Medicine@Yale

Advancing Biomedical Science, Education and Health Care

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Acquisition of Bayer site will accelerate biomedical research

Yale President Richard Levin (left) and West Haven Mayor John Picard swapped hats to mark the purchase of the Bayer campus.

Yale University's recent purchase of the 136-acre Bayer HealthCare campus in the municipalities of West Haven and Orange, Conn., offers the School of Medicine an unprecedented opportunity to expand and quicken the pace of its biomedical research programs, school officials say.

Yale President Richard C. Levin announced the acquisition, which includes 550,000 square feet of laboratory space, on June 13.

"Yale is already in the midst of a boom in the expansion of its science and medical facilities," said Levin. "The addition of this ready-made, state-of-the-art research space will allow that growth to accelerate at an unprecedented level—potentially making it possible for Yale scientists to develop new discoveries, inventions and cures years earlier. The availability of Bayer's science laboratories will enable us to undertake research programs that we would not have had space to develop for a decade or more."

School of Medicine Dean Robert J. Alpern, M.D., says plans for how to use the space are not finalized, but the medical school will be a major participant. "There are programs we would really like to grow in which growth has been limited by space," he says.

However, Alpern also says he

Bayer, *page 6*

Passing the torch

A shared life in research inspires $2.5 million gift to aid young scientists

Franklin and Lois Top (left) drew on their own experiences when making a gift to the Yale Scholars program started by Dean Robert Alpern (right) to help beginning scientists get a foothold in their fields.

When Franklin H. Top Jr., M.D., and his wife, Lois Top, M.N.ED., paid a visit to the School of Medicine recently, it was a homecoming for them both. In the late 1950s, Lois was a nursing student at the University of Connecticut and living in a dormitory the program maintained then near Grace-New Haven Hospital (now Yale-New Haven Hospital), the hospital where she was born. Franklin, her husband-to-be, had earned an undergraduate degree in biochemistry from Yale College and was working toward his medical degree at the School of Medicine. "I needed a date for the Yale-Dartmouth game, so I went over to the UConn mixer," Franklin recalls. "And that's how we met."

That meeting marked the beginning of an eventful life in biomedical research that would take the couple from New Haven to Minneapolis to Bethesda to Bangkok. Having each paid their dues at the lab bench, the Tops experienced firsthand the challenges of beginning a career in biomedical research. To help smooth the way for young scientists just entering the field, the couple recently made a $2.5 million gift to the School of Medicine to establish the Lois and Franklin Top, Jr. Yale Scholar. The Yale Scholars program is a recent initiative of Dean Robert J. Alpern, M.D., which provides four years of research funding to the most promising new researchers recruited at the medical school.

"To be able to take talent that's already been recognized in a postdoctoral program and let that person run with it makes an awful lot of sense," Franklin says. "If you want to encourage good people to get into this field, this is a good way of doing it."

Lois agrees. "It's really time-consuming to pursue a research career, and you can use all the help you can get, from ideas to funding to good lab space to do your work," she says. "This should help alleviate some of the roadblocks."

After Franklin graduated from the medical school in 1961, he completed his internship and residency in pediatrics at the University of Minnesota, where Lois also obtained a master's degree in nursing education.

In 1966, Franklin joined the Army, where he spent 22 years doing infectious disease research at the Walter Reed Army Institute of Research (WRAIR), including a three-year stint that he, Lois and their three young sons spent together in Thailand, where Franklin worked at a laboratory affiliated with the WRAIR.

Franklin eventually rose to the rank of colonel and served as director and commandant of the WRAIR. When the children were all in school,

Yale Scholar, *page 6*

International effort rewrites the book on the human genome

When the Human Genome Project wrapped up in 2003, the world got its first complete instruction manual on how to build a human. The only problem? No one knew how to read most of it.

Michael Snyder

That's because just a tiny fraction of the 3 billion letters in the manual form words that can be easily interpreted. Scientists have long relegated the rest, for the most part, to the trash heap.

But the results of a new study published in the June 14 issue of *Nature* reveal that there's a lot more going on in the vast, uncharted regions of the genome than previously supposed, and suggest that so-called "junk DNA" may not be junk after all. Now the challenge is to figure out what all that DNA is for. Doing so may prove crucial for understanding complex human diseases.

"It's sort of like Lewis and Clark," says Michael Snyder, PH.D., Lewis B. Cullman Professor of Molecular, Cellular and Developmental Biology and of molecular biophysics and biochemistry. "We're trying to map out what's there."

Toward that end, Snyder's lab is part of the Encyclopedia of DNA

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As teacher, mentor, physician and valued advisor, cardiologist Lawrence Cohen has touched the lives of students, colleagues, patients and leaders of the School of Medicine for more than three decades.

Clinical master, consummate teacher

For 35 years, students have learned how to listen from 'Larry the Heart'

A beating heart has its own sonic signature, the steady lub-dub of the chambers opening and closing as blood flows, backs up and flows again through the only muscle in the body that never rests. To the trained ear, these murmurs, whooshes, gallops and rubs speak volumes, and provide clear information about heart disease or defects.

For more than three decades, teaching the language of heart sounds to medical students has been the job of Lawrence S. Cohen, M.D., the Ebenezer K. Hunt Professor of Medicine. Deliberate, concise and always impeccably dressed, Cohen is the sort of professor whom medical students notice enough to honor with a nickname, recalls Jeffrey R. Bender, M.D., who served as a resident under Cohen in the early 1980s.

"He was known as 'Larry the Heart,' " recalls Bender, now the Robert I. Levy Professor of Preventive Cardiology, "and he was the consummate teacher."

At 74, Cohen still teaches every Yale medical student how to listen to the heart; he estimates that he's instructed some 3,000 students over the past three decades. When he thinks back to the early days of his academic career, the advancements in cardiac care fill him with wonder. "The No. 1 difference between then and now," he says, "is that someone practicing today has the tools to prevent heart disease and reverse its course."

Those tools exist in part thanks to Cohen, who was a key player in studies showing that heart attacks are caused by the rupture of a plaque from coronary artery walls and the clotting that follows.

Lifelines
Lawrence Cohen

He was also the principal investigator at Yale for the first three Thrombolysis in Myocardial Infarction (TIMI) trials, which were multicenter studies demonstrating that clot-busting drugs could limit or prevent damage during heart attacks and dramatically increase survival rates.

Known for his calm, effective approach to decision-making, Cohen has served as deputy or special advisor to medical school deans for 16 years, overseeing faculty appointments and promotions, raising money for endowed professorships and promoting the responsible conduct of scientific research. Cohen recently stepped down from this role and will be succeeded by Linda C. Mayes, M.D., the Arnold Gessell Professor of Child Development in the Child Study Center. However, he is continuing on full-time as a practicing and teaching cardiologist.

That's good news for the medical school, says John A. Elefteriades, M.D., the section chief and William W.L. Glenn Professor of Cardiothoracic Surgery (see story below), who himself learned to listen to the heart from Cohen as a member of the School of Medicine's Class of 1976. In February, Elefteriades and Cohen published their second book (Cohen's fourth), *Your Heart: An Owner's Guide* (Prometheus Books).

