Medicine@Yale

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Advancing Biomedical Science, Education, and Health Care

Yale's new Research Accelerator will bring scientists together

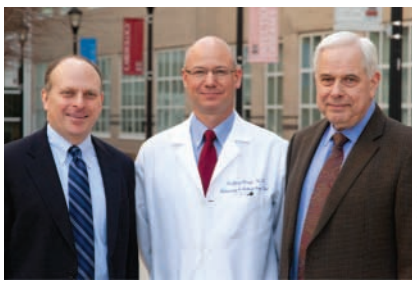
As a pulmonologist who conducts a great deal of translational research on diseases of the airway and lungs, Geoffrey L. Chupp, M.D., associate professor of medicine and director of the Yale Center for Asthma and Airway Disease, often finds himself in unfamiliar scientific territory. "I'll find a molecule that's interesting or I'll come upon some piece of data where I don't really know what I'm dealing with," Chupp says.

But in the fast-moving world of biomedical research, finding people with specific expertise using traditional methods—searching the literature or Internet, for instance—are often inefficient. "There may be people in my own building that I don't even know about whom I could work with or get information from," Chupp says.

Chupp hatched an idea for a Web-based resource that would make interdisciplinary scientific collaboration quicker and easier. In 2008, he approached longtime friend Steven Greenberg, a Westport, Conn.-based journalist and attorney who recently launched Jobs4.0, an online employment resource designed to help people over age 40 find meaningful work in a tough economy.

Chupp and Greenberg built a prototype, which they demonstrated for Robert S. Sherwin, M.D., the C.N.H. Long Professor of Medicine. As director of the Yale Center for Clinical Investigation (YCCI), Sherwin oversees many of the School of Medicine's efforts to accelerate the pace of clinical and translational research.

"We presented our site to Dr. Sherwin because we felt that the goals of YCCI and // Chupp *(page 4)*



WILLIAM SACCO

With the backing of the Yale Center for Clinical Investigation (YCCI) and YCCI Director Robert Sherwin (right), Steven Greenberg (left) and Geoffrey Chupp (middle) have launched the YCCI Research Accelerator, a new Web-based platform that makes collaboration easier for Yale scientists.

Ten years on: a new genomic revolution

A decade after the first human genome map, Yale's new DNA sequencing facility provides a wealth of information at unprecedented speed

In June 2000, the human genome revolution began with a bang. At a White House ceremony, genome pioneers Francis S. Collins, M.D., PH.D., and J. Craig Venter, PH.D., joined then-president Bill Clinton and British Prime Minister Tony Blair to announce the completion of a "working draft" of the 3 billion base pairs of DNA that comprise our genetic endowment. That effort took 10 years, $3 billion, and the work of 900 automated DNA sequencing machines scattered in laboratories around the world.

Ten years later, one technological advance after another has driven the speed of genomic analysis up and the cost down: the latest DNA sequencing technology is eight orders of magnitude faster than that used in 1987; over the last decade, costs have plummeted 14,000-fold. In a recent issue of the journal *Nature* that marked the 10th anniversary of the human genome's first draft, Collins, now director of the National Institutes of Health, provided a vivid description of what these developments mean for biomedical research. "For example," Collins writes, "the search for the cystic fibrosis gene finally succeeded in 1989 after years of effort by my lab and several others, at an estimated cost of US$50 million. Such a project could now be accomplished in a few days by a good graduate student with access to the Internet, appropriate DNA samples, some inexpensive reagents, a thermal cycler and a DNA sequencer."

As a result of this stunning progress, DNA sequence information has become a common currency for scientific discovery—every life scientist seems to be making use of it in one way or another, and it is hard for those who oversee sequencing facilities to keep up with the demand. For researchers today, a single human genome won't do—they want many, and they want to be able to compare them in detail.

MICHAEL MARSLAND

Shrikant Mane (left), director of the Yale Center for Genome Analysis (YCGA) and Kira Fitzsimons, biotechnology assistant, discuss data produced by the YCGA's latest gene sequencers, which can sequence the equivalent of more than 300 complete human genomes per month.

At Yale, scientists can now obtain this 21st century research staple from the Yale Center for Genome Analysis (YCGA), a new high-speed sequencing facility that opened in January. Housed in a newly renovated space perched atop a hill at Yale's West Campus, the YCGA is // YCGA *(page 5)*

Homecoming for a top cell biologist is packed to rafters

For several years, the School of Medicine's Department of Cell Biology has invited a distinguished scientist to Yale each year to deliver the George Palade Lecture, named in honor of a beloved former Yale faculty member and Nobel Prize winner whose integration of electron microscopy and biochemistry helped lay the foundation of modern cell biology.

Following Palade's death at age 95 in 2008, the department decided to "elevate the status of the lectureship to a university-wide event, a major international lectureship renamed the George E. Palade Memorial Lectureship in Cell Biology," says Chair James E. Rothman, PH.D., the Fergus F. Wallace Professor of Biomedical Sciences.

In a fitting tribute, on April 4, the inaugural Palade Memorial Lecture was given before a standing-room-only crowd by world-renowned cell biologist Marilyn G. Farquhar, PH.D., Palade's widow and his frequent scientific collaborator, now Distinguished Professor of Molecular and // Palade *(page 7)*

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INSIDE THIS ISSUE

ALSO

HAROLD SHAPIRO

Gerald Shulman has mapped out the metabolic disruptions at the root of type 2 diabetes. Until recently, this disease was mostly diagnosed in those over 40, but there has been a sharp increase in type 2 diabetes in younger adults and in children. The illness is also on the rise in China and India, and it is estimated that it will affect more that a third of a billion individuals in the world by the year 2020.

Turning the tide on type 2 diabetes

Work on insulin resistance sparks researcher's hopes for prevention and a cure

Gerald I. Shulman, M.D., PH.D., a world-renowned authority on diabetes, says he can't remember a time when he wasn't interested in science and medicine. He was partly inspired by his father, a Detroit physician who occasionally took the younger Shulman on hospital rounds. But as a biophysics major at the University of Michigan, Shulman "fell in love with physics and biochemistry," he says, and knew that research would figure prominently in his career.

After his second year of medical school at Wayne State University, Shulman took a break to study in the laboratory of Alan D. Cherrington, PH.D., at Vanderbilt University School of Medicine. There, Shulman administered the newly discovered hormone somatostatin to animals to suppress the pancreatic secretion of glucagon and insulin, allowing him to eliminate the effects of these two hormones and show that the amount of glucose produced by the liver can be affected by changes in blood glucose levels alone.

Following a residency in internal medicine at Duke University Medical Center, Shulman did his endocrine fellowship training at Massachusetts General Hospital. During the research portion of the fellowship, he studied the insulin receptor but he was keen to return to studies of metabolism in animals, such as those he had done at Vanderbilt.

Fortuitously, magnetic resonance spectroscopy (MRS) was just beginning to blossom. Based on the same principles as MR imaging, MRS allows scientists to noninvasively create precise, real-time chemical profiles of small regions of tissue in live animals, including humans. For Shulman, who was searching for a noninvasive method to study intracellular metabolism in living systems, MRS was the answer. In 1984 he persuaded his Mass General mentors to let him travel to Yale to complete his fellowship, since Robert G. Shulman, PH.D. (no relation), an MRS pioneer, had just joined the faculty. "It's been 25 years," jokes Shulman, who has been at Yale ever since, and is now the George R. Cowgill Professor of Physiological Chemistry. "And they keep asking me when I'm coming back."

In two decades of research that has earned him election to the National Academy of Sciences and many other honors, Shulman, also professor of medicine and of cellular and molecular physiology, and a Howard Hughes Medical Institute investigator, has combined MRS studies of patients with experiments using transgenic mice to elucidate the mechanisms of insulin resistance, the metabolic dysfunction at the core of type 2 diabetes.

His group has found that insulin resistance in muscle is mainly caused by defective insulin-stimulated glucose transport, which reduces glycogen synthesis. On the other hand, increased synthesis of glucose from amino acids and lactate in the liver is the main cause of the fasting hyperglycemia seen in type 2 diabetes.

In a novel unifying hypothesis of insulin resistance, Shulman and colleagues have proposed that an imbalance between the delivery and oxidation of fatty acids in liver and muscle cells causes biochemical changes that block insulin signaling. Recently his group identified two common genetic variants that predispose individuals to nonalcoholic fatty liver disease (NAFLD) and insulin resistance, providing new insights into gene–environment interactions that promote the development of type 2 diabetes. His work is revealing new drug targets and exercise and dietary strategies to "melt fat away" from liver and muscle, which will reverse insulin resistance and prevent type 2 diabetes.

Shulman is optimistic that type 2 diabetes—an illness that is the leading cause of blindness, end-stage renal disease, and nontraumatic loss of limbs in the U.S., currently costing the U.S. economy more than $180 billion annually—will be beaten. "Just about every drug that we currently have to treat type 2 diabetes was discovered serendipitously," he says, "and just treats the symptom of diabetes: hyperglycemia. Now that we are beginning to understand the cellular mechanisms of insulin resistance, which is at the root of type 2 diabetes, we have better therapeutic targets, and I'm quite excited about it."

Insulin pump innovator receives high honor for diabetes research

The American Diabetes Association (ADA) has selected William V. Tamborlane, M.D., to receive its Outstanding Physician Clinician Award, one of the highest honors bestowed by the ADA each year.

A professor of pediatrics and a world-renowned figure in the understanding and treatment of childhood diabetes, Tamborlane is chief of pediatric endocrinology at the School of Medicine.

