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 50 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 emotion and health-related behavior, is a highly productive scholar of human epidemiology and Public Health, and chair of the School of Management, is a fellow of the American Association for the Advancement of Science, and is a member of the American Academy of Arts and Sciences.

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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 system.

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’

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 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 electrical activity within the cells.

As director of the Yale Stress Center, Rajita Sinha balances a passion for research with a desire to improve patients’ lives.

Starting up a lab today means competing for scarce resources, but new funding avenues provide some relief.

A Yale-led team of scientists unravels the role of non-inherited genetic mutations in congenital heart defects.

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LIFELINES

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 multi-disciplinary collaboration among various specialists, says Daniel Pelleiter, 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 Pelleiter. “This is the infrastructure we’ve been waiting for to build a complete MS team.”

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 whom, 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 1,108 physicians.

“Yale physicians are simply world-class,” says Paul Tahteri, 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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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, Margaret King, Ph.D., a co-investigator 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 ‘product’ is 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 targeted for young scientists in the first stages of their careers. While these funding avenues are not 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 support their work with a gift of $500,000 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 a $1 million over three years to help establish her lab.

Yale study in the July issue of American Journal of Human Genetics 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 a $1 million over three years to help establish her lab. Goodman was named the McCluskey Scholar in 2011, an honor that helped him get his lab off the ground in its earliest days.

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 as young as age 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 KIAA1293. In a new study, published on July 1 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 the age of 7, 75 percent will be reading at grade level even two years after completing it. Testing for both DCDC2 and KIAA1293 variants could identify the children who would benefit most from intervention.”

Support tomorrow’s cures

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. 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 researchers, and, by design, the application doesn’t require the volume of preliminary data that the traditional grant system demands. 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 RO1 awards going to new investigators.

“It is an incredible collection of grants that can give young, established investigators an edge,” says Jesse Rinehart, Ph.D., assistant professor of cellular and molecular physiology, and founder of her lab with the help of grants from the Alfred 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., and administrator of the program, which is matched by NIH, Yale established a named $1 million fund that provides $1 million in startup funds over four years to a promising new tenure-track investigator. Donald S. McCluskey, M.E.N.G., 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 becoming 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 ROI—and the expectation was that within five years you’ll get a second ROI,” King says. “Now the renewal rate is 48 percent of NIH’s (NIH) sought-after renewal grants. ‘That’s no longer really feasible.’” The statistics bear her out: in 2001, the renewal rate for RO1 was 51 percent, but in 2012, it was 33 percent.

For scientists of all ages submitting proposals for new RO1 prospects are an even grimmer. In 2001, the NIH funded 25 percent of new RO1 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 RO1s to fund a lab, according to Goodman. And virtually all RO1 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

A helping hand for tomorrow’s scientists

Imagine the satisfaction of supporting the important work of your favorite researcher, and the pride you’ll feel knowing that your generosity will alter the future of medical science?

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.”

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 the age of 7, 75 percent will be reading at grade level even two years after completing it. Testing for both DCDC2 and KIAA1293 variants could identify the children who would benefit most from intervention.”

How did the human hand evolve? A Yale study in the July 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 ancestral 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.”
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., chair and Sterling Professor 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. Akiko Iwasaki, Ph.D., professor of immunobiology and of molecular, cellular, and developmental biology, Medzhitov, Tita de Lange, Ph.D., Leon Hess Professor at The Rockefeller University, Flavell, and Madlyn Flavell.

April 23–28 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.

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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.

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.

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A clotting disorder’s immune origins

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, Ravita Dhopal, M.B.B.S., 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 interferes (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.

“Typhoid fever strikes people worldwide. Understanding how the disease is caused is 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. A 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 essential for the orderly development of the 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 outcomes 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.

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

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 Songsong Jonathan Lorgunpa ’15 (right) and James D. Jamieson, M.D., Ph.D., professor of cell biology and director of the M.D./Ph.D. Program. Lorgunpa 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.
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 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 cell biology 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. Unlike 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 indicator proteins (GEVIs), these proteins can serve as visual indicators of electrical activity. Pieribone and other neuroscientists have been engineering GEVIIs 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 Neurosci-ence, Neurodegeneration and Repair. The GEVI described in the Cell paper, dubbed ArcLight, has a fortress mutation that “showed up by accident, like divine interven- tion,” 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, but 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 these cells, ArcLight recor-dings 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 thresh-old to generate an action potential each comprise a little-understood but fundamental part of the neural calculus. These small voltage fluctua-tions 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 informa-tion processing and electrical integra-tion 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 inacces-sible locations.” The neural voltage 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 Ox-ford and a former associate professor of cell biology at the School of Medicine. While at Yale, Mie-senböck 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 the optogenetic develop By using light, or fluorescence, to visualize neural activity, which Miesenböck calls “an important milestone.”

