Medicine@Yale

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Advancing Biomedical Science, Education, and Health Care

As science moves faster, the world gets smaller

In a giant leap forward for personalized medicine—one of the most highly anticipated benefits of the Human Genome Project—Yale researchers have applied new technology to diagnose and recommend therapy for a rare intestinal disorder in a seriously ill baby half a world away.

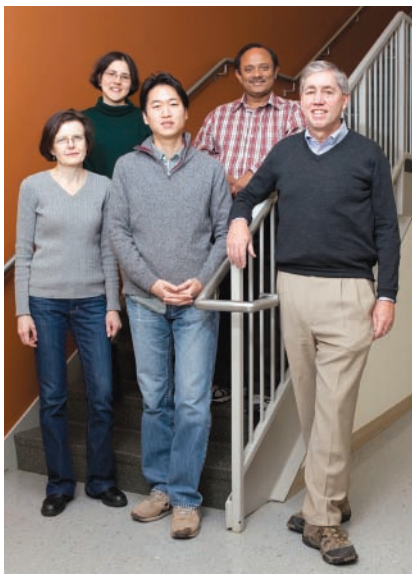
Doctors in Ankara, Turkey, were stumped as to the cause of chronic dehydration in a 5-month-old baby boy, and they called on the School of Medicine's Richard P. Lifton, M.D., PH.D., chair and Sterling Professor of Genetics, for help. After obtaining samples of the baby's DNA from the Turkish doctors, Lifton and colleagues at the newly launched Yale Center for Genome Analysis (YCGA) used an emerging technique to quickly and completely map the "exome," those regions of the boy's genome that contain protein-coding genes and their associated regulatory sequences.

In just 10 days, the Lifton team was able to determine that the baby harbored a rare mutation in an intestinal protein which causes congenital chloride diarrhea, a disorder in which the gastrointestinal tract fails to properly absorb chloride and water. Armed with this information, the baby's doctors were able to tailor a successful treatment program.

The feat was a landmark in personal genetics, marking the first time that a patient has been diagnosed, and treated, based on a comprehensive genetic scan. Moreover, it provided a preview of things to come from the YCGA, a centerpiece of the School of Medicine's research expansion onto Yale's West Campus.

"We believe this heralds the dawn of a new era in genetics and personalized medicine," says Lifton, also professor of medicine and a Howard Hughes Medical Institute investigator. "The results show that new technology can generate clinically useful results quickly, bringing doctors and patients closer to the day when comprehensive sequencing information will be a routine part of medical care."

Though the exome comprises only 1 to 2 percent of the genome, it includes crucial **// Genes** *(page 7)*



JERRY DOMIAN

(From left) Irina Tikhonova, Ute Scholl, Murim Choi, Shrikant Mane, and Richard Lifton used the latest genomic techniques to diagnose an illness in a baby 5,000 miles away in Turkey.

Fighting the fallout of childhood cancer

A personal encounter with a deadly cancer inspires a $3 million contribution to advance psychosocial care, research for child survivors

Riva Ariella Ritvo, PH.D., has a favorite quote from Gandhi: "The best way to find yourself is to lose yourself in the service of others."

For much of her life, Ritvo, known to friends as "Ari," has aimed to follow that maxim, treating and studying children with autism spectrum disorders at the Los Angeles–area Ritvo Clinic and as a clinical instructor of long standing at the Yale Child Study Center (YCSC). Ritvo's husband, Alan B. Slifka, M.B.A., a 1951 alumnus of Yale College and founder of New York–based Halcyon Asset Management, is similarly known for his public-spiritedness. In addition to being the major donor to the Joseph Slifka Center for Jewish Life at Yale (named in honor of his father), Slifka has been instrumental in advancing the cause of peaceful coexistence. Through the Alan B. Slifka Foundation, he launched The Abraham Fund, which promotes equality and peace between Arabs and Jews in Israel, and he endowed the Alan B. Slifka Program in Intercommunal Coexistence, a master's degree program in coexistence and conflict studies at Brandeis University.

"Alan is a visionary," says Ritvo. "He likes to sponsor things that don't exist yet. He was founding chairman of the Big Apple Circus. He was the first to release dolphins in captivity into the wild." **// Ritvo** *(page 5)*

MAGGIE HEINZEL-NEEL

(Clockwise from left) Max Ritvo with his parents, Ariella Ritvo and Alan Slifka. The Slifka Foundation has endowed a new professorship at the Yale Child Study Center focused on the psychosocial needs of children who survive cancer.

Medical school mounts mission of mercy for Haiti

On January 18, Martin Luther King Day, people around the world were still struggling to grasp the extent of the devastation wrought in Haiti by a magnitude 7.0 earthquake, the epicenter of which lay just 15 miles from the nation's densely populated capital, Port-au-Prince.

That day, David J. Leffell, M.D., the David Paige Smith Professor of Dermatology and Surgery and deputy dean for clinical affairs, conferred with Paul D. Cleary, PH.D., dean of the Yale School of Public Health and Anna M.R. Lauder Professor of Public Health, about the crisis.

Leffell speedily convened a meeting with Roberta L. Hines, M.D., chair and Nicholas M. Greene Professor of Anesthesiology; Martha C. Highsmith, PH.D., deputy secretary of Yale University; Gregory Luke Larkin, M.D., M.S.P.H., professor of emergency medicine; Linda C. Degutis, DR.P.H., M.S.N., associate professor of emergency medicine and **// Haiti** *(page 7)*

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INSIDE THIS ISSUE

ALSO

TERRY DAGRADI

"That's what my mind looks like," says neurobiologist Amy Arnsten of her office blackboard, where the data, sketches, and speculations that flow from her research on the prefrontal cortex of the brain make up an ever-changing mural. Arnsten's work has led to new treatments for attention-deficit hyperactivity disorder and post-traumatic stress disorder.

Keeping the brain in balance

A scientist's lifelong quest to make a difference for the mentally ill

Amy F. T. Arnsten, PH.D., is one of those lucky souls who discover at a fairly young age what their life's work will be. While a student at Columbia High School in Maplewood, N.J., in the early 1970s, Arnsten spent summers working with children with mental illness, an interest that was "crystallized," she says, when she volunteered at the Greystone Park Psychiatric Hospital in nearby Morris Plains. At Greystone, only two psychiatrists served a population of 2,000 patients, many of whom, in an age of limited legal rights for psychiatric patients and relatively crude medications, had been institutionalized for their entire adult lives. "It was like we were still in the Middle Ages," she says, "and I knew this was an area where one could make—and needed to make—a huge difference."

As an undergraduate at Brown University, Arnsten largely designed her own course of study in the "irresistibly fascinating" field of neuroscience. Having noted at Greystone that even mild stress could greatly worsen patients' symptoms, Arnsten devoted her doctoral research at the University of California, San Diego (UCSD), to norepinephrine (NE), a brain chemical released in response to stress. She had arranged a postdoctoral fellowship at the University of Cambridge to continue this work, but a seminar given at UCSD by the late Patricia Goldman-Rakic, PH.D., a scientist visiting from Yale, changed her plan, and altered the course of her scientific career. "She talked about her research on the development of the prefrontal cortex," Arnsten recalls, "and I said to myself, 'That's what I have to know.'"

In 1982, Arnsten began postdoctoral studies at Yale. Under Goldman-Rakic's tutelage, she began the exploration of the neurochemistry of the prefrontal cortex (PFC) that has captivated her ever since.

The PFC is a region at the front of the brain that is crucial to so-called executive functions—decision-making, planning, predicting, and suppressing distracting thoughts or socially unacceptable behaviors. For such an important structure, there is remarkably little room for error in the PFC, says Arnsten, who has playfully dubbed it the brain's Goldilocks: it functions best "when everything is just right." When we are fatigued or stressed, which can happen many times over the course of a single day, the relative levels of PFC neurotransmitters fluctuate, and its function declines. In extreme situations, or as a result of genetic factors, mental illness can result, and the list of psychiatric disorders associated with PFC dysfunction—post-traumatic stress disorder (PTSD), schizophrenia, obsessive-compulsive disorder, bipolar disorder, attention-deficit hyperactivity disorder (ADHD), anxiety disorders, and many more—is long and varied.

