Medicine@Yale

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Advancing Biomedical Science, Education, and Health Care

New alliance with Gilead Sciences is 'transformative'

Research collaboration pairs Yale experts with industry scientists to accelerate the development of new drugs to treat cancer

When Robert J. Alpern, M.D., dean of the School of Medicine, was asked recently to prepare a brief overview of the current state of drug discovery for a symposium at Yale's West Campus, a familiar phrase came quickly to mind: "It was the best of times, it was the worst of times . . . "

It's an apt description. On the one hand, we live in what some call the "post-Gleevec era," a time when basic research conducted over decades is bearing fruit in the form of remarkably effective, targeted drugs. But the cost of drug development has risen exponentially as clinical trials and regulations have grown more complex. The average total cost to develop a single approved drug is now pegged at a staggering $1.3 billion, a 60 percent increase since 2005.

Early-stage research carried out by academic scientists in settings like the School of Medicine is unveiling more potential drug targets than ever. But research grants are not designed to sustain the many additional steps involved in drug discovery, and academic researchers lack resources to explore these targets further. The expense and complexity of bringing drugs to the marketplace have understandably made pharmaceutical companies risk-averse and selective about which targets to pursue. The resulting gap between academia and industry has become known as the Valley of Death: only a miniscule number of promising discoveries manage to traverse this chasm, and even fewer result in drugs approved for clinical use.

To begin to bend this troubling curve, some pharmaceutical companies have been building scientific alliances with universities, a trend that has picked up steam during the past few years. In March, President Richard C. Levin announced that Yale University had forged a multi-year research alliance with Gilead Sciences, Inc., a biopharmaceutical company based in Foster City, Calif., to accelerate the discovery and development of new drugs to treat cancer.

Gilead will provide up to $40 million to support cancer research at the School of Medicine over four years, and a total of up to $100 million—the largest corporate commitment in Yale's history—for the full 10 years outlined in the agreement. Yale maintains ownership of all intellectual property generated by medical school research, and Gilead will have the first option to develop any compound it deems promising.

"The collaboration brings together one of the world's top research universities and a biopharmaceutical company dedicated to addressing unmet medical needs, with the goal of finding new treatments for cancer," Levin said. "This truly is transformative support that leverages Yale Cancer Center's top scientists, our West Campus technology investments, and the resources of the new Smilow Cancer Hospital. I can't think of a better partner to have in this collaboration than Gilead."

The project will be governed by a six-member Joint Steering Committee chaired by Joseph "Yossi" Schlessinger, PH.D., chair and William H. Prusoff Professor of Pharmacology at the School of Medicine. The committee will also include medical school scientists Richard P. Lifton, M.D., PH.D., chair and Sterling Professor of Genetics and Howard Hughes

COURTESY OF GILEAD SCIENCES

Prime movers at Gilead Sciences in the new initiative with the School of Medicine are (clockwise from left) Howard Jaffe, a 1982 alumnus of the medical school and president and chairman of the board of the Gilead Foundation; Linda Slanec Higgins, vice president, Biology; and William Lee, senior vice president, Research.

Medical Institute investigator, and Thomas J. Lynch Jr., M.D., the Richard Sackler and Jonathan Sackler Professor of Medicine, director of Yale Cancer Center, and physician-in-chief at Smilow Cancer Hospital. They will be joined by Gilead scientists Howard Jaffe, M.D., a 1982 alumnus of the School of Medicine and president and chairman of the board of the Gilead Foundation; William A. Lee, PH.D., senior vice president, research; and // Gilead *(page 8)*

Donation from leading Asian foundation will advance stem cell science

The Li Ka Shing Foundation (LKSF), Asia's largest philanthropic organization, has made a $1.5 million donation to the Yale Stem Cell Center (YSCC). The donation will fund improvements in two of the YSCC's four core laboratories that will benefit the work of more than 60 faculty members and numerous trainees across the campus.

In announcing the contribution, Yale University President Richard C. Levin said, "We are grateful for the Li Ka Shing Foundation's generosity, which benefits today's medical research in order to develop tomorrow's cures. This significant donation will allow the Yale Stem Cell Center

Li Ka-shing

to continue to make available to its members the most current technologies used in stem cell research."

YSCC Director Haifan Lin, PH.D., professor of cell biology, first met LKSF Director Solina Chau during a trip to Hong Kong last year, but Chau says it was more than the proposal on behalf of the YSCC Lin sent later that won LKSF's support.

"We have all been great admirers of the work of Yale for 100 years in China," says Chau, who visited the School of Medicine in 2010. "The team at Yale seems to be very open, and wants to support and leverage each other's work to accelerate science. At the Stem Cell Center, I felt that Haifan has developed a unique sense of community and bonding between the different teams."

In the YSCC's human embryonic stem cell (hESC) facility, the donation will support the introduction of induced pluripotent stem cell (iPSC) technology, which will bring scientists closer to tailoring patient-specific cells for the treatment of disease.

Discovered in 2006, iPSCs are typically derived from ordinary adult cells such as skin cells—not embryonic cells—but, like hESCs, they can self-regenerate indefinitely and can develop into any kind of bodily cell or tissue. Because iPSCs are genetically matched to the donor, they may not induce a rejection response by the immune system, an important characteristic in developing personalized treatments for individual patients.

The new iPSC initiative at the YSCC will be supervised by In-Hyun Park, PH.D., assistant professor of genetics, one of the world's first scientists to develop iPSC technology. Park's work has focused on the basic biology of stem cells and on the use of stem cells to // Li Ka Shing *(page 7)*

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INSIDE THIS ISSUE

ALSO

HAROLD SHAPIRO

Brian Smith, who leads the medical school's Department of Laboratory Medicine, says that the technologies that are making personalized medicine a reality pose daunting challenges to his field. The sheer quantity of patient information that can now be obtained from genomic analysis and other techniques raises a multitude of practical and ethical questions, and will require informatics experts to devise innovative ways to manage and interpret highly complex data.

Tackling an information explosion

Chair worries that the U.S. is not ready for the coming deluge of medical data

For a leader in a field at a pivotal moment of transition, Brian R. Smith, M.D., is modest, equating his role as chair of the Department of Laboratory Medicine to mostly "filling out pieces of paper." But Smith's department, with a mission that combines both service and research, is critical to patients at Yale-New Haven Hospital (YNHH) and many other institutions in New England and beyond, as well as to the work of other medical school departments.

Members of the department study the components of blood and other bodily fluids to better understand and treat disease, including those measured in the familiar lab tests ordered by doctors. Each day the department produces about 75,000 lab results for patients at YNHH and for Yale Medical Group, the medical school's clinical arm.

The department's research mission is necessarily broad, says Smith, professor of laboratory medicine, medicine, and pediatrics, because "our discipline covers essentially all of physiology and pathophysiology," with the strongest focus on immunology, hematology, and cellular therapy. Smith's own research has explored the interface between the immune and coagulation (clotting) systems in blood diseases, cardiovascular disorders, and metastatic cancer. His work on these two critical physiologies may ultimately help to reduce complications associated with heart-lung bypass machines and the administration of blood transfusions.

After attending Princeton as an undergraduate, Smith received his M.D. from Harvard Medical School, and completed his internship and residency in internal medicine at the Peter Bent Brigham Hospital in Boston. He completed fellowships in hematology, oncology, hematopathology, and research pathology at the Brigham, the Dana-Farber Cancer Institute, and Children's Hospital in Boston before joining Harvard's faculty in 1981. He came to Yale in 1989.

Fifty years ago, a patient's laboratory tests might include analyses of two or three factors, and a technologist might spend a full day generating the results. Now, Smith says, it often takes less than an hour to obtain 20 or more results for one patient. As technology alters the medical landscape, the field is facing an information explosion that demands new ways of managing and interpreting the data. Genomics alone, which now allows rapid sequencing of the billions of base pairs in the human genome, has brought formidable challenges to laboratory medicine.

Labs will soon routinely perform complex genomic and proteomic analyses impossible just a few years ago, vastly improving diagnosis but increasing reliance on informatics. "Humans are very good at some qualitative pattern recognition, but computers are far better at consolidating multiple quantitative analyses for diagnostics or following the results of therapy." But aside from technical problems, maintaining vast stores of patient information raises ethical questions. If whole genomes of patients are sequenced many years before genetic advances reveal new risk factors for diseases, "Do we try to find every patient previously sequenced and call each of them back with the new information?" Smith asks. He predicts an ever-increasing interaction of specialists in laboratory medicine with other physicians to evaluate the clinical significance of the rapidly proliferating options available in laboratory diagnostics.

The increasing adoption of electronic medical records may help pave the way for improved informatics systems. But the information overload about to take place in medicine is unprecedented, Smith says. "We need a national debate, and I think we're moving in that direction," he says.

A famously funny man backs Yale work on a deadly serious disease

For author, blogger, raconteur, and talk-show host Dick Cavett, when the topic is depression, it's personal. Cavett had his first bout with the illness a year after graduating from Yale College in 1958, and debilitating episodes continued to dog him during his storied reign as host of the various incarnations of *The Dick Cavett Show,* which first debuted on ABC in 1968.

