**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 adviser 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 $5 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 antitumor 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 multicentered Biomarker-Based Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) trial, //Cancer (1997) 8, 607–614

**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.

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 more 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**

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)

INSIDE THIS ISSUE

1 Lifelines Kimberly Davis, section chief and trauma surgeon, puts patients’ lives back together while raising her department’s profile

2 New options for glaucoma Physician-scientists at the Yale Eye Center carry on a long tradition of expert care combined with pathbreaking research

3 Give your brain a break Studies by Yale scientists reveal that trauma affects the brain, as do the more minor slings and arrows life may send our way

ALSO

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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 (YNH), 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 sort 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 biology 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, YNH 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 Master of Business Administration degree 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 co-ordinated 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, D.P.H., recognized that there was an unmet mental health need among mothers in New Haven.

With a network of 35 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.

“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 accolades as Physician of the Year

Richard L. Edelson, M.D., M.B.A., 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.
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 Isabel 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 under- went a procedure called laser trabeculoplasty, which was effective in reducing the optic nerve. However, before the treat- ment 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 sched- uled by her ophthalmologist to receive a trabeculectomy, a well-established pro- cedure 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 lines 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 out- side 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. Three months later, Soukup herself noticed a big differ- ence. “It’s a wonderful thing they’ve created,” she says. “I can read, which I love, and TV viewing has cleared up consider- ably.” 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 2 million. Typically af- flicting 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, usu- ally 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 wasn’t until 1971 that it was made a full-fledged department, the Department of Ophthalmology and Visual Sciences, with Current chair James C. Tsai, M.D., M.B.A., as its inaugural chair. Throughout the department’s history, a deep understand- ing of glaucoma has remained a calling card for Yale oph- thalmologists. In 1978, the Food and Drug Administration approved the drug timolol, developed by Sears, for glauco- ma—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 physi- cian–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.”

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. It fills 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 pres- sure 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 intra- ocular pressure.

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

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 medical treatment. "I hope that the therapeutic medications available are not effective, we can also perform laser or surgical procedures to help those patients retain their vision."

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December 6, 2011 At the 45th 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.

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 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 ’13. 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.

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.

OUT & ABOUT

November 17, 2011 The 19th Annual Hunger and Homelessness Auction, sponsored by Yale students in the health professions, raised more than $50,000 to benefit New Haven charities. 1. Richard Bellisky, M.D., Harold W. Jackers 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, perused the auction program. 2. (Foreground, left to right) Ferrin Ruiz ’13, Joel Bockett ’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.
Trauma significantly affects brain structure, but so can more common challenging events when our ability to control them is limited

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 stressful events independent of whether individuals perceive that the events caused stress, adds first author Emily Ansell, Ph.D., assistant professor of psychiatry.

Yale, Chinese university team up for mental health

New program integrates professional development and intercultural education

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 professor. 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

Stress, adversity take a toll on the brain

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 Michael Marsland, Ph.D., chair and Goizueta Foundation Professor of Biomedical Engineering, Research Scientist Zhaozhong Jiang, Ph.D., and Associate Research Scientist Jiangzhou 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 area.”

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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 area.”
Non-federal

