Medicine@Yale

JULY/AUGUST 2011
VOLUME 7, ISSUE 3
Advancing Biomedical Science, Education, and Health Care

Couple's passion for the arts inspires unique scholarship fund

Having majored in philosophy and history as an undergraduate at Trinity College, in Hartford, Conn., David Leof, M.D., a member of the School of Medicine's Class of 1964, initially found life at the medical school to be "quite terrifying." On his very first day, then-Dean Vernon W. Lippard, M.D., issued a sobering call to responsibility, reminding the new students that medical school is only a brief chapter in the life of a physician. Though the day would come when each student would receive a medical degree, "you have the rest of your life to earn it," said Lippard.

"I've never forgotten that," says Leof, now a Distinguished Life Fellow of the American Psychiatric Association and a Jungian psychoanalyst and psychiatrist in private practice in San Francisco.

But Leof's terror quickly evaporated, and "as things unfolded, I was just like a little kid at Christmas," he says. "I had an absolutely joyful time in medical school."

In gratitude, Leof and his wife, Colleen, have made a bequest to the School of Medicine of several million dollars, which will support medical students who have distinguished themselves in the arts or humanities. To enable students in this year's entering class to be eligible for the new scholarships, the couple has made an additional gift of $150,000, an amount that has already been doubled thanks to contributions from others, including a matching gift from the School of Medicine to mark the school's Bicentennial year.

Another major influence on Leof was Lippard's successor as dean, Frederick C. Redlich, M.D., a legendary chair of the Department of Psychiatry from 1950 to 1967 who built the department into one of the nation's finest. It was Redlich, Leof says, who encouraged him to go into psychiatry himself. After graduating, Leof interned at Dartmouth College's Mary Hitchcock Memorial Hospital and then served two years on a U.S. Public Health commission working for the Food and Drug Administration in Washington, D.C.

// Leof *(page 7)*

ELISABETH FALL

David and Colleen Leof's new bequest will support medical students who have attained distinction in the arts and humanities.

A young scientist scores another first

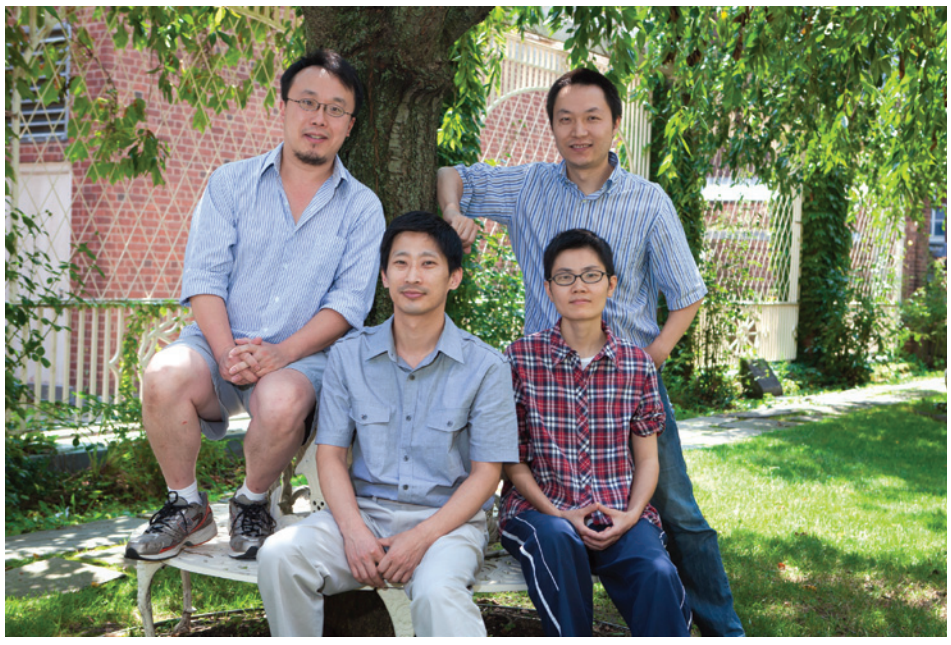
Following up on groundbreaking work of 2006, Yale structural biologist's team strikes again, cracking enzyme akin to an Alzheimer's culprit

"This is the material that's not in the biochemistry textbooks yet," says Ya Ha, PH.D. "This is preliminary work, but it's still a breakthrough."

The work in question is Ha's research team's recent determination of the atomic structure (known in the trade as "solving" the structure) of FlaK, an enzyme found in an evolutionarily ancient microorganism native to the salt marshes of the southeastern U.S. It may seem improbable that knowing a tiny piece of this tiny creature in such intimate detail could be a biomedical breakthrough. But the research, three years in the making, marks the first time that anyone has cracked the structure of an aspartyl membrane protease, a family of enzymes of which FlaK is a member.

Moreover, FlaK has an infamous cousin—presenilin, an enzyme that plays a major role in

// FlaK *(page 6)*



TERRY DAGRADI

A team led by Ya Ha (left) has determined the structure of the enzyme FlaK, a member of a family of proteins linked to early-onset Alzheimer's disease. Ha's colleagues and co-authors on the study, Sangwon Lee (center), Yi Xue (seated, right), and Jian Hu (standing, right). The team's work, a technical tour de force, represents the second time that the Ha lab has solved an important structure that had eluded other scientists.

Innate immunity pioneer receives international prize

Ruslan Medzhitov

Ruslan M. Medzhitov, PH.D., the David W. Wallace Professor of Immunobiology, is one of three scientists awarded the 2011 Shaw Prize in Life Science and Medicine.

A member of Yale Cancer Center and a Howard Hughes Medical Institute investigator, Medzhitov has made groundbreaking contributions to the understanding of Toll-like receptors (TLRs), an evolutionarily ancient component of the innate immune system that provides rapid, first-line defense against infections. Medzhitov's work has elucidated how TLRs sense microbial infections, TLR signaling, and TLR activation of inflammatory and adaptive immune responses.

In 1997, Medzhitov and the late Yale immunobiologist Charles A. Janeway Jr., M.D.,

// Medzhitov *(page 7)*

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INSIDE THIS ISSUE

ALSO

TERRY DAGRADI

In addition to his role as chair of the medical school's Section of Comparative Medicine, Tamas Horvath is founding director of the Yale Program in Integrative Cell Signaling and Neurobiology of Metabolism. The new program will explore the complex interrelationships between brain function and a variety of metabolic processes throughout the body, which have implications for understanding obesity, diabetes, neurodegenerative diseases, and the life span.

Peripheral vision

To fully fathom the brain we can't forget the body, says neuroendocrinologist

When it came time to choose a career as a young man in his native Hungary, family history was a strong influence for Tamas L. Horvath, D.V.M., PH.D. His father's side of the family is lined with veterinarians, his mother's with physicians. His older brother was already planning to be a doctor, so although Horvath was both allergic to and afraid of animals, he thought his destiny must lay in veterinary medicine.

But Horvath had a deep interest in basic biomedical research, and after receiving a degree from the University of Veterinary Sciences in Budapest he changed course, coming to the School of Medicine as a postdoctoral fellow in 1990. "The flexibility of the American system was what brought me here," Horvath says. "I didn't really want to be a vet, so I immediately came to Yale."

At the medical school Horvath worked with fellow Hungarian Csaba Leranth, M.D., now professor of obstetrics, gynecology, and reproductive sciences, and with Frederick Naftolin, M.D., PH.D. (now at New York University School of Medicine), both leading researchers in the neural and hormonal bases of reproductive physiology and behavior. He joined the Yale faculty in 1996, and, in 2000, was awarded a PH.D. in neurobiology from Attila József University in Hungary.

Horvath is now in his seventh year as chair of the medical school's Section of Comparative Medicine, a discipline that dates back to the 1960s, when veterinarians in academic medicine and the pharmaceutical industry began applying insights from their research to the human condition. The field was a natural fit for Horvath, who also holds an appointment in the Department of Neurobiology, and who earlier this year was named the inaugural Jean and David W. Wallace Professor of Biomedical Research.

In the mid-1990s Horvath realized that the brain circuitry governing reproduction also plays a major role in hunger, eating, and obesity. He shifted his research focus, showing that ghrelin, a hunger hormone released when the stomach is empty acts on the hypothalamus, a relatively primitive brain region that regulates feeding and a variety of other basic functions.

But Horvath wondered whether ghrelin could also affect higher brain functions. In 2006, he and his research team reported in *Nature Neuroscience* that mice with higher blood levels of ghrelin performed significantly better on learning and memory tasks, and that the hormone stimulated the formation of significantly more synapses in the hippocampus, a brain structure crucial to memory. These findings could lead to ghrelin-based therapies for neurodegenerative illnesses like Alzheimer's disease.

Findings like these have given Horvath a new and paradoxical perspective on neurobiology: by studying how the mammalian brain interacts with basic bodily systems, like the digestive system, to regulate metabolism, he believes we can better understand why humans have evolved with such a complex central nervous system.

