Medicine@Yale

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Advancing Biomedical Science, Education, and Health Care

Kavli neuroscience institute to cast an even wider scientific net

Building upon a grant made in 2003 that established the Kavli Institute for Neuroscience at Yale, The Kavli Foundation has announced that it will contribute additional endowment funds to diversify and strengthen the institute's interdisciplinary brain research.

Since the beginnings of neuroscience research, Yale researchers have excelled in the quest to understand the fundamental mechanisms of how the human brain develops and functions. Such findings from basic neuroscience may have profound implications for understanding brain disorders such as autism, schizophrenia, mental retardation, dyslexia, and neurodegenerative diseases.

Under the direction of Pasko Rakic, M.D., PH.D., Kavli Institute scientists have conducted influential research on the molecular, cellular, and functional organization of the cerebral cortex, the part of the brain responsible for higher brain functions such as language and reasoning.

The new commitment will enable the Kavli Institute to expand its mission to embrace Yale research on the nervous system more broadly, drawing on the expertise of the nearly 100 neuroscientists working in 20 departments across the Yale campus.

"Understanding the human brain is considered the ultimate challenge of science in the 21st century," says Rakic, chair and Dorys McConnell Duberg Professor of Neurobiology at the School of Medicine. "To achieve this laudable goal we must embrace a multidisciplinary approach, using the most advanced technologies in a variety of experimental model systems. It also requires collaboration and frequent exchange of ideas between scientists of different backgrounds. All of these will be cultivated at the Kavli Institute."

Pasko Rakic

To realize this wider vision, the institute's Steering Committee will set the institute's research agenda, foster scientific collaborations at Yale, and build ties with researchers at Kavli Institutes elsewhere. The disciplines expected to contribute to the Yale Kavli Institute's research range from genetics to psychology, and the institute will also foster the development of novel concepts and technologies to investigate the functional properties of the living brain.

In addition to providing research support, the new funds will provide support to top Yale graduate students in neuroscience, who will be designated as Kavli Scholars.

"We are very excited by the expanded approach to neuroscience research the Kavli Institute for Neuroscience at Yale is undertaking," says Fred Kavli, founder and chairman

// Kavli *(page 7)*

New line of attack on a dreaded disease

In honor of a friend fighting a brain tumor, Turkish financier's multimillion-dollar gift funds genomic analysis of deadly glioblastomas

Few diseases are as feared, or as deadly, as glioblastoma multiforme (GBM), the most aggressive and most common form of brain cancer, which accounts for about 60 percent of all brain tumors diagnosed in the United States each year. Over the past five years, improvements in radiotherapy and surgical techniques, and the advent of drugs that block blood vessel formation in tumors have significantly increased survival time in patients with GBM. But despite these advances, on average these patients live less than one year after diagnosis.

One promising avenue for transforming the prognosis faced by GBM patients is genomic research, which can identify aberrant genes present in GBM tumors and determine how such genes vary from patient to patient. Recent genetic sequencing research on GBM has already paid dividends: four new classifications of GBM based on genomic data are guiding the development of more precisely targeted therapies, as well as personalized approaches to treatment based on the genetic makeup of a given patient's tumor.

Last year's launch of the Yale Center for Genomic Analysis (YCGA) placed the School of Medicine at the forefront of genomic sequencing research. Now, with a $12 million, multi-year gift from Turkish financier Mehmet Kutman, M.B.A., to launch a new Yale Program in Brain Tumor Research, researchers at Yale School of Medicine will be bringing the power of the latest genomic techniques to better understand brain tumors, with a particular focus on GBM and related illnesses.

MICHAEL MARSLAND

Yale University President Richard Levin (center) joined neurosurgeon and geneticist Murat Günel (left) and financier Mehmet Kutman (right) at Woodbridge Hall to mark Kutman's donation establishing the Yale Program in Brain Tumor Research. The new program will apply genomic techniques to the study of brain tumors, especially glioblastoma multiforme, the most common and most aggressive form of brain cancer.

"Mehmet Kutman's generous support for Yale's genomic research will spur the effort to find new treatments for patients whose lives are threatened by these brain cancers," says Yale President Richard C. Levin.

The new program will be directed by Murat Günel, M.D., Nixdorff-German Professor of

// GBM *(page 7)*

In life and work, alumnus touched countless hearts

Donald Baim

There could be no greater gratification for a physician–scientist than seeing the fruits of his or her own research become an integral part of medical practice, providing patients with a better treatment than any that had existed before.

The late Donald S. Baim, M.D., a member of the medical school's Class of 1975 and an internationally renowned innovator in the field of interventional cardiology, had that rare privilege.

Baim, who died unexpectedly in 2009 at age 60, served as chief medical and scientific officer at Boston Scientific Corp. (BSC), a global developer, manufacturer, and marketer of medical devices, since 2006. Despite his relatively short four-year tenure, Baim was greatly beloved and admired by

// Baim *(page 7)*

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INSIDE THIS ISSUE

ALSO

TERRY DAGRADI

Three of Carolyn Slayman's grandparents, and both parents, were teachers, an influence that steered her toward academics. After earning her PH.D. in the Rockefeller University laboratory of Nobel Prize winner Edward Tatum, a postdoctoral stint at Cambridge University, and a brief tenure at Case Western University, Slayman joined the School of Medicine faculty in 1967, rising through the ranks to be the medical school's first female department chair, and the first woman to be named a deputy dean.

Taking it in stride

Deputy dean is stalwart in a whirlwind of change in biomedical research

Many awards and mementos, collected over decades in science and academia, line the office shelves of Carolyn W. Slayman, PH.D., but one stands out: a certificate from the Bob Bondurant School of High Performance Driving for excellence in skid control.

Slayman visited the Arizona school on a corporate field trip, donning a full-body racing suit and taking the wheel of some seriously powerful automobiles. In most of the day's activities—threading a car through traffic cones at speed, for example—Slayman was an average performer. But when it came to pulling out of a skid, she nailed it.

An impressed instructor surmised that Slayman honed this skill on snowy roads in her home state of Maine. But it couldn't have hurt that Slayman's demeanor is almost preternaturally calm, an unflappability that serves her well in the demanding, unpredictable role of Deputy Dean for Academic and Scientific Affairs at the School of Medicine. "No two days are alike," she says. "And you never know what's coming when an e-mail pops up or the telephone rings."

In 1995, Slayman became the first woman appointed as a deputy dean at the medical school, and she came well-prepared, having also been the first woman to head a department when she was named chair of the Department of Human Genetics (now Genetics) in 1984.

Slayman has witnessed a sea change in the status of women in science and medicine since the late 1950s, when she enrolled at The Rockefeller University for doctoral studies. In those days, each entering class at Rockefeller, hand-picked by Detlev Bronk, PH.D., the University's president, had 14 men and one woman. When asked at a question-and-answer session for new students why this 14:1 ratio persisted, Bronk coolly replied, "Because that's the right number." At Yale today, women make up a third of the total medical faculty, and since 1998, there have been more women than men in each entering medical school class.

The changes in biomedical science have been no less dramatic. Having graduated from Swarthmore College just five years after Watson and Crick's landmark paper on the structure of DNA, Slayman, also Sterling Professor of Genetics and professor of cellular and molecular physiology, has enjoyed helping to create a gene-sequencing facility at Yale's West Campus that can generate the equivalent of 300 complete human genomes per month, "opening up thinking in ways people couldn't have begun to imagine even a few years ago." Imaging techniques, from microscopes that bring a cell's individual proteins into view to scanners that map out functions in the living human brain, have transformed the scientific landscape. And through it all, once-impenetrable walls between fields and departments have tumbled down, as research became an increasingly multidisciplinary endeavor, "driven," Slayman emphasizes, "by the science itself, not declared from above."

