

Two newly appointed chairs for School of Medicine departments

Clifford Bogue is appointed to pediatrics chair after two years in an interim role

Clifford W. Bogue, M.D., professor of pediatrics (critical care), has been appointed chair of the Department of Pediatrics. The appointment became effective August 1. Bogue had been serving as the department's interim chair since 2015.

"Cliff has been a strong advocate for the department. He is committed to strengthening its research mission, developing a cadre of new leaders in pediatrics, and seeing faculty and staff flourish," says Robert J. Alpern, M.D., dean and Ensign Professor of Medicine.

Bogue says he would like to raise the stature of Pediatrics so that it is



Clifford Bogue

one of the pre-eminent departments in the country. He plans to accomplish this by bolstering and expanding the range of high-quality clinical services the department delivers in conjunction with Yale New Haven Children's Hospital and fortifying research within the department and with other programs. Plans are underway, for example, to merge the department's neurodevelopmental services with the Yale Child Study Center to provide opportunities for joint clinical care and research collaborations.

He also is committed to preparing the next generation of pediatric clinician scientists // **Pediatrics** (page 4)

New surgery chair with strong cancer background is coming from Johns Hopkins

Nita Ahuja, M.D., M.B.A., has been named chair of the Department of Surgery at the School of Medicine and chief of surgery at Yale New Haven Hospital, effective February 1.

Ahuja is currently the Jacob C. Handelsman Professor in Abdominal Surgery and professor of surgery, oncology, and urology at the Johns Hopkins University School of Medicine, and chief of surgical oncology at Johns Hopkins Hospital. She also serves as vice chair of academic affairs for the Department of Surgery and associate director of the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins.



Nita Ahuja

"Nita is widely respected for innovative patient care, renowned for her research on cancer epigenetics, and passionate about mentoring the next generation of surgeon scientists.

Her ability to be a collaborative leader will make her a welcome addition to the School of Medicine community," says Robert J. Alpern, M.D., dean and Ensign Professor of Medicine.

At Johns Hopkins, Ahuja leads the integration and expansion of surgical oncology programs across the health system. Her surgical specialization is in gastric, rectal, and pancreatic cancers. She has developed // **Surgery** (page 8)

A million-dollar fund will support junior researchers

Donor, an alumnus, sees vast potential in the work of early-career neuroscientists

With a goal of spurring new discoveries in neuroscience by bright young investigators, and supporting the work of the next generation of leaders in the field, Reynold Spector, M.D. '66, and his wife Michiko Spector have established a \$1 million fund to foster the education and training of junior faculty members.

The Reynold and Michiko Spector Fund for Neuroscience celebrates—and looks to help through philanthropy—Yale's long history of neuroscience discovery, which has contributed a great deal to the understanding of brain anatomy, physiology, and chemistry. "Yale is a strong place for neuroscience research," says Reynold Spector. "The university is committed to it, and I am hopeful that bright young scientists will come up with ideas that are new and valuable."

"The Sectors' gifts are timely, coming at a moment when young investigators are increasingly valued as indispensable partners for the medical school's senior faculty," says Robert J. Alpern, M.D., dean and Ensign Professor of Medicine. "We realize more than ever how talented young scientists bring creative and innovative approaches to the school's research programs."

As a physician and researcher, Spector has had a strong interest in the neurosciences since his Yale days. He completed his medical school thesis with the late professor and chief of neuropathology Elias Manuelidis, M.D., a world-renowned expert in Creutzfeldt-Jakob disease, a degenerative disease of the nervous system. Spector has also closely followed the work of Manuelidis' wife, Laura Manuelidis, M.D., professor of surgery (neuropathology).

"Elias Manuelidis thought a little bit differently than many other neuroscientists. He taught me an offbeat approach to things, and that



COURTESY: REYNOLD AND MICHIKO SPECTOR

turned out to be exceedingly useful, because I heard my own drummer," says Spector. "We need strong, smart, young people // **Researchers** (page 5)

Reynold Spector (right) and Michiko Spector have created a \$1 million fund to support early-career researchers in neuroscience, expressing hope that the most valuable ideas in a vital discipline will come from "bright young scientists."



Carla V. Rothlin

Carla Rothlin has devoted much of her research to properties of the immune system—which promotes tissue repair but also can degrade health through autoimmune disease. Rothlin's early-career work has earned her recognition as an inaugural Howard Hughes Medical Institute Faculty Scholar.

HAROLD SHAPIRO

Spurring the body to repair itself

Investigator seeks new pathways toward guiding immune system's ability to heal and restore

Growing up in Buenos Aires, Argentina's capital city, Carla V. Rothlin, Ph.D., associate professor of immunobiology and of pharmacology, and her three sisters listened to dinnertime conversations steeped in science. Their mother, a physician, regularly shared dermatological case studies from her practice. Their father, a pharmacology researcher, gave incremental progress updates on his lab.

At age 17, Rothlin had to choose her undergraduate specialization before entering the University of Buenos Aires. She did so without hesitation: biochemistry. "I knew it would give me human-oriented biomedical training," she says, "and also a solid foundation in mathematics, physics, biology, and medicine."

She remained there for her doctoral studies, also in biochemistry, and met world-renowned scientist Ana Belén Elgoyhen, Ph.D., who became her advisor and mentor. At the time, Elgoyhen studied the neurobiological mechanisms of how humans hear and comprehend sound. Fascinated, Rothlin decided to focus her dissertation on biochemical mechanisms that tune the sensitivity of the inner ear.

"Let's say you and I are in a noisy bar, and you want to focus only on what I am saying," Rothlin says, condensing the complex into an everyday analogy as she very frequently does.

"The brain has a way to signal back to the inner ear and tune it."

Intrigued by neurobiology's complexity, Rothlin pursued that field for her postdoctoral fellowship at the Salk Institute for Biological Studies in California under the tutelage of Greg Lemke, Ph.D. At the time, Lemke and his lab team were just beginning to better understand how a family of three receptor tyrosine kinases, called TAM receptors, which Lemke had discovered in the 1990s, are linked to the immune system. Rothlin felt drawn to immunology. She enthusiastically embraced the field and mastered its jargon and major tenets.

"When you are surrounded by smart, experienced researchers, you can take on a challenge like that," says Rothlin, noting that even with that sudden change in career focus, an important constant remained. Research questions into the "mechanisms that regulate the magnitude, duration, and types of responses in the body" have guided her work throughout, including in the immunobiology lab she established when she arrived at Yale in 2009.

In a short time, Rothlin has been recognized for her basic science work within various autoimmune diseases, including asthma, lupus, Crohn's disease, and colitis. In 2016, the Howard Hughes Medical Institute (HHMI), the Bill & Melinda Gates Foundation, and the Simons Foundation made Rothlin one of their inaugural group of HHMI Faculty Scholars, part of a program to support early-career scientists who

pursue primarily basic research projects. "It is a huge honor—a very special thing," Rothlin says of the award, which included funding to support her lab. "Everything I do is with my lab and this award gives us enthusiasm to continue working on basic science."

Also in 2016, in a paper published in *Science*, Rothlin and colleagues identified a receptor called TYRO3, located on innate immune cells, that controls the strength of the immune response, and could be a potential drug target for treating allergies.

This past May, Rothlin, Sourav Ghosh, Ph.D., associate professor of neurology and of pharmacology, and colleagues detailed in *Science* how the presence of the cytokine interleukin 4 (IL4) near a damaged site in the body caused macrophages to release growth factors needed to rebuild tissue (see "Advances," p. 3).

After discovering that significant relationship, Rothlin and her team will now focus on understanding exactly how macrophages, considered sentinel cells of the innate immune system, coordinate the healing and rebuilding of damaged tissue. "It's clear that the molecular program that induces different genes and expression of proteins for macrophages to help with tissue repair is a very different program from the one that drives inflammation, the first line of immune defense," Rothlin says. To untangle that puzzle is to search for nothing less than how the body heals and rebuilds itself. For Rothlin, it is one more puzzle she wants to solve.

Accomplishments in primary care earn Leffell Prize



Matthew Ellman

Matthew S. Ellman, M.D., associate professor of medicine (general medicine) and director of Yale Internal Medicine Associates, is the 2017 recipient of the David J. Leffell Prize for Clinical Excellence.

The prize, established by David J. Leffell, M.D., David P. Smith Professor of Dermatology and professor of surgery (otolaryngology and plastic), and his wife, Cindy, is awarded each year to "an individual who best demonstrates the highest level of clinical expertise, commitment to teaching, and the highest standards of care and compassion for patients." Robert J. Alpern, M.D., dean and Ensign Professor of Medicine, presented the award.

In accepting the prize on June 26, Ellman emphasized his passion for primary care medicine, which, he says, gives him "the gift and honor of knowing people over a lifetime, and the ability to partner with them to make life as good as it can be and to help those nearing the end of their life to make that transition." Adds Ellman, "Primary care gives me the opportunity to use my mind in concert with my heart."

In addition to his work as a clinician, Ellman is a scholar and educator in the area of palliative and end-of-life care, in which he first developed a strong interest during the 1980s while a resident at Bellevue Hospital in New York City, when the AIDS epidemic was at its peak and no effective treatments were available.

Ellman earned his M.D. degree at Harvard Medical School and was a Robert Wood Johnson Clinical Scholar at Yale.

