Medicine@Yale

NOVEMBER/DECEMBER 2012
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Advancing Biomedical Science, Education, and Health Care

Yale-New Haven and Saint Raphael are "healthier together."

> Page 3

Levin leaves indelible mark on Yale medicine

In 2004, when Yale President Richard Levin was hoping to recruit Robert J. Alpern, M.D., as the 16th dean of the School of Medicine, he told Alpern during a visit to New Haven that the medical school was excellent, but should be better, and that he was prepared to make the investment with the right person to make it as great as it should be.

Alpern had no plans to leave his position as dean of UT Southwestern Medical School in Dallas, Texas, an institution where he had been on the faculty for 17 years.

But over the course of many e-mails and conversations, Alpern recalls, "Rick convinced me that working with him, I could join a school that was already great and make it even greater. He had a vision for the school and recognized that it would require substantial investment that he was willing to commit to."

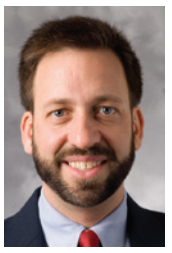
Levin, who has announced that he plans to retire from the presidency next June after a 20-year tenure, made good on that commitment, fully integrating the School of Medicine into his vision of Yale's role in the world in the 21st century.

In his inaugural address in 1993, Levin had emphasized the importance of university-based scientific research, and throughout his tenure he has pursued a vision **// Levin** *(page 6)*

MICHAEL MARSLAND

During President Richard Levin's 20-year tenure, biomedical science has flourished at Yale, with unprecedented increases in funding, research space, faculty hires, and the launch of novel interdisciplinary institutes.

Newly appointed Ob/Gyn chair has deep roots at Yale



Hugh Taylor

At the beginning of October, Hugh S. Taylor, M.D., took up his new posts as chair of the Department of Obstetrics, Gynecology, and Reproductive Sciences at the School of Medicine and chief of Obstetrics and Gynecology at Yale–New Haven Hospital (YNHH). With plans that include new cross-disciplinary clinical programs and translational research, Taylor aims to further strengthen an already highly regarded department.

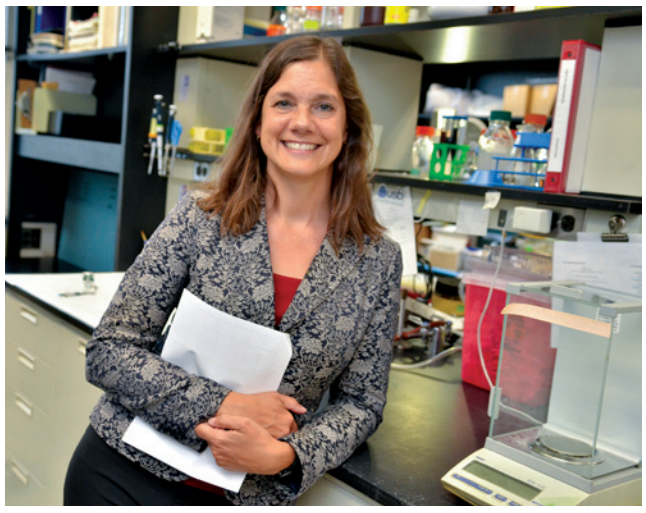
"I'm inheriting a department with a fabulous reputation and legacy," Taylor says, noting that Yale's past achievements in Ob/Gyn include major advances in fetal heart monitoring, obstetric ultrasound, and in vitro fertilization (IVF). "I'm very fortunate to have taken on the role of chair in a department that has trained more leaders in the field than any other Ob/Gyn department in the country."

As a former resident and fellow at Yale, Taylor is himself one such leader. Colleagues spotted his promise early. Dean Robert J. Alpern, M.D., recalls a conversation some years ago with Charles Lockwood, M.D., Taylor's predecessor as chair, now dean of the College of Medicine **// Taylor** *(page 7)*

Neuroscientist joins Institute of Medicine

Expert on neurobiology of addiction elected to branch of National Academies charged with providing advice on health to policymakers

"We're never going to understand all the molecules necessary for an entire behavior," says Marina Picciotto, PH.D., the Charles B.G. Murphy Professor of Psychiatry and professor of neurobiology and pharmacology, of her work on the molecular underpinnings of tobacco and alcohol abuse, depression, and eating behaviors. "But the overall philosophy—that you can say something meaningful about molecules in the brain that can inform how we think about the molecular basis of behavior—that's something that's approachable, and it's worth doing."



MICHAEL MARSLAND

Marina Picciotto is one of 70 American scientists elected in 2012 to the Institute of Medicine (IOM), "one of the highest honors in the fields of health and medicine [recognizing] individuals who have demonstrated outstanding professional achievement and commitment to service" according to the IOM website. Part of the National Academies, the IOM's mission is "to provide unbiased and authoritative advice to decision makers and the public."

The molecules that have attracted most of Picciotto's interest are nicotinic acetylcholine receptors (nAChRs), proteins embedded in nerve cell membranes that are activated by the neurotransmitter acetylcholine, but also respond to chemicals like nicotine. In addition to a fundamental involvement in tobacco addiction, nAChRs have been implicated in Alzheimer's disease and in the dysfunctional sensory processing seen in schizophrenia.

Her scientific achievements and their relevance to human health received major recognition this October with her election to the Institute of Medicine (IOM), the arm of the National Academies that provides science-based advice on medicine and health to policymakers, professionals, and the public at large.

"Marina has made important strides in the area of nicotine addiction research, and her contributions to our understanding of the many roles played by nicotinic acetylcholine receptors have been seminal," says Robert J. Alpern, M.D., dean and Ensign Professor of Medicine. "She's a world-class scientist, and I couldn't be prouder of her election to the Institute of Medicine."

Picciotto began studying nAChRs as a postdoctoral fellow in the lab of Jean-Pierre Changeux, PH.D., at **// IOM** *(page 6)*

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TERRY DAGRADI

As lauded for her advocacy for women scientists as for her own research, Joan Steitz has been a leader among women faculty at the School of Medicine and contributed to the influential National Academy of Sciences report "Beyond Bias and Barriers," on the status of women in science and engineering. She recently won the Vanderbilt Prize in Biomedical Science for her "stellar record of research accomplishments and . . . her mentorship of women in science."

"But you're a woman . . ."

Breaking down barriers, sidestepping bias to build a bright career in science

Lining a shelf in the office of Joan A. Steitz, PH.D., is a row of champagne bottles, each label signed in a rite of passage by graduate students when they completed their doctoral work in Steitz's lab, almost all of whom moved on to faculty positions or careers in industry. It may seem unremarkable to today's students that the bottles added from recent years are signed by roughly equal numbers of women and men, but Steitz knows that the labels carrying women's signatures mark just the beginning of a challenging road.

