Medicine@Yale

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Gift brings personalized cancer therapy a step closer to reality

When Roy S. Herbst, M.D., PH.D., joined Yale as professor of medicine, associate director for translational research, and chief of medical oncology at Smilow Cancer Hospital at Yale-New Haven last March, his arrival was seen as an important step toward the vision Yale Cancer Center (YCC) Director Thomas J. Lynch, M.D., had begun articulating in 2009.

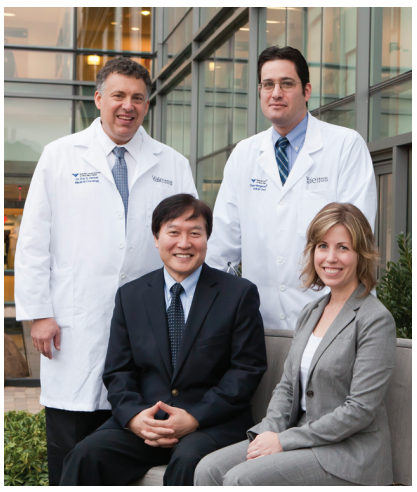
That vision centers on "personalized" cancer treatment—therapy regimens tailored to individual patients' tumors based on DNA sequencing of tissue biopsies. That vision is now closer to becoming a reality thanks to the generosity of David B. Heller, a grateful former patient of Herbst's.

Prior to joining Yale's faculty, Herbst was professor and chief of the Section of Thoracic Medical Oncology at MD Anderson Cancer Center at the University of Texas in Houston. At MD Anderson, Herbst met Heller, a patient from Chicago, Ill., who had been diagnosed with lung cancer and referred to Herbst. "We got to know each other as I advised him on his care, helped him with his diagnosis, and talked about different protocols and treatments," Herbst says.

Although Herbst left MD Anderson and Heller continued his treatment at Northwestern University in Chicago, the two maintained a close relationship. Now through the Diane and David B. Heller Charitable Foundation, Heller and his wife, Diane, have made a $1 million gift to support Herbst's efforts to advance translational research and cancer treatment at Yale.

The gift will support efforts that Herbst, an expert in lung cancer research and clinical care, has been leading for some time. Over the last several years, Herbst has spearheaded clinical studies of many anticancer drugs. His work using erlotinib (Tarceva) in combination with bevacizumab (Avastin) was among the first to combine multiple targeted agents for non-small cell lung cancer (NSCLC). As co-principal investigator of the multifaceted Biomarker-Based Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE-1) trial,

// Cancer *(page 4)*



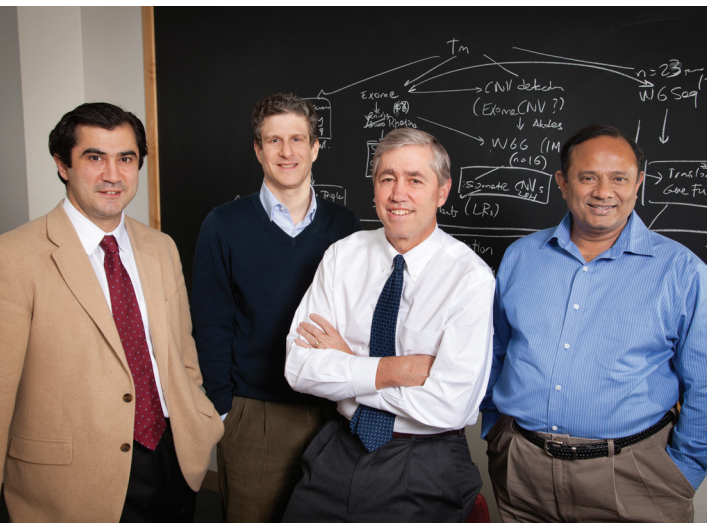
TERRY DAGRADI

(From left) Roy Herbst, pictured with colleagues Peter Koo, Daniel Morgensztern, and Julie Boyer, is spearheading efforts in personalized treatments for cancer.

Center will study rare genetic diseases

$11 million grant makes Yale home to one of three national centers tasked with unraveling the genetic causes of rare inherited diseases

For complex diseases like cancer and diabetes, there's no crystal ball that can tell you for sure whether you'll develop the illness during your lifetime. A tangled interplay between your environment, your behaviors, and the genes you inherited from your parents determines your risk of such diseases. But for some disorders—dubbed Mendelian—a mutation in a single gene is the direct and clear-cut cause of disease. And the inheritance patterns of Mendelian disorders are also straightforward, but discovering the genes responsible for these inherited diseases is not always easy.



HAROLD SHAPIRO

(From left) Murat Günel, Mark Gerstein, Richard Lifton, Shrikant Mane, and colleagues at the Center for Mendelian Genomics at Yale will use next-generation sequencing tools to study the genetic causes of inherited diseases.

More than 6,000 rare Mendelian disorders (defined by Congress as disorders affecting fewer than 200,000 Americans) have been identified. Some, such as cystic fibrosis, are well-known, but many others affect only a handful of individuals. The fewer patients with a disease, the harder it is to study, because of limited funding and limited genetic samples to compare, and scientists have so far found the genetic cause of only about half of the known Mendelian disorders. But all together, these rare diseases afflict 25 million individuals in the U.S., and uncovering their genetic causes could not only lead to treatments for these disorders, but would bring broader insights into human biology that may aid our understanding of common diseases. For example, by studying familial hypercholesterolemia, a Mendelian disorder causing very high cholesterol levels, scientists have developed new ways to treat more common causes of high cholesterol.

Now, a four-year, $11.2 million grant from the National Institutes of Health has established the Center for Mendelian Genomics at Yale (CMGY), providing researchers with the resources to tackle the genetics of these rare disorders.

"There are roughly 22,000 genes in the human genome," says Richard P. Lifton, M.D., PH.D., chair

// Center *(page 6)*

Now a department, urology recruits its inaugural leader

Peter Schulam

In January, Dean Robert J. Alpern, M.D., and Marna P. Borgstrom, M.P.H., president and CEO of the Yale-New Haven Health System, announced the appointment of Peter G. Schulam, M.D., PH.D., as chair of the Department of Urology at the School of Medicine and chief of the urology department at Yale-New Haven Hospital.

Urology, which had been organized as a section within the Department of Surgery since the section's founding by Clyde L. Deming, M.D., in 1921, has recently been elevated to departmental status by the Yale Corporation.

Schulam, a native New Havener, comes to the School of Medicine from the Ronald Reagan Medical Center at the University of California at Los Angeles,

// Urology *(page 7)*

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INSIDE THIS ISSUE

ALSO

CLAUDIO BASSO

As chief of the Department of Surgery's Section of Trauma, Surgical Critical Care, and Surgical Emergencies, Kimberly Davis has raised Yale-New Haven Hospital's profile as a leader in treating victims of traumatic injury.

On the night shift

For Yale trauma surgeon, saving patients' lives is an everyday occurrence

Since the days of her childhood in Larchmont, N.Y., Kimberly A. Davis, M.D., has had a penchant for taking things apart, finding out what's wrong with them, and putting them back together. It's one of several reasons, Davis says, that she chose to become a trauma surgeon: "I wanted to be able to intervene in the acute episode of a patient's illness and get them back to their normal level of functioning."

Now, Davis spends her days—and often her nights—helping to repair patients' bodies, and their lives, following traumatic injury. As professor of surgery and chief of the Section of Trauma, Surgical Critical Care, and Surgical Emergencies at the School of Medicine, Davis sees patients during their initial care in the emergency department (ED) at Yale-New Haven Hospital (YNHH), where she is trauma medical director.

In the ED, patients are resuscitated, given fluids, and sometimes ventilated; their injuries are assessed; and physicians determine what sorts of surgical interventions, if any, they require. "Most of what we see is blunt trauma," Davis says, meaning injuries caused by car or motorcycle accidents, falls, and, less commonly, gunshot and stab wounds.