For his work in raising awareness of depression and his efforts to eliminate the stigma associated with the disorder, the School of Medicine's Department of Psychiatry gave Cavett its Mental Health Research Advocacy Award in 2009. On March 9 of this year, Cavett joined department faculty at the Yale Club of New York City as a special guest for a presentation of some of the department's latest research on depression and bipolar disorder.

John H. Krystal, M.D., department chair and Robert L. McNeil Jr., Professor of Translational Research, introduced talks by Hilary Blumberg, M.D., associate professor of psychiatry and diagnostic radiology, and Ronald S. Duman, PH.D., Elizabeth House and Jameson Mears Professor of Psychiatry. Blumberg presented brain-imaging studies elucidating the development of bipolar disorder, while Duman discussed the role of neurogenesis (the birth of new nerve cells) in the brain's hippocampus in depression, research that throws light on the very rapid antidepressant action of the drug ketamine recently demonstrated by Krystal and colleagues.

Dick Cavett

In 1975, Cavett was successfully treated with antidepressants, and he overcame his worst episode, in 1980, with electroconvulsive therapy, which he deemed "miraculous." But existing therapies do not work for everyone, and Cavett stressed that new and better treatments are sorely needed.

Translational work by diabetes expert is cited in award

William Tamborlane

William V. Tamborlane, M.D., professor of pediatrics and a world-renowned figure in the understanding and treatment of childhood diabetes, has been awarded the T2-Translation Award by the Society for Clinical and Translational Science (SCTS).

The award recognizes the translation of research from early clinical use to applicability for widespread clinical practice. The award honors Tamborlane's pioneering clinical research, which has led to new delivery methods for physiological replacement of insulin, preventing many of the major long-term complications of childhood diabetes.

Tamborlane is chief of the Section of Pediatric Endocrinology and deputy director of the Yale Center for Clinical Investigation. His major achievements have included pioneering work in the development of insulin pump therapy, continuous glucose monitoring, sensor-augmented pumps, and a prototype design for an artificial pancreas. Tamborlane has also demonstrated the role of insulin resistance in pediatric metabolic disorders, including obesity and type 2 diabetes.

The SCTS presented Tamborlane with the award on April 28, at the national joint meeting of the Association for Clinical Research Training, the American Federation for Medical Research, and the SCTS, in association with the Association for Patient-Oriented Research.

Tamborlane's multitude of honors and distinctions include the Outstanding Physician Clinician in Diabetes Award from the American Diabetes Association in 2010.

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Food on the brain: craving vs. self-control

CORBIS IMAGES

Obese individuals and substance abusers exhibit similar patterns of brain activation: overactive reward regions in response to images of palatable food or drug paraphernalia, respectively, but reduced activity in regions involved in self-control when actually consuming food or drugs. It was unknown whether these patterns exist in "food addiction," a compulsive eating disorder that can affect both obese and lean individuals.

As reported in the April 4 online edition of the *Archives of General Psychiatry*, a team led by psychology doctoral student Ashley N. Gearhardt, M.S., M.PHIL., compared brain activity in food addicts and non-addicts. Images of a milkshake or a glass of water were presented, and subjects received a taste of the drink shortly after. In those diagnosed with food addiction, the milkshake images elicited increased activity in regions linked to motivation and craving, while tasting the shake led to lower activity in self-control regions.

"That food-related cues may trigger pathological properties is of special concern in the current food environment, where highly palatable foods are constantly available and heavily marketed," Gearhardt says.

What helps patients to survive a heart attack?

Rates of mortality after heart attack vary as much as twofold between the highest- and lowest-performing hospitals, a discrepancy that has not been fully explained.

To explore this question, Research Scientist Leslie Curry, PH.D., M.P.H.; Elizabeth H. Bradley, PH.D., professor of public health; and Harlan M. Krumholz, M.D., the Harold H. Hines Jr. Professor of Medicine, visited 11 U.S. hospitals ranked in either the top or the bottom five percent in mortality rates. As reported in the March 15 issue of the *Annals of Internal Medicine*, the team interviewed 158 staff members, and identified five factors at work in the best hospitals: an organizational culture emphasizing top-notch care; deep involvement of senior managers; participation in clinical decision-making by all health care professionals, including nurses and pharmacists; clear communication and coordinated efforts among departments; and an approach to solving problems based on sharing knowledge and learning from mistakes rather than pointing fingers.

"These essential ingredients are not expensive," Bradley says. "If we could implement our findings in more hospitals, we could improve quality without adding to costs."

Symposium is 'once-in-a-lifetime event'

A roster of top biomedical scientists visits Yale for two days of talks and intellectual exchange, along with a generous helping of good cheer

It was the hottest ticket in town—and you didn't even need a ticket.

This spring, 15 of the top minds in science converged on New Haven for the School of Medicine's Bicentennial Symposium, "Biomedicine in the New Century."

Held on April 28 and 29 and open to the public, the symposium drew capacity crowds, filling the nearly 450 seats of the Mary S. Harkness Auditorium, the medical school's largest lecture hall, and overflowing to a nearby 150-seat auditorium at the Anlyan Center for Medical Research and Education, where a live broadcast of the sessions was available.

The throng had come to hear the latest thoughts and research updates from a star-studded scientific cast, which included seven Nobel Prize winners, on topics ranging from the neurobiology of memory to the crisis of inequality in health care to the next generation of targeted cancer drugs.

The symposium was a signature event in the celebration of the School of Medicine's Bicentennial, which has been marked during the 2010–2011 academic year with the publication of *Medicine at Yale: The First 200 Years*, a richly illustrated book-length history of the school; a documentary film by Emmy Award–winning director Karyl Evans; a performance by the Yale Medical Symphony Orchestra of an original musical composition commissioned for the occasion; and, most recently, the Association of Yale Alumni in Medicine's June Reunion Weekend, which featured several special Bicentennial-related talks, events, and exhibits.

"This bicentennial symposium was a once-in-a-lifetime event for the School of Medicine," says Robert J. Alpern, M.D., dean and Ensign Professor of Medicine. "We find ourselves in a great era of advances in biomedical research. When we got together to decide how best to celebrate our anniversary there was uniform agreement that it had to include a scientific symposium featuring a group of scientists of the highest regard."

MICHAEL MARSLAND

HAROLD SHAPIRO (2)

TOP **Many of the speakers at the Bicentennial Symposium joined Yale President Richard Levin, Dean Robert Alpern, and medical school faculty for a dinner on April 28. (Front row, from left) Levin, Charles Sawyers, Joseph Goldstein, David Baltimore, Eric Kandel, Elizabeth Blackburn, Elaine Fuchs, Robert Lefkowitz, and Alpern. (Back row, from left) Peter Kim, Phillip Sharp, Harold Varmus, Michael Brown, and Michael Marmot. Symposium speakers Robert Califf, Susan Lindquist, and Huda Zogby were unable to attend the dinner.** ABOVE LEFT **Every seat at Mary S. Harkness Auditorium, and in a nearby auditorium featuring a live video broadcast, was filled on the symposium's opening day.** ABOVE RIGHT **Robert Califf, director of the Duke Translational Medical Institute at the Duke University School of Medicine, delivered the final address, "Translational Medicine: Moving from Better Ideas to Better Health."**

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60	4.5%	7%	11.5%
65	5.5%	9.5%	15%
70	7.5%	14%	15%

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MEDICINE tomorrow

OUT & ABOUT

February 18 With a gift from **Andrew Bronin**, M.D., associate clinical professor of dermatology (left), the Department of Dermatology established the **Dr. Andrew Bronin Clinical Scholarship in Dermatology**, one of two new endowments that will support young clinician–scholars in dermatology. **Richard L. Edelson**, M.D. (right), chair and Aaron B. and Marguerite Lerner Professor of Dermatology, says that the funds from the new endowments will enhance "the academic endeavors of clinician–scholars and their ability to shape the field." The first endowment was started with a $1 million gift from School of Medicine alumna Marie-Louise T. Johnson, M.D., PH.D., in 2010.

TERRY DAGRADI

March 17 On **Match Day** each spring, fourth-year students at medical schools across the country receive word of acceptance in residency training programs. At Yale, all of the 77 graduating medical students who had entered the National Resident Matching Program learned they had "matched." **1. Adelina Hung** congratulates **Rajendra Sawh-Martinez**. **2. Kseniya Golubets** and **Annie Engberg**. **3. Macdale Elwin**, **Samrawit Goshu**, **Charisse Mandimika**, and **Tamara Carroll**.

JOHN CURTIS (3)

April 15 Members of the U.S. Army held an event at the School of Medicine to describe the Army Medical Department's humanitarian operations around the world. **General Stanley McChrystal** (Ret.), former commander of U.S. forces in Afghanistan and now a senior fellow at Yale's Jackson Institute for Global Affairs, was a featured speaker at the event, titled **Common Ground: Army Medicine in Support of Humanity**. **1. Carolyn W. Slayman**, PH.D., Sterling Professor of Genetics, professor of cellular and molecular physiology, and deputy dean for academic and scientific affairs (left), with McChrystal (center) and Army personnel. **2.** A medical Deployable Rapid Assembly Shelter (DRASH) unit was on display in Harkness Ballroom. The unit, which includes a surgical bed and a variety of essential medical equipment, can be set up and functioning in less than an hour and represents the next level of care after battlefield treatment.