Medicine@Yale

Managing Editor Robert Forman

Contributors Jenny Blair, Jeanna Canapari, Charles Gershman, Michael Greenwood, Rick Harrison, Bill Hathaway, Ziba Kashef, Jill Max, Kathleen Raven, Barbara Steinberger, Natasha Strydhorst, Ashley P. Taylor, Sarah C.P. Williams, and William Weir

Design Jennifer Stockwell

Web Coordinator/Proofreader Cheryl Violante

Medicine@Yale is published four times each year by: Yale School of Medicine, Office of Communications 1 Church Street, Suite 300, New Haven, CT 06510-3330 Telephone: (203) 785-5824 Fax: (203) 785-4327

Email medicine@yale.edu

Website medicineat.yale.org

Copyright ©2017 by Yale University. All rights reserved.

If you have a change of address or do not wish to receive future issues of *Medicine@Yale*, please write to us at the above address or via email at medicine@yale.edu.

Postal permit held by Yale University, 155 Whitney Avenue, New Haven, CT 06520

Yale SCHOOL OF MEDICINE

Robert J. Alpern, M.D., *Dean and Ensign Professor of Medicine*

Charles Turner
Associate Vice President for Development and Director of Medical Development (203) 436-8560

Mary Hu
Associate Dean for Communications and Chief Communications Officer



Printed on recycled paper ♻️

Yale innovative-thinking center headed by medical school professor

A School of Medicine professor is the inaugural faculty director of the recently opened Tsai Center for Innovative Thinking at Yale (Tsai CITY), where trainees in numerous Yale disciplines are invited to network, interact, and exchange ideas. Peter



Peter Schulam

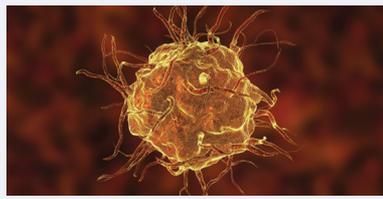
G. Schulam, M.D., Ph.D., professor and chair of urology, hopes that Tsai CITY will inspire members of Yale's health community to think about problems and opportunities in unprecedented ways.

"There's an opportunity to create relationships based on innovation amongst the entire university bridging relationships between the various schools and leveraging their unique expertise and perspectives,"

says Schulam. "Linking the medical school, the medical center, and the [Yale Medicine] health system to this process will provide a unique opportunity for innovation in health care delivery. At many institutions the medical school is a little bit isolated and separated. I think this is going to be another dimension of collaboration that will be unique for Yale."

Schulam says President Peter Salovey, // **Tsai CITY** (page 7)

Activating immune properties that heal



The human body's macrophages—a type of immune cell—not only fight off invading pathogens, but also help repair injured tissue after an infection. Yale researchers have now discovered what triggers macrophages to switch from attack mode to rebuilding mode.

In a study published on June 9 in *Science*, Carla V. Rothlin, Ph.D., associate professor of immunobiology and of pharmacology, Sourav Ghosh, Ph.D., associate professor of neurology and of pharmacology, and colleagues found that when they blocked the ability of macrophages to sense the presence of cells that had died, the macrophages no longer switched on genes required to repair tissue, even when the immune molecules IL-3 or IL-4, which help both to activate macrophages and to signal early stages of infection, were also present.

Their finding in mice that signaling molecules and dead cells were both needed to activate cell repair may help scientists learn how better to spur healing after infections, and to develop therapies for chronic inflammatory diseases such as colitis.

Aiming cancer meds within the brain

Treating brain tumors can depend on getting drugs into the brain, but the blood-brain barrier makes that difficult. In recent years, researchers have bypassed the barrier using nanoparticles that function like invisibility cloaks for drugs. Now, W. Mark Saltzman, Ph.D., Goizueta Foundation Professor of Biomedical Engineering and professor of chemical engineering and molecular physiology, and colleagues, are working to ensure that once in the brain, drug-carrying nanoparticles will actively target tumors—as opposed to either damaging healthy cells or occupying vacant space in the brain with no therapeutic effect.

Saltzman's team treated the brains of rats with nanoparticles bearing several different coatings. Some coatings had "stealth properties," which help the nanoparticles evade the immune system but also can prevent cancer cells from recognizing them. For others, stealth properties were combined with bioadhesive coatings designed to make the nanoparticles stick to cells.

As reported on May 17 in *Nature Communications*, the bioadhesive nanoparticles targeted all cell types at a higher rate than particles with stealth properties alone. Tumor cells internalized the bioadhesive nanoparticles at the highest rates of all. The result may signal a future ability to target therapies far more precisely, and with greater safety and effectiveness.

Yale enhances its cytometry capabilities

Becomes one of the first U.S. centers to adopt a technology that reveals far more than past methods about the compositions of specimens

When clinicians need diagnostic data across fields as diverse as hematology, transplantation, and tumor immunology, among others, flow cytometry is traditionally the tool they choose to identify cell markers. Investigators use flow cytometry for purposes that include analyzing cells, detecting biomarkers, and protein engineering. The technique has been essential to basic bench researchers and clinicians alike.

The methods and equipment used to probe cellular questions are rapidly advancing—including, at Yale, through the addition in 2014 of CyTOF, or Cytometry Time-Of-Flight, and this past June of the CyTOF Imaging Mass Cytometer (IMC). The latter acquisition distinguishes Yale as one of the first academic medical centers in this country to host a CyTOF IMC. Both instruments greatly expand upon the types of samples and numbers of components that can be analyzed—30 to 40 different biomarkers—where flow cytometers are more limited and can generally detect only eight. While on its own the CyTOF analyzes cells in suspension, the IMC, by contrast, can produce labeled images of tissues with spatial accuracy and provide position details of cells in an intact tissue.

The process of converting a tissue sample to a labeled, spatially accurate, microscopic image begins with a thin cross section of tissue mounted on a glass slide. Researchers add antibodies to the tissue, each antibody tagged with a different heavy metal that lets it be tracked as it binds with a specific protein. The whole assemblage goes into the IMC, where a laser vaporizes the sample from its slide, hurtling the heavy metal markers into the CyTOF instrument. Each marker, based on its mass, will have a different "time of flight" to travel through the machine. The instrument translates the times-of-flight into signals that are mapped back to where they were ablated by the laser—each one corresponding to the protein tagged with the metal—while also measuring the abundance of each protein of interest at a specific tissue location.

The IMC "means that you can detect much more in the same sample, and you can detect it with more certainty," says Ruth R. Montgomery, Ph.D., associate professor of medicine (rheumatology), associate dean for scientific affairs, and director of Yale's CyTOF facility. "Things we couldn't have dreamed of measuring—now you can get them in an afternoon."

Examples include identifying tissues that respond favorably to medication and comparing them to those that don't, or classifying immune cell responses to illness. Montgomery, for example, has used the CyTOF to compare the makeup of cells from individuals who were unperturbed by infection with West Nile virus with those from patients who developed severe symptoms of the disease.

The nascent applications for IMC are extensive, particularly in the field of pathology. "I haven't seen a disease with bodily fluids and tissues where CyTOF or [IMC] wouldn't be helpful," Montgomery says. Her team has already begun taking advantage of the instrument's vast potential. "We've started by demonstrating the power of the instrument and how to use it in a reproducible, validated, quantitative manner," Montgomery says. "And our pathology guys do that as well or better than anybody."

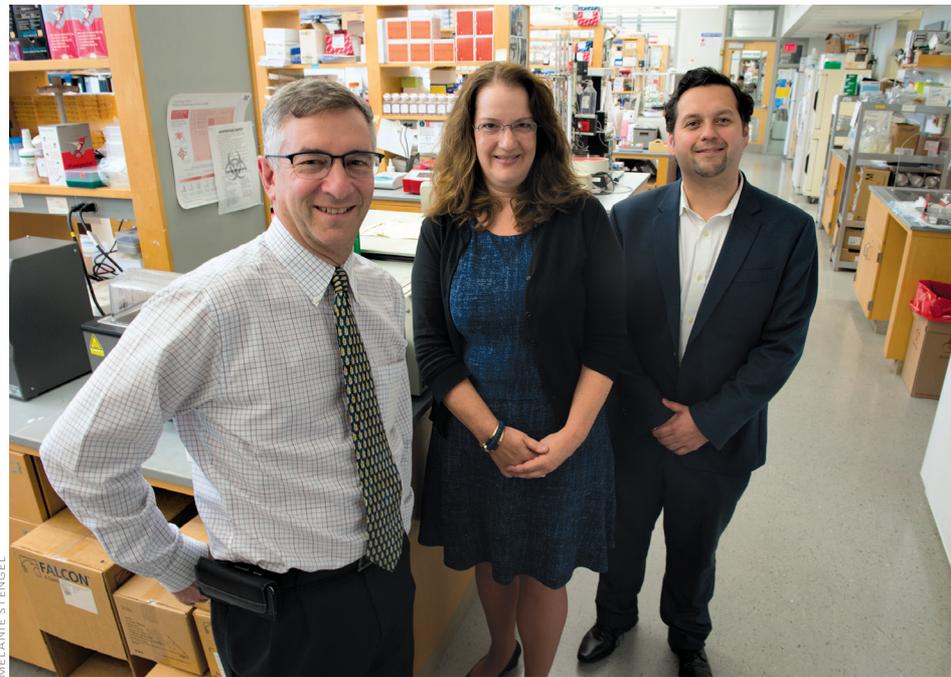
Montgomery is referring to Kurt Schalper, M.D., Ph.D., assistant professor of pathology and director of the

translational immune-oncology laboratory, and David L. Rimm, M.D., Ph.D., professor of pathology and of medicine (medical oncology), director of pathology tissue services, and director of translational pathology. Both have used the IMC to advance their cancer research: Schalper primarily investigates tumors in the lung, and Rimm focuses on breast cancer.

