Medicine@Yale

Advancing Biomedical Science, Education and Health Care

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NEW HAVEN REGISTER

Thomas Lynch at the new Smilow Cancer Hospital, slated to open this fall.

New Cancer Center head: 'aspire to cure cancers'

Thomas J. Lynch Jr., M.D., an alumnus of Yale College and the School of Medicine who is renowned for his research on the relationship between genetic variations and the effectiveness of cancer therapies, has been named director of Yale Cancer Center (YCC) and physician-in-chief of the new Smilow Cancer Hospital, which will open in October 2009. YCC is southern New England's only comprehensive cancer center designated by the National Cancer Institute and one of only 40 in the nation.

At a February reception marking his appointment, Lynch urged his new School of Medicine colleagues to think big. "I think we need to aspire to cure cancers, not just to help people live a bit longer," Lynch said. "We need to actually say, 'We're going to increase the cure rate of women with breast cancer, of men with lung cancer or prostate cancer, of men and women with colon cancer.' And I can't think of a better place than Yale Cancer Center to begin that process."

Lynch comes to Yale from Harvard Medical School and Massachusetts General Hospital (MGH), where he was professor of medicine and chief of hematology/oncology at MGH Cancer Center. "Tom is an incredibly dynamic thinker and leader," says Dean Robert J. Alpern, M.D., Ensign Professor

Lynch, *page 4*

A continuous infusion of philanthropy

The abiding legacy of a trailblazing entrepreneur of intravenous therapy

According to family lore, Ralph Falk, M.D., a physician and surgeon who practiced in Boise, Idaho in the early to mid-20th century, was nothing if not inventive. His daughter-in-law, Suzanne McDonough, recalls Falk telling her of an emergency operation he performed during the 1920s at a home in a remote mountainous area where he and a friend had gone fishing. "They had to hang a mirror over the patient's kitchen table in order to reflect Dr. Falk's automobile lights so he could see well enough to operate," says McDonough.

Falk's commitment to improving patients' lives through innovation is sustained in the Dr. Ralph and Marian Falk Medical Research Trust, established in 1991 with $50 million from the estate of Falk's late wife, Marian Citron Falk of Chicago.

At the School of Medicine, the trust has contributed over $2 million toward research on repairing spinal cord injuries and on neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease by Stephen M. Strittmatter, M.D., PH.D., the Vincent Coates Professor of Neurology and co-director of the Program for Cellular Neuroscience, Neurodegeneration and Repair.

COURTESY OF NICOLE KOHL

Ralph and Marian Falk on the deck of an ocean liner in the 1930s. By helping to make intravenous therapy and blood transfusions practical and safe, Baxter Laboratories, the medical supply firm Ralph Falk co-founded, grew into one of the world's largest medical supply companies. In 1991, Marian Falk established the Dr. Ralph and Marian Falk Medical Research Trust, which has provided support for School of Medicine research on spinal cord injury and neurodegenerative disorders such as Alzheimer's disease.

Strittmatter is well known for his work on NogoReceptor, a versatile protein that blocks recovery after spinal cord injury, but also clears the damaging amyloid buildup seen in Alzheimer's disease. In January of this year, Strittmatter's group published a report demonstrating that ibuprofen aids recovery from spinal cord trauma by protecting tissue, stimulating the sprouting of axons, and promoting regeneration of cells. Most recently, Strittmatter and colleagues have shown that prion protein, which in a misshapen form plays a role in mad cow disease, also contributes, in its normal form, to Alzheimer's disease (see related story p. 3).

"Support from the Falk Trust has been key in our developing new therapies for spinal cord injury," says Strittmatter. "It has also been essential for our exploration of the links between trauma, degeneration, and regeneration, revealing new pathways in Alzheimer's disease."

Falk, *page 8*

Alpern reappointed to new term as dean of medical school

Robert J. Alpern, M.D., who has led the School of Medicine through a period of sustained growth and increased stature since coming to Yale in 2004, has been reappointed to a second five-year term as dean, effective July 1.

Yale President Richard C. Levin cited the dean for his leadership, his rapport with the medical school and hospital communities, and his achievements in the areas of recruitment and program development.

Robert Alpern

"Faculty and staff expressed enthusiastic support for Dean Alpern's reappointment, noting his accessibility and willingness to listen, his clear vision, and the school's upward trajectory," Levin said in a message to the Yale community. "He is valued for his pursuit and recruitment of faculty and staff leadership of the highest quality, and for his excellent judgment in deciding among scientific priorities. Dean Alpern has transformed the school's relationship with Yale-New Haven Hospital, a profound change that will have a lasting impact on the school's clinical mission.

Alpern, *page 7*

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HAROLD SHAPIRO

Microbiologist Jorge Galán, chair of the medical school's Section of Microbial Pathogenesis, says that advances in molecular biology and imaging will bring more accurate diagnoses of infectious diseases, and more precisely targeted drugs to treat them.

Beyond bug-killing 'nukes'

Expert on Salmonella *says outsmarting microbes beats exterminating them*

In the late 1960s, when antibiotics and vaccines had all but vanquished smallpox, polio, and rheumatic fever, Surgeon General William H. Stewart, M.D., appeared before Congress and declared, "It is time to close the book on infectious disease." Within a few years, medical school microbiology departments, including Yale's, were closed down across America.

This declaration of victory was premature, says Jorge E. Galán, PH.D., D.V.M., the Lucille P. Markey Professor of Microbial Pathogenesis, pointing out that scores of new and deadly infectious diseases have emerged, including HIV/AIDS, Legionnaire's disease, and Lyme disease. And tuberculosis, sexually transmitted diseases (STDs), and influenza are still very much with us, sometimes in stubbornly drug-resistant forms.

In the late 1990s, then-Dean David A. Kessler, M.D., lured Galán, renowned for his work on the *Salmonella* bacterium, to Yale to launch the Section of Microbial Pathogenesis (SMP), a program distinguished by a multidisciplinary and holistic approach to the study of microbial pathogens. Bacteria, viruses, and parasites have developed elaborate survival strategies over evolutionary time, but in tandem, we humans have evolved our own mechanisms to deal with them.

The SMP's mission is to gain a deeper understanding of microbial pathogens within the context of the host cells they infect and the immune systems they sometimes defeat.

While earning a doctorate in veterinary medicine at The National University of La Plata (UNLP) in his native Argentina, Galán's clinical work with animals sparked an interest in infectious diseases. Finishing first in his class with what he calls a "ridiculously high GPA," he was awarded a fellowship to study in the PH.D. program in microbiology at Cornell University, which had a longstanding academic relationship with UNLP.

Lifelines
Jorge Galán

After postdoctoral work on *Salmonella* in the laboratory of Roy Curtiss III, PH.D., at Washington University in St. Louis, Galán moved on to Stony Brook, and then to Yale, where he has built the SMP into a team of seven distinguished scientists who bring a diversity of research methods to bear on infectious diseases ranging from tuberculosis to Legionnaire's disease to tropical parasitic diseases.

One insight that has emerged from recent research, Galán says, is that it may be time to rethink the militaristic jargon—microorganisms "attack," hosts "mount a defense," and so forth—that has so permeated his field. Most of the time, pathogens go about their business without causing great harm, he says, and the blunt antibiotic weapons we use to treat infections can do more harm than good in the long run.

"Conceptually, antimicrobials haven't changed since Fleming came up with penicillin," says Galán. "We kill the bugs." Because such a strategy attacks very basic biological processes, normal bacterial flora can also be targeted, potentially causing serious side effects, and any microbes that survive are highly resistant. "Using 'nukes' because we don't know enough about the culprit," says Galán, "will be history very soon."

Galán's own research toward this end focuses on the *Salmonella* type III protein secretion system, made up of a syringe-like tube, or "needle complex," through which the bacterium injects bacterial proteins into host cells, modulating their function for the bacterium's own advantage. In 2005 Galán joined forces with electron microscopist Vinzenz M. Unger, PH.D. (see related story, p. 5), to produce the first three-dimensional image of the needle complex in all its terrible beauty, pointing the way to the development of precise new anti-*Salmonella* regimens.

"This is truly an exciting time in terms of what the field is going to be able to contribute to the solution to the pressing problem of infectious disease," says Galán, "and our group is going to be in the thick of it."

Expert on spinal cord injury receives VA's highest scientific award

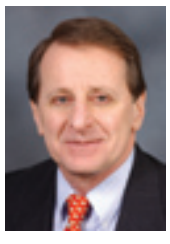
Neuroscientist Stephen G. Waxman, M.D., PH.D., whose research focuses on new therapeutic strategies to restore functions such as sensation and the ability to walk after spinal cord, nerve, and brain injuries, has received the William S. Middleton Award, the highest scientific honor of the Department of Veterans Affairs (VA).

The award was established in 1960 to honor William S. Middleton, M.D., a distinguished educator, physician–scientist, and chief medical director at the VA from 1955 to 1963.

In ceremonies that included a reception at the U.S. Capitol in Washington on April 29, Waxman, chair of neurology and the Bridget Marie Flaherty Professor of Neurology, Neurobiology, and Pharmacology, received the award for his work on spinal cord injury, multiple sclerosis, and painful nerve disorders.

Waxman has identified key molecules that are responsible for chronic pain after nerve and spinal cord injury, and his research group was the first to show molecular changes within nerve cells that permit remissions—recovery of previously lost functions such as vision and motor control—in multiple sclerosis.

Waxman directs the Neuroscience and Regeneration Research Center (NRRC), a collaboration of Yale University, the VA, the Paralyzed Veterans of America, and the United Spinal Association. The NRRC is located at the VA Connecticut Healthcare System in West Haven, Conn. He is also visiting professor and co-director of the Yale-London Collaboration on Nervous System Injury at University College London.



Stephen Waxman

"Each month we move closer to cures for spinal cord injury, nerve injury, and multiple sclerosis," Waxman says. "I am confident that, ultimately, we will conquer these disorders."

Five medical school faculty are elected to a venerable group

The Association of American Physicians (AAP), a nonprofit professional organization founded in 1885, has announced that Richard Bucala, M.D., PH.D., Lloyd G. Cantley, M.D., Erol Fikrig, M.D., David M. Rothstein, M.D., and Lawrence H. Young, M.D., have been elected as AAP members.