"The mechanisms that set the brain's ability to function are really driven by the peripheral tissues," explains Horvath. "I'm not saying what makes us human is our liver or muscles, but these periphery systems are part of what shapes us to make decisions at the right time to keep us alive."

Yale has become a new tradition for the Horvath family. Horvath's wife and scientific collaborator, Sabrina Diano, PH.D., is professor of obstetrics, gynecology, and reproductive sciences at the School of Medicine. And that older brother who wanted to become a doctor? That's Balazs Horvath, M.D., assistant professor of anesthesiology.

Nobelist is elected as a member of world's oldest scientific society

Thomas A. Steitz, PH.D., Sterling Professor of Molecular Biochemistry and Biophysics, Howard Hughes Medical Institute investigator, and co-recipient of the 2010 Nobel Prize in Chemistry, is one of 8 scientists elected as Foreign Members of the Royal Society, the United Kingdom's national academy of science.

Founded in 1660, the Royal Society is the world's oldest scientific academy in continuous existence. Through its history, the roster of the Society's Fellows and Foreign Members, elected for life on the basis of scientific excellence, has included Isaac Newton, Charles Darwin, Ernest Rutherford, Albert Einstein, Dorothy Hodgkin, Francis Crick, James Watson, and Stephen Hawking. Today there are approximately 1,500 Fellows and Foreign Members, including more than 80 Nobel Laureates.

Along with colleague Peter B. Moore and other Yale researchers, Steitz conducted groundbreaking research during the 1990s that determined the atomic structure of the ribosome, a protein-making machine in cells that is necessary to life. This work, which earned Steitz the Nobel Prize, has led to the creation of a new generation of antibiotics now in clinical trials.

According to a statement from the Society, Steitz was selected "for his pioneering contributions to the mechanisms involved in the processes of gene replication, transcription, control, and translation, that are fundamental to all life."

Thomas Steitz

In addition to its role as a worldwide fellowship of top scientists, the Royal Society provides independent scientific advice to government agencies in the U.K., publishes eight scientific journals, and provides funding for scientific research, all, according to the Society's website, "for the benefit of humanity and the good of the planet."

Radiology chair is elected president of national society

James Brink

James A. Brink, M.D., professor and chair of the Department of Diagnostic Radiology and chief of diagnostic radiology at Yale-New Haven Hospital, has been elected president of the American Roentgen Ray Society (ARRS).

The ARRS, which publishes the *American Journal of Roentgenology*, is the oldest radiology society in America. Formed in 1900, soon after the discovery of the X-ray by German physicist and Nobel laureate Wilhelm Roentgen, PH.D., the society is dedicated to the advancement of medicine through radiology and allied sciences.

Brink received a B.S. at Purdue University and an M.D. at Indiana University. He completed his residency and fellowship at Massachusetts General Hospital in Boston, and came to Yale in 1997 from the Mallinckrodt Institute of Radiology at Washington University School of Medicine in St. Louis.

Brink has pioneered technologies for maximizing resolution in CT scanning while minimizing radiation dosage and risk to patients. His work evaluating the general underpinnings of image reconstruction has helped manufacturers to develop and implement image-processing algorithms that have brought advanced applications such as CT colonography and CT angiography into clinical use.

Among his numerous awards, honors, and leadership positions, Brink is a member of the Board of Chancellors of the Academy of Radiology Research, and also serves on the board of directors for the National Council on Radiation Protection.

Medicine@Yale

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Medicine@Yale is published five times each year by the Office of Institutional Planning and Communications, Yale School of Medicine, 1 Church St., Suite 300, New Haven, CT 06510-3330 Telephone: (203) 785-5824 Fax: (203) 785-4327

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Knocking out itch with a BAM

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Many of us turn to antihistamines to deal with itch caused by seasonal nuisances such as mosquito bites, poison ivy, or allergies. As the name implies, these medications work by blocking the actions of histamine, a chemical in the body that causes skin inflammation.

But some itches, including debilitating chronic itch, do not respond to antihistamines. Scientists recently discovered that a peptide called BAM8–22 caused scratching in mice by activating neural pathways not related to histamine production.

In the May 18 issue of *The Journal of Neuroscience*, a research team led by Robert H. LaMotte, PH.D., professor of anesthesiology and neurobiology, reported that when BAM8–22 was applied to human subjects' skin, the subjects unanimously experienced increased itch and burning sensations that could not be calmed by antihistamine treatment.

"BAM8–22 binds to a receptor that is found in sensory nerve fibers in human skin," says LaMotte. "Development of an antagonist of this receptor may prove useful in the treatment of itch that is not relieved by antihistamines."

Opioid abusers have supplies close to home

The widespread illicit use of opioid painkillers begins more in bathroom medicine cabinets than back alleys, according to new Yale research published in the *Archives of Internal Medicine*.

School of Medicine investigators led by William C. Becker, M.D., an instructor in the Department of Internal Medicine, mined data from the National Survey on Drug Use and Health to get a picture of the current landscape of nonmedical use of opioid analgesics, such as oxycodone (e.g., Percodan, OxyContin) and hydrocodone (e.g., Vicodin). The data show that during the decade between 1997 and 2006, the strength of such opioids in prescriptions filled by pharmacies quadrupled, and sales doubled between 2002 and 2006. Moreover, between 2008 and 2009 the number of new recreational users of opioids increased 13 percent, to 1.2 million.

Recreational use of opioids carries risks of addiction, overdose, and even death, so the researchers were eager to uncover users' paths to the pills. One-third of nonmedical opioid users said they obtained prescriptions from a doctor, but most users said they relied on a supply from family and friends, sources that deserve more vigilance from public health officials fighting opioid abuse, say the researchers.

A crash course in real-world research

The School of Medicine's summer internships immerse high school students in research projects and take science education beyond the classroom

John Solder, a 17-year-old who will be a senior at Staples High School, in Westport, Conn., this fall, has a summer internship in the School of Medicine laboratory of Ralph J. DiLeone, PH.D., associate professor of psychiatry and neurobiology. But Solder isn't fetching coffee for the lab—instead, he is collaborating with DiLeone on experiments using optogenetics, a cutting-edge technique in which specific brain circuits can be selectively activated when exposed to light.

Solder is one of more than 100 high school students doing research internships in labs at the medical school this summer, according to Sara Rockwell, PH.D., professor of therapeutic radiology and pharmacology and associate dean for scientific affairs. "Student interns have to complete a summer project with a mentor, and in doing so they find out what it means to be a scientist," Rockwell says.

Solder, who was a member of a Staples High robotics team that won a world championship this spring, is no stranger to the medical school campus, having spent last summer working in the laboratory of Amy F.T. Arnsten, PH.D., professor of neurobiology. In Arnsten's lab, Solder explored potassium channels in nerve cells of the brain's prefrontal cortex, which are a promising target for drugs to forestall age-related memory loss. Solder presented his work at the Connecticut Science Fair and at the Connecticut Junior Science and Humanities Symposium (JSHS), where he and four other students were chosen to represent the state at the national JSHS meeting held this spring in San Diego.

Solder says that he has learned from Yale scientists both inside and outside the lab. "It's interesting hearing what they talk about at lunch," he says. "It's not just about last night's football game."

Some high school students who wish to work in a Yale lab follow Solder's approach, independently e-mailing a professor whose work matches his or her interests. Others come to the School of Medicine through established programs, such as the Discovery to Cure internship created in 2004 by ovarian cancer expert Gil Mor, M.D., PH.D., of the Department of Obstetrics, Gynecology, and Reproductive Sciences.

"I was afraid all of the smart, ambitious students would go into business to make money," Mor says. "There is a misconception that science is dark and lonely for a bright person."

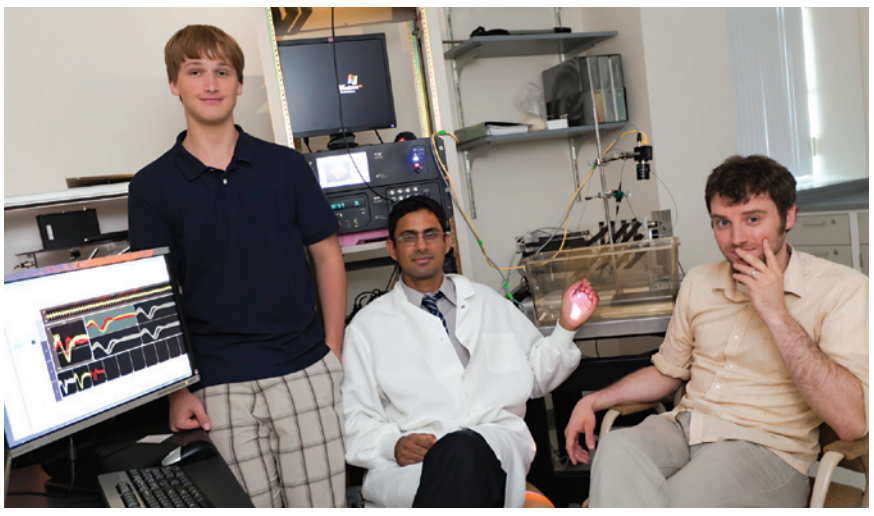
Students are nominated to participate in the six-week program by their high school science teachers, and then selected by School of Medicine faculty. This year, Mor had 140 applications, and he says the program has grown from just two students in its first year to 27 this summer. Since the inception of the Discovery to Cure internship, five interns have had the heady experience of being coauthors on papers published in the scientific literature. And in addition to doing experiments, interns are given comprehensive training in other aspects of science, including lab safety.

