INSIDE STANFORD MEDICINE

Volume 11, No. 6 ■ March 25, 2019 ■ Published by the Office of Communication & Public Affairs

How a nighttime dream changed the focus of a scientist's research into what causes a deadly heart defect.

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On Match Day, plenty of anxiety, joy, balloons

By Julie Greicius

STEVE FISCH

Medical student Carolyn Sinow on March 15 at the Li Ka Shing Center for Learning and Knowledge.

Four-hundred flutes for sparkling wine and cider lined the tables, awaiting the morning's celebratory toast. Hundreds of red, gold and white balloons were suspended on the ceiling like a held breath. With their loved ones close by, 85 Stanford medical students were about to learn where they would train to be doctors over the next several years.

Match Day, the most suspenseful day of the year for medical students, is the day that medical students nationwide open envelopes at the same time — on the West Coast, that means 9 a.m. — revealing where they will spend their residencies. This year, Match Day fell on March 15.

Lloyd Minor, MD, dean of the School of Medicine, addressed the gathering, at the Li Ka Shing Center for Learning and Knowledge, about 8:30 a.m., encouraging students to recognize the support of their friends and family not just today but throughout their upcoming careers.

"Personal resilience and the resilience we build up through our friends and our family is always going to be a constant force enabling us to remain vibrant and engaged and healthy ourselves as we seek to improve the health of those who entrust their care to us," Minor said. "This is yet the next stage in what we know is going to be — already has been and will continue to be — a brilliant career for each of you. We couldn't be more proud of you as you enter into this match process."

In the moments leading up to the big reveal, anticipation was high.

"It's been a long road to get to this point — not just the years of medical school, but the many months of applying and interviewing for residency," said Nathaniel Fleming, a fifth-year medical student from Eugene, Oregon. Fleming and fellow matching medical student Veronica Manzo met and married during medical school at Stanford, and were both hoping the envelopes held the same destination for them — she in internal medicine, he in neurology. "I'm ready to take the next step," Fleming said.

"Nervous" was how Rebecca Gao described herself ahead of Match Day. Her desired specialty, otolaryngology, "has a projected 40 percent match rate this year, so just being able to match anywhere at all is difficult," she said. Her husband — an engineer at Tesla who would be going with her to wherever her residency would be — and her mother were at her side.

Mariposa Garth-Pelly was a nurse before starting medical school at Stanford four years ago. Match Day would mark a major turning point in her journey to becoming a family medicine physician. With her husband, Sam Kim, and her parents, Celine Pele and Charles Garth, close by, Garth-Pelly prepared for what the envelope had in store for her.

Neil Gesundheit, MD, senior associate dean for medical education, was attending his 14th Match Day event at Stanford. "Given the level of student stress, I'm proud to still be standing," he quipped. Still, Gesundheit said, he enjoys celebrating with the students once they know where they've matched. "I enjoy the lower stress and tremendous relief the students feel, whether they've matched at their first choice or their 12th."

A complete match

In his remarks before the reveal, Gesundheit noted some statistics that students would soon learn for themselves. "We have a complete match today," Gesundheit said, meaning that all of the students had been matched to a residency program. "This only happens about once in a decade here at Stanford. So we're very proud." It was especially impressive, Gesundheit noted, because this year's match had a lot of people going into competitive subspecialties.

Stanford's 85 students matched in 19 fields of training: 15 in internal medicine, nine in dermatology, seven in general surgery, seven in obstetrics and gynecology, seven in anesthesiology, six in psychiatry, four in neurological surgery, four in radiology/interventional radiology, four in orthopaedic surgery, four in otolaryngology, three in pediatrics, three in emergency medicine, three in radiation oncology, two in plastic surgery, two in urology, two in family medicine, one in neurology, one in child neurology and one See MATCH, page 6

Drug could alleviate side effects of chemotherapy in breast cancer patients

By Mandy Erickson

Researchers at the School of Medicine have demonstrated a method of forecasting which breast cancer patients will suffer heart problems from a commonly used chemotherapy drug.

The researchers also found that a class of medications already approved by the Food and Drug Administration may mitigate these side effects.

Joseph Wu

"We could use this method to find out who's going to develop chemo-related toxicity and who's not," said Joseph Wu, MD, PhD, professor of cardiovascular medicine and of radiology and director of the Stanford Cardiovascular Institute. "And now we have an idea about the cardioprotective medications we can give them."

A paper describing the work was published online March 14 in *Circulation.* Wu, who is the Simon H. Stertzer, MD, Professor, is the senior author. Former research fellow Tomoya Kitani, MD, now a clinical assistant professor at the Kyoto Prefecture University of Medicine in Japan, is the lead See CANCER, page 7

Immune profile two days following stroke predicts dementia a year later, study finds

By Bruce Goldman

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A pattern of inflammatory activity in circulating blood cells two days after a stroke strongly predicts the likelihood of losing substantial mental acuity one year later, investigators at the School of Medicine report in a new study.

The findings, based on a longitudinal analysis of all major immune cell types in the blood of stroke patients, have potentially profound clinical implications. In developed countries such as the United States, 3 out of 4 stroke patients survive for substantial periods of time. However, these survivors are at twice the normal risk for dementia over the next decade, even if their cognition was initially unimpaired by the stroke.

"Being able to identify, early on, patients who are at risk for dementia is a first step toward figuring out how to treat those at-risk patients," said Marion Buckwalter, MD, PhD, associate professor of neurology and of neurosurgery.

If replicated in a larger study now underway, the findings could lead to targeted immune therapies that forestall dementia by tweaking activity in particular immune cell types during the crucial first days following a stroke, Buckwalter said.

The findings were published online March 12 in *Brain*. Buckwalter shares senior authorship with Brice Gaudilliere, MD, PhD, and Nima Aghaeepour, PhD, who are both assistant professors of anesthesiology, perioperative and pain medicine at Stanford. The lead author is Amy Tsai, a former research assistant in Gaudilliere's lab who's now a medical student at UC-Davis.

The investigators recruited study participants from among patients at Stanford Hospital who had experienced an ischemic stroke within the previous 24 hours. Blood was drawn from the 25 participants on multiple days during the first week, then See STROKE, page 6

Democracy linked to health gains in study of various nations

By Beth Duff-Brown

Most studies that look at whether democracy improves global health rely on measurements of life expectancy at birth and infant mortality rates. Yet those measures disproportionately reflect progress on infectious diseases — such as malaria, diarrheal illnesses and pneumonia — which relies heavily on foreign aid.

A new study led by Stanford Medicine and the Council on Foreign Relations suggests that a better way to measure the role of democracy in public health is to examine the causes of adult mortality, such as noncommunicable diseases, HIV, cardiovascular disease and transportation injuries. Little international assistance targets these noncommunicable diseases.

Tara Templin

When the researchers measured improvements in those particular areas of public health, the results proved dramatic.

"The results of this study suggest that elections and the health of the people are increasingly inseparable," the authors wrote.

A paper describing the findings was published March 13 in The Lancet. Tara Templin, a graduate student in health research and policy at Stanford Health Policy, shares lead authorship with Thomas Bollyky, JD, director of the Global Health Program at the Council on Foreign Relations.

"Democratic institutions and processes, and particularly free and fair elections, can be an important catalyst for improving population health, with the largest health gains possible for cardiovascular and other noncommunicable diseases," the authors wrote.

Templin said the study brings new data to the question of how governance and health inform global health policy debates, particularly as global health funding stagnates.

"As more cases of cardiovascular diseases, diabetes and cancers occur in low- and middle-income countries, there will be a need for greater health care infrastructure and resources to provide chronic care that weren't as critical in providing childhood vaccines or acute care," Templin said.

Free and fair elections for better health

In 2016, the four mortality causes most ameliorated by democracy — cardiovascular disease, tuberculosis, transportation injuries and other noncommunicable diseases — were responsible for 25 percent of total death and disability in people younger than 70 in low- and middle-income countries. That same year, cardiovascular diseases accounted for 14 million deaths in those countries, 42 percent of which occurred in individuals younger than 70.

Over the past 20 years, the increase in democratic experience reduced mortality in these countries from cardiovascular disease, other noncommunicable diseases and tuberculosis between 8-10 percent, the authors wrote.

"Free and fair elections appear important for improving adult health and noncommunicable disease outcomes, most likely by increasing government accountability and responsiveness," the study said.

The researchers used data from the Global Burden of Diseases, Injuries and Risk Factors Study; V-Dem; and Financing Global Health databases. The data cover 170 countries from 1970 to 2015.

What Templin and her co-authors found was democracy was associated with better noncommunicable disease outcomes. They hypothesize that democracies may give higher priority to health care investments.