The work is intense, but methodical. "Trauma surgery requires that you address things in specific order," Davis says. "You stop the bleeding first. You [then] stop any contamination occurring from holes in the gastrointestinal tract. And depending on whether the patient is stable, you either surgically address all of the patient's needs at that time or you get them up to the intensive care unit, and you come back to fight another day."

Davis first came to Yale in the 1980s as an undergraduate, majoring in molecular biophysics and biochemistry. But after college, a two-year stint as a research assistant in virology at the Rockefeller University helped her realize she wanted to pursue a medical degree. "While I found the basic science research very interesting, I decided that I missed the human contact," she says.

Davis earned her M.D. at Albany Medical College, then completed a residency in general surgery at Brown University's Rhode Island Hospital and a fellowship in trauma and surgical care at the University of Tennessee Medical Center. In 2006, she returned to Yale from Loyola University Medical Center in Chicago, with an appointment as associate professor of surgery. She was promoted to professor in 2011.

Because the need for rapid care is paramount and the stakes are so high, trauma physicians face unique personal demands. "When you finish caring for a sick patient, you're absolutely exhausted. You've had this huge rush of adrenaline, then you crash." It's a field, Davis says, in which physicians need to be emotionally resilient. "We often have to tell family members that their loved ones have died. To see a family fall apart, and realize the magnitude of what they're going through, is difficult to do over and over again without being compartmentalized."

If urgent care on the wards has taught her to compartmentalize, it's a skill Davis has put to good use. Her tenure as section chief has seen the recruitment of eight new surgeons, a continued focus on education and mentorship, and a deepened commitment to clinical research. Under her watch, YNHH became the first Level-I Trauma Center in Connecticut for pediatric patients, a designation bestowed by the American College of Surgeons on centers that offer the highest level of surgical care. And as if she weren't busy enough, in her spare time Davis is working toward an executive Leadership in Healthcare M.B.A. at Yale School of Management, and will graduate this spring.

How has she managed? "I juggled," she says, "and I have a group of very supportive partners."

Outreach program supports mental health of New Haven mothers

The New Haven Mental Outreach for Mothers (MOMS) Partnership, a coordinated effort by the medical school's Department of Psychiatry, the city of New Haven, and New Haven mothers, was conceived in 2010, when Megan V. Smith, DR.P.H., recognized that there was an unmet mental health need among mothers in New Haven.

With a network of 513 mothers living in New Haven, the New Haven MOMS Partnership works to meet complex needs of mothers who may be struggling with mental health issues. Now, the program is able to expand its reach thanks to a $2.5 million award from the U.S. Department of Health and Human Services Office on Women's Health. New Haven mothers who have been trained in research methods and mental health outreach will conduct workshops for mothers throughout the city. The grant will support the program's work over the next five years.

Megan Smith

"The program's aim is to ensure the emotional health of the city's families through the delivery of evidence-based mental health interventions in community settings," says Smith, assistant professor of psychiatry and in the Child Study Center and principal investigator on the grant.

The New Haven MOMS Partnership consists of the Clifford Beers Child Guidance Clinic, New Haven Healthy Start, the New Haven Health Department, All Our Kin, the Diaper Bank, the state of Connecticut Department of Children and Families, and the Housing Authority of New Haven. The MOMS Partnership's advisory committee includes more than 40 state and local leaders.

Dermatology chair receives accolade as Physician of the Year

Richard Edelson

Richard L. Edelson, M.D., chair and Aaron and Marguerite Lerner Professor of Dermatology, has been named one of three National Physicians of the Year by a committee of medical peers. The committee, assembled by the firm Castle Connolly Medical, chose Edelson from among 150 nominees for the award.

Edelson has served as chair of the Department of Dermatology since 1986, when he came to Yale from Columbia University's Comprehensive Cancer Center, where he was head of the Immunology Group. His major research interests include the immunology of cutaneous T-cell lymphoma, autoimmune disorders, epidermal T-cell interactions, and extracorporeal photochemotherapy.

At the School of Medicine, Edelson has served as director of Yale Cancer Center (YCC), director of YCC's Lymphoma Research Program, and as deputy dean for clinical affairs. He is a member of the American Society for Clinical Investigation and the Association of American Physicians. Edelson received his M.D. from Yale School of Medicine in 1970 and completed his internship in internal medicine at the University of Chicago and residency in dermatology at the Massachusetts General Hospital.

Castle Connolly Medical is best known as the firm that publishes the "Top Doctors" series of books and as the producer of the Top Doctors database that appears on the website of *U.S. News and World Report*. The organization, whose mission is "to help consumers find the best healthcare in America," was founded in 1991.

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Sex, drugs . . . and self-control

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Substance abusers who kick the habit are much more likely to relapse when stress or certain "cues"—sights or sounds associated with their drug of choice—stimulate cravings.

In a new study published in an advance online issue of the *American Journal of Psychiatry,* Marc N. Potenza, M.D., PH.D., and colleagues at the Yale Stress Center found that the pattern of brain activity elicited in cocaine-dependent women by stress or drug-related cues was remarkably different from that seen in male counterparts. In women, brain regions associated with drug craving were significantly more activated by stress than by cues; men showed the opposite pattern.

"There are differences in treatment outcomes for people who experience stress-induced drug cravings and those whose cravings are induced by drug cues," says Potenza, professor of psychiatry and director of the Women and Addictive Disorders Core of Women's Health Research at Yale. "It is important to understand the biologic mechanisms that underlie these cravings."

Getting under the skin of melanomas

What makes melanomas one of the most dangerous forms of cancer is the speed and aggressiveness with which these skin cancers spread to other parts of the body. In about a third of melanomas, the protein β-catenin is dysregulated, but the significance of this has been unclear. Now, Yale researchers have shown that β-catenin helps drive melanomas' aggressive metastasis.

In work described in the December issue of *Cancer Cell,* a team led by Marcus W. Bosenberg, M.D., PH.D., associate professor of dermatology and pathology, studied mice with genetic mutations that make them extremely prone to melanomas. When these mice were further engineered to lack β-catenin they didn't develop melanomas as quickly, and their tumors did not spread to lymph nodes, as they usually do in this mouse model. When β-catenin levels were increased by stabilizing the protein in melanoma cells, the mice developed severe skin tumors that spread to lymph nodes and lungs within a few weeks.

"This shows that a gene can enhance metastasis when activated and dramatically reduce metastasis when inactivated," says Bosenberg, but "there is still much work to be done to see exactly how this happens."

Heading off the 'silent thief of sight'

Research and treatment at the Yale Eye Center are leading to better therapies for glaucoma, a disease that robs millions of their eyesight

About a decade ago, when Isobel Soukup went for a routine eye exam, her primary ophthalmologist discovered that the pressure inside her right eye, known as intraocular pressure (IOP; see "A Glaucoma Glossary"), was nearly twice as high as it should be. Soukup didn't feel anything unusual, but she was exhibiting a classic early sign of glaucoma. She underwent a procedure called laser trabeculoplasty, which was effective in reducing IOP for about five years before the treatment needed to be repeated, not an unusual situation.

But one aspect of Soukup's medical history is unusual. Some time after the second laser treatment, the IOP in both her eyes shot up, and Soukup was diagnosed with advanced glaucoma. She was scheduled by her ophthalmologist to receive a trabeculectomy, a well-established procedure that creates a drainage hole in the eye to reduce IOP, on her right eye. But due to complications with her conjunctiva, a thin layer of cells that covers the sclera (the "white" of the eye) and lines the eyelids, that surgery was aborted and she was swiftly referred to the Yale Eye Center (YEC).

During a lengthy surgery YEC doctors sutured a robust silicone device to the outside of Soukup's right eye, which stabilized IOP. A few months later, her left eye also needed surgery, but this time YEC surgeons inserted an innovative shunt device still in clinical trials that does not require normal conjunctiva. Inserting the new device, known as the SOLX gold shunt, into Soukup's left eye was far easier and quicker than using the silicone device, and Yale doctors and clinical researchers could now directly compare the effectiveness of the two treatments in the same patient.