Arnsten has seen her research bear fruit in medications that meet the PFC's "molecular needs." Based on work in her lab, the generic compound prazosin is now used to treat PTSD. And last September, for ADHD, the Food and Drug Administration approved Intuniv, a new formulation of a compound that was inspired by Arnsten's research. Arnsten is now working with Yale's Office of Cooperative Research to develop a plant-derived compound that has shown promise for treating schizophrenia, bipolar disorder, PTSD, and related conditions.

"This is a tremendously collaborative environment," says Arnsten. "We are at a point of revolution in psychiatry and neuroscience, and Yale is a place where a lot of that is happening."

Yale Netcast
"This Is Your Brain on Stress"
Available on iTunesU or at medicineatyale.org

Medical historian lauded by Yale's graduate school for mentorship

John Harley Warner, PH.D., chair and Avalon Professor of the History of Medicine and an expert on the cultural and social history of medicine in the United States during the 19th and 20th centuries, is a recipient of a 2010 Graduate Mentor Award in the humanities from Yale University's Graduate School of Arts and Sciences.

The award, the university's top honor for teaching, advising, and mentoring, recognizes teachers and advisors for exceptional support of the professional, scholarly, and personal development of their students. Warner will be honored in February during the university's Mentoring Week and at the Graduate School Convocation in May.

John Harley Warner

After receiving his doctorate in the history of science from Harvard University in 1984, Warner was a postdoctoral fellow at the Wellcome Institute for the History of Medicine in London. He joined the medical school faculty as assistant professor of the history of medicine in 1986 and became chair of the section in 2002.

Under Warner's leadership of the Program in the History of Science and Medicine, Yale College's undergraduate major in the History of Science/History of Medicine (one of Yale's 10 largest majors) attracts about 40 new students per year.

Warner is the author of numerous scholarly articles and three books. In 2009, Warner and James S. Edmonson, PH.D., chief curator of Case Western Reserve University's Dittrick Medical History Center, published *Dissection: Photographs of a Rite in Passage in American Medicine, 1880–1930*, to wide critical acclaim.

Also receiving Graduate Mentor Awards were Suzanne H. Alonzo, PH.D., assistant professor of ecology and evolutionary biology, for the sciences, and Kelly D. Brownell, PH.D., professor of psychology and epidemiology, for social sciences.

Radiotherapists honor Yale expert on tumor biology

Sara Rockwell

Sara Rockwell, PH.D., professor of therapeutic radiology and pharmacology, and associate dean for scientific affairs, has been named a fellow of the American Society for Radiation Oncology (ASTRO). She received the award at ASTRO's 51st Annual Meeting, held in Chicago last November.

Rockwell, who joined the medical school in 1974, is an expert on the biology of solid tumors. Many regions of these tumors are profoundly oxygen- and nutrient-deprived, factors that have diverse effects on their physiology and on their response to treatment with radiation and anticancer drugs. In over 200 scientific publications, Rockwell has described these distinctive features and reported on approaches aimed at using these features to improve cancer therapy.

Rockwell, editor-in-chief of *Radiation Research*, teaches in courses on radiation biology, pharmacology, cancer biology, and ethics. She directs the Tracking and Evaluation Program for the Yale Center for Clinical Investigation (YCCI), and is a member of its executive committee. Rockwell is the medical school's representative to the American Association of Medical Colleges' Group on Research and Development, and Yale University's representative to the Federal Demonstration Partnership.

ASTRO is the largest radiation oncology society, with more than 10,000 members worldwide. A small number of long-standing ASTRO members who exemplify "excellence in research, patient care, education, and leadership/service" are chosen as fellows each year.

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ZHAOXIA SUN

Bending the curve: drug halts kidney cysts

About one-half of patients with the most common form of polycystic kidney disease (PKD), which affects about 600,000 Americans, will eventually succumb to kidney failure requiring transplant or dialysis.

Researchers studying zebrafish have noted that kidney cysts in these animals are often accompanied by a distinctive body curvature (see photo). Using this curve as a guide, Associate Professor of Genetics Zhaoxia Sun, PH.D., and colleagues report in the December 22, 2009 issue of *Proceedings of the National Academy of Sciences* that kidney cysts could be suppressed in the fish with valproic acid, a drug used for epilepsy and bipolar disorder under the trade name Depakote. The effectiveness of the compound was then confirmed in mice by PKD expert Stefan Somlo, M.D., the C.N.H. Long Professor of Internal Medicine.

"This is exciting," says Sun, "because valproic acid is also in clinical trials as a potential cancer drug and has a known safety profile."

A good drug is better when parents can help

Children with pervasive developmental disorders (PDDs)—autism, Asperger disorder, and related disorders—may be impulsive and aggressive to an extent that severely affects their daily lives.

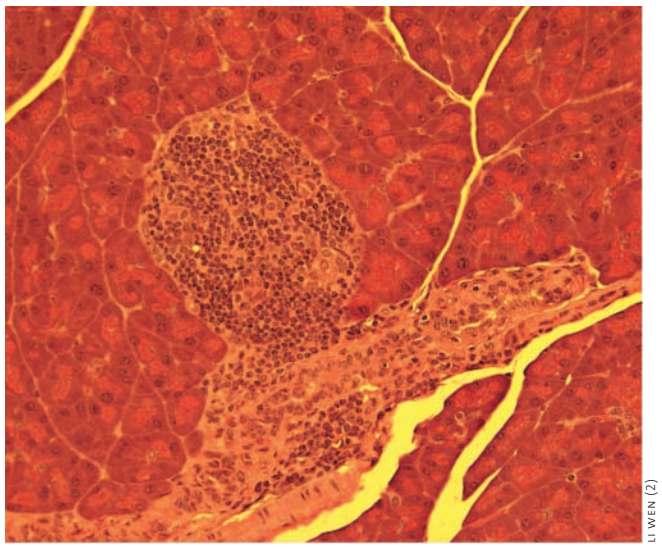
In previous work with colleagues in the National Institute of Mental Health (NIMH) Research Units on Pediatric Psychopharmacology (RUPP) Autism Network, Lawrence D. Scahill, M.S.N., PH.D., professor of nursing and child psychiatry, has shown that the drug risperidone can temper the "Richter-scale" tantrums of children with autism. But the drug does not improve the core symptoms of PDDs, and it has side effects, including weight gain and its associated health effects.

In the December 2009 issue of the *Journal of the American Academy of Child and Adolescent Psychiatry*, RUPP researchers report that supplementing risperidone treatment with parent training allowed them to significantly reduce the dose of the drug while retaining its benefits.

Scahill and RUPP colleagues have a new NIMH grant to assess the efficacy of parent training alone in preschool-age children with PDDs accompanied by disruptive, noncompliant behavior. The study, the first of its kind, will enroll 180 children through five medical centers.

Autoimmunity: finding common ground

The shared biological mechanisms of diverse autoimmune disorders inspire a united research effort



LI WEN (2)

A pancreatic islet from a mouse with diabetes (above) shows extensive lymphocyte infiltration, compared to the islet seen in the pancreas of a healthy mouse (right). Islets contain insulin-producing beta cells, which autoreactive lymphocytes attack.

Among researchers who study the adaptive immune system, generally speaking, you're a T cell person or a B cell person. Kevan Herold, M.D., professor of immunobiology and medicine, studies T cells, so called because they mature in the thymus. Herold's colleague, Eric Meffre, PH.D., associate professor of immunobiology, studies B cells, which mature in bone marrow. T cells play a central role in the immune responses mounted by cells themselves; the primary job of B cells, in contrast, is to produce antibodies that target specific pathogens. Both play key roles in immunity, but Herold, an expert on type 1 diabetes, recalls that when he was doing postgraduate work at the University of Chicago in the 1980s, "the T cell people were in one building, and the B cell people were in another building," he says. "And we never talked to them."

Thanks to Herold, at Yale, things are moving in the opposite direction. He is a driving force behind the School of Medicine's recent designation as an Autoimmunity Center of Excellence (ACE) by the National Institutes of Health (NIH), an achievement that Yale scientists see as a catalyst for a new burst of collaborative work on the dysfunctions of the immune system that underlie diverse diseases such as diabetes, lupus, and multiple sclerosis.

"We're extremely strong in basic immunology, and our immunobiology department is one of the best in the country," says Robert J. Alpern, M.D., dean and Ensign Professor of Medicine. "What we have focused on in the last five years is to take advantage of our best basic science and use that as a nidus to spin off translational research. And the new emphasis on autoimmunity is an example of that."

