Medicine@Yale

JULY/AUGUST 2010
VOLUME 6, ISSUE 3
Advancing Biomedical Science, Education, and Health Care

Gift will support troops still troubled after the battle ends

Described in Homer's *Iliad* and called by a succession of names ever since—from mere "exhaustion" to "shell shock" and "battle fatigue"—the distinctive condition that often afflicts soldiers after stressful wartime experiences, now known as post-traumatic stress disorder (PTSD), still carries a strong social stigma. And scientists still have much to learn about its psychological and physiological underpinnings.

Though the investment firm headed by Yale College alumnus Glenn H. Greenberg, M.A., M.B.A., is known as Brave Warrior Advisors, Greenberg knew little about PTSD until he began hearing that increasing numbers of veterans of the wars in Iraq and Afghanistan had returned home with deep psychological scars left by those conflicts. For Greenberg's wife, Linda Vester, who had worked for years as a war-zone correspondent for NBC News, the cluster of symptoms that make up PTSD were all too familiar.

"She also came back with stress disorder," Greenberg says, "and she told me how debilitating it was, such that when there was a thunderstorm she'd dive under the dining room table—literally, with her family there."

The School of Medicine, in partnership with the VA Connecticut Healthcare System (VACHS), has been in the vanguard of PTSD research and treatment for decades. When Greenberg, a member of the Class of 1968, contacted his alma mater to find out about Yale

Glenn Greenberg

research on PTSD, he "was not appreciative of the long history of really original work," he says, and he soon decided to help continue that work with a major gift that establishes the Greenberg Professorship in Psychiatry, Post-Traumatic Stress Disorder, and Resilience.

In the mid-1960s, after completing a residency in psychiatry at Yale, Arthur S. Blank Jr., M.D., saw the Vietnam War first hand, working in hospitals in Long Binh and Saigon. Soon after the war ended, Blank reviewed the charts of 60 veterans and concluded that many had been misdiagnosed with maladies ranging from alcoholism to schizophrenia. In 1973, Blank, now a psychiatrist in Bethesda, Md., invited those men to a therapy group at the veterans hospital in West Haven, Conn. (now the VACHS), which helped to lay the groundwork for PTSD's eventual acceptance as an official psychiatric diagnosis in 1980. Soon after, Yale recruited Walter Reed Army Medical Center endocrinologist John W. Mason, M.D., who led the first studies of disturbances in stress-related hormones in soldiers with PTSD. In 1989, Yale became home to the Clinical Neurosciences Division and the Health Services Division of the VA National Center for PTSD,

// Greenberg *(page 8)*

Cell biologist awarded top science prize

2010 Kavli Prize in Neuroscience honors researcher's deciphering of membranes' role in shuttling proteins within and between cells

On June 3, James E. Rothman, PH.D., the Fergus F. Wallace Professor of Biomedical Sciences and chair of the medical school's Department of Cell Biology, was named a recipient of the 2010 Kavli Prize in Neuroscience. The biennial $1 million award, which has become one of the most prestigious in science, was established in 2008 by a partnership of the Norwegian Association of Science and Letters, the U.S.-based Kavli Foundation, and the Norwegian Ministry of Education and Research.

Rothman is one of the world's foremost experts on membrane trafficking, the means by which proteins and other materials are transported within and between cells. The Kavli Prize highlights his contributions to the understanding of exocytosis, a form of trafficking in which spherical sacs called vesicles fuse with cell membranes to deliver their contents outside the cell.

This process is ubiquitous in biology—it is essential to cell division and insulin secretion, for example—but exocytosis plays a particularly crucial role in the nervous system. In neurons, vesicles carrying neurotransmitters fuse with cell membranes at synapses, emptying their cargo to pass on the chemical messages that govern movement, perception, cognition, memory, and mood. For three decades, Rothman has performed elegant, focused biochemical and

COURTESY OF COLUMBIA UNIVERSITY

James Rothman, winner of this year's Kavli Prize in Neuroscience.

cell biology experiments that have revealed the molecular machinery of membrane trafficking in fine detail. Much of this work was done using a "cell-free" approach, in which Rothman sidestepped the complexities of working with complete cells by isolating the intracellular components crucial to membrane trafficking. This strategy allowed him to propose that complexes of membrane-associated proteins known as SNAREs are required for vesicles to fuse with membranes.

Rothman shares the Kavli Prize with Thomas Südhof, PH.D., of the Stanford School of

// Rothman *(page 8)*

Innate immunity innovator joins National Academy

Ruslan Medzhitov

In April, Yale immunobiologist Ruslan Medzhitov, PH.D., received one of the highest honors bestowed on American scientists when he was elected to the National Academy of Sciences (NAS), the elite corps of researchers from the nation's top scientific institutions.

The David W. Wallace Professor of Immunobiology and a Howard Hughes Medical Institute investigator, Medzhitov has done pioneering research on the innate immune system, an evolutionarily ancient physiological system that launches rapid first-line defenses against bacteria and viruses.

"We are all delighted by Ruslan's election to the NAS, which honors his seminal research on innate immunity," says Carolyn W. Slayman, PH.D.,

// Medzhitov *(page 8)*

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INSIDE THIS ISSUE

ALSO

TERRY DAGRADI

In addition to leading the medical school's ophthalmology department and caring for his many patients, James Tsai is an active researcher on topics including patient adherence to glaucoma medication regimens, the development of new diagnostic technology, and the application of molecular biology to regenerate damaged retinal nerve cells in glaucoma and other eye diseases.

Leading with vision

Yale glaucoma specialist is also helping to bring eye cancers into the light

Patients go out of their way to see Yale ophthalmologist James C. Tsai, M.D., M.B.A. One traveled four-and-a-half hours from Long Island. Another takes a car service each week from Garden City, N.Y., for post-operative care. For his weekly follow-ups, a Wall Street trader journeys to New Haven each Wednesday on the Metro-North Railroad.

Tsai, an expert in glaucoma research and treatment, came to Yale in 2006 from Columbia University College of Physicians and Surgeons, where he was director of the Edward S. Harkness Eye Institute. Now chair and Robert R. Young Professor of Ophthalmology and Visual Science at the School of Medicine, Tsai is also chief of ophthalmology at Yale-New Haven Hospital (YNHH) and director of the Yale Eye Center.

Liz Whall, one of his patients, says Tsai's stamina is matched by his empathy: "I don't know how he has time to take care of so many people and still stop and listen." But for Tsai, listening is key. "You have to tailor every treatment for every individual," he explains. "It's not one size fits all."

Characterized by elevated pressure of fluid inside the eye, glaucoma can damage the optic nerve and cause irreversible vision loss. But in as many as one-third of cases, low to normal pressure measurements (a thin cornea can skew test results) can leave glaucoma undiagnosed until there is significant visual damage. Whall's undiagnosed glaucoma was affecting her ability to do basic tasks as a mother and interior designer. After a proper diagnosis, a New York surgeon performed pressure-reducing surgery on her left eye, but it yielded only short-term results. Medication to lower pressure in her right eye had severe side effects.

Whall consulted Tsai, who suggested "revising" the previous surgery on her left eye, and advised against surgery on her right eye altogether. Today, with glasses, the combined vision of Whall's eyes is 20/20.

Born in Taiwan and delivered by his grandmother, an obstetrician, Tsai is a fourth-generation physician. But there is also a darker family legacy. "I'm in a family where there definitely is a cancer gene," says Tsai. As a teenager, he watched his father fight lung cancer; three decades later, his father is being treated at Yale for a brain tumor. At just 5 months old, Tsai's eldest daughter underwent chemotherapy and surgery for liver cancer. (She is now a healthy and athletic 12-year-old.)

This history inspired Tsai to raise the profile of ocular oncology at Yale. Though little-known, eye cancer can cause blindness and can even be fatal. Metastasizing breast cancers often reach the eye, and the most common cancer that originates in the eye, choroidal melanoma, can spread to the liver, lungs, and brain. The recent opening of Smilow Cancer Hospital at YNHH helped Tsai to recruit "the first fully trained ophthalmic oncologist in the state of Connecticut," Miguel A. Materin, M.D., assistant professor of ophthalmology and visual science and director of ocular oncology.

In his personal life, Tsai's abundant energy fuels a passion for tennis. A recent bout of tendonitis, which brought him to a physical therapist, was a worthwhile result of winning a match against his coach. "The physical therapist asked, 'How did you do this?' And I said, 'I tried to learn a kick serve,' and he said, 'Yeah, but you're not in your twenties anymore!'"

Yale Netcast "A Discussion of the Importance of Glaucoma Screening"
Available on iTunesU or at medicineatyale.org

Expert on causes of kidney disease will lead physiology department

Michael J. Caplan, M.D., PH.D., who studies how membrane proteins find their proper location on the cell surface, and disruptions in this process that are associated with polycystic kidney disease (PKD), has been named chair of the Department of Cellular and Molecular Physiology.

Caplan, the C.N.H. Long Professor of Cellular and Molecular Physiology and professor of cell biology, also serves as associate director for basic research for the School of Medicine's M.D./PH.D. Program.

In PKD, a common genetic disease, the normal architecture of kidney tubules is replaced by large, fluid-filled cysts. Caplan and colleagues study the cellular and molecular pathways responsible for this process. They have made the surprising discovery that many receptor and signaling proteins involved in the sense of smell are also expressed in the kidney, a finding that suggests that olfactory signaling mechanisms may play an important role in regulating kidney function in response to chemosensory cues.

