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. 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 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.”

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.

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. “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.

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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.

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 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 first 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 1935 to 1963. In ceremonies that included a reception at the U.S. Capitol in Washington on April 29, Waxman, chair of neurology and the Bridge 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 (NRRRC), a collaboration of Yale University, the VA, the Paralyzed Veterans of America, and the United Spinal Association. The NRRRC 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.

“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.
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 changes in the protein known as amyloid-beta 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 a small fragment 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 aggregates 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 that bound 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 it is the protein that 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.

Strittmatter says, “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-beta 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 electrical activity in a brain slice.” Second, Strittmatter wants to examine further the cascade of neuron damage that occurs after amyloid-beta binds to prion protein. “We need to understand which genes and proteins come into play after prion protein and disrupt synaptic connections.”

“We must work needs to be done,” says Haakon B. Nygaard, M.D., Ph.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.”

(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


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 1968, 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.

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 of what’s next,” said Bennett, who added, “and Tom’s that person.”

An authority on lung cancer, Lynch has conducted dozens of studies of how small differences in patients’ genotypes, or 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 gefitinib (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 Martha 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 reeducate our efforts to make major advances in cancer therapy.”
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 virologists 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 Lenarr 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. Lipton, M.D., Ph.D., chair and Sterling Professor of Genetics, and Ute E. Scholl, M.D., a postdoctoral associate in Lipton’s lab, has implicated a gene known as KCNQ1 in a previously unreported medical syndrome.

Mutations in KCNQ1, 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 1 issue of Proceedings of the National Academy of Sciences, Scholl and colleagues report KCNQ1 mutations in two 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 SAMS syndrome because it features seizures, sensorineural deafness, ataxia, mental retardation and electrolyte imbalance. “If you had this study would have taken years in the past,” says Lipton, a Howard Hughes Medical Institute investigator, but with new techniques, “it was accomplished in a few weeks by a single fellow in the lab.”

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. Others, including De Camilli—who’s lab first established the curvature-generating properties of proteins containing BAR domains—found that a type of BAR 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 first established the curvature-generating properties of proteins containing BAR domains—found that a type of BAR 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.

Finally, the micrographs showed that the angle at which BARs side 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 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 cell 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 for July/August 2008

Federal

Claire Abraham, NIH, Mechanisms of Chronic Nod2-Mediated Effects in Human Macrophages, 4 years, $1,655,000 • Sarap Akopyan, NIH, Thyro-Transduction after Adjunct Thyroidectomy, 5 years, $581,717 • Frederick Altich, NIH, Enhanc- ing Health Outcomes among MyTV's Substance Abusers, 4 years, $74,954 • Laleh Ardeshirpour, NIH, Anabolic Response of Skelatal after Lacta- tion, 4 months, $77,470 • Peter Aronson, NIH, Mother of 11: The Longevity of Female Chromosomes, 4 years, $1,203,430 • Declan Barry, NIH, Chronic Pain and Opioid Dependence Assessment and Treat- ment, 4 years, $1,486,450 • Gerald Friedland, NIH, Effect of Traffic and Air Pollution on Blood Birth Outcomes, 4 years, $3,086,647 • James Boyer, NIH, T清爽 Characteristics and Comorbidity and Functional Outcomes in Older Adults with Health Status, 5 years, $359,997 • C. Y. Shen, NIH, Optical Imaging of Offic- iated Sensory Code Transformation, 5 years, $1,754,440 • Keith Choate, NIH, Genetics and Pathologi- cal Functions of Primate Dopamine Neurons to Toxicity during Development, 4 years, $811,150 • Elizabeth Hilton, NIH, Sta- tement of Mental Health Settings: A Qualitative-Quantitative Analysis, 3 years, $531,203 • Bill Forbush, NIH, Molecular Physiology of the Fas-KC-Cytotaxon, 4 years, $1,489,500 • Julie Goodwin, NIH, The Role of Vascular Smooth Muscle GR in Acute Glucos- cumetabolism in the Mouse, 5 years, $422,000 • Steven Goller, NIH, Targeting Placental Pathophysiol- ogy in IVF and Preimplantation, 1 year, $316,985 • Thomas Huesgen, NIH, Behavioral and Leptin Signaling Detect-Sent Point of the Adult Melanocortin System, 4 years, $7,758,440