Autoimmune diseases vary greatly in symptoms, but in all cases the underlying cause is the failure of the immune system to recognize one's own normal cells and tissues as "self"; rather, the immune system mistakes these benign cells and tissues as foreign, and attacks them, causing inflammation and cell death. Because these diseases affect a wide range of organ systems, about 70 Yale Medical Group physicians in diverse specialties treat some form of autoimmune disease. However, the underlying mechanisms in apparently quite different diseases, such as diabetes and multiple sclerosis (MS), are remarkably similar—a fact that has great implications for further research (see sidebar, page 7). Yale's ACE will, Herold hopes, stimulate collaborative research and pave the way for a greater understanding of common mechanisms of and potential treatments for autoimmune diseases.

The ACE program is a collaborative effort between the National Institute of Allergy and Infectious Diseases, the lead institution funding ACE; the Office of Research on Women's Health; and the National Institute of Diabetes and Digestive and Kidney Diseases, all agencies of the NIH. In late 2009, Herold and Insoo Kang, M.D., associate professor of medicine, applied for and received the grant that established Yale's ACE, now one of nine such centers in the U.S., which conduct collaborative research among themselves under the auspices of a national steering committee. The ACE grant, which is renewable at five-year intervals, enables the Yale scientists to participate in clinical trials and to initiate trials at Yale. Yale's ACE will be a center in a trial of a new immunologic in Sjögren's syndrome—an autoimmune disease of the tear ducts and salivary glands—for instance. And "we are looking into trials for scleroderma," says Herold.

It is an auspicious time for a melding of efforts in autoimmunity at Yale, says Herold, who came to the School of Medicine three years ago to direct the autoimmunity research in the Department of Immunobiology's Human and Translational Immunology (HTI) program. HTI, directed by Jordan S. Pober, M.D., PH.D., professor of immunobiology, dermatology, and pathology, aims to move advances in basic immunology into a clinical setting.

"It was very clear to me, when I came here, that scattered across the campus there were outstanding people doing translational work in autoimmunity," says Herold, who explores why overactive immune T cells mistakenly destroy the insulin-producing beta cells in the pancreas, causing type 1 diabetes. "But there hadn't really been an outlet" for translation into clinical trials that would "enable the investigators to get more in depth into the clinically relevant immunologic questions," he says. "Hopefully this center will do it."

Crucial to these efforts is the arrival in 2009 of David A. Hafler, M.D., chair of the medical school's Department of Neurology and Gilbert H. Glaser Professor. Hafler, also chief of neurology at Yale-New Haven Hospital (YNHH), came to Yale from Harvard Medical School, bringing a wealth of expertise in MS. Hafler is a leader in the effort to define the molecular basis and causes of MS, and he was among the first to apply the technique of T cell cloning to human disease, identifying the targets of activated immune cells in MS patients.

But in keeping with Yale's focus on the commonalities of autoimmune diseases, Hafler has also done extensive research on the mechanisms of type 1 diabetes, and currently has an NIH-funded grant to study that disease. "If you look at the genetics of autoimmune disease, there's a striking commonality of genetic variants. Presumably there is also an underlying similarity in terms of the immune system," Hafler says. "We don't truly understand the pathogenesis of any of these diseases at the level that we want to, but they have a commonality in terms of treatment. Some treatments are different, some are very similar, and some are paradoxical," he says, citing as an example anti-TNF, which improves rheumatoid arthritis symptoms but seems to worsen MS. "These curious paradoxes give us great insight into these diseases. It's not a luxury—it's almost a requirement—to look to the mainstream

// ACE *(page 7)*

MEDICINE tomorrow

Campaign gifts can sustain the "stimulus package"

As described on page 6, researchers at the School of Medicine landed over $100 million in grants from the American Recovery and Reinvestment Act of 2009 (ARRA) to fund their research for the next two years.

These investigators will answer many important questions in areas like cancer, Alzheimer's disease, autism, and heart disease, but they will also uncover mysteries and new opportunities for further study. In three years' time, when ARRA funds are no longer available, how will those new studies be funded?

Private gifts to create research endowments are a lasting and satisfying answer. Endowed funds provide secure funding, in perpetuity, for research in areas of mutual interest to donors and scientists. These gifts are invested in the Yale Endowment and historically, have enjoyed both secure, annual income, and solid growth of principal—a permanent stimulus for top science.

For more details, contact Jancy Houck at (203) 436-8560.

Endow a research fund: $100,000 and up

OUT & ABOUT

November 19 The 17th annual **Hunger and Homelessness Auction** sponsored by the Yale Health Professional Schools raised nearly $20,000 to benefit New Haven–area charitable organizations. A silent auction that began on Nov. 16 included offerings of clothing, dinners, food, and lessons in language, arts, dance, and sports. The live auction featured such prizes as tarot card readings, a vintage Epiphone guitar, and a chance to challenge a team fielded by Dean Robert J. Alpern, M.D., in a softball game this spring. **1. Wade Brubacher**, a professional auctioneer from Kansas and father of fourth-year medical student **Jake Brubacher**, handled the bidding at the live auction. **2. Nancy R. Angoff**, M.P.H., M.D., associate dean for student affairs (right), and **Margaret J. Bia**, M.D., professor of medicine, raised $800 with their "Girls' Night Out," which promised "good food, great company, juicy gossip, and worldly wisdom." **3.** Second-year medical students **Kristina Liu** (left) and **Ferrin Ruiz** displayed one of the auction items, a rendering of the medical school's official coat-of-arms. **4.** Second-year medical students **Amy Forrestel** (left) and **Julia Lubsen** (right) peruse offerings at the silent auction. **5.** First-year medical students **Bixiao "Brian" Zhao** (left) and **Michael Alpert** (at piano) provided musical entertainment during the silent auction. **6.** First-year Physician Associate Program student **Jennifer Paeske** makes a bid.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JOHN CURTIS (6)


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November 26 With his wife, **Beth Balschi**, **John W. Blanton**, M.D., assistant clinical professor of pediatrics, hosted 10 School of Medicine students for **Thanksgiving Dinner** at their home in New Haven. (Front, from left) Balschi, Blanton, **Warren Perry**, and **Hao Feng**. (Back, from left) **Timothy Law**, **Nyasha George**, **Debra Smith**, **Tammi Marie-Phillip**, **Charles Odonkor**, **Samrawit Goshu**, **Juliana Tolles**, and **Bing Zhang**.

COURTESY OF JOHN BLANTON

TERRY DAGRADI

November 30 A reception celebrating the appointment of **David A. Hafler**, M.D., as the inaugural **Gilbert H. Glaser Professor** was held at the Cushing/Whitney Medical Historical Library. Hafler, chair of neurology at the School of Medicine and chief of neurology at Yale-New Haven Hospital, is a leader in the effort to better understand the molecular basis of multiple sclerosis (see related story, page 3). The new professorship was established by friends and colleagues of Glaser, professor emeritus of neurology and chair of the Department of Neurology from 1971 to 1986. A widely recognized pioneer in the field, Glaser led Yale's epilepsy program to become one of the foremost in the world. (From left) Hafler, Glaser, and **Stephen G. Waxman**, M.D., PH.D., Bridget Marie Flaherty Professor of Neurology, Neurobiology, and Pharmacology, and chair of the Department of Neurology from 1986 to 2009.

HAROLD SHAPIRO

December 7 Officials from PepsiCo marked the opening of a new **PepsiCo Research Laboratory** at Yale with a visit to New Haven. Research at the new lab, at 25 Science Park, adjacent to the Yale campus, will focus on the development of healthier food and beverage products. PepsiCo will also fund a graduate fellowship to support research related to nutritional science as part of the School of Medicine's Medical Scientist Training Program (MSTP), known informally on campus as the M.D./PH.D. Program. The new lab is PepsiCo's ninth global regional research center. (Front, from left) **Carolyn W. Slayman**, PH.D., Sterling Professor of Genetics, deputy dean for academic and scientific affairs, and professor of cellular and molecular physiology; **Robert J. Alpern**, M.D., dean and Ensign Professor of Medicine; **Mehmood Khan**, M.D., chief scientific officer, PepsiCo; **Mark Pirner**, M.D., PH.D., director, clinical and scientific development strategy, PepsiCo. (Back, from left) **Mary Resseguie**, PH.D., senior scientist, PepsiCo; **Derek Yach**, M.B.CH.B., M.P.H., senior vice president, global health policy, PepsiCo; **George A. Mensah**, M.D., director, heart health and global health policy, PepsiCo; **Robert S. Sherwin**, M.D., the C.N.H. Long Professor of Medicine; **Kevan Herold**, M.D., professor of immunobiology and medicine; **Gregory Yep**, PH.D., global vice president, long-term research, PepsiCo; **Patricia E. Pedersen**, PH.D., associate vice president for development and university director of corporate and foundation relations at Yale; **James D. Jamieson**, M.D., PH.D., professor of cell biology and director of the MSTP; **Kenneth R. Williams**, PH.D., adjunct professor of research in molecular biophysics and biochemistry, and director of the School of Medicine's W.M. Keck Foundation Biotechnology Resource Laboratory, the Yale/NHLBI Proteomics Center, and the Yale/NIDA Neuroproteomics Center; **Amy P. Rich**, M.P.H., senior associate director of corporate and foundation relations in Yale's Office of Development; **Heidi Kleinbach-Sauter**, PH.D., senior vice president, research and development, global foods, PepsiCo.

