

New chair in interventional radiology honors '24/7' physician

Robert I. White Jr., M.D., professor of diagnostic radiology and director of the Yale Vascular Malformation Center, is a tireless, passionate evangelist for his chosen field of interventional radiology, a medical subspecialty that offers image-guided, catheter-based therapy for disorders of virtually every major organ in the body. So it's fitting that a new endowed chair at the School of Medicine in interventional radiology—only the third such chair in the nation—carries his name.

And White says he "can think of no better person" to hold the Robert I. White Jr., M.D., Professorship of Interventional Radiology than its inaugural appointee, Jeffrey S. Pollak, M.D., professor of diagnostic radiology and

surgery, and co-chief of the medical school's Section of Vascular and Interventional Radiology. "Jeff is the model of a clinical scientist," says White, who has combined research and patient care throughout his career.

A graduate of Columbia University, Pollak earned his medical degree at Columbia University College of Physicians and Surgeons. He did his diagnostic radiology residency at the Columbia-Presbyterian Medical Center. His fellowship in vascular and interventional radiology was at the Hospital of the University of Pennsylvania.

"Dr. Pollak is an exceptional interventional radiologist who practices continuously on the forefront of his field," says James A. Brink, M.D.,

professor and chair of the Department of Diagnostic Radiology. "The Robert White professorship will allow him to broaden the scope of his activities in this important discipline."

As director of Yale's interventional radiology fellowship program, Pollak is an important mentor to the subspecialty's future practitioners. Ashraf Thabet, M.D., a 2004 graduate of the School of Medicine who now works an interventional radiologist at Massachusetts General Hospital in Boston, Mass., calls Pollak "an insightful, brilliant, but low-key" physician, "a truly gifted interventionist," and an ideal choice for the new White Chair.

White is world-renowned for his expertise in the // Chair (page 7)



Jeffrey Pollak (right) is the inaugural appointee to a new endowed chair in interventional radiology named in honor of Robert White (left).

Unlocking access to HIV care worldwide

Indonesian foundation's \$5 million gift will enable innovative Yale researcher to expand work on links between HIV, substance abuse

A pioneering HIV/AIDS researcher, epidemiologist, and clinician, Frederick L. Altice, M.D., M.A., has traveled the world pursuing his work on the interface between infectious diseases and substance abuse. He has helped to improve access to care and treatment programs for HIV-infected drug users in Malaysia, the Ukraine, Iran, Russia, Kazakhstan, and Peru. Director of Clinical and Community Research and the founder of the School of Medicine's HIV in Prisons program, he also provides care to current and former prisoners very close to home, at the New Haven Community Correctional Center, less than two miles from the medical campus.

Altice's global commitment has now been recognized with a gift from the Indonesia-based Nusantara Trust Fund Foundation, a private philanthropic organization that provides aid and assistance for humanitarian programs in Southeast Asia, particularly through projects that address rural development, education, and health disparities. The gift, which includes a resource fund of \$2 million, will enable Altice, professor of medicine and public health, to expand on the research infrastructure he's helped to build in Southeast Asia over the last decade.

"We have been impressed with the research programs that Dr. Altice has developed in Malaysia and hope to encourage an expansion of these programs to Indonesia // Gift (page 6)



Frederick Altice has researched HIV in prisons, including the New Haven Community Correctional Center, for two decades.

A time and a place: a new window on the life of the brain



Nenad Sestan

A new study of remarkable size and scope offers clues to how the human brain develops, from its early stages into old age.

The landmark research, led by Nenad Sestan, M.D., PH.D., associate professor of neurobiology and a member of Yale's Kavli Institute for Neuroscience, found that gene expression in the human brain is exquisitely choreographed across developmental periods and brain regions. This tailoring of gene expression occurs particularly during the prenatal period, during which there are rapid changes in brain structure and function. In addition to its contribution to our knowledge of normal neural development, the study may help clarify why some people are more susceptible to particular psychiatric // Brain (page 8)



Margaret Bia

Margaret "Peggy" Bia directs the medical school's Clinical Skills Program, a key component of the curriculum that includes both classroom instruction and experience in patient care. The program emphasizes patient-centered medicine, which Bia believes is increasingly important to sustain in the rapidly changing arena of modern medical practice.

TERRY DAGRADI

Carrying the torch

Physicians must hold fast to a focus on the patient, says clinician-educator

That Margaret J. Bia, M.D., is a perennially favorite target in the annual Second Year Show—a traditional night of song and dance in which Yale medical students poke fun at their faculty mentors—is a measure of the deep impression she makes on each class. But it's not who she is, Bia says, but what she stands for, that accounts for her impact.

Raised in Brooklyn in a largely Irish neighborhood, Bia, professor of medicine, lost her father when she was 11. With seven children to care for, Bia's mother began taking in foster children for income. "There were tons of babies," Bia says. "And I had tons of cousins. Practically every woman was either the mother of seven or eight kids, or a nun. I didn't want to be a mother of ten children, and I didn't want to be a nun. I wanted to do something women didn't do."

So Bia entered medical school in the late 1960s—when fewer than 8 percent of American physicians were women. "They hardly ever made women doctors," she says, "but I thought it looked like a good way to serve."

Bia and her husband, Frank J. Bia, M.D., M.P.H., professor emeritus of medi-

cine, attended Weill Cornell Medical College as a couple, and were accepted jointly to residency programs at the University of Pennsylvania Health System.

"I was going to be an internist, but all the smartest people there, the best teachers, were nephrologists," Bia says. So she changed course and—again, with her husband—came to Yale for a fellowship in nephrology. "I was fascinated with the hard body of knowledge of nephrology. That I could understand it, and then teach it to others, really turned me on."

Now director of the medical school's Clinical Skills Program—a program she built with several colleagues over many years—Bia is responsible for seeing that medical students gain hands-on experience through practice sessions and by interviewing and examining patients with the guidance of clinical tutors. It's a valuable opportunity, she says, for students to build the skills required for truly understanding their patients.

Bia joined the faculty of Yale's Department of Internal Medicine as a transplant specialist in 1978. At that time, a kidney transplant's odds of success were about 50 percent, only young patients were allowed to have the procedure, and the powerful immunosuppressant medications given to patients were harmful. Today, the

rate of success for kidney transplants is over 90 percent for the first year after surgery, and over 80 percent for the first five years. A vastly expanded body of knowledge and refinements in technology and medications account in large part for this difference in outcomes. But equally important, Bia insists, is a patient-centered approach to treatment, in which transplant clinicians work as a team and apply a particular set of skills in order to learn what influences a given patient's behavior.

"You could know everything in the medical textbooks," she says, "but if you don't know other things, like your patient's culture and the context in which they live, a lot of your efforts are squandered."