But for all the momentum toward "big science," Slayman believes that scientists will always form working units on a human scale, never relinquishing "the ability to talk around a table." She sees her role as one of "balancing resources and possibilities," providing individual teams with the wherewithal to succeed while also playing matchmaker, urging researchers to "reach out, interact, communicate, collaborate," to make an academic whole bigger than the sum of its parts.

"There are 1,212 really smart people on our faculty doing important things, so there are bound to be problems," Slayman says. "But there's also a constant, positive ferment—good things coming from all directions."

'Old Blues' support ALS research to honor a friend and classmate

When John Tagliaferro, Cary Koplin, and Greg Weiss of the Yale College Class of 1966 learned that classmate Charles A. Skubas was ill with amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease), they knew they would find a way to honor him.

Skubas, a member of the Delta Kappa Epsilon fraternity and a lifelong athlete, was diagnosed with the progressive and neurodegenerative disease in 2007. He passed away on January 3, 2011. After visiting an increasingly frail Skubas in New Haven, Tagliaferro, Koplin, and Weiss pledged to start a fund that would not only pay tribute to Skubas but would also support the fight against ALS and related diseases. What emerged was The Charles Skubas YC '66 Fund for ALS Clinical Support and Research.

By reaching out to classmates, former teammates, and fraternity brothers, Tagliaferro, Koplin, and Weiss, in collaboration with members of Yale's Office of Development, have raised more than $283,400 so far. The fund will support enhanced patient care and research in ALS and related diseases, and will be used at the discretion of David A. Hafler, M.D., Gilbert H. Glaser Professor and chair of neurology at the School of Medicine, and chief neurologist at Yale-New Haven Hospital.

COURTESY OF AMANDA TAGLIAFERRO

A lifelong athlete, Charles Skubas was a member of Yale's varsity football team in the mid-1960s.

Advocate for the mentally ill backs young scientists

In January, the National Alliance for Research on Schizophrenia and Depression (NARSAD), the leading charity providing funds for research on psychiatric illness, announced that 10 School of Medicine scientists had won NARSAD Young Investigator awards. The awards—which provide up to $60,000 over two years to "the most promising young scientists conducting neurobiological research" relevant to understanding mental illnesses including schizophrenia, mood disorders, bipolar disorder, autism, and anxiety disorders such as obsessive-compulsive disorder and post-traumatic stress disorder—went to:

Jessica A. Cardin, PH.D.
Assistant professor of neurobiology

Silvia Corbera, PH.D.
Postdoctoral associate in psychiatry

Douglas J. Guarnieri, PH.D.
Associate research scientist in psychiatry

Jason K. Johannesen, PH.D.
Assistant professor of psychiatry

Roger J. Jou, M.D., M.P.H.
Clinical fellow in the Child Study Center

Janghoo Lim, PH.D.
Assistant professor of genetics

Ruth Sharf, PH.D.
Postdoctoral associate in psychiatry

Megan V. Smith, DR.PH., M.P.H.
Assistant professor of psychiatry

Bao-Zhu Yang, PH.D.
Assistant professor of psychiatry

Lingjun Zuo, M.D., PH.D.
Associate research scientist in psychiatry

In 2011, NARSAD will distribute $12.6 million in Young Investigator awards to 214 scientists around the world. Since 1987, the group has awarded more than $274 million in such grants, which can enable young scientists to pursue studies that will attract major grants from federal agencies or the private sector. On average, Young Investigators have gained sufficient leverage from their grants to raise 19 times the amount of their original NARSAD grant.

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Managing Editor Peter Farley

Assistant Editor Charles Gershman

Contributors Helen Dodson, Jill Max, Suzanne Taylor Muzzin, Janelle Weaver

Design Jennifer Stockwell

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Telephone: (203) 785-5824 Fax: (203) 785-4327

E-mail medicine@yale.edu

Website medicineatyale.org

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Yale SCHOOL OF MEDICINE

Robert J. Alpern, M.D.
Dean and Ensign Professor of Medicine

Jancy L. Houck
Associate Vice President for Development and Director of Medical Development (203) 436-8560

Mary Hu
Director of Institutional Planning and Communications

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A cellular doorkeeper's role in hypertension

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From their perch atop the kidneys, the adrenal glands help to control blood pressure by secreting the hormone aldosterone. In aldosteronism, often caused by adrenal tumors called adenomas, excessive levels of this hormone cause severe hypertension, but the mechanisms of tumor-induced aldosteronism have been poorly understood.

In the February 11 issue of *Science*, a team led by Richard P. Lifton, M.D., PH.D., chair and Sterling Professor of Genetics, reports that many adenomas carry mutations in the gene *KCNJ5*, which encodes channels that selectively allow potassium ions through cell membranes. The mutated channels are less selective, allowing sodium to enter and unleashing a signaling cascade that causes adenoma cells to secrete aldosterone and to overproliferate. A *KCNJ5* mutation was also found in a family with aldosteronism *not* caused by adenomas, suggesting that these mutations can also cause noncancerous adrenal cells to overproliferate and secrete too much aldosterone.

"This gene was not on anybody's list to sequence in an investigation of this disease," Lifton says. "We really hit the jackpot."

Uncovering genes that orient organs

Our bodies exhibit symmetry—two eyes, ears, arms, legs, and so on. But internal organs such as the heart, liver, and stomach must develop asymmetrically to function normally. In heterotaxy (Htx), a rare and potentially deadly birth defect, left–right asymmetry is disrupted, causing organs to be malformed or in the wrong position.

In a new genomic study published online January 31 in *Proceedings of the National Academy of Sciences*, Htx patients were found to be twice as likely as control subjects to harbor copy number variations (CNVs), stretches of duplicated or missing genetic material. Many genes disrupted by these CNVs have counterparts in the frog *Xenopus tropicalis*, and when the authors knocked out *Xenopus* genes they thought might be involved in left–right patterning, they identified five that are essential for proper development, none of which had previously been tied to asymmetry.

"Combining human genetics with model systems such as the frog will allow us to rapidly identify genes that affect embryonic development and better understand the causes of these childhood diseases," says co-author Mustafa K. Khokha, M.D., associate professor of pediatrics and genetics.

A big birthday for Child Study Center

A century of child development research and compassionate care for childhood disorders is marked by world-renowned Yale department


CUSHING/WHITNEY MEDICAL LIBRARY

Arnold Gesell, founder of the clinic that would become the Yale Child Study Center and a pioneer in research on children, employed the relatively new medium of motion pictures to record and observe behavioral patterns in infants.

As the School of Medicine's bicentennial year draws to a close, Yale's venerable Child Study Center (CSC) has begun celebrating a milestone of its own—its 100th anniversary.

One of the School of Medicine's 28 departments, the CSC was born in 1911 when Wisconsin native Arnold Gesell, PH.D., M.D., a young assistant professor in Yale University's new graduate Department of Education, persuaded medical school Dean George Blumer, M.D., to give him a single room in the New Haven Dispensary (a community clinic at the medical school founded in the late 19th century) for use in a study of mentally retarded children. From these humble beginnings, the CSC has become a world-renowned center for the study and treatment of developmental disorders and other psychological conditions affecting children.

In 1921, Gesell was named to lead an expanded Clinic of Child Development, where his work profoundly influenced a burgeoning field. As one of the first researchers to attempt a quantitative study of development by measuring the responses of infants and children to different stimuli, Gesell used the relatively new medium of film to record and study behavioral patterns, eventually filming about 12,000 children. He concluded that mental development occurs in identifiable stages, similar to those seen in physical development. Although some of his views have since fallen out of favor, Gesell's overall influence on American psychology, as well as on child-rearing practices, has been a lasting one.