HIV-free life expectancy at age 15, for example, improved significantly — on average by 3 percent every 10 years during the study period — after countries transitioned to democracy. Democratic experience also explains significant improvements in mortality from cardiovascular disease, tuberculosis, transportation injuries, cancers, cirrhosis and other noncommunicable diseases, the study said.

And yet, this connection between fair elections and global health is little understood.

"Democratic government has not been a driving force in global health," the researchers wrote. "Many of the countries that have had the greatest improvements in life expectancy and child mortality over the past 15 years are electoral autocracies that achieved their health successes with the heavy contribution of foreign aid."

They note that Ethiopia, Myanmar, Rwanda and Uganda all extended their life expectancy by 10 years or more between 1996 and 2016. The governments of these countries were elected, however, in multiparty elections designed so the opposition could only lose, making them among the least democratic nations in the world.

Yet these nations were among the top two-dozen recipients of foreign assistance for health.

Only 2 percent of the total development assistance for health in 2016 was devoted to noncommunicable diseases, which was the cause of 58 percent of the death and disability in low-income and middle-income countries that same year, the researchers found.

"Although many bilateral aid agencies emphasize the importance of democratic governance in their policy statements," the authors wrote, "most studies of development assistance have found no correlation between foreign aid and democratic governance and, in some instance, a negative correlation."

Autocracies such as Cuba and China, known for providing good health care **See DEMOCRACY, page 3**

Heart research shows ability of wearables to detect atrial fibrillation

Researchers from the School of Medicine presented preliminary results of the Apple Heart Study, an unprecedented virtual study with over 400,000 enrolled participants, on March 16. The researchers reported that wearable technology can safely identify heart rate irregularities that subsequent testing confirmed to be atrial fibrillation, a leading cause of stroke and hospitalization in the United States.

The study was launched with sponsorship by Apple Inc. in November 2017 to determine whether a mobile app that uses data from a heart-rate pulse sensor on the Apple Watch can identify atrial fibrillation. The condition often remains hidden because many people don't experience symptoms.

Key findings from the study include:

- Overall, only 0.5 percent of participants received irregular pulse notifications, an important finding given concerns about potential over-notification.
- Comparisons between irregular pulse-detection on Apple Watch and simultaneous electrocardiography patch recordings showed the pulse detection algorithm (indicating a positive tachogram reading) has a 71 percent positive predictive value. Eighty-four percent of the time, participants who received irregular pulse notifications were found to be in atrial fibrillation at the time of the notification.
- One-third (34 percent) of the participants who received irregular pulse notifications and followed up by using an ECG patch over a week later were found to have atrial fibrillation. Since atrial fibrillation is an intermittent condition, it's not surprising for it to go undetected in subsequent ECG patch monitoring.
- Fifty-seven percent of those who received irregular pulse notifications sought medical attention.

"The results of the Apple Heart Study highlight the potential role that innovative digital technology can play in creating more predictive and preventive health care," said Lloyd Minor, MD, dean of the School of Medicine. "Atrial fibrillation is just the beginning, as this study opens the door to further research into wearable technologies and how they might be used to prevent disease before it strikes — a key goal of precision health."

For the study, each participant was required to have an Apple Watch (series 1, 2 or 3) and an iPhone. The most recent Apple Watch, which features a built-in ECG, wasn't part of the study, as it was released after the study's launch. The Apple Heart Study app intermittently checked the heart-rate pulse sensor for measurements of an irregular pulse. If an irregular pulse was detected, the participant received a notification and was asked to schedule a telemedicine consultation with a doctor involved in the study through American Well. Participants were then sent ambulatory ECG patches through BioTelemetry, which recorded the electrical rhythm of their hearts for up to a week.

COURTESY OF APPLE

Examples of notifications received by participants in the Apple Heart Study, which set out to determine whether a mobile app that uses data from an Apple Watch sensor could identify atrial fibrillation.

The study's findings have the potential to help patients and clinicians understand how devices like the Apple Watch can play a role in detecting conditions such as atrial fibrillation, a deadly and often undiagnosed disease," said Turakhia. "The virtual design of this study also provides a strong foundation upon which future research can be conducted to explore the health implications of wearable technology."

"The performance and accuracy we observed in this study provide important information as we seek to understand the potential impact of wearable technology on the health system," said Perez. "Further research will help people make more informed health decisions."

Researchers from the Lankenau Heart Institute, Jefferson Medical College, the University of Colorado School of Medicine, Cooper Medical School of Rowan University, StopAfib.org, the American Foundation for Women's Health, and Duke University also contributed to the study.

The Apple Heart Study was funded by Apple Inc. **ISM**

INSIDE STANFORD MEDICINE

Inside Stanford Medicine is published monthly in July and December and semi-monthly the rest of the year.

is produced by
Office of Communication & Public Affairs
Stanford University
School of Medicine
3172 Porter Drive
Palo Alto, CA 94304
Mail code 5471
(650) 723-6911
http://med.stanford.edu/news/

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STANFORD MEDICINE

Molecular data can predict cancer recurrence, scientists say

By Krista Conger

Molecular data obtained from breast cancer cells can be used to predict which patients are at a high risk for recurrence even decades after their diagnosis, according to a new study jointly conducted by researchers at the School of Medicine and the Cancer Research UK Cambridge Institute, as well as several other institutions.

In particular, some patients whose tumors express the estrogen receptor but not another receptor called HER2 are at a persistent risk of relapse over time. Until now, there has been no way to identify those women among their peers.

The study also identifies a subgroup of women with what are known as triple-negative breast tumors whose cancers are unlikely to return after five years. The researchers also learned where and when in the body certain breast cancers are likely to metastasize.

The findings provide researchers and clinicians with a powerful new tool with which to predict a patient's prognosis and potentially direct clinical decision-making.

"For the first time, we've been able to study the rates and routes of breast cancer metastases at unprecedented resolution," said Christina Curtis, PhD, assistant professor of medicine and of genetics at Stanford and co-director of the Molecular Tumor Board at the Stanford Cancer Institute. Curtis first defined the distinct subgroups of patients in a study published in *Nature* in 2012.

"Once we compiled the rich, clinical follow-up data, it became strikingly apparent that distinct relapse trajectories characterized patients in each of the genomic subgroups we had previously defined," Curtis said.

In particular, about 25 percent of women with estrogen-receptor-positive, or ER-positive, tumors have a 42 to 55 percent chance of seeing their cancers return within 20 years, the researchers found.

"We found that about 25 percent of women whose tumors express the estrogen receptor and not HER2 have an exceedingly high risk of late distant relapse and account for the vast majority of these events," Curtis said. "These are the women who seem to be cured but then present with systemic disease many years later. Until now, there has been no good way to identify this subset of women who might benefit from ongoing screening or treatment."

The new study was published online March 13 in *Nature*. Curtis shares senior authorship with Carlos Caldas, MD, director of the Cambridge Breast Cancer Research Unit and professor of cancer medicine at the University of Cambridge. Oscar Rueda, PhD, a senior research associate at the University of Cambridge, is the lead author.

"A clinical challenge in breast cancer management has been distinguishing which tumors pose greatest risk of late recurrence," said Harold Burstein, MD, PhD, associate professor of medicine at Harvard Medical School, who was not involved in the research. "This important scientific paper identifies molecular features that determine the timing of cancer recurrence. In the future, this type of genomic classification should help us separate patients who remain at jeopardy — and might warrant additional or ongoing treatment — and those who do not."

'Unprecedented resolution'

Importantly, in many cases the study also identified the likely genomic drivers of specific tumors, many of which the researchers believe could serve as targets for drug development.

Traditionally, physicians have relied primarily on clinical variables — such as the size and grade of the tumor at diagnosis, the degree of lymph node involvement and the age of the patient — when making treatment decisions and prognoses. More recently, genomic tests to determine which, if any, molecules are expressed by the cancer cells have been used to subcategorize breast cancers and guide treatment decisions.

For example, a tumor that expresses high levels of estrogen, indicating it relies on estrogen to grow, might be successfully treated by drugs that block the binding of the hormone to the cancer. The presence or absence of HER2 is also routinely used to categorize breast cancers and plan treatment.

Curtis and her colleagues studied the long-term medical histories of more than 3,000 women diagnosed with breast cancer in the United Kingdom and Canada between 1977 and 2005 to learn more about whether, when and where specific breast cancer types are likely to spread after initially successful treatment. For 1,980 of these women, the database also contained molecular details about their cancers, including information about estrogen receptor and HER2 expression, the levels of the expression of other specific cancer-associated genes and the presence or absence of specific, acquired genetic aberrations known as copy number variations. Integrating all this information, they developed a computer model that identified four tumor subgroups that express the estrogen receptor but not HER2 that have a high risk of recurrence, as well as other ER-positive/HER2-negative breast cancer subtypes that were less likely to recur.

