Medicine@Yale

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Life-changing care forges a family-physician bond

Following a global trek for the right care, a family finds success, and calm, at Yale

Hal Blumenfeld, M.D., PH.D., the recently named Mark Loughridge and Michele Williams Professor of Neurology, has spent his career trying to prevent loss of consciousness in people with epilepsy.

Earlier this year his team reported in the journal *Epilepsia* that impaired consciousness during and after focal seizures can be reversed by deep brain stimulation. Now he is working toward making the treatment available for patients. The discovery comes after more than a decade of research on the mechanisms of consciousness loss in focal seizures, including a landmark article recently published in *Neuron*, as well as research on the physiological changes in what are called absence seizures and generalized tonic-clonic seizures.

Says Blumenfeld, "My research is one hundred percent motivated [by a desire to] improve the lives of people with epilepsy. Consciousness impacts their ability to drive a car and to function at school or in other social situations."

Blumenfeld is making significant progress, and few know better how important that is than the family who earlier this year endowed his professorship.

Meghan Loughridge's father, Mark Loughridge, and stepmother, Michele Williams, had taken Meghan around the world looking for a way to control her epilepsy. Eventually they found themselves in Houston, at another hospital, waiting for yet another test. Meghan was scared, but this was nothing unusual.

Mark describes Meghan's life as "a movie with every fifth frame missing." She would have 30 seizures in a single minute and one daily grand mal seizure, the kind characterized by a loss of consciousness and violent muscle contractions. // Chair *(page 7)*

TERRY DAGRADI

Inspired by the care their daughter received, Mark Loughridge and Michele Williams have endowed a new professorship in neurology.

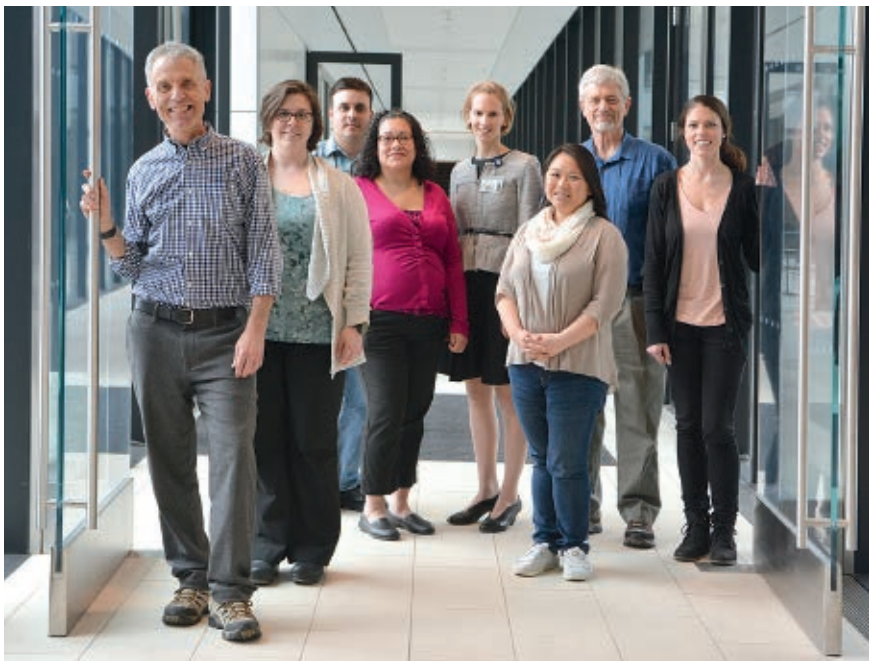
A more precise approach to dyslexia

Pediatrician aims to reduce the impact of a broad range of learning disabilities

Jeffrey R. Gruen, M.D., professor of pediatrics and genetics, is taking a holistic view in working to remedy learning disabilities. Focusing on reading, attention, and mathematics disabilities, Gruen and his colleagues are preparing to follow around 3,200 first-graders in New Haven Public Schools (NHPS) over five years.

The new study, called the New Haven Lexinome Project (NHLP) and supported by a grant from the New York-based Manton Foundation, focuses on "genes-by-environment" effects: Gruen's team is studying how home and cultural environments interact with a child's genetics to influence his or her learning.

Says Gruen, "Disabilities in schoolchildren cost billions for federal, state, and local intervention programs. We hope to improve the effectiveness of those efforts by harnessing the predictive tool of genetics to target the kids who can benefit most from help, and to precisely match them with their optimal intervention."



MICHAEL MARSLAND

Using "precision education," a team led by Jeffrey Gruen (left) is collecting data on about 3,200 first-graders in New Haven schools to further our understanding of and ability to predict and address dyslexia. A gift from the Manton Foundation is supporting the team's research.

The NHLP builds on Gruen's previous work in the field. In 2005 the journal *Science* described his discovery of the gene *DCDC2*—one of just a handful of genes associated with dyslexia—as the fifth most important breakthrough of that year. In 2008 Gruen coined the term *human lexinome* to capture all of the genes and specific // Dyslexia *(page 8)*

Foundation enables continued progress in stem cell research

Earlier this year, Haifan Lin, PH.D., director of the Yale Stem Cell Center (YSCC), and colleagues discovered a potentially unique ability of stem cells: they can avert the damaging effects of stress better than regular cells. Stem cells are biologically valuable because they can both differentiate into other kinds of cells and divide to produce more stem cells. The team's findings suggest that stem cells are designed to avoid passing on damaged DNA that could cause molecular-level irregularities, like cancer. The research was published in the journal *Stem Cell Reports*.

A $1.86 million grant from the Li Ka Shing Foundation made to YSCC earlier this year will help the Center continue similarly innovative research. The grant will help fund new research equipment and strengthen collaborations between Yale and Shantou University (STU), in southeastern China.

The Hong Kong businessman Li Ka-shing founded STU. A self-made billionaire, Li dropped out of high school to help earn money for his family. He has spent his career building his company, which he // Stem Cell *(page 7)*

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EDDIE TORRES

Akiko Iwasaki enjoys asking basic science questions whose answers might be right under our noses, or inside them. Her research on the immune system's interactions with the rhinovirus made national headlines earlier this year. Not satisfied to focus on one area of research, her work spans a range of immunologic topics, including the herpes simplex virus and autophagy.

Heeding the call of basic research

A willingness to question dogma keeps a Yale immunologist motivated

For as long as she could, Akiko Iwasaki, PH.D., resisted a call to basic science research. She grew up outside Osaka, in the Kensai region of Japan, with a physicist father who spent long nights studying. The lifestyle initially did not appeal to her. But later, as an undergraduate at the University of Toronto, she discovered immunology, and found she could no longer deny her innate attraction to science.

Iwasaki, professor of immunobiology and of molecular, cellular, and developmental biology and a Howard Hughes Medical Institute investigator, has built a career asking research questions that examine accepted tenets within the field of immunology. Her doctoral thesis, also at the University of Toronto, created a wave of surprise in 1998 by suggesting that vaccines work by presenting antigens to T cells through white blood cells—not muscle cells, as previously thought.

More recently, Iwasaki and her lab members set out to challenge conventional thought about why the common cold spreads more readily in the winter months. Researchers assumed rhinoviruses evolved to function best in cooler climes—and in the nasal cavity, usually colder than the rest of the body. But when her team incubated the virus in airway cells in a warm environment, it not only survived, but grew, when the host's immune cells lacked key defense genes.

These studies suggested it may be the host immune response, rather than the virus, that determines the virus's growth. The immune system itself appears "impaired at the lower body temperature compared to the core body temperature," Iwasaki says. The findings, published in *Proceedings of the National Academy of Sciences* last January, suggest that colder temperatures "dampen" cell receptors designed to detect rhinoviruses, and therefore the immune system never gets a memo to attack.

In parallel, Iwasaki's team is investigating the immune defense against influenza viruses, particularly among older adults. In the U.S., more than 90 percent of deaths from influenza occur among adults over 65. A vaccine that helps older adults fight the flu would mark a huge breakthrough—and Iwasaki is hopeful that will come.

Since she started her lab at Yale in 2000, Iwasaki's peers have frequently recognized her work. In 2003 she received the Wyeth Lederle Young Investigator award from the Infectious Diseases Society of America. The Burroughs Wellcome Fund recognized her research on the pathogenesis of infectious diseases in 2005. The American Association of Immunologists awarded her the BD Biosciences Investigator Award in 2011. And in 2012 the American Society for Microbiology honored her work on the role of autophagy, or "self-eating," in antiviral immunity with the Lilly Research Award.

What drives Iwasaki's productivity? "The fun of it," she says. Next, she wants to figure how to fight viruses by harnessing the infection-fighting power of T cells, rather than relying only on antibodies, as most current vaccines do. Such work could have implications for the treatment of HIV and the herpes simplex type 2 virus.

At home, Iwasaki can puzzle out experiments with her husband, Ruslan M. Medzhitov, PH.D., the David W. Wallace Professor of Immunobiology and a Howard Hughes Medical Institute investigator. And their two daughters, ages 5 and 7, routinely drop immunology-related vocabulary into conversation, she says.

This suggests yet another accomplishment: she's passed on the fun of science.

School of Nursing alumna returns to lead the school

Ann Kurth

Ann Kurth, PH.D., M.P.H., R.N., M.S.N., a global health expert and a Yale School of Nursing (YSN) alumna, will return to Yale as YSN's new dean on January 1, 2016.