Cohen is "the cardiologists' cardiologist. When any of us is ill, we go to him," Elefteriades says. "And whenever there's a difficult or complex case that requires exceptional judgment, cardiologists from all over the region will send their patients to him."

The Brooklyn-bred Cohen came to Yale in 1958 as an intern, following college at Harvard and medical school at New York University. Twelve years later, after stints at Johns Hopkins, Harvard, the National Institutes of Health and the University of Texas, he returned to Yale as chief of cardiology.

Cohen has mentored dozens of influential cardiologists and leaders in academic medicine. John M. Lasala, M.D., PH.D., director of interventional cardiology at Washington University in St. Louis, was a fellow under Cohen in 1989 and 1990. Lasala recalls, "The most amazing thing was his ability to synthesize great amounts of information into simple and factually correct assessments. He could say an awful lot with very little."

Cohen has no intention of putting aside his clinical duties any time soon.

"Being able to make a difference in patients' lives" he says, "is a privilege."

Top heart surgeon is named Glenn Professor

John Elefteriades

Internationally known heart surgeon John A. Elefteriades, M.D., professor of surgery, has been named the William W.L. Glenn Professor of Cardiothoracic Surgery. Elefteriades is chief of the Section of Cardiothoracic Surgery at the medical school and program director of the Thoracic Surgery Residency Program at Yale-New Haven Medical Center.

Elefteriades' research and clinical practice focus on aortic aneurysms, advanced left ventricular failure and heart transplantation. He received both his B.A. and M.D. from Yale and he has spent his entire professional career in New Haven. Elefteriades joined the School of Medicine's faculty in 1983, and became full professor in 1993. He has repeatedly been included in lists of the best heart surgeons in the Northeast and in the country.

Under the leadership of Lawrence S. Cohen, M.D. (see story above), the Glenn professorship was established with generous gifts from family, friends and colleagues to honor Glenn, a former chief of cardiothoracic surgery at Yale who was a world-renowned pioneer of cardiovascular surgery.

During his long career, Glenn created early mechanical heart pumps and developed the first radio frequency pacemaker. Glenn also was the first surgeon elected president of the American Heart Association. He died in 2003.

Yale scientist is new president of Wellesley College

H. Kim Bottomly, PH.D., former deputy provost for science, technology and faculty development at Yale and professor of immunobiology and molecular, cellular and developmental biology, was named president of Wellesley College in May.

Kim Bottomly

Bottomly is a widely published researcher on immune responses to allergens. She has served as a member of the Immunobiology Study Section at the National Institutes of Health (NIH), was appointed to the Advisory Council of the National Institute of Allergy and Infectious Diseases and received the prestigious MERIT award from the NIH.

Bottomly was instrumental in spearheading Yale's faculty diversity initiative, a plan to add 30 new women and 30 minority faculty members over the next seven years. Bottomly's deputy provost position, which combined two roles to meet her personal interests—faculty development and science—has not yet been filled.

Bottomly's departure adds to a growing roster of women who have moved on from Yale's Provost's Office to head other prestigious institutions. Former Provost Judith Rodin, PH.D., left Yale in 1994 to become president of the University of Pennsylvania; Alison Richard, PH.D., became head of the University of Cambridge in 2003; the following year, Susan Hockfield, PH.D., was named the 16th president of the Massachusetts Institute of Technology.

Medicine@Yale

Peter Farley, *Managing Editor*

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Advances

Health and science news from Yale

Putting a squeeze on Lyme disease

The Centers for Disease Control and Prevention recently reported that the incidence of Lyme disease, caused by the tick-borne bacterium *Borrelia burgdorferi*, has more than doubled in the past 15 years, with most cases concentrated in New England. Now, Yale scientists have found a loophole in the bacterium's life cycle that offers a way to stop ticks from ever carrying the disease, which they pick up as larvae when they suck blood from mice.

Erol Fikrig, M.D., professor of medicine, epidemiology and microbial pathogenesis, and colleagues discovered that *B. burgdorferi* takes advantage of a protein that ticks inject into mice when they bite to prevent an immune response and swelling. When the researchers blocked this protein, either by stopping ticks from producing it in their salivary glands, or by coaxing the mice to obstruct it, the *B. burgdorferi* couldn't go from mouse to tick.

The findings, published in the inaugural issue of *Cell Host & Microbe* in July, may eventually help curb infections in humans by targeting the bacterium at this early stage in its lifecycle. "You could reduce the number of ticks carrying Lyme disease," says Fikrig. "That's the long-term goal."

These mice like to spend time chilling

When breath mints are called "cool" on television, it's truth in advertising, according to a new study by Sven-Eric Jordt, PH.D., assistant professor of pharmacology, and colleagues from the University of California at San Francisco and the University of Wisconsin.

The team reports in the July 12 issue of *Nature* that mouse neurons engineered to lack TRPM8, an ion channel receptor involved in detecting the cooling sensation produced by menthol, were profoundly less sensitive to both menthol and cool temperatures.

In further experiments, when mice lacking TRPM8 were placed on test surfaces that included cool areas, they were far less likely than normal mice to avoid those spots. However, if these areas were cooled below 15 °C (59 °F), TRPM8-deficient mice avoided them as much as normal mice, suggesting that temperatures below this threshold may stimulate pain pathways that do not rely on TRPM8.

The importance of TRPM8 in detecting menthol is well-established, but some researchers disputed its role in cold detection. For now, it seems, the issue's been iced.

Finding a new chink in cancer's armor

Close-up view of protein offers hope for new, highly targeted cancer drugs

In the July 27 issue of *Cell*, a research team led by Joseph Schlessinger, PH.D., William H. Prusoff Professor and chair of pharmacology, reports solving the atomic-level structures for the active and inactive forms of a protein that has been implicated in several types of cancer. The results highlight previously unidentified changes in the protein's structure that seem to be crucial for its activation. Drugs designed to block these changes could represent a novel class of therapies with the potential to work against a broad range of cancers.

"It gives us totally new avenues for developing drugs for a large group of target proteins that are responsible for several cancers," says Schlessinger.

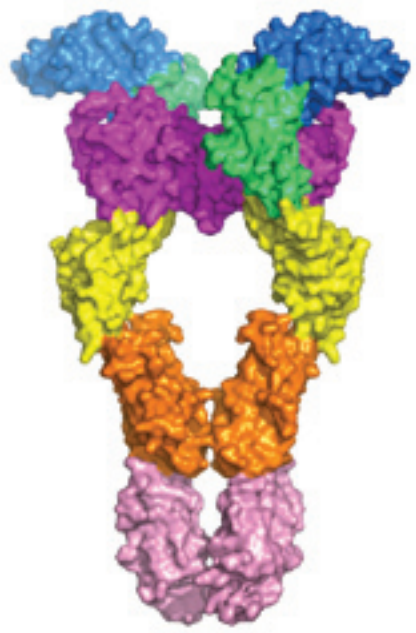
The study focused on one of 59 receptor tyrosine kinases (RTKs), a set of related proteins that normally become active only under particular circumstances to help cells proliferate, differentiate and survive. Certain mutations in RTKs can turn the proteins on inappropriately, causing aberrant cell proliferation that may ultimately lead to cancer. Blocking the activities of RTKs has become a major strategy in anticancer drug design, so knowing the structures of the proteins can tell researchers which parts are important for turning the proteins on and would therefore make good drug targets.