With about 1,000 active members and approximately 550 emeritus and honorary members from the United States, Canada, and other countries, the AAP supports the pursuit of medical knowledge and the application of basic and clinical science to clinical medicine. Each year, 60 exceptional individuals are nominated for membership by the AAP's council. Members have included Nobel laureates and members of the National Academy of Science and Institute of Medicine.

Bucala, professor of medicine, pathology, and epidemiology, is an expert on the role of the cytokine MIF in inflammatory and infectious diseases. Cantley, professor of medicine and of cellular and molecular physiology, studies the development and repair of tubules in the kidney (see related story, p. 8). Fikrig, who is Waldemar von Zedtwitz Professor of Medicine as well as professor of microbial pathogenesis and epidemiology, is a leading researcher on Lyme disease and West Nile virus. Rothstein, associate professor of medicine, studies immunosuppression and the induction of tolerance in the immune system. Young, professor of medicine and of cellular and molecular physiology, studies the cellular and molecular mechanisms of adaptation to myocardial ischemia.

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Advances

Health and science news from Yale

Relax—for your heart's sake

It is well known that stress and anger are not heart-healthy, but a new School of Medicine study, published in the March 3 issue of the *Journal of the American College of Cardiology*, provides new evidence of the harmful effects of mental stress on the heart.

Rachel J. Lampert, M.D., associate professor of medicine, and colleagues sought to learn whether anger would increase T-wave alternans (TWA), which measure electrical instability in the heart, and whether anger-induced electrical instability would predict future problems in patients being treated for arrhythmias. Asking 62 patients with enlarged hearts and recently implanted defibrillators to perform math problems under pressure and to recall situations in which they were angry while undergoing standard heart monitoring, they found that those with greater anger-induced TWA were more likely to experience arrhythmias in the future.

"Further studies are needed to determine whether there is a role for therapies which may reduce anger and the body's response to stress," Lampert says, "thereby preventing arrhythmias in those at risk."

Drug can curb both smoking and drinking

That roughly 60 percent of alcoholics smoke is not surprising, since scientists have shown that nicotine appears to enhance alcohol's "buzz." And while the harm that can be caused by abusing either drug is widely acknowledged, trying to quit using them has long proven an elusive challenge.

Now, it may be easier to fight both addictions at once. A new School of Medicine study has found that varenicline, a popular smoking cessation drug sold under the trade name Chantix, also dramatically reduces the amount of alcohol a heavy drinker will consume.

In an advance issue of *Biological Psychiatry* published online in February, first author Sherry McKee, PH.D., associate professor of psychiatry, and colleagues report that, after taking varenicline in a laboratory setting, 80 percent of heavy-drinking smokers did not drink alcohol that was made available to them, compared to 30 percent of those who were given a placebo. At the doses studied, there were no adverse effects when varenicline was combined with alcohol.

"A medication such as varenicline, which may target shared biological systems in alcohol and nicotine abuse, holds promise as a treatment for individuals with both disorders," says McKee.

A protein's surprise role in Alzheimer's

Medical school researchers find that an unexpected culprit plays a part in triggering dementia

In 1906, the German psychiatrist Alois Alzheimer first described the disease that now bears his name, noting that clumps of protein known as plaques had built up between nerve cells in the brain of one of his patients who suffered from dementia. But in the century since, scientists studying Alzheimer's disease (AD), a terminal degenerative disease that afflicts more than 26 million people worldwide, have been befuddled by the questions of what triggers plaques to begin forming in the brain in AD, and precisely how plaques may damage, and ultimately destroy, memory function.

In the February 26 issue of the journal *Nature*, a team from the laboratory of Stephen M. Strittmatter, M.D., PH.D., co-director of the medical school's Program in Cellular Neuroscience, Neurodegeneration and Repair, reported an unexpected piece in this puzzle that may lend a new direction to the next wave of Alzheimer's research. The group found that the normal form of prion protein—the abnormal form of which is notorious for its role in mad cow disease and other neurodegenerative conditions—is one of the initial players in the disease process that leads to the deposition of plaques and dementia seen in AD.

"We had been interested in Alzheimer's disease for a while, because a longstanding interest in my lab is recovery from various kinds of injury," says Strittmatter, a member of Yale's Kavli Institute for Neuroscience who is well known for his work on Nogo, a protein that blocks nerve regeneration in the injured spinal cord. "We're interested in whether the damaged brain in Alzheimer's could also recover in some way."

It has long been known that Alzheimer's plaques are large aggregations of a protein called amyloid-beta (A-β). But over the last several years, scientists have realized that A-β oligomers—much smaller, soluble structures consisting of as few as two A-β molecules—are toxic to synapses, the communication nodes of the brain, and probably represent the beginning stage in a destructive cascade that culminates in amyloid plaques.

The Strittmatter team first synthesized A-β oligomers and showed that the oligomers bound to nerve cells from the hippocampus, a brain region that is crucial to memory. The scientists then created a binding assay in which 225,000 DNA sequences from the mouse brain were expressed in non-neuronal cells, and they tested which of these sequences would bind the A-β oligomers. In a process lasting several months, "one at a time we expressed each of the genes from the brain in non-neuronal cells," Strittmatter, the Vincent Coates Professor of Neurology and professor of neurobiology, recalls. Out of the hundreds of thousands of sequences, only one, which encodes the mouse version of the normal prion protein, bound with the oligomers. "We wouldn't have predicted prion protein," Strittmatter says. "We might have predicted some protein that nobody had ever studied before, one that we didn't know anything about."

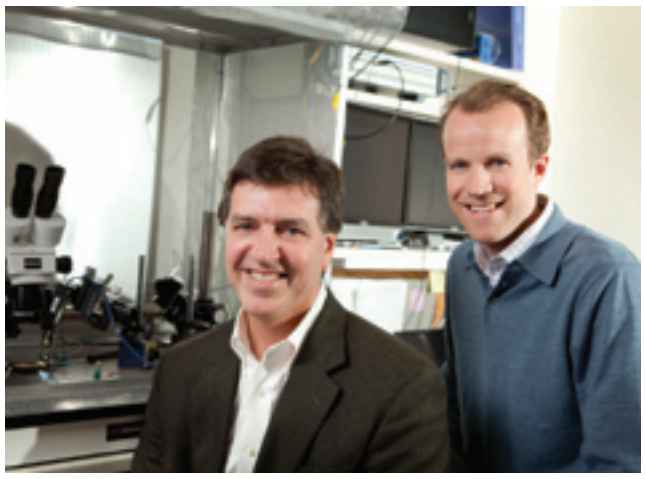
In fact, scientists know a good deal about prion protein, because a misfolded, infectious version of the protein has been implicated in neurodegenerative diseases such as mad cow disease and Creutzfeldt-Jakob disease. "Everybody has prion protein," Strittmatter says, adding that the protein is important for normal brain function. "But in those diseases, it changes its shape and becomes a self-replicating infectious particle, which can spread the disease to other people or animals. That infectious, twisted conformation of prion protein is not what we're seeing in Alzheimer's disease."

Though the version of the prion protein studied by the Strittmatter group is not infectious, the researchers provided evidence that it disrupts memory function when bound to A-β oligomers. When brain slices from normal mice were treated with A-β oligomers, the treatment suppressed an electrophysiological process known as long-term potentiation, or LTP, which is considered to be essential to memory formation. However, brain slices of mice that lacked the gene for prion protein had normal LTP after treatment with A-β oligomers, indicating that binding with the prion protein is necessary for the oligomers to exert their deleterious effects. Though there is much to be studied to understand precisely how prion/A-β complexes damage nerve cells, "the key thing is that now we have a first step, a molecular handle," says Strittmatter.

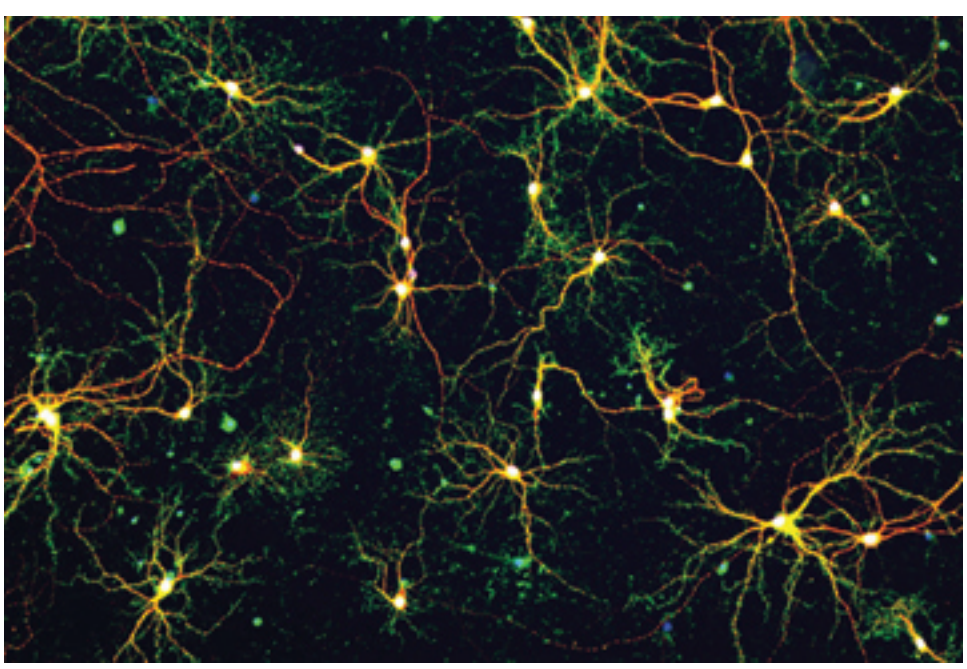
This "handle" may give researchers a better grip on developing new therapies for Alzheimer's disease. With the identification of prion protein as an essential player in the disease process, scientists now have new drug targets to explore to slow or prevent the havoc A-β wreaks on the brain. "Many of the therapeutic approaches now focus on the idea that the best thing to do would be just lower the amyloid-β concentration in the brain," Strittmatter says, adding that a new therapy may lie in preventing the interaction of A-β with the prion protein pathway. "We're trying to develop ways to block this pathway, and then test them in animal models."

