Medicine@Yale

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Advancing Biomedical Science, Education, and Health Care

Yale Cancer Center benefits doubly from generosity

United Technologies supports 'the power of innovation' in Yale's cancer care and research

United Technologies Corporation (UTC), a Hartford-based multinational manufacturer and Connecticut's largest private employer, has donated $3 million to establish a new endowed professorship at Yale Cancer Center (YCC).

The gift, which establishes the United Technologies Corporation Professorship in Cancer Research, stems from UTC's long-time commitment to supporting cancer care and research, and represents a deepened commitment by UTC to what its leaders see as a track record of success at Yale. In July 2008, UTC announced a $1 million gift to Smilow Cancer Hospital at Yale-New Haven, which was then under construction and which opened in 2009.

"Smilow Cancer Hospital is now delivering great service to the community, including UTC employees," says Louis Chênevert, chairman and CEO of United Technologies. "Our company has a long history of supporting leading organizations in our communities, and Yale Cancer Center is a proven leader."

The new professorship, which will support the full-time research activities of a faculty member whose primary research focus is cancer, is also part of what Chênevert describes as UTC's "broader efforts of promoting employee wellness."

Mark Reitsma, UTC's manager of Global Human Resources Support Operations, is one of many United Technologies employees who have been treated for cancer at Smilow. Diagnosed with stage 4 lung cancer in 2010, Reitsma was initially told that he had only a few months or years

COURTESY OF UNITED TECHNOLOGIES CORP

(From left) Mark Reitsma, a UTC employee and patient at Smilow Cancer Center, and Louis Chênevert, CEO of UTC.

to live. And then, at his supervisor's recommendation, he sought a second opinion at Smilow.

Under the care of Scott N. Gettinger, M.D., associate professor of medicine, Reitsma's treatment has included chemotherapy and new Phase I clinical trial drugs. Not only has his disease been stable, but // UTC *(page 7)*

Easing suffering, giving support at the end of life

Jennifer Kapo

The Palliative Care Program at Yale Cancer Center (YCC) has received a $1 million gift from the Milbank Foundation for Rehabilitation.

Directed by Jennifer M. Kapo, M.D., associate professor of internal medicine and chief of palliative medicine at Smilow Cancer Hospital at Yale-New Haven, the Palliative Care Program focuses on managing symptoms and quality of life issues for adult patients with serious, chronic, progressive, or terminal cancers at the hospital. The donation will support the program's services, research, and palliative care // Milbank *(page 7)*

New CEO will lead medical school's clinical practice

Executive arrives at a time of major growth in Yale's practice, and change in American medicine as a whole

Paul Taheri, M.D., M.B.A., has joined the School of Medicine as deputy dean and chief executive officer of Yale Medical Group (YMG), following a nationwide search. Taheri began his new role at Yale in early March.

Taheri was the senior associate dean for clinical affairs and president and CEO of the University of Vermont (UVM) Medical Group in Burlington as well as a professor of surgery at UVM. There, he was responsible for overseeing and managing a 500-member multispecialty practice with more than 1,000 staff and $250 million in annual revenue. Taheri has been credited with preparing the group, both financially and operationally, for the future of health care reform.

He comes to Yale at a pivotal time for the school's clinical practice, which has expanded remarkably over the past decade. The size of the clinical faculty has grown dramatically, clinical revenues have nearly doubled, and there has been a significant expansion in the breadth and depth of clinical programs. With these developments has come the need for a more centralized and unified physician group practice.

On a national scale, the passage and implementation of the Affordable Care Act represents a sea change for American medicine—particularly for academic medical centers such as Yale's—and the nation's serious shortage of primary care physicians presents an ongoing challenge.

"We know Obamacare is going to be here. We have to go with a very strong primary care base," says Taheri. "As long as we are data-driven, thoughtful, and methodical, we can manage the changes and balance all the missions of the enterprise, and come out more able to bear risk."

Taheri has been charged with establishing a strong management structure for YMG and maintaining its high-performing clinical operation. // YMG *(page 6)*

This month, Paul Taheri joins the School of Medicine as CEO of Yale Medical Group. Among other goals, Taheri aims to standardize the operations of the clinical practice across its many sites, fully integrate electronic medical records, and oversee an expansion of Yale's role in addressing the nation's continuing shortage of primary care providers.

RAJAN CHAWLA

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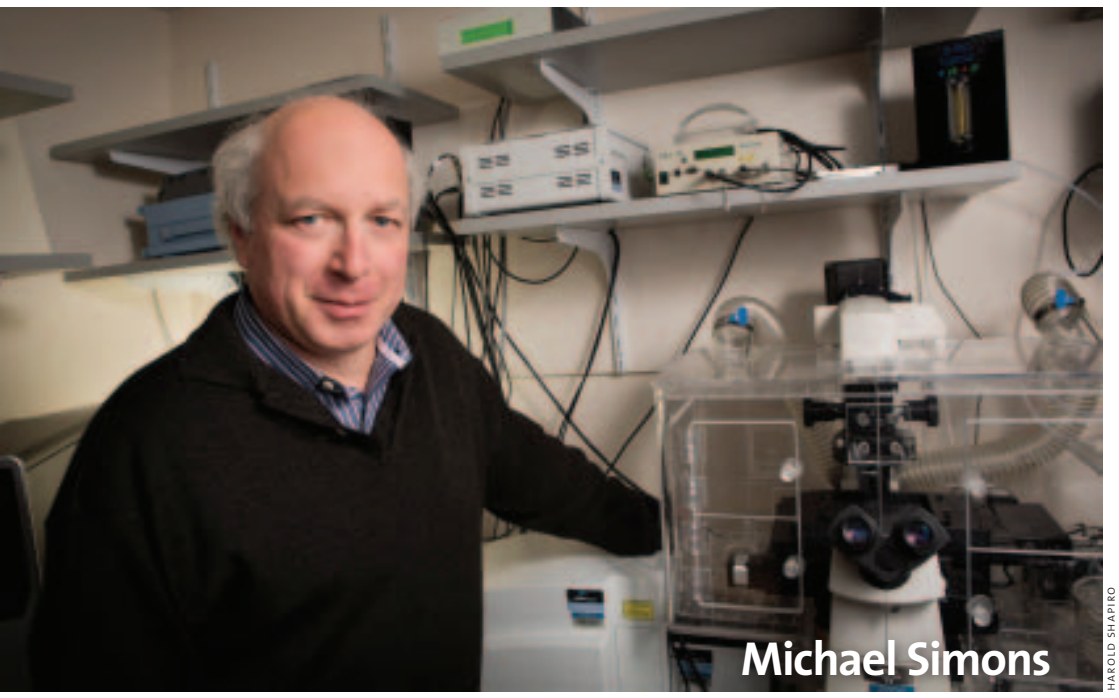

HAROLD SHAPIRO

Michael Simons, a leading researcher on the role of arteriogenesis in cardiovascular diseases, directs the Yale Cardiovascular Research Center (YCVRC). The YCVRC's collaborative spirit and unique scientific climate has attracted top cardiovascular scientists to the School of Medicine and has opened up new research directions and avenues of funding.

Getting to the heart of disease

Scientist works toward molecular therapies for cardiovascular diseases

Born in Leningrad (now St. Petersburg), Russia, to Jewish parents before the fall of the Soviet Union, Michael Simons, M.D., says a medical career was "sort of a default." Anti-Semitism barred Jews from many scientific pursuits, so his parents, both doctors, encouraged his interest in medicine as the basis for a strong natural science education.

Simons' family immigrated to Boston in 1978. Simons had begun a 6-year medical program immediately after high school in Russia, so he was admitted to Boston University School of Medicine as a third-year student, but he chose instead to start anew, as an undergraduate. "I thought, if I continue in a medical program, I'll forever have an inadequate undergraduate education," he says, speaking with a mild accent and an understated intensity.

Knowing nothing about the nearby Massachusetts Institute of Technology (MIT), Simons walked inside and introduced himself. "I figured it's probably a state school, so it can't be too expensive," he says, laughing. He applied and was offered a spot and a scholarship.

After graduating, Simons went to medical school at Yale, where he began to explore cardiology, crossing paths with influential figures in the field such as Barry L. Zaret, M.D., now professor emeritus of medicine, and S. Evans Downing, M.D., professor emeritus of pathology, an adviser for his thesis research in coronary physiology.

In 1993 Simons joined the faculty at Harvard Medical School and Boston's Beth Israel Hospital (now Beth Israel Deaconess Medical Center), whose chief of cardiology was William Grossman, M.D., whose success in recruiting leading molecular cardiologists soon transformed the program into one of the world's best. "I never knew if it happened by design or by accident, but we were able to do what nobody else could do," Simons says.