Michael Caplan

Caplan earned his M.D. and PH.D. degrees at Yale School of Medicine in 1987. He became an assistant professor in 1988 and was promoted to full professor in 1998.

In April, Caplan was named as the first recipient of Yale's Postdoctoral Fellows Mentoring Award. He has been given numerous other honors, including the School of Medicine's Charles W. Bohmfalk Teaching Prize, the Young Investigator Award of the American Society of Nephrology, and the Henry P. Bowditch Award Lectureship of the American Physiological Society.

Caplan has served as interim chair since the death of his colleague Steven C. Hebert, M.D., a distinguished nephrologist and kidney researcher who served as chair from 2000 to 2008.

VA hospital with Yale affiliation gets top marks for care

Gary Desir

The U.S. Department of Veterans Affairs (VA) has ranked the VA Connecticut Healthcare System (VACHS) in West Haven, Conn., first in the country among the system's tertiary facilities for its clinical care.

"We're not one of the largest or most well-funded facilities, but we tend to be very efficient and provide outstanding care," says Gary Desir, M.D., professor of medicine and chief of medical services at the VACHS. "The challenge is going to be that our patient population is increasing yet our funding is not, so we have to maintain the same level of care but with fewer resources."

The VACHS, one of 153 VA hospitals nationwide, achieved a perfect score in performance measures in three of nine categories: acute myocardial infarction, tobacco screening, and heart failure. For behavioral health screening, community-acquired pneumonia, and surgical complications it achieved a rating of "exceptional." For diabetes, ischemic heart disease, and heart-disease prevention, the VACHS, which has a long-standing affiliation with the School of Medicine, also had very high ratings.

There are more than 200,000 visits to VACHS clinics each year. The hospital offers a full range of medical, surgical, and psychiatric services to veterans, with particular strengths in epilepsy, stroke, rehabilitation for the blind, post-traumatic stress disorder, alcoholism, schizophrenia, and virology. In addition, its medical research program is the second-largest in the VA system.

Medicine@Yale

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Medicine@Yale is published five times each year by the Office of Institutional Planning and Communications, Yale School of Medicine, 300 George St., Suite 773, New Haven, CT 06511
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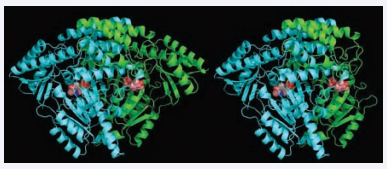


KUAKARUN KRUSONG

Faulty histamine gene is a factor in Tourette's

Best known for triggering symptoms of hay fever, histamine also acts as a neurotransmitter in the brain. A new genetic study led by Matthew W. State, M.D., PH.D., the Donald J. Cohen Associate Professor of Child Psychiatry, suggests that histamine plays a role in Tourette's syndrome.

As reported in the May 20 issue of *The New England Journal of Medicine*, in a rare family in which the father and all eight children, but not the mother, have Tourette's, affected family members all carried the same mutation in *HDC*, a gene involved in histamine synthesis.

Normally, HDC molecules pair up in a symmetrical complex (above left) to synthesize histamine. The mutation, which truncates the HDC protein, is found on only one of two chromosomes, and inhibits the enzymatic activity of the normal copy by forming an abnormal complex (above right).

Histamine-boosting drugs reduce Tourette's-like behaviors in mice lacking *HDC*, and several are in human clinical trials for neuropsychiatric conditions, says State, also co-director of the Yale Neurogenetics Program. "This may mean that we have the opportunity to go directly from a rare genetic finding to a trial of a new approach to treatment. In our field, that would be very unusual, and very exciting," he says.

A new sort of stem cell is aimed at Parkinson's

Parkinson's disease, which degenerates motor function and speech, results from a loss of dopamine-producing brain cells. Drug treatments cannot always relieve the tremor and loss of balance caused by the disorder.

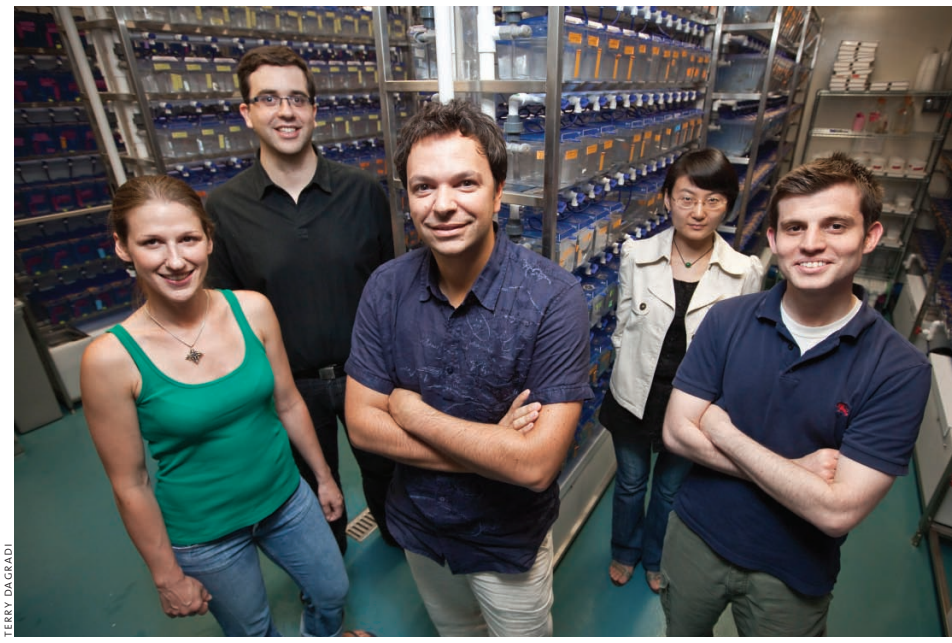
Embryonic stem cells (ESCs) have shown promise as a means of regenerating the lost cells, but scientists have been on the lookout for alternatives to ESCs that can be easily obtained from adult patients.

In experiments reported online in the April issue of the *Journal of Molecular and Cellular Medicine*, Yale researchers led by Hugh Taylor, M.D., professor of obstetrics, gynecology, and reproductive sciences, explored the therapeutic potential of cells from the lining of the uterus, or endometrium. Regularly regenerated after menstruation, this tissue is a rich source of stem-like cells in adults. In a mouse model of Parkinson's, transplanted endometrial cells migrated to damaged brain tissue and differentiated into dopamine-producing neurons, significantly raising dopamine levels.

"Endometrial tissue is probably the safest, most easily attainable source of stem cells currently available," says Taylor. "I think this is just the tip of the iceberg for what we will be able to do with these cells."

A big shift in our knowledge of small RNAs

New pathway found for microRNAs, powerful and versatile regulators



TERRY DAGRADI

Antonio Giraldez (center), leader of a study that revealed a new pathway for microRNA processing, in the medical school's zebrafish facility with co-authors (from left) Heather Patnode (research assistant), Daniel Cifuentes (postdoctoral fellow), Huiling Xue (postdoctoral fellow), and David Taylor (graduate student in molecular biophysics and biochemistry).

Lively, hardy, and inexpensive, the zebrafish is a popular species for beginning tropical-fish hobbyists. An attractive small fish native to the Ganges River and other freshwater sites in South Asia, it is also a darling of developmental biologists because, in addition to being easy to maintain in large numbers, zebrafish develop rapidly—their major organ systems undergo substantial development in just 24 hours—a phenomenon made all the more remarkable by the transparency of the fish's embryos. Through a microscope, says zebrafish specialist Antonio J. Giraldez, PH.D., scientists have an intimate, clear view as the fish's adult form swiftly unfolds.

Some basic principles of molecular biology have lately seemed to change just as dramatically. The wholly unexpected discovery about 20 years ago that short stretches of genetic material called microRNAs (miRNAs) exert profound and pervasive control of gene expression is a case in point. The study of miRNAs has since become one of the fastest-growing areas in biology, and now, by taking advantage of the zebrafish's unique qualities, research in the laboratory of Giraldez, assistant professor of genetics and the Lois and Franklin H. Top, Jr. Yale Scholar (see box below), is prompting scientists to rethink strongly held ideas on how miRNAs are formed.

Until the early 1990s, it was thought that, for the most part, genes are activated or suppressed by transcription factors, which bind to DNA to promote or inhibit the transcription of genes into messenger RNA (mRNA), and hence determine which genes are ultimately translated into proteins. But while studying the development of the microscopic roundworm *Caenorhabditis elegans* (another handily transparent organism), Victor Ambros, PH.D., then at Harvard University, made the startling discovery that a tiny stretch of RNA, only 22 genetic letters long, switched off a crucial gene that orchestrates the timing of developmental events in *C. elegans*.

Over the next 10 years, scientists determined that small RNAs like that discovered by Ambros are a ubiquitous, fundamental regulator of gene expression throughout the plant and animal kingdoms. More than 700 miRNAs have been identified in humans, each of which may regulate hundreds (or even thousands) of genes; with such wide reach, miRNAs may interact with more than 60 percent of our genome. These findings have revealed that miRNAs "have deep implications not only in how humans and animals are made, but in the development of human diseases," says Giraldez, also a member of the Yale Stem Cell Center. In 2006, the Nobel Prize in Physiology or Medicine was awarded to two American scientists for elucidating one of the main mechanisms by which miRNAs silence genes, an extraordinary turn of events considering that just 15 years earlier miRNAs were not even known to exist.

