$3 billion Yale campaign will benefit science and medicine

Nearly a decade after the close of its last major fundraising campaign, Yale has launched “Yale Tomorrow,” a five-year drive to raise $3 billion, a major portion of which will be directed toward science and medicine. At the public launch of the campaign in September, President Richard C. Levin announced that donors had already committed $1.3 billion in gifts and pledges during the campaign’s quiet phase, which began in mid-2004.

The campaign is organized around four major themes: “Yale College,” “The Arts,” “The Sciences” and “The World.” Within the sciences, under the rubric “Medicine Tomorrow,” Yale will seek support for many research, educational and clinical programs, with the ultimate goal of finding new and better ways to diagnose and treat illness, says Dean Robert J. Alpern, M.D., Ensign Professor of Medicine.

According to Inge T. Reichenbach, Yale’s vice president for development, the campaign’s goals for the medical school are quite specific. These goals include increased support for research, the establishment of new endowed professorships, increased financial aid for students, new buildings for research and clinical care, improved technology, educational innovation and support for the Yale Campaign, page 6

New genes found in Crohn’s disease, serious eye ailment

A decade ago, finding genes that contribute to human diseases was labor-intensive, time-consuming and prohibitively expensive. But today, cutting-edge research tools are changing all that, and two School of Medicine researchers are at the forefront of the revolution. Last month, in the journal Science, Josephine J. Hoh, Ph.D., associate professor of epidemiology and ophthalmology, and Judy H. Cho, M.D., associate professor of medicine, reported that their research teams had homed in on genes involved in two genetically complex human disorders: age-related macular degeneration (AMD), the leading cause of vision loss and blindness in the elderly in the developed world, and Crohn’s disease (CD), an inflammatory disorder of the gastrointestinal tract.

The key to the research strategy used by Hoh and Cho is the natural variability in the 3 billion “letters” in the human genome, the genetic instruction book that encodes all the proteins in the body. Compare the genomes of a large group of people and you’ll find single-letter differences in the DNA sequences of genes that are more common in some people than others. The idea is to identify those single-letter differences, called polymorphisms, that are associated with particular diseases or traits. The polymorphisms are markers for the genes that are responsible for these diseases or traits.

Hoh and Cho’s research strategy is actually a variation of the classical gene-mapping technique, which involves comparing the DNA of people who have a disease with that of those who do not to try to identify the genes that contribute to the disease. But whereas classical gene mapping can take years and thousands of people, Hoh and Cho’s strategy can take a fraction of the time and involves analyzing only a few dozen people. The key is to look at not only the people who have a disease but also their healthy relatives in order to identify any differences in DNA sequences that are associated with disease.

By doing this, Hoh and Cho have been able to identify some previously unsuspected genetic markers that are associated with the development of AMD, which leads to blindness, and Crohn’s disease, a serious eye ailment.

These new findings have generated enormous excitement among the scientific community, and they are already spurring new research. But perhaps even more exciting is the potential for these findings to lead to new treatments for these diseases. For example, if a particular gene is found to be a key contributor to AMD, it may be possible to develop drugs that block the action of that gene to prevent or delay the disease.

Hoh and Cho say they are particularly excited about this potential because they have already begun looking for gene therapies that could be used to treat these diseases. Gene therapy involves introducing a normal copy of a gene into a person’s body to replace a faulty or missing gene. This approach is already approved for use in treating certain rare genetic disorders, and it is being actively investigated for treating other diseases, including AMD and Crohn’s disease.

For Robert J. Alpern, M.D., the medical school’s dean and Ensign Professor of Medicine, the warm feelings are mutual. “One of my great pleasures as dean has been the opportunity to come to know the Israel family closely,” Alpern says. “Their enthusiasm for Yale and the medical school continues a family legacy that has helped shape what we are and where we can go. I am especially appreciative that Tom and Barbara had the confidence in Yale and in me to place no restrictions on how this gift is used.” All told, Israel and his wife, Barbara, have donated more than $7 million to the medical school, including a $1 million commitment toward establishing a professorship in memory of Donald J. Cohen, M.D., a renowned child psychiatrist and director of the Yale Child Study Center (YCSC) who died in 2001. These gifts complement a $1.25 million donation made by Adrian Israel in 1986 to establish the School of Medicine’s Magnetic Resonance Research Center.

Both Thomas and Adrian Israel have also been active and longstanding supporters of the Yale School of Management (SOM), where the Adrian C. Israel Professorship of International Trade and Finance was established in 1976. After Adrian’s death, Thomas, who serves on the SOM’s advisory board, combined money from his father’s estate with his own 25th reunion gift to Yale to establish the International Finance Center at the Yale School of Management, page 6

Following in his father’s footsteps

Yale alumnus, investor makes unrestricted gift to School of Medicine

Carrying on a philanthropic tradition begun by his late father, Adrian C. “Ace” Israel of the Yale Class of 1936, investor and Yale alumnus Thomas C. Israel has made a gift of $5 million to the School of Medicine. Israel, who says his family has long had a deep interest in medical science, placed no restrictions on the new gift, saying that confidence in the medical school’s leadership overruled any need to earmark the funds.

