Medicine@Yale

Advancing Biomedical Science, Education and Health Care

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New look at how resistant bugs dodge drugs

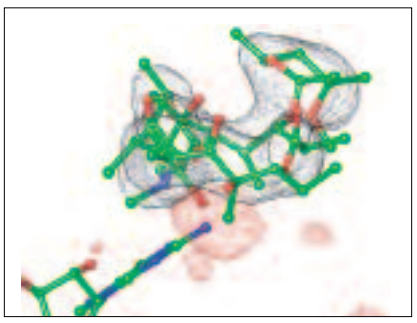
Yale biologists have opened a new front in the war on antibiotic-resistant bacteria by creating the first high-resolution pictures that show how some resistant bacterial strains, which threaten to undo years of progress against infectious disease, thwart commonly used antibiotics.

The new research, published in the April 22 issue of *Cell*, provides scientists with a fresh battle plan for creating new antimicrobial drugs.

Many widely used antibiotics work by latching onto and inhibiting ribosomes, the protein factories present in all cells. Using X-ray crystallography, Thomas A. Steitz, PH.D., Sterling Professor of Molecular Biophysics and Biochemistry and a Howard Hughes Medical Institute investigator, and Peter B. Moore, PH.D., Sterling Professor of Chemistry and professor of molecular biophysics and biochemistry, determined the atomic-level structure of five common antibiotics when the drugs were bound to the ribosomes of sensitive or resistant bacteria.

Although the antibiotics used in the study have quite different chemical structures, Steitz and Moore found that they all bind to the same site on the ribosome's large subunit and that resistance to all of them is generated by the same change in just

Ribosome, *page 8*



In the ribosome of a resistant bacterium (lower left), a "bulge" (red area at center) keeps the antibiotic erythromycin (upper right) from binding tightly.

YALE PROJECTS FOR GLOBAL HEALTH RECEIVE MAJOR FUNDING

Richard Flavell will spearhead a new approach to vaccine development with a $17 million grant from the Grand Challenges in Global Health initiative, which is supported by the Bill and Melinda Gates Foundation, the Wellcome Trust and the Canadian Institutes of Health Research and managed by the Foundation of the National Institutes of Health.

Mouse breakthrough will speed vaccines

All progress in biomedicine is made on the horns of a dilemma. The testing of drugs or other therapies in humans before they are shown likely to be safe and therapeutically promising in preclinical studies is prohibited by ethical considerations. But the tools available for preclinical work—laboratory animals or isolated cells in a dish—are no substitute for testing in the living human body.

Bringing a potential cure from laboratory science to human clinical trials often requires an unsettling leap across an unavoidable

Foiling malaria mosquitoes, p. 6

gap in knowledge, and only a small fraction of the drugs that enter clinical testing are eventually approved for use in medicine.

This state of affairs has presented particular challenges in immunology research, says Richard A. Flavell, PH.D., chair and Sterling Professor of Immunobiology. Mice, the most commonly used research animal, have immune systems that are tailored to deal with the bacteria and viruses that the species has been subjected to over evolutionary time, not the same set of pathogens that infect humans. And, as its name implies, the immune system isn't a unitary organ like the liver, but a multifaceted mechanism distributed throughout the body, which is difficult to emulate faithfully in a petri dish.

"You don't really want to be studying mouse cells; you want to study human cells, and ultimately you study humans, in clinical trials," says Flavell, who is also a Howard Hughes Medical Institute

Flavell, *page 6*

Using laser light, team guides flies by remote control

Researchers at the School of Medicine have created a high-tech puppet show, only their marionettes are alive and have no strings attached. With the help of some genetic tweaking, the team got fruit flies to walk, jump and fly on command—simply by flashing a light at them.

Over centuries, to better understand the brain's normal functions and the roots of disease, scientists have devised many methods of manipulating animal behavior, but they have had to rely on invasive tech-

Flies, *page 7*

Fund will honor mentor, aid students

This spring, when Applera Corp. of Foster City, Calif., asked members of its board of directors to suggest worthy recipients for gifts from the corporation, Carolyn W. Slayman, PH.D., the medical school's deputy dean for academic and scientific affairs, suggested a grant that would do double duty to promote her ideals in biomedical education.

Slayman, a director of Applera—the parent company of Applied Biosystems, a manufacturer of scientific equipment, and Celera, which played a major role in sequencing the

Fund, *page 6*

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Form leads to function

Solving the puzzles of protein folding may shed new light on Alzheimer's

Lifelines
Arthur L. Horwich

Arthur Horwich (third from right) in his element—amongst the graduate students, postdoctoral fellows and research scientists with whom he shares the lab bench.

It's true that biologist Arthur L. Horwich, M.D., received last year's Gairdner International Award for having "revolutionized our understanding about basic cellular functions," but to hear him talk, he's not much different from the twenty-something postdoctoral researchers who staff his lab.

"I just have never matured beyond postdoc," says Horwich, the Eugene Higgins Professor of Genetics, professor of pediatrics and a Howard Hughes Medical Institute (HHMI) investigator. "I still work at the bench every day. I still like to do my own experiments. I like to be able to live with and suffer through the problems of understanding how things work side by side with my own people, and I always have one or two things for myself that I consider my own laboratory struggle."

In his first-floor lab at the Boyer Center for Molecular Medicine, Horwich has helped to solve, bit by bit, one aspect of what has long been known as "the protein-folding problem," the question of how newly made proteins transform from long chains of amino acids into three-dimensional structures. This folding step is essential, because the shapes of folded proteins determine their functions; for proteins, loosely speaking, anatomy is destiny.

Horwich's work has built upon that of Nobel laureate and biochemist Christian B. Anfinsen, PH.D., who showed in the early 1960s that the sequence of amino acids in a nascent protein contains all the information it needs to fold from a chain into the three-dimensional sheets and helices of a functioning protein.

But in 1987, Horwich and colleagues discovered that sometimes proteins need help from other specialized proteins, aptly known as "chaperonins," which serve as intracellular protein-folding machines. Horwich was impressed to discover that these molecular chaperones will try up to 20 times to properly fold an intractable protein. In terms of the energy the cell must expend, Horwich notes, "it's a very expensive process," but misfolding is costly, too: misfolded proteins are linked to hundreds of devastating disorders, including Alzheimer's, Parkinson's and mad cow disease.

"This work is as basic to biology as understanding the nature of genes and how genes are expressed and translated into proteins," says Richard P. Lifton, M.D., PH.D., an HHMI investigator who is chair and Sterling Professor of Genetics at the medical school.

Colleagues are amazed that, at 54, Horwich still enjoys the rigors of running experiments. "He seems to have retained the enthusiasm for science that people who are more senior seem to lose—the day-to-day excitement," says Tony Hunter, PH.D., a cell biologist at the Salk Institute and a fellow Gairdner winner who was one of Horwich's early mentors.

In his spare time, Horwich enjoys fly-fishing, tennis and backpacking. But after a few days on the river or in the mountains, he's eager to get back to the Boyer Center. Each day in the lab holds out the chance, however small, he says, "to see something that's not been seen before. There's no substitute for it."

Lifelines *profiles the people who carry out the scientific, educational and clinical missions of the Yale School of Medicine.*

Student explorations in the world of research

For Doris Duke fellows and classmates, research event celebrates discovery

As he delivered the 18th annual Farr Lecture at Student Research Day in May, Arthur L. Horwich, M.D., described his own path to a career in research. He trained as a pediatrician, but the lure of the laboratory ultimately proved too strong to resist. Still, he found a balance. "Research and the bedside," he said, "are inextricably linked." Horwich, a geneticist whose work has shown how proteins fold (see *Lifelines* above), still consults on clinical cases.

"You cannot predict exactly what you will be doing in some balance of research and clinical medicine," said Horwich. "Make sure it is a balance that really causes you to have fun."

Student Research Day is an annual celebration of the Yale System of medical education, established in the 1920s by then-Dean Milton C. Winternitz, M.D.

The first two years of medical school at Yale are absent of grades, and students are encouraged to pursue their own interests. A thesis based on original research has been a requirement for graduation since 1839. Yale is the only medical school in the United States with this long-standing tradition.