Joseph Schlessinger

In general, RTKs have three major parts: an intracellular component, a portion embedded in the cell's membrane, and an extracellular domain that extends to the outside of the cell. Normally, each RTK binds specifically to an external signaling molecule called a ligand via its extracellular domain. Binding permits two molecules of the RTK to come together, forming a paired structure known as a dimer. Once dimerized, pockets within the intracellular portions of the RTKs bind to adenosine triphosphate, or ATP—an energy-storing molecule found inside cells—and use it to modify themselves in such a way that they are active and able to modify and assemble other factors inside the cell to promote cell growth.

Two recently developed and highly successful cancer-fighting drugs, Gleevec and Sutent, work by preventing the intracellular regions of some RTKs from binding ATP. Gleevec is effective against particular stomach cancers and leukemias; Sutent also works against specific stomach cancers and fights some kidney cancers. "As we speak," says Schlessinger, "hundreds of people are being saved by these two drugs."

But Schlessinger, who helped discover Sutent, says there's still an urgent need for new drugs. Many cancers don't respond to Gleevec or Sutent, and those that do typically develop resistance to the drugs within a few years.



The crystal structure of the extracellular portion of the Kit receptor in its active form. The binding of Kit's ligand, stem cell factor (magenta), has caused two Kit molecules (blue, green, yellow, orange, pink) to form a paired structure in which some regions (orange, pink) closely interact.

With that in mind, Schlessinger has spent the last 10 years putting together a detailed atomic-level view of the extracellular domain of an RTK called Kit. All that effort has yielded a picture of the protein at atomic resolution—about a million times smaller than the thickness of a sheet of paper.

The results suggest that after binding to their ligands and forming dimers, Kit molecules change their shape such that certain portions of the extracellular domain in one Kit molecule move close enough to interact with their counterparts on the other Kit molecule in the dimer.

These interacting regions represent completely new targets for cancer drugs. And since Kit is part of a family of RTKs with similar extracellular domains, the targets represented by this study probably exist in more than a half dozen other RTKs that have been implicated in various cancers. "It's a mechanism that is likely to be universal to quite a few of these RTKs," Schlessinger predicts.

Because the targets are in the extracellular portion of the protein, scientists won't have to worry about getting the drugs inside cells, a major challenge in drug design. And because the interactions involve relatively small portions of the extracellular domain, researchers may be able to design more effective drugs, says Mark A. Lemmon, PH.D., of the University of Pennsylvania School of Medicine.

Lemmon, who wrote a commentary accompanying Schlessinger's report in *Cell*, explains that previous drug design efforts targeting the extracellular domains of Kit and Kit-related RTKs have sought to block dimerization, which involves many interactions over large portions of the protein. But it takes a big molecule—an antibody, for example—to disrupt enough of these interactions to have an impact on dimerization, and that's not ideal.

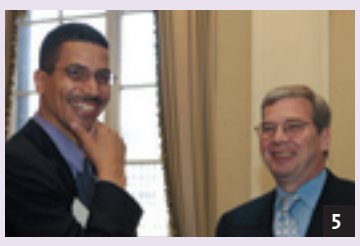
"They're really sledgehammer drugs, and they're not particularly good," says Lemmon. "These are the first kinds of interactions in the extracellular domains for which you could devise small molecule inhibitors," and that could lead to much better drugs in the long run.

Most importantly, drugs aimed at these new targets might be effective against Gleevec- and Sutent-resistant cancers, offering hope to many cancer patients who are trying to stay one step ahead of the enemy.

Out & about

April 21: The 8th annual LA CASSA MAGICA, a black-tie gala to benefit Yale Cancer Center (YCC), was held at The Belle Haven Club in Greenwich, Conn. The event raised over $400,000 to support the creation of a clinical-trials unit within the new Yale-New Haven Cancer Hospital, which is now under construction. **Kathryn Anderson Adams** of Greenwich chaired the event. **Debbie and Louis Chênevert** were vice chairs for the evening, which was hosted by CNN television news anchor and Yale Cancer Center YCC board member **Paula Zahn**. Corporate chairs for La Cassa Magica included **George E. Crapple**, **Paul K. Kelly**, **Nicholas T. Makes**, **Joseph R. Perella**, **Hal Parmelee**, and **Richard S. Sackler**, M.D. Adams and Zahn were honored for their continued support for YCC with plaques that will be displayed in the new Cancer Hospital. **1.** (From left) **Edward Chu**, M.D., professor of medicine and YCC deputy director; Debbie and Louis Chênevert. **2. Duke Brodsky**, **Erica Feingold**, **Howard Brodsky**, **John Moccia**. **3.** (From left) **Jeff and Karin Keith** with **Sean and Duffy Kilbride**. **4. Lucy Day**, **Carol Crapple** and **Margie Warwick**. **5.** (From left) Zahn; **Richard L. Edelson**, M.D., professor of dermatology and YCC director; and Adams.

April 29: In the ANNUAL FACULTY-STUDENT SOFTBALL GAME, the faculty team fielded by Dean **Robert J. Alpern**, M.D., "Bob's Bulldogs," jumped out to an early lead, thanks to (says a highly-placed faculty source) fine fielding, daring base running, and a tremendous home run by **Dennis L. Cooper**, M.D., professor of medicine. The lead eventually built up to 10-3, and the faculty may have gotten a bit complacent. In the 7th inning, the students staged a spirited comeback, but their efforts fell short. The final score was 10-9 in favor of the faculty, in the closest, best-played and most injury-free game in the legendary three-year rivalry between Alpern's heroic team and Class of 2008 Captain **Misaki Kiguchi**'s youthful challengers. The Dean donates chances to join the game to bidders at the students' annual Hunger and Homelessness Auction. (Front row, from left): **David L. Rimm**, M.D., PH.D., associate professor of pathology; **Peter M. Glazer**, M.D., PH.D., Robert E. Hunter Professor of Therapeutic Radiology; **Sam Glazer**; Alpern; Cooper; **Diane Kowalski**, M.D., assistant professor of pathology and surgery; **James S. Duncan**, PH.D., professor of diagnostic radiology and biomedical engineering; **Maritza Martel**, M.D., assistant professor of pathology; and **Richard A. Silverman**, director of admissions. (Back row, from left): **Kelvin C. Lau** '08; **Gabriel A. Widi** '08; **Saif S. Rathore** '10; **Indy M. Wilkinson**, '08; **Scott T.O. Kennedy** '08; **Maulik P. Shah** '08; **Karl R. Laskowski** '08; Kiguchi; **Reid Sansone**; **Susan A. Sansone**, registrar, M.D./PH.D. Program; **Mark H.J. McRae** '08; and **Matthew C. McRae** '09.