Following Gesell's retirement, Milton J.E. Senn, M.D., was recruited in 1948 to serve as both chairman of the Department of Pediatrics and director of the renamed and reorganized CSC. The designation as a center reflected the University's desire for a multidisciplinary approach to the study of children and child development. An innovator in pediatrics, Senn was a pioneer in bringing mental health principles into pediatric practice, and as the CSC's new leader he welcomed the insights of social workers, early childhood educators, and other nonmedical child specialists.

Senn was succeeded in 1966 by Albert J. Solnit, M.D., who had been the first resident in child psychiatry at Yale. Solnit was a child psychiatrist, pediatrician, and psychoanalyst who pioneered work on social policy and child custody. He built even more interdisciplinary connections, fostering collaborations with Yale Law School and overseeing the formal establishment of the CSC as a department of both the medical school and Yale-New Haven Hospital.

The CSC also was deeply influenced by its fourth director, the late Donald J. Cohen, M.D., one of the most influential American child psychiatrists of his generation. Cohen upended tradition, rejecting conventional notions that development can be explained in either environmental or genetic terms and seeking to bridge these two viewpoints. In Cohen's studies of autism, for example, he blended the latest research findings, and he came to view the disorder as both genetically and neurologically based—a break from the then-common belief that autism resulted from flawed parenting.

In the difficult period following Cohen's death in 2001, John E. Schowalter, M.D., now professor emeritus in the CSC, filled in as interim director until 2002, when Alan E. Kazdin, PH.D., now John M. Musser Professor of Psychology at Yale and a leader in the development of evidence-based treatments for mental disorders in children, was named the CSC's fifth director. The current director, Fred R. Volkmar, M.D., the Irving B. Harris Professor of Child Psychiatry, Pediatrics, and Psychiatry, was inspired by Cohen's work, and initially came to the CSC in 1980 to work with him. Volkmar has gone on to become a leading scholar in autism and related disorders.

Over the last 100 years the CSC has been home to generations of faculty and trainees who have shaped both the science and social policy surrounding childhood development and mental health issues. The Center now includes the Edward Zigler Center in Child Development and Social Policy, named for Edward F. Zigler, PH.D., Sterling Professor Emeritus of Psychology and chief architect of the Head Start and Early Head Start programs. The Zigler Center has dramatically changed the landscape of services for children and families locally, regionally, and globally. James P. Comer, M.D., M.P.H., the Maurice Falk Professor of Child Psychiatry in the CSC and associate dean for student progress at the School of Medicine, began developing a plan to improve low-achieving elementary schools in New Haven in 1968. Modeled on the understanding that development and learning are inextricably linked, that program, now known as the School Development Program, or SDP, informs state and national education policy and practice and has been implemented in hundreds of schools around the world.

Today the CSC remains at the forefront of the field of child development. Researchers at the Center are making significant strides in many areas, using brain-wave technology, genomics, and neuroimaging, and conducting clinical trials to study such diverse phenomena as the lasting effects of stress and trauma during early brain development; accurate diagnosis of autism in infancy; psychosocial care for children diagnosed with cancer; the genetic and neural bases of autism, Tourette's syndrome, and other developmental disorders; and the efficacy of drugs in treating childhood disorders. The Albert J. Solnit Training Program, established in 2004 as a lasting tribute to the former CSC director, perpetuates Solnit's dedication to clinical excellence and superior education. This six-year, combined clinical and research program admits only two students per year, qualifying graduates for both the adult and child psychiatry board exams and preparing them to help children and families who face the potential disruptions and devastations of a diagnosis of a mental health disorder.

Volkmar credits the center's broad, multifaceted approach for its continued success. "Because there's so much going on here, it means there's more potential for cross-disciplinary work," he says, a model that will guide the CSC through its second century of achievement.

The next century of progress

According to recent data from the National Health and Nutrition Examination Survey, approximately one in five children in the U.S. will meet the diagnostic critera for a mental health disorder such as Tourette's syndrome, autism, anxiety, bipolar disorder, or depression. For 100 years, researchers and physicians at the Yale Child Study Center (csc) have provided compassionate care for children and adolescents, rapidly translating scientific discoveries into practical treatments in the clinic, the home, and the community. Your gifts to these csc programs will sustain this legacy into the next century:

The Albert J. Solnit Integrated Training Program (up to $15 million) A highly selective six-year program (see story above) that gives future clinicians intensive training to provide crucial treatment and support to children with mental disorders, and their families.

Clinical Excellence Fund ($250,000–$1 million) Enables the translation of scientific research to innovative therapies in the Child Study Center's general and specialty clinics (autism, Tourette's syndrome/OCD, trauma, and anxiety disorders).

Community Program Fund ($100,000) Provides support for international programs that work with governments and organizations around the world to improve children's mental health.

For more details, contact Zsuzsanna Somogyi at (203) 436-8559.

MEDICINE tomorrow

OUT & ABOUT

January 11 Yale's Child Study Center (CSC) kicked off its 100th year with a **Centennial Series Symposium** on infant mental health in honor of Arnold Gesell, M.D., the CSC's founder (see related story, p. 3). From left: **Linda Mayes**, M.D., Arnold Gesell Professor of Child Psychiatry; **Helen Egger**, M.D., visiting assistant professor in the CSC; (back row) **Fred R. Volkmar**, M.D., director of the CSC and the Irving B. Harris Professor of Child Psychiatry, Pediatrics, and Psychiatry; **Katarzyna Chawarska**, PH.D., associate professor in the CSC; and **Walter S. Gilliam**, PH.D., associate professor in the CSC and director of The Edward Zigler Center in Child Development and Social Policy.

TERRY DAGRADI (2)

JOHN CURTIS (5)

February 18 The Class of 2013 carried on a 62-year tradition, poking fun at the medical school's faculty and administration in "Staph Inception," this year's **Second Year Show**. **1.** "Boy band" member **Wayne Gui** in one of the dance numbers. **2.** From left: **Maria Koenigs**, **Kara Furman**, **Stephanie Meller**, **Irina Shklyar**, and **Meg Whicker** as members of a glee club that faces off with the boy band. **3. Amanda Hernandez** plays the lead in "Fashion Design Girl." **4. Misia Yuhasz**, the lead dancer in "Dean Belitsky." **5.** From left: **Matt Garner**, **Michael Alpert**, **Chris Sauer**, **Kyle Ragins**, **Ray Chen**, and **Dhruv Kullar** in "Residency."

January 20 89 people from the medical campus were in attendance at a **School of Medicine Night at Mory's**, held in the venerable York Street bar and eatery that reopened last November after a two-year hiatus. **1.** From left: Ralph Brooks; Sheela Shenoi, M.D., instructor in internal medicine; and **Auguste H. Fortin VI,** M.D., M.P.H., associate professor of medicine. **2. Karen Peart**, J.D., associate director of media relations in Yale's Office of Public Affairs and Communications, and her son, Jordan. **3.** Mory's general manager **Robin Soltez** (left) and hostess **Jennifer Dunne**. **4.** Yale College's all-female a capella group **Proof of the Pudding** performed for the crowd. **5.** From left: **Christopher G. Burd**, PH.D., associate professor of cell and developmental biology at the University of Pennsylvania School of Medicine; Dean and Ensign Professor of Medicine **Robert J. Alpern**, M.D.; and **James E. Rothman** , PH.D., the Fergus F. Wallace Professor of Biomedical Sciences and chair of the Department of Cell Biology.

HAROLD SHAPIRO (5)

EMILY HAU

February 18 A **Reception Honoring Flora M. Vaccarino**, M.D., who was named Harris Professor of Child Psychiatry in October, was held in the School of Medicine's Beaumont Room. **Carolyn M. Mazure**, PH.D., associate dean for faculty affairs, professor of psychiatry and psychology, and director of Women's Health Research at Yale (left), celebrates with the honoree, who recently founded the Program in Neurodevelopment and Regeneration, an interdepartmental initiative that will use induced pluripotent stem cells as a research tool to understand neuronal development in individuals with specific neuropsychiatric disorders.