Tamborlane's major achievements have included pioneering work in the development of insulin pump therapy,

William Tamborlane

continuous glucose monitoring, sensor-augmented pumps, and, most recently, designing a prototype of an artificial pancreas.

Tamborlane has also demonstrated the role of insulin resistance in pediatric metabolic disorders, including obesity and type 2 diabetes.

In late 2009, Tamborlane was honored by the Diabetes Technology Society with the Diabetes Technology Leadership Award for his extraordinary lifetime accomplishments in diabetes research and technological innovation.

Also in 2009, Tamborlane was one of six members of the YSM faculty elected to the Connecticut Academy of Science and Engineering, in recognition of his original contributions to "theoretical or applied science or engineering."

Tamborlane will be presented with the award at the annual ADA meeting in Orlando, Fla., in June.

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Diabetes expert is named head of endocrinology

Robert Sherwin

Robert S. Sherwin, M.D., an internationally renowned diabetes researcher and director of the Yale Center for Clinical Investigation (YCCI), has been appointed chief of endocrinology in the department of internal medicine at Yale-New Haven Hospital (YNHH) and Yale School of Medicine. The endocrinology section at YNHH provides diagnosis and therapy to people with hormonal and metabolic diseases.

Sherwin, the C.N.H. Long Professor of Medicine, has been an attending physician at YNHH since 1974, as well as a consulting physician at the VA Connecticut Healthcare System in West Haven, Conn.

In addition to his role at YCCI, Sherwin directs the medical school's Diabetes Endocrinology Research Center, and he has served as the program director of Yale's General Clinical Research Center.

Sherwin received his undergraduate degree from Union College in Schenectady, New York, and his M.D. from Albert Einstein College of Medicine. He did his residency at Mount Sinai Hospital and was a clinical associate at the NIH before becoming a fellow in medicine (metabolism) at Yale.

He is a former president of the American Diabetes Association (ADA) and a winner of the ADA's Banting Medal for lifetime scientific achievement in diabetes. He has published over 300 papers in scientific journals, edited textbooks and book chapters related to diabetes, and has served on national professional committees for the past 30 years.

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Immune system fights stem cells' dark side

If proteins were celebrities, OCT4 would be on the A-list. In 2007, in a dramatic advance, several researchers showed that inserting the gene for OCT4 and just a few other genes transformed adult skin cells into stem cells capable of generating any tissue in the body.

But in addition to the vast healing potential of stem cells, some fear that using them for therapy may cause tumors, and others believe that tumors regrow in cancer patients when a tiny number of stem cells in tumors survives therapy and continues regenerating.

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OCT4 is commonly expressed in germ-cell tumors (GCTs) such as testicular cancer and some ovarian cancers. In the April 17 online edition of *Proceedings of the National Academy of Sciences,* a team led by Madhav V. Dhodapkar, M.D., the Arthur H. and Isabel Bunker Professor of Hematology, found that the immune system commonly targets this protein and that this immune response correlates with the development of GCTs. Only 35 percent of newly diagnosed GCT patients had an immune response to OCT4, compared to more than 80 percent of healthy humans. Interestingly, after chemotherapy, an anti-OCT4 immune response was seen in 83 percent of the GCT patients.

The work could lead to trials of immune therapies for cancer that target pathways involving stem cells.

Zeroing in on genes to head off aneurysms

In a massive new genomic study, an international team led by School of Medicine researchers has identified three new regions, or loci, containing genetic variants that increase the risk of intracranial aneurysms, weaknesses in the brain's blood vessels. Ruptured aneurysms occur in 500,000 people worldwide each year, causing hemorrhagic stroke, but most have no symptoms. Rupture is fatal in up to 40 percent of cases, and survivors usually have severe neurological damage.

The team compared nearly 900,000 variable spots in the genomes of almost 6,000 aneurysm patients with those of 14,000 healthy subjects. In the May issue of *Nature Genetics,* they describe the new loci and confirm that two previously identified loci are strongly associated with aneurysms. A person carrying variants in all five loci is five to seven times more likely to develop an aneurysm than an individual carrying none.

"These five findings explain about 10 percent of the genetic risk," says lead author Murat Günel, M.D., the Nixdorff-German Professor of Neurosurgery. "This is 10 percent more than we understood just a couple of years ago, but there is a long way to go."

Cellular 'neighbors' spur cancer's spread

Genetic flaws in separate cells interact with one another to form tumors, Yale researchers find

One reason cancer is so difficult to understand and to treat is that tumors are a genetic muddle. A cell can become cancerous via a number of pathways, so the cancer-causing mutations found in one tumor cell may be quite different from those found in neighboring cells. One consequence of this genetic heterogeneity is that a treatment that successfully kills some cells may be ineffective against others. As these surviving cells proliferate, the tumor may become resistant to treatment.

Cancer researchers are beginning to decipher how genetic defects interact within individual cells and lead them awry. However, very little is known about the far more daunting question of whether, in the complex biological milieu that scientists call the "tumor microenvironment," mutations in one cell can interact with those in other cells to promote cancer.

In an article in *Science* published in 2003, Tian Xu, PH.D., vice chair and professor of genetics, and colleagues noted that tumors in the fruit fly *Drosophila melanogaster* "display many characteristics observed in human cancers." In order to emulate the genetic patchwork of human tumors, Xu and School of Medicine colleagues have created a "mosaic" form of *Drosophila* in which a tiny number of cells with mutant genes can exist in a fly with mostly normal cells. In an elegant series of experiments reported in the journal *Nature* in January, Xu and colleagues used this model to demonstrate that interactions between separate cells carrying different mutations are indeed possible, and that they can have a profound effect on how cancers grow and metastasize.

In the new studies, Xu, along with graduate student Ming Wu, PH.D., and postdoctoral fellow José Carlos Pastor-Pereja, PH.D., the lead authors, first created mosaic flies in which a well-known cancer-causing gene known as *Ras* is expressed in some cells along with a mutant, non-functional form of *scribbled* (abbreviated *scrib*), a tumor-suppressor gene. To track the effects of these manipulations, these cells were tagged with green-fluorescent protein (GFP).

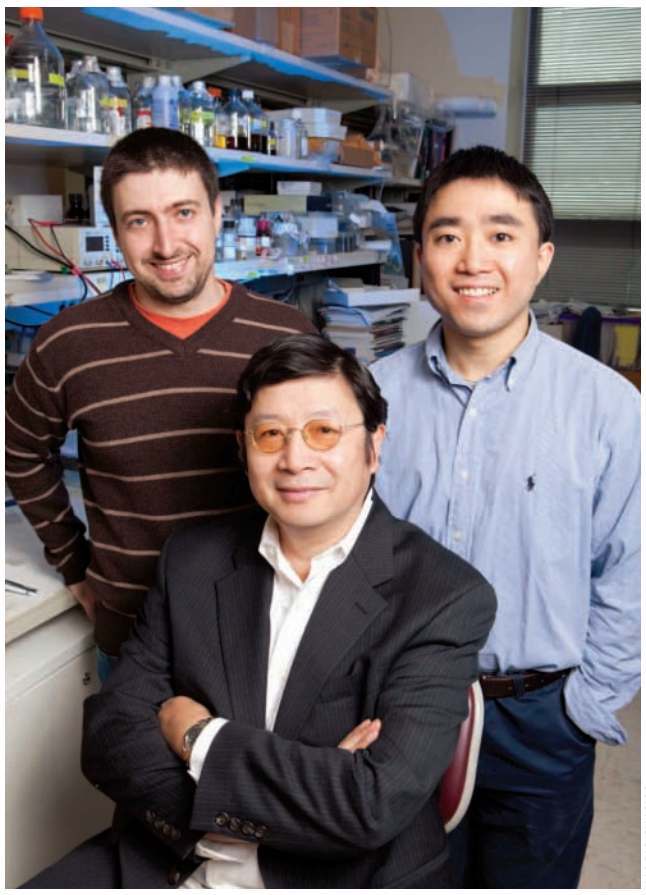
The result was explosive: GFP-tagged tumors soon engulfed the normal cells in the flies' brains, and spread to adjacent tissues as well. In these cells, the presence of mutant *scrib* signals that the cells are damaged, which activates a stress-related signaling pathway called JNK (pronounced "junk"). If the cells had been carrying mutant *scrib* alone, the activation of the JNK pathway would have caused the cells to die, while simultaneously triggering another pathway in adjacent cells known as JAK-STAT, which promotes proliferation. This makes up for the loss of the lost *scrib* mutant cells in a process known as compensatory proliferation. However, the presence of *Ras* and the *scrib* mutation together in the same cells overrides the JNK cell-death signal, while preserving the JAK-STAT proliferation signal, putting the *Ras* carrying cells on a path to tumor development and progression.

The most intriguing observation, however, was that when *Ras* was expressed alone in some cells, and the *scrib* mutation alone in other, adjacent cells (with most cells being normal, as before), rampant tumor growth and metastasis was seen again, just as when the two mutants occurred together in the same cells (see photo).

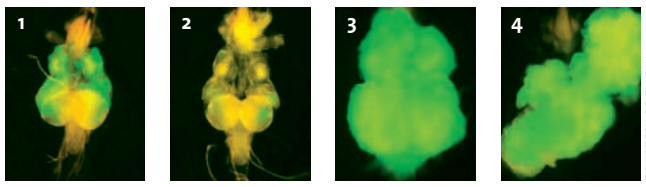
This phenomenon had never been observed, and indicated that some intercellular interaction between *Ras* and *scrib* mutant cells could fuel the growth and spread of cancer. The researchers discovered that the JNK pathway is activated as usual in the *scrib* mutant cells, causing them to die, but JNK signaling in these cells is also somehow propagated to adjacent cells carrying *Ras*. In those cells, JNK activates the JAK-STAT proliferation pathway, causing tumors and metastasis.