ROBERT LISAK

James Tsai

Tomas Grippo

Nils Loewen uses a device known as a slit lamp to detect early glaucoma in patients at the Yale Eye Center (YEC). Along with YEC colleagues, Loewen uses the most advanced devices and noninvasive surgical techniques to treat the disease in later stages if it cannot be managed by medication.

Three months later, Soukup herself noticed a big difference. "It's a wonderful thing they've created," she says. "I can read, which I love, and TV viewing has cleared up considerably." Her left eye is "working wonderfully," she says, but the right "still has its moments when it leaks."

Glaucoma is an irreversible, progressive disease in which elevated IOP damages the optic nerve. (However, for reasons that are not fully understood, 20 to 25 percent of patients suffer from "normal-tension glaucoma," in which optic nerve damage has occurred despite normal IOP measures). If left untreated, glaucoma can lead to blindness. Of the 60 million people worldwide suffering from glaucoma (the latest figures are from 2010), the disease caused blindness in 12 million. Typically afflicting people in their 60s and older, it is known as "the silent thief of sight," because it often goes undetected until 95 percent of the optic nerve is permanently destroyed. Medication, usually in the form of eye drops, is generally the first weapon used to treat IOP. In more complicated and aggressive cases, laser trabeculoplasty or trabeculectomy can be employed.

The School of Medicine has a long history in studying and treating diseases of the eye, having first incorporated ophthalmology as a distinct subject into the curriculum in 1876, but it would be nearly a century before the discipline was represented by a freestanding department. In 1961, the Connecticut Lions donated $18,000 to recruit Marvin L. Sears, M.D., from Johns Hopkins University to Yale to launch the Section of Ophthalmology in the Department of Surgery. The section grew rapidly, and in 1971 it was made a full-fledged department, the Department of Ophthalmology and Visual Sciences, with Sears—a glaucoma expert—as its inaugural chair.

Throughout the department's history, a deep understanding of glaucoma has remained a calling card for Yale ophthalmologists. In 1978, the Food and Drug Administration approved the drug timolol, developed by Sears, for glaucoma—the first effective new treatment for the disease since the early 1900s—and the drug is still used today. Sears' successor as chair, M. Bruce Shields, M.D., now professor emeritus of ophthalmology and visual sciences, also made significant advances in the diagnosis and treatment of the disease during his 15-year career at Yale.

Current chair James C. Tsai, M.D., M.B.A., the Robert R. Young Professor of Ophthalmology and Visual Sciences, is also an internationally recognized glaucoma clinician and researcher. To further enhance the department's expertise in glaucoma, he recruited Nils Loewen, M.D., PH.D., in 2009, and Tomas M. Grippo, M.D., in 2011. Both are leading physician–scientists who use state-of-the-art surgical techniques to treat glaucoma and also conduct research on the disorder's causes and mechanisms.

"In my opinion, the glaucoma subspecialty can be viewed as the internal medicine of ophthalmology, because we get to know our patients for years or possibly decades," says Tsai. "But if the therapeutic medications available are not effective, we can also perform laser or surgical procedures to help those patients retain their vision."

In a healthy eye, a clear liquid, the aqueous humor, passes through the pupil and drains through a membrane called the trabecular meshwork, which filters the fluid and allows it to exit the eye and join the general circulation. In glaucoma, this membrane is blocked, much like a clogged sink, leading to increased IOP and possible optic nerve damage. "At its most basic level, glaucoma is a plumbing problem," says Loewen, assistant professor of ophthalmology and visual sciences and director of the YEC's Glaucoma Section. "You've got to improve the flow."

// Glaucoma *(page 7)*

A glaucoma glossary

anterior chamber The part of the eye between the cornea and iris, filled with aqueous humor.

aqueous humor A clear gelatinous-like fluid continually produced in the eye's anterior chamber. This fluid exits the eye via drainage canals in a region called the anterior chamber angle.

glaucoma A complex eye disease characterized by optic nerve damage and resulting loss of vision. Abnormally high pressure within the eye is usually, but not always, present in the condition.

intraocular pressure (IOP) The pressure inside the eye that results from the combined production and drainage of aqueous humor, measured in millimeters of mercury (mmHg). Normal IOP ranges between 10 and 21 mmHg.

laser trabeculoplasty A laser beam procedure that targets the eye's drainage channels to improve flow and lower intraocular pressure.

optic nerve The nerve tract that transmits visual information from the retina to the brain.

optic head drusen Calcified deposits in the region where the optic nerve enters the back of the eye. Optic head drusen are associated with visual field loss, and may be present in glaucoma.

shunt An artificial drainage device surgically implanted in the eye to lower intraocular pressure. The SOLX shunt, still in clinical trials, is made of inert, highly purified gold. The SOLX device is far smaller than conventional shunts and can be quickly implanted in a minimally invasive procedure.

trabecular meshwork Cellular tissue in the anterior angle chamber that allows aqueous humor to drain from inside the eye.

trabectome A recently developed, minimally invasive procedure that removes sections of the trabecular meshwork that are damaged in glaucoma.

trabeculectomy A well-established surgical treatment for glaucoma, in which a small drainage hole is created in the sclera ("white") of the eye. The surgery carries some risks, and may need to be repeated if the drainage hole becomes obstructed by scar tissue.

OUT & ABOUT

November 15, 2011 **David Leof**, M.D. '64 (left), and his wife **Colleen Leof** (right) visited the medical school to mark the awarding of the first **Dr. David and Colleen Leof Scholarship** to **Isha Marina di Bartolo** '15. The fund was established in 2011 to provide support for Yale medical students with distinction in the humanities or arts. Colleen Leof, an artist, will present each Leof Scholar with a sculpture honoring that student's selection.

TERRY DAGRADI

JOHN CURTIS

November 28, 2011 To mark **World AIDS Day**, Yale medical students and faculty brought **Stephen Lewis**, co-founder and co-director of international advocacy organization AIDS-Free World, to campus to deliver a talk called "AIDS at 30" as part of the Global Health Seminar, an interprofessional course organized by the schools of medicine, nursing, and public health.

December 5, 2011 At the **4th Annual Andrews Lecture**, sponsored by the Donaghue Foundation and titled "A Caregiver's Journey," **Lee Woodruff** spoke about her family's experience caring for her husband, ABC news anchor Bob Woodruff, who suffered a traumatic brain injury while traveling with the U.S. military in Iraq in 2006.

JOHN CURTIS

CARL KAUFMAN

December 7, 2011 In the **Pop to Stop Addison's** campaign, **Emma Florian**, **Adam Florian**, and **Benjamin Florian** raised $900 by selling homemade necklaces made from pop-tops to increase awareness of Addison's disease in memory of their brother Joshua. The family presented a check to **Susan D. Boulware**, M.D., assistant clinical professor of pediatrics, at her clinic in Guilford, Conn. (From left) Boulware, Emma, Adam, Benjamin, and their mother, **Eliza Florian**.

November 17, 2011 The **19th Annual Hunger and Homelessness Auction**, sponsored by Yale students in the health professions, raised more than $30,000 to benefit New Haven charities. 1. **Richard Belitsky**, M.D., Harold W. Jockers Associate Professor of Medical Education, deputy dean for education, and associate professor of psychiatry; and **Nancy R. Angoff**, M.P.H., M.D., M.ED., associate professor of medicine and associate dean for student affairs, peruse the auction program. 2. (Foreground, left to right) **Ferrin Ruiz** '13, **Joel Beckett** '13, and **Kristina Liu** '13 take part in the bidding. 3. **Wade Brubacher**, professional auctioneer from Kansas and father of Jake Brubacher '10, returned to the School of Medicine by popular demand to conduct the proceedings.

JOHN CURTIS (3)

// Cancer *(from page 1)* Herbst and his colleagues made significant advances in personalized therapy of NSCLC by using molecular analysis of tissue biopsies to determine the most appropriate targeted treatment available for each patient.