MICHAEL MARSLAND (2)

April 26 At the Yale Club of New York City, **Carolyn M. Mazure**, PH.D., professor of psychiatry and psychology, associate dean for faculty affairs, and director of **Women's Health Research at Yale** (WHRY), spoke about the latest biomedical research that WHRY is supporting and conducting. (From left) WHRY Advisory Council members **Diane Young Turner**; **Kitty Northrop Friedman**, J.D.; Mazure; **Roslyn Milstein Meyer**, PH.D.; and **Fran DeToro**.

CHI CHI UBIÑA

MICHAEL MARSLAND (2)

April 27 The 32nd annual **Seton Elm and Ivy Awards**, presented at Yale's Woolsey Hall, honored people and organizations that further partnership between New Haven and Yale. **1.** New Haven Mayor **John DeStefano Jr.** (left) and Yale University President **Richard Levin** (right) with medical students **Oluwarotimi Okunade**, **Charisse Mandimika**, **Amy Moreno**, and **Jorge Ramallo-Pardo** of the Yale chapters of the Student National Medical Association and Latino Medical Student Association, which were honored with an Ivy Award for their work encouraging New Haven high school students to pursue careers in the sciences and health professions. **2. Georgina Lucas**, deputy director of the Robert Wood Johnson Foundation Clinical Scholars Program at Yale, also received an Ivy Award.

Turner syndrome seen sooner with new test

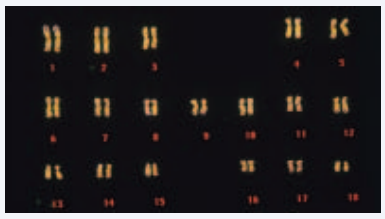


PHOTO RESEARCHERS, INC.

Turner syndrome (TS) is a relatively common genetic condition in females in which some or all of the X chromosome is deleted, causing stunted growth and heart and kidney problems. TS can be diagnosed with a karyotype (above), but these are labor intensive and impractical as a routine test, so the disorder often goes undetected until girls reach 10 years of age.

In the March issue of the *Journal of Clinical Endocrinology & Metabolism*, Scott A. Rivkees, M.D., professor of pediatrics, and colleagues describe a genetic test for TS that is quicker, less expensive, and more amenable to large-scale use than karyotyping. The new screen, which analyzes variations in DNA at 18 sites on the X chromosome, diagnosed TS with almost perfect accuracy in 132 females without TS and 74 females known to have TS based on prior karyotype analyses.

The team notes that very short girls could be tested early for TS, enabling intervention with growth hormone and treatments for organ defects. "If broadly used in the clinical setting at young ages, this test can prevent the delayed recognition of TS," Rivkees says.

Small brains reveal a gene's outsize role

Microcephaly is a developmental disorder characterized by significantly reduced brain size and a smaller number of neurons, as well as profound mental retardation. Although several genes have been implicated in this disorder, little is known about its cellular and molecular underpinnings.

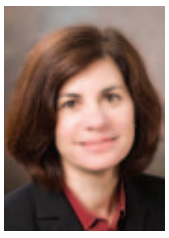
In a study published May 13 in *The American Journal of Human Genetics*, Murat Günel, M.D., Nixdorff-German Professor of Neurosurgery and professor of genetics and neurobiology, and collaborators analyzed DNA from three families affected by an extreme congenital form of this condition resulting in a 90 percent reduction in brain size and abnormal layering of cells in the cerebral cortex.

The team homed in on mutations shared by family members in a gene known as *NDE1*. In the developing nervous system, NDE1 proteins accumulate at centrosomes—structures critical for cell division—in cells that generate neurons, but the *NDE1* mutations found in these families undermine this clustering. These data are evidence for crucial roles of *NDE1* and centrosomes in normal production and organization of neurons during development. Also, Günel says, evolutionary changes in *NDE1* over 5 million years may underlie the greater size and complexity of human brains relative to those of non-human great apes.

A new alternative for asthma patients

"Breakthrough treatment" offers an option for those asthma patients whose attacks cannot be controlled with conventional drug therapies

Asthma can be difficult to treat, so physicians at the Yale Center for Asthma and Airway Disease (YCAAD) are always searching for novel therapeutic approaches to treat severe cases for which drug treatment has proved ineffective. A case in point is bronchial thermoplasty (BT), a new minimally invasive procedure made possible by a device recently approved by the FDA that uses radiofrequency energy to treat moderate to severe asthma.



Lauren Cohn

Geoffrey Chupp

Each year thousands of patients visit YCAAD, which recently became the first center between Boston and New Jersey to offer BT. Because YCAAD's multidisciplinary approach creates an ideal setting for performing and refining the procedure, the center is one of 30 in the country participating in a phase IV post-market trial of the new device.

Asthma symptoms result from an excess of smooth muscle cells in the airways of the lungs. When various triggers cause airway inflammation, bronchial muscle cells contract and constrict the airways, making breathing difficult. In BT, a flexible camera known as a bronchoscope is adapted with the BT device to gently heat and eliminate smooth muscle. This prevents the airways from constricting.

The studies that led to FDA approval of the BT procedure showed that it significantly mitigated asthma symptoms and flare-ups of the disease, improving asthma patients' quality of life.

"With this breakthrough treatment, we are confident we will be able to alleviate much of the suffering of our patients with severe asthma," says Geoffrey L. Chupp, M.D., associate professor of medicine and YCAAD director. "In the past, these patients received high doses of medication and continued to suffer from frequent asthma attacks and limitations on routine daily activities, as well as frequent emergency room visits. Bronchial thermoplasty gives new hope to these asthmatic patients and a non-drug option to control their disease. "

Jonathan T. Puchalski, M.D., assistant professor of medicine and director of the Thoracic Interventional Program in the medical school's Section of Pulmonary and Critical Care Medicine, performs the BT procedure with the help of a team that includes Kimberly Ebel, R.N., Suzanne Koshis, R.N., and Kelsey Johnson, P.A. Patients are sleepy during the procedure but breathing on their own, and they are usually able to go home afterwards.

Because the BT procedure itself can sometimes trigger an asthma attack, it is generally performed in three outpatient sessions in which different regions of the lungs are treated, spaced about three weeks apart.

One patient who was recently treated with the procedure at YCAAD had suffered from severe asthma his entire life. With poor lung function, he was chronically short of breath and had trouble exercising.

Like many patients who undergo BT, this patient's symptoms worsened for a brief period immediately after the procedure. After four months, however, he had decreased his medications and no longer used a rescue inhaler when playing sports. He has increased his heart rate by 20 points when exercising on a treadmill, and his lung function has also slightly improved.

"This is exactly the clinical response you would predict based on the trials evaluated by the FDA. The patient is pleased he went through the procedure," says Chupp.

Patients who undergo BT receive follow-up care from a team that includes Nicole Grant, R.A., and Carol Holme, who provide assessment immediately after the procedure, and Radhika Nandlal, R.N., who provides care and advice to BT patients who return to YCAAD over the long term.

As the only major asthma center in the Northeast, YCAAD physicians and scientists enjoy unique opportunities to conduct research aimed at understanding the biological pathways at the root of asthma as well as to improve treatments like BT.

The center maintains a large repository that includes clinical and physiological data, DNA samples, plasma, and lung specimens from asthma patients who are stable or are experiencing flare-ups. All of this data is regularly uploaded into a Web-supported database so that information is readily available, making it easier to recruit patients for clinical trials and identify those who could benefit from specific treatments like BT.

HAROLD SHAPIRO

Jonathan Puchalski performs bronchial thermoplasty (BT) at the Yale Center for Asthma and Airway Disease, one of the few sites in the Northeast equipped for this recently approved, minimally invasive procedure. BT targets the muscle tissue that causes airway constriction, offering a new medical option for asthma patients whose symptoms cannot be successfully controlled with medications.

"We're trying to get better at figuring out what therapy is best for what person," says Lauren E. Cohn, M.D., assistant professor of internal medicine and YCAAD co-director. "Because we see so many patients with this disease, we really are starting to understand how to group our patients and how to get the sense of who might need BT."

In 2007, Chupp and Jack Elias, M.D., chair and Waldemar Von Zedtwitz Professor of Medicine, reported in *The New England Journal of Medicine* that asthmatic patients have high levels of a protein called YKL-40 that helps regulate the immune response and can cause lung inflammation. They went on to show that those with a particular mutation in the YKL-40 gene are at greater risk of developing asthma and have lower lung function.

Cohn has joined Chupp and Elias in a search for biomarkers that can predict patients' response to BT. The team believes that the YKL-40 mutation or levels of the protein in the blood may be a good candidate, since YKL-40 levels appear to decrease significantly after BT.

"We customize the treatment approach for every patient and determine if they're a candidate for BT or some other advanced or investigational treatment," says Chupp. "YKL-40 might be a clinically useful marker of responsiveness."