As noted above, JNK signaling is induced by stress, such as when tissue is wounded. When the researchers damaged wing discs in *Drosophila* larvae with cells carrying *Ras*, tumors resulted, indicating that stress-induced JNK signaling alone is sufficient to turn cells carrying *Ras* toward cancer.

"A lot of different conditions can trigger JNK stress signaling," says Xu. "Physical stress, emotional stress, infections, inflammation – all these things." The Xu team's view of stress-induced tumor growth is consistent with recent findings of other researchers, who have shown that tumors and wounds have similar traits, and that there is a close relationship between chronic inflammation and cancer.



HAROLD SHAPIRO



COURTESY OF TIAN XU

(Top) Tian Xu (seated) and (standing, from left) postdocs José Carlos Pastor-Pereja and Ming Wu discovered that distinct genetic mutations occurring in different cells can cooperate to fuel cancer. (Bottom) In the fruit fly brain, cells carrying a cancer-promoting *Ras* mutation alone (panel 1, green) show moderate overgrowth, while a mutant *scribbled* gene alone (2) has little effect. When *Ras* and mutant *scribbled* are together in cells, tumors invade the entire brain (3), an effect also seen when these genes are each expressed alone in different, but adjacent, cells (4).

Xu believes that his group's findings on cell–cell interaction in tumors are a powerful demonstration of how the precise genetic control offered by *Drosophila* can shed new light on the biology of cancer. "The bad news is that it is much easier for a tissue to accumulate mutations in different cells than in the same cell," says Xu, a Howard Hughes Medical Institute investigator and director of the Institute of Developmental Biology and Molecular Medicine at Fudan University in Shanghai, China. "Better understanding of the underlying mechanism causing cancer always offers new tools to battle the disease."

OUT & ABOUT

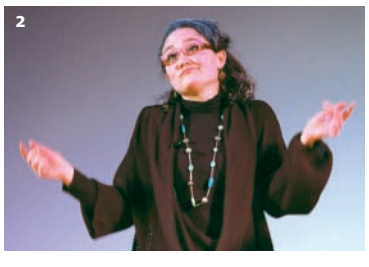
January 21 The **Status of Women in Medicine** (SWIM) held a reception celebrating the contributions of women to the School of Medicine. From left: **Merle Waxman**, M.A., associate dean for academic development, ombudsperson of the School of Medicine, and director of the Office of Women in Medicine; SWIM co-chair **Paula B. Kavathas**, PH.D., professor of laboratory medicine, genetics, and immunobiology; SWIM co-chair **Jennifer M. McNiff**, M.D., professor of dermatology and pathology; **Robert J. Alpern**, M.D., Dean and Ensign Professor of Medicine; SWIM co-chair **Joann B. Sweasy**, PH.D., professor of therapeutic radiology and genetics; **Carolyn M. Mazure**, PH.D., professor of psychiatry and psychology, associate dean for faculty affairs, and director of Women's Health Research at Yale; and **Nancy H. Ruddle**, PH.D., the John Rodman Paul Professor of Epidemiology and professor of immunobiology.

JERRY DOMIAN

January 29 **John Allen Jones**, an alumnus of Yale College and the Graduate School of Arts and Sciences, made a major gift in support of the student-run **HAVEN Free Clinic**. The clinic, which opened in 2005, offers medical services to uninsured patients in the Fair Haven neighborhood of New Haven. From left: HAVEN student leaders **Rachel Jamison** '15; **Sara Crager** '12; **Audrey Provenzano** '10; Jones, **Richard Belitsky**, M.D., Harold W. Jockers Professor of Medical Education, deputy dean for education, and associate professor of psychiatry; and **Olatokunbo "Toks" Famakinwa** '11.

COURTESY OF JANCY HOUCK

February 19 and 20 The Class of 2012 affectionately mocked faculty while carrying on a 61-year-old tradition at this year's **Second Year Show**, entitled "Love in the Time of Swine Flu." **1.** The show's finale featured the full cast. **2. Whitney Sheen** '12 portrayed Nancy R. Angoff, M.P.H., M.D., associate dean for student affairs. **3. Julius Oatts** '12, the show's director, as star-crossed lover Steven. **4. Alyssa Nylander** '12 (in red), the director of choreography, and Oatts (with bow tie) lead a dance number in the Cadaver Ball scene that accompanies the song "Thriller," choreographed by **Carina Preskill** '12 (not pictured).



JOHN CURTIS (4)

JOHN CURTIS (3)

March 18 Each year, fourth-year medical students experience a welcome sense of relief on **Match Day**, when they receive word of acceptance in residency training programs. Students from the Class of 2010 matched at top programs across the country, including at Harvard-affiliated hospitals; Yale-New Haven Hospital, the University of California–San Francisco; the Hospital of the University of Pennsylvania; Memorial Sloan-Kettering Cancer Center; Stanford University; New York Presbyterian Hospital; Columbia University; the Hospital of St. Raphael; Johns Hopkins Hospital; and the University of Southern California. **1. Frederick Wang** '10 and **Leah McNally** '10. **2. Stephanie Nguyen** '10 (left) and **Laura Cooney** '10. **3. Matty Vestal** '10 (left) and **Andres Martin**, M.D., M.P.H., Riva Ariella Ritvo Professor of Pediatric Oncology Psychosocial Services.

// Chupp *(from page 1)* Yale's Clinical and Translational Science Award—collaboration, breaking down barriers and resource sharing—were remarkably well aligned with the focus of our new platform," Greenberg says, and Sherwin agreed. "Our goal is to more effectively link scientists across the Yale campus to promote new interdisciplinary research collaborations," Sherwin says.

Sherwin provided support that allowed Greenberg and Chupp to proceed on their project, and two years of discussions, consultations, and testing followed. "We spoke to dozens of researchers and clinicians, from lab assistants to department chairs, to make the platform as valuable as possible to the entire Yale scientific community," says Chupp.

Finally, in March, Chupp saw his concept made real, as the new resource—dubbed the YCCI Research Accelerator (RA)—was launched. Since then, more than 300 members of the Yale community have registered to use the RA.

Yale is the first institution to have full access to this type of technology for scientific collaboration and resource sharing. The RA offers Yale scientists a comprehensive online tool they can use to share and discuss research projects, data, lab protocols, results, news of clinical trials, and advances in clinical care.

"A cancer researcher studying a particular gene has no systematic way of finding other researchers, say in immunology, asthma, or even botany, who might be studying the same gene," Greenberg says. "The YCCI Research Accelerator is designed to facilitate those potentially rewarding collaborations."

The service uses a novel system called data-driven collaboration to quickly and easily identify potential research partners, Chupp explains. "Other software programs allow researchers to easily find published papers or biographical information," he says, "but we wanted to create the first-ever platform that identifies potential collaborators on the basis of a mutual interest in the substance of the data or reagents, not on purely social factors."

Greenberg notes there is great flexibility built into the website, so that each scientist can use it in his or her own way, and each scientist can choose his or her own level of disclosure. In addition, the site can be customized for other institutions, and many institutions can be linked together, so the RA can allow scientists to reach beyond Yale to forge new research connections.

But for the site to be valuable to members of the Yale community, Greenberg says, scientists need to log on and post data. He and Chupp are encouraging all Yale researchers across the university campus to join the RA community.

"The real benefit of having this type of technology is that it will help communication about complex diseases and disorders," says Debbie Hilibrand, chair of the Yale Child Study Center's Executive Council. Hilibrand's son David has both scoliosis and autism. "Autism, for instance, is [connected with] learning disabilities and obsessive-compulsive disorder. And those may also be worked on in multiple departments." Technologies like the RA "will help research at the university become better-integrated and more effective."

"We've had listings from a wide range of Yale scientists who are sharing data, reagents, antibodies, human samples, research projects, and more. The response has been extremely strong. We're also about to post information on over 90,000 peptides available from the Keck Lab," Greenberg says, referring to one of Yale's main centers for protein analysis. "Much more is in the works."

The RA is secure, password-protected, and free of charge for all Yale users. To learn more about using this powerful new tool for scientific collaboration, visit YCCI.researchaccelerator.org.

GETTY IMAGES

An engineered tissue's surprising development

Christopher K. Breuer, M.D., and Toshiharu Shinoka, M.D., PH.D., have been studying the use of tissue-engineered vascular grafts (TEVGs) to treat congenital heart defects. TEVGs—created by seeding a biodegradable scaffold with a patient's bone marrow cells (BMCs)—make living vessels that will grow as a child grows and could last a lifetime.

Breuer and Shinoka, both associate professors of surgery and pediatrics, and Yale colleagues explored how BMCs are transformed to vessels in TEVGs. BMCs are stem cells, so many scientists thought that BMCs differentiate into the endothelial and smooth-muscle cells that comprise blood vessels.

But in the March 9 issue of *Proceedings of the National Academy of Sciences*, the group reports that BMCs were undetectable soon after TEVGs were implanted into mice. Instead, the graft appeared to initiate an inflammatory response that drew white blood cells to the scaffold, replacing the BMCs. These cells were also soon replaced, with the mouse's own blood vessel cells.