Kurth, associate dean for research at New York University College of Global Public Health and the inaugural Paulette Goddard Professor of Global Health Nursing at New York University College of Nursing (NYUCN), is a clinically trained epidemiologist with a career-long interest in the prevention, detection, and care of HIV and other sexually transmitted infections.

"[Kurth's] leadership in promoting health care around the world fits ... with the YSN mission of promoting better health for all," Yale President Peter Salovey wrote to the University community.

At NYUCN Kurth is also professor of medicine and executive director of NYUCN Global, which supports research and improved health care infrastructure globally. In addition to her M.S.N. from YSN, she holds an A.B. magna cum laude from Princeton University, an M.P.H. from Columbia University, and a PH.D. in epidemiology from the University of Washington. She is a fellow of the National Academy of Medicine and a member of the U.S. Preventive Services Task Force that sets screening guidelines for the country.

Kurth succeeds Margaret Grey, DR.PH., R.N., the Annie W. Goodrich Professor of Nursing, who stepped down in August. Holly Powell Kennedy, PH.D., executive deputy dean and the Helen Varney Professor of Midwifery, is serving as interim dean.

International collaboration opens doors for student researchers

When Daniel Colón-Ramos, PH.D., associate professor of cell biology, arrived from Puerto Rico as a freshman at Harvard in 1994, things didn't quite go as planned. Once in his dorm room, he felt dizzy and recalls telling his roommate, "I'm dying. You have to take me to the hospital."

The hospital physicians suspected meningitis, but results on a spinal tap were negative. Following a phone call between Puerto Rican and American physicians, it came to light that "these were all the symptoms of dengue fever. I was coming in with a tropical disease," Colón-Ramos says.

With this global context in mind, Colón-Ramos has spearheaded a new M.D./PH.D. collaboration with the University of Puerto Rico (UPR). Starting this year, students accepted in the M.D. program at UPR can apply to Yale's Combined Program in the Biological and Biomedical Sciences and will be assigned mentors while studying for their PH.D.s in New Haven. After completing their research, they will return to UPR for the final year of medical school.

The training that UPR students receive at Yale will prepare them for careers as physician-scientists, currently a small community in Puerto Rico's medical community. But they will also bring their island experiences to enrich the environment at Yale.

MICHAEL MARSLAND

Peter Salovey (left) and University of Puerto Rico President Uroyoán Walker at an event celebrating the universities' collaboration.

"We're training our next generation," says Uroyoán Walker, PH.D., president of UPR. "And when I say ours, I mean the world's."

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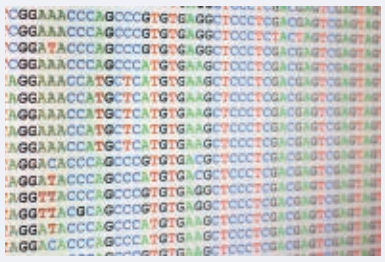
ADVANCES
Health & Science News

What's *not* behind a rare lymphoma



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While most cancers are caused by mutations in single nucleotides of DNA, like changing some letters in a sentence, cutaneous T cell lymphoma is often driven by large deletions of whole genes, like removing whole pages from a book. A better understanding of how these deletions cause the rare lymphoma, which affects skin cells and causes rashes, could lead to better treatments.

To gain insight, Yale researchers studied blood samples from 40 patients with cutaneous T cell lymphoma. Comparing DNA sequences in cancerous cells with those in healthy cells revealed that the large deletions affected 17 different genes. Many of the genes, the team reported July 20 in *Nature Genetics*, control similar molecular pathways, suggesting that the misregulation of these pathways may be key to causing the lymphoma and suggesting that drugs targeting these pathways could help treat it.

"This cancer has a very distinctive biology," said Jaehyuk Choi, M.D., PH.D., assistant professor of dermatology and lead author of the study.

Solving a multiple sclerosis mystery

In the autoimmune disease multiple sclerosis (MS), the immune system's T cells attack the myelin sheaths surrounding nerve cells, potentially leading to neurodegeneration. But the reasons T cells attack in cases of MS have eluded researchers for years. Now, scientists from Yale and MIT have found a piece of the puzzle.

The team generated over 14,000 T cell libraries using blood samples from 23 MS patients and 22 healthy controls, and discovered that T cells from MS patients caused more inflammation than those from healthy patients. In MS patients, autoreactive T cells produce factors that signal the body's inflammatory immune response, but those same autoreactive cells in healthy patients secrete anti-inflammatory agents instead.

"In most people, these T cells are acting to repair tissue, but in MS patients, they do damage to the nervous system," said David Hafler, M.D., chair and the William S. and Lois Stiles Edgerly Professor of Neurology, professor of immunobiology, and senior author of the study, published in *Science Translational Medicine* in May. The authors contend that the anti-inflammatory agents produced by healthy controls may limit disease progression. The findings suggest a similar mechanism may be at work in other autoimmune diseases.

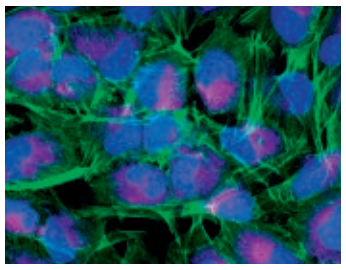
The art, and science, of collaboration

A world-class center on Yale's West Campus is 'on-call' for scientists, offering tools and services critical for precision medicine

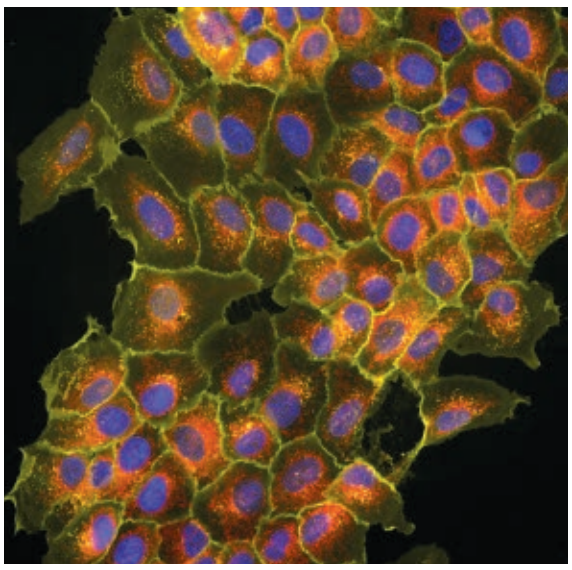
In the field of cancer research, one of the most significant discoveries in the last two decades is the finding that most cancers are caused by overactive cell division due to genetic mutations. The concept of "precision medicine" now uses a patient's specific mutations to help treat his or her cancer. For a subset of patients, this approach—matching patients with appropriate targeted drugs—works exceedingly well. But unfortunately, many patients develop treatment resistance over time, after which the cancer can make an aggressive return. "For people like me in the signaling field, it was a pretty major disappointment that resistance can readily develop," says David F. Stern, PH.D., professor of pathology and associate director of shared resources at Yale Cancer Center (YCC). "And it's been a real practical problem for the clinicians."

Cancer cells, just like healthy cells, try to maintain internal stability, or homeostasis. When single drugs are introduced that interfere with the cells' division pathways, many eventually switch to parallel pathways that cause the cells to continue dividing.

For Stern, who was researching melanoma, it eventually became clear that these single-agent therapies weren't going to work well enough. He needed to find a cocktail of drugs that could hit enough targets in the cell to shut down the cancer for good. Six years ago, he and collaborator Marcus W. Bosenberg, M.D., PH.D., associate professor of dermatology and pathology, turned to the Yale Center for Molecular Discovery (YCMD) for help. "We brought the project to them and they said, 'Yes, we can do this,' even though no one had done this kind of combination screening here, or really anywhere," Stern recalls.



DENTON HOYER



(Above) Biologists and chemists at the Yale Center for Molecular Discovery (YCMD) specialize in molecular screening and development to aid biomedical research at Yale. From left: Shelia Umlauf, Will Hungerford, Jacquelyn McGrath, Peter Gareiss, Mark Plummer, Janie Merkel, Yulia Surovtseva, Laura Abriola, and Denton Hoyer. Using fluorescence microscope imaging, dyes, and stains, YCMD staff stain cells for analysis, including (left) breast epithelial MCF10A cells and (above left) human epithelial HeLa cells.

The YCMD, one of the core resource facilities on Yale's West Campus in West Haven, Conn., specializes in drug screening and development. "We help faculty access and correctly implement a suite of technologies for early-stage drug design," explains Janie Merkel, PH.D., director of biology at the YCMD.

The YCMD's staff includes both biologists and chemists with industry experience. The Center has a range of technologies to screen small molecules for particular effects and to quantify the results in almost any small study system, from plant seeds to nematode eggs to cell lines. Its library contains 150,000 compounds, covering a wide swath of chemical structures that can pass through the cell membrane. Once useful compounds are identified in a screen, the chemists take over, tinkering with their molecular structures to maximize their effectiveness.

When Stern and Bosenberg brought their project to the YCMD, they started with a small single-agent screen on a melanoma cell line, then worked up to a much larger assay using 41 different agents in combination with each other.