“If we trust the people and the institution we give money to, we should feel that they’ll use good judgment as to how it’s used,” says Israel, a 1966 Yale graduate and chair of A.C. Israel Enterprises, a New York City-based firm that invests in private equity funds and makes direct private equity investments.

For Robert J. Alpern, M.D., the medical school’s dean and Ensign Professor of Medicine, the warm feelings are mutual. “One of my great pleasures as dean has been the opportunity to come to know the Israel family closely,” Alpern says. “Their enthusiastic support for Yale and the medical school continues a family legacy that has helped shape what we are and where we can go. I am especially appreciative that Tom and Barbara had the confidence in Yale and in me to place no restrictions on how this gift is used.”

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The Israel family—Wendy, Thomas, Barbara and (far right) Emily—has strong ties with the medical school and with Dean Robert J. Alpern (second from right).
Biologist cited for structural insights in action of antibiotics

In a ceremony and commemorative symposium held at Keio University in Tokyo in November, Thomas A. Steitz, Ph.D., Sterling Professor of Molecular Biophysics and Biochemistry at Yale, was awarded the 11th Keio Medical Science Prize.

Steitz, also a Howard Hughes Medical Institute investigator, was honored for X-ray crystallography research that in 2000 led to publication of the structure of the large subunit of the ribosome, which is crucially involved in translating instructions contained in messenger RNA (mRNA) into proteins.

Many antibiotics work by interfering with the translation of mRNA by the ribosome of bacteria, but some bacteria develop mutations that change the ribosome’s structure and render the bacteria resistant to treatment. From their crystallographic work, Steitz and collaborators have identified the structural basis of antibiotic drug function and resistance, and he and several Yale colleagues founded Rib-X, a company developing new compounds to combat drug-resistant bacteria.

The Keio award, the only prize of its kind awarded by a Japanese university, recognizes outstanding research achievements in the medical or life sciences, and includes an honorarium of 20 million Japanese yen, or about $173,000.

Steitz has been on the Yale faculty since 1970, arriving directly after completing postdoctoral training at Harvard University and at the Medical Research Council Laboratory in Cambridge, England.

The recipient of numerous awards, Steitz was appointed full professor in 1979 and named Sterling Professor in 2001.
A crystal-clear look at a puzzling protein

An enzyme's structure may provide new clues on Alzheimer's disease

Biologists and chefs alike know that oil and water don’t mix. So several years ago, when researchers first discovered intramembrane proteases—a class of hydrophobic (“water-loving”) enzymes that inexcpliably appeared to function smack in the middle of the oily membrane that surrounds cells—many scientists were perplexed. Some were downright skeptical.

By publishing the first-ever crystal structure of one such enzyme, Ya Ha, Ph.D., assistant professor of pharmacology, and colleagues may have reeled the intramembrane proteases’ recipe for success.

In addition to providing a solution to a slippery biological mystery, Ha’s work could shed light on the mechanisms underlying Alzheimer’s disease.

Chewing up proteins, a process known as proteolysis, is the job of proteases. But protein-splitting reactions require water, a substance that is normally excluded from the greasy interior of cell membranes.

In 1997, Nobel laureates Joseph L. Goldstein, Ph.D., and Michael S. Brown, Ph.D., published intriguing data in Cell suggesting that a protease involved in regulating cholesterol somehow did its work within the cell membrane. Goldstein and Brown acknowledged that this protease must be “unusual,” but they proposed that gamma-secretase, the enzyme that cleaves amyloid protein into the toxic fragments seen in the brains of Alzheimer’s patients, might operate in the same manner.

When structural biologist Ha came to the School of Medicine from Harvard University five years ago, he first set his sights on gamma-secretase to try to crack the paradox of intramembrane proteases. Ha was convinced that obtaining structural information through X-ray crystallography was the key to understanding how these controversial enzymes worked.

But despite the Ha research team’s best efforts, gamma-secretase could not be coaxed into forming crystals, the first step in determining a protein’s molecular structure. Without a crystal, there was little chance of grant support from the National Institutes of Health, so Ha scraped together funds from the Department of Pharmacology and private foundations to continue his work.

When a family of bacterial enzymes with similar activity known as rhomboid proteins was discovered, Ha seized on those as an alternative. From there, he and postdocs Yongcheng Wang, Ph.D., and Yingjiu Zhang, Ph.D., worked for more than four years before they successfully formed a rhomboid protein crystal and obtained the first X-ray data.

At last, they saw how an intramembrane enzyme is built: in the middle of a sea of fat, the rhomboid protease creates a protective bubble to shelter water molecules in its active site. The protein is serpentine, crisscrossing the cell membrane six times. Five of these segments bundle together to create a water-filled chamber within the membrane.