To reach that goal, says Strittmatter, "we'd like to move to a model that's even closer to Alzheimer's. We'd like to prove that prion protein is required for memory loss—not just electric activity in a brain slice." Second, Strittmatter wants to examine further the cascade of neuron damage that occurs after amyloid-β binds to prion protein. "We need to understand which genes and proteins come into play after prion protein and disrupt synaptic connections."

"Much more work needs to be done," says Haakon B. Nygaard, M.D., a member of Strittmatter's lab who took part in the research along with first author Juha Laurén, M.D., PH.D., medical student David A. Gimbel, and M.D./PH.D. student John W. Gilbert. "But it's nevertheless a very exciting finding, and one we hope will further stimulate current research."



HAROLD SHAPIRO



COURTESY OF STEPHEN STRITTMATTER

(Above) Stephen Strittmatter (left) and Haakon Nygaard were involved in a study showing that proteins known as prions play a crucial role in triggering the accumulation of amyloid-beta into the toxic plaques found in the brains of Alzheimer's disease patients. (Below) In the mouse hippocampus, a region that is crucial for memory, prion protein (red) and amyloid-beta protein (green) bind extensively to information-receiving dendrites. Areas where both proteins are present appear yellow.

Out & about

January 22: New Haven's Long Wharf Theatre hosted **GLOBAL HEALTH & THE ARTS.** The event combined a world premiere performance of award-winning South African playwright Athol Fugard's "Coming Home" with a symposium on scientific, technological, and economic aspects of conquering infectious disease in developing countries. **1.** Keynote speaker **Gerald Friedland**, M.D., professor of medicine and epidemiology and director of the AIDS program at Yale-New Haven Hospital, described his two decades of experience treating HIV/AIDS and tuberculosis in New York, New Haven, and South Africa. **2. Valerie A. Ceva**, M.B.A., of consulting firm The Strategic Choice, with **Paul R. Pescatello**, J.D., PH.D., president and CEO of Connecticut United for Research Excellence (CURE). **3.** Pulitzer Prize–winning playwright **Paula Vogel**, Eugene O'Neill Professor and chair of the Yale School of Drama's department of playwrighting, is greeted by **Gordon Edelstein**, Long Wharf's artistic director and director of "Coming Home." **4.** Professor of Medicine **Asghar Rastegar**, M.D., and **Adeoye Y. Olukotun**, M.D., M.P.H., of CardioVax, Inc. **5. William H. Prusoff**, PH.D., professor emeritus of pharmacology and co-discoverer of the anti-HIV drug Zerit, with **David I. Scheer**, president of Scheer and Company, Long Wharf Theatre Trustee, and organizer of the event.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HAROLD SHAPIRO (5)


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5


HAROLD SHAPIRO

April 4: At the Department of Psychiatry's 2009 neuroscience symposium, "Recovery Across the Lifecycle," famed talk show host and *New York Times* blogger **Dick Cavett** (right) received the department's annual **MENTAL HEALTH RESEARCH ADVOCACY AWARD. John H. Krystal**, M.D. (left), the Robert L. McNeil Jr. Professor of Translational Research and deputy chair for research, presented the award to Cavett, a member of the Yale College Class of 1958, for his openness about his lifelong battle with clinical depression in his writings, interviews, and speeches, and for informing the public of the many treatment options available to patients who suffer from depression.


1

JOHN CURTIS (3)


2


3

February 19: Continuing a 60-year-old tradition, the School of Medicine's Class of 2011 put on the annual **SECOND YEAR SHOW**, a satirical musical revue, in Harkness Auditorium. This year's offering, "The Great ST Depression," presented an exaggerated version of the nation's current fiscal crisis: facing a deflated endowment, layoffs, and a drop in financial aid, faculty and students must come up with creative ways to earn money. Associate Dean for Student Affairs Nancy R. Angoff, M.P.H., M.D.; Dean and Ensign Professor of Medicine Robert J. Alpern, M.D.; and Margaret J. Bia, M.D., professor of medicine, were played by **Larissa Chiulli**, **Derek Kennedy**, and **Lauren Hackney**, respectively, and all received considerable skewering. **1. Odayme Quesada** and **Mona Sadghepour**. **2.** With support from dancer **Yehoda Martei** (left), **Matthew Singleton** portrayed anatomy professor Lawrence J. Rizzolo, PH.D., in a number called "My Goodies/Rizzilicious," based on Ciara and Petey Pablo's "My Goodies" and Fergie's "Fergilicious." **3. Adam Kaufman**, **Mei Elansary**, **Henry Park**, and **Lauren Graber** in a sketch in which students get part-time jobs at S'wings, a Crown Street eatery.

Lynch *from page 1*

of Medicine. "He brings enormous vision and experience in cancer care, research, and education. We needed someone who knows what we need to do and with a vision to take us there, and Tom's that person."

An authority on lung cancer, Lynch has conducted dozens of studies of how small differences in patients' genomes, or in the genetic makeup of tumors, can have a significant impact on the success of anti-cancer agents.

For example, in 2008, the *Journal of Clinical Oncology* published the results of a multicenter clinical trial led by Lynch which showed that lung cancer patients with mutations in a gene known as *EGFR* did twice as well after treatment with the drug gefenitib (Iressa) than do patients in the general population after standard chemotherapy.

Lynch believes that such research will make "personalized" therapy for many more cancers available very soon. "There are several reasons why this is so important," he says. "First, patients want drugs that work. Second, insurance companies and society want to pay for drugs that are given to patients whom they will benefit —they want to pay for things that actually make a big difference."

Lynch will also oversee a new institute for cancer biology at Yale's 136-acre West Campus, for which he will recruit a director and senior and junior scientists in the fields of cell signaling, cancer immunology, and drug development.

As a founder of the Boston-based Kenneth B. Schwartz Center for the Promotion of Caregiver/Patient Relations, Lynch says he believes the very best care for cancer patients is as important as cutting-edge research, and that he will continue to focus on patient care at Yale.

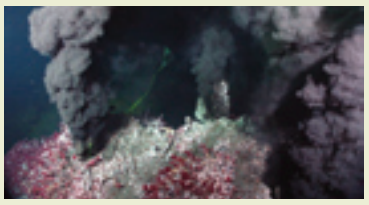
"We're delighted that Dr. Lynch will provide the medical leadership that interweaves clinical expertise with compassionate, family-centered care for our patients," says Marna P. Borgstrom, M.P.H., CEO and president of Yale-New Haven Hospital. Smilow Cancer Hospital at Yale-New Haven, opening this fall, is expected to become the most comprehensive cancer care facility in New England.

Lynch received his undergraduate degree from Yale College in 1982 and his medical degree from the School of Medicine in 1986. He completed his internship and residency at MGH, and after completing a fellowship in medical oncology at the Dana-Farber Cancer Institute, joined the MGH medical staff in 1993.

"For far too long," Lynch says, "we've accepted very modest gains as being triumphs in cancer therapy, but patients and family members want to know, 'Can I be cured of this?' We need to rededicate our efforts to make major advances in cancer therapy."

Advances

Health and science news from Yale



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Living dangerously, in more ways than one

Evolutionary biologists are intrigued by *Methanopyrus kandleri*, a single-celled organism that thrives near hydrothermal vents on the ocean floor where water temperatures can reach 752 degrees Fahrenheit (see photo). Thanks to new work in the laboratory of Dieter Söll, PH.D., Sterling Professor of Molecular Biophysics and Biochemistry, *M. kandleri* may soon be a darling of virologists.

In the May 1 edition of *Science* a Yale team reports that *M. kandleri* carries a mutation that swaps cytosine (C) for uracil (U) in 30 crucial genes. The mutation would probably be fatal, but the researchers found that *M. kandleri* also has an enzyme that corrects the mutation.

The enzyme is a member of a family that interests HIV researchers because of its antiviral activity, and "may be of biotechnological interest if we can engineer it to mutate C to U at any desired location within an RNA molecule," says Lennart Randau, PH.D., postdoctoral associate in the Söll lab and a lead author of the paper.

A new syndrome, a new role for a gene

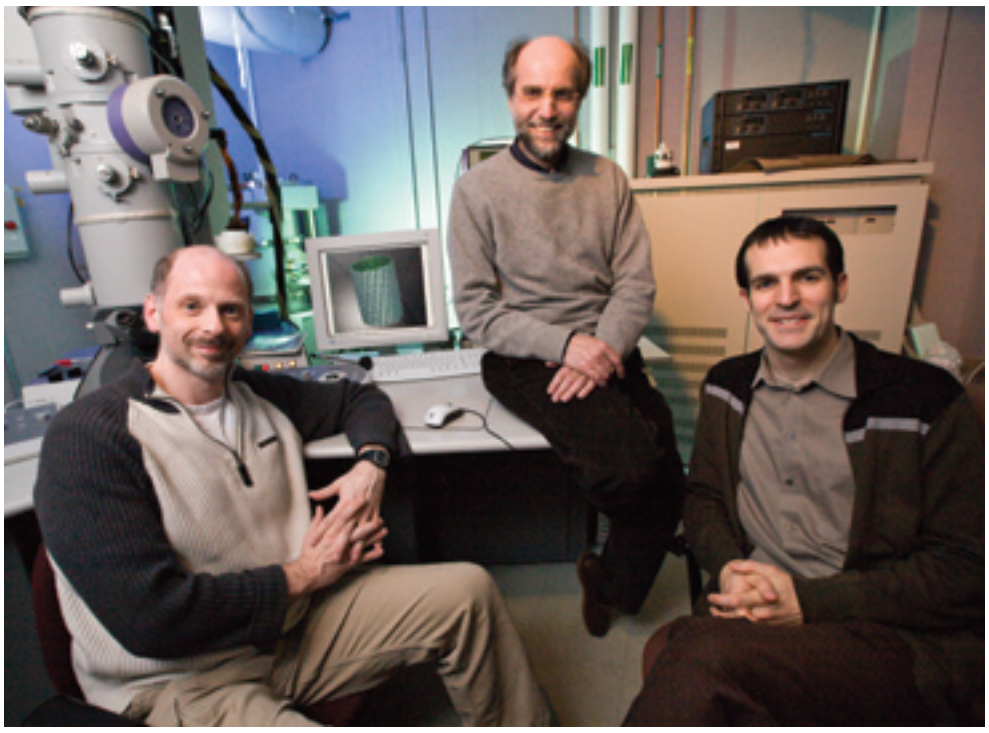
An international team led by Richard P. Lifton, M.D., PH.D., chair and Sterling Professor of Genetics, and Ute I. Scholl, M.D., a postdoctoral associate in Lifton's lab, has implicated a gene known as *KCNJ10* in a previously unreported medical syndrome.