Five prize-winning students gave oral presentations, and 75 took part in this year's poster session.

Among them was second-year student Mary Dombrowski, who examined whether transplants of olfactory ensheathing cells can regenerate myelin. She chose the topic because her father has multiple sclerosis. In her experiments with rats she found that the cells did encourage myelin growth. "It has stimulated my interest in neurology as a career choice," she said.

Fourth-year student Hardean E. Achneck found the bright side to a devastating disease. Ascending aortic aneurysms are associated with a decrease in systemic atherosclerosis. "If we find out what the genes are, we may find the mechanism of this and, eventually, treat atherosclerosis," he said.

Alison H. Norris, an M.D./PH.D. student, studied the HIV risk for workers on a sugar plantation in Tanzania. Helena Hansen, who completed the M.D./PH.D. program in May, studied faith-based substance abuse treatment in a Pentecostal community in Puerto Rico.

Eight students won fellowships from the Doris Duke Clinical Research Fellowship Program for Medical Students, a national program started in the fall of 2001 by the Doris Duke Charitable Foundation (DDCF), with Yale as one of 10 participating universities. The yearlong program starts in July with three classroom courses before students embark on their own research projects.

According to John N. Forrest Jr., M.D., professor of medicine and director of student research, there must be a clinical element to the Doris Duke-funded projects. "Someone in the research group touches the patient," he said. "It can't be a mouse model of diabetes."

Yale received an initial grant of $480,000 in 2001 from DDCF, and its participation in the program was extended this year with an additional $500,000 to carry it forward through June 2009.

Notable teachers receive high honors at Commencement

At the medical school's Commencement ceremony on Harkness Lawn in May, the Class of 2005 enjoyed their day in the sun, basking in the admiration of family and friends. But faculty, too, were honored for their many contributions to education.

Peter Aronson

Marie-Louise Landry

For the first time, the Bohmfalk Prize for teaching basic sciences was awarded to a husband-and-wife team, Marie-Louise Landry, M.D., professor of laboratory medicine, and Peter S. Aronson, M.D., the C.N.H. Long Professor of Medicine and professor of cellular and molecular physiology. The Bohmfalk Prize for teaching clinical science went to Michael K. O'Brien, M.D., PH.D., assistant clinical professor of surgery.

Sharon K. Inouye, M.D., M.P.H., professor of medicine, received the Leonard Tow Humanism in Medicine Award, while Catherine Chiles, M.D., associate clinical professor of psychiatry, won the Leah M. Lowenstein Prize, for excellence in the promotion of egalitarian medical education. The first annual Alvin R. Feinstein Award for outstanding clinical skills was awarded to Ronald R. Salem, M.D., associate professor of surgery.

Robert D. Auerbach, M.D., lecturer in obstetrics, gynecology and reproductive sciences, was awarded the Francis Gilman Blake Award for outstanding teaching.

Public health students chose Elizabeth H. Bradley, M.B.A., PH.D., associate professor of public health, for the Award for Excellence in Teaching, the third in her nine-year career at Yale.

Medicine@Yale

Peter Farley, *Managing Editor*

Contributors: Lakshmi Bangalore, Douglas Barnes, John Curtis, John Dillon, Michael Fitzsousa, Renee Gaudette, Andrea Gendrachi, Maureen Grieco, Jane Hadjimichael, Lauragene Lyons, Jill Max, Pat McCaffrey, Christopher Pates, Cathy Shufro, Marc Wortman
Photographs and Illustrations: Aaron Berger, Isabel Chenoweth, John Curtis, Terry Dagradi, Jerry Domian, Hannah Fairfield, Peter Moore, Rockefeller Archive Center, Harold Shapiro, Hugh Sturrock/The Wellcome Trust, Elaine Ubina, Paul Webster/House Ear Institute, S. Mark Williams, Sandra Wolin
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Telephone: 203.785.5824 Fax: 203.785.4327
E-mail: medicine@yale.edu
Website: medicineatyale.org

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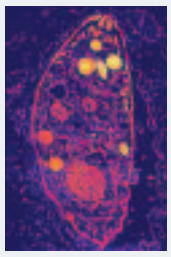
Advances

Health and science news from Yale

Taking a toll on parasitic infections

In 1997, a blockbuster article by two Yale scientists, the late Charles A. Janeway Jr., M.D., and Ruslan M. Medzhitov, PH.D., professor of immunobiology, kicked off one of the hottest research areas in immunology. Janeway and Medzhitov reported that innate immune system molecules called *toll*-like receptors, or TLRs, give early warning of microbial or viral invaders to the acquired immune system, which marshals the body's array of defenses against infection.



Scientists have since identified over a dozen types of TLRs, which work by detecting distinctive genetic signatures or proteins found in bacteria and viruses but not in the eukaryotic cells that make up our bodies.

But some pathogens—such as *Toxoplasma gondii* (above), the parasite that causes toxoplasmosis—are also eukaryotes, and a team at Yale and the National Institutes of Health wondered whether TLRs could recognize them.

In the June 10 issue of the journal *Science*, the group reported that TLR11, discovered at Yale in mice just last year, detects a protein in *T. gondii* and triggers a robust immune response.

The global impact of parasitic infections such as toxoplasmosis is tremendous. Sankar Ghosh, PH.D., professor of immunobiology and a member of the research team, says that while it is not yet clear whether humans have a functional version of TLR11, "insight obtained from these studies should lead to development of novel strategies to combat these infections."

New kidney discovery may help heart

The kidneys filter waste and excess water from the body and keep sodium and other electrolytes in balance, but they also secrete crucial protein hormones that regulate heart function and the production of red blood cells.

Eight million Americans suffer from kidney impairment, some 500,000 of whom have end-stage renal disease (ESRD), for which dialysis is a lifesaving treatment. Dialysis paired with dietary restrictions can substitute for the kidney's filtering and electrolyte-balancing roles, but even with medications that replace important hormones ESRD patients are prone to serious, sometimes fatal, heart problems.

Gary V. Desir, M.D., professor of medicine, and research scientist Jianchao Xu, M.D., PH.D., suspected that there might be additional kidney hormones that promote cardiac health. In May, the scientists announced in *The Journal of Clinical Investigation* that they had discovered a new kidney protein, renalase, that lowers blood pressure and improves heart function.

Xu says the discovery "has immediate implications for therapy." Desir agrees: "We are hopeful that renalase will impact the treatment of chronic kidney disease and change the way in which we treat patients with chest pain and heart attacks."

A quest to detect earliest signs of autism

Child Study Center begins major effort to track autism markers in infancy

(From left) Ami Klin, Warren Jones and Katarzyna Chawarska have set their sights on detecting signs of autism as early as possible.

A recent issue of the journal *Science* with the theme "What Don't We Know?" was organized around 125 of the most pressing and difficult scientific questions of our time. There, alongside the grandiose, perennial puzzlers like "What is the universe made of?" was a somewhat different, but no less vexing, sort of question: "What causes autism?"

More than 60 years after autism was first identified, it remains among the most mysterious and intractable psychological disorders. And the disability at the heart of autism—profound isolation that emerges in early childhood—undermines social bonds that are basic to human nature.

For autistic children and their families, the medical school's Child Study Center (CSC), a landmark facility for the study of child development, is both a source of comfort in their day-to-day struggles and a beacon of hope for future scientific breakthroughs. Most institutions devoted to autism focus either on research or on clinical care, but at the CSC, cutting-edge research—in genetics, diagnostic techniques, neuroscience and pharmacology—is tightly intertwined with the most effective treatments in the clinic.

Autism is often described as arising "out of nowhere" during the second year of life. But according to Katarzyna Chawarska, PH.D., assistant professor and director of the CSC's autism screening program, many parents say in retrospect that they noticed subtle anomalies in their child's behavior well before full-blown symptoms first appeared. Chawarska says that developing methods to consistently, accurately measure behavioral differences as early as possible—a strategy *Science* cited as the key to successful intervention in autism—is now "one of the hottest topics in the field."