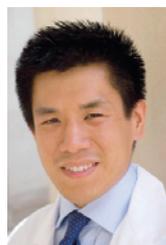
Recognizing the value of patient-centered medicine is especially critical in today's atmosphere of medical practice, Bia says, because "the patient is no longer at the center of patient care. It's profit. The more procedures you do, the more money you make." But thanks to advocates like Bia, patient-centered medicine is now a core part of Yale's medical curriculum, and educators can point to a body of data showing that this approach yields better outcomes.

"Talking to patients doesn't always pay well, but good patient care means you have to connect," Bia says. "I see myself as a torchbearer."

Medical student is first to receive newly endowed Baim Scholarship

Jeffrey Low, of the Class of 2015, is the first recipient of the Donald S. Baim, M.D. '75 Scholarship, established by Boston Scientific Corporation in February 2011 with a \$1.7 million endowment. The scholarship honors Baim, an interventional cardiology pioneer who served as Boston Scientific's chief medical and scientific officer from 2006 until his death in 2009.

As a middle school and high school student in San Francisco, Jeffrey Low found an early love for medicine. While volunteering in the spine center of a community hospital, Low had the opportunity to perform clinical research for surgeons who had invented a successful orthopaedic device. While still



Jeffrey Low

in high school, Low had co-authored papers published in prominent medical journals. As a Harvard undergraduate, Low did consulting for health care firms and the government of Tanzania, where

he worked on a project to develop a low-cost device for monitoring HIV.

The Baim scholarship will be awarded each year to an incoming Yale medical student according to both financial need and intellectual and clinical drive, and covers half of his or her tuition for four years. According

to a press release, Low received the scholarship based on his "demonstrated pursuits in innovation, invention and blending business and technology with a grounded interest in clinical medicine and biomedical science."

"Dr. Baim had a profound and enduring impact on an entire generation of cardiologists and the clinical practice at Boston Scientific, where he served as the 'voice of the patient,'" said Tim Pratt, executive vice president, chief administrative officer, general counsel, and secretary of Boston Scientific. "This fund ensures that his spirit and legacy will live on in outstanding students like Jeffrey and future scholarship recipients."

VA Connecticut Healthcare System appoints director



Janice Boss

In July, Janice M. Boss, M.S., was named director of the VA Connecticut Healthcare System.

Boss brings a wealth of experience to her

new position. Since 1983 she has held a variety of leadership posts at VA medical centers around the country, most recently as director for the VA Medical Center (VAMC) in Wilkes-Barre, Penn.

Boss began her career in the Department of Veterans Affairs (VA) at the VAMC in Boston, Mass., where she started as an administrative resident and went on to serve in four other administrative positions. She then moved to Baltimore, Md., to join the VA's Eastern Division office.

During the Clinton administration, when the VA was reorganized and decentralized into 22 Veterans Integrated Service Networks (VISNs), she returned to Boston to establish the first network office, for VISN 1.

In 1996, Boss moved to California to become director of network operations for VISN 22, based in Long Beach. She held subsequent positions as associate director at VAMC San Diego, as director of the VAMC in Iron Mountain, Mich., for two-and-a-half years, and as interim director at the Philadelphia VAMC.

Boss received her bachelor's degree from Trenton State College and a master's degree in healthcare administration from the University of Houston. She is a Certified Healthcare Executive in the American College of Healthcare Executives.

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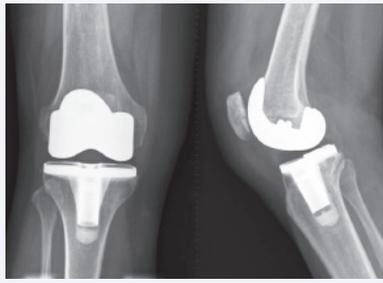
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Are 'better' devices a good choice for all?



Innovations in medical devices—such as artificial joints, pacemakers, and defibrillators—aren't always beneficial in the long run. Small refinements in function or durability can come at huge cost to patients, with only minor improvements in long-term failure rates. To assess such trade-offs, a group led by Lisa G. Suter, M.D., assistant professor of medicine, developed a computer model that simulates patient outcomes with new devices, focusing on total knee replacement (above) as a test case.

Someone who has a knee replacement in their fifties has an 18 percent chance the device will wear out within 20 years and have to be replaced again. But because of the higher risk of death among older patients, only 9 percent of those in their 70s who receive a knee replacement will need a second replacement. The Suter team reports in the November 4 issue of the *New England Journal of Medicine* that, as a group, older patients may not live long enough for longer-lasting devices to be worth their additional cost.

The researchers say their model can be easily applied to other device innovations to evaluate their true benefits.

Getting a close look at a virus-detecting RIG

Viruses ranging from common influenza to hepatitis C rely on strands of RNA to infect human cells and spread their genetic information. Yale researchers have now made a step toward understanding how the human immune system recognizes viral RNA strands to mount an immune response, work that could reveal new ways to target such viruses with drugs.

Scientists knew that a protein called RIG-I binds to viral RNA that's entered a human cell and alerts the cell of its presence. To find out more about how RIG-I recognizes viral infection, Anna Marie Pyle, PH.D., the William Edward Gilbert Professor of Molecular, Cellular, and Developmental Biology, along with postdoc Dahai Luo, PH.D., and Brett Lindenbach, PH.D., assistant professor of microbial pathogenesis, determined the 3-D structure of RIG-I bound to double-stranded RNA (dsRNA), which is produced when viruses replicate.

As reported in the October 14, 2011 issue of *Cell*, the group discovered that when bound to dsRNA, RIG-I undergoes a dramatic change in shape, in which one section of the protein folds out to make room for the RNA. The authors write that their work on RIG-I's structure "reveals multiple strategies for therapeutic design."

HIV/AIDS: Yale covers the waterfront

School of Medicine researchers and physicians are working at home and abroad to tackle the worldwide HIV/AIDS pandemic

Since it was first clinically observed in 1981, HIV/AIDS has become perhaps the greatest epidemiological challenge of the last half-century. The last two decades have seen significant advances in scientists' understanding of and ability to treat the disease, but in epidemiological terms, with more than 34 million cases worldwide and 2.7 million new HIV infections per year, HIV/AIDS remains a dangerous pandemic.

The diverse group of Yale scientists working in the field mirrors the complexity of the disease itself: at Yale, not only are biologists, epidemiologists, and clinicians working in tandem to understand, treat, and prevent the spread of HIV/AIDS, but so are economists and mathematical modelers.

With colleagues in social work and nursing, Warren A. Andiman, M.D., professor of pediatrics and epidemiology, established the Yale AIDS Care Program in 1986. The program expanded as the patient population grew, and in 1991 Gerald Friedland, M.D., a renowned clinician and researcher, joined the faculty. Andiman then became director of the Pediatric AIDS Care Program, and Friedland, professor of medicine and epidemiology, became director of its adult counterpart, the Yale AIDS Program. Since then, Yale scientists and clinicians have been at the front lines of care for those with HIV.