Ha says his lab’s first picture of the rhomboid protease is merely a snapshot. A small dent in the protein facing outward from the cell might be an entryway for water molecules, and a protein flap just outside the central chamber could be a gate that controls the entry of proteins to be cleaved.

He wants to capture more views of the protein to find out how this gate might work and how the enzyme’s activity is regulated.

However improbable this enzyme’s mechanics, they are medically important. The rhomboid proteases are part of the family that includes human gamma-secretase, which cleaves a large transmembrane protein in the brain to release the amyloid fragments thought to cause Alzheimer’s disease.

“Compounds that inhibit the production of toxic amyloid peptides are now believed to be one of the most promising approaches to the development of drugs for Alzheimer’s disease,” says Vincent T. Marchesi, M.D., Ph.D., Anthony N. Brady Professor of Pathology and an expert on both membrane protein structure and Alzheimer’s disease. “Ha’s findings are an important contribution to this effort.”

Ha says that the rhomboid protease is a good model system for intramembrane proteases in general, but he confesses that he still has his eye on gamma-secretase. “I would love to see it,” he says.

While the two enzymes are not related by their protein sequence or by evolution, Ha believes that they share common features because they face the same challenge of mixing water with oil. “Once you have a few structures, you’ll see a pattern start to emerge,” Ha explains. “That will give us a better understanding of how inhibitors might work, and then maybe we can design better inhibitors, and maybe those inhibitors can be used as drugs.”

Now that a protein structure that proves that intramembrane proteoly- sis is possible is in hand, Ha says, “the doubters can be satisfied.” And other researchers, doubters or not, are certainly taking note: the Ha lab’s paper was published in the online version of the journal Nature at 1 p.m. on October 11; four hours later, scientists were ringing Ha’s phone requesting his raw data to apply to their own studies.

Structural biologists Ya Ha (seated) and Yongcheng Wang worked with Yingjiu Zhang to unlock a quirky enzyme’s secrets.
August 27: Over 300 cyclists gathered in Fairfield, Conn., for the second annual Connecticut Challenge, a noncompetitive bike ride benefiting programs for cancer survivors at the Yale Cancer Center (www.ctchallenge.org). Sponsored riders at this year’s event rode 25, 50 or 100 miles, raising $500,000 for the ycc.

1. Riders line up at the start of the event.
2. Connecticut Challenge cofounder Jeff Keith, of Westport, Conn., with Richard L. Edelson, M.D., professor of dermatology and director of the ycc.
3. From left: Aaron and Elizabeth Roberts joined their father, Kenneth B. Roberts, M.D., associate professor of therapeutic radiology, for the ride.
4. Yale Cycling Team members (from left) Curtis Eastin, Stephen Kriss, Anna Milkowski, Chris Ritacco, Jacob S. Hacker, Ph.D., professor of political science, Bruce McGalliard (a friend of the team), David A. McCormick, Ph.D., professor of neurobiology, and Steven Felix took part in the Challenge.

October 4: A dinner to support the Children’s Health Council (CHC), a volunteer leadership group dedicated to raising funds to support research in the medical school’s Department of Pediatrics, was sponsored by David H. Dreyfuss, principal of Dreyfuss Integrated Communications Group and a CHC founding member, and his wife, Lauren Tarshis. The event was held at the Birchwood Country Club in Westport, Conn. 1. From left: Jonathan Lach, Albert Hallac and Dreyfuss. 2. Tarshis and Margaret K. Hostetter, M.D., chair and Jean McLean Wallace Professor of Pediatrics. 3. Andrew and Jennifer Kanter. 4. Standing, from left: Harold D. Bornstein Jr., M.D., and Maureen L. Bornstein. Seated, from left: Carol Hallac, Dave Evans and Albert Hallac. 5. Standing, from left: Leo Dreyfuss, Andrew Tarshis, Robert Blondi, M.D., associate clinical professor of pediatrics, and Pat Thornton. Seated, from left: Karen Tarshis, Penny Kaestli and Marie E. Egan, M.D., associate professor of pediatrics and cellular and molecular physiology.

September 20: The St. Baldrick’s Foundation, founded on St. Patrick’s Day in 1999 by three Irish-American executives, has raised over $20 million for childhood cancer research by holding head-shaving events that encourage solidarity with children undergoing chemotherapy treatments. During a visit to the School of Medicine, the foundation presented St. Baldrick’s supporter Jack Van Hoff, M.D., associate professor of pediatrics, with a check for $25,000 to fund pediatric oncology research.

1. From left: Cheryl Davidson, Nina Kadan-Lottick, M.D., assistant professor of pediatrics, Van Hoff, Kathleen Ruddy, St. Baldwin’s executive director, Joli Lyn Gross and Peter Maloney. 2. The “shavee” team from St. Augustine’s Church in Seymour, Conn., included (from left) Dan Wasilewski, Cindy Hannon, Fr. Brian Jeffries and Linda Bojarczyk.