"The advantage of having the screening center here is that we developed this whole system," he says. "Nobody showed us how to do it. Five or six years ago, there was little published literature in combination work." It took his team nearly a year to analyze their data: they have since published their work in the journal *Cancer Discovery* and are hoping to move into clinical trials, while also coordinating similar projects using lung and pancreatic cancer cell lines.

Early-career researchers at the School of Medicine have also benefited substantially from collaborations with the YCMD. Ranjit Bindra, M.D., PH.D., assistant professor of therapeutic radiology and of pathology, met with Merkel before joining the faculty three years ago. He received a YCMD pilot grant and began investigating drugs that would block DNA repair in tumors. Standard therapies—chemotherapy and radiation—largely tackle cancer by damaging cellular DNA, but cancer cells have DNA repair mechanisms that can diminish the therapies' effectiveness. Bindra's team is seeking a class of compounds that inhibit these repair mechanisms, making the cancer more susceptible to treatment.

"It's easy to think you could do it all yourself," Bindra says, "but you really need a screening, like these folks, who are going to keep you on track and make sure you design a screen which will get you meaningful hits." Bindra's lab has worked on four different projects with the YCMD, two of which are currently running. His work has generated two manuscripts, and Bindra plans to use the preliminary data in an application for federal grant funding.

An initial project with the YCMD often leads to funding from larger institutions, as Qin Yan, PH.D., associate professor of pathology, discovered when he began research at Yale. Like Bindra, Yan was awarded a YCMD pilot grant shortly after he joined the medical school's faculty in 2008. He had discovered a category of enzymes that act as major epigenetic regulators, altering gene expression globally—and realized that inhibiting these enzymes might lead to a potential cancer treatment. Searching for a compound to do so, he first screened 15,000 compounds at the YCMD, then increased that number to 106,000 in a second screen, looking for samples where the enzymes had failed to react. His lab discovered a handful of candidates, which later led to a patent and the promise of related research projects. He has successfully applied for two Department of Defense grants as an extension of the work he did at the YCMD and has developed a partnership with the National Cancer Institute.

The YCMD not only provides assay development and drug screening technologies, but also consults on projects and provides grant-writing assistance. The Center is subsidized to provide the best possible costs to School of Medicine faculty. For many researchers, it adds translational potential to their basic science research. And its highly trained staff pride themselves on creating long-term relationships and offering a custom approach to help develop any research project brought to their doorstep. "We'll be emailing Saturday at seven a.m. going back and forth," Bindra says. "They're almost on-call, [as if] we're in the hospital."

Says Denton Hoyer, PH.D., director of chemistry at the YCMD, "It starts with a conversation. Just call us."

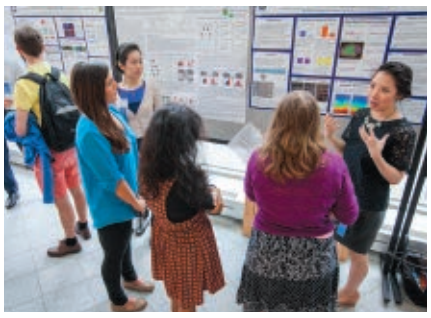
OUT & ABOUT

March 27–29 Entrepreneurs, physicians, and engineering students convened at a **Hackathon** sponsored by Yale's Center for Biomedical and Interventional Technology (CBIT) and Center for Outcomes Research and Evaluation (CORE) to brainstorm ways to improve clinical care. **1.** Yale University President **Peter Salovey**, PH.D., the Chris Argyris Professor of Psychology, delivered opening remarks. **2.** Winners of the Best Patient Experience Solution Award included (from left) nursing student **Angela Hasler** '16; **Catherine Jameson**, Yale College '16; **Justin Koufopoulos**; and graduate student **Linda Fong** '17. **3.** A group presented its project to judges. (From left) **Shervin Etemad**; **Dylan Visher**, Yale College '16; **Malipeddi Phanindra Kumar Reddy**; **Katia Barnave**; and **Iulia Tamas**, Yale College '16.

WILLIAM SACCO (3)

JOHN CURTIS (3)

May 21 **Medical Education Day** gave members of Yale's medical community a chance to share educational projects and research as well as engage in numerous educational sessions. **1.** (From left) **David M. Irby**, PH.D., keynote speaker and professor of medicine at the University of California, San Francisco; **Janet P. Hafler**, ED.D., professor of pediatrics, associate dean for educational scholarship, and director of the Teaching and Learning Center (TLC); **Richard Belitsky**, M.D., the Harold W. Jockers Associate Professor of Medical Education, associate professor of psychiatry, and deputy dean for education; and **Michael L. Schwartz**, PH.D., associate professor of neuroscience and associate dean for curriculum. **2.** Participants at a workshop included **Andrea G. Asnes**, M.D., M.S.W., associate professor of pediatrics, and **Benjamin Doolittle**, M.D., associate professor of medicine and pediatrics. **3.** A panel of judges made up of students, faculty, and staff from Yale School of Medicine, Yale School of Nursing (YSN), and Yale School of Public Health evaluated poster presentations. (From left) **Rosana Gonzelez-Colaso**, PHARM.D., M.P.H., assistant professor of medicine; **Susan H. Forster**, M.D., associate clinical professor of nursing; YSN student **Eileen Condon** '20; **Monica R. Ordway**, PH.D., APRN, assistant professor of nursing; **Kathleen H. Ang**, M.D., clinical fellow in pediatric endocrinology; **Oladoyin Oladeru**, M.P.H. '15; **John A. Encandela**, PH.D., assistant professor of psychiatry and associate director for curriculum and educator Assessment at the TLC; **Dippy Bhattacharya** '18; **Jake Wang** '17; and **Tracie Addy**, PH.D., assessment program manager at the TLC.



JOHN CURTIS

May 5 At **Student Research Day**, medical students presented their thesis research for members of the community. M.D./PH.D. student **Genevieve Yang** '17 (left) stands in front of her poster on schizophrenia research while M.D./PH.D. student **Wendy Xiao** '17 (right) discusses her research project, showcasing data on consciousness collected from electrodes implanted in the brains of patients.

May 18 At the School of Medicine's **Commencement Ceremonies**, Howard Koh, M.D. '77, the Harvey V. Fineberg Professor of the Practice of Public Health Leadership at Harvard University's T.H. Chan School of Public Health, encouraged members of the Class of 2015 to stay humble. **1.** (From left) **Adriana Blakaj** and **Christopher Bartley** graduated from the M.D./PH.D. Program. **2. Jessica S. Wang** poses with her diploma. **3.** (From left) **Ryan Aronberg**, **Katherine Davis**, **Nour Kibbi**, **Abhijeet Gumadavelli**, and **Brian Letzen**.

JOHN CURTIS (1), TERRY DAGRADI (2)

JOHN CURTIS (1), TERRY DAGRADI (3)

May 29 Scores of alumni returned to campus on **Reunion Weekend**. **1.** (From left) **Kim Fish** and her husband **Guy Fish**, M.D. '85, with classmates **Julie Danaher**, M.D. '85, and **Sara Cartmell**, M.D. '85. **2.** (From left) **Linda Maxwell**, M.D. '00; **Robert H. Gifford**, M.D., former deputy dean for education; and **Oscar R. Colegio**, M.D. '00, PH.D. '00, assistant professor of dermatology. **3.** (From left) **Ben Zabar**, M.D. '11; **Natalie Spicyn**, M.D. '11; **Barbara Ann (Hirschman) Chaiyachati**, M.D. '15, PH.D. '15; and her husband, **Krisda Chaiyachati**, M.D., M.P.H. **4. James W. Bonz,** M.D., assistant professor of emergency medicine, gave a demonstration at the Yale Center for Medical Simulation.

KATHLEEN RAVEN

July 20 At a reception for the **Covidien Clinical Immersion Program**, engineers and workers at the medical device company Covidien were recognized for their successful completion of a yearlong program that includes observing surgeries at Yale-New Haven Hospital and attending lectures given by School of Medicine faculty and hospital administrators. (From left) **Justin Williams**, **Mark Rodbourn**, **Corrie O'Donnel**, **Jeff Varesio**, **Brett Roesler**, **Matthew Chowaniec**, **Rob Satti**, **Rich Fillion**, and **Dave Jermine**.

COURTESY OF CARINA DEHNER

July 21 **Carina Dehner**, M.D. (second from left), postgraduate fellow in immunobiology, attended the **Lindau Nobel Laureate Meeting** in Germany as a Young Scientist Fellow. Dehner joined **Peter C. Doherty**, PH.D. (center), a 1996 recipient of the Nobel Prize in Physiology or Medicine, and colleagues for a lunch.

ADVANCES
Health & Science News

Addiction treatment can start in the ED

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Opioid-addicted patients who show up in the emergency department (ED) are typically treated for symptoms then referred elsewhere for follow-up. Now, new research from Yale shows that ED-initiated buprenorphine, a medication used to treat opioid dependence, could help expand access to addiction treatment.

Gail D'Onofrio, M.D., M.S., chair and professor of emergency medicine, and David A. Fiellin, M.D., professor of medicine and public health, and colleagues randomly assigned 329 opioid-dependent ED patients. About a third of the patients received information about treatment resources, a third participated in interventions before receiving information and help in attending a treatment program, and a third were given buprenorphine in the ED and follow-up care afterward.

ED-initiated buprenorphine, the team reported April 28 in *Journal of the American Medical Association*, increased engagement in addiction treatment, reduced self-reported illicit opioid use, and decreased use of inpatient treatment services.