Now? Later? Brain cells help us make the call

ISTOCKPHOTO.COM

We all prefer receiving large rewards right away, but we typically must choose between small, quick payoffs and bigger ones that occur later. Neuroscientists have determined that a brain region called the basal ganglia is crucial in helping us evaluate the size and timing of such incentives.

As reported in the January 13 issue of *Neuron*, a team led by Daeyeol Lee, PH.D., associate professor of neurobiology and psychology, determined which basal ganglia structures govern these choices. Lee and colleagues recorded the activity of neurons in the caudate nucleus and ventral striatum of the basal ganglia in monkeys that shifted their gaze toward different patterns on a computer screen to receive either a tiny amount of apple juice delivered instantly or a larger quantity provided seconds later. The team found that the caudate nucleus contributed more to these judgments than did the ventral striatum. Neurons in the caudate seemed to compare the values of the treats based on their delay and magnitude, revealing a new role of this brain region in decision-making.

The work may help to explain psychiatric conditions characterized by a bias toward immediate gratification. "We don't know the anatomical basis of . . . problem gambling or impulsive behavior," Lee says. "Now we are starting to pinpoint those areas, even down to individual neurons."

Sorting out the steps in *Salmonella* infection

Salmonella bacteria invade the gut by piercing a needle-like structure through the intestinal lining to inject their own proteins into cells. First the needle complex moves into place, and then, in sequence, proteins called translocases and effectors infiltrate the host cell.

In a report published online February 3 in *Science*, a team led by Jorge E. Galán, D.V.M., PH.D., the Lucille P. Markey Professor of Microbial Pathogenesis, analyzed the molecular choreography underlying this step-by-step process.

They found that a protein known as SpaO prepares the bacterium for attack by forming a large complex that includes components of the needle and translocases, but few effectors. However, mutant bacteria that lacked translocases showed high levels of effectors in the SpaO complex, indicating that the complex acts as a sorting platform, queuing up translocases and effectors to deliver them sequentially.

Galán says that understanding such mechanisms could lead to new therapies that do not kill microbes but prevent them from doing harm, an approach that could thwart the development of drug resistance in pathogens.

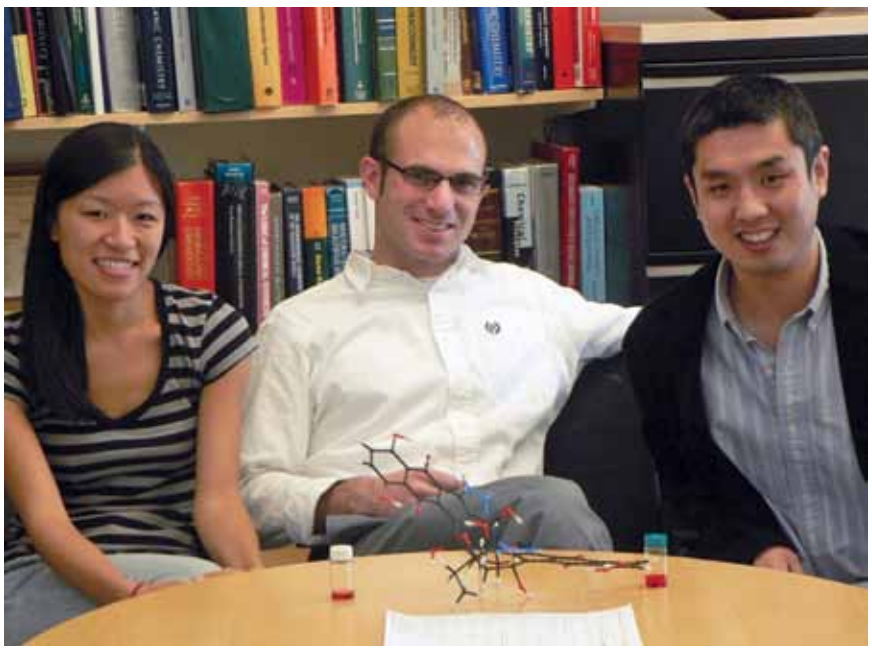
In 11 steps, chemists make a giant leap

The 'blood, sweat, and tears' of Yale researchers push them over the top to crack the daunting, decade-old puzzle of a potent anticancer agent

In the latest chapter of a 15-year scientific story spanning the globe from the South Pacific to New Haven, a team of scientists in Yale's Department of Chemistry has achieved the first synthesis of an elusive chemical compound, opening the door to the development of a new class of molecules to target and destroy cancer stem cells. Many researchers believe that these cells are a root cause of some of cancer's deadliest characteristics, including resistance to chemotherapy, tumor relapse, and metastasis.

The story begins in 1996, when a team of scientists from Wyeth-Ayerst Research (now part of Pfizer) and the University of Utah were analyzing marine organisms they had collected in Fiji in the hopes of finding useful chemicals for drug development. From a bright orange sea squirt retrieved from the seabed, the group isolated a chemical that killed cancer cells and microbial pathogens such as staph bacteria with remarkable potency. The structure of the compound suggested that it might have a bacterial origin itself, and after five years of subsequent analysis the team discovered a previously unknown species of symbiotic bacterium living on the sea squirt that produced yet another chemical with impressive anticancer and antibacterial properties, which they called lomaiviticin.

But the bacterium that produces lomaiviticin is extremely rare, and it cannot be easily coaxed into creating the molecule in the laboratory. For the past decade, chemists worldwide have been striving without success to synthesize lomaiviticin to obtain sufficient quantities for exploring its anticancer properties more deeply. Now, as reported online January 31 in the *Journal of the American Chemical Society*, a team at Yale, led by Seth Herzon, PH.D., has managed to synthesize a form of the compound known as lomaiviticin aglycon for the first time.



COURTESY OF SETH HERZON

(From left) Graduate student Cristina Woo, Seth Herzon, and postdoctoral fellow Liang Lu solved the "extremely difficult" problem of synthesizing a chemical that has drawn worldwide attention for its potential in fighting a variety of cancers.

"About three quarters of anticancer agents are derived from natural products, so there's been lots of work in this area," says Herzon, assistant professor of chemistry. "But this compound is structurally very different from other natural products, which made it extremely difficult to synthesize in the lab."

Herzon's team, which managed to synthesize the molecule in just 11 steps starting from basic chemical building blocks, has been working on the problem since 2008 and spent more than a year on just one step of the process involving the creation of a carbon–carbon bond. It was an achievement that many researchers deemed impossible, trying to work around it using other techniques, but the Herzon team's persistence paid off.

"A lot of blood, sweat, and tears went into creating that bond," Herzon says. "After that, the rest of the process was relatively easy." **// Herzon** *(page 8)*

Surgeons-turned-detectives explore the dawn of chemotherapy

Thanks to the unearthing of long-lost medical records by two dogged surgeons, the full story of the first use of intravenous chemotherapy for cancer, which occurred at Yale in the early 1940s, can now be told.

The general outlines of this event—that a lymphoma patient, known only as "J.D." in the medical literature, received the first known chemotherapy at New Haven Hospital (now Yale-New Haven Hospital) in 1942—have been recounted by historians based on the recollections of those involved in the case, but the specifics have until now remained a mystery.

Two years ago, Clinical Professor of Surgery John E. Fenn, M.D. and Robert Udelsman, M.D., M.B.A., chair and William H. Carmalt Professor of Surgery, became fascinated by J.D.'s case and determined to try to locate his medical records. The problem was that they had no name, date of birth, medical record number, or precise dates of treatment—only the patient's initials.

For months the two pursued records from that era, including pathology reports, of every "J.D." they could find. Michael Kashgarian, M.D., professor emeritus and senior research scientist in the Department of Pathology, whom they'd enlisted to help, finally found a report that looked promising, but the medical record number contained errors. Thanks to the help of a persistent archivist, they eventually narrowed the possibilities down to one patient. In a moment of triumph, Fenn sent Udelsman a one-word e-mail: FOUND!