"There weren't any women doing this sort of thing when I was being educated," says Steitz, Sterling Professor of Molecular Biophysics and Biochemistry and one of the world's foremost authorities on RNA biology. In the early 1960s, when she received her undergraduate degree in chemistry women in science almost always worked as research associates, not faculty members, she says, so she planned to attend Harvard Medical School after college—to become a physician instead of a scientist.

But the summer before she was to start, Steitz worked in the cell biology lab of Joseph G. Gall, PH.D., at the University of Minnesota (a Yale alumnus, Gall would later join Yale's faculty), and "got so excited about it that I decided I wanted to continue doing research and discovering how things work. I didn't care if I was ever in a position that the men would be in."

In 1963, Steitz entered Harvard's graduate program in biochemistry and molecular biology graduate program, the sole woman in a class of 10. She recalls that when she approached a scientist about doing her thesis research in his lab, which did similar work to that she did in Minnesota, "he said, 'But you're a woman, you'll get married, you'll have kids, and what good will all this education be then?'"

So Steitz got her "second choice," as the first female graduate student in the lab of James D. Watson, PH.D., who had just shared the Nobel Prize as co-discoverer of the structure of DNA. Though Watson was known to fancy "cute girls," she says, when it came to science "he judged people purely on the basis of what they could contribute, regardless of gender."

When Steitz moved on, to a postdoctoral position at Cambridge University, one of the "big, burning questions" in molecular biology was how the cell's protein-making machinery determines where on a strand of messenger RNA (mRNA) to begin translating its message into proteins.

The lab's other postdocs, all men, shied away from this problem because the probability of obtaining an answer, especially in two years' time, was slim. "I'm never going to have a job anyhow," Steitz recalls thinking, so she took it on. She soon had the answer, which she published in a now-classic 1969 paper in the journal *Nature*.

Steitz *did* "get a job"—at the School of Medicine in 1970, where she has since accumulated a long list of accomplishments. Notable among them was her 1979 discovery of snRNPs ("snurps"), RNA–protein complexes crucial to the proper splicing of mRNA.

Steitz, a Howard Hughes Medical Institute investigator since 1986, acknowledges that she had "good timing": the women's movement of the 1970s brought women into many fields that had been dominated by men. But she also credits molecular biology's embrace of "open, adventuresome, trailblazing" people in her success. "RNA," she says, "has been a very good field for women."

Recent graduate's documentary film garners top award at film fest

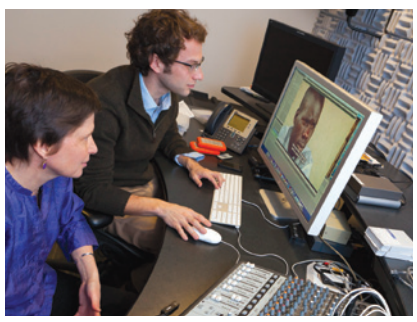
Michael Otremba, M.D., a 2012 graduate of the School of Medicine and now a postdoctoral fellow in the Department of Surgery, has won the award for best documentary feature in the New York Los Angeles International Film Festival.

Otremba's film, "*Twero*: The Road to Health," explores the practice of many Ugandan doctors detaining patients who are unable to pay their bills. *Twero* means "right to health" in Luo, one of the languages spoken in Uganda. The Ugandan government's promise of free medical services to all Ugandans "has been very difficult to translate into reality," Otremba says.

"In all my prior research, I had never encountered the phenomenon of clinics being turned into debtors' prisons. My hope is that the film will be used to advocate for health care reform in all communities where patients are unable to access basic health services."

Otremba devoted his fifth year of medical school to the project, which combines his interests in human rights and visual arts. He worked under the mentorship of Gretchen K. Berland, M.D., associate professor of medicine and recipient of a MacArthur "genius" grant for her own documentary work.

In August, Otremba's film was honored by the international Networked Digital Library of Theses and Dissertations consortium, which promotes the creation and distribution of "electronic" thesis projects.



TERRY DAGRADI

Michael Otremba, at work on his documentary film *Twero* (right), was advised by physician-filmmaker Gretchen Berland (left).

Medical school alumnus awarded a Nobel Prize

Brian Kobilka

Brian K. Kobilka, M.D., a 1981 graduate of the medical school and professor of molecular and cellular physiology and of medicine at Stanford University School of Medicine, has won the 2012 Nobel Prize in Chemistry. He shares the prize with Robert J. Lefkowitz, M.D., of Duke University Medical Center, for their work on sensors lodged in the cell membrane known as G-protein-coupled receptors (GPCRs).

Kobilka and Lefkowitz's work has contributed greatly to our understanding of the ways cells sense and respond to their environment—about half of all medications achieve their effects through GPCRs.

At Duke in 1968, Lefkowitz began using radioactively labeled hormones to identify their receptors, and soon unveiled the β-adrenergic receptor, which binds adrenaline at the cell surface and sets off a biochemical cascade inside the cell.

In the 1980s, Kobilka joined Lefkowitz's lab as a postdoctoral fellow. Together, Kobilka and Lefkowitz isolated the gene that codes for the β-adrenergic receptor. After noticing the gene's similarity to a light-sensitive receptor in the retina, they found that both were members of a large family of receptors, now recognized as GPCRs, that play a role in a variety of vital functions from seeing to digestion to memory.

In 2011, Kobilka's team captured an image of the β-adrenergic receptor at the moment that it is activated and sends a signal into the cell. In announcing the prize, the Nobel committee declared, "This image is a molecular masterpiece–the result of decades of research."

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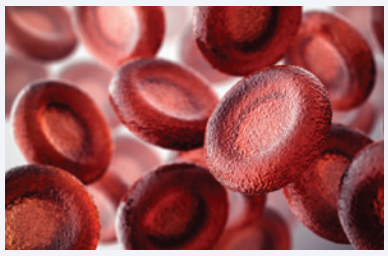


ISTOCKPHOTO.COM

Healthy blood cells take a beating during chemotherapy. New work by Yale researchers suggests a strategy to help repair the damage.

A team led by Jun Lu, PH.D., assistant professor of genetics, scanned a library of molecules known as microRNAs (miRNAs) to see if any affected the recovery of bone marrow cells injured by the cancer drug 5-fluorouracil. One, called miR-150, stood out: cells that had extra miR-150 recovered slowly, and cells that completely lacked miR-150 recovered the fastest.

miRNAs are short stretches of genetic material that bind to messenger RNA (mRNA), blocking the cell from making protein coded in that mRNA. Lu and colleagues discovered that miR-150 binds to the mRNA for a gene called *c-myb*, and if the group shut down *c-myb* through other means, they could partially replicate the slowed recovery seen in cells with high levels of miR-150.

