Medicine@Yale

MARCH/APRIL 2014
VOLUME 10, ISSUE 1
Advancing Biomedical Science, Education, and Health Care

Two on Yale faculty elected to Institute of Medicine

Leaders in emotional intelligence and immunity join prestigious corps

Yale University President Peter Salovey, PH.D., and immunologist Ruslan M. Medzhitov, PH.D., the David W. Wallace Professor of Immunobiology, have been elected to the Institute of Medicine (IOM), one of the most prestigious bodies in health and medicine.

Salovey's research has focused on how effective communication and promotional techniques can persuade people to change risky behaviors relevant to cancer and HIV/AIDS. His lab compared the effectiveness of contrasting interventional approaches—either presenting the benefits accrued by adopting a healthier behavior or warning of the risks of not adopting that behavior. Investigative studies by Salovey, the Chris Argyris Professor of Psychology, and professor of Epidemiology and Public Health and in the School of Management, have been widely used in tailoring educational and public health messages about adopting healthier behaviors to prevent or detect disease.

Along with John D. Mayer, PH.D., of the University of New Hampshire, Salovey was a pioneer in developing the concept of emotional intelligence—the belief that people have a wide range of emotional and intellectual skills that can be developed and monitored to better guide their thinking and actions. His seminal research on the ways that human moods and emotions affect behavior and decision-making, and his lab's development of methods to study and measure these factors, laid the groundwork for the establishment of the Yale Center for Emotional Intelligence. The principles of emotional intelligence arising from Salovey's work have since been applied around the world.

Peter Salovey

Ruslan Medzhitov

Medzhitov, a Howard Hughes Medical Institute investigator, has made pioneering contributions to the understanding of innate immunity, which provides immediate defense against infection. His studies helped elucidate the critical role of toll-like receptors (TLRs) in sensing microbial infections, mechanisms of TLR signaling, and activation of the inflammatory and immune response.

// IOM *(page 8)*

Genetics chair receives major new prize

KIMBERLY WHITE/GETTY IMAGES

$3 million Breakthrough Prize honors geneticist's research on hypertension

Richard P. Lifton, M.D., PH.D., chair and Sterling Professor of Genetics and professor of medicine, was among six scientists awarded the Life Sciences Prize by the Breakthrough Prize in Life Sciences Foundation on December 12. The prize, which carries an award of $3 million, honors Lifton's breakthrough work in genetics.

Lifton, a Howard Hughes Medical Institute investigator, uses genetic approaches to identify the genes and pathways that contribute to common human diseases, including cancer, and cardiovascular, renal, and bone disease. The prize recognizes his pioneering work in identifying the genetic and biochemical underpinnings of high blood pressure, or hypertension, which affects more than 1 billion people worldwide

// Prize *(page 7)*

Richard Lifton's work has demonstrated the fundamental role of salt reabsorption by the kidney in the regulation of blood pressure.

In new Yale-AbbVie research partnership, a 'true symmetry'

With the aim of advancing understanding of the molecular, cellular, and genetic underpinnings of autoimmune and inflammatory diseases, and to find new and better treatments, Yale School of Medicine (YSM) has entered into a research partnership with the global pharmaceutical company AbbVie. The North Chicago, Ill.-based AbbVie, formed in 2013 when Abbott Laboratories divided into two companies, will provide $14.5 million over a five-year period to fund research led by YSM faculty.

According to the American Autoimmune Related Diseases Association, autoimmunity is the second-leading cause of chronic disease in the U.S., affecting some 50 million individuals. There is also growing recognition among scientists that immune-mediated inflammatory processes are at the root of a wide array of common and deadly disorders, including cancer, heart disease, and Alzheimer's disease.

Catalyzed by Yale's preeminence in immunobiology research, the partnership marks another milestone in the formation of

// Partnership *(page 6)*

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INSIDE THIS ISSUE

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HAROLD SHAPIRO

Robert Sherwin's research on Type 1 diabetes has paved the way for some of today's most common therapeutics. For 26 years, Sherwin served as director of the School of Medicine's training program in diabetes and metabolism, funded by the National Institutes of Health.

The art and science of diabetes care

A career spent shaping knowledge of diabetes, and improving lives

When Robert S. Sherwin, M.D., began a fellowship in 1972 in the medical school's Department of Internal Medicine, his plan was to deepen his knowledge of metabolism and return to New York City's Mount Sinai Hospital, where he'd completed his residency, to establish a diabetes research program. 42 years later and still at Yale, he hasn't looked back.

Now the C.N.H. Long Professor of Medicine and chief of the Section of Endocrinology, Sherwin has been at the forefront of research that has fundamentally improved medicine's ability to address the body's lack of insulin production in Type 1 diabetes, an autoimmune disease that results in unregulated levels of blood glucose and, if untreated, can cause organ damage and death.

A Bronx-born New Yorker with a passion for art, Sherwin minored in art history while at Union College. After earning his M.D. at Albert Enstein College of Medicine, he planned to research kidney disease at the National Institutes of Health (NIH), but was instead accidentally offered, and accepted, a research position in a diabetes lab there. At the NIH and afterward, he came to see that treatments for Type 1 diabetes—which affects nearly 3 million Americans today—could be vastly improved.

In 1974 Sherwin joined Yale's Department of Internal Medicine. Working with Professor of Pediatrics William V. Tamborlane, M.D., he played a critical role in the development of insulin pump therapy—in which a small pump slowly delivers insulin, stabilizing blood glucose levels. "As late as 1980 our treatments kept people with Type 1 diabetes alive, but we had no real way to monitor what we were doing or much to offer therapeutically," says Sherwin, also director of the Yale Center for Clinical Investigation (YCCI). However, the advent of continuous infusion, along with ancillary advances like the finger prick blood test and the ability to measure glucose over an extended period, dramatically enhanced treatment.

In later research, Sherwin defined how the brain senses glucose and activates defenses against low blood sugar, or hypoglycemia—the major complication of insulin therapy. "There are adaptations in the brain that make glucose-sensing cells more efficient so people are less aware of their hypoglycemia," he explains.

Sherwin's research today relies on cutting-edge imaging techniques, including functional magnetic resonance imaging (fMRI) and positron-emission tomography (PET), and aims to clarify the neurological bases of hypoglycemia and obesity. Working with a diverse group of researchers—from psychiatrists to pediatricians—his research into areas of the brain that control emotion, motivation, and reward has revealed dramatic differences between the brain responses of lean and obese children. Interdisciplinary collaboration of this kind is central to the research being supported by YCCI's five-year $45.4 million Clinical Translational Science Award—the university's largest NIH grant—and is, he believes, key to the future of medicine.

Today, Sherwin continues to see patients despite a busy research schedule and broad administrative duties. The creativity in research and the prospect of improving the lives of many continue to excite him, he says, while acknowledging that working with patients helps keep him grounded.

"The creative struggle in research is similar to what happens when you're trying to achieve a vision in art," Sherwin says. "The excitement comes when things reveal themselves."

National Cancer Institute renews Yale Cancer Center's designation

Yale Cancer Center (YCC)'s designation as a comprehensive cancer center by the National Cancer Institute (NCI) was recently extended for an additional 5 years following an extensive grant submission and review process. The award includes $12.2 million in funding over five years to support YCC's research programs and shared resources, along with the continuation of YCC's comprehensive status, the most prestigious level of designation from the NCI. The designation is given to centers that meet strict criteria for patient care, cancer research, clinical trials, and community outreach and education.

The renewed designation is "a reflection of the groundbreaking research efforts in our laboratories and the increasingly fast pace of translating our research findings to improved patient care and treatment options for our patients," says Thomas J. Lynch Jr., M.D., director of Yale Cancer Center and physician-in-chief at Smilow Cancer Hospital at Yale-New Haven. "Our successes in cancer treatment, research, and education over the past five years, and those promised to come, will ensure Yale Cancer Center is exceeding the NCI's expectations for comprehensive cancer centers," Lynch says.

Thomas Lynch

One of 41 comprehensive cancer centers in the nation, YCC is the only designated center in Connecticut. Among the many advantages of receiving care at a comprehensive cancer center are access to a large variety of oncologists specializing in specific types of cancer, and the close link between research and clinical care, which ensures that patients receive the most innovative and targeted treatments available.

Widely acclaimed hematologist joins Cancer Center

Steven Gore

Yale Cancer Center (YCC) and Smilow Cancer Hospital at Yale-New Haven have appointed Steven D. Gore, M.D., an internationally known hematologist, as director of hematologic malignancies at Smilow Cancer Hospital (SCH). Gore comes to Yale from The Johns Hopkins University School of Medicine (JHUSOM), where he was professor of oncology and a faculty member in the Program in Cellular and Molecular Medicine. He came to Yale in November.

"Dr. Gore's national leadership on clinical trials for patients with leukemia and meylodysplastic syndromes and focus on translational research will elevate our hematology program," says Madhav V. Dhodapkar, MBBS, the Arthur H. and Isabel Bunker Professor of Medicine, professor of immunobiology, and chief of hematology at YCC and SCH.