This "better understanding of how TEVGs develop *in vivo* will lead to improved second-generation TEVGs," the authors write.

New pathways toward growing new arteries

Stimulating arteriogenesis, the growth of new arteries, in adults with cardiovascular disease is a holy grail of cardiology. Many efforts have focused on vascular endothelial growth factor (VEGF), which creates new blood vessels during embryonic development. However, VEGF has shown little success in adults, especially in those with cardiovascular disease or diabetes.

A team led by Michael Simons, M.D., the Robert W. Berliner Professor of Medicine and Cell Biology, and chief of Yale's Section of Cardiovascular Medicine, focused instead on two interacting signaling pathways, ERK1/2 and PI3K. ERK1/2 is activated in growing arteries and suppressed in quiescent vessels, so the group searched for some PI3K inhibitory factor. In the April issue of *The Journal of Clinical Investigation*, they name the culprit, a PI3K-regulated enzyme known as Akt1. Suppressing Akt1 released the PI3K brake on ERK1/2 and successfully activated growth of new arteries in mice and zebrafish.

"Because we've located this inhibitory pathway, this opens the possibility of developing a new class of medication to grow new arteries," Simons says. "The next step is to test this finding in a human clinical trial."

Lifelong friends, also joined in giving

Two members of the Class of 1956 who fondly recall their Yale years make gifts to the medical school

Rear Admiral William M. Narva, MC, USN, and Captain Mitchell Edson, MC, USN, met as members of the School of Medicine's Class of 1956, and have remained friends throughout their adult lives. More than 50 years later, with their medical school years firmly etched in memory and their careers largely behind them, they still speak on the phone regularly.

The two met, Narva says, because "the class was an intimate class. The whole community was very close." Narva and Edson's first days on Cedar Street in the fall of 1952 coincided with the arrival of Dean Vernon W. Lippard, M.D. "His pitch was, 'I'm a freshman like you are, I'm just starting like you. You're my class—we're going to do this together,'" Narva recalls. "Everybody at Yale was on your side."

The two old friends have also joined together in giving back to Yale. Edson has generously contributed to the Annual Fund for years, and he added to this long record of support in 2005 by establishing the Mitchell Edson, M.D., Endowment for International Clinical Rotations. At that time, Edson was the gift chair for his 50th reunion, and discussions with Narva planted the seed for Narva making a new $200,000 bequest in honor of his and Edson's 55th reunion next spring. In happy coincidences, that event falls at the close of the School of Medicine's Bicentennial celebration and at the conclusion of the University's five-year "Yale Tomorrow" fundraising campaign.

After medical school, Narva interned at the National Naval Medical Center (NNMC) in Bethesda, Md. He then completed a three-year residency in dermatology that included stints at the U.S. Naval Hospital in San Diego and Los Angeles County General Hospital. From 1966 to 1986, as a medical officer in the Navy, he was a consulting physician to the White House and the United States Congress, and in 1986 he became Attending Physician of the United States Congress. Edson, also a career Navy man, completed residencies in surgery and urology at the St. Albans Naval Hospital in New York City, where he eventually became chief of urology in 1966. Edson subsequently became chair of the Department of Urology at the NNMC, and then at Washington Hospital Center in Washington, D.C., where at 82 he still practices four days a week.

COURTESY OF MITCHELL EDSON

COURTESY OF WILLIAM NARVA

In 1963, both William Narva (left) and Mitchell Edson were stationed in Oakland, Calif., but Edson soon received orders to head to the U.S. military base at Okinawa, Japan, where many American soldiers and Marines received training before joining forces in Vietnam. From 1963–64, Edson (above) was Commanding Officer, Third Medical Battalion, Third Marine Division, Okinawa.

Although their military careers took them on different courses, the friends' paths did cross. When Narva was assigned to the U.S. Naval Hospital in Oakland, Calif., Edson, having finished his residency, joined the Department of Urology there. Edson and Narva met again **// Narva** *(page 8)*

// YCGA *(from page 1)* home to 13 state-of-the-art sequencers that churn out more than 900 billion base pairs of new information every 30 days, or the equivalent of more than 300 complete human genomes per month.

"Advancing science in these areas now requires the ability to produce very large volumes of sequence data and analyze them efficiently," says Richard P. Lifton, M.D., PH.D., chair and Sterling Professor of Genetics, who chairs YCGA's Advisory Board. "The YCGA permits us to do this at a scale that has been matched by few places in the country."

The immense computational power of the medical school's newest sequencers is belied by the machines' quiet operation and unremarkable appearance. Lined up behind a glass wall, through which YCGA Director Shrikant Mane, PH.D., keeps a watchful eye, these multimillion dollar marvels could be mistaken for a group of blue dorm fridges.

The YCGA had its beginnings in a much smaller DNA sequencing core Mane launched at Yale's Keck Foundation Biotechnology Resource Lab in 2006. Through the Keck facility, for which he remains director of microarray services, Mane provided sequencing services to Yale researchers using just three automated machines.

Last fall, Yale University made the decision to invest significantly in large-scale DNA sequencing technologies, to support research by investigators across the entire campus. Mane was named to head the new facility. He moved rapidly to acquire seven new Illumina Genome Analyzers, three machines at various campus locations, and three sequencers housed at the Keck facility, and to consolidate all the equipment at the West Campus. But that was just the beginning. "Scaling up an operation of this size by a factor of at least 100 in data output over the course of several months is a Herculean task," Lifton said. The job included building "wet bench" infrastructure to prepare samples as well as other building modifications to accommodate high-performance computing; hiring and training new personnel; and developing and refining bioinformatics techniques and software. With round-the-clock efforts from Mane and his staff, the pieces fell into place quickly, and the facility was up and running within two days after the move to West Campus.

These labors have already yielded a significant scientific payoff. In a pilot project last fall, Lifton and Mane used whole-exome sequencing—a genomic shortcut in which researchers sequence only the few percent of a person's DNA that actually encodes proteins, where disease-causing mutations are most likely to occur—to pinpoint the cause of a baby's rare kidney disease. Their success marked the first use of whole-exome scanning to diagnose a patient, an important new milestone in personalized medicine.

Richard Lifton

The investment in large-scale sequencing has also enabled a raft of new research projects. In last year's competition for research funds under the American Recovery and Reinvestment Act, Yale received five major NIH awards totaling $21 million, all dependent on the resources of the YCGA.

In his 25 years in science, Mane has not witnessed the level of enthusiasm among researchers for any technology as he sees now for large-scale sequencing. "When I wrote a grant to purchase our first genome analyzer back in 2005, I had 38 investigators sign on. Now, for my latest grant I have 150 interested. That kind of response tells you how important this technology is. It's the most exciting thing I've ever been involved in."

In just a few years, researchers predict, it will take only 15 minutes and a few hundred dollars to decode an individual's genome. Sequencing will be a routine part of medical care, and doctors will use genetic information to drive the diagnosis and treatment of many diseases. As Lifton sees it, "We have already had innumerable new insights into disease biology from having the genome sequence, but I think the best is yet to come."