JANICE CARR/CORBIS

Sniffing out a strategy to defeat malaria

Humans spend $10 billion per year on deodorants, but to mosquitoes—including *Anopheles gambiae*, carriers of malaria in sub-Saharan Africa (see photo)—our sweat is the sweetest perfume.

In the February 3 online edition of *Nature*, John R. Carlson, PH.D., the Eugene Higgins Professor of Molecular, Cellular, and Developmental Biology, and colleagues report that they expressed a variety of *A. gambiae* odorant receptors in a neuron on the antennae of mutant fruit flies. First author Allison Carey, a student in the School of Medicine's M.D./PH.D. program, then recorded over 27,000 responses to 110 different odors.

The team found that many *A. gambiae* receptors are precisely tuned and highly sensitive to components of human body odors, which helps them locate and infect the hundreds of millions of people afflicted with malaria each year.

"Compounds that jam these receptors could impair the ability of mosquitoes to find us," says Carlson. "Compounds that excite some of these receptors could help lure mosquitoes into traps or repel them."

Appreciating RNA in a whole new way

Not so long ago, biology textbooks depicted proteins as the workhorses that carry out most biochemical reactions in cells, while pigeonholing RNA as a mere middleman between DNA and proteins. But over the past twenty years, it has become clear that RNA can play far more complex roles.

In the December 3, 2009 issue of *Nature,* scientists in the laboratory of Ronald R. Breaker, PH.D., the Henry Ford II Professor of Molecular, Cellular, and Developmental Biology and Howard Hughes Medical Institute Investigator, describe a slew of previously unknown RNA-based structures that may carry out complex biochemical functions.

First author Zasha Weinberg, PH.D., and colleagues in Breaker's lab report in detail on two large, intricate structures built entirely of RNA in bacteria. One, GOLLD, appears to help viruses that infect bacteria to burst out of infected cells so that they can seek new targets. Another, HEARO, might be a mobile genetic element that causes spontaneous genetic change.

Breaker says the research helps us come to grips with how cells such as our own really function. "Every time we feel as though we're giving RNA just about the right amount of credit," he says, "we find more amazing RNAs."

Study finds improved heart attack care

Using new guidelines, hospitals are unblocking arteries more quickly, and improving patients' outcomes

Patients with heart disease have benefitted enormously from advances in cardiology over the last few decades, including cholesterol-lowering statin drugs and better blood pressure medications. And if a heart attack should occur, percutaneous coronary intervention (PCI; more commonly known as balloon angioplasty) can be a lifesaver, opening up blocked arteries to restore blood flow to the heart.

But with PCI, time is of the essence. In 2006, in order to minimize lasting damage to heart cells from oxygen deprivation, the American College of Cardiology and 38 partner organizations launched a national campaign known as the D2B Alliance. To shorten "door-to-balloon" (D2B) times—the time from when a patient enters the hospital to the point when blood flow is restored to the heart by opening a blockage with angioplasty—the alliance set a goal of 75 percent of patients receiving this life-saving heart attack care within 90 minutes of hospital arrival.

In 2005, less than half of hospitals studied met those guidelines for D2B times. But in a study of the most recent data from the National Cardiovascular Data Registry (NCDR) published by a Yale-led team in the December 15, 2009 issue of the *Journal of the American College of Cardiology*, more than 80 percent of hospitals met the guidelines.

The study team surveyed D2B times in 831 hospitals participating in the NCDR's CathPCI Registry from April 1, 2005 to March 31, 2008. The survey showed marked reductions in unnecessary delays in treatment and widespread adoption of recommended strategies to improve care. The improvement was seen not just in select hospitals or certain states, but across the nation.

"The key is to have a leader and a team devoted to a single goal and to be persistent, even in the face of setbacks," says senior author Elizabeth H. Bradley, PH.D., professor of public health at the Yale School of Public Health and associate clinical professor of nursing. "This campaign has changed the way heart attack care is delivered—for the benefit of patients."

TERRY DAGRADI

In a study evaluating emergency heart attack care at 831 U.S. hospitals, Elizabeth Bradley (above), Harlan Krumholz (left), and colleagues found a significant improvement in "door-to-balloon" (D2B) times—the time period between arrival at the hospital and completion of angioplasty—following the implementation of new D2B guidelines set by the American College of Cardiology and 38 partner organizations.

Some examples of strategies to reduce D2B times include having emergency department staff able to activate the catheterization laboratory with a single call, taking steps to ensure that a catheterization team can be in the lab within 20–30 minutes of being paged, and promptly reporting data on D2B times to staff.

Bradley's co-author Harlan M. Krumholz, M.D., the Harold H. Hines Jr. Professor of Medicine and Public Health, said patients are now being treated so rapidly that in some cases the heart attack is aborted, damage is avoided, and patients rapidly experience a full recovery. "This remarkable leap in performance is a tribute to the nation's interventional cardiologists and other healthcare professionals who quickly adopted effective systems that were developed by NIH-sponsored research," he says.

"Most of what we read about in health care reform is about health care financing," Bradley adds. "This effort shows that the way care is organized can have tremendous impact, and with relatively little added resources."

// Ritvo *(from page 1)*

Late last year, the Slifka Foundation built on its tradition of innovative philanthropy with a $3 million gift to the School of Medicine establishing the Riva Ariella Ritvo Professorship in pediatric oncology psychosocial services at the YCSC.

"In providing this gift to Yale, Ariella Ritvo and Alan Slifka are providing essential help for children with cancer," says Robert J. Alpern, M.D., dean of the medical school and Ensign Professor of Medicine. "The psychosocial challenges faced by young cancer patients are an important problem, and in great need of philanthropic support."

The new gift has very personal roots. In October 2007, Ritvo and Slifka's world was turned upside-down when Ritvo's 16-year-old son, Max, fell ill with mysterious symptoms. Complaining of minor back pain, which he first attributed to a possible sports injury—he is a second-degree black belt in martial arts—Max Ritvo soon developed a fever, which got steadily worse, and he was finally raced to a Santa Monica, Calif., hospital for evaluation.

"Within a week," recalls Ari Ritvo, "I went from having a boy with a fever and a minor backache to admitting him to the emergency room."

Max was ultimately diagnosed with Ewing sarcoma, a cancer of the bone and soft tissue that mainly affects teenage boys. It is an insidious disease: like ovarian cancer, Ewing sarcoma generally has no definitive symptoms until after it has metastasized. Because of his advanced illness, Max was flown to Sloan-Kettering.

After several rounds of grueling chemotherapy, Max's cancer regressed to the point that he was eligible for surgical treatment. Finally, following surgery and a subsequent course of radiotherapy, he was declared to be in remission in June 2008.

Throughout his ordeal, Max and his family relied heavily on the counsel and support of Abraham S. Bartell, M.D., a psychiatrist and psychopharmacologist at Sloan-Kettering specializing in the psychosocial needs of young people with cancer and their families.

In one of Ari Ritvo's frequent phone calls with Fred R. Volkmar, M.D., the Irving B. Harris Professor of Child Psychiatry and director of the YCSC, Volkmar said that the YCSC had provided seed money for a Yale program providing psychosocial services to pediatric oncology patients. Because of the difference such services had made in her family's life, Ritvo encouraged Volkmar to submit a pilot program proposal to the Slifka Foundation, which agreed to take over funding for the program. Then she and Slifka decided to establish the new professorship.

