Medicine@Yale

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Changing of the guard: Salovey becomes 23rd president of Yale

Gifted administrator, teacher, and scholar is champion of cross-campus collaboration

On June 30, Peter Salovey, PH.D., the Chris Argyris Professor of Psychology, became Yale University's 23rd president, replacing President Richard Levin, who stepped down after 20 years at the helm, having served his institution longer than any other president currently in the Ivy League or the 61-member Association of American Universities.

Salovey's selection for the presidency by the Yale Corporation from a pool of 150 candidates was unanimous. He has walked the campus for 31 years, first as a graduate student in psychology, then as professor, department chair, dean of the Graduate School of Arts and Sciences, and dean of Yale College. For the past four years, he has been the university provost.

That broad and deep Yale experience, together with his upbeat and genial personal style, made him seem like a natural for the job to many insiders. "People at the medical school were very enthusiastic about the appointment. I certainly was," says Robert J. Alpern, M.D., dean and Ensign Professor of Medicine. "Across the university, he would have been my number-one choice."

Salovey, also professor of Epidemiology and Public Health and in the School of Management, is a highly productive scholar of human emotion and health-related behavior, having written or edited 13 books and 350 articles or essays. He is perhaps best known for having helped pioneer the now-commonplace concept of emotional intelligence.

No stranger to the medical school, Salovey holds an appointment in the School of Public Health, where he researches the development of effective messages about // President *(page 7)*

MICHAEL MARSLAND

Peter Salovey, a psychologist with deep roots at Yale, made the transition from provost to president on June 30.

Honoring a leader in innate immunity

German foundation names School of Medicine scientist the first recipient of €4 million prize for pioneering research in immunobiology

On June 5 in Berlin, Germany, School of Medicine researcher Ruslan M. Medzhitov, PH.D., received the inaugural Else Kröner Fresenius Award, an international prize for distinguished immunology research created in 2012 by the Else Kröner-Fresenius-Foundation (EKFF), one of Germany's largest philanthropic organizations.

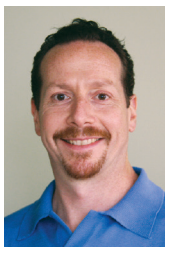
The award recognizes Medzhitov's pioneering contributions to our understanding of the innate immune system, which mounts an immediate defense against infection and provides the slower-acting adaptive immune system with the necessary information to create custom-made cells that target specific bacterial or viral invaders.

Medzhitov, the David W. Wallace Professor of Immunobiology and a Howard Hughes Medical Institute (HHMI) investigator, has done seminal studies elucidating the critical role of innate immune // Award *(page 8)*

COURTESY OF THE ELSE KRÖNER-FRESENIUS-FOUNDATION

The Else Kröner Fresenius Award was presented to Yale's Ruslan Medzhitov (center) in a ceremony in Berlin by Germany's Federal Minister of Education and Research, Johanna Wanka (left), and Susanne Schultz-Hector (right), a board member of the Else Kröner-Fresenius-Foundation, one of the largest philanthropic organizations in Germany.

Lighting a new path to understanding the brain's 'language'



Michael Nitabach

When President Barack Obama announced the $100 million neuroscience initiative called Brain Research through Advancing Innovative Neurotechnologies (BRAIN) in April, the journal *Nature* called it "a bold bid for the neuroscientist's ultimate challenge," but pointed out that "if researchers are to make sense of the frenzy of electrical signals coursing through the brain's circuits, they will need to record simultaneously from as many neurons as possible," a capability that has been sharply limited by available technology.

But School of Medicine scientists have now made significant strides toward meeting this challenge by inserting a fluorescent protein in neurons that emits light of varying intensity to mirror changes in electrical activity within the cells. As reported online August 8 in the journal *Cell*, using // Brain *(page 7)*

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INSIDE THIS ISSUE

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HAROLD SHAPIRO

At the Yale Stress Center, Rajita Sinha and colleagues provide a peaceful environment for patients grappling with addictions, as well as those who seek to minimize the health effects of everyday stress. In addition to its clinical programs, the center conducts research on the behavioral and brain mechanisms underlying substance abuse and other damaging responses to stress.

Giving refuge, advancing research

Yale Stress Center head promotes healing of the body, mind, and brain

Rajita Sinha, PH.D., says that the emotional expressiveness of the Indian classical dance studies of her youth laid the foundation for a lifelong interest in the brain-body tango that regulates mood and behavior. As an undergraduate in her native Delhi, she studied biopsychology, conducting research on the effects of marijuana and working at a counseling center. For her graduate work at the University of Oklahoma Health Sciences Center, she studied how emotion is manifested physiologically, a thread that she has carried through her subsequent work on the brain-altering effects of drugs and alcohol.

Throughout, Sinha has observed and studied how people cope with stress and with *wanting*—"The abundance of choices available in the world, and easy access to commodities, including drugs, challenges the body's motivational systems in novel ways," she says.

Sinha, now Foundations Fund Professor of Psychiatry at the School of Medicine, is director of the Yale Stress Center (YSC), an interdisciplinary program dedicated both to treating the problems that can arise when people modulate emotions through drugs, alcohol, and eating, and to studying the brain mechanisms underlying stress, cravings, and addiction.

The YSC's holistic approach is apparent upon setting foot in the door. The waiting room, which Sinha helped design, is decorated in calming muted colors, and a mini rock garden and soothing music contribute to an air of tranquility. The clinical side of the center, which opened last year, offers behavioral techniques, including biofeedback, nutrition, and yoga, to help people manage life stressors. One study in progress at the center is looking at the efficacy of mindfulness, a technique that Sinha says has helped her personally deal with stress.

After receiving her clinical psychology doctorate at Yale in 1992, Sinha joined the medical school faculty and developed models of how stress induces brain and body changes that stimulate addictive behaviors. New imaging methods helped Sinha, also professor of neurobiology and in the Yale Child Study Center, to characterize and validate the concept of stress-induced craving, an increase in motivation to seek out something mood-altering. "The conventional approach to addiction was, 'People like to get high. If you take away the high, that stimulus won't be reinforcing anymore, and they'll stop using.' It's a behavioral model that didn't work," she says.

Missing from the equation, she says, was stress. In one of her experiments, stress increased subjects' craving for alcohol, an effect that was more pronounced in binge drinkers. Drinking is relaxing in the short term, says Sinha, but over time it raises stress hormones, leading to a vicious cycle where more alcohol is needed to achieve the same relaxing effect. Changes in the brain that mediate these effects lead to cravings and addictive behaviors; similar changes are seen in food and gambling addictions, also being studied at the YSC.

Because her passion is science, Sinha says, "there's always been tension between applying and seeing treatments work, versus understanding the mechanism." It seems, though, that at the YSC the tension between clinic and lab is melting away: the center's interventions for mind and body ultimately target the brain, and Sinha and colleagues can then study patients' brains to come up with even more powerful treatments for stress and addiction.

Yale-New Haven Health System opens Multiple Sclerosis Center

May 15 marked the opening of the new Multiple Sclerosis (MS) Center at the Yale-New Haven Hospital North Haven Medical Center. The North Haven, Conn., center provides state-of-the-art treatments for MS and rheumatic and digestive diseases, and will also provide patients with the opportunity to enroll in clinical trials to advance the understanding of the biology of these diseases and to improve treatment options.

MS patients often find themselves visiting different specialists in multiple locations. But the new center is a "one-stop shop" that allows for multidisciplinary collaboration among various specialists, says Daniel Pelletier, M.D., professor of neurology and diagnostic radiology and chief of the MS Center.

The center boasts seven exam rooms, a procedure room, an infusion room, and offices for clinicians and researchers. It also includes an on-site laboratory and blood-draw services, as well as diagnostic radiology services and equipment, including a powerful 3-Tesla magnetic resonance imaging (MRI) scanner. Parking is free, easing access for patients with canes and wheelchairs.

"It's a new time," says Pelletier. "This is the infrastructure we've been waiting for to build a comprehensive MS team."

Daniel Pelletier

Noting that scientists are beginning to understand the common mechanisms underlying many autoimmune diseases, David A. Hafler, M.D., chair and Gilbert H. Glaser Professor of neurology and professor of immunobiology, says, "The treatment that works in one disease can work in another. We're finally beginning to learn about how to treat this disease."