Puchalski believes that BT is a promising treatment for some patients who obtain unsatisfactory results from asthma inhalers or oral medications such as beta-agonists. "This new procedure offers a potential upgrade for treatment over inhaled drugs or other medications because we are attacking the problem at its very root," he says. Chupp agrees: "For those with severe asthma, this is a terrific option where medication can fall short."

Grants and contracts awarded to Yale School of Medicine

July/August, 2010

Federal

David J. Adle, NIH, *Functional Characterization of an ER-Resident Ligase in Yeast*, 3 years, $150,234 **Serap Aksoy**, NIH, *Evidence-Based Control Strategies of Sleeping Sickness Vectors*, 3 years, $176,780 **Allen E. Bale**, NIH, *Genetic Epidemiology of Early-Onset Basal Cell Carcinoma*, 2 years, $165,500 **Michael H. Bloch**, NIH, *Longitudinal Structural MRI Study of Adulthood Outcome in Tourette Syndrome*, 5 years, $902,154 • **Titus Boggon**, NIH, *Regulation of Polycystin-2 Channel Activity*, 4 years, $1,730,781 • **Angelique Bordey**, U.S. Army Medical Research Acquisition Activity (Department of Defense), *Understanding the Etiology of Tuberous Sclerosis Complex*, 3 years, $730,792 • **Richard Bucala**, NIH, *Defining Signatures for Immune Responsiveness by Functional Systems Immunology*, 1 year, $53,738 • **William B. Cafferty**, NIH, *Plasticity of Intact Circuits Restores Function after Spinal Cord Injury*, 3 years, $747,000 • **Michael J. Caplan**, Department of Defense, *A New Therapeutic Strategy for Autosomal Dominant Polycystic Kidney Disease: Activation of AMP Kinase by Metformin*, 3 years, $1,241,250 • **Sreeganga S. Chandra**, NIH, *The Physiological Functions of Synucleins*, 1 year, $1,851,531 • **Marek C. Chawarski**, NIH, *Behavioral Drug and HIV Risk Reduction Counseling with MMT in China*, 5 years, $3,123,146 • **Yung-Chi Cheng**, NIH, *Biochemical Pharmacology of Anti-HIV Compounds*, 5 years, $2,068,750 • **Tian H. Chi**, NIH, *Epigenetic CD4 Regulation Stability and Epimutations*, 11 months, $413,275 • **Elizabeth B. Claus**, NIH, *The Meningioma Consortium: Genome-Wide Association Study*, 3 years, $3,828,168 **Joseph E. Craft**, NIH, *Immune Response in Lupus*, 5 years, $2,146,502 • **Michael C. Crair**, NIH, *Neurobiology of Cortical Systems*, 5 years, $1,002,485 **Charles S. Dela Cruz**, NIH, *Molecular and Cellular Interaction Between Cigarette Smoke Exposure and RSV in the Lung*, 5 years, $669,600 • **Richard L. Edelson**, NIH, *Dermatology Training Grant*, 5 years, $1,629,774 • **Tore Eid**, NIH, *Glutamine Synthetase and the Mechanism of Seizures in Mesial Temporal Lobe Epilepsy*, 5 years, $1,810,155 • **Stephanie C. Eisenbarth**, NIH, *Role of the NLRP3 Inflammasome in Adaptive Immunity*, 5 years, $667,575 **Jack A. Elias**, NIH, *Training in Respiratory Biology and Pathobiology*, 5 years, $2,908,390 • **Veeraragavan P. Eswarakumar**, NIH, *Mechanisms of FGFR2 Signaling in Salivary Gland Branching Morphogenesis*, 5 years, $2,056,899 • **Erol Fikrig**, NIH, *Defining Signatures for Immune Responsiveness by Functional Systems Immunology*, 1 year, $210,864 **Harald G. Foellmer**, NIH, *Development of a Flavivirus E Protein Fusion Loop Vaccine*, 2 years, $165,500 **Brian W. Forsyth**, NIH, *Development of an International Guide to Monitor and Support Child Development*, 5 years, $2,583,807 • **Jorge E. Galán**, NIH, *Molecular Genetic Analysis of* Salmonella *Cell Invasion*, 5 years, $2,602,374 • **Mark B. Gerstein**, Department of Energy, *Tools and Models for Integrating Multiple Cellular Networks*, 2 years, $1,170,951 • **Michael Girardi**, NIH, *Local Immunoregulation of Carcinogenesis*, 5 years, $1,809,151 **Abha R. Gupta**, NIH, *Identification of Candidate Genes at the Synapse in Autism Spectrum Disorders*, 4 years, $681,027 • **David Hafler**, NIH, *Defining Signatures for Immune Responsiveness by Functional Systems Immunology*, 1 year, $2,430,086; NIH, *Costimulatory Mechanisms of Autoimmunity*, 5 years, $8,540,473; NIH, *Costimulatory Mechanisms of Autoimmunity*, 1 year, $2,859,450 • **Isaac E. Hall**, NIH, *Urinary Biomarkers for Recovery After Acute Kidney Injury and Prognosis in Hospitalized Patients*, 1 year, $65,841 • **Mark W. Hochstrasser**, NIH, *Predoctoral Program in Cellular and Molecular Biology*, 5 years, $11,541,618 **Dewan Syed Fahmeed Hyder**, NIH, *Multivalent PARACEST Agents for Quantitative Molecular Imaging*, 4 years, $1,347,079; NIH, *Translation of Smart Contrast Agents for Brain Tumor Characterization by MR*, 5 years, $1,613,701 • **Karl L. Insogna**, NIH, *Impact of a Protein Supplement on Bone Mass in Older Women*, 1 year, $424,412; NIH, *Role of CSF-1 in Osteoclast Function*, 1 year, $413,750 **Shuta Ishibe**, NIH, *Role of Focal Adhesion Kinase (Fak) in Nephrosis and Nephritis*, 5 years, $2,068,750 • **James D. Jamieson**, NIH, *Medical Student Training Program*, 5 years, $10,965,240 **Susan Kaech**, NIH, *Defining Signatures for Immune Responsiveness by Functional Systems Immunology*, 1 year, $210,200 • **Insoo Kang**, Department of the Army, *Studying the Role for CD4+ T Cell Subsets in Human Lupus*, 3 years, $1,241,250; Department of Defense, *Studying the Role for CD4+ T Cell Subsets in Human Lupus*, 3 years, $3,723,750 • **Barbara I. Kazmierczak**, NIH, *Innate Immune Responses to Type III Secretion System Components and Effectors*, 4 years, $1,799,161 • **Tae Hoon Kim**, NIH, *Analysis of Higher Order Chromatin Structures in Normal and Cancer Epigenomes*, 5 years, $1,717,065 • **Steven H. Kleinstein**, NIH, *Defining Signatures for Immune Responsiveness by Functional Systems Immunology*, 1 year, $241,804 • **Albert I. Ko**, NIH, *Disease Determinants of Urban Leptospirosis*, 5 years, $3,472,193; NIH, *Natural History of Urban Leptospirosis*, 4 years, $1,221,739 • **Diane S. Krause**, NIH, *MKL in Megakaryocytopoiesis*, 4 years, $1,443,989 **James F. Leckman**, NIH, *Training Program in Childhood Neuropsychiatric Disorders*, 5 years, $2,274,453 • **Csaba Leranth**, NIH, *Bisphenol A Effect on Primate Brain*, 2 years, $1,413,822 • **Ethan P. Marin**, NIH, *The Role of Protein Palmitoylation in Endothelial Cell Function*, 5 years, $673,650 **Graeme F. Mason**, NIH, *Ethanol as Fuel for the Brain in Rats*, 2 years, $439,405 • **Carolyn Mazure**, NIH, *Yale BIRCWH Scholar Program on Women's Health and Addictive Behaviors*, 5 years, $2,476,819 • **Sherry McKee**, NIH, *Does Tobacco Legislation Reduce Alcohol Consumption?* 2 years, $512,190 • **Ruth R. Montgomery**, NIH, *Defining Signatures for Immune Responsiveness by Functional Systems Immunology*, 1 year, $596,225 **Christopher Moore**, Agency for Healthcare Research and Quality/DHHS, *Identifying Unnecessary Irradiation of Patients with Suspected Renal Colic*, 4 years, $1,973,901 • **Michael H. Nathanson**, NIH, *Ca^{2+} Waves in Hepatocytes: Mechanisms and Effects*, 5 years, $2,396,796 • **Ingrid M. Nembhard**, Agency for Healthcare Research and Quality/DHHS, *Understanding the Implementation of New Practice in Health Care Organizations*, 10 months, $488,402 • **James Noonan**, NIH, *Identifying Enhancers with Human-Specific Developmental Functions*, 5 years, $3,352,861 • **Marcella Nunez-Smith**, NIH, *Measuring Racial/Ethnic Discrimination/Bias on Health Care Delivery*, 2 years, $395,959 • **Kevin Pelphrey**, NIH, *A fNIRS System to Further Research on Neurodevelopmental Disorders*, 1 year, $444,700 • **Francheska Perepletchikova**, Nat'l Inst. of Mental Health and Neuro Sciences (India), *Adapting Dialectical Behavior Therapy for Children with Suicidality and/or Self-Harm Behaviors: Pilot Randomized Clinical Trial with Maltreated Children in Foster Care*, 1 year, $180,074 • **Ismene L. Petrakis**, NIH, *Translational Neuroscience Research in Alcoholism*, 5 years, $1,072,316 • **Christopher Pittenger**, NIH, *Pathophysiologically Realistic Mouse Models of Neuropsychiatric Disease: Tourette Syndrome*, 5 years, $2,214,743 • **Katerina Politi**, NIH, *Mechanisms of Mutant Epidermal Growth Factor Receptor–Induced Lung Tumorigenesis*, 3 years, $810,141 **Lori A. Post**, Agency for Healthcare Research and Quality/DHHS, *ED Disability Diagnostic Tool: A HIT Feasibility Study*, 5 years, $2,485,754 • **Marc N. Potenza**, NIH, *Translational Research of Cocaine, Striatum, and Impulsivities*, 4 years, $3,834,967 **Vincent J. Quagliarello**, NIH, *Program of Research in Infectious Diseases of Elders*, 5 years, $671,625 **Yibing Qyang**, NIH, *Derivation and Functional Characterization of Heart Cells from Human Embryonic and Induced Pluripotent Stem Cells*, 5 years, $504,930 • **David L. Rimm**, NIH, *Predicting Metastasis in Melanoma*, 4 years, $1,505,671 **Jesse J. Rinehart**, NIH, *Investigation of Electrolyte Homeostasis via Quantitative Proteomics*, 5 years, $771,560 • **Scott A. Rivkees**, Food and Drug Administration, *Radioactive Iodide Therapy of Pediatric Graves' Disease*, 4 years, $1,600,000 **Joseph S. Ross**, NIH, *Impact of Publicly Reporting Hospital Outcomes Measures for Older Adults*, 3 years, $442,710 • **Douglas L. Rothman**, NIH, *13C MRS Studies of Human Brain Mitochondrial Metabolism in Healthy Aging*, 4 years, $2,052,625 **James E. Rothman**, NIH, *Mechanisms of Intracellular Membrane Fusion*, 5 years, $3,646,441 **Jonathan Saxe**, NIH, *Investigating the Role of a Novel PIWI-Interacting Protein in Spermatogenesis*, 2 years, $105,508 • **Richard S. Schottenfeld**, NIH, *INVEST Drug Abuse Research Fellowship*, 1 year, $39,000 • **William C. Sessa**, NIH, *Regulation of Vascular Remodeling and Angiogenesis by Nogo*, 5 years, $2,566,184 • **Albert C. Shaw**, NIH, *Defining Signatures for Immune Responsiveness by Functional Systems Immunology*, 1 year, $713,174 • **Haina Shin**, NIH, *Antigen-Specific CD8 T Cell Migration and Protective Immunity in Permissive and Restrictive Tissues*, 3 years, $143,670 **Satinder K. Singh**, NIH, *Transport and Inhibition in a Biogenic Amine Transporter*, 3 years, $741,325 **David L. Snow**, NIH, *Research Training Program in Substance Abuse Prevention*, 5 years, $1,542,175 **Daniel J. Spergel**, NIH, *Calcium Signaling in the Pubertal Activation of the GnRH Pulse Generator*, 15 months, $17,928 • **Thomas A. Steitz**, NIH, *Structures of DNA and RNA Polymerases and Functional Complexes*, 4 years, $1,871,229 • **Hanna E. Stevens**, NIH, *Prenatal Stress and the Development of Inhibitory Neurons in the Forebrain*, 5 years, $870,435 • **Stephen M. Strittmatter**, NIH, *Prion Protein in Alzheimer's Disease Pathophysiology*, 5 years, $1,696,375 • **Nancy E. Suchman**, NIH, *Fostering Mothers' Emotionally Responsive Parenting*, 5 years, $2,108,700 • **Patrick Sung**, NIH, *DNA Repair Genes and Proteins of the RAD52 Group*, 5 years, $2,124,273 • **Joann B. Sweasy**, NIH, *DNA Polymerase Beta Variants in Cancer*, 5 years, $2,021,612 • **Hemant D. Tagare**, NIH, *Fast 3D Reconstruction Algorithms for Cryo-EM*, 4 years, $1,666,512 • **Elisabetta Ullu**, NIH, *RNA Metabolism in Trypanosomes*, 5 years, $3,953,019 • **Emily Wang**, NIH, *Improving Cardiovascular Outcomes in Individuals with a History of Incarceration*, 5 years, $689,855 • **Sherman M. Weissman**, NIH, *Transcriptome and Methylome Analysis of Single Cells*, 2 years, $455,177 • **Lynn D. Wilson**, NIH, *Racial Disparities in Clinical Outcomes and the Therapeutic Use of Radiotherapy for Patients with Cutaneous Lymphoma*, 1 year, $82,750 • **John J. Wysolmerski**, NIH, *Function of the Calcium Sensing Receptor in the Breast*, 5 years, $1,623,595 **Andrew Xiao**, NIH, *A Novel Enzymatic Activity of WSTF and its Role in Tumorigenesis*, 3 years, $747,000 • **Kimberly A. Yonkers**, NIH, *Project START: Screening to Augment Referral to Treatment*, 5 years, $3,541,448 • **Herbert Yu**, NIH, *Epidemiologic Study of Hepatocellular Carcinoma in the U.S.*, 5 years, $6,987,938 • **Yongli Zhang**, NIH,*Single-Molecule Manipulation of SNARES*, 5 years, $1,551,550 • **Heping Zhang**, NIH, *Research Training in Mental Health Epidemiology*, 5 years, $2,243,687 • **Yong Zhu**, NIH, *Can Shift-Work Shift Epigenetic Patterns?* 2 years, $445,035 • **Lingjun Zuo**, NIH, *Deep Sequencing of CNR1 Gene Network in Substance Dependence*, 5 years, $909,090