May 5: THE SCIENCE OF AUTISM AT YALE brought scientists and clinicians from the medical school's Child Study Center (CSC) to the Yale Club of New York City to present the latest research findings and treatment options for autism. The event also celebrated the naming of the CSC as an Autism Center of Excellence by the National Institutes of Health, a highly competitive and prestigious designation that includes $7.5 million in direct research funding for the research program headed by autism expert **Ami J. Klin**, PH.D., Irving B. Harris Associate Professor in the Child Study Center. **1.** (From left) Klin with **Matthew W. State**, M.D., PH.D., Irving B. Harris Associate Professor of Child Psychiatry and associate professor of genetics; CSC Director **Fred R. Volkmar**, M.D., Irving B. Harris Professor of Psychiatry, Pediatrics, and Psychology; and **Robert T. Schultz**, PH.D., associate professor in the CSC and associate professor of diagnostic radiology. **2. Debbie Hilibrand**, chair of the Executive Council of the Child Study Center Associates, and **Barbara de Kwiatkowski**. **3.** (From left) **Judy Higgins** with **William and Barbara Epifanio**. **4. Wendy Pillsbury** and **Christopher Eichmann**. **5. Jesse Mojica** and **Josh Needelman**.

May 28: At GRADUATION FOR THE CLASS OF 2007, **Karen S. Morris-Priester**, M.D., spoke to a reporter from New Haven's WTNH News Channel 8. Morris entered the School of Medicine as a 40-year-old grandmother and mother of five in 2002. The week before graduation, Morris-Priester's teachers had lured her to a classroom for "an important graduation meeting." Instead, Oprah Winfrey appeared on a video screen to tell Morris-Priester and her assembled classmates that she would be honored for her achievements on the "Cheers to You!" segment of the *Oprah Winfrey Show*. "Oprah was saying my name!" said the shocked Morris-Priester as her fellow students cheered. "You don't expect Oprah to be talking about you!" During her appearance on the program, Morris-Priester learned that AMBI Skincare, a Johnson & Johnson company, will pay her medical school debt, and that Johnson & Johnson is establishing a scholarship in her honor to increase the number of minority women in the sciences. Morris-Priester has begun an internship at Lehigh Valley Hospital in Allentown, Pa., to be followed by an anesthesiology residency at Brigham and Women's Hospital in Boston.

Advances

Health and science news from Yale

Hearing voices: a brain out of sync?

Some 200 milliseconds before you speak, brain cells in your motor cortex fire in concert, predicting the sounds you are about to produce. This electrical discharge instructs your auditory cortex to disregard any matching signals coming from your ears, which keeps you from being distracted by the sound of your own voice.

But the story may be different for patients with schizophrenia, as Judith Ford, PH.D., and collaborators suggest in the March issue of the *American Journal of Psychiatry*. The researchers found that brain activity synchronized shortly before the onset of speech, possibly reflecting communication between the motor and sensory cortex. However, in patients with severe auditory hallucinations, this pre-speech synchronization is weaker, and the brain's reaction to self-generated speech is not dampened: patients who hear voices seem less able to recognize their own.

Next on the authors' list is to repeat the study for the "inner speech" that accompanies thinking to see whether a lack of synchronization may cause patients with schizophrenia to mistakenly perceive their inner thoughts as external voices.

Stem cells show promise in Parkinson's

The symptoms of Parkinson's disease (PD)—muscle rigidity, tremor and a general slowing of movement—have been successfully treated in monkeys using human stem cells.

PD is caused when large numbers of dopamine-producing cells (DA cells) die off in a brain region known as the substantia nigra.

In the July 17 issue of *Proceedings of the National Academy of Sciences*, a team headed by D. Eugene Redmond Jr., M.D., professor of psychiatry and neurosurgery, reports that human neural stem cells implanted into one side of the substantia nigra in monkeys with severe Parkinsonian symptoms migrated and survived on both sides, where many displayed biochemical markers indicating that they had matured into DA cells. Other implanted cells also migrated to key regions and appeared to play a nurturing role, creating a protective microenvironment that restored the function of the monkeys' own surviving DA cells.

Over a four-month period, the monkeys treated with stem cells had vastly improved. "Not only are stem cells a potential source of replacement cells," says Redmond, "they also seem to have a whole variety of effects that normalize other abnormalities."

Research center aims to make rickets history

$5 million grant brings cutting-edge science to bear on age-old disease

Study Coordinator Elizabeth Olear (left) works alongside Thomas Carpenter on two clinical studies of rickets, part of a new initiative funded by the School of Medicine's first Center of Research Translation (CORT) grant.

When we think of rickets, the bone-softening disorder that causes short stature and bowing deformations of the legs, we're likely to imagine that the disease is a relic of the distant past. But rickets is still very much with us, says Thomas O. Carpenter, M.D., professor of pediatrics and a leading rickets researcher.

Carpenter first encountered rickets in the 1970s as a resident at Children's Hospital at the University of Alabama in Birmingham. Most of the cases he saw were nutritional in origin—a lack of calcium and vitamin D in the diet are the two main causes of rickets and have accounted for a rising incidence of the disease over the past 20 years.

But Carpenter was particularly intrigued by children with X-linked hypophosphatemia, or XLH, an inherited form of the disease caused by a mutation on the X chromosome.

As the disease's name implies, these children have very low levels of phosphate because they excrete too much of this mineral in their urine; however, unlike children with dietary rickets, XLH patients have normal levels of both calcium and vitamin D. Carpenter, who directs the Yale Center for X-Linked Hypophosphatemia (YC-XLH), says that 30 years ago he found these contradictory lab findings "baffling."

However, recent studies have revealed a previously unknown system governing mineral balance and bone growth, and biomedical science is on the cusp of a new understanding of XLH, Carpenter says. With the help of a $5,000,000 Centers of Research Translation (CORT) grant, one of four awarded nationwide last fall by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, he and YC-XLH co-director Karl L. Insogna, M.D., professor of medicine,

Rickets, *page 7*

Brewing a new treatment for kidney disease

Swirled in a cup, tea leaves are said to offer a glimpse into the future. Now, Yale researchers have shown that one kind of Chinese tea may change the future for patients with polycystic kidney disease (PKD), an inherited genetic disorder in which the formation of multiple renal cysts leads to kidney failure. The disease is the most common life-threatening genetic disorder worldwide, affecting some 12 million people. There is no cure, and the only effective treatments for PKD-induced renal failure are dialysis and kidney transplants.

A team led by biochemist Craig M. Crews, PH.D., recently showed that triptolide, a compound found in the thunder god vine, a medicinal plant used to make the traditional Chinese tea known as *lei gong teng*, activates a cascade of molecular events that stops kidney cysts from forming.

"Triptolide has been looked at, and is still being looked at, as an anti-tumor agent," explains Crews, associate professor of molecular, cellular and developmental biology, chemistry and pharmacology. "Yet they don't know how it works. Our thinking all along is that we'd love to know how it works so that we can anticipate potential side effects as well as come up with different compounds that work in the same way."

Biochemist Craig Crews found a powerful medicine for polycystic kidney disease in a traditional Chinese herbal tea.

To find out, Crews made a radioactive version of triptolide, added it to kidney cells and tracked where it went. He found that the compound clustered around a protein called polycystin-2, a calcium channel found in kidney cells that is mutated in many cases of PKD.

During normal development, kidney cells arrange themselves into tubules that course through the organ. When the cells finish this assembly, urine flows through the tubules and bends a protein called polycystin-1, which is found on tiny hair-like extensions of the cells. Polycystin-1 then signals a partner protein, polycystin-2, to release calcium from internal stores, which stops the tubule growth. In people with inherited mutations in either polycystin gene, this message to stop tubule formation is silenced.