Mutations in *KCNJ10*, which codes for an ion channel that is expressed in the brain, kidney, and inner ear, cause seizures and deafness in mice. In the April 7 issue of *Proceedings of the National Academy of Sciences*, Scholl and colleagues report *KCNJ10* mutations in five patients from four families with a syndrome that features—in addition to complex neurological problems—a defect in the kidney's ability to manage potassium and magnesium levels.

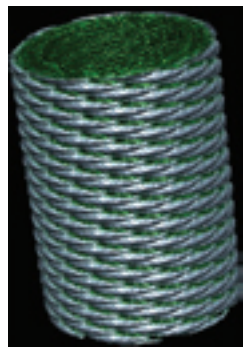
These electrolyte abnormalities are attributed to a loss of the ion channel's contribution to maintaining the activity of the kidney's sodium-potassium pump.

The authors dubbed the disorder SeSAME syndrome because it features seizures, sensorineural deafness, ataxia, mental retardation and electrolyte imbalance.

"A study like this would have taken years in the past," says Lifton, a Howard Hughes Medical Institute investigator, but with new techniques, "it was accomplished in a few weeks by a single fellow in the lab."



TERRY DAGRADI



(Left) Vinzenz Unger, Pietro De Camilli, and Adam Frost used electron microscopy to determine how proteins known as BAR domains help to bend membranes into the tubes, spheres and other curved structures that make normal cellular function possible. (Above) Many banana-shaped BARs (gray) interact with one another to form a helical scaffold around membranes (green) to form tubes.

How membranes get the bends

Yale team's close-up look at membrane bending was named a top scientific paper of 2008

In cells, as in people, flexibility is important. To move, communicate, divide, or shuttle cargo about their interiors, cells must shape membranes—the fatty sheets that form their outer boundaries and the borders of their internal organelles—into tubes, spheres, and other curved structures. Such shape-shifting of cell membranes is crucial to all life on Earth. In humans, impairments of mechanisms involved in membrane curvature are thought to be associated with several diseases, including muscle disorders, epilepsy, and mental retardation.

In a paper published in March 2008 in the journal *Cell*, a School of Medicine team led by Vinzenz M. Unger, PH.D., associate professor of molecular biophysics and biochemistry, gave researchers a clear new view of this process and answered some of the unresolved questions in the field. That paper was recently selected by the journal *Nature* as one of the most significant scientific contributions of 2008.

Over the past several years, scientists around the world, including Pietro De Camilli, PH.D., the Higgins Trust Professor of Cell Biology, have used molecular biology, electron microscopy (EM), and X-ray crystallography to determine that banana-shaped protein modules called BAR domains help membranes assume tubular or spherical shapes.

But the precise role played by BARs in the transformation of flat membranes to curved structures was unknown. Some scientists proposed a scaffolding model, in which attractive forces acting between membranes and the curved face of BAR domains create tubes and spheres in a passive manner. Other researchers, including De Camilli—whose lab first established the curvature-generating properties of proteins containing BAR domains—found that a type of BARs known as N-BARs include, or are flanked by, a molecular "wedge." It was suggested that this wedge is inserted into the membrane, causing the membrane to buckle and bind to the BAR domains' curvature.

While each of these processes may contribute to membrane bending to some extent, it has been difficult to appreciate the sequence of events that lead to membrane deformation, because no one had ever directly visualized BAR domains at work. "In structural biology, there is a complete black box at the interface between the membrane and water," says Unger. "But it's there that molecules come together, forming complexes of different compositions, and it's those dynamic events that make a lot of biology happen."

Unger and his colleagues are breaking open that black box with a technique known as cryoelectron microscopy (cryoEM), which preserves the biological integrity of membranes and their associated proteins. In cryoEM, a biological structure of interest is preserved in a near-native aqueous environment by plunging the sample into liquid ethane, which cools the water at the rate of 100,000 degrees Celsius per second and suspends the structure at minus 172 degrees Celsius in a protective, utterly transparent ice-like solid.

To get a close-up view of how BARs might operate in cells, Adam Frost, M.D., PH.D., a student in Unger's lab who began a postdoctoral fellowship at the University of California–San Francisco in April, created artificial membranes that closely mimic those found in cells and then added protein domains in the BAR family known as F-BARs. "It was a little less than a year of biochemistry to get a sample that generated a great image," Frost explains. "Then it was another two years of taking images and analyzing them."

In the paper lauded by *Nature*, on which Frost was first author, one of the most surprising things those images revealed is that BARs can bind to membranes while lying on their sides, like individual bananas sitting on a kitchen counter. Previous experiments had not identified any membrane-binding regions in this part of BAR proteins, but the cryoEM images clearly showed sidewise binding.

The team also examined BARs on tubular membranes. (The smallest were less than 600 angstroms across. By comparison, a sheet of paper is about 1 million angstroms thick.) Images of these showed that abundant BAR proteins had formed a dense outer coat on the tubes by binding on their curved surfaces and by interacting with one another at sites on their sides and at their tips; complementary experiments performed in De Camilli's lab showed that mutations in these lateral or tip-to-tip binding sites disrupt tubule formation in cells.

Finally, the micrographs showed that the angle at which BARs sidle up to one another when forming a tube's coat helps to determine the tube's diameter.

Based on these combined results, the authors propose that, on flat membranes, BARs accumulate on their sides, nesting within one another until attractive forces at their lateral surfaces cause them to turn onto their tips en masse, pulling the membrane into a rounded shape as the binding regions on their curved surfaces come into play. The BARs then interact with one another to provide a stabilizing coat and to determine the diameter of tubular structures.

As the authors write in *Cell*, at least in the case of F-BARs, the work demonstrates that "tubule formation … results through a shape-based scaffolding system that is amplified by the self-assembly of a helical coat," with no apparent contribution of molecular wedges.

Some of the most important cellular processes, including many involved in human disease, take place at membranes, but Unger says that the limitations of most imaging methods in this realm mean that cell biology textbooks have so far had to rely on "cartoons"—artists' renderings largely based on inference. As *Nature*'s top paper designation indicates, however, scientists are increasingly turning to cryoEM to get a truer picture of these interactions. "We'll never stand a chance of targeting any of these molecules for drug development," Unger says, "if we don't use imaging to replace those cartoons with the real thing."