The Yale AIDS Program's Nathan Smith Clinic (NSC), established in 1990, was the first in Connecticut dedicated exclusively to the care of adults with HIV. Today the NSC is the largest HIV clinic in Connecticut, serving more than 850 patients, including those on Medicaid and Medicare and the uninsured. All patients are assigned a primary care provider and also have access to specialty services, including psychiatry and women's health, and linkages with substance abuse programs—particularly important given the prevalence of mental illness and substance abuse among the HIV-infected population.

Embracing not only patient care but also clinical research and the training of medical students, residents, and fellows, the Yale AIDS Program—a part of the Section of Infectious Diseases in the Department of Internal Medicine—reflects the School of Medicine's three missions of research, education, and patient care. But it also has a fourth mission of community, says Merceditas S. Villanueva, M.D., associate professor of medicine and the program's director since 2009. "Community" can refer to both the local and international communities, but in some regards, Villanueva says, the two are closely linked.

A number of successful programs that have been piloted in New Haven have seen subsequent implementation around the world. In the early 1990s, Edward H. Kaplan, PH.D., and Robert Heimer, PH.D., and Kaveh Khoshnood, PH.D., M.P.H., demonstrated the success of New Haven's needle/syringe exchange program (NSEP), one of the first in the nation. Established with special permission from the Connecticut state legislature, the program's goal was to slow the spread of HIV infection among injection drug users (IDUs) by providing them with free, sterile syringes. By 1992, Kaplan, now the William N. and Marie A. Beach Professor of Management Sciences at the School of Management, professor of public health at the School of Medicine, and professor of engineering and the School of Engineering and Applied Sciences; Heimer, professor of epidemiology and public health and associate professor of pharmacology; and Khoshnood, associate professor of epidemiology; had accumulated enough data to show, via mathematical models, that the program was reducing new HIV infections by a third.

Kaplan, Heimer, and Khoshnood's work was the first to offer hard evidence of the efficacy of NSEPs as an HIV prevention strategy. Since then, Yale faculty have worked to implement NSEPs in broader domestic and international settings. For instance, Heimer has evaluated NSEPs in Russia and Estonia, and Frederick L. Altice, M.D., M.A., professor of medicine and public health, has implemented a needle exchange in Malaysia, where he's worked since 2005 (see related story, page 1).

Another local initiative that has seen global implementation is the HIV in Prisons program, launched in

Connecticut in 1991. Altice and colleagues in the Yale AIDS Program, including Sandra A. Springer, M.D., assistant professor of medicine, and R. Douglas Bruce, M.D., M.A., M.Sc., assistant professor of medicine and epidemiology, have worked to treat HIV-infected inmates in prisons around the U.S. and abroad—not only for HIV, but also for the other ailments that often affect them, such as tuberculosis, mental illness, and substance abuse.

Although the success of New Haven's NSEP has dramatically reduced the rate of HIV infection via shared needles, there is still a wide overlap between those with HIV and those with substance abuse disorders, particularly among prisoners. "HIV is a proxy for risk-taking behavior,"



Since 2009, R. Douglas Bruce (right) has worked with the Pangaea Global AIDS Foundation on the implementation of Tanzania's methadone treatment programs, the first use of methadone as a public health intervention in sub-Saharan Africa.

explains Bruce. And because drug addiction can interfere so drastically with successful treatment of HIV, "often we have to address that before we can address HIV care."

Bruce came to Yale in 2000 and worked alongside Altice and Springer for several years, treating HIV-infected inmates in New Haven's prison system. "As things evolved, I realized that some of the treatments we were offering in mobile settings and in the jail weren't sufficient," he says. Specifically, he was dissatisfied with the amount of time it took to get drug users on methadone—a synthetic opioid used to treat addiction to opioids like painkillers and heroin. Due to its low cost, methadone is a practical means of addiction treatment, but, due to regulations in clinics, it used to take up to eight weeks to get a person into methadone treatment in New Haven. Within that lengthy period, substance-dependent people who were struggling in the community or who had been released from prison and were unable to stop using drugs on their own usually ended up in the hospital, jail, "or worse, dead," Bruce says. The cycle simply wasn't ending. "Eight weeks was too long."

In a clinic at New Haven's Hill Health Center, as well as one in the Fair Haven section of New Haven, Bruce set out to make quick treatment more accessible // HIV (page 7)

Support medical advances by giving from your IRA

Why now?

There is still time for individuals aged 70 and older to make charitable gifts directly from individual retirement accounts (IRAs). Contributions up to \$100,000 can satisfy minimum distribution requirements and will not be treated as taxable income. But hurry—this opportunity is set to expire on December 31, 2011.

Why Yale School of Medicine?

By using the charitable IRA rollover to make your gift to the School of Medicine, you benefit from significant tax savings while helping to secure the excellence and strength of the School. Your gifts can support groundbreaking medical research that will impact generations of patients. Or, you can fund scholarships that assist talented students on their path to becoming the physicians of tomorrow.

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OUT & ABOUT

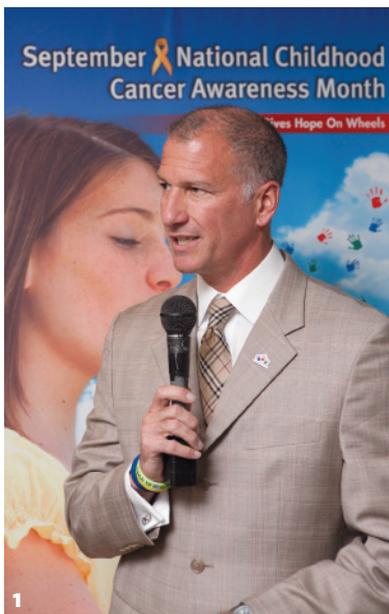
September 18 Students and faculty brought their competitive spirit to Yale's Cullman-Heyman Tennis Center for the **Student/Faculty Tennis Classic**. **1.** (From left) **Ben Albright '15**, Dean and Ensign Professor of Medicine **Robert J. Alpern, M.D.**; **Jovana Pavusic '13**; and **Robert Udelsman, M.D., M.B.A.**, chair and William H. Carmalt Professor of Surgery. **2.** A volley by **Agnès Vignery, D.D.S., PH.D.**, associate professor of orthopaedics and rehabilitation. **3.** **Eileen Harder '14**, the event's organizer, with **Pasquale Patrizio, M.D.**, professor of obstetrics, gynecology, and reproductive sciences.



TERRY DAGRADI (3)

September 20 As part of its **Hope on Wheels** program, which supports pediatric cancer research and treatment programs around the U.S., representatives of Hyundai Car Sales named **Gary Kupfer, M.D.**, professor of pediatrics and pathology, chief of the Section of Pediatric Hematology and Oncology, and director of the Pediatric Oncology Program at Smilow Cancer Hospital at Yale-New Haven, a Hope on Wheels Scholar, and donated \$100,000 for his work.

1. **Peter DiPersia**, general manager of the eastern region at Hyundai Motor America. **2.** (From left) **Cynthia N. Sparer, M.P.A.**, executive director of Yale-New Haven Children's Hospital (YNHCH); **Clifford W. Bogue, M.D.**, associate professor of pediatrics, interim chair of the Department of Pediatrics, and physician-in-chief at YNHCH; Kupfer; and DiPersia.