For many teens in the Discovery to Cure program, which places students in labs across the medical campus, the internship is their first exposure to the excitement of formulating a scientific research question, something impossible to grasp when performing well-trodden experiments in their high school's labs. "They come in and within six weeks they are talking like a scientist, seeing what happens when a research question works, or doesn't," says Mor. At the end of the internship, all participants give a 10-minute PowerPoint presentation on their work.

Michael H. Bloch, M.D., M.S., assistant professor in the Child Study Center and assistant director of the medical school's Obsessive-Compulsive Disorder (OCD) Research Clinic, regularly invites high school students to join him as summer interns. Typically, he says, students interested in OCD or Tourette's syndrome approach him after reading about his work online. "I've been really impressed with how knowledgeable and enthusiastic they are," he says. "It's nice to have a fresh set of eyes in the lab. Often interns ask questions that many experienced people don't ask." Bloch, who worked in labs while in college, says of the high schoolers, "I think the experience gives them a glimpse into what clinical research is like, what mental illness is like, and also teaches them valuable skills for the workplace."

According to Rockwell, because many Yale graduate students don't have an opportunity to teach, having a high school student in the lab gives them an opportunity to flex their mentoring muscles. Interns come from around the world, but most come from Connecticut, and Rockwell believes that "anything that brings a higher level of involvement between the local community and Yale is a good thing."

Taylor DeRosa, 17, who attends Sacred Heart Academy in Hamden, Conn., is working this summer for both Mor and Assistant Professor of Chemistry Seth Herzon, PH.D. on an antibiotic with the potential to attack tumors. DeRosa says that her summer internship has made a deep impression, and that she is seriously considering a career in research. "There was a moment when I was holding a compound in my hand, and I just felt like it was important work," she says. "That's not something you feel in Chemistry class."



TERRY DAGRADI

High school senior John Solder (left), of Westport, Conn., is one of more than 100 high school students who are getting a taste of biomedical research at the School of Medicine this summer. Solder is working with M.D./PH.D. student Nandakumar Narayanan (center) and Benjamin Land (right) in the laboratory of Yale neurobiologist Ralph DiLeone on experiments employing optogenetics, a cutting-edge technique in which specific brain circuits can be activated by exposure to light.

OUT & ABOUT

May 23, 2011 Members of the Class of 2011 marked the beginning of their careers as physicians at this year's **Commencement** ceremonies. Of the 100 students in the class, 76 chose to spend a fifth year at the School of Medicine; those graduating this year were joined by students from the previous year who had taken a fifth year, as well as three students in the M.D./PH.D. Program. **1.** (From left) **Westin Amberge**, **Sumayya Ahmad**, **Elie Balesh**, **Isaac Benowitz**, **Larissa Chiulli**, **Jessica Crawford**, **Nicole Cabbad**, and **Noah Capurso** marched in the annual Commencement procession. **2. Bibhav Acharya** received the Arnold P. Gold Humanism in Medicine Award, which honors a graduating student who demonstrates the highest standard of compassion and sensitivity in his or her interaction with patients. **3. L.J. McIntosh**. **4. Bridget Hopewell**, **Nina Ni**, **Lauren Hackney**, and **Maya Hasan**. **5. John N. Forrest Jr.**, M.D., professor of medicine and director of the Office of Student Research; **Matthew Hornick** (in background); and **Irwin M. Braverman**, M.D., professor of dermatology. **6. Benjamin Goldberg**, who will begin a psychiatry residency at the University of California-San Francisco, with family members.

TERRY DAGRADI (6)

TERRY DAGRADI

JOHN CURTIS (2)

June 3, 2011 **Reunion Weekend** brought more than 300 alumni and guests to the School of Medicine. **1. Richard Silverman**, director of admissions (second from right), led a tour of the medical campus, including the Healing Garden on the seventh floor of Smilow Cancer Hospital. **2.** Dean and Ensign Professor of Medicine **Robert J. Alpern**, M.D., (right) chats with **Christine Duranceau**, M.D. '81, class social chair; **Christine Walsh**, M.D. '73, incoming president of the Association of Yale Alumni in Medicine; and her husband, **Sean Walsh**, at a leadership reception. **3.** (From left) **Tricia Gibbs**, M.D. '87, **Richard Gibbs**, M.D. '86, and **Nancy R. Angoff**, M.P.H. '81, M.D. '90, associate dean for student affairs, at "The Paths We've Traveled," a Friday afternoon panel.

June 27, 2011 Delegations from Yale and University College London (UCL) met with government leaders at the House of Commons of the United Kingdom to raise awareness of the **Yale-UCL Collaborative**, a transatlantic clinical and research partnership created in 2009. **1. George Freeman**, M.P. (left), the member of Parliament who hosted the event, chats with **James E. Rothman**, PH.D., the Fergus F. Wallace Professor of Biomedical Sciences and chair of the Department of Cell Biology. **2.** (From left) **Mark Marsh**, PH.D., director of UCL's Laboratory for Molecular Cell Biology; Rothman; **John Martin**, M.D., professor of cardiovascular medicine at UCL and co-director of the Yale-UCL Collaborative; **Sir John Tooke**, M.D., vice provost (health) of UCL, head of the UCL School of Life & Medical Sciences, and head of the UCL Medical School; **Robert J. Alpern**, M.D., dean and Ensign Professor of Medicine; **Michael Simons**, M.D., the Robert W. Berliner Professor of Medicine and Cell Biology, chief of the Section of Cardiovascular Medicine, and co-director of the Yale-UCL Collaborative; and **Michael Worton**, PH.D., vice provost (academic and international) of UCL.

COURTESY OF UNIVERSITY COLLEGE LONDON (2)

Study finds key player in polycystic diseases of both kidney and liver

Autosomal dominant polycystic kidney disease (ADPKD), the most common form of polycystic kidney disease, is an inherited disorder in which the formation of multiple renal cysts leads to kidney failure. ADPKD, in which cysts can also form in the liver, is the most common potentially life-threatening genetic disorder worldwide, affecting some 12 million people. There is no cure, and the only effective treatments are dialysis and kidney transplantation.

For more than a decade, scientists have known that mutations in a gene known as *PKD1* are associated with ADPKD, but new research led by Stefan Somlo, M.D., the C.N.H. Long Professor of Medicine, professor of genetics, and chief of the Section of Nephrology, shows that polycystin-1 (PC1), the protein product of *PKD1*, is a central player in a five-gene network that underlies not only ADPKD, but two other polycystic diseases as well.

Stefan Somlo

In the June 19 issue of *Nature Genetics*, a team led by Somlo, along with Craig M. Crews, PH.D., professor of molecular, cellular, and developmental biology, professor of chemistry, and professor of pharmacology, reports that knocking out the two genes involved in polycystic liver disease also decreased levels of functional PC1, and that the severity of polycystic disease was directly correlated with the genetic "dosage" of PC1—increasing expression of *PKD1* dampened cyst formation.

In addition, low levels of PC1 promoted cyst formation in ARPKD, a less common recessive form of polycystic kidney disease. "We found that these conditions are not the result of an all-or-nothing phenomenon," says Somlo. "The less *PKD1* is expressed, the more cysts develop. Conversely, expressing more *PKD1* can slow the process."

The genes mutated in isolated human polycystic liver disease regulate quality control in protein production. When they are compromised, cellular trash collectors called proteasomes take up the slack, cleaning up improperly processed proteins and probably degrading PC1 in the process. When the researchers administered drugs that inhibit proteasomes—some of which have shown promise as cancer treatments—PC1 levels rose and cyst formation decreased. "The data suggest the exciting possibility that targeting the activity of *PKD1* may be beneficial for treatment of isolated polycystic liver disease, childhood recessive polycystic kidney disease, and even a subset of adult ADPKD," says Somlo.

Carolyn W. Slayman, PH.D., Sterling Professor of Genetics and deputy dean for academic and scientific affairs, says, "Steve Somlo's lab has been at the forefront of PKD research for many years, and this new paper makes an important contribution by showing the interactions among five genes in cyst formation."

Diet, diabetes, and a gene called *MINDY*

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Tamping down expression of the fruit fly gene *Indy* improves mitochondrial function, mimicking the effects of a low-calorie diet and prolonging the life span of the flies (hence the name, an abbreviation for "I'm not dead yet"). But scientists have lacked details on the precise physiological bases for these changes.

To find out, a group led by Gerald I. Shulman, M.D., PH.D., George R. Cowgill Professor of Physiological Chemistry and professor of Medicine and Cellular and Molecular Physiology, knocked out *MINDY*, a mammalian version of the gene. As reported In the August 3 issue of *Cell Metabolism*, the manipulation improved mitochondrial function and fatty acid metabolism in the liver. The mice were protected from diet- and age-related accumulation of fat in the liver, which leads to hepatic insulin resistance, and, in humans, can evolve into type 2 diabetes.