Faculty medical practice boasts 49 'top docs' in region

New York magazine's 2013 list of the metropolitan region's top doctors includes more than four dozen of the physicians of Yale Medical Group (YMG), the medical school's faculty practice. This year, the magazine named 49 YMG physicians in the magazine's annual "Best Doctors" issue.

Castle Connolly Medical Ltd., a New York City research and information firm, determines the rankings via a regional peer-review survey that asks thousands of licensed physicians to nominate the physicians who, in their judgment, are the best in their field and related fields. The list is based on the annual *Top Doctors New York Metro Area* guidebook.

According to the company, the annual New York guidebook lists the top 10 percent of the metro area's physicians. *New York* magazine's list is more selective—the top quarter of the top 10 percent. This year, the magazine featured a total of 1,198 physicians.

"Yale physicians are simply world-class," says Paul Taheri, M.D., M.B.A., deputy dean for clinical affairs and chief executive officer of YMG. "We recruit and retain physicians who have superlative training, educate future leaders, and support research innovations. The fact that 49 of our physicians were identified reflects our strength in a region with many academic medical centers."

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ADVANCES
Health & Science News

Getting a leg up during evolution

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How did the human hand evolve? A Yale study in the July 3 issue of *Cell* describes some of the genomic changes that may have modified limb development during human evolution.

Using a biochemical marker, James P. Noonan, PH.D., associate professor of genetics, and colleagues globally identified DNA sequences that promote and enhance gene expression in developing fore- and hindlimbs (or hands and feet) of mice, monkeys, and humans. They found that 13 percent of sequences have significantly increased activity in human limbs compared to monkey and mouse, gains pointing to over 300 genes that show increased expression in the human embryonic limb.

"It has been difficult to understand how human traits evolved, because we didn't know where the important genetic changes might be," Noonan says. "Now we do, and we have the tools to determine what biological effects these changes may have. Our study provides a roadmap for understanding other human-specific traits that arise during development, such as increased brain size and complexity."

Dyslexia more severe if two genes affected

The consequences of dyslexia, a reading disorder that affects as much as 17 percent of the population, can be greatly minimized by early educational intervention. Because the condition has a strong genetic component, researchers have been eager to develop a genetic test to identify children at risk at as young an age as possible.

In 2005, a team led by Jeffrey R. Gruen, M.D., linked variations in a gene called *DCDC2* to dyslexia risk, and other researchers made a similar connection between dyslexia and a gene known as *KIAA0319*. In a new study, published on July 11 in *The American Journal of Human Genetics*, Gruen and colleagues found that children carrying variations in both genes scored significantly lower on tests of reading and other language skills than those with variations in one or the other.

The robustness of the effect on test scores of this genetic double-whammy could provide the basis for a reliable and practical genetic screen, which is sorely needed, says Gruen: "Research shows that if children with dyslexia receive intensive intervention before middle school, 75 percent will be reading at grade level even two years after completing it. Testing for both *DCDC2* and *KIAA0319* variants could identify the children who would benefit most from intervention."

A helping hand for tomorrow's scientists

In an age of unprecedented competition for research grants, philanthropists are helping to kickstart the careers of young scientists

When she arrived at Yale after a successful postdoctoral fellowship, Megan C. King, PH.D., assistant professor of cell biology, was ready to hit the ground running. But she soon found that setting up a brand-new lab isn't easy, and has a lot in common with starting a small business from scratch. "You have to find the people, you have to find the 'investment' money, you have to decide what your 'products' are going to be, and then you have to get something done so you can return something to those investors," King says. "And that is not at all what being a postdoc is about."

For new investigators it's always been a challenge to win grants. But today even experienced researchers are facing funding cutoffs, making it all the more difficult for those just starting out. Fortunately, corporations, foundations, and private individuals are stepping into the breach, offering young investigators welcome supplements and even alternatives to federal funds. And the federal government itself is following suit, establishing funding streams specifically tailored for gifted scientists in the first stages of their careers. While these funding avenues are no substitute for bread-and-butter federal research grants, they provide a measure of relief to a select group of investigators.

For example, in 2011 King was named a Searle Scholar, an honor awarded to 15 new tenure-track scientists annually that supports their work with a gift of $300,000 over three years. Funded by the estates of Mr. and Mrs. John G. Searle, the Searle Scholars Program supports exceptional young faculty in the biomedical sciences and chemistry. King's recruitment to Yale in 2009 was also supported in part by the G. Harold and Leila Y. Mathers Charitable Foundation, which awarded her $1.1 million over three years for her work using fission yeast to study the DNA repair functions within cells.

This spring, Andrew Goodman, PH.D., assistant professor of microbial pathogenesis, and Bo Chen, PHARM.D., PH.D., assistant professor of ophthalmology and visual science and of neurobiology, were named 2013 Pew Scholars in the Biomedical Sciences. Offered to just 22 scholars nationwide, the prestigious prize from the Pew Charitable Trusts offers $240,000 over four years, and is awarded only to early-career scholars. Elena Gracheva, PH.D., a new assistant professor of cellular and molecular physiology, runs her lab with the help of grants from the Alfred P. Sloan Foundation, the Arnold and Mabel Beckman Foundation, and the Rita Allen Foundation.

Through the Yale Scholars program, founded in 2006 by Dean and Ensign Professor of Medicine Robert J. Alpern, M.D., donors contribute $2.5 million, which is matched by Yale to establish a named $5 million fund that provides $1 million in startup funds over four years to a promising new tenure-track investigator. Donald S. McCluskey, M.ENG., an alumnus of Yale College and Yale's Faculty of Engineering, endowed the first Yale Scholarship in the name of his brother (now deceased), Robert T. McCluskey, M.D., also a Yale College alum. Goodman was named the McCluskey Yale Scholar in 2011, an honor that helped him get his lab off the ground in its earliest days.

These initiatives are more important than ever because federal grants—traditionally the largest source of funding for the biomedical sciences—are extremely difficult to land now for all researchers, but especially for junior scientists. "It used to be easy: Do decent work, put in a reasonable grant, listen to the comments, resubmit it maybe once, and you'll get an R01—and the expectation was that within five years you'd get a second R01," King says, referring to the National Institutes of Health's (NIH) sought-after renewable grants. "That's no longer really feasible." The statistics bear her out: in 2001, the renewal rate for R01s was 51 percent, but in 2012, it was 33 percent.

For scientists of all ages submitting proposals for new R01s, prospects are even grimmer. In 2001, the NIH funded 25 percent of new R01 grant applications; in 2012 funding had declined to 15 percent, and within some individual NIH institutes, the success rate has dipped into the single digits. Yet it takes the equivalent of two R01s to fund a lab, according to Goodman. And virtually all R01 applications submitted by young researchers are for new grants. So young principal investigators expend large amounts of time on federal and private grant applications that they could be devoting to research.

Gracheva says that grantwriting consumes 30 percent of her 70-hour work week, while Valentina Greco, PH.D., assistant professor of genetics and dermatology, estimates she writes five or six applications for every grant she receives. "My time goes into writing grants rather than doing science or mentoring my people," Greco says, "but I must do the grants. I work six times as much so I can cover all my functions." Applying for grants, says King, takes a good deal of emotional fortitude, and young researchers can't always look to more seasoned colleagues for guidance: "Even our mentors can't give us a whole lot of advice, because they've never been junior when the NIH was like it is now," she says.

Recognizing the plight of young investigators, federal agencies have in recent years set aside grants specifically for those in the early stages of their careers. Since 2007, the NIH Director's New Innovator Award has funded a small number of grants for exceptionally original early-career research, and, by design, the application doesn't require the volume of preliminary data that the traditional grant system does. Goodman was an awardee in 2012 and King in 2011. And policy changes adopted in 2007 have substantially increased the number and the percentage of R01 awards going to new investigators.

HAROLD SHAPIRO

In today's economic climate, with increased competition for funding, young scientists like cell biologist Megan King are relying more than ever on honorific grants to jumpstart their research careers.

"I am lucky, because there are mechanisms in place to give young, unestablished investigators an edge," says Jesse Rinehart, PH.D., assistant professor of cellular and molecular physiology, one of the first scientists to set up a lab at Yale's West Campus in Orange, Conn. "It's in the best interest of the NIH and other funding institutions to make sure that we have scientists for the future."