Grants and contracts awarded to Yale School of Medicine

July/August, 2009

Federal

Serap Aksoy, NIH, *Tsetse Fecundity Reduction for Tryopanosomiasis Control*, 5 years, $2,064,820 • **Karen Anderson**, NIH, *Exploring Novel Targeting Strategies for AIDS Protozoal Pathogens*, 1 year, $413,750 • **Robert Beech**, NIH, *Stress-Related Changes in Gene Expression as Biomarkers of Relapse Vulnerability*, 2 years, $453,547 • **Vineet Bhandari**, NIH, *Role of Angiogenic Agents in Alveolar Maturation and Injury*, 2 years, $827,500 • **James Boyer**, NIH, *Silvio O. Conte Digestive Diseases Research Core Centers*, 10 months, $296,930 **Richard Bucala**, NIH, *MIF and the Host Response to Infection*, 5 years, $2,068,750 **David Calderwood**, NIH, *Structure and Function of the IPP Complex*, 4 years, $1,390,200 **Michael Caplan**, NIH, *Ion Pump Partners: Regulators of Sorting and Function*, 10 months, $566,331 • **Herta Chao**, NIH, *Imaging the Effects of Androgen Deprivation Therapy on Cognitive Functions in Patients with Non-Metastatic Prostate Cancer*, 2 years, $130,400 **Lauren Cohn**, NIH, *Immune Regulation in the Respiratory Tract by the Epithelial Protein PLUNC*, 2 years, $455,125 • **Michael Crair**, NIH, *Mechanisms of Visual Map Development in the Superior Colliculus*, 4 years, $2,388,716 **Gary Desir**, NIH, *The Molecular Physiology of Renalase*, 22 months, $645,588 • **Kavita Dhodapkar**, NIH, *FCγ Receptor–Mediated Regulation of Dendritic Cell Function*, 4 years, $1,655,000 • **Ralph DiLeone**, NIH, *Leptin Receptor Signaling and Function in Dopamine Neurons*, 4 years, $1,294,726 • **Hester Doyle**, NIH, *The Contribution of Protein Methylation to the Development of SLE*, 2 years, $164,912 **Jack Elias**, NIH, *Cigarette Smoke, RIG-Like Helicases and Alveolar Remodeling*, 4 years, $1,655,000 • **Americo Esquibies**, NIH, *Role of VEGF in Lung Development and Hyperoxic Injury*, 5 years, $665,550 • **Lynn Fiellin**, NIH, *An Interactive Video Game for HIV Prevention in At-Risk Adolescents*, 5 years, $3,983,099 **Brian Forsyth**, NIH, *Addressing Adherence to PMTCT and Early Care of Women and Infants in South Africa*, 2 years, $348,450 • **Alison Galvani**, NSF, *Dynamic Risk Perceptions about Mexican Swine Influenza*, 1 year, $57,125 **Charles Greer**, NIH, *Genetic Determinants of Local Circuit Organization*, 5 years, $1,758,440 **Yongtao Guan**, NSF, *CAREER: New Statistical Methods for Massive Spatial, Temporal and Spatial-Temporal Process*, 5 years, $400,000 **Seth Guller**, NIH, *Targeting Placental Pathophysiology in IUGR and Preeclampsia*, 2 years, $827,500 • **Ann Haberman**, NIH, *In Vivo Imaging of T and B Interactions in Germinal Center Initiation*, 4 years, $1,655,000 • **Marc Hammarlund**, NIH, *Horseman, Pass By: Finding Post-Development Functions of Essential Genes*, 4 years, $1,324,000 • **Jonas Hannestad**, NIH, *Validation of Beta2-Containing Nicotinic Acetylcholinergic Receptors as a Potential Therapeutic Target in Bipolar Disorder*, 22 months, $382,516 • **Hoby Hetherington**, NIH, *B1-Based Localization for MRSI of Human Brain at 7T*, 4 years, $2,001,728 **Minoti Hiremath**, Dept of Defense (US), *Role of PTHrP and Mesenchymal Wnt Signaling in Mediating the Effects of PTHrP in the Mammary Gland*, 3 years, $243,000 • **Jeannette Ickovics**, NIH, *Interdisciplinary HIV Prevention Training Program*, 5 years, $2,240,148 **Jessica Illuzzi**, NIH, *Duration of Intrapartum Antibiotic Prophylaxis for Group B Streptococcus*, 2 years, $158,175 • **Karl Insogna**, NIH, *Core Center for Musculoskeletal Biology and Medicine*, 5 years, $3,310,000 • **Melinda Irwin**, NIH, *RCT of Exercise on Aromatase Inhibitor Side Effects in Breast Cancer Survivors*, 4 years, $2,542,898 • **Yasuko Iwakiri**, NIH, *Arterial Remodeling in Chronic Liver Disease*, 5 years, $1,863,470 • **Susan Kaech**, NIH, *Transcriptional Control of IL-7 receptor (IL-7R) in T Cells*, 3 years, $166,476 • **Mustafa Khokha**, NIH, *Developing Transposon Methods for Insertional Mutagenesis in Xenopus*, 2 years, $455,125 • **Kenneth Kidd**, NSF, *ALFRED: Ongoing Growth of an Anthropological Resource*, 3 years, $731,577 • **Robert LaMotte**, NIH, *Neural Mechanisms of Itch*, 5 years, $6,256,393 • **Brian Leaderer**, NIH, *Traffic and Respiratory Morbidity in the Northeast*, 5 years, $3,179,812 • **Qiang Leng**, NIH, *Identification, Characterization and Regulation of Intermediate Conductance K Channels in the Kidney*, 5 years, $1,559,347 • **Becca Levy**, NIH, *Positive Age Stereotypes across the Life Span*, 2 years, $826,221 • **Chiang-Shan Li**, NIH, *Thalamic Processes of Self-control in Cocaine Dependence*, 22 months, $383,635; NIH, *Imaging Cognitive Control in Cocaine Dependence*, 5 years, $639,090 • **Brett Lindenbach**, NIH, *Molecular Determinants of Hepatitis C Virus Infectivity*, 4 years, $1,655,000 **Shuangge Ma**, NIH, *Effective Clustering Penalized Methods for Genomic Biomarker Selection*, 2 years, $173,605; NSF, *Novel Methods for Pharmacogenomic Data Analysis using Gene Clusters*, 3 years, $99,998 **Suzanne Macari**, NIH, *Perceptual Factors Affecting Social Attention in Autism Spectrum Disorders*, 2 years, $165,500 • **Arya Mani**, NIH, *Investigation of Genetic and Physiological Causes of Inherited Vascular and Metabolic Diseases*, 5 years, $2,068,750 **John McCormack**, NIH, *The Role of SSD1 in Handling of Oxidized RNAs in* Saccharomyces cerevisiae, 3 years, $148,974 • **Eric Meffre**, NIH, *Loss of B Cell Tolerance in Rheumatoid Arthritis*, 2 years, $788,236 • **Alexandra Miller**, NIH, *A Role for Migrating Olfactory Placode Cells in Olfactory Nerve Development*, 2 years, $90,254 • **Andrew Miranker**, NSF, *Protein–Protein Recognition Motifs Based on Solenoid Display*, 3 years, $450,000 **Alan Morrison**, NIH, *The Rac2-Induced Macrophage Proteome and Vascular Pathology*, 3 years, $165,858 • **Michael Nathanson**, NIH, *Investigative Training in Hepatology*, 5 years, $1,249,731 • **Alexander Neumeister**, NIH, *Serotonin 1B Receptor Imaging in Pathological Gambling and Alcohol Dependence*, 2 years, $355,679 • **Laura Niklason**, NIH, *Research Training in Anesthesiology*, 5 years, $843,747 **Kevin Pelphrey**, NIH, *Neuroimaging of the Development of Neural Mechanisms for Social Cognition*, 2 years, $999,085 • **Kitt Petersen**, NIH, *Mechanisms of Insulin Resistance in the Aged*, 1 year, $413,750 • **Anna Rhoades**, NSF, *Single-Molecule Studies of Tau Conformations and Dynamics*, 5 years, $761,404 • **David Rimm**, NIH, *Optimal Predictors of Response to Trastuzumab*, 2 years, $1,172,590 • **Marc Rosen**, NIH, *Abstinence-Linked Money Management*, 4 years, $2,017,242 • **Bruce Rounsaville**, NIH, *Psychotherapy Development Research Center*, 5 years, $11,029,918 • **Eric Rubenstein**, NIH, *Nuclear Localization and Function of the Transmembrane DOA10 Ubiquitin Ligase*, 3 years, $148,974 • **Nancy Ruddle**, NIH, *Lymphotoxin: Regulation and Biologic Function*, 4 years, $839,245 • **Gerard Sanacora**, NIH, *Effects of Stress and Glutamatergic Agents on Glutamate Cycling and Behavior*, 5 years, $1,903,013 • **Richard Schottenfeld**, NIH, *Pain and Opioid Dependence (POD)*, 4 years, $1,484,772 • **Nenad Sestan**, NIH, *Development and Organization of the Human Frontal Cortex*, 5 years, $5,707,948; NIH, *Molecular Control of Cortical Projection Neuron Identity and Connectivity*, 5 years, $1,810,155 • **Gordon Shepherd**, NIH, *Sense Lab: Integration of Multidisciplinary Sensory Data*, 5 years, $3,523,649 • **Robert Sherwin**, NIH, *Diabetes Mellitus and Disorders of Metabolism*, 5 years, $1,637,270 • **Frederick Sigworth**, NIH, *Fluctuations in Ionic Current through Membrane Channels*, 4 years, $1,710,451 • **Rajita Sinha**, NIH, *Development of Guanfacine to Decrease Drug Craving, Anxiety and Cocaine Relapse Risk*, 3 years, $1,056,114 • **Carla Stover**, NIH, *Integrated Treatment for Fathers Who Perpetrate Domestic Violence*, 5 years, $784,663 **Stephen Strittmatter**, NIH, *Molecular Determinants of Adult CNS Axon Growth*, 2 years, $963,898 • **Scott Strobel**, NSF, *IRES: U.S./Ecuador/Peru/International: Undergraduate Rainforest Expedition and Laboratory*, 3 years, $115,065 • **Bindu Sukumaran**, NIH, *Characterization of an* Anaplasma phagocytophilum *Protein Interfering with Eukaryotic Vacuolar Transport Pathway*, 2 years, $165,500 • **Jane Taylor**, NIH, *Motivation in Addiction: PKA Mechanisms*, 5 years, $1,399,507 • **Mary Tinetti**, NIH, *Universal Outcomes as a Common Metric across Multiple Diseases in Elders*, 2 years, $373,203 • **Flora Vaccarino**, NIH, *Environmental Enrichment and Neuronal Turnover in the Brain*, 2 years, $331,000 • **Fei Wang**, NIH, *Frontotemporal Neural Systems in Bipolar Disorder and Schizophrenia*, 5 years, $897,352 • **Tong Wang**, NIH, *Axial Flow Effects in Proximal Tubule*, 5 years, $2,050,925 **Anne Williamson**, NIH, *Glutamate–Glutamine Metabolism in Primary Human Brain Tumors*, 2 years, $455,125 • **Lawrence Young**, NIH, *AMP-Activated Protein Kinase in the Ischemic Heart*, 4 years, $1,655,000 • **Dejan Zecevic**, NIH, *Voltage-Sensitive Dye Imaging from the Nervous System*, 4 years, $1,446,842 • **Caroline Zeiss**, NIH, *Building a Better AMD Mouse*, 2 years, $455,125 • **Tongzhang Zheng**, NIH, *Research Training for Cancer Epidemiology and Biostatistics in China*, 5 years, $1,107,087

