Medicine@Yale

Advancing Biomedical Science, Education and Health Care

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New endowment honors a spirited St. Louis 'symbol of Yale'

The family of William R. Orthwein Jr. and the William R. Orthwein Jr. and Laura Rand Orthwein Foundation, a St. Louis, Mo.-based philanthropic organization, have made a combined $2.5 million gift to the School of Medicine to endow a new Yale Scholar in Ophthalmology and Visual Sciences.

The Yale Scholars program, a recent initiative of Dean Robert J. Alpern, M.D., provides four years of research funding to the most promising new faculty members recruited at the medical school.

William Orthwein

Orthwein, a 1938 graduate of Yale College, did a brief stint after graduation as a salesman for the General American Life Insurance Company, but soon moved to McDonnell Aircraft Corporation (later to become McDonnell Douglas, now part of the Boeing Company), where he would enjoy a 45-year career. According to his daughter, Nettie O. Dodge, of Wheatland, Wyo., Orthwein began in the personnel division of the company and eventually headed that unit. He later became the first president and chairman of McDonnell Douglas Automation Company, or McAuto, which pioneered systems integration in the aircraft industry, particularly in the realm of computer-aided design and manufacturing.

Although Orthwein is dealing with complications of a stroke he suffered in 2003, he gathered in February with family and friends to celebrate his 90th birthday. Stephen Jones, J.D., a 1970 graduate of Yale College and trustee of the Orthwein Foundation who attended the celebration, consid-

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'What else would you do with money?'

Yale's wartime help inspires gifts from most generous alumnus, wife

Each day, a bustling community of 6,000 faculty, students and staff tend to the business of the School of Medicine—teaching the art and science of medicine, studying, taking care of patients and conducting research in one of the world's leading academic centers.

But to spend an hour with John Anlyan, M.D., a retired thoracic and oncologic surgeon and member of the medical school's Class of 1945, is to glimpse a more intimate time in the education of young doctors, an era when the first-year class had 46 students and the school's complement of tenured professors was only a few dozen. "It was just a beautiful experience," Anlyan says during a phone call from San Rafael, Calif., where he lives with his wife of 60 years, Betty Anlyan.

Born in Egypt to Armenian parents, Anlyan came to Yale as an undergraduate in 1939, as World War II loomed on the horizon. During the war years, Anlyan's family's overseas assets were frozen, so he and his younger brothers, William and Frederick, relied on Yale for financial support during their education.

Betty and John Anlyan have made a lasting mark on the School of Medicine.

"Yale gave me my start," he says. "It gave all three of us our start."

In gratitude for the aid Yale provided to John and his brothers at a difficult time in their lives, John and Betty Anlyan made arrangements in 1990 to leave their estate to the School of Medicine, setting in motion the largest-ever alumnus gift to the medical school. Once fully realized, the Anlyans' pledge could yield more than $50 million. Thanks to their desire to see their philanthropy in action at Yale, they have transferred millions of dollars to the school already. In addition, at Betty Anlyan's request, their estate will endow a professorship in the humanities at Yale.

William, who graduated with the Yale College Class of 1945w and the medical school's Class of 1949, went on to become the chancellor of Duke University Medical Center. Frederick, a 1951 alumnus of Yale College, also entered medicine and is now a retired pathologist living on Long Island. John, who graduated from Yale College in 1942, will return to New Haven in June for his 65th college reunion.

John Anlyan would have finished medical school a year earlier had he not contracted tuberculosis at the start of his first year. The disease

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Gene defect plays role in early-onset heart disease

Yale scientists led by cardiologist Arya Mani, M.D., have identified a rare defect in a single gene associated with early heart disease and metabolic syndrome, a cluster of risk factors that includes high levels of harmful LDL cholesterol and triglycerides, low HDL, or "good," cholesterol, hypertension and diabetes.

"The belief is that coronary artery disease and most other diseases are caused by mutations in several genes. Each gene, in combination with environmental factors, exerts a small effect, so it is very difficult to identify them in the general population," says Mani, assistant professor of medicine. "But if we find families in which some members have an extreme form of the disease, such as very early onset, while other family members are unaffected, they are optimal for genetic research."

As reported in the March 2 issue of the journal *Science*, on a research trip to his native Iran, Mani discovered one such extreme case: a man with high blood pressure, high cholesterol and diabetes who had suffered a heart attack at age 48. Although the man had been treated with coronary artery bypass surgery, atherosclerotic plaque continued to build up in his grafted heart arteries and in his carotid arteries, and he eventually died of a stroke.

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From Ethiopia to your local emergency department, Elizabeth Bradley's hard-nosed research is promoting improved hospital care and management.

Making hospitals better

For management expert, the key to good health care is all in the details

As a teenager in New Britain, Conn., Elizabeth H. Bradley, PH.D., volunteered at the local hospital, but she had little interest in being a physician. "The adults I knew were in manufacturing as engineers or management," says Bradley. "To me, the interesting part of a hospital was how it was organized and managed—and how much it was *not* like a regular business."

Now a professor of public health at the School of Medicine, director of its Health Management Program and co-director of the Robert Wood Johnson Clinical Scholars Program, Bradley is still drawn to the organizational aspects of health care. "I guess I've never changed," she says.

After receiving her undergraduate degree at Harvard University, Bradley went on to earn an M.B.A. in health administration at the University of Chicago Graduate School of Business. She then completed an administrative fellowship at Massachusetts General Hospital in Boston, where she stayed on as an administrator for several years.

"As a hospital administrator at Mass General, I helped make lots of changes—in staffing levels, work flow, admissions practices," Bradley says, "but we never had the time to evaluate whether the changes were making a difference." Physicians conduct randomized trials to assess the safety and effectiveness of drugs and procedures, but Bradley says there was no equivalent scrutiny of organizational changes made by hospital managers. "I was eager to step back from what I was doing and apply the same rigorous methodology to evaluate management practices as those used to evaluate medical care," she says.

After obtaining her PH.D. in public health from Yale in 1996, Bradley embarked on just the kind of management systems research she felt was lacking. She has since published many research articles on the organizational and other factors involved in translating our best health care knowledge into the best possible systems of care for real-world patients. Bradley has worked in the areas of hospital care, long-term care, and hospice care; since 1996 she has collaborated with the John D. Thompson Hospice Institute for Education, Training and Research, Inc., in Branford, Conn.

Lifelines
Elizabeth Bradley

Recently, Bradley was part of a team led by Harlan M. Krumholz, M.D., the Harold H. Hines Jr. Professor of Medicine, that enlisted researchers from the School of Medicine, the School of Nursing, Yale-New Haven Hospital and several other institutions to devise ways to shorten "door-to-balloon time," the critical period between a heart attack patient's arrival at a hospital and the completion of an angioplasty procedure in a cardiac catheterization lab. The group identified six best practice strategies, published in the *New England Journal of Medicine* in 2006, which have formed the basis for a national alliance of more than 800 hospitals devoted to improving outcomes for heart attack patients.

There are large differences among hospitals in severity-adjusted mortality rates after heart attack, and the two researchers now plan to determine which organizational strategies are linked to reduced mortality.

Bradley is also using her management skills in Ethiopia, where government officials requested help in improving hospital care. With a team of 23 Yale-Clinton Foundation Fellows in International Healthcare Management, she has developed a strategy to implement fundamental elements of good hospital management, including triage systems, inventory management, practices to reduce hospital-acquired infections, and quality improvement methods.

Although her work in Ethiopia might seem far removed from streamlining heart attack patients' trips to the catheterization lab, Bradley says the goal in both cases is encouraging hospitals to adopt best practices.

Both projects also include an evaluation component, ensuring that these practices are supported by objective evidence.

"We want to learn what distinguishes the hospitals that get the best results," Bradley says, but she won't settle for assumptions or anecdotes. "We need the evidence to back it up."

Student-run auction for New Haven charities has a banner year

Eager bidders at the silent auction.

The annual student-run Hunger and Homelessness Auction, held last November, raised more than $36,000 for seven community agencies in New Haven, the most ever raised by the auction and an increase of $5,000 over the previous year.