Despite tough times, the struggle is well worth it, they all agree. Goodman calls it a great privilege to work with his team members, and Greco puts in as many hours as she possibly can. "My job is not my job—it's my hobby, my passion," she says. "You just can't be afraid," King says. "It is kind of a brave new world, but it's not hopeless. We're figuring it out."

Support tomorrow's cures

In 2006, the School of Medicine launched the Yale Scholars program, an initiative that supports the most promising new investigators as they launch their scientific careers.

Under the program, a donor can create a Yale Scholar endowment with a gift of $2.5 million, which is matched, dollar for dollar, by Yale. The resulting $5 million fund produces income that provides crucial support to a young scientist for his or her first four years as an independent investigator.

In year five, when the scientist has established a research portfolio that can secure federal grants and other outside funding, the award passes on to another top recruit, and the cycle continues in perpetuity.

Imagine the satisfaction of supporting the important work of the scientists profiled on this page, such as Megan King, Andrew Goodman, or Elena Gracheva. Who knows how their creativity and new ideas will alter the future of medical science?

We welcome your interest and participation in the Yale Scholars program. For more information, contact Zsuzsanna Somogyi, deputy director for medical development at 203-436-8559 or zsuzsanna.somogyi@yale.edu.

OUT & ABOUT

CLINT SPAULDING/PATRICKMCMULLAN.COM

April 1 A **Vilcek Prize** was awarded jointly to **Ruslan M. Medzhitov**, PH.D., the David A. Wallace Professor of Immunobiology; and **Richard A. Flavell**, PH.D., chair and Sterling Professsor of Immunobiology, who were honored for their influential work on the innate immune system. The awards, given by the Vilcek Foundation, recognize significant contributions to American science and the arts made by immigrants. **1. Marica Vilcek**, co-founder and vice president of the Vilcek Foundation, and Flavell. **2.** (From left) **Akiko Iwasaki**, PH.D., professor of immunobiology and of molecular, cellular, and developmental biology; Medzhitov; **Titia de Lange**, PH.D., Leon Hess Professor at The Rockefeller University; Flavell; and **Madlyn Flavell**.

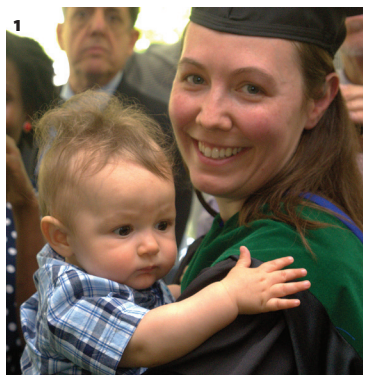
LIZ LIGON PHOTOGRAPHY

April 24–28 A laser light sculpture titled ***Night Rainbow | Global Rainbow New Haven*** was projected from East Rock Park to commemorate the 375th anniversary of the city's founding. The sculpture's creator, Yvette Mattern, has worked in cities around the world, using specially designed lasers to project a large-scale rainbow pattern, seen here above Congress Street on the medical school campus.

HAROLD SHAPIRO

TERRY DAGRADI (3)

May 15 A ribbon-cutting marked the opening of the **Multiple Sclerosis (MS) Center** at the Yale-New Haven Hospital North Haven Medical Center in North Haven, Conn. (see related story, p. 2). **1. Daniel Pelletier**, M.D., professor of neurology and diagnostic radiology and chief of the new center, with **Elizabeth Jameson**, an artist with MS whose works hang on the center's walls. **2. Lisa Gerrol**, president of the National MS Society's Connecticut Chapter. **3.** (From left) **David A. Hafler**, M.D., the Gilbert H. Glaser Professor and chair of neurology and professor of immunobiology; Jameson; Pelletier; and Gerrol.



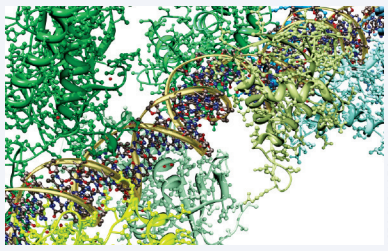
JOHN CURTIS (4)

May 20 At **Commencement** the Class of 2013 looked back at four years at Yale, and ahead to medical careers. **1. Sarah Johnson** and her son **Eli**. **2. Kristina Liu** (left) and **John Millet**. **3. Charles Odonkor** (left) and **Johannes Adomako-Mensah**. **4.** (From left) **Justin Steinberg**, **Lydia Shook**, **William Thomas Clarke**, **Madison Hustedt**, and **Joshua Hustedt**.

TERRY DAGRADI (6)

May 31–June 2 **Reunion Weekend** brought 360 alumni and friends to campus, with record turnouts from classes celebrating 5th, 10th, and 15th reunions. **1. Robert J. Alpern**, M.D., dean and Ensign Professor of Medicine, at the Welcome Dinner, held at Edward S. Harkness Memorial Hall. **2. Richard Belitsky**, M.D., deputy dean for education and Harold W. Jockers Associate Professor of Medical Education, gave a progress report on the rebuilding of the medical school's curriculum. **3.** Members of the Class of 1988 gathered on Harkness Lawn. (Seated, from left) Frederick Godley, M.D., husband of **Kathleen Carney-Godley**, M.D.; **Janice Janas**, M.D.; **Joi Barrett**, M.D.; **Susan Valley**, M.D. (Standing, from left) **David Galbraith**, M.D.; **Joe Dizon**, M.D., and **Steve Slovic**, M.D. **4.** (From left) **Maya Lodish**, M.D. '03, with daughter **Isabelle Zimmerman**, and Carney-Godley during a family-friendly treasure hunt at the medical school's Historical Library. **5.** Members of the Class of 1973 marked their 40th reunion, including (from left) **Randy Zusman**, M.D.; **Richard Boland**, M.D.; **Christine Walsh**, M.D.; **Harold Mancusi-Ungaro**, M.D.; **Andrew Kadar**, M.D.; and **Thomas Romano**, M.D. **6. G. Morris Dillard,** PH.D., M.D., (left) catches up with **Peter Gregory**, M.D. '63.

A clotting disorder's immune origins



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Immune thrombocytopenia (ITP), a bleeding disorder characterized by low blood platelet numbers, can result in excessive bleeding during injuries.

While ITP is known to be an autoimmune disorder, the precise mechanisms of both the disease and a common treatment, intravenous immunoglobulin (IVIG) administration, have been unclear.

In a study published on July 10 in *Science Translational Medicine*, Kavita Dhodapkar, MBBS, associate professor of pediatrics, and colleagues detail the unique genetic signature of children with ITP. They show that this signature is mediated by elevated levels of both infection-fighting proteins called interferons (see photo) and innate immune cells called plasmacytoid dendritic cells found in ITP patients.

The research team also showed that IVIG treatment diminishes the elevated gene expression, but only temporarily, a finding that is consistent with the treatment's short-lived efficacy. These studies therefore provide potential targets for new therapies against ITP by directly attacking the underlying innate immune cells.

Typhoid toxin's deadly design

Typhoid fever, one of the longest-known diseases in human history, still claims more than 200,000 lives a year globally. But the molecular factors that make *Salmonella* Typhi far more virulent than closely related *Salmonella* bacteria that cause the temporary abdominal distress associated with food poisoning have been a mystery.

A Yale study has now revealed how *S.* Typhi packs its lethal punch, a discovery that could lead to the development of effective vaccines and other new therapies against typhoid fever.

Nearly a decade ago, a research team led by Jorge Galán, PH.D., D.V.M., chair and Lucille P. Markey Professor of Microbial Pathogenesis, identified a toxin unique to *S.* Typhi. In follow-up work published in the July 11 issue of *Nature*, Galán and colleagues report that delivering the toxin alone to mice produced the main symptoms of typhoid fever. The team also solved the atomic structure of the toxin and identified the cellular receptors that guide the toxin to its site of action.

"What makes this so exciting for us is that vaccines and therapeutics that target toxins have an excellent track record of success" in diseases such as tetanus and botulism, says Galán, whose lab has begun a search for new typhoid fever treatments.

