Yale physiologist elected to National Academy of Sciences

Steven C. Hebert, M.D., spent the early part of his career exploring the kidney’s basic processes using the tools of traditional physiology—radioactive tracers to track ions as they cross cell membranes and light microscopy to measure the volume of cells in the nephron, the complex and convoluted structure that forms the kidney’s basic unit.

Then in the late 1980s, he faced a choice: continue with the tried-and-true laboratory methods at his disposal or risk a leap headlong into the world of molecular genetics. Using a technique called expression cloning, in which genes are isolated according to their function, Hebert and his colleagues saw the chance to identify the molecules that transport salts across membranes and regulate calcium levels in the blood. Maintaining these functions is critical to a healthy heart, strong bones and normal blood pressure.

“My feeling at that time was the gamble was worth it, because I didn’t see that we could advance in our understanding without doing these things,” Hebert said on May 3, the day he was elected to the National Academy of Sciences (NAS). Hebert is the chair and C.N.R. Long Professor of Molecular and Cellular Physiology and professor of medicine. “It was do or die.”

Apparently, the risk paid off. In the early 1990s, Hebert’s laboratory made three fundamental discoveries about how the kidney handles potassium, sodium and calcium. His group identified a channel that regulates potassium excretion and is involved in Bartter’s syndrome type II, an inherited disorder that causes sodium and potassium to be lost in the urine. He and his colleagues also identified two sodium chloride transporters that Hebert, page 6

You don’t have to meet Gus Berkes to learn about his accomplishments. They’re right in front of you whenever you pick up a magazine.

Berkes, who turned 80 in March, spent his working life as a production director at Esquire, Better Homes & Gardens and McCall’s, where he pioneered the use of innovations we now take for granted—bound-in subscription cards and advertising supplements, foldout pages and the legendary (and wonderfully self-explanatory) ad gimmick known as “Scratch-n-’Sniff.”

“See all these cards?” Berkes asks as he riffls through a copy of Better

Welcome to Medicine@Yale

This is the inaugural issue of a new publication created to keep you up-to-date with the many exciting things happening at the School of Medicine. Every other month, we will report on the accomplishments that make the school one of the world’s great biomedical institutions.

The school’s mission is to provide outstanding education to our students, to advance the frontiers of science, and to serve the medical, public health and educational needs of the residents of Connecticut, the Northeast and the world over. We are excited to have the opportunity to share our achievements in these many areas with you.

I hope you will enjoy reading this premiere issue. Please drop us a line at the address on page 2 and tell us how you like it.

Robert J. Alpern, M.D., Dean

New Kavli center for neuroscience research will untangle mysteries of the human brain

A mere 2 millimeters may separate us from other members of the animal kingdom. That’s the approximate thickness of the cerebral cortex, a sinuously folded sheet of tissue on the outermost surface of the brain where the neural machinery resides for many capabilities, such as language and reasoning, that we think of as distinctively human.

Pasko Rakic, M.D., Ph.D., the chair and Dorris McConnell Duberger Professor of Neurobiology, has spent a lifetime deciphering how the nervous system cells present at birth manage to arrange themselves into the highly ordered, densely interconnected and immensely complex circuitry of the adult cortex.

Now, thanks to the unique philanthropic vision of the Kavli Foundation, formed by California industrialist Fred Kavli, Rakic and other Yale neuroscientists with a special interest in the cortex have the tools to dig even more deeply into the mysteries of the human brain. Last year, the foundation announced the establishment of the Kavli Institute for Neuroscience at Yale, one of only three such centers in the world devoted to brain research.

David Auston, Ph.D., president of the foundation, says that he and Kavli believe that Yale’s “outstanding group of neuroscientists will make important advances in understanding the basic functioning of the brain.”

Nigerian-born engineer and philanthropist Fred Kavli at his home in Goleta, Calif.

Most organizations that fund biomedical research, whether public or private, have a quite specific mission, often focused on finding treatments for particular diseases. But the Kavli Foundation bears the distinctive stamp of its Norwegian-born founder, a man with a sweeping Kavli, page 6

Magazine innovator celebrates 101 years with gifts for his medical school “family”

Gus Berkes

Home at East Hill Woods, the retirement community in Southington, Conn., where he has made his home since 1953, “That’s me.”

Thirty years ago, just after being treated at Yale by Clarence T. Sasaki, M.D., the Charles W. Oluse Professor of Surgery, Berkes and his wife, Josephine, who were childless, created trust funds and placed instructions in their wills to support their favored charities. Because of his gratitude to Sasaki and the warm rapport the two men enjoyed, the School of Medicine was at the top of Berkes’ list in his bequest.

But four years ago, with his 100th birthday on the horizon, Berkes happened upon a magazine story detailing Sasaki’s recent research in head and neck surgery, and he

Berkes, page 3

Field work for field mice

Recruiting wildlife in the fight against Lyme disease, p. 4

Shaping minds

Bristol-Myers Squibb and graduate education, p. 5

Also

Advances, pp. 4-6; Grants, p. 7; Awards, p. 8

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E-mail us at medicine@yale.edu or phone (203) 737-8241
Kidney researchers celebrate a banner year

First Stefan Somlo, M.D., Yale’s chief of nephrology, learned that he would be heading off to Singapore in late June to accept the field’s top award for research on polycystic kidney disease, a life-threatening condition that affects more than 12.5 million people worldwide.

Next Steven C. Hebert, M.D., the chair of physiology, was tapped to receive the A.N. Richards Award at the same June meeting, the World Congress of Nephrology.

Then another Yale kidney researcher, Walter Boron, M.D., Ph.D., was selected for the Horner W. Smith Award from the American Society of Nephrology (ASN). Finally, Hebert was elected to the National Academy of Sciences (see related story, Page 1) for his discoveries leading to new drugs that benefit more than 1 million kidney patients worldwide.

Is there something in the water? “It’s just that Yale has great strength and depth in this area of science,” says Dean Robert J. Alpern, M.D., a nephrologist himself, who was attracted to Yale in part by its long tradition in the field dating to the work of John Peters, M.D., during the 1950s.