"*MINDY* may be a novel therapeutic target for the treatment of hepatic insulin resistance, a major factor in the pathogenesis of type 2 diabetes," says Shulman, also a Howard Hughes Medical Institute investigator.

Could digestive woes be contagious?

In the digestive system, many trillions of bacteria subsist in a delicately balanced ecosystem known as the microbiome. If that balance is disturbed, one result can be irritable bowel disorder (IBD), an ailment that causes cramping, constipation, and diarrhea.

When the gut's bacterial equilibrium is out of whack, sentinel proteins called NLRs can detect tissue damage. If activated, NLRs join other proteins to form complexes known as inflammasomes, which in turn promote the production of cytokines, protective proteins that can restore balance.

In a study published May 27 in *Cell*, a team led by Richard A. Flavell, PH.D., chair and Sterling Professor of Immunobiology and Howard Hughes Medical Institute investigator, knocked out a vital piece of the NLRP6 inflammasome in mice, which lowered levels of the cytokine IL-18. In the absence of IL-18, one family of gut bacteria overproliferated, displacing others and causing IBD-like inflammation.

In a startling finding, a similarly altered microbiome and propensity for inflammation was picked up by normal mice housed with NLRP6-deficient mice. "The fact that IBD may be transmitted from a susceptible mouse to an ostensibly normal one has potentially profound implications for IBD and other human diseases in which microbiota contribute," says Flavell.

A surgeon's rare skills heal a man in need

International medical organization brings a patient from Haiti to a Yale neurosurgeon, who successfully treats a dangerous brain aneurysm


JOHN CURTIS

Ketan Bulsara performs a neurological examination on Norbert Tibeau to assess the results of the minimally invasive aneurysm surgery that Bulsara carried out pro bono in cooperation with the international medical organization Partners in Health.

While still in high school in Haiti in 2001, Norbert Tibeau began having severe headaches, but it would be seven years before he finally saw a doctor. By then Tibeau's headaches were lasting for up to a week. He was seeing flashes of light, his vision was impaired, and the pain was incapacitating. "I would have to lie down," Tibeau, now a 28-year-old studying for the priesthood, recalls. "Sometimes I couldn't eat."

In January of last year, the international medical organization Partners in Health (PIH), which had organized Tibeau's doctor visit, made arrangements for him to travel to the neighboring Dominican Republic for an MRI scan, which revealed a brain aneurysm that could kill or cripple him if left untreated.

Through its Right to Health Care Program, PIH searched for physicians and hospitals across the United States willing to donate their services to treat Tibeau, finally settling on Yale because of the unique skills of Ketan R. Bulsara, M.D., associate professor of neurosurgery at the School of Medicine and director of neuroendovascular and skull-base surgery at Yale-New Haven Hospital (YNHH).

Bulsara, who came to Yale in 2007, is one of a handful of neurosurgeons in the world who is dual-fellowship trained in both traditional cerebrovascular/skull base microsurgery and in endovascular neurosurgery, a minimally invasive method in which a catheter is inserted through a leg artery into the brain to treat aneurysms, strokes, tumors, and other ailments. Along with YNHH and medical device manufacturers, Bulsara agreed to donate his services to treat Tibeau.

At YNHH on April 26, Bulsara, guided by state-of-the-art imaging technology, threaded a catheter less than 1 millimeter wide from the femoral artery in Tibeau's thigh into the aneurysm, which had grown to a diameter of 2 centimeters and bordered on critical structures, including the optic nerve and pituitary gland. "Platinum coils about as fine as human hair were placed inside the aneurysm to allow it to clot," Bulsara says, adding that, until recently, the standard treatment for aneurysms such as Tibeau's involved opening the skull, clamping off the artery, and performing a bypass. "Without treatment the risk of this aneurysm bleeding within five years would be close to 50 percent. If the aneurysm bled, the chances of him being severely incapacitated or dead would be 30 to 50 percent."

Two days after the procedure Tibeau was sitting up in bed and joking with one of his nurses. He said he was feeling better and that his headaches had not recurred. Bulsara says he was glad to help, and attributed the successful outcome to close collaboration among colleagues in neurosurgery, anesthesia, radiology, intensive care, nursing, and surgical and radiological technologists. He says Tibeau was doing well, and that he expected he would make a full recovery.

"It can be difficult to find a hospital that can fix this kind of problem, let alone agree to do the surgery for free," says Sybill Hyppolite of PIH, who accompanied Tibeau from Haiti and served as his interpreter during his stay in New Haven. "We are very grateful to Yale and Dr. Bulsara for offering to do this case."

Must kicking the tobacco habit cause weight gain?


Marina Picciotto


Yann Mineur

Yale scientists have thrown new light on an ugly truth about smoking: though cigarettes can kill you, most smokers are thinner than their non-smoking peers. Many people take up smoking, or resist quitting, because nicotine lowers body weight.

"We have known for a very long time that some smokers use cigarettes to try to control their weight," says Marina Picciotto, PH.D., Charles B.G. Murphy Professor of Psychiatry and professor of neurobiology and pharmacology. "And we have now identified one of the molecular mechanisms underlying this effect."

A major subset of the brain's nerve cells are studded with "nicotinic" receptors, which activate the cells when coupled with nicotine molecules. Tobacco addiction is thought to result from the interaction of these neurons with other neural circuits that govern the brain's reward systems. But the physiological link between nicotine and weight loss has been poorly understood.

During research on the potential antidepressant effects of several nicotine-like drugs, some of which is reported in the current issue of *Behavioural Pharmacology*, Associate Research Scientist Yann S. Mineur, PH.D., M.SC., noticed that, like smokers, mice treated with the drug ate less than the control mice and gained less weight. The robustness of these effects hinted at a possible mechanism, and Mineur obtained a pilot grant from Yale's Transdisciplinary Tobacco Use Research Center to undertake further studies.

For this research, Picciotto and Mineur teamed up with Xiao-Bing Gao, PH.D., associate professor of comparative medicine, and Tamas Horvath, D.V.M., PH.D., the Jean and David W. Wallace Professor of Biomedical Research and chair of the Section of Comparative Medicine (see related story, page 2).

In the June 10 issue of *Science*, the group describes experiments demonstrating that a specific type of nicotinic receptor found on cells known as POMC neurons is the crucial trigger for nicotine's effects on eating and weight gain in the mice. When the scientists disabled this particular receptor, the mice ate as much as normal mice, even when given a nicotine-like drug.

POMC neurons are located in the hypothalamus, a brain region known to regulate feeding and metabolism, where they generate hunger and fullness cues that direct us when to seek food and when to put the fork down. "The interesting aspect of our finding," says Picciotto, "is that the receptors that are expressed in the POMC neurons are not the same ones that are responsible for nicotine reward."

Smokers are about 10 pounds lighter than non-smoking peers on average, but they gain weight once they've kicked the tobacco habit, which discourages many smokers from quitting. By understanding how to control nicotine receptors in the hypothalamus, Picciotto says, researchers may be able to develop a drug that would prevent weight gain for smokers trying to quit, and would perhaps be useful for the treatment of obesity in non-smokers as well. "It is possible," says Picciotto, "that a nicotinic medication could be one more tool to help motivate and assist those struggling with obesity to lose weight."

// FlaK *(from page 1)* the development of hereditary, early-onset forms of Alzheimer's disease. Ha, associate professor of pharmacology, hopes that knowledge of FlaK's structure will help shed light on presenilin's form and function, which in turn could reveal new opportunities to treat or prevent Alzheimer's in its more common forms.

"Presenilin is similar to FlaK—there's a suggested similarity between the structures," says Ha, who is senior author of the report of FlaK's structure published in *Nature* on July 28. "We have evidence to believe that they are evolutionarily very closely related."

This is the second time that the Ha team has solved a structure that had eluded other researchers. In a 2006 paper in *Nature*, Ha, then an assistant professor, and colleagues published the atomic structure of GlpG, a rhomboid protease that does its work within cell membranes. GlpG's unusual intramembrane hydrolytic activity is similar to that of gamma-secretase, a protein complex that cleaves amyloid precursor protein (APP) into the fragments that form insoluble plaques in the brains of patients with dementia. (Ha's lab is covering the waterfront in the Alzheimer's realm, having also done significant structural work on APP since 2004.)

No one has yet solved the structure of presenilin, but Ha says that comparisons of FlaK's structure with biochemical analyses of presenilin reveal three common segments that cross the cell membrane. He believes those segments are the site where APP is cleaved, the first enzymatic step down the long road that leads to Alzheimer's disease.

Ha's group solves structures using X-ray crystallography, the same technique Rosalind Franklin used to produce the images James Watson and Francis Crick relied on when they deciphered the double-helix structure of the DNA molecule in the 1950s.