This year's auctioneer was Wade Brubacher, father of first-year medical student Jake Brubacher. State Attorney General Richard Blumenthal, J.D., made a guest appearance to auction his own donation—lunch and a personal tour of the State Capitol.

Recipients of this year's funds are the Community Health Care Van; HAVEN Free Clinic; Community Soup Kitchen; Domestic Violence Services of Greater New Haven; Immanuel Baptist Shelter; Leeway Inc.; Loaves and Fishes; and the St. Thomas More Catholic Chapel and Center at Yale University.

As in past years, the fundraising began with a silent auction from November 13 to 16, followed by a live auction in the Harkness Ballroom on November 16.

Tumor virus expert will direct research at Cancer Center

Daniel C. DiMaio, M.D., PH.D., the Waldemar Von Zedtwitz Professor and vice chair of genetics and professor of therapeutic radiology, has been named scientific director of Yale Cancer Center (YCC). In this new role, DiMaio will broadly oversee all basic science research at the YCC.

As director of the YCC's Molecular Virology Program since 1993, DiMaio has guided collaborations among 17 independent but interactive laboratories with a common interest in cancer. His own laboratory is focused on papillomaviruses, an important cause of human cancers, particularly in women. DiMaio's research group has explored how these viruses control cell growth and proliferation, revealing potential new drug targets for cancer, and is using the viruses as novel research tools to manipulate the behavior of normal cells.

Daniel DiMaio

After graduating summa cum laude from Yale College in 1974, DiMaio earned his M.D. and PH.D. degrees from the Johns Hopkins University School of Medicine.

In announcing DiMaio's appointment, YCC Director and Professor of Dermatology Richard L. Edelson, M.D., said, "Dan brings a wide range of experience to this senior leadership role, which is critical to YCC's efforts to successfully expand our research initiatives. In addition to his own internationally recognized scientific accomplishments, he has shaped our Molecular Virology Program into one which serves as a superb example of first-rate interactive science."

Medicine@Yale

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Advances

Health and science news from Yale

For better health, can the soft drinks

The annual U.S. production of soft drinks exceeds 600 8-ounce servings per person. These bubbly beverages have become a fixture of our culture despite numerous studies correlating soft drink consumption with health problems.

Kelly D. Brownell, PH.D., professor of psychology and epidemiology and director of Yale's Rudd Center for Food Policy and Obesity, recently led a thorough analysis of 88 previous reports on the health effects of drinking soda.

In the March issue of the *American Journal of Public Health*, Brownell's group reports that soda increases caloric intake and body weight, decreases intake of calcium and other nutrients and raises the risk of type 2 diabetes.

Moreover, the additional calories associated with soft drink consumption add up to more than those in the drinks themselves, suggesting that drinking soda may increase hunger or decrease a sense of fullness.

When cancer is a family affair

In life's genetic lottery, we often inherit unfavorable characteristics. Some, like mom's wiry hair, are innocuous, but certain defective genes can slowly wreak biological damage over time. In two such genes, ***BRCA1*** and ***BRCA2***, mutations predispose their carriers to developing cancers, especially breast and ovarian cancers.

To determine how prevalent and risky ***BRCA*** mutations are, Harvey A. Risch, M.D., PH.D., professor of epidemiology, and colleagues in Ontario, Canada, asked ovarian cancer patients to report the incidence of cancers among their first-degree relatives. The patients were tested for ***BRCA1/2*** mutations, which were correlated with the family histories.

In the December 6 issue of the *Journal of the National Cancer Institute*, the team estimates that ***BRCA1/2*** mutations lurk in 1 of every 99 individuals (1.01 percent) in the general population—a much higher frequency than previously thought—and that carriers are 4.6 to 102 times more likely than noncarriers to develop ovarian, testicular, pancreatic and female and male breast cancers.

"Families with appreciable histories of any cancers, not just breast and ovary and not just cancers in females, should think about mutation screening because methods of prevention are becoming available," Risch says.

Forty years of research, teaching and healing

A bold experiment in mental health care reaches a new milestone

Psychiatry Chair Benjamin "Steve" Bunney (seated) and Deputy Chair John Krystal have witnessed the many successes of the Connecticut Mental Health Center. Bunney will retire this year after 38 years on the Yale faculty, including 20 years as department chair.

When Yale psychiatrist Frederick C. "Fritz" Redlich, M.D., met with newly elected Governor Abraham A. Ribicoff in 1955 to discuss how services for Connecticut's mentally ill might be improved, he came prepared, according to Benjamin S. Bunney, M.D., the Charles B.G. Murphy Professor of Psychiatry. Redlich, who served as psychiatry chair from 1950 to 1967, had given a great deal of thought to public policy issues surrounding mental health, much of which he later crystallized in *Social Class and Mental Illness*, a classic 1958 book he wrote with Yale sociologist August B. Hollingshead, PH.D.

When Redlich appealed to Ribicoff for more services for Connecticut citizens with psychiatric disorders, particularly the poor, Ribicoff shot back, "Well, Fritz, what is Yale going to do about mental health?" In reply, Redlich described the innovative department he had built in his first five years as Yale's Psychiatry chair. Based on a graduate-school model, the basic and clinical research done by its faculty members formed the foundation for all of its teaching and patient care. Redlich argued that a mental health center adhering to the same philosophy would provide the best, most scientifically sound psychiatric treatment to Connecticut's citizens.

Over the next four years the Department of Psychiatry and the state of Connecticut hammered out a joint partnership that proposed a wholly new approach to mental health care: a community-based center in which psychiatric treatment, training and research would be brought together under one roof.

In the summer of 1966, with the opening of the Connecticut Mental Health Center (CMHC), Redlich's vision became a reality. The 65,000-square-foot facility featured space for day patient and outpatient services, 22 beds for inpatients, an additional 22 beds for clinical research, an emergency unit, a 140-seat auditorium, classrooms and a library. Redlich served as the CMHC's first director; the research facilities were later named in honor of Governor Ribicoff.

Today, the CMHC still stands as a model for research-based mental health training and patient care. Under the direction of Professor of Psychiatry Selby C. Jacobs, M.D., the center complements its scientific and educational roles with inpatient and outpatient psychiatric services for over 7,000 New Haven-area residents each year. As part of the "Yale Tomorrow" capital campaign, the medical school has launched a special fundraising drive to expand and improve upon CMHC's facilities.

"The ideas that research would define care and training, and that all parties—psychotherapists, psychoanalysts, social psychologists and biological psychiatrists—would be brought together within one building were really revolutionary," Bunney says. "The CMHC has an entire floor where one side is basic laboratories and the other is an inpatient research ward for biological psychiatry. This brought basic scientists and clinical investigators together long before the term 'translational research' was ever invented. At the CMHC, basic researchers learned about clinical problems and clinical researchers learned the vocabulary of the basic scientists, which made communication possible between these two groups. This in turn spawned all kinds of collaborations, including hypothesis-driven clinical research."

Beginning in the early 1970s, CMHC scientists led by George K. Aghajanian, M.D., made the first electrophysiological recordings in the brain regions that make use of the neurotransmitters noradrenaline and serotonin. By studying the functioning of these neurotransmitters, these scientists laid the groundwork for drug treatments for opiate dependence, depression, anxiety disorders and attention deficit disorder. Meanwhile, basic scientist Bunney made similar recordings in brain regions that use the neurotransmitter dopamine; Robert H. Roth Jr., PH.D., studied the biochemistry of dopamine systems; and clinical researcher Malcolm B. Bowers Jr., M.D., studied the dopamine system in patients with schizophrenia. This work lent support to the emerging concept that some of the brain's dopamine systems are hyperactive in schizophrenia, which ultimately led to a new generation of antipsychotic medications with greater efficacy and fewer side effects.

Another important early research accomplishment at the CMHC, the discovery of clonidine as the first non-opiate treatment for opiate dependence, vividly illustrated the power of Redlich's integrated model of psychiatry.

In work with animals, Aghajanian and D. Eugene Redmond, M.D., now professor of psychiatry and neurosurgery, found that inhibiting the noradrenaline system with clonidine decreased the symptoms of opiate withdrawal, making rapid and relatively painless withdrawal possible for addicted individuals.