Somo, the C.H. Long Professor of Medicine, and a colleague will share the Lillian Jean Kaplan International Prize for Advancement in the Understanding of Polycystic Kidney Disease for their work in discovering genes that cause polycystic kidney and liver diseases.

Somlo and frequent collaborator Gregory G. Germaine, M.D., of the Johns Hopkins School of Medicine will receive $500,000 each from the F.K. Foundation in the International Society of Nephrology. National Academy Honoree Hebert will receive the A.N. Richards Award from the International Society of Nephrology (ISN) for his fundamental discoveries about how the kidney regulates salt balance.

The Richards Award, which carries a $10,000 cash prize, is the ISN’s highest award for basic research. It is presented every two years at the World Congress and is named for Alfred Newton Richards (1876–1966), a member of the Yale College Class of 1897.

Boron, a professor of cellular and molecular physiology, has performed pioneering work on the processes that determine intracellular pH, which must be maintained in the normal range for normal cell function. His contributions include the development of methods to measure and manipulate intracellular pH, the use of these methods to discover several new transport processes for acids and bases across cell membranes and the cloning of cDNAs that encode several of these transporters.

For new deputy dean, focus is on top-notch care, service to patients

As the new deputy dean for clinical affairs, David J. Leffel, M.D., continues a task he began 10 years ago when he added a new portfolio to his work as a dermatologist: improving the business side of medicine.

As head of the Yale Medical Group (YMG), the medical school’s 750-member faculty practice, Leffel has encouraged physicians and other caregivers to move outside traditional departmental boundaries into interdisciplinary, disease-based teams.

“Because our knowledge of disease is so much more refined, we understand that solutions to illness are not limited to a particular organ in which the disease is expressed,” says Leffel, who will oversee the growth and development of the practice in his new role.

In addition to helping move scientific knowledge from the bench to bedside, Leffel is focused on making sure the day-to-day operations of the practice run flawlessly for the sake of patients and referring physicians.

Ensuring that the world-class medical care at Yale reaches patients quickly and efficiently all boils down to good communication and good coordination, Leffel says.

“To teach medical students to be doctors of the 21st century,” he adds, “and to take care of patients with new technology and medications of the 21st century, you have to have a clinical practice of the 21st century.”

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Present at the creation

Expert on gene swapping joined molecular biology at its very beginnings

Charles M. Radding, M.D., professor emeritus of genetics, did sculpture as a hobby in medical school, and his portrait demonstrated a natural aptitude for plastic surgery, according to an influential mentor who also happened to be his older brother, Philip. The elder Radding, an orthopaedic surgeon, hoped the two would someday practice in side-by-side offices.

Although the scheme had some appeal, Charles already knew his passion was biochemistry, not medicine.

It was 1953, and Watson and Crick’s double helix model of DNA had opened a new door to understanding for biologists, a door the fledgling biochemist Radding eagerly entered. Radding, who recently retired after 37 years at Yale, went on to become a leader in illuminating the theoretical and biochemical underpinnings of genetic recombination.

Also known as gene swapping, recombination orchestrates the orderly transmission of genes from generation to generation in all organisms, and it is now recognized as an important anti-cancer defense that human cells use to repair tumor-causing mistakes in the genome.

In the mid-1970s, while traveling on a bus filled with fellow scientists through the Scottish Highlands, Radding and Matthew Meselson of Harvard University hatched a new theoretical model of recombination. The 1975 paper they co-authored describing the model formed the basis for much of the experimental work in recombination in the years that followed.

Radding’s experimental approach combined his expertise in enzymes with that of advancement in the understanding of polygenic kidney disease in their work in discovering genes that cause polycystic kidney and liver diseases. Somlo and frequent collaborator Gregory G. Germaine, M.D., of the Johns Hopkins School of Medicine will receive $500,000 each from the F.K. Foundation in the International Society of Nephrology. National Academy Honoree Hebert will receive the A.N. Richards Award from the International Society of Nephrology (ISN) for his fundamental discoveries about how the kidney regulates salt balance. The Richards Award, which carries a $10,000 cash prize, is the ISN’s highest award for basic research. It is presented every two years at the World Congress and is named for Alfred Newton Richards (1876–1966), a member of the Yale College Class of 1897.

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Pfizer and Yale join forces for research and education

Like many enterprises with international reach, Pfizer Inc. makes its corporate home in New York. But the company has deep roots in southeastern Connecticut, having built what was then the world’s largest manufacturing plant for antibiotics in Groton in 1943.

Today, more than 6,000 Pfizer scientists and R&D personnel continue to do much of the company’s work in drug discovery and testing in laboratories in Groton and at its Global Research and Development headquarters in nearby New London.

With the April opening of the $35 million New Haven Clinical Research Unit (CRU), a 3-story dedicated facility for Phase I drug trials, Pfizer further strengthened its ties to Connecticut and added new luster to a multifaceted Pfizer-Yale research alliance that began three years ago.

At the CRU, one of only 4 such Pfizer facilities in the world (the others are in Ann Arbor, Mich.; Brussels, Belgium; and Singapore), volunteers will take part in studies in which they will receive potential medicines that have cleared several years of safety studies in the laboratory. Although the CRU is wholly owned and operated by Pfizer, some studies there will be collaborations between Pfizer and biotechnology experts at the School of Medicine, who will use positron emission tomography (PET) and other technologies to track where and how drugs under study are acting in the body.

Diane K. Jorkasky, M.D., Pfizer’s vice-president of clinical pharmacology, says that the ability to draw on the expertise of Yale scientists in a mutually beneficial partnership figured heavily in the company’s decision to locate the CRU in New Haven, citing “a world-class medical imaging center with a strategic interest in PET scanning and research on the central nervous system and a university that understood the value of academic-industrial relationships.”

But the planned collaborative studies at the New Haven CRU are just one example of Pfizer’s research and education partnerships with Yale.