The most painstaking part of X-ray crystallography is growing a pure crystal comprised of numerous copies of a molecule of interest, a trial-and-error process that requires great skill. For certain molecules, like the membrane proteins Ha's group studies, this process can take years. Once a suitable crystal is attained, it is mounted in an apparatus and exposed to a fine X-ray beam. Because crystals are orderly structures, the beam scatters in an orderly way. The resulting diffraction pattern, which provides an indirect glimpse of the electron density of various parts of the molecule under study, is captured by detectors for later analysis.

This procedure is repeated many times, with the crystal slightly rotated each time, until diffraction patterns have been obtained from all orientations of the crystal.

Finally, with the help of computers and whatever biochemical or other information may exist about their molecule, scientists begin the process of deriving a structure from their data. The end result depicts the position of every atom in the molecule in three dimensions.

The Ha group's new FlaK structure, a technical tour de force, is based on X-ray crystallography data obtained at a resolution of 3.6 angstroms; a sheet of paper is about 1 million angstroms thick.

Ha's also careful not to expect too much right away from the solving of FlaK's structure, and says it will require further research to make the leap from structure to function.

"I have a blueprint of a machine, but now we need to put gas in it and take it for a test drive," says Ha. "We'll be able to see if it's a car or if this is a plane that can fly."

To do this, Ha has been working with Jonathan A. Ellman, PH.D., Eugene Higgins Professor of Chemistry and professor of pharmacology. The two hope to gain additional structural information that will give them insights into how FlaK operates in cell membranes.

"We're developing and designing substrate-mimicking inhibitors to try to co-crystallize with FlaK to see how they interact," Ha explains. "This is the next step to understand how these structures work, and it will be a collaborative effort."

Ha was one of the first new faculty members hired by Joseph Schlessinger, PH.D., William H. Prusoff Professor of Pharmacology, when Schlessinger became chair of the Department of Pharmacology in 2001. Ha says Schlessinger's support and patience have been essential for those in his lab to complete the long-term research projects required in structural biology.

Solving FlaK's structure, the latest stroke of good fortune in Ha's lab, comes at a point in his career when he has adopted a measured response to scientific success: the years of work just completed have opened up many new avenues of research yet to be begun.

"If this had happened when I was a postdoc I would have been jumping up and down," he says. "It still excited me to be the first to produce this structure, but now I know how slow research can go—how many years it can take."

Grants and contracts awarded to Yale School of Medicine

September/October, 2010

Federal

Hervé Agaisse, NIH, *Host Factors Involved in* Listeria monocytogenes *Spread from Cell to Cell*, 9 months, $413,305 • **Sandra Alfano**, NIH, *Promoting and Developing Human Research Protection Programs in International Settings*, 1 year, $53,726 **Frederick Altice**, NIH, *Prison Interventions and HIV Prevention Collaboration*, 5 years, $2,195,538 **George Anderson**, Department of Defense, *Biomarkers for Autism and for Gastrointestinal and Sleep Problems in Autism*, 3 years, $472,129 **Marcus Bosenberg**, Department of Defense, *UVL, ROS, Pigmentation, Genetic Predisposition, and Epigenetic Gene Silencing in Melanoma*, 3 years, $381,886 • **Douglas Brash**, Department of Defense, *UVL, ROS, Pigmentation, Genetic Predisposition, and Epigenetic Gene Silencing in Melanoma*, 3 years, $540,363 • **Catalin Buhimschi**, NIH, *DAMP-RAGE Signaling and Fetal Injury in Inflammation-Induced Preterm Birth*, 5 years, $1,989,170 • **Lloyd Cantley**, NIH, *Center for Polycystic Kidney Research at Yale*, 5 years, $1,517,657 **Michael Caplan**, NIH, *Center for Polycystic Kidney Research at Yale*, 5 years, $2,621,551 **Sandy Chang**, NIH, *Telomere-Induced Senescence as a Suppressor of Tumorigenesis*, 2 years, $793,777 **John Chidlow**, NIH, *Physiological Regulation of Vascular Function by Mutant Caveolin-1*, 3 years, $143,670 • **Mark Cicero**, Health Resources and Services Administration/DHHS, *Small Victims, Big Challenges: Refining Pediatric Disaster Triage Education and Assessing Triage Algorithms in the Pre-hospital Setting*, 3 years, $852,415 • **Robert Constable**, NIH, *Null Spacing Imaging: A Novel Approach to Accelerating MR Imaging*, 5 years, $3,461,146 • **Larry Davidson**, NIH, *Effectiveness and Cost-Effectiveness of Peer Mentors in Reducing Hospital Use*, 4 years, $3,701,164 • **Isabelle Derre**, NIH, *Identification of Human Host Factors Involved in Chlamydia Development*, 2 years, $455,229 • **Francesco D'Errico**, National Science Foundation, *Superheated Emulsions for Nuclear Material Detection*, 1 year, $389,180 • **James Duncan**, NIH, *Extraction of Functional Subnetworks in Autism Using Multimodal MRI*, 1 year, $384,865 • **John Elsworth**, NIH, *Dopamine Modulation of Cortical Spine Synapses and Cognition in MPTP Monkeys*, 5 years, $2,338,028 • **Richard Flavell**, NIH, *Understanding Hematopoietic Neoplasias using Humanized Mice*, 5 years, $5,444,073 **Amanda Foust**, NIH, *Optical Imaging of Information Processing in CNS Axons*, 3 years, $115,840 **Thomas Gill**, NIH, *Epidemiology of Disability and Recovery in Older Persons*, 5 years, $4,503,758 **Bonnie Gould Rothberg**, NIH, *Prognostic Markers in Metastatic Melanoma*, 5 years, $530,195 **Eduardo Groisman**, NIH, *Regulation of* Salmonella *Virulence by the PhoP Protein*, 6 months, $248,250; NIH, *Molecular and Functional Analyses of the PMRA/PMRB Regulatory System*, 3 years, $997,641 • **David Hafler**, NIH, *Regulatory T Cells in Autoimmune Disease*, 1 year, $848,779 **Ruth Halaban**, Department of Defense, *UVL, ROS, Pigmentation, Genetic Predisposition, and Epigenetic Gene Silencing in Melanoma*, 3 years, $273,752 • **Robert Heimer**, NIH, *Influences on HIV Prevalence and Service Access among IDUs in Russia and Estonia*, 5 years, $1,775,423 • **Kevan Herold**, NIH, *Human and Translational Immunology*, 5 years, $1,043,354; NIH, *Innate and Adaptive Immune Responses in Pre–Type 1 Diabetes*, 2 years, $399,089 • **Raimund Herzog**, NIH, *Adaptations of Brain Energy Metabolism to Hypoglycemia*, 5 years, $776,520 • **Christopher Hoimes**, Department of Defense, *Engineered Histone Deacetylase Inhibitor Nanoparticles for Durable Suppression of Androgen Receptor Target Genes in Prostate Cancer*, 2 years, $119,792 • **Tamas Horvath**, NIH, *Hypothalamic AgRP Neurons are Determinants of Healthy Lifespan and Higher Brain Functions*, 5 years, $4,130,467 • **Leora Horwitz**, NIH, *Heart Failure Readmissions in Older Adults: A Systems Perspective*, 4 years, $648,465 • **Akiko Iwasaki**, NIH, *Antiviral CTL Mobilization to the Genital Mucosa*, 2 months, $403,434 • **Kenneth Kidd**, Department of Justice, *Developing a Forensic Resource/Reference on Genetics Knowledge Base*, 2 years, $643,771 • **In-Jung Kim**, NIH, *Molecular Specification of Direction Selectivity in the Visual System*, 3 years, $747,000 • **Peter Krause**, Centers for Disease Control and Prevention/DHHS, *Lyme Disease Reduction Via Deer-Targeted Interventions*, 1 year, $95,000 • **Harlan Krumholz**, NIH, *Center for Cardiovascular Outcomes Research at Yale University*, 4 years, $6,817,443 • **Chandrika Kumar**, Health Resources and Services Administration/DHHS, *Medical Resident Rotation in Ambulatory Geriatrics*, 5 years, $374,955 • **Robert Leeman**, NIH, *Difficulties with Self-Control and High-Risk Alcohol Use in Young Adults*, 5 years, $750,033 • **Judith Lichtman**, Centers for Disease Control and Prevention/DHHS, *Cardiovascular Disease Trends in Elderly*, 8 months, $45,000 **Haifan Lin**, NIH, *Toward a Central Question on Epigenetics: A Major Epigenetic Programming Mechanism Guided by piRNAs*, 5 years, $4,150,417 **Elias Lolis**, NIH, *Crystal Structures of CXCR4 Complexed to CXCL12*, 2 years, $455,125 • **Shuangge Ma**, NIH, *Novel Methods for Integrative Analysis of Cancer Genomic Data*, 4 years, $1,344,185 • **Ruslan Medzhitov**, NIH, *Integration of Cytokine Receptors and Immunoreceptors Signaling Pathways*, 1 year, $413,750 • **Joshua Motelow**, NIH, *Subcortical Control of Neocortical Slowing During Focal Hippocampal Seizures*, 3 years, $138,225 **Terrence Murphy**, NIH, *Enhanced Evaluation of Second Stage Translational Research (EESTR)*, 9 months, $232,001 • **Rafael Perez-Escamilla**, NIH, *Stress Management Among Latinos with Type 2 Diabetes*, 5 years, $1,725,273 • **Scott Rivkees**, NIH, *Graves' Disease Therapy Risks to Mother and Fetus*, 4 years, $2,562,440 • **Carla Rothlin**, NIH, *TAM Receptor Tyrosine Kinases in Inflammatory Bowel Disease*, 4 years, $1,632,874 • **Gerald Shulman**, NIH, *Genetic and Cellular Mechanisms of NAFLD and Hepatic Insulin Resistance*, 5 years, $7,143,910 **Albert Sinusas**, NIH, *Training in Multi-Modality Molecular and Translational Cardiovascular Imaging*, 5 years, $1,182,836 • **Megan Smith**, Department of Health and Human Services, *New Haven Mental Health Outreach for Mothers (MOMS) Project 4*, 1 year, $100,000 • **Dieter Söll**, Department of Energy, *Engineering Selenoproteins for Enhanced Hydrogen Production*, 3 years, $581,935 • **Stefan Somlo**, NIH, *Center for Polycystic Kidney Research at Yale*, 5 years, $1,529,318 **Sandra Springer**, NIH, *Naltrexone for Opioid Dependent Released HIV+ Criminal Justice Populations*, 5 years, $4,213,200 • **Eugene Swenson**, NIH, *Investigation of the Liver Progenitor Cell Niche Using CK19 Lineage Tracing*, 2 years, $165,500 **Michal Tal**, NIH, *A Role for Autophagy in Cytosolic Viral Recognition and Aging*, 2 years, $67,480 **Mary Tinetti**, Agency for Healthcare Research and Quality/DHHS, *Beta-Blocker Effect on a Range of Health Outcomes in Older Adults with CAD and COPD*, 1 year, $361,109 • **Adam Trexler**, NIH, *Single-Molecule Fluorescence to Characterize Alpha Synuclein Transition to Toxic Oligomeric States*, 2 years, $82,760 • **Xiao-Jing Wang**, NIH, *CRCNS: Uncovering Neural Circuit Mechanisms of Category Computation and Learning*, 5 years, $1,664,436 **Scott Weatherbee**, NIH, *Center for Polycystic Kidney Research at Yale*, 5 years, $82,750 • **John Wysolmerski**, NIH, *PTHrP in Mammary Development*, 4 years, $1,406,750 • **Xiaoyong Yang**, NIH, *O-GlcNAc Modification in Metabolic Homeostasis*, 5 years, $2,068,750 • **Hongyu Zhao**, NIH, *Loss-of-Function Variants in the 1000 Genomes Data Set and Implications for GWAS*, 2 years, $732,963