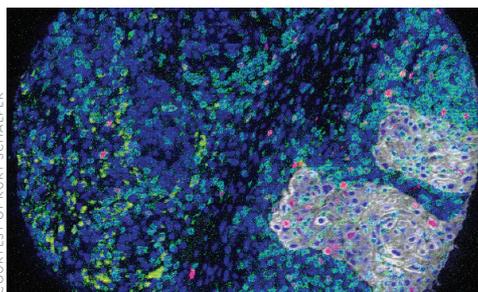
Tumor heterogeneity (the metabolic, metastatic, and morphological nuances distinguishing one patient's tumor from another's, and even cells within a single tumor) makes positional information a prized research commodity that traditional flow cytometry cannot match. "Having that spatial context [from IMC] turns out to be a very important point," Schalper says. It means researchers can study not only the components of a specimen, but also their interactions. "It's really a way of amplifying—massively—the amount of information we can obtain from samples," says Schalper.

Much as Montgomery investigates varying responses to the West Nile virus, Schalper uses IMC to interrogate what distinguishes immune cells that recognize and attack tumor cells from those that fail to sense the threat. Rimm uses the same technology to study the range of responses breast tumors exhibit to treatment with an anti-cancer drug.

"We've got a drug; now we can ask a question," Rimm says. "Can we look at relationship of expression and predict a response to therapy? That's something that will be really valuable to patients. You can see how this gets



ABOVE Ruth Montgomery (center) is director of the Cytometry Time-Of-Flight (CyTOF) facility at the School of Medicine. David Rimm (left) and Kurt Schalper (right) have been primary investigators as the facility's new CyTOF Imaging Mass Cytometer (IMC) comes into active use.



LEFT An image produced by the CyTOF IMC shows T-cells (represented in green) in the stroma of human non-small cell lung carcinomas that are positive for cytokeratin (white). The signal for Ki-67 (red), a proliferation marker, appears in both tumor and stromal cells. Nuclei are shown in blue. This image goes far beyond the detection capabilities of previous methods of cytometry.

from a very technical, highly scientific question, all the way to patient care." Rimm and Schalper do not see the IMC arriving in clinics anytime soon. For now, the instrument is too specialized and expensive for that setting. In its academic realm, however, IMC is used to track tens of variables in tissues—identifying which ones differentiate cancer-ignoring from cancer-fighting ones, for example—and then apply that knowledge to more readily available methods. Once researchers know which variable to look for—thanks to the IMC—the more limited capabilities of standard techniques no longer pose the same restrictions.

"We use all the tools we can to get at the puzzles we're looking for," Montgomery says. This includes collaborating with Yale's Department of Mathematics and other sources of quantitative expertise, to consolidate the sheer volume of data that IMC produces. The digital image of a single patient's tissue sample in Rimm's lab contains 400,000 to 600,000 pixels, and the // **Cytometry** (page 5)

OUT & ABOUT

April 25 At an **Alumni Grand Rounds** event, medical students gathered insights and shared stories with family medicine veterans **Richard Gibbs**, M.D. '86, and **Tricia Hellman Gibbs**, M.D. '87, both professors of clinical medicine at the University of California, San Francisco, and co-founders of the San Francisco Free Clinic. From left, medical students **Zola Chihombori Quao**, Class of 2018; **Dervin Cunningham**, Class of 2019; **Aishwarya Pillai**, Class of 2020; Richard and Tricia Gibbs; and **Nicolas Muñoz**, Class of 2020.



JOHN CURTIS

June 15 The Department of Internal Medicine established the **Iva Dostanic Physician-Scientist Trainee Award** five years ago to honor a physician researcher who died of ovarian cancer in 2011 while at Yale. The 2017 awardee is **Sarah Huen**, M.D., Ph.D., then an instructor in medicine (nephrology) and now an assistant professor at the University of Texas Southwestern Medical School. (l-r): Iva's parents, **Predrag Dostanic**, and **Dragana Dostanic**, M.D.; **Gary V. Desir**, M.D., chair of internal medicine; Huen; and **Peter S. Aronson**, M.D., C.N.H. Long Professor of Medicine and professor of cellular and molecular physiology, and award committee chair.



MARY-LOUISE LANDRY

June 2-4 At **Reunion Weekend**, alumni attended research talks, met current medical students, and renewed class ties. **1. Dervin Cunningham**, Class of 2019 (right), joins **Ahmed Abou-Zamzam Jr.**, M.D. '92, and his wife, **Sharon S. Lum**, M.D., on a campus tour. **2.** Dean **Robert J. Alpern**, M.D. (left), gives the Distinguished Alumni Service Award to outgoing Alumni Association President **Richard Kayne**, M.D. '76, joined by incoming president **Harold Mancusi-Ungaro**, M.D. '73. **3.** From left, **Mat Massicotte**, M.D. '92, **Jenny Williams**, M.D. '92, **Julie Lund Sharpless**, M.D. '92, and her husband, **Ned Sharpless**, M.D.



ROBERT A. LISAK (1, 2, 3)



June 21-22 The 2017 **Lung Cancer SPORE Workshop**, held at Yale West Campus Conference Center, invited discussion in wide areas of lung cancer. **1.** Keynote speaker (with plaque) **Tyler Jacks**, Ph.D., director of the Koch Institute for Integrative Cancer Research at MIT, stands with fellow researchers, from left, **Peter Ujházy**, M.D., Ph.D., deputy associate director of the Translational Research Program of the National Cancer Institute; **Charles S. Fuchs**, M.D., M.P.H., Richard Sackler and Jonathan Sackler Professor of Medicine and director of Yale Cancer Center (YCC); **Roy S. Herbst**, M.D., Ph.D., Ensign Professor of Medicine and professor of pharmacology, and chief of medical oncology at YCC; Tyler Jacks; **Katerina A. Politi**, Ph.D., associate professor of pathology at Yale; and **Christine M. Lovly**, M.D., Ph.D., assistant professor of medicine and of cancer biology at Vanderbilt-Ingram Cancer Center. **2.** **Ellen Sigal**, Ph.D., chair and founder of Friends of Cancer Research, talks with Roy Herbst during a panel discussion.



CARL KAUFMAN (1, 2)



ROBERT A. LISAK (1, 2, 3)

August 10 During the annual **White Coat Ceremony**, students heard from keynote speaker **Darin A. Latimore**, M.D., the medical school's deputy dean for diversity and inclusion and chief diversity officer. **1.** **Joana Andoh**, Class of 2021, stands with her mother, **Sally Andoh**, and former dean of the residential Silliman College **Hugh M. Flick Jr.** **2.** From left, **Jonathan Avery**, **Victoria Bartlett**, and **Elisa Berson** sit with the rest of the Class of 2021 after receiving their white coats. **3.** Dean **Robert J. Alpern**, M.D., recognizes **Richard A. Silverman**, who is retiring after 18 years as director of the school's Office of Admissions.

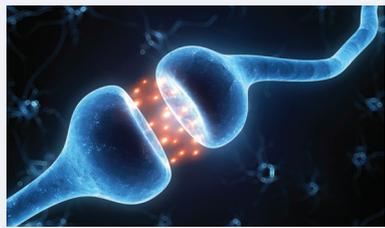
// **Pediatrics** (page 1) and has been actively involved in training students, residents, and fellows. He wants to develop a research pathway with expanded infrastructure and mentorship for residents and fellows who are interested in biomedical research. Under his leadership, the department will expand its efforts to enhance the number of faculty and trainees from underrepresented minorities in medicine, an effort that he already has begun.

Bogue, who was named chief medical officer at Yale New Haven Children's Hospital in 2014, has held a number of medical school and hospital leadership positions since he joined the faculty in 1993. He has served as director of pediatric critical care transport, medical director of the pediatric intensive care unit, director of the pediatric critical care fellowship, chief of pediatric critical care medicine and associate chair for strategic planning.

For more than 20 years he has directed a research program funded by the National Institutes of Health on the developmental biology of the lung, liver, and cardiovascular system. His laboratory has made important contributions to the discovery of genetic pathways involved in embryonic organ development, including the identification of genetic pathways essential to the formation of the liver and biliary system, as well as the cardiovascular system.

Bogue has received the Mae Gailani Junior Faculty Award, the Norman J. Siegel Faculty Award, and a pediatric fellow teaching award, among other honors. He graduated with distinction from the University of Virginia in 1981 and completed his M.D. at his alma mater in 1985. He was chief resident in pediatrics at Vanderbilt University before completing his fellowship in pediatric critical care medicine at Yale.

Alzheimer's damage reversed by a drug



An experimental drug improves the learning and memory skills of mice with Alzheimer's disease, and reconnects cells in their brains, according to new Yale-led research.

Stephen M. Strittmatter, M.D., Ph.D., professor of neurology and of neuroscience, and colleagues had previously found that the receptor mGluR5, found on the surface of brain cells, was a key to explaining how Alzheimer's affects the brain. mGluR5, they discovered, transmits the damaging effects of amyloid beta and prion proteins to the inside of brain cells, causing the hallmark dysfunction associated with Alzheimer's. But mGluR5 is also required for normal brain function, so fully blocking it is not an option to treat disease.

In the new work, published July 5 in *Cell Reports*, Strittmatter's team tested the Silent Allosteric Modulator (SAM) drug BMS-984923, which keeps mGluR5 from interacting with amyloid beta and prion proteins without blocking its normal function. While the drug did not lower levels of the usually damaging proteins, it prevented them from diminishing brain cell function. The treatment also reversed existing Alzheimer's symptoms in the mice.