In 2000, the company established a fellowship in memory of the late Patricia S. Goldman-Rakic, a renowned Yale neurobiologist, which provides tuition, health insurance and a stipend every year to a promising graduate student in neuroscience in Yale’s Combined Program in the Biological and Biomedical Sciences (see related story on Page 3). Through Pfizer Faculty Development grants, five assistant and associate professors in the School of Medicine have been granted up to $50,000 worth of research time at the medical school’s Magnetic Resonance Research Center.

And in a new joint effort of Pfizer’s Women Leaders Network and the medical school’s Office for Women in Medicine, a visiting professorship has been created that allows a woman on the medical school faculty to spend 2 weeks working alongside Pfizer researchers in Groton and New London each year.

In the most ambitious Yale-Pfizer partnership to date, construction is under way on a PET research center, where high-resolution scanners will allow Yale scientists to pinpoint drug action in the human body, especially in the brain. In addition to an initial start-up investment of $5 million, Pfizer has pledged $20 million over 10 years for the new center, which is slated to open this fall.

“The relationship is one of win-win for both,” says Jorkasky, “and the biggest winners will be the patients who will benefit from the science that the partnership explores.”

Class of 1954 makes a lasting impact with scholarship gift

The School of Medicine’s Class of 1954, the last of the “small classes” of 65 students, is a tight-knit group.

Through the years, class members have kept in touch via birthday cards and holiday greetings. Until his death in 1996, Class Agent John K. Rose, M.D., conveyed frequent messages to members that nurtured the class’s unusual closeness over the past five decades.

But to mark their 50th reunion last June, its members looked squarely the future by establishing the Class of 1954 Memorial Scholarship.

In creating the fund, which will provide a permanent source of support to students with financial need, the class joined a select group of medical school alumni who have established class-based scholarships.

When the class was considering a 50th reunion gift, Frank L. Gruskay, M.D., of Woodbridge, Conn., suggested establishing a scholarship fund honoring all members of the class, and the medical school’s Class of 1954, the last of the “small classes” of only 65 students.

Berkes continued from page 1

decided to give half of his trust immediately to support Sasaki’s work. Berkes called Sasaki on the phone, and in the no-nonsense manner well-known to his East Hill Woods neighbors, he said, “Do you remember me? You treated me 30 years ago, and I want to give you some money.”

He did just that, in the form of a $40,000 endowment for Sasaki’s Section of Otolaryngology. Berkes’ beloved wife, Jo, had since died from heart disease, so he soon followed up his first gift with a second endowment for Yale’s Section of Cardiothoracic Surgery, headed by John A. Eleftheriades, M.D.

Berkes went on to set up two charitable annuities for the Department of Surgery, but because he had little need for the income they generated, he deposited the money in yet another trust earmarked for the School of Medicine. This newest trust has appreciated to the point where he may be able to leave Yale an additional gift that matches his original donation, Berkes says with a laugh, adding, “I feel like I’ve discovered perpetual motion.”

In sum, Berkes’ gifts to the medical school will total as much as $1.4 million, and he says it was the right decision to donate sooner rather than later, because his gifts are a “two-way street”: he takes great joy from seeing the fruits of his generosity. Berkes says it was “the greatest thrill” to pay a recent visit to the medical school and discuss current research with Eleftheriades and a group of medical students.

Berkes stresses that the germ of his proud association with Yale physicians and fundraisers—he calls them “family”—lies in the solid doctor-patient bond he formed with Sasaki all those years ago, and he fondly hopes that doctors-in-training will learn to engage deeply with their patients.

Among Berkes’ inventions at Esquire was a small symbol placed at the end of articles that alerted readers when a piece had come to an end. In his honor, we’ve placed one below. But at a vigorous 101, Berkes’ story is far from over. Instead, he seems increasingly likely to see a $200,000 contribution from the Class of 1954. That may lie on the next page. M.K.

Medicine @ Yale June/July 2005
Vaccinating wildlife suggests a new strategy in continuing battle against Lyme disease

In the summer of 1975, children from the rural towns near Lyme, Conn., began developing an odd type of arthritis. Yale rheumatologists Allen Steere, M.D., and Stephen Malawista, M.D., were called in to investigate, and they quickly determined that the strange seasonal flare-up had all the markings of an infectious disease. Eventually, Steere and other Yale investigators discovered that a corkscREW-shaped bacterium known as a spirochete was responsible for the condition they dubbed Lyme disease. Malawista, Steere and colleagues went on to show that humans contracted Lyme disease after being bitten by deer ticks, which pick up the bacterium themselves from wild mice. Yale scientists went on to develop successful antibiotic treatments for the disease that prevent the painful arthritis and other neurological problems that occur in some people.

But these stunning early successes of Yale scientists in the diagnosis and treatment of Lyme disease have not been matched by equal gains in prevention. Residential development in rural areas has placed more people in contact with ticks. A Lyme disease vaccine proved unpopular with consumers and was taken off the market. The disease now ranks as the most common tick-borne illness in the United States, with the number of new infections rising 35-fold since 1982. In 2002, over 32,000 cases were reported to the Centers for Disease Control and Prevention (Cdc).

Entomologist Durland Fish, Ph.D., of Yale’s Department of Epidemiology and Public Health, decided to revisit the vaccine strategy, but instead of humans he targeted the white-footed mouse, a key player in the spread of Lyme disease.

Working in the woods outside New Haven, Fish and his colleagues captured nearly 1,000 mice and injected them with the Lyme vaccine. As reported in the Proceedings of the National Academy of Sciences, the next year the researchers found lower rates of Lyme infection in both mice and ticks in the study areas.

“This is the first field study to show that we can decrease natural infection rates for a tick-borne disease by immunizing wildlife,” says Fish.

"Obviously it’s not feasible to catch all the mice in a large area and inject them, but an edible vaccine, something you could incorporate into bait, should work as well.”