"When these cells can't sense or can't respond to urine flow, they think they are at an earlier stage in development," says Crews. "And they say 'Well, you know what? We need to make a tubule' and they keep growing and they form a cyst." People with inherited polycystin mutations usually start noticing symptoms of kidney disease around age 25, Crews says. "Then they go from a kidney that's twice the size of normal at diagnosis to kidneys that can be upwards of 2 liters, the size of a big soda pop."

Working with Postdoctoral Associate Stephanie Leuenroth, PH.D., and Stefan Somlo, M.D., the C.N.H. Long Professor of Medicine and chief of nephrology, and colleagues, Crews went on to show that triptolide, when it binds to polycystin-2, stops kidney cysts from growing: in mice engineered to have polycystin-2 mutations, triptolide reduced the size of kidney cysts by 50 percent. Somlo, one of the world's leading experts on PKD, was the first scientist to identify polycystin-2.

Triptolide is now in early clinical trials as a cancer treatment, and the researchers hope their PKD findings will help accelerate clinical tests of triptolide in kidney disease.

Crews says the new findings strengthen his opinion that traditional Chinese remedies hold vast untapped potential for new medicines.

"Clearly, these mixtures have some type of effect or they wouldn't have been used for literally millennia," he says. "The challenge for Western researchers is to try to identify what the active ingredient is. Then, as I did with triptolide, we can find out how it works."

Bayer *from page 1*

could envision the new campus as a place for other parts of the university to converge with the medical school. "It would be terrific if we could also have faculty from the other side of campus over there," he says. "It could act as a meeting space to bring together different parts of the university."

George Zdru, director of the Yale School of Medicine Capital Program, manages lab and office space at the medical school. "Up until now, planning has always been constrained by lack of space," he says, "and the planning process was almost like a game of checkers, requiring the movement of a lot of people to get to the endpoint. Now it can become something a little more elegant, allowing us to think of planning more holistically."

Zdru says that the Bayer campus adds both flexibility and immediacy to the planning process.

"When you build a project, it's usually a five-year process from the initial ideas until the time you can actually use the space," says Zdru. "These particular laboratories are designed in a flexible, universal manner that should make it very easy to occupy them without much renovation. It's a good package."

In addition to lab space, the Bayer complex includes office buildings and warehouses, which may be used as storage space for the Yale University Art Gallery and the Peabody Museum of Natural History.

The financial details of acquiring the 136-acre campus will be disclosed at the time of closing.

While Bayer is not planning to vacate all the office buildings and warehouses until 2008, Alpern says that lab space is already available and that Yale programs could begin relocating as early as the fall.

The purchase of the Bayer HealthCare complex is the largest space acquisition in the university's history, says Alpern, and the purchase complements other recent building initiatives at Yale.

The 457,000-square-foot Anlyan Center for Medical Research and Education, which opened in 2003, is Yale's largest building. The Amistad Building, which will officially open this fall, will house laboratories for interdepartmental programs in stem cell biology, human translational immunology and vascular biology and transplantation. President Levin also emphasized that the acquisition of the Bayer campus will not affect plans to build more than 2 million square feet of new Yale facilities in New Haven over the next six years, and that the heart of the campus will remain in the city.

In addition to payment in lieu of taxes (PILOT) funds that the state of Connecticut will provide to the city of West Haven and town of Orange, Yale has agreed to make additional voluntary payments to the municipalities proportional to the voluntary payments the university now makes to the city of New Haven.

Yale will also invest $1 million over the next three to four years to enhance science education in the Greater New Haven area.

Yale Scholar *from page 1*

Lois joined the Metabolism Branch of The National Institutes of Health's National Cancer Institute, where she worked as a clinical research nurse on some of the earliest studies of gene therapy and on treatments for adult T-cell leukemia/lymphoma.

But the most significant chapter in the Tops' lives began in 1988, when Franklin retired from the Army to become executive vice president of a fledgling biotechnology company called Molecular Vaccines; two years later the company changed its name to MedImmune.

The company, based in Maryland, where the Tops now make their home in Rockville, went on to make biotech history in 1998 when the U.S. Food and Drug Administration approved MedImmune's Synagis, the first monoclonal antibody treatment for an infectious disease. Synagis is now the standard treatment to prevent serious illness from respiratory syncytial virus, a lung infection common in early childhood that can be dangerous to premature infants or children with heart or lung problems. Since then, MedImmune has successfully developed FluMist, a flu vaccine in nasal-spray form, and Ethyol, which protects cancer patients' salivary gland against damage from radiation treatments.

In June, MedImmune was acquired by global pharmaceutical giant AstraZeneca for $15.6 billion. The company will retain its name, and Franklin remains on board as executive vice president of MedImmune Ventures, which identifies companies that may be suitable for MedImmune partnerships or investments.

Franklin Top inherited his interest in medicine and in infectious disease from his father, Franklin H. Top Sr., M.D., who edited *Communicable and Infectious Diseases*, a leading textbook that saw nine editions published between 1955 and 1981.

"There have been huge changes in my lifetime," Franklin says. "When I was an intern and resident, we were just beginning to influence childhood leukemia. We were not keeping children alive. We were giving them a longer duration of reasonably good health, but we always lost them. Now 85 percent of those children are essentially cured. In my own field, infectious diseases, most cases of childhood meningitis were caused by the pneumococcus or *Haemophilus influenzae*. As a result of good work—basic research and then applied development work—these infections are pretty well eliminated from the United States."

The Tops believe that such accomplishments will occur at an even more rapid pace in the future. "We both appreciate the gains medical science has made in our lifetimes," Franklin says. "We'd like to give back the fruits of our good experience with the Army and with MedImmune to keep that going."

"It has been a pleasure for me to come to know Frank and Lois Top," says Dean Robert J. Alpern, M.D., Ensign Professor of Medicine. "When I first met Frank, he told me of his deep gratitude to the School of Medicine, and when he and Lois recently acquired funds from the sale of MedImmune, they were swift in making a commitment to the Yale Scholars program. Frank's accomplishments are a credit to the quality of the medical school's educational program, and I am also very grateful that Frank has agreed to serve on the newly formed Dean's Council, providing us with sage advice based on his many experiences over the years."

ENCODE *from page 1*

Elements (ENCODE) project, a mammoth undertaking of the National Human Genome Research Institute (NHGRI; part of the National Institutes of Health) involving a consortium of 35 groups of researchers at 80 institutions in 11 nations. These researchers have spent the last four years sifting through more than 400 million data points to make sense of just one percent of the human genome. That may not sound like much, but scrutinizing even this small portion of our DNA has turned up some surprises.