Grants and contracts awarded to Yale School of Medicine

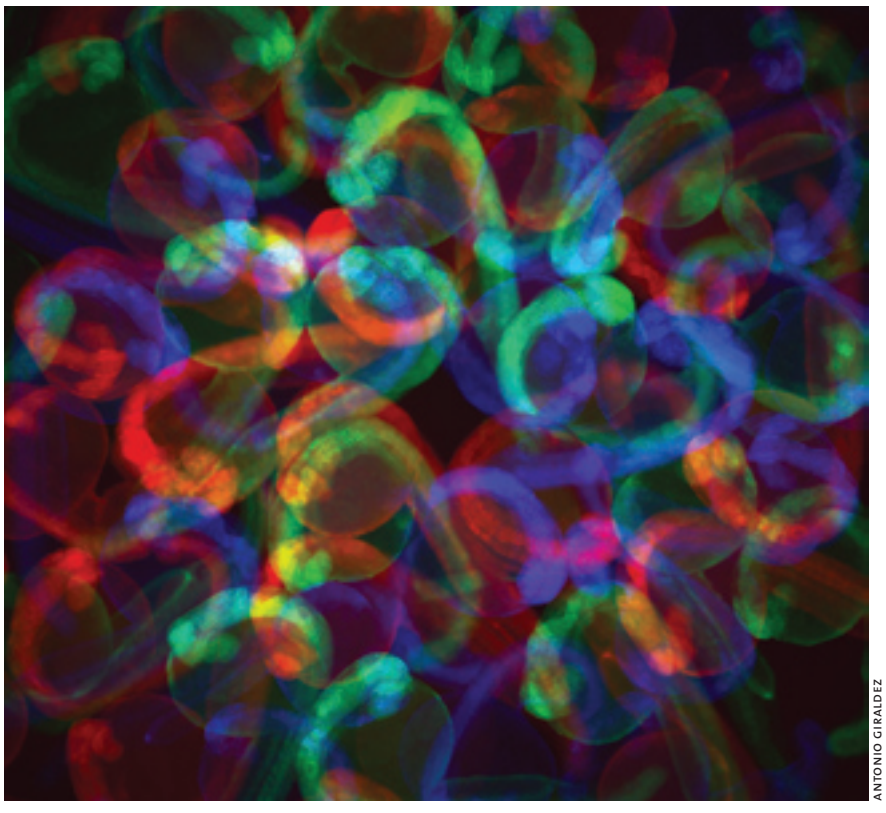
July/August 2008

Federal

Clara Abraham, NIH, *Mechanisms of Chronic Nod2-Mediated Effects in Human Macrophages*, 5 years, $1,655,000 • **Serap Aksoy**, NIH, *Tsetse-Transmitted African Trypanosomiasis*, 4.5 years, $581,717 • **Frederick Altice**, NIH, *Enhancing Health Outcomes among HIV+ Substance Abusers*, 5 years, $923,368 • **Laleh Ardeshirpour**, NIH, *Anabolic Response of Skeleton after Lactation*, 4 years, $777,492 • **Peter Aronson**, NIH, *Methods in Nephrologic Research*, 5 years, $2,405,330 • **Declan Barry**, NIH, *Chronic Pain and Opioid Dependence Assessment and Treatment*, 5 years, $894,320 • **Kathleen Belanger**, NIH, *Effect of Traffic and Air Pollution on Birth Outcomes*, 4.5 years, $3,084,687 • **James Boyer**, NIH, *Mechanisms of Bile Secretion and Cholestasis*, 5 years, $4,370,907 • **Elizabeth Bradley**, Agency for Health Care Research and Quality (AHRQ), *Yale Training Program in Health Services Research*, 5 years, $1,121,640 • **Janet Brandsma**, NIH, *Langerhans Cell-Mediated Immune Modulation of HPV8 Expression and Tumorigenesis*, 2 years, $409,613 • **Sarwat Chaudhry**, NIH, *Comorbidity and Functional Outcomes in Older Patients with Heart Failure*, 5 years, $539,997 **Wei Chen**, NIH, *Optical Imaging of Olfactory Sensory Code Transformation*, 5 years, $1,758,440 **Keith Choate**, NIH, *Genetics and Pathobiology of Ichthysosis en Confetti*, 5 years, $646,650 **Lydia Chwastiak**, NIH, *Brief Motivational Interviewing to Improve Diabetes Self-Care in Schizophrenia*, 5 years, $901,800 • **Steven Coca**, NIH, *Long-Term Prognosis of Acute Kidney Injury in Cardiac Surgery*, 5 years, $958,290 • **Ned Cooney**, NIH, *Concurrent Alcohol and Smoking Treatment: Effects on Alcohol Relapse Risk*, 4 years, $1,780,859 • **Madhav Dhodapkar**, NIH, *Anti-Tumor Immunity in Myeloma*, 10 months, $321,696; NIH, *Targeting Myeloma via Dendritic Cells*, 2 years, $763,829 • **Ronald Duman**, NIH, *Research Training—Biological Sciences*, 5 years, $1,424,660 • **John Elsworth**, NIH, *Susceptibility of Primate Dopamine Neurons to Toxicity during Development*, 4.5 years, $1,810,155 • **Elizabeth Flanagan**, NIH, *Stigma within Mental Health Settings: A Qualitative-Quantitative Analysis*, 3 years, $531,203 • **Biff Forbush**, NIH, *Molecular Physiology of the Na-K-Cl Cotransporter*, 4 years, $1,489,500 • **Julie Goodwin**, NIH, *The Role of Vascular Smooth Muscle GR in Acute Glucocorticoid-Mediated HTN*, 5 years, $807,356 • **Seth Guller**, NIH, *Targeting Placental Pathophysiology in IUGR and Preeclampsia*, 1 year, $316,985 **Tamas Horvath**, NIH, *Developmental Insulin/Leptin Signaling Determines Set-Point of the Adult Melancortin System*, 4 years, $1,758,440 **Beth Jones**, NIH, *Cancer Screening Behavior in Hispanic/Latinas Living in the Northeast United States*, 5 years, $3,417,316 • **Mustafa Khokha**, NIH, *Characterization and Cloning of* X. tropicalis *Craniofacial Mutants*, 5 years, $1,621,900 • **Ami Klin**, NIH, *The Ontogeny of Social Visual Engagement in Infants at Risk for Autism*, 5 years, $3,054,456 • **Michael Koelle**, NIH, *Biochemical and Genetic Analysis of Regulator and G Protein Signaling (RGS) Proteins in the* C. elegans *Nervous System*, 20 months, $372,376 • **John Krystal**, NIH, *The Interactive Impact of Cocaine and Schizophrenia on Prefrontal Function*, 2 years, $389,125 • **Becca Levy**, NIH, *Racial Disparities in Heart Attack Recovery: Role of Stigma and Stress*, 4 years, $3,020,752 **Tene Lewis**, NIH, *Everyday Discrimination and Cardiovascular Disease in African-American Women*, 5 years, $758,418 • **Shuangge Ma**, NSF, *Collaborative Research: Novel Semiparametric Two-Part Models: New Theories and Applications*, 3 years, $177,501 • **Laura Manuelidis**, NIH, *Experimental Creutzfeldt-Jakob Disease*, 4 years, $2,065,776 • **Steve Martino**, NIH, *Effectiveness of Motivational Interviewing Supervision in Community Programs*, 5 years, $2,438,322 • **David McCormick**, NIH, *Cellular Mechanisms of Visual Cortical Function*, 3 years, $1,241,205 • **Diane McMahon-Pratt**, NIH, *Vector/Host-Parasite Interface of Leishmaniasis in Colombia*, 4.5 years, $709,890 • **Andrew Miranker**, NIH, *Predoctoral Program in Biophysics*, 5 years, $2,554,331 **Gilbert Moeckel**, NIH, *Role of COX2 in Medullary Interstitial Cell Survival and Function*, 9 months, $58,498 • **Michelle Monette**, NIH, *An Investigation of the Renal Na-K-Cl Cotransporter*, 2 years, $96,472 • **Brent Moore**, NIH, *Computer-Based Treatment for Drug Dependence*, 4 years, $725,326 • **Gil Mor**, NIH, MyD88-*Bearing Tumors in Immune Regulation and Chemoresistance*, 5 years, $1,717,013 • **Rhea Paul**, NIH, *Studies of Prosody in Individuals With Autistic Spectrum Disorders*, 6 months, $30,043 • **Ismene Petrakis**, NIH, *Mecamylamine for the Treatment of Alcohol Dependence*, 5 years, $1,460,250; Dept. of the Army, *Prazosin for Treatment of Patients with PTSD and Comorbid Alcohol Dependence*, 4 years, $1,686,555 • **Marina Picciotto**, NIH, *Galanin-Opiate Interactions*, 5 years, $1,779,125 **Jennifer Pluznick**, NIH, *Olfactory Proteins in the Kidney and Regulation of Glomerular Filtration Rate*, 2 years, $174,920 • **Alessandro Santin**, NIH, *Treatment of Chemotherapy-Resistant Human Ovarian Cancer by Administration of CPE*, 4 years, $1,376,743 • **Patrick Sung**, NIH, *Formation and Resolution of Recombination Intermediates*, 4 years, $1,191,600 • **Richard Sutton**, NIH, *Probing Blocks to Infectious HIV Release in Mouse Cells*, 4.5 years, $1,886,700 • **William Tamborlane**, NIH, *Training in Pediatric Endocrinology/Diabetes Research*, 5 years, $1,052,280 **Peter Tattersall**, NIH, *Predoctoral Training Program in Virology*, 5 years, $553,696 • **Jane Taylor**, NIH, *Sex Differences in Alcohol Habit Formation in Rats: Corticostriatal Mechanisms*, 2 years, $141,500 • **Mary Tinetti**, NIH, *Claude D. Pepper Older Americans Independence Center at Yale*, 5 years, $6,023,697 • **Susumu Tomita**, NIH, *Regulation of Glutamate Receptors by Calcium-Dependent Protein Kinase*, 5 years, $1,489,500 **Alda Tufro**, NIH, *Functions of VEGF-A in Podocytes: Implications for Renal Disease*, 6 months, $284,991 • **Flora Vaccarino**, NIH, *Astroglial Cells in Perinatal Brain Injury*, 5 years, $1,827,301 **Jon Vermeire**, NIH, *Molecular Characterization of a Hookworm Macrophage Migration Inhibitory Factor*, 3 years, $161,898 • **Carol Weitzman**, Health Resources and Services Administration, *MCH Leadership Education in Developmental-Behavioral Pediatrics*, 1 year, $192,467 • **Bao-Zhu Yang**, NIH, *Mapping Genes for Comorbidity of SUDs and Depression*, 5 years, $854,422 **Dejan Zecevic**, NSF, *Dendritic Signal Integration Underlying Plasticity*, 4 years, $700,002 • **David Zenisek**, NIH, *Retinal Synaptic Transmission*, 4 years, $1,655,000 • **Z. Jimmy Zhou**, NIH, *Synaptic Function and Organization of the Mammalian Retina*, 3 years, $1,275,522; NIH, *Physiology and Development of the Vertebrate Retina*, 4 years, $1,823,685