The study, published October 25 in *Cell Reports*, is the first to use a miRNA screen in living mice to study an active physiological process, and the first to implicate a miRNA in the recovery of bone marrow cells after chemotherapy.

Before eyes open, brain gets ready to see

For weeks after birth, a newborn mouse is blind, with eyes that have yet to open. But to prepare the animal to see when its eyes do open, neural circuits in the brain's visual system must begin developing. This same situation, which is in place before birth in humans, is a scientific puzzle, because the proper development of many brain regions involved in vision generally requires sensory input through the eyes.

New research shows that waves of spontaneous neural activity in the retinas of still-closed eyes in mice are necessary to properly wire up the brain: when their eyes finally open, the mice are able to see. "If you interfere with this activity, the wiring details are all wrong," says Michael C. Crair, PH.D., William Ziegler III Professor of Neurobiology and professor of ophthalmology and visual science.

As reported in the October 11 issue of *Nature,* Crair's team simultaneously recorded the activity of neurons in the eyes and brain of newborn mice. They found that waves of activity in the retina were relayed through the brain and produced corresponding activity in the visual cortex, where information from the retina is processed. This occurred for at least a week of a mouse's life.

The work sheds light on how similar neural activity in unborn fetuses shapes the human visual system.

With acquisition, hospital broadens reach

With Hospital of Saint Raphael acquisition, Yale-New Haven Hospital becomes the fifth largest hospital in the United States

On September 11, in a historic ceremony, officials from Yale-New Haven Hospital (YNHH) and the Hospital of Saint Raphael (HSR) signed final documents. Hours later, at 12:01 a.m. the next day, the two hospitals officially became a single 1,519-bed institution with two main campuses.

"We are delighted that with all of the necessary approvals and due diligence behind us, we can begin the important work of integrating these two great hospitals," said Marna P. Borgstrom, M.P.H., CEO of YNHH and president and CEO of Yale-New Haven Health System. "We believe that as one unified hospital, we'll be able to enhance access to high-quality health care resources in a more cost-effective manner. This integration will be critical to meeting the extraordinary health care challenges that lie ahead."

The integration will allow YNHH to provide the region with more coordinated care, to reduce redundancy of clinical services and financial investments, and to become more efficient. It also gives YNHH 511 much-needed beds and provides financial stability for the HSR campus.

While volume at most Connecticut hospitals has been flat or declining over the past several years, YNHH has seen an increase, resulting in significant capacity constraints; the HSR acquisition will allow YNHH to avoid an estimated $650 million investment in a new patient tower.

The transaction helps HSR to preserve a deeply rooted legacy as an exceptional care provider and to honor its traditions as a Catholic hospital, while also taking on the future as part of a nationally recognized academic medical center.

"For the Hospital of Saint Raphael, the integration represents an opportunity to assure financial stability in an uncertain time. Proceeds from the $160 million transaction will allow the hospital to pay off its debt and will help address its pension liabilities," said Christopher O'Connor, HSR president and CEO. "We are intent on making this integration go as smoothly as possible for our patients, our employees, physicians, and the community. This represents a Connecticut solution to a Connecticut challenge."

To better prepare for the 21st century health care landscape, HSR leaders began discussions with potential partners two years ago, including both state and national hospitals and systems; Catholic and secular hospitals; and for-profit and non-profit companies. In March 2011, HSR and YNHH signed a letter of intent to explore integration, followed by a definitive agreement in September, in which YNHH agreed to purchase HSR's assets, to invest in HSR buildings and technology, and to honor HSR's Catholic heritage at that campus.

The Sister Anne Virginie Grimes Health Center, Saint Raphael's 125-bed skilled nursing and short-term rehabilitation facility, is also being acquired as part of the transaction.

Both hospitals worked for the past year to minimize job losses by keeping vacant positions open and managing attrition. About 3,400 HSR employees are transitioning to positions in the Yale-New Haven Health System. Additionally, 400 members of the HSR medical staff have been newly credentialed as members of the YNHH medical staff.

ROBERT LISAK

Marna Borgstrom, CEO of Yale-New Haven Hospital, and Christopher O'Connor, president and CEO of the Hospital of Saint Raphael, sign the final agreement to make official the integration between the two historic New Haven-based hospitals.

"The integration has the opportunity to increase quality outcomes and provide better access to the entire continuum of care for patients," said Peter N. Herbert, M.D., chief of staff and senior vice president of medical affairs at YNHH and clinical professor of medicine at the School of Medicine. "Care will be better coordinated as clinical information and data will be accessible to all patients and providers though a new, state-of-the-art integrated electronic medical record system."

Following the signing of the definitive agreement, there was a months-long approval process that included the Connecticut Attorney General, the Federal Trade Commission and Connecticut Office of Health Care Access.

Local and state elected officials, community leaders and regional businesses were overwhelmingly supportive of the integration.

Genomic study of bowel disorders is a global effort

In one of the largest studies of its kind ever conducted, an international team of scientists has thrown new light on the genetic basis of inflammatory bowel disease (IBD), a group of chronic autoimmune digestive disorders affecting 2.5 million people worldwide.

The new study links variations in 163 regions of the human genome, 71 of which are newly discovered, to increased risk of contracting IBD. These regions showed a striking overlap with those implicated in other autoimmune diseases, and suggest that IBD results from overactive immune defense systems that evolved to fight off serious bacterial infections.

In the two most common forms of IBD, Crohn's disease (CD) and ulcerative colitis, (UC) the immune system produces an ongoing inflammatory reaction in the intestinal tract that injures the intestinal wall, leading to diarrhea and abdominal pain. IBD patients typically need lifelong treatment with drugs, and often need surgery to repair tissue damage.

Judy Cho

"Up until this point we have been studying Crohn's disease and ulcerative colitis separately," says Judy H. Cho, M.D., the Henry J. and Joan W. Binder Professor of Gastroenterology (see related story, page 4) and professor of genetics, a lead author of the study, which was published in the journal *Nature* on November 1. "We created this study on the basis that there seems to be a vast amount of genetic overlap between the two disorders."

As a first step, the researchers conducted a "meta-analysis" of 15 previous genomic studies of either CD or UC, creating a large dataset that combined genetic information from some 34,000 individuals who took part in those studies. The results then formed part of a second meta-analysis that included data from new genome-wide scans of more than 41,000 DNA samples from CD or UC patients and healthy comparison subjects collected at 11 centers around the world by the International IBD Genetics Consortium.