September 20: A sold-out evening with Judy Collins was held at Yale’s Sprague Hall to benefit Women’s Health Research at Yale (WHRY). 1. From left: The singer was escorted to a pre-concert reception in the President’s Room in Woodbridge Hall by Linda Koch Lorimer, J.D., vice president and secretary of Yale University, and Carolyn M. Mazure, Ph.D., professor of psychiatry, associate dean for faculty affairs and WHRY director. 2. From left: Richard C. Levin, president of Yale University and his wife, Jane Levin, join Collins at the reception.
How the stressed become depressed

Some individuals persevere in hardship, others crumble like paper dolls. Mental fortitude in the face of stress has been linked to variations in a gene that regulates the neurotransmitter serotonin. Individuals with a short version of the gene have a greater propensity to fall into depression under stress, while those with the longer version are more resilient.

To gain a glimpse of how these genetic differences might interact with stress to produce depression, R. Todd Constable, Ph.D., professor of diagnostic radiology and biomedical engineering, and colleagues in New York and Germany used brain imaging while individuals carrying short or long forms of the gene looked at images of faces. Other work had suggested that short-gene carriers who had experienced life stress would show an elevated response to sad or fearful faces in brain areas involved in depression and anxiety.

But in the October 24 issue of Proceedings of the National Academy of Sciences, Constable and colleagues reported less activation in short-gene carriers under these conditions and greater activation at rest. This pattern may reflect “a chronic state of vigilance, threat, or rumination” in short-gene carriers that makes them more vulnerable to depression under stress.

The immune system in a sticky situation

Neutrophils, critical cells of the early immune response, travel quickly through the bloodstream to sites of infection to engulf and kill bacteria. If genetic defects slow down this neutrophil migration, more severe infections may result.

School of Medicine researchers have now identified a key gene that regulates neutrophil movement through the body, which may clarify why some individuals are more susceptible to infection and inflammation.

A team led by Richard A. Flavell, Ph.D., Sterling Professor and chair of Immunobiology and Howard Hughes investigator, reports in the October 6 issue of Science that mice lacking the gene Myo1f have neutrophils that adhere more readily to their surroundings and are therefore markedly slower in reaching sites of infection. Myo1f, not previously known to play a role in immunity, limits the number of proteins known as integrins on the cell surface. In the gene’s absence, more integrins are released, making neutrophils more sluggish. “Without Myo1f, immune cells get too sticky and cannot move fast,” says first author Sang-won V. Kim, Ph.D., now at Memorial Sloan-Kettering Cancer Center. “So the host becomes vulnerable to acute infection.”

A robot arrives in the operating room

Operating room nurse Elizabeth Lasorso, R.N., did a double take when she walked into the operating room in late August and saw four robotic arms looming over a patient undergoing a radical prostatectomy. “I saw those arms just moving away, and nobody touching them,” she recalls, “and I thought, ‘Wow!’ ”

Seated across the room was Associate Professor of Surgery John W. Colberg, M.D., his face pressed to a screen, his hands inserted in gloved controls and his feet on pedals that manipulated the arms of Yale-New Haven Hospital’s newly acquired da Vinci Surgical System. To remove the patient’s prostate gland, Colberg controlled three of the da Vinci System’s arms for cutting and suturing; the fourth held a tiny binocular camera inserted into the patient’s pelvis.

“The experience was phenomenal,” says Colberg, the first physician to use the new $1.8 million device manufactured by Intuitive Surgical of Sunnyvale, Calif. Since then he has performed more than a dozen urological procedures using the da Vinci System.

As with other minimally invasive surgical procedures, robot-assisted surgery has distinct advantages, Colberg says. In the minimally invasive prostatectomy developed in the early 1990s using laparoscopic techniques, incisions are smaller than in open surgery and patients recover more quickly. According to Colberg the robotic version is even better, causing “virtually no bleeding.”

The da Vinci device increases the surgeon’s dexterity and improves the ability to see. The magnification of the operating field provided by the da Vinci System’s camera is four to eight times greater than that provided by a standard surgeon’s loupe, the viewfinder on the robotic console provides surgeons with a three-dimensional view. The equipment’s “wristed” robotic arms can rotate 360 degrees, far greater than the human arm, which is limited by the shoulder joint to about 270 degrees. And robotic “hands” never shake.

Physicians train by observing three surgeries, practicing for two days and then doing cases protoned by a physician credentialed in robot-assisted surgery. Colberg says that his patients have sought out the robotic procedure after hearing about it from their physicians, from friends or on the Internet.

Although the first robot-assisted prostatectomy was performed just six years ago and there are only about 400 such machines nationwide, Colberg says that 32,000 of the 80,000 radical prostatectomies performed in the United States in the near future will be robot-assisted.

Robert Udelsman, M.D., M.B.A., M.S.B., chair of the Department of Surgery and Lampman Professor of Surgery, calls the da Vinci System a major innovation: “The optics and the coordination that the surgeon gets with his hands are unbelievable.”