By that time, physicians were routinely using procedures like balloon angioplasty and stenting to treat coronary artery disease, but Simons was interested in doing so by stimulating the growth of new arteries, a process known as arteriogenesis. To that end, he began studying whether recently discovered angiogenic growth factors might be used to accomplish that goal. Animal research had shown promise, but studies in humans were inconclusive. To better understand arteriogenesis, Simons studied the molecular controls that determine blood vessel growth. He continued this research for seven years as the A.G. Huber Professor of Medicine at Dartmouth Medical School, uncovering new and unexpected mechanisms controlling how the signals of growth factors are processed in their target cells.

Returning to Yale in 2008, Simons succeeded Zaret as the Robert W. Berliner Professor of Medicine and chief of the medical school's Section of Cardiovascular Medicine, and he launched the Yale Cardiovascular Research Center, which has become a research powerhouse under his direction.

Simons' work holds great promise beyond the treatment of coronary disease. "There are distinct signals that control cell fate and thus the type of vasculature that's formed," says Simons, also professor of cell biology. By manipulating these signals, his work suggests, the growth of arteries, veins, and lymphatic vessels can be stimulated in a targeted way to treat arterial, venous, and lymphatic diseases—and he also believes that manipulating the vessels that supply blood to tumors may one day lead to new possibilities for treating cancer.

Women's Health Research at Yale celebrates 15 years of success

Women's Health Research at Yale (WHRY), whose mission is to ensure that women are included in research studies, gender differences in health are examined, and health outcomes are analyzed by gender, celebrated its 15th anniversary in February.

Since its inception, WHRY has awarded more than $4.4 million in "seed" grants to more than 60 Yale investigators. Many of these scientists used the results from WHRY-funded studies to obtain a total of nearly $50 million in grants that further their work in key areas of research. Some of these areas include developing new models for treating breast cancer and preventing tumor metastasis; smoking and other addictive behaviors; cardiovascular disease; depression; osteoporosis; and adaptation of returning women combat veterans.

WHRY's mission also includes building interdisciplinary research cores, training the next generation of researchers, and engaging the community through outreach.

"Three-fourths of the pilot investigators are junior and mid-level faculty who need initial funding to launch their research on women's health and gender differences," says Carolyn M. Mazure, PH.D., director of WHRY, professor of psychiatry and psychology, and associate dean for faculty affairs. "More than half of the funded investigators obtained external funding using their pilot results, at least five times the success rate for new investigator-initiated National Institutes of Health grant applications."

Carolyn Mazure

WHRY was founded in 1998 with funding from the Patrick and Catherine Weldon Donaghue Medical Research Foundation.

Medical student is ahead of the curve, and still under 30

Nicholas Downing

Nicholas Downing, a student in the School of Medicine's Class of 2014, has been named one of *Forbes* magazine's 30 most influential people under the age of 30. In 2011, as a first-year student, Downing began comparing the speed with which the U.S. Food and Drug Administration (FDA) approves new drugs to the speeds of drug approval by comparable agencies in Europe and Canada.

His work, funded by the Pew Foundation and published in 2012 in *The New England Journal of Medicine* (Downing is one of the youngest-ever first authors published in the prestigious journal) showed that, contrary to popular belief, the FDA was faster than regulators in other countries at approving new medicines.

The report concluded that given the FDA's lead over its peer institutions, criticisms about the inefficiency of the agency's review process for novel drugs may be unfounded.

The idea for the FDA study emerged from the impending reauthorization of the Prescription Drug User Fee Act (PDUFA), which was first enacted in 1992 to allow the FDA to collect fees from drug companies to fund the process of new drug approval.

Downing says that his study "injected some objective information into what had become a relatively subjective debate."

CORRECTION In our September/October profile of Joan A. Steitz, PH.D., the description of the discovery of single-nucleotide ribonuclear proteins (snRNPs) should have indicated that this work was conducted with Michael Lerner, M.D., PH.D., then a student working in Steitz's lab.

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Proteins folding badly: havoc ensues

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When exposed to the antibiotic streptomycin, bacterial cells begin making mistakes in protein production. The error-ridden proteins fold improperly and accumulate in the cell, clumping into toxic aggregates that eventually kill the bacteria.

Such aggregates are of broad interest because they are also a hallmark of neurodegenerative conditions such as Alzheimer's disease. A research group led by Dieter Söll, PH.D., Sterling Professor of Molecular Biophysics and Biochemistry and professor of chemistry, Jesse Rinehart, PH.D., assistant professor of cellular and molecular physiology, and Jiqiang Ling, PH.D., postdoctoral associate, have found that proteins misfolded due to streptomycin are unusually prone to oxidation, a chemical state more likely to damage the bacterial cell. When the group amplified the expression of certain genes related to oxidation and reduction, streptomycin induced far less damage.

The results, published in the December 14, 2012 issue of *Molecular Cell*, could shed light on protein aggregates related to human disease.

How bad timing befalls the brain

In patients with Parkinson's disease (PD), carefully timed actions, such as the coordinated behaviors that make up body movements, can be severely disrupted. The brain's prefrontal cortex, which is involved in planning behavior, receives input from the ventral tegmental area (VTA), a cluster of neurons in the midbrain that produce the neurotransmitter dopamine. Since dopamine neurons are damaged in PD, a team of Yale scientists wanted to know whether VTA neurons could play a role in temporal dysfunction.

Ralph J. DiLeone, PH.D., associate professor of psychiatry and neurobiology, and colleagues trained mice to press their noses against a wall for food rewards, which would only be given if at least 20 seconds had elapsed since the last reward. Over time, the mice learned to wait 20 seconds before touching the wall.

As reported in the December 11, 2012 issue of *Proceedings of the National Academy of Sciences*, when the team precisely targeted dopamine receptors in prefrontal neurons to alter their activity, the mice were much less accurate on the 20-second test—they frequently tried to get a reward after only 10 or 15 seconds. The findings could provide a new target for drugs to help PD patients who have difficulty timing their behaviors.

Mapmakers of the living human body

Positron emission tomography is a vital tool for School of Medicine researchers studying psychiatric diseases, diabetes, and cancer

Imagine trying to develop a drug and being able to see how and where that drug acts inside the body of a living person. Just such a tool is provided by positron emission tomography (PET), an imaging technology that is aiding drug development and research on the mechanisms of disease at the School of Medicine's state-of-the-art PET Center.

Animal models are useful for many aspects of biological research, but when the aim is translating research discoveries into applicable treatments for humans, particularly for brain disorders, research in living humans is critical. "It's only through imaging that you can begin to understand the complexity of the human brain," says Robert S. Sherwin, M.D., the C.N.H. Long Professor of Medicine and director of the Yale Center for Clinical Investigation (YCCI).

It is precisely the inaccessibility of the human brain that makes *in vivo* imaging technologies like PET so valuable. "If you suffer from an illness of nearly any organ of your body, it's perfectly acceptable to donate a piece of that organ for analysis" via biopsy, says John H. Krystal, M.D., Robert L. McNeil Jr. Professor of Translational Research and chair of the Department of Psychiatry. "But the preciousness of brain tissue has prohibited psychiatry from developing the kind of understanding of the organ that it studies relative to what is possible in other areas of medicine."

In addition to the critical role it has played in neuroscience research at Yale, PET is now beginning to see wide use in research on diseases such as cancer and diabetes.

Led by Richard E. Carson, PH.D., professor of diagnostic radiology and biomedical engineering, the PET Center's mission—to provide the highest quality of nuclear imaging to the medical school's researchers—is embodied in numerous collaborations both on campus and off, all relying on an intricate and well-choreographed network of technology and personnel.

At the heart of the 22,000-square-foot facility is a cyclotron, which accelerates atomic particles to produce short-lived radioactive isotopes. A team of radiochemists led by Yiyun Henry Huang, PH.D., director of chemistry at the Center and associate professor of diagnostic radiology, uses these isotopes to synthesize radioactive versions of drug molecules or other biologically active substances. These radioactive molecules are called tracers: they trace the paths of molecules that are important in human physiology, such as glucose, and they're administered to research subjects in extremely small, trace amounts.

A subject lies within a PET scanner (similar in appearance to a CT scanner) while radiochemists, working under great time constraints due to the short half-life of PET isotopes, create the labeled compounds. When these compounds are injected into the subject's body they navigate and bind to specific organ sites. The PET scanner is able to detect the accumulation of radioactivity at these various sites and convert this data into color-coded maps. But PET provides more than pretty pictures: the images are based on precise quantitative physiological and pharmacological information that can be useful in its own right.