Non-federal

Nancy Angoff, American Medical Association Foundation, *Food, Medicine, and Wellness Event*, 7 months, $400 • **Richard Belitsky**, Gilead Foundation, *HAVEN Primary Care Clerkship*, 1 year, $69,382 • **Benjamin Blagogee**, American College of Occupational and Environmental Medicine, *Injury and Return to Work Issues among Truck and Bus Drivers*, 1 year, $35,439 • **Hal Blumenfeld**, Children's Hospital (Cincinnati), *Impact of Initial Therapy and Response on Long-Term Outcome in Children with CAE*, 1 year, $8,801 • **Angelique Bordey**, Connecticut Innovations, Inc., *Mechanical Control of Neural Stem Cell Fate*, 4 years, $928,954 • **Elizabeth Bradley**, Bill and Melinda Gates Foundation, *Diffusion, Dissemination and Widespread Take up: What Works?*, 1 year, $362,571; Doris Duke Charitable Foundation, *Global Health Leadership Institute Conference*, 1 year, $25,000 • **Peter Broer**, Plastic Surgery Educational Foundation, *The Role of Leptin in Calciphylaxis*, 1 year, $9,500 • **Ketan Bulsara**, Micrus

// Leof *(from page 1)* "When I went to my internship, Redlich said, 'You're going to be a psychiatrist, and consider this a declaration of intention.'" Redlich then promised Leof a residency at Yale following his public health commission. Though Leof chose the University of California-San Francisco instead, he has indeed spent his life in psychiatry.

The Leofs' decision to support students with distinction in the arts and humanities stems from lifelong passion. David Leof says his medical training was enhanced by many trips to see a friend's workshop productions at the Yale School of Drama and time spent at the School of Art and Architecture (as it was then called). A year in London as a James Hudson Brown Fellow was another highlight of his Yale years, he says. In addition to walking the wards, rowing, and playing rugby for St. Thomas's Hospital Medical School, Leof completed a seminal research project, mapping out for the first time the innervation of the human lung, and published the results in the *Journal of Anatomy* in 1964.

Colleen Leof is an accomplished artist whose work has appeared in numerous solo and group exhibitions and is part of private collections around the world.

Richard Belitsky, M.D., Harold W. Jockers Associate Professor of Medical Education, deputy dean for education, and associate professor of psychiatry, says, "This gift supports and acknowledges the notion that the study of the humanities and the arts is a worthwhile and valuable part of the preparation for becoming a caring, compassionate, and skilled physician."

From David Leof's perspective, "It only seemed morally right that the bulk of my estate—which was created by me being a physician, which was created by Yale—should be returned to Yale."

// Medzhitov *(from page 1)* published the results of seminal experiments in the journal *Nature* showing that TLRs provide the adaptive immune system with the necessary information to create custom-made B and T cells that target specific bacterial or viral invaders.

Since then, TLRs have become the subject of intense research activity in laboratories around the world. Because of their ability to potently stimulate adaptive immune responses, TLRs are promising drug targets.

Medzhitov shares the prize with Jules A. Hoffman, PH.D., director of the Institute of Molecular and Celluar Biology at the University of Strasbourg, France, and president of the French Academy of Sciences, and Bruce A. Beutler, M.D., founding director of the new Center for the Genetics of Host Defense at UT Southwestern Medical Center in Dallas, Texas.

TLRs were discovered in fruit flies, in which they were believed to serve only a developmental role, but Hoffman showed TLRs also acted as immune sensors in insects. Beutler demonstrated that the receptor identified by Janeway and Medzhitov, now known as TLR4, acts by detecting distinctive molecular patterns in the outer membranes of bacteria.

"I am delighted that The Shaw Prize has recognized Ruslan Medzhitov's outstanding research," says Robert J. Alpern, M.D., dean and Ensign Professor of Medicine. "Ruslan demonstrated the role of the innate immune response in the adaptive response and then identified the mechanism by which this occurs."

Medzhitov has received many honors for his large body of work. Last year, he won the Lewis S. Rosenstiel Award for Distinguished Work in Basic Medical Research. Medzhitov was also elected last year to the National Academy of Sciences, the elite corps of scientific advisors selected from the nation's top institutions.

The Shaw Prizes, international honors that carry a monetary award of $1 million (U.S.), are given by the Hong Kong-based Shaw Prize Foundation for achievement in the life sciences, astronomy, and mathematics. Established in 2002 by filmmaker and philanthropist Run Run Shaw, the awards are "dedicated to furthering societal progress, enhancing quality of life, and enriching humanity's spiritual civilization." Medzhitov will receive the award in Hong Kong in September.

Medzhitov was born in 1966 in Tashkent, Uzbekistan, then part of the Soviet Union. He received his undergraduate education at Tashkent State University and obtained his PH.D. from Moscow State University in 1993. Medzhitov first came to the School of Medicine in 1994 as a postdoctoral fellow in Janeway's laboratory. He was named assistant professor in 1999 and professor in 2003.

"I am very honored to be a recipient of this prestigious award," Medzhitov says. "Awarding this prize in the field of innate immunity is a reflection of the great advances made by many investigators in the field."