New light on congenital heart disease

Up to 10 percent of congenital heart defects caused by non-inherited gene mutations similar to those previously implicated in autism

When a baby is born with a severe heart defect, there is usually no obvious explanation. In the majority of cases the family has no history of such heart problems, and most often the parents carry no known genetic mutations related to the defect that they could have passed along. Recently School of Medicine scientists contributed to a sweeping new search for genetic mutations in children with unexplained heart abnormalities that uncovered several hundred non-inherited mutations that may help shed light on how such problems arise during fetal development.

The new study, published June 13 in the journal *Nature*, was led by scientists from the School of Medicine as part of a multicenter collaboration that included patients and scientists from seven U.S. centers and from University College London. The study compared the genomes of children with severe congenital heart disease (CHD) to the genomes of their healthy parents to try to determine whether *de novo* mutations—mutations that, rather than being passed from parent to child, arise spontaneously in egg, sperm, or early embryo cells—are involved in these disorders.

"Because many affected patients are the offspring of healthy parents, we speculated that new mutations might play a significant role in CHD," says Richard P. Lifton, M.D., PH.D., chair and Sterling Professor of Genetics, professor of medicine, and a lead author of the study along with Martina Brueckner, M.D., associate professor of pediatrics and genetics. Children with heart defects, they found, were 7.5 times more likely to have damaging *de novo* mutations in genes expressed in the developing heart than were healthy children, and such mutations appear to contribute to more than 10 percent of all cases. Most interestingly, many of the newly identified mutations affect proteins that orchestrate normal development by helping to turn genes on and off at the proper times by altering the chemical marks on histone proteins, which provide a scaffold that DNA is wrapped around in the cell nucleus. This mechanism is known as epigenetic control.

The scientists analyzed the genomes of 362 trios, each comprising two unaffected parents and one child with severe CHD. These families were participants in the National Institutes of Health–funded Pediatric Cardiac Genomics Consortium; the team also studied the genomes of a control group of 260 parent-child trios with no history of CHD. The study used a rapid and inexpensive method of sequencing all the genes in the genome—called exome sequencing—pioneered at Yale over the last decade. The DNA sequencing for the study was performed at the Yale Center for Genome Analysis at Yale's West Campus, and the analysis was led by two members of Lifton's lab: Samir Zaidi '16, a student in Yale's M.D./PH.D. Program, and Murim Choi, PH.D., a postdoctoral fellow.

When the researchers examined the genes with *de novo* mutations, they found a common thread. "There's a pathway that seems to be particularly hit by these *de novo* mutations, not only in congenital heart diseases, but in autism as well," says Brueckner. "That suggests that this pathway plays a vital role in diverse aspects of fetal development."

Ten of the *de novo* mutations found in CHD patients occurred in genes required for the addition or removal of methyl groups at two sites on one of the histones. These two methylation sites play a critical role in turning genes on and off. Most interestingly, one of these marks activates gene expression, while the other represses expression. In embryonic stem cells and in developing embryos, key developmental genes appear to have both of these marks, and scientists have hypothesized that this methylation pattern is particularly important in the developing embryo, when genes must turn on and off at precise times in particular cell types to ensure proper development.

"As development proceeds, cells become committed to a specific fate by removing either the repressive or the activating marks, resulting in either activation of gene expression or long-term repression," says Lifton, also a Howard Hughes Medical Institute investigator. "It appears that subtle alteration in the dosage of these histone modifications—either increasing or decreasing methylation—can perturb development. This is particularly interesting because it raises the possibility that environmental perturbations might produce the same outcome in the absence of a mutation."

CHD is only the second disease for which a large search for *de novo* mutations has been performed. In 2012, Yale researchers studying autism also found a role for *de novo* mutations, and the most frequently mutated gene in autism plays a role the same methylation pathway. These findings suggest a broad role of this pathway in the development of the heart and brain, and possibly other organs. The next steps in understanding the process, the scientists say, will be uncovering which genes show altered expression as a consequence of changes in histone methylation.

TERRY DAGRADI

(From left) Richard Lifton, Samir Zaidi, and Martina Brueckner are part of a team who analyzed hundreds of genomes in their quest to determine the influence of genetic mutations on congenital heart disease.

The team plans to follow up on the genes pinpointed in the study, both those affecting the methylation pathway and those associated with other cellular functions. And since *de novo* mutations only explain roughly one in 10 cases of CHD, they're still on the hunt for other causes. "The long-term goal," Brueckner says, "is to be able to understand these congenital abnormalities well enough that we can tailor medical and surgical care specifically to each individual patient, leading to the best lifetime outcome for the growing population of individuals living with congenital heart disease."

Pulse

TERRY DAGRADI

One of the distinguishing features of the "Yale System" of medical education is the requirement that each student write a thesis—a requirement that dates back to 1839. At Student Research Day, held each spring, medical students present the results of their thesis research to members of the School of Medicine community. Pictured above are Songprod Jonathan Lorgunpai '15 (right) and James D. Jamieson, M.D., PH.D., professor of cell biology and director of the M.D./PH.D. Program. Lorgunpai is investigating therapeutic competition in older adults, or situations in which older adults with multiple chronic conditions are prescribed medications that may benefit one condition while adversely affecting a coexisting condition.

