INSIDE STANFORD MEDICINE

Volume 11, No. 20 ■ November 4, 2019 ■ Published by the Office of Communications

The rate at which California's newborns receive antibiotics varies dramatically depending on the hospital, a study found.

Page 3

New Stanford Hospital dedicated at ceremony

By Grace Hammerstrom

STEVE FISCH

The new Stanford Hospital was dedicated Oct. 23 at a ribbon-cutting ceremony. The 824,000-square-foot medical facility will open its doors to patients Nov. 17.

Stanford Health Care marked a key milestone Oct. 23 with a ribbon-cutting ceremony to dedicate the new Stanford Hospital, more than 10 years in the making.

The 824,000-square-foot medical facility, at 500 Pasteur Drive in Palo Alto, will open its doors to patients Nov. 17.

"For so long, the Stanford Hospital has been a distant dream, something on the horizon," said David Entwistle, president and CEO of Stanford Health Care, in his opening remarks. "The fact that we're here today to celebrate the culmination of more than a decade of work is truly amazing. We're here today because of the thousands of hours of effort from dedicated individuals. We should all take great pride in what we've been able to accomplish together."

On hand for the celebration were university leaders, faculty, medical staff, patients, public officials and donors, who gathered in the atrium of the new building.

Lloyd Minor, MD, dean of the Stanford School of Medicine, said the opening of the new hospital ushers in an era of even greater collaboration and discovery.

"We want to drive biomedical research that changes health care here at Stanford and around the world," Minor said. "Having a world-class hospital and world-leading clinicians to collaborate with vastly increases the power and speed with which we will be able to translate our discoveries to the benefit of all people."

Designed by the internationally recognized firm Rafael Viñoly Architects, in association with medical planners from Perkins Eastman, the new hospital was built to accommodate the most advanced medical technology, increase capacity for patients and meet California's stringent seismic safety standards.

Plans for the hospital began in 2006 with the selection of the architect. From there, a collaborative and extensive community planning process began, which included 100 public meetings with the city of Palo Alto. Vice Mayor Adrian Fine spoke at the ceremony.

"With the opening of the new Stanford Hospital, Stanford Health Care will continue its role as an important resource for Palo Alto and the larger community," said Fine, who was born at Stanford Hospital in 1986. "Having a world-class hospital right here in our neighborhood, in our backyard, delivering care informed by the latest

See DEDICATION, page 3

Robots to join workforce at new Stanford Hospital

By Daphne Sashin

The more than 5,500 Stanford Health Care employees who work at the new Stanford Hospital will be joined by a fleet of robots programmed to deliver linens, packages and medical supplies; keep track of the hospital's medication inventory; and count out pills for nurses to administer.

The new hospital opens Nov. 17.

Handing off repetitive and

See ROBOTS, page 2

KEVIN MEYNELL PHOTOGRAPHY

Tug robots will serve as autonomous couriers, hauling heavy loads of supplies between the central loading dock at 300 Pasteur Drive and the new hospital at 500 Pasteur Drive — a half-mile round-trip.

Scrambled cytoplasm of frog eggs organizes itself into cell-like structures, study finds

By Jack J. Lee

Can scrambled eggs unscramble themselves? Well, sort of.

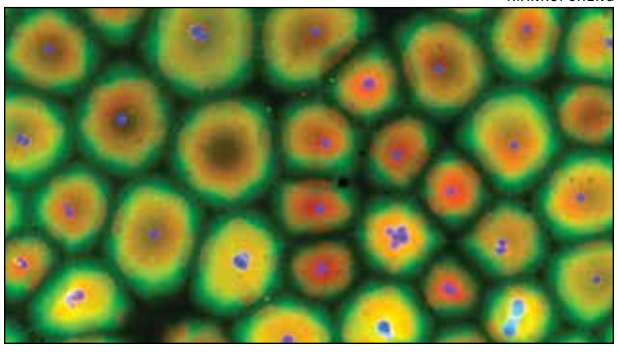
The cytoplasm of ruptured *Xenopus* frog eggs spontaneously reorganizes into cell-like compartments, according to a study by researchers at the School of Medicine.

"We were gobsmacked," said James Ferrell, MD, PhD, professor of chemical and systems biology and of biochemistry. "If you blend a computer, you'd end up with tiny bits of computer, and they wouldn't even be able to add two and two. But, lo and behold, the cytoplasm reorganizes."