Lyme disease prevention expert Joseph Piesman of the Cdc hopes that Fish’s results will stimulate more studies of wildlife vaccination. “We need more options for controlling and preventing Lyme disease, and these ecological, host-targeted approaches are very important,” Piesman says.

Newborn deer ticks are infected with the Lyme disease bacterium during a single, summertime feeding on a mouse, and the bacterium spreads the winter inside the tick’s gut. In spring, when the ticks feed on humans, the bacterium can be released into the bloodstream, causing Lyme disease.

According to professor of medicine Erol Fikrig, how the bacterium sets up residence in the tick during winter has been a mystery, but late last year, Fikrig’s group wrote in the journal Cell that they had discovered a receptor that serves as a docking station in the tick gut for the Lyme disease bacterium. If “You manipulate the ticks so that they no longer have this receptor, you reduce the spirochetes,” says Fikrig, who envisions the creation of a receptor-blocking vaccine that would prevent ticks from carrying the Lyme disease bacterium.

Possible cancer inhibitor found in worm study

Yale scientists studying the microscopic worm C. elegans have discovered a cellular brake on a gene implicated in about 20 percent of human cancers, especially lung cancer. The finding opens up new possibilities for cancer diagnosis and treatment, says Frank M. Slack, Ph.D., assistant professor of molecular, cellular and developmental biology.

Slack and his colleagues found that a snippet of genetic material in the worms called let-7 shuts down the activity of an oncogene that can cause cell proliferation to spiral out of control, as happens in cancer. In Slack’s experiment, in developing worms that lacked let-7 cells continued to divide instead of differentiating.

Scientists use C. elegans in the laboratory because the worms share many genes with more complicated animals. According to Slack, let-7 and Ras are almost identical in humans and C. elegans, and Ras protein, the product of the oncogene, is abundant in human lung cancers.

Lung cancer has a poor prognosis, but the lungs may be an ideal target for inhalable gene therapy agents. This may not cure the cancer, Slack said, but “gene therapy with let-7 may be a way to alleviate it or slow it down.”

A heart is repaired, the patient grows up

Program helps growing number of adult survivors of congenital disease

Congenital heart disease (CHD), the most common of birth defects, affects more than 32,000 children born in the United States each year. Three decades ago, many of these children would have died shortly after birth, but thanks to great advances in surgical and medical techniques most children with CHD can now expect to live well into adulthood.

To meet the special medical needs of this group, the Yale Medical Group recently launched the Adult Congenital Heart Program, the first program of its kind in Connecticut and one of only two dozen in the country. “We are looking at a population of patients that hardy existed 20 or 30 years ago,” says James C. Perry, M.D., who staffs the program’s outpatient clinic with coordinator Nicole K. Boramand, A.P.R.N.

The multidisciplinary program provides treatment for common medical problems experienced by survivors of CHD, especially arrhythmias caused by irregularities in the heart’s electrical system and heart failure, which can occur when structural or electrical abnormalities impede the heart’s ability to pump blood.

“Pediatric heart patients were often discharged based on age, but adult cardiologists are not usually trained to manage congenital heart disease. Those patients had nowhere to go,” Perry says. “Our program offers access to pediatric and adult cardiologists and other medical staff with essential expertise.”

The program also offers specialized patient education. “Our focus is on preventive maintenance,” Boramand adds. “What treatments and lifestyle adjustments can increase the length and quality of life? For instance, we emphasize that the old notion that all people with adult CHD should avoid exercise is no longer accepted.”

Those who survive congenital heart disease into adulthood also experience a full range of other health concerns, of course, from catching the flu to developing arthritis to managing pregnancy. Perry notes that the new program will help clinicians learn more about how common health problems affect this population.

Perry and Boramand predict that vanguard programs like Yale’s will inspire future clinicians to specialize in treating adult survivors of congenital heart disease. “This is a group of patients we are just beginning to learn about,” Perry says. “But to see people with complex congenital heart defects going strong into middle age is remarkable.”

James Perry and Nicole Boramand specialize in a new group of patients.

www.medicinenet.com
A long, fruitful collaboration: Bristol-Myers Squibb and Yale

Thirty-year partnership fosters innovations in education and research

Continuing a partnership with the School of Medicine that was forged more than 30 years ago, the Bristol-Myers Squibb Co. has renewed its fellowship support for graduate students in the Combined Program in the Biological and Biomedical Sciences at Yale.

The Combined Program, commonly known as the RSS Program, has transformed the university's graduate education in the life sciences since its inception in 1966. At that time, Bristol-Myers Squibb (BMS) made a substantial, multiyear gift that contributed decisively to both the initial success of the RSS Program and its long-term efficacy.

Directed by Lynn Cooley, Ph.D., professor of genetics and cell biology, the program spans faculty and laboratories in both the School of Medicine and on Science Hill, where the life sciences departments of Yale's Graduate School of Arts and Sciences are located. Underpinning the program is the conviction that intellectual and educational experiences should reflect the increasingly fluid, interdisciplinary nature of biological science. Students select an area of study—such as immunology or neuroscience—but they choose courses and lab work in numerous departments which together comprise more than 285 faculty. For Tomomi Tsuochi, a member of the RSS Class of 2005, the final year of the program has been a heady experience. Tsuochi uses yeast to study the basic mechanism of cell division known as meiosis, and she recently observed a chromosomal mutation that had never before been seen since meiosis was discovered in the 1880s. This May, Tsuochi and her mentor, G. Shirleen Roeder, Ph.D., Eugene Higgins Professor of Molecular, Cellular, and Developmental Biology, published the findings in the Journal of Cell Science.

Tsuochi says that the RSS program has broadened her scientific horizons. "I hope that what I do will affect medicine in some way," she says, "so I'm glad that RSS has combined biology and medicine in one big program."

Bristol-Myers Squibb's support for the RSS Program is part of a broader collaboration with Yale to advance shared educational objectives. For example, the Yale/Bristol-Myers Squibb Educational Alliance—which set up in 1996—has enabled Yale graduate students to gain exposure to private-sector biomedical research through summer rotations at BMS' research and development campus in nearby Wallingford, Conn.