Editing away a genetic disorder

The genetic disease cystic fibrosis is caused by a mutation in the cystic fibrosis gene *CFTR*, normally involved in the production of digestive fluids and mucus. Patients can have difficulty breathing, frequent lung infections, and other complications, and while symptoms can be managed, the disorder has no known cure.

New research reported April 27 in *Nature Communications* by Yale scientists suggests that inhaling a nasal spray containing tiny nanoparticles, specially engineered to carry genetic information, might be the next big treatment for cystic fibrosis.

The team, led by Marie E. Egan, M.D., professor of pediatrics and of cellular and molecular physiology, Peter M. Glazer, M.D., PH.D., chair and professor of therapeutic radiology, and W. Mark Saltzman, PH.D., the Goizueta Foundation Professor of Biomedical Engineering, designed bits of DNA that cause cells to turn on their gene-editing program and repair the *CFTR* mutation. When they implanted these molecules inside nanoparticles and applied the nanoparticles to the noses of mice, close to 10 percent of the animals' airway cells became mutation-free—enough to change airway function.

"The technology could be used as a way to fix the basic genetic defect in cystic fibrosis," Egan said.

Alzheimer's research accelerates at Yale

A federally funded research center will support interdisciplinary efforts and pool resources to focus on Alzheimer's disease

2015 has been a banner year for the study of Alzheimer's disease (AD) at Yale. School of Medicine researchers recently published papers about an experimental drug that helps mice with a form of the disease, the role of immune cells in warding it off, and how cellular "garbage disposal" systems may be involved. In June, those discoveries and several recent expansions and investments in research, equipment, and faculty helped win the university an $8.9 million, five-year grant from the National Institutes of Health to fund a new Alzheimer Disease Research Center (ADRC).

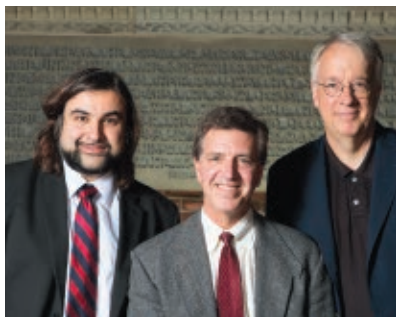
Stephen M. Strittmatter, M.D., PH.D., the Vincent Coates Professor of Neurology, professor of neurobiology, and founding director of the Yale Memory Disorders Clinic (YMDC), is the grant's principal investigator. He leads the ADRC with co-director Christopher H. Van Dyck, M.D., professor of psychiatry, neurology, and neurobiology and the director of the Alzheimer's Disease Research Unit (ADRU). The two will help coordinate a small army of Yale physicians and scientists to accelerate research on this debilitating form of dementia.

As one of 29 federally funded AD research centers around the U.S., the Yale ADRC will coordinate the efforts of clinical and research units across the university, among them the ADRU; the Program in Cellular Neuroscience, Neurodegeneration and Repair (CNNR); the Yale/NIDA Neuroproteomics Center; the Program on Aging; and the YMDC. It will also offer mentorship and pilot funding to up-and-coming researchers who are interested in Alzheimer's.

Three major lines of research, with an emphasis on the cell biology of Alzheimer's disease, will headline the ADRC's efforts. One, headed by Shawn M. Ferguson, PH.D., assistant professor of cell biology, will study how nerve fibers' waste-processing units, or lysosomes, can malfunction, potentially contributing to AD. In the second, Strittmatter and Van Dyck will study a key signal-receptor protein in neurons called mGluR5, one that could be targeted by new drugs. Finally, Chun-Hay Alex Kwan, PH.D., assistant professor of psychiatry and neurobiology, will study how circuits of neurons involved with the neurotransmitter GABA may play a role in the disease.

The ADRC will also establish five new cores, including a Clinical Core built upon the 24-year-old ADRU, and a Biomarker/Pathology Core that will develop new ways to monitor the disease. Both cores will also aggregate samples like blood, brain tissue, and stem cells for broad sharing and study. An Outreach Core will recruit subjects and conduct Alzheimer's-related community education, particularly for minorities.

Changes at Yale in recent years have paved the way for the university to become a center for Alzheimer's research. For example, hiring in the Department of Neurology has increased since David Hafler, M.D., the William S. and Lois Stiles Edgerly Professor of Neurology, became chair: its full-time members now number 50, compared with 20 or fewer a decade ago. The YMDC was founded in 2013 under Strittmatter's direction. Last year, the medical school made an $8.8 million investment in imaging technologies like magnetic resonance (MR) and positron emission tomography (PET). And a general expansion of basic neuroscience research, Van Dyck says, has also made a crucial difference



HAROLD SHAPIRO

As the principal investigators of the Alzheimer's Disease Research Center (ADRC), Stephen Strittmatter, M.D., PH.D. (center), and Christopher Van Dyck, M.D. (right), will spearhead cross-campus research efforts. Arash Salardini, M.D. (left), is associate leader of the ADRC's Clinical Core.

"With the CNNR and other people ... increasingly getting involved, it really gave us the critical mass to be able to do this," Van Dyck says. "It's a huge achievement."

Team-based science is the focus of new clinician-scholars program

When the Robert Wood Johnson Foundation (RWJF) ended its longstanding Clinical Scholars Program last year, the city of New Haven stood to lose deep health care expertise and free help.

The national program began in 1972 with the goal of bringing an academic approach to the training of clinician-investigators. Yale was one of the earliest participants in the program, starting in 1974 under the leadership of the late Alvan R. Feinstein, M.D., the Sterling Professor of Medicine and Epidemiology.

Since then, more than 175 RWJF scholars at Yale have worked on diverse projects, with a common theme of translating research into action. Scholars have conducted community-based research on a range of topics including the availability of healthy foods, HIV/AIDS status, gun violence, immigrant and refugee health, and access to health care for the homeless.

Though the RWJF decided last year to stop funding the Clinical Scholars Program, four host sites—the University of California Los Angeles; University of Michigan; University of Pennsylvania; and Yale—took up the mantle to begin a new, independent fellowship similar in spirit to the original program.

"I feel fortunate to be part of a training program that is blessed with so much loyalty, appreciation, and dedication among the alumni, the faculty, and the institutional and community partners," says Cary Gross, M.D.,

ROBERT LISAK

The newest members in what will be the last cohort of Robert Wood Johnson Foundation Clinical Scholars include (from left) Sanket Dhruva, Courtney McMickens, Alicia Agnoli, Joshua Elder, Dowin Boatright, Alon Peltz, Anita Arora, and Carolyn Presley.

professor of medicine and co-director of the new National Clinician Scholars Program (NCSP) at Yale. "That is why we simply had to find a way to continue training the next generation of scholars who will lead our efforts to improve the health care system and enhance the health of individual patients, our communities, and the nation."

The NCSP, which will start in 2016, shares many features of the original program but incorporates changes that consider today's changing health care landscape. Among these, it emphasizes team-based approaches to research and clinical care. As a result, the NCSP will train doctoral-level nurse-scientists alongside physicians.

In clinical practice, team-based models such as patient-centered medical homes—which bring together physicians, nurses, physician associates, and others to care collaboratively for patients—are increasingly common. "Team-based care is a common and effective part of our health care system, yet we're still struggling to learn how to do it well," says Gross, who is leading the planning of the NCSP at Yale.

The decision to include nurse-scholars in the NCSP builds on the interdisciplinary framework of the RWJF program, which trained physicians from various specialties, including internists, surgeons, pediatricians, and others, together.

"No profession can do it all themselves, and we each have important roles to play in the // Scholars *(page 7)*