Gore is a member of the American Society of Hematology, the American Society of Clinical Oncology, and the American Association for Cancer Research, among other organizations. He received his B.S. from Yale College and his M.D. from Yale School of Medicine. He completed his residency in internal medicine at the University of Chicago Hospitals and Clinics and a fellowship in oncology at JHUSOM. He has authored more than 200 peer-reviewed articles and book chapters on hematologic malignancies and myelodysplastic syndromes.

CORRECTION

In our last issue, we incorrectly labeled our *Grants and contracts* listing "July-August 2012." We reported grants and contracts from September-October 2012. We regret the error.

Medicine@Yale

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Medicine@Yale is published quarterly by the Office of Institutional Planning and Communications, Yale School of Medicine, 1 Church St., Suite 300, New Haven, CT 06510-3330
Telephone: (203) 785-5824 Fax: (203) 785-4327

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

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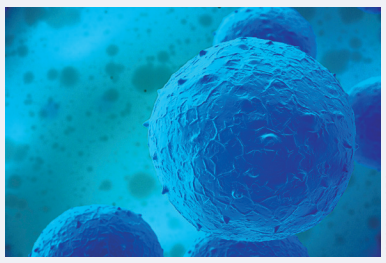
Printed on recycled paper

For stem cells, fate depends on location



ISTOCKPHOTO

Stem cells are widely studied in part because they can transform: they can become heart, liver, and even brain cells. Research on stem cell "fate" has largely focused on the cells' intrinsic properties and genetic patterns.

A Yale study implicates a different factor: a cell's original location in its "niche." The lab of Valentina Greco, PH.D., assistant professor of genetics and dermatology and senior author, developed a novel form of microscopy to track individual stem cells in the hair follicles of living mice. Monitoring these cells dynamically as a hair grew, first author Panteleimon Rompolas, PH.D., postdoctoral fellow in genetics, and colleagues found that cells from the lower part of the follicle niche tended to end up in the hair structure, while those at the top of the niche tended to remain stem cells. When they killed only cells in one area, other cells moved in and began behaving like the cells they'd replaced.

The findings, published online October 6 in *Nature*, suggest that stem cell location has far more influence on cell fate than previously thought.

An organelle's role in appetite, weight gain

Mitochondria, organelles that serve as the powerhouses of living cells, generate and maintain proper energy levels in complex organisms. But they do more than just generate energy.

A new School of Medicine study shows that the size and shape of mitochondria in specialized brain cells is key to controlling appetite and weight gain in mice. Analyzing AgRP neurons in mice, known to play a role in appetite, the team found that in a fasting state, the neurons had many small mitochondria. When the mice were fed high fat diets, the mitochondria fused together: they were fewer in number, but larger. To test whether these changes were integral to how AgRP functioned, the team blocked mitochondria from fusing in the AgRP neurons of some mice. The mice not only had impaired neuron signaling when they ate, but failed to gain weight on a high-fat diet.

The findings, reported September 25 in *Cell*, show a direct link between mitochondria changes and whole-body metabolism. "Mitochondra need to have ongoing dynamic plasticity in order to support neurons, which are necessary for appetite and for the maintenance of life," said lead author Tamas L. Horvath, DVM, PH.D., the Jean and David W. Wallace Professor of Biomedical Research and chair of the Section of Comparative Medicine.

Medical education is new center's focus

Using an array of tools, Teaching and Learning Center supports pedagogical innovation at the School of Medicine

Accomplished faculty at medical schools across the United States often receive little formal training in pedagogy, and academic medicine is known for rewarding research accomplishments while not always incentivizing excellence in teaching. At the School of Medicine, however, the teaching of medicine is not only benefiting from a new, central home on campus; it is also quietly attracting national attention.

In 2012, the medical school introduced a new means of supporting medical education: the Teaching and Learning Center (TLC). As the TLC enhances faculty teaching, measures students' learning, assesses the curriculum, and delivers digital educational tools, it is supporting the teaching of medicine at Yale with an array of new resources.

The TLC is part of the Strategic Plan for Medical Education, a vision for YSM's future advanced in 2010 by a group of stakeholders under the leadership of Deputy Dean for Education Richard Belitsky, M.D., the Harold W. Jockers Associate Professor of Medical Education and associate professor of psychiatry. The Strategic Plan called for the school to rebuild its curriculum "from the ground up" and to elevate the status of teaching.

Education has been center-stage at the School of Medicine since its founding in 1810, and was the subject of intense focus when the "Yale System" of medical education, which prizes students' independence and their original research, was established in the 1920s. However, the instructor support the TLC provides is unprecedented.

Led by Janet Hafler, ED.D., associate dean for educational scholarship and professor of pediatrics, the TLC has a team of experts who work together to develop innovative assessment strategies, incorporate technology into the learning process, and support educators by drawing upon and conducting educational scholarship. "Faculty are very interested in effective teaching strategies to promote learning," says Hafler.

The new curriculum—set to launch in 2015—will emphasize small-group student-centered learning. The TLC offers resources to support this format: educators can ask the TLC's experts for confidential feedback on their teaching styles or request help with course objectives, curriculum, slides, or written materials. TLC experts offer many workshops on teaching strategies, including, for example, a workshop on how best to teach clinical reasoning skills; some 100 faculty have taken it. The Center has also offered a faculty fellowship for the past four years that covers subjects like offering feedback, making talks interesting, and keeping learners engaged.

"The Teaching and Learning Center has been a godsend for clinician-educators like me," says Dana W. Dunne, M.D., assistant professor of medicine, who worked with Hafler to implement a curriculum in humanistic bedside teaching. "Some of us hadn't been immersed in adult learning theory, or had any access to education experts. If you have an interest in educating faculty, students, or residents, the Center can help with a framework and the tools to get going."

Some of those tools are digital. Gary B. Leydon, the TLC's associate director for technology services, works with faculty to create tailor-made educational apps and websites, some of which are used during class time. Leydon developed an interactive pharmacology website that lets students plug in different values to explore how the body processes a drug. He has also built websites for posting faculty-generated curricular videos supporting a variety of courses and clerkships, and to facilitate faculty development in areas like the teaching of clinical reasoning.

In the fall of 2011, the School of Medicine drew national attention by doing away with paper copies of course materials and instead, providing medical students with iPads that allow easy access to specially developed digital tools. Using the iPads, "we're actually integrating these tools into the curriculum," says Michael L. Schwartz, PH.D., associate dean for curriculum and associate professor of neurobiology, who spearheaded the initiative.

One of the TLC's biggest challenges may be assessment of faculty, students, and the curriculum itself. To meet this challenge, two experts in the TLC are devoted to assessment. Assistant Professor of Psychiatry John A. Encandela, PH.D., associate director for curriculum and educator assessment in the TLC, develops methods of weighing faculty members' teaching skills and educational scholarship that can count toward reappointments and promotions. Professor of Medicine Michael L. Green, M.D., M.SC., as associate director for student assessment, faces a particular challenge. Schwartz says, "it's a very complicated task: how to create assessments that are useful to the learner, but still allow us to validate our programs and graduate physicians that are appropriately trained. We don't want to integrate things that are the antithesis of the Yale System."

WILLIAM SACCO

The Teaching and Learning Center (TLC) supports the medical school's educational mission with an array of new resources. The TLC's leadership includes (from left) Anna Reisman, John Encandela, Gary Leydon, Janet Hafler, Michael Green, Jacqueline Fordiani, Frederick Haeseler (retired), and Dorothy DeBernardo.

Green's role is to examine ways assessment can aid the School of Medicine's educational mission while preserving—and contributing to—the school's unique spirit of independence and collegiality.

One of the TLC's functions is to draw on pedagogical research. With Hafler's expert help in accessing and interpreting such scholarship, faculty can make more informed decisions about how to approach education-related tasks. The TLC also guides faculty in conducting // TLC *(page 4)*

The future of education

Yale School of Medicine must prepare students to excel in a rapidly changing health care landscape. The school's educational mission requires stable and continuous support to thrive, and you can help in the following ways:

Endowing the Teaching and Learning Center $10 million
Leaders in medical education collaborate with faculty to support excellence and innovation in teaching.

Endowed Professorships $3 million
For distinguished faculty members whose scholarship in education represents the highest standards.

Endowed Programs for Teaching $500,000 to $1 million
Providing sustainable faculty development and programmatic support for innovative curriculum development and teaching.

Endowed Faculty Advisors $500,000
For faculty who give individualized career and life guidance to students throughout their years at Yale.

Endowed Educational Technology Fund $250,000 and up
Facilitating access to and utilization of cutting-edge technologies.

Endowed Clinical Mentor $250,000
For faculty who provide formative personalized feedback and concentrated guidance to students in a clinical environment.

Endowed Educational Resource Fund $100,000 and up
Enhancing the learning experience by supporting scholarship, curricular innovation, unique training opportunities, and professional development.

For more information about these or other gift opportunities, contact Eric Schonewald at eric.schonewald@yale.edu or 203-436-8557 or visit www.medicine.yale.edu/support.