The Heller Foundation's new gift supports Herbst's vision for building translational research at Yale, including an expansive National Cancer Institute (NCI)-funded BATTLE-2 trial, which Herbst designed. The trial's objective is to further improve the efficacy of targeted therapies by identifying the NSCLC patients most likely to benefit from them. Herbst is committed to promoting similar studies initiated by Yale investigators, and has recently supported translational research collaborations among groups of three or more faculty members—including basic and clinical scientists, and junior and senior investigators—through an internal award mechanism called T-TARE (Translational-Targeted Area of Research Excellence). Out of seven applications received, four were awarded seed funds to strengthen the collaboration and facilitate the submission of new multi-investigator grant applications to the NCI.

New translational research initiatives at Yale will be highly collaborative, drawing on Yale's strengths in anticancer drug design and genome analysis and integrating resources at the Yale Center for Genome Analysis and the new Cancer Biology Institute on Yale's West Campus. In addition to launching BATTLE-2 and other similar translational research programs, the Hellers' gift will enable Herbst and colleagues to build an infrastructure that will benefit similar studies of other forms of cancer. The BATTLE-2 trial and other future translational research initiatives will be conducted under the auspices of YCC's new Translational Research Program, which opened last fall under the leadership of Herbst and Julie L. Boyer, PH.D., associate director for translational research administration at YCC. Peter (Ja Seok) Koo, PH.D., associate professor of medical oncology, was also recruited to this effort at Yale from MD Anderson in October.

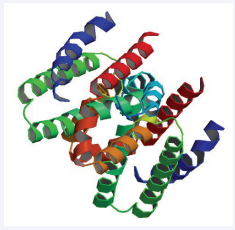
"By facilitating the expansion of our molecular profiling capacity, this gift allows us to develop an innovative translational medicine program under Dr. Herbst's leadership," says Lynch, the Richard Sackler and Jonathan Sackler Professor of Medicine. "Ultimately, we want to use molecular profiling to help guide every patient's treatment."

The founder of the Chicago-based investment management firm Advisory Research, Inc., Heller is himself a beneficiary of genetic screening and personalized medicine. He is also, he takes care to point out, a Harvard man. "I went to Harvard on a scholarship. I never had any money, [and] I got very lucky in life." The Heller Foundation has a long track record of philanthropy, particularly for academic medicine and scholarships benefiting students from lower-income families. "What greater gift could any human being have than to be able to help other people?" asks Heller. "My wife Diane and I are thrilled that we're in a position to be helpful to Dr. Herbst and Yale."

David J. Leffell, M.D., the David Paige Smith Professor of Dermatology, professor of surgery, and deputy dean for clinical affairs, says, "True progress in translational research, which will have a direct impact on our ability to cure disease, depends on the generosity of people like the Hellers. Only with the support of grateful patients and their families can we truly leverage our research and clinical strength to create new breakthroughs."

Herbst says, "This is a truly special gift from a man for whom I have enormous respect. I am thankful for the Hellers' investment in our plans, and I am especially grateful for their astute appreciation of the importance of flexible support in building translational research programs like this at Yale."

Mighty mouse shows diabetes drug in action



YOON ET AL., *J. BIOL. CHEM.* 281, 35088–35096

Preclinical research has long relied on mice, which share genes and biochemical pathways with humans. But mice are not an ideal stand-in when it comes to the immune system. Immunity must differentiate an animal's own cells from foreign cells, so each species' system is unique. To sidestep this problem, Yale researchers have worked for several years on a mouse model in which grafted human stem cells coax the mice to produce human immune cells.

To test the utility of this new model, a group led by Kevan C. Herold, M.D., professor of immunobiology, and Richard A. Flavell, PH.D., chair and Sterling Professor of Immunobiology, used the mice to determine the mechanism of action of teplizumab, a type 1 diabetes drug currently in human clinical trials.

As reported in the January 25 issue of *Science Translational Medicine*, in mice the drug caused human white blood cells to exit the circulation and migrate to the small intestine, where they produce an anti-inflammatory protein called interleukin-10 (above). The findings were then replicated in patients, suggesting that the mouse can reliably be used for preclinical tests of other drugs affecting immunity.

Tiny particle a big step in cancer gene therapy

Gene therapy is an attractive concept with great promise. But in practice, delivering therapeutic genes to diseased cells has been undermined by limited efficiency and considerable toxicity.

To overcome these hurdles, a group led by W. Mark Saltzman, PH.D., chair and Goizueta Foundation Professor of Biomedical Engineering, Research Scientist Zhaozhong Jiang, PH.D., and Associate Research Scientist Jiangbing Zhou, PH.D., synthesized nanoparticles combining sticky DNA-binding regions with regions that protect the genetic material and ferry it safely into target cells.

As reported online in *Nature Materials* on December 4, when these biodegradable polymer-based particles were loaded with a gene that promotes cell death and injected into cancer-bearing mice, the growth of tumors in the mice was significantly inhibited, and they suffered no toxic side effects.

Saltzman hopes to someday use a nanoparticle delivery system in gene therapy for several human diseases, particularly brain tumors. "We've been developing techniques for introducing particles like these directly into the brain to treat malignant brain tumors for some years," Saltzman says. "Our hope is that these polymers give us another tool—a very safe tool—that we can potentially use in that arena."

Stress, adversity take a toll on the brain

Trauma significantly affects brain structure, but so can more common challenging events when our ability to control them is limited

Rajita Sinha

Emily Ansell

Enduring adversity as a child, losing your job, a nasty divorce—many types of stress have been associated with serious illnesses, from addiction and depression to diabetes and even cancer.

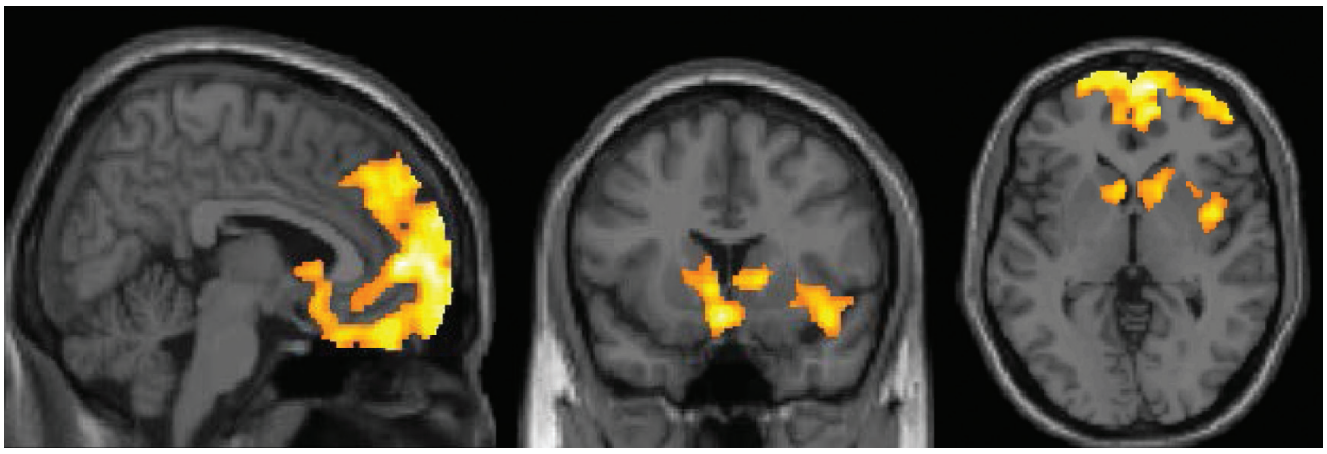
The brain is particularly vulnerable to stress-induced damage, but how stress changes the brain is not fully understood. Using magnetic resonance imaging (MRI), two new studies by School of Medicine researchers have linked stress to a reduction in the volume of nerve cells, or gray matter, in the prefrontal cortex (PFC), a region that controls emotions, abstract thinking, and impulses. Understanding how these changes develop over time could help researchers identify individuals most vulnerable to stress. Ideally these patients could be steered toward exercise, social support, and other clinical interventions known to offset the harmful effects of stress.