Non-Federal

Vikki M. Abrahams, American Heart Association, *Effect of Antiphospholipid Antibodies on Trophoblast Function and Vascular Remodeling in Pregnant APS Patients*, 3 years, $196,405 • **Amy M. Ahasic**, Cystic Fibrosis Foundation, *Cystic Fibrosis Center*, 1 year, $26,980 • **Jeremy Baskin**, Jane Coffin Childs Memorial Fund, *Investigation of a Protein Complex Implicated in P14P Synthesis in the Brain*, 3 years, $143,500 • **Ariel Bazzini**, Pew Latin American Fellows Program, *Regulation of the Maternal to Zygotic Transition in Zebrafish*, 4 years, $65,000 • **Michael H. Bloch**, American Academy of Child and Adolescent Psychiatry, *Double-Blind, Placebo-Controlled Trial of N-acetylcysteine for Childhood Tourette Syndrome*, 2 years, $60,000 • **Daniel J. Boffa**, CALGB Foundation, *Evaluation of Novel Molecular NSCLC Classification System*, 1 year, $33,000 • **Elizabeth H. Bradley**, Commonwealth Fund, *All-Cause Hospital Readmission Rate for Patients with Heart Failure and Acute Myocardial Infarction: What Hospital Practices Make a Difference and How Are They Adopted?* 2 years, $390,850; South Essex Partnership NHS Foundation Trust, *SEPT Leadership Workshop*, 1 year, $140,000 • **Joseph Brennan**, Abbott Laboratories Inc., *Cardiovascular Training Fellowship Grant*, 1 year, $34,434 **Ketan R. Bulsara**, Stryker Instruments, *Skull Base Cerebrovascular Dissection Fund*, 1 year, $7,700 **Jessica A. Cardin**, Esther A. & Joseph Klingenstein Fund, *Distinct Sources of Inhibition Differentially Regulate Cortical Activity*, 1 year, $50,000; Whitehall Foundation, Inc., *Role of Inhibition in Visual Gain Modulation and Perception*, 3 years, $225,000 • **Tobias Carling**, Doris Duke Charitable Foundation, *Systematic Analysis of Human Endocrine Tumor Genomes*, 3 years, $255,000; Damon Runyon Cancer Research Foundation, *Molecular Genetics of Endocrine Tumor Disease*, 3 years, $225,000 • **Anees Chagpar**, University of Louisville, *Louisville Breast Cancer Update*, 1 year, $7,108 **Jaehyuk Choi**, Dermatology Foundation, *Genetic Screen for Tumor Suppressors in Mouse Skin Using PiggyBac Transposon Mutagenesis*, 1 year, $30,000 **Jennifer N. Choi**, Dermatology Foundation, *Isotretinoin Versus Doxycycline as Preemptive Therapy for EGFR Inhibitor–Induced Papulopustular Rash*, 1 year, $20,000 • **Chuhan Chung**, National Pancreas Foundation, *Regulation of Pancreatic Fibrotic Responses by Pigment Epithelium-Derived Factor (PEDF)*, 1 year, $44,516 • **Gary W. Cline**, Medical College of Georgia, *Database Mining of Phenotype Induced by High-Fat Diets*, 1 year, $3,000 • **Susan R. Compton**, ACLAM Foundation, *Assessment of Risk of Transmission of Mouse Parvovirus from Immunodeficient C57BL/6 Mice*, 1 year, $30,000 • **William E. Damsky**, Joanna M. Nicolay Melanoma Foundation, Inc., *Joanna M. Nicolay Melanoma Foundation Award*, 1 year, $10,000 • **Kamil Detyniecki**, National EpiFellows Foundation, *Patient Recognition of Seizures During In-patient Video-EEG Monitoring*, 1 year, $19,000 • **Kavita Dhodapkar**, Charles A. Dana Foundation, Inc., *Targeting Human Glioma Stem Cells via Dendritic Cells*, 3 years, $200,000 **Xuemei Dong**, Arthritis Foundation, *The Transcription Factor Mash2 in Follicular Helper T Cell Differentiation*, 2 years, $100,000 • **Jamie L. Duke**, PhRMA Foundation, *Computational Modeling of Genome-Wide Targeting of Somatic Hypermutation*, 2 years, $33,333 • **Ronald S. Duman**, Repligen Corporation, *Influence of Uridine on Behavior in the Forced Swim Test*, 1 year, $19,569 • **Daniel R. Duncan**, Howard Hughes Medical Institute, *Elucidating the Role of PDGF in Neovessel Formation*, 1 year, $27,000 • **E. Jennifer Edelman**, Society of General Internal Medicine, *Prescription Opioids and their Impact on Quality of Life, HIV Progression, and CART Adherence*, 1 year, $5,000 • **Paul S. El-Fishawy**, American Academy of Child and Adolescent Psychiatry, *A Pilot Study of Whole-Exome Sequencing and Homozygosity Mapping in the Identification of Genes that Contribute to Autism*, 15 months, $15,000 • **Gerald Friedland**, Albert Einstein College of Medicine, *Impact of HIV Co-Infection and TB Genotype on Treatment Outcomes in MDR*, 1 year, $108,069 • **Anna-Rachel Gallagher**, American Heart Association (Founders Affiliate), *The Role of Fibrocystin in Wnt signaling and Mechanism of Repair*, 3 years, $231,000 **Mark B. Gerstein**, Brigham and Women's Hospital, *Analysis of Patterns of Structural Variation in the 1,000 Genomes Data Set*, 21 months, $442,594 **Daniel R. Goldstein**, American Society of Transplantation, *Nanoparticles: A Novel Approach to Deliver Tolerogenic Agents in Experimental Transplantation*, 1 year, $40,000 • **Jose L. Gomez-Villalobos**, Aerocrine Inc. USA, *Characterize the Relations Between FENO and Asthma Severity in the YCAAD Cohort*, 1 year, $25,000 • **Christopher H. Gottschalk**, Teva Pharmaceuticals USA, *Multiple Sclerosis Fellowship-TEVA*, 1 year, $50,000 • **Jeffrey Grotzke**, Cancer Research Institute, Inc., *Membrane Receptors and Associated Signaling Pathways in Cross-Presentation*, 3 years, $144,000 **David Hafler**, Brigham and Women's Hospital, *TIM Family of Genes: Role in T Cell Immunity and Tolerance: Project 2*, 3 years, $862,257