Király Beck, Center for Medicine for Greater New Haven, Pediatrics same-sate patient Program at North Haven Middle School, 7 months, $2,890 & Daryn David, American Psychiatric Association Foundation, Supporting Participants for Mothers Diagnosed with Serious Mental Illness, 1 year, $12,000 & Charles Duncan, Synthsys, USA, 2011 APA Course, 1 year, $7,000 & Marie Egert, Hartwell Foundation, Synthetic Nanomaterials for Gene Conver- sion of Cytofbis, 3 years, $300,000 & Paul El-Fishawy, American Psychiatric Association, Study Research Fellowship, 1 year, $45,000 & Joel Gelernter, Virginia Commonwealth University (VA), Stress-Induced Drinking in Veterans: The Role of Combat History and PTSD, 1.2 years, $109,671 & David Hafler, National Institute of Neurological Disorders and Stroke (NIH), Discovery of a Gene for Cosinophilic Inflammatory Diseases Using High-Throughput Robotic Platforms, 2 years, $2,500,000 & Robert Herron, Weill Cornell Medical College for Community Research (NY), 4P Recruitment Dynamics and Network Structure in Responder Driven Samples, 3 years, $18,325 & Kristina Hernandez, Bur- roughs Wellcome Fund, Regulation of MicroRNA Biogenesis Through the Core Microprocessor Components, 1.8 years, $10,000 & Michael Higley, Richard and Susan Smith Family Foun- dation, Study of Neuronopathy, Neuroplasticity, and Psychosocial Functioning in the Prepontal cerebral cortex, 3 years, $500,000 & Debbie Humphries, Connecticut Association of Directors of Health, Connecticut Local Health Department (LAH) fee for Service Structure and Service Profiles Across LAHs and Within LAHs Over Time, 9 months, $34,000 & Jeanette Ickovics, Aetna Foundation, Inc., Childhood Obesity: Exploring the Childhood Obesity Context on Risk Behaviors and Health Out- comes, 15 years, $100,000 & Nils Loewen, Amer- ican Gastroenterology Association, 2011 Young Clinician Scientist Award, 1 year, $40,000 & Ruian Medhotirg, University of North Dakota, Mechanisms of Susceptibility to Viral-Bacterial Co-Infection, 6 months, $165,500 & Peter Morgan, Mind Science Foundation, Lucid Dreaming and Performance, Supporting Cognitive and Social Coping Task, 1 year, $15,000 & Angus Nairn, Rockefeller University (NY), Thalamic Striatopallidal Pathways and Actions of Psychostimulants, 1 year, $73,712 & Chirag Parikh, Tufts- New England Medical Center (MA), The Aging Kidney: Chronic Kidney Injury, Impaired Functions and Clinical Outcomes, 1.5 years, $17,955 & Franceska Peretepkichova, Green Chimneys: Adopting Dialectical Behavior Therapy for Children in Residential Care, Pilot Randomized Clinical Trial with Children with Severe Emotional and Behavioral Dysregulation, 1.3 years, $71,000 & Margaret Pitsalidis, Vanderbilt University Medical Center (TN), The anova US Study, 5 years, $18,990 & Carole Redlich, South- ern Illinois University School of Medicine (Dept. of Defense), Phase II Clinical Trials: D-Methio- nine to Reduce Nocice-Induced Hearing Loss, 2 years, $138,867 & Harvey Risch, Johns Hopkins University (MD), Validation and Final- ise Mapping of Pancreatic Cancer Susceptibil- ity (LA), 5 years, $55,200 & Carla Raths, Lulu Research Institute, Inc., Taming the Pathogenic Type I Interferon Response in in vitro, 3 years, $500,000 & Marianne San, Academic Pediatrics, New York, Pilot Study to understand IVIG Pharmacokinetics in the NICU, 1 year, $130,000 & Andrew Scherlis, United States Social Security Administration, Afflicted the Rickety- ness of the Pediatric Waiting Room, 1 year, $346,999 & Martin Schwartz, Uni- versity of Colorado at Denver, Understanding the Rh0(D) Mediator Suppressor Gene, 1.4 years, $115,069 & Qin Yan, Melanoma Research Foundation, Roles of Fatty Regu- lation on Melanoma Metastasis, 2 years, $90,000 & Yong Zhu, The Genevra Foundation (Dept. of Defense), Circadian Genes and Risk for Prostate Cancer, 1 year, $17,613

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 Torrent Proton sequencer, produced by San Diego-based company 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 alumni Jonathan Hruby and Kevin Biegel, PhD.

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 medical researchers and genetic counselors in their effort to uncover the causes of rare genetic diseases.

“Cost, speed, and ac- curacy are key elements in the use of dna sequencing for both disease-gen design- discovery and clinical utility,” says the school of Medicine’s Richard Lifton. “The technological advances in the new instrument promise to be game-changers for both research and clinical applications.”