Grants and contracts awarded to Yale School of Medicine

September 2014–December 2014

Federal

Clara Abraham, NIH, *Mechanisms Regulating Innate Immune Responses*, 1 year, $416,250
Alan Anticevic, NIH, *Neuropsychiatric Classification via Connectivity and Machine Learning*, 1.9 years, $145,022 • **John Beckmann**, United States Department of Agriculture, *Molecular Mechanism of Cytoplasmic Incompatibility and Insect Control*, 2 years, $150,000 • **Maria Bonarrigo**, NIH, *Recovery-Oriented Structures, Practices and Outcomes in CMHCS: A National Study*, 3.8 years, $2,893,919 • **Jessica Brown**, NIH, *Elucidating the Inhibitory Mechanisms of RNA Triple Helices in Nuclear Decay*, 1.9 years, $177,894
Nancy Carrasco, NIH, *Molecular Characterization of the Sodium/Iodide Symporter (NIS)*, 3.8 years, $1,710,869 • **Xi Chen**, NIH, *Old-Age Pension, Household Behavior Change and the Well-Being of the Elderly*, 2 years, $333,000 • **Won-Kyung Cho**, NIH,*Interleukin-13-Mediated Mechanisms of Pulmonary Vascular Remodeling*, 5 months, $133,514 • **Geoffrey Chupp**, NIH, *Pre-Clinical Development of a Novel Anti-YKL-40 Biologic to Treat Severe Asthma*, 1.8 years, $3,311,540 • **Mark Cicero**, DHHS, *Computer-Based Simulation Pediatric Disaster Triage Training for Emergency Medical Services Providers*, 3 years, $720,455 • **Gary Cline**, NIH, *Imaging Pancreatic Beta-Cells with PET Neuroimaging Agents*, 2.9 years, $496,756
Theodore Cohen, NIH, *Evaluating Health and Economic Effects of Targeted Strategies in TB/HIV*, 3.8 years, $2,583,370 • **Christian Connell**, **Jacob Tebes**, DHHS, *MPSY Rhode Island Child and Family Wellbeing: Wraparound Services for CPS-Identified Families*, 3 years, $250,000 • **Charles Dela Cruz**, NIH, *Host-Pneumococcal Interaction in the Lung*, 5 years, $2,090,555 • **Kumar Dharmarajan**, NIH, *Geriatric Conditions and Readmission after Acute Myocardial Infarction*, 4.8 years, $861,382
Vishwa Dixit, NIH, *Thymic Adipogenesis and Age-Related Thymic Demise*, 4 years, $1,665,000
Gail D'Onofrio, SAMHSA, *Yale-SBIRT Medical Health Professional Training Program*, 3 years, $943,785 • **Ronald Duman**, NIH, *Synaptic Mechanisms Underlying the Rapid Antidepressant Actions of Scopolamine*, 4.8 years, $2,207,943
Leigh Evans, **Lori Post**, DoD, *Evaluation of the Effectiveness of LTR Training versus Simulation Training and Stress Inoculation*, 6 months, $417,751 • **Jorge Galan**, NIH, *Typhoid Toxin and* Salmonella Typhi *Pathogenesis*, 5 years, $2,526,770 • **Patrick Gallagher**, NIH, *Regulation of Erythrocyte Volume Homeostasis*, 2 years, $412,088 • **Alison Galvani**, NSF, *RAPID: Optimal Allocation of Both Non-Pharmaceutical and Pharmaceutical Interventions toward Controlling Ebola Transmission in West Africa*, 1 year, $199,890 • **Mary Germino**, NIH, *Hybrid Parametric/Non-Parametric Direct Reconstruction for Dynamic PET*, 2 years, $72,552 • **David Glahn**, DoD, *Genetic and Diagnostic Biomarker Development in ASD Toddlers Using Resting-State Functional MRI*, 2 years, $187,935; NIH, *Gene Networks Influencing Psychotic Dysconnectivity in African Americans*, 5 years, $3,880,154 • **Peter Glazer**, NIH, *Bifunctional Antibodies for Melanoma Therapy*, 5 years, $2,230,305; NIH, *Hypoxia, DNA Repair, and Gene Silencing*, 5 years, $1,873,125 • **Charles Greer**, NIH, *Piriform Cortex: Sequential Developmental Events*, 5 years, $1,769,065 • **Daniel Greif**, NIH, *Pathological Arterial Muscularization and the Role of Integrins*, 4 years, $1,665,000 • **Elena Grigorenko**, Department of Education, *Foundation for Alliance for Education*, 1 year, $399,963
Cary Gross, NIH, *Impact of Social Contagion on Physician Use of Unproven Cancer Interventions*, 4 years, $2,222,343 • **Jaime Grutzendler**, NIH, *Angiophagy a Mechanism Linking Microvascular and Alzheimer's Pathologies*, 1.7 years, $457,875; NIH, *Postnatal Development of the Neuro-Glio-Vascular Unit*, 5 years, $1,821,095 • **Michelle Hampson**, NIH, *Biofeedback of Activity in the Orbitofrontal Cortex for OCD*, 4.8 years, $2,521,700
Shilpa Hattangadi, NIH, *Elucidating the Role of Nuclear Protein Export in Erythroid Nuclear Condensation*, 3.8 years, $1,332,000 • **Raimund Herzog**, NIH, *Regulation of Brain Glucose Metabolism by Alternate Fuels in Type 1 Diabetes*, 4.8 years, $1,873,125 • **Robert Hill**, NIH, *Cellular Mechanisms of Cortical Myelin Plasticity and Regeneration* In Vivo, 3 years, $165,354
Elizabeth Jonas, NIH, *Mitochondrial Ion Channels in Hypoxic Neurons*, 3.8 years, $1,665,000
Naftali Kaminski, NIH, Mir-29 Mimicry as a Therapy for Pulmonary Fibrosis, 1.8 years, $2,729,729 • **Min-Jong Kang**, NIH, *NLRX1 and MAVS in Cigarette Smoke-Induced Inflammation and Alveolar Remodeling*, 1 year, $428,498 • **Robert Kerns**, NIH, *Pain, Care, Quality and Integrated and Complementary Health Approaches*, 5 years, $2,258,491 • **Kenneth Kidd**, National Institute of Justice/Department of Justice, *Continued Development of FROG-kb: A Forensic Resource/ Reference on Genetics Knowledge Base*, 2 years, $314,468 • **Michael Koelle**, NIH, *Neuromodulator Signaling and Activity in the* C. Elegans *Egg-Laying Circuit*, 3.9 years, $1,426,617 • **Diane Krause**, NIH, *Molecular Basis of Dominantly Inherited Kidd-Null Phenotype*, 2 years, $457,875
Eli Lebowitz, NIH, *Explanatory Clinical Trial of a Novel Parent Intervention for Childhood Anxiety*, 3.9 years, $702,893 • **Becca Levy**, NIH, *Stress Biomarkers as a Potential Link Between Age Benefits and Health*, 1.8 years, $332,999 • **Aaron Levy**, NIH, *Integrin-Arg-SHP2 Signaling Regulates NMDAR Function and Neuron Morphology*, 3 years, $90,978 • **Chiang-Shan Li**, NIH, *Cognitive Control and Cocaine Dependence: Thalamic Noradrenergic Processes*, 5 years, $2,621,904 • **Chenxiang Lin**, NIH, *Cell-Free Membrane Remodeling Guided by DNA Nano-Templates*, 4.8 years, $2,497,500
Kasia Lipska, NIH, *Predicting Severe Hypoglycemia among Older Adults with Diabetes*, 4.8 years, $777,933 • **Shuangge Ma**, NIH, *Penalization Methods for Identifying Gene Environment Interactions and Applications to Melanoma and Other Cancer Types*, 3 years, $434,565 • **John MacMicking**, NIH, *GBPs as New Inflammsome Regulators during Mammalian Host Defense*, 5 years, $2,081,250 • **Mark Mamula**, NIH, *Post Translational Modifications in Tolerance and Autoimmunity*, 5 years, $2,081,250 • **Arya Mani**, NIH, *Hepatic Wnt/LRP6 Regulation of Plasma Lipids*, 4 years, $2,080,864 • **Darryl Martin**, DoD, *Targeting Prostate Cancer with Multi-Functional Nanoparticles*, 3 years, $374,625 • **James Mazer**, NIH, *CRCNS: Model-Driven Single-Neuron Studies of Cortical Remapping*, 2.9 years, $666,000
Don Nguyen, NIH, *A Novel Lineage Pathway Controls Metabolic Adaptation by Metastatic Lung Cancers*, 5 years, $1,901,390 • **Michael Nitabach**, NIH, *Synaptic Microcircuits Controlling Sleep*, 4.8 years, $2,029,622 • **In-Hyun Park**, NIH, *Investigation of the Function of Methylated DNA Binding Protein in Reprogramming*, 5 years, $1,602,565 • **Dana Peters**, NIH, *Detection of Atrial Remodeling by MRI: Validation and Emerging Significance*, 4 years, $1,665,000 • **Marina Picciotto**, NIH, *Nicotine and Food Intake*, 4.7 years, $2,081,250 • **Katerina Politi**, DoD, *Cellular Plasticity and Heterogeneity of EGFR Mutant Lung Cancer*, 1 year, $166,500 • **Neil Romberg**, NIH, *Blocking Autoantibody Secretion in CVID Patients with ITP by IL-2 Restored Tregs*, 5 years, $897,350
Carla Rothlin, NIH, *TAM Receptor Tyrosine Kinases in Inflammatory Bowel Disease*, 5 years, $2,081,250 • **James Rothman**, NIH, *Mechanism of Membrane Fusion by SNARE Proteins*, 4 years, $2,630,700 • **Nenad Sestan**, NIH, *Functional Genomics of Human Brain Development*, 4.9 years, $215,803 • **Matthew Simon**, NIH, *Integrating RNAs into Signaling Pathways by Engineering Covalent RNA Modifications*, 4.7 years, $2,497,500 • **Megan Smith**, NIH, *SCH:INT Harnessing the Power of Technology: MOMBA for Postpartum Smoking*, 4 years, $1,779,556
Benjamin Toll, NIH, *Novel Treatments to Enhance Smoking Cessation before Cancer Surgery*, 1.9 years, $398,352 • **Vasilis Vasiliou**, NIH, *A Novel Aldehyde Dehydrogenase (ALDH16A1) in Gout*, 2 years, $396,401; NIH, *Mouse Models for Alcohol Metabolism and Tissue Injury*, 3.3 years, $1,084,055; NIH, *Role and Molecular Mechanisms of Corneal Aldehyde Dehydrogenase*, 7 months, $225,752; NIH, *The Role of GSH in Cornea and Lens Development*, 8 months, $132,591 • **Narendra Wajapeyee**, NIH, *Metabolic Drivers of Melanoma Initiation, Progression and Therapy Response*, 2 years, $398,352 • **Scott Woods**, NIH, *8/9 Predictors and Mechanisms of Conversion to Psychosis*, 5 years, $2,306,236 • **Dianqing Wu**, NIH, *Mechanisms for Wnt Signaling*, 3.7 years, $1,465,200
Mingyi Xie, NIH, *Noncanonical microRNA Biogenesis and Function in a Gamma Herpesvirus and Mammals*, 2 years, $177,895 • **Xiangru Xu**, NIH, *Study DNA Methylation Changes in Brain Aging and Rapamycin Treatment*, 1 year, $248,997
Qin Yan, DoD, *Targeting an Epigenetic Regulator to Suppress Breast Cancer Metastasis*, 3 years, $1,165,498 • **Wei Zhang**, NIH, *The Essential Role of Gamma-Secretase in Human Papillomavirus Infection*, 3 years, $159,906