"It's a wonderful program, and I give Ari Ritvo and Alan Slifka tremendous credit for doing all of this. These are children who have a tremendous range of mental health needs, and so do their families," says Volkmar. "We want to be there to help address pressing issues, but we can also help to prevent future problems. We want to be involved at all levels, and the vision behind this gift is to do just that."

With improvements in diagnosis and therapy, more children than ever before survive cancer. But the psychological aftermath, which in addition to emotional distress can include the development of serious learning disabilities in children who undergo chemotherapy, is often overlooked.

"The world needs to accommodate" the ever-increasing number of survivors, says Ritvo. "It's going to cost some money to do epidemiologic surveys and conduct research to determine who these kids are, and what their specific needs are during and after treatment."

Max Ritvo, now a Yale freshman in Jonathan Edwards College in the Directed Studies program, continues to do well. He has joined the board of Kids Kicking Cancer, a Detroit-based nonprofit organization that helps pediatric oncology patients manage stress through meditation and the martial arts.

Grants and contracts awarded to Yale School of Medicine

May/June 2009

Federal

Philip Askenase, NIH, *The Role of AIDS in Contact Sensitivity*, 2 years, $455,125 • **Sonia Caprio**, NIH, *Metabolic Markers and Predictors of Childhood Obesity*, 5 years, $1,373,650 • **Kelly Cosgrove**, NIH, *Dopaminergic and Endocannabinoid Interactions in Nicotine Dependence*, 1 year, $194,700 • **Jared Davis**, NIH, *Investigating the Mechanism of mRNA Cleavage in the Ribosomal A-Site*, 2 years, $96,856 **Robin de Graaf**, NIH, *Cerebral Metabolic Flux Mapping using Oxygen-17 NMR*, 2 years, $903,284 **Ralph DiLeone**, NIH, *Development of Neuronal Tracers to Study Leptin Modulation of Dopamine Circuits*, 2 years, $389,125 • **Maria Diuk-Wasser**, NIH, *Determining the Reservoir for Host-Targeted Control Measures to Prevent Lyme Disease*, 2 years, $165,500 • **Robert Dubrow**, NIH, *Framework Program for Global Health at Yale University*, 2 years, $270,000 • **Barbara Ehrlich**, NIH, *Regulation of Cholangiocytes by InsP3 Receptor Isoforms*, 4 years, $1,729,897 • **Sorin Fedeles**, NIH, *Molecular Pathogenesis of Autosomal Dominant Polycystic Liver Disease (ADPLD)*, 2 years, $50,988 • **Erol Fikrig**, NIH, *Circadian Regulation of Innate Immune Mechanisms of Viral Recognition*, 2 years, $455,125 **Jorge Galán**, NIH, *Molecular Mechanisms of* Salmonella typhi *Pathogenicity*, 2 years, $631,892 **Alison Galvani**, NIH, *Impacts of Individual and Social Behavior on Influenza Dynamics and Control*, 5 years, $2,986,225 • **Kevan Herold**, NIH, *Yale Autoimmunity Center of Excellence*, 5 years, $3,886,266 • **Sohail Husain**, NIH, *Ryanodine Receptor in Pancreatitis*, 5 years, $1,731,406 • **Melinda Irwin**, NIH, *Impact of Exercise on Ovarian Cancer Prognosis*, 5 years, $3,375,064 • **Akiko Iwasaki**, NIH, *NLR Control of Antiviral Defense in the Respiratory Mucosa*, 2 years, $455,125 • **Susan Kaech**, NIH, *Determining How Adjuvants Alter Effector and Memory T Cells during Vaccination*, 2 years, $455,125; NIH, *Control of Effector and Memory T Cell Development by Inflammatory Signals*, 5 years, $2,060,662 • **Barbara Kazmierczak**, NIH, *Regulation of Motility and Organelle Assembly at the* Pseudomonas aeruginosa *Pole*, 2 years, $820,950 **David Kingery**, NIH, *Exploring the Transition State of Ribosomal Peptide Bond Catalysis*, 2 years, $41,176 • **Anthony Koleske**, NIH, *Regulation of Invadopodia Formation in Breast Cancer Cells*, 2 years, $618,142 • **Haiqun Lin**, NIH, *Longitudinal Study of Transitions in Disability and Death among Older Persons*, 3 years, $989,825 • **James Mazer**, NIH, *Allocation and Control of Visual Attention*, 2 years, $768,627 • **Gil Mor**, NIH, *Function of Toll-Like Receptors Throughout Gestation*, 5 years, $5,491,503 • **Sukanya Narasimhan**, NIH, *Tick Midgut Proteins Critical for* Borrelia *Transmission*, 2 years, $455,125 • **Alexander Neumeister**, NIH, *Serotonin 1B Receptor Imaging in Major Depressive Disorder*, 2 years, $353,386 • **Michael Nitabach**, NIH, *Novel Analgesics from Australian Funnel-Web Spider Venom*, 2 years, $455,125 • **Samuel Sathyanesan**, NIH, *Role of Transcription Factors in the Action of Antipsychotic Drugs*, 2 years, $389,125 **Albert Sinusas**, NIH, *Hybrid Volumetric SPECT/CT Imaging System*, 1 year, $500,000 • **Jeffrey Sklar**, NIH, *Trans-Splicing of RNA in Endometrial Stroma and Other Tissues*, 5 years, $1,665,114 • **Thomas Steitz**, NIH, *Structural Bases of the Functions of RNA-Protein Machines*, 5 years, $7,732,270 **Stephen Strittmatter**, NIH, *Axonal Growth Cone Signal Transduction*, 3 years, $1,422,273 • **Scott Strobel**, Dept. of Defense (U.S.), *Investigation of Diesel Producing Fungi as a Renewable Source of Fuel*, 5 years, $4,175,381 • **Joann Sweasy**, NIH, *DNA Polymerase Beta and Mutagenesis*, 5 years, $1,628,932 • **Cenk Tek**, NIH, *Lifestyle Modification to Reduce Weight and Related Morbidity in Mental Illness*, 2 years, $1,345,812 • **Timur Yarovinsky**, NIH, *Type I Interferon-Induced Protection from Staphylococcal Pore-Forming Toxins*, 2 years, $443,892