Grants and contracts awarded to Yale School of Medicine

March 2012–June 2012

Federal

Achyuta Adhvaryu, NIH, *The Intra-Household Distribution of Food and Health Resources Amongst Children*, 5 years, $652,175 • **Ather Ali**, NIH, *MBSR for Fibromyalgia: A Dose-Finding Study*, 5 years, $670,529 • **Frederick Altice**, NIH, *Expanding Medication-Assisted Therapies in Ukraine*, 5 years, $2,778,068 • **Peter Aronson**, NIH, *Roles of* SLC26A6 *in Renal NaCl Transport and Prevention of Oxalate Urolithiasis*, 5.1 years, $2,803,831 • **Anton Bennett**, NIH, *Signaling by Gain-of-Function* Shp-2 *Mutants in Noonan Syndrome*, 3.8 years, $1,429,694 **Thomas Biederer**, NIH, *Defining Roles of Synapse-Organizing SynCAM Molecules in Drug Addiction*, 2 years, $415,521 • **Linda Bockenstedt**, NIH, *A New Cytokine-Based Immunoassay for the Diagnosis of Lyme Borreliosis*, 2.2 years, $465,656 • **Titus Boggon**, NIH, *Structure-Directed Investigations into the Regulation of Ste20 Kinases*, 3.8 years, $1,232,602 • **Nicholas Carnevale**, NSF, *Collaborative Research: ABI Development: Building a Community Resource for Neuroscientists*, 3 years, $99,317 • **Nancy Carrasco**, NIH, *Molecular Characterization of the Sodium/Iodide Symporter (NIS)*, 1.9 years, $182,463 • **Kathleen Carroll**, NIH, *Computer-Based Training in CBT for Spanish-Speaking Substance Users*, 5 years, $2,217,591 • **Brenda Cartmel**, NIH, *Effect of Exercise on Cortisol Dysregulation in Ovarian Cancer Survivors*, 2 years, $120,373 • **Michael Centrella**, NIH, *Regulators of Osteoblast Protein Synthesis Initiation*, 2 years, $315,613 • **Bo Chen**, NIH, *HDAC4-Mediated Photoreceptor Protection in Retinal Degeneration*, 5 years, $2,079,583 **Murim Choi**, NIH, *Discovery of Rare Genomic Variants Affecting Blood Pressure Phenotype in Humans*, 9 months, $133,110 • **Kelly Cosgrove**, NIH, *Imaging Genetics in Tobacco Smokers*, 1 year, $634,110 • **Joseph Craft**, NIH, *A Novel B Cell Marker And Therapeutic Target In Lupus*, 2 years, $392,386 • **Peter Cresswell**, NIH, *Quality Control of MHC Class I Restricted Antigen Processing*, 4 years, $1,616,732 • **Robin de Graaf**, NIH, *Acquisition of a 500-MHz NMR System for Metabolic Studies*, 1 year, $893,000; NIH, *Multi-Coil Shimming of the Human Brain at 7 Tesla*, 4 years, $1,447,409 • **Madhav Dhodapkar**, NIH, *Anti-tumor Immunity in Myeloma*, 5 years, $1,438,868 • **Maria Diuk-Wasser**, NIH, *Babesiosis Emergence in the United States*, 4.2 years, $1,782,202 • **Deepak D'Souza**, NIH, *FAAH-Inhibitor for Cannabis Dependence*, 3 years, $1,625,128; NIH, *Imaging Brain Cannabinoid Receptors in Schizophrenia*, 2 years, $372,488 • **Myun Hwa Dunlop**, NIH, *Live Cell Imaging of Rapidly Induced Golgi Unstacking and its Effects on Intra-Golgi Trafficking*, 2 years, $101,404 • **Jason Fletcher**, NIH, *Examining the Sources and Implication of Genetic Homophily in Social Networks*, 2 years, $458,376 • **John Forrest**, NIH, *Short-Term Research Training: Students in Health Professionals Schools*, 5 years, $1,114,665 • **William Gaines**, NIH, *Role of the Shu Complex in Homology-directed Chromosome Repair*, 3 years, $155,346 • **Kathryn Gardner**, NIH, *Investigating Rb/E2F Control Over Gene Expression During Germline Differentiation*, 3 years, $155,346 • **Murat Günel**, NIH, *Molecular Genetic Pathogenesis of Intracranial Aneurysms*, 5 years, $3,489,792 • **David Hafler**, NIH, *Yale Clinical Neuroscientist Training Program*, 5 years, $239,224 • **Michelle Hampson**, NIH, *Biofeedback of Activity in the Supplementary Motor Area for Tourette Syndrome*, 5 years, $2,079,896 • **Erica Herzog**, NIH, *Significance of Circulating Semaphorin 7a+ve Cells in Pulmonary Sarcoidosis*, 3 years, $502,017 • **James Howe**, NIH, *Single Channel Properties and Structure of Glutamate Receptors*, 1.2 years, $414,792 • **Manisha Juthani-Mehta**, NIH, *Cranberry Capsules for Prevention of UTI in Nursing Home Residents*, 4 years, $2,557,617 • **Trace Kershaw**, NIH, *Using Cell Phones to Understand Social Networks of Young Men*, 2 years, $457,011 • **Hochang Lee**, NIH, *Intracranial Atherosclerosis and Predictors of Post-CABG Depression*, 3 years, $1,596,021 • **Shan Liu**, NIH, *Using Adenoviral Vectors to Express Broadly Neutralizing Anti-gp160 Antibodies*, 2 years, $84,464 • **Shuangge Ma**, NIH, *Robust Rank-based Methods and Detection of GxE in Cancer Etiology and Survival*, 3 years, $344,397 **Robert Malison**, NIH, *Validation of a Remote Wireless Sensor Network (WSN) Approach to the Individualized Detection of Cocaine Use in Humans*, 2 years, $691,492 • **Heather Marshall**, NIH, *Mechanisms of CD4 T Cell Memory Development During Viral and Bacterial Infections*, 2 years, $106,132 • **David McCormick**, NIH, *Neurotransmitter Actions in Neocortex and Thalamus*, 5 years, $1,934,852 • **Eric Meffre**, NIH, *Impact of Regulatory T Cells on Human Peripheral B Cell Tolerance*, 2 years, $412,811 **Wang Min**, NIH, *Stress Signaling Pathways Linking Endothelial Injury to Graft Arteriosclerosis*, 4 years, $1,621,593 • **Gil Mor**, NIH, *Discovery to Cure Summer Program*, 5 years, $491,613 **Walther Mothes**, NIH, *Monitoring Single Conformational Events During HIV Assembly*, 2 years, $431,154 • **Michael Nathanson**, NIH, *Trafficking of the EGF Receptor to the Nucleus: Mechanisms and Effects*, 2.7 years, $196,895 **Hengyao Niu**, NIH, *Mechanisms and Crosstalk of DNA Break Resection Pathways*, 2 years, $180,000 • **Stephanie O'Malley**, NIH, *1/2-Multi-site Study: Varenicline Treatment of Alcohol Dependent Smokers*, 4 years, $2,107,866 • **Chirag Parikh**, NIH, *Mentoring Program for Translational and Patient Oriented Research in AKI*, 4.9 years, $895,878; NIH, *Novel Biomarkers in Cardiac Surgery to Detect Acute Kidney Injury*, 4 years, $3,002,979 **Jordan Pober**, NIH, *Proteins of the Endothelial Cell Surface*, 4 years, $1,864,914 • **Karin Reinisch**, NIH, *Regulatory Mechanisms in Membrane Trafficking*, 4 years, $1,369,604 • **James Rothman**, NIH, *Cortical ER Biogenesis in Mammalian Cells*, 4 years, $1,330,672 • **Douglas Rothman**, NIH, *Console for 4T Human MR System*, 1 year, $599,195 • **David Schatz**, NIH, *Immunoglobulin and T Cell Receptor Gene Assembly*, 5 years, $1,871,812 • **Patrick Skosnik**, NIH, *CB1 Mediation of Cerebellum Versus Forebrain-Dependent Associative Learning*, 2 years, $353,430 • **Brian Smith**, NIH, *Immunohematology/Transfusion Medicine Research Training*, 5 years, $2,111,503 • **Stephen Strittmatter**, NIH, *Cortical Plasticity During Recovery from Spinal Cord Injury*, 5 years, $1,819,636; NIH, *Functional Genomics of Axonal and Synapse Regeneration*, 1 year, $324,639 • **Scott Strobel**, NIH, *Mechanisms of Ribosomal Reactions: Peptide Bond Formation, Peptide Release and MRNA Cleavage*, 3.8 years, $1,260,422 • **Denis Sukhodolsky**, NIH, *EEG Coherence in Children with TS: Association with ADHD and Tic Severity*, 2 years, $157,807 • **Zhaoxia Sun**, NIH, *Investigate Kidney Cyst Formation and a CiliaMediated Signaling Network*, 4 years, $1,447,282 **Joann Sweasy**, NIH, *Base Excision Repair and Autoimmunity*, 2 years, $456,665 • **Edwin Thrower**, NIH, *The Role of Cigarette Smoke Toxin and Alcohol in Pancreatitis*, 2 years, $332,732 • **Anthony Van den Pol**, NIH, *Vesicular Stomatitis vsvrp30 Selectively Destroys Human Metastatic Melanoma*, 5 years, $1,536,008 **Chen Wang**, NIH, *Modulation of Endothelial Cell Allo-Immunogenicity by Rapamycin*, 2 years, $94,464 • **Emily Wang**, NIH, *The Impact of Incarceration and Substance Abuse on HIV-Infected Veterans*, 2 years, $332,416 **Joanne Weidhaas**, NIH, *MicroRNAs to Understand Cause and Outcome in Breast Cancer*, 5.1 years, $1,726,315 • **Li Wen**, NIH, *Role of TLR9 in Beta Cell Function and Diabetes*, 4.9 years, $1,790,768 • **Tian Xu**, NIH, *Mechanism of Cell-Cell Interaction in Tumor Growth and Metastasis in Flies*, 4.8 years, $1,344,700; Department of Defense, *A Genetic Interaction Screen for Breast Cancer Progression Driver Genes*, 2 years, $831,061 • **Heping Zhang**, NIH, *Analysis of Genomic Data for Complex Traits*, 5 years, $1,443,046 • **Z. Jimmy Zhou**, NIH, *Visual Science Training Grant*, 5 years, $744,488