State makes first stem-cell grants to Yale

Yale fared well in the first group of grants awarded in November by the state of Connecticut from a $100 million fund established last year to promote stem cell research. Scientists at Yale received $7.7 million of the $9.8 million allocated by the State of Connecticut Stem Cell Research Advisory Committee for 21 research projects; $12 million went to investigators in New Jersey, Maryland, Missouri and Illinois—have decided to fund stem cell research.

Michael P. Snyder, Ph.D., professor of molecular, cellular and developmental biology, received the largest state grant, $3.8 million to investigate how human embryonic stem cells (hESCs) differentiate into nerve cells. Haifan Lin, Ph.D., director of the Yale Stem Cell Program (YSCP), received $2.5 million to support a new core facility that will accommodate federal funding restrictions on hESC research. Diane S. Krause, M.D., Ph.D., associate professor of laboratory medicine and pathology and co-director of the YSCP, received $836,654 to study a leukemia gene using hESCs.

Other Yale researchers who received funding include Yingjun Joan Huang, M.D., Ph.D., an assistant professor of obstetrics, gynecology and reproductive sciences who received $200,000 to study the fragile X mutation, a leading cause of mental retardation, in early human development; Eleni A. Markakis, Ph.D., assistant professor of psychiatry, who was awarded $84,407 to direct the isolation of neuronal stem cells from hESCs; and Erik Shapiro, Ph.D., assistant professor of diagnostic radiology, who received $199,975 for magnetic resonance imaging studies of the migration of neural progenitor cells.

“With this first allotment of money, Connecticut becomes a national leader in the area of stem cell research,” said Gov. M. Jodi Rell in a statement announcing the grants. “We have proven ourselves able to provide a place where such research can be done safely, ethically and effectively, in addition to providing investment dollars for the growth of the bioscience industry in Connecticut, and making an investment intended to improve the health of generations to come.”
In addition to his father, his daughter Wendy and himself, Yale alumni in Thomas’s family include an uncle, a brother (now deceased) and a nephew.

Of his own undergraduate years as an American Studies major, Israel says that although he didn’t fully realize it at the time, the Yale of the mid-1960s provided an unusually rich setting for a young man with a keen interest in our country’s history and culture. John F. Kerry, future war hero, senator and presidential candi- date, was Israel’s classmate and a fel- low member of the Yale soccer team.

Genes from page 1

ences at about one in every 1,300 let- ters. In all, there are about 10 million sites sprinkled throughout the human genome where common variations occur. Most of these variations, which are known as single-nucleotide poly- morphisms, or SNPs (pronounced “snips”), have no relevance to health. But some SNPs may influence one’s risk of developing a particular disease.

Genetic variations lying close to one another on a chromosome are often inherited together in chunks. By looking for chunks of variations that are always found in people with a particular disease but rarely in healthy individuals, scientists can narrow the search for disease genes and eventually pinpoint their locations. To effectively scan the SNPs in the entire genomes of large groups of people, however, one must compare hundreds of thousands of variations, which would have been impossible until quite recently.

Last year, Hoh’s research group was among the first to complete such a whole-genome analysis by combinin- g the SNP information compiled in public databases with the power of microarrays—silicon or plastic chips that are coated with hundreds of thousands of precisely arranged microscopic fragments of DNA.

The chip the Hoh team used al- lowed them to rapidly compare the genomes of more than 100 people with and without AMD for 100,000 different SNPs. As reported in the April 15, 2005, issue of Science, the research- ers pinpointed a single-letter variation strongly associated with the so-called “dry” form of AMD, a common form of the disease that causes vision loss but which rarely leads to complete blindness.

Using the same approach, Hoh and colleagues have now identified a variation associated with the “wet” form of AMD, a rarer but far more damaging form of the disorder in which a proliferation of leaky blood vessels causes irreversible damage to the retina. In the November 10, 2006, issue of Science, the team reports that people who had inherited a particular SNP from both parents near a gene called htra1 are 11 times more likely to get AMD than those lacking the variant.

The disease-associated SNP dis- covered by Hoh’s team seems to increase the expression of the gene, but she cautions that her results do not definitively establish that the variation itself causes AMD. The SNP may just lie close to some other disease-promoting genetic variation, she says, and it is still not clear how overexpression of htra1 would cause the blood vessel growth characteristic of the disease. However, previ- ous research has demonstrated that htra1 protein is present in the eyes of patients with wet AMD.

“It’s a long way, probably many years, to prove it,” Hoh says, but she adds that every clue is valuable when tackling poorly understood disorders like AMD. Hoh says that he know very little about the biological pathways causing AMD and that identifying po- tential disease-promoting genes like htra1 may lead to a greater understand- ing of those pathways.

Cho and other consortium members publish results from a study comparing DNA from 147 CD patients and 548 healthy people. They used microarray technology that simultaneously examines more than 300,000 SNPs in the genome—80 percent of the known SNP varia- tions of European ancestry, who are most susceptible to CD—and identified a vari-ation in the healthy people that is absent in those with CD.