In July 2004, the Simons Foundation, a philanthropic organization headed by the husband-and-wife team of Marilyn Hawrys Simons and James H. Simons, announced a major new initiative to fund autism research, and they asked the CSC's Ami J. Klin, PH.D., Irving B. Harris Associate Professor of Child Psychiatry, to propose a project that would decisively advance the field.

In studies of older children and adults using special cameras and software that calculates precisely where a subject's gaze is directed at any point in time, Klin and research scientist Warren Jones had shown that autistic subjects pay far less attention to socially relevant information—facial expressions, for example—than do normal subjects when viewing human interactions on a screen. Klin suggested that an adaptation of the technique could harmlessly track the eye movements of newborns and infants. By pinpointing the time during early development when autistic children's patterns of gaze begin to reflect a shift away from social engagement, Klin reasoned, it might be possible to provide interventions that steer them in a more normal direction.

Klin's audacious plan called for a study on a scale never seen before in autism research: screening 150 infants—including 120 high-risk siblings of older children with autism—immediately after birth, every month for the first six months, every three months until 18 months of age and every six months after until age 3.

The ambitious scope of Klin's proposal won over the foundation, which awarded $2.6 million to launch the project in the newly constructed Simons Laboratory of Social Neuroscience in Infancy.

"In our field there are very few things more expensive than a prospective study of the unfolding of socialization in the first two years of life," Klin says. "But the social mind and brain develop at great speed, and disruption of this process in autism could happen at any stage. Sampling a child's development only once or twice would greatly reduce the power of our methods." Emboldened by the foundation's vote of confidence, he says, "we might be able to find vulnerability to autism as early as the first month of life."

Yale visit brings hope to paralyzed veterans

In the highly specialized world of modern biomedical research, it is all too easy for scientists to lose themselves in the microscopic complexities of the intracellular world—the genes, molecules and signaling pathways that are the keys to understanding disease and finding new treatments.

But at least once a year, the scientists at Yale's Center for Neuroscience and Regeneration Research receive a bracing reminder of what's really at stake in their work on spinal-cord repair when members of Paralyzed Veterans of America (PVA) roll through the center's front door in their wheelchairs. This year, PVA, which has supported the center since 1988, brought its largest contingent ever, along with a check for $225,000.

"PVA has been a wonderful partner in the battle against spinal-cord injury, but they give us more than money," says Stephen G. Waxman, M.D., PH.D., the center's director and the Bridget Marie Flaherty Professor of Molecular Neurology. "They have given us a sense of vision and mission which are felt throughout this building."

(From left) Stephen Waxman describes a new microscopy facility at the Center for Neuroscience and Regeneration Research, located on the West Haven campus of the VA Connecticut Healthcare System, to Delatorro McNeal and John Bollinger of Paralyzed Veterans of America.

John Bollinger, PVA's deputy executive director, says there was new excitement in the air during this year's visit because the latest scientific strategies, including stem cell research, provide the clearest route he's seen to successful therapies for spinal-cord injury.

"Every one of us probably heard a doctor say within hours after our injury, 'You're never going to walk again,'" says Bollinger, who was paralyzed while serving in the Navy. "Now people can actually talk about the cure. We feel very optimistic that they're going to make significant advances at this center."

Waxman agrees. "As someone who chooses words carefully, I didn't feel I could use the word 'cure' 10 years ago. Now I'm saying it's on the table. It's not going to be easy, but it's an achievable goal."

Connecticut's $100 million stem cell program good news for Yale

In her Yale laboratory in 2001, Diane S. Krause, M.D., PH.D., surprised the scientific community with her discovery that adult stem cells taken from the bone marrow of mice can produce liver, lung, intestine and skin cells. To her dismay, her studies and similar findings have provided ammunition to opponents of embryonic stem cell research, who have used her results to argue that research with stem cells derived from human embryos is unnecessary. Speaking in January at a hearing of the Connecticut General Assembly, Krause told legislators that "[closing] off this avenue of research based on the early promise of adult stem cells is to play the odds with people's lives." She called upon the legislature to support both adult and embryonic stem cell research in the state.

In May the General Assembly did just that as it approved a bill to commit $100 million to embryonic stem cell research over 10 years. At a ceremony in Farmington a few weeks later, with Krause and medical school Dean Robert J. Alpern, M.D., looking on, Gov. M. Jodi Rell signed the bill into law. The bill's passage is expected to boost this stem cell research at both Yale and the University of Connecticut. The legislation establishes a two-step process in which experts in both science and ethics review requests for funding.

Unlike adult stem cells, which have shown a limited ability to develop into other cells, embryonic stem cells can generate virtually any type of cell in the body. Biologists believe they have the potential to help treat diseases such as diabetes and Alzheimer's and to repair the spine, heart and other organs.

This field of study has been limited in the United States by guidelines established by President Bush that restrict federal funding exclusively to specific embryonic stem cell lines established prior to August 9, 2001. Supporters of the research contend that many of those pre-existing lines have been tainted by cells from other animals, such as mice, and that the limited number of lines hampers opportunities for study.

Krause is spearheading the effort to establish a stem cell program at Yale, and is one of more than 20 scientists at the university doing stem cell-related work. Recruitment of a senior leader for the Yale program began this past winter with an international search and will likely be followed by the hiring of five to seven new faculty members whose work is focused solely on stem cell biology.

Once established, the new program will likely have investigators performing both adult and embryonic stem cell research, with separate laboratories for any research using embryonic cell lines not approved for federal funding.

Out & about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April 16: **LA CASSA MAGICA,** the sixth annual Yale Cancer Center (YCC) gala, was held at the Country Club of Fairfield, Conn. The event, chaired by **Kathryn Anderson Adams** of Greenwich, raised more than $400,000 to support clinical trials at the center. **Dr. Richard** and **Beth Sackler** were vice-chairs and **Louis Chênevert**, **Paul Kelly**, **Nicholas Makes**, and **Joseph Perella** served as corporate chairs. The Honorable **Rudolph W.** and **Judith S. Giuliani** were honorary chairs for the evening, which was hosted by CNN anchor and YCC board member **Paula Zahn**. **1.** (From left) Dean **Robert J. Alpern,** M.D., Rudolph Giuliani, YCC director **Richard L. Edelson**, M.D. **2.** From left: Adams, actress **Blythe Danner**. **3. Arlene** and **Mel Goldstein**. **4.** (From left) Zahn, **Carol Crapple, Lucy Day.**


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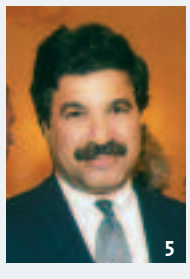
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April 21: **WOMEN OF VISION AWARDS** were bestowed by Women's Health Research at Yale (WHRY) on renowned feminist author and activist **Gloria Steinem** and **Roslyn Milstein Meyer**, PH.D., co-founder of Leadership, Education and Athletics in Partnership (LEAP) and New Haven's annual International Festival of Arts and Ideas, at a celebration held at the Omni Hotel. **1.** (From left) Steinem, Meyer, **Carolyn Mazure**, PH.D., WHRY director. **2. Linda Koch Lorimer**, J.D., vice president and secretary of Yale University. **3.** Chief Justice **Margaret H. Marshall**, J.D., of the Supreme Judicial Court of Massachusetts. **4.** Lt. Gov. **Kevin B. Sullivan**. **5. William W. Ginsburg**, CEO, Community Foundation for Greater New Haven.


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June 2: **THE SURGEON AS ARTIST,** an exhibit of artwork by Yale-affiliated surgeons, was placed on display at the Harvey Cushing/John Hay Whitney Medical Library in conjunction with the 10th Annual Spring Reunion of the Yale Surgical Society (YSS). **1. Harold Spear**, M.D., and **Suzanne Spear**. **2. Ralph S. Greco**, M.D., with his sculpture "Travertine Torso." **3.** (From left) **James M. Dowaliby II**, M.D.; **A. John Anlyan**, M.D.; Greco; **Bernard S. Siegel**, M.D.; **Paul Barcewicz**, M.D.; **Eiji Yanagisawa**, M.D.; **Michael K. O'Brien**, M.D., PH.D. **4.** Enjoying a snack are **Katie** and **Emily Malison**, daughters of **Eugenia M. Vining**, M.D., clinical instructor in surgery and YSS board member, and **Robert T. Malison**, M.D., associate professor of psychiatry.