Marc Hammarlund, Ellison Medical Foundation, *Mechanisms of Age-Related Decline in Axon Regeneration*, 4 years, $400,000 • **Jonas O. Hannestad**, Nancy Taylor Foundation for Chronic Diseases, Inc., *Glutamate Receptor Type 5 During Interferon-Alpha Treatment of Hepatitis C*, 2 years, $218,040 • **Jorge Henao-Mejia**, Leukemia and Lymphoma Society, *Role of the MicroRNA-181 Family in Hematopoiesis and Leukemopoiesis*, 3 years, $162,100 • **Gretchen Hermes**, American Psychiatric Institute for Research and Education, *Psychosocial Regulation of Mood Disorders: Translational Models of Depression*, 1 year, $2,500 **Kevan Herold**, Juvenile Diabetes Research Foundation International, *IL-1RA and Oral Insulin on Reversal of Diabetes in NOD Mice*, 1 year, $88,000 **Yoko Ibuka**, Social Science Research Council, *Cost-Effective Strategies of Influenza Vaccination in the U.S. and Japan*, 1 year, $55,931 • **Shuta Ishibe**, Satellite Healthcare, Inc., *The Role of Synaptojanin-1 in Regulation Podocyte Homeostasis*, 3 years, $150,000 • **Roger J. Jou**, Pfizer Inc., U.S. Pharmaceuticals Group, *The Neural Basis of Weak Central Coherence in Autism Spectrum Disorders*, 1 year, $32,500 • **Nina Kadan-Lottick**, American Cancer Society, Inc., *Comparing Two Models of Cancer Survivorship Care: A Randomized Trial*, 4 years, $720,000 • **Anil K. Karihaloo**, American Heart Association (Founders Affiliate), *Understanding the Role of Chemokine Receptor CXCR4 in Kidney Development*, 3 years, $198,000 • **Barbara I. Kazmierczak**, Mayo Foundation, *Evaluating Innate Immune Responses to* Staphylococcus aureus *Acquisition and Carriage in Cohorts of Persistent Carriers and Non-Carriers*, 10 months, $100,000 • **Robert D. Kerns**, The Mayday Fund, *Implementing a VA Stepped Care Model of Pain Management*, 5 years, $400,000; Patrick and Catherine Weldon Donaghue Medical Research Foundation, *Implementing a VA Stepped Care Model of Pain Management*, 5 years, $400,000 **Ami Klin**, Simons Foundation, *Brain-Behavior Growth Charts of Altered Social Engagement in ASD Infants*, 3 years, $751,048 • **Felix Knauf**, National Kidney Foundation, *Molecular Physiology of Urinary Oxalate Excretion*, 2 years, $100,000 • **Narae Ko**, American Society of Nephrology, *Transepithelial Oxalate Transport in the Proximal Tubule of Kidney*, 11 months, $25,500 **Harlan M. Krumholz**, Robert Wood Johnson Foundation, *The RWJF Clinical Scholars Program CORE Grant, 2010–2012*, 2 years, $1,035,425; Robert Wood Johnson Foundation, *The RWJF Clinical Scholars Program Cohort Grant, 2010–2012*, 2 years, $1,020,995; Robert Wood Johnson Foundation, *The RWJF Clinical Scholars Program: 3rd year Cohort (2010–2011)*, 1 year, $98,875 **David S. Lee**, American Society for Clinical Pharmacology and Therapeutics, *Development of Risk Prediction Models in Older Adults on Antihypertensive Medications for Cardiovascular and Falls Outcomes*, 1 year, $35,000 • **Mathieu Lemaire**, Kidney Foundation of Canada, *Novel Insights into Proximal Tubule Function: Finding Novel Disease-Causing Genes in a Large Cohort of Patients with Dent's Disease Without Mutation in CLCN5 or OCRL1 Using Whole-Exome Capture*, 3 years, $195,000 • **Chiang-Shan Li**, Tourette Syndrome Association, Inc., *Cognitive Motor Control in Tourette Syndrome: Subcortical Noradrenergic Processes*, 1 year, $75,000 • **Yilun S. Liu**, Elsa U. Pardee Foundation, *Elucidation of the Molecular Basis of RECQ4 Deficiency in Cancer Pathogenesis*, 1 year, $100,000 • **Charles J. Lockwood**, Eastern Connecticut Health Network Services, Inc., *Eastern Connecticut Health Network, Inc. Oncology Affiliated Hospital Agreement FY10*, 5 months, $7,500 • **Nils Loewen**, Lumenis Ltd., *Selective Laser Trabeculoplasty Repeatability*, 15 months, $10,000 **Xiaomei Ma**, Regents of the University of California, *Environmental and Molecular Epidemiology of Childhood Leukaemia*, 1 year, $5,989 • **John D. MacMicking**, Crohn's and Colitis Foundation of America, *Functional Importance of Immunity-Related GTPases in IBD Development*, 3 years, $386,100 • **Una Makris**, American College of Rheumatology, *Epidemiology of Restricting Back Pain in Older Persons*, 2 years, $153,000 • **Robert W. Makuch**, IMD Marketing Consulting Co., Ltd, *Yale University: Food, Drug & Medical Device Administration Training*, 6 months, $64,300 **Jaime G. Maldonado-Aviles**, Hilda and Preston Davis Foundation, *Role of the Prefrontal Cortex and Related Molecular Mechanisms in Altered Feeding Behaviors*, 3 years, $165,000 • **Lisa M. Mattei**, American Heart Association (Founders Affiliate), *Control of Lymph Node Vascular Growth by CD4 T Cells*, 2 years, $44,000 • **James C. McPartland**, Simons Foundation, *Brain–Behavior Growth Charts of Altered Social Engagement in ASD Infants*, 3 years, $245,205 • **Charlotte Mitchell**, American Lung Association, *Interferon-Gamma Effects on the Airway Epithelium Modulate Lung Disease*, 1 year, $65,000 • **Masahiro Murakami**, American Heart Association, *Mechanisms of Heart Failure Development in Mice Lacking Cardiomyocyte FGF Signaling*, 4 years, $308,000 • **Thomas S. Murray**, Charles H. Hood Foundation, *The Role of Lactate Metabolism in* P. aeruginosa *Biofilm Formation*, 2 years, $150,000 **Marcella Nunez-Smith**, Josiah Macy Jr. Foundation, *Promotion and Retention of Diversity in Medical Education (PaRoDime)*, 2 years, $250,000 **Haakon B. Nygaard**, American Foundation for Aging Research, *The Role of Cellular Prion Protein in Beta-Amyloid-Induced Epilepsy and Early Death in Alzheimer's Disease Mouse Model*, 1 year, $50,054 **Lynda U. Odofin**, University of Vermont, *Prevalence of* Clostidium difficile (C. diff.) *in Connecticut Swine Farms*, 17 months, $12,520 • **A. David Paltiel**, Massachusetts General Hospital, *The Cost-Effectiveness of Preventing HIV Complications*, 1 year, $20,788 • **Alexander Panda**, Brookdale Foundation Group, *Dendritic Cell Immunoscenescence: Characterizing TLR Function of Human Dendritic Cells in the Elderly*, 2 years, $175,911 • **Eon Joo Park**, American Heart Association (Founders Affiliate), *Role of Nogo-B and NgBR in Vascular Function and Cholesterol Homeostasis*, 2 years, $83,000 **In-Hyun Park**, Charles H. Hood Foundation, *Investigation of Functional Myogenic Progenitors from Reprogrammed IPS cells for Duchenne Muscular Dystrophy*, 2 years, $150,000 • **Anup Patel**, Plastic Surgery Educational Foundation, *A Novel Approach to Measuring the Impact of Surgery in Craniosynotosis with ERPS*, 1 year, $10,000 • **Rhea Paul**, International Society for Autism Research, *Slifka/Ritvo Innovation in Autism Research*, 1 year, $12,500 • **Kevin Pelphrey**, Simons Foundation, *Brain–Behavior Growth Charts of Altered Social Engagement in ASD Infants*, 3 years, $503,747 **Jamy Peng**, American Cancer Society, Inc., *Molecular Mechanism of Gene Regulation by Polycomb Proteins*, 14 months, $62,461 • **Marc N. Potenza**, University of Maryland, *Genetic Contributions to Adolescent HIV Risk Behavior*, 5 years, $401,307 **Peter M. Rabinowitz**, Mary Imogene Bassett Hospital, *Infection Risk in Swine Workers*, 1 year, $14,999 • **Ziba Razinia**, American Heart Association, *Characterization of the Role of Filamins, Important Regulators of Cardiovascular Development, in Cell Migration* 2 years, $44,000 **Anamika M. Reed**, American Gastroenterological Association, *The Role of Pathologic Calcium Signaling in Low pH Effects in the Pancreatic Acinar Cell*, 2 years, $80,000 • **Michael Robek**, Sunshine Lake Pharma Co., Ltd, *Anti-HBV Activity of GLS4 In Transgenic Mice*, 9 months, $99,563 • **Robert M. Rohrbaugh**, Gilead Foundation, *Gilead Didactic Curriculum and Clinical Elective FY11*, 1 year, $200,000 • **Neil D. Romberg**, Clinical Immunology Society, *Functional Defects and Molecular Compensation in the B Cells of Patients Carrying TAC1 Mutations*, 1 year, $30,000 • **Joseph S. Ross**, American Federation for Aging Research, *AFAR*, 3 years, $252,183 • **Jennifer P. Ruger**, Greenwall Foundation, *Ethical Issues in Health Policy*, 3 years, $232,073 • **Christian Schlieker**, Ellison Medical Foundation, *Deciphering the Nuclear Quality Control Network and its Relation to Aging*, 4 years, $400,000; Charles H. Hood Foundation, *Investigating Nuclear Envelopathies from the Perspective of Protein Quality Control*, 2 years, $150,000 **Amy R. Schwartz**, New York University School of Medicine, *Tailoring Clinical Guidelines to Comorbidity*, 8 months, $57,994 • **Ambika R. Shenoy**, Cystic Fibrosis Foundation, *CFTR Function in Macrophages and Neutrophils*, 1 year, $68,250 **Robert S. Sherwin**, American Diabetes Association, Inc., *CNS Responses to Hypoglycemia in Diabetes*, 2 years, $81,000 • **Warren D. Shlomchik**, University of Pittsburgh, *Peripheral Mechanisms of Immunologic Tolerance*, 1 year, $812,961 **Francesco Strino**, American-Italian Cancer Foundation, *Development of Complex System Tools for Fingerprinting Subclonal Tumor Composition*, 1 year, $35,000 • **Zhaoxia Sun**, American Cancer Society, Inc., *Functional Connections Between the Tor Pathway and the Cillium in Zebrafish*, 4 years, $720,000 • **Grace C. Teng**, Cancer Research Institute, Inc., *Genome-wide Mapping of RAG1 and RAG2 Protein Binding*, 3 years, $141,000 • **Mary E. Tinetti**, American Federation for Aging Research, *2010 Competitive National CoE Program Award Application*, 1 year, $123,921 • **Robert J. Tomko**, American Cancer Society, Inc., *American Cancer Society New England Division: Massachusetts Biotechnology Council Cancer Research Challenge, Millennium: The Takeda Oncology Company Postdoctoral Fellowship*, 3 years, $150,000 • **Lucy A. Truman**, University of Edinburgh, *Do Pro-Inflammatory T Cells Home to Tertiary Lymphoid Organs in Sjögren's Disease and Cultivate Lymphoma?* 1 year, $104,130 • **Amelia Villagomez**, American Psychiatric Association, *APA Fellowship*, 1 year, $34,470 • **Narendra Wajapeyee**, American Association for Cancer Research, *Understanding the Mechanisms of BCR-ABL-Mediated Transformation*, 2 years, $100,000 • **Jason S. Weinstein**, Arthritis Foundation, *T Follicular Help Cells in Immunity and Autoimmunity*, 2 years, $100,000 **Sherman M. Weissman**, University of Massachusetts, *HOX Cluster Intergenic Non-Coding RNAs in Myeloid Differentiation and Function*, 4 years, $1,765,487 • **Carol C. Weitzman**, Lulac Head Start Inc., *Lulac Head Start*, 1 year, $30,000 **Marney A. White**, American Heart Association, *Internet-Administered Smoking Cessation Treatment for Overweight and Obese Smokers*, 3 years, $197,659 • **Robert I. White**, University of California, San Francisco, *Rare Diseases Clinical Research Consortia (RDCRC) for the Rare Disease Clinical Research Network*, 1 year, $82,251 • **Yong Xiong**, Alex's Lemonade Stand, *Elucidating the Initiation Mechanism of the Fanconi Anemia Pathway of DNA Damage Repair*, 2 years, $200,000 • **Yang Yang**, American Federation for Aging Research, *Nicotinic Restoration of Prefrontal Cortex Physiology in Aged Monkeys*, 1 year, $45,710 • **James J. Yue**, Orthopaedic Research and Education Foundation, *Yale Comprehensive Spine Fellowship*, 1 year, $69,500