Non-Federal

Khalid Abbed, American Assoc. of Neurological Surgeons, *Prospective Outcomes Evaluation of One-Level Transforaminal Lumbar Interbody Fusion Performed with a Minimally Invasive Approach Versus a Conventional Open Approach*, 1 year, $50,000 • **Jean Adnopoz**, Community Health Center Assoc. of Connecticut, *CPCA Title IV*, 1 year, $245,735 • **George Anderson**, Alan B. Slifka Fdn., *Melatonin in Infants with Autism: A Longitudinal Study of Excretion Patterns*, 3 years, $209,346 • **Robert Beech**, Donaghue Medical Research Fdn., *Gene-Expression Algorithms to Predict Lithium Response*, 3 years, $240,000 • **Carlo Bernardino**, American Geriatrics Soc., *Geriatrics for Specialists Initiative*, 2 years, $37,600 • **Sumita Bhaduri-McIntosh**, Charles H. Hood Fdn., *The Role of Regulatory T Cells in Immune Evasion*, 2 years, $150,000 **Michael Bloch**, American Psychiatric Inst. for Research and Education, *Longitudinal Follow-Up Study of Long-Term Outcome in Pediatric OCD*, 2 years, $45,000 • **Elizabeth Bradley**, Children's Investment Fund Fdn., *External Evaluation of the Clinton Fdn. HIV/AIDS Initiative*, 3.5 years, $656,277 • **Martina Brueckner**, American Heart Assoc.—Founders Affiliate, *Cilia in Cardiac Morphogenesis*, 3 years, $198,000 • **Gordon Buchanan**, Jazz Pharmaceuticals, *Chemosensitive Serotonergic Neurons Mediate Hypercapnia-Induced Arousal*, 16 months, $50,000 • **Sonia Caprio**, American Diabetes Assoc., *Mechanisms of Insulin Resistance in Childhood Obesity*, 4 years, $800,000 • **Sarwat Chaudhry**, American Federation for Aging Research, *Supplement to Comorbidity and Functional Outcomes in Older Patients with Heart Failure*, 5 years, $300,000 **Keith Choate**, Fdn. for Ichthyosis and Related Skin Types, *First Ichthyosis Clinical Scholar*, 1 year, $40,000 • **Steven Coca**, American Soc. of Nephrology, *Effect of Acute Kidney Injury on Long-Term Kidney Function in Elderly Patients*, 2 years, $95,800 • **Justin Cohen**, Howard Hughes Medical Inst., *Assessing Plasticity: The Populations and Mechanisms Responsible for Epithelial Engraftment of Bone Marrow-Derived Cells*, 2 years, $76,000 • **Oscar Colegio**, Dermatology Fdn., *Epithelial to Mesenchymal Transitions in the Development of Metastases*, 1 year, $30,000 **Susan Compton**, ACLAM Fdn., *Effect of* Helicobacter hepaticus *or MNV on Mouse Parvovirus Infection*, 1 year, $25,000 • **Mauro Cortez Veliz**, Pew Charitable Trusts, *Regulation of Iron Uptake in the Intracellular Protozoan Parasite* Leishmania amazonensis, 6 months, $95,000 **Peter Cresswell**, American Asthma Fdn., *Redox Regulation of the Inflammatory Response in Asthma*, 3 years, $750,000 • **Michael Crowley**, Nat'l Alliance for Research on Schizophrenia and Depression, *Negative Affect Regulation in Oppositional Defiant Disorder*, 2 years, $59,670 **Pietro De Camilli**, American Diabetes Assoc., *Spatiotemporal Regulation of Phosphoinositides by SHIP2 in Insulin Signaling*, 1 year, $45,000 **Robin de Graaf**, Resonance Research, *Dynamic Shimming for* In Vivo *NMR Applications*, 1 year, $61,199 • **Charles Dela Cruz**, Parker B. Francis Fdn., *The Role of Cigarette Smoke Exposure in Respiratory Infections*, 3 years, $150,000 • **Neil Desai**, Hoard Hughes Medical Inst., *Exploring Causality in the Link between ERBB2/HER2/NEU and Genomic Instability*, 2 years, $76,000 • **Ralph DiLeone**, Mount Sinai School of Medicine, *Studies of Feeding Peptides in Animal Depression Models*, 1 year, $66,647 • **Ronald Duman**, Mount Sinai School of Medicine, *Studies of CAMP Signaling and CREB in Nucleus Accumbens in Depression*, 1 year, $45,802 • **Marie Egan**, Cystic Fibrosis Fdn., *Quality Improvement: Learning and Leadership Collaborative VI: Yale ACT Project*, 1 year, $10,800 • **Richard Ehrenkranz**, PGS Medical Research and Electronic Design, LLC, *Wireless Cardiorespiratory Monitor for Neonates*, 1 year, $15,000 • **Aymen Elfiky**, American Soc. of Clinical Oncology, *Targeting Phosphoinositide-3 Kinase in Renal Cell Cancer*, 1 year, $50,000 • **Donald Engelman**, Univ. of Rhode Island, *PHLIP Nanotechnology Platform for Cancer Imaging and Therapy: Nanoscience and Nanotechnology in Biology and Medicine*, 1 year, $198,544 • **Thomas Fernandez**, American Academy of Child and Adolescent Psychiatry, *Genetic Investigation of Childhood Movement Disorders*, 16 months, $15,000 • **Carlos Fernandez**, American Heart Assoc.—Nat'l Center, *Role of Protein Kinase AKT1 in Atherosclerosis*, 3 years, $198,000 • **Gerald Friedland**, Newman's Own Fdn., *Project Access*, 1 year, $20,000; Vanderbilt Univ. Medical Center, *Genot*, 1 year, $69,292 **Antonio Giraldez**, Pew Scholars Program in the Biomedical Sciences, *The Role of MicroRNAs in Vertebrate Development*, 5 years, $300,000 **Julie Goodwin**, Nat'l Kidney Fdn., *The Role of the Vascular Endothelial Glucocorticoid Receptor in Glucocorticoid-Mediated Hypertension*, 1 year, $40,000 • **Elena Grigorenko**, Columbia Univ.-Teachers College, *Substance Abuse among Suburban Youth: A Prospective Study*, 1.5 years, $146,769 • **Baiba Grube**, Susan G. Komen Breast Cancer Fdn., *Interdisciplinary Breast Fellowship Grant*, 2 years, $90,000 • **Jonas Hannestad**, Soc. of Nuclear Medicine Education and Research Fdn., *Neuroinflammation and Depression during Interferon-Alpha Treatment of Hepatitis C: A SPECT Study*, 2 years, $100,000 • **Ilan Harpaz-Rotem**, Philadelphia Research and Education Fdn., *CBT for Nightmares in OEF/OIF Veterans*, 4 years, $604,638 • **Kenneth Harrison**, American Heart Assoc.—Founders Affiliate, *Role of Nogo-B Receptor in Intracellular Cholesterol Homeostasis*, 2 years, $42,000 • **Daniel Hawiger**, Nat'l Multiple Sclerosis Soc., *The Novel RhoGAP/HOP/NET Tolerance-Inducing Pathway in Myelin-Specific T Cells*, 5 years, $570,428 • **Octavian Henegariu**, American Lung Assoc., *Changes in Th2 Responses and Lung Inflammation in Mice with Conditional PPARG Deletion in CD4 T Cells*, 1 year, $35,110 • **Erica Herzog**, State of CT Dept. of Public Health, *Innate Immunity and Pulmonary Progenitor Cells in Smoking Induced Lung Disease*, 20 months, $239,938 • **Scott Heysell**, American Soc. of Tropical Medicine and Hygiene, *Enhancing Diagnosis of* Mycobacterium tuberculosis *in Children in Rural South Africa*, 2 years, $140,000 • **Tamas Horvath**, American Diabetes Assoc., *Insulin Determines Developmental Organization of Hypothalamic Circuits*, 4 years, $180,000 • **Zhiwei Hu**, State of CT Dept. of Public Health, *Targeting Tumor Blood Vessels for Immunotherapy and Photodynamic Therapy of Human Lung Cancer*, 20 months, $374,240 **Bahman Jabbari**, Solstice Neurosciences, *Botulinum Neurotoxin Center of Excellence at Yale*, 1 year, $25,000; Allergan Sales, *Movement Disorder Fellowship Program*, 1 year, $40,000 • **Roger Jou**, American Psychiatric Inst. for Research and Education, *Autism Spectrum Disorders/ACE Fellowship*, 1 year, $45,000 • **Nina Kadan-Lottick**, CogniFit Ltd., *A Pilot Study of the Feasibility and Efficacy of the Computer-Based Mindfit Intervention*, 1 year, $50,000; St. Baldrick's Fdn., *Career-St. Baldrick's Fdn. Scholar*, 3 years, $330,000 **Insoo Kang**, American College of Rheumatology, *ACR/REF/Amgen Wyeth Rheumatology Fellowship Award*, 1 year, $25,000 • **Ivana Kawikova**, Tourette Syndrome Assoc., *The Role of the Immune System in Tourette's Syndrome*, 1 year, $75,000 • **Kenneth Kidd**, Wenner-Gren Fdn. for Anthropological Research, *Genetic Relationships among East African Populations Based on Single Nucleotide Polymorphisms*, 1 year, $35,000 **Tae Hoon Kim**, Sidney Kimmel Fdn. for Cancer Research, *Analysis of Chromatin Barriers in Cancers*, 2 years, $200,000 • **Harlan Krumholz**, Robert Wood Johnson Fdn., *RWJ Clinical Schol-*



ANTONIO GIRALDEZ

"Embryonic Dance," an image by Antonio J. Giraldez, PH.D., assistant professor of genetics and the inaugural Lois and Franklin Top Jr. Yale Scholar. With support from the Pew Scholars Program in the Biomedical Sciences, Giraldez studies vertebrate development using zebrafish as a model system. Here, messenger RNA in zebrafish embryos that is repressed by microRNAs encodes a fluorescent protein. The shorter embryos are mutants that lack microRNAs.