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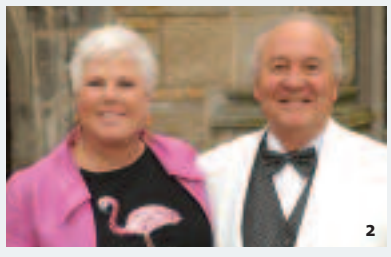
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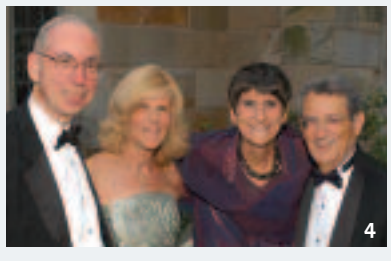
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June 11: At the second **DISCOVERY TO CURE GALA**, Congresswoman **Rosa DeLauro** (D-CT) was a featured speaker. The event, held under a festively decorated tent at Yale's Branford College, netted $256,000 for cancer screening for women at high risk, the training of high school students for careers in biomedical research, and the translation of basic research in gynecological oncology into practical treatments. In one of the evening's highlights, it was announced that two new endowments in the names of **Debra Levin** and **Marie Malouf** had been established with funds contributed by family and friends. **1.** (From left) **Rosanne Malouf**, gala chair, Levin, Marie Malouf. **2.** Gala committee members **Christine** and **Edward Fleischli**, D.V.M. **3. Thomas J. Rutherford**, PH.D., M.D., associate professor of obstetrics, gynecology and reproductive sciences **4.** (From left) **Peter E. Schwartz**, M.D., John Slade Ely Professor of Obstetrics, Gynecology and Reproductive Sciences, **Arlene Schwartz**, DeLauro, **Stanley Greenberg**, president of Greenberg-Quinlan Research.

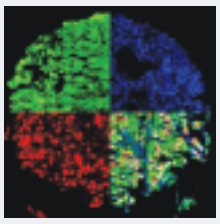
Advances

Health and science news from Yale

A chink in malignant melanoma's armor?

Pathologists have an eagle eye for subtle abnormalities in tissue that may signal disease, but even the best of them cannot discern aberrant protein patterns within individual cells.

Such patterns are the hallmark of many diseases, especially cancer, so David L. Rimm, M.D., PH.D., and Robert L. Camp, M.D., PH.D., of the Department of Pathology, devised AQUA (Automated Quantitative Analysis), a technique that combines sophisticated mathematics and microscopy to reveal and precisely measure the expression of up to five proteins in tissue at once—automatically (see photo).



In the July 7 issue of *Nature*, Rimm and collaborators reported that with the help of AQUA they discovered that MITF, a protein involved in cell survival, is "amplified"—abnormally copied many times over—in malignant melanoma cells.

In a commentary on the paper, Glenn Merlino, PH.D., a researcher at the National Cancer Institute, writes that malignant melanoma cells appear to depend utterly on MITF amplification for their survival. The protein "could be a weak link in an otherwise unbreakable chain," he notes, leading to new, targeted therapies for a deadly cancer that is notoriously difficult to treat.

Patient to surgeon: I hear a symphony

Operating rooms can be noisy, stressful places. For decades, doctors and nurses have turned to recorded music to mask the din and soothe nerves, and anxious patients being prepared for surgery have found solace in favorite melodies.

And there appear to be measurable medical benefits to music in the OR. Several studies have found that patients need less anesthesia when music is playing during surgery. But Zeev N. Kain, M.D., professor of anesthesiology, pediatrics and child psychiatry at the School of Medicine, wondered whether this phenomenon was due to music's aesthetic qualities or merely its ability to drown out the racket in the operating room.

Kain and colleagues at Yale and the American University of Beirut designed a study in which patients undergoing minor urological surgery who could control the dosage of a sedative—they had received spinal anesthesia but were awake—listened through headphones to either music or white noise generated by a relaxation device. As reported this May in the journal *Anesthesia and Analgesia*, the white noise blocked out the sounds of the operating room as effectively as music, but the patients who listened to music used significantly less sedative.

Ovarian cancer test exposes quiet killer

For women and their doctors, ovarian cancer is "the disease that whispers," says Yale's Gil Mor, M.D., PH.D., associate professor of obstetrics, gynecology and reproductive sciences. In many cases, this deadly cancer grows silently, or sends out easily misread signs such as indigestion or bloating. If caught early, the disease has a 90 percent cure rate, but for most women the first sign of trouble comes when they are diagnosed with advanced, largely incurable tumors.

Trying to hear and heed that first whisper, Mor and colleagues have developed a new test for the early detection of ovarian cancer. Based on the levels of four cancer-related proteins in a sample of blood, the test accurately and sensitively picks out women with early-stage cancers.

The promising advance came from basic research in Mor's laboratory, coupled with the work of Yale-New Haven Hospital clinicians in the Discovery to Cure program for ovarian cancer (see *Out & About*, page 4). The program was initiated two years ago to bring researchers and clinicians together to accelerate the application of basic research to the diagnosis and treatment of women's reproductive cancers.

"This detection system, which could give a tremendous boost to early diagnosis of ovarian cancer, started out as absolutely basic science," says Peter E. Schwartz, M.D., the John Slade Ely Professor of Obstetrics, Gynecology and Reproductive Sciences and executive director of the program. "Within the framework of the Discovery to Cure initiative, we were able to move the test quickly into our early detection program."

Mor found the four proteins by a process of elimination, starting with 165 cancer-related candidate marker proteins. In collaboration with David C. Ward, PH.D., then in Yale's Department of Genetics and now director of the Nevada Cancer Center in Las Vegas, he used protein chip technology to measure each potential marker in blood samples from nearly 100 women, including newly diagnosed patients and healthy, age-matched controls. No one protein was found that could reliably distinguish between women with and without cancer, but further analysis revealed a set of four protein hormones whose combined profiles indicated with 95 percent accuracy which women had ovarian cancer.

The test is now being used experimentally in the Yale Early Detection Program for Ovarian Cancer, where it has delivered promising results under the direction of Thomas J. Rutherford, PH.D., M.D., associate professor of obstetrics, gynecology and reproductive sciences, and Discovery to Cure's clinical director.

For example, one young high-risk patient who had been previously treated for breast cancer elected to have her ovaries removed because she was concerned about the possibility of ovarian cancer. Although her ovaries appeared to be normal and she had no other signs of the disease, pathologists who examined the tissue after the surgery found a stage 1A cancer, "the earliest stage you can recognize," says Mor. When blood that had been drawn from the patient before surgery was examined with the new test, it scored positive. "From 40 high-risk patients screened so far in this manner, we've had 3 positives who had all been shown to have cancer in the pathology lab."

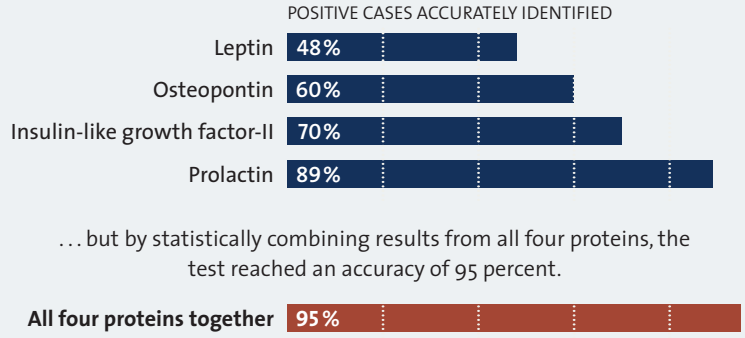
Despite its potential, the test is not ready for prime time: 95 percent accuracy means that 5,000 out of every 100,000 women tested would obtain a false-positive result. For widespread use, the screen needs to achieve more than 99 percent accuracy. Mor hopes to reach that benchmark by identifying additional protein markers, and plans are in the works to screen up to 1,000 more women in cooperation with the National Cancer Institute.