Non-Federal

Neil Aggarwal, American Psychiatric Association, *APA/SAMHSA Minority Fellowship*, 1 year, $32,895 • **Diego Alvarez**, Pew Medical Fellowships, *The Cell Biology of Hepatitis C Virus Entry*, 3 years, $90,000 • **Marc Auerbach**, R Baby Foundation, *A Multi-Center Study to Evaluate the Effectiveness of Simulation of Patient Outcomes*, 1 year, $90,000 **Henry Binder**, Bill and Melinda Gates Foundation, *Planning for the Delivery of a More Effective Oral Rehydration Solution to Improve Diarrhea Control Worldwide*, 2 years, $1,803,724 • **Elizabeth Bradley**, Commonwealth Fund, *Hospital Variation in Survival Rates after Acute Myocardial Infarction*, 2 years, $203,185; South Essex Partnership NHS Foundation Trust, *Leadership Workshop*, 14 months, $140,000 • **Christopher Breuer**, Advanced Technologies and Regenerative Medicine, LLC, *Development of a Murine Model for Evaluating Tissue Engineered Vascular Graft (Aortic Interposition Model)*, 1 year, $63,765 • **Natalia Buza**, Cap Foundation Scholars Program, *Scholars Research Fellowship*, 1 year, $25,000 • **Ilana Chefetz-Menaker**, Life Sciences Research Foundation, *Identification and Characterization of Ovarian Cancer Stem Cells*, 3 years, $168,000 **Hyung Chun**, Howard Hughes Medical Institute, *Role of the Apelin-APJ Pathway in Vascular Wall Disease*, 4 years, $307,663 • **Oscar Colegio**, Dermatology Foundation, *Defining the Role of the Innate Immune System in Tumor Progression and Metastasis*, 1 year, $55,000; Damon Runyon Cancer Research Foundation, *Defining the Role of the Innate Immune System in Tumor Progression and Metastasis*, 3 years, $275,667 • **Daniel Colón-Ramos**, Esther and Joseph Klingenstein Fund, Inc., *Molecular Factors Directing Orchestrated Circuit Formation during the Development of the Thermotaxis Circuits in* C. clegans, 3 years, $150,000 • **Eve Colson**, Boston University, *Study of Attitudes and Factors Affecting Infant Care*, 1 year, $56,244 **Joseph Contessa**, American Society for Radiation Oncology, *Targeting N-Linked Glycosylation to Radiosensitize Malignant Gliomas*, 2 years, $250,000 • **Neera Dahl**, Plexxikon, Inc., *A PKD Patient Registry*, 1 year, $64,940 • **Charles Dela Cruz**, Flight Attendant Medical Research Institute, *Mechanisms of Synergy between Cigarette Smoke and RSV*, 3 years, $325,500 • **Kavita Dhodapkar**, Doris Duke Charitable Foundation, *Regulation of Fc Gamma Receptors in Immune Thrombocytopenic Purpura*, 3 years, $405,000 • **Antonette Dulay**, Society for Maternal-Fetal Medicine, *A Role for Soluble Modulators of Innate Immunity in Regulating the Intra-Amniotic Inflammatory Response to Infection*, 3 years, $300,000 • **Stephanie Eisenbarth**, College of American Pathologists Foundation, *Evaluating the Role of IL-1beta in the Generation of Immunity Following Nalp3 Inflammasome Activation by Aluminum Adjuvants*, 1 year, $25,000 • **Jack Elias**, Flight Attendant Medical Research Institute, *Cigarette Smoke and RIG-Like Helicase Innate Immunity*, 3 years, $325,500 **Eran Elinav**, Cancer Research Institute, *Role and Mechanism of Inflammasome Dysregulation in Autoimmunity*, 3 years, $145,500 **Ada Fenick**, The Children's Fund of Connecticut, *Enhancement of Developmental Screening in the Medical Home*, 20 months, $115,000 • **Liana Fraenkel**, American College of Rheumatology, *Improving Risk Communication and Decision Making in RA*, 2 years, $400,000 • **Xiao-Bing Gao**, Foundation for Prader-Willi Research, *Hypocrelin/Crexin Deficiency in Prader-Willi Syndrome Animal Models*, 1 year, $50,000 • **Arnar Geirsson**, The Thoracic Surgery Foundation for Research and Education, *Role of MicroRNA in Cardiac Ischemia and Heart Failure*, 2 years, $100,000 • **Jonathan Grauer**, Stryker Spine, *Biochemical Comparison of Uniaxial Screws and Monoaxial Screws*, 8 months, $26,685 **Hamada Hamid**, Epilepsy Foundation of America, *Characterizing Hippocampal–Frontal Circuits in Epilepsy and Depression*, 1 year, $40,000; Nat'l EpiFellows Foundation, *White Matter Changes in Epilepsy and Depression*, 1 year, $20,000 • **Marc Hammarlund**, Arnold and Mabel Beckman Foundation, *Strategies to Study the Function of Essential Genes in Neurons*, 3 years, $300,000 **Jamie Harrington**, Howard Hughes Medical Institute, *Evaluation and Characterization of Nanomaterials for Noninvasive Monitoring of Human Embryonic Stem Cell–Based Tissue Engineered Vascular Grafts*, 22 months, $38,000 • **Lyndsay Harris**, CALGB Foundation, *Biomarker Incubator to Define and Validate Predictors of Response to Paclitaxel and Trastuzumab*, 1 year, $44,967 • **Kevan Herold**, American Diabetes Association, Inc., *Beta before Alpha: The Importance of Residual Beta Cell Function for Alpha Cell Secretion of Glucagon in Response to Hypolycemia*, 2 years, $150,000; Juvenile Diabetes Research Foundation Int'l, *Preclinical Studies of Anti-CD3 mAb and IL-1 Antagonists*, 2 years, $324,020 • **Hoby Hetherington**, Resonance Research, Inc., *Optimization of Human Head MRI and MRS using High Order Shim Insert*, 6 months, $54,968 • **Narutoshi Hibino**, American Heart Association, Founders Affiliate, *Nanomaterials for Noninvasive Monitoring of Mouse Induced Pluripotent Stem Cell–Based Tissue Engineering Vascular Graft*, 2 years, $87,000 • **Theodore Holford**, MD Anderson Cancer Center, *Microsimulation of Longitudinal Smoking and Lung Cancer Risk*, 2 years, $250,241 • **Henry Huang**, University of Montana, *PET Imaging Tracers to Quantify Norepinephrine Transporter in the Brain*, 1 year, $138,439 • **Beth Jones**, University of Miami, *Effectively Communicating Mammography Results to Underserved Women*, 1 year, $3,333 • **Kaveh Khoshnood**, China CDC, *Multidisciplinary HIV and TB Implementation Sciences Training in China*, 9 months, $129,983 • **Felix Knauf**, Amgen, Inc., *Role of Transporter SLC26A2 in Oxalate Homestasis*, 1 year, $40,000 • **Christine Ko**,