For more than three decades, BMS—or Bristol-Myers, as the company was known prior to its 1999 merger with Squibb—has encouraged Yale education and research in genetics, therapeutics for cancer and the HIV and perinatal medicine. Most recently, the School of Nursing's

More integrated care for cancer patients, collaboration of scientists and clinicians are goals of proposed new YNHH building

According to Yale-New Haven Hospital President and CEO Joseph A. Zaccagnino, M.P.H., the hospital's planned new pavilion for cancer care is one of the biggest projects ever proposed in New Haven. The facility's impact can be measured in cost ($430 million), size (14 stories, 497,000 square feet), new patient beds (112) and the number of permanent jobs the center is expected to bring to New Haven (400).

These figures are undeniably impressive, but the plans for a new clinical center also represent something that numbers alone can't capture, says Yale Cancer Center Director Richard L. Edelson, M.D.; Edward Chu, M.D., the center's director of clinical research and Ira Melman, Ph.D., its scientific director: a rare opportunity to provide state-of-the-art patient care while advancing the science of cancer therapy.

The proposal derives from "an intense focus on cancer that is truly unique among the medical schools, Yale-New Haven Hospital and the university as a single effective team," says Edelson, a cancer immunologist who developed a widely used immunotherapy for T-cell lymphoma. "The people whom we're recruiting are leaving outstanding positions at other university medical centers to come to Yale because they recognize that this new facility is not just another building at another cancer center. Something quite special is happening in the field of cancer at Yale."

From the patient's perspective, too, the proposed 14-story clinical center will be far more than bricks and mortar, Chu says, because it will consolidate services now scattered around the medical complex, including diagnostic imaging, surgery, radiation treatment, social services and palliative care. "For the first time, we'll actually have a dedicated facility for the clinical care of our cancer patients," says Chu. "We're really making the patient the focus."

To achieve a marriage between basic and clinical research, Chu says, the School of Medicine has hired nine clinical investigators, most of whom will arrive this summer. The heart of the new effort, says Melman, will be an unusually close collaboration between these investigators and the teams of basic scientists who will develop new therapies and test and refine them in clinical trials.

An architect's rendering of the proposed new pavilion for cancer care at Yale-New Haven Hospital.

Mellman says that the construction of the new center comes at an auspicious time, when basic research on the molecular biology of cancer is ripe for translation to human treatments.

"Increasingly, Yale faculty on the basic science side are becoming deeply committed to applying what we have learned in the laboratory to problems of human biology in general and human cancer in particular," says Mellman, the Sterling Professor of Cell Biology and a prominent figure in cancer research, "because the problems are so great from a human point of view, and the challenges are so great from a scientific point of view."

And although researchers can learn a great deal studying fruit flies

and mice, Mellman says, clinical trials are vital to advancing cancer care. "The only true model for human cancer is human cancer."

The proposed new Clinical Center is part of a larger Yale Cancer Center endeavor, which will have as a central goal the combination of scientific advances with creative and seamless delivery of the best available clinical care.

According to Mellman and Chu, because understanding cancer requires a multidisciplinary approach, the Yale Cancer Center's new focus will not be on particular tumor types but on disciplines: cancer immunology, cancer genetics, imaging, stem cell biology and drug development. "The new clinical facility is, therefore, a central part of the broader Yale cancer effort."

Once the construction cranes are gone and the hard hats are hung up, Mellman says he looks forward to seeing clinicians, students, laboratory staff and basic scientists brainstorming over the new clinical building. "The first step in any new scientific collaboration," he says, "is communication."
Drive to cure blindness hits $5 million

The Medical School's Arlundy Center was granted with white linem and fresh flowers at a March celebration to mark the successful completion of a five-year, $5 million campaign to build a new center for macular degeneration research at Yale.

The campaign was given a jump-start at the outset, thanks to a $300,000 donation from the Connecticut Lions Club Eye Research Foundation in 2000. On its needs came a $1 million challenge grant from Foresight Inc., a Connecticut-based eye-research charity founded by former patients of Yale ophthalmologists.

Kenneth and Christine Lo, who traveled from Taiwan to attend the effort, two Yale Vision Galas organized by Cecilia Teitell of Stamford, Conn., raised another $385,000.

Rocky Cingari, a longtime Connecticut plastic surgeon, donated $60,000 from Darien, crisscrossed the state during the campaign seeking additional contributions from local Lions Clubs, friends and business contacts.

Cingari coordinated a separate appeal to employees and customers of ShopRite supermarkets, including the seven he owns in southwestern Connecticut with his brothers Sam and Dominic, and he planned charity golf tournaments held in conjunction with ShopRite and the Darien Lions.

With donations from the Darien-based E. Matilda Ziegler Foundation for the Blind and from William Ziegler, the campaign reached its $5 million goal in January. Offering thanks to all who made contributions toward building the center, which will be known as the Connecticut Lions Macular Degeneration Research Center, Bruce Shields, M.D., chair and Marvin Sears Professor of Ophthalmology and Visual Science, said, "We have been very blessed with an incredible number of dedicated and talented people, to whom we are grateful beyond words."

As donors mingled with Yale doctors and scientists during a cocktail reception, the vast Starr Atrium echoed with strains of the Beatles' "Blackbird" played on classical guitar. Lemon and McCartney's lyrics—"Take these tired eyes and learn to see"—were never more apt.

Habert, continued from page 1

are the target sites for important diabetic drugs and explain their mechanisms of action. His subsequent discovery of a calcium-sensing receptor known as CaSR led to the development of a new drug, Angen's Senopar, which is used to treat hyperparathyroidism, a hormonal disorder that affects more than 1 million patients worldwide with end-stage kidney disease.

"What's really amazing," says fellow nephrologist Peter S. Aronson, M.D., "is that Steve has made breakthroughs in three quite different areas. What he's done is really remarkable."

Habert is a past recipient of the Homer Smith Award, the top prize given by the American Society of Nephrology, and he is traveling in May to Singapore to accept the A.J. Richards Award from the International Society of Nephrology (see related story, Page 2).