In addition to confirming that 92 regions identified in previous studies confer a significant risk of CD, UC, or both, the study linked 71 additional stretches of the genome to IBD. The IBD-linked variants largely fall in genomic regions that regulate the expression of immune-system genes implicated in other autoimmune diseases, particularly the skin disease psoriasis and a joint disorder // IBD *(page 8)*

OUT & ABOUT

September 3 Psychiatry faculty, residents, and their families ran in the 35th annual **New Haven Road Race**. (From left) **Audra Crutchfield**, PH.D., local recovery coordinator at the VA Connecticut Healthcare System in West Haven, Conn.; **Ilan Harpaz-Rotem**, PH.D., associate professor of psychiatry; **Ismene L. Petrakis**, M.D., professor of psychiatry and chief of psychiatry at the VA; **Shana Ross**, principal of Vili and Ve Solutions, and her son **Micah Ross**; **Kurt Shaffert**, chaplain at the VA; **Catherine Zaneski**, APRN, psychiatric nurse practitioner at the VA; **Michael J. Sernyak**, M.D., professor of psychiatry and CEO of the Connecticut Mental Health Center; **Kirsten Wilkins**, M.D., assistant professor of psychiatry; **Louis Trevisan**, M.D., associate clinical professor of psychiatry; **David Ross**, M.D., PH.D., assistant professor of psychiatry; **Donna LaPaglia**, PSY.D., assistant professor of psychiatry; **Don Slone**; **Adam Mecca**, M.D., PH.D., resident in psychiatry, with his daughter **Lily Mecca**; and **Marcia Mecca**, M.D., clinical fellow in geriatric medicine.

COURTESY OF KIRSTEN WILKINS

September 9 As part of its **Hope on Wheels** program, which supports pediatric cancer research and treatment programs around the U.S., representatives of Hyundai Car Sales donated $250,000 to Yale. 1. **Gary Kupfer**, M.D., professor of pediatrics and of pathology and chief of the Section of Pediatric Hematology/Oncology at Smilow Cancer Hospital at Yale-New Haven (third from left) with Hyundai representatives **Jim Sullivan**, **Dave O'Brien**, **Craig Salera**, **Ken Bloech**, and **Tony Yantosca**. 2. (Back, from left) **Cynthia N. Sparer**, M.P.A., executive director of Yale-New Haven Children's Hospital (YNHCH); Kupfer; and **George Lister**, M.D., chair and professor of pediatrics and physician-in-chief at YNHCH. (Front, from left) **Faith Nelson**, **Andrew Cohen**. 3. Faith Nelson, ready to make a handprint.

HAROLD SHAPIRO (3)

September 8 At the annual **Closer to Free** bicycle ride, members of the School of Medicine and Yale-New Haven Hospital (YNHH) communities came together to raise money for cancer treatment and research at Yale Cancer Center (YCC) and Smilow Cancer Hospital at Yale-New Haven. 1. **Thomas J. Lynch** Jr., M.D., the Richard Sackler and Jonathan Sackler Professor of Medicine, director of YCC, and physician-in-chief at Smilow Cancer Hospital. 2. **Elizabeth Kunz**, MSW, LCSW, clinical social worker at YNHH. 3. **Jeremy Kortmansky** (left), M.D., physician at YCC, and **Howard S. Hochster**, M.D., professor of medicine and associate director for clinical research at YCC, share a triumphant moment. 4. A crowd of cyclists convenes waves to patients inside Smilow Cancer Hospital.

CHRIS VOLPE (4)

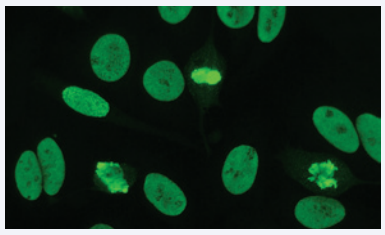
September 17 **The Shaw Prize in Life Science and Medicine** was awarded to **Arthur L. Horwich**, M.D., at a reception in Hong Kong. Horwich, Sterling Professor of Genetics and professor of pediatrics, shares the prize with longtime collaborator Franz-Ulrich Hartl, M.D., DR.MED., of the Max Planck Institute of Biochemistry in Germany. Horwich has devoted his career to understanding protein folding, a process that is disrupted in neurodegenerative conditions such as amyotrophic lateral sclerosis. **Leung Chun-ying** (right), Chief Executive and President of the Executive Council of Hong Kong, presented the award to Horwich (left).

COURTESY OF THE SHAW PRIZE FOUNDATION

TERRY DAGRADI (2)

September 20 A reception was held in the Medical/Historical Library honoring the appointment of **Judy H. Cho**, M.D., professor of medicine and of genetics, as the inaugural **Henry J. and Joan W. Binder Professor of Gastroenterology** (see related story, page 3). 1. Cho (second from right) with members of her lab (from left) **Ken Hui** '15; **Mónica Bowen** '15; **Wei Zhang**, M.D., PH.D., associate research scientist; biostatistician **Kaida Ning**, M.SC.; and **Sok Meng Evelyn Ng**, research assistant. 2. **Henry J. Binder**, M.D., professor emeritus and senior research scientist in the Department of Medicine, who established the Binder Professorship earlier this year with his wife, Joan W. Binder.

Damaging in lupus, useful in cancer . . .



SIMON CAULTON

An antibody generated in lupus can weaken or kill tumor cells, offering both a new type of cancer treatment and an explanation for the low rates of some cancers seen in individuals with lupus.

In lupus a person's immune system goes awry, creating "autoantibodies" that target normal cellular components. One such antibody derived from a mouse model of lupus, 3E10, enters the nuclei of cells, where DNA resides. As reported in the October 24 issue of *Science Translational Medicine*, a team led by Peter M. Glazer, M.D., PH.D., chair and Robert E. Hunter Professor of Therapeutic Radiology and professor of genetics, was using 3E10 as a vehicle to carry other molecules into cancer cell nuclei, but they noticed that 3E10 alone was sufficient to make the cells more susceptible to radiation and cancer drugs. The group found that 3E10 binds to broken, loose ends of DNA, disrupting normal DNA repair mechanisms.

Many cancer treatments—including radiation and some chemotherapeutic drugs—aim to damage the DNA of tumor cells, and 3E10 may make such treatments work better. In cancers that already have deficiencies in DNA repair, 3E10 alone can kill the cells.