While ArcLight is the most favor-able GEVI available at the moment, says Miesenböck, it still remains in improving optical instrumentation for even better local-ization of neural signals in both space and time.

Pieribone envisions the two strands of optogenetics coming together in a way that will 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 numer-ous labs and the genetic construct is freely available online. Both Pieribone and Lawrence B. Cohen, Ph.D., pro-fessor of cellular and molecular physi-ology, 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.”

Vincent Pieribone

**Highlights**

**Achievements**

- Pieribone collaborated with Nitabach to develop ArcLight, a genetically encoded fluorescence indicator protein that allows for direct measurement of neural activity.
- ArcLight allows for simultaneous optical control and recording of the nervous system, providing a full circuit diagram of the brain.
- Progress on using ArcLight continues to accelerate, with the distribution of ArcLight flies to numerous laboratories.

**Implications**

- ArcLight promises to revolutionize the understanding of neural activity.
- The use of ArcLight in combination with optical imaging could provide insights into neurological and psychiatric diseases.
- ArcLight's ability to measure membrane voltage directly at inaccessible locations could advance our understanding of neural physiology.

**Future Directions**

- Further refinement of ArcLight for use in human brains.
- Continued research into the applications of optogenetics for disease treatment and neural circuit mapping.

**Contributions**

- Pieribone and Nitabach's work on ArcLight has implications for a variety of fields, including neurobiology, optogenetics, and neuroscience.
- Their efforts have the potential to revolutionize the way we study the brain and understand neural function.

**Acknowledgments**

- Pieribone acknowledges the contributions of Nitabach and the broader scientific community in advancing the field of optogenetics.
- The work on ArcLight is supported by various grants and collaborations, underscoring the interdisciplinary nature of their research.

**Impact**

- ArcLight has the potential to transform our understanding of neural circuits and their role in disease.
- The development of ArcLight highlights the importance of interdisciplinary collaboration in advancing scientific knowledge.

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**Awards & Honors**

- Stephanie C. Eisenbarth, M.D., Ph.D., assistant professor of cell biology, and Andrew Goodman, Ph.D., right, assistant professor of microbiological pathogenesis, have been named 2013 Pew Scholars in the Biomedical Sciences. Chen and Goodman are among 22 recipients selected from 154 nominees from major research institutions. Chen, who is developing gene delivery techniques to generate new neural circuits, received the award to continue his research on degenerative retinal diseases.
- Goodman studies how the body's resident bacteria affect human health and drug metabolism.

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**President**

- President Salovey has said he hopes to make Yale “more unified…innovative…accessible… and excellent.” As he said in an interview with Yale Magazine, “By unified, I mean interconnected or interdependent. When depart-ments, programs, and schools col-laborate, the whole becomes greater than the sum of the parts.”

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**Medical School**

- Salovey notes that Yale's compact geography eases the way for cross-campus collaboration—as with the Department of Biomedical Engi-neering, 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?"

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**Alpert**

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

Boehringer Ingelheim Professor is expert on the genomics of pulmonary diseases

Lieping Chen, M.D., Ph.D., professor of immunobiology, dermatology, and medicine, has been appointed the United Technologies Corporation Professor in Cancer Research. Also on his faculty of the Translational Medicine 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 method 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. 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.

Badger's new award in immunobiology

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

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 came 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.

Kaminski’s research focuses are the role of microRNAs in lung pathobiology, with a specific interest in regulatory roles in pulmonary fibrosis. The research involves developing clinical diagnostics to monitor disease severity and therapeutic response, as well as developing new therapeutic approaches.

Kaminski comes to Yale from the University of Pittsburgh, where he was founding director of the Program in Systems Biology and associate professor of medicine, computational biology, and human genetics.

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.

Levchenko combines molecular biology, microfabrication, and imaging technologies 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 1964 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.

Biology award recognizes the field’s increasing prominence in contemporary biomedical research.

“Immunity is not only essential for understanding infections 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 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 2007 Vital Vlcek Prize for Biomedical Science. In addition, Medzhitov was one of three scientists awarded the Shaw Prize in Life Science and Medicine for 2011, and in 2010, he was the recipient of the 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 research institutions. Since 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.

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 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.