Pathway affects blood vessel actions

Blood vessel development depends on the fibroblast growth factor (FGF) signaling pathway, suggests a study published on May 11 in *Nature*.

Researchers already knew that another growth factor, VEGF, played a role in vascular development, so Michael Simons, M.D., Robert W. Berliner Professor of Medicine (Cardiology) and professor of cell biology, investigated whether FGF might do the same. Mouse embryos genetically engineered to lack FGF receptors in their blood vessels developed smaller and less-branching vascular networks than embryos with the receptors, Simons' team found. The absence of FGF also hampered the development of lymphatic vessels.

Further, blood vessels were found to need FGF receptors in order to metabolize sugars through glycolysis, a process where enzymes break down glucose. FGF receptors are necessary for production of the transcription factor c-Myc, which leads to generation of the essential glycolytic enzyme HK2.

Knowledge of molecules important for vascular development could lead to drugs that block the blood vessel formation that often sustains cancer tumors, Simons says. It may also point the way toward regrowing blood vessels in patients with vascular problems such as coronary artery disease.

Boost for method to curb youth smoking

Video games that have shown effectiveness in trials will have their use expanded through funding from the CVS Health Foundation

Lynn E. Fiellin, M.D., associate professor of medicine and in the Yale Child Study Center, has spent much of her recent career determining how best to use video games to empower adolescents to avoid risky behaviors that affect life outcomes. Fiellin's work has just received a substantial boost in the form of a \$1.4 million gift from the CVS Health Foundation. The three-year gift is a part of "Be The First," a \$50 million commitment by CVS Health to help deliver the first tobacco-free generation.

This gift aims to further smoking prevention by helping to bring *smokeSCREEN*, a game Fiellin's group has developed, to a broader audience across the United States. The game, currently played on an iPad, conveys anti-tobacco messaging via character-based graphic novel-like images and multiple-choice questions. Results of a New Haven- and Los Angeles-based study indicate a significant impact on health risk perceptions and knowledge about both cigarette and electronic cigarette use among young people exposed to *smokeSCREEN*.

The game is part of a series that has focused on HIV prevention, sexual risk, drugs, alcohol, bullying, and cheating, Fiellin says, and has recently been expanded with additional NIH and Food and Drug Administration funding to significantly emphasize smoking prevention. Among other support, in 2009 the National Institutes of Health (NIH) awarded her a \$4 million, five-year grant to support research on using the games to influence adolescent behavior. In 2015, Fiellin founded the Center for Health & Learning Games at the School of Medicine, which focuses on serious game development and evaluation, and their applications to health and behavioral science.

CVS first approached Fiellin in March of this year, two years after it made headlines by announcing plans to ban all cigarette sales at its stores. "That spoke volumes to me," Fiellin says, noting the company's commitment to smoking prevention even though its decision to stop

selling cigarettes cut off a significant source of revenue. "CVS showed they were speaking with their feet," she says. "This is an opportunity to really get this game out there in a meaningful way such that it can become part of the after-school experience." The new aim is to implement *smokeSCREEN* nationally in 2018, following the launch of a pilot program this fall with a group of national partners led by CVS.

"Through our support of Yale's *smokeSCREEN* gaming app we do hope to reach more youth and young adults who use tobacco or who are at risk of becoming regular tobacco users, encouraging them to quit or discouraging them



(l-r): Lynn Fiellin directs the Center for Health & Learning Games, Tyra Pendergrass is associate director, and Kimberly Hieftje is deputy director. A CVS Health Foundation gift will expand use of their method to reduce adolescent smoking.

from ever starting to smoke," says Eileen Howard Boone, president of the CVS Health Foundation and senior vice president of corporate social responsibility & philanthropy at CVS Health. "Over the next year, we're aiming to expose hundreds of thousands of students to the game, which is a very unique approach to cessation and tobacco control."

The CVS Health Foundation, created by CVS Health more than 25 years ago, works with nonprofit entities throughout the U.S. to support and expand health care for underserved populations, create innovative approaches to chronic disease management, provide tobacco cessation and youth prevention programming, and mitigate prescription drug abuse.

// **Researchers** (page 1) who hear a different drummer to undertake innovative neuroscience research so we can make real progress against many currently untreatable brain diseases."

"I know my husband's interest in neuroscience research started at Yale," says Michiko Spector. "Neuroscience is still an area with many unknowns. We need young, innovative blood to figure out our brain."

The endowed fund will provide research and teaching support in perpetuity to junior faculty working in the field. This year, Ellen J. Hoffman, M.D., Ph.D., assistant professor in the Yale Child Study Center, has been selected to receive research support from the fund. "As a junior faculty member, I believe the Spector Fund Award will greatly contribute to the development of my research program. The award will give me the opportunity to expand my research in new directions with the aim of advancing our understanding of the neurobiology of autism."

Reynold Spector, now retired, focused his research on understanding the blood-brain and blood-cerebrospinal fluid barriers.

He also had a long career in clinical pharmacology, culminating in a position at Merck, where he oversaw the development of breakthrough medications including Zocor®, Singulair®, Fosamax®, and Cozaar®; and vaccines for human papillomavirus and shingles. Prior to his tenure at Merck, where he served as head of development, Spector conducted neuroscience research at Harvard for seven years, and then at the University of Iowa, where he was director of the university's Clinical Research Center as well.

The Sectors' daughter, June T. Spector, M.D., M.P.H., is also a graduate of Yale School of Medicine, Class of 2005. She now is an associate professor of medicine (general internal medicine), and of environmental and occupational health sciences, at the University of Washington. The Sectors view their contribution to Yale as a crucial investment in an institution that has done much for them, and for all of its students. "Both June and I benefitted greatly from Yale," Reynold Spector says, "so we decided to give back."

// **Cytometry** (page 3) IMC measures 30 to 40 selected proteins within each pixel for more than 60 patients. That adds up to 120 million data points for one small pilot study, so Rimm has recruited Yuval Kluger, Ph.D., associate professor of pathology, a bioinformatics expert affiliated with Yale's Applied Mathematics Program, to help analyze the data. Collaboration among disciplines and departments is "a requirement, at this point," says Montgomery. "We have the technology to create giant datasets. And, to make sense of them—to interpret them for relevance to our health questions—we need to have computational colleagues."

Once investigators learn its capabilities, Montgomery sees CyTOF IMC moving far beyond its initial uses, and becoming an essential tool for labs across the School of Medicine. "Now that we can really make use of it, we can advance into many different areas," she says. "A lot of people come in here to see me with their great ideas about what they want to do, and I tell them to go ahead and use the machine."