For one thing, the genome hosts a lot more activity than anyone expected. For over four decades, the canonical view has been that the important bits of our DNA—the readily decipherable genes making up 1.5 percent of the genome—get converted into RNA via a process called transcription. RNA, in turn, instructs the cell to make proteins, the molecular movers and shakers that do all the heavy lifting in the cell. Scientists have long assumed that, in general, each gene is transcribed into one RNA fragment and that the gene-free portions of our DNA—a whopping 98.5 percent of the genome—aren't transcribed at all. Not so, according to results from the ENCODE pilot project. They show that most of the letters in the genomic instruction manual wind up being transcribed. This happens, in part, because each gene is often transcribed along with a surprisingly large number of non-protein-coding sequences to produce some extraordinarily long RNA fragments. The results also indicate that a single gene can be transcribed into many different RNA fragments of varying lengths such that each gene is represented, on average, by more than five transcripts that share overlapping sequences.

"That's a lot more than we thought there would be," says Snyder, adding that it's unclear what all these extra transcripts are for.

Even more perplexing is the prevalence of RNA molecules transcribed entirely from gene-free portions of the genome. Non-protein-coding (NPC) RNA transcripts were previously known to exist, but the ENCODE project identified many new ones. Again, their purpose is unknown.

As intriguing as these findings are, Snyder is even more excited that the project has identified new regulatory regions—portions of the genome that do not encode proteins but instead, control when, where and how much genes are expressed. A slew of recent studies have linked complex diseases with variations in NPC regions of the human genome that could have regulatory functions.

The surprising results of the ENCODE study garnered worldwide attention after publication in *Nature* in June.

In May, for example, two independent groups linked heart disease with DNA variations in NPC portions of chromosome 9, and in April, a diabetes-linked variation was found in the same NPC region, along with six other variations found elsewhere in the genome. Might some of these variations in NPC DNA promote disease by interfering with the expression of genes at distal sites?

Snyder and his collaborators hope to answer questions like this by mapping out where all the regulatory regions are and how they work. "To me," he says, "this is really what the ENCODE project is all about."

The next step is for scientists to go from looking at just 1 percent of the genome to analyzing the whole thing. As daunting as that sounds, Elise A. Feingold, PH.D., the program director for ENCODE at NHGRI, believes there's good reason to be optimistic.

"The pilot project was a success," says Feingold, who earned one of the first PH.D. degrees from the School of Medicine's Department of Genetics (then Human Genetics) in 1986. "It shows we can do this."

And because cheaper, faster technologies keep popping up, Feingold believes it won't be prohibitively expensive or time-consuming to do. NIH has set aside $100 million to fund the scaled-up project for the next four years. This might not be enough to fully analyze the whole genome, Feingold concedes, but "we'll get a good way there."

Foundation supports Yale research "of practical benefit"

Two School of Medicine researchers received 2006 Investigator Awards from the Patrick and Catherine Weldon Donaghue Medical Research Foundation, a West Hartford, Conn.-based philanthropic organization devoted to supporting biomedical research "of practical benefit to human life."

Hal Blumenfeld, M.D., PH.D., associate professor of neurology, neurobiology and neurosurgery, will apply his award to a study of the effects of epileptic seizures on driving. While patients with epilepsy operate virtual-reality driving simulators, Blumenfeld will use neuroimaging and electroencephalography to determine which brain regions are involved in epileptic seizures and the effects of seizure-induced loss of consciousness on driving safety. "This will be the first time that driving impairment during seizures will be directly measured," says Blumenfeld, who hopes to design improved treatments to preserve consciousness and prevent car accidents among individuals with epilepsy.

Becca Levy, PH.D., associate professor of epidemiology and psychology, studies how psychological factors, particularly how older individuals perceive aging, affect health in old age. Her research demonstrated for the first time that positive age stereotypes can improve the physical and cognitive functioning of older individuals and that positive self-perceptions of age are associated with increased longevity. With her Investigator Award, Levy will conduct a randomized controlled trial to test whether healthy behaviors can be promoted by positive beliefs about aging in older individuals.

Hal Blumenfeld

Becca Levy

"It is exciting to have the opportunity to build on our findings and apply them to health promotion," Levy says, adding that the interventions she is studying are likely to benefit high-risk groups of older individuals in Connecticut, particularly African-Americans.

The foundation launched the Donaghue Investigator program in 1998 to support scientists at Connecticut academic institutions whose work promises "a direct, near-term impact on improving public health, clinical practice or community health interventions." The program, now in its final year, provides five-year, $600,000 awards to investigators.

In announcing the 2006 awards, Raymond S. Andrews Jr., co-trustee of the Donaghue Foundation with Bank of America, said, "We are pleased that Donaghue can provide the type of support to talented researchers that will allow them to pursue innovative and important answers to significant health problems."

Rickets *from page 5*

are using this new knowledge to embark on an ambitious, multipronged scientific attack on XLH, the most common inherited form of rickets.

"Over the past 10 years, the science really opened up and revealed an entirely novel mechanism of phosphate regulation," Carpenter says. In 1995, the mutated gene that causes XLH was identified as *PHEX*; this discovery has allowed scientists to create mouse models of the disease that exhibit a pattern of phosphate depletion, bone deformation and dental abnormalities similar to those seen in human patients.

It was subsequently discovered that a protein known as fibroblast growth factor 23 (FGF23) plays a crucial role in autosomal dominant hypophosphatemic rickets (ADHR), a rare inherited form of the disease that closely resembles XLH. More recently, yet another protein, DMP1, has been shown to be central to a third form of inherited rickets (autosomal recessive hypophosphatemic rickets) that also closely resembles XLH. Most strikingly, the PHEX protein, FGF23 and DMP1 have been found to be most abundantly expressed in the same specialized bone cell, the osteocyte. Carpenter believes that PHEX (an enzyme), DMP1 and FGF23 must all work in the same pathway that is involved in XLH. "This is the most convincing evidence to date," Carpenter says, "for an intimate connection between skeletal biology and systemic mineral balance in the body."

The standard treatments for XLH are calcium and phosphate supplements, but the levels of these minerals must be carefully monitored to avoid serious side-effects. Carpenter says that the CORT grant will allow him and his colleagues to advance more precise and effective molecular therapies.

The three main lines of inquiry that comprise the CORT are being pursued with the support of a Research Core facility directed by Caren M. Gundberg, PH.D., professor of orthopaedics and rehabilitation. Carpenter and Insogna will lead two clinical studies: one will determine what biochemical markers best predict the severity of XLH cases; a second will focus on the role of parathyroid hormone excess in the disease, and will apply a specific therapy to correct this complication of XLH. Marie B. Demay, M.D., associate professor of medicine at Massachusetts General Hospital in Boston, will lead a project exploring her recent finding that phosphate regulates cell death in cartilage cells. Finally, Joseph Schlessinger, PH.D., the William H. Prusoff Professor and chair of Pharmacology (see related story, page 3) will join Veraragavan P. Eswarakumar, PH.D., newly appointed assistant professor of orthopaedics and rehabilitation, to identify and characterize the cell-surface receptor for FGF23. Based on the FGF23 studies, members of the YC-XLH will develop small molecules to inhibit activation of the receptor and test them in preclinical trials, and, if successful, Phase 1 clinical trials. In addition to the research projects, the YC-XLH has co-sponsored a Bone Seminar Series with the NIH-sponsored Yale Core Center for Musculoskeletal Disorders, and will soon be launching a pilot and feasibility program for further work in this related field.

To complement his work on XLH, Carpenter continues to study and treat nutritional rickets in inner-city New Haven children with the help of a 3-year, $844,000 grant he received in 2005 from the Gerber Foundation.