ars Program Third Year Cohort, 1 year, $179,435; Robert Wood Johnson Fdn., *RWJ Clinical Scholars Program CORE 2008–2010*, 2 years, $1,017,744; Robert Wood Johnson Fdn., *RWJ Clinical Scholars Program 2008–2010 Cohort*, 2 years, $1,079,036 • **Gary Kupfer**, Newman's Own Fdn., *Pediatric Oncology Research Program*, 3 years, $75,000 • **Dori Laub**, International Psychoanalytical Assoc., *Scenic Microanalysis of Video-Testimonies*, 1 year, $5,000 • **John Leventhal**, State of CT Dept. of Children and Family Services, *Child Sexual Abuse Clinic—DCF*, 3 years, $453,281 • **Paula Licona Limon**, Pew Charitable Trusts, *Th17 vs. Treg Development in Multiple Sclerosis*, 4 years, $120,000 • **Yilun Liu**, American Cancer Soc., *Understanding the Role of RAD51C Complexes in Recombination and Repair*, 2 months, $30,000 • **John MacMicking**, Burroughs Wellcome Fund, *Immune Control of Human Phagosomal Pathogens by a Novel GTPase Superfamily*, 5 years, $500,000 • **Arya Mani**, Doris Duke Charitable Fdn., *The Genetic Etiology of Atherosclerosis and Metabolic Syndrome*, 3 years, $405,000 • **Arnaud Marlier**, American Heart Assoc.—Founders Affiliate, *The Role of p204 in Mesenchymal-Epithelial Transition*, 2 years, $90,000 • **Stephanie Massaro**, American Soc. of Hematology, *Regulation of Megakaryocytic Differentiation in Human Embryonic Stem Cells*, 1 year, $50,000 • **Kristin Mattocks**, American Fdn. for AIDS Research (amfAR), *What They're Not Telling Me: Veterans, Trust and HIV Care in the VA*, 2 years, $108,480 • **Linda Mayes**, Univ. of North Carolina at Chapel Hill, *Neural Circuitry of Parent Attachment in Substance Abuse*, 10 months, $433,269 • **Sean McEvoy**, Howard Hughes Medical Inst., *The Effect and Mechanism of Genetic Deletion of Serotonin Neurons on Respiratory Control*, 2 years, $76,000 • **Sherry McKee**, Health Research, Inc. *Smoke-Free Policies Alter Smoking and Drinking Behavior*, 1 year, $28,860 • **Diane McMahon-Pratt**, Intelligent Optical Systems, *Serological Diagnostic Immunoassay Test Strip for Leishmania*, 1 year, $92,463 **Michael Miller**, Medimmune, *Clinical and Epidemiologic Investigation of the Newly Identified Polyomaviruses, WUV and KIV*, 1 year, $35,000 **Rebecca Miller**, State of CT Dept. of Mental Health and Addiction Services, *BE HIP: The Healthy Information Program*, 2 months, $7,500 **Aaron Mishara**, Nat'l Alliance for Research on Schizophrenia and Depression, *Performance Monitoring and Reward Processing in Schizophrenia: A combined ERP and fMRI Study*, 2 years, $60,000 • **Yasha Modi**, Howard Hughes Medical Inst., *Effects of HuR Gene Deletion on Angiogenic Responses*, 2 years, $76,000 • **Bart Muhs**, American Geriatrics Soc., *Effect of Aging on Regional Aortic Compliance Before and After Endografting*, 2 years, $150,000 • **Anita Nag**, Leukemia and Lymphoma Soc., *Understanding How KSHV-Encoded PAN RNA Escapes Nuclear RNA Surveillance*, 3 years, $165,000 • **Nikhil Nayak**, Howard Hughes Medical Inst., *Genetics of Intracranial Aneurysm*, 2 years, $76,000 • **Marcella Nunez-Smith**, Assoc. of American Medical Colleges, *2008 Herbert W. Nickens Faculty Fellowship*, 2 years, $15,000 • **A. David Paltiel**, Massachusetts General Hospital, *Optimizing HIV Care in Less Developed Countries*, 1 year, $20,694 **Melissa Perkal**, American Geriatrics Soc., *Geriatrics Education for Specialty Residents*, 1 year, $25,000 • **Christopher Pittenger**, Doris Duke Charitable Fdn., *Glutamate in OCD: Explorations in the Pathophysiology and Treatment of Refractory Obsessive Compulsive Disorder*, 3 years, $405,000; Tourette Syndrome Assoc., *An Animal Model of Tourette Syndrome: Targeted Ablation of Striatal Fast-Spiking Interneurons*, 1 year, $74,876 • **Jean-Claude Platel**, Tuberous Sclerosis Alliance, *Contribution of Neonatal Neural Progenitors to TSC Lesions*, 3 years, $196,563 • **Christopher Ransom**, Nat'l Epifellows Fdn., *Voltage Dependence of Tonic Inhibition in Rat Hippocampus*, 1 year, $20,000 • **Priscilla Ridgway**, Nathan Kline Inst., *Center to Study Recovery in Social Contexts*, 1 year, $10,067 • **Kasandra Riley**, American Cancer Soc., *Investigating the Role of Epstein-Barr Viral MicroRNAs in Apoptosis*, 3 years, $138,000 • **David Rimm**, State of CT Dept. of Public Health, *Development of 2 Protein-Based Tests to Determine which Patients with Early Stage Non-Small Cell Lung Cancer are Cured by Surgery Alone*, 20 months, $186,642 **Scott Rivkees**, JS Genetics, *Identification of Oligodendrocyte Stimulators*, 6 months, $49,788 **Bradley Rubin**, American Heart Assoc.—Heritage Affiliate, *Insulin Regulation of Glucose Transporter and Aminopeptidase Trafficking*, 2 years, $42,000 • **Aybala Saricicek**, Nat'l Alliance for Research on Schizophrenia and Depression, *Quantification of Endogenous 5-HT in Man Using a Novel PET Radioligand*, 2 years, $60,000 **Gerald Shadel**, Emory Univ., *Mitochondrial Genome Instability and ROS in Tumorigenesis*, 5 years, $5,663,591 • **Erik Shapiro**, Dana Fdn., *Dynamic MRI of Immune Cell Infiltration in Experimental Stroke*, 2 years, $200,000 • **Timothy Shutt**, United Mitochondrial Disease Fdn., *Identification of the DNA Required for Replication of mtDNA in Human Cells*, 2 years, $99,998 **Arthur Simen**, American Federation for Aging Research, *Epigenetic Factors in Vulnerability to Aging and Stress*, 3 years, $300,000 • **Arietta Slade**, FAR Fund, *Minding the Baby*, 2.5 years, $815,948 • **David Snow**, Consultation Center, Inc., *Personnel Service Agreement 2008/2009*, 1 year, $560,569 • **Steven Southwick**, CogState, Inc., *CogState Fellowship: Robert Pietzrak*, 1 year, $63,970 • **Antoine Sreih**, American College of Rheumatology, *Determination of the Frequency and Pathologic Significance of the MIF Gene Polymorphism in Patients with Vasculitis*, 3 years, $150,000 • **Stephen Strittmatter**, Amyotrophic Lateral Sclerosis Assoc., *Optimizing Motor Neuron Transplantation in ALS for Nerve Fiber Growth*, 3 years, $213,000 • **Matthew Strout**, American Soc. of Hematology, *Targeting of Activation-Induced Cytidine Deaminase during Somatic Hypermutation*, 2 years, $100,000 **Yajaira Suarez**, American Heart Assoc.—Nat'l Center, *MicroRNAs as Regulators of Endothelial Cell Biology and as Potential Therapeutic Targets*, 4 years, $308,000 • **Joann Sweasy**, Univ. of Southern California, *DNA Polymerase Fidelity Mechanisms: Theory and Experiment*, 1 year, $161,885 • **Sina Tavakoli**, American Heart Assoc.—Founders Affiliate, *αvβ3-Targeted Imaging of Injury-Induced Vascular Remodeling and Response to Rosiglitazone in Type 2 Diabetic Mice*, 2 years, $88,000 • **Jane Taylor**, Mount Sinai School of Medicine, *Accumbens/Amygdala Delta FosB/CREB and Incentive Motivation*, 10 months, $63,503; Mount Sinai School of Medicine, *Studies of Motivation for Food in Animal Depression Models*, 1 year, $33,323 • **Masaaki Torii**, Vanderbilt Univ. Medical Center, *Development of Reciprocal Neural Circuitry*, 1 year, $60,821 • **Marianne Ulcickas Yood**, Henry Ford Health System, *Building a Pharmacovigilance Population-Based Laboratory*, 20 months, $58,411 • **Shobha Vasudevan**, Leukemia and Lymphoma Soc., *Translation Regulation of Cytokine mRNAs by AREs and MicroRNAs in HL*, 3 years, $195,000 • **Matthew Vestal**, Howard Hughes Medical Inst., *Functional Neuroimaging of the Effects of Ethosuximide on Epileptogenesis*, 2 years, $76,000 • **Fei Wang**, Nat'l Alliance for Research on Schizophrenia and Depression, *Structural and Functional Connectivity of the Perigenual Anterior Cingulate in Adolescents with Bipolar Disorder*, 2 years, $60,000 • **Stuart Weinzimer**, Jaeb Center for Health Research, *Automated Closed Loop Glucose Control in Type 1 Diabetes Mellitus*, 1 year, $394,261 • **Sherman Weissman**, Elsa U. Pardee Fdn., *Development of a New Method for Treatment of Hematological Malignancies*, 1 year, $100,000 • **Jason Wilken**, Marsha Rivkin Center for Ovarian Cancer Research, *sErbB3: A Novel Ovarian Cancer Prognostic Biomarker*, 1 year, $59,691; Marsha Rivkin Center for Ovarian Cancer Research, *Overcoming Primary Herceptin Resistance in Ovarian Cancer*, 1 year, $29,963 • **Wendol Williams**, Soc. of Nuclear Medicine Education and Research Fdn., *Serotonin 1B Receptor Imaging in PTSD*,1 year, $25,000 • **Tim Willinger**, Cancer Research Inst., *Role of Dynamin 2 in T Cell Homeostasis and Trafficking*, 3 years, $145,500 **Joseph Woolston**, State of CT Dept. of Children and Family Services, *Outpatient Psychiatric Clinic for Children*, 3 years, $617,548; State of CT Dept. of Children and Family Services, *Neighborhood Youth Center*, 3 years, $111,010 • **Yong Xiong**, Charles H. Hood Fdn., *Molecular Dissections of the Fanconi Anemia Pathway of DNA Damage Response*, 2 years, $150,000 • **James Yu**, RSNA Research and Education Fdn., *The Promise of Intensity Modulated Radiation Therapy for Head and Neck Cancer: Patterns of Care, Access to Treatment, and Functional Outcomes*, 1 year, $30,000 • **James Yue**, Depuy Spine, *2008-2009 DePuy Spine Surgery Fellowship Program*, 1 year, $80,000 • **Huiping Zhang**, Alcoholic Beverage Medical Research Fdn., *Association Study of a Subfamily (Rz) of Regulator of G-Protein Signaling (RGS) Genes in Alcohol Dependence*, 2 years, $100,000 • **Howard Zonana**, Univ. of Connecticut, *Correctional Managed Health Care*, 1 year, $130,809

Alpern *from page 1*

He cares deeply about the school and is ambitious for its future success."

Alpern, a nephrologist and researcher who is also the Ensign Professor of Medicine, came to Yale from the University of Texas Southwestern Medical School in Dallas, where he served as dean and, before that, chief of the division of nephrology. In his time at Yale, Alpern has overseen an expansion of the medical school's research and clinical operations, the establishment of several key multidisciplinary programs and a large number of faculty recruitments.

Alpern notes that he focused early in his term on expanding the facilities available for research. A building at 10 Amistad St., originally planned as office space, was converted to a research facility that opened its doors in 2007. The medical school also leased a large amount of space at 300 George St. that had already been converted for laboratory use by biotechnology companies, and Alpern has participated in the development of Yale's West Campus, which will be home to a number of new research institutes and core facilities.

The additional space has supported formation of the Yale Stem Cell Center, the Program in Cellular Neuroscience, Neurodegeneration and Repair and the Human and Translational Immunology Program. Likewise, it has supported continued growth in areas in which the School of Medicine is already known for its excellence, such as genetics, immunobiology, and internal medicine.

One of the results of these investments has been a steady increase in grants and contracts to the school from the National Institutes of Health (NIH). Since 2004, Yale has moved from eighth place to fifth place in the ranking of total annual NIH grants to medical schools. "NIH dollars are not the endpoint," Alpern says, "but they do indicate the quality of the research and they indicate what your peers think about its value."

Alpern says he is most proud of the administrative team he has built and credits them for the school's continued success. Deputy Deans Richard Belitsky, M.D., David J. Leffell, M.D., Carolyn W. Slayman, PH.D., Cynthia Walker, M.B.A., and her predecessor, Jaclyne W. Boyden, all provided extraordinary leadership during his first term, Alpern says, as have Jancy L. Houck, M.A., director of medical development and alumni affairs, and Mary J. Hu, M.B.A., director of institutional planning and communications.