OUT & ABOUT

September 7 At the annual **Closer to Free** bicycle ride, members of the medical school and Yale-New Haven Hospital communities raised more than $1.2 million for cancer treatment and research at Yale Cancer Center and Smilow Cancer Hospital at Yale-New Haven. 1. (From left) **William Casey King**, PH.D., executive director of the Yale Center for Analytical Sciences at the School of Public Health; **Susan T. Mayne**, PH.D., C.-E.A. Winslow Professor of Epidemiology; and her husband, **James Mayne**. 2. **Ken Pelletier**, of Onyx Pharmaceuticals. 3. **Sajid A. Kahn**, M.D., assistant professor of surgery. 4. Cyclists at the ride's opening ceremony.




CHRIS VOLPE (4)

October 7 After the news broke that the 2013 **Nobel Prize in Physiology or Medicine** had been awarded to **James E. Rothman**, PH.D., chair and Fergus F. Wallace Professor of Cell Biology and professor of chemistry, a press conference was held in the medical school's Historical Library. Rothman is one of the world's foremost experts on membrane trafficking, the means by which proteins and other materials are transported within and between cells. The prize highlights his contributions to the understanding of exocytosis, a form of trafficking in which spherical sacs called vesicles fuse with cell membranes to deliver their contents outside the cell. 1. In his remarks, Rothman, also director of the Nanobiology Institute on Yale's West Campus, touched on the challenges posed today by the uncertainty surrounding federal funding of science. 2. **Robert J. Alpern**, M.D., dean and Ensign Professor of Medicine (left), and Yale President **Peter Salovey**. 3. A crowd awaits Rothman's entrance.



TERRY DAGRADI (3)

October 26 Past Yale recipients of the **Homer W. Smith Award**, the American Society of Nephrology's top honor, gathered at New Haven's Roia Restaurant with **Stefan Somlo**, M.D., the C.N.H. Long Professor of Medicine, professor of genetics, chief of the Section of Nephrology in the Department of Internal Medicine, and the 2013 recipient of the award. (From left) Somlo; Somlo's wife, **Joan O. Cho**, assistant clinical professor of medicine; **Deborah Lifton**; **Richard P. Lifton**, M.D., PH.D., chair and Sterling Professor of Genetics, professor of medicine, and a Howard Hughes Medical Institute investigator; **Marie-Louise Landry**, M.D., professor of laboratory medicine and of medicine; **Peter S. Aronson**, M.D., the C.N.H. Long Professor of Medicine and professor of cellular and molecular physiology; **Betty Boulpaep**; **Emile L. Boulpaep**, M.D., professor of cellular and molecular physiology; **Gerhard H. Giebisch**, M.D., professor emeritus of and senior research scientist in cellular and molecular physiology; **Patricia A. Preisig**, PH.D., professor of medicine and of cellular and molecular physiology; and **Robert J. Alpern**, M.D., dean and Ensign Professor of Medicine.

TERRY DAGRADI

September 15 A **reception** for minority faculty, residents, students, and fellows was held at the home of **Gary V. Desir**, M.D., professor of medicine and of forestry and environmental studies, interim chair of the Department of Internal Medicine, and co-chair of the School of Medicine's Minority Organization for Retention and Expansion (MORE), whose goal is to attract and support minority faculty members. 1. **Nadia A. Ameen**, MBBS, associate professor of pediatrics and of cellular and molecular physiology (left), and **Linda K. Bockenstedt**, M.D., the Harold W. Jockers Professor of Medicine. 2. **James P. Comer**, M.D., Maurice Falk Professor in the Child Study Center (CSC), professor of psychiatry, and associate dean for student affairs (left), and **Forrester A. "Woody" Lee,** M.D., professor of medicine and assistant dean for multicultural affairs. 3. (From left) **Carla E. Marin**, PH.D., associate research scientist in the CSC; Marin's partner, **Anthony Jones**; **Giselle Gutiérrez**, predoctoral fellow in psychiatry; **Hanako Shishido**, M.A., ATR-BC, predoctoral fellow in psychiatry; and **Katrina Roundfield**, predoctoral fellow in psychiatry.



JOHN CURTIS (3)

MICHAEL MARSLAND

October 13 **Inauguration Ceremonies** marked the start of **Peter Salovey**'s tenure as Yale's 23rd president. Pictured with Salovey are **Kimberly M. Goff-Crews**, J.D., secretary and vice president for student life (left), and **Margaret H. Marshall**, J.D., former chief justice of the Supreme Judicial Court of Massachusetts and the senior fellow of the Yale Corporation.





CARL KAUFMAN (6)

October 27 School of Medicine students and faculty took their talents to the court at the **Faculty-Student Tennis Classic**. 1. 52 students and faculty members participated in the tournament, an annual tradition begun in 2011. 2. **Mark Youngblood** '20, a student in the Medical Scientist Training Program (known informally as the M.D./PH.D. Program), delivers a serve. 3. (From left) **Karel F. Liem Jr.**, M.D., PH.D., assistant professor of pediatrics; **Vikram Jairam**, '15, **Sriram Ramanan**, postgraduate associate in neurology, and **Ketan R. Bulsara**, M.D., associate professor of neurosurgery. 4. **Ysabel Ilagan**, Yale College '14. 5. **Lance H. Linke**, PH.D., associate research scientist in psychiatry. 6. **Lee Ying**, '20, a student in the M.D./PH.D. Program, gives it his all.

// TLC *(from page 3)* their own educational research for publication in peer-reviewed journals.

The popularity of the TLC's activities attests to a widespread interest at Yale in medical pedagogy. The Center's Medical Education Discussion Group draws crowds, as did its first annual Medical Education Day last year. A new medical education elective offers students the chance to work with simulators and Web-based tools to gain advanced educational experience.

When a Medical Education Interest Group launched last year, it drew in some 300 students and faculty. "[The TLC] is seen as a great asset," says Ray Chen '14, a fourth-year medical student and former president of the interest group, who adds that students directly seek out TLC resources for their own research.

The School of Medicine is not alone in prioritizing formal pedagogical support: other top-tier medical schools have taken similar steps in recent years. For example, the Stanford Faculty Development Center for Medical Teachers offers workshops and consultations to faculty, while the Institute for Excellence in Education at the Johns Hopkins School of Medicine provides faculty with educational research support and training seminars. Similarly, the University of Pennsylvania's Center for Teaching and Learning offers resources to instructors across the university.

But Yale School of Medicine's successes with original educational scholarship and its creative use of technology are nudging the school into the spotlight. In April, the school will host the Association of American Medical Colleges' Northeast Group on Educational Affairs; and Schwartz is frequently approached by medical schools curious about Yale's use of iPads and video technology in the curriculum.

Outside attention aside, the TLC's innovations are designed to fit Yale's strengths. Belitsky has told students that these changes in medical education are intended to strike a balance between the School of Medicine's collegial, collaborative values and the need to innovate responsibly, keeping apace with the times. And in all the interactions with faculty and students, Hafler says, the TLC harmonizes with the Yale System by emphasizing a supportive approach.

"We want the Teaching and Learning Center to be a safe place to explore teaching, make mistakes, learn how to teach from uncertainty, and not be judged," says Hafler. "And we want the same learning environment for the students."

Triggering the 'domino' of life

ISTOCKPHOTO

In its first day of development, a human embryo follows instructions produced by its mother's nearby cells. Afterward, the embryo begins following its own genetic instructions. Scientists haven't yet uncovered the instructions that cause this transition, but new Yale research offers clues.

In shifting from dependent to self-directing, an embryo must turn on three specific genes, the team reported online September 22 in *Nature*.

Sequencing the genomes of zebrafish embryos, the team found that among genes that are turned on first, *Nanog*, *SoxB1*, and *Pou5f1* had the highest expression levels. When the scientists blocked these genes, the embryos failed to continue developing. Interestingly, these same three genes have been found to reprogram adult human cells into stem cells resembling those found in an embryo.

These genetic factors "provide an entry point to understanding the first domino to fall in the creation of life," says Antonio J. Giraldez, PH.D., associate professor of genetics and senior author of the study.

Molecule links aging and inflammation

Inflammation in the body is most often thought of as a healthy defense against an invading bacteria or virus. But inflammation can also occur separately from outright infection, and scientists know that as people age, constant low-level inflammation of many organs becomes more common and is thought to contribute to many chronic diseases.

A team of scientists led by Vishwa Deep Dixit, D.V.M., PH.D., professor of comparative medicine and immunobiology at the School of Medicine, has found a new piece of this puzzle: a molecule that controls this age-related inflammation. The protein, NLRP3, was already known to be linked to unusual types of inflammation: that associated with obesity and diabetes, for example.

Dixit's team reported October 1 in *Cell Metabolism* that removing the NLRP3 protein in mice prevented many physiological changes that typically accompany aging, including changes to the immune system, eyes, bones, metabolism, and brain cells. Mice without NLRP3, they found, had a longer "healthspan"—the portion of a lifespan free of serious illness.

The study is the first to show that inflammation is causally linked to functional decline in aging and suggests that drugs altering NLRP3 in humans may extend healthspans.