Dermatology Foundation, *Comparison of Squamous Cell Carcinoma and Keratoacanthoma*, 1 year, $20,000 • **Peter Krause**, Tufts University, *Xenodiagnosis of Lyme Disease*, 1 year, $37,569 • **Harlan Krumholz**, Robert Wood Johnson Foundation, *Clinical Scholars Program*, 1 year, $93,543; Robert Wood Johnson Foundation, *Clinical Scholars Program*, 2 years, $1,085,855 • **Rachel Lampert**, Emory University, *Mechanisms Linking Depression to Cardiovascular Risk*, 1 year, $18,423 • **Adam Lazorchak**, The Leukemia & Lymphoma Society, *The Role of mTOR Signaling in the Regulation of RAG Recombinase Expression*, 3 years, $146,510 • **Patty Lee**, Flight Attendant Medical Research Institute, *TLR-Mediated Emphysema: Role of Aging and Gender*, 3 years, $325,500 • **Seung Lee**, Rotary International District 3690 Club of Korea, *Therapeutic Implication of PKD, Histone Deacetylase Inhibitors*, 1 year, $56,802 • **Ralf Leonhardt**, Cancer Research Institute, *Characterization of TAP- and Tapasin-Independent MHC Class-1 Restricted Melanoma Epitope*, 3 years, $145,500 • **Chiang-Shan Li**, Tourette Syndrome Association, Inc., *Imaging Cognitive Motor Control in Tourette Syndrome*, 1 year, $75,000 • **Susan MacLauchlan**, American Heart Association, Founders Affiliate, *Thrombospondin 2 Regulation by Nitric Oxide Levels in Wound Angiogenesis*, 2 years, $42,000 • **Praveen Mannam**, American Heart Association, Nat'l Center, *Endothelial MKK3 Mediates Sepsis and Lung Injury*, 1 year, $65,000 • **Linda Mayes**, Hope for Depression Research Foundation, *Understanding Abnormal Cortical Activation in Infants of Depressed Mothers*, 2 years, $110,000 **Carolyn Mazure**, Maximilian E. & Marion O. Hoffman Foundation, Inc., *Women's Health Research at Yale*, 2 years, $50,000 • **Brannon McCullough**, American Heart Association, Nat'l Center, *Mechanics of Cofilin-Induced Actin Filament Severing*, 2 years, $42,000 **Thomas McGlashan**, University of Oslo, *Collaborative Research Agreement*, 1 year, $37,000; Stavanger University Hospital, *Collaborative Research Agreement*, 1 year, $18,500 • **Carsten Mim**, Cancer Research Institute, *Structural Studies on BAR-proteins and their Role in Membrane Remodeling*, 3 years, $145,500 • **Wang Min**, Oklahoma Medical Research Foundation, *Epsin in Angiogenesis and Vascular Remodeling*, 1 year, $13,659 • **Sukanya Narasimhan**, L2 Diagnostics, LLC, *Nanoparticle-Based Vaccines against Flaviviruses*, 1 year, $34,401 **Abhinav Nath**, American Heart Association, Nat'l Center, *Single-Molecule Insights into Detoxification Catalysis and the Response to Oxidative Stress*, 2 years, $78,000 • **Ali Ozturk**, Congress of Neurological Surgeons, *Genetics of Intracranial Aneurysms*, 1 year, $25,000 • **Anisha Patel**, Endocrine Fellows Foundation, *Obesity and Metabolic Changes Associated With Transgenic Marshmallow Mice*, 1 year, $20,000; Lawson Wilkins Pediatric Endocrine Society, *Obesity and Metabolic Changes Associated with Transgenic Marshmallow Mice*, 1 year, $50,000 • **Kevin Pelphrey**, University of Pittsburgh, *Biological and Information Processing Mechanisms Underlying Autism*, 7 months, $44,238 **Salley Pels**, Nat'l Hemophilia Foundation, *Clinical Hemostasis Fellowship*, 2 years, $192,498 • **Kitt Petersen**, American Diabetes Association, Inc., *Distinguished Clinical Scientist Award*, 4 years, $760,000 • **Yibing Qyang**, American Heart Association, Nat'l Center, *Wnt Signaling and Functional Characterization of Isl+ Cardiovascular Progenitor Cells*, 4 years, $308,000 • **Lynne Regan**, Mary Kay Ash Charitable Foundation, *Development of a Novel Class of Hsp90 Inhibitors as Anti-Cancer Therapeutics*, 2 years, $100,000 **Robert Rosenheck**, The Feinstein Institute for Medical Research, *Recovery after an Initial Schizophrenic Episode (RAISE): Schizophrenic Episode Recovery*, 6 months, $94,795; Duke University, *Comparison of Long-Acting Antipsychotic Medications for Schizophrenia (CLAMS)*, 1 year, $94,795 • **James Rothman**, G. Harold and Leila Y. Mathers Charitable Foundation, *Regulation of Vesicle Transport Pathways Established by Genome-Scale Function Scans*, 1 year, $197,068 • **Lauren Saunders**, American Heart Association, Nat'l Center, *Characterization of Autotaxin, a Lysophospholipase D*, 2 years, $42,000 • **Montrell Seay**, United Negro College Fund, *UNCF-Merck Postdoctoral Fellow*, 18 months, $85,000 • **Hua Shen**, International Society for Heart and Lung Transplantation, *The Impact of CD14 and CD36 Signaling in Costimulatory Blockade Extension of Allograft Survival*, 1 year, $40,000 • **Anushree Shirali**, Nat'l Kidney Foundation, *Nanoparticle-Encapsulated Delivery of Immunosuppression during Transplantation*, 2 years, $100,000 **Mark Shlomchik**, Boston University, *Activation and Regulation of Autoimmunity by Innate Immune Sensing Pathways*, 5 years, $2,293,327 • **Gerald Shulman**, American Diabetes Association, Inc., *Mentor Based Award*, 4 years, $144,000 • **Frederick Sigworth**, Princeton University, *Improved Algorithms for Macromolecular Structure Determination by Cryo-EM + NMR Spectroscopy*, 5 years, $500,000 • **Mark Solomon**, American Heart Association, Nat'l Center, *Pseudosubstrate Inhibition of the Anaphase-Promoting Complex*, 3 years, $198,000 • **Ajay Srivastava**, American Society of Nuclear Cardiology, *Determining Myocardial Blood Flow Reserve in Cardiac Transplant Recipients by 82-Rb PET*, 1 year, $30,000 • **Gary Stack**, College of American Pathologists Foundation, *Delayed Hemolytic Transfusion Reactions*, 1 year, $10,000 • **Hanna Stevens**, American Psychiatric Institute for Research and Education, *Wyeth Research Fellowship*, 1 year, $45,000 • **Michael Strambler**, Nat'l Research Council, *Diversity Fellowship*, 1 year, $41,500 • **Stephen Strittmatter**, Craig H. Neilsen Foundation, *Screening the Genome for Axonal Regeneration Control*, 2 years, $250,000 • **Patrick Sung**, New York University, *Mechanisms of DNA Motor Proteins in Homologous Recombination*, 10 months, $99,176 • **Hugh Taylor**, The John B. Pierce Laboratory, Inc., *Compromised Microcirculation in Women with Polycystic Ovary Syndrome*, 1 year, $20,421 • **David Tuck**, Philips Medical Systems, *Integration of Imaging and Genomic Data in Breast Cancer*, 2.5 years, $475,662 • **Flora Vaccarino**, Tourette Syndrome Association, Inc., *Interneuron Deficit and Functional Compartments of the Striatum in Tourette Syndrome*, 1 year, $71,892 **Vivian Vlamakis**, American College of Rheumatology, *An Analysis of CD4 T-Cell Subsets in Patients with SLE*, 3 years, $150,000 • **Fei Wang**, The Klingenstein Third Generation Foundation, *The Neural Circuitry of Adolescent Major Depressive Disorder: A Multi-Modality Magnetic Resonance Imaging Study*, 2 years, $60,000 • **Stuart Weinzimer**, Juvenile Diabetes Research Foundation Int'l, *Prevention of Nocturnal Hypoglycemia with Automatic Pump Suspension*, 1 year, $241,873 **Sherman Weissman**, American Society of Hematology, *A Biochemical Approach to Isolate Extracellular and Intracellular Interacor(s) of the Stem Cell Antigen CD34*, 6 months, $4,000 • **Carol Weitzman**, Lulac Head Start Inc., *Head Start*, 1 year, $30,000 **Dawn Wetzel**, Pediatric Infectious Diseases Society, *Phagocytosis and* Leishmania *Invasion*, 2 years, $90,000 • **Bruce Wexler**, Nat'l Inst. of Mental Health & Neurosciences, *fMRI during Simulated Social Interactions in Schizophrenia: Emotion- and Cognition-Related Brain Activations*, 3 years, $965,500 **Dianqing Wu**, University of Connecticut, *Interactive Signaling Modules and Vascular Phenotypes*, 10 months, $409,069 • **James Yue**, Depuy Spine, Inc., *Clinical Spine Fellowship*, 1 year, $80,000; Medtronic Spinal and Biologics, *Charitable Spine Fellowship*, 1 year, $80,000 • **Hitten Zaveri**, ITN Energy Systems, Inc., *Wireless Multimodal Brain Monitoring*, 2 years, $265,341

// Palade *(from page 1)* Cellular Medicine at the University of California–San Diego (UCSD).

In 1973, Farquhar came to Yale with Palade and with James D. Jamieson, M.D., PH.D. (now professor of cell biology and director of the medical school's M.D./PH.D. Program) to establish a new Section of Cell Biology, ultimately spending 17 years on the faculty and rising to Sterling Professor.

For Farquhar, the occasion was suffused with nostalgia, with many familiar faces dotting the capacity crowd at the medical school's Anlyan Center auditorium. For her listeners, the lecture was a tour de force of scientific exposition by a researcher with five decades' experience in the lab.

In a pair of classic 1957 papers that she published as a postdoctoral fellow at the University of Minnesota in collaboration with Robert A. Good, M.D., and Robert L. Vernier, M.D., Farquhar used electron microscopy to examine biopsies from children with kidney diseases and made the first descriptions of the structural abnormalities that compromise renal function in these patients.

CHRIS VOLPE

The inaugural George E. Palade Memorial Lecture, sponsored by the Department of Cell Biology, was delivered to a capacity crowd by Marilyn Farquhar of the University of California–San Diego. Farquhar, a distinguished scientist whose career spans more than 50 years, is the widow of Palade, a Nobel Prize winner whose integration of electron microscopy and biochemistry helped to launch the modern era of cell biology. Farquhar and Palade (along with James Jamieson, now director of Yale's M.D./PH.D. program) came to the School of Medicine in 1973 to establish the Section of Cell Biology, now a full-fledged department, and were members of the Yale faculty for 17 years.

After joining Palade's cell biology lab at The Rockefeller University in 1959 as a postdoctoral fellow, Farquhar continued her work on kidney structure and function. In 1963 she discovered tight junctions, crucial sites of cell–cell interactions, and in her subsequent work at the University of California–San Francisco, Rockefeller, Yale, and UCSD she has made seminal contributions to our understanding of membrane trafficking, the process by which proteins and other materials are transported within and between cells. This diverse body of work has earned Farquhar many accolades, including the A.N. Richards Award from the International Society of Nephrology, the Homer W. Smith Award from the American Society of Nephrology, the E.B. Wilson Medal from the American Society for Cell Biology, and membership in the National Academy of Sciences and the American Association of Arts and Sciences.

In her April lecture at Yale, Farquhar crisply presented a new line of work centered on GIV, a protein recently discovered in her lab which appears to play a role in cancer growth and metastasis.

GIV binds to Gαi, a member of a family known as G proteins, which are usually found on cells' outer membranes, where they act as middlemen between receptors that detect extracellular signals and effectors that induce actions inside the cell. By contrast, Farquhar's group and others found Gαi to be abundantly expressed in the Golgi apparatus, an intracellular structure, with no associated receptor; when Gαi was localized with a red fluorescent protein, explained Farquhar, underscoring a vivid micrograph projected behind her, the Golgi "lit up like a Christmas tree."

Further studies of this peculiar protein led to the discovery that GIV regulates and activates Gαi: when Gαi is in an active state, cells tend to migrate, whereas inactive Gαi prompts cells to divide. Because unregulated cell migration and division are hallmarks, respectively, of the metastasis and rampant proliferation seen in cancer, Farquhar's team next explored the potential role of GIV–Gαi interactions in human cancers.