"The newly discovered mechanisms by which our bodies regulate phosphate are very exciting, and have broad implications in human biology," says Carpenter. "We have learned so much from the patients who have contended with so many long-term consequences of XLH that it is only fitting that we may soon be able to apply these discoveries to new therapies that should significantly improve their quality of life."

Grants and contracts awarded to Yale School of Medicine

November/December 2006

Federal

Walter Boron, NIH, *Physiology of Electrogenetic Na/HCO_3 Cotransporters*, 5 years, $1,900,958 **Junjie Chen**, NIH, *Study the Role of Chfr in Tumorigenesis*, 4.5 years, $1,427,343 • **Wonsun Han**, NIH, *Regulation of Na,K-ATPase Distribution and Function by Arrestin and Spinophilin*, 2 years, $94,772 • **Jonathan Kagan**, NIH, *Cellular and Molecular Aspects of Toll-Like Receptor Signal Transduction*, 1 year, $89,996 • **Chun Geun Lee**, NIH, *Genetic Factors Controlling Effector Function of TGF-Beta in COPD and Fibrosis*, 5 years, $2,066,770 • **Daeyeol Lee**, NIH, *Dynamics of Cortical Communication*, 1.5 years, $262,321 • **Michael Nitabach**, NIH, *Calcium Signaling in Circadian Clock Neurons*, 4 months, $386,500 • **Harvey Risch**, NIH, *Case-Control Study of Pancreas Cancer in Shanghai, China*, 5 years, $3,596,491 • **Bing Su**, NIH, *Regulation and Function of MEKK3 in Dendritic Cells*, 1 year, $349,191; NIH, *Molecular Mechanisms of MEKK3*, 1.5 years, $143,759 • **Patrick Sung**, NIH, *Molecular Basis of BRCA2-Mediated DNA Repair and Cancer Avoidance*, 5 years, $1,841,689 **Terrence Town**, NIH, *Blocking TGF-Beta Immune Signaling as a Therapeutic Target for Alzheimer's Disease*, 1 year, $90,000 • **Anthony Van den Pol**, NIH, *Hypocretin Neurons*, 4 years, $1,447,487

Non-Federal

Zane Andrews, Foundation for Research Science & Technology, *Molecular and Neuroanatomical Mechanisms of Ghrelin Signaling in the Brain: Implications for Obesity*, 1 year, $58,464 • **Aydin Arici**, Serono, Inc. (U.S.A.), *The Role of AKT Signaling Pathway in the Pathogenesis of Endometriosis*, 2 years, $56,824 **Xueying Chen**, American Heart Assoc. (Heritage Affiliate), *Computational Screening for Dosage-Sensitive Genes Involved in Cardiovascular Diseases*, 1 year, $18,334 • **Robert Constable**, Pfizer, Inc., *A Study to Investigate the Utility of Magnetic Resonance Endpoints for Defining Liver Disease in Subjects with Chronic HCV*, 1 year, $195,568 • **Karen Dorsey**, St. Luke's-Roosevelt Institute for Health Sciences, *Metabolic Effects of Differential Organ Growth Rates*, 6 months, $151,411 • **Marie Egan**, Cystic Fibrosis Foundation, *Cystic Fibrosis Clinical Research Facilitation Awards*, 1 year, $64,800 • **Gerald Friedland**, Institute for Clinical Research Inc., *International Network for Strategic Initiatives in Global HIV Trials*, 4.5 years, $513,621 • **Bryan Hains**, American Pain Society, *Supraspinal Modulation of Pain after SCI by Microglia*, 1 year, $20,000 • **Kevan Herold**, Juvenile Diabetes Research Foundation Int'l, *Phase II Trial of hOKT3yl*, 1 year, $82,537 • **Fenghua Hu**, Paralyzed Veterans of America, *Mechanisms of Amino-Nogo Inhibition*, 2 years, $100,000 **Henry Huang**, GlaxoSmithKline Research & Development, Ltd., *Evaluation of the PET Ligands [^{11}C]GSK981352 and [^{11}C]PHNO to Image Dopamine D3 Receptor in Rhesus Monkey*, 9 months, $210,495; GlaxoSmithKline Research & Development, Ltd., *Development of [^{11}C]/[^{18}F]AFM for First-in-Human Trial of the Serotonin Transporter Ligand AFM*, 1 year, $50,000 • **Ivana Kawikova**, Nat'l Alliance for Autism Research, *Is Autoimmunity Involved in Pathogenesis of Autism?* 2 years, $120,000 **John Krystal**, Nat'l Alliance for Research on Schizophrenia and Depression, *GABRA2 Modulation of NMDA Receptor Deficit-Related PFC Dysfunction*, 1 year, $100,000 • **Daeyeol Lee**, University of Rochester, *Neural Interactions Among Multiple Motor Structures*, 3.5 years, $922,312 • **Aliza Leiser**, The Ovarian Cancer Research Fund, Inc., *Clinical Implications of the TLR-4/MYD88 Pathway in Epithelial Ovarian Cancer*, 2 years, $75,000 • **Yorgo Modis**, Roche Organ Transplantation Foundation, *The Structural Basis of Innate Immune Sensing and Signaling by Toll-Like Receptors*, 3 years, $242,484 • **Mary Schwab-Stone**, Leon Lowenstein Foundation, Inc., *Greenwich Needs Assessment*, 1 year, $25,000 • **Patrick Sung**, Lawrence Berkeley Nat'l Laboratories, *Modulation of the Functionality of Homologous Recombinational Repair*, 9 months, $120,649 • **James Tsai**, Synabridge Corporation, *Instrument for Glaucoma Early Detection and Monitoring*, 1.5 years, $102,881 • **Carol Weitzman**, Robert Wood Johnson Foundation, *Identifying and Treating Maternal Depression in Underserved, Minority Women in a Pediatric Primary Care Setting*, 2 years, $202,976 • **Sandra Wolin**, Ellison Medical Foundation, *Investigating the Role of Oxidative RNA Damage in Aging*, 4 years, $991,688 • **Yong Xiong**, Richard & Susan Smith Family Foundation, *Mechanisms of HIV Suppression by Human Antiviral Protein APOBEC3 and HIV's Countermeasures*, 2 years, $200,000

Awards & honors

Richard P. Lifton, M.D., PH.D., chair and Sterling Professor of Genetics and professor of medicine and molecular biophysics and biochemistry, has received the Alfred Newton Richards Award from the International Society of Nephrology. This award, the highest scientific honor of the society, cited Lifton's pioneering contributions to understanding the molecular and genetic basis for renal and cardiovascular disease.

Bernard Lytton, M.B.B.S., F.R.C.S., Donald Guthrie Professor Emeritus of Surgery, is president of the American Association of Genito-urinary Surgeons (AAGUS). The AAGUS is a professional association of academic urologists from around the world. Lytton, who joined the faculty of the School of Medicine in 1962, performed the first kidney transplant in Connecticut in 1967.