A new first: rewriting the genetic code

By editing its genome, scientists from Yale, Harvard, and MIT re-engineered a bacteria to better protect against a virus

Imagine that you wanted to remove every instance of the letter Q from the English language without losing meaningful words spelled with Q, and without adding any new letters to the alphabet. You'd have to choose an alternate letter to take Q's place—C or K, perhaps—then rewrite books with the new letter and re-teach people to spell and read using the new alphabet. Such an undertaking is what a team of Yale, Harvard, and MIT researchers have recently completed. Rather than altering the English language, however, they removed a letter from the genetic alphabet of a bacteria.

Farren Isaacs

The re-engineered bacteria didn't just contradict classic rules of biology: it also was able to better fight off invading viruses that normally relied on the host's language to function.

In all living organisms, genes are made up of long strings of four nucleotides. Every set of three nucleotides in a row—64 different possible combinations—codes for one amino acid, the building block of a protein. Each of these so-called codons is translated into its corresponding amino acid through a unique tRNA molecule. At one end, the tRNA binds the three nucleotides; at the other it carries the associated amino acid. The team of scientists, which includes the School of Medicine's Jesse Rinehart, PH.D., assistant professor of cellular and molecular physiology, and Farren J. Isaacs, PH.D., assistant professor of molecular, cellular, and developmental biology, wanted to remove one of these codons from a strain of bacteria.

"No one had ever entirely removed a codon from a genetic code," Rinehart says. "But if we could remove a codon and the organism was fine, biologists could start utilizing that codon for their own engineering purposes."

If Qs, for example, were no longer used in words like "quick" and "mosque," then Q could be assigned a different meaning—like a new punctuation mark. For synthetic biologists, having an unassigned codon is key to adding new amino acids to a protein to give it new properties.

To show that removing a codon was possible, Rinehart, Isaacs, and George Church, PH.D., professor of genetics at Harvard Medical School, set their sights on the least common codon: a string of the three nucleotides U-A-G. Rather than code for an amino acid in a protein's structure, UAG is a stop codon: it tells the translation machinery that the end of a gene has been reached, like a period. But two other codons serve the same function: UAA and UGA. So, using precise gene editing techniques that they had previously developed, the scientists changed every occurrence of UAG in a strain of *Escherichia coli*, 321 in all, to UAA.

"What's really powerful about these techniques is that we can take these oligonucleotides and insert them with high efficiency, and it allows us to simultaneously target many sites across the genome," Isaacs says.

Jesse Rinehart

The codon replacement worked, but that wasn't the end of the project. The team then introduced a genetic mutation into the protein that normally interprets the UAG as a stop codon—called release factor 1 (RF1). In a normal cell, deleting RF1 would lead to a jumble of misread genes: one protein would run into the next with no break, since the stop codon wouldn't be read between genes. But in the newly engineered *E. coli*, there were no UAG sequences to be read. Unlike other strains of bacteria, removing RF1 from this strain had no effects. Or, at least, no negative effects: when the altered *E. coli* was infected with a bacteriophage, a type of virus that infects bacteria, the invading phage could no longer function.

"When the phage infects the cell, its genes contain stop codons, including UAG stop codons," Rinehart says. "And it relies on the bacteria's release factor to read those codons." By removing a codon from the bacteria's entire language, the scientists had given the bacteria a new defense against the virus. The research was published October 18 in the journal *Science*.

"This is an important advance in understanding the genetic code," Rinehart says. "But it also shows that we are in an exciting new reality where we can take the lessons we've learned from biology, from understanding the genome and the proteome, and we can go forward into a more exciting time where we can engineer new properties into cells."

The advance opens up the door to a new way of adding amino acids to proteins—by assigning UAG to a new tRNA, with a completely novel amino acid on the protein side.

The team plans to continue optimizing the techniques and pushing the boundaries of what's possible in protein engineering. "We could now introduce entirely new properties into these organisms by assigning this codon to a new amino acid," Isaacs says. "That we were able to change the code, as well as introduce new biological functions, is exciting and satisfying."

Digital tomosynthesis enhances accuracy of breast cancer detection

For more than 50 years, radiologists have screened women for breast cancer using 2-D mammography, a low-energy X-ray imaging technology that aids diagnosis, and also sometimes leads to false alarms and "callbacks" for further screening.

Now, thanks to a new technology, accuracy is improving. In a little more than two years, digital breast tomosynthesis, or 3-D mammography, is significantly reducing callbacks while picking up more cancers. It's working so well that all eligible patients who visit the Yale Breast Center (YBC) for mammography are receiving tomosynthesis in addition to 2-D mammography. The results, says Liane E. Philpotts, M.D., professor of diagnostic radiology and chief of breast imaging for the YBC at Smilow Cancer Hospital at Yale-New Haven, have outpaced expectations.

"We've seen a 20 percent increase in cancer detection rates over 2-D mammography," Philpotts says. Before tomosynthesis was used, YBC radiologists were calling back more than 10 percent of all women. With tomosynthesis, that number has been reduced by 30 percent.

The procedure was approved by the U.S. Food and Drug Administration in 2011 following trials at Yale-New Haven Hospital and four other medical centers. It is the first technology to deliver three-dimensional images in mammography, allowing radiologists to view the breast in detailed 1 mm sections. "We can characterize lesions better. You get a better view of the margins [the area at the edge of the tumor], which makes for a better assessment," Philpotts says.

ROBERT LISAK

Since incorporating the use of digital tomosynthesis in breast cancer screening, Liane Philpotts and colleagues at the Yale Breast Center have seen an increase in accuracy.

In 2013 Philpotts and colleagues reported online in the journal *Radiology* that the technology is most beneficial for patients aged 40 to 50 and those with dense tissue, but that it also has significant benefits for patients into their 70s.

Says Philpotts, "The bottom line is that every patient benefits."