. . . and lupus holds yet another surprise

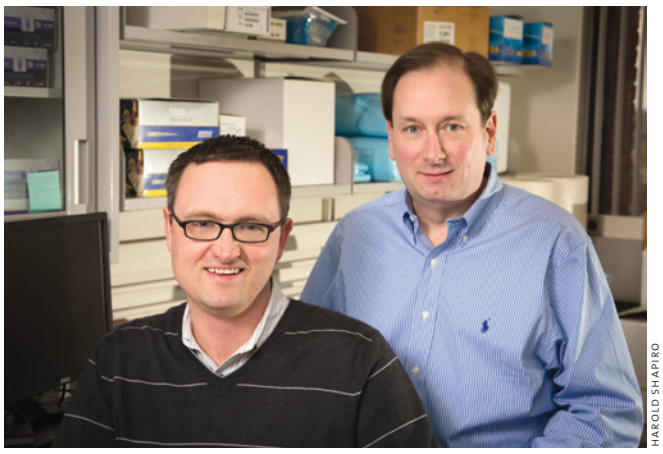
A hypothesis on the molecular underpinnings of lupus has been turned on its head in a new Yale study. Lupus is characterized by attacks on the DNA and RNA of normal cells by the immune system, but researchers have struggled to understand the source of the antibodies against the genetic material.

One theory is based on the everyday destruction of neutrophils, the most abundant type of white blood cell. When neutrophils undergo a particular kind of cell death, their DNA is packaged into a neutrophil extracellular trap (NET) and released. Scientists have suspected that an accumulation of NETs could stimulate the formation of antibodies against DNA.

Mark J. Shlomchik, M.D., PH.D., professor of laboratory medicine and immunobiology, and colleagues tested this theory by crossing mice that cannot form NETs with mice prone to lupus: if the theory were correct, such mice would be less likely to develop full-blown lupus. Instead, the mice had more severe lupus, with a different pattern of autoantibodies. The results, published October 24 in *Science Translational Medicine*, suggest that neutrophils may be important sources of immune-system stimulation in lupus, but that NETs could play a protective, rather than aggravating, role.

A rare mutation offers wide possibilities

Lessons gleaned from a rare blood disease could lead to treatments for more common disorders of the blood, including sickle cell anemia



HAROLD SHAPIRO

In studying the cellular dehydration that occurs in xerocytosis, Jesse Rinehart (left) and Patrick Gallagher identified mutations in the gene for the protein PIEZO1, which may also cause dehydration in sickle cell anemia.

As they flow through veins and arteries, most red blood cells are plump with water. Channels lining the membrane of each red blood cell help ensure that it has the right balance of salts and liquids, keeping the cells elastic and healthy. It's a process vital to human biology, but also one that's been hard for researchers to fully explain. A team including scientists at the School of Medicine has now uncovered a protein that is key to how blood cells maintain their hydration, and which could have implications for treating sickle cell anemia, the most common inherited blood disorder in the United States.

The discovery came out of a quest to understand a much rarer inherited blood disorder called xerocytosis. In this disease, the equilibrium of red blood cells is off: extra potassium and water seep out of cells as they careen against the sides of blood vessels, leaving the cells fragile and causing anemia, a shortage of red blood cells. Sickle-cell anemia, which affects some 70,000 Americans, is characterized by misshapen red blood cells, and a common complication, apart from the clumping of the misshapen cells, is cell dehydration. "Some of the mechanisms that cause the dehydration are known, but we've never uncovered what is that channel at the top of the mountain that starts the avalanche going," says Patrick G. Gallagher, M.D., professor of pediatrics, genetics, and pathology.

Gallagher and a team of collaborators thought that if they could understand dehydration in hereditary xerocytosis, it might help explain the similar phenomenon they see in sickle cell patients. So, in a study supported by the Doris Duke Foundation and conducted in collaboration with a team from the University of Manitoba, they analyzed the genomes of two large, multi-generational families affected by xerocytosis. As reported in the August 30, 2012, issue of *Blood*, in both families they identified mutations in the gene for a protein called PIEZO1.

Fortuitously, the PIEZO1 protein had been characterized for the first time in late 2010 as a channel that senses mechanical force or pressure on a cell's outer membrane—such as the change in pressure that could be caused by swelling or shrinkage of the cell. "This is the first example of a human disease connected to the protein," says Jesse Rinehart, PH.D., assistant professor of cellular and molecular physiology, who joined Gallagher to study the protein's role in xerocytosis.

Rinehart showed that PIEZO1 is indeed found in the membrane of red blood cells and went on to analyze its structure. He hasn't yet uncovered the effect of the xerocytosis-linked mutations on PIEZO1's function, but that's a next step. "The first take away from this is that here is what causes xerocytosis," says Gallagher, director of the Yale Center for Blood Disorders. "But the second is that it looks like PIEZO1 is a very good candidate to be what initiates dehydration in sickle cell."

The cause of sickle cell anemia—a mutation in the oxygen-carrying protein hemoglobin—has been known for decades. Though scientists haven't established what causes the cellular dehydration seen in the disease, many suspect that another protein initiates the dehydration process. If PIEZO1 is that long sought-after protein, says Gallagher, drugs targeting PIEZO1 could treat some of sickle cell's symptoms as well as those of hereditary xerocytosis.

At an international meeting on red blood cells at Yale this winter, investigators from around the world will be sharing their data on PIEZO1 to help complete the story. "Already, this really validates the idea that studying the rarest diseases can help us understand biology more broadly," says Rinehart.

Hybrid technique is a new option for arrhythmias

Implantable defibrillators are devices that can prevent sudden cardiac death in patients with ventricular tachycardia (VT), a potentially life-threatening fast heart rhythm that originates in one of the ventricles of the heart, by delivering a shock to terminate the abnormal rhythm.

While most patients tolerate these devices very well, the shocks are unpredictable, and for some people, even a few of them can be psychologically devastating. This uncertainty may cause tremendous anxiety that limits a patient's quality of life.

Doctors often start medical therapy once a shock occurs, but this does not always prevent future shocks. For some of those patients, radiofrequency catheter ablation is needed to eliminate the short circuits causing the abnormal rhythm.

However, in patients with weak hearts, "the ablation procedure itself can be quite taxing," says Pramod Bonde, M.D., assistant professor of surgery. "In fact, there are a lot of patients who are turned down for this procedure because of their poor heart function." To give such patients an option, in October, Yale physicians successfully performed what they believe were Connecticut's first ablations for VT using a new hybrid technique that takes advantage of an extracorporeal membrane oxygenation (ECMO) machine, which provides temporary support of heart and lung function for patients whose weak hearts would have otherwise made the ablation procedure extremely risky.