Non-federal

Clara Abraham, Pfizer Inc., U.S. Pharmaceuticals Group, *JAK-Dependent Modulation of Pattern Recognition Receptors in Human Myeloid-Derived Cells*, 2 years, $200,000; Icahn School of Medicine at Mount Sinai (ISMMS), *RNA Sequencing of Human Monocyte-Derived Macrophages*, 8 months, $39,060 • **Heather Allore**, **Ramachandran Ramani**, Icahn School of Medicine at Mount Sinai (ISMMS) (NIH), *Trajectory of Recovery in the Elderly*, 1.6 years, $73,723 • **Alan Anticevic**, Vanderbilt University (NIH), *Thalamocortical Networks in Psychosis*, 11 months, $18,939 • **Marc Auerbach**, R Baby Foundation, *Mobile Pediatric Simulation: IMPACTS*, 1.4 years, $169,800 • **Mary Bailey**, University of California, San Francisco (NIH), *Treatment of Multiple Sclerosis with Siponimod*, 8 months, $11,409 • **Brian Biroscak**, University of South Florida (DHHS), *Community-Based Prevention Marketing for Systems Change: Reducing Disparities*, 1 year, $59,507 • **Demetrios Braddock**, Connecticut Innovations, Inc., *Validation of NPP1 Enzyme Replacement to Treat Diseases of Ectopic Bone Mineralization*, 2 years, $500,000 • **David Calderwood**, **Benjamin Turk**, Gilead Sciences, *Gilead-Yale Collaboration in Cancer - Genome Wide shRNA Screening*, 2 years, $2,306,716 • **Mian Cao**, Parkinson's Disease Foundation, *Functional Study of the Newly Identified Autosomal Recessive Early-Onset Parkinsonism-Associated Mutation in Sac1 Domain of Synaptojanin1*, 1 year, $50,000 • **Michael Caplan**, Epigen Biosciences, Inc. (NIH), *Development of Novel Agents for the Treatment of Renal Fibrosis*, 1 year, $143,180 • **David Carlson**, Dartmouth College (NIID), *Comparing* In Vivo *Biodosimetry with EPR to Independent Physical Dosimetry Methods*, 9 months, $50,000 • **Keith Choate**, Doris Duke Charitable Foundation, *Genetics and Pathobiology of Cutaneous-Skeletal Hypophosphatemic Syndrome and Erythrokeratodermia Variabilis*, 1.5 years, $64,800 • **Theodore Cohen**, Harvard University (NIH), *MIDAS Center for Communicable Disease Dynamics*, 11 months, $143,300 • **Zachary Cooper**, Commonwealth Fund, *Understanding the Pricing Dynamics in the U.S. Health Care Industry: An Analysis Using HCCI Data*, 2 years, $384,845 • **Chris Cotsapas**, Mayo Clinic College of Medicine (NIH), *Uncovering Genetic Determinants of Influenza Vaccine Response in Humans – A HIPC Project*, 10 months, $162,657 • **Robin de Graaf**, University of Minnesota (NIH), *Imaging Brain Function in Real World Environments & Populations with Portable MRI*, 9 months, $39,884 • **Francesco D'Errico**, University of Michigan (Dept. of Energy), *Consortium for Verification Technology*, 1 year, $160,000 • **James Farrell**, Cook Medical, Inc., *Comparing a 25G EUS-FNA with a 20G EUS ProCore FNB Device*, 1 year, $5,000
Richard Formica, Icahn School of Medicine at Mount Sinai (ISMMS) (NIH), *Effects of Inhibiting Early Inflammation in Kidney Transplant Patients*, 1 year, $76,240 • **Alison Galvani**, University of Warwick, *Evaluating the Feasibility of the WHO 2020 Goal for HAT Elimination*, 3.2 years, $381,071
Thomas Gill, University of Massachusetts (NIH), *Advancing Geriatrics Infrastructure and Network Growth*, 3.6 years, $39,620 • **David Glahn**, University of Southern California (NIH), *ENIGMA Center for Worldwide Medicine, Imaging and Genomics*, 8 months, $61,845; Brain & Behavior Research Foundation (formerly NARSAD), *Testing the Influence of the Glutamatergic Gene Pathway on Neurocognitive and Neuroimaging Endophenotypes for Schizophrenia*, 2 years, $98,464
Fred Gorelick, University of California, Los Angeles (NIH), *Organelle Disorders in Pancreatitis*, 1 year, $251,108 • **Jaime Grutzendler**, Alzheimer's Association, *Angiophagy a Mechanism Linking Microvascular and Alzheimer's Pathologies*, 3 years, $250,000 • **Mihaly Hajos**, Forum Pharmaceuticals, Inc. (formerly En Vivo Pharmaceuticals, Inc.), *Proposal for Developing* in Vivo *Efficacy Assays for a7 nAChR Agonist Studies to Support PK/PD Modeling and Establishing Neurophysiology-Based Translational Biomarkers*, 1 year, $402,241 • **Ilan Harpaz-Rotem**, Icahn School of Medicine at Mount Sinai (ISMMS) (NIH), *Fear Learning and Reconsolidation After Trauma Exposure - A Computational Approach*, 1 year, $239,977
Kevan Herold, L2 Diagnostics, LLC (NIH), *STTR Phase 2: Measurement of Beta Cell Death in Diabetes*, 1 year, $277,551; **Kevan Herold**, **David Hafler**, Juvenile Diabetes Research Foundation International, *Cellular Biomarkers of Progression in the T1D At-Risk Setting*, 2 years, $175,000
Michael Higley, Tuberous Sclerosis Alliance, *Analysis and Treatment of Altered Cortical Network Dynamics in TSC*, 2 years, $150,000 • **James Howe**, University of Texas Health Science at Houston (NIH), *TARP Modulation of AMPA Receptors*, 1 year, $53,280 • **Yiyun Huang**, UCB Pharma S.A., *PET Imaging of SV2A Receptors with [11C]UCB-J ([11C]APP311))*, 7 months, $258,313 • **Christoph Juchem**, National Multiple Sclerosis Society, *Study of MS Tissue Injury and Repair with* In Vivo *Magnetic Resonance Spectroscopy of Lipids and Proteins*, 1 year, $43,944 • **Naftali Kaminski**, University of Pittsburgh (NIH), *Center for Casual Modeling and Discovery of Biomedical Knowledge from Big Data*, 7 months, $108,761 • **Steven Kleinstein**, Stanford University (NIH), *The Center for Expanded Data Notation and Retrieval (CEDR)*, 7 months, $94,316; U.S.-Israel Binational Science Foundation, *Models and Methods for Mining B cell Repertoire Dynamics from Next-Generation Sequencing Studies*, 4 years, $105,000 • **Peter Krause**, Columbia University (NIH), *Babesiosis Emergence in the United States*, 1 year, $43,054
Diane Krause, Burroughs Wellcome Fund, *Collaborative Studies for Single Cell Epigenetic Analyses*, 1 year, $12,000 • **Michael Krauthammer**, SUNY Stony Brook (NIH), *Tools to Analyze Morphology and Spatially Mapped Molecular Data*, 5 years, $6,290 • **Haifan Lin**, G. Harold and Leila Y. Mathers Charitable Foundation, *Applying Nono-Physics to Epigenetics: Solving the Structure of Piwi-piRNA-Chromatin Complex by Atomic Force Microscopy*, 4 years, $1,708,593 • **Kasia Lipska**, American Federation for Aging Research, *Predicting Severe Hypoglycemia among Older Adults with Diabetes*, 4.7 years, $50,000 • **Elias Lolis**, U.S.-Israel Binational Science Foundation, *CD74 Intracellular Domain (ICD) as a Transcription Factor- Structure and Function*, 4 years, $105,000
John MacMicking, Kenneth Rainin Foundation, *Immunity-Related GTPases: A New Network Hub Model for IBD*, 1 year, $100,000 • **Mark Mamula**, Juvenile Diabetes Research Foundation International, *Protein BioMarkers of Beta Cells in T1D*, 1 year, $100,000 • **Praveen Mannam**, American Thoracic Society, *Mitochondrial Quality Control as a Therapeutic Target in Sepsis*, 1 year, $40,000
Ruslan Medzhitov, The Leona M. and Harry B. Helmsley Charitable Trust, *Exploring the Vulnerabilities of the Developing Intestinal System and its Role in VEO IBD*, 3 years, $627,000 • **Ruth Montgomery**, Mayo Clinic of Rochester (NIH), *Novel Technologies to Define Functional Attributes of T Cells in West Nile Virus*, 10 months, $50,033
Don Nguyen, Astra Zeneca AB, *Role of AZD9291 in Treating Brain and Leptomeningeal Metastasis*, 1 year, $83,000 • **Michael Nitabach**, John B. Pierce Laboratory Inc. (NIH), *Development of*