The researchers were also able to identify a subgroup of women with triple-negative breast cancers — considered to be an aggressive and more difficult form of the disease to treat — who are unlikely to see their cancers recur after five years.

Distinct patterns of metastasis

Curtis and her colleagues found that they could predict the course of the disease at different points during a patient's clinical follow-up. They also found that the subgroups display distinct patterns of recurrence in terms of timing and the sites of metastasis.

PAUL SAKUMA

A researcher at Stanford, joined by collaborators at several other institutions, has subcategorized tumors to predict recurrence, guide treatment decisions and improve drug development.

"Our model uniquely accounts for the chronology of a patient's disease and is based on a genome-driven classification scheme that can inform personalized therapeutic approaches," Curtis said.

One unavoidable limitation of a retrospective study spanning decades such as this means the researchers are studying patients diagnosed and treated many years ago.

"This is a retrospective, observational cohort," Curtis said. "Since then, treatment paradigms have changed for some patient subgroups. Most notably, trastuzumab — which specifically targets the HER2 receptor and has dramatically improved outcomes for patients with HER2-positive breast cancer since it was approved for use in early stage breast cancer in 2006 — was not an option for many of the women in this study. It will be important to take what we've learned here and determine whether we can similarly improve the outcomes of these patient subgroups at high risk of recurrence with new therapies that target their specific genomic drivers."

Curtis and her colleagues are currently planning clinical trials to do just that. They also developed a web-based research tool that may ultimately help clinicians more accurately predict an individual's risk of relapse and guide treatment decisions.

"We've shown that the molecular nature of a woman's breast cancer determines how their disease could progress, not just for the first five years, but also later, even if it comes back," Rueda said. "We hope that our research tool can be turned into a test doctors can easily use to guide treatment recommendations."

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

Curtis is a member of the Stanford Cancer Institute and Stanford Bio-X.

Other Stanford co-authors of the study are instructors of medicine Jose Seoane, PhD, and Jennifer Caswell-Jin, MD. Researchers from the British Columbia Cancer Research Center; the Research Institute in Oncology and Hematology in Winnipeg, Canada; the University of Nottingham; King's College London; and the University of Valladolid in Spain also contributed to the work.

The research was supported by Cancer Research UK, the Experimental Cancer Medicine Center, the National Institute for Health Research in the United Kingdom, the Breast Cancer Research Foundation, the American Association for Cancer Research and an NIH Director's Pioneer Award.

A patent application has been filed on aspects of the research findings by Curtis, Caldas, Rueda and Seoane.

Stanford's departments of Medicine and of Genetics also supported the work.

ISM

Democracy

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at low cost, have not always been as successful when their populations' health needs shifted to treating and preventing noncommunicable diseases. A 2017 assessment, for example, found that true life expectancy in China was lower than its expected life expectancy at birth from 1980 to 2000 and has only improved over the past decade with increased government health spending. In Cuba, the degree to which its observed life expectancy has exceeded expectations has decreased, from four-to-seven years higher than expected in 1970 to three-to-five years higher than expected in 2016.

"There is good reason to believe that the role that democracy plays in child health and infectious diseases may not be generalizable to the diseases that disproportionately affect adults," Bollyky said. Cardiovascular diseases, cancers and other noncommunicable diseases, according to Bollyky, are largely chronic, costlier to treat than most infectious diseases, and require more health care infrastructure and skilled medical personnel.

The researchers hypothesize that democracy improves population health because:

- When enforced through regular, free and fair elections, democracies should have a greater incentive than autocracies to provide health-promoting resources and services to a larger proportion of the population.
- Democracies are more open to feedback from a broader range of interest groups, more protective of media freedom and might be more willing to use that feedback to improve their public health programs.
- Autocracies reduce political competition and access to information, which might deter constituent feedback and responsive governance.

Various studies have concluded that democratic rule is better for population health, but almost all of them have focused on infant and child mortality or life expectancy at birth.

Over the past 20 years, the average country's increase in democracy reduced mortality from cardiovascular disease by roughly 10 percent, the authors wrote. They estimate that more than 16 million cardiovascular deaths may have been averted due to an increase in democracy globally from 1995 to 2015. They also found improvements in other health burdens in the countries where democracy has taken hold: an 8.9 percent reduction in deaths from tuberculosis, a 9.5 percent drop in deaths from transportation injuries and a 9.1 percent mortality reduction in other noncommunicable disease, such as congenital heart disease and congenital birth defects.

"This study suggests that democratic governance and its promotion, along with other government accountability measures, might further enhance efforts to improve population health," the study said. "Pretending otherwise is akin to believing that the solution to a nation's crumbling roads and infrastructure is just a technical schematic and cheaper materials."

Other researchers from the Council on Foreign Relations, as well as researchers from the University of Washington-Seattle and Bilkent University in Turkey, also contributed to the study.

Funding for the research came from Bloomberg Philanthropies and the Bill & Melinda Gates Foundation.

Stanford's Department of Health Research and Policy also supported the work. **ISM**

Mystery novel, dream spur key scientific insight into heart defect

By Bruce Goldman

Jim Spudich isn't the kind of avid reader who devours a book in two days and moves immediately to the next on his nightstand. He just reads himself to sleep on evenings when he wants to reroute his brain from thinking about his work. Which is most of the time.

"Creative research is not a job — it's a full-time, almost childlike obsession driven by the curiosity that all kids have," said Spudich, PhD, professor of biochemistry. "I see myself as a kid who's never had to grow up."

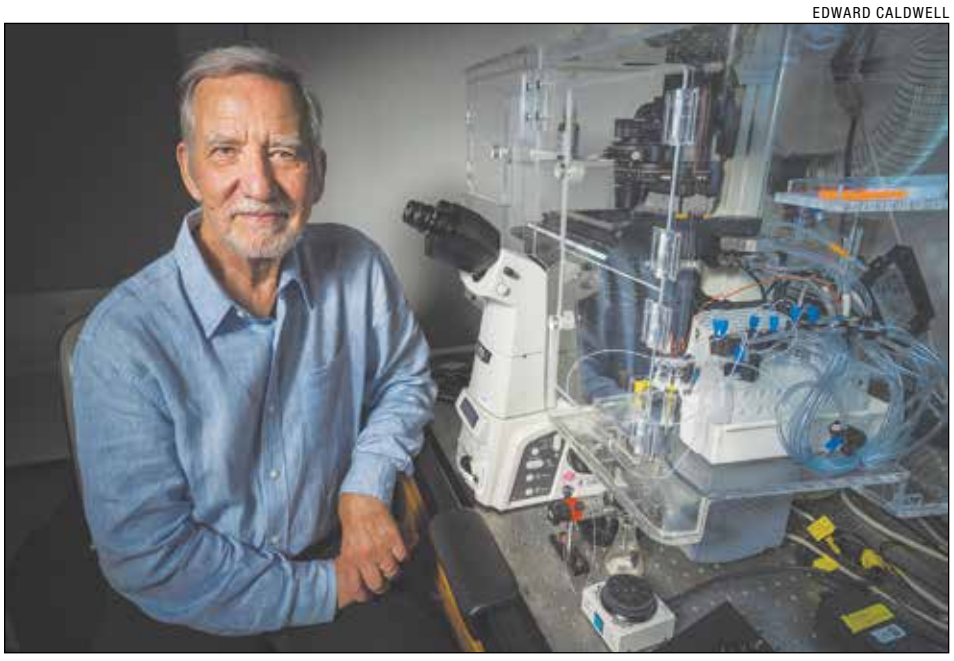
Yet even scientists have to sleep. Spudich, 77, ordinarily gets his fair share — close to eight hours a night. But when he needs some help winding down, a good murder mystery will do it, especially if it's set in the American Southwest, where he spent several years as a child and whose mesa-strewn terrain he's flown over many times in the pilot's seat of a small plane. (He's a licensed pilot.)

Flying is the ultimate escape for Spudich, the Douglass M. and Nola Leishman Professor in Cardiovascular Disease. "I can go out once every couple of weeks for an hour, climb up into the clouds and get some perspective as everything down below disappears," he said. In particular, his taste in bird's-eye views favors mesas, which look like what you'd get if you sawed the top off a mountain.