HAROLD SHAPIRO (2)

October 3 Representatives of University College London (UCL) gathered with their Yale counterparts for a meeting of the **Yale-UCL Collaborative**. **1.** (From left) **Natasha Lewis, LL.B.**, director of legal services at UCL; **Lori Manders**, director of development and alumni relations at UCL; **William C. Sessa, PH.D.**, Alfred Gilman Professor of Pharmacology; and **John Martin, M.D.**, professor of cardiovascular medicine at UCL and co-director of the Yale-UCL Collaborative. **2.** (From left) Woodbridge Fellow **Sarika Arya**; Sessa; Martin; **David Price, PH.D.**, vice-provost (research) at UCL; Manders; **Sir Cyril Chantler**, chair of UCL Partners; **Michael Simons, M.D.**, the Robert W. Berliner Professor of Medicine and Cell Biology, chief of the Section of Cardiovascular Medicine, and co-director of the Yale-UCL Collaborative; **Robert J. Alpern, M.D.**, dean and Ensign Professor of Medicine; **Mary J. Hu, M.B.A.**, director of Institutional Planning and Communications at the School of Medicine; **Cynthia Carr, J.D., LL.M.**, visiting lecturer at Yale Law School;



Steven M. Girvin, PH.D., deputy provost for Science and Technology and the Eugene Higgins Professor of Physics and Applied Physics; **Richard Lifton, M.D., PH.D.**, chair and Sterling Professor of Genetics; **Stephanie S. Spangler, M.D.**, deputy provost for health affairs and associate vice president for West Campus planning; **Donald L. Filer**, associate secretary and director of international affairs; Lewis; and **Michael Whorton, PH.D.**, vice-provost (international) and Fielden Professor of French Language and Literature at UCL.



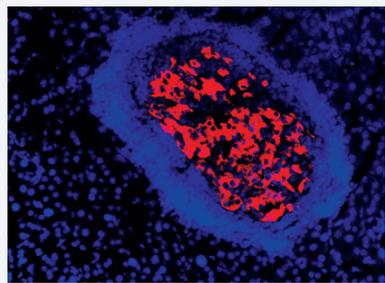
TERRY DAGRADI (2)

October 27-28 Yale's Child Study Center (CSC) held its annual meeting of the **Child Study Center Associates**, the final event in a series of four marking the CSC's hundredth year, in honor of the late Albert J. Solnit, M.D., who served as CSC director from 1966 to 1983. **1.** (From left) **Barbara F. Nordhaus, M.Sc., M.S.W.**, assistant clinical professor in the CSC, and **Ruth Lord**. **2.** (From left) **Joan Harris, Carol Schaefer**, and **Chuck Schaefer**.



TERRY DAGRADI (2)

Telltale DNA aids early diabetes diagnosis



COURTESY OF KEVAN HEROLD

In type 1 diabetes, the immune system kills insulin-producing beta cells (above) in the pancreas. By the time the illness is diagnosed, most beta cells have been destroyed, creating a challenge for potential treatments to be effective.

When cells die they rupture, and the DNA in their nuclei escapes into the bloodstream. Though the DNA sequence in every cell is identical, the body's organs have diverse functions, so DNA is "marked" with tissue-specific modifications that enable or suppress the expression of appropriate genes.

In an early edition of *Proceedings of the National Academy of Sciences*, a group led by Kevan C. Herold, M.D., professor of immunobiology and medicine, describe a marker found only in beta-cell DNA. In a mouse model of type 1 diabetes, the team saw a rise in blood-borne beta-cell DNA just as the cells began to die, long before diabetes symptoms appeared. Higher levels of beta-cell DNA were also seen in newly diagnosed type 1 diabetes patients.

"Early detection of cell death may allow for better monitoring and earlier interventions in people at risk for developing type 1 diabetes," says Herold.

New one-two punch brings down bacteria

Recent experiments in which stretches of proteins and genetic material are inserted into bacteria to silence genes have shown great promise as a means of treating bacterial infection. By inactivating genes such as those a bacterium needs to copy its genome, or those that help it to resist antibiotics, the method can kill the cells directly or make them more vulnerable to antibiotic drugs.

Yale scientists have now developed a technique that gets these molecules into bacterial cells more efficiently, making the procedure more effective than ever. The new method, which was developed in the laboratory of Nobel laureate Sidney Altman, PH.D., Sterling Professor of Molecular, Cellular, and Developmental Biology and professor of chemistry, combines a fragment of protein based on a molecule in human immune cells with a stretch of genetic material that can bind to and inactivate a bacterial gene.

In the October 4, 2011, issue of *Proceedings of the National Academy of Sciences*, Altman's team reports that when they used the method to inactivate genes that underlie bacterial resistance to the antibiotics penicillin and chloramphenicol, it was as much as a hundred times more effective than similar compounds tested thus far.

Common threads seen in autoimmune diseases

As genes conferring risk for autoimmunity are revealed, the shared pathways underlying seemingly different illnesses are coming to light

Researchers studying what goes wrong in autoimmune diseases now have a road map to guide future work, thanks to two ambitious international studies published in August in which School of Medicine researchers played key roles. One, reported in *Nature*, doubles the number of known genetic culprits in multiple sclerosis (MS). The other, in *PLoS Genetics*, finds that the genetic basis of autoimmunity is largely shared among autoimmune disorders.

Autoimmune diseases, which occur when the immune system attacks the body's healthy tissue, are three times more common among women than men, and rank among the top 10 causes of death for women under age 65 in the United States, according to Chris Cotsapas, PH.D., assistant professor of neurology and genetics and lead author of the *PLoS* paper.

"All autoimmune diseases have a substantial heritability," Cotsapas says, much of which is due to variants in the major histocompatibility complex, a section of chromosome 6 that is well populated with immune-related genes.

Other genes also play a role. For example, recent genome-wide association studies (GWAS) have implicated over 20 additional genomic regions in MS, a condition in which the immune system targets myelin, a fatty sheath around nerve cell extensions that is crucial for efficient neural transmission. But these studies left much of the heritability of the disease unexplained, leaving researchers wanting a bigger and better study.

"Everyone realized that no one could do it individually," says MS expert David Hafler, M.D., the Gilbert H. Glaser Professor and chair of neurology, part of the team that published the study in *Nature*. That paper, authored by the International MS Genetics Consortium and the Wellcome Trust Case Control Consortium 2, involved 11 years of work by nearly 250 researchers in 15 countries.

In genome-wide comparisons of DNA from about 10,000 people with MS and from 20,000 unaffected people, Hafler and colleagues confirmed 23 out of 26 previously reported genetic associations with MS, and they identified an additional 29 gene regions that had never before been tied to the illness.