"When you go to your physician's office, you might get your insulin levels checked out, and your doctor will use it to recommend treatments," says Rajita Sinha, PH.D., Foundations Fund Professor of Psychiatry and director of the Yale Stress Center, who was involved in the new studies. "We need to be able to get there with the brain, to treat it just like any other organ system."

Scant human research to date has explored stress and the brain, and these reports have tended to focus on either people with disorders or healthy adults who were exposed to a single traumatic event, such as those who directly experienced the 9/11 attacks.

In one of the new Yale studies, researchers instead focused on the accrual of adversity—the death of a loved one, a robbery, or even moving to a new city—over a person's lifetime. "We were interested in the effects of stressful life events independent of whether individuals perceive that the events caused stress," explains first author Emily Ansell, PH.D., assistant professor of psychiatry.

The researchers employed a 140-question survey called the Cumulative Adversity Interview to tally **// Stress** *(page 7)*



COURTESY OF RAJITA SINHA

In a recent Yale study, magnetic resonance imaging scans showed a correlation between the number of stressful events an individual has experienced—even those that might be considered only mildly stressful—and reduced volume (yellow and orange) of the medial prefrontal cortex, anterior cingulate, and right insula. These brain areas serve important functions related to self-control and the regulation of emotions.

Yale, Chinese university team up for mental health

New program integrates professional development and intercultural education

MICHAEL MARSLAND

Elizabeth Bradley (front, center) welcomes Chinese leaders in psychiatric care to the Yale GHLI-Fudan Mental Health Program.

Yale University's relationship with China is an old and storied one, with roots dating to the 1830s, when Yale graduates began traveling to China to perform missionary work. Today, this relationship is strong and multifaceted, and it continues to grow: among the newest Yale-China initiatives is a joint program with Shanghai's Fudan University focused on mental health education and professional development.

In January and February, seven Chinese leaders in psychiatric care and policy traveled to New Haven to enhance their professional development as part of a new program designed by the Yale Global Health Leadership Institute (GHLI). A three-week conference, the Yale GHLI-Fudan Mental Health Program is a forum for Chinese psychiatrists to learn current best practices in psychiatric treatment and to improve their leadership and management skills.

The program included lectures, seminars, panel discussions, hands-on learning exercises, and site visits to treatment facilities and recovery programs throughout Connecticut for people with psychiatric illnesses and addictions. Topics covered in the various sessions included research practices and methodologies, ethics, paths to publication, workforce restructuring and expansion, and the relationship of law to mental health policy, among others.

Yale and Fudan University are no strangers: the relationship dates back to 1905, when Li Denghui, of the Yale College Class of 1899, became Fudan's first director of studies, and, subsequently, the university's first president. In 2003 the two universities launched the Shanghai-based Fudan-Yale Biomedical Research Center, whose mission is to conduct research on the molecular causes of human diseases.

Martha Dale, M.P.H., GHLI's director of China Programs, says the GHLI-Fudan Mental Health Program benefits not only the participants but also the broader Yale-Fudan University relationship. "This program is a trial of a relationship with Fudan University for health care leadership education. Our hope is that it will create a new venue for relationship-building and collaboration on health care leadership and systems strengthening. It's a mutually beneficial program in that sense."

Elizabeth H. Bradley, PH.D., professor of public health and GHLI's faculty director, says, "One goal of the program is to start to build the relationships necessary to work with China to improve the quality and capacity of the [Chinese] mental health system."

Grants and contracts awarded to Yale School of Medicine

March/April, 2011

Federal

Hervé Agaisse, NIH, *Regulation of Bacterial Pathogen Actin-Based Motility by Host Cell Kinases*, 2 years, $455,125 • **Emily Ansell**, NIH, *Interpersonal Behaviors, Stress, and Addiction*, 5 years, $906,132 • **Albert Arias**, NIH, *Alcohol Dependence: Pharmacotherapy, Pharmacogenetics, and Genetics*, 2.9 years, $608,138 **Thomas Biederer**, NIH, *Mechanisms of SynCAM-Induced Synapse Formation*, 5 years, $735,220 **Ronald Duman**, NIH, *Role of mTOR and Synaptic Protein Synthesis in the Rapid Antidepressant Actions of NMDA Receptor Blockade*, 5 years, $2,648,873 • **Erol Fikrig**, NIH, *Tissue-Specific* Borrelia *Gene Expression*, 5 years, $2,076,876 **Emily Freed**, NIH, *The Role of Ribosome Biogenesis*, 1.3 years, $30,462 • **Daniel Greif**, NIH, *Morphogenesis of the Pulmonary Artery Smooth Muscle Layer*, 4 months, $411,744 • **Eduardo Groisman**, NIH, *Regulation of* Salmonella *Virulence by the PhoP Protein*, 5 years, $2,076,458 **Erol Gulcicek**, NIH, *Nano-UPLC LTQ-Orbitrap Velos MS System for Yale University Keck Laboratory*, 1 year, $777,269 • **Yiyun Huang**, NIH, *PET Imaging of Kappa Opioid Receptors: Tracer Validation and Sex/Age Effect Study*, 3.8 years, $2,590,011 • **Jeannette Ickovics**, NIH, *School Wellness Policy: RCT to Implement and Evaluate Impact on Childhood Obesity*, 5 years, $2,927,148 • **Leonard Kaczmarek**, NIH, *Expression of Ion Channels in the Auditory System*, 5 years, $1,524,069; NIH, *Design of Slack Channel Activators*, 2 years, $500,133 **Harriet Kluger**, NIH, *Models to Predict Prognosis and Benefit from Adjuvant Therapy in Renal Cell Carcinoma*, 5 years, $1,816,127 • **Yilun Liu**, NIH, *The Molecular Basis of RECQ4 Associated Genetic Disorders and Cancer Predisposition*, 7 months, $83,965 • **Paul Lombroso**, NIH, *The Role of STEP in Schizophrenia*, 5 years, $1,722,071 **Jun Lu**, NIH, *The Role of MicroRNAs in Leukemia Initiation and Maintenance*, 5 years, $1,723,634 **Diane McMahon-Pratt**, NIH, *Improved Treatment of American Cutaneous Leishmaniasis by Immunomodulation*, 4 years, $2,686,096 **Ruslan Medzhitov**, NIH, *Memory of DNA Damage*, 5 years, $1,830,591 • **Andrew Miranker**, NIH, *Insight into Pathological Self-Assembly Using Alpha-Helical Mimetics*, 4 years, $1,237,047 • **Girish Neelakanta**, NIH, Anaplasma phagocytophilum *Induce* Ixodes scapularis *Antifreeze Glycoprotein Gene Expression to Enhance Tick Survival in the Cold*, 2 years, $165,500 • **Mehmet Sofuoglu**, NIH, *Cognitive Enhancement as a Target for Cocaine Pharmacotherapy*, 11 months, $1,582,569 **Edward Snyder**, NIH, *Recipient Epidemiology and Donor Evaluation Study-III (REDS III)—Domestic Sites*, 2 years, $2,360,528 • **Dawn Wetzel**, NIH, *Cytoskeletal Control of* Leishmania *Infection*, 3 years, $166,360 • **Sandra Wolin**, NIH, *Recruitment of Host Noncoding RNAs by XRN1*, 2 years, $494,793 • **Yawei Zhang**, NIH, *Air Pollution and Fetal Growth in China*, 5 years, $504,179 • **Yong Zhu**, NIH, *Molecular Epidemiology/Functional Analysis of MicroRNAs in Non-Hodgkin's Lymphoma*, 4 years, $1,584,663 **Lingjun Zuo**, NIH, *Deep Sequencing of Glutamatergic Pathway Genes in Alcohol and Nicotine Co-Dependence*, 2 years, $343,613