Scientists have revised many of their ideas over the past 20 years regarding how miRNAs work and how they are formed, but one character in the miRNA story has remained unchanged: Dicer, an enzyme that, as its name implies, snips complex precursors into the 21- to 23-nucleotide length that characterizes functional miRNAs. In addition to the zebrafish's other attributes, the species is also amenable to precise genetic manipulations. In recent work with zebrafish mutants, Giraldez has confirmed Dicer's central role, showing that fish develop abnormally if the enzyme's function is compromised. Though diagrams in journals and textbooks have varied in their depictions of the early and intermediate steps of miRNA maturation, up to now Dicer has always stood toward the end of the line, the enzymatic gateway through which all precursors must pass to become miRNAs.

But miRNAs continue to surprise. Giraldez and Yale colleagues, collaborating with scientists from Massachusetts to Japan, have now shown that some miRNAs can be processed by an alternative pathway that does not require Dicer. Moreover, the researchers provide evidence that miR-451, a Dicer-independent miRNA they analyzed in depth, is necessary for the normal production of red blood cells. In the new research, published in the June 25 issue of the journal *Science*, Giraldez and colleagues expanded on his earlier work with zebrafish mutants. After introducing a mutation to suppress the activity of Dicer, the researchers looked to see whether any functional miRNAs were present in these mutant fish. Using high-throughput genomic sequencing tools, the group found that several miRNAs had indeed been successfully processed. Giraldez recalls that, because the belief that Dicer is essential to miRNA processing was so firmly established, he and his team found this result "extremely weird, and in fact it took us almost two years to believe it," during which time the group conducted every imaginable experiment until they were satisfied that the finding held up.

Eventually, they concentrated on one Dicer-independent miRNA called miR-451, because it is present in many species (in March, for example, researchers at Ohio State University proposed that miR-451 may regulate the growth of brain tumors in humans), and because its distinctive configuration is a bad structural match for Dicer processing, which suggested that some other pathway was at work.

In typical miRNA processing, once Dicer has cut miRNA precursor strands to a proper-length miRNA, the strands are loaded into a molecule known as the RNA-Induced Silencing Complex (RISC), where the business of gene-silencing actually takes place. Inside RISC, a second enzyme called Argonaute 2 (Ago2) slices up any mRNA strand containing a sequence that exactly matches the loaded miRNA, **// Giraldez** *(page 7)*

MEDICINE >> tomorrow

Yale Scholars: a gift that yields scientific dividends

In 2007, medical school alumnus Frank Top, M.D., and his wife, Lois (right), made a $2.5 million gift to the School of Medicine to establish a Yale Scholar endowment, a fund that smooths the way for a promising young scientist beginning his or her career. Yale Scholars receive four years of research funding; by year five, when a researcher generally has independent grant funding, the award passes on to another top recruit. Exciting new work by Antonio Giraldez, the Lois and Franklin J. Top, Jr. Yale Scholar, is described on this page. "To take talent that's already been recognized in a postdoctoral program and let that person run with it makes an awful lot of sense," says Frank, and Lois agrees. "It's really time-consuming to pursue a research career," she says, "and you can use all the help you can get."

A named Yale Scholar position can be endowed with a gift of $2.5 million, which is matched dollar for dollar by Yale University, creating a $5 million endowment. Donors receive Yale Tomorrow campaign and reunion credit for the full amount. For more information, contact Jancy Houck at (203) 436-8560.

A familiar voice speaks up for Alzheimer's patients, research

It began with a sweatshirt. In December 2007, when Tony- and Emmy-Award-winning actor David Hyde Pierce appeared on the *Today* show to promote *Curtains,* the Broadway comedy in which he was then appearing, an alert viewer in New Haven noticed that the illustrious Yale College alumnus wore a sweatshirt bearing the name of An Important Medical School That Is Not Yale.

A package was soon delivered to Hyde Pierce's dressing room at the Al Hirschfeld Theater with a tongue-in-cheek note from Dean Robert J. Alpern, M.D., that read, in part, "I have been remiss in not providing you with the relevant clothing associated with your alma mater . . . and am enclosing a Yale School of Medicine sweatshirt, hat, and scarf." The hat, a baseball cap, was a hit: Hyde Pierce, best-known for his portrayal of the cultured, persnickety Niles Crane, M.D., PH.D., in the long-running CBS sitcom *Frasier*, says he wears the cap "religiously." (The fictional Crane earned his undergraduate, M.D., and PH.D. degrees at Yale.)

But Alpern's letter also had a serious purpose. During his career, Hyde Pierce has lent his voice to animated characters as various as *The Simpsons*' Cecil Terwilliger and Slim the stick-insect in *A Bug's Life*. But for 15 years, he has also been one of the most visible and articulate spokesman for The Alzheimer's Association, raising awareness of the urgent need for better diagnostic tools and effective treatments for Alzheimer's disease (AD). Because Alpern has made the expansion of research on neurodegenerative diseases a touchstone of his tenure as dean, he invited Hyde Pierce to visit the School of Medicine to learn about the school's diverse research efforts in AD.

"Statistically, this is a disease that's going to affect everybody in one way or another," Hyde Pierce says, and this trend has been borne out in his own life. The disease killed his beloved grandfather, and advancing dementia would likely have claimed his father but for a fatal bout with pneumonia. "When he died, he still knew us," says the actor, a former national board member (now an honorary member) of the Alzheimer's Association.

Hyde Pierce took Alpern up on his offer to visit New Haven, and met with scientists exploring AD on every front in the search for new treatments. "When you see these bristling intellects working on this thing, and how much has been done," Hyde Pierce says, "it gives you hope." He was "pleased and proud, having gone to Yale, to find out about the medical school's vibrant neurodegenerative research community," and this past March he joined Alpern and a group of School of Medicine scientists at the Yale Club of New York for a presentation of the School of Medicine's Alzheimer's disease research.

The session was moderated by John H. Krystal, M.D., the Robert McNeil Professor of Translational Research, chair of the Department of Psychiatry, and an authority on neuropsychiatric disease. To lead off the talks, Associate Professor of Pharmacology Ya Ha, PH.D., whose team published the first-ever crystal structure of an enzyme that acts inside cell membranes in 2007, discussed how his work relates to human gamma-secretase, the enzyme that creates the amyloid fragments involved in AD. Stephen M. Strittmatter, M.D., PH.D., the Vincent Coates Professor of Neurology and co-director of the Yale Program in Cellular Neuroscience, Neurodegeneration, and Repair, then presented his surprising recent findings on how the amyloid-beta (A-β) protein that comprises the "plaques" found in AD patients' brains may begin the destructive cascade that eventually erases memories (see related story, p. 5). Finally, Christopher H. van Dyck, M.D., professor of psychiatry and neurobiology and director of Yale's Alzheimer's Disease Research Unit, reported on progress using imaging techniques such as positron emission tomography (PET) to measure brain levels of A-β, which may soon achieve the elusive goal of early AD diagnosis, providing doctors with enough time for treatments to make a difference.

In his own remarks, Hyde Pierce navigated "the twin horns of the Alzheimer's dilemma" that he says frame most of his talks on the subject. It is essential, he says, to "keep hope alive and let people know there's progress," but also to drive home the urgency of the current situation. "We have no treatments, and we need to be candid about this disease."

The prolific Hyde Pierce has received many accolades since he graduated from Yale College in 1981, including a Tony Award in 2007 for his work in *Curtains*, and four Emmys for *Frasier*. But earlier this year he brought home a different sort of prize, one that is particularly appropriate for a man who has made his name as both actor and advocate: the Tony Awards' 2010 Isabelle Stevenson Award, which honors his "substantial contribution" to the Alzheimer's Association.

TERRY DAGRADI

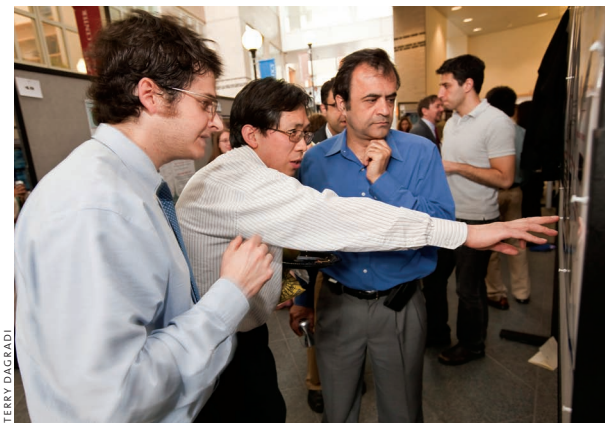
Actor and Yale alumnus David Hyde Pierce of *Frasier* fame joined researchers Stephen Strittmatter (left) and John Krystal (right) at a Yale Club session on Alzheimer's disease.

OUT & ABOUT

April 15 During their annual visit to the medical school's Center for Neuroscience and Regeneration Research (CNRR), members of the **Paralyzed Veterans of America** (PVA) had dinner with CNRR scientists in Branford College's Common Room and received scientific updates at CNRR labs the following day. From left: Yale University President **Richard C. Levin** accepts a PVA donation of $300,000 from **Gene A. Crayton**, national president of PVA, joined by **Stephen G. Waxman,** M.D., PH.D., CNRR director and Bridget Marie Flaherty Professor of Neurology, Neurobiology, and Pharmacology. PVA has been a steadfast supporter of the CNRR for over 20 years, and has made donations totaling millions of dollars to fund the center's research.