The scientists' analysis of specimens from rapidly spreading cancers versus those from localized cancers revealed that GIV was far more abundant in the former than the latter, findings that were replicated in pancreas, colon, and breast cancers.

Taken together, the results indicate that drug compounds that target GIV and prevent activation of Gαi may slow the metastatic progression that proves lethal in many cases of cancer, a direction now being pursued by Farquhar's trainees.

Farquhar summed up her talk with a straightforward acknowledgment of the remaining mysteries in this latest research, and with thanks to the many young scientists who have helped her probe these questions in the lab.

Then, with the wisdom gained during a life in science, she elegantly tied a bow around both sentiments. "After all, these young people all need something to do," she said. "So we need to leave some questions on the table for them."

Expert on autoimmunity is appointed Paul Beeson Professor

Joseph E. Craft, M.D., newly named as the Paul B. Beeson Professor of Medicine, is an internationally recognized expert on the pathogenesis of systemic autoimmune diseases, including lupus and rheumatoid arthritis.

He and his research team seek to define the mechanisms of loss of self-tolerance and activation of autoreactive T cells in systemic autoimmune diseases, and the differentiation and regulation of T cells in normal immune responses. His research has been continually funded by the National Institutes of Health (NIH) since 1985, and he is the current recipient of an NIH MERIT Award and directs an NIH-funded center in the rheumatic diseases.

Craft joined the School of Medicine as an assistant professor in 1985 after completing an internship and residency

Joseph Craft

at Yale-New Haven Hospital (YNHH) and a fellowship in rheumatology. He became a professor of medicine in 1997, a professor of immunobiology in 1999.

The chief of the Section of Rheumatology since 1991, Craft has also directed the Yale Investigative Medicine Program since 2004. He is chief of rheumatology at YNHH.

Craft won the School of Medicine's Charles W. Bohmfalk Teaching Prize in Basic Sciences in 2004. He has been elected a fellow of the American Association for the Advancement of Science and to the American Society for Clinical Investigation, among other professional honors.

Craft has served numerous national research organizations, including as chair of two standing study sections at NIH and on the scientific advisory board of the Alliance for Lupus Research. He is a member of the Board of Scientific Counselors at the NIH's National Institute of Arthritis, Musculoskeletal, and Skin Diseases (NIAMS), and he is a member of the boards of the Arthritis Foundation and the Lupus Clinical Trials Consortium. Craft is a co-founder and serves on the board of L2 Diagnostics, a biotechnology company in New Haven.

An associate editor of *Arthritis & Rheumatism*, Craft also serves on the editorial board of *Autoimmunity*. He is active in a number of community service endeavors, including serving as a volunteer for the Connecticut Chapter of the Lupus Foundation of America.

The professorship was established in 1981 by the late Elisha Atkins, M.D., to honor his colleague Paul B. Beeson, M.D., a beloved clinician, researcher, and teacher who served as chair of Yale's Department of Internal Medicine from 1952 to 1965. An expert in infectious disease, Beeson provided an ideal by which Yale medical students, residents, and faculty members have measured themselves for decades. Upon his retirement from academia in 1981, his two chief residents summarized Beeson's legacy: "In short," they said, "he is the kind of physician all of us aspire to be."

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Ritvo Professor to address psychosocial needs of children with cancer

Andrés S. Martin, M.D., M.P.H., a child and adolescent psychiatrist on the faculty of the Yale Child Study Center (YCSC), has been named the inaugural Riva Ariella Ritvo Professor of Pediatric Oncology Psychosocial Services by the Yale Corporation.

The new professorship was established in September 2009 with a gift from Riva Ariella Ritvo, PH.D., an autism expert and clinical instructor at the YCSC, and her husband, Alan B. Slifka, M.B.A., a noted philanthropist and member of the Yale College Class of 1951.

The professorship was created to hasten the pace of YCSC research in this area, with the aim of creating a model of comprehensive psychosocial care for children diagnosed with cancer and their families. Childhood cancer affects not only children's physical health, but can threaten their social and emotional adjustment, educational performance and cognitive abilities.

After receiving his medical degree from Anahuac University in Mexico City in 1990, Martin completed a fellowship and residency in psychiatry at Harvard Medical School, followed by a residency in internal medicine at the University of Miami's Miller School of Medicine. He received his M.P.H. degree from the Yale School of Public Health.

Since 2002, Martin has been medical director of the Children's Psychiatric Inpatient Service (CPIS) at Yale-New Haven Children's Hospital, which serves children with serious neuropsychiatric disorders and is an

Andrés Martin

important clinical interface between the YCSC and the hospital. In addition to providing clinical care, the CPIS has evolved into a model training facility for house staff and for medical students from Yale and other institutions.

Martin is director of medical studies at the YCSC. He is also associate training director of both the child and adolescent psychiatry program and an innovative program in child psychiatry funded by the National Institute of Mental Health that integrates clinical and research training. The latter program has served as a model for other teaching institutions.

Martin has helped develop a medical student mentorship program in child psychiatry that has been replicated at 10 other institutions across the nation, and a separate international mentorship program for early career academic psychiatrists.

Martin is editor-in-chief of the *Journal of the American Academy of Child and Adolescent Psychiatry*. He is co-editor of the fourth edition of *Lewis's Child and Adolescent Psychiatry: A Comprehensive Textbook*; the forthcoming second edition of *Pediatric Psychopharmacology: Principles and Practice*; and of *Life Is with Others: Selected Writings in Child Psychiatry*, which features essays by his late mentor and father-in-law, Donald J. Cohen, M.D., who served as YCSC director from 1983 to 2001.

// Narva *(from page 5)* in Washington. Narva had moved from Oakland to San Diego when, "out of nowhere, I got a set of orders after eight months to go back to be the chief of dermatology at the NNMC in Bethesda," Narva says. Soon afterwards, Edson also was assigned to Bethesda, initially to serve as assistant chief of urology.

In Washington, Narva saw and treated members of Congress, the Supreme Court, and five U.S. presidents, and Edson once had President Richard Nixon as a patient. Narva "was never intimidated by any of these folks," he says. "Every one of them was very appreciative and compliant." But he soon corrects himself: "Lyndon Johnson was truly an intimidating personality."

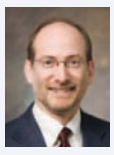
Edson, who attends class reunions at Yale every five years, says of himself and Narva, "It was a very exciting time for us. And that's why we feel so strongly that we should continue to support the School of Medicine, financially and in other ways."

Narva, of course, agrees: "Everybody was so receptive. Everybody was so supportive. It really was a pleasant, warm experience. That's what I conjure up every time I think about New Haven and the medical school."

Awards and Honors

Daniel A. Colón-Ramos, PH.D., assistant professor of cell biology, has won a two-year Sloan Foundation Fellowship for "outstanding promise." Colón-Ramos studies how neuronal circuits form during development. The awards, given annually by the Alfred P. Sloan Foundation to 118 early-career researchers, include funding of $50,000.

David A. Hafler, M.D., Gilbert H. Glaser Professor and chair of Neurology, has been awarded the John J. Dystel Prize for Multiple Sclerosis Research from the American Academy of Neurology. The Prize recognizes outstanding contributions to research in the understanding, treatment, or prevention of multiple sclerosis.



John H. Krystal, M.D., the Robert L. McNeil Jr., Professor of Translational Research and chair of the Department of Psychiatry, has received the Stanley Dean Research Award from the American College of Psychiatrists for research leading to "promising new approaches to the neurobiology and treatment of schizophrenia."

GERSTEIN

ROEDER

SHULMAN

Mark B. Gerstein, PH.D., Albert L. Williams Professor of Biomedical Informatics; **G. Shirleen Roeder**, PH.D., Eugene Higgins Professor of Molecular, Cellular, and Developmental Biology; and **Gerald I. Shulman**, M.D., PH.D., George R. Cowgill Professor of Physiological Chemistry and professor of medicine and of cellular and molecular physiology, have been elected Fellows of the American Association for the Advancement of Science (AAAS). AAAS is an international nonprofit organization dedicated to advancing science around the world. Among other activities, AAAS publishes the journal *Science*.

CAPLAN

CAPPELLO

CARSON

FISH

HAFLER

INSOGNA

MAZURE

MAYNE

ROEDER

Michael J. Caplan, M.D., PH.D., chair and C.N.H. Long Professor of Physiology and professor of cell biology; **Michael Cappello**, M.D., professor of pediatrics, microbial pathogenesis, and epidemiology; **Richard E. Carson**, PH.D., professor of diagnostic radiology and biomedical engineering; **Durland Fish**, PH.D., professor of epidemiology; **David A. Hafler**, M.D., Gilbert H. Glaser Professor and chair of the Department of Neurology; **Karl L. Insogna**, M.D., professor of medicine; **Susan T. Mayne**, PH.D., professor of epidemiology; **Carolyn M. Mazure**, PH.D., professor of psychiatry and psychology, associate dean for faculty affairs, and director of Women's Health Research at Yale; and **G. Shirleen Roeder**, PH.D., Eugene Higgins Professor of Molecular, Cellular, and Developmental Biology and professor of genetics, have been elected members of the Connecticut Academy of Science and Engineering (CASE). Founded in 1976 and patterned after the National Academy of Sciences, CASE is a private, nonprofit institution devoted to advising state government and industry "in the application of science and engineering to the economic and social welfare."