Protein-Based Voltage Probes, 11 months, $32,804 • **John Pachankis**, Hunter College, City University of New York (NIH), *Building Mobile Health HIV-Prevention Capacity for MSM in Romania*, 8 months, $37,028 • **A. Paltiel**, Harvard School of Public Health (DHHS), *Prevention Policy Modeling Lab*, 1 year, $187,218 **In-Hyun Park**, University of Texas at Dallas (NIH), *Analysis of Higher Order Chromatin Structures in Normal and Cancer Epigenomes*, 1 year, $56,478 • **Godfrey Pearlson**, Mount Sinai Medical Center (NIH), *Deconstructing Psychoses Based on Patterns of Abnormal Brain Activity*, 11 months, $97,319; Hartford Hospital (NIH), *Neural Architecture of Emotion Regulation, Adolescent Development & Depression*, 4 years, $19,764 • **Kitt Petersen**, Atara Biotherapeutics, Inc., *ATA 842 Preclinical Mouse Study*, 9 months, $402,930 • **Virginia Pitzer**, Bill and Melinda Gates Foundation, *Typhoid Modeling Studies for Typhoid Conjugate Vaccine Cost Effectiveness and for Typhoid Delivery Strategy*, 3 years, $609,151 • **Lajos Pusztai**, University of Michigan, *Financial Support for the Breast Cancer Intergroup Correlative Science Studies*, 1 year, $50,000 • **David Rimm**, Breast Cancer Research Foundation, *Targeted and Immune Therapies in Breast Cancer*, 1 year, $250,000 • **Carla Rothlin**, Kolltan Pharmaceuticals, Inc., *Specificity of TAM RTK Immune Function*, 3 years, $742,250 **Alessandro Santin**, The Honorable Tina Brozman Foundation, *Brozman Consortium Planning Grant*, 1 year, $15,000; The Honorable Tina Brozman Foundation, *Brozman Consortium Sample Collection Grant*, 1 year, $30,000 **Jennifer Sherr**, The Leona M. and Harry B. Helmsley Charitable Trust, *Effect of LX4211 on Control to Target Automated Insulin Delivery*, 2 years, $479,900 • **Robert Sherwin**, **Raimund Herzog**, Juvenile Diabetes Research Foundation International, *Development of Agents to Diminish the Risk of Hypoglycemia-Induced Brain Injury in T1DM*, 2 years, $491,784 • **Richard Shiffman**, NORC (DHHS), *Standardized and Shareable Opioid Clinical Decision Support for Electronic Health Records*, 1 years, $146,436 **Wendy Silverman**, Florida International University (NIH), *Attention Bias Modification Training in Youth with Subthreshold Impairing Anxiety*, 9 months, $55,638 • **Satinder Singh**, U.S.-Israel Binational Science Foundation, *Bacterial Homologues of Vesicular Neurotransmitter Transporters: Tools for Understanding Mechanism*, 4 years, $84,698 • **Michael Skonieczny**, South Essex Partnership NHS Foundation Trust, *Training and Development*, 1 year, $160,000 • **Serena Spudich**, Henry M. Jackson Foundation (DoD), *Study of NeuroHIV Cure Consortium (Protocols: RV217, RV254, RV397, RV398 RV412)*, 1 year, $182,654; Brigham and Women's Hospital (NIH), *AIDS Clinical Trials Group (ACTG) Leadership and Operations Center*, 1 year, $59,532 **Tami Sullivan**, University of New Mexico, *Financial, Therapeutic, Health and Deterrence Outcomes for Domestic Violence Tort Plaintiffs: Interdisciplinary Study in Law & Psychology*, 1 year, $6,882 • **Alda Tufro**, Georgia Regents University (NIH), *S-Nitrosylation of Extracellular Matrix Proteins in Diabetic Nephropathy*, 1 year, $100,000 • **Benjamin Turk**, University of Minnesota (NIH), *Multiplexed Kinase Biosensor Technology to Detect Leukemia Signaling with Mass Spectrometry*, 11 months, $20,723 • **Christopher Van Dyck**, Medical University of South Carolina (NIH), *Apathy in Alzheimer's Disease Methylphenidate Trial (ADMET II)*, 9 months, $86,780 **Stuart Weinzimer**, Nemours Children's Clinic, Jacksonville (NIH), *T1D and the Brain in Children: Metabolic Interventions*, 9 months, $186,920; Stanford University, *Outpatient Closed-Loop Studies - EPID Controller*, 1 year, $227,248 • **Adam Wisnewski**, American Chemistry Council, *Identification of Primary Reaction Products of Hexamethylene Diisocyanate (HDI) in the Respiratory Tract*, 1 year, $65,608 • **Wendell Yarbrough**, Adenoid Cystic Carcinoma Research Foundation, *Targeting Cancer Stem Cells in Salivary Adenoid Cystic Carcinoma*, 1 year, $27,500

// Stem Cell *(from page 1)* founded in 1950, into the Cheung Kong Group, now a multinational conglomerate. He established the Li Ka Shing Foundation in 1980 in part to help spur education reforms and medical innovation. His new gift to Yale builds on a gift of $1.56 million made in 2011.

"Training side-by-side with leading scientists in stem cell research will be a transformative experience for the students and faculty at Shantou University Medical College, and I want to express my heartfelt appreciation to Professor Haifan Lin and the YSCC for this amazing opportunity," Li said.

"Continued support from Li Ka-shing allows us to accelerate the pace and broaden the scope of our work," says Lin, also professor of cell biology; of genetics; and of obstetrics, gynecology, and reproductive sciences. "We are extremely grateful to Mr. Li for his generosity," Lin says.

As YSCC's founding director, Lin created four core facilities for basic stem cell research and has supported more than 80 research labs at Yale on projects covering a range of critical topics. The YSCC's core facilities focus on research in human embryonic stem cells and induced pluripotent stem cells, cell imaging, genomics, and cell manipulation.

COURTESY OF THE LI KA SHING FOUNDATION

Li Ka-shing (left) and Haifan Lin attend a commencement ceremony at Shantou University (STU), in China. A new gift from the Li Ka Shing Foundation to the Yale Stem Cell Center supports research and a continued international collaboration between Yale and STU.

In addition to independent research, scientists in these core labs work with researchers across the university who need assistance in any of these areas.

Since its founding in 2006, YSCC resources have contributed to hundreds of research projects at Yale. Just this year, researchers showed how stem cells could be used to create miniature human brain models to better understand autism. Another group tracked stem cell development in mouse hair follicles and found that the cells' development appeared to be influenced extrinsically by the surrounding microenvironment. Yet another Yale team found that a variant of the gene *CCNE1* appears critical for reprogramming mature cells.

"Yale is enormously grateful to the Li Ka Shing Foundation for its continued support of basic science, translational research, and scholarly exchange," said Carolyn Slayman, PH.D., Sterling Professor of Genetics, professor of cellular and molecular physiology, and deputy dean for academic and scientific affairs. "This grant will help expedite the development of therapeutic treatments for some of the world's most debilitating diseases."

// Scholars *(from page 5)* delivery of health care across the health continuum," says Margaret Grey, DR.PH., R.N., the Annie Goodrich Professor of Nursing and former dean of the School of Nursing. "The more we educate people in silos—whether for clinical practice or clinical research, or health services research—the less likely it is they will work collaboratively when they get out in the real world."

Also, Grey says, post-doctoral training slots for nurses are limited, and the NCSP will provide a much-needed avenue for nurses who seek to combine clinical work with research.

The new two-year program will select approximately five physician- and nurse-scholars per year to complete coursework together at Yale, sharing mentors from across the professions. NCSP scholars will lead their own policy-relevant research projects, guided by faculty and community partners.

Says Gross, "We place a great emphasis on teaching scholars not just how to do research, but how to instill change. And we're applying the same principles to the design of the program itself, changing it to reflect the needs of today's communities and tomorrow's health care system."

// Chair *(from page 1)* "The world made no sense to her," Mark says.

That day in Houston, Meghan ran from the hospital. She led Mark and Michele down a freeway, running the wrong way in traffic. They eventually convinced her to return. Mark sat in a room at a psychiatric facility alone with Meghan and attempted to soothe her. Michele sat outside and warned a police officer that she should not enter the room until Mark had more time with Meghan. But the officer entered, and Meghan punched her in the face.

Hal Blumenfeld

Years later, the storm has calmed: the family began a new chapter when Meghan visited the Yale Comprehensive Epilepsy Center (YCEC). She's been seizure-free for nearly two years under Blumenfeld's care. His gentle demeanor made it easy for Meghan to buy into working with the YCEC, Mark says: "Meghan really trusts Hal." With a thorough review of her long and complicated history, the team came up with a strategy to bring the seizures under control.

Meghan's family offered annual support to Blumenfeld's epilepsy research for several years before endowing the professorship. Says Mark, "This was an opportunity for us to pay back to the community ... and to a facility that had done so much for our family."

In addition to his research on loss of consciousness during seizures, Blumenfeld, also professor of neuroscience and neurosurgery, has delved into the prevention of epilepsy. In 2008 he reported in *Epilepsia* that giving the anti-seizure medication ethosuximide to animals with absence epilepsy before onset of seizures markedly reduced seizures and continued to do so for months after the treatment. He continues to explore the possibility of very early treatment for human patients to change the course of the disease.