CHRIS VOLPE

May 11 At the School of Medicine's annual **Student Research Day**, held in the atrium of the Anlyan Center, M.D./PH.D. student **Daniel Balkin**, one of 71 students who presented original research, discussed his work with Associate Research Scientist **Zhi-Jia Ye**, PH.D., and Associate Professor of Medicine **Arya Mani**, M.D. The Farr Lecture, the culminating event of Student Research Day, was delivered by **Lewis Landsberg**, M.D., Irving S. Cutter Professor of Medicine and dean emeritus of Northwestern University's Feinberg School of Medicine.



TERRY DAGRADI

May 24 The members of the Class of 2010 launched their careers as physicians at this year's **Commencement** ceremonies. Graduate **David Myles** '10, who will join the Pediatric Residency Program at Johns Hopkins Children's Center, celebrated with his family. This year's Commencement address was given by **Donald M. Berwick**, M.D., M.P.P., professor at the Harvard School of Public Health, newly appointed by President Obama to head the Centers for Medicare and Medicaid Services. Many students graduated with joint degrees at this year's Commencement: 15 received M.D./PH.D. degrees; 22 received M.D./M.H.S. degrees; one received an M.D./M.B.A.; and one received an M.D./M.P.H.

TERRY DAGRADI

June 3–6 Medical school alumni turned out in droves for **Alumni Weekend**, which featured symposia on "Doctor as Patient" and "When Illness Strikes the Leader"; an academic review of the legacy of pioneering neurosurgeon Harvey Cushing, M.D.; and guided tours of the Medical Library, campus improvements, the new Smilow Cancer Hospital, and the 136-acre West Campus. Saturday marked the dedication of the new Harvey Cushing Center, which includes a dramatic display of Cushing's whole-brain specimens, clinical drawings and photographs, and memorabilia. Class Dinners, including one in honor of the Class of 1960's 50th reunion, took place at New Haven–area restaurants. Members of the Class of 2000, including (from left) **Carl J. Seashore**, M.D., **Daniel Jacoby**, M.D., **Linda Maxwell**, M.D., **John D. Mahoney**, M.D., **Darren L. Lish**, M.D., and **Felix Adler**, M.D., celebrated their 10th reunion.

JOHN CURTIS

Getting 'pumped' aids kids' diabetes control

In type 1 diabetes, autoimmune damage to insulin-producing cells in the pancreas causes abnormally high levels of glucose in the blood. Unchecked, diabetes can cause blindness, kidney failure, and heart disease.

To keep harmful hyperglycemia at bay, patients rely on dietary adjustments and injections of insulin. But successfully managing blood sugar using current methods of self-testing and multiple daily insulin injections is difficult. In adults, continuous glucose monitoring technology and insulin pumps (see photo) have each proven to better control blood sugar, but these approaches have not worked as well in children.

In a year-long, randomized, multicenter trial known as STAR 3, led at the School of Medicine by William V. Tamborlane, M.D., professor of pediatrics and chief of that department's Section of Pediatric Endocrinology and Diabetes, sensor-augmented insulin pumps, which combine insulin infusion with continuous glucose monitoring, better controlled blood sugar in type 1 diabetics of all ages than did daily insulin injections. The study, published on June 29 in the online edition of *The New England Journal of Medicine*, is the first to show consistent results in children.

Building a case against an Alzheimer's culprit

In 2009, a team from the lab of Stephen M. Strittmatter, M.D., PH.D., reported in *Nature* that small amyloid beta (A-β) molecules— which aggregate to form the plaques seen in Alzheimer's disease (AD) patients' brains—bind to neurons expressing cellular prion protein (PrP^c), a ubiquitous protein in the normal brain. When A-β bound to PrP^c, neural processes believed to underlie memory formation were compromised, leading the researchers to hypothesize that PrP^c binding of A-β is a key early player in the cognitive decline of AD.

In the May 5 issue of the *Journal of Neuroscience*, Strittmatter and colleagues present more evidence. Studying a mouse model of AD, the group found that mice bred to lack PrP^c showed no impairment in spatial learning and memory—even though their brains were riddled with A-β plaques. Mice expressing PrP^c showed marked memory deficits and died significantly earlier than their counterparts.

"Cellular prion protein is the essential mediator that leads to Alzheimer's-like memory dysfunction and reduced survival in these model mice," says Strittmatter, the Vincent Coates Professor of Neurology and co-director of the Program in Cellular Neuroscience, Neurodegeneration, and Repair.

Ixodes scapularis? There's an app for that!

Yale-designed iPhone application provides Lyme disease information, employs user's location to assess risk

Thanks to faculty and students at the Yale School of Public Health (YSPH), users of Apple's popular iPhone can better protect themselves against Lyme disease, the most prevalent insect-borne disease in the United States.

The new application presents data on the abundance of infected ticks at the location of the user anywhere within the U.S., based on information from the phone's Global Positioning System (GPS) hardware. If ticks are determined to be present, the user is given a list of precautions to avoid bites. A chart with life-size photos is provided to aid in the identification of black-legged ticks (*Ixodes scapularis,* also known as deer ticks) at each life stage, useful information because these ticks cannot transmit Lyme disease during some stages. If the user has been bitten, the program provides instructions on how to properly remove a tick, along with a narrated video.

"This is the first health application for smartphones that could have an immediate impact on a major disease" said Durland Fish, PH.D., professor of epidemiology at YSPH, who oversaw the development of the application.

Lyme disease can be transmitted after 48 hours of feeding by an infected tick, and most physicians will treat patients who experience such bites with a short course of antibiotics to prevent the disease. To help users determine when they were bitten, the application depicts ticks at various stages of blood engorgement and advises patients to seek medical attention if the photos suggest that a removed tick had been attached for 48 hours or longer. A panel of photos of skin rashes characteristic of Lyme disease along with a list of other symptoms also prompts users to seek immediate medical attention if they believe they are infected. To help users obtain medical care in unfamiliar locations, a GPS-based physician locator finds nearby doctors and provides the phone number and directions to each physician's office.

"You can only get Lyme disease in certain areas, only by certain ticks, and only after a tick has remained attached for a certain amount of time," says Fish. "Information provided by this app should help many people prevent Lyme disease."

HAROLD SHAPIRO (2)

Along with Maria Diuk-Wasser (right), assistant professor of epidemiology, and Francesica Tizard (left), senior administrative assistant at the Yale School of Public Health, Durland Fish (seated) has crafted a new Lyme disease application for the Apple iPhone. The software uses location-based services to inform users of the presence of deer tick populations, and also includes clear depictions of ticks at various life stages (left), which can help determine whether tick bites require quick medical attention.

Content for the application is provided by Lyme disease researchers at the School of Medicine—where Lyme disease was first identified—in cooperation with the U.S. Centers for Disease Control and Prevention, the American Lyme Disease Foundation, and IntuApp, an applications development company in New York City. It is available through the Apple iTunes Store for $1.99, with proceeds supporting the research and education mission of the American Lyme Disease Foundation based in Lyme, Conn.

Grad student lauded for malaria mosquito research

Allison Carey, M.D., PH.D., who just completed her doctoral studies in Yale's Interdepartmental Neuroscience Program, is a winner of the 2010 Harold M. Weintraub Graduate Student Award. The award, sponsored by the Basic Sciences Division of the Fred Hutchinson Cancer Research Center (FHCRC) in Seattle, Wash., recognizes outstanding achievement by graduate students in the biological sciences.

Carey is one of 13 graduate students in North America to receive the award this year. The awardees participated in a scientific symposium on May 7 at the FHCRC.

Carey, who received her M.D. in 2009 and her PH.D. at Commencement this past June, has focused her research at Yale on odorant receptors in the mosquito *Anopheles gambiae*, the primary carrier of malaria in sub-Saharan Africa. Carey will soon begin a postdoctoral fellowship at the Institut Pasteur in Paris, France.

In the February 3 issue of *Nature*, Carey and colleagues, including her advisor John R. Carlson, PH.D., the Eugene Higgins Professor of Molecular, Cellular, and Developmental Biology, identified *A. gambiae* odorant receptors that are precisely tuned and highly sensitive to components of human body odors, which may help them to locate and infect the hundreds of millions of people afflicted with malaria each year. In this research, which formed the basis of her PH.D. thesis, Carey recorded over 27,000 responses to 110 different odors from a variety of *A. gambiae* receptors expressed in the antennae of mutant fruit flies. This work "was of epic proportion," Carlson says. "It required an enormous amount of effort, a high level of skill, and a great deal of creativity. Allison was also a wonderful colleague."

TERRY DAGRADI

Allison Carey has studied the highly sensitive olfactory system of malaria-carrying *Anopheles* mosquitoes, work that may help prevent them from infecting humans or lure them into traps.

A major goal of the Carlson lab is to apply knowledge of the molecular basis of *A. gambiae* olfaction to reduce the mosquitoes' attraction to human odors or to lure them into traps, strategies that may slow the transmission of malaria.

The Weintraub Award, established in 2000, honors the late Harold M. Weintraub, PH.D., a founding member of the FHCRC's Basic Sciences Division and a leading researcher in developmental biology. Carey is one of two students in Carlson's lab to win the award recently: Elissa Hallem, PH.D., was an awardee in 2005.