Biofilm, NIH, Cationic Genes: Behavior in Human/Pathogenic Living in the Northeast United States, 5 years, $3,417,316 • Mustafa Khokha, NIH, Characterization and Clogging of Proteins by the H-Ras GTPase in Nodu- la Tufo, NIH, Functions of V1-R in Podo- cytogenic Lesions for Renal Disease, 6 months, $283,000 • Flavo Vaccarino, NIH, Astroglial Cells in Perinatal Brain Injury Stand-By, NIH, Studies on Autism Spectrum Disorders/Neural Cell Function, 5 years, $1,796,300 • Zhi Huo Yang, NIH, Mapping Genes for Comor- bidity and Depression, 5 years, $854,422 • Dejan Zoric, NIH, Retinal Synaptic Transmission, 4 years, $410,959 • Zoran Zivkovic, NIH, Sympatic Function and Organization of the Mamm- alian Retina, 3 years, $127,522 • Carol Weitzman, NIH, Physiology and Development of the Ventrolateral Retina, 4 years, $823,685

Non-Federal

Khalid Abbas, American Asso- ciation of Neurological Surgeons, Prospective Outcomes Evaluation of One-Level Transforaminal Lumbar Interbody Fusion performed with new technology Approach Versus a Conventional Open Approach, 1 year, $15,000 • Jean Adolph, Community Health Center Association, Title IV, 1 year, $425,753 • Gary Anderson, Alan B. Milstein, in Infants with Autism, Long-Term Effects of Ecotaxation Patterns, 3 years, $209,346 • Robert Baeck, Dona- guez Medical Research Fdn., Gene-Expression Algorithms to Predict Lithium Response, 3 years, $240,000 • Carl Manzoni, American Geri- atric Soc., Geriatrics for Specialist Interventions, 2 years, $157,500 • Craig McCracken, NIH, Role of the Role of Regulatory T Cells in Immune Evasion, 2 years, $150,000 • Michael Black, American Psychiatric Inst. for Research and Education, for Study of Long-Term Outcome of Pediatric ccd, 4 years, $450,000 • Elizabeth Bradley, Children’s Innova- tion Fund Effec- tiveness Trial, 5 years, $698,570 • Martin Buechner, American Heart Assoc., founders, 3 years, $198,900 • Gordon Buchanan, Jazz Pharmaceuticals, Chromobi- ological Studies in the Mouse, 4 years, $198,500 • Caro Caprio, American Diabetes Assoc., Mechanisms of Hemoglobin Derivatives in Rodent Cells, 4 years, $800,000 • Sarat Chaudhury, American Federation for Aging Research, Supplement to the Biomedical Sciences, The Role of Microvis- cosities in Vertebrate Development, 5 years, $1,000,000 • Julie Goodwin, Nati’l Kidney Fdn., The Role of the Vascular Endothelial Glucose Recep- tor-Glucocorticoid-Mediated Hypertension, 4.5 years, $1,610,000 • Elena Girzdanova, Columbia University—Teachers College, Substance Abuse among Suburban Youth: A Prospective Study, 1.5 years, $146,769 • Balba Grewe, Susan G. Komen Breast Cancer Fdn., Interdisciplinary Breast Fellowship, 2 years, $90,000 • Jonas Hennestad, NIH, Society of Nuclear Medicine and Research Fdn., Neuroimaging and Depression during Interdural Alpha Blockade of NPY, 3 years, $208,000 • Ivan Hapuz- rot, Stanford University and Research Fdn., cnp for Nephritis as a cause of VTE, 4 years, $604,638 • Kenneth Harrison, American Heart Assn.—Founders Affiliate, Role of Nogo-B Receptor in Intracellular Calcium Homeostasis, 2 years, $42,000 • David Hawiger, Nat’l Multiple Sclerosis Soc., The Novel Rhodoid Peterman: Teasing-Inducing Pathway in Muscle, 2 years, $57,720 • Octave Henegar, American Lung Assn., Changes in the Lung Nerve Nerve in Children with Asthma, 2 years, $1,000,000 • Tommaso Horvath, American Diabetes Assoc., Nod2 Determinant Developmental-Organization of Hypothalamic Circuits, 4 years, $180,000 • Zhehui He, State of CT Dept. of Public Health, Preventing Tumor Blood Vessels for Immunotherapy and Photodynamic Therapy, Pan-African Kidney Health, 20 months, $332,440 • Bahamn Iraberti, Social Science, Ruth num Neurocenter of Excellence at Yale, 1 year, $25,000 • Allergan Sales, Movement Disorder Fellow- ship Program, 4 years, $140,000 • Roger Jon, American Psychiast for Research and Education, Autism Spectrum Disorder/ACE Fol- low-up, 1 year, $141,000 • Nina Kallendorf, CogniPharm, Ltd., A Pilot Study of the Feasibility and Efficacy of the Computer-Based Mindfulness interven- tion, 1 year, $90,000 • St. Baldwin’s Fdn., Center- St. Baldwin’s Fdn. Scholar, 3 years, $331,000 • Insoon Kang, American College of Rheumatol- ogy, 1 year, $250,000 • Nguyen Wurhistology Rheumatol- ogy Fellowship Program, for the Wurhistology in Rheumatological Drugs, 2 years, $345,200 • Tourette Syndrome Assoc., The Role of the Immune System in Tourette’s Syndrome, 1 year, $75,000 • Kenneth Kidd, Winner-Gren Fds. 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 Cancer, 3 years, $200,000 • Harlan Krumholz, Robert Wood Johnson Fdn., Myrick Schol-