Remarkably, the self-assembled compartments retain the ability to undergo division and can form smaller compartments. Previous studies have shown that some subcellular structures, such as centrosomes and endoplasmic reticulum, can self-assemble outside cells from their purified components, demonstrating that these structures have some ability to self-organize. However, the new study provides the first example of self-organization at the scale and complexity of entire cells.

Ferrell is the senior author on the study, which was published Nov. 1 in *Science*. The lead author is postdoctoral scholar Xianrui Cheng, PhD.

XIANRUI CHENG



After being scrambled, the cytoplasm of *Xenopus* frog eggs spontaneously reorganizes into cell-like compartments. Nuclei are blue, microtubules are green and the endoplasmic reticulum is red.

The discovery relied on Cheng's observations. While studying a molecular process known as programmed cell death, he noticed the nuclei in a tube of cytoplasmic extract from frog eggs were behaving unexpectedly. After 30 minutes or so, the nuclei had organized so the distance between two nuclei was almost equal, Cheng said. When he imaged the cytoplasmic extract on microscope slides, he saw that it had formed distinct compartments that resembled a sheet of cells.

"If you take the cytoplasm of the frog egg — note that the cytoplasm has been

See EGGS, page 2

Eggs

continued from page 1

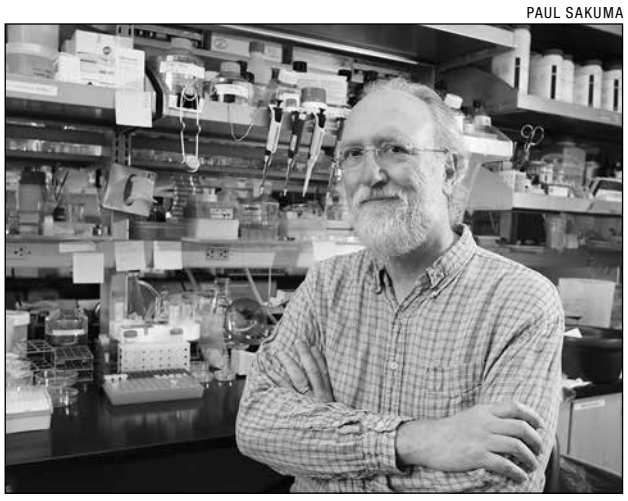
homogenized, so whatever spatial structure that was there has been completely disrupted — and just let it sit at room temperature, it will reorganize itself and form small cell-like units. That's pretty amazing," Cheng said. These cell-like compartments formed whether or not *Xenopus* sperm nuclei were added, suggesting that the behavior relied on something intrinsic to the egg.

To understand the mechanism underlying the phenomenon, the researchers tested whether compartment formation was affected by the addition of chemical inhibitors to cytoskeletal proteins, motor proteins and kinases, which activate other proteins. This approach revealed that ATP, the primary source of energy in the cell, and microtubules, cytoskeletal filaments that provide structural support, were required for compartments to form. Dynein, a type of motor protein, was also required for proper microtubule localization.

Self-organized compartments divide

These cell-like compartments not only looked like cells; they divided like them, too. The egg extract that the researchers used when they identified compartment formation contained a chemical that prevented the cells from entering the cell cycle. When this chemical was removed, and sperm nuclei were added, the egg extract formed compartments that divided into smaller compartments.

PAUL SAKUMA



James Ferrell is co-author of a study whose findings suggest that *Xenopus* egg cytoplasm has the intrinsic ability to generate the basic spatial organization of the cell, and even has some of its functions.

The researchers saw that these compartments could undergo over 25 rounds of division, indicating that the process was very robust. The division was also reductive, Cheng said, since the total amount of cytoplasm remained constant and was being divided into smaller and smaller compartments with each cycle. "You're taking the material from the egg, and it divides in a mode that's reminiscent of embryonic development," he said. "Just like they're supposed to in a real egg."

Future directions

All of these findings suggest that the *Xenopus* egg cytoplasm has the intrinsic ability to generate the basic spatial organization of the cell and even has some of its functions. An open question, however, is what role this phenomenon plays in the normal physiology of the egg. Another question is whether this ability to self-organize is peculiar to eggs or is shared by other types of cells.

The researchers also hope to further understand what's needed for self-organization to occur. "My favorite question right now," Ferrell said, "is can we make a simple model that explains the basics of this organization process? Or do we have to do something extremely complicated, like account for every single thing that we know a microtubule can do?"