According to Richard P. Lifton, M.D., Ph.D., chair and Sterling Professor of Genetics, Habert's election to the NAS was no surprise, given the major contributions he has made to his field.

"One of the major thrusts of Steve's work has been to put a molecular face on the abstract principles that have been defined by Gerhard [Giebisch] and other members of the physiology department here at Yale," Lifton said at a ceremony honoring Habert. "By identifying these molecules, he has really allowed us to begin to see how this very intricate and complex machine works in all its integrated glory."

At the ceremony, Dean Robert J. Albery, M.D., called election to the NAS "the greatest honor you can have as a scientist in the United States and certainly one that is reserved for a select few." For his part, Habert was clearly elated, and in his remarks he returned to the development of Senopar as one of the most meaningful events in his career. "Being involved with the translation of your science into medicine," he said, "is the greatest joy you can have as a scientist at a medical school."

Kavli, continued from page 1

intellectual interest in the fundamental scientific questions of our age.

The foundation has distributed more than $400 million in grants to create Kavli Institutes that embrace science writ both enormously large and exceedingly small. Four institutes dedicated to astrophysics foster study of the origin and structure of the universe, while three others concentrate on nanoscience, a cutting-edge field devoted to the manipulation of matter at the molecular and atomic levels.

For Rakic, who serves as director of Yale's Kavli Institute, it is no accident that the foundation has chosen neuroscience to bridge these extremes. "Fred Rakic understands that only the human brain is capable of grasping both the whole universe and the tiniest particle," Racik says, "so it has great intellectual appeal for him to learn how the human brain works."

Kavli also firmly believes that unfettered inquiry is the best route to cracking these great puzzles, and the foundation has won great respect among scientists for its nonintrusive style. "For a typical grant, we must provide a timetable, even specifying what we will do in three years," Rakic says. "Kavli realizes that in three years you might have changed your mind and decided that you need to do something else."

Often a scientist has an intriguing idea, but not enough data for a full-blown grant proposal. The Kavli Institute for Neuroscience at Yale has created several of these great puzzles, and the foundation has won great respect among scientists for its nonintrusive style. "It is very clear to us that the very nature of neuroscience is such that we need the flexibility to move forward as the science evolves," Rakic says. "It is wonderful that we can do this work and have the freedom to explore new lines of research. The institute has also sponsored lectures and informal brainstorming sessions with leading neuroscientists from around the world. Finally, the institute is planning annual symposia where acclaimed researchers will present the latest thinking in neuroscience. "We are confident," says Fred Kavli, "that the expert scientific team at Yale will make important progress in gaining understanding of some of the most complex and baffling secrets in nature hidden in the brain and mind."
Analysis of genome reveals clues to macular degeneration

Biomedical research into the genetic basis of disease has progressed at a rapid clip since the sequence of the human genome was announced in 2000, but March saw the scientific equivalent of a triple play. Three research teams, including one led by Josephine J. Hoh, Ph.D., of Yale’s Department of Epidemiology and Public Health, simultaneously announced that they had identified a gene variant associated with a greatly increased risk of age-related macular degeneration (AMD), a progressive disease leading to blindness that affects more than 10 million elderly Americans (see related story, Page 6).

The human genome can be thought of as a vast string of 3 billion letters in which each letter represents one of the four nucleotides that provide instructions to the body’s protein-building machinery. The genome is 99.9% percent identical among humans, but after every 100- to 300-letter stretch on average is single nucleotide polymorphisms, or SNPs (pronounced “snips”), sites where one nucleotide is substituted for another. Scientists believe that these single-letter variations may help explain why some people are predisposed to certain diseases or respond differently to drug therapies.

Remarkably, all three of the teams who published their findings in March independently zeroed in on the same SNP, a spot on chromosome 1 that is thought to be a gene that codes for an immune system protein known as complement factor H (CFH). In its usual form, CFH acts as a brake on the complement system, a component of the body’s immune response. According to Hoh, whose group scanned the full genomes of 98 individuals with AMD and those of 90 controls, those who carry two copies of the newly identified variant in the CFH gene are nearly 2.5 times more likely than the rest of the population to develop AMD. “This is only an association,” Hoh emphasizes. “It doesn’t really tell you that this is the cause of the disease.”

But a faculy version of CFH may indeed be a culprit in AMD, which has many features of an autoimmune disease. For example, yellowish deposits at the back of the eye known as drusen, the clinical hallmark of AMD, contain complement proteins.

Hoh, an assistant professor, credits the Raymond and Beverly Sackler Fund for the Arts and Sciences for making the study possible. “This particular kind of study is expensive, not the normal thing a junior faculty member can perform,” she says. “I am extremely grateful for the support from the Sackler family.”

Michael B. Bracken, Ph.D., M.P.H., the Susan Dwight Bliss Professor of Epidemiology and Hoh’s collaborator, adds that the work represents a wholly new way of doing epidemiology. “For the past 100 years, we’ve used a hypothesis-testing approach, where hypotheses were generated from animal studies or small human studies and then we did large epidemiology studies.”

By contrast, whole-genome searches for SNPs are “hypothesis-free”: “The association between a gene and disease is established first, and the biology is done after,” Bracken says. “This takes all that we’ve thought about doing science and turns it on its head, and it’s likely to have major payoffs in the future.”