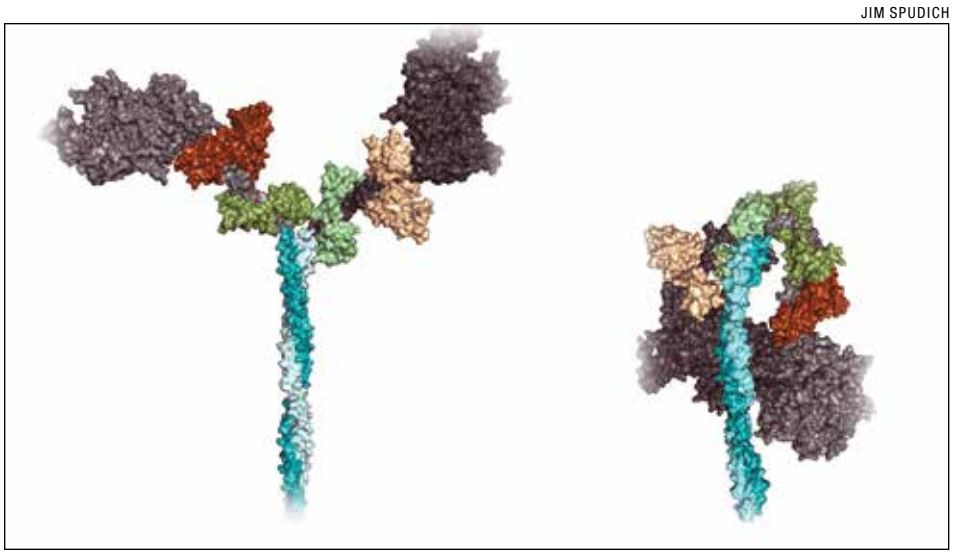
One evening, in December 2014, Spudich's wife of 54 years, Anna, who knows his tastes well, slipped him some bedtime reading, a murder mystery. Spudich knocked off a few chapters before falling asleep, only to awaken in the dark with the germ of a vision that would solve a mystery he'd been brooding over for more than a year.

"It's not so unusual that we scientists go to bed dreaming about our research," Spudich said. "What was different about this dream was that it changed the entire course of our work."

EDWARD CALDWELL



JIM SPUDICH



COURTESY OF JIM SPUDICH

(Top left) Jim Spudich studies how mutations in cardiac myosin could play a role in a deadly heart disorder. (Below left) An illustration of a myosin molecule in an "open" and "folded" position. (Above) An avid pilot, Spudich, shown here in the mid-1990s, has flown over many mesas. He had a dream about a mesa that provided an insight about what may be at the root of the disorder.

Dying young

When he was 5, Spudich moved with his family from Illinois to Phoenix because his older sister had severe heart trouble, and her doctor had warned that she'd never make it through another cold winter. In the warm, dry Arizona climate, she survived for five more years before succumbing to a heart attack.

The heart beats because it's made of muscle cells that rhythmically shrink in sync and then relax, pumping blood throughout the vascular system. Since 1969, Spudich has zeroed in on a pair of proteins that make all muscular contraction possible. His interest has led him to focus on a particular disorder called hypertrophic cardiomyopathy.

"HCM, as we often call it, was first recognized as a genetics-based disease only about 25 years ago," Spudich said. "It's epitomized by the phenomenon of young athletes in their prime keeling over from sudden death when nobody even knew anything was wrong with them."

HCM's defining clinical symptom is a hypercontractile heart. "It's as if you're out for a short run," Spudich said. "The problem is, you're doing that 24 hours a day, every day of your life."

In response, the heart muscle thickens and eventually stiffens, choking off blood flow through the organ. The progression can end in sudden death.

One in every 500 people is affected by HCM. "The number of patients keeps getting bigger," Spudich said. "We used to have no idea how many there were, because people weren't checking." But with the discovery that HCM could — and usually did — arise from genetic mutations, intensive gene screening has turned up hundreds of different mutations, mostly in a small number of the proteins of the muscle-contraction machinery, that can cause the disorder.

A riddle that has stymied Spudich for years is this: "We usually think of mutations as causing a protein not to work as well as the unmutated version does; they're messing with what was a beautiful evolutionary design," he said. "But HCM mutations are doing the opposite. They're somehow causing the protein to work 'better.'" The result is a heartbeat that's too powerful.

More than a third of those mutations occur in the gene coding for a protein that's intimately involved in every move we make and every beat of the heart. Spudich knows a thing or two about that protein, called myosin. He won the coveted Lasker Award in 2012, largely for inventing novel ways to study individual myosin molecules and their interactions with another protein called actin.

Of the 40 or so nearly identical versions of myosin produced in every cell of the body, Spudich pays the most attention to cardiac myosin, the version produced and used by heart muscle cells. In fact, Spudich's eight-person lab is one of the few in the world bearing down on human cardiac myosin in a serious way, he said. "So, I have an obligation to keep working on this until we cross the finish line."

Current HCM therapies leave much to be desired. Physicians rely on conventional heart drugs that, for example, slow the heartbeat. The ultimate treatment comes later: open-heart surgery to cut away excess heart muscle. "You can only do this once," Spudich said.

Looking for clues

A myosin molecule's general structure, known since the 1960s, resembles a two-headed monster: two large globular "heads" protruding from a stalklike tail. It's long been known that myosin sometimes adopts a posture in which its heads fold over and snuggle up against its tail, reminiscent of a sleeping flamingo with its head tucked under a wing.

"But the relevance of this to HCM was essentially unknown," Spudich said.

To see why it's important, it helps to know how healthy muscles contract. Spudich has played a major role in explaining this in precise molecular detail.

A cardiac muscle cell contains perhaps a hundred repeating structural subunits called sarcomeres, arranged one after another in a series. A sarcomere is composed of myosin-rich "thick filaments" alternating with parallel "thin filaments" made of actin.

Closer inspection reveals that each thick filament is knitted from the bottom halves of myosin molecules' tails. In response to electrical impulses traversing the heart, the myosin heads protruding from the thick filament chomp down on the nearest actin filament, then tug against it like sailors tugging in tandem on a rope, pulling the sarcomere walls closer together and making the muscle fiber contract, before relaxing again.

That's a heartbeat. And if those myosin sailors are tugging too hard on those actin ropes? That's hypercontractility, the hallmark of HCM.

But why would this happen?

About 35 to 40 percent of all known HCM-inducing mutations are in cardiac myosin, making it an obvious candidate for intense scrutiny. But until about a dozen years ago, nobody could study the effects of cardiac myosin mutations, Spudich said, because the biotechnology for making significant amounts of it that would work didn't exist yet.

Then one of his frequent collaborators at the University of Colorado figured out a way to pull it off. Spudich dropped everything else he'd been doing and began systematically characterizing the effects of HCM-inducing mutations on the function of cardiac myosin molecules, asking: Why would so many diverse mutations all cause myosin to be hypercontractile?

Most of these mutations pop up on the molecule's head. Another big batch are in the top part of its tail. Spudich hypothesized that the mutations somehow made each individual cardiac-myosin molecule faster-moving or more forceful than normal.

"But in the many mutations we studied, neither molecular speed nor strength were accounting for mutation-induced hypercontractility," he said. "We were missing something."

Dreaming

On Dec. 14, 2014, after many months of not getting expected results, Spudich lay awake in bed late at night wondering what clue he'd been overlooking.

"For just one night, stop thinking about your work," Anna told him. She gave him a book she was sure he was going to like: *The Haunted Mesa*, by Louis L'Amour. The book's plot unfolded in the setting of a Southwestern mesa similar to many Spudich had spied from above during his airborne sojourns in the Southwest.

He nodded off about 20 pages in, awakening hours later from a vivid dream in which the image of a mesa morphed into a myosin molecule. **See DREAM, page 5**

Modified immune cells issue alert when cancer detected

By Hanae Armitage

Immune cells imbued with the power to detect and reveal tumors could be a new method of diagnosing cancer, according to a study from the School of Medicine.

The research, performed in mice, involved modifying a specific class of immune cells to patrol the body for cancer and send a signal through blood or urine when they found trouble.

"We've been after early cancer diagnostics for years, but this time, we came at it from another angle," said Sanjiv "Sam" Gambhir, MD, PhD, professor and chair of radiology and director of the Canary Center at Stanford for Cancer Early Detection. "We said, if nature doesn't give you sufficient signal that cancer is present, can we force the body to make one? In this case, can we force immune cells to emit detectable markers if cancer exists somewhere in the body?"

The question prompted the engineering of a sort of immune cell-turned-informant, which Gambhir said is possibly the first in-animal example of a phenomenon called "immunodiagnostics." Like immunotherapy, immunodiagnostics repurposes the body's own cells to perform a task — in this case, reporting the presence of disease or damaged cells.

Currently, the technique can detect tumors as small as 4 millimeters in diameter — about the size of a pencil top eraser — which outperforms some of the most advanced early tumor detection methods out there, said Gambhir, who is also the director of the Precision Health and Integrated Diagnostics Center at Stanford.