Grants and contracts awarded to Yale School of Medicine March/April, 2011

Federal

Hervé Agassiz, nih, Regulation of Bacterial Pathogen Action-Based Host Response by Host Cell Kinases, 2 years, $515,143 & Emily Ansell, nih, Interpersonal Behaviors, Stress, and Addiction, 3 years, $590,832 & Albert Arias, nih, Alcohol Dependence: Pharmacotherapy, Pharmacoge- netics, and Genetics, 2 years, $680,318

Thomas Biederer, nih, Mechanisms of Synaptic- Induced Synapse Formation, 5 years, $2,235,200 & Ronald Duman, nih, Role of receptor and Synaptic Plasticity in the Development of Antidepressant Actions of nMDA Receptor Blockade, 5 years, $2,612,873 & Erol Gulcicek, nih, Tissue-Specific Barreloid Gene Expression, 5 years, $2,078,876 & Evelyn Hu, nih, The Role of Ribosome Biogen- esis, 3 years, $15,360 & Daniel Greif, nih, Morphogenesis of the Pulmonary Artery Smooth Muscle Layer, 4 years, $1,194,260 & Eduardo Gussian, nih, Regulation of Sallamine Venu- lation by the Phox Protein, 5 years, $2,076,428 & Erol Culicier, nih, Nano-Utral-231-Orchop- Vets MS System for Yale University-Kent Labo- ratory, 1 year, $777,400 & Hao Huang, nih, Art Imaging of Kapoor Oocyte Receptor. Transition Value and Sexification Effect Study, 3 years, $2,590,011 & Jeannette Ickovics, nih, School Wellness Policy, 3 years, $2,659,557 & Eva Kunkel, nih, Evaluate Impact on Childhood Obesity, 5 years, $2,921,148 & Leonid Kazmazek, nih, Expression of Iron Channels in the Auditory System, 5 years, $2,224,357 & Mun Yee, nih, Robotic Platform Functional Genes in Non- Human Primates, 2 years, $1,285,723 & Lingjun Zuo, nih, Deep Sequencing of Glutama- tergic Pathway Genes in Alcohol and Nicotine Co-Dependence, 2 years, $353,919

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 machin- ery 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 connec- tions 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 muta- tions are present and walking around somewhere,” says Lifton. It’s the goal of the CMG2 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 pos- sibilities 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 rec- ognition of what happens when genes are mutated in humans.”

And beyond the therapeutic im- plications 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 hu- man body. And this tells us a great deal about how entire pathways work, which is very important to future drug development.”
Stress at kidney stone treatment center and the sive surgery, and director of both the endo urology and minimally inva-

micro-incision, contains tubular the risk of infection. The tiny plate, highly purifi ed gold, an inert mate-

Solx wider range of patients to avoid these fail after fi ve years, while permanent-

standard—but it’s another tool that we have if we identify the right patient.”

These results “suggest that childhood stress may afect brain develop-

mental, 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 someone on treatment,” says Mayes, the Arnold Gesell Profes-

or of Child Psychiatry, who has been studying a group of 350 such chil-

dren, including the 42 whose brain scans are reported on in the new research. In this study, participants fi lled out the Childhood Trauma Question-

naire, which assesses perceived physi-

cal and emotional adversity. Again using structural imaging, 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.

In a separate collaborative study by researchers in the Department of

prostate, and kidney cancer; donor nephrectomy 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 Hous-

Texas.

He then served as general surgically and conventionally treated surgical and urology residencies at the Johns Hop-

kips Hospital in Baltimore, Md.

Schulam succeeds Robert M. Weiss, M.D., the Donald Guth-

rie 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 urologic practice in 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 eff orts 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 de-

partment’s inaugural chair.”

Glaucoma (from page 3) But current surgical therapies are far from ideal, says Loewen. In trabeculotomy, for example, surgeons create a small hole in the eye underneath the eyelid to drain fl uid, but in many cases scar tis-

ue builds up and causes failure.