Grants and contracts awarded to Yale School of Medicine

January/February 2005

Federal

Karen Anderson, NIH, A Novel Approach for Studying Transient Enzyme Intermediates, 4 years, $1,209,662 • Susan Borger, NIH, Assembly, Localization and Function of the U3 SnRNP, 4 years, $1,531,473 • Kevin Behar, NIH, NER Studies of Brain Energics and HypoxiGenia In Vivo, 4 years, $1,248,400

Walter et al., NIH, Through the Channel, 3 years, $1,243,060 • Iluminar Corp., Gas Transport Through Channels, 3 years, $1,208,489 • Peter Bowers, NIH, Identification of a Gene Causing Acute Necrotizing Alkalosis, 5 years, $458,611 • Lawrence Brass, NIH, Storied Hospitalization in the United States and Functional FFR (SHEP) Study, 3 years, $1,243,097 • Cecilia Canessa, NIH, Regulation of ENG by EGF, 3 years, $1,207,500 • Michael Cappello, NIH, The Role of MIF in Host-directed Immunity and Disease, 5 years, $1,207,857 • James Duncan, NIH, Inhibition of Function/Structure Image Analysis in Autism, 5 years, $1,201,274 • Cynthia Epperson, NIH, Nonsmoker’s Serrato, GABA and Glutamate, in PMED, 3 years, $1,254,412 • Martin Hildebrand, NIH, Degradation of Short-Used Regulatory Proteins in Yeast, 4 years, $1,245,574 • Stuart Katz, NIH, Studies on Genetics in Heart Failure, 5 years, $1,203,304 • Kenneth Kedd, NIH, ADRH and ALDRH Genes in Tastebuds in Population, 3 years, $1,202,000 • Walther Mothes, NIH, Retinovascular Eflux via Multidrug Transport, 5 years, $1,197,555 • Ching Parikh, NIH, Renal Failure in Non-Myeloablative Stem Cell Transplant, 3 years, $1,204,312 • Archival Poole, NIH, Leukemic Transformation of the AML1/ MDS/EVI, Protein, 3 years, $1,207,211 • Robert Schaul, NIH, The Fatburner Genetik and Amygdala in the Pathobiology of Autism, 5 years, $1,206,559 • Frederick Sigworth, NIH, Fibrillation in Ionic Current through Membrane Channels, 4 years, $1,214,219 • Elif Pinar Ulku, NIH, BRAK Mutation in Trypanosoma, 5 years, $1,192,787 • Anthony Van Der Pol, NIH, Response Properties of Hypothalamic MCH Neurons, 3 years, $1,207,450 • Shu-Mei Wong, NIH, Acquiescence and Low Risk During Pregnancy, 3 years, $1,256,000

Non-Federal

Thomas Biedner, March of Dimes, Analysis of a Molecular Link Between Synapse Formation and Neuronal Developmental Disorders, 5 years, $1,350,000 • Jonathan Bogen, American Diabetes Association, Novel Probing of Glucose Transporter Traffic, 1 year, $100,000 • Mary Boguski, Sekino Inc., SCRA Optimy for Firefighter Proton, 3 years, $1,199,999 • Michael Cappello, The Gerber Foundation, Biometers of Dietary Calcium Insufficiency in Inner-City, 5 years, $284,433 • Joseph Craf, The Arthritis Foundation, CNS Migraine, Mechanical Dopamine, 3 years, $1,200,000 • Richard Edelson, American Cancer Society, American Cancer Society Institutional Research Grant, $150,000 • Ramon Feliciano, Bayer Healthcare, Molecular Pathogenesis of Antibody Deficiency Disorders, 5 years, $1,270,260 • Sotan Ghephlante, American Heart Association, Identification of Signaling Pathway for Cardiac Morphogenesis, 4 years, $65,000 • Thomas Gill, University of Florida, Exercise to Prevent Disability—Pilot Study, 7 months, $15,000 • Helen Gilliam, The William Casper Gunn Memorial Fund, Provocative in Crosslinking Community Data to a National Pre-K Contract, 1 year, $8,120 • Robert Kerns, The Patrick Institute, Catherlind Warden Donoghue Medical Research Foundation, CRF for Paediatrical Neurology, 3 years, $1,212,295 • Darin Lahm, The International Psychosocial Association, Video Toxicology Study of Chemicals, 4 years, $1,205,000 • Shu-Mei Wong, American Thoracic Society, Genetic Factors Controlling TGF-beta in the Pathogenesis of COPD, 2 years, $950,000 • Gene Gun, Pfeifer, Development of Non-Occipial, Multi-Volume GABA MRI at a Tacle—An Investigators Initiated Proposal, 2 years, $727,859 • Daniel Matulka, Alkalstic Beverage Medical Research Foundation, Automatic Processing of Alcohol Intoxication in Chronic Alcoholics: EPP and FHR Data, 2 years, $700,000 • Sherry Mcgill, Alkalstic Beverage Medical Research Foundation, Effect of Alcohol on Reactivity to Tobacco Smoke—Phase III, 8 months, $215,990 • Tiaann Caff, The PKD Foundation, Study of Polycystic Ovaries; Localization and Trafficking and the Molecular Underpinnings, 3 years, $65,000 • Michael Ogden, Cystic Fibrosis Foundation, The Effect of Carcinogen Treatment on the Function of Gamma Fos CFTR, 1 year, $108,000 • Thomas Carpenter, The Gerber Foundation, Biometers of Dietary Calcium Insufficiency in Inner-City, 5 years, $1,200,000 • Timothy Quinn, Scoliosis Foundation, The Role of Fibroblasts in Nephrogenic Fibrosing Dermopathy, 3 years, $100,000 • Joseph Schnellinger, Ludwig Institute for Cancer Research, Intracellular Signal Pathway for Cell Signaling in Cancer and Other Diseases, 1 year, $137,000 • Neal Sestan, Whitehall Foundation, Molecular Control of Prionyel Cell Identity and Connectivity, 3 years, $120,000 • Rosanna Soler, American Cancer Society, Prohysical Factors, Race and Cancer Survival, 5 years, $250,000 • Julie Annona, Association for Academic Surgery, Effects of Persiodynsociety on Neurocognitive Function in Primary Hyoperapathobilary, 3 years, $90,000 • Stephen Stenimtm, Christopher Reuze Pahysoth Foundation, Asograflogilrh Pharmacokinetics for Recovery from Spinal Cord Injury, 5 years, $90,000 • Mary Tinetti, The John A. Hartford Foundation, Key to Quality of Excellence in Aging, 3 years, $600,000 • Li-Xin Xu, The Sasho Institute, Dental Cell Therapy for Autoimmune Disease, 3 years, $120,000 • James Tur, Abbott Spine, ESD in a Caprise Model, 1 year, $134,241 • Hangwu Zhao, Bionolmic Support for the Analysis of Dynamic Data in Order to Identify Potential Biomarkers and Mechanisms of Drug-Induced Vascular Injury, 1 year, $250,000