The records revealed that an immigrant from Poland first came to New Haven Hospital in 1941 for treatment of massive tumors in and around his neck that had diminished his ability to eat, sleep, breathe, and turn his head. Radiation treatments were quite effective at first, but by August of the following year the tumors had recurred and had developed resistance to treatment with X-rays. As no other therapeutic options for cancer had yet been developed, doctors had nowhere else to turn. **// Surgeons** *(page 8)*

CHARLES GERSHMAN

Robert Udelsman (left) and John Fenn took on the task of locating the misplaced medical records of the first patient treated for cancer with intravenous chemotherapy, an event that grew out of wartime research seeking antidotes for chemical weapons conducted at the School of Medicine in the 1940s.

Grants and contracts awarded to Yale School of Medicine

May/June, 2010

Federal

Choukri Ben Mamoun, NIH, *Transcriptional Regulators of the Malarial var Multigene Family*, 2 years, $447,316 • **Angelique Bordey**, NIH, *Cerebellar Neurogenesis*, 5 years, $2,017,031 • **Michael J. Caplan**, NIH, *Cell Biology of Renal Sodium Pump: Sorting and Function*, 5 years, $2,952,924 • **Sonia Caprio**, NIH, *Study to Investigate the Pathophysiology of Type 2 Diabetes in Youth*, 5 years, $2,077,807 • **Richard E. Carson**, NIH, *State-of-the-Art PET/CT Instrumentation*, 1 year, $2,300,000 **Christopher M. Colangelo**, NIH, *5500 QTRAP Mass Spectrometer for Yale Keck Lab*, 1 year, $491,747 **Todd Constable**, NIH, *Method for Measuring Functional Subunits in Human Cortex*, 4 years, $1,613,625 • **Pietro De Camilli**, NIH, *Molecular Mechanisms in Synaptic Vesicle Recycling*, 4 years, $1,469,133 • **Gary V. Desir**, NIH, *Renalase in Acute Kidney Injury: Utility as Biomarker and Therapeutic Agent*, 1 year, $500,000 • **Daniel C. DiMaio**, NIH, *Cell Transformation by Bovine Papillomavirus*, 5 years, $2,678,587 • **Ronald S. Duman**, NIH, *Antidepressants: Signal transduction and gene expression*, 5 years, $1,768,750 • **Leah Ferrucci**, NIH, *Epidemiology, Genetics and Behaviors in a Study of Basal Cell Carcinoma*, 3 years, $113,436 **Helen Fox**, NIH, *Cognitive Processes for Pharmacotherapy and Treatment Outcome in Cocaine Dependent Individuals*, 5 years, $773,253 • **Cary P. Gross**, NIH, *Use and Outcomes of Radiation Therapy for Medicare Patients with Common Cancers*, 3 years, $1,565,949 • **David Hafler**, NIH, *Autoimmune Centers of Excellence: Investigation of Innate Immunity in Multiple Sclerosis*, 5 years, $1,653,739; NIH, *T Cell Recognition of Myelin in Multiple Sclerosis*, 1 year, $390,668 • **Nathan Hansen**, Nat'l Inst. of Mental Health, *Intervention to Reduce Acute Stress and HIV Risk in Newly HIV Diagnosed Men*, 3 years, $732,594 • **Fumiaki Imamura**, NIH, *Molecular Mechanisms Regulating Mitral Cell Development*, 3 years, $496,500 **Akiko Iwasaki**, NIH, *Autophagy in Antiviral Immunity*, 5 years, $2,046,572 • **Themis Kyriakides**, NIH, *MCP-1 and Attenuation of the Foreign Body Response*, 4 years, $1,357,100 • **Daeyeol Lee**, NIH, *Decision Making and Orbitofrontal Cortex*, 5 years, $1,861,875 • **Ifat Levy**, NIH, *Cognitive Bases of Risk-Taking Over the Lifespan: Psychophysics and Brain Imaging*, 5 years, $1,661,141 • **Paul J. Lombroso**, NIH, *Molecular and Cellular Analysis of Brain Enriched PTPs*, 5 years, $2,098,409 • **James C. McPartland**, NIH, *Connectivity in Social Brain Systems in Autism*, 2 years, $454,660 • **Ruslan M. Medzhitov**, NIH, *Role of Basophils in Initiating Th2 Immune Responses*, 5 years, $2,066,130 **Walther H. Mothes**, NIH, *Two-Photon Microscope for Intravital Imaging*, 1 year, $487,929 **Michael H. Nathanson**, NIH, *A Laser Scanning Confocal Microscope for Research and Education*, 5 months, $931,206 • **Karin Reinisch**, NIH, *Structural Studies of the MHC Class 1 Peptide Loading Complex*, 2 years, $413,750 • **Scott A. Rivkees**, NIH, *Periventricular White Matter Injury Prevention*, 4 years, $1,603,281 • **Marc I. Rosen**, NIH, *Improving Clinician Ratings of Money Mismanagement: Addictions Impact*, 4 years, $1,295,519 **Michael Rowe**, NIH, *Citizenship and Mental Illness*, 2 years, $455,125 • **Alan C. Sartorelli**, NIH, *Hypoxia-Activated O6-Benzylguanine Prodrugs*, 3 years, $955,802 • **John Schell**, NIH, *Using vsv Vectors to Elicit Broadly Neutralizing Antibodies Against SIV Envelope*, 3 years, $156,438 • **Sunny Shin**, NIH, *Molecular and Cellular Characterization of Host Response Pathways Triggered by Vacuolar Bacterial Pathogens*, 7 months, $94,770 • **Jody Sindelar**, NIH, *Aging Research at the 2010 through 2014 ASHEcon Biennial Conferences*, 5 years, $125,000 • **Carter Takacs**, NIH, *Roles of miRNAs During Vertebrate Brain Morphogenesis*, 3 years, $155,538 • **Seyedtaghi Takyar**, NIH, *MIR-1 is a Critical Regulator of VEGF-Induced Angiogenesis*, 2 years, $237,600 • **Taiwo Adedapo Togun**, NIH, *Identification of Genomic Biomarkers of Trastuzumab Response*, 3 years, $82,760 • **Derek K. Toomre**, NIH, *Super-Resolution Structured Illumination Microscope (SIM)*, 1 year, $496,785 **Mikhail Torban**, Nat'l Inst. on Drug Abuse, *INVEST Drug Abuse Research Fellowship*, 1 year, $44,000 **Benjamin E. Turk**, NIH, *Identification of Exosite-Targeting Inhibitors of Anthrax Lethal Factor*, 1 year, $165,500 • **Li Wen**, NIH, *Environment, Innate Immunity and Type 1 Diabetes*, 4 years, $1,655,000