Non-federal

Kirsten Bechtel, Community Foundation for Greater New Haven, *Pediatrics SANE-SAFE-T Program at North Haven Middle School*, 7 months, $2,890 • **Daryn David**, American Psychological Foundation, *Supported Parenting Participants for Mothers Diagnosed with Serious Mental Illness*, 1 year, $12,000 • **Charles Duncan**, Synthes (USA), *Resident 2011 RUNN Course*, 1 year, $7,000 • **Marie Egan**, Hartwell Foundation, *Synthetic Nanoparticles for Gene Correction of Cystic Fibrosis*, 3 years, $300,000 • **Paul El-Fishawy**, American Psychiatric Association, *APA/Lilly Research Fellowship*, 11 months, $45,000 • **Joel Gelernter**, Virginia Commonwealth University (NIH), *Stress-Induced Drinking in OEF/OIF Veterans: The Role of Combat History and PTSD*, 1.2 years, $109,673 • **David Hafler**, Nancy Taylor Foundation for Chronic Diseases, *Discovering Genetic Variations in Human Inflammatory Diseases Using High-Throughput Robotic Platforms*, 2 years, $230,000 • **Robert Heimer**, Institute for Community Research (NIH), *IDU Peer Recruitment Dynamics and Network Structure in Respondent Driven Sampling*, 3 years, $85,123 • **Kristina Herbert**, Burroughs Wellcome Fund, *Regulation of MicroRNA Biogenesis Through the Core Microprocessor Components*, 1.8 years, $10,000 • **Michael Higley**, Richard and Susan Smith Family Foundation, *Neuromodulation of Synaptic Transmission in the Prefrontal Cortex*, 3 years, $300,000 **Debbie Humphries**, Connecticut Association of Directors of Health, *Connecticut Local Health Department (LHD) Fee-for-Service Structures and Service Profiles Across LHDs and Within LHDs Over Time*, 9 months, $34,000 • **Jeannette Ickovics**, Aetna Foundation, Inc., *Childhood Obesity: Exploring the Role of Environmental Context on Risk Behaviors and Health Outcomes*, 1.5 years, $150,000 • **Nils Loewen**, American Glaucoma Society, *AGS 2011 Young Clinician Scientist Award*, 1 year, $40,000 • **Ruslan Medzhitov**, Harvard Medical School (NIH), *Mechanisms of Susceptibility to Viral-Bacterial Co-Infection*, 6 months, $165,500 • **Peter Morgan**, Mind Science Foundation, *Lucid Dreaming and Performance on Prefrontal Cortical Tasks*, 1 year, $15,000 • **Angus Nairn**, Rockefeller University (NIH), *Striatal Phosphoproteins and Actions of Psychostimulants*, 1 year, $277,128 **Chirag Parikh**, Tufts-New England Medical Center (NIH), *The Aging Kidney; Chronic Injury, Impaired Functions and Clinical Outcomes*, 5 years, $187,954 • **Francheska Perepletchikova**, Green Chimneys, *Adapting Dialectical Behavior Therapy for Children in Residential Care: Pilot Randomized Clinical Trial with Children with Severe Emotional and Behavioral Dysregulation*, 3 years, $171,109 • **Margaret Pisani**, Vanderbilt University Medical Center (NIH), *The MIND USA Study*, 5 years, $218,990 • **Carrie Redlich**, Southern Illinois University School of Medicine (Dept. of Defense), *Phase II Clinical Trials: D-Methionine to Reduce Noise-Induced Hearing Loss*, 4 years, $386,897 • **Harvey Risch**, Johns Hopkins University (NIH), *Validation and Fine-Scale Mapping of Pancreatic Cancer Susceptibility Loci*, 1 year, $55,949 • **Carla Rothlin**, Lupus Research Institute, Inc., *Taming the Pathogenic Type 1 Interferon Response in SLE*, 3 years, $300,000 • **Marianne San Antonio**, Academic Pediatric Association, *Do the Conditions of Administration Affect the Reliability of Developmental Screening in the Pediatric Waiting Room?* 1 year, $14,996 • **Martin Schwartz**, University of Colorado at Denver, *Understanding the RhoGD12 Metastasis Suppressor Gene*, 1.4 years, $118,069 • **Qin Yan**, Melanoma Research Foundation, *Roles of Epigenetic Regulator JARID1B in Metastatic Melanoma*, 2 years, $90,000 • **Yong Zhu**, The Geneva Foundation (Dept. of Defense), *Circadian Genes and Risk for Prostate Cancer*, 1.4 years, $15,833

// Center *(from page 1)* and Sterling Professor of Genetics, one of the principal investigators of the new grant. "Right now we know what diseases result when about 3,000 of those are mutated. We know almost nothing about what happens when the remaining ones are mutated."

The new grant, announced last December, will also fund two other national centers devoted to the genetics of Mendelian diseases—one at the University of Washington, in Seattle, Wash., and one operated jointly by Baylor College of Medicine, in Houston, Texas, and at Johns Hopkins University, in Baltimore, Md.

"Between all the institutions, we collectively want to solve all of the remaining Mendelian diseases," says Lifton, also a Howard Hughes Medical Institute investigator. "And we'll be working as a consortium. So each group has its own strengths in particular clinical areas, and the goal is to minimize any overlap of work that's done." Genetic samples submitted from clinicians through a single Web portal, Lifton explains, will be distributed to the three centers based on their interests.

At Yale, other principal investigators at the new center will include Murat Günel, M.D., the Nixdorff-German Professor of Neurosurgery and professor of genetics and neurobiology; Shrikant Mane, PH.D., senior research scientist in genetics; and Mark B. Gerstein, PH.D., the Albert L. Williams Professor of Molecular Biophysics and Biochemistry and co-director of the Yale Computational Biology and Informatics Program.

Over the last decade, Yale has spearheaded the development of exome sequencing, the gene sequencing method that the new project relies on. Rather than spell out every nucleotide in the human genome, as genomic studies have traditionally done, exome sequencing allows researchers to focus only on those parts of the genome that encode proteins, the physical machinery of cells. A large fraction of inherited diseases are thought to be due to mutations in the exome.

"The new sequencing technologies enable us to pinpoint disease-causing genes even with only a few affected subjects," says Lifton. "This has really opened up the field." (See "The bench-top revolution.")

There is already a network of clinicians around the world who refer patients with rare diseases to School of Medicine researchers for genetic and other testing, follow-up, and possible treatment. Lifton and his colleagues have focused especially on connections with doctors in the Middle East, where culturally sanctioned marriages between cousins lead to a higher rate of rare genetic disorders than is seen in the U.S. "With 7 billion people on the planet, even the rarest mutations are present and walking around somewhere," says Lifton. It's the goal of the CMGY to identify patients with all these rare mutations and learn the consequences of each genetic deviation. In the process, they may also learn how to treat some patients.

"Identifying the specific genetic causes of these diseases will be useful diagnostically; the therapeutic possibilities will only be revealed when we can link mutations to disease traits," Lifton says. But he anticipates that by discovering the genetic causes of some of the disorders, doctors will be able to develop better ways to treat them. "If you look at the most promising targets in the pharmaceutical industry today, almost all of them arose from the recognition of what happens when genes are mutated in humans."

And beyond the therapeutic implications of the new project, the Yale team expects to learn some lessons in basic biology. The link between a given gene mutation and the disease it causes can teach scientists a great deal about what function that same gene performs normally, Lifton explains. "It really tells us how each gene works in the context of the human body. And this tells us a great deal about how entire pathways work, which is very important to future drug development."

The bench-top revolution

It's not just funding pushing forward the pace of genetic research at Yale, it's also technological innovation. On the heels of receiving the grant establishing the Center for Mendelian Genomics (see main story), Yale is acquiring a state-of-the-art DNA sequencer that has the potential to analyze an entire human genome in 24 hours for only $1,000.

The Ion Proton Sequencer, produced by San Francisco-based Life Technologies Corp., is currently one of just three worldwide—the others are being deployed at Baylor College of Medicine, in Houston, Texas, and the Broad Institute, in Cambridge, Mass. The machine, about the size of a laser printer, was developed in part by Yale alumnus Jonathan M. Rothberg, PH.D., a pioneer in DNA sequencing technology.

Most sequencers require weeks or months, and many thousands of dollars, to sequence a human genome. The Ion Proton's power and speed are due to advanced semiconductor chips that capture the chemistry of a DNA sample in much the same way as a digital camera captures light. The new equipment promises to be a boon to many projects undertaken at Yale, including the new effort to uncover the causes of rare genetic diseases.