Ferrell is a member of Stanford Bio-X, the Stanford Cancer Institute and the Wu Tsai Neurosciences Institute at Stanford.

The research was supported by the National Institutes of Health.

Stanford's departments of Chemical and Systems Biology and of Biochemistry also supported this work. **ISM**

Robot

continued from page 1

mechanical tasks to machines — 23 delivery robots that will travel on pre-programmed routes throughout the hospital and three pharmacy robots that will store and package medication — will prevent employee injuries, reduce medication errors and free up staff to focus on the more valuable and satisfying work of assisting clinicians and caring for patients, said Gary Fritz, vice president and chief of applications for Stanford Health Care.

"The real value of pharmacists and pharmacy technicians comes when they use their clinical knowledge to care for patients, not to count pills," Fritz said. "Similarly, in the supply chain, routine activities like pushing a cart 30 minutes in each direction isn't really job enriching, but what is enriching is if those people can talk to patients or spend time figuring out how to get better supplies."

Autonomous robots tug supplies

At 4 feet high, the Tugs will serve as autonomous couriers, hauling heavy loads of supplies between the central loading dock at 300 Pasteur Drive and the new hospital at 500 Pasteur Drive — a half-mile round-trip via tunnel. The Tugs move about 2 miles per hour and can pull more than half a ton.

"We're automating the heavy movement across long distances to protect our employees," said Shaheed Hickman, supply chain project manager at the hospital.

The robots use lasers and GPS to create a 3D map of their surroundings and determine if they need to stop or move to get around an obstacle. The robots convert that 3D map to a 2D image, so managers and staff can remotely track them in real time. The Tugs have the capability to open doors wirelessly and stop when they sense movement that may interfere with their path. They can distinguish between stationary or moving obstructions within a 10-foot radius and alter their course accordingly.

While you can't have a conversation with them, they do speak a few phrases — including "crossing hallway" and "Tug has arrived" — and they stop the moment they are touched. If a fire alarm goes off, the robots pull off to the side of the hallway to get out of the way.

Initially, the Tugs will be used to carry carts full of small packages, bulk food, nonurgent medical supplies and linens to the basement level of the new hospital, where, for now, a staff member will get the items to their final destination. The Tugs also will haul dirty linens, used food trays and garbage from the new hospital and ferry it back to the dock.

In between jobs, the Tugs automatically return to recharge at their docking stations.

Robotic pharmacy

You won't see many pills in the new hospital pharmacy. That's because most of them are stored inside three giant robotic machines, which don't get tired, rushed or make mistakes as they're filling drug orders for patients.

Two of them, the BoxPickers, aren't what you imagine when you think of a robot. They are more like giant cabinets with a computer interface on the outside. Inside, there are stacks of drawers containing boxes of medications and a mechanical arm, or picker, that moves up and down the aisles. The BoxPickers currently store nearly $5 million worth of medications — about 80 percent of what's stored in the patient care unit's medication dispensing cabinets, located in the medication areas on the hospital floors.

KEVIN MEYNELL PHOTOGRAPHY

Joel Rivera, a pharmacy technician, next to the PillPick robot, which can package 1,000 doses of medicine per hour. The same work would take a technician 10 hours to complete.

Each day, when it's time to restock the dispensers with medications, the technician checks the BoxPicker's computer to determine which are needed and in what quantities. On the other side of the cabinet, the arm locates the box containing that specific medication and moves it into a drawer that unlocks for the technician.

Besides the time savings afforded by the pharmacy robots, the machines reduce the chance of pill-selection errors, said Douglas Del Paggio, PharmD, assistant director of pharmacy.

"Instead of me going over to a bin and pulling a drug and looking at it — and if I'm in a rush, I may accidentally pull the wrong one, or the wrong drug is in the wrong bin — in these robots, it is all bar-code scanned and checked, so it's very accurate — like 99.9 percent," Del Paggio said.

The BoxPickers also keep a running inventory and automatically generate new orders for the drug wholesaler on a daily basis.

"You have more seamless control of inventory, because you're not just eyeballing and saying, 'I think I need more of that,' which is how we've been doing it for decades," Del Paggio said.

Across the room, a third robot — a suction-powered machine called the PillPick — counts out bulk medications and slides them into individual, bar-coded packets.