Grants and contracts awarded to Yale School of Medicine

September/October, 2009

Federal

Serap Aksoy, NIH, *Molecular Aspects of Tsetse and Trypanosome Transmission*, 5 years, $2,326,195 (A) • **Colleen Barry**, NIH, *Expanding Treatment for Opioid Dependence among the Privately Insured*, 4 years, $1,746,305 • **Robert Beech**, NIH, *Progesterone-Induced Gene Expression Changes and Risk of Relapse to Cocaine Use*, 2 years, $496,500 (A) • **Hilary Blumberg**, NIH, *Biomarkers of Suicide Risk in Adolescents and Young Adults: Factors that Contribute to High Risk in Bipolar Disorder*, 2 years, $998,276 (A) • **Hal Blumenfeld**, NIH, *Preventing Spike-Wave Epileptogenesis: Critical Period and Neuroimaging Biomarkers*, 2 years, $821,933 (A) • **Clifford Bogue**, NIH, *Hex: A Homeobox Gene Essential for Liver Development*, 22 months, $824,822 (A) • **Martina Brueckner**, NIH, *Genetic Determinants of Human Heterotaxy and Aortic Arch Malformation*, 6 years, $4,394,539 • **Richard Bucala**, NIH, *Innate and Adaptive Mechanisms in Arthritis*, 5 years, $1,859,375 • **Lloyd Cantley**, NIH, *Cellular Repair of Kidney Injury*, 21 months, $706,903 (A) • **Thomas Carpenter**, NIH, *Classical and Non-Classical Responses to Vitamin D in Children: The Role of DBP Genotype*, 2 years, $999,475 (A) • **Judy Cho**, NIH, *Beyond Single-Point GWAS: Genetics of Crohn's Disease in Ashkenazi Jews*, 22 months, $1,001,477 (A) • **Hyung Chun**, NIH, *Role of Apelin in the Systemic and Pulmonary Vasculature*, 5 years, $667,575 • **Paul Cleary**, CDC/DHHS, *Category 1: Meeting Community Needs Across the Prevention Spectrum*, 5 years, $5,316,317 • **Joan Cook**, NIH, *Theory-Driven Mixed-Methods Evaluation of PTSD Treatment Implementation in VA Residential Settings*, 2 years, $918,498 (A) • **Lynn Cooley**, NIH, *Dynamic and Super-Resolution Imaging of Endogenous Proteins in* Drosophila *Tissues*, 2 years, $946,752 (A) • **Cindy Crusto**, NIH, *The Study of Multiple Social Determinants of Young Children's Health*, 2 years, $1,035,964 (A) • **Pietro De Camilli**, NIH, *OCRL and the Pathogenesis of Lowe Syndrome and Dent Disease*, 4 years, $1,117,760 • **Daniel DiMaio**, NIH, *Molecular Basis of Viral and Cellular Transformation*, 5 years, $6,413,248 • **Peniel Dimberu**, NIH, *Role of TRIM Protein in Cellular Innate Anti-viral Responses to HCV*, 2 years, $82,352 (A) • **Claudia Dominguez**, NIH, *Infection and CD8 T Cell Memory: Development, Maintenance, and Plasticity*, 3 years, $108,128 • **Deepak D'Souza**, NIH, *GABA Deficits and Vulnerability to Cannabinoid-induced Psychosis*, 2 years, $374,461 • **Lynn Fiellin**, NIH, *Reducing Heavy Drinking to Optimize HIV/AIDS Treatment and Prevention*, 5 years, $3,911,127 • **Richard Flavell**, NIH, *Understanding the Role of AMCase in Asthma*, 2 years, $1,000,000 (A) • **Ewa Folta-Stogniew**, NIH, *Biacore T100 SPR for Yale Keck Lab*, 1 year, $363,515 • **Joel Gelernter**, NIH, *Genetics of Alcohol Dependence in African-Americans*, 5 years, $3,193,349; NIH, *Genome-wide Association Study of Cocaine Dependence in Two Populations*, 2 years, $4,207,355 (A) • **Sarah Gray**, NIH, *Mechanisms Underlying Leptin's Attenuation of Cocaine-seeking Behavior in Rats*, 2 years, $60,732 (A) **Cary Gross**, Agency for Healthcare Research and Quality/DHHS, *Multimorbidity and Cancer Screening: Achieving Patient Understanding*, 2 years, $299,340 • **Murat Günel**, NIH, *Functional Genomics of the Cavenous Malformation Gene*, 5 years, $2,978,125; NIH, *Molecular Variants that Determine Genetic Susceptibility to Intracranial Aneurysm*, 5 years, $3,265,832; NIH, *Gene Discovery in Recessive Structural Brain Disorders through Whole-Exome Sequencing*, 2 years, $2,906,138 (A) **David Hafler**, NIH, *The Role of Rare Variants in Multiple Sclerosis Risk*, 2 years, $1,917,986 (A) **Kevan Herold**, NIH, *Type 1 Diabetes TrialNet: Clinical Center at Yale University*, 5 years, $2,028,525 **Karl Insogna**, Department of Agriculture, *Mechanisms of Dietary Protein-Induced Changes in Calcium Absorption Efficiency*, 3 years, $499,123 **Elizabeth Jonas**, NIH, *Role of Bcl-xL in Synaptic Plasticity in the Hippocampus*, 2 years, $870,314 (A) **Leonard Kaczmarek**, NIH, *Biochemical Control of Excitability in Neurons*, 2 years, $909,360 (A) **Insoo Kang**, NIH, *Studying the Effects of Vitamin D on FOXP3 and IL-17 Expression in Human CD4+ T Cells*, 2 years, $413,750 • **Walter Kernan**, NIH, *Insulin Resistance Intervention after Stroke (IRIS) Trial*, 5 years, $24,307,862 • **Trace Kershaw**, NIH, *Randomized Controlled Trial to Enhance Dual Protection among PLHIV in India*, 4 years, $1,455,414 **Ami Klin**, NIH, *Performance Indices of Social Disability in Toddlers with Autism*, 2 years, $993,553 (A) **Michael Krauthammer**, NIH, *Advancing Literature Mining through Processing and Analysis*, 3 years, $1,016,452 • **Suchitra Krishnan-Sarin**, NIH, *Incentive-Based Intervention for Smoking Cessation and Prevention in High School*, 2 years, $761,988 (A) **Chiang-Shan Li**, NIH, *Amygdala Processes and Early Habitual Drinking*, 2 years, $384,975 **Charles Lockwood**, NIH, *Women's Reproductive Health Research Career Development Program*, 5 years, $2,410,115 • **Xiaomei Ma**, NIH, *Myelodysplastic Syndromes: Patterns of Care and Outcomes*, 2 years, $417,476 • **Robert Malison**, NIH, *DBH, D2High and Cocaine Paranoia/Aversion: A [11C]PHNO PET Study*, 2 years, $413,520 (A) • **Sadie Marjani**, NIH, *Analyzing Allele-Specific Gene Expression and Regulation in* C. albicans, 2 years, $101,764 • **Linda Mayes**, NIH, *ERP Neurobehavioral Assessment of Negative Reinforcement in Adolescents*, 2 years, $455,125 • **Ellena McCarthy**, NIH, *Cellular Dissection of Neuropeptide Signaling in the Circadian Neural Network*, 3 years, $148,974 **Justin McDonough**, NIH, *A Systems Biology Approach for Investigating* Coxiella burnetii *Infection*, 2 years, $97,264 (A) • **Sherry McKee**, NIH, *Dose-Ranging Study of Varenicline on Human Alcohol Self-Administration Behavior*, 3 years, $1,054,468 • **David Merrick**, NIH, *Characterization of the Cleaved Carboxy-Terminal Tail of Polycystin-1*, 2 years, $92,352 • **Wang Min**, NIH, *Inhibiting JNK: A New Anti-Inflammatory Strategy*, 2 years, $1,059,124 (A) • **Arie Mobley**, NIH, *Mechanisms of Embryonic Olfactory Sensory Neuron Axon Targeting*, 2 years, $101,764 **Shelby Montague**, NIH, *Translation of Olfactory Input into Behavioral Output in the* Drosophila *Larva*, 3 years, $93,073 • **Walther Mothes**, NIH, *Targeting HIV Cell-to-Cell Transmission*, 4 years, $2,218,363 • **Michael Nathanson**, NIH, *Silvio O. Conte Digestive Diseases Research Core Center*, 5 years, $6,007,650 (A) • **Lynda Odofin**, NIH, *Prevalence of Community-Acquired MRSA in Live Pigs and their Handlers*, 2 years, $85,077 (A) • **Stephanie O'Malley**, NIH, *Career Support and Mentoring of Interdisciplinary Alcohol Research*, 5 years, $1,236,542 • **Charisse Orme**, NIH, *Role of TUG in the Formation of Insulin-Responsive GLUT4 Vesicles*, 3 years, $114,132 • **Godfrey Pearlson**, NIH, *Genetic Architecture of Alcohol Misuse Candidate Endophenotypes*, 2 years, $996,533 (A) • **Margaret Pisani**, NIH, *Feasibility of Measuring Sleep in a Critical Care Environment*, 2 years, $438,880 (A) **Saif Rathore**, Agency for Healthcare Research and Quality/DHHS, *Race and Cardiac Catheterization Use in the Setting of Acute Myocardial Infarction: Classifications, Associations, and Long-Term Outcomes*, 14 months, $34,800 • **Carrie Redlich**, Center for Construction Research and Training, *Assessment and Prevention of Isocyanate Exposures in the Construction Industry*, 1 year, $149,986; NIOSH/CDC/DHHS, *Isocyanate Skin and Air Exposure: Assessment and Control*, 4 years, $1,648,387 **Scott Rivkees**, NIH, *Adenosinergic Mechanism of Intrauterine Growth Retardation*, 2 years, $823,948 (A) • **James Rothman**, NIH, *"Suspended" Bilayers: New Technology to Study the Dynamics of Membrane Structure and Function*, 2 years, $969,272 (A) • **Nenad Sestan**, NIH, *Transcriptional Atlas of Human Brain Development*, 2 years, $9,889,558 (A) • **Mark Shlomchik**, NIH, *Murine Memory B Cell Development and Function*, 5 years, $2,833,059 • **Michael Simons**, NIH, *Supporting New Faculty Recruitment to Enhance Research Resources through Biomedical Research Core Centers*, 2 years, $1,153,026 (A) • **Jeffrey Sklar**, NIH, *The JAZF1 Gene and Type 2 Diabetes*, 3 years, $1,076,754 • **Mehmet Sofuoglu**, NIH, *Sensitivity to Intravenous Nicotine: Genetic Moderators*, 2 years, $379,824 • **Mark Solomon**, NIH, *Pseudosubstrate Inhibition of the Anaphase Promoting Complex*, 2 years, $662,000 (A) • **Sandra Springer**, NIH, *Alcohol Pharmacotherapies among Released HIV+ Prisoners*, 5 years, $4,011,217 • **Vinod Srihari**, NIH, *Specialized Treatment Early in Psychosis (STEP): A Community Health Center-Based Cost-Effectiveness Study*, 2 years, $749,840 (A) **Matthew State**, NIH, Genomic Profiling and Functional Mutation Analysis in Autism Spectrum Disorders, 2 years, $2,245,837 (A) • **Stephen Strittmatter**, NIH, *Yale Cellular Neuroscience, Neurodegeneration, and Repair (CNNR) Program*, 2 years, $1,524,000 (A) • **Matthew Strout**, NIH, *Regulation and Dysregulation of Antibody Diversification*, 5 years, $872,100 • **Susumu Tomita**, NIH, *Genome-Wide Screening of Transmembrane Subunits of Ion Channels*, 2 years, $1,000,000 (A) **Federico Vaca**, NIH, *Development and Crash Injury Risk in Adolescent Latino Males*, 3 years, $436,867 • **Flora Vaccarino**, NIH, *Biological Correlates of Altered Brain Growth in Autism*, 2 years, $1,987,576 (A); NIH, *Cellular and Genetic Correlates of Increased Head Size in Autism Spectrum Disorder*, 2 years, $491,452; NIH, *Injury and Recovery in Developing Brain*, 5 years, $6,906,861 • **Neil Vasan**, NIH, *Structural Studies of the Exocyst*, 4 years, $123,364 • **Stuart Weinzimer**, NIH, *Closed-Loop Effectiveness and Ambulatory Regimens (CLEAR)*, 3 years, $2,189,034 • **Robert Weiss**, NIH, *Targeted siRNA Nanotechnology for Intravesical Treatment of Urological Diseases*, 22 months, $985,031 (A) • **Li Wen**, NIH, *Effect of Diet and Commensal Bacteria on Diabetes Outcome in NOD Mouse*, 2 years, $991,054 (A) • **Kenneth Williams**, NIH, *YALE/NIDA Neuroproteomics Research Center*, 5 years, $8,448,566 • **Stephanie Young**, NIH, *Novel Signaling between Striatal Neurons and Postnatal Neural Progenitors*, 2 years, $51,192 **Huiping Zhang**, NIH, *Association and Function of Opioid Receptor Gene Variants to Substance Dependence*, 3 years, $786,849 (A)