"With ECMO, patients with weak hearts become candidates for VT ablation. This is important for those who must endure repeated shocks from their defibrillators as a result," says Bonde, director of Yale's ECMO program, who performed the procedures alongside electrophysiologist Joseph G. Akar, M.D., PH.D., associate professor of medicine and director of the Cardiac Electrophysiology Laboratory. "We can maximize their chances of survival and chances of success with this new technique."

The first patient treated at Yale with the procedure was a man with a weak heart and so-called "VT storm," characterized by incessant life-threatening heart rhythms that trigger multiple repetitive defibrillator shocks. The patient, who had already had two open-heart operations, had been receiving as many as six shocks in less than one minute from his defibrillator, and Akar wanted to perform a radiofrequency catheter ablation to pinpoint the source of the problem and treat it.

COURTESY OF JOSEPH AKAR

More patients are eligible for heart arrhythmia surgery thanks to a new procedure being used by cardiac surgeon Pramod Bonde (right).

The physicians performed what they say is typically a 4- to 6-hour procedure with a team of about 15 people, including surgeons, electrophysiologists, nurses, perfusionists, technologists and // Heart *(page 6)*

// IOM *(from page 1)* the Institut Pasteur in Paris, France, and she describes these beginnings the way many describe their first cigarette: "Once I started," she says, "I was hooked."

Picciotto has also done important studies of nicotine exposure during gestation and adolescence and its effects on learning and memory, and of the neuropeptide galanin, which modulates ACh release and may exert a protective effect against addiction to drugs of abuse such as cocaine, amphetamines, and opiates.

Picciotto received her undergraduate degree in biological sciences from Stanford University in 1985, and a PH.D. in molecular neurobiology in 1992 from The Rockefeller University in New York City, where she worked in the Laboratory of Molecular and Cellular Neuroscience under Paul Greengard, PH.D. She became a member of the Yale faculty in 1995.

Also vice chair for basic science research in the Department of Psychiatry and associate director of the School of Medicine's Medical Scientist Training Program (informally known as the M.D./PH.D. Program), Picciotto serves on the National Advisory Council of the National Institute on Drug Abuse. In 2000 she was awarded the Presidential Early Career Award in Science and Engineering by President Clinton, and in 2007 she was honored with the Jacob P. Waletzky Award by the Society for Neuroscience.

The IOM, established in 1970 by the National Academy of Sciences, is a national resource for independent, scientifically informed analyses and recommendations on issues related to human health. Those elected to the institute are judged to have made significant contributions to the advancement of medical science, health care, and public health, and election is considered one of the highest honors in the health sciences.

// Heart *(from page 5)* others—a procedure that patients with weak hearts can tolerate with ECMO.

Akar was pleased that the ECMO support allowed him to take the time he needed to perform the ablation procedure carefully. Most importantly, he says, ECMO support allowed him to induce the dangerous heart rhythm long enough for him to locate its source.

"The VT procedure is potentially long and technically complicated," Akar says. "Many patients have such severe underlying heart disease that they would really be unable to withstand the stress of this procedure if it was not for the hemodynamic support provided by the ECMO."

Bonde says the development of Yale's adult ECMO program in the past year—at first as a temporary measure for patients with adult respiratory distress syndrome, acute heart failures, catheter-lab emergencies and other serious events—laid the foundation for the successful hybrid ablation procedures.

"We've matured the adult ECMO program and are having very good outcomes, and these procedures are an extension of that," he says. "We waited until now to do it because we wanted to make sure the team is confident and that complex procedures such as VT ablation can be supported with ease."

Other centers in the country have offered the hybrid procedure, either with ECMO or with pumps that take over the function of the heart, but not the lungs. "This is the first such case at Yale and to my knowledge in Connecticut," Akar says. "I look forward to offering this important therapy as we build our ECMO and VT programs to treat challenging cases."

The two doctors predict Yale will treat at least 20 to 30 patients next year with the hybrid procedure, and more as patients and referring physicians learn the procedure is available.

// Levin *(from page 1)* of preeminence in medicine and science at Yale. "Today, the scientific capability of American universities is the envy of the world," he said in 1993. "We neglect its support at our peril."

Levin's unwavering commitment to medicine and science in the years since is a direct outgrowth of his often-stated goal of transforming Yale into an institution with global reach, Alpern says. "Rick understood that science and medicine," as fields that interest and benefit people worldwide, "are a powerful form of 'international currency' in academia."

In January 2000 Levin announced the greatest investment in biomedical science in the university's 300-plus-year history. *The New York Times* called his dedication of $500 million to science and engineering "one of the largest one-time building plans ever" made by a university.

Less than a month later Levin said that an additional $500 million investment would go to the School of Medicine over the coming decade.

That investment funded outstanding infrastructure for modern biomedical science—new laboratories, core technology facilities, and high-tech teaching centers—that could have never have been shoehorned into the medical school's existing facilities.

In 2003, the medical school opened the largest academic building in Yale history, the 457,000-square-foot Anlyan Center for Medical Research and Education. Alpern, who became dean in 2004, says that the facility is so crucial that "I can't imagine what the medical school would look like if it weren't here."

Together with the 120,000-square-foot Amistad Street Building, which opened in 2007, the medical school increased its existing laboratory space by half.

In academic medicine, increased space drives increased quality: construction projects enacted under Levin made possible a 76 percent boost in medical school faculty, from 1,300 when he took office to 2,300 today. Collectively these faculty propelled a nearly four-fold jump in the school's annual grant funding, from about $140 million in 1992 to about $540 million, according to the latest figures.

Levin's strong backing for medicine and science also spurred Yale's adoption of critical new technologies and the recruitment of accomplished and visionary scientists. In addition, many scientists who were offered positions at other schools chose to stay at Yale, appreciating the university's commitment to them.

The school's principal teaching hospital, Yale-New Haven Hospital (YNHH), also grew, especially through the 2009 opening of the 14-story Smilow Cancer Hospital at Yale-New Haven, which united all of Yale Cancer Center's myriad clinical services under one roof.

"It is a day of inspiration, a day that we've all waited for for many years," Levin said on Smilow's opening day. "It will allow this hospital and this medical school to take their places among the leaders in the world in the care and treatment of cancer." Alpern credits Levin, who as Yale President serves on the hospital's board, with fostering an excellent working relationship between the university and medical school and YNHH. "He has had a huge commitment to the hospital's success and to the success of its relationship with the medical school," says Alpern.

In June 2007, Levin spearheaded the purchase of the former Bayer Healthcare North American pharmaceutical headquarters in West Haven, Conn. Now known as West Campus, the purchase added 136 acres and more than 1.5 million square feet of space, including many purpose-built biomedical research labs.

Levin called on the university to make West Campus Yale's home for innovative biomedical and clinical science programs that cross and challenge disciplinary boundaries and take risks for the chance at making revolutionary advances.