Grants and contracts awarded to Yale School of Medicine

July-August 2012

Federal

Morris Bell, NIH, *Research Training in Functional Disability Intervention*, 5 years, $1,211,422 **Choukri Ben Mamoun**, NIH, *Function and Inhibition of Plasmodium Lipid Decarboxylases*, 5 years, $2,040,256 • **Steven Bernstein**, NIH, *Implementation of HIT-Enhanced Tobacco Treatment for Hospitalized Smokers*, 4 years, $3,065,704 • **Jonathan Bogan**, **Varman Samuel**, NIH, *Vesicle Translocation and the Metabolic Syndrome*, 2 years, $490,072 • **Jonathan Bogan**, NIH, *Regulation of Insulin Sensitivity by TUG Acetylation*, 1.9 years, $445,678 • **Kathleen Carroll**, NIH, *A Stage I Study of Computer Based Training in CBT for Alcohol Use Disorders*, 2 years, $358,209 • **Sarwat Chaudhry**, NIH, *Risk Stratification in Older Persons with Acute Myocardial Infarction: SILVER-AMI*, 4.8 years, $11,336,130 • **Katarzyna Chawarska**, NIH, *Pivotal Response Treatment for Infants at Risk for ASD: A Pilot Intervention*, 1.8 years, $162,900 • **Tian Chi**, NIH, *Remodeling-Independent Function of the BAF Complex in T Cells and Beyond*, 2 years, $444,701 • **Daniel Colon-Ramos**, NIH, *Cellular and Molecular Mechanisms that Temporally and Spatially Restrict Synaptic Development*, 4.9 years, $1,877,535 • **Christian Connell**, NIH, *Effects of the Wraparound Service Model for Maltreated Youth in a System of Care*, 1.7 years, $455,634 • **Joan Cook**, DHHS, *Advancing the Science of Education, Training and Practice in Trauma*, 1 year, $49,989 **Kelly Cosgrove**, NIH, *Yale SCOR Translational Center to Develop Gender-Sensitive Treatment for Tobacco Dependence*, 4.9 years, $644,116 **Michael Crowley**, NIH, *Neural Correlated of Negative Reinforcement in Adolescence & Substance Use Risk*, 5 years, $823,250 • **Ralph DiLeone**, NIH, *Exploring the Neural and Molecular Basis for the Effects of Vitamin D on Diet-Induced Obesity*, 2 years, $384,017 • **Clare Flannery**, NIH, *Effect of Insulin on Estrogen Receptor Alpha Activity in Human Endometrial Cells*, 4.9 years, $658,350 **Jackie Fretz**, NIH, *Regulation of Podocyte Differentiation by the Transcription Factor (EBF1)*, 1.8 years, $180,000 • **Gerald Friedland**, **Sheela Shenoi**, NIH, *Implementing Point of Care CD4 Analysis to Decentralize HIV Care in Rural Africa*, 2 years, $340,649 • **Vamsi Gangaraju**, NIH, *Novel Role of Piwi/piRNA Pathway in Developmental Robustness*, 1.1 years, $180,000 • **Antonio Giraldez**, NIH, *Functional Analysis of the Zebrafish Genome Through RNA-seq and Ribosome Profile*, 4.7 years, $2,452,353; NIH, *Molecular Mechanisms of MicroRNA Mediated Regulation*, 3.8 years, $1,253,302; NIH, *Development of RNA Interference in Zebrafish*, 2.1 years, $444,513 • **Daniel Goldstein**, **Timothy Nottoli**, NIH, *Hyaluronan as an Innate Ligand that Induces Inflammation after Transplantation*, 2 years, $444,701 • **Fred Gorelick**, NIH, *Training Program in Investigative Gastroenterology*, 5 years, $1,649,153 • **Ann Haberman**, NIH, *Analysis of B Cell Transcriptome Shifts Prior to Lineage Divergence* In Vivo, 2 years, $439,893 • **David Hafler**, **Kevan Herold**, NIH, *The Role of the Innate Immune System on Treg Reprogramming in Human Autoimmune Disease*, 5 years, $3,776,077 • **Tamas Horvath**, NIH, *Hypothalamic AgRP Neurons are Determinants of Healthy Lifespan and Higher Brain Functions*, 3 years, $2,445,532 • **John Hwa**, NIH, *Hyperglycemia, Thromboxane and Platelet Hyperactivity in Diabetes Mellitus*, 4 years, $1,643,874 • **Elizabeth Jonas**, NIH, *Role of Bcl-xL in Synaptic Plasticity*, 1.5 years, $385,300 • **Samuel Katz**, NIH, *Cell Death Regulation by Pro-Apoptotic BOK During Hematopoiesis*, 3 years, $402,055 **Young-Shin Kim**, NIH, *The Roles of Environmental Risks and GEX in Increasing ASD Prevalence*, 4.8 years, $2,737,179 • **Martin Kriegel**, NIH, *Role of Gender-Associated Microbiota in Organ-Specific Autoimmunity*, 3.9 years, $537,466 • **Haifan Lin**, NIH, *Toward a Central Question on Epigenetics: A Major Epigenetic Programming Mechanism Guided by piRNAs*, 3 years, $2,445,532 • **Jun Lu**, NIH, *Novel Bioinformatics Tools for Mammalian MicroRNA Target Prediction*, 9 months, $281,465 **Robert Malison**, NIH, *Clinical Neuroscience Research Training in Psychiatry*, 5 years, $1,222,658 **Thomas Manes**, NIH, *Identification of Human PECAM-1 Receptor*, 2 years, $83,021 • **Praveen Mannam**, NIH, *MKK3 is a Mediator of Sepsis and Lung Injury in the Elderly*, 2 years, $161,692 • **Steve Martino**, **Kimberly Yonkers**, NIH, *Three Strategies for Implementing Motivational Interviewing on Medical Inpatient Units: See One, Do One, Order One*, 5 years, $3,693,694 • **Carolyn Mazure**, NIH, *Yale SCOR Translational Center to Develop Gender-Sensitive Treatment for Tobacco Dependence*, 4.9 years, $306,566 • **James McGrath**, NIH, *Investigations of Mouse Interspecies Hybrids*, 1.9 years, $446,511 • **Sherry McKee**, NIH, *Yale SCOR Translational Center to Develop Gender-Sensitive Treatment for Tobacco Dependence*, 4.9 years, $286,522; NIH, *Yale SCOR Translational Center to Develop Gender-Sensitive Treatment for Tobacco Dependence*, 4.9 years, $524,505 • **Jaimie Meyer**, NIH, *Evaluating and Improving HIV Outcomes in Community-Based Women Who Interface with the Criminal Justice System*, 5 years, $821,147 **Perry Miller**, NIH, *Biomedical Informatics Research Training at Yale*, 5 years, $4,398,925 • **Andrew Miranker**, NIH, *An Orderly Approach to Toxic Mechanism by Disorderly Peptides*, 4.1 years, $1,505,890 • **Arie Mobley**, NIH, *Activity Dependent Mechanism of Olfactory System Development*, 3 years, $490,675 • **Yorgo Modis**, NIH, *The Structural Basis of Nucleic Acid Recognition by Toll-Like Receptors*, 4 years, $1,238,602 • **Marcella Nunez-Smith**, NIH, *Validating the Patient-Reported Experiences of Discrimination in Care Tool (PreDict)*, 4.9 years, $3,228,664 • **Kevin O'Connor**, **David Hafler**, DoD, *Commensal Microorganisms Affect Autoimmunity in Multiple Sclerosis*, 1 year, $132,037 • **Stephanie O'Malley**, NIH, *Moderators and Predictors of Response to Treatments for Alcohol Dependence*, 2 years, $410,801 **Chirag Parikh**, NIH, *Novel Kidney Injury Tools in Deceased Organ Donation to Predict Graft Outcome*, 3.9 years, $2,769,709 • **Sunil Parikh**, NIH, *Innate Immune Responses in Populations with Differing Susceptibility to Malaria*, 1.9 years, $381,807 • **Jamy Peng**, NIH, *Epigenetic Regulation of* Drosophila *Germline Development*, 10 months, $114,380 • **Marina Picciotto**, NIH, *Yale SCOR Translational Center to Develop Gender-Sensitive Treatment for Tobacco Dependence*, 4.9 years, $638,571 **Christopher Pittenger**, NIH, *Glutamate in OCD: A Magnetic Resonance Spectroscopy Study*, 4.9 years, $1,759,560 • **Marc Potenza**, NIH, *Clinician Scientist Training Program (CSTP)*, 5 years, $2,622,099 • **James Rothman**, NIH, *Regulation of Exocytosis at Neuronal Synapses*, 4 years, $2,980,834 • **Craig Roy**, NIH, *Genetic Analysis of Legionella Phagosome Trafficking*, 5 years, $2,630,046 • **Gary Rudnick**, NIH, *Ion and Biogenic Amine Transport Mechanism*, 5 years, $1,650,680 **Mehran Sadeghi**, NIH, *Imaging Protease Activation in Calcific Aortic Valve Disease*, 5 years, $2,060,020 • **William Sessa**, NIH, *Institutional National Research Service Award*, 5 years, $1,696,871 • **Albert Shaw**, NIH, *Midcareer Award in Translational Immunology of Aging*, 5 years, $836,640 • **Robert Sherwin**, NIH, *Yale University Clinical and Translational Science Award*

// Partnership *(from page 1)* industry-academia partnerships at Yale. "This is a collaboration between an industry leader in the treatment of autoimmune diseases and one of the best academic immunology research programs," says Richard A. Flavell, PH.D., chair and Sterling Professor of Immunobiology and a Howard Hughes Medical Institute (HHMI) investigator. "Our shared goal is the development of better treatments for immunologic diseases."

The AbbVie-Yale Collaboration in Immunobiology will be directed by a five-member joint steering committee. Members from Yale are Flavell; Jordan S. Pober, M.D., PH.D., Bayer Professor of Translational Medicine, professor of dermatology and pathology, and director of the Department of Immunobiology's Human and Translational Immunology Program; and Akiko Iwasaki, PH.D., professor of immunobiology and of molecular, cellular, and developmental biology, and an HHMI investigator. Members from AbbVie are Lisa M. Olson, PH.D., vice president of immunology, and Hamish Allen, PH.D., director of global external research in immunology. "We're very excited because we see it as a new way to strengthen our science," Olson says.

Since the founding of Yale's immunobiology program in 1988 it has become a world leader in basic immunology research. Among the key breakthroughs made at Yale was the 1997 discovery by the late Charles A. Janeway Jr., M.D., and Ruslan M. Medzhitov, PH.D., David W. Wallace Professor of Immunobiology and an HHMI investigator, that components of the innate immune system called toll-like receptors (TLRs) prompt the expression of genes that provide the adaptive immune system with the necessary advance intelligence to do its job. The study of TLRs is now one of the most active and important research areas in immunobiology.

Flavell's recent work on metabolic syndrome, a condition associated with the Western high-fat diet, suggests that interactions between our genes, our diet, and the microbes that inhabit our bodies have an important influence on inflammatory responses and on the incidence of such diseases as obesity, nonalcoholic fatty liver disease, Type 2 diabetes, and heart disease.

WILLIAM SACCO

Members of the AbbVie-Yale Collaboration in Immunobiology's steering committee include (from left) Richard Flavell, Lisa Olson, Akiko Iwasaki, Jordan Pober, and Hamish Allen.

Pober, an authority on changes in vascular endothelial cells (which form the lining of blood vessels) that target white blood cells to particular sites, recently discovered that pericytes, the cells that support endothelium in small blood vessels, also regulate inflammation by restricting the number of white blood cells that exit vessels, a finding that could lead to new drugs to treat inflammatory diseases.

Iwasaki and colleagues have recently developed a novel vaccine technology that recruits immune cells into vaginal tissue to provide long-term protection against genital herpes infections. Her group is now exploring ways to adapt this strategy to other tissues to fight a range of infections, including HIV and infectious disorders of the skin, respiratory tract, and digestive system.

AbbVie, in turn, is known not only for its pharmaceutical research and drug discovery capabilities, but for an array of specialized strengths. "They're superb at certain kinds of automation of processes, at chemistry, and at generating biological reagents," says Flavell, adding that the Collaboration will give Yale researchers access to proprietary AbbVie molecules known as dual-variable domain antibodies, which combine two targets, making them valuable experimental and treatment tools.

"Yale and AbbVie have highly complementary skills and interests in the field of immunology, and we look forward to a productive collaboration," says Carolyn W. Slayman, PH.D., deputy dean for academic and scientific affairs, Sterling Professor of Genetics, and professor of cellular and molecular physiology.