TERRY DAGRADI

With funding from the National Institutes of Health, Linda Mayes (left) and associate research scientist Michael Crowley (right) use dense-array electroencephalography (EEG) to measure subtle changes in brain function that result from early childhood stress, whether caused by prenatal exposure to cocaine or broader, more all-encompassing stressors such as poverty and violence. Crowley's daughter, Lia, is wearing a net containing dozens of electrodes, which detect the differences in electrical potentials across the surface of the brain.

Non-federal

Kathleen Akgun, University of Washington, *Risk, Severity, and Outcome of Bacterial Pneumonia in an HIV +/- Veteran Cohort*, 10 months, $135,707 (A) **Joel Beckett**, American Vascular Association, *Effect of Polyphenols in Olive Oil on Smooth Muscle Cell Proliferation*, 4 months, $3,000 **Richard Belitsky**, Gilead Foundation, *HAVEN Primary Care Clerkship*, 1 year, $75,000 • **Michael Bloch**, Trichotillomania Learning Center, Inc., *Double-Blind, Placebo-Controlled Trial of N-Acetylcysteine for Childhood Trichotillomania*, 1 year, $20,000 • **Donald Botta**, CoolSpine, LLC., *Intraventricular Cooling Catheter*, 2 years, $153,659 (A) **Cynthia Brandt**, Massachusetts General Hospital, *Rare Cancer Genetics Registry*, 2 years, $72,277 (A) **Robert Bruce**, Liberty Community Service, Inc., *Services in Supportive Housing*, 1 year, $130,000 **Matthew Burg**, Columbia University, *Comparison of Depression Interventions after Acute Coronary Symptoms*, 10 months, $71,443 (A) **Thomas Carpenter**, Thrasher Research Fund, *Assessing Vitamin D Requirements: The Role of Vitamin D Binding Protein in the Response to Vitamin D Supplementation in Infants*, 3 years, $417,736 • **Peter Charpentier**, Hebrew Rehabilitation Center for the Aged, *HRC/IFAR*, 1 year, $8,742 **Lauren Cohn**, Tufts University, *The Role of STAT3 in Allergic Inflammation and Airway Remodeling*, 1 year, $18,215 • **Larry Davidson**, Illinois Institute of Technology, *Adherence And Empowerment: Service Participation and Meaningful Outcomes*, 1 year, $196,796 • **Madhav Dhodapkar**, Leukemia and Lymphoma Society, *Combination Therapy Targeting Natural Killer T Cells*, 3 years, $600,000 **Maria Diuk-Wasser**, University of Minnesota, *Eco-epidemiology of Leptospirosis in Latin Americans: Understanding Transmission Dynamics in a Community*, 1 year, $15,373 • **Wawrzyniec Dobrucki**, Society of Nuclear Medicine Education and Research Foundation, *Noninvasive Quantitative MicroSPECT/CT Assessment of Myocardial Angiogenesis and Remodeling Post-MI in Diabetic Rats Subjected to Therapy with Bi-Functional Angiotensin II Receptor Blocker*, 1 year, $25,000 **Donald Engelman**, University of Rhode Island, *PHLIP Nanotechnology Platform for Cancer Imaging and Therapy: Nanoscience and Nanotechnology in Biology and Medicine*, 2 years, $215,450 (A) • **Jorge Galán**, Columbia University, *Type III Secretion Antigen Delivery System Assembled in Non-Replicating Platform*, 5 months, $155,509 • **Mark Gerstein**, Brigham and Women's Hospital, *Analysis of Patterns of Structural Variation in the 1000 Genomes Data Set*, 10 months, $170,445 (A); Massachusetts Institute of Technology, *NIH modENCODE DAC GO Grant*, 1 year, $140,000 • **Frank Giordano**, Williams Syndrome Association, *Williams Syndrome*, 2 years, $320,000 • **Tina Goldsmith**, Organization for Autism Research, *Comprehension of Pretense in Young Children with Autism: The Development of Assessment and Teaching Techniques*, 16 months, $2,000 • **Elena Grigorenko**, King Faisal University, *Etiological Bases of Giftedness*, 3 years, $467,620 • **Ruth Halaban**, Melanoma Research Alliance, *Sequencing of the Melanoma Exome, Transcriptions and Epigenome*, 3 years, $999,999 **Lyndsay Harris**, Breast Cancer Research Foundation, *Biomarker Incubator to Define and Validate Predictors of Response to Paciltaxel and Trastuzimab*, 1 year, $199,999 • **Robert Heimer**, Biomedical Center, St. Petersburg, Russia, *International Feasibility Study of Pharmacy-Based HIV Prevention: St. Petersburg*, 9 months, $38,593; Duke University, *Drug Policy, Incarceration, Community Reentry, and Race Disparities in HIV/AIDS*, 10 months, $391,623; United Nations Population Fund, *Developing an Evaluation Platform for UNFPA's Y-PEER Projects*, 9 months, $168,000 • **John Hwa**, American Heart Association, *Prostanoid Receptor Pharmacogenetics and Environmental Trace Metals*, 28 months, $240,372 • **Karl Insogna**, Dairy Management, Inc., *The Impact of Protein Supplement on Bone Mass in Older Men and Women*, 2 years, $109,975 • **Megan King**, G. Harold and Leila Y.

(A) **Denotes new grant funding received under the American Recovery and Reinvestment Act of 2009 (ARRA).**

New fellowships memorialize Annie Le, 'an exemplary student'

When Annie Marie Le, an idealistic and ambitious doctoral student in Yale's Combined Program in the Biological and Biomedical Sciences (BBS), lost her life in a homicide last September, the Yale community—and the larger world—reacted with grief and dismay.

In the wake of Le's death, members of many parts of the Yale community came together to forge a scholarship fund that would commemorate her life and exemplary spirit in a lasting way by supporting the work of current graduate students. Soon after, the Yale Corporation established the Annie Le Fellowship to provide assistance to doctoral candidates in the BBS program "whose demonstrated commitment to bettering the world around them and outstanding record and research exemplify the qualities represented in the life and career of Annie Le."

Two graduate students in the BBS program—Julie Button, a fifth-year graduate student in microbiology; and Jason Wallace, a fourth-year graduate student in molecular, cellular, and developmental biology—have been named the inaugural Annie Le Fellows and will receive funding for the 2010–2011 academic year.