He said the immune cell signals are flagging a specific class of malfunctioning cells, which includes tumor cells, but is not limited to them. The technique also could be tailored to detect more than just cancer, and could potentially flag other disorders, such as multiple sclerosis or chronic inflammation, he said.

A paper detailing the findings of the study was published online March 18 in *Nature Biotechnology*. Gambhir, who is the Virginia and D.K. Ludwig Professor for Clinical Investigation in Cancer Research, is the senior author. Amin Aalipour, an MD-PHD student, is the lead author.

Natural detective, engineered narc

As tumors grow, little bits of their DNA slough off and float out into the bloodstream. A simple blood draw should be able to detect the cancerous scraps, theoretically, but the reality is that circulating tumor DNA is not always plentiful, and so the chances of capturing enough of it in a blood draw or urine sample are usually slim, especially when the tumor is relatively small.

"As you look for evidence of cancer at earlier points in the diseases, there are fewer and fewer circulating tumor molecules in the bloodstream," Gambhir said. But finding cancer earlier could be crucial to treating it more successfully.

In searching for a new solution, Gambhir and his team tapped into one particular subclass of immune cells, known as macrophages, that naturally scout for damaged or malfunctioning cells in the body.

The challenge then became one of determining when the macrophage had detected a possible tumor environment. And that's where Gambhir's team came up with a solution.

The team played to the macrophage's natural strengths. Many immune cells, including macrophages, change on a genetic level when they prepare to perform immunological duties. Certain genes are known to turn on when a macrophage comes into contact with the tumor environment, helping to activate the macrophage's main job: gobbling up malfunctioning or dead cells. Gambhir's engineering feat harnesses the process that spurs these genes into action.

Prompted by the promoter

Every gene contains something called a promoter, which is a sequence of DNA that primes gene activation. Once a promoter is awakened — in this case, by the macrophage's detection of tumor cells — the rest of the gene's activation process ensues, and the gene becomes fully functional.

Gambhir and his team were able to repurpose the promoters of the genes that perk up when macrophages detect a suspicious cell. The team is integrating these tumor-associated promoters into new genes that, when turned on, send out a signal that scientists can see in the blood or urine.

STEVE FISCH

Sam Gambhir and his team have come up with a way to re-engineer immune cells known as macrophages to detect and flag cancer in mice.

"The molecular marker is called Gaussia luciferase, and under certain chemical circumstances, it glows," Gambhir said. "So the idea is, we pick a gene that turns on when a macrophage senses a tumor cell, we link that gene's promoter to Gaussia luciferase and finally, we integrate it into the macrophages."

These re-engineered immune cells can then roam the body in their usual manner, only this time, if they find a damaged cell, they tell you. Gambhir and his team tested the refined macrophages in mice and were able to detect mouse models of breast cancer from a vial of blood or urine when the tumor was just 4 millimeters in diameter. At this nascent stage of the tumor, the new immunodiagnostic outperformed other cancer detection methods: Because the tumor is so small, it's not producing enough circulating DNA to reliably show up in blood; and a PET scan, which is a standard, image-based cancer detection method, is only sensitive enough to find tumors 8 millimeters in diameter.

To see if macrophages have stumbled across a possible tumor, scientists add a special molecule to the blood or urine sample that reacts to the presence of Gaussia luciferase and causes it to glow. Fluorescing fluid means the modified macrophage has activated its tumor-associated genes.

Refining the diagnosis

Although a fluorescing vial likely reveals the presence of cancer, it's not a definitive diagnosis at this point in the development of the technique, Gambhir said. Macrophages activate certain sets of genes that can correspond to a handful of off-kilter cells, such as a tumor or a wound. Once the macrophage sends its signal, Gambhir said, doctors would use one of several other tests to determine whether it's reacting to a cancerous target.

He added that the engineering trick done with Gaussia luciferase is modular and can apply to just about any other reporter, such as a PET scan reporter or tracer. That way, a tumor-activated macrophage would likewise glow under a PET scan, making it easy for doctors to spot cancer cells. What's more, Gambhir added, the immunodiagnostic strategy is not restricted to macrophages; the technique could also work in other immune cells, such as T-cells.

In the immediate future, Gambhir said that he plans to continue to test the detection method in other types of cancers and animal models, likewise refining the method to home in on tumor cells only, rather than cells with other types of damage. **ISM**

Dream

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It was 5:30 a.m. Aflame with inspiration, Spudich jumped out of bed and beelined to his computer, a new hypothesis in his head.

Protein molecules are born as linear sequences of chemical building blocks called amino acids, but that one-dimensionality doesn't last long. Almost as soon as each molecule gets produced in a cell, it folds up into a characteristic three-dimensional shape it will retain for the rest of its working life.

With molecular-modeling software now widely available, researchers including Spudich can speedily rotate a molecule of interest in any of three dimensions onscreen. Viewed from the right perspective, one part of the myosin head's surface is a broad expanse, as flat as the mesa of the dream that had just awakened the sleeping scientist.

Those who study myosin have known about this mesalike surface since 1993, Spudich said. But until now, nobody had given much thought to its significance.

Every amino acid sequence of a protein molecule is specified by the gene encoding that particular protein. There are 20 different amino acid varieties to choose from, each with its own distinctive biochemical quirks: for example, a negative versus positive versus neutral electrical charge.

One typical type of mutation results in the substitution of one amino acid for another.

Spudich's team had previously generated computer models flagging points along cardiac myosin's linear sequence where a mutated amino acid had been found to cause HCM. These mutations' locations seemed to be scattered pretty randomly along the molecule.

But viewed on the properly folded molecule, as Spudich was now doing, many of these mutations could be seen to fall somewhere on the mesalike surface of the head of myosin. Many others fell along the part of the tail against which the head rested when the molecule was assuming its "sleeping" position.

Spudich's group had been studying 15 or so of the most common HCM-inducing cardiac myosin mutations. They knew that most of those mutations had the effect of changing or eliminating the electrical charge the amino acid in the unmutated molecule would have had.

Now it hit him: Opposites attract. Surfaces with lots of positive charges on them are drawn to surfaces with lots of negative charges on them. Any mutation that reduces this charge opposition could result in the myosin head's spending less time tucked up against its tail and more time on duty tugging on its nearby actin filament. These mutations aren't changing myosin molecules' strength or speed; they're just making more heads available to do the tugging.

All hands on deck

What Spudich and others had been overlooking was this: Most of the time, many of the myosin heads in the thick filament are on break — at least in healthy heart muscle. Thick fibers normally host a huge reserve army of loafing myosin heads, which is a good thing; those loafing heads can be recruited by normal physiological responses when needed. But HCM mutations effectively nudge them back on the job, even when they're not needed.

A sarcomere's contractile force, Spudich reasoned, is proportional to the number of myosin heads that are "grabbing" onto the actin filament at any given moment. Normally, the mesalike surface of a cardiac myosin molecule spends much of its time in coordinated proximity with a portion of the "tail" section, sequestering the head so it can't grab the actin filament.

Looking at the folded cardiac-myosin molecule on his computer screen, Spudich realized that by weakening the overall attraction between a myosin molecule's head and tail, HCM-inducing mutations were freeing up myosin heads to grab onto a neighboring actin filament, increasing the number of myosin heads actually pulling their weight at any one time. Hence, the hypercontractile heart. Not quite proof, but a hypothesis with a bright future.

Spudich's group has since shown that mutations at these suspect sites do actually alter cardiac myosin's posture and put more heads in play. A 2018 *Proceedings of the National Academy of Sciences* paper co-authored by Spudich suggested that a drug called mavacamten, now in phase-3 clinical trials for HCM, may be successful in reversing the hypercontractility induced by a wide range of HCM-inducing mutations on the myosin mesa.

All patients in two earlier trials of mavacamten showed significant improvement. These trials have been sponsored by a South San Francisco-based biotechnology company, MyoKardia Inc., that Spudich co-founded in 1998 to speed the translation of his findings into drugs that could be used in clinical practice to treat HCM. Mavacamten was the fruit of this discovery effort.

"The drug is pushing available heads into the unavailable state — the opposite of what I believe most of these mutations are doing," Spudich said.

In principle, this approach might apply to most HCM-causing mutations.

As for *The Haunted Mesa*, Spudich eventually finished it and, he said, enjoyed it. But the thing that sticks with him was that image of a mesa and its prophetic power, as revealed in his dream that night.

What if Spudich's wife hadn't given him that book to read that night? "I think someone else would have stumbled on the same idea," he said. "The dream just jump-started it, accelerating progress by a number of years."