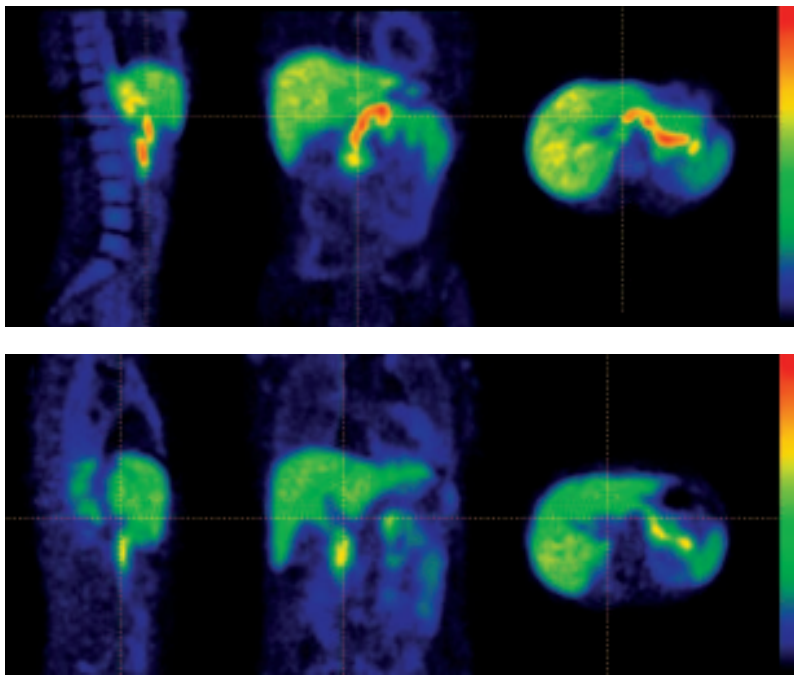
In psychiatry, imaging technologies like PET have enabled some of the most critical discoveries in recent decades. Since the early 1960s, psychiatrists had hypothesized, for instance, that psychosis—a set of symptoms seen in schizophrenia that includes hallucinations and delusions—was a consequence of hyperactivity of the brain's dopamine signaling system. "But until recently, we had no way to test that hypothesis," Krystal says. This changed in the 1990s, when new research approaches in imaging made it possible to measure dopamine release noninvasively in a living person. "Now that we have PET," Krystal says, "we've identified a number of pathological mechanisms that might be targeted with treatments for psychiatric disorders."

In the quest to find such treatments, brain imaging has become essential. Single-photon emission computed tomography, or SPECT, is a complementary imaging tool (often used during cardiac stress tests) that is more widely available than PET and does not require a cyclotron, because SPECT tracers, often based on iodine or technetium, are longer-lived and can be ordered from suppliers. But PET has become more popular thanks to the development of the PET isotope Fluorine-18, which has a longer half-life than most PET tracers and is widely used in clinical // **PET Center** *(page 7)*

Richard Carson

Yiyun Henry Huang

Evan Morris



COURTESY OF RICHARD CARSON

An example of the Yale PET Center's expansion of its research portfolio beyond neuroscience and psychiatry, these images were made using a tracer for insulin-producing pancreatic β-cells. (Top) In three views of a healthy subject there is robust uptake of the tracer (red) in the pancreas, indicating a substantial population of β-cells. (Bottom) In a patient with type 1 diabetes, cooler colors in the pancreatic region indicate a compromised population of insulin-producing cells.

Scanning the horizon

There is no shortage of great ideas at Yale School of Medicine, as evidenced by the story on this page describing the number and variety of investigators using positron emission tomography (PET) to study psychiatric diseases, diabetes, and cancer. The strengths of Yale's basic science, translational, and clinical research continues to provide extraordinary opportunities to pioneer many promising and crucial medical discoveries. We have invested strategically in technology and core equipment that assists many researchers in their work, making the School of Medicine one of the largest and most productive biomedical research institutions in the world.

Medical school faculty are active in hundreds of fields, working to discover basic biological mechanisms, understand disease processes, develop new diagnostic and therapeutic strategies, and analyze disease incidence and treatment outcomes across populations. Our research enterprise is robust and highly collaborative and it is among the top five recipients of funding from the National Institutes of Health.

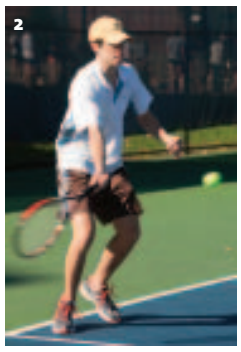
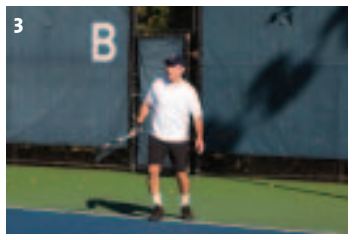
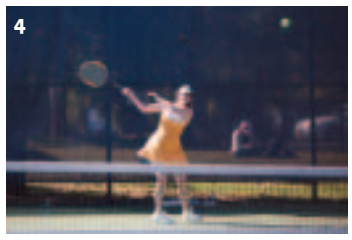
The generosity of individual donors can accelerate Yale's groundbreaking research. With independent funds, Yale researchers are able to harness the power of cutting-edge technology—like PET imaging—and pursue tomorrow's most significant biomedical discoveries. There are many ways you can participate:

Create a research fund to support new investigations	*$100,000*
Endow a Yale Scholar fund to support a young investigator (eligible for 100% matching funds from Yale University)	*$2.5 million*
Fund a professorship to assist a distinguished researcher	*$3 million*

For information about these and other ways to support the School of Medicine, contact Jancy Houck, associate vice president for development and director, medical development, at (203) 436-8560 or jancy.houck@yale.edu

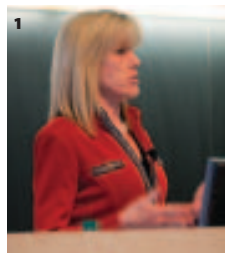
OUT & ABOUT

September 23 School of Medicine students and faculty took their talents to the courts at the **Faculty-Student Tennis Classic**. **1.** (From left) Medical students **Anton Safonov** '15, **Joel Winer** '15, **Jia Liu** '15, and **Michael Chang** '15. **2. Alex Scherer** '18. **3. Robert Udelsman**, M.D., M.B.A., chair and William H. Carmalt Professor of Surgery and surgeon-in-chief at Yale-New Haven Hospital, attends the baseline. **4. Jennifer A. Galvin**, M.D., assistant professor of ophthalmology and visual science and pediatrics, keeps her eye on the ball. **5. Jordan Gruskay** '15, gives it his all.

TERRY DAGRADI (5)

October 9 **1.** The Donaghue Foundation's annual **Andrews Lecture** was given by **Sue Sheridan**, M.B.A., deputy director of patient engagement at the Washington, D.C.-based Patient-Centered Outcomes Research Institute. **2. Mark R. Mercurio**, M.D., M.A., professor of pediatrics and director of the School of Medicine's Program for Biomedical Ethics (left), and **Moreen Donahue**, D.NP., R.N., senior vice president, patient care services, and chief nursing officer, Western Connecticut Health Network, take questions. **3. Raymond S. Andrews Jr.**, a trustee of foundation from 1993 to 2007 for whom the lectureship is named, enjoys a light moment.




TERRY DAGRADI (3)

October 18 A reception was held in the medical school's Historical Library honoring the **appointment of George Lister, M.D., as chair of the Department of Pediatrics**. Lister, seen here with a patient, **Jonathan Narducci**, is a 1973 graduate of the School of Medicine and former member of its pediatrics faculty. Lister is Jean McLean Wallace Professor of Pediatrics, professor of cellular and molecular physiology, and physician-in-chief at Yale-New Haven Children's Hospital.


HAROLD SHAPIRO



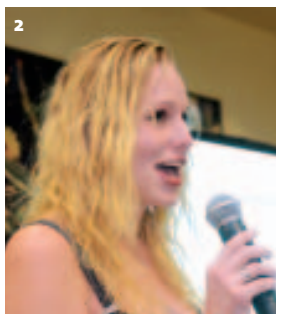
GALE ZUKER (3)


November 2 The Jane Coffin Childs Memorial Fund for Medical Research held a **Symposium** in honor of its 75th anniversary. **1. Huda Y. Zhogbi**, M.D., of Baylor College of Medicine. **2.** Members of the board include (front, from left) **Stephen J. Elledge**, PH.D., of Harvard Medical School; **Randy W. Schekman**, PH.D., of the University of California–Berkeley; **Cynthia J. Kenyon**, PH.D., of the University of California–San Francisco; and (back, from left) **Haifan Lin**, PH.D., professor of cell biology and genetics at the School of Medicine and director of the Yale Stem Cell Center; **Richard M. Losick**, PH.D., of Harvard University; Zhogbi; **John Kuriyan**, PH.D., of the University of Califorania–Berkeley; and **Thomas D. Pollard**, M.D., Sterling Professor of Molecular, Cellular and Developmental Biology, professor of molecular biophysics and biochemistry, and dean of the Yale Graduate School of Arts and Sciences. **3.** (From left) **Bronwen A. Childs**, member of the Fund, and **James E. Childs**, SC.D., senior research scientist and lecturer in epidemiology at the School of Public Health and chairman of the Fund's board of managers.