"This has transformative potential, frankly—only some of which we can envision today," Levin said as the planning for West Campus got under way. "We've given our successors an opportunity to dream in ways we can't imagine today."

Both Alpern and Carolyn W. Slayman, PH.D., deputy dean for academic and scientific affairs at the School of Medicine for most of Levin's presidency, say that one of Levin's greatest strengths as an administrator is that he is an "incredible listener."

But Slayman stresses that Levin's is not a passive form of listening, but one to which he brings the ability to take what he hears and "integrate it and fit it together. He builds a framework in his mind, so he's not just hearing random things and remembering them–he's putting them together in a very logical, connected way."

By combining these skills, say Alpern and Slayman, during his tenure Levin developed extremely well-informed views on academic medicine that guided his decisions.

But most important, says Alpern, "He followed through."

Pulse
The life of Yale School of Medicine

Hunger and Homelessness Auction

The Hunger and Homelessness Auction, an annual event held at the School of Medicine that raises funds to help alleviate hunger and homelessness in the New Haven area, turned 20 this year.

The first auction was organized in 1993, when medical student Jeffrey Meyerhardt, M.D. '97, M.P.H., now associate professor of medicine at Harvard Medical School, proposed the idea to Robert H. Gifford, M.D., professor emeritus of medicine and associate dean of student affairs at the time. "He and I cooked up the first auction, which was held in Harkness Ballroom," Gifford recalls. That year, the auction raised about $3,500. In 1994, the proceeds were $7,000.

Organized by students from the School of Medicine, the Physician Associate Program, and the School of Nursing, the event now typically generates more than $25,000. The auction has grown into a week-long slate of activities, including a football game between the first- and second-year classes, panel discussions, performances, and films—all culminating in both silent and live auctions of donated items. Past recipients of proceeds from the auction include the Community Health Care Van, Loaves and Fishes, Domestic Violence Services of Greater New Haven, and New Haven Home Recovery, and Youth Continuum.

Project to explore roots of autism in girls

NIH awards grant of $15 million for research at Center of Excellence

STAN GODLEWSKI

Kevin Pelphrey, pictured here with his three children, two of whom have autism spectrum disorders (ASDs), is the lead investigator of a five-year, $15 million Yale study that will investigate the causes of autism in girls, who are about five times less likely than boys to be diagnosed with an ASD. The School of Medicine's Autism Center of Excellence is one of nine institutions participating in the $100 million project, which is funded by the National Institutes of Health.

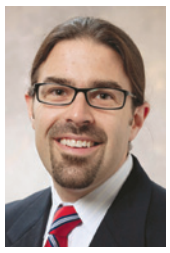
The reasons why autism spectrum disorders (ASDs) are almost five times more common among boys than among girls may soon be revealed, thanks to a five-year, $15 million National Institutes of Health (NIH) grant awarded to the School of Medicine's Autism Center of Excellence (ACE) research program.

Led by principal investigator Kevin Pelphrey, PH.D., the Harris Family Associate Professor in the Child Study Center (CSC), the Yale ACE award is part of a $100 million National Institutes of Health program that will provide funding to nine institutions to investigate the causes of and treatments for ASDs.

"It is my hope that this award will invigorate research in autism at Yale and allow us to maintain our outstanding history of cutting-edge work in this field," says Pelphrey, also associate professor of psychology and director of the Center for Developmental Neuroimaging.

Pelphrey and a collaborative team of researchers from Yale, UCLA, Harvard, and the University of Washington will investigate the poorly understood nature of autism in females. Other labs at the School of Medicine that will participate include that of James C. McPartland, PH.D., assistant professor in the CSC and assistant professor of psychology, and director of the Yale Developmental Disabilities Clinic.

The team will study an unprecedented number of girls with ASDs



James McPartland

and will focus on genes, brain function, and behavior throughout childhood and adolescence. ASDs are complex developmental disorders that affect how a person behaves, interacts with others, communicates, and learns. According to the Centers for Disease Control and Prevention, ASDs affect approximately 1 in 88 children in the United States.

NIH created the ACE Program in 2007 to launch an intense and coordinated research program that supports large collaborative efforts to advance broad research goals. The program expanded this year to examine such issues as children and adults who have limited or no speech, possible links between ASDs and other genetic syndromes, potential treatments, and the possible reasons why ASDs are more common among boys than girls, according to Alice Kau, PH.D., of the Intellectual and Developmental Disabilities Branch at the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), one of five institutes funding the ACE program.

Other supporters of the ACE program include the National Institute on Deafness and Other Communication Disorders, the National Institute of Environmental Health Sciences, the National Institute of Mental Health, and the National Institute of Neurological Disorders and Stroke.

// Taylor *(from page 1)* and vice president for Health Sciences at The Ohio State University. "Charly told me that someday, when he left or retired, I would do a national search, and after I had looked at candidates all across the country, I would appoint Hugh Taylor as the next chair," Alpern recalls with a laugh. "And that's exactly what happened. We're absolutely delighted."

Alpern says that Taylor is "spectacular" and brings a unique constellation of talents to the job. "He's a great clinician, great teacher, and an outstanding researcher. He's got it all, in addition to being an incredibly nice person, and he's quite mature administratively for someone who hasn't been a department chair yet."

That maturity may be owing to Taylor's national leadership experience. Among other positions, he is a member of the boards of directors of the Society for Gynecologic Investigation and of the American Society for Reproductive Medicine, both premier organizations in the field. He also served for two years as clinical director of the Society for Assisted Reproductive Technology, the nation's most important group of IVF professionals, and he is editor of the journal *Reproductive Sciences*.

In addition to seeing patients, Taylor has been continuously funded by the National Institutes of Health for over 20 years for his research into endometriosis, adult stem cells, and reproductive developmental biology, among other areas. He has also long been a lauded mentor to students, residents, and faculty.

Taylor has deep Yale roots. He graduated from Yale College and the University of Connecticut School of Medicine, then completed his residency at YNHH in 1992. Pursuing parallel careers at bench and bedside at the School of Medicine, he completed a postdoctoral fellowship in molecular biology as well as a fellowship at Yale's Division of Reproductive Endocrinology and Infertility (REI). He has been a Yale faculty member since then, going on to serve as chief of REI. During his six-year tenure in that position, Taylor turned around REI's fiscal deficit and expanded its patient volume, range of services, and IVF success rate, positioning REI as a national leader in the field.