For this, all hail Morpheus. "Sleep is amazing," Spudich said. "You've been thinking and thinking and thinking about something for such a long time. Then suddenly the dream solves the puzzle for you." **ISM**

Match

continued from page 1

in ophthalmology.

About 25 percent of the matching students will be staying at Stanford for their residencies, Gesundheit said. Another 25 percent will be staying in California but not at Stanford. The rest of the students will go to 13 other states.

It was the sixth Match Day at Stanford for Mijiza Sanchez, EdD, MPA, associate dean for medical student affairs. Her team — including student life manager Tanicia Perry and operations coordinator Dale Lemmerick — produces the event each year, ensuring it is unique for each class and also supportive of every student's unique experience on such a fateful day.

"Match Day is a very highly charged and emotional event," Sanchez said. "We provide rooms so that students can open their envelopes in private if they don't want to do it in the large room." From orientation to graduation, Sanchez and her team support the students' progress. "The Office of Medical Student Affairs plays an integral role in each of the matching students reaching this milestone," she said. "It's a very happy day for all of us."

Christian O'Donnell, a fourth-year medical student who had been deployed to Iraq in the 1st Infantry Division in 2004, said he was "excited to move to the next phase of training." His wife, Raphaelle, was at his side, and his parents and mother-in-law had also flown in from Boston and Chicago, respectively, to be there.

The envelope, please

As the hour approached, students were directed to the four corners of the room, where their academic advising deans — Susan Knox, MD, PhD, associate professor of radiation oncology; Nounou Taleghani, MD, PhD, clinical associate professor of emergency medicine; Eric Sibley, MD, PhD, professor of pediatric gastroenterology; and Amy Ladd, MD, professor of orthopaedic surgery and the Elsbach-Richards Professor of Surgery — were standing by with the envelopes. After the final seconds of countdown, the balloons dropped from the ceiling and students tore open their red envelopes.

Looking surprisingly calm, O'Donnell learned he'd be staying at Stanford to train in anesthesiology, with a focus on critical care. He smiled, visibly relieved and happy, and embraced his wife. His father's eyes welled with tears, and his family cheered.

Garth-Pelly got the news that she matched at the Institute for Family Health/Mount Sinai family medicine residency program in Harlem. "I'm thrilled!" she said. She'll be finishing up packing and moving to New York with her husband next weekend.

"I matched at Michigan!" Gao said. She got her first choice, adding, "I'm already planning ahead for a busy but rewarding new few years." Her husband, she said, was "even more relieved I matched at Michigan so he can find a job!"

Fleming and Manzo were beaming, having matched at the University of California-San Francisco together.

Gesundheit led the room in a toast to students and families, and then invited everyone to enjoy a catered brunch. Students went on hugging, cheering and sharing their news with each other throughout the morning. They'd reconvene in the evening for a celebratory dinner. **ISM**

STEVE FISCH

STEVE FISCH

(Above) Madeline Grade, who matched in emergency medicine at UC-San Francisco, with Dean Lloyd Minor. (Right) Associate Dean of MD Admissions Iris Gibbs, center, on Match Day with medical students who had learned where they would be spending their residencies.

Stroke

continued from page 1

at two weeks, one month, three months and one year after their strokes. Using mass cytometry, the researchers assessed the properties and activation states of the 10 million or so individual immune cells obtained in each blood draw.

Measuring cognitive ability

At days 3, 30, 90 and 365 after their strokes, participants also took the Montreal Cognitive Assessment, or MoCA. The test measures several aspects of cognition, including spatial knowledge, memory and ability to calculate. It is designed to detect cognitive deficiencies. In particular, the scientists compared each participant's MoCA performance on day 90 with the participant's performance on day 365.

Nima Aghaeepour

"Nearly one-third of the participants' MoCA scores showed declines between three months and one year out from their stroke," Buckwalter said.

Each participant's mass cytometry results and MoCA scores were fed into an algorithm developed in Aghaeepour's laboratory. This algorithm was specifically designed for its ability to reduce massively complicated collections of highly correlated data to more manageable data sets.

The investigators identified three distinct phases — recognizable at post-stroke days 2, 5 and 90 — through which the immune system progresses before returning to normal about a year after the event. Each phase is marked by its own unique set of deviations in relative numbers and activation levels of a small number of immune cell types in the blood.

It was the first, or acute, phase, peaking just two days after the stroke, that grabbed the researchers' attention. The more exaggerated the deviations among the handful of immune cells identified as defining that phase, the more likely a participant was to suffer a drop in performance on the mental test between three months and one year out from the event, the study found.

Brice Gaudilliere

The correlation, which was big enough to achieve statistical significance in this small study, was independent of age, sex, body mass index, location of the stroke or type of treatment given when the participants initially reached the hospital. Remarkably, cognitive loss was also unrelated to the initial size of the stroke.

"We didn't know what to expect," Aghaeepour said. "This was an exploratory study looking to understand how cells function after stroke. We had no idea we'd find a correlation with long-term cognitive outcomes. It was an exciting accident."

Predictive power of acute phase

Intermediate- and late-phase analysis added nothing to the acute phase's predictive capacity. The investigators speculate that maybe later on, whatever immune cells are disrupting a patient's cognitive apparatus are acting within the brain itself, so their activity might not get picked up in screenings of blood circulating peripherally.

"A lot more needs to be done to differentiate the people who will go on to have post-stroke dementia from those who won't," Buckwalter said. But with the key cellular players predictive of long-term dementia at least tentatively identified, the job gets much simpler.

"Being able to detect something in the bloodstream would be much easier than doing a brain biopsy," Gaudilliere said. "Mass cytometry lets you measure the entire haystack in order to find the needle. Once you have the needle, you don't need the haystack anymore. You can focus on just a few features of a few cell types," opening the door to clinical applications.

Marion Buckwalter

A study Gaudilliere conducted in 2014 with other Stanford researchers, including Martin Angst, MD, professor of anesthesiology, perioperative and pain medicine and a co-author of the new study, used mass cytometry to detect whether differences in immune signatures of patients after undergoing hip-replacement surgery, an intensive and traumatic procedure, could serve as telltale indicators of a patient's ability to recovery fully and quickly from the operation.

Gaudilliere said there were "provocative similarities" in the post-event immune trajectories of participants in the surgical and stroke trials. "In both studies, we found similar patterns among participants in the activation of certain signaling molecules in certain immune cell types," he said. "It suggests a shared immune response between surgical and neurological injury may be implicated in the neurocognitive dysfunction seen after stroke or major traumatic injury."

Buckwalter and study co-author Maarten Lansberg, MD, PhD, associate professor neurology and neurological sciences, are now running a scaled-up trial to try to validate the results of the small study.

Buckwalter is a member of Stanford's Wu Tsai Neurosciences Institute and of Stanford Bio-X. Gaudilliere is a member of Stanford's Maternal & Child Health Research Institute. Aghaeepour is a member of Bio-X.

Other Stanford co-authors are former clinical research assistant Kacey Berry; former visiting medical resident Maxime Beneyto, MD; Dyani Gaudilliere, DMD, MPH, clinical assistant professor of plastic & reconstructive surgery; research scientist Edward Ganio, PhD; research data analyst Anthony Culos; postdoctoral scholar Mohammad Ghaemi, PhD; former visiting medical resident Benjamin Choisy, MD; former visiting researcher Karim Djebali, DMD; visiting medical-student researcher Jakob Einhaus; visiting student researcher Basile Bertrand; research assistant Athena Tanada; postdoctoral scholars Natalie Stanley, PhD, and Ramin Fallahzadeh, PhD; Quentin Baca, MD, PhD, clinical instructor of anesthesiology, perioperative and pain medicine; former research assistant and lab manager Lisa Quach; clinical research coordinator Elizabeth Osborn; and neuropsychologist Lauren Drag, PhD.

The work was funded by a Big Ideas in Neuroscience grant from the Wu Tsai Neurosciences Institute at Stanford and by the National Institutes of Health.

Stanford's departments of Anesthesiology, Perioperative and Pain Medicine, of Neurosurgery and of Neurology and Neurological Sciences also supported the work. **ISM**

OBITUARY

Innovative transplant surgeon Oscar Salvatierra dies at 83

By Erin Digitale

Oscar Salvatierra Jr., MD, professor emeritus of surgery and of pediatrics at the Stanford University School of Medicine and a leader in the effort to enact national legislation regulating organ donation, died March 16 at his home in Menlo Park, California. He was 83.

The cause was complications from Parkinson's disease, according to his wife, Pam Salvatierra.