Building on this research, Mark S. Gold, M.D., now Distinguished Professor of Psychiatry at the University of Florida, Professor of Psychiatry Thomas R. Kosten, M.D., and Herbert D. Kleber, M.D., now professor of psychiatry at Columbia University, found that patients being treated at

CMHC, *page 4*

The rewards of life on the front lines

Jane Halbing Stitelman, editor of Yale Psychiatry, *the* Yale Psychiatry Bulletin *and the CMHC newsletter* CenterPages, *wrote the following essay to commemorate the CMHC's 40th anniversary.*

After we read over CMHC's Annual Reports from the past 40 years, we felt like we'd eaten 40 boxes of Rye Krisp. There's nothing like reducing an institution to a four-page bureaucratic report to drain the life out of a place. This was a particular problem for me, because I wrote most of them.

The reports told of our annual caseload of 5,000 patients and initiatives that organized and reorganized people and programs to accommodate a burgeoning caseload and limited resources. The line that captured it best, perhaps, was "We are doing more and more with less and less."

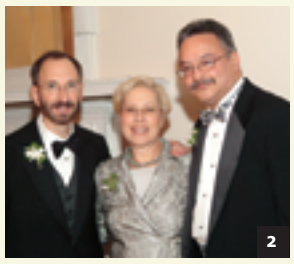
If I had it to do over again, I'd write about the day-to-day life of the place. I'd start by reminding the reader that mental illness is a wide and subtle confluence of factors, of genes and stressors, which can be countered by strengths and supports. Our understanding of the causes of mental illness is still evolving, and our treatments continue to evolve as well.

The life of this place is on the front line of a struggle with a terrible illness, played off against the possibility of health, comfort and normal life. It's a struggle that occurs with each interaction that attempts to fine-tune reality, ability and acceptance. How do you keep score? Ann Joy, our director of psychosocial rehabilitation services, once said that Professor of Psychiatry Michael Hoge had explained, "For some of the people we treat, just being able to sit with other people for 15 minutes is a success. Small steps are big gains." Happily, there are also those for whom success has meant much more, including joining the ranks of caregivers.

CMHC's vitality is where the caregivers of all kinds—physicians, nurses, psychologists, social workers, mental

Rewards, *page 6*

Out & about



September 29: The **40TH ANNIVERSARY GALA OF THE CONNECTICUT MENTAL HEALTH CENTER** (CMHC), a treatment, research and teaching partnership of the medical school and the State of Connecticut (see related story, p. 3), featured dinner and dancing at the New Haven Lawn Club. **1.** The keynote speaker for the event was television personality **Jane Pauley**, author of *Skywriting: A Life Out of the Blue*, a memoir of her struggle with bipolar disorder. **2.** From left: CMHC Chief Operating Officer and gala emcee **Robert Cole**, M.H.S.A.; **Susan Woodall**, executive director of the CMHC Foundation; and **Tomàs Reyes Jr.**, the CMHC's manager of communications and public information. **3.** Clockwise from left: **Sheila Allen Bell**, director of the Housing Authority of New Haven; **John DeStefano Jr.**, mayor of the city of New Haven; **Audrey Tyson**; and **Barbara Lamb**, director of cultural affairs for the city of New Haven. **4.** From left: **Candace Buchanan** and **Katura Bryant**.

March 17: **ALUMNI OF THE SCHOOL OF MEDICINE'S PHYSICIAN ASSOCIATE PROGRAM** and their guests joined **Mary Warner**, M.M.SC., PA-C, assistant dean and director of the program, for a relaxed evening get-together in Hanover, N.H. Hanover-area alumni regaled Warner with stories of their days in New Haven and beyond. Warner hopes to expand the program's alumni outreach program by meeting with as many graduates as possible within the next year. Clockwise from lower left: **Gayle Spelman**, PA-C '93; **Kathy De Rham**, PA-C '77; **John Bond**, PA-C '76 (behind Kathy De Rham); **Cary Stratford**, PA-C '80; **Jack Cassidy**, PA-C '73; **Alice (Hofmann) Mello**, PA-C '99; **Tim Mello**, PA-C '99; Warner; and **Abbott De Rham**.

March 6: A **CEREMONY IN HONOR OF CONNECTICUT STATE SENATOR TONI HARP** was held in the Historical Library of the School of Medicine's Harvey Cushing/John Hay Whitney Medical Library. In Washington, D.C., in February, the American Medical Association (AMA) presented Harp with its Dr. Nathan Davis Award for Outstanding Government Service. The award, named for the founder of the AMA, is the highest honor the association confers on public officials. Harp was recognized for her advocacy of community health centers, pediatric dental care, expanded access to health care and regulating medical insurance premiums and co-payments for the economically disadvantaged. From left: **Michael M. Deren**, M.D., chair of the board of trustees of the Connecticut State Medical Society (CSMS); **Gary J. Price**, M.D., immediate past president and councilor-at-large of the CSMS; **Toni N. Harp** (D-New Haven); and Dean and Ensign Professor of Medicine **Robert J. Alpern**, M.D.

April 9: **THE FAMILY OF SYDNEY HOFF AND FRIENDS** visited the medical school's Center for Neuroscience and Regeneration Research to present checks totalling $50,000 to **Stephen G. Waxman**, M.D., PH.D., chair and Bridget Marie Flaherty Professor of Neurology, to support his research on the molecular basis of erythromelalgia (EM), a rare, incurable neurological disorder that causes burning pain in the hands, feet and other extremities. Eleven-year-old **Sydney Hoff** of Briarcliff Manor, N.Y., was recently diagnosed with the disorder; her mother, **Sharon Hoff**, and friends raised the funds with appeals to their families and the wider community. Front, from left: Sharon Hoff, **Alex Martucci**, Sydney Hoff, **Marty Hoff**, **Drew Shaulson**. Back, from left: Waxman and **Karen Shaulson**.

CMHC *from page 3*

the CMHC for opiate abuse recovered even more rapidly if given an opiate blocker along with clonidine.

John H. Krystal, M.D., who was a student at the School of Medicine at the time, was greatly impressed by the CMHC's pioneering research on clonidine.

"This research was a landmark in psychiatry," says Krystal, the Robert McNeil Jr. Professor of Clinical Pharmacology and an expert on posttraumatic stress disorder. "It may have been the first time a clinical condition was understood at the cellular level, leading to the development of a novel treatment based on scientific principles. It exemplifies the Yale tradition of translating basic science insights into treatment advances."

The unusual productivity of the CMHC's translational approach continued into the 1990s, as Eric J. Nestler, M.D., PH.D., now the Lou and Ellen McGinley Distinguished Chair in Psychiatric Research at UT-Southwestern Medical Center in Dallas, led groundbreaking studies on the neurobiological basis of drug addiction. Today, Ronald S. Duman, PH.D., the Elizabeth House and Jameson Mears Professor of Psychiatry, is one of the leading proponents of the neurogenic theory of antidepressant drug action, one of the most significant advances in the understanding of mood disorders in decades (see related story, p. 5).

This record of achievement is all the more remarkable given the organizational and cultural differences between a university and a government agency, say the psychiatry department's state partners at the Connecticut Department of Mental Health and Addiction Services (DMHAS).

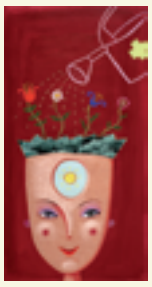
According to Thomas A. Kirk Jr., PH.D., DMHAS commissioner, "The fact that this partnership has been sustained so long is really a statement about the shared commitment to clinical services, research and teaching. The National Alliance on Mental Illness recently reviewed the mental health systems of each of the states and assigned grades. Connecticut was one of the top two states in the nation, and I think our relationship with CMHC was clearly a contributor to our high grade." DMHAS Deputy Commissioner Wayne Dailey, PH.D., agrees. "A lot of the policy questions that we deal with are pretty complicated, and they affect thousands of people's lives. In a university setting, tenured faculty have a rather long view of things, but the median term of office of a commissioner of mental health in the United States is about 21 months," Dailey says. "There's a lot of pressure on commissioners to act quickly, and often the evidence and data available to a commissioner in making a key policy decision are not very good because of that pressure. But when you have a university partner that is bringing research that's been used in developing evidence-based practices into the policymaking process, you have a much stronger basis for making those decisions."