TERRY DAGRADI (3)

November 6 A celebration of the election of **Marina Picciotto**, PH.D., Charles B.G. Murphy Professor of Psychiatry and professor of neurobiology and pharmacology, to the **Institute of Medicine** was held in the medical school's Historical Library. **1.** Members of Picciotto's lab (from left) include **Mary Burke**, **Seth Taylor**, **Cali Calarco**, **Emily Einstein**, PH.D., Picciotto, **Margreet Plantenga**, **Yann S. Mineur**, PH.D., **Yon Woo Jung** , **Samantha M. Sheppard**, and **Sam R.S. Blakeman**. **2.** (From left) **John H. Krystal**, M.D., chair of the Department of Psychiatry and Robert L. MacNeil Jr. Professor of Translational Research; Picciotto; **Robert J. Alpern**, M.D., dean and Ensign Professor of Medicine; and **Pietro De Camilli**, M.D., Eugene Higgins Professor of Cell Biology and professor of neurobiology. **3.** Picciotto and her husband, **Angus C. Nairn**, PH.D., Charles B.G. Murphy Professor of Psychiatry and professor of pharmacology.


JOHN CURTIS (4)

November 15 Yale students in the health professions came together to organize the **20th Annual Hunger & Homelessness Auction**. This year, more than $27,000 was raised for charities and service agencies in the New Haven area. **1.** (From left) **Linh Vu** '16, **Richard Kim** '16, and **Lucas Butler** '16, make a bid. **2. Amanda King** '15, one of the auction's co-organizers. **3. James J. Abrahams**, M.D., professor of diagnostic radiology and surgery, with a friend. **4.** Students in the Physician Associate program with (in bow tie) **William B. Stewart**, PH.D., associate professor of surgery.

Cracking one of *Salmonella*'s secrets

WIKIMEDIA COMMONS

Some *Salmonella* bacteria are flexible—a mouse or a monkey is as good a host as a human. But *Salmonella* Typhi (*S.* Typhi), which causes typhoid fever, is picky: it survives *only* in human cells. In the November 16, 2012 issue of *Science*, Jorge E. Galán, chair and Lucille P. Markey Professor of Microbial Pathogenesis, and postdoctoral fellow Stefania Spanò, PH.D., explain why *S.* Typhi dies off inside non-human cells.

In many types of *Salmonella*, a protein called GtgE keeps a group of enzymes away from the vacuole, a membrane that surrounds the bacteria inside host cells. But *S.* Typhi lacks GtgE, and in non-human cells the membrane becomes studded with these enzymes, including one called Rab32. In mouse immune cells Rab32 delivers antimicrobial factors to the *S.* Typhi-containing vacuole, but in humans, "the immune system is still firing bullets, but this pathogen has learned how to dodge them," Galán says. When the scientists blocked Rab32 or added the *GtgE* gene to *S.* Typhi, the bacterium successfully infected mice for the first time, results that could lead to new treatments for typhoid fever.

What's behind a risky cellular shift

Yale scientists have pieced together a molecular program that sustains endothelial cells, which line blood vessels throughout the body. Researchers had proposed only recently that in a process called Endo-MT, these cells transition into another type, mesenchymal cells, which prompt the buildup of scar tissue in vessel walls, heart valves, and other tissues. The Endo-MT shift is suspected to play a role in many conditions, including atherosclerosis and hypertension, but it wasn't fully understood how the change takes place.

In the December 27, 2012 issue of *Cell Reports*, a team led by Michael Simons, M.D., Robert W. Berliner Professor of Medicine and section chief of cardiovascular medicine, shows that a signaling molecule called fibroblast growth factor (FGF) maintains levels of *let-7*, a snippet of genetic material known as a microRNA. In turn, *let-7* puts the brakes on expression of the receptor for a signaling molecule called transforming growth factor beta (TGF-β). When TGF-β binds to its receptor it directly induces Endo-MT, so when FGF expression was blocked, *let-7* levels plummeted, and TGF-β did its damage.

"The loss of FGF signaling input may be the root cause of a number of the most common cardiovascular illnesses," says Simons.

Stem cells reveal a long-hidden mosaic

The cells that make up each human body are discovered to be surprisingly different from one another at the level of the genome

Although the many cells in a human body have distinct functions and appearances, it's generally been assumed that they all share the same genetic blueprint. So when adult cells are reprogrammed into their most basic, stem cell state, it's assumed that the resulting stem cells will all be the same. Such induced pluripotent stem cells (iPSCs), the thinking goes, could then be coaxed to develop into one of a number of different cell types that genetically match a donor. But a new discovery by a team of Yale researchers has upended this reasoning: cells accumulate so many genetic changes during a human's lifetime, they've found, that even a single tissue can give rise to genetically diverse iPSCs.

"These cells are increasingly used as models for disease and potentially can be used as the basis for treatments," says Flora M. Vaccarino, M.D., Harris Professor in the Child Study Center and professor of neurobiology, who led the new study. "But there was evidence based on other experiments that there was genetic variation among populations of iPSCs, which could be bad news for the field."

The variation had been spotted when other researchers compared the genomes of iPSCs that they expected to be identical, since they'd all been reprogrammed from the same tissue in a single individual. Instead, when the iPSC genomes were compared to one another, huge chunks of DNA were found to be duplicated or deleted—a phenomenon called copy-number variation (CNV). Scientists began to fear that reprogramming creates unstable genomes and an increased ability to develop mutations, which would undermine the promise of iPSCs for both research and therapy.

But Vaccarino and her collaborators, including first author Alexej Abyzov, PH.D., associate research scientist, and co-senior authors Mark B. Gerstein, PH.D., the Albert L. Williams Professor of Biomedical Informatics, and Alexander Urban, PH.D., of Stanford University School of Medicine, thought more work was needed to show exactly what was causing these CNVs, so they launched a detailed genomic study of a group of iPSC cell lines that originated from skin cells of seven individuals. Whole-genome DNA sequences were obtained from three iPSC lines from each donor and were compared through several bioinformatic approaches to that of the donor's skin cells.

"The first thing we found was that there was, in fact, an alarming number of copy number variations, both duplications and deletions," says Vaccarino. Each iPSC line had an average of two CNVs, she says, though some had as many as five. "But we were still not convinced that this was due to the reprogramming." Then they were surprised to notice that two different iPSC cell lines that originated from the same person had an identical CNV. For both lines to have developed precisely the same variation independently was highly unlikely, and the observation suggested that the variation already existed in the donor's skin cells and was not due to the reprogramming used to make the iPSCs.

TERRY DAGRADI

Participants in a new study that used stem cells to reveal an unexpected degree of genetic mosaicism in human skin cells included (standing, from left) Livia Tomasini, Anna Szekely, Mike Wilson, Sherman Weissman, Anita Huttner, Elena Grigorenko, and Ying Zhang. (Seated, from left) Alexej Abyzov and Flora Vaccarino, the study's senior author.

// Stem cells *(page 7)*

Spine Center lets patients in pain get back on track

Susan Cusano and Nina Kadan-Lottick, M.D., share an unhappy distinction: Far too early, they felt like frail, elderly women. Cusano, 55, could barely walk. Kadan-Lottick, associate professor of pediatrics, spent her early 40s gradually cutting back on activities until she was no longer playing outside with her children.

Both women are patients at the new Yale-New Haven Hospital Spine Center in New Haven, where spine surgeons Khalid M. Abbed, M.D., and Jonathan N. Grauer, M.D., stopped their debilitating pain and helped them reclaim their lives. Abbed, assistant professor of neurosurgery, and Grauer, associate professor of orthopaedics and rehabilitation and of pediatrics, are part of an interdisciplinary team at the Spine Center that brings a variety of specialists under the same roof for optimal treatment of any spinal ailment, surgical or not, in the most convenient and efficient manner possible.