Button, who works in the laboratory of *Salmonella* expert Jorge E. Galán, PH.D., D.V.M., the Lucille P. Markey Professor of Microbial Pathogenesis, studies the roles that "chaperone" proteins play in the Type III Secretion System, an appendage used by many Gram-negative bacteria to help them infect a host's cells by moving factors into those cells that promote the bacteria's survival and replication. Wallace, a doctoral student in the lab of Ronald R. Breaker, PH.D., the Henry Ford II Professor of Molecular, Cellular, and Developmental Biology and Howard Hughes Medical Institute Investigator, studies large, non-coding RNAs that were recently discovered in several species of bacteria, which appear to be important for helping the bacteria survive extreme stress.

In addition to their academic work, both fellows are public-spirited. Button participates in the Hill Neighborhood Mentoring Program, has served on the Graduate Student Assembly for two years, and has sung with the Academia Nuts, the graduate school's all-female a cappella group. Wallace provides Spanish-English translation for his church and has served as a career mentor for the Boy Scouts of America.

"Annie Le was an exemplary student, and someone who was concerned about the community in which she lived. And so we thought that the fellowship really would emphasize those two qualities—that is, the capacity of someone to really be an absolutely outstanding student, who also was concerned about the larger world in which he or she lives. We thought it was a really appropriate way to commemorate her life and her time at Yale," says Jon Butler, PH.D., the Howard R. Lamar Professor of American Studies, History, and Religious Studies. Butler was dean of Yale's Graduate School of Arts and Sciences when Le died, and he oversaw the implementation of the new fellowship.

"Annie came to Yale to study and train as a biomedical scientist," says Elias Lolis, PH.D., associate professor of pharmacology and Le's former doctoral supervisor. "She also cared about people and treated everyone with respect. It is for these reasons that Yale University established this fellowship in her memory."

HAROLD SHAPIRO

Julie Button and Jason Wallace, doctoral candidates in the Combined Program for Biological and Biomedical Sciences, have been named the inaugural Annie Le Fellows for 2010–2011.

An initial $100,000 endowment from the Yale Corporation has been increased by additional gifts from friends and members of the Yale community. In April, the Association of Asian American Yale Alumni, the Association of Yale Alumni, the Yale Alumni Association of Metropolitan New York, the Yale Life Sciences Alumni Association, and several other groups collaboratively organized a benefit concert for the fund in New York City.

After earning her undergraduate degree in cell and developmental biology at the University of Rochester, Le came to Yale for graduate work in 2007. Working in the laboratory of her advisor, Anton M. Bennett, PH.D., associate professor of pharmacology, Le was exploring the effects of metabolic stresses on an enzyme connected with mitochondrial function in muscle cells. She planned to devote her life to biomedical research, and had dreamed of having a scientific career at the National Institutes of Health.

"One of the many tragic aspects about losing Annie was that it was only after her death that the Yale community at large learned about her and her wonderful qualities," says John D. Alvaro, PH.D., administrative director of BBS. "The fellowship in her name now enables us to identify and celebrate other talented and selfless students, some of the hidden gems among the student body."

The Annie Le Fellowship will be awarded each year by the Graduate School of Arts and Sciences, at the recommendation of faculty in the biological and biomedical sciences. To contribute to the fellowship fund, contact Wesley Poling, PH.D., at wesley.poling@yale.edu or (203) 432-7919.

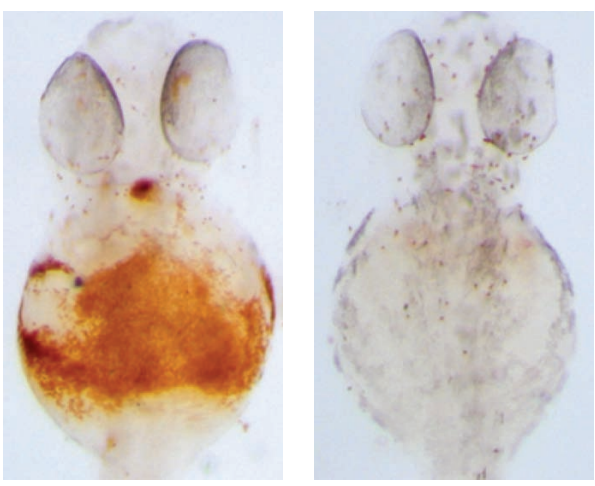
Mathers Charitable Foundation, *Mechanical Communication between the Nucleus and the Cytoplasm*, 3 years, $1,100,000 • **Michael Koelle**, Merck/United Negro College Fund, *2009 UNCF Merck Undergraduate Science Research Scholarship Award*, 1 year, $10,000 • **Richard Lifton**, Columbia University, *A GWAS for IgA Nephropathy, the Most Common Form of Glomerulonephritis*, 10 months, $344,355 A • **Nils Loewen**, American Glaucoma Society, *Application for Mentoring for Advancement of Physician-Scientists (MAPS) Enabling Award Program*, 1 year, $10,000 • **Paul Lombroso**, Institute for the Study of Aging, *Screening for Inhibitors of STEP*, 1 year, $138,600 • **Charles Lusk**, G. Harold and Leila Y. Mathers Charitable Foundation, *Connecting Chromatin to the Lumen: Making Pores in the Nuclear Envelope*, 3 years, $1,100,000 **Steven Marans**, NewAlliance Foundation, Inc., *Child Development Community Policing Program*, 1 year, $5,000 • **Richard Marottoli**, Research Foundation for Mental Hygiene, *Health and Aging Policy Fellowship*, 1 year, $30,000 • **Kathleen Martin**, Flight Attendant Medical Research Institute, *Effects of Secondhand Cigarette Smoke Exposure on Adiponectin, MTOR and Vascular Disease*, 22 months, $216,000 • **Eric Meffre**, Mount Sinai School of Medicine, *Loss of B Cell Tolerance in Primary Immunodeficiencies*, 1 year, $310,645 A • **Leonard Milstone**, TransDerm, Inc., *Delivery of Biologically Active Nucleic Acids to Epidermal Cells*, 2 years, $885,279 A • **Marc Potenza**, University of Minnesota, N-*Acetyl Cysteine Plus Behavioral Therapy for Nicotine Dependent Pathological Gambling*, 1 year, $237,204 A • **Peter Rabinowitz**, Harvard School of Public Health, *Chronic Occupational Noise, Stressors, and Susceptibility in Cardiovascular Illness*, 1 year, $22,223 • **Harvey Risch**, Fred Hutchinson Cancer Research Center, *Barrett's and Esophageal Adenocarcinoma Consortium Genetic Susceptibility Study*, 1 year, $20,889 • **Alan Sartorelli**, National Foundation for Cancer Research, *Approaches to the Therapy of Leukemia*, 3 years, $151,940 • **Margretta Seashore**, Children's Nat'l Medical Center, *Longitudinal Studies for Urea Cycle Disorders*, 6 months, $6,594; Children's Research Institute, *Longitudinal Studies for Urea Cycle Disorders*, 5 years, $500,000 • **Sachin Shah**, American Heart Association, *Variations of Inpatient Spending and Patient Outcomes with Acute MI*, 6 months, $11,000 • **Robert Sherwin**, Columbia University, *Hydrozyuera (HU) Use in Sickle Cell Disease*, 9 months, $79,087 • **Michael Simons**, Fondation Leducq, *Transatlantic Network on Therapeutic Arteriogenesis and Metabolism Modulation*, 5 years, $936,220 • **Stephen Strittmatter**, Alzheimer's Association, *Neuronal Receptor Mediating the Disease-Causing Effects of A-Beta Oligomers*, 3 years, $200,000 • **Vinzenz Unger**, Johns Hopkins University, *Structural Biology of Copper Homeostasis*, 1 year, $261,490 • **Tong Wang**, University of Cincinnati, *Apical Chloride/Bicarbonate Exchangers in Small Intestine and Kidney*, 10 months, $41,843 • **Nadia Ward**, Research Triangle Institute, *Yale University GEAR UP Partnership Grant*, 1 year, $24,000 • **Sherman Weissman**, Stanford University, *Mapping Transcription Factors Binding Sites in the Mouse Genome*, 6 months, $48,102 A • **Scott Woods**, University of California, Los Angeles, *Prevention Trial of Family Focused Treatment in Youth at Risk for Psychosis*, 2 years, $150,597 A • **Qin Yan**, The V Foundation for Cancer Research, *Roles of Histone Demethylase Retinoblastoma Binding Protein 2 in Cancer*, 2 years, $200,000 • **Herbert Yu**, Brigham and Women's Hospital, *Genome-Wide Association Study of Endometrial Cancer*, 1 year, $126,628 A

// Giraldez *(from page 3)*

destroying the genes in that mRNA. Since Ago2 has its own slicing activity, the Giraldez team hypothesized that Ago2, rather than Dicer, might process miR-451, and this supposition proved to be correct: in a zebrafish mutant with faulty Ago2, levels of miR-451 were sharply reduced. Previous studies had shown that miR-451 is essential for normal red blood cell production, and the Ago2-mutant zebrafish were found to be anemic (see photo).

This observation nicely complements another new study by a Cold Spring Harbor Laboratory research team (two members of which also worked with Giraldez and colleagues on the zebrafish study), who found that mice with compromised Ago2 also had reduced levels of miR-451 and anemia. Because the Ago2 processing pathway for miR-451 and other miRNAs has been conserved in vertebrate animals over evolutionary time to regulate processes as basic to life as red blood cell production, Giraldez believes that these seeming exceptions to the Dicer-based rule may prove to have much wider implications.