"Embodying Dance," an image by Antonio J. Giraldes, m.d., assistant professor of genetics and the inaugural Lois and Franklin L. Topf Jr. Yale Scholar. With support from the Pew Scholars Program in the Biomedical Sciences, his research focuses on how the nervous system uses limbic structures and the cerebellum as a model system. Here, messenger RNA in zebras, which is expressed by microarrays, encodes a fluorescent protein. The shorter embryos are mutants that lack microns.
One of the results of these invest- ments has been a steady increase in grants and publications 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 funding is not the "be all-end all," Alpern says, "but 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 administration and faculty who have credits them for the school’s continued success. Deputy Deans Richard Belitsky, M.D., David J. Leffell, M.D., Carolyn W. Slawyer, Ph.D., Cynthia Walker, M.B.A., and her predecessor, Jacquie W. Boyen, have all provided extraordinary leadership during his first term, Alpern says, as have Janey L. Houck, M.A., director of medical development and alumni affairs, and Mary J. Hu, M.B.A., director of institutional advancement. He also cites the "outstanding" work of the department chairs and fac- ulty, and points to several key external recruitments to leadership positions— notably, Jane L. Houck, new chair of the Department of Cell Biology; Hai Yan, 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 interdisci- plinary programs. "The 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 National Institutes of Health Roadmap of the NIH Clinical and Transla- tional 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 from 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 Simonds, M.D., who arrived last summer and is building the section’s strengths in interventional cardiology, treatment of heart failure, electrophysiology, and basic research. The 24-story Smilow Cancer Hospital at Yale University New Haven, which opened in May, is ready 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, page 70). With this premier designation, the opening 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 VHHH," says Alpern, who has worked very closely with Marna P. Bogrerson, M.P.H., president and CEO of VHHH.

"We’ve improved the relationship be- tween the medical school and hospital in a way that neither institution would have imagined just 10 years ago," 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 of medical 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 in part on teaching as well as the 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, has become one of the most selective medical schools in the nation, with 4,089 applications for the 160 places in the Class of 2013. Just as closer collaboration with VHHH has strengthened the entire clinical enterprise, so too have collabora- tions with the university leadership have paid major dividends across the entire Yale campus, Alpern says.

"[President] Rick Levin made a com- mitment to translational research, which inspired me to come here, and he delivered. To take a school as good as Yale and make it better is excit- ing, and we’ve come a long way. The reason I’ve signed on for another five years is to continue that ascent."
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. 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 evaluate 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 clinical 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. 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.

Falk from page 7

In the early 1990s, 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, a Cali-

fornia entrepreneur who had begun to study hemostasis and fluid delivery of solutions after seeing many patients die from cholaera-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. The trust is committed to funding research on diseases with no known cure, the trust has backed proj-

ects 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 sup-
port. Though Ralph Falk died before she was born, Vere Nicoll believes that the trust is an apt expression of his insatiable curiosity and generous spirit. Ryan, who remembers Mar-

ian Falk as “a very interesting lady, a woman of enormous energy,” agrees 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.”

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 nephrologist who studies the forma-

tion and repair of tubules in the kidney, structures that are crucial to the organ’s function.

When the kidney is injured following blood loss or exposure to toxins, the remaining epithelial cells regenerate as 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.

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.

Named endowed scholarship fund: $10,000 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 func-

tion, by creating four new advisory positions. Faculty members in these new positions will advise students on academic and career planning issues.

M E D I C I N E T O M O R R O W