Non-Federal

Mert O. Bahtiyar, American Inst. of Ultrasound in Medicine, *Fetal Cardiac Response to Intra-amniotic Infection*, 2 years, $10,000 • **Richard E. Carson**, Mount Sinai School of Medicine, *5HTT and 5-HT2A Receptors in Impulsive Aggression and Effects of Fluoxetine*, 1 year, $217,675 • **Susan R. Compton**, American Association for Laboratory Animal Science, *Evaluation of Risk Factors for Mouse Parovirus Transmission*, 1 year, $43,545 **Weiguo Cui**, Burroughs Wellcome Fund, *Burroughs Wellcome Fund 2010 Travel Grant Program*, 1 month, $3,500 • **Patrick G. Gallagher**, Doris Duke Charitable Foundation, *Erythrocyte Hydration Pathways as Modifiers in Sickle Cell Disease*, 3 years, $486,000 • **Joel E. Gelernter**, Butler Hospital, *Dex/CRH Test Response Endophenotypes*, 1 year, $16,545 • **Susan Michelle Goebel Goody**, FRAXA Research Foundation, *STEP: A Novel Therapeutic Drug Target in Fragile X Syndrome*, 2 year, $90,000 • **Albert Ko**, Chembio Diagnostic Systems, Inc., *Rapid Test for Leptospirosis*, 2 years, $421,715 • **Mark J. Mamula**, Academy for Applied Science, *Research and Engineering Apprenticeship Program 2010*, 2 months, $2,600 • **Luis N. Marenco**, University of Alabama at Birmingham, *OR-ModelDB: A Resource for the Computational Biology of Chemosensory Receptors*, 1 year, $24,930 **Richard A. Marottoli**, American Medical Association Foundation, *Medical Fitness to Drive*, 8 months, $8,000 • **Linda C. Mayes**, University of Maryland at College Park, *Novel Behavioral Activation Intervention, Reward Processing, and Youth Smoking Cessation*, 3 years, $80,623 **Diane McMahon-Pratt**, Intelligent Optical Systems, Inc., *Rapid Field Test Kit for Differentiation of Human and Animal* Leishmania *in the Sand Fly Vector*, 6 months, $10,000 • **Pramod Kumar Mistry**, Genzyme Corporation, *Biomarker Discovery and Validation in Gaucher Disease*, 1 year, $148,345 • **Yorgo Eugene Modis**, Burroughs Wellcome Fund, *Burroughs Wellcome Fund Travel Grant*, 5 months, $1,000; Burroughs Wellcome Fund, *Burroughs Wellcome Fund Seminar Grant*, 10 months, $1,000 • **Deepak Narayan**, Plastic Surgery Educational Foundation, *Hemangioma: Stem Cell Tumor of Pericyte Origin*, 1 year, $10,000 • **Ali Kemal Ozturk**, American Association of Neurological Surgeons, *Whole Exome Sequencing in Five Large Intracranial Aneurysm Families*, 1 year, $15,000 • **A. David Paltiel**, Harvard Medical School, *Modeling the Impact of HIV Prevention Interventions*, 4 years, $263,253 • **Chirag R. Parikh**, Northern California Institute for Research & Education, *The Aging Kidney in HIV Infection: Biomarkers of Early Detection for Kidney Injury*, 1 year, $2,312,475 **Marc N. Potenza**, Mount Sinai Medical Center, *Norepinephrine Transporter Imaging in Alcohol Dependence and Obesity*, 3 years, $201,255; Mount Sinai School of Medicine, *Norepinephrine Transporter Imaging in Alcohol Dependence and Obesity* (ARRA supplement), 1 year, $433,730; Mount Sinai School of Medicine, *Serotonin 1B Receptor Imaging in PTSD with and without Co-morbid Depression*, 1 year, $30,878; Mount Sinai School of Medicine, *Serotonin 1B Receptor Imaging in Major Depressive Disorder*, 1 year, $7,614 • **Valerie Reinke**, March of Dimes, *Control of Cell Proliferation by VRK1 in Mouse Germ Cells and Embryos*, 3 years, $324,099 • **Harvey A. Risch**, Cancer Research Center of Hawaii, *Collaborative Genetic Study of Ovarian Cancer Risk*, 1 year, $28,828 • **Scott A. Rivkees**, JS Genetics, *Identification of Oligodendrocyte Stimulators*, 10 months, $227,346 • **Lara Elise Rosenbaum**, Howard Hughes Medical Institute, *Evaluating the Role of E-Cadherin in Melanoma Invasion and Metastasis*, 2 years, $38,000 • **Mark Shlomchik**, University of Buffalo, *Identification of Specific Roles for Ets-1 in B Cell Tolerance*, 5 years, $168,572 **Gerald I. Shulman**, Covidien AG, *Rat Model of Surgical Alleviation of Type 2 Diabetes by RYGB or Catheterization of the Small Intestine*, 2 years, $352,515 • **Janis Lee Tondora**, Columbus House, *PCP Training for Columbus House*, 8 months, $10,706 • **Xiao-Jing Wang**, The Swartz Foundation, *Sloan/Swartz Summer Meeting*, 2 months, $24,934 • **Stephen Waxman**, Nancy Taylor Foundation for Chronic Diseases, Inc., *Proof-of-Principle of Novel Pharmacotherapies for Neuropathic Pain: Production of Gene-slicing Molecules for Studies on Pain*, 2 years, $223,038

New grant from VA supports a fresh look at primary care training

The United States faces a severe shortage of physicians in the coming decades. As the health care needs of the aging Baby Boomers grow rapidly, the number of medical school students electing to enter the field of primary care is in sharp decline. According to the National Resident Matching Program, students choosing residency training in general internal medicine fell from 575 in 1999 to 264 in 2008.

One of the factors that has been found to influence students' views of general internal medicine as a career choice is the quality of the educational experience in internal medicine.

The VA Connecticut Healthcare System (VAHCS) is now poised to address that issue with a new $5 million grant from the Department of Veterans Affairs to establish a Center of Excellence in Primary Care Education. The Yale-affiliated VAHCS is one of only five facilities in the country to receive the five-year grants, which will support a new approach to training internists and other health care professionals. Traditionally, internal medicine residents have spent most of their time training in inpatient settings, but the majority of patients are now treated in outpatient settings. "Training hasn't really kept up with the reality of how internists practice," says the School of Medicine's Patrick G. O'Connor, M.D., M.P.H., professor of medicine and section chief of general medicine.

Rebecca Brienza

Under the existing system, residents spent just one half-day a week at the VAHCS, but they will now go there for training every day for two months at a time, a total of 10 months of intensive training over the three years of residency. Interns and first-year residents will continue to spend a half day per week at the VA in between the two-month intensive blocks. "Restructuring their schedule will allow them to really learn what a primary care doctor actually does, which is to be there every day for their patients and have longitudinal relationships," says Assistant Professor of Medicine Rebecca Brienza, M.D., M.P.H., who will serve as director of the new center.

Patrick O'Connor

The center will also establish a one-year postgraduate fellowship in primary care for nurse practitioners, becoming the first program in the country to offer such training. Residents and nurse practitioners will train in teams, taking care of patients together for a 12-month period, with the nurse practitioners providing continuity of care during the time residents are training at other locations between their two-month stints.

"The current way we train postgraduate M.D.s and nurse practitioners is really a 'silo' model, where there's no cross-pollination for collaboration," says Brienza. "We've learned that caring for patients in multidisciplinary care teams is a better approach, with better outcomes for patients." The center will provide training in interprofessional collaboration to residents and nurse practitioners, as well as students in medical school, undergraduate nursing programs, pharmacy, and health psychology. They will learn how to work effectively as members of a team, how to appreciate the input of others and their contribution to caring for patients, and conflict management. "All those things with regard to teamwork that are assumed that health professionals know but that there's actually no real training for," says Brienza.

The new training model fits in well with changes brought about by the recent health care reform legislation, with its concept of a "medical home," an outpatient-based primary care practice through which care is coordinated.

The program is itself a collaboration between the VA, Yale School of Medicine, Yale School of Nursing, University of Connecticut School of Medicine, and Fairfield University School of Nursing. The five institutions will contribute a total of over 200 trainees over a five-year period.

"Training programs need to prepare physicians not only for the present, but also for the future, when they'll have more responsibility for team care and organization of services for patients," says O'Connor.

// GBM *(from page 1)* Neurosurgery at Yale and an accomplished researcher on genetic causes of brain disorders, who was the recipient of Kutman's donation. "This gift brings unprecedented opportunities for us to extend our expertise in genomic sequencing to one of the deadliest diseases, and hopefully, to make a difference for patients," says Günel, also professor of neurobiology and genetics and co-director of the Yale Neurogenetics Program.