When a physician puts a patient's order into the electronic health record system for one of these drugs, the only human work required is for a pharmacist to verify the order. Then the robot goes to work, whirring and hissing. Within seconds, a day's worth of medicine slides down a conveyor belt, organized on a plastic ring.

The PillPick can package 1,000 doses per hour — the same amount that it would take a pharmacy technician about 10 hours to pack by hand.

"This allows our pharmacists and technicians to instead spend more of their time with physicians, nurses and, most importantly," Del Paggio said, "directly with patients and family members." **ISM**

Editor's Note

The next issue of *Inside Stanford Medicine* will be published Nov. 25.

INSIDE STANFORD MEDICINE

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

is produced by

Stanford Health Care | School of Medicine
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Redwood City, CA 94063
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STANFORD MEDICINE

Antibiotic use in newborns varies widely among state's hospitals

By Erin Digitale

The rate at which California's newborns receive antibiotics varies dramatically depending on the hospital, a study led by researchers at the School of Medicine has found: Percentages were as low as 1.6 and as high as 42.5.

BRIDGET COILA/FLICKR

Researchers compared data from 121 California hospitals that have neonatal intensive care units, looking at 326,845 babies born during 2017. A paper describing the work was published Oct. 22 in *Pediatrics*.

They calculated the percentage of newborns at each hospital who received antibiotics, as well as the number who received antibiotics per proven case of sepsis, or bloodstream infection.

The number of babies receiving antibiotics ranged from 11.4 to 335.7 infants treated per case of early-onset sepsis, defined as sepsis diagnosed within two days of birth. (These rates were calculated based on the entire population of babies in the study, not just the ill or premature infants cared for in hospitals' neonatal intensive care units.)

The rates of antibiotic use were not linked to hospitals' rates of newborn sepsis, indicating that there does not seem to be a medical explanation for the differences.

"We have an extremely low rate of actual infection, and we have loads and loads of patients, even after four or five years of antibiotic stewardship work, being treated with antibiotics for reasons we don't understand," said Jeffrey Gould, MD, the study's senior author and a professor of neonatal and developmental medicine. The lead author is Joseph Schulman, MD, of the California Department of Health Care Services.

Since 2014, California clinicians and researchers have been trying to reduce unnecessary antibiotic use in newborns. Giving newborns unneeded antibiotics may put them at risk for developing diseases such as asthma, and it contributes to increasing antibiotic resistance among bacteria that cause infections. Research published last year showed that California hospitals are making progress in reducing antibiotic use for newborns, but the new study shows there is still more work to do, Gould said.

> "We want to know what's driving quality and what's holding people back."

Holdover from prior era

Antibiotic overuse is a holdover from a prior era of neonatology, when many newborns received prophylactic antibiotics because of concerns about whether sepsis could be detected quickly enough in babies.

"In the past, we were very crude in terms of our perception of the subtleties of the disease," Gould said.

Today, after decades of research, doctors have a much better understanding of the early signs of sepsis in newborns, including those born after full-term pregnancies and those who arrive prematurely. Watching and waiting for these signs before starting antibiotics is now an accepted approach, along with culturing a blood sample from babies suspected of having sepsis to confirm if they are actually experiencing an infection.

Research has also indicated that caregivers can stop giving antibiotics once a baby improves, or if their blood culture results are free of infection, even if they haven't completed the full course of medication initially prescribed. But these changes have been slow to catch on.

Using new data

Gould and his colleagues at the California Perinatal Quality Care Collaborative are using the data from the study as a springboard for helping hospitals that overprescribe antibiotics.

"We're figuring out what to do if a group is challenged, and we're also starting to identify the teams that are high achievers to identify the things that allow them to perform well," he said. "We want to know what's driving quality and what's holding people back, so we can understand what we have to do to change this."

Other Stanford co-authors of the study are William Benitz, MD, professor of neonatal and developmental medicine; Jochen Profit, MD, associate professor of neonatal and developmental medicine; and Henry Lee, MD, associate professor of neonatal and developmental medicine.

Gould, Benitz, Profit and Lee are members of the Stanford Maternal & Child Health Research Institute; Lee is also a member of Bio-X.

Researchers at the California Perinatal Quality Care Collaborative contributed to the article. **ISM**

Dedication

continued from page 1

research and discovery is an immense benefit to those who call the Bay Area home."