Patients with early to moderate glaucoma have recently been treated at the YEC with a new procedure called a trabeculotomy, 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 trabeculotomy—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 trabeculotomy is that it up to 50 percent of procedures fail after fi ve years, while permanent-

ly increasing the risk for a devastat-

ing eye infection.”

Loewen hopes that the SOLX gold stent received by Isabel Soukup received will provide an alterna-
tive to trabeculotomy for a much wider range of patients to avoid these complications.

About the size of a fl attened grain of rice, the SOLX device is made of highly purifi ed gold, an inert mater-

e that can be inserted just 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 depriv es 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 dedi-

cated to using new medical science from all fi elds, including stem cell and gene therapies, to advance the under-

standing and treatment of glaucoma. Loewen conducts basic research to understand why IOP increases. He is currently working on a gene therapy designed to improve outfl ow by re-

placing the tissue that regulates fl ow, the trabecular meshwork. Grippo has also a special interest in optic disc drusen, calcifi ed 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 24 percent of eyes—some have been seen in patients who also present risk factors for glaucoma. “It’s very dif-

cult 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 diffi cult to detect. Adding to this diffi culty is the fact that both conditions may cause similar visual field loss.”

At present there is also no proven treatment for optic head drusen. Gripp-

po hopes to launch long-term prospec-
tive studies at Yale to better understand the relationship between drusen and glaucoma and to seek better therapies.

Tais believes that people who develop glaucoma may have unusu-

ally sensitive optic nerves that are easily damaged by fluctuations in IOP. Based upon this idea, Tais 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 col-

league Steven M. Strittmatter, M.D., Ph.D., the Virginia Professor of Neurology and professor of neuro-

biology, to study the role of a protein called Nogo that blocks nerve regen-

eration. 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 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 eff ects of fl uctuating IOP, and regen-

erate those optic nerve fi bers that have been damaged by the disease.”

“This is indeed an exciting time to be engaged in glaucoma research and treatment,” says Tais.

Honor a great physician on Doctor’s Day

The glaucoma experts of the Yale Eye Center are exemplars of the compassionate, skilled doctors of Yale Medical Group (YM), the largest academic multi-specialty medical practice in New England. When they joined the School of Medicine, YM physicians chose not only to provide world-class patient care, but to innovate within their fields by translating promising research into new treatments. In recognition of this dedication, YM doc-

tors earned a spot in New York magazine’s annual list of the region’s top doctors.

For more than 20 years, March 30th has been set aside as Doctor’s Day, a day to express admiration and gratitude to those who im-

prove our health and our lives. This year, become a friend to YM by making a charitable gift to help support our physicians in their important work.

Your contribution, large or small, will send a clear message to our hardworking doctors. Thank you for your support. To learn more, visit ymgyfund.org or contact us at 860-687-6747.
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 benefits and malleability of human development, and the way children grow and mature. Using 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 disorders. Her work 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 350 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 Gwynhyfare 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 interactions with genetic risk 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 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 Amary Winslow, M.S., D.R.P.H., who served as chair of the department from its founding in 1905 until his retirement in 1945. A scholar with an international reputation and a firm belief in the philosophers 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.

Each year, the presidents of 50 universities nomi- nate 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 $185,000 over five years.

Herzon’s past honors include the Searle Scholar Award and the Synthesis/Syntell 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-elect of the American College of Neuro-psychopharmacology. The ACNP is the leading organization focusing on the brain science related to neuropsychiatric disorders.

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 on Regional Anesthesia and Adult Anesthesia in the Department of Anesthesiology, and chair of the Health Professions Advisories Board at Yale College, Rosenbaum is a co-editor of the reference book Anesthesia Emergencies, and of numerous book chapters, articles, and other publications.

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 intern for 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 Biochemis-try 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, which in small, noncod- ing RNA molecules rather than proteins affect gene expression, was an important genetic regulator in the parasite.

In supporting her nomination, Shulamith Michaeli, M.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.