The Spine Center team, which also includes spine surgeons Peter G. Whang, M.D., and James J. Yue, M.D., both associate professors of orthopaedics and rehabilitation, and Maxwell S. Laurans, M.D., assistant professor of neurosurgery, and Associate Professor of Neurosurgery Michael L. DiLuna, M.D., are aiming to set up a system that will allow a patient under a surgeon's care to be sent down the hall to a medical spine specialist or some other caregiver. "We can send them to physical therapists whom we routinely communicate with," says Grauer. The center also plans to recruit a physiatrist—a clinician who specializes in treating pain and helping patients regain function.

The new center, at One Long Wharf, is located in a large suite complete with X-ray machines, and the physical therapy gym has windows that overlook Long Island Sound. Clinicians work in a hub surrounded by exam rooms, so it is simple for providers to review a diagnostic scan together or collaborate on a treatment plan.

Cusano and Kadan-Lottick were treated with surgery, but they say they found it reassuring that they were able to evaluate all their options.

Cusano came to Grauer with significant symptoms in her legs related to her lumbar spine. She had seen other doctors, but was still looking for a physician who would spend the time necessary to get to the root of her complex problem. "I felt like I was 100," remembers Cusano. Grauer recommended surgical treatment known as decompression and fusion. Though Cusano didn't relish having an operation, she is now happy with her decision. "I'm raking. I'm shoveling snow. I just lifted a

ROBERT LISAK

Donna Riccitelli, a registered technologist in radiology, helps a patient prepare for an X-ray at the Spine Center.

// Spine Center *(page 6)*

Grants and contracts awarded to Yale School of Medicine

November 2011–February 2012

Federal

Hervé Agaisse, NIH, *Mechanisms of Intracellular Pathogen Dissemination*, 5 years, $2,078,958 **Hal Blumenfeld**, NIH, *Functional Neuroimaging in Childhood Absence Epilepsy*, 5 years, $1,819,456 • **Titus Boggon**, NIH, *The Mechanism of Arg Kinase Activation by Integrin B1*, 4 years, $546,898 • **Maria Diuk-Wasser**, U.S. Environmental Protection Agency, *Novel Behavioral Intervention for Prevention of Tick-Borne Infection on Block Island*, 2 years, $150,296 **Peter Glazer**, NIH, *Novel Triplex-Engineered, BRCA1-Mutated Cell Lines for Research*, 2 years, $431,517 • **Mark Hochstrasser**, NIH, *Function and Assembly of Eukaryotic Proteasomes*, 4 years, $1,280,017 • **Ellen Hoffman**, NIH, *A Novel Zebrafish Model for the Functional Analysis of Genes in Autism*, 5 years, $752,967 • **Susan Kaech**, NIH, *The Role of STAT3 in Effector and Memory CD8 T Cell Longevity and Metabolism*, 2 years, $456,292 **Maria Kamenetska**, NSF, *Unwinding DNA: Measuring Mechanical Stiffness of a Single DNA Molecule to Understand Histone Control over Gene Expression*, 2 years, $113,000 • **Anthony Koleske**, NIH, *The Mechanism of Arg Kinase Activation by Integrin B1*, 4 years, $739,728 • **Miler Lee**, NIH, *Characterizing Modes of Maternal RNA Degradation during Vertebrate Development*, 3 years, $161,802 • **Nandakumar Narayanan**, NIH, *Prefrontal Dopamine and Cognitive Symptoms of Parkinson's Disease*, 5 years, $871,290 • **Laura Niklason**, NIH, *Molecular Mechanisms of Arteriogenesis*, 5 years, $122,888 • **Polloneal Ocbina**, NIH, *Investigating the Requirement of microRNAs in VEGF Signaling* In Vivo, 1 year, $8,291 • **Craig Roy**, NIH, *Deciphering Ubiquitin-Regulation Host Responses to the Intracellular Pathogen* Legionella pneumophila, 2 years, $428,117 **Martin Schwartz**, NIH, *Molecular Mechanisms of Arteriogenesis*, 5 years, $387,901 • **William Sessa**, NIH, *Molecular Mechanisms of Arteriogenesis*, 5 years, $485,877 • **Gerald Shulman**, NIH, *Mechanisms of Fat-Induced Insulin Resistance*, 4 years, $1,363,421 • **Michael Simons**, NIH, *Molecular Mechanisms of Arteriogenesis*, 5 years, $574,110 **Albert Sinusas**, NIH, *Molecular Mechanisms of Arteriogenesis*, 5 years, $147,208 • **Richard Sutton**, NIH, *Production of HIV Vector Supernatant Using Helper-Dependent Adenovirus*, 1 year, $221,284 • **Daniela Tirziu**, NIH, *Molecular Mechanisms of Arteriogenesis*, 5 years, $139,108 **Christian Tschudi**, NIH, *Transcriptome Analysis of* Leishmania panamensis *Developmental Stages*, 2 years, $166,042 • **Tobias Walther**, NIH, *Cellular Functions of Plasma Membrane Organization by Eisosomes*, 3.9 years, $1,231,956 • **Min Wang**, NIH, *Nicotinic Receptor Effects on Neurophysiology of Dorsolateral Prefrontal Cortex*, 3.8 years, $1,356,627 • **Dianqing Wu**, NIH, *Identification of Novel Genes as Being Important for Neutrophil Functions*, 2 years, $456,553