Blumenfeld is director of the Yale Clinical Neuroscience Imaging Center and a member of the Kavli Institute for Neuroscience. A graduate of Harvard University, Blumenfeld earned his M.D. and PH.D. from Columbia University. He completed his internship in internal medicine at Columbia Presbyterian Medical Center and his neurology residency at Massachusetts General Hospital. He then served as a fellow in epilepsy at Yale School of Medicine (YSM).

Blumenfeld's research draws on such varied areas as imaging, bioengineering, and neurochemistry. Excellence across disciplines and a culture of collaboration keep him at YSM, he says: "It's really a team effort that brings us happy stories such as Meghan's."

Meghan has neurological impairment from the epilepsy that began when she was a year old. Now that she's seizure-free, there is finally a window to work on the behavioral issues that have presented such challenges to Meghan and her family.

Mark Loughridge is the former chief financial officer of IBM, and is currently lead director of Vanguard and independent director at the Dow Chemical Co. He serves on the Council on Chicago Booth for the University of Chicago Booth School of Business, where he earned an MBA.

Michele serves on the board of Mercy Learning, a group that provides literacy and life skills training to low-income women. One day one of the women Michele was tutoring had a seizure. Although almost 30, she had never been under a doctor's care for her epilepsy.

Michele's first call was to Blumenfeld, and the woman was referred to the YCEC for care. Says Michele, "She got exactly the same treatment that Meghan did."

Physiologist joins National Academy of Sciences

Nancy Carrasco, M.D., professor of cellular and molecular physiology, has been named to the National Academy of Sciences (NAS) as a foreign associate. She is among 84 new members and 21 foreign associates selected for membership this year in recognition of their achievements in original scientific research. The new cohort includes three other Yale faculty members.

Carrasco's work explores the mechanisms of transport across the cell membrane. Her research on the Na+/I- symporter (NIS), the key plasma membrane protein that mediates active iodide transport in the thyroid, lactating breast, and other tissues, ranges from biochemical, biophysical, and physiological investigations to translational studies, including development of new cancer treatments. Her research group was the first to discover the mechanism for cellular uptake of iodide, after cloning NIS.

A native of Mexico, Carrasco received her M.D. and an M.S. in biochemistry from the National Autonomous University of Mexico, and completed a postdoctoral fellowship at the Roche Institute of Molecular Biology. She joined the School of Medicine's faculty in 2011 following an appointment at the Albert Einstein College of Medicine in New York City.

Nancy Carrasco

"My election stands as a counterargument to some of the claims we hear every now and then regarding the contribution that immigrants—those from Mexico, like myself—are making in the U.S. and around the world. I think that one of the most beautiful things about science is that it's an international pursuit," she said.

> "I think that one of the most beautiful things about science is that it's an international pursuit."
>
> —Nancy Carrasco, M.D.

The NAS is a private, non-profit institution established under President Abraham Lincoln at the height of the Civil War to serve as an advisory group. With the National Academy of Engineering, National Academy of Medicine, and National Research Council, today it provides science, technology, and health policy advice to the federal government and other organizations.

Carrasco and the other newly elected members will be formally inducted at the NAS annual meeting next year, bringing the total number of active members to 2,250 and the total number of foreign associates to 452.

Yale immunologist named HHMI investigator

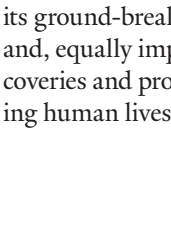
John D. MacMicking, PH.D., associate professor of microbial pathogenesis, is one of 26 scientists named in May as investigators of the Howard Hughes Medical Institute (HHMI).

MacMicking is a leading expert in the emerging field of cell-autonomous immunity—the ability of most nucleated cells, not just those of the immune system—to defend against infection via sophisticated antimicrobial strategies evolved to deal with a wide array of microbial pathogens. Many of these strategies are orchestrated through interferon (IFN) signaling pathways essential for host resistance to major infectious diseases such as tuberculosis, AIDS, and malaria. In work begun at The Rockefeller University and continued at Yale School of Medicine (YSM), he and his lab members identified a new superfamily of enzymes termed IFN-inducible GTPases in both immune and non-immune cells that play a critical role in this unusual form of host defense.

An HHMI announcement about MacMicking's selection noted that his "discoveries about how individual cells protect themselves against viruses, bacteria, and other pathogens is forcing scientists to reconsider what constitutes the boundaries and breadth of the traditional immune system."

MacMicking earned his B.SC. at the Australian National University in Canberra and his PH.D. at the Sloan-Kettering Institute-Cornell University Medical College in New York City. He was a HHMI Life Science Research Foundation Fellow and adjunct assistant professor at The Rockefeller University before being recruited to YSM.

MacMicking has been recognized as a Searle Scholar, an Edward Mallinckrodt Jr. Foundation Fellow, a Cancer Research Institute Investigator, and a Burroughs-Wellcome Fund



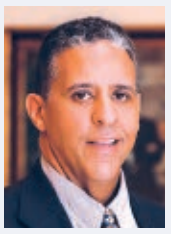
John MacMicking

Investigator in the pathogenesis of infectious disease. In 2014 he was named both an American Asthma Foundation Scholar and the Kenneth Rainin Foundation Innovator.

A non-profit medical research organization with an endowment of more than $16 billion, HHMI was founded by businessman Howard Hughes in 1953. The HHMI's grants to scientists from 19 institutions across the United States for basic biomedical research are worth $153 million over the next five years. The new investigators—who include four current HHMI early career scientists—were selected for their individual scientific excellence from 894 eligible applicants, and are expected to begin their appointments this fall.

Awards & Honors

Pietro De Camilli, M.D., chair and the John Klingenstein Professor of Neuroscience and professor of cell biology, has been named president-elect of the American Society of Cell Biology. His term will begin in 2017. De Camilli is also director of the Kavli Institute for Neuroscience at Yale and a Howard Hughes Medical Institute investigator.



Benjamin A. Fontes, M.P.H., biological safety officer, has received the American Biological Safety Association's Arnold G. Wedum Distinguished Achievement Award for his "outstanding contributions to biological safety accomplished through teaching, research, service, or leadership." In 2014 he was Yale's Environmental Health and Safety Employee of the Year.

Dennis D. Spencer, M.D., the Harvey and Kate Cushing Professor of Neurosurgery, has received an Ambassador for Epilepsy Award from the International League Against Epilepsy. The award recognizes Spencer's outstanding contributions to activities advancing the cause of epilepsy internationally. He has helped develop epilepsy surgery programs in Asia, Africa, and Latin America.

Joan A. Steitz, PH.D., Sterling Professor of Molecular Biophysics and Biochemistry and a Howard Hughes Medical Institute investigator, received the 2015 Connecticut Medal of Science for her seminal research on the structure and function of RNA. The medal is Connecticut's highest honor for scientific achievement in fields crucial to the state's economic competitiveness.

// Dyslexia *(from page 1)* loci on human chromosomes that appear to play a role in the development of language, expression, and reading.

In recent years Gruen has worked to hone an approach he calls "precision education." In 2009, with the support of a $5 million grant from the Manton Foundation, he was the principal investigator of a multicenter genetic study of dyslexia in minorities, focusing on Hispanic-American and African-American children, called the Yale Genes, Reading, and Dyslexia (GRaD) Study. Its goal was to find genetic markers that can identify children at risk for dyslexia well before the children begin to fail in school, so that intervention could be started early, when it's most effective.

The NHLP takes this research a step further. Children with dyslexia can have additional disabilities that span more than one domain, and hence the need to gather more information. Gruen's aim is to know as much as possible about how genes and the type of learning intervention a child receives interact with each other. Whereas the GRaD Study focused on presymptomatic screening, the goal of the NHLP is to use genetics to predict response-to-intervention, and to inform the optimal intervention for each student with learning disabilities.

The team will selectively enroll qualified students for individual cognitive assessments, classroom and testing performance, family life and background, culture, serial magnetic resonance imaging of brain structure and function, and comprehensive genomic analyses. Once they reach the second grade, some students will also participate in an intense intervention with specially trained teachers.

By mid-October the NHLP had enrolled 87 families. The researchers are focused on recruitment and testing in first grade classes. The target for the study's conclusion and results is 2021.

"The School of Medicine is deeply appreciative of this further encouragement and support from the Manton Foundation, an institution that has a strong record in the advancement of important work on behalf of underserved, urban communities," said Dean Robert J. Alpern, M.D., Ensign Professor of Medicine. "This new grant allows the school to continue its ground-breaking genetics research and, equally important, to apply discoveries and progress toward improving human lives."

Sometime in the future, Gruen says he hopes district-wide screening can be implemented to identify children at high risk for learning disabilities, and then to match them to a precisely-designed curriculum effective for a child's unique genomic sequence.

"We know that dyslexia can respond to intervention programs that address multiple learning modalities and are offered in early grades," Gruen says. However, "often the diagnosis and intervention come too late after a child has experienced repeated academic failures, and when the child is less likely to respond," he says.

The Manton Foundation was established in New York City in 1991 by Sir Edwin and Lady Manton to support the arts, education, health care, cultural preservation, and medical research.