Advances

Health and science news from Yale

Growing out of depression

For decades, people suffering from mood disorders have found relief with antidepressants, but the biological basis for the action



of these highly prescribed medications remains unclear. One theory, based on landmark studies by Ronald S. Duman, PH.D., the Elizabeth House and Jameson Mears Professor of Psychiatry, proposes that these drugs exert their effects by stimulating neuronal growth factors; these proteins generate new nerve cells in certain brain areas that lead to changes in mood and behavior.

With Jennifer Warner-Schmidt, PH.D., a former graduate student now at Rockefeller University, Duman has identified vascular endothelial growth factor, or VEGF, as one such protein.

In the March 13 issue of the *Proceedings of the National Academy of Sciences*, the team reports that VEGF is produced in the brain's hippocampal region following administration of various antidepressants. Higher VEGF levels led to increased cell division and positive behavioral responses in well-established rat models of depression. Conversely, blocking VEGF action inhibited these effects.

These findings point to the VEGF pathway as a possible target in the development of new and better antidepressant drugs.

A closer look at bacterial insurgents

American troops in Iraq are battling on yet another front, one as ancient as war itself, yet as modern as the post-penicillin era. Over 240 wounded soldiers have been afflicted with bloodstream infections of the antibiotic-resistant bacterium *Acinetobacter baumannii*. Left unchecked, this bacterium causes urinary tract infections, pneumonia, meningitis, sepsis and even death.

Using DNA sequencing technology from 454 Life Sciences, a Branford, Conn., biotech company, Michael Snyder, PH.D., the Lewis B. Cullman Professor of Molecular, Cellular and Developmental Biology, and colleagues analyzed the bacterium's entire genome.

In the March 1 issue of *Genes and Development*, Snyder's group revealed that a surprising 17 percent of *A. baumannii*'s genetic material originated in other microorganisms. Over half of these "alien islands" contain genes that are critical to the bacterium's ability to harm humans.

The study shows that the organism has gained a tactical advantage by incorporating foreign DNA. Understanding these evolutionary adaptations will bolster the antibiotic armamentarium.

Building new bridges from lab to patient

Over the past two decades, researchers in the School of Medicine's immunobiology group have led the way in unlocking the secrets of the immune system. Richard A. Flavell, PH.D., chair of the newly designated Department of Immunobiology pioneered the use of genetically engineered mice to study the fundamental principles of organization and regulation of immune responses. Using mice to mimic human diseases, researchers found evidence of immune system involvement in many maladies, including cancer and heart disease.

But there are enough differences between the immune systems of mice and humans that Flavell and his colleagues hit a wall when it came time to test their theories in people with diseases. Frustrated by the barriers to moving laboratory findings into the clinic, Flavell devised a plan to bridge the chasm between mouse and man.

His solution, embedding clinical researchers in the Department of Immunobiology, resulted in the medical school's newly launched program in Human and Translational Immunology (HTI), which will eventually include six new faculty members whose research spans both basic and human experimentation. The program will also reach out to clinical researchers in a variety of medical departments with an interest in immunology.

The new program will be headed by Jordan S. Pober, M.D., PH.D., the founder and former director of Yale's highly successful interdepartmental translational research program in Vascular Biology and Transplantation. Pober, whose own research has elucidated the role of the immune system in vascular disease and organ transplantation, became the vice-chair of the Department of Immunobiology for the Section of HTI in January.

"To make translation work, you need a way to connect physicians and basic scientists, and that is best done by people with both interests who are willing to work in the middle," says Pober. "That's what HTI is going to provide."

The work of the program's first recruit, Kevan Herold, M.D., is a model of translational research. While at Columbia University, Herold, now professor of immunobiology and medicine at the School of Medicine, advanced the most promising new treatment for type 1 diabetes in children. The disease starts when the immune system mistakenly attacks insulin-producing islet cells in the pancreas. As the cells die, insulin production declines, and children become dependent on multiple daily injections of insulin.

Jordan Pober

First in mice, and then in human clinical trials, Herold and Jeffrey A. Bluestone, PH.D., of the University of California, San Francisco, and their research teams have shown that administering antibodies designed to inhibit a particular immune response in children with early symptoms of type 1 diabetes delays, and may even prevent, the full-fledged development of the disease. The antibody formulation, further refined by MacroGenics of Rockville, Md., under the name MGA301, is currently in advanced-phase clinical trials for Food and Drug Administration (FDA) approval. The FDA recently named MGA301 an "orphan drug," a designation that provides special incentives to companies developing compounds to treat rare diseases.

Herold and his work represent "the best kind of bridge," says Carolyn W. Slayman, PH.D., Sterling Professor of Genetics and deputy dean for academic and scientific affairs at the School of Medicine. "He brings together a track record for excellent basic research with a new treatment for an important human disease." Slayman adds that Herold's work links immunobiology with another strong Yale academic unit, the internal medicine/endocrinology group led by diabetes researcher Robert S. Sherwin, M.D., the C.N.H. Long Professor of Medicine.

The HTI initiative comes at an opportune time for translational research at Yale. In October, the newly formed Yale Center for Clinical Investigation received a five-year, $57 million Clinical and Translational Science Award from the National Institutes of Health, funding that will help provide the infrastructure HTI investigators need to conduct research and to train a new generation of clinical immunologists.

By removing roadblocks to clinical research, Flavell, Pober and their HTI colleagues hope to see Yale discoveries turned into treatments for a wide range of diseases, from diabetes and cancer to heart disease and stroke.

"For 18 years, immunobiology has been focused on studying the basic mechanisms of immunology and applying that to disease, but almost all our focus has been on mice," Flavell explains. "So the new program is the same thing, really, just now in humans."

Two Yale RNA experts receive Ellison awards

The Ellison Medical Foundation (EMF) has named two Yale scientists Senior Scholars in Aging, an award that recognizes creative and productive research into processes that affect lifespan and age-related diseases and disabilities.

Frank J. Slack, PH.D., associate professor of molecular, cellular and developmental biology, and Sandra L. Wolin, M.D., PH.D., professor of cell biology and of molecular biophysics and biochemistry, will each receive $150,000 per year for four years to support their research.

Slack studies the role of microRNAs, or miRNAs, short strands of genetic material that act as "switches," orchestrating development and aging by activating or shutting down patterns of gene expression over time. In research on the microscopic roundworm *C. elegans*, Slack and his colleagues have elucidated how two miRNAs known as *lin-4* and *let-7* ensure that organs emerge at their proper time during the worm's development. Slack has also shown that the miRNA *let-7*, which he discovered as a postdoctoral associate at Harvard Medical School, is poorly expressed in human lung cancers, a finding that has led him to propose that many cancers may be caused by dysfunctions in miRNA regulation over the lifespan.

Slack joined the Yale faculty in 2000 after doctoral work in molecular biology at Tufts University School of Medicine and postdoctoral training at Stanford University School of Medicine and at Harvard. He is a member of Yale Cancer Center.

Wolin studies how RNA molecules fold into intricate shapes inside the cell and how a protein known as Ro binds RNAs that have been misfolded. She and her research team have shown that RNA binding by Ro helps cells survive damage from ultraviolet radiation.

They also found that mice lacking Ro develop an autoimmune disease that resembles lupus, indicating that the normal function of Ro could be important for preventing autoimmunity.

Damaged small RNAs have been detected in the brains of aging animals and patients with neurodegenerative diseases such as Alzheimer's and Parkinson's. With the help of the Senior Scholar in Aging award, Wolin hopes to identify genes involved in detecting and degrading damaged RNAs and to determine how they may contribute to aging and neurodegeneration.

Frank Slack

Sandra Wolin

Wolin joined the medical school faculty in 1991. She received her M.D. and her PH.D. degree in molecular biophysics and biochemistry from Yale, and completed her postdoctoral training at the University of California, San Francisco. She is also a member of the Yale Cancer Center.

The Bethesda, Md.-based EMF was created by Lawrence J. Ellison, founder and chief executive officer of software giant Oracle Corporation, and Joshua Lederberg, PH.D., who received his doctoral degree at Yale and went on to share the 1958 Nobel Prize in Physiology or Medicine for his studies of genetic recombination.