To his new job, Taylor brings a slew of ambitious goals. He plans to expand the department's research efforts in translational medicine, such as research in cancer genomics that may lead to personalized treatments. Also on his agenda is improved clinical care through collaboration. Already hard at work to create a cross-disciplinary incontinence program, Taylor plans to organize medical teams for other challenging clinical problems. "We're working with pediatrics and pediatric surgery to increase our offerings in fetal therapy," he says, "and collaborating in maternal-fetal medicine with neonatology, to be more closely aligned on high-risk pregnancies and in the neonatal intensive-care unit." This multispecialty approach, he says, is the future of medicine. "Rather than be siloed into departments, we bring all the different areas of expertise that might have relevance to a patient's disease together under one roof."

Taylor plans to act on YNHH's recent acquisition of the Hospital of Saint Raphael (see related story, page 3) to strengthen the department's relationships with community Ob/Gyn physicians. He will also recruit new faculty leaders and expand the department's involvement with international capacity-building.

"We've got tremendous opportunities, starting on a fabulous foundation," he says. "I hope to be able to take the department to even greater heights."

Chair of immunobiology honored by the Cancer Research Institute

Richard A. Flavell, PH.D., chair and Sterling Professor of Immunobiology and a Howard Hughes Medical Institute (HHMI) investigator, has received the 2012 William B. Coley Award for Distinguished Research in Basic Immunology.

The award was given by the Cancer Research Institute (CRI) jointly to a group of three scientists for their work to define the gene transcription factors that regulate differentiation of CD4+ T cells, a crucial component of the adaptive immune response. Flavell shares the award with Laurie H. Glimcher, M.D., the Stephen and Suzanne Weiss Dean and provost for medical affairs at Weill Cornell Medical College, and Kenneth M. Murphy, M.D., PH.D., the Eugene Opie First Centennial Professor of Pathology and Immunology and HHMI investigator at Washington University School of Medicine in St. Louis.

Flavell studies the molecular basis of T-cell differentiation. His research team has used genomic approaches to identify the genes that are selectively expressed in T-cell lineages, and has used gene targeting, transgenic mice, and retroviral technology to elucidate the function of these genes and their target sequences.

Richard Flavell

A member of the Institute of Medicine (see related story, page 1) and National Academy of Sciences, he also studies the mechanisms of programmed cell death using mice lacking death-effector molecules, and the molecular and cellular bases of autoimmune disease.

The CRI was established in 1953 to transform cancer patient care through the discovery and development of safe and effective immune system-based strategies to treat and eventually cure all cancers. The Coley Award is one of the CRI's highest honors for those who have made seminal contributions to the fields of immunology and cancer immunotherapy. The award was presented at the CRI's 26th Annual Awards gala on October 17 in New York City by James P. Allison, PH.D., director of the CRI Scientific Advisory Council.

Research of two medical school scientists is boosted by NIH Director's Awards

Two School of Medicine scientists were honored recently with National Institutes of Health (NIH) Director's Awards.

Alan Anticevic, PH.D., associate research scientist in psychiatry, received the NIH Director's Early Independence Award, and Andrew L. Goodman, PH.D., assistant professor of microbial pathogenesis, has received the NIH Director's New Innovator Award.

The Early Independence Award will support Anticevic's work, which combines neuroimaging, computational modeling, and pharmacology to better understand the cognitive dysfunction seen in schizophrenia, an aspect of the illness for which there are no effective treatments. Anticevic, administrative director of the National Institute on Alcohol Abuse and Alcoholism's Center for the Translational Neuroscience of Alcoholism, is one of only 14 scientists in 2012 to receive the Early Independence Award, which is designed to provide junior scientists of exceptional merit "with the opportunity to conduct independent biomedical or behavioral research by skipping the conventional postdoctoral training period." Anticevic received his doctorate from Washington University School of Medicine in 2011.

Alan Anticevic

Andrew Goodman

Goodman's project, titled "Defining the Contribution of Interpersonal Microbial Variation to Drug Metabolism," explores the influence of microbial communities in the gastrointestinal tract on drug metabolism.

Taking a novel approach that combines microbial ecology, robotics, and pharmacokinetics, Goodman seeks to understand why drugs commonly used to treat ulcerative colitis are ineffective for 35 percent of patients despite compelling evidence implicating gut microbes in both drug activation and inactivation.

The New Innovator awards, established in 2007, support investigators who are within 10 years of their terminal degree or clinical residency, but who have not yet received a Research Project Grant (R01) or equivalent NIH grant, to conduct exceptionally innovative research. They are a part of the NIH's Common Fund High Risk-High Reward program, which "provides opportunities for innovative investigators in any area of health research to take risks when the potential impact in biomedical and behavioral science is high," according to NIH Director Francis S. Collins, M.D., PH.D.

Pediatrician recognized by international body for work on preventing, treating child abuse

John M. Leventhal, M.D., professor of pediatrics and in the Child Study Center, has been honored with the C. Henry Kempe Memorial Lectureship Award from the International Society for the Prevention of Child Abuse and Neglect (ISPCAN). The award is given to an individual who has made "significant contributions to the welfare of children and demonstrate[d] teaching experience."

John Leventhal

The award's namesake, C. Henry Kempe, published a classic article in 1962 called *The Battered Child Syndrome*, and helped establish the Society. Leventhal delivered the Kempe Lecture in September in Istanbul, Turkey, at ISPCAN's biennial congress.

Leventhal's clinical and research interests center on the evaluation and treatment of physically abused, sexually abused, and neglected children; development and behavior; and the primary care of children. Also clinical professor of nursing and medical director of the Child Abuse Program at Yale-New Haven Children's Hospital, he received his M.D. from Tufts University School of Medicine and completed his residency and fellowship at Yale-New Haven Hospital, where he was a Robert Wood Johnson Clinical Scholar.

// IBD *(from page 3)* known as ankylosing spondylitis. Genes affected by these regulatory regions are also involved in the production of immune cells that fight infection by mycobacteria, a family of microbes that cause diseases such as leprosy and tuberculosis.

"We see a genetic balancing act between defending against bacterial infection and attacking the body's own cells," says Jeffrey C. Barrett, D.PHIL., of the Wellcome Trust Sanger Institute in Cambridge, England, also a lead author of the study. "Many of the regions we found are involved in sending out signals and responses to defend against 'bad' bacteria. If these responses are over-activated, we found it can contribute to the inflammation that leads to IBD."

Nearly 100 scientists in 15 countries contributed to the new work, which "highlights the incredible power that working together in a large team can have," says Cho, director of Yale's Inflammatory Bowel Disease Center in the Department of Internal Medicine's Section of Digestive Diseases. "This would not have been possible without the thousands of DNA samples from patients with these conditions assembled by the International IBD Genetics Consortium. Collectively, our findings have begun to uncover the biological mechanisms behind this disease."