Non-federal

Vikki Abrahams, March of Dimes, *Understanding, Predicting and Preventing Adverse Pregnancy Outcomes in Women with Anti-phospholipid Antibodies*, 3 years, $200,000 **Hilary Blumberg**, International Bipolar Foundation, *Development of Bipolar Disorder in Adolescence*, 1 month, $29,400 • **Michael Bracken**, Wayne State University (NIH), *PREGNANT Trial Re-Analysis and Review*, 7 months, $60,813 • **Susan Busch**, Johns Hopkins Bloomberg School of Public Health (NIH), *Implementation of Federal Mental Health Parity*, 2 years, $207,898 • **Alexandra Byrne**, Christopher and Dana Reeve Foundation, *Identification of Intrinsic Regulators of Neuronal Regeneration*, 1.1 years, $25,000 • **Richard Carson**, Bristol-Myers Squibb Company, *Exhibit A-1-Proj Plan for Proj 2*, 2 years, $379,462 • **Andrew Dewan**, Brown University (NIH), *Fetal Genetic Contributions to Preeclampsia*, 2 years, $159,325 **John Geibel**, Elsa U. Pardee Foundation, *A Novel Apoptosis-Inducing Therapy Targeted to Mitochondria in Cancer Cells*, 1 year, $131,050 **Antonio Giraldez**, March of Dimes, *The Role of microRNAs During Vertebrate Development*, 3 years, $334,313 • **David Glahn**, The Mind Research Network (NIH), *Mining the Genome-wide Scan: Genetic and Structural Imaging Covariation in Schizophrenia*, 5 years, $302,429 **David Hafler**, Questcor Pharmaceuticals Inc., *Understanding the Effects of ACTH on CD4+ T-Cell Function in Multiple Sclerosis Patients*, 2 years, $285,324 • **Mihaly Hajos**, Cure Huntington's Disease Institute Foundation, *Auditory Gating Mechanisms in Transgenic Animal Models of Huntington's Disease: Application to Translational Research and Therapeutic Evaluation of Phosphodiesterase 9 Inhibitor CHDI-00396436*, 1 year, $231,990 • **Nathan Hansen**, Columbia University (NIH), *Efficacy Trial of a Brief Health Enhancement Intervention for Newly Diagnosed Men*, 1.2 years, $73,794 **Kevan Herold**, University of Michigan, *Innovative Studies to Dissect the Pathoetiology of Long Term Type 1 Diabetes Mellitus with Residual Beta Cell Function*, 7 months, $44,543; Juvenile Diabetes Research Foundation International, *Studies of Patients with Long-Standing Type 1 Diabetes and Residual Insulin Production*, 5 years, $77,000 • **Erica Herzog**, Sanofi U.S., *Role of Bi-Specific IL4 and IL13 Blockade and Macrophages in IPF*, 1.5 years, $400,000 **Yiyun Huang**, New York University School of Medicine (NIH), *CB1 Receptor Imaging in Anorexia Nervosa*, 2 years, $150,503; New York University School of Medicine (NIH), *Kappa Opioid Receptor Imaging in PTSD*, 2 years, $235,375 • **Leonard Kaczmarek**, FRAXA Research Foundation, *Potassium Channel Modulators for the Treatment of Fragile X*, 2 years, $134,000 • **Anil Karihaloo**, Epigen Biosciences, Inc. (NIH), *The Synthesis of Novel Selective LPA-1 Receptor Antagonists for Evaluation of an Animal Model of Renal Fibrosis*, 1.5 years, $123,143 • **Mark Kidd**, University of Verona, *G15 Expression in Gastroenteropancreatic Neuroendocrine Tumors: Functional Analysis and Signaling Pathway*, 1 year, $6,500 **Albert Ko**, University of California, Berkeley (NIH), *Global Health Fellows and Scholars Program*, 4.9 years, $336,687 • **John Leventhal**, Children's Memorial Hospital (NIH), *Clinical Decision Rules to Discriminate Bruising Caused by Physical Child Abuse*, 2 years, $23,584 • **Joseph Madri**, Case Western Reserve University (NIH), *Clinically Translatable Nanotechnology: Hemostasis and Neuroprotection*, 1 year, $51,191 • **Mark Mamula**, Juvenile Diabetes Research Foundation International, *Protein Modifications in the Development of Type I Diabetes*, 2 years, $199,871 **Mark Michalski**, Society of Interventional Radiology Foundation, *Real-Time Hepatic Vessel Mapping for Interventional Procedures using a Hierarchical Learning Computer Vision Architecture*, 8 months, $5,000 • **Wang Min**, Gilead Sciences, *Gilead-Yale Collaborative Research on ASK1 Inhibitors*, 2 years, $386,613 • **Pramod Mistry**, Genzyme Corporation, *Biomarkers in Gaucher Disease*, 1.7 years, $115,496 • **Marcella Nunez-Smith**, American Medical Association Foundation, *Joan F. Giambalvo Memorial Scholarship*, 1 year, $5,000 • **Elaine O'Keefe**, State of Conn. Dept. of Public Health, *Quality Improvement Training for Local Public Health System Partners*, 6.9 months, $42,748 **Marina Picciotto**, Klarman Family Foundation, *Acetylcholine: A Novel Regulator of Circuits Involved in Food Intake and Eating Disorders*, 2 years, $400,000 • **Christopher Pittenger**, Massachusetts General Hospital, *A Translational Model of Autoimmune Neuropsychiatric Illness*, 2 years, $200,000 • **Katerina Politi**, Vanderbilt University (NIH), *Overcoming Acquired Resistance to EGFR Inhibitors in Lung Cancer*, 11 months, $66,197 • **Marc Potenza**, University of Connecticut Health Center (NIH), *Neuroimaging of Adolescents in Treatment for Cannabis Use Disorder*, 1 year, $8,616 **Peter Rabinowitz**, National Pork Board, *Determining Viral Load and Persistence of Influenza A in Aerosols and on Surfaces in Swine Production Facilities*, 1 year, $101,105; Schmidt Family Foundation, *Animal and Human Sentinels for Natural Gas Extraction Hazards*, 1 year, $100,000 • **Michael Robek**, Tangdu Hospital, *Interleukin-7 in HBV Replication and Therapy*, 1 year, $49,417 • **Marc Rosen**, University of California, Los Angeles (NIH), *Centralized Off-Site Adherence Enhancement Program (CARE)*, 1.2 years, $173,256 • **Gerard Sanacora**, Massachusetts General Hospital (NIH), *Rapidly Acting Treatments for Treatment-Resistant Depression (RAPID)*, 2.3 years, $202,037 • **Frederick Shic**, Hand Hold Adaptive, *Handheld Technology for Speech Development in Students with Autism Spectrum Disorders*, 7 months, $49,672 • **Anne Song**, Lupus Foundation of America, Inc., *Competition Between TLR7 and TLR9 for UNC93B in a Murine Model of Lupus*, 3 months, $4,000 • **Serena Spudich**, Brigham and Women's Hospital (NIH), *AIDS Clinical Trials Group Leadership and Operations Center*, 1 year, $58,198 • **Derek Steinbacher**, KLS Martin L.P., *Pharmacological Inhibition of FGFR2 Prevents Premature Suture Closure in a Mouse Model of Crouzon Syndrome*, 1 year, $15,000 • **Richard Taylor**, American Institute of Ultrasound in Medicine, *A Prospective Study on Point-of-Care Focused Cardiac Ultrasound in Assessing for Thoracic Aortic Dimensions, Dilation, and Aneurysm in Correlation with CT Angiogram in Suspected Cases of Pathology*, 2 years, $9,998 • **Nicholas Theodosakis**, Joanna M. Nicolay Melanoma Foundation, Inc., *Determination of the Mechanisms of Melanoma Metastasis*, 1 year, $10,000 • **Abdou Thiam**, National Center for Scientific Research (France), *Direct Imaging of Budding and Fusion of Lipid Droplets Mediated by Proteins in Emulsion Droplets Based on Microfluidics—Dynamics of Protein Interactions, Assembly and Metabolism Energy*, 2 years, $102,988 **Benjamin Toll**, Duke University (NIH), *Effects of Message Framing on Cessation among Couples Where Both Partners Smoke*, 2 years, $24,927 • **Federico Vaca**, State of Conn. Dept. of Transportation, *Mapping Alcohol Problems and Statistics in Crashes (MAPS-C)*, 7 months, $229,120 • **Anthony Van den Pol**, University of Utah (NIH), *Ivermectin-Activated Human Glycine Receptor Attenuated Epilepsy*, 1 year, $136,373 • **Christopher Wendler**, University of Florida (NIH), *Graves' Disease Therapy Risks to Mother and Fetus*, 1.2 years, $195,205

// Brain *(from page 1)* optical detectors, the scientists could precisely measure electrical signals in complex neural circuits in a living fruit fly.

"Electrical signals are the language the nervous system uses to transmit information," says Vincent A. Pieribone, PH.D., professor of cellular and molecular physiology and of neurobiology and an author of the new paper. "Now we can look at this electrical information optically and non-invasively."

Achieving the ultimate goals of BRAIN, "to better understand how [humans] think, learn, and remember" and to apply these insights to neurological and psychiatric disease, will first require a deep understanding of simpler nervous systems—those of worms, flies, zebrafish, or mice, for instance—and alternatives to the electrode, the neurophysiologist's staple tool of the past half-century. Recording electrodes "always cause damage, and are rejected by the brain," Pieribone says, and in living systems there are physical limits that constrain the number and proper placement of electrodes.