Grants and contracts awarded to Yale School of Medicine

September 2016–November 2016

Federal

Clara Abraham, DoD, *Modulation of Host Responses to Microbial Products*, 3 years, \$2,005,800 • **Frederick Altice**, NIH, *Integrating Addiction Treatment and HIV Services into Primary Care Clinics in Ukraine*, 4.8 years, \$4,373,313 • **Karen Anderson**, NIH, *Mechanism and Inhibition of HIV Reverse Transcriptase*, 3.7 years, \$2,356,149 • **Morris Bell**, NSF, *CHS: Large: Collaborative Research: Computational Science for Improving Assessment of Executive Function in Children*, 4 years, \$1,205,294 • **Joerg Bewersdorf**, NIH, *Enabling Nanoscale Dynamic Imaging of Vesicles and Organelles*, 3.9 years, \$3,350,000 • **Dipankar Bhattacharya**, NIH, *Elucidating a Novel Function for *slco1a2*, an Organic Anion Transporter, in Left-right Patterning and Cardiac Development*, 3 years, \$105,108 • **Hilary Blumberg**, NIH, *Ultra High Field Strength MRI and MRS Study of Bipolar Disorder in Adolescents*, 2 years, \$460,625 • **Hal Blumenfeld**, NIH, *Remote Effects of Focal Hippocampal Seizures on Neocortical Function*, 5 years, \$1,816,970; NIH, *Network Mechanisms of Seizure-induced Cardiorespiratory Impairment*, 5 years, \$1,808,194 • **Emanuela Bruscia**, NIH, *CFTR and Toll-like Receptor Signaling*, 3.8 years, \$1,675,000 • **Sonia Caprio**, NIH, *Pathogenesis of Youth Onset Pre-diabetes and Type 2 Diabetes*, 4.9 years, \$3,301,226 • **Madeleine Chalfant**, NIH, *Determining the Role of Nucleoporins in Ciliogenesis and Heart Development*, 3 years, \$100,064 • **Lawrence Cohen**, NIH, *New Approaches for Better Protein Voltage Sensors*, 2.9 years, \$1,929,501 • **Chris Cotsapas**, NIH, *Genomics of NfκB-mediated Gene Regulation in Multiple Sclerosis*, 4 years, \$2,933,202 • **Joseph Craft**, NIH, *Training Program in Investigative Rheumatology*, 5 years, \$1,920,515 • **Forrest Crawford**, NIH, *Network-based Epidemiology for Hidden and Hard-to-Reach Populations*, 5 years, \$2,512,500 • **James Daley**, NIH, *The Role of Small RNAs in Homologous Recombination*, 2 years, \$460,625 • **Larry Davidson**, SAMHSA, *Peer Leadership Training Curriculum Development*, 1 year, \$138,541 • **Francesco D'Errico**, **Lawrence Staib**, **Michael Choma**, DHS, *Evaluation and Demonstration of Technologies Related to Threat Detection*, 5 years, \$349,964 • **James Duncan**, NIH, *Sub-network-based Quantitative Imaging Biomarkers for Therapy Assessment in Autism*, 4.7 years, \$1,876,784 • **David Fiellin**, NIH, *3/6 COMpAAAS U01: Intervention Study*, 5 years, \$2,405,512 • **Terri Fried**, NIH, *Enhancing Engagement in Advance Care Planning*, 3.8 years, \$2,185,029 • **Alison Galvani**, NIH, *Sustainable Capacity in Liberia for Informing Surveillance and Response Through Modeling, Biostatistics and Computational Tools*, 11 months, \$50,000 • **Mark Gerstein**, NIH, *Methods and Software to Enhance Genomic Privacy and Sharing of RNA-Seq Data*, 2.8 years, \$727,728 • **Carlos Grilo**, NIH, *Behavioral and Pharmacologic Treatment of Binge Eating and Obesity*, 4.9 years, \$3,578,388 • **Shangqin Guo**, NIH, *Molecular Definition of Cancer Cell-of-Origin*, 4.7 years, \$2,512,500 • **Marc Hammarlund**, NIH, *Mechanisms and Regulation of Neuronal Aging*, 11 months, \$606,339 • **Kevan Herold**, NIH, *Phase II Trial of Extended Release Exenatide (Bydureon) and Teplizumab in Patients with New Onset Type 1 Diabetes*, 1 year, \$251,250 • **Raimund Herzog**, NIH, *Reversing Brain Metabolic Adaptations to Recurrent Hypoglycemia in Older Adults with Type 1 Diabetes Using a Predictive Low Glucose Management (PLGM) System*, 3.9 years, \$1,925,295 • **Joy Hirsch**, NIH, *Neural Mechanisms for Social Interactions and Eye Contact in ASD*, 4.8 years, \$3,215,009 • **Jaclyn Hughto**, NIH, *Intervention to Overcome Mental Health Disparities in Criminally Justice Involved Transgender Women*, 2 years, \$87,152 • **John Hwa**, NIH, *Hyperglycemia, Aldose Reductase, miRNA and Cardiovascular Disease in Diabetes Mellitus*, 3.8 years, \$1,675,000 • **Kevin Jensen**, NIH, *The Effect of Nicotine Delivery Rate on Reinforcement*, 1.9 years, \$196,350 • **Nikhil Joshi**, NIH, *Investigating the Development and Maintenance of Tumor-associated Tertiary Lymphoid Structures in an Autochthonous Mouse Model of Lung Adenocarcinoma*, 3 years, \$586,764 • **Amy Justice**, NIH, *1/6 COMpAAAS U24: Coordinating Center*, 5 years, \$1,207,008; NIH, *2/6 COMpAAAS U01: Observation Study*, 5 years, \$4,970,166 • **Naftali Kaminski**, DoD, *Large Noncoding RNAs as Therapeutic Targets in IPF*, 3 years, \$2,009,813 • **Brian Kiluk**, NIH,

Identification of a Meaningful Cocaine Use Outcome Measure, 2 years, \$455,675 • **Amanda King**, NIH, *Convection-enhanced Delivery of Radiosensitizer-Encapsulating Nanoparticles for the Treatment of Pediatric Brainstem Gliomas*, 3 years, \$83,444 • **Saurabh Kulkarni**, NIH, *Understanding the Molecular and Cellular Regulation of Cilia Assembly and Regeneration in Multiciliated Cells*, 2 years, \$256,500 • **Patty Lee**, DoD, *MIF-based Therapies in Cigarette Smoke-related COPD and Pneumonia*, 3 years, \$2,994,748 • **Carrie Lucas**, NIH, *PI3K Signaling in Regulation of CD8 T Cell Senescence and Death*, 2.8 years, \$745,057 • **Steven Marans**, SAMHSA, *Childhood Violent Trauma Center (CVTC)*, 5 years, \$3,000,000 • **Olga Morozova**, NIH, *Optimizing Medication-assisted Therapy for Opioid Dependence in Ukraine: HIV Impact Modeling and Cost-effectiveness Evaluation*, 2 years, \$98,290 • **Michael Nitabach**, NIH, *Peptide Modulation of Physiology and Behavior*, 3.8 years, \$1,578,428 • **Chirag Parikh**, NIH, *Novel Kidney Injury Tools in Deceased Organ Donation to Predict Graft Outcome*, 4.9 years, \$3,074,178 • **Abhijit Patel**, DoD, *Early Detection of Lung Cancer via Tumor DNA Fragments in Blood*, 1 year, \$166,500 • **Godfrey Pearson**, DOT, *Examine the Feasibility of a Standardized Field Test for Marijuana Impairment: Laboratory Evaluations*, 3.3 years, \$742,046 • **Melinda Pettigrew**, DHHS, *Identification of Microbial Disruption Indices (MDI) Predictive of Colonization and Dominance by Multi-drug Resistant Pseudomonas Aeruginosa*, 1.2 years, \$459,721 • **Christopher Pittenger**, NIH, *Histamine Regulation of Basal Ganglia Function*, 1.9 years, \$404,250 • **Adele Ricciardi**, NIH, *Nano-particles for Site-specific Genome Editing in Utero*, 3 years, \$105,108 • **Aaron Ring**, NIH, *Uncoupling Pleiotropy in the LIGHT/HVEM/LTBetaR Signaling Network*, 5 years, \$2,093,750 • **Joseph Ross**, DHHS, *Yale-Mayo FDA Center for Excellence in Regulatory Science and Innovation*, 1.9 years, \$5,292,624 • **Arash Salardini**, NIH, *Imaging Innate Immune Responsiveness of Microglia in Alzheimer's Disease Brain*, 1.7 years, \$460,625 • **Lauren Sansing**, NIH, *Dynamic Neuroimmune Profiling in Patients with Acute Intracerebral Hemorrhage*, 4.8 years, \$2,760,717; NIH, *Efferocytosis and the Resolution of Inflammation After Intracerebral Hemorrhage*, 5 years, \$1,832,030 • **Mahnoosh Sharifi**, DHHS, *Using Electronic Health Records to Support Decision-making in Pediatric Obesity Care*, 3 years, \$462,052 • **Albert Shaw**, NIH, *Training in Investigative Infectious Diseases*, 5 years, \$1,540,923 • **Brian Shuch**, NIH, *Genomic Heterogeneity and the Small Renal Mass*, 4 years, \$694,388 • **Patrick Skosnik**, NIH, *Multimodal Imaging of Recovery from Cannabis Dependence*, 3.9 years, \$2,942,206 • **Dieter Söll**, DOE, *Engineering Selenoproteins for Enhanced Hydrogen Production*, 1 year, \$450,000 • **Sandra Springer**, NIH, *The Impact of HIV Infection on Immunologic, Transcriptomic, and Metabolic Signatures of Medication-assisted Therapy for Opioid Addiction*, 4.7 years, \$5,756,801 • **Stephen Strittmatter**, NIH, *Characterizing and Targeting Pyk2 Kinase in Alzheimer's Disease*, 4.8 years, \$2,090,105; NIH, *Evaluation of Novel Targets for Retinal Ganglion Cell Axon Regeneration*, 3 years, \$2,044,890 • **Patrick Sung**, DOE, *Structural & Cell Biology of DNA Repair Machines*, 5 years, \$73,700 • **Hemant Tagare**, NIH, *Comprehensive Local Resolution Analysis for Cryo-EM*, 3 years, \$981,061 • **Janet Tate**, NIH, *5/6 COMpAAAS U24: Resource in Informatics and Biostatistics (RIB)*, 5 years, \$1,433,439 • **Jeffrey Testani**, DHHS, *Evaluating Predictive Methods and Product Performance in Healthy Adults for Pediatric Patients, Case Study: Furosemide*, 2 years, \$398,650 • **Christian Tschudi**, NIH, *Integrating Roles of Noncoding RNPs in RNA Biogenesis, RNA Decay and Cell Survival*, 3.8 years, \$2,120,896 • **Emily Wang**, NIH, *Building Resilient Neighborhoods and Positive Social Networks to Prevent Gun Violence*, 2.7 years, \$1,357,992 • **John Wysolmerski**, DoD, *Targeting CaSR/GABAB R1 Heterodimers to Treat Bone Metastases in Breast Cancer*, 3 years, \$628,125 • **Jiansong Xu**, NIH, *Nitric Oxide Facilitates Nicotine Absorption During Cigarette Smoking*, 2 years, \$460,625 • **Ke Xu**, NIH, *Methylome-wide and mQTL Analysis of HIV Progression in the Context of Cocaine Use*, 3.9 years, \$1,606,005 • **Qin Yan**, DoD, *CA150340: Dissecting the Roles of ARID2 Tumor Suppressor in Metastatic*

Melanoma, 2 years, \$665,999 • **Lee Ying**, NIH, *Regulation of Adipogenesis in Obesity by hydroxymethylation*, 2 years, \$59,060 • **Shang-Min Zhang**, DoD, *Epigenetic Regulation of Histone Demethylase JARID1B in Melanoma*, 1 year, \$124,874