Endovascular Corporation, *Micrus PAC Trial: Evaluation of Presidio and Cerecyte Coils in Large and Giant Aneurysms*, 1 year, $21,790 • **Herta Chao**, William O. Seery Foundation, *Imaging the Effects of R-CHOP Chemotherapy on Cognitive Function in Patients with CD20-Positive High-Grade Lymphoma*, 1 year, $68,000 • **Ee-Chun Cheng**, Connecticut Innovations, Inc., *The Role of Epigenetic Factor HP1 in Regulating Human Embryonic Stem Cell Pluripotency and Differentiation*, 2 years, $200,000 • **Daniel Colón-Ramos**, Alfred P. Sloan Foundation, *Molecular Factors Directing Synaptic Specificity in the* C. elegans *Brain*, 2 years, $50,000 • **Sukru Emre**, University of Texas Southwestern Medical Center at Dallas, *A Multi-Center Group to Study Acute Liver Failure*, 1 year, $95,153 • **Adrienne Ettinger**, University of New Mexico, *A Prospective Birth Cohort Study Involving Uranium Exposure in the Navajo Nation*, 1 year, $24,908 • **Richard Flavell**, U.S.-Israel Binational Science Foundation, *Elucidation of Leptin's Immuno-modulatory Effects on the Gastrointestinal Immune Response*, 2 years, $49,700; Connecticut Innovations, Inc., *Characterization of Human Hematopoiesis* in vivo *in an Improved Model of Humanized Mice Engrafted with Embryonic Stem Cell-Derived Hematopoietic Stem Cells*, 5 months, $1,000,000; Bill and Melinda Gates Foundation, *A Mouse Model for Human Malaria Infection*, 2 years, $2,983,165 • **Richard Formica**, Mount Sinai School of Medicine, *Individualizing Therapy for Kidney and Heart Transplant Recipients*, 1 year, $190,850 • **Gigi Galiana**, L'Oréal USA, *Faster MRI with a B1 Accelerated Reconstruction Sequence* (*BARS*), 1 year, $60,000 • **Xiao-Bing Gao**, Foundation for Prader-Willi Research, *MCH Neurons in Prader-Willi Syndrome Animal Models*, 1 year, $50,000 • **Xin Quan Ge**, Connecticut Innovations, Inc., *The Role of Dormant Organs in Ensuring Genome Integrity in Human Embryonic Stem Cells*, 2 years, $200,000 **Joel Gelernter**, Medical University of South Carolina, *Exploration of GxE Interactions for PTSD in Disaster-Affected Youth*, 1 year, $104,006 • **Frank Giordano**, Angion Biomedica Corp., *SBIR: A Phase II Pilot Study to Evaluate the Safety and Activity of BB3 as an Adjunct to Percutaneous Coronary Intervention (PCI) in Subjects Presenting with Acute ST Segment Elevation MI (STEMI)*, 2 years, $1,188,559 **John Giuliano Jr.**, Children's Hospital of Philadelphia, *Multi-Center NEAR4KIDS*, 7 months, $1,000 • **Daniel Greif**, Pulmonary Hypertension Association, *Morphogenesis of the Pulmonary Artery Smooth Muscle Layer*, 3 years, $203,521 **Cary Gross**, Dana Farber Cancer Institute, *Accountability and the Role of the Principal Investigator in Multicenter Trials*, 9 months, $15,925 **Caren Gundberg**, Rensselaer Polytechnic Institute, *Effects of Osteocalcin and Osteopontin on Damage Morphology and Bone Fragility*, 5 years, $209,314 • **David Hafler**, Brigham and Women's Hospital, *Project 4 Analysis of Pathogenic T Cell Response in MS*, 1 year, $62,755; Dana Farber Cancer Institute, *Antigen Presentation in Human Autoimmune Diseases* (*Project 4*), 1 year, $332,868; Massachusetts Institute of Technology, *Analytical Microtools for Discovering Autoreactive Lymphocytes*, 1 year, $133,500; University of California, San Francisco, *A Haplotype Map for Multiple Sclerosis*, 7 months, $116,200 • **Lyndsay Harris**, Breast Cancer Research Foundation, *Biomarker Incubator to Define and Validate Predictors of Response to Paclitaxel and Trastuzumab*, 1 year, $222,982 • **Erica Herzog**, American Thoracic Society, *Semaphorin 7A and Alternative Macrophage Activation in IPF*, 2 years, $100,000 **Raimund Herzog**, Rockefeller University, *The Role of GSAP in the Pathophysiology of Type 2 Diabetes Mellitus*, 7 months, $15,000 • **Theodore Holford**, Pacific Institute for Research and Evaluation, *Lung Cancer Group for NCI's CISNET Program*, 1 year, $79,314 • **Leora Horwitz**, American Federation for Aging Research, *AFAR*, 4 years, $99,968 **Changyun Hu**, Juvenile Diabetes Research Foundation International, *Anti-CD20 and Oral Anti-CD3 Prevents and Reverses Diabetes in NOD Mice*, 3 years, $246,048 • **Steven Kleinstein**, U.S.-Israel Binational Science Foundation, *Modeling Competition and Genetic Diversification in Adaptive Immunity*, 4 years, $82,350; Mount Sinai School of Medicine, *Program for Research on Immune Modeling and Experimentation* (*PRIME*), 5 years, $1,284,931 • **Diane Krause**, Connecticut Innovations, Inc., *Use of Human Embryonic Stem Cells and Inducible Pluripotent Stem Cells to Study Megakaryoblastic Leukemia*, 3 years, $2,000,000 **Gary Kupfer**, U.S.-Israel Binational Science Foundation, *Analysis of Congenital Dyserythropoietic Anemia* (*CDA*) *Through Creation and Manipulation of Patient-Derived Induced Pluripotent Stem Cells*, 4 years, $53,500 • **Alexandra Lansky**, Nakuuruq Solutions, LLC, *Women's Heart Health Awareness*, 1 year, $127,500 • **Eun Jung Lee**, Connecticut Innovations, Inc., *Maturation of Human Embryonic Stem Cell (hESC)-Derived Cardiomyocytes* In Vivo *Using 3D Engineered Tissue Model System*, 2 years, $200,000 • **Ben Lin**, American Society of Echocardiography, *Analysis of Regional Myocardial Strain and Vortical Flow Dynamic as Predictors of Left Ventricular Remodeling after Infarction*, 1 year, $35,000 • **Haifan Lin**, Ellison Medical Foundation, *piwi-piRNA Mechanism in Maintaining Genome Integrity and Longevity*, 4 years, $993,000 • **Shuangge Ma**, University of Texas Southwestern Medical Center at Dallas, *Predicting Adjuvant Chemotherapy Responses in Lung Cancer*, 5 months, $20,159 • **Robert Makuch**, IMD Marketing Consulting Co., Ltd., *Yale University: Crisis Management Training*, 2 months, $49,800; IMD Marketing Consulting Co., Ltd, *Yale University: Hospital Management Training*, 1 year, $22,025 • **Pramod Mistry**, National Gaucher Foundation, *Mechanism of Gaucher Disease in a New Conditional KO Mouse Model of Type 1 Gaucher Disease*, 1 year, $70,000 • **Gil Mor**, U.S.-Israel Binational Science Foundation, *Preparation of the Uterus for Implantation*, 4 years, $32,000 **Angus Nairn**, Rockefeller University, *Functional Analysis of Signaling Proteins in Dendritic Spines*, 5 years, $1,298,988 • **Don Nguyen**, V Foundation for Cancer Research, *Tumor–Microenvironment Interactions That Regulate the Therapeutic Response of Lung Cancer Brain Metastasis*, 2 years, $200,000 • **Elaine O'Keefe**, Boston University, *CT Partnership for Public Health Workforce Development*, 5 years, $700,000 • **Efrat Oron**, Connecticut Innovations, Inc., *Molecular Mechanisms of Germ Layer Induction in Human Embryonic Stem Cells*, 2 years, $200,000 • **Michael Paidas**, Talecris Biotherapeutics, Inc., *Antithrombin Levels Preceding Placenta-Mediated Complications*, 1 year, $236,460 • **Lori Post**, Michigan State University, *Health Information Technology to Prevent Abuse, Neglect, and Exploitation*, 1 year, $83,906 **Caihong Qiu**, Connecticut Innovations, Inc., *Regulations of Lin28 in Human Embryonic Stem Cell Self-renewal and Differentiation*, 3 years, $750,000; Connecticut Innovations, Inc., *Efficient Gene Targeting in Human Embryonic Stem Cells via Recombineering-Based Long Arm Targeting Vector*, 2 years, $200,000 • **Peter Rabinowitz**, Mary Imogene Bassett Hospital, *Infection Risk in Swine Workers*, 1 year, $14,999 • **David Rimm**, University of Michigan, *Automated Quantitated Analyses of Epidermal Growth Factor Receptor, HER2, HER3, HER4, and PTEN in N9831 Primary Breast Tumors Using Tissue Microarrays*, 1 year, $50,000 • **Lawrence Rizzolo**, Connecticut Innovations, Inc., *Co-Differentiation of KESC-Derived Retinal and Retinal Pigment*, 3 years, $832,608 **Matthew Rodeheffer**, Connecticut Innovations, Inc., *Identification and Characterization of Multipotent Cell Populations from Human Adipose Tissue for Application in Regenerative Therapies*, 2 years, $200,000 • **Erik Shapiro**, Connecticut Innovations, Inc., In Vivo *Evaluation of Human ES, IPS and Adult Brain–Derived Neural Progenitor Cell Transplantation and Migration Using MRI*, 2 years, $200,000 • **Gordon Shepherd**, University of California, San Diego, *Operation, Support, and Enhancement of Neuroscience Information Framework*, 1 year, $214,000 • **Arthur Simen**, American Foundation for Suicide Prevention, *Prefrontal and Genetic Determinants of Suicidality and Depression in the Elderly with Cardiac Disease*, 2 years, $75,000 • **Dieter Söll**, Boston University, *2-Selenouridine Formation in Archaea*, 1 year, $16,550 **Serena Spudich**, Washington University in St. Louis, *Neurological AIDS Research Consortium*, 1 year, $33,100 • **Stephen Strittmatter**, Association for Frontotemporal Dementias, *Imaging the Role of Progranulin Interaction with Sortilin in Fronto-Temporal Lobar Degeneration*, 1 year, $60,000 • **Scott Strobel**, Howard Hughes Medical Institute, *Rainforest Expedition and Laboratory: Engaging Undergraduate Students in Research Through Project Ownership*, 4 years, $600,000 • **Joann Sweasy**, University of Vermont, *Structure and Function of DNA Repair Enzymes*, 5 years, $251,840 • **William Tamborlane**, Juvenile Diabetes Research Foundation International, *InsuPatch: A Novel Approach to Accelerate Insulin Absorption and Action*, 1 year, $585,341 **Mary Tinetti**, Research Foundation for Mental Hygiene, *Health and Aging Policy Fellows Application*, 1 year, $132,000 • **Li Wen**, Juvenile Diabetes Research Foundation International, *Role of Intestinal Segmented Filamentous Bacteria in Diabetes Development*, 1 year, $110,000 • **Herbert Yu**, Albert Einstein College of Medicine, *Serum Levels of EGFR-Signaling-Network*, 1 year, $65,080