Non-federal

Nancy Angoff, Arnold P. Gold Foundation for Humanism in Medicine, *Arnold P. Gold Foundation 2012*, 5 months, $2,000 • **Baptiste Barbot**, Spencer Foundation, *Identity (re)Creation in Delinquent Adolescents*, 1.5 years, $38,900 **Henry Binder**, Flinders University, *Development of New Strategies to Improve Zinc Status in Children with Environmental Enteropathy at Risk of Diarrhea*, 3 years, $55,524 • **Linda Bockenstedt**, Nat'l Research Fund for Tick-Borne Diseases, Inc., *Regulation of* Borrelia burgdorferi*-induced Inflammation by TAM Receptors*, 1 year, $60,000 **Jonathan Bogan**, American Diabetes Association, Inc., *Diet-Induced Insulin Resistance in Adipocytes*, 3 years, $339,250 • **Elizabeth Bradley**, Commonwealth Fund, *Hospital Strategies to Reduce Risk-Standardized 30-Day Mortality for Patients with Heart Attacks*, 1.5 years, $194,931; Management Sciences for Health, *Sustainable Leadership, Management, and Governance*, 4.4 years, $86,016 • **Jessica Brown**, American Cancer Society, Inc., *Do ENE-like Structures Stabilize Cellular Noncoding RNAs?* 3 years, $150,000 **Jean-Marie Buerstedde**, Nat'l University of Ireland, Galway, *Locus Specificity of Immunoglobulin Gene Diversification*, 2 years, $31,032 **Jersey Chen**, American Heart Association, *Incidence, Outcomes, and Treatment of Cardiotoxicity After Breast Cancer*, 3 years, $197,874 • **Hyung Chun**, American Heart Association (Founders Affiliate), *Apelin-Targeted microRNAs in Pulmonary Arterial Hypertension*, 3 years, $198,000 **Eve Colson**, Association of American Medical Colleges, *Identifying Beliefs About Barriers to Interprofessional Education Services*, 8 months, $5,000 • **Shawn Cowper**, University of Pittsburgh (NIH), *University of Pittsburgh Clinical and Translational Science Institute*, 4 months, $4,478 **Sabrina Diano**, American Diabetes Association, Inc., *Minority Undergraduate Internship*, 1 year, $3,000 • **Kyle Draheim**, American Cancer Society, Inc., *Elucidating the Significance of ILK/Integrin Tail Interactions*, 3 years, $150,000 **Marie Egan**, Cystic Fibrosis Foundation, *Cystic Fibrosis Therapeutics Development Center*, 1 year, $69,535 • **John Elefteriades**, Ministry of Education and Science of the Russian Federation, *MESRF Scholarship for Bulat Ziganshin*, 8 months, $30,415 • **Elisabeth Erekson**, American Urogynecologic Society, *Frailty and Functional Status in Older Women with Urinary Incontinence*, 2.1 years, $25,000 • **Irina Esterlis**, Charles A. Dana Foundation, Inc., *Brain Imaging of the Glutamatergic System in Depression*, 3 years, $200,000 • **Terri Fried**, Patrick and Catherine Weldon Donaghue Medical Research Foundation, *Development and Implementation of Patient-Centered Guidelines*, 4 years, $880,000 **Thomas Gill**, University of Florida (NIH), *The LIFE Study*, 1.4 years, $1,899,930 • **Peter Glazer**, Doris Duke Charitable Foundation, *Nanoparticle-Mediated Correction of the Sickle Cell Disease Mutation*, 3 years, $486,000 • **Andrew Goodman**, Crohn's & Colitis Foundation of America, *Dissecting the Role of the Human Gut Microbiota in Aminosalicylate Metabolism*, 1 year, $347,490 • **Valentina Greco**, American Cancer Society, Inc., *Stem Cell Deregulation during Tumor Regression*, 4 years, $720,000 • **David Greer**, University of Texas Health Science Center at Houston (NIH), *University of Texas Specialized Program in Acute Stroke*, 1.3 years, $22,500 **Elena Grigorenko**, Florida State University (NIH), *Genomic Sequence Pattern Analyses in African-American Families with Severe SRD*, 1 year, $202,362 • **Malini Harigopal**, American Society of Cytopathology, *HPV16 DNA Methylation for Improved Triage of ASCUS*, 2 years, $50,000 **Kevan Herold**, Benaroya Research Institute, *JDRF/ITN Partnership in Immune Tolerance*, 1 year, $50,000 • **Michael Higley**, Epilepsy Foundation of America, *Inhibitory Control of Dendritic Excitability in Epilepsy*, 1 year, $50,000 • **Martha Kaiser**, Autism Speaks, *Near-Infrared Spectroscopy for Studies of Early Neural Signatures of Autism*, 3 years, $449,809 • **Janghoo Lim**, National Ataxia Foundation, *Molecular Pathogenesis Studies of Spinocerebellar Ataxia Type 1*, 1 year, $50,000 • **Carolyn Mazure**, Grace J. Fippinger Foundation, *Women's Health Research at Yale: Research Cores*, 1 year, $10,000 **Gail McAvay**, Universal American, T*he Prevalence and Impact of Depressive and Anxiety Disorders in a Medicare Population*, 2 months, $11,008 **Ruth Montgomery**, Mayo Clinic of Rochester (NIH), *High-Throughput Immunophenotypic Analyses of Humoral Responses to West Nile Virus*, 1 year, $74,475 • **Gil Mor**, Wayne State University (NIH), *Services in Support of the Perinatology Research Branch*, 9 months, $138,606 • **Adam Naples**, Autism Speaks, *Brain Electrophysiology of Interactive Social Stimuli*, 2 years, $107,443 **Don Nguyen**, National Lung Cancer Partnership, *Identifying Metastasis-Propagating Cells and Their Niche in Lung Adenocarcinoma Progression*, 2 years, $108,000 • **Katerina Politi**, Thomas G. Labrecque Foundation, *A Translational Pilot Study on Serum Biomarkers of Lung Cancer Using Transgenic Mouse Models of Lung Adenocarcinoma*, 1 year, $70,000 • **Scott Pope**, American Cancer Society, Inc., *Regulation of Inflammation by Single Dependent Transcriptional Repression*, 3 years, $150,000 • **Faye Rogers**, Breast Cancer Alliance, Inc., *Gene-Targeted Apoptosis as a Therapeutic Strategy for HER2-Positive Breast Cancer*, 1 year, $100,000 • **Alessandro Santin**, Honorable Tina Brozman Foundation, *Iron Oxide Nanoparticles Complexed to CPE Peptide for the Early Detection and Treatment of Chemotherapy-Resistant Ovarian Cancer Stem Cells*, 2 years, $200,000 **Lynn Selemon**, Texas A&M University (U.S. Dept. of Defense), *The Root Cause of Post-traumatic and Developmental Stress Disorders*, 1.4 years, $324,987 • **Mark Shlomchik**, Merck KgaA, *Autoimmunity and the Role of BLyS Signaling Pathways*, 2 years, $296,616 • **Michael Simons**, European Commission, *Biodegradable Magnetic Stent for Coronary Artery Luminal Regeneration*, 4 years, $641,567 • **Matthew State**, Simons Foundation, *Whole-Exome Sequencing of Simons Simplex Quads*, 2 years, $2,646,852 • **Asim Tarabar**, American Academy of Clinical Toxicology, *Lily of the Valley Ingestion: Epidemiology, Laboratory Diagnosis, and Treatment of* Convallaria *Toxicity*, 1 year, $3,750 • **Narendra Wajapeyee**, Elsa U. Pardee Foundation, *Pre-Clinical Evaluation and Development of the Secreted Tumor Suppressor IGFMP as a Novel Lung Cancer Therapeutic*, 1 year, $100,000 • **Sandra Wolin**, Lupus Research Institute, Inc., *The role of Ro60-Bound RNAs in SCLE*, 3 years, $300,000 • **Yanling Wu**, Genzyme Corp., *Towards Cell Therapy for Guacher's Disease: Use of Triplex-Forming Peptide Nucleic Acids to Correct Glucocerebrosidase*, 2 years, $211,179 • **Luyang Yu**, American Heart Association, *SENP1-Mediated GATA2 desumoylation is Critical for Endothelial Activation in Graft Arteriosclerosis*, 4 years, $308,000

// YMG *(from page 1)* Working with department chairs, faculty, and clinical partners, he says, he plans to develop and implement measures that improve and standardize clinical operations, enhance revenues, and make the best possible use of precious available space.

"There are huge benefits to standardization. We could do better than we do now" across the many sites in the Yale-New Haven Healthcare System, Taheri says. "Whether [patients] go to New Haven or Bridgeport, it should be the same experience."

Taheri is past chair of the Group on Faculty Practices for the Association of American Medical Colleges and an examiner for the American Board of Surgery. He has lectured broadly on various business topics related to medicine, including the cost of care, physician leadership, and optimizing systems. He received his undergraduate degree from St. Lawrence University and his medical degree from New York University, then completed his general surgical residency at Tulane University.

Taheri succeeds David J. Leffell, M.D., the David P. Smith Professor of Dermatology, professor of surgery, and chief of the medical school's Section of Dermatologic Surgery and Cutaneous Oncology.

Leffell, who spearheaded the branding of the clinical practice under the Yale Medical Group name, has served in successive YMG leadership positions since 1996. "Dr. Leffell is responsible for much of the transformation of Yale's clinical practice over the past 15 years, while continuing to serve as an extraordinarily successful section chief," says Robert J. Alpern, M.D., dean and Ensign Professor of Medicine. "His leadership has significantly advanced YMG's reputation for quality of care and service, and he has spearheaded many initiatives, including the selection of the medical center's first integrated electronic health record system."

Michael Berman, M.D., has overseen YMG's operations as interim director and CEO during the past year, and he led the search process that recruited Taheri. During the transition to Taheri's leadership, Berman is serving as a special advisor to the clinical practice.

// Spine Center *(from page 5)* dishwasher with my daughter," she says.

As for Kadan-Lottick's symptoms, she says, "I really had to psych myself up to walk from my garage to my office" due to compression of her spinal cord that caused her severe pain. An associate professor of pediatrics at the School of Medicine, Kaddan-Lottick says she was immediately impressed with Abbed, whose training includes fellowships in orthopaedic and neurosurgical spine surgery. Ultimately, she chose a surgical procedure that drew on this specialized training—a multilevel, minimally invasive decompression and stabilization procedure that dramatically decreased her recovery time, blood loss, muscle injury, and hospital stay compared with conventional surgical options.

Kadan-Lottick was walking the day after surgery, and Abbed helped her craft a rehabilitation plan.

"I really feel like I had been living the life of someone decades older," says Kadan-Lottick, now two years out from her surgery. She says she is now hiking, skiing, and biking with her family again.

Most patients don't need surgery, so Abbed and Grauer always seek alternatives for those who can benefit from them. "It used to be the hardest part of my job when I saw someone who was hurting and they weren't candidates for surgery, so I couldn't help them," Abbed says. "Now we have the ability to get them the nonoperative treatment they need."

The Spine Center's physicians stay in close touch with physical therapists, who routinely discuss the patient's progress with the surgeon and adjust rehab techniques when necessary.

"Therapy is very specific to the individual," says Jhasson Brooks, lead physical therapist for the center. "We can bring them to a point where we reduce their pain, teach proper body mechanics, and prevent further injuries," he says.

Cusano first saw the Spine Center's new facility on a recent follow-up visit, and she says she loved it. But the change she sees in herself is even more impressive, she says. Of her first visit, she says, "I remember sitting there crying," but today there are no more tears.

// Stem cells *(from page 5)* So Vaccarino and her collaborators—a multidisciplinary team that included stem cell biologists, bioinformaticians, and geneticists—turned to a new, high-resolution technology called digital PCR to scour the original skin cells for CNVs. Unlike older technologies, digital PCR is sensitive enough to detect variations present in only 0.1 percent of the cells. The team discovered that around half of the CNVs they'd pinpointed in the iPSC lines could also be found in the fibroblasts. "It could be that even more than half are present," says Vaccarino, "but that's what we were able to detect with this method."

The study's most intriguing twist is that the researchers found iPSCs to be remarkably stable—reprogramming does not appear to significantly alter the genomes of donor cells. Instead, it is donor cells that show an unexpected amount of variation.