Non-federal

Clara Abraham, Icahn School of Medicine at Mount Sinai (NIH), *Integrative Genomic Analyses of Macrophages in Crohn's Disease*, 11 months, \$150,750 • **Fuad Abujarad**, Michigan State University, *Licensing and Regulatory Affairs, Health Information Technology to Prevent Abuse, Neglect, and Exploitation: Child Care Background Checks*, 1 year, \$35,742 • **Marc Auerbach**, Johns Hopkins University (DHHS), *Improving Rural Pediatric Emergency Care Through Tele-simulation*, 10 months, \$15,966; Children's Hospital of Philadelphia (DHHS), *Advancing Family Centered Care and Quality Self-assessment for Pediatric Resuscitation Readiness*, 3 years, \$49,699 • **Helene Benveniste**, University of Rochester Medical Center (NIH), *Para-vascular Basis of Small Vessel Disease URF AWD00001203*, 4.7 years, \$1,193,250; University of Rochester (NIH), *Glymphatics Function In a Transgenic Rat Model of Alzheimer's Disease URF AWD0527901*, 2.6 years, \$411,367 • **Anne Black**, Wellesley College (NIH), *Risk Behavior Among Offspring of Teen Parents: Effects of Parenting on the Next Generation*, 2 years, \$47,913 • **Theodore Blaine**, U.S. Lacrosse, *A Biomechanical Analysis of the Protective Effect of Shoulder Pads in Preventing Major Shoulder Injury in Men's Lacrosse*, 1.3 years, \$32,987 • **Douglas Brash**, Leo Pharma A/S, *Chemixcitation in Human Disease*, 1 year, \$41,718 • **Christopher Bunick**, Foundation for Ichthyosis & Related Skin Types (FIRST), *Deter-mining the Structural Mechanisms of Ichthyosis-causing Mutations by X-ray Crystallographic Analysis of Keratins 1 and 10*, 1 year, \$50,000 • **Susan Busch**, Dartmouth College (NIH), *Mental Health Care Under New Payment Strategies*, 3.8 years, \$35,287 • **Linda Cantley**, Stanford University (NIH), *Disease, Disability and Death in an Aging Workforce*, 11 months, \$348,889; Board of Trustees of The Leland Stanford Junior University (NIH), *Occupational Exposure to PM2.5 and Cardiovascular Disease (CVD)*, 4 years, \$39,845 • **Richard Carson**, Pfizer, U.S. Pharmaceuticals Group, *Preclinical Evaluation of PF-06874354 Using PET*, 1 year, \$286,791; Molecular Neuroimaging (NIH), *A Program for Innovative PET Radioligand Development and Application: A Translational Toolbox for Treatments for Mental Health*, 3.8 years, \$146,767; Indivior, *Project 1: Preclinical Evaluation of APV202701A Using [¹¹C]PHNO PET*, 1 year, \$389,411 • **Dana Cavallo**, Sewanee The University of the South, Andrew W. Mellon Foundation, *Development of a School-wide Tobacco Survey to Inform a Smoking Prevention and Cessation Program in a Southern Appalachian High School*, 1 year, \$5,599 • **Anees Chagpar**, Connecticut Breast Health Initiative, *SHAVE2, A Multi-center Randomized Controlled Trial of Routine Cavity Shave Margins vs. Standard Partial Mastectomy*, 1 year, \$50,000 • **Katarzyna Chawarska**, University of South Carolina (NIH), *Emergence, Stability and Predictors of Anxiety in Fragile X Syndrome*, 1 year, \$22,077 • **Paul Cleary**, University of Connecticut Health Center, *State Innovation Models: Round Two of Funding for Design & Test Assistance-Evaluation*, 1 year, \$225,000 • **Daniel Colon-Ramos**, Howard Hughes Medical Institute, *2016 Faculty Scholars Competition: Eligibility Responses*, 5 years, \$900,000 • **Zachary Cooper**, National Institute for Health Care Management Foundation, *Analyzing the Frequency, Causes and State Responses to Surprise Out-of-Network Billing*, 1 year, \$49,570 • **Philip Corlett**, University of Aarhus, *Proxemics and Trust in Serious Mental Illness*, 1 year, \$10,770 • **Patrick Cudahy**, Infectious Diseases Society of America, *Composition of Multi-drug Resistant Mycobacterium Tuberculosis Strains during Treatment*, 1 year, \$30,000 • **Gary Desir**, **Fred Gorelick**, Bessor Pharma (NIH), *Acute Pancreatitis: Renalase as a Novel Target and Analogues as New Therapy*, 1 year, \$100,000 • **Marcelo Dietrich**, The John B. Pierce Laboratory, *Uncovering a Novel Circuit Linking Neurons Encoding Homeostatic Needs to Motor Output Areas in the Brainstem*, 1 year, \$23,239 • **Vishwa Dixit**, Glenn Foundation for Medical Research, *Glenn Award for Research in Biological Mechanisms of Aging (the Glenn Award)*, 2 years, \$60,000 • **George Dragoi**, Charles H. Hood Foundation, *Neuronal Mechanisms Underlying Brain Development of Internal Representations During Childhood*, 2 years, \$150,000 • **Marie Egan**, Cystic Fibrosis Foundation (CFF), *Implementation of Pediatric Clinical Pharmacy Services at Yale New Haven*

Hospital, 3 years, \$119,556 • **Denise Esserman**, Patient-centered Outcomes Research Institute, *Expansion of Methods for Two-Stage Trial Designs for Testing Treatment, Self-selection and Treatment Preference Effects*, 3.2 years, \$515,511 • **Carlos Fernandez-Hernando**, Mayo Clinic Jacksonville Florida (NIH), *Role of MicroRNA-33 in Alzheimer's Disease*, 4.7 years, \$26,368 • **John Forrest**, Doris Duke Charitable Foundation, *Pilot Twinning Model for Doris Duke Charitable Foundation International Clinical Research Fellowship Program for Medical Students*, 1 year, \$12,000 • **Lisa Fucito**, Medical University of South Carolina (NIH), *Gain-framed Messages and NRT Sampling to Promote Smoking Cessation in Lung Cancer Screening Programs*, 5 years, \$247,800 • **Jean-Francois Geschwind**, Boston Scientific Corporation, *Paclitaxel-Eluting-Beads Transarterial Chemoembolization using OncoSpheres in a Rabbit VX2 Liver Cancer Model*, 1 year, \$232,181 • **Antonio Giraldez**, Howard Hughes Medical Institute, *Molecular Analysis of the Maternal to Zygotic Transition*, 5 years, \$600,000 • **Valentina Greco**, Howard Hughes Medical Institute, *Capturing Basic Principles of Tissue Regeneration and Disease by Live Imaging*, 5 years, \$900,000 • **Jaime Grutzendler**, National Multiple Sclerosis Society, *Local Astrocyte Contributions to Myelin Repair*, 3 years, \$330,000 • **Stephanie Halene**, Edward P. Evans Foundation, *Study of MDS Biology and Response to Targeted Therapeutics in a MDS Xenotransplantation Model*, 1 year, \$200,000 • **Christos Hatzis**, Breast Cancer Research Foundation, *Biological Interpretation of the Cancer Genome*, 1 year, \$250,000 • **Erica Herzog**, NAVITOR Pharmaceuticals, *Efficacy of Selective mTORC1 Inhibition in IPF*, 1.5 years, \$228,629; Imago Pharmaceuticals, *Evaluation of JNK Inhibition in Experimentally Induced Lung Fibrosis*, 1 year, \$55,893 • **Michael Hines**, SUNY Downstate Medical Center (NIH), *Embedded-ensemble Encoding*, 2.8 years, \$39,910; Brown University (NIH), *Human Neocortical Neurosolver*, 9 months, \$147,859 • **Tamas Horvath**, Biogen MA, *Neurophysiological Evaluation of AD-related Transgenic Rats and Mice*, 1 year, \$296,101 • **Henry Hsia**, Rutgers, The State University of New Jersey (NIH), *Multi-functional Nanoparticles Containing sRAGE Potentiated Bioactive Peptides for Wound Healing*, 1.6 years, \$50,250 • **Yiyun Huang**, Bristol-Myers Squibb Company, *Milla Tracer Development for PD-L1 Imaging in Humans*, 1 year, \$127,119 • **Melinda Irwin**, Breast Cancer Research Foundation, *Physical Activity Diet, Weight and Breast Cancer Survivorship*, 1 year, \$258,696 • **Elizabeth Jonas**, New York University (NIH), *Molecular Composition of the Mitochondrial Permeability Transition Pore*, 1 year, \$112,826 • **Amy Justice**, University of California, San Francisco (NIH), *Protein Biomarkers for CVD Prediction in HIV-Infected and Uninfected Veterans*, 10 months, \$83,346; New York University School of Medicine (NIH), *Should Screening and Treatment Strategies for Unhealthy Alcohol Misuse in HIV-infected Persons Vary with Smoking, Depression, and Substance Abuse?*, 9 months, \$66,924 • **Arie Kaffman**, Brain & Behavior Research Foundation (formerly NARSAD), *Early Life Stress Impairs Normal Hippocampal Development by Inhibiting Expression of IRF8 in Microglial Cells*, 2 years, \$99,817 • **Robert Kerns**, The Consortium of Multiple Sclerosis Centers, *Perceived Pain-related Illness Intrusiveness Among Persons with Multiple Sclerosis*, 1 year, \$40,000 • **Richard Kibbey**, University of Massachusetts (NIH), *Metabolomics Administrative Supplement: Disruption of Parity-induced Tumor Suppressor Pathways by Xenoestrogen Exposures During Pregnancy*, 3.8 years, \$52,205 • **Kenneth Kidd**, Massachusetts Institute of Technology (DoD), *Datasets for Forensic Research*, 1 year, \$199,119 • **Jonathan Koff**, Cystic Fibrosis Foundation (CFF), *Implementation of Outpatient Clinical Pharmacy Services: Award for a Pharmacist and/or Pharmacy Technician*, 3 years, \$119,880 • **Robert LaMotte**, Johns Hopkins University (NIH), *Peripheral Neuronal Mechanisms of Itch*, 11 months, \$221,000 • **Christine Lattin**, Graduate Women in Science, *Using Positron Emission Tomography (PET) to Assess Tissue-specific Energetic Trade-offs Between Immune Function and Reproduction in a Wild Bird*, 1 year, \$10,000 • **Daeyeol Lee**, California Institute of Technology (NIH), *Neuronal Substrates of Hemodynamic Signals in the Prefrontal Cortex*, 4.9 years, \$74,942 • **Chiang-Shan Li**, Brown University (NIH), *Large-scale Network Modeling for Brain Dynamics: Statistical Learning and Optimization*, 9 months, \$74,198 • **Mark Mamula**, Alliance for Lupus Research (New Name: Lupus Research Alliance), *Therapeutic Inhibitors of Antigen Presentation Pathways in SLE*, 3.2 years, \$579,020