So far, Mor's lab has been a wellspring of important clinical prospects in ovarian cancer. A few years ago he uncovered phenoxodiol, a new compound that is in Phase II clinical testing at Yale under a fast-track designation from the FDA. Now Mor is working on a personalized medicine approach that uses tumor samples from patients and laboratory tests to select the best course of chemotherapy for each individual woman.

"Whatever Gil can come up with in his lab," Schwartz says, "we are happy to move quickly into our translational laboratory and then on into the clinic."

Greater than the sum of its parts

In developing a new blood test for ovarian cancer, Yale researchers tested four different proteins, each of which showed some promise . . .



. . . but by statistically combining results from all four proteins, the test reached an accuracy of 95 percent.

Source: Gil Mor.

From humble start at Yale, REMEDY thrives

In 1991, after several volunteer missions to Latin America, anesthesiologist William H. Rosenblatt, M.D., made an observation that was to have far-reaching effects: many of the hospitals he visited were in dire need of medical supplies, while at Yale-New Haven Hospital (YNHH) many of those same supplies were discarded without being used.

Thus was born REMEDY (Recovered Medical Equipment for the Developing World), a nonprofit committed to recovering surplus medical supplies and teaching others how to do it.

What started as a local program at YNHH to collect opened but unused surgical supplies—which have never touched a patient but can't be reprocessed due to liability concerns—has grown into a grass-roots organization involving hundreds of hospitals around the United States. From Yale alone, the REMEDY program has donated more than 30 tons of medical supplies to hospitals overseas. "Each of these pieces of material, whether it be a suture, a glove or a sponge, is going to wind up in another part of the world and be useful," says Rosenblatt. The program has also saved the hospital over $30,000 in disposal costs since its inception, at a cost of only about $200 per year for disinfecting and bagging the supplies.

Today, REMEDY trains hospitals to organize their own programs and has helped 358 hospitals begin recovery activities. The organization provides teaching packets free of charge, and with Yale's Office of International Health, has developed a notification program called AIRE-mail, in which medical supplies donated by hospitals and vendors are advertised via e-mail to 125 nonprofit humanitarian organizations. It has also developed a catalog called the REMEDY Atlas, consisting of the 240 supplies most often recovered, which will help ensure that recipients are getting supplies they need.

Meanwhile, the collecting, sorting, packing and shipping of surplus medical supplies has largely been taken over by students. In 2001, RYSA (REMEDY at Yale Students Association) was started by Jonathan S. Cohen, PA-C, a physician associate who is now a surgical resident at The Johns Hopkins Hospital. Between last August and January, RYSA volunteers shipped 3,500 pounds of supplies from the New Haven area to eight countries. Information about the program is available on the Web at www.remedyinc.org.

Finding new perfumes to foil a femme fatale

The female mosquito that spreads malaria might be felled by smell

With the notable exception of the West Nile virus, the industrialized world is blessedly free of mosquito-borne diseases. But according to the World Health Organization (WHO), malaria causes over 300 million acute illnesses and kills at least a million people each year, mostly children in developing countries. The WHO estimates that an African child dies of malaria every 30 seconds. "We don't think about it much in this country," says John R. Carlson, PH.D., the Eugene Higgins Professor of Molecular, Cellular and Developmental Biology, "but as a world health problem this is just staggering."

Carlson, an expert on the sense of smell in insects, has thought about malaria a great deal, and with the help of a five-year, $8.5 million grant offered by the Grand Challenges in Global Health initiative to Vanderbilt University, he and a team of scientists on three continents are launching an ambitious and innovative plan of attack against this dreaded disease.

John Carlson

In 1999, researchers in Carlson's lab identified the genes that encode the exquisitely sensitive odor receptors found in fruit fly antennae—the first such genetic mapping of any insect olfactory system. The mosquitoes that spread malaria, females of the genus *Anopheles*, use similar receptors to find their human hosts, and Carlson was eager to apply the techniques he had developed to

A female of the species *Anopheles stephensi*, the insect that transmits malaria on the Indian subcontinent, seen in flight and full of blood. *Anopheles* mosquitoes find their human hosts by following odors.

Anopheles. "After doing all this basic research for many years at Yale," he says, "I thought we should see whether any of it could be useful in addressing real-world problems."

Carlson contacted Laurence J. Zwiebel, PH.D., an associate professor of biological sciences at Vanderbilt who studies mosquito olfaction, and the two collaborated to identify the genes for *Anopheles* odor receptors in 2001. Because fruit flies are far easier to study in the lab than *Anopheles*, Carlson's lab devised a method to place *Anopheles* receptors in fruit fly antennae, and by 2004 Carlson, in collaboration with graduate student Elissa Hallem, had pinpointed an antenna protein in the *Anopheles* female that specifically responds to a chemical compound in human sweat.

"That was exciting," Carlson says, "because it suggested the possibility that we could then identify compounds that either excited or blocked those receptors, thereby inhibiting the ability of the mosquitoes to find us. You could sort of jam the system."

The discovery came at an auspicious time. In 2003, the Grand Challenges initiative was seeking novel, practical solutions to the world's most massive public health problems. Zwiebel assembled a proposal to design new repellents and traps that specifically target *Anopheles* and to test them in field settings in Africa—precisely the sort of "deliverable technology" the initiative was encouraging.

In the wide-ranging project, Zwiebel, the principal investigator, and Carlson will test hundreds of chemical compounds using fruit flies genetically engineered with *Anopheles* odor receptors to see which elicit the most robust response. Colleagues at Wageningen University in the Netherlands will then assess whether the candidate chemicals actually alter *Anopheles* behavior. Compounds that pass this test will be analyzed again in specially designed mosquito enclosures in Tanzania. Finally, the repellents and attractants deemed effective will be deployed in villages in the Gambia, a nation in West Africa, to see whether they can reduce the incidence of malaria.

This multi-tiered approach was a good fit with the goals of the Grand Challenges initiative, Carlson says. "They didn't want just lab research in America. They actually wanted to develop real, practical solutions to these problems, and for that we needed real expertise in the field in Africa."

Carlson hopes the findings from the new project will prove useful in curbing other mosquito-borne illnesses, such as yellow fever. "With insect-borne diseases, the best way to control the disease is often to control the insect," he says. "We smell good to the mosquitoes, so if we can understand in molecular detail how the insects are attracted to us, we might be able to devise new means of controlling them."

Flavell *continued from page 1*

investigator. "But most of the studies needed are really invasive, and therefore cannot safely be performed in people. There are enormous difficulties making sure that what you do in clinical trials is safe and isn't going to adversely affect the patient."

But a remarkable advance in a Swiss laboratory may provide a long-sought bridge between the bench and the bedside for immunologists. In 2004, Markus G. Manz, M.D., and his colleagues at the Institute for Research in Biomedicine managed to create a rudimentary but functional human immune system in mice by injecting human umbilical-cord blood containing stem cells and other progenitor cells into a mutant strain of mice that are born without immune systems of their own.

Manz's paper appeared just as the Grand Challenges in Global Health initiative began accepting grant proposals. Flavell, seeing the vast potential of combining Manz's technique with his own molecular genetic approaches in the mouse to streamline the development of new vaccines, proposed that his team join forces with Manz and with Tarrytown, N.Y.-based biotech company Regeneron Pharmaceuticals to perfect a mouse model of human immunity.

In late June, Flavell received the happy news that the Grand Challenges initiative had offered him a $17 million grant to oversee the project.

"It's akin to a 'Manhattan Project,' to make this work like a true human immune system, so you could really do experimentation that is predictive of the human response," Flavell says. "The present system doesn't work exactly like human immunity, but we think we have an understanding of the deficiencies, and we're going to make it work."

A mouse model of human immunity would allow scientists to test many human vaccines in mice, including experimental HIV vaccines, which has heretofore been impossible because mice are normally not susceptible to the virus.

But Flavell says that the technique will have any number of applications. "This system, once it's up and running, could be used to study all kinds of things," he says. "It will be a big step forward."

Elizabeth E. Eynon, PH.D., a research scientist in Flavell's lab, says that the model could make clinical trials much more efficient. "The FDA will require people to do just as many Phase I and Phase II trials as they do now," she says, "but the likelihood of failure at those stages would be reduced if we can show safety and efficacy beforehand."