Anlyan *from page 1*

stranded him in a sanitarium near New Haven—playing poker, as he recalls, with his fellow patients and waiting to be liberated from his confinement. His recollection of medical school in the early 1940s is a parade of larger-than-life professors whose personalities, one gets the sense, were matched at times by that of their student. He recalls Harry Zimmerman, M.D., the eminent neuropathologist and friend of Albert Einstein, as a lively teacher who would go on to become the first dean of the Einstein School of Medicine.

Anlyan and his classmates were also impressed by Milton C. Winternitz, M.D., another professor of pathology who had transformed the medical school during his deanship from 1920 to 1935.

Anlyan remembers him as "a little short guy who was just like dynamite. He *made* the medical school." Students called him "Winter" when he wasn't listening, and a high-spirited Anlyan used the same moniker one morning when passing Winternitz in the hall.

"I said, 'Good morning, Winter,'" he recalls, his companions falling silent. There was a moment's pause, and then "he put his arm around me and said, 'Call me Milt. It's more informal.'" The tension dissolved in a burst of laughter.

Richard Breck, M.D., a retired geriatrician in Wallingford, Conn., and classmate of Anlyan, remembers Anlyan as a popular student and life of the party. "He was well known for his ability to tell stories and jokes," Breck recalls.

After medical school, Anlyan completed a surgical internship and residency at the University of Chicago Clinics, then spent two years at Ohio State as a resident in thoracic surgery and graduate student in enzyme chemistry. In 1949, then-surgery Chief Gustaf Lindskog, M.D., invited him back to Yale as an instructor at a salary of $5,000 a year. ("You could hardly live on that," Anlyan says, "but we had fun.") After two years he moved to New York, spending the next three years as a Damon Runyon Fellow at the Sloan-Kettering Institute and Memorial Hospital.

In 1957, with John having completed his clinical training and his Navy service, he and Betty set off across the country in a Mercury sedan in search of a suitable place to settle and launch his surgical practice. As he tells it, "I couldn't stop coughing in L.A.; San Diego was boring. But the minute we hit the Golden Gate, we said, 'This is it.'" San Francisco became their home.

During John's long surgical career specializing in cancer treatment, he and Betty invested in California real estate; their bequest of the return from those investments would eventually fuel the growth of the medical school through the construction of Yale's largest building, the 457,000-square-foot Anlyan Center for Medical Research and Education, which opened in 2003.

The Robert Venturi design, which combines a north and a south building across a central atrium, significantly increased the space available at the medical school for bench science and translational research, provided

The 457,000-square-foot Anlyan Center for Medical Research and Education, Yale's largest building, provides state-of-the-art facilities for bench science, education and magnetic resonance imaging studies.

badly needed facilities for anatomy and histology instruction and included an extensive vivarium, a state-of-the-art magnetic resonance research center and a new auditorium.

Lawrence J. Rizzolo, PH.D., an associate professor of surgery who teaches anatomy in the Anlyan Center, says that when the Anlyans toured the new building in 2005, John looked down the long third-floor hallway and joked, "This is too stark. I want to give the students something to laugh at." An avid painter, he provided photographic reproductions of his favorites among the oils he had created to Yale's Office of Development, which had them framed and displayed them along the corridor. Soon after, Rizzolo says, canvases started arriving—followed by more canvases. Now, the third-floor hallway of the Anlyan Center's north building is lined with dozens of brightly colored canvases depicting San Francisco scenes, landscapes, flowers and a few portraits. Rizzolo says that since 2003 he has noticed Anlyan's brush strokes getting broader and his colors brighter. Perhaps in explanation, Anlyan says macular degeneration has limited his sight in recent years.

But the place Yale occupies in Anlyan's memories and sentiments is undimmed. John has long been involved in alumni and development activities, serving on the Yale Development Board and the last Yale capital campaign, which raised $1.7 billion for the university from 1992 to 1997. The Anlyans are deeply involved in Yale's current capital campaign, the $3 billion "Yale Tomorrow" fundraising effort.

Yale made a lasting impression on John Anlyan, and his and Betty's legacy has changed the shape of the medical school in a lasting way. But Anlyan, the most generous alumnus in the school's history, is self-effacing when he explains his and his wife's gifts to the School of Medicine. "We don't have any children," he says. "What else would you do with money?"

Gene *from page 1*

When Mani looked at the medical records of 58 of this man's blood relatives, he found that 28 had been diagnosed with early CAD—before the age of 50 in men and 55 in women—and that 23 of those 28 died at young ages; family members without CAD died much older. Test results from the 13 available family members with early CAD showed that nearly all of them had high LDL cholesterol and triglyceride levels, high blood pressure and diabetes, meeting National Institutes of Health criteria for metabolic syndrome.

With evidence of a strong genetic component in this family's metabolic syndrome and early CAD, Mani obtained blood samples from affected and unaffected family members and returned to the School of Medicine to complete genomic analyses. Working in collaboration with Richard P. Lifton, M.D., PH.D., chair and Sterling Professor of Genetics, Mani eventually zeroed in on a mutation that affected family members had in a gene on chromosome 12 known as *LRP6*.

One change in an amino acid in the *LRP6* gene altered the activity of the protein it encodes, which acts in the Wnt (pronounced "wint") signaling pathway, a network of proteins involved in normal development and

Arya Mani

in certain malignant tumors.

The family studied by Mani exhibits an extreme case of heart disease and associated metabolic risk factors, and the mutation he identified is quite rare. However, genes with similar functions to *LRP6* and the Wnt pathway itself have been highly conserved over evolutionary time in species as diverse as frogs and humans. This suggests that the pathway has basic physiological importance, and Mani believes that further study of Wnt-related genes will reveal that defects in the pathway are involved in more common forms of cardiovascular disease.

"The main finding is the role of Wnt signaling in the development of metabolic syndrome and CAD," Mani says. "That is where science has to focus now to understand the basic molecular mechanism of the disease."

Lifton agrees. "We expect that studies of the Wnt signaling pathway in patients with early CAD and metabolic syndrome will provide new insight into the basic biology of disease causation and allow new approaches to disease prevention," he says.

Rewards *from page 3*

health workers, occupational and rehab therapists—champion their patients in countless ways.

This is a time to acknowledge every clinician who has called around the state to find a bed; every doctor who has weighed the benefits and costs of medications for his or her patient; every case manager or peer advocate who has worried where someone's next meal or coat would come from. We acknowledge every clinician who hoped a shelter could overlook this one last outburst; and every clinician who tried to keep a released prisoner out of trouble. This is the time to thank everyone who has taught us to understand the nuances of human spirit and behavior.

We thank our researchers for their work on the complicated pathways to the causes and treatment of mental illness and addictions, as well as those who prepare the endless grants, and who keep the labs and clinics running smoothly. We thank the many agencies of the Community Services Network of Greater New Haven that give life to the phrase "a network of services." The very nature of our work requires the highest degree of collaboration.

It is a time to acknowledge the CMHC environment itself: our able public safety department, our switchboard operators, our computer and records staff, and the myriad of people—carpenters, electricians, housekeeping and building crews—who keep the place clean and safe, warm and even welcoming. And there is the true front line of our work: the secretaries and administrative supervisors, who are often the first responders to crises of all kinds. The place would close without you.

CMHC exists because of everyone who comes to work each day—or night—to meet whatever surprising developments his or her shift may hold. The remarkable thing about CMHC is that regardless of the thinking, the funding or the treatments available, for 40 years we have been here to help steer a difficult, sometimes heartbreaking, often hopeful process.

Hardly a box of Rye Krisp at all.