Grant renewed for infectious disease surveillance

School of Public Health joins with state to track flu, Lyme, HPV, other threats

The Connecticut Emerging Infections Program (EIP), a collaboration between Yale School of Public Health (YSPH) and the state's Department of Public Health, has been awarded \$20.9 million to continue research and surveillance of infectious diseases in Connecticut for another five-year cycle. \$14 million of this award from the federal Centers for Disease Control and Prevention (CDC) is earmarked to support the efforts of the YSPH office of EIP.

The Yale EIP tracks a wide range of infectious diseases that affect state residents. According to James I. Meek, M.P.H., EIP's associate director, staffers annually monitor and investigate approximately 1,400 cases of food-borne illness, 1,500 cases of *Clostridium difficile* infection, 1,000 flu hospitalizations and 2,000 cases of high-grade cervical lesions caused by human papillomavirus infection. In addition, EIP staff survey approximately 1,500 hospital or nursing home residents to estimate the burden of health care-associated infections in these institutions and engage thousands of Connecticut residents in studies to assess the burden and evaluate prevention measures for tick-borne diseases.

Tracking these diseases allows EIP staff and state public health officials to better understand risk factors for contracting these diseases, identify targets for future public health interventions, and evaluate the effectiveness of current interventions.

"We are thrilled to be able to continue to build on the success of the past 20 years in conducting public



With new funding, an effort by the School of Public Health and the state to track infectious disease continues for five more years. Leaders from Yale are (l-r) Robert Heimer and Linda Niccolai, co-principal investigators; and James Meek, associate director.

health surveillance for Connecticut. Collectively, the diseases we monitor affect more than 10,000 residents every year, and monitoring trends is essential for informing public health practice and policy. We are also excited about our role in continuing to train students and fellows, who will be the public health workforce of the future," says Linda M. Niccolai, Ph.D., associate professor of epidemiology (microbial diseases), who is co-principal investigator of the program along with Robert Heimer, Ph.D., professor of epidemiology (microbial diseases) and of pharmacology. Matthew Cartter, M.D., M.P.H., the state epidemiologist, serves as the Department of Public Health's principal investigator.

"Emerging infectious diseases are a reality for Connecticut and tackling these infections in partnership with the CDC and the Connecticut Department of Public Health has enabled a robust response to protect Connecticut residents for over 20 years," says Sten H. Vermund, M.D., Ph.D., dean

and Anna M.R. Lauder Professor of Public Health, and professor of pediatrics. "We are especially pleased with the role that YSPH students are playing in specific projects, both contributing substantially and learning about public health practice in the process."

Yale is one of 10 sites that have received renewed funding as part of the CDC's Emerging Infections Program, a national network that monitors disease outbreaks in order to inform policy surrounding methods of preventing and treating infectious disease. Communities covered by the national EIP approximate the composition of total U.S. population in terms of age, race, gender, and other health indicators.

Yale was one of the first EIP sites funded in 1995, when the national program began.

// **Tsai CITY** (page 2) Ph.D. '86, and Provost Ben Polak recruited him for his role in Tsai CITY because the university's Center for Biomedical and Interventional Technology (CBIT), which he co-founded with W. Mark Saltzman, Ph.D., the Goizueta Foundation Professor of Biomedical Engineering and professor of chemical engineering and of molecular physiology, has already been a successful catalyst for innovation. He says imagination also has flourished in many other pockets within the university. "People ask, 'How innovative is Yale?' Yale is very innovative, and there are a lot of innovative efforts," Schulam notes. "There are many successful innovative efforts on the campus but they did not share a common portal. By creating a foundation for innovative efforts there will be increased networking and improved visibility for all the programs."

According to Schulam, success will not be measured by the number of entrepreneurial ventures Tsai CITY spawns. While startups are desirable, Schulam says, how many participants the center attracts

and the variety of disciplines they represent will mean more. "That level of connectivity, that level of interaction, that level of networking, that level of collegiality, is what we are hoping to create," he says. "And what will be the results of that? It is difficult to predict but we are hopeful this center will enhance the impact Yale students have in their future careers by broadening how they approach problem solving."

Tsai CITY's executive director is Andrew McLaughlin, whose prior roles include deputy chief technology officer of the United States in the Obama White House, CEO and executive chair of Digg, and senior fellow at Columbia University's School of International and Public Affairs. The center's current home is at 254 Elm Street. Construction of a permanent location on Becton Plaza on Yale's main campus should be completed in 2019.

A large grant from the Joe and Clara Tsai Foundation has provided funding to create and build Tsai CITY. Joseph C. Tsai, B.A. '86, J.D. '90, says it is a way to pay tribute to the formative role that

innovative thinking has played in his own life, which includes co-founding and serving as executive chair of the global e-commerce company Alibaba. Tsai's prior contributions to Yale include the law school's Paul Tsai China Center, named for his father; and gifts to the Department of Computer Science and to Yale Athletics, particularly the men's and women's lacrosse programs.

Faculty elevated to endowed professorships



Jaime Grutzendler, M.D., becomes the Dr. Harry M. Zimmerman and Dr. Nicholas and Viola Spinelli Professor of Neurology. He also is director of the Center for Experimental Neuroimaging.



Francis Y. Lee, M.D., Ph.D., has been named Wayne O. Southwick Professor of Orthopaedics and Rehabilitation. He also is professor of pathology.

Angela Montgomery, University of North Carolina at Chapel Hill (NIH), *Environment, Epigenetics, Neurodevelopment & Health of Extremely Preterm Children*, 6.9 years, \$1,394,073 • **Sunil Parikh**, University of California, San Francisco (NIH), *Optimizing ACT Use for African Children in the Setting of HIV and Malnutrition*, 5 years, \$251,250 • **Robert Pietrzak**, Icahn School of Medicine at Mount Sinai (ISMMMS) (DHHS), *A Randomized Controlled Trial of Internet CBT for PTSD in WTC Responders*, 1 year, \$54,086 • **Jordan Pober**, Icahn School of Medicine at Mount Sinai (ISMMMS) (NIH), *Effects of Inhibiting Early Inflammation in Kidney Transplant Patients*, 1 year, \$76,430 • **David Reiss**, Regents of the University of California (NIH), *Interdisciplinary Research Network on Early Adversity & Later Life Reversibility*, 3 months, \$22,932 • **David Rimm**, Breast Cancer Research Foundation, *Targeted and Immune Therapies in Breast Cancer*, 1 year, \$250,000 • **Daphne Robakis**, Columbia University (NIH), *Planning Grant: Columbia-Yale-Bilkent Study: Genetic Study of Essential Tremor*, 2 years, \$26,810 • **Joseph Ross**, Regents of the University of Minnesota (NIH), *Diffusion of Clinical Evidence into Practice: Physician Networks, Delivery Organizations, and Markets*, 1 year, \$40,220 • **Carla Rothlin**, U.S.-Israel Binational Science Foundation, *Elucidating the Role of Gas6 as a Key Regulator of Host-commensal Interactions in the Oral Mucosa*, 4 years, \$90,000; Howard Hughes Medical Institute, *Immune Checkpoints at the Interface of Innate and Adaptive Immunity*, 5 years, \$600,000 • **Douglas Rothman**, Pfizer, U.S. Pharmaceuticals Group, *An Open-label, Two-period, Fixed-sequence Study to Validate the Utilization of 31P-Magnetic Resonance Spectroscopy to Quantify Hepatic Fructose Metabolism and Evaluate Repeatability in Healthy Male Subjects*, 11 months, \$171,136 • **Helena Rutherford**, Margaret S. Mahler Child Development Foundation, *Fetal Autonomic System Development and Mother-Infant Outcomes in Depression*, 1 year, \$5,000 • **Kurt Schalper**, Moderna Therapeutics, *Measurement of OX40 Pathway and Immune Contexture in Human Solid Tumors Using Objective Methods*, 1 year, \$234,051; Millennium Pharmaceuticals, *Quantitative Analysis of SYK, FLT3, and Immune Composition in Human Lung, Head & Neck and Breast Carcinomas*, 1 year, \$262,430 • **Michael Schilsky**, Wilson Disease Association, *Development of a Registry for Patients with Wilson Disease*, 1 year, \$9,350; University of Texas Southwestern Medical Center at Dallas (NIH), *ALFSG-potential Use of Rotational Thromboelastometry (ROTEM) to Explore Hemostatic Abnormalities in Patients with Acute Liver Failure*, 4 years, \$6,030 • **Eve Schneider**, Arnold and Mable Beckman Foundation, *The Molecular Basis of Mechanotransduction in Vertebrate Glabrous Skin*, 2 years, \$137,825 • **Patrick Skosnik**, Charles A. Dana Foundation, *In vivo Imaging of Synaptic Density in Schizophrenia*, 3 years, \$200,000 • **Mark Solomon**, Melanoma Research Foundation, *The Role of the Anaphase-Promoting Complex in Human Melanoma*, 2 years, \$200,000 • **Serena Spudich**, Henry M. Jackson Foundation (NIH), *Critical Role of Cytotoxic T Cells in HIV Neuropathogenesis*, 9 months, \$78,561 • **Mario Strazabosco**, Partners Seeking a Cure, *Upregulation of Biliary Epithelia Innate Immune Responses in PSC*, 2 years, \$60,000 • **Stephen Strittmatter**, Dr. Ralph & Marian Falk Medical Research Trust, *Therapeutic Targets to Rescue Synapse Loss in Alzheimer's Disease*, 2 years, \$1,000,000 • **Stephanie Thorn**, MicroVide (NIH), *Proteolytic Imaging of Remodeling Myocardium*, 1 year, \$132,519; University of South Carolina, Amgen, *Amgen Amendment 7: Cardiac MMP Imaging with Intracoronary Delivery of TIMP*, 5 months, \$95,459 • **Jeffrey Townsend**, Temple University (NIH), *Evolutionary Bioinformatics of Tumor Profiles*, 11 months, \$48,082 • **Christian Tschudi**, U.S.-Israel Binational Science Foundation, *The Role and Mechanism of RNA Pseudouridylation and Sugar Methylation (Nm) During the Development Cycle of Trypanosomes*, 4 years, \$55,355 • **Flora Vaccarino**, Simons Foundation, *Somatic Mosaicism in Autism Spectrum Disorders*, 3 years, \$823,359 • **Tamara Vanderwal**, Klingenstein Third Generation Foundation, *The Use of Movies to Assay Brain Network Dynamics in ADHD*, 2 years, \$60,000 • **Pamela Ventola**, George Washington University (NIH), *Multi-modal Developmental Neurogenetics of Females with ASD*, 1 year, \$305,126 • **Sherman Weissman**, University of Hawaii at Manoa (NIH), *An Integrative Bioinformatics Platform with Application in Single Cancer Cells*, 4 years, \$111,645 • **John Wyslowski**, XOMA Corporation, *PTH Receptor Antibodies in HHM*, 1 year, \$90,971 • **Xiao Xu**, University of Michigan (NIH), *How Does Health Interface with Living Arrangements?*, 3.7 years, \$49,626