Michael Cappello and colleagues are investigating the molecular pathogenesis of hoekworm infection, which erects physical and mental development in as many as 1 billion people around the world. This photomicrograph shows the worm’s mouth at lower right.
Unconventional physician-filmmaker receives “genius” grant

When Gretchen K. Berland, M.D., embarked on a research project in 2000 aimed at improving health care for the disabled, she took an unusual approach: she gave video cameras to three people in wheelchairs and asked them to record their lives. Berland, an assistant professor of medicine who had worked as a producer for public television before medical school, hoped to make an intimate, first-person film that would give physicians and policymakers a fresh perspective on the day-in, day-out realities of coping with life in a wheelchair. The film that resulted, titled Rolling, won the Grand Jury

New HHMI investigator says appointment liberates his science

Ronald R. Breakey, Ph.D., has never shied away from uncharted scientific waters, but he says the best thing about his selection in March as a Howard Hughes Medical Institute (HHMI) investigator is that the institute’s largely unrestricted support will “allow me to become much more aggressive in taking bigger risks.”

Breakey’s penchant for unconventional science has served him well. In his pathbreaking work on “riboswitches,” Breakey has shown that cells can regulate their function in ways that biologists would only recently have considered possible. In the laboratory, RNA strands can fold into intricate three-dimensional structures known as aptamers, which precisely recognize targets, much like antibodies do. For example, Breakey has engineered aptamers to detect minute quantities of potential bioterrorism agents. But most biologists thought of aptamers as just a handy tool, and few imagined that they played any role in living things.

However, because aptamers work so well in the lab, Breakey was convinced that they must exist in nature. Three years ago, he stunned the scientific world by showing not only that aptamers exist in bacteria, but also that they switch genes on and off, a function previously thought to be the sole province of proteins acting on DNA. These natural aptamers, which Breakey calls riboswitches, may be important new drug targets in humans, and Breakey has co-founded a company to search for aptamer-based gene therapies.

Breakey, the Henry Ford II Professor of Molecular, Cellular and Developmental Biology, is one of 43 newly appointed HHMI investigators. He joins 15 other Yale HHMI investigators among the 54 designers at biomedical research centers across the United States.

Awards & honors

Hal Blumenfeld, M.D., Ph.D., assistant professor of neurology, has received the Dreifuss-Perry Epilepsy Award for his research on epilepsy and impaired consciousness. The award is made by the American Academy of Neurology to recognize physicians in the early stages of their careers who have made an independent contribution to epilepsy research.

Albert C. Lo, M.D., Ph.D., associate professor of medical genetics, received a Presidential Early Career Award for Scientists and Engineers from the White House Office of Science and Technology Policy at a reception at the White House last September. Lo was honored for his contributions to new therapeutic strategies to restore function in people with multiple sclerosis.

John D. MacMicking, Ph.D., assistant professor in the Section of Microbial Pathogenesis, has been selected as a Senior Scholar by the Illinois-based Kinsbarg Foundation. The award is one of the most prestigious given to junior scientists. MacMicking also received the Mallinckrodt Foundation Program Scholar Award in 2004, given annually to scientists starting their careers.

Linda Degenhis, M.D., Ph.D., associate professor of surgery (emergency medicine) and of epidemiology and public health, was elected chair of the executive board of the American Public Health Association (APHA). The APHA, with 37,500 members from a variety of disciplines, is the primary association for public health professionals and practitioners.

Robert J. Grozyczak, M.D., professor of medicine and director of the Section of Gastroenterology, Digestive Diseases at the VA Connecticut Healthcare System in West Haven, received the 2004 Isarur Bous Medal from the German Society of Digestive and Metabolic Diseases in Leipzig, Germany, for his scientific contributions to gastroenterology, hepatology and metabolic diseases.

Susan T. Mayne, Ph.D., professor of epidemiology, was appointed to the nutrition sub-committee of the Food Advisory Committee of the Food and Drug Administration’s Center for Food Safety and Applied Nutrition, which provides advice to the center’s director and the commissioner of food and drugs regarding emerging food safety, food science, nutrition and other biodes-related issues.

Raymond R. Russell, M.D., assistant professor of medicine (cardiology), has been named the 2004 Bayer Fellow. The award, endowed by the Bayer Pharmaceuticals Corp., provides a fellowship each year to a faculty member making significant advances in medicine or health care management.

Brian S. Reidenberg, M.D., Ph.D., professor of neurology; pharmacology and neurobiology and chair of the Department of Neurology, has been named the first recipient of the National Multiple Sclerosis Society’s Stephen C. Reingold Award. The award recognizes the contributions of Stephen C. Reingold, Ph.D., who, until his recent retirement, was responsible for the Society’s national research and training programs.

Ronald Breakey

Robert S. Sherwin, M.D., the C.H.H. Long Professor of Medicine, has received the Long-Standing Achievement Award from the Novartis Pharmaceutical Corp. for his role in developing insulin pump therapy, a crucial advance in diabetes care, in which insulin is infused continuously via a small pump. He also helped develop the most widely accepted method for measuring cells‘ sensitivity to insulin.

Robert Udelsman, M.D., Ph.D., an endocrinologist, has been named the American Association of Endocrine Surgeons (AAES), a society of board-certified surgeons who have a major interest in and devote significant portions of their practice or research to endocrine surgery.

Hamid Reza Razvi, M.D., professor of neurology and the executive director of the National Multiple Sclerosis Society’s Peter J. Reingold Award.

The award recognizes the contributions of Stephen C. Reingold, Ph.D., who, until his recent retirement, was responsible for the Society’s national research and training programs.