// Li Ka Shing *(from page 1)* treat neuromuscular and liver diseases.

The contribution will also significantly enhance the DNA sequencing capabilities of the YSCC's genomics core. Genomics has become central to biology in recent years, and the field of stem cell research is no exception.

"Stem cell study is becoming increasingly a study at the genetic level and epigenetic level," Lin says. "Now you need to use deep sequencing to look at the entire genome, instead of just one of your favorite genes."

The LKSF donation has funded the replacement of the core's Illumina sequencer with a newer model, as well as the hiring of a new research associate and the enhancement of analytical software—improvements that Lin says will increase the core's sequencing output threefold.

These changes will benefit not only Yale faculty conducting stem cell research, but also graduate students and postdoctoral fellows, and visiting scientists from elsewhere in Connecticut who make use of the core's DNA sequencing abilities.

Haifan Lin

One such project is research by Jun Lu, PH.D., assistant professor of genetics, on the role of non-coding RNAs in development and disease, which relies on the deep genome sequencing that the new Illumina sequencer will enable. The availability of deep sequencing will also allow Andrew Xiao, PH.D., assistant professor of genetics, and colleagues to examine the entire genome in his research on chromatin, a DNA–protein complex that controls the genome's integrity. A third example is Lin's own work in understanding the role that bits of genetic material called small RNAs play in stem cell biology.

Lin studies how piRNAs, a class of small RNAs discovered in his lab, guide epigenetic factors to specific points within the genome. "We've now found over 60,000 of these RNAs," Lin says. "To study these RNAs, the only effective way is to use this deep sequencing."

An additional benefit of the donation, Lin says, derives from the LKSF's status as a private foundation. The use of federal funding, such as grants awarded by the National Institutes of Health (NIH), is restricted to certain lines of stem cells approved by the U.S. government; these grants cannot be used to fund work on other cell lines. However, "very often these non-NIH-approved cell lines are much more important and better than the few government-approved lines," Lin says. "This donation really gives us a huge advantage."

Dean and Ensign Professor of Medicine Robert J. Alpern, M.D., says, "We're delighted that the Li Ka Shing Foundation has chosen to support Yale's Stem Cell Center. One of the key features of the center is its ability to offer core services that enhance stem cell research across the university. This donation will allow these cores to provide the most up-to-date equipment and services."