Non-Federal

Steven Bernstein, Montefiore Medical Center & Hospital, *Trial to Test the Efficacy of a Tailored Intensive Smoking Cessation Intervention in Persons Living with AIDS*, 1 year, $12,793 • **Linda Bockenstedt**, Nat'l Research Fund for Tick-Borne Diseases, Inc., *Real-Time Imaging of Vector-Borne* Borrelia burgdorferi *Infection in Mice*, 1 year, $60,000 • **Mary Bogucki**, Spectral Energetics, Inc., *Non-Ionizing Radiation Vision for a New Army (NIRVANA)*, 5 months, $27,234 • **Angelique Bordey**, Elsa U. Pardee Foundation, *Control of Blood Flow in Glioma*, 1 year, $123,963 • **Michael Cappello**, March of Dimes, *Mucosal Immunity to Hookworm Infection and Disease*, 3 years, $300,000 • **Sreeganga Chandra**, W.M. Keck Foundation, *Mechanisms of Synapse Maintenance: Role in Neurodegenerative Disorders*, 1 year, $25,000 • **Robert Collins**, Jane Coffin Childs Memorial Fund for Medical Research, *Engineering of TPR Domains to Recognize Cell-surface Receptors*, 2 years, $94,583 **Pietro De Camilli**, Nat'l Alliance for Research on Schizophrenia and Depression (NARSAD), *Phosphoinositide Metabolism and Psychiatric Diseases*, 1 year, $99,999 • **Clare Flannery**, Endocrine Fellows Foundation, *Effect of Hyperinsulinemia on Endometrium*, 1 year, $15,000 • **Martín García-Castro**, Connecticut Innovations Inc., *Molecular Profiling and Cell Fate Potential of hESC Derived Early Neural Crest Precursors*, 2 years, $200,000 **Nathan Hansen**, Duke University, *Brief Care-Based HIV Prevention for Newly Diagnosed Men*, 1 year, $2,483 • **Kevan Herold**, Duke University, *Pilot, Optimization and Testing of Nanoparticulate-Based Non-Invasive Imaging in Autoimmune Disease (ACE)*, 1 year, $165,500; Connecticut Innovations Inc., *Induction and Differentiation of Beta Cells from Human Embryonic Stem Cells*, 2 years, $200,000 • **Yingqun Huang**, Connecticut Innovations Inc., *Molecular Function of Lin28 in Human Embryonic Stems Cells*, 4 years, $500,000 • **Jeffery Kocsis**, Connecticut Innovations Inc., *Cellular Transplantation of Neural Progenitors Derived from Human Embryonic Stem Cells to Remyelinate the Nonhuman Primate Spinal Cord*, 4 years, $500,000 **Graciela Krikun**, Aniara Diagnostica, *Detection of Plasma TF Expression and Activity in Women with Endometriosis*, 1 year, $5,000 • **Harlan Krumholz**, National Bank of Egypt, *Improving Healthcare in Egypt*, 2 years, $534,492 • **Maria Lara-Tejero**, Columbia University, *The Interactions of Type III Secretion Effector Proteins*, 10 months, $82,750 **Qi Li**, Connecticut Innovations Inc., *Neural Stem Cell Responses to Hypoxia*, 2 years, $200,000 **Jun Lu**, Connecticut Innovations Inc., *MicroRNA Regulation of hESC Fates*, 4 years, $500,000 **Stephanie Massaro**, Connecticut Innovations Inc., *The Influence of Aberrant Notch Signaling on RB Mediated Cell Cycle Regulation in Acute Megakaryoblastic Leukemia*, 2 years, $200,000 • **Eric Meffre**, Juvenile Diabetes Research Foundation Int'l, *Loss of B Cell Tolerance That is Common to RA, SLE and T1D*, 7 months, $220,000 • **Angus Nairn**, Michael Stern Parkinson's Research Foundation, *Identification of Neuron-Specific Protein Expression and Post-Translational Modifications Involved in Parkinson's Disease*, 1 year, $495,280 • **Kevin Pelphrey**, Duke University, *Longitudinal Functional Imaging of Early Childhood Anxiety Disorders*, 1 year, $20,709 • **Marc Potenza**, Nat'l Center for Responsible Gaming, *The Yale Gambling CORE (Center of Research Excellence)*, 3 years, $402,498 **Yibing Qyang**, Connecticut Innovations Inc., *Derivation and Functional Characterization of Heart Cells from Human Embryonic Stem Cells*, 2 years, $200,000 • **Carrie Redlich**, Center to Protect Workers' Rights, *Risk of Isocyanate Exposure in the Construction Industry*, 1 year, $30,000 • **David Rimm**, Associazione "Sandro Pitigliani" per la Lotta Contro i Tumori, *Evaluation of Topoisomerase IIa Protein by a Novel Approach (AQUA, Automated Quantitative Analysis)*, 1 year, $27,390; SAIC-Frederick, Inc., *Intrinsic Controls for Formalin-Fixed, Paraffin-Embedded Tissue*, 3 years, $569,643 **Craig Roy**, Columbia University, *Pathogenic Mechanisms of* Coxiella burnetii, 10 months, $329,103 **Joseph Sarhan**, American Heart Association—Founders Affiliate, *hnRNPs as MK2 Substrates in Leukocyte Integrin-Induced Interferon-Gamma mRNA Stabilization*, 4 months, $5,000 • **Masanori Sasaki**, Talecris Biotherapeutics, Inc., *Combined Intravenous Immunoglobulin and Cell Therapy for Spinal Cord Injury*, 2 years, $225,000 • **Nenad Sestan**, March of Dimes, *Molecular Control of Cortical Projection, Neuron Identity, and Connectivity*, 3 years, $295,255 • **Eva Sevcsik**, Max Kade Foundation, Inc., *Role of Oxidative Stress in Aggregation and Membrane Interaction of Alpha-Synuclein*, 1 year, $49,000 • **Steven Southwick**, Mount Sinai School of Medicine, *WTC RHC Data and Coordination Center*, 1 year, $76,155 • **David Stern**, Harry J. Lloyd Charitable Trust, *Identifying New Targets for Personalizing Melanoma Therapies*, 1 year, $120,000 • **Stephen Strittmatter**, Wings for Life Spinal Cord Research Foundation, *Imaging of Axonal Growth after Human Spinal Cord Injury*, 1 year, $126,426 • **Richard Sutton**, Connecticut Innovations Inc., *Genome-Wide Screen to Identify hESC-Specific DNA Transcription Elements*, 4 years, $500,000 • **Oyebode Taiwo**, Stanford University, *Disease, Disability and Death in an Aging Workforce*, 1 year, $688,344 **Hugh Taylor**, John B. Pierce Laboratory Inc., *Estrogen & Progesterone Effects on Orthostatic Tolerance*, 2 years, $82,579 • **Penghua Wang**, Northeast Biodefense Center, *Roles of Autophagy in Flaviviral Immunity*, 10 months, $82,750 • **Sandra Wolin**, Connecticut Innovations Inc., *Investigating the Role of Nuclear RNA Surveillance in Embryonic Stem Cells*, 2 years, $200,000 • **Tian Xu**, Connecticut Innovations Inc., *piggyBac Transposon for Genetic Manipulation and Insertional Mutagenesis in Human Embryonic Stem Cells*, 4 years, $500,000

'Stimulus package' grants saving jobs, building infrastructure, advancing research at Yale

The $787 billion American Recovery and Reinvestment Act of 2009 (ARRA), colloquially known as "the stimulus package," is helping to construct and repair roads and bridges, weatherize buildings, and create a new energy infrastructure based on renewable resources.

But ARRA is also helping to build biomedical knowledge at Yale, and creating or saving American jobs in the bargain.

At press time, Yale University as a whole had received $121.6 million in ARRA grants, $101.5 million of which was awarded to the School of Medicine for research during the next two fiscal years.

During the spring and early summer of 2009, medical school faculty and staff submitted more than 775 applications for ARRA grants, a full 25 percent of which were funded. In addition to 200 awards already approved, another 41 proposals totaling $52 million for construction projects and high-end instrumentation are still under review.

As the largest employer in New Haven and the third largest employer in Connecticut, Yale is a major contributor to the Connecticut economy. According to the Connecticut Center for Economic Analysis, salaries, wages, and benefits paid by Yale contributed $1.3 billion to the Connecticut economy in 2007.

Medical school scientists are already putting ARRA funds—and Connecticut's citizens—to work, beefing up research programs in areas as diverse as cancer, Alzheimer's disease, autism, heart disease, multiple sclerosis, addiction, and preventing suicide among adolescents.

Moreover, in recent years, discoveries by scientists at the School of Medicine have fueled a growing biotech industry in the New Haven area, which itself employs approximately 1,400 people. ARRA funding will provide further momentum to this trend by helping Yale researchers to commercialize technologies and stimulate investments to start new companies by establishing "proofs of concept" for early-stage treatments.

For example, Stephen M. Strittmatter, PH.D., Vincent Coates Professor of Neurology and professor of neurobiology, received $481,000 in ARRA funds for his research on repairing injuries of the brain and spinal cord. Strittmatter recently helped to found Axerion, a new company that is developing drugs based on Strittmatter's work. Within the next six months, New Haven-based Axerion plans to hire as many as 20 researchers and managers.

Likewise, a $331,000 ARRA grant to Peter M. Glazer, M.D., PH.D., the Robert E. Hunter Professor of Therapeutic Radiology and professor of genetics, will help him to pursue an exciting new approach to treating disease using a genetic "fix-it kit" that can provide a sustained cure for diseases such as sickle-cell anemia, HIV/AIDS, and many cancers. A local start-up company, Helix Therapeutics, has licensed patents for Glazer's technology from Yale, and last year secured its first $965,000 of seed capital from the state of Connecticut and other investors to hire scientists and begin research operations.

Six of the largest grants, made through the NIH's ARRA-funded Grand Opportunities (GO) program, are based around the Yale Center for Genome Analysis, which will be up and running on Yale's West Campus by the end of 2009 (see related story, page 1).

"The medical school's impressive success rate in ARRA applications is a testament to the very high caliber of science conducted at Yale," says Dean Robert J. Alpern, M.D., "and also to the phenomenal energy of our investigators and their research and administrative teams."

CORRECTION

In a story in our last issue about a new professorship established by Jonathan and Richard Sackler, we misprinted the first name of the Sacklers' father, Raymond, and mistakenly stated that Raymond and his wife, Beverly, had endowed the Sackler Wing at the Royal Academy of Arts, rather than the Raymond and Beverly Sackler Galleries at the British Museum. We regret the errors.