"Cost, speed, and accuracy are key elements in the use of DNA sequencing for both disease-gene discovery and clinical utility," says the School of Medicine's Richard Lifton. "The technological advances in the new instrument promise to be game-changing for both research and clinical applications."

// Stress *(from page 5)* stressful events in the lives of 103 adults with no history of psychiatric problems. These volunteers then underwent structural MRI scans, which reveal the shape and volume of various brain regions.

As reported January 2 in *Biological Psychiatry*, participants who reported more adverse experiences had significantly less gray matter in the medial PFC, anterior cingulate, and insula, three brain areas involved in self-control and emotion regulation. "These regions concern us because the changes could affect an individual's ability to deal with their stress in the future," says Ansell. "It may lead to problems with negative thinking and feeling down, or drinking more alcohol, smoking more cigarettes, or overeating reward-based foods like fats or sugars."

In a separate collaborative study by researchers in the Department of

Hilary Blumberg

Linda Mayes

Psychiatry and the Child Study Center, published in the December issue of *Archives of Pediatric and Adolescent Medicine*, principal investigators Hilary P. Blumberg, M.D., and Linda C. Mayes, M.D., and colleagues reported similar volume reductions in the PFC and several other brain regions in 42 adolescents who had been at a higher risk of maltreatment.

These results "suggest that childhood stress may affect brain development, leading to brain differences by adolescence that may increase vulnerability to developing disorders of emotion and impulse regulation," says Blumberg, associate professor of psychiatry and director of the Mood Disorders Research Program.

"This group was identified for a variety of reasons, such as exposure to drugs prenatally, or coming from a depressed mother or severe poverty," says Mayes, the Arnold Gesell Professor of Child Psychiatry, who has been studying a group of 350 such children, including the 42 whose brain scans are reported on in the new research, for nearly two decades.

In this study, participants filled out the Childhood Trauma Questionnaire, which assesses perceived physical and emotional adversity. Again using structural MRI, the researchers found that the higher a child's score on the questionnaire, the smaller the volume of gray matter in the PFC and several other brain regions. Intriguingly, when analyzed separately, different types of adversity were found to have different effects on the brain. For instance, physical trauma was linked to reduced volume in the ventral striatum—involved in reward processing and addictive behaviors—whereas emotional neglect was tied to reduced volume of the amygdala, a deep-brain structure that regulates emotions.

Mayes plans to follow these adolescents for many more years, to see how adversity, combined with genetic and social factors, may shape their behaviors and, eventually, parenting skills.

Since both studies analyzed people without psychiatric diagnoses, the findings suggest that certain resilience factors help people combat the physical fallout of stressful events. "All of these are questions that are not yet clear," Mayes says, "but very important for intervention."

// Urology *(from page 1)* where he was vice chair of urology, chief of the division of endourology and minimally invasive surgery, and director of both the kidney stone treatment center and the surgical living kidney donor program. Schulam was also professor of urology at UCLA, and founder and co-director of UCLA's Center for Advanced Surgical and Interventional Technology.

Schulam has long-standing clinical interests in adrenal disorders; bladder, prostate, and kidney cancer; donor nephrectomy; and kidney stones and kidney reconstruction; and he is nationally known for his expertise in minimally invasive surgery and laparoscopic techniques.

With an award from the Medical Scientist Training Program, Schulam received his medical degree as well as his doctorate in immunology from Baylor College of Medicine in Houston, Texas.

He then served as general surgical intern and completed surgical and urology residencies at the Johns Hopkins Hospital in Baltimore, Md.

Schulam succeeds Robert M. Weiss, M.D., the Donald Guthrie Professor of Surgery, who has served as chief of the Section of Urology, director of the urology residency program, and director of the pediatric urology program for 25 years. Weiss will continue his laboratory research and his active urology practice at Yale.

"The transition of Urology to a department recognizes its increased importance in clinical medicine and the commitment of Yale and Yale-New Haven Hospital to expand our efforts in urologic care, research, and education," says Alpern. "I can think of no one better than Pete Schulam to lead us in these efforts as the department's inaugural chair."

// Glaucoma *(from page 3)* But current surgical therapies are far from ideal, says Loewen. In trabeculectomy, for example, surgeons create a small hole in the eye underneath the eyelid to drain fluid, but in many cases scar tissue builds up and causes failure.

Patients with early to moderate glaucoma have recently been treated at the YEC with a newer procedure called a trabectome. This operation, which removes damaged portions of the trabecular meshwork, takes just a few minutes to perform, and the after-care only involves the use of drops for one or two months. "It requires much less maintenance, and the risks of severe complications are much less over the short term and the long term," Loewen says. "It's not going to replace the trabeculectomy—still the gold standard—but it's another tool that we have if we identify the right patient."

Loewen adds that "one of the bad things about classical trabeculectomy is that up to 50 percent of procedures fail after five years, while permanently increasing the risk for a devastating eye infection."

Loewen hopes that the SOLX gold shunt received by Isobel Soukup received will provide an alternative to trabeculectomy for a much wider range of patients to avoid these complications.

About the size of a flattened grain of rice, the SOLX device is made of highly purified gold, an inert material that can remain entirely on the inside of the eye without increasing the risk of infection. The tiny plate, which is implanted through a single micro-incision, contains tubular channels that create a new drainage pathway to reduce IOP. The shunt can be inserted in about 20 minutes, and the patient's vision returns to normal after only a couple of days. The device is undetectable by the patient and is intended to last indefinitely.

"Glaucoma is a devastating disease that causes disability and deprives us of our primary sense. Yet as we live longer, it's only going to become more and more common," says Loewen. "To have these new technology-driven micro-surgeries available to us is very gratifying."

Besides surgery, the YEC is dedicated to using new medical science from all fields, including stem cell and gene therapies, to advance the understanding and treatment of glaucoma. Loewen conducts basic research to understand why IOP increases. He is currently working on a gene therapy designed to improve outflow by replacing the tissue that regulates flow, the trabecular meshwork.

Grippo has also a special interest in optic disc drusen, calcified deposits in the back of the eye that are associated with optic nerve degeneration. Optic disc drusen are a relatively frequent condition—studies have reported evidence of optic disc drusen in up to 2.4 percent of eyes—sometimes seen in patients who also present risk factors for glaucoma. "It's very difficult to make a diagnosis of glaucoma when someone has optic disc drusen, mainly because the drusen obscure the normal anatomy of the optic nerve head, making optic nerve changes due to glaucoma very difficult to detect. Adding to this difficulty is the fact that both conditions may cause similar visual field loss."

At present there is also no proven treatment for optic head drusen. Grippo hopes to launch long-term prospective studies at Yale to better understand the relationship between drusen and glaucoma and to seek better therapies.

Tsai believes that people who develop glaucoma may have unusually sensitive optic nerves that are easily damaged by fluctuations in IOP. Based upon this idea, Tsai has undertaken extensive basic and translational research, investigating neuroprotective agents in animal models of glaucoma, developing novel techniques for vision testing, and evaluating the surgical outcomes of glaucoma tube-shunt implants.

He has collaborated with colleague Steven M. Strittmatter, M.D., PH.D., the Vincent Coates Professor of Neurology and professor of neurobiology, to study the role of a protein called NOGO that blocks nerve regeneration. By inactivating NOGO, it may be possible in the future to regenerate optic nerves that have already been damaged by glaucoma, Tsai says.

Tsai believes that advances in both biomedical engineering and neuroscience are the keys to future innovations in glaucoma research and treatment. In 10 or 20 years, he says, he hopes a new three-part paradigm for glaucoma treatment will have emerged, including therapies that rebuild the trabecular meshwork, protect the optic nerve from the effects of fluctuating IOP, and regenerate those optic nerve fibers that have been damaged by the disease. "This is indeed an exciting time to be engaged in glaucoma research and treatment," he says.