The Hong Kong–based LKSF was founded in 1980 by global entrepreneur and philanthropist Li Ka-shing. The LKSF supports projects that propel social progress and create a cycle of charity in the world by expanding access to quality education and health care, encouraging cultural diversity and exploration, and stimulating community involvement and sustainable development. To date, the foundation has given approximately $1.6 billion in charitable donations.

Through ventures in a variety of industries, including container terminals, telecommunications, retail, real estate, hotels, infrastructure, and energy, Li Ka-shing has built a $26 billion fortune that makes him the 11th wealthiest person in the world, according to *Forbes* magazine. In 2006, Li pledged to donate one third of his fortune, or about $10 billion, to philanthropic projects. Li, who has two sons, is known to refer to the LKSF as his "third son."

"This is a wonderful contribution from LKSF, and reflects the visionary insight of its founder about what's needed to effectively promote stem cell research," says Lin, "and it is a demonstration of the important role of philanthropists in science."

Benefactors of Boyer Center receive medical school's highest honor

In April, Herbert Boyer, PH.D., a towering figure in molecular medicine for almost 50 years, and his wife, Marigrace, received the Peter Parker Medal, the medical school's highest honor, for their outstanding contributions to the School of Medicine.

The award presentation was an anniversary of sorts, as it has been 20 years since the dedication of the Boyer Center for Molecular Medicine, one of the medical school's most important research buildings. Boyer, who was a postdoctoral fellow at the School of Medicine from 1963 to 1966, made the construction of that building possible with a $10 million gift, given in gratitude to Yale for helping him start his research career.

"The Boyer Center has been critical to the medical school during the past two decades, and its twentieth year marked the time to honor Herb and Grace Boyer with the Peter Parker Medal," says Dean Robert J. Alpern, M.D., Ensign Professor of Medicine.

As a doctoral student at the University of Pittsburgh in the early 1960s, Boyer wrote to Edward A. Adelberg, PH.D., then chair of the Department of Microbiology at the School of Medicine, to ask for bacterial strains he needed for an experiment. Within a week, the strains were in the mail and a scientific collaboration had begun. In 1963 Boyer came to Yale as a postdoc in Adelberg's lab.

"The fruit of my career," said Boyer at an award ceremony held in the Medical Historical Library, "dates back to Ed Adelberg and my association with him."

Boyer's greatest contribution to medicine came after he met Stanley Cohen, PH.D., a Stanford professor, at a conference in Hawaii. Boyer had found a way to use enzymes to cut snippets of DNA that maintained their genetic code and could be spliced onto other bits of DNA. Once inserted into circular strands of DNA known as plasmids, which Cohen was studying, Boyer's snippets could be inserted into bacteria, which could then produce a desired protein in large quantities.

This technology—which Boyer and Cohen used to develop recombinant insulin by inserting human genes into *E. coli* bacteria—launched the biotech industry, and opened the door to later developments in genetic engineering and gene therapy. With venture capitalist Robert Swanson, they formed Genentech, now a leader in the pharmaceutical industry.

TERRY DAGRADI

Herbert and Marigrace Boyer are presented with the Peter Parker Medal by Dean Robert Alpern.

"Herb had the incredible good sense to apply recombinant technology to develop treatments that would make people better, and he was able to create recombinant insulin and recombinant growth hormones," Alpern said. Boyer broke boundaries not only in science, Alpern noted, founding his company when academic scientists considered alliances with business the equivalent of "embracing the dark side." Now, Alpern said, it is common practice.

Boyer was also prescient in another way. "Now we all talk about interdisciplinary science," Alpern said. "Twenty years ago it wasn't obvious that it was the way to go—the Boyer Center was a collection of faculty from many different departments, all working together on many different problems."

In his brief remarks, Boyer paid tribute to his mentor, Adelberg, who died in 2009. "Not only was he a fine scientist, but he was a gentleman of the first order," Boyer said. Under Adelberg's tutelage, Boyer continued, he discovered how he wanted to spend his career. "I appreciate all the things that happened here at Yale."

Expert on food-borne infectious bacteria is recognized with a top microbiology prize

Jorge Galán, PH.D., D.V.M., the Lucille P. Markey Professor of Microbial Pathogenesis, has won the 2011 Robert Koch Award, one of the highest honors in microbiology, for his work on the mechanisms of infection by food-borne pathogens such as *Salmonella* and *Campylobacter*. These bacteria cause millions of cases of infectious gastroenteritis worldwide each year, a major public health burden in both industrialized and developing countries.

Jorge Galán

"With his fundamental research on mechanisms of bacterial pathogenesis [Galán] contributed substantially to the foundation of cellular microbiology as a scientific field," stated the award citation from the Robert Koch Foundation, based in Berlin, Germany.

Galán chairs the School of Medicine's multidisciplinary Section of Microbial Pathogenesis, in which faculty with expertise in genetics, immunology, and cell biology study pathogenic microbes.

He and members of his lab study the molecular "cross-talk" that occurs between pathogens and their hosts during infection. Galán is particularly well-known for his studies of a bacterial nanomachine known as the type III secretion system, which many pathogenic bacteria use to deliver virulent proteins into host cells. Understanding this nanomachine could lead to a new classes of vaccines and antimicrobials to prevent many important bacterial infections.

The Robert Koch Award, which includes a prize of 100,000 euros, is named in honor of the German physician who formulated Koch's postulates, the first systematic criteria guiding research on microbial diseases.

Koch, one of the founders of the field of microbiology, was awarded the 1905 Nobel Prize in Physiology or Medicine for his seminal work on tuberculosis and other infectious diseases.

Leader in blood vessel biology and disease is appointed as Alfred Gilman Professor

William C. Sessa, PH.D., a leading researcher on blood vessel function and vascular disease, has been designated as Alfred Gilman Professor of Pharmacology.

William Sessa

Sessa's research focuses on the vascular endothelium, cells that line all blood vessels and form the largest endocrine organ in the human body.

His laboratory is investigating the factors, including genes, that can cause dysregulation of the endothelium and contribute to cardiovascular diseases, such as atherosclerosis, and other diseases. He is also using proteomics techniques to discover novel proteins that may regulate blood vessel function.

Sessa earned his PH.D. at New York Medical College and was a postdoctoral fellow and senior scientist at the William Harvey Research Institute at St. Bartholomew's Hospital Medical College in London.

Sessa joined the Yale faculty in 1993 as an assistant professor of pharmacology, and has been a full professor at the School of Medicine since 1999. He serves as director of the interdepartmental Vascular Biology and Therapeutics Program, and as vice chair of the Department of Pharmacology.

Sessa has authored or co-authored more than 200 research articles or papers.

His numerous honors include the American Heart Association's Established Investigator Award; the Young Alumnus Award from the Philadelphia College of Pharmacy and Sciences; the American Society of Pharmacology and Experimental Therapeutics' John J. Abel Award in Pharmacology; a MERIT Award from the National Institutes of Health; the Robert M. Berne Distinguished Lectureship from the American Physiological Society; and the William Harvey Medal.

// Gilead *(from page 1)* Linda Slanec Higgins, PH.D., vice president, biology.

"Yale's faculty in this partnership bring critical, complementary skills to form an optimal team," says Alpern. "Tom Lynch brings experience in clinical trials, Rick Lifton has been a leading innovator in genetics and genomics, and Yossi Schlessinger has unparalleled success in cancer drug development."

Gilead's Chief Scientific Officer, Norbert W. Bischofberger, PH.D., executive vice president, research and development, says that pairing with Yale dovetails well with the company's current focus on oncology. "Based on the strong track record of the Yale cancer research team, I am confident this collaboration will lead to important advances in the understanding of the genetic basis of cancer as we collectively seek to develop novel targeted therapies for patients in areas of unmet medical need."

Jaffe says that the collaboration was inspired because "Yale had succeeded in bringing together a critical mass of fantastic talent" in genomics, drug development, clinical trials, and personalized medicine. He agrees with Alpern that Schlessinger is an ideal leader for the initiative, because of his role in the development of two of the most significant targeted cancer therapies of recent years: Sutent, a treatment for stomach and kidney cancers, and PLX-4032, a compound that has had unprecedented success in the treatment of malignant melanoma, one of the deadliest and most intractable cancers. (PLX-4032 is expected to receive FDA approval in the coming months.) "Dr. Schlessinger has a pedigree that is unique," says Jaffe. "He's been intimately involved in the creation of two transformative medications."

In the collaboration, tumor samples will be analyzed to identify gene mutations that disrupt normal cellular functions and promote the uncontrolled cell growth and metastasis seen in cancer. Mutations are believed to underlie the development of drug resistance in cancer, and the team will explore this phenomenon as well. Next, the painstaking process of crystallizing the mutated protein to discern its structure begins, with the aim of revealing sites where drug molecules or antibodies can block cells' aberrant behavior. After a compound is refined for maximum effectiveness, it can be tested in animals, and finally in humans. Genomics may then enter the picture again to determine the profile of each patient's tumors to create personalized therapies.

"When we find cancer targets that are new, we will work with Gilead on designing drugs, which they can then test in the clinic," Schlessinger says. "This is a tremendous opportunity for Yale and Gilead."