Genomic variation in the cells of a single individual is called mosaicism, after the differently colored tiles that make up a mosaic. Mosaicism is known to result from the cell dysregulation seen in cancer and other diseases. But significant genetic differences among cells in healthy individuals were thought to be rare, especially among cells in a single tissue.

The new findings, which were published in the December 20, 2012, issue of the journal *Nature*, suggest that such variation has been "markedly underestimated," write the authors.

"In the skin, this mosaicism is extensive and at least 30 percent of skin cells harbor different deletion or duplication of DNA, each found in a small percentage of cells," Vaccarino explains. "This has far-reaching consequences for genetic analyses, which currently use only blood samples. When we look at the blood DNA, it's not exactly reflecting the DNA of other tissues such as the brain. There could be mutations that we're missing."

The good news for researchers moving forward, says Vaccarino, is that iPSC cell lines provide a straightforward way to reveal genetic diversity within individuals. "We can now use the stem cells as a discovery tool to look at these rare events." she says.

// UTC *(from page 1)* Reitsma, a long-time cyclist, has twice completed Smilow's annual 100-mile Closer to Free bicycle ride while in treatment. His care at Smilow, he says, "has been fantastic. There's an attitude of optimism. You feel that there's hope, not only because of the people you interact with, but also knowing that you have access to the latest treatments available."

According to Chênevert, United Technologies and YCC are linked by a spirit of innovation. "UTC's support of Yale Cancer Center reflects both the unfortunate fact that cancer touches almost every UTC employee in some form as well as our belief in the power of innovation," says Chênevert, the current chair of the YCC Director's Advisory Board and, along with his wife, Debbie, a long-time supporter of cancer research and treatment at the School of Medicine.

"In our businesses, we've seen how our investments in innovation can transform an industry and change the world. We know the same is true in the fight against cancer."

YCC Director Thomas J. Lynch, M.D., sees UTC as an important ally. "UTC's continued support enables us to broaden and deepen our reach in the fight against cancer, so that we can continue to help improve the lives of people like Mark Reitsma," says Lynch, the Richard Sackler and Jonathan Sackler Professor of Medicine and physician-in-chief at Smilow Cancer Hospital.

UTC has more than 215,000 employees worldwide, about 26,000 of them in Connecticut. Its business units produce Pratt & Whitney aircraft engines, Sikorsky helicopters, Carrier air conditioning and heating systems, Otis elevators and escalators, UTC aerospace systems, and Kidde fire safety and detection systems.

// Milbank *(from page 1)* fellowships. "We are very grateful for the generous support of the Milbank Foundation and for their confidence in our vision to build palliative care, education, and research over the coming years to benefit our patients and their families," Kapo says. "This gift will ensure that we have the resources needed to help train the next generation of palliative care physicians, and to provide for the palliative care and end-of-life needs for all of our patients."

Kapo came to Yale from the University of Pennsylvania in 2012 to build the Palliative Care Program into a model clinical service that provides world-class, comprehensive supportive and palliative care to patients and their families who face cancer and other serious, life-threatening illnesses.

"A commitment to care with dignity at end of life says much about our humanity as a society," says YCC Director Thomas J. Lynch. M.D., the Richard Sackler and Jonathan Sackler Professor of Medicine and physician-in-chief at Smilow Cancer Hospital. "The Milbank gift sets a terrific example of supporting efforts to help patients and families deal with some of life's hardest experiences. With their support Yale will be well on its way to establishing one of the nation's very top palliative care units for patient care, education, and research."

The Milbank Foundation for Rehabilitation was created in 1995 to realize the vision of philanthropist Jeremiah Milbank (Yale College 1909) to integrate people with disabilities into all aspects of American life. His grandson Jeremiah Bogert, of the Yale College Class of '63, currently serves as the Foundation's chairman. Bogert's father, brother, and son, Jeremiah Jr., are also Yale graduates (Classes of '34, '60, and '89).

"My grandfather, Jeremiah Milbank, was one of the great philanthropists of his time," says Bogert. "We are proud of our historic ties to Yale and honored to follow in his philanthropic footsteps by supporting the Yale Palliative Care Program."

// PET Center *(from page 3)* cancer settings. PET instrumentation is expensive, but it offers a number of advantages over SPECT: the cost per study is lower; spatial and temporal resolutions are higher; imaging is more sensitive and contains less "noise"; and a greater variety of tracers can be used.

Kelly P. Cosgrove, PH.D., assistant professor of psychiatry, uses PET to study the effects of nicotine-induced dopamine release in the brain. In 2009, a team including Cosgrove, Irina Esterlis, PH.D., assistant professor of psychiatry and diagnostic radiology, and the late Julie Staley-Gottschalk, PH.D., published a study in *Archives of General Psychiatry* in which they used SPECT imaging to demonstrate that, after quitting, smokers have an increase in nicotine receptors that lasts up to a month, and that this increase in receptor availability is correlated with craving for cigarettes.

Cosgrove, also assistant professor of diagnostic radiology and neurobiology, is building on that work, using PET to study effects of variables like sex, psychiatric status, and genetic makeup on nicotine-induced dopamine release, as well as cognitive changes that occur when a person stops smoking.

Krystal has used PET to examine the effects of post-traumatic stress disorder and early emotional trauma on the brain. Others in the Department of Psychiatry are using PET to study depression, schizophrenia, Tourette's syndrome, and various addictions.

Marc N. Potenza, M.D., PH.D., uses PET to analyze brain reward circuits in cocaine, alcohol, and gambling addictions. "PET offers distinct advantages over other widely used imaging measures in that it allows for investigation of specific receptors," which is "critical to understanding pathophysiology, particularly with respect to developing new pharmacotherapies," says Potenza, professor of psychiatry, neurobiology, and in the Child Study Center.

Yale Cancer Center (YCC) is one of the PET Center's newest partners in research applications outside psychiatry. Like YCCI, which has provided significant funding and other resources to help initiate collaborative work, YCC has contributed pilot funding to facilitate collaborations using PET.

One such project involves work by Joseph N. Contessa, M.D., PH.D., assistant professor of therapeutic radiology, who is using PET to analyze the actions of the anti-cancer drug erlotinib (Tarceva) in non-small cell lung cancer by labeling erlotinib and using it as the PET scan tracer.

Others at YCC—including David J. Carlson, PH.D., assistant professor of therapeutic radiology, and Sara Rockwell, PH.D., professor of therapeutic radiology and pharmacology, and associate dean for scientific affairs—are using newly designed PET tracers to study hypoxia (low levels of oxygen) in the tumors of both humans and mice.

PET has also proven valuable in assessing recovery from spinal cord injury. In 2011, Stephen M. Strittmatter, M.D., PH.D., the Vincent Coates Professor of Neurology and professor of neurobiology, published a paper in *Annals of Neurology* showing that after treatment with an agent that unlocks regeneration mechanisms in the nervous system, mice with spinal cord injury showed marked recovery, which Strittmatter's team observed by using PET to measure the density of nerve fibers, using a tracer originally developed to study depression. His work may lead to new treatments for spinal cord injury in humans.

One of PET's benefits is the unlimited potential of radiochemistry to create and test new labeled compounds. As in Strittmatter's research, often a compound will turn out to have important unexpected uses. In recent studies led by Gary W. Cline, PH.D., associate professor of medicine, Kitt Falk Petersen, M.D., professor of medicine, and Kevan Herold, M.D., professor of immunobiology and medicine, researchers found that a tracer originally designed to measure neural activity in Parkinson's Disease could be used to measure the mass of insulin-producing β-cells in the pancreas. "The ability to look at and measure them *in vivo* in human beings over time is a hugely valuable tool" for diabetes research, Carson says (see figure, page 3).

As noted, PET is extremely valuable in drug design, and the ability of the PET Center's radiochemistry team to create a wide range of tracers underlies a mutually beneficial relationship the Center enjoys with the pharmaceutical industry. Pfizer contributed $5 million in 2007 to help establish the Center and the company provides ongoing support for PET studies of its large library of compounds. The expertise of PET Center scientists has now spurred collaborations with more than 10 pharmaceutical companies.

But the Center's relationship with industry is equally beneficial for Yale scientists. Having been designed to accommodate industry studies—which typically occur at a faster pace and larger scale than federally funded academic studies—the Center has the advantage of high-quality instrumentation.

The Center has a scanner able to image the human brain at a resolution of 2.5 millimeters, for instance, one of only 17 such scanners in the world. The scanner can also track and compensate for patients' head movements 20 times per second to eliminate blurring.