The vast majority of genes in the implicated regions play a role in the immune system. Many affect white blood cells, particularly helper T cells, which prime their B cell cousins to fight perceived threats. In addition, the researchers noted that over a third of the genes associated with MS had been previously flagged as possible culprits in at least one other autoimmune disorder, findings that should "put to rest" any doubts that MS is primarily an autoimmune disease, says Hafler.

The *PLoS Genetics* study, on which Hafler, Cotsapas, and others joined a group organized by the Federation of Clinical



Chris Cotsapas



David Hafler

Immunology Societies (FOCIS), investigated whether seven common autoimmune disorders share genetic influences, as would be expected from the way these disorders co-occur within individuals and families. "People often get more than one," says Hafler.

Cotsapas, Hafler, and colleagues on the FOCIS team analyzed data from previous GWAS of celiac disease, lupus, type 1 diabetes, Crohn's disease, MS, rheumatoid arthritis, and psoriasis, focusing on 107 genetic variants that had been tied to autoimmune disease. They found that nearly half the genes were associated with increased risk of multiple autoimmune disorders. "I was really surprised that the degree of sharing was that high," says Cotsapas.

Next, the researchers grouped the variants by their associated diseases and found that many affected genes code for proteins that closely interact in networks. "They talk to each other, and that suggests that there are entire pathways that underlie risk to multiple diseases," Cotsapas says. Crohn's disease, MS, and psoriasis have symptoms that are "about as different as you can get," but these conditions share a pathway involving helper T cells. Other autoimmune conditions might converge on a different protein network, says Hafler. "If you look at a certain pathway, certain diseases share that pathway, and others do not."

The new findings, Hafler says, are examples of the "brave new world" of autoimmune disease research in the post-genomic era, a world in which we will find treatments for these diseases by seeing them in completely new ways.

Gift links tribal colleges with Child Study Center

When Charles W. Carl Jr., M.D., talks about his 2005 trip to the Navajo Nation—a 27,000 square-mile Native American reservation in the Southwestern U.S.—his voice fills with emotion. Carl and his wife, Dianne, visited the reservation after making a donation to the American Indian College Fund, which works to improve opportunities in higher education for Native Americans. The experience was "profoundly moving," says Carl, a 1952 graduate of Yale College and 1963 graduate of the School of Medicine. "It turned me on to the need in the Native American community for services, [especially] for child mental health services."

The trip inspired Carl to donate \$450,000 in 2008 to the School of Medicine's Child Study Center (CSC) to establish an exchange program known as the Charles W. Carl Jr., M.D. Training Fellowship Program in Child Development and Mental Health. Now in its third year, the fellowship enables Native American students and teachers from tribal colleges to visit the CSC for a two-week educational immersion in

child development and mental health each July. It will also support the deployment of CSC faculty to reservations and tribal colleges, to increase understanding of Native American culture and child care priorities.

The program's goal, says Carl, a psychiatrist in private practice in Massachusetts, is "to create a knowledge base and a skill base in the Native American community. There's a huge need on the reservations for information and training. I hope that by having an exchange, we'll be able to help Native Americans to help their own people."

In 2010, the CSC welcomed its first group of five fellows, who attended a structured series of workshops with

CSC faculty, informational sessions about research and clinical programs at the CSC and elsewhere on the medical campus, and tours of New Haven and Yale. The fellowship includes travel expenses, lodging, and a small stipend.

The program is already growing, says CSC Director Fred R. Volkmar, M.D., the Irving B. Harris Professor of Child Psychiatry, Pediatrics, and Psychology; in 2011, 13 fellows were accepted from a pool of more than 60 applications. Volkmar says the program is designed to "help people become more aware of the range of excellent clinical and research models, interventions, and other resources that exist. The hope is that it can be inspiring."



Charles Carl



Twelve students and one faculty member from Native American tribal colleges came to Yale last summer for training in child development and mental health at the Child Study Center. Fred Volkmar (standing, second from left) and Barbara Nordhaus (not pictured) coordinate the program.

Tablets an excellent prescription for School of Medicine's students

This fall, all 518 medical students at Yale received Apple iPad tablets to download course curricula, take notes in class, and assist them in their clinical training. "It's hard to think of anything else that has had such a profound and rapid impact," says Michael Schwartz, PH.D., assistant dean for curriculum.

The initiative grew out of a remarkably successful pilot program in which a handful of students at the School of Medicine were given iPads during the spring 2011 semester. Though originally a move to make the School of Medicine a greener campus, the response from both professors and students suggested that in addition to being an efficient and environmentally smart way to deliver learning materials, tablet computers have the potential to transform medical education at Yale.

Robert Camp, M.D., PH.D., who teaches pathology to first- and second-year students, says the iPad is ideal for small-group teaching. "Computer screens, which we used to use, create a barrier between you and the person you are talking to. It's not interactive. But the iPad is more like a piece of paper. You hold it more like a book and you can pass it around. It tends to engender more group thinking and group discussion."

A self-described "paper person," Vicki Bing of the Class of 2014 says she had "huge reservations" before

joining the pilot program. "I absolutely have to have everything printed out, so I didn't know how an iPad could replace that." But after a semester of using the tablet, she says, "I really, really loved it." Bing says she appreciates having access to all the course material while listening to a lecture, and also welcomes the iPad's portability. "I travel a lot, and I used to bring paper copies of everything with me to study on the road," she says. "With the iPad it's so much easier. It's all right there with the touch of a finger."

The School of Medicine's iPad initiative is part of a growing trend at medical schools across the country, including those at Brown; the University of California, Irvine; Stanford; and the University of Minnesota. But Yale's program is different in that all students, not just those in their first and second years, have received the tablets. Yale has securely encrypted its iPads, a feature that will allow third- and fourth-year students to protect patients' privacy when they use the tablets in their clinical work. It takes students about 30 minutes to download the entire curriculum for one year on the



Seeing is believing: the printed curriculum materials formerly used by a single School of Medicine student in one year, held by Richard Belitsky, deputy dean for education, tower over Assistant Dean for Curriculum Michael Schwartz's iPad tablet.

iPad, although they are advised to download the fall, winter, and spring courses separately because faculty continue to update documents until the start of the course.

Nicholas Bergfeld, a member of the pilot group who is now in his second year at the medical school, says he can foresee the iPad enhancing his interaction with patients during his clinical studies. "You and the patient can look at their lab

test results, X-rays, or whatever else together. It enables a greater level of personal connection."

Schwartz, says it had cost roughly \$1,000 per student to provide paper copies of all course materials, about the same price as an iPad and supporting applications. "We pretty much break even," he says, "but the iPad is better for the environment—and as an information delivery system, it's much more versatile."

// Gift (from page 1) and other countries in the region . . . in line with the vision and mission of the foundation," says Tatag Wiranto, PH.D., chairman of the Nusantara Trust Fund Foundation and Deputy Minister for the Development of Disadvantaged Regions in Indonesia. "We believe that through strategic partnership with researchers and educators from the best institutions in the world, such as Yale, we will be able to build our capacity to ensure success and the sustainability of our efforts to improve the lives of our people."