Flavell and Eynon are gearing up to hire a dozen new scientists to begin the mouse project in earnest, but the magnitude of the Grand Challenges grant, the largest foundation grant in the history of the School of Medicine, is only slowly sinking in.

"Our heads are still spinning," Flavell says.

Fund *continued from page 1*

human genome—took advantage of the company's offer by earmarking their $300,000 gift to endow a fund that will support Yale's Combined Program in the Biological and Biomedical Sciences (BBS) and honor the memory of her mentor and thesis advisor, Edward L. Tatum, PH.D.

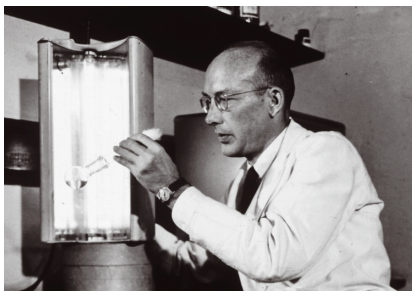
Slayman met Tatum at Rockefeller University, where she earned her doctorate under his supervision in the 1960s, just after he won the Nobel Prize in physiology or medicine for pioneering work on genetic regulation of metabolism in the cell. "For a very famous man—he was at the height of his career—he nonetheless took extraordinary measures to work closely with every student and every postdoc in his lab group," recalls Slayman, Sterling Professor of Genetics and professor of cellular and molecular physiology.

Carolyn Slayman

Tatum did part of the research that led to the Nobel at Yale in the late 1940s with his graduate student Joshua Lederberg. The two discerned how bacteria exchange and recombine genetic material, findings that paved the way for gene sequencing and genetic engineering. They shared the prize with another Tatum collaborator, George W. Beadle, PH.D.

Slayman and Ira Mellman, PH.D., chair and Sterling Professor of Cell Biology, were the chief architects of the BBS program. Founded in 1996, the program has become a cornerstone of graduate science education at Yale, transforming the curriculum to reflect the increasingly interdisciplinary nature of biological science. Knowing Tatum's dedication to nurturing aspiring scientists, Slayman thought that a fund commemorating him should be linked to the program, and she hopes that the new Edward L. Tatum Fund will support an outstanding BBS student in the field of genetics.

Ever the scientist, Slayman says she hopes the Applera gift will be "autocatalytic"—a term from chemistry for the mechanism by which the products of a reaction provide fuel for further reactions—and will inspire others to support the BBS program. The gift already shows signs of self-replication: it will benefit from a university policy that matches endowment gifts to the School of Medicine, which will double its impact.



Edward Tatum in his Rockefeller University laboratory in the late 1950s.

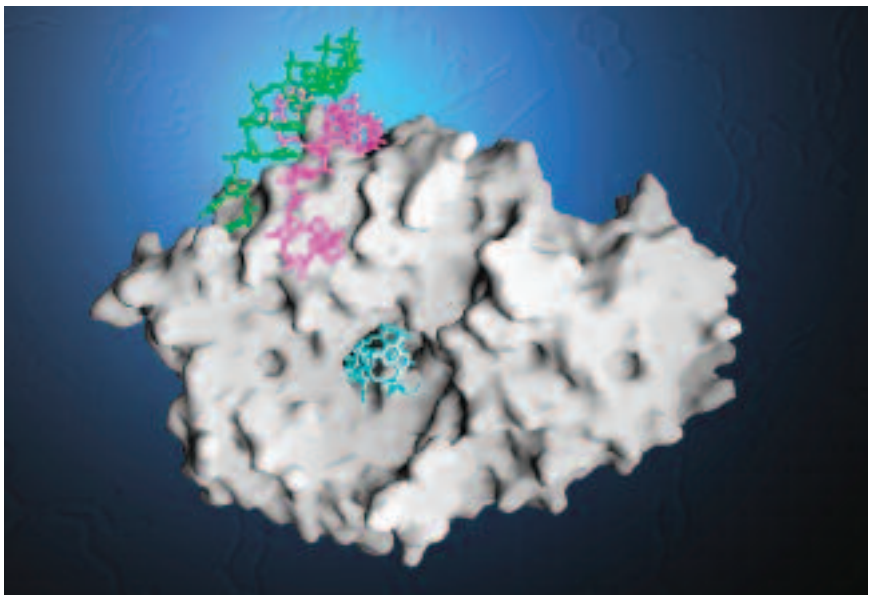
Grants and contracts awarded to Yale School of Medicine, *March/April 2005*

Federal

George Aghajanian, NIH, *Psychotogenic Drug Action on Chemically Defined Neurons*, 4 years, $931,200 • **Thomas Biederer**, NIH, *Mechanisms of Syncam-Induced Synapse Formation*, 5 years, $1,445,391 • **Jonathan Bogan**, NIH, *Proteomic Characterization of Insulin Signaling Targets*, 2 years, $327,000 • **Richard Bungiro**, NIH, *Mucosal Immune Responses in Hookworm Infection*, 2 years, $163,500 • **Edward Chu**, NIH, *Molecular Regulation of Translational Regulation*, 4 years, $886,720 • **Lauren Cohn**, NIH, *T Cell Control of Airway Mucus Production*, 5 years, $2,043,750 • **Ralph DiLeone**, NIH, *Investigating the Role of Leptin Signaling in the Ventral Tegmental Area*, 2 years, $400,125 • **Gail D'Onofrio**, NIH, *Enhancing Emergency Room Physician-Performed Alcohol Interventions in the Emergency Department*, 5 years, $3,461,863 • **Durland Fish**, Department of Agriculture, *Eco-Epidemiology of Emerging Arthropod-Borne Pathogens in the Northeast*, 1 year, $300,781 • **Gerald Friedland**, NIH, *New England Program for AIDS Clinical Trial—PROACT*, 1 year, $802,492 • **Guadalupe Garcia-Tsao**, NIH, *Cirrhosis and Its Complications*, 5 years, $775,659 • **Peter Glazer**, NIH, *Cisplatin Damage Response and Cell-to-Cell Communication*, 5 years, $1,446,633 • **Ruth Halaban**, NIH, *Epigenetic Chromatin Changes as Melanoma Markers*, 2 years, $281,220 • **Hatim Hassan**, NIH, *Mechanisms of Regulation of Anion Exchanger SLC26A6*, 5 years, $710,100 • **Michael E. Hodsdon**, NIH, *Structural Basis of Prolactin Receptor Recognition*, 5 years, $1,465,139 • **Mark Horowitz**, NIH, *Regulation of Bone Remodeling by Megakaryocytes*, 5 years, $1,798,500 • **Themis Kyriakides**, NIH, *MCP-1 and Attenuation of the Foreign Body Response*, 5 years, $1,524,640 • **Linda Mayes**, NIH, *Neurocognitive Development in Children Living in Poverty*, 5 years, $2,529,478 • **David McCormick**, NIH, *Neurotransmitter Actions in Neocortex and Thalamus*, 4 years, $1,660,477 • **Laura Ment**, NIH, *Multicenter Randomized Indomethacin Intraventricular Hemorrhage Prevention Trial*, 5 years, $6,965,242 • **Pramod Mistry**, NIH, *Patient-Oriented Research in Inherited Metabolic Liver Diseases*, 5 years, $738,291 • **Michael Nathanson**, NIH, Ca^{2+} *Waves in Hepatocytes: Mechanisms and Effects*, 5 years, $486,127 • **Paul Noble**, NIH, *Regulation of Pulmonary Fibrosis by CXCR3*, 4 years, $1,635,000 • **Lynne Regan**, NIH, *High-Throughput Assays for Inhibitors of Protein-Protein Interactions*, 3 years, $975,058 • **Jennifer Ruger**, NIH, *Economic Evaluation of Addiction Services*, 3 years, $445,818 • **Raymond Russell**, NIH, *Function and Regulation of Cardiac Uncoupling Proteins*, 4 years, $1,308,000 • **Joseph Santos-Sacchi**, NIH, *Membrane Properties of Cells Comprising the Outer Hair Cell System*, 5 years, $2,388,206 **Gerald Shadel**, Department of the Army, *Nuclear-Mitochondrial Signals That Control Oxidative Stress Resistance and Longevity*, 3 years, $294,034 • **Albert Shaw**, NIH, *Top3 Homologues in Lymphocyte Genome Stability and Aging*, 5 years, $355,175 • **Dieter Soll**, NIH, *Studies on Transfer RNA*, 4 years, $5,345,449 • **Stefan Somlo**, NIH, *Genetics of Autosomal Dominant Polycystic Liver Disease*, 5 years, $2,401,172 • **Carlos Stocco**, NIH, *Regulation of Estradiol Production by Prostaglandin F2alpha*, 2 years, $163,500 • **Stephen Strittmatter**, NIH, *Molecular Determinants of Axonal Regeneration*, 4 years, $1,512,376 • **Peter Takizawa**, NIH, *Mechanism of mRNA Transport by Myo4p*, 5 years, $1,379,288 • **Sandra Wolin**, NIH, *RNA Quality Control and Environmental Stress*, 4 years, $1,316,769 • **Lawrence Young**, NIH, *Regulation of Glucose Transport in the Ischemic Heart*, 4 years, $1,471,500