The SNP, in a gene known as IL23R, tamps down the expression of a receptor for interleukin-23 (IL-23), a protein that promotes inflammation. Cho speculates the SNP protects healthy people from CD by interfering with the protein’s function, and she suggests that developing drugs to block the IL-23 may provide a new therapy for CD.

“We knew this was an unbelievably hot finding,” says Cho, who believes that whole-genome analyses will lead to important advances in treating previously intractable diseases.
Magnetic resonance system will open new scientific vistas

State-of-the-art magnet will enhance studies of metabolism and epilepsy

The School of Medicine has been awarded a $2 million grant from the National Center for Research Resources (NCRR) for the purchase of a powerful new 7 Tesla (7T) magnetic resonance system. The 7T system, one of only a dozen in the world, will be installed in the medical school’s Anlyan Center this summer. The system will allow Yale researchers to perform ultra-high-resolution MR studies of epilepsy, diabetes, psychiatric diseases, cancer and learning disorders.

The new equipment, obtained with funds from the NCRR’s High-End Instrumentation Program, will be a shared resource for several investigators funded by the National Institutes of Health under the leadership of Douglas L. Rothman, Ph.D., professor of radiologic engineering.

According to Rothman, the equipment will be used primarily for magnetic resonance spectroscopy (MRS) studies of humans, which create profiles of the chemicals present in various tissues, or in different regions of the same tissue. The 7T system can chemically analyze areas of tissue as small as 3 cubic centimeters. As a complement to the new imaging initiative, the medical school has recruited the research team of Eliza Hetherington, Ph.D., from Albert Einstein College of Medicine.

Moving to the School of Medicine is a scientiﬁc homeowner for Hetherington and Pan, who along with Rothman received their doctoral degrees in the laboratory of Robert G. Shulman, Ph.D., Sterling Professor Emeritus of Molecular Biophysics and Biochemistry and a pioneer of MRS research.

Since 1998, first at Brookhaven National Laboratory and then at Einstein, Hetherington and Pan have generated biochemical brain images that have used as a guide to surgery. “You can tell exactly where in the brain I want to operate,” Hetherington says. “New 7T system will allow us to see, using magnetic resonance spectroscopy, the chemistry of the brain during surgery. The researchers hope the 7T system will allow them to accurately predict which patients will go on to develop epilepsy following a first seizure.”

Hetherington says that MRS is a particularly powerful technique for studying neurological diseases, because it can detect depletions of a brain-specific chemical that occurs not only in epilepsy, but also in neurodegenerative diseases like Alzheimer’s disease and multiple sclerosis.

“Very clearly it is there better sensitivity for a number of pathologies, especially epilepsy, using spectroscopic imaging,” he says. “But for almost any neurological disorder, there’s an advantage. Alzheimer’s is a prime example of where spectroscopy works well for early detection.”

According to Pan, the high resolution of the 7T system changes the landscape of her research. “The 7T system is critical because it allows us to draw conclusions at a volume size that makes sense. At 1.5 T, you have to make a measurement from the entire brain, but with 7T you can make a measurement on the order of a few cubic centimeters,” she says. “Having a measurement of the whole brain is interesting, but it doesn’t tell me anything speciﬁc. With a 7T system I can tell exactly where in the brain I want to look and be accurate about it.”

The NCRR makes one-time awards to support the purchase of sophisticated instruments costing more than $500,000 to advance biomedical research and increase knowledge of the underlying causes of human disease.

“The High-End Instrumentation Program provides numerous investigators access to essential equipment, often beneﬁting entire research communities and dramatically advancing their research projects,” says Barbara M. Alving, M.D., the NCRR’s acting director. “These awards spurs the kind of scientiﬁc discoveries necessary for the development of treatments for a broad spectrum of diseases.”

The School of Medicine will contribute approximately half of the system’s cost, as well as the cost of installation in the recently constructed 30,000-square-foot Magnetic Resonance Research Center in the Anlyan Center.

“The new 7T system will provide Yale scientists with the capability of imaging biochemical and functional activity of the brain and limbs at unprecedented levels of spatial resolution,” says Rothman. “The research will be unique among ultra-high-field MR systems in its focus on developing and applying MR biochemical imaging for the understanding, diagnosis and treatment of disease.”