Altice's interest in HIV/AIDS took root three decades ago. As a medical student in the early 1980s, while conducting research at the Centers for Disease Control and Prevention, Altice began to describe the early epidemiology of the disease. Later that decade, he was part of a group of Yale researchers who had established one of the first needle exchange programs in the U.S., providing drug users in New Haven with clean syringes in an effort to prevent the spread of HIV (see related story, page 3). Since 1991, Altice's prison program has promoted HIV prevention and care for prisoners and former prisoners in Connecticut and elsewhere. In 1993, Altice established the Community Health Care Van, a free mobile clinic connected with New Haven's needle/syringe exchange program (NSEP), which integrates drug treatment and care.

In 2005, Malaysia's former Prime Minister, Abdullah Ahmad Badawi, announced health policy changes that included implementing NSEPs and

introducing methadone, a synthetic opioid used to treat addiction to opioid drugs such as heroin.

Earlier that year, Altice had formed a close collegial relationship with Adeeba Kamarulzaman, M.B.B.S., F.R.A.C.P., professor of medicine and now dean of the Faculty of Medicine at the University of Malaya in Kuala Lumpur and president of the Malaysian AIDS Council from 2006 to 2010. Aware of Altice's expertise as an interventionist, Kamarulzaman enlisted his help in implementing Badawi's changes throughout Malaysia.

"I said, 'Sure, but I need to understand the epidemic,'" Altice recalls. Altice's role in fighting the Malaysian HIV/AIDS epidemic has been broad, but he began with both feet on the ground—literally. His outreach took him to many locations on the streets of Malaysia, including "under bridges where people shot up drugs," he says.

In persuading Malaysian leaders to adopt some of his recommendations, Altice was able to point to his past work in Iran—like Malaysia, a Muslim country—where he provided guidance in the introduction of methadone treatment in prisons.

"Rick understands cultural and religious sensitivity. These things can make or break partnerships with countries like Malaysia," says Kamarulzaman. "We love him because of his accessibility, generosity of spirit, and knowledge."

Working with the Malaysian anti-drug agency Agensi Anti Dadah Malaysia (AADK), the Ministry of

Health, and the Prison Department, Altice has been deeply involved in expanding methadone, HIV, and tuberculosis (TB) treatment in Malaysian prisons and community settings. His current work in Malaysia includes the introduction of preventive HIV and TB therapies into prisons and a program for reforming compulsory drug detention centers that detain suspected drug users without fair trials.

The new resource fund donated by the Nusantara Trust Fund Foundation will enable Altice to expand on and replicate these efforts in other Southeast Asian countries, especially Indonesia, where Altice plans to expand and adapt innovative care delivery models for prisons and rural settings.

"We are developing new research methods and adapting innovative models of care that are transcending the usual academic boundaries to create new knowledge," Altice says. Eager to collaborate with colleagues at other universities and research institutions throughout Asia, he says his work is "less about ownership and more about mission." Before seeking funding on an even larger scale, "we're going to examine multiple pilot projects initially," he says, "and expand our training . . . to get more people interested. I would really like to shift the mentality towards research and treatment."

Altice, who holds an appointment as a visiting professor at the University of Malaya, received his M.D. from the Emory University School of Medicine and completed his residency in the Department of Internal Medicine and a



Frederick Altice (right) met Tatag Wiranto, chairman of the Nusantara Trust Fund Foundation in Jakarta, Indonesia, in November for a check presentation.

fellowship in the department's Section of Infectious Diseases at Yale. From 1991 to 1992, he received additional training in the Robert Wood Johnson Clinical Scholars program. In 1993, after observing the untreated health problems of many people participating in the New Haven NSEP, Altice helped to launch the Community Health Care Van, a mobile clinic offering a range of health care services to members of the New Haven community.

"Rick has always been committed to helping less fortunate people, in New Haven and throughout the world," says Robert J. Alpern, M.D., dean and Ensign Professor of Medicine. "This gift acknowledges this and provides ongoing support for his research efforts at the interface between substance abuse and the spread of HIV."

// **HIV** (from page 3) for people with substance abuse disorders. “We’ve made it so you can get into treatment in 24 hours, and have captured a larger piece of a very ill pie,” he says.

Springer’s work focuses on the adherence of HIV-positive prisoners to antiretroviral (ARV) medications, particularly during and following release from prison, when patients are most likely to relapse into patterns of alcohol and opioid use. Her novel research involves evaluating the use of extended-release naltrexone—which can be given just before release from prison but has longer-lasting benefits than comparable treatments—to manage addiction and to improve HIV treatment outcomes.

In recent years, Bruce has worked to implement methadone treatment programs internationally. In 2009, he was invited to Tanzania to help launch what was the first use of methadone as a public health intervention in sub-Saharan Africa. Despite the success of such programs, there is much work yet to be done. To decrease the number of new HIV infections each year, “we have to take a significant number of people with HIV out of the injection pool,” Bruce says. “To do that, we have to get tens of thousands of people into treatment.”

The advent of ARV therapies in the mid-1990s was a major breakthrough, effectively changing HIV/AIDS from a fatal disease to what is now considered a chronic, manageable disease. “People are not dying in the numbers they used to,” Villanueva says. One of the earliest ARV medications, stavudine, was developed at Yale by the late Professor of Pharmacology William Prusoff, PH.D., and the late Tai-Shun Lin, PH.D., senior research scientist. In 1994, stavudine—which works by thwarting replication of the retrovirus—was approved by the Food and Drug Administration as a treatment for HIV. Known more commonly under the trade name Zerit, it has been used in combination with other drugs to extend the lives of many thousands with HIV.

Today, clinical trials of new antiretroviral therapies are an active component of the School of Medicine’s efforts to better understand

and treat HIV/AIDS. Michael J. Kozal, M.D., professor of medicine, uses new sequencing technologies such as DNA micro-arrays and ultra-deep genomic sequencing methods, to understand the genetic factors that make patients resistant to ARV medications. As director of HIV Clinical Trials at Yale and chief of the Section of Infectious Diseases at the VA Connecticut Healthcare System in West Haven, Conn., Kozal spearheads trials of new HIV medications, and has been able to offer patients alternatives when older treatment modalities fail.

In the clinical realm, one of the most encouraging recent successes has been the eradication of transmission of HIV from mother to child during pregnancy and childbirth. At Yale-New Haven Hospital, the virus has not been transmitted from an infected mother to a child in more than 15 years. Yale’s Pediatric AIDS Clinic, in fact, has only several dozen patients still on treatment, the youngest of whom is sixteen. When these last patients reach adulthood, they will transition to adult clinics, and then the clinic will likely close its doors, says Andiman, the clinic’s director.

Andiman credits this achievement—part of a trend taking place across the U.S.—to the implementation of HIV screening of pregnant women. If a woman is known to be HIV-positive, certain precautions, such as tailored ARV regimens for mothers and the use of breast-milk substitutes for infants, can be taken to drastically reduce the chances of transmission.