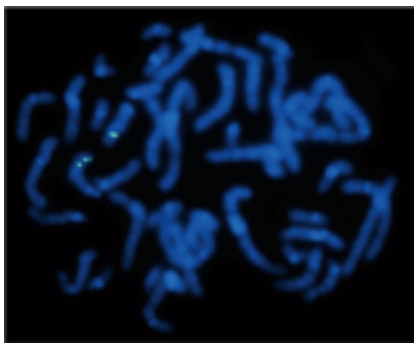
Grants and contracts awarded to Yale School of Medicine
September/October 2006

Federal

Maria Teresa Baquero, Department of the Army, *Microtubule-Associated Protein Expression and Predicting Taxane Response*, 3 years, $96,120 • **Clifford Bogue**, NIH, *Hex—A Homeobox Gene Essential for Liver Development*, 2 years, $432,300 • **Lloyd Cantley**, NIH, *Stem Cells in Organ Maintenance and Repair*, 1 year, $12,000 • **Thomas Carpenter**, NIH, *Center of Research Translation Program* (CORT), 5 years, $8,213,600 • **Kathleen Carroll**, NIH, *Computer-Based Training for Cognitive Behavioral Therapy*, 3.5 years, $1,407,143 • **Junjie Chen**, NIH, *Study of the Role of DNA Damage Reponses in Tumorigenesis and Senescence*, 4.5 years, $1,265,587; NIH, *Analysis of BRCA1 Function in DNA Repair*, 4.5 years, $1,334,551; Department of Defense, *Genomic Instability and Breast Cancer*, 4 years, $825,000 • **Yung-Chi Cheng**, NIH, *Nucleoside Analogs as Anticancer Compounds*, 4.5 years, $1,495,498 • **Judy Cho**, NIH, *Mapping Chromosome 3q Inflammatory Bowel Disease*, 3 years, $867,270 • **Jimmy Choi**, NIH, *Motivation and Learning in Schizophrenia*, 1 year, $56,199 • **Vladimir Coric**, National Geospatial-Intelligence Agency, *Efficacy of Forensic Analysis in Detecting Deception During High Stress Situations*, 1 year, $119,632 • **Kelly Cosgrove**, NIH, *Brain Imaging of Sex Differences in Tobacco Smokers*, 5 years, $893,700 • **Joseph Craft**, NIH, *Genetic Analysis of T Cells in Lupus*, 5 years, $1,818,504 • **Alan Dardik**, NIH, *Flow Responses to Carotid Angioplasty*, 4.5 years, $665,550 • **Christopher DeFeo**, NIH, *Structure and Function of the Human Copper Transporter*, 2 years, $66,060 • **James Duncan**, NIH, *LV Strain Quantification from 4D Echocardiography*, 4.5 years, $7,244,829 • **Brian Elbel**, Agency for Health Care Research and Quality, *Choice Sets and Consumer Selection of Health Plans*, 1 year, $32,400 • **Julia Etchin**, Department of the Army, *Molecular Basis for BRCA2-Mediated DNA Repair and Breast Tumor Supression*, 3 years, $97,200 • **Leigh Evans**, Agency for Health Care Research and Quality, *Simulation Training for Ultrasound Guided Central Venous Catheter Insertion*, 2 years, $532,681 • **John Forrest**, NIH, *Yale Predoctoral Clinical Research Training Program*, 1 month, $581,683 • **Jorge Galán**, NIH, *Predoctoral Training Program in Microbial Pathogenesis*, 5 years, $1,061,569 • **Joel Gelernter**, NIH, *Genetics of Cocaine Dependence*, 4 years, 7 months, $5,980,328 • **Harindarpal Gill**, NIH, *NBCe1 and n1: Crystal Structure Determination*, 2 years, $85,989 • **Charles Greer**, NIH, *Mechanisms of Aging in the Olfactory System*, 5 years, $6,652,339 • **Mridu Gulati**, National Institute for Occupational Safety and Health, *Longitudinal Study of Respiratory Function in Aluminum Smelter Workers*, 3 years, $291,600 **Noam Harel**, NIH, *Nogo's Role in Intracellular Trafficking*, 4.5 years, $782,316 • **George Heninger**, NIH, *Substance Abuse Education for Medical Students*, 2.5 years, $652,532; NIH, *Clinical and Basic Neurobiology of Nervous System Diseases*, 2 years, $134,362 • **Henry Huang**, NIH, *New PET Radioligand for Serotonin Transporter*, 2 years, $714,183 • **Karl Insogna**, NIH, *Impact of a Protein Supplement on Bone Mass in Older Women*, 4 years, $1,876,418 • **Sven-Eric Jordt**, NIH, *TRPA1 Channels in Sensory Neurons as Targets for Environmental Irritants*, 5 years, $2,390,822; NIH, *Sensory Neural Mechanisms of Pulmonary Agent and Vesicant Toxicity*, 4.5 years, $2,446,733 • **Amy Justice**, NIH, *Veterans Aging Cohort Study*, 5 years, $13,928,272 • **Joan Kaufman**, NIH, *Genetic and Environment Modifiers of Child Depression*, 4.5 years, $1,858,595 **Trace Kershaw**, NIH, *HIV/STD Risk Among Young Expectant Fathers: Relationship Attachment and Transition*, 4.5 years, $2,537,672 **Michael Krauthammer**, NIH, *Text Mining as a Translational Tool in Biomedicine*, 3 years, $439,857 • **Daeyeol Lee**, NIH, *Cortical Mechanisms of Sequence Learning*, 7 months, $303,729 **Chiang-Shan Li**, NIH, *Imaging Inhibitory Control in Cocaine Dependence*, 1 year, $208,800 **Haifan Lin**, NIH, *Regulation of Germline Stem Cell Division in* Drosophila, 1 year, $94,875 **Brett Lindenbach**, NIH, *Hepatocellular Carcinoma: Targeting HVC Replication*, 3.5 years, $613,302 • **Xiaomei Ma**, NIH, *Myelodysplastic Syndromes: Previous Exposures, Survival, and Quality of Life*, 5 years, $698,600 • **Robert Malison**, NIH, *Genetics of Opioid Dependence in a Hmong (Thai) Isolate*, 2 years, $553,320 **Irvin Modlin**, NIH, *Molecular Strategies to Define Carcinoids and Rationalize Surgical Intervention*, 3.5 years, $1,173,350 • **Laura Niklason**, NIH, *Biological Vascular Grafts*, 4 years, 7 months, $3,477,864 • **Jordan Pober**, NIH, *Chronic DTH and IFN-gamma in Human Graft Arteriosclerosis*, 5 years, $11,635,495 **Vazhaikkurichi Rajendran**, NIH, *Role of IK Channels in Rat Distal Colon*, 5 months, $1,614 **Faye Rogers**, NIH, *Altered Helical Structures: Repair and Induction of Genomic Instability*, 3 years, $445,161 • **Robert Sherwin**, NIH, *Clinical and Translational Science Award TL1*, 4.5 years, $57,330,994 • **Arthur Simen**, NIH, *Epigenetic Factors in Stress-Enhanced Acquisition of Cocaine Self-Administration*, 2 years, $330,083 **Dennis Spencer**, NIH, *Origin of Extracellular Glutamate in Human Temporal Lobe Epilepsy*, 3.5 years, $2,056,128 • **Matthew State**, NIH, *The Role of SLITRK1 in Tourette and Related Disorders*, 5 years, $2,217,291 • **Rebecca Sweet**, NIH, *Autoimmune Memory Development and Maintenance*, 2.5 years, $127,392 • **Fred Volkmar**, NIH, *Autism and Related Disorders: Development and Outcome*, 5 years, $5,906,778 **Kathleen Wilson**, Department of the Army, *The Roles of NFBD1, 53BP1, and BRCA1 in the DNA Damage Response*, 3 years, $96,746 **Dianqing Wu**, NIH, *Wnt Signaling and Bone Biology*, 3 years, 6 months, $1,521,756; NIH, *Molecular Function of Chemoattractant-Mediated Signaling*, 3 years, 6 months, $1,776,906