Twenty years and counting for Women's Health Research at Yale

The center funds research that illuminates specific health needs of women

BRCA2, a gene associated with increased risks of breast cancer, can be mutated in thousands of ways—but only some of those mutations are dangerous. The key question for oncologists, genetic counselors, and women with breast cancer is: which ones?

Ryan B. Jensen, Ph.D., associate professor of therapeutic radiology, is sorting through thousands of BRCA2 mutations to spot the red flags. His work could greatly improve counseling and cancer treatment for breast cancer patients.

Jensen is moving his research forward in part thanks to a grant from Women's Health Research at Yale (WHRY), a self-supporting center within Yale School of Medicine that will celebrate its 20th anniversary in February. With data developed through \$5 million in WHRY grants to date, Yale scientists have gone on to secure \$95 million in external grants to further their research into women's health.

"Women continue to be underserved in terms of research knowledge," says Carolyn M. Mazure, Ph.D., the Norma Weinberg Spungen and Joan Lebson Bildner Professor of Psychiatry and Psychology, who founded the center in 1998 and has been executive director ever since.

The center focuses on the need to fully account for sex and gender in biomedical research. Women suffer higher rates of Alzheimer's disease, for instance, and can present with different symptoms than men when experiencing heart attacks. But studies of these diseases traditionally pay

inadequate attention to sex differences, Mazure says.

It was not until 1994 that the National Institutes of Health (NIH) required researchers to include women participants in clinical studies and to analyze data by sex or gender. It was not until last year that the NIH required female animals and tissue and cell samples in laboratory studies. To this day, many studies are still not designed to tease out sex differences.

WHRY-funded research, though, has already helped women and girls.

In 2002, for example, a landmark paper published in *The Lancet* led to better advice for breast cancer patients and those at higher risk for breast cancer. WHRY grant recipient Bruce G. Haffty, M.D., then of the Department of Therapeutic Radiology, showed that certain mutations in the genes BRCA1 and BRCA2 predisposed breast cancer patients to new tumors in either breast.

Girls with autism also stand to benefit from the center's grants. Because boys outnumber girls in autism diagnoses, many studies include few if any girls.

"They've been orphaned from autism research," says Pamela Ventola, Ph.D., assistant professor in the Yale Child Study Center.

With a 2015 WHRY grant, Ventola tested for the first time a behavioral intervention called Pivotal Response Therapy on girls with autism. The girls made bigger gains in social engagement and functioning than boys in the study—despite having started with more severe impairments.

"Without these pilot data, girls would still be under-studied," Ventola says. "We are extremely grateful for the funding from WHRY. Without the work supported through this



HAROLD SHAPIRO

grant, we wouldn't know the value of this therapy in girls."

Jensen, too, says the funds were crucial to his work. When he arrived at Yale as a junior faculty member, he had recently made a crucial breakthrough, becoming the first in the world to purify the BRCA2 protein. But there was no way to follow up without seed money that would let him establish the preliminary data necessary for the larger NIH grants he later received and that continue to fund his work today.

"The pilot grants are great for young investigators—I got this within a year of when I came to Yale," he says. "It gives you practice writing grants at this level, and then you get some feedback. It really helps you start preparing for the big NIH grants. And it keeps your lab going."

WHRY-funded researchers at Yale study colon cancer and autoimmune disease in women, as well as ovarian cancer, infections during pregnancy, intimate partner violence, and other topics to advance women's health or discover sex differences to benefit women and men.

Women's Health Research at Yale, led since its founding by Carolyn Mazure (left), is a leader in building research knowledge of health issues as they relate to women. Ryan Jensen is investigating gene mutations' varied effects on breast cancer.

Mazure advocates for women's health research in Washington, D.C., and has frequently spoken at other universities about how they might build programs similar to Yale's and fully integrate a focus on sex and gender into a medical school curriculum.

"We have been enthusiastic about helping others to build these centers," says Mazure. "We want more people focusing on the importance of studying women and investigating sex and gender differences. It is vital to help women, and it can also help men. Because in studying differences, we learn things that are very important for the care and treatment of disorders that affect us all."

Looking back over nearly 20 years, Mazure is quick to turn her attention toward the road that lies ahead. "We have made great progress," she says. "But there is an enormous amount left to do."

// **Surgery** (page 1) an international reputation for the management of peritoneal cancer metastases with cytoreduction, a technique to remove the maximum number of cancer cells that is possible, and heated intraperitoneal chemotherapy.

As an investigator, Ahuja directs a National Institutes of Health-funded cancer research laboratory focused on improving outcomes for gastrointestinal cancers. In addition to her widely recognized work in translational

epigenetics—the expression of our genetic code—she recently has been a leading member of the Stand Up To Cancer Dream Team "Bringing Epigenetic Therapy to the Forefront of Cancer Management." She conducts investigator-initiated clinical trials in colorectal cancer, pancreatic cancer, and other solid tumors and has developed biomarkers for the early detection of colorectal and pancreatic cancers. She also leads a National Cancer Institute Clinical and Laboratory Training

Program for developing a pipeline of academic surgical oncologists.

"I am the poster child for the tripartite academic mission," she says. "I strongly believe in it."

Building upon the growth of the department, she says she would like to add to its stature by setting the tone for care delivery and being at the forefront of clinical outcomes, research programs, and faculty mentorship. "Health care is being disrupted by market forces, but at the same

time there is lots of opportunity," she notes. "It is our job to seek out those opportunities and fashion how health care delivery will happen in the next 20 to 30 years."

Ahuja obtained her medical education at the Duke University School of Medicine and her training in general surgery at Johns Hopkins. After completing a fellowship in surgical oncology at Johns Hopkins focused on hepatobiliary malignancies, she joined the faculty in 2003.

Awards & Honors



Philip W. Askenase, M.D., professor of medicine (immunology), and chief of the Section of Allergy and Clinical Immunology from 1985 through 2011, will receive the 2018 Distinguished Scientist Award from the American Academy of Allergy, Asthma & Immunology.



James S. Duncan, Ph.D., Ebenezer K. Hunt Professor of Radiology and Biomedical Imaging and professor of electrical engineering, has received the Medical Image Computing and Computer Assisted Intervention Society's top honor, the Enduring Impact Award.



Rosemarie L. Fisher, M.D., professor of medicine (digestive diseases) and of pediatrics, and, until last year, associate dean of graduate medical education, is honored with Distinguished Service Membership from the American Association of Medical Colleges.



Peter M. Glazer, M.D., Ph.D., chair and Robert E. Hunter Professor of Therapeutic Radiology and professor of genetics, has received the National Cancer Institute's Outstanding Investigator Award.



Chirag R. Parikh, M.D., Ph.D., professor of medicine (nephrology) and director of the Program of Applied Translational Research (PATR), receives the American Society of Nephrology's Young Investigator Award.



Jessica M. Pollard, Ph.D., assistant professor of psychiatry and clinical director of the Specialized Treatment for Early Psychosis (STEP) Program, becomes chair-elect of the Mental Health Section of the American Public Health Association. She will assume her role as chair in 2019.