More than two-thirds of Stanford Hospital patients live in Santa Clara and San Mateo counties, said Stanford President Marc Tessier-Lavigne, PhD. "People come here from around the world for life-saving and life-changing care, but I find it particularly meaningful that we are serving our communities and neighbors as well," he said.

"We truly are Palo Alto's community hospital," Entwistle said. "I'm deeply grateful to everyone who believed in the vision for this facility and worked so hard over the past decade to make it a reality. Today is a testament to their efforts." Also in attendance were Amir Dan Rubin, Stanford Health Care's previous president and CEO, and Mariann Byerwalter, who served as interim president and CEO.

The seven-story hospital includes 368 private patient rooms, an entire floor dedicated to surgical and procedural care, and 4 acres of public gardens. An emergency department, more than double the size of the current one, will serve adults and trauma patients. Pediatric emergency services will continue to be provided at the existing emergency department. Stanford Hospital is the only Level 1 trauma center on the Peninsula.

'Bold new chapter in medicine'

Toward the end of the ceremony, John Levin, chair of the Stanford Health Care board of directors, called leaders up to a stage.

"While we're here to dedicate a building constructed of steel, concrete and glass, its heart, its essence, its purpose are its people," Levin said. "The opening of this hospital represents a bold new chapter in medicine, a proud legacy of caring for our local community and for patients from around the country and across the globe."

Then Levin spoke: "On behalf of the dedicated clinicians who provide world-leading clinical care within these walls; on behalf of the biomedical researchers whose discoveries fuel that world-leading care; on behalf of the educators who will use this exceptional facility to teach the next generation of health care professionals; on behalf of hospital and university leaders, government officials, community members, faculty and staff, design and construction professionals, volunteers, donors, countless collaborators who worked so hard to bring us to this day; and most of all, on behalf of the patients and families whose hope will be restored, whose lives will be touched for decades to come, by the dream we have realized together, it is my distinct honor on behalf of the Stanford Health Care board of directors to formally accept this building."

To cheers and a rousing round of applause, Entwistle — with Minor on his left and Levin on his right — cut a red ribbon stretched across the stage. **ISM**

STEVE FISCH

David Entwistle, left, president and CEO of Stanford Health Care, with state Assemblyman Marc Berman, whose district includes the main campus of Stanford. Below, Lloyd Minor, dean of the School of Medicine, addresses the gathering at the ceremony.

STEVE FISCH

Stanford researchers awarded close to $9 million for opioid, pain studies

Five Stanford researchers were awarded grants from the National Institutes of Health's Helping to End Addiction Long-Term Initiative. The HEAL grants address the nation's opioid crisis by funding research into opioid misuse, as well as alternatives to pain treatment.

LAURA SIMONS, PhD, associate professor of anesthesiology, perioperative and pain medicine, was awarded $5.4 million to study biological and behavioral processes in adolescents with high-impact chronic musculoskeletal pain.

LUIS DE LECEA, PhD, professor of psychiatry and behavioral sciences, and **XIAOKE CHEN**, PhD, associate professor of biology, received $1.64 million to investigate the connection between brain circuits involved in opioid use and sleep regulation.

RAAG AIRAN, MD, PhD, assistant professor of radiology, and **NOLAN WILLIAMS**, MD, assistant professor of psychiatry and behavioral sciences, received $1.4 million to study the delivery of ketamine to the brain as a treatment for chronic pain. ISM

OF NOTE

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


Shipra Arya


Gheorghe Chistol


Lawrence Fung


Tamar Green


Debra Kaysen


Jonathan Lin


Julia Noel


Johannes Reiter


Vipul Sheth


Hiroyuki Shimada


Surbhi Sidana


Taia Wang


Irving Weissman


Jason Yeatman

SHIPRA ARYA, MD, an associate professor of vascular surgery, was elected secretary of the Surgical Outcomes Club. She will ascend to the presidency in two years.

GHEORGHE CHISTOL, PhD, was appointed assistant professor of chemical and systems biology, effective Sept. 1. His research employs single-molecule approaches to understand the mechanisms that safeguard the integrity of our genomes and what happens when these mechanisms fail.

LAWRENCE FUNG, MD, PhD, was appointed assistant professor of psychiatry and behavioral sciences, effective July 1. He is the director of the Stanford Neurodiversity Project and specializes in autism spectrum disorder. His research interests include neurodiversity, phenomenology and neurobiology of autism, as well as novel interventions for the condition.