Other researchers have recently reported successes in the optical measurement of neural activity in zebrafish. But co-author Michael N. Nitabach, PH.D., J.D., associate professor of cellular and molecular physiology and of genetics, says that the method used by these scientists, which tracks calcium levels in neurons, provides only an indirect measure of electrical activity, while the tools developed at Yale provide a precise, direct measure.

Pieribone's specialty is collecting fluorescent proteins where they occur naturally, such as in deep sea tropical fish. When expressed in neurons as so-called genetically encoded fluorescence voltage indicator proteins (GEVIs), these proteins can serve as visual indicators of electrical activity. Pieribone and other neuroscientists have been engineering GEVIs for the past 15 years, but they have all turned out to be duds when moved from cell culture to the brains of living animals. "None of them have had sufficient signal size" to be useful, says Nitabach, also a faculty affiliate of the Program in Cellular Neuroscience, Neurodegeneration and Repair.

The GEVI described in the *Cell* paper, dubbed ArcLight, has a fortuitous mutation that "showed up by accident, like divine intervention," says Pieribone. This genetic alteration gives ArcLight a strong and exquisitely sensitive fluorescence signal that directly reflects the membrane voltage of the neuron in which it is expressed: it gets dimmer as the voltage rises, and brighter when the voltage diminishes.

Genetically engineering a brain that glows in response to voltage changes may seem innovative enough on its own, but Pieribone knew that ArcLight would only be useful if it reflects brain activity as well as recording electrodes, the gold standard in neuroscience research. To this end, Pieribone collaborated with Nitabach, an expert on the nervous system of the fruit fly *Drosophila melanogaster*.

Having screened hundreds of fluorescing constructs over the years, Pieribone was stunned when he and Nitabach performed their initial experiments. "The first time we recorded ArcLight in *Drosophila* I thought there must be something wrong with the traces, because they looked too good," says Pieribone. "You seldom get those kinds of surprises where things work better than imagined."

Nitabach and Pieribone decided to express ArcLight in a group of neurons that are well-characterized and known to regulate the fly's circadian clock. In simultaneous electrode recordings and optical imaging of fluorescing neurons, they showed that results from ArcLight are consistent with those using wires to poke nerve cells. As a bonus, they showed for the first time something that had been suspected in the field but not proven, that the membranes of these cells are more active in the morning than in the evening. "This can't be recorded any other way," says Nitabach. "It's like opening uncharted territory."

The ArcLight signal is faster than calcium detectors, and there are subtle electrical events that are significant for neural processing that calcium-based methods, and even electrodes, miss entirely, says Nitabach. Action potentials, the Morse code of neurons seen as spiking voltage changes on recordings, are important, he says, but non-spiking signal propagation along neural branches and the synaptic input to neurons that doesn't reach the threshold to generate an action potential each comprise a little-understood but fundamental part of the neural calculus. These small voltage fluctuations are undetected when the signal of interest is the binary "spike-or-silence" from the neuron's cell body, the only part of a neuron accessible with an electrode.

ArcLight allows imaging of discrete parts of neurons, a key to understanding this hidden neural computation. "A lot of the information processing and electrical integration is happening in distal parts of the cell that you can't put an electrode on," says Nitabach. "With ArcLight you can measure membrane voltage directly at those otherwise inaccessible locations." The neural volume that can be studied with optical imaging compared with electrodes is also expanded, because light can penetrate deeper into brain tissue without damaging it.

"Seeing electrical activity in the brain directly is a long-standing dream that now seems tangible," says Gero A. Miesenböck, M.D., director of the Center for Neuronal Circuits and Behavior at the University of Oxford and a former associate professor of cell biology at the School of Medicine. While at Yale, Miesenböck pioneered optogenetics, the use of light to control behavior via genetically encoded photosensitive components in neurons. What Pieribone, Nitabach, and colleagues have done is the flip side of optogenetics, using light, or fluorescence, to visualize neural activity, which Miesenböck calls "an important milestone."

Vincent Pieribone

While ArcLight is the most favorable GEVI available at the moment, says Miesenböck, a big challenge still remains in improving optical instrumentation for even better localization of neural signals in both space and time.

Pieribone envisions the two strands of optogenetics coming together in a way that would allow simultaneous optical control and recording of the nervous system. This dovetails well with the ultimate goal of the BRAIN initiative, creating a full circuit diagram of the brain.

"Right now we have lots of snapshots, but we don't know how the nervous system processes things from start to finish," Pieribone says. An understanding of the whole loop, from sensing to action, in flies or worms is required before the same questions can even be broached for human brains.

Progress on this front should now accelerate considerably, as ArcLight flies have been distributed to numerous labs and the genetic construct is freely available online. Both Pieribone and Lawrence B. Cohen, PH.D., professor of cellular and molecular physiology, are poised to release results using ArcLight in the mouse brain. "The mutation of ArcLight turned out to be a big hit," says Pieribone. "I feel this represents a revolution in the way we're studying the brain."

// President *(from page 1)* disease prevention for inner-city populations, and is a member of Yale Cancer Center. He was also critical in helping to develop the National Institutes of Health–funded Yale Center for Interdisciplinary Research on AIDS (CIRA). As provost, Salovey has worked with Alpern and with Carolyn W. Slayman, PH.D., deputy dean for academic and scientific affairs, Sterling Professor of Genetics, and professor of cellular and molecular physiology, to review potential faculty slots, as well as settling administrative questions at the medical school.

"He's got a structure in his mind about how the medical school is organized, how it works, and what our priorities are," says Slayman. "That fund of knowledge will get us off to a quick start in working with him in his new role." In addition, she says, "I'm impressed at his ability to listen to a complicated set of issues, really pay attention to what people are saying, and synthesize an approach that can allow people to arrive at consensus."

Salovey is also a popular educator who has mentored numerous graduate students and taught introductory psychology for decades. On the national stage, Salovey has held prominent national leadership positions, serving on panels and working groups with the National Institute of Mental Health and the National Science Foundation.

Salovey has said he would like to focus on entrepreneurial opportunities and economic development, as exemplified by Yale's Science Park and by West Campus, in Orange, Conn. Collaboration is also a priority: in his acceptance speech, Salovey said he hopes to make Yale "more unified . . . innovative . . . accessible . . . and excellent." As he said in an interview with *Yale Alumni Magazine*, "By 'unified,' I mean interconnected or interdependent. When departments, programs, and schools collaborate, the whole becomes greater than the sum of the parts."

Slayman points out that Yale's compact geography eases the way for cross-campus collaboration—as with the Department of Biomedical Engineering, a young and highly innovative department staffed by both the medical school and the School of Engineering and Applied Science. "Peter, of course, has helped to foster this," she says. "I think he will continue to help us build joint programs with other parts of Yale. Who knows what it'll be next?"

Alpern says that "there's every reason to believe Peter's going to be a fantastic president. We will miss Rick Levin, because Rick has been so terrific for the medical school. But I think Peter is just going to continue that."

Awards & Honors

Stephanie C. Eisenbarth, M.D., PH.D., assistant professor of laboratory medicine and immunology, has received the Individual Biomedical Research Award from the Hartwell Foundation. As a Hartwell Investigator, Eisenbarth will receive $100,000 per year for three years to support her research on allergen tolerance in children with asthma.

Bo Chen, PHARM.D., PH.D., (left), assistant professor of ophthalmology and visual science and of neurobiology, and **Andrew Goodman**, PH.D., (right), assistant professor of microbial pathogenesis, have been named 2013 Pew Scholars in the Biomedical Sciences. Chen and Goodman are among 22 recipients selected from 134 nominees from major research institutions. Chen, who is developing gene delivery techniques to generate new retinal cells, will use his award to continue his research on degenerative retinal diseases. Goodman studies how the body's resident bacteria affect human health and drug metabolism.

Innovator in immune therapies for cancer named United Technologies Corp. professor

Lieping Chen, M.D., PH.D., professor of immunobiology, dermatology, and medicine, has been appointed the United Technologies Corporation Professor in Cancer Research. Also director of the cancer immunology program at Yale Cancer Center, Chen focuses his research on developing new immunotherapeutic treatment options for cancer. His laboratory was the first to apply costimulation as a means for cancer therapy and, working more than a decade, discovered the B7-H1/PD-1 immune inhibitory pathway and established the principle of cancer therapy by blocking this pathway.