Non-Federal

Ali Abu-Alfa, Genzyme, *Genzyme–Yale Educational Conferences*, 7 months, $20,700 • **Diana Beardsley**, University of Massachusetts, *Prevention of the Complications of Bleeding Disorders*, 1 year, $23,189 • **Henry Binder**, Christian Medical College Hospital, *Comprehensive Studies of a New Improved Oral Rehydration Solution for Diarrheal Disease*, 1 year, $69,250 **Hilary Blumberg**, National Alliance for Research on Schizophrenia and Depression, *Frontal Markers of Vulnerability and Resilience to Bipolar Disorder*, 2 years, $100,000 • **James Boyer**, Mount Desert Island Biologic Laboratory, *Development of a Comparative Toxicogenomics Database*, 5 years, $22,890 • **Michael Bracken**, Johns Hopkins University, *Genome-Wide Association Studies of Asthma in Populations of African Descent*, 3 years, $188,881 **David Brissette**, Physician Assistant Education Association, *Physician Assistants as Medicine Hospitalists*, 1 year, $4,972 • **Richard Bucala**, Bay Pines Foundation, *Release of MIF Protein Complexes* in Vivo*: Response to Inflammation*, 11 months, $13,272 • **David Calderwood**, U.S.-Israel Binational Science Foundation, *Cytoplasmic Regulation of LFA-1 Assemblies Underlying Lymphocyte Adhesion Transmigration and Immune Cell Recognition: The Talin Link*, 4 years, $71,564 • **Michael Carrithers**, National Multiple Sclerosis Society, *T Lymphocyte Surveillance and the Neuroprotective Barriers in Health and Disease*, 3 years, $415,719 • **Owen Chan**, Juvenile Diabetes Research Foundation International, *Role of GABA in Modulation of Counterregulatory Responses to Hypoglycemia*, 3 years, $89,308 • **Junjie Chen**, Susan G. Komen Breast Cancer Foundation, *Understanding the Tumor Suppression Function of BRCA1*, 1 year, 7 months, $120,080; Mayo Clinic of Rochester, *Mayo Clinic Breast Cancer SPORE*, 1 year, $178,326 • **Paul Cleary**, Harvard University, *National Implementation of Medicines Consumer Assessment of Healthcare Providers and Systems*, 7 months, $117,978 • **Michael DiGiovanna**, Breast Cancer Research Foundation, *Activated HER2 as a Predictor of Therapeutic Response and as a Target in Novel Combination Therapies*, 1 year, $249,263 • **Wawrzyniec Dobrucki**, Juvenile Diabetes Research Foundation International, *Noninvasive Assessments of Myocardial and Peripheral Therapeutic Angiogenesis in Animal Models of Type-1 Diabetes Mellitus*, 3 years, $88,214 • **Glen Farr**, American Cancer Society, *Regulation of Na,K-ATPase Function by the Tetraspanin Protein CD81*, 3 years, $138,000 • **Simmie Foster**, United Negro College Fund, *An Adaptive Response of the Innate Immune System*, 2 years, $52,000 **Gerald Friedland**, AIDS Project Hartford, *HIV Prevention Intervention Research with HIV-positive Incarcerated Populations*, 2 years, $123,048 • **Alison Galvani**, James S. McDonnell Foundation, *Developing and Applying Game Theoretic Vaccination Models with Psychological Data*, 6 years, $442,905 • **Alexandria Garino**, Physician Assistant Education Association, *Improving Clinical Anatomy Recall and Spatial Reasoning in Physician Assistant Students*, 1 year, $2,500 • **Walter Gilliam**, Child Health & Development Institute of Connecticut, *Preschool Mental Health Climate Scale: A Tool for Preschool Mental Health Consultants and Other Professionals*, 1 year, $50,000 • **Bryan Hains**, Dana Foundation, *Neuroimmune Modulation of Chronic Pain after Spinal Cord Injury*, 2 years, $200,000 • **Robert Heimer**, Gilead Foundation, *Evaluating the Effects of Expanded Hours for Syringe Exchange Programs in Connecticut*, 1 year, $25,000; Gilead Foundation, *Pilot Intervention Research: Brief Care-Based HIV Prevention for Newly Diagnosed Men*, 1 year, $25,000 • **Erica Herzog**, Edward Mallinckrodt, Jr. Foundation, *Mechanisms of Bone Marrow: Epithelial Fusion in the Murine Lung*, 3 years, $210,000 • **Amy Justice**, University of California, San Francisco, *Treatments for Complex Patients in New Settings*, 1 year, $24,800 • **Mark Mamula**, L2 Diagnostics, LLC, *Modified HER-2 Tumor Antigens for Vaccination in Cancer*, 11 months, $264,075 • **Aaron McGee**, Burroughs Wellcome Fund, *Inhibition of Plasticity in the Adult Central Nervous System by Nogo-66 Receptor Signaling*, 5 years, $500,000 **Haiying Meng**, International Dyslexia Association, *A Deletion in Intron 2 of DCDC2 Gene Regulates Protein Expression in Developmental Dyslexics*, 1 year, $10,000 • **Yorgo Modis**, L2 Diagnostics, LLC, *Broad Spectrum Therapeutic Human Antibodies for Dengue Virus Infections*, 1 year, $77,122; L2 Diagnostics, LLC, *Antivirals Targeting Flavivirus Envelope Proteins*, 1 year, $153,384 • **Kitt Petersen**, Novartis Pharmaceuticals, *Regulation of Muscle PDH Flux in Different Populations*, 9 months, $202,010 • **Marc Potenza**, University of Maryland at Baltimore, *Genetic Contributions to Adolescent HIV Risk Behavior*, 1 year, $28,655 • **Joseph Santos-Sacchi**, Stanford University, *New Technologies for Investigation of the Hair Cell Afferent Fiber Synapse*, 1 year, $74,587 • **Gerald Shadel**, American Federation for Aging Research, *Mouse Models of Aging and Age-Related Pathology via Mitochondrial DNA Transformation*, 1 year, $124,296 • **Wei-Xing Shi**, National Alliance for Research on Schizophrenia and Depression, *Prefrontal Control of DA Neurons in the VTA*, 2 years, $100,000 • **Gerald Shulman**, Medical College of Georgia, *Coordinating and Bioinformatics Unit for the Mouse Metabolic Phenotyping Center*, 5 years, $511,500 • **William Sledge**, Eli Lilly and Company, *Recovery Guide Treatment Program for Recurrent Psychiatric Hospitalization*, 1 year, $99,193 • **Stefan Somlo**, Plexxikon, *Graft Inhibitors in Polycystic Kidney Disease*, 1.5 years, $89,542; Icagen, *Icagen Research Agreement*, 1 year, $41,214 • **Scott Strobel**, Howard Hughes Medical Institute, *Bioprospecting for Natural Products in the World's Rainforests: An Undergraduate Science Expedition*, 4 years, $1,000,000 • **Fattaneh Tavassoli**, Calibrant Biosystems, *Breast Cancer Proteome via Laser-Free Microdissection and Gemini Technologies*, 2 years, $37,196 • **Terence Trow**, CoTherix, *Educational Grant Agreement*, 1 year, $5,000 • **Ping Wang**, American Heart Association (Heritage Affiliate), *Role of PLC-beta3 in the Initiation and Progression of Atherosclerosis*, 1.5 years, $70,000 • **Dianqing Wu**, University of Connecticut, *Vascular Remodeling: Macrophage/Monocyte Signaling in Vascular Pathophysiology*, 8 months, $148,873; University of Connecticut, *Polarity in Networks and Pathways: The Study of Neutrophil Polarity*, 7 months, $70,307 • **Zhinan Yin**, Amino UP Chemical, *AHCC Reduces Chemotherapy Side Effects*, 1 year, $19,800 • **Yufeng Zhou**, U.S.-Israel Binational Science Foundation, *Activation Gating of Potassium Channel Pores: A Unifying Mechanism Controlled by Hydrophobic Interactions*, 4 years, $19,205



With support from the National Institutes of Health, Matthew State, M.D., PH.D., Harris Associate Professor of Child Psychiatry in the Child Study Center, is studying the role of a gene known as *SLITRK1* (bright blue areas at left of photo) in Tourette's syndrome and related disorders.

Orthwein *from page 1*

ers Orthwein a "surrogate father" and often refers to him as "Uncle Bill." "He is one of the guys who, when I was faced with a particularly vexing question, I would ask 'What would my father do?' and then 'What would Bill Orthwein do?' " Jones says. "It's a role that he has always played, and will always play in my life."