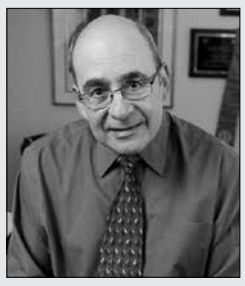
A pediatric kidney transplant surgeon, Salvatierra was the physician most involved in the development and passage of the National Organ Transplant Act of 1984, which established a nationwide network to enable the fair and equitable allocation of donor organs to patients across the country.

The law, on which Salvatierra collaborated with then-Congressman Al Gore, also banned buying and selling donor organs. It has served as a model for laws regulating organ transplantation around the world.

"It saddens me to hear of the passing of my friend and former colleague Dr. Oscar Salvatierra," said Gore, who went on to serve as vice president to President Bill Clinton. "Oscar's tireless dedication to the development of the National Organ Transplant Act helped revolutionize the medical field and human rights in the United States."

Salvatierra was also a beloved clinician and prominent scientist whose research profoundly improved pediatric kidney transplantation.

"Dr. Salvatierra dedicated his career to making organ transplants safer, more successful, and more widely and fairly accessible," said Lloyd Minor, MD, dean of the Stanford School of Medicine. "His work in transplantation helped restore health to thousands of people around the globe, including the many children he cared for in the world-class kidney transplant program he founded at Lucile Packard Children's Hospital Stanford."



Oscar Salvatierra

Salvatierra developed methods that enabled small children to be successfully transplanted with adult-sized kidneys. He also pioneered an immune-suppression protocol for pediatric kidney transplant recipients that avoided steroid medications, which have harmful side effects in children, such as severe growth suppression.

"He was always looking for the perfect transplant," said Waldo Concepcion, MD, professor of surgery and of pediatrics, who was mentored by Salvatierra and succeeded him as chief of pediatric kidney transplantation at Packard Children's Hospital. "So many of the techniques we use now in pediatric kidney transplant are because of him."

Native of Phoenix

Salvatierra was born April 15, 1935, in Phoenix, Arizona, one of six children of Josefina Garcia and Oscar Salvatierra Sr. The first in his family to attend college, Salvatierra earned a scholarship to Georgetown University, graduating cum laude in 1957. He completed medical school at the University of Southern California in 1961, followed by residencies in pediatric urology and urology.

Salvatierra served in the U.S. Army Medical Corps in Vietnam and worked as a physician in Pomona, California, before beginning a postdoctoral fellowship in transplant surgery at the University of California-San Francisco in 1972. Salvatierra was chief of the UCSF transplant service from 1974 to 1991, when he moved to Pacific Presbyterian Medical Center, now known as California Pacific Medical Center. He was part of a group of surgeons and staff who came from the center to Lucile Packard Children's Hospital Stanford to establish the hospital's pediatric liver and kidney transplantation programs in 1994.

"He was a gifted clinician and one of the best doctors I have ever known, much loved by his patients and their families," said Steven Alexander, MD, professor of pediatrics and division chief of pediatric nephrology at Packard Children's.

At Stanford, Salvatierra pushed for better and safer kidney transplants. He conducted magnetic resonance imaging studies of blood flow in small children who had received kidneys from adults, determining that about 20 percent of such transplants were failing because the child's smaller blood volumes left the transplanted organs vulnerable to blood clots.

A new fluid-management protocol Salvatierra developed raised the success of such transplants to nearly 100 percent.

Salvatierra also questioned the need for corticosteroid medications for immune suppression. The drugs had been considered essential to prevent rejection of kidney transplants, but had serious side effects in children, causing growth suppression, high blood pressure, acne, vision problems and weight gain.

In the early 2000s, Salvatierra conducted clinical trials of an immune-suppressing antibody called daclizumab, demonstrating that the steroid-free regimen not only prevented rejection but also did less damage to the transplanted kidneys than steroids.

Salvatierra **See SALVATIERRA, page 8**

OBITUARY

Ed Rubenstein, pioneer in intensive care medicine, dies at 94

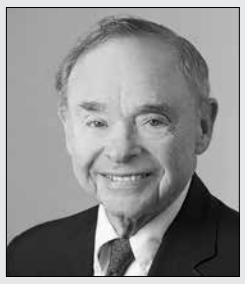
By Mandy Erickson

Edward Rubenstein, MD, professor emeritus of primary care and population health at the Stanford University School of Medicine and the author of an early textbook on intensive care medicine, died March 11 of natural causes. He was 94.

Described by many as a Renaissance man, Rubenstein researched treatments for sickle cell anemia, developed a diagnostic imaging system using synchrotron radiation, explored the role of cerebrospinal fluid in age-related mental disorders, and studied a possible link between dietary nonprotein amino acids and disease. He was also a founding editor of *Scientific American Medicine.*

"Ed was a one-person transdisciplinary research project because he had such broad knowledge," said Kevin Grimes, MD, professor of chemical and systems biology at the School of Medicine who was working with Rubenstein on the role of nonprotein amino acids in multiple sclerosis. "He could talk to you about the importance of the size of the sun and how that affects cobalt's being on the planet."

Rubenstein's son John Rubenstein said his father was perhaps most proud of his work on synchrotron radiation, which is used in research and diagnosis. "That's probably what he would say is his biggest research success," the son said.



Edward Rubenstein

Native of Cincinnati

Born in Cincinnati on Dec. 5, 1924, Rubenstein was inspired to become a physician by his own pediatrician, who cared for him when his family feared he had contracted polio. The son of a state assemblyman, he attended the University of Cincinnati as an undergraduate, graduated from its College of Medicine in 1947 and was a resident at Cincinnati General Hospital and Barnes Hospital at Washington University in Saint Louis.

When the Korean War started, he learned that doctors were in short supply in the military and enlisted. From 1950 to 1952, he was head of medicine at March Air Force Base in Riverside County, California.

Rubenstein briefly returned to the Midwest to join the faculty at the University of Cincinnati, then headed back to California, where he started a medical practice in San Mateo. He joined Stanford in 1955 as a clinical instructor at San Mateo County General Hospital. He became a clinical professor in 1960, and was named associate dean for postgraduate medical education in 1972. He retired in 1993 but remained actively engaged in research. The Department of Medicine holds an annual lecture named for him.

"I had the pleasure of getting to know him during the Rubenstein Lectureships and recognize the breadth of his interests, from small molecules to clinical observations," said Abraham Verghese, MD, professor of medicine at Stanford and the Linda R. Meier and Joan F. Lane Provostial Professor. "He was interested in the individual, their place in society, disease, epidemiology, the molecular structure of the cell — it was all medicine. I only wish I had been one of his trainees."

Rubenstein was a member of the National Academy of Medicine. He won several Stanford awards, including the Albion Hewlett Award and the Kaiser Award for Innovation and Outstanding Contributions to Medical Education.

He is survived by his wife, Nancy, of Hillsborough; sons John and James, both UCSF physicians, and William, an educator and writer in Los Angeles; and two grandchildren: Tess, a nurse practitioner at the San Francisco Veterans Administration Health Care System, and Thomas, a musician and composer.

The family is planning a memorial service. ISM

Cancer

continued from page 1

author.

Between 15 and 20 percent of breast cancer patients have the HER2-positive variety, for which the most effective treatment is the chemotherapy drug trastuzumab, sold under the brand name Herceptin. But trastuzumab also causes more heart problems than other breast cancer drugs; about 15 percent of patients taking it will develop cardiac dysfunction, likely because of a genetic predisposition. The side effects include a reduction in the amount of blood the heart pumps with each contraction and, less commonly but more seriously, heart failure. Except for quitting trastuzumab, there currently is no treatment for the side effects.

Knowing which patients will develop heart problems — and having medications to treat them — could allow patients to receive the most effective cancer-fighting therapy.

From stem cells to heart cells

The researchers conducted the study in a lab, using blood from three healthy participants and from seven participants with breast cancer, including five who had experienced cardiac dysfunction due to trastuzumab. They derived stem cells from the white blood cells, then coaxed those stem cells to develop into heart cells, or cardiomyocytes.

When they applied trastuzumab to the cells from breast cancer patients who showed heart dysfunction, the cells contracted less vigorously. But when they applied trastuzumab to the cells of breast cancer patients who had not suffered side effects, the cells showed little change. The cells from patients who suffered more severe heart problems in reaction to trastuzumab showed more pronounced weakening than those from patients with less severe problems.

The researchers hypothesize that trastuzumab disrupts the cells' energy pathway in some patients. "It changes the way the heart cells consume energy," Wu said.

The researchers then applied medications known as AMPK activators to the weakened cells. This class of medications includes metformin, a drug commonly used to treat Type 2 diabetes. As the researchers expected, the weakened cells ate up more glucose and contracted more vigorously with AMPK activators.