He also cites the "outstanding" work of the department chairs and faculty, and points to several key external recruitments to leadership positions—notably, James E. Rothman, PH.D., as chair of the Department of Cell Biology; Haifan Lin, PH.D., as director of the Yale Stem Cell Center; and Paul D. Cleary, PH.D., as dean of the Yale School of Public Health—as well as nearly a dozen major internal recruitments for department and program leaders.

An equally important focus of his first term, says Alpern, was expansion of the clinical practice and the creation of centers of excellence and interdisciplinary programs. "The key thing for a school like Yale is to tie these efforts to the excellent science here through translational research," he notes. In 2006, the school competed successfully for a landmark grant under the first round of the NIH Clinical and Translational Science Awards (CTSA) Program. The $57 million CTSA grant—Yale's largest ever—has been critical in building infrastructure linking the School of Medicine's research base to the clinical practice, notes the dean.

One of the clinical initiatives is a new transplant program, with renowned liver and kidney specialists, headed by Sukru H. Emre, M.D. A new chief of cardiology, Michael Simons, M.D., arrived last summer and is building the section's strengths in interventional cardiology, treatment of heart failure, electrophysiology, and basic research. The 14-story Smilow Cancer Hospital at Yale-New Haven Hospital (YNHH) is set to open this fall, and in February Alpern announced the appointment of Thomas J. Lynch Jr., M.D., as director of Yale Cancer Center (see related story, p. 1). With this progress and the addition of a cancer biology institute planned for West Campus, Alpern says, Yale is poised to be a world leader in cancer research and treatment.

"All of this progress has benefited from close collaboration with YNHH," says Alpern, who has worked very closely with Marna P. Borgstrom, M.P.H., president and CEO of YNHH. "We've improved the relationship between the medical school and hospital in a way that makes both institutions better," he notes.

The medical school's educational program remains extraordinarily strong, Alpern says, and has been bolstered by the 2006 appointments of Belitsky as deputy dean for education and Laura R. Ment, M.D., as associate dean for admissions. The school launched a strategic planning process for medical education in 2008, focusing on innovation in teaching as well as reinforcement of the Yale system, the unique philosophy of medical education adopted by the School of Medicine in the 1920s. Yale School of Medicine, which will celebrate its bicentennial in 2010, continues to be one of the most selective medical schools in the nation, with 4,081 applications for the 100 places in the Class of 2013.

Just as closer collaboration with YNHH has strengthened the entire clinical enterprise, excellent relations with the university leadership have paid major dividends across the entire Yale campus, Alpern says. "[President] Rick Levin made a commitment to science and medicine, which inspired me to come here, and he delivered. To take a school as good as Yale and make it better is exciting, and we've come a long way. The reason I've signed on for another five years is to continue that ascent."

Yale Netcast
"The Yale School of Medicine, Past, Present and Future"

Dean of Public Health is Anna M.R. Lauder Professor

Paul D. Cleary, PH.D., the newly named Anna M.R. Lauder Professor of Public Health, has devoted much of his career to understanding how to improve the quality of patient care.

Paul Cleary

Cleary, dean of the School of Public Health and director of the Center for Interdisciplinary Research on AIDS, is interested in developing better methods for using patient reports about their care and health status to elevate the quality of medical care.

His recent research includes a study of how organizational characteristics affect the costs and quality of care for persons with AIDS; a national evaluation of a continuous quality improvement initiative in clinics providing care to HIV-infected individuals and a study of the long-term impact of patient-centered hospital care.

He is the principal investigator of one of the Consumer Assessment of Healthcare Providers and Systems grants funded by the Agency for Healthcare Research and Quality. These grants support research to develop surveys of consumers about their health plans and services. He also is leading a Robert Wood Johnson Foundation project to facilitate and stimulate research on public health systems.

Cleary's work with people infected with HIV dates back to the 1980s. His first study in the field was a randomized trial of an education and support program for blood donors discovered to be infected with HIV. He has since continued to investigate the ways in which HIV infection affects people's lives and the factors affecting the quality of the medical care they receive.

Cleary taught at the University of Wisconsin and at Rutgers University before joining the faculty at Harvard Medical School, where he was a professor of medical sociology in the Departments of Health Care Policy and Social Medicine. In 1997 he received Harvard's A. Clifford Barger Award for Excellence in Mentoring. Cleary joined the faculty of the School of Medicine in 2006.

Cleary is a member of the Institute of Medicine. He was selected as a distinguished fellow of the Association for Health Services Research in 1996, and in 2002 received the Distinguished Investigator Award from the Academy of Health Services Research and Health Policy.

Berliner Professor envisions blood vessel growth as therapy

Michael Simons, M.D., recently appointed the Robert W. Berliner Professor of Medicine, is a leading researcher on angiogenesis—the growth of new blood vessels—in cardiovascular diseases.

Michael Simons

Simons came to Yale in 2008 as chief of the Department of Internal Medicine's Section of Cardiovascular Medicine at the School of Medicine and Yale-New Haven Hospital.

His research interests include fibroblast growth factor signaling in the vascular system, regulation of arterial development and branching, and endothelial signaling. He is developing strategies to deliver and assess various biological agents—genes, proteins, antibodies, and receptor "traps"—and in identifying and validating novel biomarkers that predict individual responses to therapies.

He has been an advocate for using biological therapies to stimulate new vessel growth to improve circulation in damaged regions of the heart or in blood-deprived limbs.

Before coming to Yale, Simons was the A.G. Huber Professor of Medicine, and professor of pharmacology and toxicology, at Dartmouth Medical School. He was also chief of cardiology at Dartmouth-Hitchcock Medical Center and the director of its Cardiovascular Center.

Simons received his M.D. from Yale in 1984. He was a resident in internal medicine at New England Medical Center, Boston, and a medical staff fellow and postdoctoral fellow at the National Heart, Lung and Blood Institute at the National Institutes of Health. He completed a fellowship in cardiology at Beth Israel Hospital in Boston and postdoctoral training at Massachusetts Institute of Technology, where he was an associate scientist in the Program for Excellence in Molecular Biology of the Cardiovascular System.

Expert on kidney development, repair is named Long Professor

Lloyd G. Cantley, M.D., professor of cellular and molecular physiology and newly named C.N.H. Long Professor of Medicine, is a noted nephrologist who studies the formation and repair of tubules in the kidney, structures that are crucial to the organ's function.

Lloyd Cantley

When the kidney is injured following blood loss or exposure to toxins, the remaining epithelial cells regenerate functional tubules. By examining epithelial cell adhesion, migration, and tubule branching in response to growth factors, Cantley and colleagues in his laboratory are determining the intracellular signaling events critical for tubule formation during kidney development and following injury. Cantley also studies the role of adult stem cells in recovery from acute tubular necrosis, one of the most common causes of kidney failure, in which tubule cells die. His group has found that stem cells from bone marrow can sometimes home to injured tubules and differentiate into tubular epithelial cells, but that their primary beneficial effect is in secreting factors that protect existing tubular cells from death. Members of his laboratory are presently examining how stem cells can be mobilized for therapy in cases of acute renal failure.

Cantley is associate chair for research in the Department of Internal Medicine and associate director of its nephrology fellowship program. An associate editor of the *Journal of the American Society of Nephrology*, Cantley has published his research in the *Journal of Clinical Investigation*, *Molecular Cell*, and *Proceedings of the National Academy of Science*.

Cantley earned his M.D. from the West Virginia University School of Medicine. He completed his residency at North Carolina Memorial Hospital and his fellowship training in nephrology at Beth Israel Hospital and Brigham and Women's Hospital in Boston.

Falk *from page 1*

In the early 1930s, frustrated by labor-intensive and unsafe methods of providing much-needed fluids to his patients during and after surgery, Ralph Falk resolved to find a better way. Along with his brother, Harry, Falk struck a deal to form a business with Donald E. Baxter, M.D., a California entrepreneur who had begun to develop a viable system for intravenous delivery of solutions after seeing many people die from cholera-induced fluid loss as a medical missionary in China. The company was incorporated as Baxter Laboratories in 1931.

Three years later, Falk purchased Donald Baxter's interest in the company, which went on to manufacture blood transfusion products that were extensively used during World War II and to develop some of the earliest equipment for kidney dialysis. By the time of Falk's death in 1960, Baxter Laboratories was one of the world's largest medical supply companies, with annual sales of over $37 million.

The assets of the Ralph and Marian Falk Medical Research Trust have grown to about $170 million, says Catherine Ryan, a Chicago-based senior vice president at Bank of America, which serves as sole trustee. With a broad mission to support research on diseases with no known cure, the trust has backed projects ranging from biomedical engineering to cancer research to neuroscience, with renewable three-year grants.

Melanie Vere Nicoll, granddaughter of Ralph and Marian Falk and a member of the Yale College Class of 1983, works closely with Ryan to select proposals that receive the trust's support. Though Ralph Falk died before she was born, Vere Nicoll believes that the trust is an apt expression of his insatiably curious mind and generous spirit. Ryan, who remembers Marian Falk as "a very interesting lady, a grande dame of Chicago," says that the trust will continue to implement its present strategy—awarding grants for the best proposals from top institutions without imposing a narrow scientific or disease-based focus—because the track record of Falk-supported work has been a good one. "We haven't cured anything yet," says Ryan, "but there's no doubt that we've helped a lot of people."

MEDICINE tomorrow

Supporting medical education

Each spring, fourth-year students at medical schools across the country eagerly anticipate Match Day, when students receive word of acceptance in residency training programs. It is a joyous day — the reward for four years of hard work and study. But getting medical students to Match Day takes more than individual student effort; it requires private support from alumni and friends. The gift opportunities below can provide essential funding for medical education.

JOHN CURTIS

Named endowed scholarship fund: $100,000 and up

Many medical school students face significant debt upon graduation. Annual income from endowed scholarships helps students meet tuition and associated costs during their four years at Yale School of Medicine.

Named endowed mentoring fund: $250,000 and up

Academic advising and guidance is critical to medical students' success, and Yale School of Medicine has taken steps to enhance this important function, by creating four new advisory positions. Faculty members in these new positions will advise students on academic and career planning issues.