TAMAR GREEN, MD, was appointed assistant professor of psychiatry and behavioral sciences, effective July 1. Her research interests are pediatric clinical neuroscience with an emphasis on neurogenetic and neurodevelopmental syndromes. She also uses genetic models to understand attention deficit hyperactivity disorder.

DEBRA KAYSEN, PhD, was appointed professor of psychiatry and behavioral sciences, effective Aug. 16. Her research interests focus on psychological treatments for post-traumatic stress disorder as well as mood and substance use disorders following traumatic events, especially for underserved populations and in low-resource communities.

JONATHAN LIN, MD, PhD, was appointed professor of pathology and of ophthalmology, effective July 1. His research interests are the mechanisms of retinal degeneration, neurodegeneration and eye pathology.

JULIA NOEL, MD, was appointed assistant professor of otolaryngology-head and neck surgery, effective Sept. 1. She specializes in surgery of the thyroid and parathyroid glands. She also has expertise in advanced and recurrent thyroid cancer, minimally invasive approaches and ultrasound-guided techniques.

JOHANNES REITER, PhD, was appointed assistant professor of radiology, effective July 1. His research interests focus on the stochastic processes underlying cancer evolution, with the goal of improving the prognosis and treatment of tumors.

VIPUL SHETH, MD, PhD, was appointed assistant professor of radiology, effective Aug. 1. His research focuses on translating magnetic resonance imaging methods to characterize the tumor microenvironment in pelvic malignancies and improve diagnosis, staging and therapy.

HIROYUKI SHIMADA, MD, PhD, was appointed professor of pathology and of pediatrics, effective July 1. His research includes a focus on neuroblastomas, one of the most common pediatric solid tumors.

SURBHI SIDANA, MD, was appointed assistant professor of medicine, effective Aug. 1. She specializes in treating plasma cell disorders, such as multiple myeloma and amyloidosis, with treatments that include blood and marrow transplantation and CAR-T cell therapy. Her research focuses on the development of novel therapeutic approaches, biomarkers and management of treatment toxicity.

TAIA WANG, MD, PhD, assistant professor of medicine, of microbiology and of immunology, received two seven-year awards to study influenza immunity: a $1.5 million grant from St. Jude Children's Research Hospital for improving knowledge of how influenza immunity develops during infancy and childhood, and a $2.2 million grant from the Icahn School of Medicine at Mount Sinai for developing longer-lasting influenza vaccines.

IRVING WEISSMAN, MD, the Virginia and D. K. Ludwig Professor in Clinical Investigation in Cancer Research, director of the Institute for Stem Cell Biology and Regenerative Medicine, and professor of pathology and of developmental biology, received the Arthur Kornberg and Paul Berg Lifetime Achievement Award in Biomedical Sciences from the Stanford Medicine Alumni Association. The honor recognizes his contributions to stem cell research and translational therapies.

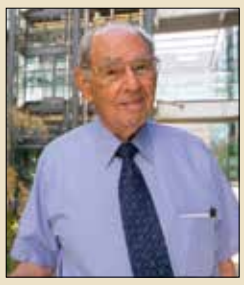
JASON YEATMAN, PhD, was appointed assistant professor of pediatrics and of education, effective Sept. 1. The director of the Brain Development & Education Lab in the Graduate School of Education, Yeatman focuses his research on the mechanisms of learning to read and how these mechanisms differ in children with dyslexia. A goal of the lab is to design literacy intervention programs that are effective across the wide spectrum of learning differences. ISM

Memorial event for Stanley Schrier set for Nov. 10

A celebration of the life of Stanley Schrier, MD, will be held from 3 to 5 p.m. Nov. 10 at McCaw Hall in the Frances C. Arrillaga Alumni Center.

Schrier, a founding member of the Division of Hematology, died Aug. 15 at the age of 90. He was a respected researcher, mentor and teacher.

RSVP to SchrierCelebrationofLife@stanford.edu. ISM


Stanley Schrier

STANFORD RESEARCH INTO THE IMPACT OF TOBACCO ADVERTISING

Blowing smoke

Early in the last century, the tobacco industry featured physicians, nurses and dentists in their advertisements, hoping to provide smoking with a healthy image. "It was a response to a public that was starting to worry about the health consequences of smoking," said Robert Jackler, MD, professor of otolaryngology-head and neck surgery. He has collected thousands of the ads, some of which are currently on display in the National Museum of American History in Washington, DC. The exhibit runs through March 2020.