The $14.5 million in funding is available to School of Medicine faculty with primary or secondary appointments in the Department of Immunobiology. Of the 14 grants awarded, six will be four-year "full research" grants of $1 million each, and eight will be two-year pilot project grants of $160,000 each, to support early-stage research. Of the annual payments, $2 million has been allocated toward funding for HHMI investigators beginning in the Collaboration's second year.

Following an application period, grant awards will be determined by members of the joint steering committee. The grants will be awarded in stages, staggered over the Collaboration's five-year term. In addition, the Collaboration enables lab meetings, a retreat, and an annual joint scientific symposium.

The Collaboration has its roots in the longstanding relationship that Flavell built with Abbott Laboratories in the 1990s. As part of that relationship, Flavell helped guide Abbott's acquisition of a research facility in Worcester, Mass. Now known as the AbbVie Bioresearch Center, that facility is less than a two-hour drive from Yale, a factor Olson cites as important. "Our proximity allows for close interactions between AbbVie and Yale scientists, which will greatly advance a deep understanding of the biology around potential new therapeutics," Olson says. "People at AbbVie are incredibly motivated to make new medicine."

Says Flavell, "This is a genuinely synergistic connection between [institutions with] two sets of complementary skills, with very common interests. It's a true symmetry."

Program-KL2, 4 years, $3,122,344; NIH, *Yale University Clinical and Translational Science Award Program-TL1*, 4 years, $1,420,989; NIH, *Yale Clinical and Translational Science Award Program-UL1*, 4 years, $3,182,021; NIH, *Yale Clinical and Translational Science Award Program-UL1*, 4 years, $3,683,748; NIH, *Yale Clinical and Translational Science Award Program-UL1*, 4 years, $25,328,536 **Mark Shlomchik**, NIH, *Role of B Cells and DCs in Lupus Pathogenesis*, 1.2 years, $458,855 • **Satinder Singh**, NIH, *Structural Studies of Vesicular Monoamine Transporters*, 1.9 years, $432,300 • **Peter Tattersall**, **Susan Cotmore**, NIH, *Molecular Basis of Parvoviral Target Cell Specificity*, 4.8 years, $2,415,877 • **Hugh Taylor**, NIH, *Environmental Estrogen Induced Epigenetic Alteration of Uterine Stem Cells*, 4.8 years, $2,058,875 • **Agnes Vignery**, NIH, *Osteoclasts Exosomes*, 1.8 years, $400,180 **Joanne Weidhaas**, **Frank Slack**, NIH, *MicroRNAs to Understand Cause and Outcome in Breast Cancer*, 4.9 years, $1,705,591 • **Brian Weiss**, NIH, *Symbiosis and Immunity in the Tsetse Fly*, 2 years, $427,199 **Yawei Zhang**, NIH, *PHAHs and Thyroid Cancer Risk in DoDSR Cohort*, 4.7 years, $3,305,686 • **Z. Jimmy Zhou**, NIH, *Synaptic Function and Organization of the Mammalian Retina*, 5 years, $2,059,188