Non-Federal

Richard Bucala, Alliance for Lupus Research, *Macrophage Migration Inhibitory Factor Inhibition in Systemic Lupus Erythematosus*, 1 year, $250,000 • **Ronald Duman**, Organon Inc., *Influence of Organon #2448 and Organon #26576 on Neurogenesis in the Adult Hippocampus*, 1 year, $221,160 • **Marie Egan**, Cystic Fibrosis Foundation, *The Effects of Curcumin Treatment on the Function of Delta F508 Cystic Fibrosis Transmembrane Conductance Regulator*, 1 year, $108,000 • **Alan Garen**, Sidney Kimmel Cancer Center, *Targeting Vessels in Tumors*, 5 years, $168,067 • **Susan Kaech**, Edward Mallinckrodt Jr. Foundation, *Identifying the Genes That Regulate Formation of Memory CD8 T Cell Precursors*, 3 years, $50,000 • **Elias Lolis**, Robert Leet and Clara Guthrie Patterson Trust, *Identification of the Allosteric Sites of CXCR4*, 1 year, $75,000 • **Stephen Malawista**, G. Harold and Leila Y. Mathers Charitable Foundation, *Leukocytes and Inflammation*, 1 year, $110,000 • **David Morris**, Robert Leet and Clara Guthrie Patterson Trust, *Pathogenesis of Fibrotic Lung Disease*, 1 year, $75,000 • **David Rimm**, Breast Cancer Alliance Inc., *Spectral-Spatial Imaging to Detect Premalignancy in Breast Tissue Samples*, 1 year, $100,000 • **Craig Roy**, Health Research Inc., Coxiella burnetii *Type IV Effector Proteins*, 1 year, $163,500 • **Gerald Shadel**, Robert Leet and Clara Guthrie Patterson Trust, *Genetic Transformation of Mitochondria: Toward Mouse Models and Human Gene Therapy for Mitochondrial Diseases and Aging*, 1 year, $75,000 • **Stefan Somlo**, Mizutani Foundation for Glycoscience, *The Role of N-Glycosylation in Human Polycystic Diseases*, 1 year, $46,442 **Zhaoxia Sun**, Edward Mallinckrodt Jr. Foundation, *Chemical Suppression of Polycystic Kidney Disease in Zebrafish*, 1 year, $50,000 **Flora Vaccarino**, Tourette Syndrome Association Inc., *Inhibitory Interneurons in the Cerebral Cortex of Patients with Tourette's Syndrome*, 1 year, $74,558 • **Li Wen**, Juvenile Diabetes Research Foundation International, *Tolerance Induction by Insulin Reactive and TGFβ Producing T Cells*, 3 years, $165,000 **Kevin White**, Columbia University, *Integrated Approaches to Hox-Regulated DNA Elements*, 1 year, $131,415 • **Graham Williams**, Astra Zeneca, L.P., *Characterization of the Neurobiological Consequences of Acute Alpha-7 Treatment in the Nonhuman Primate: Identification of the Potential for Improving Cognitive Function in Schizophrenia*, 1 year, $230,875



In NIH-funded research reported in *Cell* in May, Sandra Wolin and Karin Reinisch of the Department of Cell Biology determined how the Ro protein, a major target of the immune system in patients with autoimmune diseases such as lupus, binds to RNA. In normal cell metabolism, Ro is thought to function in quality control of noncoding RNAs, ensuring that misfolded and defective RNAs are degraded. These misfolded RNAs bind both on the outer surface of Ro (green and purple strands) and in a hole in the protein (blue strand).

Flies *continued from page 1*

niques like stimulating nerves and muscles with implanted electrodes. The new Yale study marks the first time an animal's behavior has been shaped by remote control without such invasive tactics. "We do not have to poke them with electrodes," says Gero A. Miesenböck, M.D., an associate professor of cell biology at the medical school, who led the study.

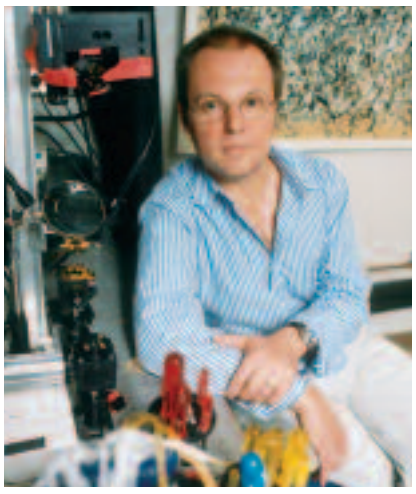
The research, which appeared in the April 8 issue of the journal *Cell*, prompted a flurry of international headlines that made comparisons to video games and mind control. It even became fodder for Jay Leno's monologues on *The Tonight Show* —twice.

But jokes aside, Miesenböck says that the research is a new way to learn how nerve cells govern behavior, and that it will open new avenues to understanding neurological illnesses. "Initially, scientists are often passive observers," Miesenböck says. "But at some point, active control becomes essential in order to establish causes and mechanisms."

Using meticulous genetic techniques, Miesenböck and graduate student Susana Q. Lima, now a postdoctoral fellow at Cold Spring Harbor Laboratory on Long Island, inserted rat ion channels, microscopic pores that admit calcium into cells, in nerve cells that control fruit flies' escape movements. In rats, these channels activate cells by opening in the presence of adenosine triphosphate (ATP), but Miesenböck and Lima injected the flies with a "caged" form of ATP that only functions when exposed to light.

The tiny flies were placed into an arena the size of a dime, where they dawdled until Lima and Miesenböck flashed laser pulses at them, which "liberated" the caged ATP and caused the flies to perform characteristic escape responses. The flies behaved on cue up to 82 percent of the time. "There was all this hope that it would work," Miesenböck says, "but I think the extent to which it did was a very pleasant surprise."

Because escape behavior also occurs when a fruit fly detects a shift from light to darkness that might signal danger—from a descending fly swatter, say—the researchers did the same experiment on a strain of flies in which the visual system was engineered to be insensitive to light, and they got the same response. In another experiment that hints at the technique's potential for restoring neural function, Miesenböck and Lima even got headless flies to perform the trick. Because of the architecture of their nervous system,



From the pages of *Cell* to *The Tonight Show*'s stage, Gero Miesenböck's remote-controlled flies have created a stir.

fruit flies can live for a day or more without their heads, but they remain motionless. However, when equipped with Miesenböck and Lima's "phototriggers," the headless flies took flight whenever the laser was turned on.

In addition to studying the escape circuit, Miesenböck and Lima placed their phototriggers in fruit fly neurons that produce dopamine, a neurotransmitter involved in movement that has been implicated in Parkinson's disease and addiction. When they activated the cells with light, the flies displayed "quite surprising" behaviors reminiscent of dopamine pathologies in humans, Miesenböck says, adding that before these experiments, "very little was known about what these neurons do."

"It's a really cool technique," says Ronald L. Davis, PH.D., a professor of molecular and cellular biology at Baylor College of Medicine, citing the study's unique strengths as "the untethering of the animal, and using light as the stimulus."