Cindy R. Miller, M.D., associate professor of diagnostic radiology and co-section chief of pediatric imaging, received the Jack O. Haller Award for Excellence in Teaching from the Society for Pediatric Radiology at the society's annual meeting in April. Miller, whose research interests include the relationship between imaging findings and clinical outcomes in premature infants, was honored for her commitment to mentoring medical students, residents and fellows in pediatrics and radiology.

Clarence T. Sasaki, M.D., Charles W. Ohse Professor of Surgery and chief of otolaryngology, is the president of the American Broncho-Esophagological Association (ABEA). ABEA is a society of physicians who convene each spring to present original research in otolaryngology. Sasaki, who received his M.D. from the School of Medicine in 1966 and now specializes in head and neck surgeries, began his term in April.

Warren D. Shlomchik, M.D., associate professor of medicine and immunobiology, has received a Clinical Scientist Award in Translational Research by the Burroughs Wellcome Fund. The $750,000 award supports physician-scientists who are dedicated to mentoring trainees and to translational research, the two-way transfer between laboratory research and patient treatment. Shlomchik studies immune system responses to allogeneic hematopoietic stem cells, such as those used in bone-marrow transplants for leukemia.

Diabetes experts win top scientific honors

Yale researchers lauded for research, development of innovative treatments

(Left) At the annual meeting of the American Diabetes Association (ADA), Robert Sherwin receives the Banting Medal from Richard Rubin, the ADA's immediate past-president for health care and education. (Right) Gerald Shulman (center) celebrates his election to the National Academy of Sciences with colleagues Roland Baron (left) and Steven Hebert.

Two School of Medicine scientists have received high honors for their contributions to diabetes research and treatment. Robert S. Sherwin, M.D., the C.N.H. Long Professor of Medicine and director of the Yale Center for Clinical Investigation, is the winner of the 2007 Banting Medal for Scientific Achievement Award from the American Diabetes Association (ADA), the association's highest honor for diabetes researchers. Gerald I. Shulman, M.D., PH.D., professor of medicine and of cellular and molecular physiology, was elected to the National Academy of Sciences (NAS), one of the highest honors in American science and engineering.

Sherwin's recent work has focused on how the brain senses blood glucose levels and activates defenses against hypoglycemia. This is an important clinical issue because this critical system becomes impaired after intensive insulin treatment of diabetes, which limits our capacity to prevent the long-term complications of the disease. These studies are the outgrowth of pioneering work by Sherwin and Professor of Pediatrics William V. Tamborlane, M.D., on a portable pump that continuously delivers insulin to treat diabetes. In addition, Sherwin's laboratory has developed a mouse model of type 1 diabetes that shares features of the human immune system; using this model, Sherwin and colleagues have identified a new target of the autoimmune response that could lead to a vaccine to prevent type 1 diabetes.

The Banting Medal is named for Sir Frederick G. Banting, M.D., a Canadian physician and scientist who shared the 1923 Nobel Prize in physiology or medicine as a co-discoverer of insulin. In presenting Sherwin with the award in June at the ADA's annual meeting in Chicago, Larry C. Deeb, M.D., the association's president, lauded Sherwin for his research and his prominence in the diabetes field. "His direct contributions to the development of insulin pump therapy and the landmark Diabetes Control and Complications Trial have led to major improvements in the care of patients with diabetes and his leadership in this area of research should be applauded," said Deeb.

Sherwin also helped organize and co-direct the seminal work of the Kroc Collaborative Study Group, which showed that long-term studies of the role of glucose in diabetes complications are possible.

Sherwin has served as president of the ADA, Chairman of the Medical Science Advisory Board of the Juvenile Diabetes Research Foundation and as a member of the Food and Drug Administration's Endocrinologic and Metabolic Drugs Advisory Committee. He has published over 300 articles in peer-reviewed journals. For his work as a clinical scientist, Sherwin received the Novartis Award for Long-Standing Achievement in Diabetes. He is the recipient of two MERIT Awards from the National Institute of Diabetes and Digestive and Kidney Diseases.

Shulman, a Howard Hughes Medical Institute investigator, is a preeminent diabetes researcher who uses magnetic resonance spectroscopy (MRS) to study insulin resistance and the metabolic roles of the liver and muscle in type 2 diabetes.

MRS is a noninvasive procedure based on the same principles as magnetic resonance imaging that allows researchers to make precise, repeated chemical profiles of regions of tissue as small as three cubic centimeters. By comparing profiles made during a brief time span, it is possible to calculate the rate of metabolism in that region of tissue.

Recent results published by Shulman's lab show that altered metabolism in mitochondria—the "power plants" of cells—in muscle may be responsible for insulin resistance. This work may one day lead to the identification of genes that make individuals more prone to diabetes, as well as treatments for insulin resistance.

Shulman also investigates the benefits of exercise in managing diabetes, using MRS and other noninvasive techniques to measure fat metabolism and fatigue during aerobic exercise.

Shulman has received numerous awards for his research, including an Outstanding Investigator Award from the American Federation for Clinical Research, the Outstanding Scientific Achievement Award and a Distinguished Clinical Scientist Award from the ADA. Shulman was elected to the NAS's Institute of Medicine in December 2005.

Obstetrics/gynecology chair is honored as leader and writer

It was an eventful spring for Charles J. Lockwood, M.D., the Anita O'Keefe Young Professor of Women's Health and chair of the Department of Obstetrics, Gynecology and Reproductive Sciences. Lockwood was named president of the Society for Gynecological Investigation (SGI) at their annual meeting in March, and he received his second Jesse H. Neal National Business Journalism Award from American Business Media (ABM) for opinion pieces he has written as editor-in-chief of *Contemporary OB/GYN* magazine.

With approximately 1,200 basic scientists and clinical researchers as members, the SGI is the world's leading scientific organization in reproductive sciences and obstetrics and gynecology. As president, Lockwood will preside over the 2008 annual meeting in San Diego along with his School of Medicine colleague Hugh S. Taylor, M.D., associate professor of obstetrics, gynecology and reproductive sciences, who will serve as program director for the meeting. Lockwood previously served as secretary treasurer for the society.

Charles Lockwood

Lockwood received his writing award from ABM for his recent editorials in *Contemporary OB/GYN*, including articles on how the Internet has affected obstetrics and gynecology practices, the politics of emergency contraception and the effectiveness of prenatal care in at-risk populations.

Since Lockwood became chair of Yale's Department of Obstetrics, Gynecology and Reproductive Sciences in 2002, the department has doubled both its National Institutes of Health (NIH) grant dollars and its clinical revenue. In addition to his duties as chair, Lockwood also serves on numerous administrative committees for the School of Medicine, Yale-New Haven Hospital and Yale University, including the Dean's Advisory Board, the Comprehensive Cancer Center Steering Committee, the Executive Committee of the Hospital Medical Board and the Provost's Budget Committee. He has been a regular member and recently served as acting chair of the U.S. Food and Drug Administration's Reproductive Health Drugs Advisory Committee.

Lockwood's laboratory research, supported by three NIH grants, focuses on the molecular mechanisms of menstruation, contraceptive-associated uterine bleeding, preterm deliveries and the pathogenesis of many adverse pregnancy outcomes. In addition, he maintains a busy faculty practice in high-risk obstetrics. He has been cited annually as a "Best Doctor" by *New York* magazine and the Castle and Connolly Survey since 1995.