Non-federal

Renata Batista Brito, Childs (Jane Coffin) Memorial Fund, *Control of Cortical Inhibition by Nrg1-ErbB4 Signaling*, 3 years, $154,500 • **Lauren Beslow-Kaye**, The Children's Hospital of Philadelphia (NIH), *Functional Connectivity & Pediatric Stroke*, 3 years, $307,152; University of Colorado at Denver (NIH), *Investigation of Prognostic Factors in Childhood-Onset AIS: Role of Stroke Subtype*, 1 year, $2,000 • **Vineet Bhandari**, Cornerstone Therapeutics, Inc., *Surfactant-Enhanced Delivery of Silencing RNA (siRNA) in Neonatal Mouse Models of Bronchopulmonary Dysplasia*, 5 years, $15,000 • **Alfred Bothwell**, The Mary Kay Foundation, (Formally The Mary Kay Ash Charitable Foundation), *Modeling Human Immune System Interaction with Breast Tumors and Treatments in Mice*, 2 years, $100,000 • **Elizabeth Bradley**, **Asghar Rastegar**, **Linda Arnold**, **Urania Magriples**, Ministry of Health, Rwanda, *Building Human Resources for Health: Yale University and the Ministry of Health of Rwanda*, 1.5 years, $1,663,080 • **Cynthia Brandt**, University of Pittsburgh (NIH), *The Risk of Types of Heart Failure Among HIV Infected and Uninfected Veterans*, 2 years, $231,389 • **Clemente Britto-Leon**, Cystic Fibrosis Foundation, *Regulation of SPLUNC1 During Airway Inflammation, Infection, and Cystic Fibrosis*, 1 year, $68,250 • **Richard Bucala**, Alliance for Lupus Research, *Function of the Polymorphic MIF Locus in SLE*, 2 years, $336,385 **Daniel Campbell**, Autism Speaks, *Improved Early Detection of Autism Using Novel Statistical Methodology*, 1.5 years, $102,846 • **Richard Carson**, UCB Pharma S.A., *Novel PET Ligand Selection Study in NHPs (Project 1 Under Research Collaboration Agreement)*, 3 years, $806,844 • **Silvia Corbera**, Hartford Hospital (NIH), *The Social Brain in Schizophrenia and Autism Spectrum Disorders*, 5 years, $319,446 • **Joseph Craft**, Rheumatology Research Foundation (Formally: American College of Rheumatology), *Novel B Cell Marker and Therapeutic Target in Rheumatoid Arthritis*, 1 year, $75,000 • **Leslie Curry**, Commonwealth Fund, *CMWF: STAAR 100 Survey*, 6 months, $49,091 • **Charles Dela Cruz**, Flight Attendant Medical Research Institute, *Mechanisms of Synergy between Cigarette Smoke and RSV*, 2 years, $217,000 • **Shawn Ferguson**, Ellison Medical Foundation, *Identification of Mechanisms Regulating Lysosome Homeostasis and Their Role in Protecting Neurons against Aging*, 4 years, $400,000 • **Thomas Fernandez**, Simons Foundation, *Genetic Investigations of Motor Stereotypes*, 2 years, $249,076 • **Liana Fraenkel**, Brigham and Women's Hospital (NIH), *Rheumatic Expertise Expanded Access to Improve Community Health: REACH:RA*, 1 year, $14,250; American College of Rheumatology, *Improving the Delivery of Care Using a Theory-Based Decision Support Tool*, 2 years, $347,324 • **Jose Gomez Villalobos**, Flight Attendant Medical Research Institute, *A 3-Gene Signature in Smoking Exposure and Asthma*, 3 years, $325,500 • **Andrew Goodman**, Global Probiotics Council, *Connecting Interpersonal Microbial Variation to Drug Efficacy*, 1 year, $50,000 • **Celeste Greer**, Pharmaceutical Research & Manufacturers of America (PhRMA) Foundation, *Transcriptional Elongation Blockade as a Mechanism of Transcriptional Repression and Anti-Cancer Activities of Histone Deacetylase Inhibitors*, 2 years, $40,000 • **Isaac Hall**, American Heart Association, *Profiling Renal Repair for Outcomes After Kidney Injury in Transplantation*, 5 years, $593,000 • **Kristin Hoffmann**, Dermatology Foundation, *Identifying Prognostic Markets in Melanoma using Tissue Microarrays and Quantitative Analysis*, 2 years, $30,000 • **Theodore Holford**, Massachusetts General Hospital (NIH), *Lung Cancer Group for NCI's CISNET Program*, 2.2 years, $246,201 • **Tamas Horvath**, DiaLean Ltd., *Dln-101 for the Treatment of Parkinson's Disease*, 2 years, $131,658 • **Evelyn Hsieh**, American College of Rheumatology, *Osteoporosis Among HIV-Infected Individuals in China*, 2 years, $125,000; University of North Carolina at Chapel Hill (NIH), *Building Research Capacity for Global Health*, 1 year, $19,687 • **Yiyun Huang**, New York University School of Medicine (NIH), *Cb1 Receptor PET Imaging Reveals Gender Differences in PTSD*, 2 years, $257,705 • **John Hwa**, University of Pennsylvania (NIH), *Personalization of Therapeutic Efficacy and Risk*, 1.8 years, $516,493 • **Natalia Ivanova**, Mount Sinai School of Medicine (NIH), *Expression2Kinases: mRNA Profiling Linked to Multiple Upstream Regulatory Layers*, 1.8 years, $24,646 • **Min-Jong Kang**, Flight Attendant Medical Research Institute, *Role of NLRX1 in COPD Pathogenesis*, 3 years, $325,500 • **Haben Kefella**, Howard Hughes Medical Institute, *Regulation of Autophagy in the Retinal Pigment Epithelium, a Punitive Target for the Treatment of Age Related Macular Degeneration*, 2 years, $39,000 • **Kaveh Khoshnood**, Bhutan Foundation, *Training the Royal Institute of Health Services Faculty and Students in Capacity Building and Curriculum Development for New Public Health Programs in Bhutan*, 11 months, $48,639 • **Richard Kibbey**, American Diabetes Association, Inc., *Compartmentalized Phosphoenolpyruvate Metabolism in Insulin Secretion*, 3 years, $212750; Pfizer Inc., U.S. Pharmaceuticals Group, *Mechanism of Improved Function and Health in Human Islets Treated with the GK Activator PF-04937319*, 2 years, $472,711 **Grace Kim**, Wilkins (Lawson) Pediatric Endocrine Society, *Nutrigenetics Study of Fatty Liver Disease in Obese Youth*, 1 year, $50,000 • **Steven Kleinstein**, Mayo Clinic of Rochester (NIH), *Development of HIPC Data Standards to Support Cross-Center Projects*, 1 year, $153,993 • **Jeffery Kocsis**, National Multiple Sclerosis Society, *Transplantation of OPCs into the Demyelinated Spinal Cord*, 4 years, $614,593 • **Peter Krause**, Immunetics, Inc. (NIH), *Screening and Confirmatory Tests for Human Babesia*, 2 years, $34,579 • **Harlan Krumholz**, Robert Wood Johnson Foundation, *The RWJF Clinical Scholars Program: 12-14 Cohort Grant*, 2 years, $522,915; Robert Wood Johnson Foundation, *The RWJF Clinical Scholars Program: 12-14 Core Grant*, 2 years, $1,035,239 • **Tassos Kyriakides**, **William King**, University of Nicosia, *The University of Nicosia-Health Research/Services Training Grant*, 2 months, $6,431 • **Robert Leeman**, Alcoholic Beverage Medical Research Foundation (ABMRF), *A Brief, Web-Based Alcohol Reduction Intervention for Undergraduates: Initial Study*, 2 years, $100,000 • **Janghoo Lim**, Charles H. Hood Foundation, *Molecular Pathogenesis Studies of Childhood Neurological Disorders: Rett and Angelman Syndromes*, 2 years, $150,000 **Jun Lu**, Health Research Inc. (NIH), *Novel Approaches to Mammalian MicroRNA Target Prediction*, 1.8 years, $554,466 • **Don Nguyen**, International Association for the Study of Lung Cancer, *Targeting Lipid Metabolic Pathways in Metastatic Lung Adenocarcinoma*, 2 years, $80,000 • **Richard Nowak**, University of Miami (DHHS), *The Effectiveness of Prednisone for the Treatment of Ocular Myasthenia (EPITOME)*, 1.2 years, $16,256 • **Roni Nowarski**, Jane Coffin Childs Memorial Fund, *Role and Mechanisms of Inflammasome Dysregulation in Colorectal Tumorigenesis*, 3 years, $154,500 • **Alexander Panda**, American Federation for Aging Research (NIH), *Age Associated Defects in Localization and Trafficking of Toll-Like Receptor 1*, 5 years, $100,000 • **Chirag Parikh**, Roche Organ Transplantation Research Foundation, *Impact of Donor Kidney Function and Injury on Kidney Transplant Recipient Allograft Function*, 2 years, $156,530 • **Sunil Parikh**, University of California, San Francisco (NIH), *Antimalarial Pharmacology in HIV Co-infected Children and Pregnant Women in Uganda*, 1.9 years, $168,667 • **Farzana Pashankar**, State of CT Dept of Public Health, *State of CT Genetics*, 5 years, $502,250 • **Daniel Pelletier**, Johns Hopkins University, *A Randomized Controlled Trial of Vitamin D Supplementation in Multiple Sclerosis*, 1.7 years, $27,555 **Ismene Petrakis**, Ernest Gallo Clinic and Research Center, *Zonisamide and CPT for Veterans with PTSD and Comorbid Alcohol Dependence*, 2 years, $449,719 • **Virginia Pitzer**, Princeton University, *Evaluation of Candidate Vaccine Technologies Using Computational Models*, 1 year, $48,738 **Srikala Raghavan**, American Cancer Society, Inc., *Investigating the Role of Integrins in Organizing the Extracellular Matrix*, 3.4 years, $624,076 **Farah Rahiem**, American Psychiatric Association, *APA Minority Fellowship*, 8 months, $46,306 • **Lissandra Ramsey**, Tourette Syndrome Association, Inc., *Behavioral, Neurochemical and Pharmacological Analysis of HDC-KO Mice, a New Animal Model for Tourette Syndrome*, 1 month, $36,362 **Harvey Risch**, H. Lee Moffitt Cancer Center and Research Inst. (NIH), *Follow-Up of Ovarian Cancer Genetic Association and Interaction Studies (FOCI)*, 2 years, $89,057 • **Kurt Roberts**, Foundation for Surgical Fellowships, *Foundation for Surgical Fellowship 2012-2013*, 1 year, $61,000 • **Matthew Rodeheffer**, American Diabetes Association, Inc., *Characterization of Brown and Beige Adipogensis in Vivo*, 3 years, $255,200 • **Joseph Schlessinger**, Gilead Sciences, *Yale-Gilead Collaboration: siRNA Libraries and Their Use for Functional Genomic Screen*, 2 years, $834,214 • **Margretta Seashore**, State of CT Dept of Public Health, *State of CT Genetics*, 5 years, $990,812 • **Robert Sherwin**, New York University (NIH), *The Norepinephrine Transporter: A Novel Target for Imaging Brown Adipose Tissue*, 2 years, $326,659 • **Mark Shlomchik**, Hoffmann (F) - La Roche, Ltd, *Investigation of Efficacy and Mechanism of GA101 in Lupus Mice*, 1 year, $80,674 • **Albert Sinusas**, NFL Charities, *Non-Invasive Quantitative Imaging of Muscle Growth and Vascularization in College Football Athletes*, 1.5 years, $100,000 • **Mark Solomon**, American Heart Association, *Transcription Factors as Substrates of the Anaphase-Promoting Complex in Budding Yeast*, 3 years, $198,000 • **Yang Song**, American Heart Association (Founders Affiliate), *Role of VSMC-Mediated Cytokine Production in Age-Associated Inflammation and Atherosclerosis*, 2 years, $45,000 **Jeongmin Song**, Columbia University (NIH), *Role of Typhoid Toxin in the Pathogenicity of* Salmonella Typhi, 1.1 years, $135,893 • **David Stern**, DE-BIOPHARM S.A., *Combination Screening Debio 0932*, 1.3 years, $118,318; DEBIOPHARM S.A., *Combination Screening Debio 1143*, 1.9 years, $167,288 **Tamara Vanderwal**, American Psychoanalytic Association, *Cross-Modal Sensory Processing in Infants: A Longitudinal Brain Mapping Study*, 1 year, $16,000 • **Vamsidhar Velcheti**, American Society of Clinical Oncology, *Prognostic and Predictive Value of Programmed Death-1 Ligands in Non-Small Cell Lung Cancer*, 1 year, $50,000 **Merceditas Villanueva**, University of Connecticut (NIH), *ART Adherence and Secondary Prevention of HIV*, 1 year, $64,602; University of Massachusetts (DHHS), *New England AIDS Education and Training Center*, 2 years, $372,501 • **Emily Wang**, Foundation for California Community Colleges (DHHS), *Transitions Clinic Network: Linking High-Risk Medicaid Patients from Prison to Community Health Care*, 2 years, $207,303 **Hanbing Wang**, American Heart Association, *Hilary Hanbing Wand AHA No. 179941620*, 4 months, $3,320 • **Stephen Waxman**, Nancy Taylor Foundation for Chronic Diseases, Inc., *Nav1.7 and Chronic Pain: Generation of a Model Human Inherited Erythromelalgi (IEM) in Rodents*, 2 years, $241,959 • **Joanne Weidhaas**, University of Texas M.D. Anderson Cancer Center - Science Park, *MicroRNA as a Prognostic Marker in Cervical Cancer Patients After Chemoradiation: Analysis of Tissues from RTOG 90-01 and an Institutional Prospective Trial*, 2 years, $30,000 • **Brian Weiss**, University of Richmond (NIH), *Sodalis Glossinidius Irion Acquisition*, 3 years, $114,787 • **Graham Williams**, **Stacy Castner**, Cure Huntington's Disease Institute Foundation (CHDI), *Evaluation of PDE9 Inhibitor CHDI-00396436 and PDE4 Inhibitor CHDI-00315447 (DG-071) on the Performance of Rhes*, 1.2 years, $535,711 • **Andrew Xiao**, Ellison Medical Foundation, *Investigating the Role of Epigenetic Mechanisms for Genome Integrity Maintenance in Stem Cells during Aging*, 4 years, $400,000 **Mingyi Xie**, Leukemia and Lymphoma Society, *MicroRNA Target Identification & Biogenesis in a T-Cell Leukemia Causative Virus*, 3 years, $165,000 • **Jie Yao**, American Heart Association, *Functional and Systematic Analysis of Gene Positioning in Muscle Cells*, 4 years, $308,000

// Prize *(from page 1)* and is the most prevalent risk factor for heart attacks, heart failure, and stroke.

Lifton has identified mutations in more than 20 genes that cause either extreme hypertension or hypotension (low blood pressure) in people. He pioneered the discovery of human disease through the study of "outliers," people and families with extreme forms of common diseases. His work has demonstrated the fundamental role of salt reabsorption by the kidney in the regulation of blood pressure, and has provided the scientific rationale for worldwide efforts to prevent hypertension and reduce morbidity and mortality by limiting dietary salt intake, and also for improved therapeutic approaches to hypertension.

