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 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 has eluded other scientists.

Innate immunity pioneer receives international prize

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., received the 2011 Shaw Prize.

Medicine@Yale

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.

A summer spent in science

More than a hundred high school students joined School of Medicine labs this summer for hands-on, real-world science internships.

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Medicine@Yale
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 came immediately to Yale.”

At the medical school Horvath worked with fellow Hungarian Csaba Larenth, 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 1600s, 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.”

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 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, 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 related 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 colongraphy 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.

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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 deblitting 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. L. Natoff, 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 treatments.

“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., Ph.D., associate professor of psychiatry and neurobiology, and Michael H. Bloch, M.D., assistant professor in the Child Study Center, found that opioid prescriptions filled by pharmacies quadrupled, and sales doubled between 2002 and 2006. Moreover, between 2002 and 2009 the number of new recreational users of opioids increased 19 percent, to 2.1 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.

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 when exposed to light.

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, M.D., 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. Arumten, Ph.D., professor of neurobiology. In Arumten’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 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.”

We’ve exceeded our goals—thanks to you!

June 30, 2011 marked the successful conclusion of the medical school’s Medicine>>Tomorrow campaign. The effort resulted in gifts and commitments to the School of Medicine totaling $583 million—surpassing our original goal of $570 million—from alumni, friends, patients, corporations, and foundations.

We are grateful to everyone who stepped up to support our missions of research, education, and clinical care.

WHAT DID THOSE GIFTS ACCOMPLISH?

Facilities: Helped to build the Smilow Cancer Hospital at Yale-New Haven Faculty support: Provided support for 17 new professorships and seven new Yale Scholar endowments Education: Funded enhanced experiences for our students here and around the globe

Financial aid: Created 27 new endowed scholarship funds to assist students pursuing M.D., Ph.D., M.P.H., and P.A. degrees

Donor restricted current use ($22m)
Unrestricted current use ($64m)
Unrestricted current use ($64m)

MEDICINE TOMORROW
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, 36 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 Amberg, Sumayya Ahmad, Elie Balesh, Isaac Benowitz, Larissa Chiuilli, Jessica Crawford, Nicole Cabbad, and Noah Capurse marched in the annual Commencement procession.

2. Bhikhav 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.


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.

June 23, 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 W. 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.

3. From left) Christine Durancon, 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.

4. (From left) Tricia Gibbs, M.D. ’97; 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.

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 the PKD1 gene underlie not only ADPKD, but also other polycystic conditions as well.

Nephrology, shows that polycystin-1 (PC1), a central player in a five-gene network that underlies not only ADPKD, but also other polycystic diseases as well.

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 ADPKD, 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 PCs in the process. When the researchers administered drugs that inhibit proteasomes—some of which have shown promise as cancer treatments—PC1 levels rise 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.”
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

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 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, 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 neuromodulation and skull base surgery at Yale-New Haven Hospital (YNNH). Bulsara, who came to Yale in 2007, is one of a handful of neurosurgeons in the world who is dual-division 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 YNNH and medical device manufacturers, Bulsara agreed to donate his services to treat Tibeau. At YNNH 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 Sybil 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?

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 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).

Picciotto is a member of Yale’s cell biology program, which focuses on how nicotine affects the brain. “We have known for a very long time that some smokers use cigarettes to control their weight,” says Mineur. “Studies have shown that nicotine causes weight loss in mice.” But scientists have lacked details on the molecular underpinnings of this weight loss. Picciotto and Mineur have now found that a specific type of nicotinic receptor controlling the brain’s reward systems. They identified a specific type of nicotinic receptor found on cells called 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 to pound cigarettes 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 which would 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.”

Could digestive woes be contagious?

Tapping down expression of the fruit fly gene indy improves mitochondrial function, mimicking the beneficial 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 Molecular Pharmacology, knocked out minyD, a mammalian version of the gene. As reported in the August 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.

“MinyD 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.

Diet, diabetes, and a gene called minyD

ADVANCES

Health & Science News

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 equilib-rium is out of whack, sentinel proteins called NLVs can detect tissue damage. If activated, NLVs 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 NR6P6 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 similarity altered microbiome and propensity for inflammation was picked up by normal mice housed with NR6P6-deficient mice. Indeed, in the face of the June 2006 transmission from a susceptible mouse to an ostensibly normal one has potentially profound implications for IBD and other human diseases in which micro- biota contribute,” says Flavell.
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 synchrotron, an instrument that uses a high-powered electron gun to fire a beam of electrons at a crystal. 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.

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 DNA molecules in the early 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.

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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 Medzhitov a residency at Yale following his public with Commis- sion. Though Medzhitov chose the University of California-San Francisco instead, he has since spent his life in psychiatry.

The Leois’ decision to support students with distinction in the arts and humanities stems from lifelong passion. David Leois says his medical training was enhanced by many trips to see a friend’s workshop produc- tions at the Yale School of Drama and time spent at the School of Art and Architecture (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 Medico School, Leois completed a seminar 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 Leois is an accomplished artist whose work has appeared in numerous solo and group exhibi- tions and is part of private collections around the world.

Richard Belinsky, M.D., Harold W. Jockers Associate Professor of Medical Education, deputied for education, and associate professor of psychiatry, says, “This gift supports and acknowled- edges the notion that the study of the humanities and the arts is a worthwhile and valuable part of the preparation for becoming a compassionate, and skilled physician.” From David Leois’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 shares the prize with Jules A. Hoffman, Ph.D., director of the Institute of Molecular and Cellular 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 Genes 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 act as immune sensors in insects. He demonstrated that the receptor identi- fied by Janeway and Medzhitov, now known as TLR4, acts by detecting dis- tinctive 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 adaptive immunity is furthered.”

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 honored last year by the National Academy of Sciences, the elite corps of scientists 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 Founda- tion 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 contributing to the civilization.” Medzhitov will receive the award in Hong Kong in September.

Medzhitov was born in 1966 in Tash- kent, 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 labora- tory. He then became 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 investi- gators in the field.”
Paul D. Cleary, Ph.D., has been reapointed by Yale President Richard C. Levin as dean of the Yale School of Public Health (YSHP) 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 YSHP 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 YSHP’s Master of Public Health (M.P.H.) program have increased 30 percent, to a record number of 1,010 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. YSHP 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 viral infectious diseases. Faculty at YSHP are conducting important studies of many diseases and disease agents including leptospirosis, Lyme disease, babesiosis, African trypanosomiasis, leishmaniasis, and HIV. These investigations are aimed at preventing infection and reducing the negative consequences of disease in vulnerable and underserved populations.

Cleary has developed and expanded YSHP’s public health service and practice activities, including a new Office of Community Health at YSHP 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 (C.A.R.E.), 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,” said Cleary. “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.”

**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-caloric food consumption, with the aim of improving health outcomes related to these maladaptive behaviors.

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 research fellowship in clinical psychology at Yale in 2004. She 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 Addiction’s national 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 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 Cardiology program. In 1998 he became a professor of dermatology.

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 a named 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 annual meeting. This year, he was elected to the Association of American Physicians and won the Ross Whipple Award from the American Society of Investigative Pathology.

**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 molecular medicine, and development biology, Cooley studies the cellular mechanisms of oogenesis.

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 oocyte development and remodeling during development.

Cooley is also director of Yale’s Combined Program in the Biological and Biomedical Sciences. She earned her B.A. at Claremont College and 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. **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. Sherrwin, 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 telephone Award to recognize outstanding achievements in the training of diabetes research scientists and the facilitation of diabetes research. Sherrwin 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.