Such advances have resulted in remarkable improvements in the U.S., but in many places where the disease is most prevalent, a lack of resources has impeded progress. In Pretoria, South Africa, for instance, where one quarter of all pregnant women have HIV, without treatment about 40 percent of children born to infected mothers become infected. Brian W. Forsyth, M.B.Ch.B., professor of pediatrics and in the Child Study Center, has conducted a number of studies aimed at improving the prevention of mother-to-child transmission in sub-Saharan Africa and other resource-poor areas, where, Andiman says, “the problem is one of access [to care], money, and political will.”

Yale AIDS Program at a glance

At Yale, HIV/AIDS is the clinical and research focus of a vast number of individuals, centers, and programs. Among them are the **Yale AIDS Program**; the **Pediatric AIDS Care Program**; and the **Center for Interdisciplinary Research on AIDS** (CIRA), a consortium of more than 100 scientists involved in research on and treatment and prevention of HIV/AIDS in the United States and abroad. CIRA’s director is **Paul D. Cleary**, PH.D., dean of the Yale School of Public Health, chair of the Department of Epidemiology and Public Health, and the Anna M.R. Lauder Professor of Public Health.



FRIEDLAND



ALTICE



BARAKAT



BRUCE



FRANCIS



KOZAL



SHENOI



SPRINGER



VILLANUEVA

As director of the Yale AIDS Program from 1991 until 2009, **Gerald Friedland**, M.D., professor of medicine and epidemiology, oversaw its growth from a regional center for patient care into a leading international center for HIV/AIDS research, treatment, and prevention. One of the program’s nine faculty members, Friedland is an expert in HIV therapies and the interface between HIV and tuberculosis. His work with vulnerable populations includes extensive research and patient care in rural South Africa. **Frederick L. Altice**, M.D., M.A., professor of medicine and public health, is a specialist in infectious diseases and addiction medicine and has worked to reform treatment strategies for prisoners and those with substance use disorders in the U.S. and around the world. **Lydia A. Barakat**, M.D., assistant professor of medicine, is medical director of the program’s Nathan Smith Clinic (NSC). Her areas of interest are quality management and enhancing HIV training within the medical residency program. **R. Douglas Bruce**, M.D., M.A., M.Sc., assistant professor of medicine and epidemiology, is an expert in the intersection of substance abuse and infectious diseases, particularly HIV and hepatitis C. **John S. Francis**, M.D., PH.D., assistant professor of medicine, has treated patients with HIV/AIDS at Yale-New Haven Hospital and the NSC for more than five years, and now cares for patients primarily at the VA Connecticut Healthcare System. Francis supervises internal medicine residents and infectious disease fellows, and also works closely with Yale medical students as an academic advisor. **Michael J. Kozal**, M.D., professor of medicine, is a specialist in the genetic determinants of HIV drug resistance and the use of new technologies to detect drug-resistant viral variants. **Sheela Sheno**i, M.D., M.P.H., assistant professor of medicine, does clinical research on HIV/AIDS and tuberculosis, particularly in resource-limited settings. **Sandra A. Springer**, M.D., assistant professor of medicine, specializes in clinical research and the care of patients with HIV/AIDS, particularly prisoners and those afflicted by substance abuse. **Merceditas S. Villanueva**, M.D., associate professor of medicine, is the current director of the Yale AIDS Program, having succeeded Friedland in 2009.

Resource allocation is of critical importance, says A. David Paltiel, PH.D., professor of public health. Paltiel uses mathematical models to predict the ways certain treatments or preventative measures—making HIV screening routine, for instance—would affect both the epidemic’s trajectory and the economics of treatment and prevention. “Our work helps decision-makers know what every dollar spent will buy,” says Paltiel, who is also a professor at the Yale School of Management.

“What’s good in the first world is good in the third world,” says Forsyth, who is working to put in place in South Africa those measures that

have bred success in the U.S.

According to Villanueva, American physicians, privileged with resources, funding, and supportive government policies, have a duty to help the less well-off, and it’s a responsibility that Yale scientists and physicians have not taken lightly.

“Yale brings to the table so many talents, and has been a conduit to improving the care for HIV/AIDS within the local and international communities,” Villanueva says. “The people that I work with are very out-of-the-box thinkers, and the research spawned in our program is motivated by their huge hearts.”

// **Chair** (from page 1) diagnosis and treatment of Hereditary Hemorrhagic Telangiectasia (HHT; also known as Osler-Weber-Rendu syndrome), a heritable genetic condition in which blood vessels in certain parts of the body tend to form without capillaries. These tiny vessels are crucial to depressurizing blood as it flows from arteries to veins, and in HHT high-pressure arterial blood flows directly into veins with full force, creating fragile sites that are prone to ruptures and bleeding.

Some symptoms associated with HHT, such as frequent nosebleeds, are fairly benign. But some patients have vascular malformations in the liver, lungs, or brain that can suddenly burst, with life-threatening consequences.

White’s treatment of hundreds of families with HHT and his involvement in the establishment of

HHT Centers of Excellence around the world has gained him a fan club among his patients that would be the envy of any rock star. In gratitude, more than a dozen of those patients and their families pooled the considerable resources needed to create the new endowed chair. White and his wife, Patricia Kelly-White, who has joined her husband in raising awareness of HHT, also pitched in.

One donor, Lisa Ruscitti of Ridgefield, Conn., whose son Jackson was diagnosed with HHT at Yale after he suffered a brain hemorrhage at four weeks old, uses the superlatives one hears again and again from White’s patients and their relatives. She calls him a “wonderful person” who “goes above and beyond what a physician needs to do.”

Another grateful HHT patient, Bradley E. Blevins, senior vice president

and senior credit officer at The Northern Trust Company in Chicago, Ill., echoes these comments. Blevins, who has served on the board of HHT Foundation International, credits White with saving his life, and marvels that he is seemingly “available 24/7” for his patients, “answering every e-mail within an hour or two.”

Diana R. Meiches of Prides Crossing, Mass., another former HHT Foundation board member, calls White “one of the most brilliant men I’ve ever met,” and says he “absolutely epitomizes compassionate care.” White treated Meiches’ husband, Marc A. Meiches, chairman, president, and chief executive officer of Electric Insurance Co., for HHT, and “there is no doubt in my mind that he saved Marc’s life,” she says.

Anna B. Lange, of Richmond, Va.,

whose family also made a contribution to the new chair, half-seriously says she thinks of White as “almost walking on water”, adding, “He literally has saved multiple lives in our family.” HHT is pervasive in the Lange family, so White has been deeply involved with the medical care of many of her loved ones. “He’s such a warm, caring person, and has such charisma,” Lange, says. “I could not adequately express our feelings, our appreciation, and our admiration for Dr. White.”