"The importance of Rick Lifton's work on the genetic basis of hypertension cannot be overstated. As a scientist and colleague, Rick represents the very best of Yale School of Medicine. We are delighted that the foundation has chosen to recognize his achievements," says Robert J. Alpern, M.D., dean and Ensign Professor of Medicine.

Said Google co-founder Sergey Brin and his wife, biologist and entrepreneur Anne Wojcicki, co-sponsors of the December 12 awards gala, "Scientists should be celebrated as heroes, and we are honored to be part of today's celebration."

Lifton earned his M.D. and PH.D. in biochemistry at Stanford University, and completed a residency in internal medicine at Boston's Brigham and Women's Hospital before coming to Yale in 1993. Among other honors, he is a member of the National Academy of Sciences, the Institute of Medicine, and a past recipient of the Wiley Prize in Biomedical Sciences.

Founded in 2013 by technology entrepreneurs, the Breakthrough Prize in Life Sciences Foundation is a nonprofit corporation dedicated to advancing breakthrough research, celebrating scientists, and generating excitement about the pursuit of science as a career. Its founders include Brin; Wojcicki; Internet entrepreneur Jack Ma; entrepreneur and venture capitalist Yuri Milner; and Facebook CEO Mark Zuckerberg.

Vilcek Foundation recognizes Yale geneticist's 'creative promise'

The Vilcek Foundation has named Antonio J. Giraldez, PH.D., associate professor of genetics, one of three recipients of the 2014 Vilcek Prizes for Creative Promise in Biomedical Science, awards that recognize significant contributions to American science made by immigrants.

Giraldez, born in Spain, focuses on the ways microRNAs (miRNAs) and other non-coding RNAs shape gene expression during embryonic development. Working with zebrafish, he and colleagues recently found that the mRNA family miR-430 is

Antonio Giraldez

responsible for the clearance of maternal mRNAs, providing insight into the mechanisms of how mRNAs regulate gene expression. His findings aid our understanding of the first steps that lead to embryogenesis after fertilization.

The Vilcek Prize for Creative Promise in Biomedical Science is awarded annually to three foreign-born scientists, age 38 or younger, for exceptional accomplishments early in their career. Each recipient receives a $35,000 cash award.

In 2013, Yale's Richard A. Flavell, PH.D., chair and Sterling Professor of Immunobiology, and Ruslan M. Medzhitov, PH.D., David W. Wallace Professor of Immunobiology, were jointly awarded the Vilcek Prize for Biomedical Science for their longstanding and influential work on the innate immune system, the first line of defense against infection by bacteria and viruses.

Yale-Jefferson Award honors couple's commitment to public service

Two alumni of the School of Medicine received the Yale-Jefferson Public Service Award for their commitment to service and social responsibility in November. Richard D. Gibbs, M.D. '86, and Patricia H. Gibbs, M.D. '87, were recognized for founding and sustaining the San Francisco Free Clinic (SFFC), which provides urgent medical care to uninsured people in San Francisco.

More than 8,000 patients visit the clinic each year to receive medications and care at no cost. Since the SFFC's founding 20 years ago, the Gibbses have taught, mentored, and inspired Yale medical students doing primary care clinical rotations at the clinic. With the precedents established by

TONY FIORINI

Yale Jefferson Public Service Award recipients (from left) Richard Gibbs, Tricia Gibbs, and Kara Scroggins (right) with Vice President Linda Koch Lorimer.

the SFFC, and with their help as early advisors, the Gibbses were instrumental in developing the HAVEN Free Clinic, the School of Medicine's student-run free clinic in the Fair Haven section of New Haven.

The award, presented at the assembly of the Association of Yale Alumni by Vice President Linda Koch Lorimer, J.D., was first given in 2012. It is conferred by Students and Alumni of Yale (STAY) to recognize individuals who inspire the Yale community through their contributions to the greater good. Candidates must have a demonstrated involvement in a Yale service project or have made substantial use of Yale facilities or services for an outside service project. The STAY awards are the local iteration of the national Jefferson Awards, given since 1972.

Video "The Yale-Jefferson Award for Public Service"
Available at youtube.com/yalecampus

Pioneer in women's health research is Spungen Bildner Professor

Carolyn M. Mazure, PH.D., professor of psychiatry and psychology and director of Women's Health Research at Yale (WHRY), has been appointed the inaugural Norma Weinberg Spungen and Joan Lebson Bildner Professor of Women's Health Research at Yale.

Carolyn Mazure

The professorship is endowed by a leadership gift from Elisa Spungen Bildner, of the Yale College Class of '75, and her husband, Robert Bildner, of the Yale College Class of '72, which complements gifts from other donors and an anonymous foundation. The professorship is named in honor of Elisa's mother and in memory of Robert's mother.

Mazure, also associate dean for faculty affairs, founded WHRY in 1998 as an interdisciplinary research center focused on women's health and gender differences. As director, she has steered WHRY through steady growth into a national model, widely known for initiating and supporting investigations on women's health and gender differences and emphasizing the translation of discoveries into practical health care advances.

The other key missions of WHRY include training new investigators in women's health, facilitating collaborations among scientists and institutions, and sharing health findings with the broader public through outreach efforts.

Since its founding, WHRY has awarded more than $4.5 million in pilot grants to nearly 70 investigators, who have obtained more than $52 million in external grants to further their research.

Mazure's contributions in women's health began with her own research in the field of depression. Her current research focuses on the interplay of stress, depression, and addictive disorders with an emphasis on gender difference.

Mazure received her doctorate in clinical psychology from Pennsylvania State University in 1980 and joined the School of Medicine's faculty in 1982.

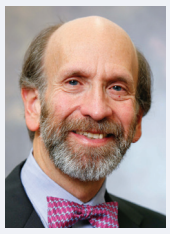
// IOM *(from page 1)* "Peter and Ruslan are two very different scientists who represent the spectrum of excellence we have among our Yale faculty," said Robert J. Alpern, M.D., dean and Ensign Professor of Medicine. "We are delighted that once again this has been recognized by the IOM."

Salovey has been honored with a National Science Foundation Presidential Young Investigator Award, a National Cancer Institute CIS Partner in Research Award, and a Substance Abuse and Mental Health Services Administration Excellence Award. In 2013 he was elected to the American Academy of Arts and Sciences.

Medzhitov was co-recipient of the 2013 Vilcek Prize for Biomedical Science, and of the Shaw Prize in Life Science and Medicine for 2011. He is also a past recipient of the Else Kröner Fresenius Award and the Lewis S. Rosenstiel Award for Distinguished Work in Basic Medical Research, and was elected to the National Academy of Sciences. His role in elucidating the workings of the innate immune system won him the Blavatnik Award for Young Scientists in 2007.

The IOM is an honorific membership body that also advises lawmakers, health professionals, and the public on health care and health policy. Salovey and Medzhitov are among 70 new members and 10 foreign associates elected to the IOM, bringing IOM's total membership to 1,966.

Awards & Honors



Gary E. Friedlaender, M.D., chair and Wayne O. Southwick Professor of Orthopaedics and Rehabilitation and professor of pathology, is the recipient of the 2014 William W. Tipton Jr., M.D. Leadership Award from the American Academy of Orthopaedic Surgeons (AAOS). The award recognizes leadership, mentorship, and significant accomplishment in and commitment to the field of orthopaedic surgery. Friedlaender has served as chair of the Department of Orthopaedics and Rehabilitation since 1986. He received the award at the AAOS's annual meeting in March.

Valentina Greco, PH.D., assistant professor of genetics and dermatology, is the 2014 winner of the International Society for Stem Cell Research's Outstanding Young Investigator Award. The award recognizes Greco's research into the interactions between stem cells and their niches, including the first direct, real-time visualization of stem cell divisions noninvasively in living mammals. Greco is a past recipient of the Dermatology Foundation's Research Career Development Award and the American Skin Association's Research Scholar Award. She came to Yale in 2009.

Becca Levy, PH.D., associate professor of epidemiology and psychology, was awarded the Ewald W. Busse Research Award for Excellence in Social and Behavioral Sciences by the International Association of Gerontology and Geriatrics (IAGG). Levy's research explores psychosocial factors that influence elders' cognitive and physical functioning, as well as their longevity. She is the recipient of numerous other honors and awards. The Busse Research Award, given once every four years, was presented at the IAGG's World Congress in Seoul, South Korea, last summer.

Two Yale scientists have been honored with National Institutes of Health (NIH) "High-Risk, High-Reward" Research Awards. **Amy F.T. Arnsten**, PH.D., professor of neurobiology and psychology, received one of 12 NIH Pioneer Awards. The five-year, $2.5 million grant supports Arnsten's research on the molecular vulnerabilities for disease in the brain's highly evolved association cortex. **Jason M. Crawford**, PH.D., assistant professor of chemistry and microbial pathogenesis, received the NIH Director's New Innovator Award—also a five-year, $2.5 million grant, awarded to early-career scientists pursuing highly promising lines of inquiry. The grant enables Crawford's research on gut-dwelling bacteria that play a role in the development of colorectal cancer. The 2013 "High-Risk, High-Reward" grants total about $123 million and support more than 78 scientists.