Chen earned his medical degree at Fujian Medical University in China, his M.S. at Beijing Union Medical College in Beijing, China, and his PH.D. at Drexel University College of Medicine. Prior to his arrival at the School of Medicine in 2010, he was a research scientist at Bristol-Myers Squibb Co. and served on the faculty at the Mayo Clinic in Rochester, Minn., and the Johns Hopkins University School of Medicine.


Lieping Chen

Chen's honors and awards include a Presidential Award from Bristol-Myers Squibb, a Clinical Investigator Award from Cancer Research Institute-New York, and the Milton Fromer Memorial Lectureship in the Case Western Reserve University. He was an American Cancer Society Research Scholar, and keynote speaker at the International Society for Biological Therapy of Cancer and the Congress of the Spanish Society of Immunology.

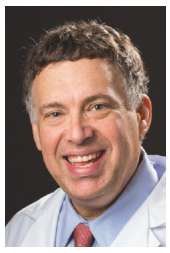
The professorship was established earlier this year with a $3 million gift from Hartford, Conn.-based United Technologies Corporation (UTC), a multinational manufacturer.

Leader in personalized lung cancer therapy named Ensign Professor of Medical Oncology

Roy S. Herbst, M.D., PH.D., a nationally recognized leader in lung cancer treatment and research, has been named the Ensign Professor of Medical Oncology. Herbst joined the School of Medicine in 2011 as professor of medicine, associate director for translational research at Yale Cancer Center, and chief of medical oncology at Smilow Cancer Hospital at Yale-New Haven. Prior to his appointment at Yale, Herbst was the Barnhart Distinguished Professor and chief of the Section of Thoracic Medical Oncology at MD Anderson Cancer Center at the University of Texas in Houston.

Herbst is best known for his work in developmental therapeutics and personalized therapy for non-small cell lung cancer (NSCLC). Over the last decade, he has spearheaded translational studies of many anticancer drugs.

He is a major proponent of personalized therapy for NSCLC. As co-principal investigator of the Biomarker-Based


Roy Herbst

Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE-1) trial, he made significant advances in personalized therapy for NSCLC by using molecular analysis of tissue biopsies to determine the most appropriate targeted treatment for each patient in real time. He now leads the BATTLE-2 clinical trial at Yale.

Herbst earned a B.S. and M.S. from Yale University. He received his M.D. from Cornell University Medical College and earned a PH.D. in molecular cell biology from the Rockefeller University. He completed fellowships in medical oncology at Dana-Farber Cancer Institute and in hematology at Brigham and Women's Hospital in Boston, where he also received a M.M.S. from Harvard University.

Boehringer Ingelheim Professor is expert on the genomics of pulmonary diseases

Naftali Kaminski, M.D., an expert on the genomics of lung disease, biomarker discovery, and pulmonary fibrosis, has joined the School of Medicine as Boehringer Ingelheim Pharmaceuticals, Inc. Professor of Medicine and chief of the Section of Pulmonary, Critical Care, and Sleep Medicine.


Naftali Kaminsky

Kaminski's research interests involve applying genomic approaches to elucidate basic mechanisms and improve diagnosis and treatment of idiopathic pulmonary fibrosis, a chronic scarring lung disease, as well as such diseases as severe chronic obstructive pulmonary disease (COPD), severe asthma, and sarcoidosis. Among his group's recent discoveries are the role of microRNAs in lung fibrosis and the identification of novel molecular and genetic biomarkers in pulmonary fibrosis.

Kaminski comes to Yale from the University of Pittsburgh School of Medicine, where he held an endowed chair for pulmonary research and was professor of medicine, pathology, computational biology, and human genetics, and founding director of the Dorothy P. and Richard P. Simmons Center for Interstitial Lung Disease.

Kaminski received his medical degree from the Hebrew University–Hadassah Medical School in Jerusalem, Israel. He completed his residency at the Hadassah Mount Scopus University Hospital in Jerusalem, and his pulmonary fellowship at Sheba Medical Center in Israel. He completed a postdoctoral fellowship at the Lung Biology Center in the Cardiovascular Research Institute at the University of California–San Francisco.

Malone Professor studies vital cell signaling pathways and how they go awry in disease

Andre Levchenko, PH.D., a leading researcher in intracellular signal transduction and cell-to-cell communication, has joined the School of Medicine and Yale's School of Engineering and Applied Science (SEAS) as John C. Malone Professor of Biomedical Engineering.


Andre Levchenko

Levchenko combines molecular biology, microfabrication, and imaging techniques with state-of-the-art modeling to investigate how living cells sense their environments and communicate with other cells. Specifically, he focuses on signal transduction pathways that have been implicated in vital cellular functions such as the cell cycle, locomotion, and cell death, and their role in pathologies including cancer and AIDS.

Levchenko comes to Yale from The Johns Hopkins University, where he was associate professor of biomedical engineering.

He holds an M.S. in biophysics from Moscow Institute of Physics and Technology, and an M.S. and doctorate in bioengineering from Columbia University.

He completed a postdoctoral fellowship in biology at the California Institute of Technology.

The Malone Professorship was established in 2011 by John C. Malone, a 1963 graduate of Yale College. Malone's commitment of $50 million established 10 senior professorships in SEAS; the Department of Biomedical Engineering is co-administered by SEAS and the School of Medicine. Levchenko is the second professor to be appointed to a Malone chair, joining Jay Humphrey, PH.D., who was named John C. Malone Professor of Biomedical Engineering in 2012.

// Award *(from page 1)* system molecules known as toll-like receptors (TLRs) in sensing microbial infections, as well as how TLR signaling activates inflammation and adaptive immunity.

The award, which includes a cash prize of €4 million—€3.5 million for Medzhitov's research, and a €500,000 personal award—was presented by Germany's Federal Minister of Education and Research, Johanna Wanka, PH.D., in a ceremony at the German Historical Museum in Berlin. In accepting the prize, Medzhitov said, "I am very grateful to the Else Kröner-Fresenius-Foundation and its scientific jury for this amazing award. It is a huge honor and privilege to be recognized this way. This award is particularly meaningful because it provides a generous support for future studies."

The award commemorates the 25th anniversary of the death of Else Kröner, who led the growth of a small pharmacy and associated business into a global medical company, the Fresenius Group, which employs more than 100,000 people in over 100 countries, and has annual sales of over €10 billion.

Kröner, who supported young scientists and was interested in novel research into the origin and development of disease, established the EKFF in 1983, dedicating it to the support of medical research and humanitarian medical work in developing countries. To date, the foundation has provided funding of approximately €150 million for more than a thousand projects.

"The Else Kröner-Fresenius-Foundation is very pleased and proud to announce Dr. Ruslan Medzhitov as the award winner. Both his past contributions as well as his very exciting future research ideas make him an ideal candidate," said Susanne Schultz-Hector, M.D., PH.D., a physician-scientist and member of the foundation board.

The EKFF's new award in immunology recognizes the field's increasingly prominent role in contemporary biomedicine. "Immunology is not only essential for understanding infectious diseases or allergies, it is also involved in autoimmune diseases such as rheumatoid arthritis, cardiovascular diseases, and cancer," Schultz-Hector said. "It is a particularly fast-moving field of research, promising important breakthroughs in the near future."

Medzhitov has received numerous honors for his large body of work. Earlier this year, he was awarded the inaugural Lurie Prize in the Biomedical Sciences from the Foundation for the National Institutes of Health, and along with Richard A. Flavell, PH.D., chair and Sterling Professor of Immunobiology and HHMI investigator, he was co-recipient of the 2013 Vilcek Prize for Biomedical Science.

In addition, Medzhitov was one of three scientists awarded the Shaw Prize in Life Science and Medicine for 2011, and he won the 2010 Lewis S. Rosenstiel Award for Distinguished Work in Basic Medical Research. Also in 2010, Medzhitov was elected to the National Academy of Sciences, the elite corps of researchers from the nation's top scientific institutions. In 2007, he received a Blavatnik Award for Young Scientists, given by the Blavatnik Family Foundation, for his contributions in elucidating the role of the innate immune system.