Plan for retrospective study

The researchers plan to follow these findings with a retrospective study of patients who were taking metformin for diabetes while they were receiving trastuzumab for breast cancer. If they find that patients on metformin had fewer cardiac side effects, they hope to conduct a trial to see if giving patients metformin with trastuzumab will show the same results.

Wu said testing drugs on cells in a lab can vastly reduce the time needed to bring drugs to patients, as well as the cost. "You can screen them in a dish first," he said. "This will significantly cut the cost of drug development, providing better and more affordable drugs to the population."

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

With metabolic profiles, center hopes to head off disease early

By Erin Digitale

Michael Snyder

Karl Sylvester

In a bid to understand the origins of many childhood diseases, a Stanford team plans to broadly characterize the metabolic profiles of thousands of patients treated at Lucile Packard Children's Hospital Stanford and Stanford Children's Health clinics.

Researchers at the Metabolic Health Center, whose launch was approved by the dean's office in February, will analyze patients' blood and urine samples with mass spectrometry to measure about 1,500 small molecules per patient, with the ultimate goal of producing a detailed metabolic profile of every patient seen at the hospital or clinics. The metabolites, indicators of what the body's cells are busy doing, will include nearly 800 individual lipids and an additional 700 nonlipid chemicals. The team plans to have their first 1,000 metabolic profiles completed by the end of 2019.

"Your metabolic signature is a really strong signifier of your health," said Michael Snyder, PhD, professor and chair of genetics and co-director of the new center.

Metabolism is the collection of chemical reactions carried out by a cell to maintain life, such as breaking down carbohydrates, fats and proteins for energy; metabolites are the products of those reactions.

At present, doctors routinely measure only a tiny handful of metabolites in the blood, such as glucose and cholesterol. Although these measurements can provide clues about specific diseases, comprehensive profiling holds the potential to provide a more detailed view into many more diseases, including how they evolve and why metabolism goes awry, Snyder said. The research team plans to link their discoveries to genetic information to better understand the genetic origins of disease.

In metabolic problems that develop slowly, such as obesity and Type 2 diabetes, medical scientists have only a limited understanding of what goes wrong in the early stages of the disease process.

Profiling healthy patients

"By profiling people first while they're healthy, we will be able to catch problems, before they become symptomatic," said Snyder, who holds the Stanford W. Ascherman, MD, FACS, Professorship in Genetics. "That will be huge in terms of enabling us to avoid complications that come later."

The team also hopes to gain a clearer understanding of rare metabolic diseases, including inherited metabolic disorders, and of the processes by which premature infants can develop serious complications and acquired diseases that are associated with being born too soon or too small. "Deep metabolomics profiles will be informative in some of these cases in helping us understand what's wrong," Snyder said. "We also hope it will lead to new therapies."

California's newborn screening program now looks for approximately 40 different metabolic diseases in babies, but because it relies on a limited number of metabolites that are already linked to known diseases, it does not pick up on children with unknown or less-understood conditions. As a result, many children with developmental delay have no formal medical diagnosis. The new project may help clarify a myriad of mystery conditions. In fact, nearly every disease has an underlying metabolic signature.

"We believe it will be possible to extend the principle of newborn screening for genetic disease to many more newborns and children at risk for acquired diseases using the center's expertise in expanded metabolic profiling," said Karl Sylvester, MD, associate dean for maternal and child health and co-director of the new center.

Other co-directors of the center are David K. Stevenson, MD, senior associate dean for maternal and child health and professor of pediatrics, and Tina Cowan, PhD, professor of pathology. Kevin Contrepois, PhD, is the center's scientific director, and Casandra Trowbridge is its administrative and operations director.

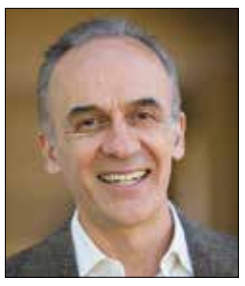
"Ultimately, our aim is to keep children healthy rather than treat them after they develop disease," Snyder said. "This project fits really well with Stanford's prowess at being able to mine big data and apply the results to improving human health."

The center is supported by Lucile Packard Children's Hospital Stanford; the medical school's departments of Genetics, of Pediatrics and of Pathology; the Stanford Precision Health Biobank; and Thermo Fisher Scientific. **ISM**

OF NOTE

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

Greg Albers



E.J. Chichilnisky

Amit Etkin

Julie Kauer

Kilian Pohl

GREG ALBERS, MD, the Coyote Foundation Professor and professor of neurology and neurological sciences, was the principal investigator of a study that received a 2019 Distinguished Clinical Research Achievement Award from the Clinical Research Forum, a national organization that honors impactful peer-reviewed studies. Albers led the DEFUSE 3 Study, a multicenter clinical trial on stroke treatment that showed the largest positive treatment effect ever achieved in a stroke study, and that immediately led to new international guidelines to extend the treatment window for stroke.

E.J. CHICHILNISKY, PhD, the John R. Adler Professor and professor of neurosurgery and of ophthalmology, received a Research to Prevent Blindness Stein Innovation Award. The three-year, $300,000 award will support his study of visual processing in the human retina and how it relates to established animal models, including a new application for high-resolution electrical recordings in the areas of the retina responsible for high-acuity vision.

AMIT ETKIN, MD, PhD, was promoted to professor of psychiatry and behavioral sciences, effective March 1. His research examines the neuroscience of emotion and cognitive regulation, as well as basic aspects of neural circuit functioning, in healthy people and people with psychiatric disorders.

JULIE KAUER, PhD, was appointed professor (research) of psychiatry and behavioral sciences, effective Jan. 1. Her research uses mouse models to understand the roles of synaptic plasticity in spinal cord circuitry, as well as the effects of pain, acute stress and drug addiction on synaptic plasticity in the brain.

KILIAN POHL, PhD, was appointed associate professor (research) of psychiatry and behavioral sciences, effective Nov. 1. His research uses computational science to identify biomedical phenotypes with the aim of improving the mechanistic understanding, diagnosis and treatment of neuropsychiatric disorders.

LAURA ROBERTS, MD, the Katharine Dexter McCormick and Stanley McCormick Memorial Professor and chair and professor of psychiatry and behavioral sciences, is the 2019 recipient of the annual lifetime service award from the American Association of Directors of Psychiatric Residency Training. The award recognizes a member who has provided significant service to the association, had an impact on psychiatric residency education nationally, demonstrated excellence in psychiatric residency education, and is committed to empowering and educating the next generation of psychiatrists.

Laura Roberts

Samuel So

SAMUEL SO, MD, the Lui Hac Minh Professor in the School of Medicine and professor of surgery and director of the Asian Liver Center, has been chosen as a 2019 Asia Game Changer Award Honoree by the Asia Society. He was recognized for his efforts to eliminate hepatitis B and reduce the burden of liver cancer in Asia and in Asian-Americans. **ISM**

Salvatierra

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helped many other physicians develop their careers, often serving as a mentor and role model.

"When I was just beginning my surgical training, I happened to see his name listed from UCSF as their kidney transplant surgeon," said Carlos Esquivel, MD, PhD, professor of pediatrics and of surgery and chief of the division of abdominal transplantation at Stanford. It was the early 1980s, a time when few surgeons came from minority backgrounds. "I thought, 'Here is somebody with a Spanish last name, and he is at a prestigious university and already has an excellent reputation. This is who I'm going to emulate.'

"He was truly dedicated to his patients — very compassionate, with a great bedside manner," added Esquivel, who led the team that moved with Salvatierra from Pacific Presbyterian to Stanford. "And he was a very deliberate and skillful surgeon."

Children who need kidney transplants are quite ill, and Salvatierra became known for his ability to connect with young patients and help calm their parents' fears.

During their years of collaboration, Esquivel learned that one of his own sons needed surgery for a kidney problem. "I chose Oscar to do his surgery," Esquivel said, adding that the decision felt especially weighty because of his own professional knowledge. "For a surgeon, to pick someone to do an operation on your own child means you think that surgeon is the best person in the world. And I did."

Salvatierra retired from his clinical responsibilities in 2006, becoming associate dean for medical students at the School of Medicine, a position he held until 2015. He received many major awards during his career.

Salvatierra is survived by his wife of 25 years, Pam; son Mark Salvatierra of San Jose, Calif.; daughter Lisa Rudloff of Centerport, New York; four grandchildren; five siblings; and many nieces and nephews.

A memorial service was held last week.

In lieu of flowers, the family requests donations to the Dr. Oscar Salvatierra Emergency Fund, PTA1191484-100HEUT, which provides emergency funds for medical students who experience financial crises. Donations can be directed to Development Services, Stanford University, P.O. Box 20466, Stanford, CA, 94309-0466. **ISM**