Beede Professor studies the causes of developmental and learning disabilities in children

Elena L. Grigorenko, PH.D., has been designated the inaugural Emily Fraser Beede Associate Professor for Developmental Disabilities. Grigorenko's research focuses on understanding how genetic and environmental risk factors contribute to developmental and learning disabilities in children.

She is particularly interested in how children with special needs, such as those infected with intestinal parasites or diagnosed with autism, succeed by capitalizing on their strengths. Her work in this area has contributed to a greater understanding of the flexibility and malleability of human development, and the way children grow and mature. Using


Elena Grigorenko

diverse methodologies, ranging from molecular genetics to cultural studies to family and educational intervention designs, Grigorenko has conducted research on international adoptees who were brought to the United States when young; the rates of learning disabilities in harsh environments with high rates of illness, intoxication, and poverty; and the interactions between genetic and environmental factors for conduct problems. She is especially interested in studying the risk factors for language and reading disabilities, autism, and criminal behaviors in pre-adolescent children. Grigorenko has worked with children and their families in Africa, India, Saudi Arabia, and Russia.

The author, co-author, or editor of more than 300 articles, book chapters, and books, Grigorenko has received awards for her work from five different divisions of the American Psychological Association (APA). Her other honors include the Gardner Lindzey Dissertation Award in General Psychology, the Sigmund Koch Early Career Award in Theoretical and Philosophical Psychology, and the Berlyne Early Career Award for Creative Achievement in Psychology of the Arts. In 2004, she won the APA Distinguished Award for an Early Career Contribution to Developmental Psychology.

Grigorenko earned a doctorate in general psychology at Moscow State University in Russia, and in 1996 earned a second doctorate at Yale in developmental psychology and genetics. She joined the School of Medicine faculty in 2002 with affiliations in the Department of Psychology, the Child Study Center, and the Department of Epidemiology and Public Health. Since 2008, she has served as director of the Yale Academic Skills Clinic. She is also an adjunct professor at Teachers College, Columbia University, and in the psychology department at Moscow State University.

Expert in the effects of lifestyle choices on cancer risk named C.-E.A. Winslow Professor

Susan T. Mayne, PH.D., an expert in the lifestyle determinants of cancer risk, has been named the C.-E.A. Winslow Professor of Epidemiology at the Yale School of Public Health (YSPH).

Mayne's research has emphasized the role of dietary factors in the etiology of several major cancers. She also studies other lifestyle factors, such as tobacco and alcohol use, and their interaction with genetics in cancer risk.

Recently, Mayne co-authored a study that found that indoor tanning significantly raises the risk of an increasingly common form of skin cancer in young people. Mayne and colleagues at the School of Public Health reported online in the *Journal of the American Academy of Dermatology*


Susan Mayne

in December that people under the age of 40 who had tanned indoors had a 69 percent increased risk of early-onset basal cell carcinoma. The team found that the association was strongest among women, and that the risk increased with years of tanning use.

Mayne is head of the Division of Chronic Disease Epidemiology, which includes 28 faculty members. She is also associate director of Yale Cancer Center, where she is responsible for Population Sciences. Mayne, who earned her doctorate from Cornell University, has led Yale's Cancer Prevention and Control Research Program for 17 years to record-high levels of National Institutes of Health (NIH) funding and productivity. She developed the Yale-National Cancer Institute partnership, which gives faculty and students access to important national cohort studies for research, as well as an NIH-funded training program in cancer epidemiology and genetics, now entering its ninth year. She has received the Distinguished Teaching Award at YSPH.

A member of several editorial boards, Mayne is a fellow of the American College of Epidemiology and of the Executive Leadership in Academic Medicine Program for Women. She has authored or co-authored over 170 articles and book chapters.

The C.-E.A. Winslow Memorial Fund was established in 1958 by an anonymous donor to support the work of a professor in the Department of Public Health (a precursor to YSPH). It recognizes Charles-Edward Amory Winslow, M.S., DR.PH., who served as chair of the department from its founding in 1915 until his retirement in 1945. A scholar with an international reputation and a firm belief in the philosophy of disease prevention, Winslow profoundly influenced both Yale's department and the burgeoning field of public health.

Awards & Honors

Yale chemist is awarded Packard Fellowship

Seth B. Herzon, PH.D., assistant professor of chemistry, has been named a 2011 Packard Fellow.

The fellowship was established in 1988 by the David and Lucile Packard Foundation to support early-career scientists in the physical sciences and engineering, and will support work in Herzon's laboratory, which is focused on two areas of research. The first involves natural products synthesis, finding ways to recreate useful complex molecules produced in nature in the laboratory; the second research area pursued by Herzon is organometallic chemistry and the development of new catalytic reactions.

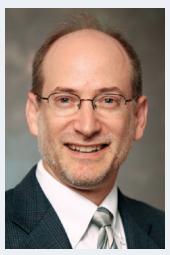

Seth Herzon

Each year, the presidents of 50 universities nominate members of their faculty for the Packard Fellowship, and a panel of scientists selects 16 fellows to receive the award. The fellowships provide individual grants of $875,000 over five years.

Herzon's past honors include the Searle Scholar Award and the Synthesis/Synlett Journal Award, among others.

Psychiatry chair is president of leading brain and behavior society

John H. Krystal, M.D., the Robert L. McNeil Jr. Professor of Translational Research, chair of the School of Medicine's Department of Psychiatry, and chief of psychiatry at Yale-New Haven Hospital, has been named president of the American College of Neuropsychopharmacology. The ACNP is the leading organization focusing on the brain science related to neuropsychiatric disorders.

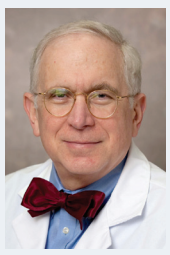

John Krystal

Krystal, also director of the Clinical Neuroscience Division of the Department of Veterans Affairs National Center for Posttraumatic Stress Disorder (PTSD) and director of the National Institute on Alcohol Abuse and Alcoholism's Center for the Translational Neuroscience of Alcoholism, is an expert in "translational neuroscience"—the effort to link concepts and approaches arising from basic brain research to the study of the neurobiology and treatment of psychiatric disorders. He has applied this strategy to developing new treatments for schizophrenia, PTSD, alcoholism, and depression.

Anesthesiologist receives lifetime achievement award

Stanley H. Rosenbaum, M.D., professor of anesthesiology, surgery, and internal medicine, has been honored with a Lifetime Achievement Award by the Society of Critical Care Anesthesiologists.

Director of the Section of Perioperative and Adult Anesthesia in the Department of Anesthesiology, and chair of the Health Professions Advisory Board at Yale College, Rosenbaum is a co-editor of the reference book *Anesthesia Emergencies*, and of numerous book chapters, articles, and other publications.


Stanley Rosenbaum

His research interests include the incidence and detection of perioperative myocardial injury, and the interaction of modern ethical principles in end-of-life care. Rosenbaum holds a B.A. from Columbia University, a master's degree in physics from Harvard University, and an M.D. from Weill Cornell Medical College. He completed residencies in internal medicine and in anesthesiology at Columbia-Presbyterian Medical Center in New York City.

Cell biologist honored for research in molecular parasitology

Elisabetta Ullu, PH.D., professor of medicine and cell biology, has received the inaugural Alice and C.C. Wang award from the American Society of Biochemistry and Molecular Biology.

Ullu received the award for her laboratory's research on a mechanism of gene silencing called RNA interference (RNAi). While examining RNA synthesis and processing pathways in the protozoan parasite *Trypanosoma brucei*, the cause of African sleeping sickness, Ullu showed that RNAi, in which small, noncoding RNA molecules rather than proteins affect gene expression, was an important genetic regulator in the parasite.


Elisabetta Ullu

In supporting her nomination, Shulamit Michaeli, PH.D., professor of life sciences at Bar-Ilan University in Israel, said Ullu's discovery of RNAi in *T. brucei* "made a revolution in the ability to investigate the function of genes in parasites."

A native of Italy, Ullu received her doctorate from the University of Rome in 1973 and joined Yale's faculty in 1984.