Jones, an attorney in the St. Louis-based firm of Armstrong Teasdale LLP, says that Orthwein has been the most prominent figure in the St. Louis community of Yale alumni, a "symbol of Yale" for as long as he can remember, and that he has given over 100 years of combined service to cultural and charitable organizations in the city, including St. Luke's Hospital, the Saint Louis Symphony Orchestra, the Saint Louis Zoo, the Saint Louis Science Center and the Missouri Botanical Garden. "His involvement in the Yale community and in the St. Louis community more generally, in terms of his time, his talent and his treasure, is remarkable."

Though he has enjoyed good vision throughout his life, Orthwein had a personal encounter with visual science in 1993, when his ophthalmologist reported on his anisocoria, or uneven pupil size, and its possible relation to the dispersion of pigment from his iris, in the *Journal of Glaucoma.*

Honoring fifty years of far-reaching scientific influence

Physiologist caps an illustrious career with nephrology award

In recognition of his 50 years of research, teaching and leadership in the field of nephrology, Gerhard H. Giebisch, M.D., Sterling Professor Emeritus of Cellular and Molecular Physiology, was awarded the 2006 John P. Peters Award from the American Society of Nephrology (ASN). Giebisch is the first Yale faculty member to receive the Peters Award, named in honor of a well-known physician-scientist who served as chief of the Metabolic Section of Yale's Department of Medicine from 1922 to 1955.

Born in Vienna, Austria, Giebisch moved from Cornell University Medical College to Yale in 1968 to chair the School of Medicine's Department of Cellular and Molecular Physiology. He won the ASN's Homer Smith Award in 1971 for his research elucidating how hormones and diuretic drugs affect the passage of ions such as potassium, sodium and chloride across cell membranes in the tubules of the kidney, a process that is crucial to maintaining chemical balance in the body's internal environment.

In this work, Giebisch used techniques known as micropuncture and microperfusion to precisely map how and where potassium is secreted and excreted at various points along the nephron, the kidney's basic structural and functional unit. He also employed patch-clamping techniques to record the movement of ions through channels within the membrane of kidney cells. Giebisch has endeavored to frame these fine-grained details in terms of how they affect kidney function in the whole organism. "You can take the system apart to do detailed analysis," he has said, "but the art is to put it all back together."

Gerhard Giebisch (left) and his longtime friend and collaborator Peter Aronson at the American Society of Nephrology's annual meeting in November 2006.

Giebisch is the author or co-author of more than 400 research articles and book chapters. With Donald W. Seldin, M.D., the William Buchanan Professor of Internal Medicine at UT Southwestern Medical Center in Dallas, he is co-editor of the pre-eminent textbook in nephrology, *The Kidney: Physiology and Pathophysiology.*

He has been a research mentor to over 75 trainees who now work as physiologists and nephrologists throughout the world. Giebisch was president of the ASN from 1971 to 1972, and he has served on numerous editorial boards for scientific journals and on study sections that review grant proposals for the National Institutes of Health. He is a member of The National Academy of Sciences and has received five honorary doctorates.

His colleague and collaborator Peter S. Aronson, M.D., the C.N.H. Long Professor of Medicine and professor of cellular and molecular physiology, says that Giebisch is driven by an insatiable curiosity and love of beauty in both his scientific and personal life, citing his annual mountaineering trips to the Alps—including one undertaken last fall at age 80—his fluency in several languages and his exhaustive knowledge of classical music and opera.

For Aronson, Giebisch was a natural choice for the Peters Award, which honors broad contributions to the field over and above a successful research career. "He's trained many, many people who have gone on to open laboratories all over the world. He's been a leader in many societies, organized many conferences and he's edited what has become the major textbook in renal physiology," says Aronson. "For the last thirty years, Dr. Giebisch has been probably the most prominent 'international statesman' of nephrology."

Dean and Ensign Professor of Medicine Robert J. Alpern, M.D., himself a nephrologist and researcher, concurs.

"While Gerhard has been honored throughout his career for his research, the Peters Award recognizes his contributions to the broader nephrology community," Alpern says. "He has directly mentored researchers all over the world, but in addition Gerhard has been an advisor and supporter for a multitude of researchers in nephrology. He is internationally recognized for his intellect and generosity."

Scientist wins Wiley Prize for research on protein-folding

Although Arthur L. Horwich, M.D., prefers to spend as much of his time as possible in the lab, he made a happy exception on April 6, when he traveled to The Rockefeller University in New York City to accept the Wiley Prize in Biomedical Sciences. The prize is given by the Wiley Foundation, which was established in 2001 by John Wiley & Sons, a 200-year-old publisher of scientific, technical and medical books and online services.

Horwich, the Eugene Higgins Professor of Genetics and Pediatrics and a Howard Hughes Medical Institute investigator, was honored along with Franz-Ulrich Hartl, M.D., DR.MED., of the Max Planck Institute of Biochemistry in Germany for their significant contributions to understanding how proteins fold. Scientists have long wondered how proteins make the transformation from chains of amino acids to three-dimensional structures whose specific shape determines their function. Over the last 17 years, Horwich and Hartl's labs have helped unravel this mystery.

"In some respects it's a recognition of our field," says Horwich. "People are beginning to recognize that chaperone-type machines are significant and play a significant role in the cell." Horwich and Hartl will divide a $25,000 grant, and each gave a special lecture at Rockefeller.

Building on the work of Nobel prize-winning biochemist Christian B. Anfinsen, PH.D., who showed that folding instructions are encoded in the sequence of amino acids that make up proteins, in 1989 Horwich's lab, in a collaboration with Hartl and his postdoctoral mentor Walter Neupert, reported in the journal *Nature* that a specialized mitochondrial protein called Hsp60 acts as a protein-folding "machine." Because of this protein's helping role, it was soon dubbed a "chaperonin." Horwich and Hartl and their colleagues then went on to elucidate the mechanism of action of the machine using the bacterial relative called GroEL.

Chaperonins are double-ringed molecules that assist in protein folding by binding unfolded proteins in an open ring and then encapsulating them under a cooperating "lid" structure (GroES) where they can fold without sticking to each other. This prevention of aggregation is an important function because such aggregates can harm the cell as in a number of neurodegenerative diseases. The two rings of a chaperonin take turns binding and folding proteins so that as one ring finishes a folding reaction, the other takes over with a new "substrate" polypeptide.

Oftentimes a protein does not fold properly with one passage into the machine and will be released from it without having reached folded form; the machine will then make another attempt, binding the non-folded

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chain and attempting once again to correctly fold it. This process of cycling consumes cellular energy in the form of adenosine triphosphate, or ATP, which binds to the machine to enable the encapsulation step and then hydrolyzes thereafter, allowing release of polypeptide.

"Art's work has beautifully demonstrated that the notion that all proteins can fold unassisted is simply wrong. In fact, emerging evidence from his lab suggests that in the absence of the protein-folding machines he has discovered and characterized, cellular life is impossible," says Richard P. Lifton, M.D., PH.D., chair and Sterling Professor of Genetics and professor of medicine and molecular biophysics and biochemistry. "His work has truly revolutionized our understanding of the most fundamental aspects of cellular physiology."

It remains unclear why the chaperone machines are unable to prevent a number of neurodegenerative diseases in which protein misfolding occurs, like Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, and mad cow disease, and these days Horwich has turned his attention to such diseases. In one approach, his group is seeking to elucidate the structure of fibrillar aggregates formed in one such disease, so-called amyloid. He is also working on a model of amyotrophic lateral sclerosis, a paralyzing movement disorder, known also as Lou Gehrig's disease, which is in some cases caused by misfolding of a specific enzyme, superoxide dismutase. Work in microscopic nematode worms has shown that misfolding of this particular protein causes a paralyzing disorder in them as well.

Horwich and Hartl have also won the 2004 International Award from Canada's Gairdner Foundation, which recognizes outstanding achievements in biomedical research, and the 2006 Stein and Moore Award from The Protein Society. Horwich was elected to the National Academy of Sciences in 2003 and was named a fellow of the American Association for the Advancement of Science last year.

Horwich has been a member of the medical school faculty since 1984, when he joined as an assistant professor of genetics. Now, as a full professor in the same department, he works as a bi-coastal scientist, splitting his time between New Haven and the Scripps Research Institute in La Jolla, Ca. He holds an A.B. and M.D. from Brown University and completed his residency and internship in pediatrics at Yale-New Haven Hospital.