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Federal

Morris Bell, Ph.D., Cognitive Training and Enhanced Supported Employment, 5 years, $2,189,756 • Christopher Breier, N.I.H., Development of Second-Generation Tissue-Engineered Vaccines, 5 years, $673,563 • Tania Burgert, N.I.H., Postprandial Glycemia in Association with Vascular Disease in Childhood Obesity, 3 years, $375,454 • Elizabeth Claus, N.I.H., Menopause: Risk Factors and Quality of Life, 5 years, $2,385,811 • Mark Colman, N.I.H., Disease, Disability and Death in an Aging Workforce, 3 years, $916,639 • Pietro De Camilli, N.I.H., Molecular Mechanisms in Synaptic Vesicle Recycling, 4 years, $1,377,200 • Robin de Graaf, N.I.H., Novel Technologies for Global Optimization of Magnetic Field Homogeneity, 2 years, $532,473 • Enrica De Leu, N.I.F., Kinetic Mechanism of PAS-Box DNA Binding, 3 years, $472,077 • John Darcy, N.I.H., TM Interactions in Membrane Protein Folding and Function, 4 years, $1,754,951 • Durland Fish, N.I.H., Spinal Fusion by Barrelin Bacteria in the U.S., 3 years, $490,000 • Sami Karim, N.I.H., Neuronal Circuits and Function, 5 years, $1,750,000 • Brian Leasure, N.I.H., Asthma Severity in Children and Fine Particle Composition, 5 years, $344,204 • Elías Lois, N.I.H., Functional and Structural Studies of CD74 Activation, 5 years, $1,905,883 • Xingxiang Luo, N.I.H., Fine-Mapping the Risk Loci for Alcoholism in 22q11 Gene Cluster and Adenex Genes, 5 years, $772,821 • Robert Malinson, N.I.H., Drug Abuse, Sleep and Cognition, 3 years, $375,309 • Rustam Modirzhanov, N.I.H., Cell Biology of TLR Signal Transduction, 5 years, $1,893,752 • Gero Miesenbock, Office of Naval Research, Computation in Neuronal Microcircuits, 3 years, $418,000 • Michael Nathanson, N.I.H., Regulation of Liver Regeneration, 5 years, $590,000 • Julie J. Noglik, N.I.H., Metabolic Neuroprotection: Creative Supplementation in Human Brain, 2 years, $29,998 • Nancy Buddle, N.I.H., Lympho- and Tumoral Neogenesis, 1 year, $134,927 • Albert Simonas, N.I.H., Hybrid Imaging of Angiogenesis and Arteriogenesis, 4 years, $1,612,083 • Anthony Van den Pol, N.I.H., Cytokine Inhibition in the Brain, 5 years, $1,790,275 • Detlev Woncker, N.I.H., Studies of Myocardial Apoptosis in Conges- tive Heart Failure, 5 years, $306,582 • Sandra Wolin, N.I.H., Biogenesis of Small RNAs, 4 years, $1,454,848 • Tingzhao Zheng, N.I.H., Environ- ment, Gene and Testicular Cancer Risk, 5 years, $1,579,226

Non-Federal

Elizabeth Clauss, Susan G. Komen Breast Cancer Foundation, Ductal Carcinoma in situ and BRCA1/2: Outcomes and Risk Prediction, 2 years, $299,823 • Robert Constable, Pfizer, Inc., MR Methodologies and Further Analysis and Reporting of Data, 2 months, $25,790 • Gail D’Onofrio, Yale-New Haven Health System, Disease Preparedness and Emergency Response Education and Research, 1 year, $15,000 • Deepak D’Souza, Zentiva, L.P., Nicotinic Modulation of a Noncompetitive N-Methyl-D-Aspartate (NMDA) Receptor Antago- nist–Induced Schizophrenia-Like Information Processing Deficits in Humans, 1 year, $546,444 • Daniel Goldstein, Boche Organ Transplantation Foundation, Role of Intratheal Lymphocytes in Neutonal Transplant Tolerance, 2 years, $161,203 • Zhehui Hu, Susan G. Komen Breast Cancer Foundation, Targeting the Neuro- limes for Immunotherapy and Photodynamic Therapy of Breast Cancer, 2 years, $210,000 • Scott-Eric Judd, Health Effects Institute, Health Effects of Air Pollution, 1 year, $80,000 • Amy Justice, University of Kentucky, Computer Alcohol Interactions for IDV, 2 years, $30,919 • Ari Kaffman, American Psychiatric Institute for Research and Education, The Effects of Postnatal Maternal Care on Neurogen- esis During Development and Their Implications for the Development of Vulnerability to Stress, 1 year, $45,000 • John Krystal, National Alli- ance for Research on Schizophrenia and Depres- sion, CARB A2 Modulation of NMDA Receptor Deficit–Related PFC Dysfunction, 1 year, $10,000 • Elías Lois, University of Florida, Viral-Induced Chemokine Receptor Antagonist, 2 months, $25,181 • Joseph Maris, Arizona, Inc., Stage I: Preliminary Characterization of a MIB Inhibitor, 2 years, $15,901 • Paul Lembosko, National Alli- ance for Research on Schizophrenia and Depres- sion, Characterization of the TRP Knock-Out Mouse, 1 year, $99,000 • John McConnell, University of Iowa, Collaborative Development of a Vaccine Against Citrus and Vascular Leishmaniasis, 2 years, $175,904 • Guillermo M. Morán, Novogen Limited, Assay of Induction Apoptosis by Phenoloxidase in Cancer Cells, 1 year, $90,940 • Prakash Nadkarni, Mount Sinai School of Medicine, N.C.T. Medical Monitoring Program Data and Prognostive Medicine, 3 years, $504,000 • Angela Nairn, National Alliance for Research on Schizophrenia and Depression, Neuroimaging Analysis of the Actions of RON2 and Other Neurotrophic Factors, 1 year, $59,900 • Jill Reiter, Susan G. Komen Breast Cancer Founda- tion, Prognostic Significance of Salable EGFR Expression in Breast Cancer, 2 years, $200,000 • Sara Rockwell, PharmMar USA, Inc., Prelimi- nary Studies of the Effects of Aplidine in Hypoxic Environments and in Combination with Radia- tiion, 1 year, $67,035