"There is an immense, vast sea of small RNAs out there, and it is difficult to sort out what is junk from what is functional," says Giraldez. "This discovery really opens the door to finding new families of these RNAs that influence many forms of biological activity. With this new 'molecular scissors,' we have another tool to find small RNAs that are important to life, that activate genes in disease, and may be important in developing new therapeutics."



COURTESY OF ANTONIO GIRALDEZ

Expression of hemoglobin (brown), a crucial component of red blood cells, in a normal zebrafish embryo (left) and in a mutant embryo lacking the gene for the enzyme Argonaute 2 (Ago2; right). In the absence of Ago2, which is part of a novel microRNA processing pathway recently discovered by a Yale-led research team, mutant fish develop severe anemia.

A 'can-do, visionary' scientist is named graduate school dean

Thomas D. Pollard, M.D., Sterling Professor of Molecular, Cellular, and Developmental Biology, has been appointed dean of Yale's Graduate School of Arts and Sciences, effective July 1.

As an undergraduate at Pomona College in his native California in the early 1960s, Pollard, also professor of molecular biophysics and biochemistry and of cell biology, was eager to understand how cells move (cell motility) and how they divide to form daughter cells (cytokinesis), questions that have guided his research ever since.

For more than three decades of research on these topics, Pollard has won some of the most prestigious awards in biomedical science, including the E.B. Wilson Medal (2004), from the American Society for Cell Biology (ASCB); the Lewis S. Rosenstiel Award for Distinguished Work


Thomas Pollard

in Basic Medical Science (2006, with James A. Spudich, PH.D., of Stanford School of Medicine); and the Gairdner International Award (2006, with Alan Hall, PH.D., of Memorial Sloan-Kettering Cancer Center).

In addition to their importance in basic biology, motility and cytokinesis have direct relevance to oncology, because these processes drive cancer's spread and the growth of tumors. Research in Pollard's laboratory, which has combined techniques from biochemistry, biophysics, cell biology, and genetics, has focused on actin filaments—long, thin protein fibers that are a basic component of the cytoskeleton, the intracellular framework that lends strength to cells and gives them their shape. Actin filaments generate force for locomotion in white blood cells and cancer cells, and form the "purse string" that pinches a cell into two daughter cells during cell division, a process that is also important in wound healing.

"Always a scientist at heart," as he was described by Yale President Richard C. Levin upon his appointment, Pollard has nonetheless gravitated to leadership roles throughout his career. He has served as president of the Salk Institute for Biological Studies, of the Biophysical Society, and of the ASCB, which has called him the "personification of [the society's] can-do, visionary spirit." He was associate editor of the *Journal of Cell Biology* for seven years.

With bachelor's degrees in chemistry and zoology from Pomona, Pollard earned his M.D., *cum laude,* at Harvard Medical School, where he was later a professor. He joined the Yale faculty as Eugene Higgins Professor of Molecular, Cellular, and Developmental Biology in 2001.

Pollard is a member of the National Academy of Sciences and the Institute of Medicine, and a fellow of the American Academy of Arts and Sciences, the Biophysical Society, and the American Association for the Advancement of Science, for which he now serves on the board of directors.

Married to his wife, Patty, since 1964 (she has been president of the Yale University Women's Organization for the past 4 years), Pollard passed on a love of science to his children, Katie and Dan, both of whom are computational biologists. In a 1992 ASCB profile, he said of his family, "We all like to see things work!"

Expert on disability in elderly elected to venerable medical society

Thomas M. Gill, M.D., an authority on the epidemiology and prevention of disability among older persons, has been elected to the Association of American Physicians (AAP).


Thomas Gill

The Humana Professor of Geriatric Medicine and professor of medicine and epidemiology, Gill seeks to understand the mechanisms underlying physical decline in community-living older people and to develop means of preventing such decline. Since 1997, Gill has been principal investigator on the Precipitating Events Project (PEP), which has revolutionized our understanding of disability in older persons. Through monthly phone interviews and regular home visits, PEP researchers have learned that, contrary to a widely held belief that disability is irreversible, older people often recover quickly from disabling events. In 2006, the National Institute on Aging backed PEP with a $3.2 million MERIT award, allowing Gill to continue the 12-year study for several more years.

More recently, Gill, co-director of both the Yale Program on Aging and the Claude D. Pepper Older Americans Independence Center, has embarked on studies of the potential benefits of testosterone treatment in symptomatic older men and the effectiveness of exercise interventions in preventing disability, and has explored strategies to promote independent bathing in community-living older people.

Gill, also director of the Yale Center for Disability and Disabling Disorders, has received many accolades, including the Paul Beeson Physician Faculty Scholars in Aging Research Award, and the Outstanding Scientific Achievement for Clinical Investigation Award from the American Geriatrics Society, and the Ewald W. Busse Research Award in the Biomedical Sciences.

After completing his M.D. at the University of Chicago in 1987, Gill came to Yale as a Robert Wood Johnson Clinical Scholar for research training in clinical epidemiology. After a year as a geriatrics fellow, Gill joined the Yale faculty in 1994. Gill oversees the Yale Research Fellowship in Geriatric Medicine and Clinical Epidemiology, and is director of the Pepper Center's Research Career Development Core.

Founded in 1885 by seven physicians (including legendary physician Sir William Osler, M.D.) the AAP elects members who make "outstanding contributions to the advancement of science and medicine."

// Rothman *(from page 1)*
Medicine, and Richard H. Scheller, Ph.D., formerly at Stanford and now executive vice president of Genentech.

While at the University of Texas Southwestern Medical Center, Südhof discovered synaptotagmin, a protein in vesicle membranes that senses intracellular calcium levels. When a neuron is stimulated, calcium binds to synaptotagmin, which prompts the vesicle to release its contents by interacting with SNARE complexes and fusing with the cell membrane. Structural, genetic, and cell biology studies in Scheller's lab have mapped out the interactions of synaptotagmin and SNAREs during exocytosis with great precision.

In addition to the neuroscience prize, Kavli Prizes in astrophysics and in nanoscience are also awarded every two years by the NASL. Rothman's is the second consecutive Kavli Prize in Neuroscience won by a School of Medicine researcher. In 2008, Pasko Rakic, PH.D., Dorys McConnell Duberg Professor of Neurobiology, shared the prize for his research on the cerebral cortex.

In 2004, the Kavli Foundation, led by Norwegian-born entrepreneur and philanthropist Fred Kavli, established the Kavli Institute for Neuroscience at Yale. Directed by Rakic, it is one of only four such institutes nationwide.

// Medzhitov *(from page 1)*
Sterling Professor of Genetics and the medical school's deputy dean for academic and scientific affairs. "Year after year, important new insights keep emerging from his lab."

As a doctoral student at Moscow State University, Medzhitov was fascinated by a new theory put forth by the late School of Medicine immunobiologist Charles A. Janeway Jr., M.D., which held that the innate immune system somehow provides guidance to the slower, but more fine-tuned responses of the adaptive immune system.

In 1994, Medzhitov came to Yale as a postdoctoral fellow in Janeway's laboratory, and the two researchers made the groundbreaking discovery that Toll-like receptors (TLRs), a component of the innate system, indeed provide the adaptive system with the necessary information to create custom-made B and T cells that target specific bacterial or viral invaders. Since then, Toll-like receptors have become the subject of intense research activity in laboratories around the world.

"Ruslan's identification of a Toll-like receptor in mammals and his studies linking innate immune responses with the triggering of specific adaptive immune responses by T cells and B cells have had a huge impact on our understanding of infectious diseases and vaccine development," says Max D. Cooper, M.D., Georgia Research Alliance Eminent Scholar, professor of pathology and laboratory medicine at Emory University School of Medicine, and NAS member. "The elucidation of TLRs by Ruslan and others has also heightened immunologists' awareness of the importance of Darwinian evolutionary principles for understanding how the immune system works."

Last December, Medzhitov was awarded the Lewis S. Rosenstiel Award for Distinguished Work in Basic Medical Science. His election to the NAS brings the number of current Yale faculty who are members to 60. The NAS, a private organization of scientists and engineers dedicated to the furtherance of science and its use for the general welfare, was established in 1863 by a Congressional Act of Incorporation signed by Abraham Lincoln. The Academy acts as an official adviser to the federal government, upon request, in any matter of science or technology.

Yale Netcast
"Arming the Immune System"
Available on iTunesU or at medicineatyale.org

// Greenberg *(from page 1)*
the world's first major interdisciplinary research initiative focusing on the disorder. Since then, Yale investigators at the VA have remained at the center of PTSD research and have helped improve the care of returning veterans nationally.

Son of National Baseball Hall of Fame member Henry "Hammerin' Hank" Greenberg, the legendary first-baseman and power hitter for the Detroit Tigers during the 1930s and 40s, Glenn Greenberg has many Yale College ties. His stepfather, the late Joe Lebworth, was a member of the Class of 1948. His son Greg is a member of the Class of 1984, and younger son Duncan graduated in 2008. Greenberg's brother, Steve, is a member of the Class of 1970.

Greenberg hopes his gift makes a difference in the understanding of PTSD, and he says that our soldiers deserve no less. "If you come home and you're suffering from PTSD—you're anxious, you're depressed, you have a hair-trigger temper, you can't sleep at night—you're not very likely to be a good father, spouse, or employee. So it's going to affect the rest of your life," he says. "And all because you accepted very low pay to go into a war zone."