The method is also extraordinarily precise: in one experiment, Miesenböck and Lima were able to place rat ion channels in just two of the 100,000 cells that make up the fly nervous system. And the procedure allows scientists to selectively turn on parts of an intact nervous system. These parts need not be next to each other, and their locations need not be known in advance. This creates enormous potential for discovering which groups of neurons control which aspects of behavior.

Both Miesenböck and Davis say that applying the technique to human illness is still far off, and for now, Miesenböck is sticking to fruit flies. Next he plans to probe the neural activity around their courtship behavior—essentially, he'll be playing Cupid. "It's not just the sex act that interests us," he says, but "it'll get us on *The Tonight Show* again, I'm sure."

New president of alumni body sees a bright future ahead

Frank Lobo, M.D., has roots that run deep at the School of Medicine. He earned his medical degree here in 1992, and for many years served as a faculty member in immunology, within the Department of Medicine. After seven years as an officer and executive committee member of the Association of Yale Alumni in Medicine (AYAM), he was elected the alumni group's president in June.

Lobo says that he's looking forward to his two-year term, in particular because of the strength of the school's current leadership. "This is an extremely positive moment for the

Frank Lobo

medical school," he says. "Our new dean [Robert Alpern] really has demonstrated a great understanding not only of what's so magical about Yale, but also of the challenges that the school faces. He appears to have a very strategic vision about how to make the appropriate changes."

Lobo, who was the AYAM vice president for the last two years, began his term July 1. He succeeds Donald E. Moore, M.D., M.P.H., and he says he'll pick up where Moore left off.

"The plans are to carry on with the mission of the AYAM, which is to involve the alumni in the affairs of the medical school and contribute to its welfare in any way we can," Lobo says. "We have a vigorous expansion of the missions of research and patient care, as well as a very appropriate sensitivity to the uniqueness of our educational mission by our new dean. That will be a very easy and exciting message to bring to the alumni."

Jocelyn S. Malkin, M.D., was elected vice president of the association. Malkin, a psychiatrist in private practice in Maryland, has served on the AYAM executive committee and as a delegate and member of the board of governors of the Association of Yale Alumni. Christine Walsh, M.D., serves as secretary until June, 2006.

The AYAM helps shape and lead all the school's alumni programs, including class reunions each June, outreach events around the country and activities in greater New Haven. The group will host an outing to the Yale-Harvard Game on November 19.

Ribosome

continued from page 1

one of 3,000-plus RNA nucleotides that, along with 21 proteins, make up the enormous structure.

"We found that the resistance results from a mutation in the RNA part of the ribosome that puts an extra bump on its surface that pushes the drug a little further away from its preferred site than it would like to be," Moore says. This minor change causes antibiotics to lose their grip on the ribosome. The binding of one drug used in the study, azithromycin, was reduced by a factor of 10,000 on ribosomes of resistant bacteria.

Bulges of the kind found by Steitz and Moore are so effective at protecting bacteria that they have developed two ways to add them. Some, such as those examined in the new study, mutate their ribosomal RNA, but more commonly they acquire an enzyme that adds the bump to unmutated RNA.

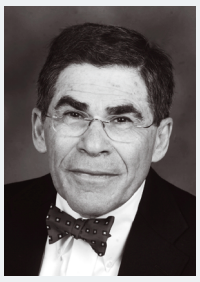
Understanding the structural basis of resistance suggests how to beat it: chemists can build new antibiotics one atom at a time, tailoring the chemical shape of the drug to accommodate that extra bump. Similar approaches have resulted in new drugs to treat AIDS and cancer.

"Without detailed structure information, you do what medicinal chemists have done for years—you randomly change the antibiotics in a kind of blind way, and keep testing them," Moore says. "Now, we can make guided changes based on the structure."

Five years ago Steitz and Moore's lab beat out the competition in a hotly contested international race to solve the high-resolution structure of the bacterial ribosome's large subunit. They quickly joined with several Yale colleagues to found Rib-X Pharmaceuticals, and the New Haven-based startup has been pursuing new antibiotic drugs ever since.

According to structural biologist Jamie H.D. Cate of the University of California at Berkeley, the quality of Steitz and Moore's structures makes them particularly valuable. "Their structures are really gorgeous," Cates says. "Steitz and Moore see more detail in the ribosome than anyone else can see, and getting those details right is important for drug discovery."

Awards & honors



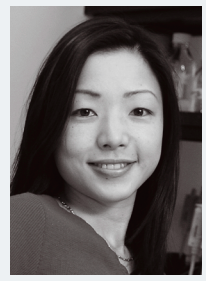
Henry J. Binder, M.D., professor of medicine and of cellular and molecular physiology, has received the Distinguished Achievement Award from the American Gastroenterological Association. The award recognizes an individual who has made a major contribution to clinical or basic research in gastroenterology or in an allied field.

Alison P. Galvani, PH.D., assistant professor of epidemiology, has received a Young Investigators' Prize from the American Society of Naturalists for her research on how evolutionary forces shape the engagement between infectious agents and the immune system of individual hosts, and on how evolution shapes host-parasite interactions.

Bryan C. Hains, PH.D., associate research scientist in neurology, has been awarded a two-year Pfizer Scholars Grant in Pain Medicine for his research on neuropathic pain in spinal-cord and peripheral nerve injury. The award supports the career development of junior faculty who are pursuing pain medicine research relevant to human health.

Josephine Hoh, PH.D., associate professor of epidemiology, has been selected as a 2005 New Scholar in Aging by the Ellison Medical Foundation. The four-year, $200,000 award will allow Hoh to further her earlier research, which identified at least one important genetic variant in age-related macular degeneration (AMD), a leading cause of blindness.

Theodore R. Holford, PH.D., the Susan Dwight Bliss Professor of Epidemiology and Public Health, was named a fellow of the American Statistical Association. Holford studies temporal trends in disease maps, models for controlling cancer, and the use of geographic information systems to assess environmental exposures and disease risk.



Akiko Iwasaki, PH.D., assistant professor of immunobiology, has been named a 2005 Investigator in the Pathogenesis of Infectious Disease by the Burroughs Wellcome Fund. The award will support her research on the interaction between host and viruses that cause diseases such as genital herpes and respiratory influenza infection.

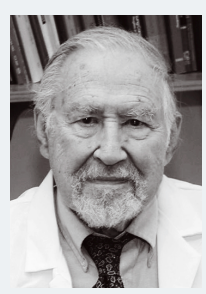
Becca Levy, PH.D., associate professor in the School of Public Health's Division of Chronic Disease Epidemiology, has been named a fellow in the Behavioral and Social Sciences section of the Gerontological Society of America (GSA). The GSA is the nation's oldest scientific organization devoted to research, practice and education in aging.

Glenn C. Micalizio, PH.D., assistant professor of chemistry, has been named a 2005 Beckman Young Investigator. The Young Investigator Awards are given annually by the Arnold and Mabel Beckman Foundation to provide support to promising young faculty members in the early stages of academic careers in the chemical and life sciences.

Stephanie S. O'Malley, PH.D., professor of psychiatry and director of the Division of Substance Abuse Research, has won the 2004 Dan Anderson Research Award. The award, sponsored by the Butler Center for Research at the Hazelden Foundation, honors a researcher who has advanced scientific understanding of recovery from addiction.

Lynne J. Regan, PH.D., professor of molecular biophysics and biochemistry and of chemistry, has won a Guggenheim Foundation Fellowship for her research on novel anti-cancer reagents. The Fellowships support research in all fields of knowledge, under the freest possible conditions, on the basis of distinguished achievement and exceptional promise.

Sandra G. Resnick, PH.D., assistant professor of psychiatry and associate director of the Northeast Program Evaluation Center of the Veterans Health Administration, received the Carol T. Mowbray Early Career Research Award from the U.S. Psychiatric Rehabilitation Association for her research on consumer-run mental health programs for veterans.



Raymond Yesner, M.D., professor emeritus and senior research scientist in the School of Medicine's Department of Pathology for more than 50 years, has been awarded the Gold Medal by the International Academy of Pathology (IAP) for excellence in research and teaching. Yesner, a longstanding member of the IAP, is an authority on pathology of the lung.