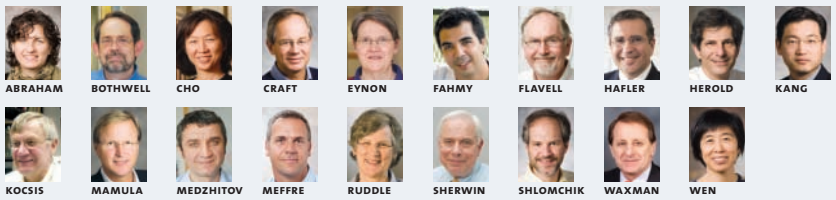
// ACE *(from page 3)*
science of immunology to explain these things."

Meffre, who joined the immunobiology faculty in 2008 and whose research is focused on B cell tolerance (the extent to which these immune cells are reactive or nonreactive to self), has uncovered similar functional abnormalities in B lymphocytes from patients with type 1 diabetes, rheumatoid arthritis, and lupus. For Meffre, the ACE grant has already led to increased collaboration with other Yale scientists. As part of one ACE project, for instance, a former colleague in Paris sends Meffre samples from Sjögren's syndrome patients, which he analyzes for B cell function. But Meffre also shares these samples with Kang, who studies T cells. "There's a lot of overlap in our research," Meffre says.

A push for contiguous laboratory space is another aspect of Yale's new collaborative research in autoimmunity. Though the particulars are yet to be determined, a group of principal investigators is slated to move this year into a single interdisciplinary autoimmunity lab dedicated exclusively to human studies. The new centralized laboratory space will also house scientists working in transplant and tumor immunology and in neurology.

"This new center for research on human autoimmunity," Herold says, "will be a very exciting place."

Autoimmunity: research on many fronts



Inflammatory bowel disease (IBD)

IBD is a group of inflammatory conditions of the colon and small intestine that includes Crohn's disease and ulcerative colitis.

- **Clara Abraham, M.D.** Assistant professor of medicine
- **Judy H. Cho, M.D.** Associate professor of medicine and genetics
- **Richard A. Flavell, PH.D.** Chair and Sterling Professor of Immunobiology
- **Ruslan M. Medzhitov, PH.D.** Professor of immunobiology

Lupus (SLE)

In this chronic disease, formally known as systemic lupus erythematosus, or SLE, the immune system attacks the skin, joints, blood, and kidneys.

- **Joseph E. Craft, M.D.** Professor of medicine and immunobiology
- **Tarek Fahmy, PH.D.** Associate professor of biomedical engineering and chemical engineering
- **Insoo Kang, M.D.** Associate professor of medicine
- **Mark J. Mamula, PH.D.** Professor of medicine
- **Eric Meffre, PH.D.** Associate professor of immunobiology
- **Mark J. Shlomchik, M.D., PH.D.** Professor of laboratory medicine and immunobiology

Multiple sclerosis (MS)

In MS, T cells (and probably also B cells) damage and scar the fatty myelin sheaths that insulate axons in the brain and spinal cord.

- **David A. Hafler, M.D.** Chair of Neurology and Gilbert H. Glaser Professor
- **Nancy H. Ruddle, PH.D.** John Rodman Paul Professor of Epidemiology and professor of immunobiology
- **Stephen G. Waxman, M.D., PH.D.** Bridget Marie Flaherty Professor of Neurology, Neurobiology, and Pharmacology
- **Jeffery D. Kocsis, PH.D.** Professor of neurology and neurobiology

Rheumatoid arthritis (RA)

RA is a chronic autoimmune disorder that involves many tissues and organs—especially the joints, where inflammation leads to pain, stiffness, and the destruction of cartilage.

- **Eric Meffre, PH.D.** Associate professor of immunology

Sjögren's syndrome

In Sjögren's syndrome, immune cells attack the glands that produce saliva and tears. Scientists believe that "misbehaving" B and T cells may be a cause.

- **Insoo Kang, M.D.** Associate professor of medicine
- **Eric Meffre, PH.D.** Associate professor of immunobiology
- **Nancy H. Ruddle, PH.D.** John Rodman Paul Professor of Epidemiology and professor of immunobiology

Type 1 diabetes

In Type 1 diabetes, T cells destroy insulin-producing beta cells in the pancreas. Some scientists implicate an autoimmune response meant to target virus-infected cells.

- **Alfred L.M. Bothwell, PH.D.** Professor of immunobiology
- **Elizabeth E. Eynon, PH.D.** Research scientist in immunobiology
- **Richard A. Flavell, PH.D.** Chair and Sterling Professor of Immunobiology
- **David A. Hafler, M.D.** Chair of Neurology and Gilbert H. Glaser Professor
- **Kevan Herold, M.D.** Professor of immunobiology and medicine
- **Mark J. Mamula, PH.D., M.S.** Professor of medicine
- **Eric Meffre, PH.D.** Associate professor of immunobiology
- **Nancy H. Ruddle, PH.D.** John Rodman Paul Professor of Epidemiology and professor of immunobiology
- **Robert S. Sherwin, M.D.** C.N.H. Long Professor of Medicine
- **Li Wen, M.D., PH.D.** Senior research scientist in medicine

// Genes *(from page 1)*
protein-coding regions where disease-causing mutations are most likely to occur. The Lifton group—which included YCGA Director Shrikant Mane, PH.D.; Postdoctoral Associates Murim Choi, PH.D., and Ute I. Scholl, M.D.; and Research Associate Irina R. Tikhonova, PH.D., of the medical school's W.M. Keck Foundation Biotechnology Resource Laboratory—worked out an exome sequencing method that combines gene-chip technology to isolate the target DNA with the latest high-throughput sequencing techniques and hardware to decode it.

The approach yields a quick and comprehensive view of an individual's genes for a few thousand dollars, or 10 to 20 times cheaper than sequencing the entire genome.

This "capture and sequence" method can be applied to virtually any disease and will accelerate the pace of discovery of new genes related to both rare and common conditions.

Even as they were developing the technology, Lifton and Mane could already envision how large-scale sequencing tools would transform the work of researchers across the medical school. They established the YCGA, a core resource that will not only accommodate a growing demand for genomic sequencing, but also keep Yale researchers at the forefront of human genetics.

With support from the American Recovery and Reinvestment Act (ARRA; see related story, page 6), 12 of the latest-generation Illumina gene-sequencing machines, which will vastly increase medical school researchers' ability to perform high-throughput genomic analysis, are being installed at the YCGA.

The medical school's early investment in this approach has already jump-started a substantial amount of new research: of six major ARRA research grants the School of Medicine received recently, five were based on this new sequencing technology.

"This is an area where we are leaders," Lifton says, "and we want to take advantage of that."

Yale Netcast: "Genes: You Are What You Inherit"
Available on iTunesU or at medicineatyale.org

// Haiti *(from page 1)*
director of the Yale Center for Public Health Preparedness; and Maria Bouffard, director of emergency management services at Yale University.

A medical team was assembled, including Larkin; Nousheh Saidi, M.D., assistant professor of anesthesiology; orthopaedic surgeon Peter Boone, M.D., of St. Vincent's Hospital in Bridgeport, Conn.; and physician assistant Donald MacMillan, PA, and nurse Tom Kimberly, APRN, of the Yale-New Haven Hospital (YNHH) emergency department. Ralph Jean-Mary, business manager for YNHH and a native of Haiti, later joined the group to assist as an interpreter and with logistics.

On January 26, a jet carrying the Yale team and a donated, 1,500-lb. cargo of much-needed medical supplies touched down in the port city of Cap-Haïtien, Haiti. A small plane then took them over mountainous terrain to the city of Hinche, about 50 miles northeast of Port-au-Prince, where earthquake victims were being evacuated to the Hôpital Sainte Thérèse, a hospital operated by the worldwide health care organization Partners in Health.

A small hotel in Hinche owned by Jean-Mary's parents provided lodging for the Yale team. For the next six days, they provided life-saving medical, trauma, and surgical care at the hospital for scores of children and adults, and also instructed local doctors and nurses in the use of monitoring and anesthesia equipment.

The group treated fractures and crush injuries, many of which were worsened by the delay in obtaining medical care. Wounds that would have been minor if treated early became grossly infected, often requiring amputation. "As horrible as something like amputation is in this country, we have paved roads, we have public transportation, we have crutches and wheelchairs and prostheses. These patients don't have any of those things," Larkin said at a February 1 press conference after the team's return to New Haven. "It's hard enough to walk around on their dirt roads with two working legs." Saidi described the team's work as a "drop of water in an ocean" of devastation, but she was glad to be able to help at least some of the victims. "If the team wasn't there I don't know when or if they would have had surgery," she said.