Grants and contracts awarded to Yale School of Medicine May/June 2006

Medicine/Yale January/February 2007
Expert on blood pressure genes is honored

It has been a busy fall for Richard P. Lifton, M.D., Ph.D., chair and Sterling Professor of Genetics and Howard Hughes Medical Institute investigator. In October, Lifton received the 2006 Robert Tigerstedt Award at the 21st Scientific Meeting of the International Society of Hypertension (ISH) in Fukuoka, Japan. A month later, he delivered the first Donald Seldin Lecture at Scientific Sessions 2006, the annual national meeting of the American Heart Association (AHA), held this year in Chicago.

The Tigerstedt Award is named in honor of a Finnish scientist who discovered renin, a kidney enzyme involved in high blood pressure. The prize is the highest scientific award of the ISH, and is presented at each biennial meeting “to honor a scientist or physician for outstanding achievements in the field of hypertension.”

Lifton was cited by the society for his identification of genetic mutations that govern human blood pressure by affecting how the kidneys handle salt. By investigating families from around the world, Lifton’s research team has identified mutations in seven genes that raise blood pressure, and eight that lower blood pressure.

The AHA lectureship was established this year to honor Donald W. Seldin, M.D., William Buchanan Chair in Internal Medicine at UT Southwestern Medical Center in Dallas.

Seldin, a 1943 graduate of Yale School of Medicine, served as an assistant professor at Yale until 1951, when he left for UT Southwestern, then a fledgling medical school with rudimentary facilities.

Over the next 35 years, Seldin was a central figure in UT Southwestern’s rise into the ranks of the world’s most elite research institutions.

Along the way, Seldin made seminal scientific observations on salt and potassium transport in the kidney, and he has been a leader in understanding the relationships between renal and cardiovascular diseases. Fittingly, Lifton’s lecture in Chicago was entitled “Molecular Genetics of Cardiovascular Risks: The Kidney as the Cause of Hypertension.”

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A member of the Yale faculty since 1993, Lifton is a member of the National Academy of Sciences and the Institute of Medicine.

He is the recipient of numerous awards for his research. These include the highest scientific awards of several other organizations, including the AHA, the American Society of Nephrology, the American Society of Hypertension and the Council for High Blood Pressure Research, as well as the Pasarow Foundation Award for Medical Research.

Education innovator wins award for work on transforming schools

School reform leader James P. Comer, M.D., the Maurice Falk Professor of Child Psychiatry at the Yale Child Study Center (YCSC), has won the 2007 University of Louisville Grawemeyer Award in Education. The award, which carries a $200,000 prize, cites Comer as a champion of improving schools by applying knowledge from child development research.

Comer is best known for the School Development Program (SDP), founded at the YCSC in 1968. The SDP promotes optimal emotional, behavioral and academic development in schoolchildren through school governance teams that give all parties—teachers, administrators, parents, students, janitorial and cafeteria workers, and school psychologists—a voice in how their schools are operated and a stake in the educational outcome.

The SDP model has been applied in over 1,000 schools in the United States, South Africa, England, Ireland and the Caribbean, and research has shown that it improves children’s performance in low-achieving schools.

Comer, author of the 2004 book Leave No Child Behind: Preparing Today’s Youth for Tomorrow’s World, joined the Yale faculty in 1968. He has received numerous awards, including the Smithsonian Institution’s John P. McGovern Behavioral Science Award, the Heinz Award in the Human Condition, the Harold W. McGraw Jr. Prize in Education, and the Charles A. Dana Award for Promising Achievement in Education. He has also received a special presidential commendation from the American Psychiatric Association and was named to Education Week magazine’s list of 100 people who helped shape American education in the 20th century.

The School Development Program, developed at Yale’s Child Study Center, has improved children’s performance in over 1,000 low-achieving schools all over the world.

The Grawemeyer Awards, which are also given in music composition, religion, psychology and other fields, were established in 1984 by H. Charles Grawemeyer, an alumnus of the University of Louisville who made his fortune as an industrialist and entrepreneur. The awards are distinguished by Grawemeyer’s belief that lay people as well as experts should judge candidates’ contributions, and his conviction thatweeping, influential ideas are as important as personal accomplishment.