School of Public Health leader begins second five-year term

Paul D. Cleary, PH.D., has been reappointed by Yale President Richard C. Levin as dean of the Yale School of Public Health (YSPH) and chair of the Department of Epidemiology and Public Health at the School of Medicine.

Cleary, the Anna M.R. Lauder Professor of Public Health, began his second five-year term on July 1.

In a letter to the YSPH community announcing the reappointment, Levin wrote that "faculty, staff and students enthusiastically support Dean Cleary's reappointment, noting his commitment to public health, his clear vision for the school, and the school's steadily upward trend during his tenure."

During Cleary's first term, applications for admission to YSPH's Master of Public Health (M.P.H.) program have increased 30 percent, to a record number of 1,049 applications in 2010. In September 2009, the program's new Global Health Concentration admitted its first cohort of students, and in 2010 it accounted for 27 percent of M.P.H. applicants. The school's faculty and doctoral program have been ranked by the National Research Council as among the finest in the nation.

The school has also expanded its research portfolio under Cleary's direction, especially in cancer prevention, one of the school's core areas of focus. YSPH researchers are studying links between nutrition and exercise and several cancers, including lung, mouth and throat, esophageal, stomach, breast, and ovarian cancers.

In addition, Cleary has strengthened the school's ongoing research on global infectious diseases. Faculty at YSPH are conducting important studies of many diseases and disease agents including leptospirosis, Lyme disease, babesiosis, African trypanosomes, hantavirsus, leishmaniasis, and HIV. These investigations are aimed at preventing infection and reducing the negative consequences of disease in vulnerable and underserved populations.


Paul Cleary

Cleary has developed and expanded YSPH's public health service and practice activities, including a new Office of Community Health at YSPH that has created a sustainable model for community service focused on programs to improve the health of New Haven–area residents. In another example of regional engagement, the school has established the Community Alliance for Research and Engagement (CARE), a collaboration with the Yale Center for Clinical Investigation and the City of New Haven's mayor's office, school system, and community organizations.

The school is also deeply involved in the Yale Global Health Initiative, which has developed a strategy for engaging a broader group of scholars at Yale who are making major contributions to global health research and education.

"Equal access to quality health care is essential for disease prevention and health promotion for every individual around the world. Faculty, staff, and students are actively engaged in the study of health disparities, health care quality, access and delivery, and public and private policy in this country and across the globe," said Levin. "Yale is fortunate to have Paul Cleary leading the School of Public Health, and I know you join me in thanking him for his willingness to serve for a second term."

Awards & Honors

Marie E. Egan, M.D., associate professor of pediatrics and of cellular and molecular physiology, has won the Hartwell Individual Biomedical Research Award for her research on the use of nanoparticles to treat cystic fibrosis (CF). The award, given to twelve scientists per year, includes a grant of $100,000 per year for three years. The technique Egan is investigating involves replacing short fragments of DNA in the gene responsible for CF, to correct a known mutation in the common genetic disease. CF affects the entire body and can cause early death.

Megan C. King, PH.D., assistant professor of cell biology, has been named one of fifteen Searle Scholars for 2011. The Searle Scholars Program was founded in 1980 and is funded through the Searle Funds at the Chicago Community Trust. The program makes grants to selected institutions to support the independent research of young scientists in the chemical and biological sciences who have recently been appointed as assistant professors on a tenure-track appointment. King will receive a grant of $300,000 over three years.

Robert S. Sherwin, M.D., the C.N.H. Long Professor of Medicine, chief of the Section of Endocrinology, and director of the Yale Center for Clinical Investigation and the Diabetes Endocrinology Research Center, has received the American Diabetes Association's Albert Renold Award. The award honors outstanding achievements in the training of diabetes research scientists and the facilitation of diabetes research. Sherwin directed Yale's training program in diabetes and metabolism for 26 years, and has mentored nearly 100 research trainees, many of whom have gone on to achieve successful academic careers.

Leading researcher on egg development named C.N.H. Long Professor of Genetics

Lynn Cooley, PH.D., an authority on oogenesis (egg development), has been named C.N.H. Long Professor of Genetics. Also professor of cell biology and of molecular, cellular, and developmental biology, Cooley studies the cellular mechanisms of oogenesis.


Lynn Cooley

Using the fruit fly *Drosophila melanogaster* as a model system, Cooley and those in her laboratory study the formation of egg chambers in which oocytes develop, the flow of information and nutrients from nurse cells to oocytes, changes in the cytoskeleton during egg development, and the role of ovarian muscles in the progression of developing egg chambers. Cooley's research in *Drosophila* highlights the central role of intercellular bridges in the formation of animal gametes, including in humans, and the importance of dynamic cytoskeletal remodeling during development.

Cooley is also director of Yale's Combined Program in the Biological and Biomedical Sciences. She earned her B.A. at Connecticut College and her PH.D. at the University of Texas-Austin, based on research conducted in the Yale laboratory of Dieter G. Söll, PH.D., Sterling Professor of Molecular Biophysics and Biochemistry and professor of chemistry. She began her research on oogenesis during a postdoctoral fellowship at the Carnegie Institution of Washington, in Baltimore, Md.

Among Cooley's many distinctions is a Pew Scholar Award from The Pew Charitable Trusts.

Authority on stress and addiction is named Foundations' Fund Professor of Psychiatry

Rajita Sinha, PH.D., has been appointed as Foundations' Fund Professor of Psychiatry. Sinha is director of the Yale Stress Center, established in 2007 with a $23 million grant from the National Institutes of Health (NIH). The interdisciplinary center brings together scientists to study the effects of stress on motivated behaviors such as excessive cigarette smoking, alcohol use, and high-calorie food consumption, with the aim of improving health outcomes related to these maladaptive behaviors.


Rajita Sinha

In her own research, Sinha has shown how stress and adversity increase desire for addictive substances such as alcohol, illicit drugs, and high-fat foods, and how chronic use of these substances and/or obesity alter biological stress responses, promoting craving and compulsive seeking of these substances. Her work is leading to new treatment strategies that target changes in stress, emotion, and craving responses.

Sinha holds a PH.D. from the University of Oklahoma Health Sciences Center and earned a respecialization in clinical psychology at Yale in 1992. She has served as director of addiction services at the Connecticut Mental Health Center and is chief of the Section of Psychology in the Department of Psychiatry. Her honors include an Independent Scientist Award, an Interdisciplinary Women's Health Research Scholar Award, and a Women's Health Research Scholar Award, all from the NIH. Sinha is an elected member of the College of Problems on Drug Dependence and the International Society for Psychoneuroendocrinology.

Expert in vascular biology, advocate for translational medicine is Ensign Professor

Jordan S. Pober, M.D., PH.D., who studies the role of the vascular endothelium in immune and inflammatory responses, has been named Ensign Professor of Immunobiology.

Pober was a student in the School of Medicine's M.D./PH.D. Program in the 1970s, completing his first year of residency in pathology at Yale-New Haven Hospital. He held a postdoctoral fellowship at Harvard University, completed his pathology training at Brigham and Women's Hospital, and taught at Harvard Medical School. Pober returned to Yale in 1991 as professor of pathology and immunobiology and director of the Boyer Center for Molecular Medicine's Molecular Cardiobiology program. In 1998 he became a professor of dermatology.


Jordan Pober

Pober is vice chair of the Department of Immunobiology for its Section of Human and Translational Immunology, and director of the interdepartmental Human and Translational Immunology program. He has been named a Searle Scholar, an Established Investigator of the American Heart Association, and a MERIT awardee of the National Heart, Lung, and Blood Institute. He has served as president of the North American Vascular Biology Organization and the co-founder and co-director of the Joint Yale-Cambridge University Biomedical Research Program.

In 2010 Pober was the Russell Ross Memorial Lecturer in Vascular Biology at the American Heart Association's national meeting. This year, he was elected to the Association of American Physicians and won the Rous Whipple Award from the American Society of Investigative Pathology.