The medical team's efforts were coordinated in New Haven by Kimberly A. Davis, M.D., associate professor of surgery, chief of the section of trauma, surgical critical care and surgical emergencies, and trauma director at YNNH.

"It should be a source of great pride for our faculty and staff that, not only did key faculty leaders like Drs. Davis, Degutis, and Larkin, respond quickly to this tragedy, but we have such a broad range of talent that was eager to help," says Leffell. "That's what doctors do. We help people in need."

(From left) Tom Kimberly, Nousheh Saidi, Rick Frechette, Gregory Luke Larkin, Donald MacMillan, Peter Boone, and Ralph Jean-Mary in Hinche, Haiti, where they provided medical care to earthquake victims. The team also delivered medical supplies to Frechette, a priest and physician who directs the St. Damien Hospital in Port-au-Prince.

DONALD MACMILLAN

Pioneer in studies of innate immunity wins Rosenstiel Award

Ruslan Medzhitov, PH.D., the David W. Wallace Professor of Immunobiology and a Howard Hughes Medical Institute investigator, has been awarded the 2010 Lewis S. Rosenstiel Award for Distinguished Work in Basic Medical Science.

The Rosenstiel Award, established in 1972 by Brandeis University, has a long record of identifying and honoring pioneering scientists. Many winners of the award have subsequently gone on to win other major prizes in biomedical research, including the Nobel Prize. A $30,000 cash prize and a medal accompanies each award.

The award to Medzhitov is for his "elucidation of the mechanisms of innate immunity." In 1997, Medzhitov

Ruslan Medzhitov

and the late Yale immunobiologist Charles A. Janeway Jr., M.D., published a seminal paper in the journal *Nature* showing that proteins known as Toll-like receptors (TLRs) performed a crucial role in sensing microbial infections and alerting the adaptive immune response to act against them.

TLRs work as a first line of defense against infection by detecting large molecules common to many pathogens. For example, the outer membranes of many infectious bacteria contain structural elements not found in mammalian cells, and TLRs quickly recognize these patterns. Because of their ability to potently stimulate adaptive immune responses, TLRs are promising drug targets.

Sharing the award this year is Jules Hoffman, PH.D., of the National Center of Scientific Research in Strasbourg, France. Hoffman discovered the immune function of TLRs, which were previously thought to play only a developmental role, in the fruit fly *Drosophila melanogaster*.

Past Yale winners of the Rosenstiel Award include: (2008) Arthur L. Horwich, M.D., Sterling Professor of Genetics and professor of pediatrics, for his work in protein folding; (2002) Joan A. Steitz, PH.D., Sterling Professor of Molecular Biophysics and Biochemistry, for her work with small nuclear ribonucleoproteins; (2001) Thomas A. Steitz, PH.D., Sterling Professor of Molecular Biophysics and Biochemistry and professor of chemistry and a winner of the 2009 Nobel Prize in Chemistry for contributions to determining the structure of the ribosome; (1996) Thomas D. Pollard, M.D., chair and Sterling Professor of Molecular, Cellular, and Developmental Biology and professor of molecular biophysics and biochemistry, for his contributions to the understanding of molecular motors; and (1989) Sidney Altman, PH.D., professor of biology, for discovering the catalytic properties of RNA. Altman won the Nobel Prize in Chemistry the same year.

Developer of new cancer drugs is honored with international award

Joseph Schlessinger, PH.D., chair and William H. Prusoff Professor of Pharmacology, has been named winner of the 2010 Pezcoller Foundation–AACR International Award for Cancer Research.

Joseph Schlessinger

The award, established in 1998, recognizes a scientist "of international renown who has made a major scientific discovery in basic cancer research or who has made significant contributions to translational cancer research."

As the winner of the award, Schlessinger will give two lectures on his work, one at the 101st annual meeting of the AACR (American Association for Cancer Research) in Washington, D.C., in April, and the 5th Annual Stanley J. Korsmeyer Lecture in Padua, Italy, in May. Schlessinger will then receive the award—which includes a prize of €75,000 and a commemorative plaque—at a ceremony in Trento, Italy, on May 7.

In a scientific career that has spanned three decades, Schlessinger has discerned the mechanism of action of a family of surface receptors and revealed their roles as critical drivers of a variety of cancers. These studies provided the conceptual foundation for the development of tyrosine kinase inhibitors as successful new drugs for the treatment of many cancers.

Schlessinger has cofounded three biotechnology companies and served as an advisor to several others—work that led to a drug approved by the U.S. Food and Drug Administration in January 2006 for advanced kidney cancer and for a stomach cancer known as gastrointestinal stromal tumor, or GIST. That drug, now marketed by Pfizer as Sutent, and other drugs based on Schlessinger's discoveries are being tested as treatments for more common renal cancers, as well as breast and other cancers.

The December 18, 2009 issue of the journal *Science* featured a news article on the remarkable clinical results obtained in metastatic melanoma with PLX4032, a new compound developed by Plexxikon, a biotech company Schlessinger cofounded. In a Phase I trial, PLX4032 had an unprecedented 70 percent response rate in treating the disease. PLX4032, which has moved into Phase III trials, has generated excitement because it appears to selectively target a cancer-causing mutation of a gene involved in metastatic melanoma without affecting normal versions of the gene, findings which suggest that other cancer-causing mutations may also be precisely targeted.

The Pezcoller Foundation was established in 1980 by Alessio Pezcoller, an Italian medical professor and surgeon. In addition to sponsoring this award, the foundation also sponsors a series of symposia, publishes a journal, and supports awards for early-career scientists from Europe who have submitted highly rated abstracts for presentation at the AACR's annual meeting. The AACR was founded by a group of 11 scientists in 1907, and now has nearly 27,000 members in more than 60 countries.

Yale Cancer Center director is named inaugural Sackler Professor

Thomas J. Lynch Jr., M.D., has been named the inaugural Richard Sackler and Jonathan Sackler Professor of Medicine and Yale Cancer Center Director. Lynch, who joined the Yale faculty in 2009, is also physician-in-chief at Smilow Cancer Hospital.

Lynch is renowned for his research on the relationship between genetic variations and the effectiveness of cancer therapies. An authority on lung cancer, he has conducted dozens of studies of "personalized" cancer therapy—taking account of small differences in patients' genomes, or in the genetic makeup of their tumors, to tailor their treatment with the most appropriate anticancer agents.

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

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

Thomas Lynch

Lynch received his undergraduate degree from Yale College in 1982 and his medical degree from Yale School of Medicine in 1986. He completed his internship and residency at Massachusetts General Hospital (MGH), and after completing a fellowship in medical oncology at the Dana-Farber Cancer Institute, joined the MGH medical staff in 1993. At Harvard Medical School and MGH, he was professor of medicine and chief of hematology/oncology.

Richard S. Sackler, M.D., and his brother, Jonathan Sackler, joined forces in 2009 to create a $3 million endowment establishing the new professorship, expressly intended to be held by those appointed as director of Yale Cancer Center (YCC). Richard Sackler, co-chairman of Stamford-based Purdue Pharma and adjunct professor of genetics at Rockefeller University, serves on YCC's Advisory Board and the Yale School of Medicine's Dean's Council. He and his wife, Beth, head the Richard and Beth Sackler Foundation. Jonathan Sackler and his wife, Mary Corson, lead the Stamford-based Bouncer Foundation.

STEITZ IN STOCKHOLM

On December 10, in the elegant and festive setting of the Stockholm Concert Hall, King Carl XVI Gustaf of Sweden presented the 2009 Nobel Prize in Chemistry to Thomas A. Steitz, PH.D., Sterling Professor of Molecular Biophysics and Biochemistry, for his seminal research in structural biology.

During the 1990s, Steitz, also professor of chemistry and Howard Hughes Medical Institute Investigator, and Yale colleagues used X-ray crystallography to determine the three-dimensional structure of the large subunit of the ribosome at 2.4 angstroms—a resolution high enough for the researchers to model each of the structure's individual atoms.

The ribosome is a cellular organelle that is crucially involved in protein synthesis. Because many antibiotics work by targeting and shutting down the ribosomes of bacteria, Steitz's research is now guiding the development of new drugs for the treatment of antibiotic-resistant infections.

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