"Mr. Kutman's selection of Dr. Günel to perform these studies is a testimony to Murat's international reputation in neuroscience. He is a gifted clinician and investigator who can use these resources to focus on the genetic basis for glioblastoma," says Joseph M. Piepmeier, M.D., Nixdorff-German Professor of Neurosurgery and director of surgical neuro-oncology at the School of Medicine. "Under Dr. Günel's leadership, the Yale Program on Neurogenetics is now positioned to discover effective treatment for this fatal disease."

The gift, which was announced at a February 17 signing ceremony at Yale's Woodbridge Hall, was made by Kutman in honor of a close friend and fellow board member at Istanbul-based Global Investment Holdings, a merchant bank with diverse interests in Turkish seaports, real estate, energy generation and distribution, and financial institutions. Kutman's colleague is currently being treated for GBM.

"I have a great deal of confidence in both Dr. Günel and Yale School of Medicine," says Kutman. "We hope very much to break ground in genomics-related GBM research in the near future."

Based on this agreement, some 400 samples of brain tumors from Turkish hospitals will be delivered to Yale, a valuable research resource that will supplement the many pathological specimens already on hand at the medical school.

"In spite of much research and the application of the latest in technology, the prognosis for survival of patients with GBM is unacceptably short," says Robert J. Alpern, M.D., Dean and Ensign Professor of Medicine. "Basic research leading to an understanding of the biology of these tumors is essential. The generous gift of Mr. Kutman will permit Murat Günel to use state-of-the-art genomics to study the molecular mechanisms responsible, thus paving the way for new treatments."

Günel says that sequencing of GBM tumors so far, while quite productive, is incomplete. "As we work to contribute to a complete catalog of the mutations present in brain tumors, we will be able to understand individual tumors and come up with better therapies," he says.

School of Medicine researchers at the YCGA led by Günel's longtime mentor and colleague Richard P. Lifton, M.D., PH.D., chair and Sterling Professor of Genetics and Howard Hughes Medical Institute investigator, have pioneered a speedy and inexpensive genomic technique known as exome sequencing, in which only those parts of the genome containing protein-coding genes are sequenced.

This approach will be valuable for studying a variety of brain tumors, says Günel, because the genomic research on other brain tumors completed by scientists so far suggests that some genes may have a major effect, and that even a single gene mutation could play a role in a large percentage of tumors. However, Günel says, it will be important to compare data from exome scans with those of the entire genome, because non-coding genomic regions are believed to play an important role in tumor formation in the brain.

Though the Yale Program in Brain Tumor Research has just been established, research on the genetic roots of GBM is already up and running at the School of Medicine, says Günel. "We're sequencing brain tumors right now," he says. "There's no time. A cure cannot wait."

// Kavli *(from page 1)* of The Kavli Foundation. "Science flourishes with collaboration and this will be a great stimulus to more innovative research."

Robert W. Conn, PH.D., president of the Foundation, adds, "The Foundation is very pleased that Yale will be significantly expanding the scope of activities at the Kavli Institute for Neuroscience. It's also wonderful that, with the establishment of the Kavli Scholar program, Yale's top graduate students in neuroscience will have even more reason to be part of this exciting research enterprise."

Founded in 2000 by Fred Kavli, a Norwegian-born businessman and philanthropist, The Kavli Foundation is dedicated to advancing science for the benefit of humanity, promoting public understanding of scientific research, and supporting scientists and their work. The Foundation's mission is implemented through an international program of research institutes in the fields of astrophysics, nanoscience, neuroscience and theoretical physics, and through the support of conferences, symposia, endowed professorships, journalism workshops and other programs and activities.

The Foundation is also a founding partner of the Kavli Prizes. First awarded in 2008, the prizes recognize scientists for seminal advances in astrophysics, nanoscience, and neuroscience. A prize in each of these areas is awarded every two years, with international prize committees independent of the Foundation choosing the recipients. For his decades of influential research on the cerebral cortex, Rakic was one of the recipients of the inaugural Kavli Prize in Neuroscience. James E. Rothman, PH.D., the Fergus F. Wallace Professor of Biomedical Sciences and chair of the Department of Cell Biology, was a recipient of the Kavli Prize in 2010 for his discoveries on the molecular mechanisms of synaptic transmission.

"We are very grateful to Fred Kavli for his continued support of the Yale Kavli Institute and our neuroscience programs," says Robert J. Alpern, M.D., dean and Ensign Professor of Medicine. "This recent gift will allow us to expand the size and scope of the Kavli Institute to provide the means to explore new directions for Yale's neurosciences."

MICHAEL MARSLAND

From left: Miyoung Chung, vice president for scientific programs at the Kavli Foundation, and Robert W. Conn, Kavli Foundation president, joined Yale President Richard C. Levin and Pasko Rakic, director of the Kavli Center for Neuroscience at Yale, to mark the foundation's renewed support for the center, which will expand its reach to embrace a broader range of neuroscience research at Yale.

// Baim *(from page 1)* his BSC colleagues, who have contributed $1.7 million to establish The Donald S. Baim, M.D., '75 Scholarship Fund at the School of Medicine. The fund will provide an annual scholarship to a promising student with financial need in each year's entering class, covering half the tuition for all four years of medical school.

"We are extremely grateful for the generosity of Boston Scientific and the contribution it is making to generations of young physicians," says Robert J. Alpern, M.D., dean and Ensign Professor of Medicine. "Dr. Baim was a remarkable alumnus who made great advancements in the field of cardiovascular medicine, and we are pleased to continue his legacy through this scholarship fund."

Baim was a founding figure and one of the most prolific innovators in interventional cardiology, the branch of cardiology focused on catheter-based delivery of therapies such as angioplasty, stents, valve repair, and ablation, the destruction of abnormal tissue to treat cardiac arrhythmias. In a 2010 remembrance published in the trade journal *In Vivo*, colleague and friend Gregg Stone, M.D., professor of medicine and director of cardiovascular research and education at the Center of Interventional Vascular Therapy (CIVT) at Columbia University Medical Center, describes Baim's "almost Zen-like relationship with devices—he intuitively understood how a device would interact with the pathology and pathophysiology of a disease and how that interaction might help an individual patient."

He was also one of those rare individuals known in academic medical circles as a "triple threat," excelling in the clinic, the lab, and the classroom.

Born in New York City, Baim spent his childhood in Miami Beach, Fla., and received his undergraduate degree in physics from the University of Chicago. Two fellow members of Baim's medical school class at Yale—Martin B. Leon, M.D., professor of medicine and associate director of CIVT at Columbia, as well as vice chairman of the Cardiovascular Research Foundation in New York; and Steven N. Oesterle, M.D., now senior vice president for science and technology at Medtronic—were Baim's lifelong friends, and also became leaders in interventional cardiology.

It was during a postgraduate fellowship in cardiology with John B. Simpson, M.D., PH.D., at Stanford University School of Medicine that Baim first displayed his uncanny skill in treating heart disease using catheter-based methods. He went on to make seminal refinements to those methods over the course of a three-decade career, including 25 years on the faculty of Harvard Medical School, during which he published more than 300 articles, treated thousands of patients, and saw interventional cardiology rise from relative obscurity to become the standard of care for any number of heart disorders.

"Don Baim was the guy who introduced science to what [in the 1980s] was a very anecdotal, almost guild-like profession," Oesterle recalled in *In Vivo*.

In announcing the scholarship fund, Ray Elliott, president and chief executive officer of BSC, said, "Boston Scientific is proud to honor our esteemed former colleague by supporting the next generation of medical leaders at his alma mater."

Wallace Professor of Biomedical Research studies role of brain circuits in metabolism

Tamas L. Horvath, D.V.M., PH.D., professor and chair of the Section of Comparative Medicine, has been named the inaugural Jean and David W. Wallace Professor of Biomedical Research.