And the Center's advanced chemistry facilities mean that scans can often be scheduled so closely that a tracer can be produced and then quickly used in two or more scans. For that to happen, "there are a lot of different parts working together," says Evan D. Morris, PH.D., co-director for imaging and associate professor of diagnostic radiology, biomedical engineering, and psychiatry.

Since its 2007 opening, the Center has increased its capacity by acquiring new PET scanners and growing its staff to more than 50, placing it among the largest, most active centers in the U.S.

The Center's abundance of resources are not only of immediate benefit for Yale research, but also enables School of Medicine scientists to make stronger cases when requesting grant funding. Says Carson, "When you're competing for grants in an always-difficult grant environment, it's helpful to be able to say, for instance, that we have the highest-resolution PET scanners available in the world."

Researchers win prize honoring exceptional immigrant scientists

On February 5, the Vilcek Foundation announced that two immune-system researchers at the School of Medicine will share one of the 2013 Vilcek Prizes, awards that recognize significant contributions to American science and the arts made by immigrants.

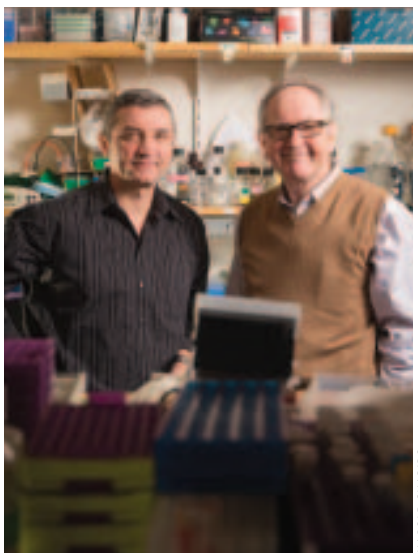
Richard A. Flavell, PH.D., chair and Sterling Professor of Immunobiology, and Ruslan M. Medzhitov, PH.D., David A. Wallace Professor of Immunobiology, were honored for their long-standing and influential work on the innate immune system, the first line of defense against infection by bacteria and viruses.

This year's Vilcek Prize in the arts and humanities will go to cello virtuoso Yo-Yo Ma. The prizes carry a cash award of $100,000.

Born in the United Kingdom, Flavell received his PH.D. in biochemistry in 1970 at the University of Hull and came to Yale in 1988 to lead its immunobiology program. Flavell and colleagues have discovered several important receptors of the innate immune system, and he has made major contributions to our understanding of how activation of the innate system triggers the adaptive immune system's more specialized responses.

Medzhitov, a member of the Yale faculty since 1999, is a native of Tashkent, Uzbekistan. He immigrated to the United States in the early 1990s, having been inspired by the then-controversial theories of innate immunity championed by the late Yale immunobiologist Charles A. Janeway Jr., M.D. At the time, innate immunity was deemed unimportant and received scant scientific attention, but by 1997 Medzhitov, Janeway, and colleagues identified an innate immune system receptor in humans that acts as a pathogen-detecting sentinel and activates adaptive immunity. The study of innate immunity has since seen explosive growth, and Medzhitov's work continues to have significant implications for autoimmune diseases, cancer, and other illnesses.

"We are pleased to honor two truly outstanding scientists. The pioneering work of Ruslan Medzhitov and Richard Flavell has led to important insights into the mechanisms of the immune responses, which has implications for many fields of biomedical studies," said Jan Vilcek, president of the Vilcek Foundation.



HAROLD SHAPIRO

Ruslan Medzhitov (left) and Richard Flavell are winners of a prize that honors significant contributions of foreign-born scientists and artists to American life.

Kent Professor's research evaluates the effectiveness of treatments for addiction

Kathleen Carroll

Kathleen M. Carroll, PH.D., recently named Albert E. Kent Professor of Psychiatry, studies behavioral, pharmacological, and combined treatments for addiction, with an emphasis on improving the quality of such therapies through rigorous research on their clinical efficacy.

Carroll graduated summa cum laude from Duke University, completed predoctoral training in the Yale Department of Psychiatry's Division of Substance Abuse, and earned her PH.D. in clinical psychology from the University of Minnesota. She joined the Yale faculty in 1990, becoming full professor in 2002.

Carroll is the principal investigator of the School of Medicine's Psychotherapy Development Research Center—the only National Institute on Drug Abuse (NIDA) center devoted to behavioral therapies research—and of the New England node of NIDA's Clinical Trials Network. She received a MERIT Award from the National Institutes of Health in 2003 for her research on computer-assisted training in cognitive-behavioral therapy.

Carroll has been designated as a Highly Cited Researcher by ISI Thompson, and she is the author of more than 220 peer-reviewed research publications as well as numerous books and book chapters.

Carroll was president of the American Psychological Association's Division 50 (Addictions) from 2002 to 2005, when she received the Division's Distinguished Scientific Contributions to Education and Training Award.

Expert in vascular biology, inflammation, and immunity is inaugural Bayer Professor

Jordan Pober

Jordan S. Pober, M.D., PH.D., recently appointed as the inaugural Bayer Professor of Translational Medicine, is an authority on the interrelations of vascular endothelial cells (which form the lining of blood vessels), inflammation, and immunity. His research aims to advance organ replacement therapy, tissue engineering, and regeneration of injured tissues.

Bayer, a global enterprise in the fields of health care, nutrition, and high-tech materials, established the professorship to recognize its shared goals with the School of Medicine: to improve and speed up the translation and delivery of fundamental scientific discoveries in human health, from the laboratory into the clinic; and to engage in innovative and collaborative research, with the broader goal to deliver improved patient care.

Pober is director of the medical school's Human and Translational Immunology Program and vice-chair of the Department of Immunobiology. He earned his M.D. at the School of Medicine in 1977 along with a PH.D. in molecular biophysics and biochemistry. He returned to Yale in 1991 as professor of pathology and immunobiology, and became professor of dermatology in 1998.

Pober founded the Vascular Biology and Transplantation Program, the medical school's first interdisciplinary program in translational medicine, in 1999. He has been honored as a Searle Scholar, an Established Investigator of the American Heart Association, and a MERIT awardee of the National Heart, Lung, and Blood Institute.

Ensign Professor has unveiled mechanisms shared by the vascular and nervous systems

Anne Eichmann

Anne Eichmann, PH.D., newly designated Ensign Professor of Cardiology, explores the factors that determine where the cells in blood vessels and lymphatic vessels grow, as well as how the vascular and nervous systems influence each other's growth and function. She has discovered that common molecular cues direct growth of blood vessels and nerves, opening new possibilities for directing blood vessel growth toward infarcted tissue or away from growing tumors. Eichmann is currently studying that link in diseases affecting both systems, notably diabetes.

Eichmann obtained her M.SC. at the Weizmann Institute in Israel, and a PH.D. in molecular and cell biology from Université Paris 13. After postdoctoral work, she moved to the Collège de France, where she was Inserm Avenir Young Investigator from 2001 to 2006 and a research director for Inserm since 2002. She joined the Yale faculty in 2010.

Her research has won her numerous honors, including a Lillian Bettencourt Prize for Life Sciences, the Chevalier de L'ordre National du Mérite, and the Jean Bernard Award from the Medical Research Foundation. She has served on the Inserm Scientific Research Council, the European Research Council, and the Fondation Lefoulon Delalande fellowship board, and the editorial boards of *Physiology Reviews* and *Endothelium*. She has been elected council member of the North American Vascular Biology Organization.

Berliner Professor studies how blood flow stimulates the formation of new arteries

Martin Schwartz

Martin A. Schwartz, PH.D., the newly named Robert Berliner Professor of Cardiology, is a noted cardiovascular researcher whose studies of cell adhesion and behavior have led to new insights into atherosclerosis and heart disease.

Professor of medicine and cell biology, Schwartz is affiliated with the Vascular Biology and Therapeutics Program. He is an expert on mechanotransduction—how cells respond to mechanical forces—and his lab's main focus is understanding how the friction of flowing blood against the endothelial cells lining blood vessels regulates the behavior of these cells, including how increased flow leads to the growth of new arteries.

Schwartz earned his PH.D. in physical chemistry from Stanford University. He conducted postdoctoral research at the Massachusetts Institute of Technology, and joined the faculty of Harvard Medical School in 1983. In 1991, he moved to the Scripps Research Institute, and then the University of Virginia. He joined the Yale faculty in 2011.

Schwartz is part of a team at the Yale Cardiovascular Research Center that received a five-year, $9.5 million grant from the National Heart, Lung, and Blood Institute to study the molecular basis of artery formation and develop a new framework for therapeutic advances.

The professorship is named for Robert W. Berliner, M.D., a renowned kidney researcher and dean of the School of Medicine from 1973 to 1983.