Tamas Horvath

Horvath's research is focused on neuronal circuits that support energy metabolism, as well as pathological conditions, such as obesity and diabetes, that affect these circuits. He also studies the role of metabolic signals in neurodegenerative diseases.

Horvath investigates the role of synaptic plasticity in the mediation of peripheral hormones' effects on the central nervous system as well as the role of mitochondrial membrane potential in normal and pathological brain functions. His research combines classical neurobiological approaches, including electrophysiology and neuroanatomy, with endocrine and genetic techniques to better understand biological events at the level of the organism.

Horvath, also a professor of neurobiology and of obstetrics, gynecology, and reproductive sciences, is the founding director of the Yale Program in Integrative Cell Signaling and Neurobiology of Metabolism, which was launched in 2009.

A winner of the National Institutes of Health Director's Pioneer Award in 2010, Horvath has also been honored with an Alexander von Humboldt Professorship by the Republic of Germany's Ministry of Science.

The Wallace Professorship in Biomedical Research was established in August 2010 by philanthropists Jean and David W. Wallace of Greenwich, Conn. The endowed chair supports the academic, research, and teaching activities of a School of Medicine faculty member whose work advances the school's strategic vision and who is recognized as among its most promising and productive researchers.

Expert on prevention of falls in the elderly is honored for a pioneering body of research

The American Geriatrics Society (AGS) has awarded Mary E. Tinetti, M.D., the Edward Henderson Award, which recognizes a distinguished clinician, educator, or researcher who has made significant contributions to the field.


Mary Tinetti

The AGS is honoring Tinetti for her pioneering work on falling in the elderly and its prevention. Tinetti will receive the award and will present the Henderson State-of-the-Art Lecture at the AGS's 2011 Annual Scientific Meeting in Washington, D.C., in May.

Tinetti is the Gladys Phillips Crofoot Professor of Medicine and Epidemiology and Public Health, and director of the Yale Program on Aging at the School of Medicine.

She was the first investigator to show that older adults at risk for falling and injury could be identified, that falls were associated with a range of serious adverse outcomes, and that multifaceted risk-reduction strategies were both successful and cost-effective.

Her work has transformed the prevailing view of falls as an inevitable consequence of aging to a preventable event with a multidimensional set of risk factors that can be identified and controlled.

Tinetti has also investigated and published extensively on functional disability and mobility impairment. She is now involved in efforts to translate these research findings into clinical and public health practice.

Most recently, Tinetti has focused her research on clinical decision-making in the face of multiple health conditions.

Tinetti has been awarded many of the highest accolades in geriatrics. In 2009, she received a MacArthur Foundation Fellowship (popularly known as a "genius" award) recognizing her contributions to the area of fall prevention in older adults.

// Herzon *(from page 5)* In 2010, Herzon was named a Searle Scholar, an award granted each year to 15 "exceptional young faculty in the biomedical sciences and chemistry," according to the program's website.

In addition to lomaiviticin aglycon, Herzon's team has also created smaller, similar molecules that have proven extremely effective in killing ovarian stem cells, says Gil Mor, M.D., PH.D., a researcher at the School of Medicine and Yale Cancer Center who is collaborating with Herzon to test the new class of molecules as cancer therapies.

But Mor and Herzon are particularly excited about lomaiviticin aglycon's potential to kill ovarian cancer stem cells because the disease is notoriously resistant to Taxol and carboplatin, two of the most common chemotherapy drugs.

"Ovarian cancer has a high rate of recurrence, and after using chemotherapy to fight the tumor the first time, you're left with resistant tumor cells that tend to keep coming back," Mor explains. "If you can kill the stem cells before they have the chance to form a tumor, the patient will have a much better chance of survival—and there aren't many potential therapies out there that target cancer stem cells right now." Cancer stem cells are thought to be precursors to tumors in a number of other cancers as well, including in the brain, lung, and prostate, and in leukemia.

Herzon, Mor, and colleagues will continue to analyze lomaiviticin aglycon to better understand its actions on cancer stem cells at the molecular level, and they hope to begin testing the compounds in animals shortly.

"This is a great example of the synergy between basic chemistry and the applied sciences," Herzon says. "Our original goal of synthesizing this natural product has led us into entirely new directions that could have broad impacts in human medicine."

New AAAS Fellows

Three School of Medicine faculty members have been elected Fellows of the American Association for the Advancement of Science (AAAS), an international nonprofit organization dedicated to advancing science around the world.

Founded in 1848, the AAAS serves some 262 affiliated societies and academies of science.

The association's mission is to "advance science, engineering, and innovation throughout the world for the benefit of all people." The AAAS also publishes the journal *Science*.

At the AAAS Annual Meeting in Washington, D.C., in February, 503 new Fellows were lauded for their exceptional contributions to science and technology.

Jorge E. Galán, PH.D., D.V.M., the Lucille P. Markey Professor and chair of the Section of Microbial Pathogenesis, is renowned for his work on the mechanisms of pathogenesis of the intestinal pathogens *Salmonella enterica* and *Campylobacter jejuni*.

Haifan Lin, PH.D., director of the Yale Stem Cell Center and professor of cell biology, is a world leader in understanding the role that bits of genetic material called small RNAs play in stem cell differentiation and self-renewal.

Hongyu Zhao, PH.D., professor of public health (biostatistics), genetics, and statistics, develops statistical, computational, and visualization tools for molecular biology and genetics.

// Surgeons *(from page 5)* At about the same time, under the auspices of the War Department's Office of Scientific Research and Development, formed by President Franklin D. Roosevelt, School of Medicine faculty members were conducting highly classified research projects to support the Allies' effort in World War II. Pharmacologists Louis S. Goodman, M.D., and Alfred Gilman, PH.D., were searching for antidotes to mustard gas, the chemical warfare agent that had been used to such devastating effect in World War I.

In studies of nitrogen mustard, a relative of the poison gas, Goodman and Gilman observed that lymph cells in animals were particularly sensitive to the compound's toxicity, which led them to wonder whether it would also kill lymphoma cells. Indeed it did: when nitrogen mustard was administered intravenously to mice with lymphoma, their tumors shrank rapidly and soon disappeared, an unexpected and unprecedented result. However, mirroring J.D.'s response to radiation treatment, the tumors recurred, and subsequent treatments with nitrogen mustard were less and less effective.

Nonetheless, the tumor regression in the mice had been dramatic and had significantly increased their survival time. Goodman and Gilman were eager to test nitrogen mustard clinically, and they approached Gustav E. Lindskog, M.D., then an assistant professor (he would ultimately go on to chair the Department of Surgery), about attempting an experimental nitrogen mustard treatment of J.D.'s terminal cancer.

On August 25, 1942, J.D., recognizing that he had no other alternatives, consented to the treatment and became the first patient to receive intravenous chemotherapy for cancer. By the end of September his tumors had completely regressed and no cancer cells were detectable in a biopsy of his lymph nodes. Unfortunately the tumor returned by mid-October, and just as Goodman and Gilman had observed in animals, the newly emerged tumor displayed increasing resistance to nitrogen mustard, which was also found to be toxic to white blood cells. On December 1, 1942, after 96 days in the hospital, J.D. died.

Fenn and Udelsman say that J.D.'s case was immensely important because it revealed three aspects of chemotherapy—tumor regression, tumor resistance, and toxic side-effects—that shaped the development of better oncology drugs thereafter. Nearly 70 years later, the pair has published a paper in the March issue of the *Journal of the American College of Surgeons* that tells the story of the sleuthing that uncovered J.D.'s medical record, and also clarifies and corrects many of the specifics of his case.

J.D.'s hospital admission record, written up by a Yale medical student, fills in the detail that had until now been missing by describing the patient's management, the events that led to the use of nitrogen mustard for treatment, the patient's social and personal history, and how the decision to attempt chemotherapy emerged. The student's drawings in the medical record are "beautiful," Udelsman says. "This was the birth of medical oncology."