White says that the new professorship will provide Pollak with the freedom to do the clinical research needed to evaluate medical outcomes and advance the field. “I want to see this specialty become important in people’s minds, and having this chair in interventional radiology will really reflect that,” says White. “Jeff is the future.”

Leader in ‘telemental health medicine’ is honored by the Department of Veterans Affairs

Linda S. Godleski, M.D., has received the David M. Worthen Award for Career Achievement in Educational Excellence from the Department of Veterans Affairs (VA), the VA’s highest recognition for academic accomplishments.

Godleski, associate chief of staff for education for the VA Connecticut Healthcare System in West Haven, Conn., and associate professor of psychiatry at the School of Medicine, has pioneered the application of telemedicine (the use of technology to provide medical care when distance separates providers from patients) to psychiatry, in an emerging field known as “telemental health medicine.”

As director of the VA National Telemental Health Center, Godleski has been a leader in developing

telemental health curricula for the VA, which has one of the largest such programs in the world.

Telemental health medicine has proved to be an efficient and economic method of providing behavioral health services for patients who live in rural areas and might not otherwise have access to mental health care professionals. Godleski and her colleagues have used the method for clinical assessments, individual and group psychotherapy, psycho-educational interventions, cognitive testing, and general psychiatry.

Godleski has chaired the Telemental Health Field Advisory Work Group for the Veterans Health Administration (VHA), which has been instrumental in developing a “toolkit” to deploy telemental health



Linda Godleski

techniques nationwide, expanding the use of clinical videoconferencing, in-home messaging, videophones, and pilot Internet applications.

Godleski has also led the VA in strategic planning for new educational initiatives, including an extensive expansion of medical and associated health programs with Yale and other VA affiliates.

Godleski received her medical degree from the University of Virginia (UVA) School of Medicine, where she also completed her psychiatry residency.

Prior to joining Yale she served on the faculty of medical schools at

Vanderbilt University, UVA, the University of Hawaii, and the University of Louisville. She has served as a consultant to a number of academic and federal agencies, as well as the American Telemedicine Association. Her work has been presented extensively at VA and academic conferences, including expert testimony before Congress, and she has published widely in peer reviewed journals.

The Worthen Award recognizes a VA employee from any health discipline who has made contributions of national significance to education in the health professions. First issued in 1988, it commemorates the late David M. Worthen, M.D., former head of VHA Academic Affairs and an inspirational leader of VA’s educational mission.

// **Brain** (from page 1) or neurological disorders, especially autism and schizophrenia, which many scientists believe are caused by perturbations in early brain development.

Sestan has long been interested in understanding the transcriptome, the term for the totality of expressed RNA molecules, of the human brain. We share most of our genes with other animals, and in Sestan’s view, it is the spatiotemporal dynamics of the brain transcriptome—when and where genes are expressed—that underlies humans’ unique attributes.

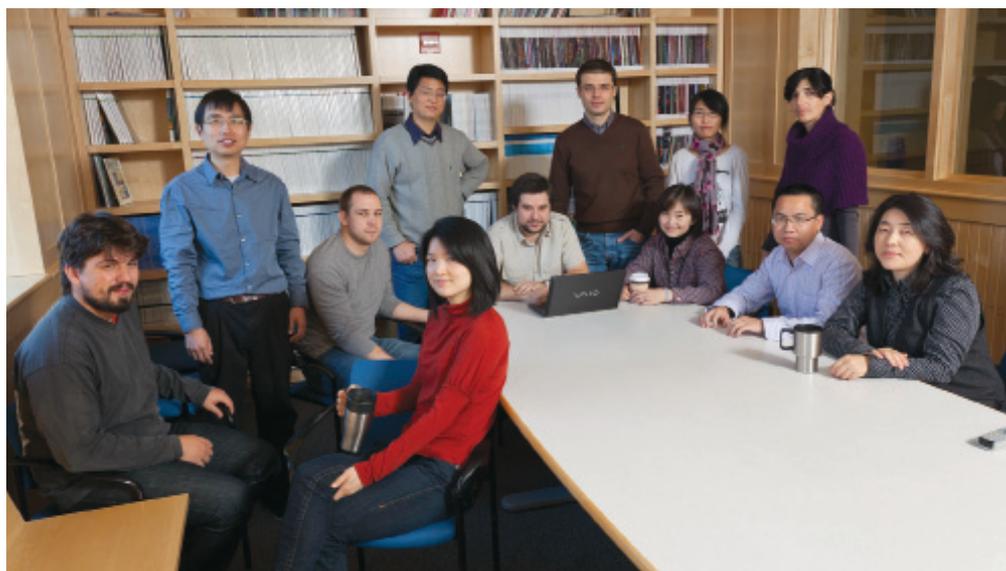
In the new research, Sestan and colleagues measured the relative abundance of messenger RNA (mRNA) molecules in 16 important brain regions at 15 developmental stages across the lifespan. Because mRNA is the molecular middleman between genes and the protein-making machinery of the cell, with some adjustments mRNA levels are a reliable indicator of which genes are slated for translation into proteins at any given time.

Previous efforts to decipher the transcriptome of the human brain have looked at only a few brain areas and/or a few time points, so when recently developed technology made it possible to interrogate most of the human genome in one swoop, Sestan saw a chance to do the study of his

dreams. Yet in thinking about the study, which would ultimately analyze more than 17,000 distinct mRNA transcripts, he decided that “this cannot be done by one person, one lab, or even one institution.”

Indeed, the study, published in the October 27 issue of *Nature*, involved an international team of collaborators, as well as several scientists from Sestan’s own laboratory: Hyo Jung Kang, PH.D.; Yuka Imamura Kawasawa, PH.D.; Feng Cheng, PH.D.; Ying Zhu; Xuming Xu, PH.D.; Mingfeng Li, PH.D.; Andre Sousa; Mihovil Pletikos, M.D.; Kyle Meyer; Goran Sedmak, M.D.; Yurae Shin; Matthew Johnson, PH.D.; Zeljka Krsnik, PH.D.; Simone Mayer; and Sofia Fertuzinhos, PH.D.

Thanks to the generosity of brain donors, Sestan’s team had access to 57 post-mortem human brains representing developmental stages from 40 days after conception to 82 years of age. They gathered 1,340 tissue samples for analysis, including from 11 areas of the neocortex, where the



It took an unusually large team of postdocs and graduate students (including some not pictured here) in the laboratory of Nenad Sestan (standing, third from right) to complete a large-scale analysis of gene expression in the developing human brain across the lifespan.

neural machinery resides for many capabilities, such as language and reasoning, that we think of as distinctively human.

This massive effort uncovered some surprising results. For starters, the study found that nearly nine of every ten genes in the human genome are expressed in the brain, “basically saying you use most of your genes to build your brain,” Sestan says. DNA “switches” can turn gene expression on or off, and expression of most of these genes varied by developmental period, brain region, or both. “What was also surprising and completely unknown before,” Sestan says, “is that most of these changes occur during prenatal and early postnatal development.”

In addition, from one brain region or time point to another, “genes switch their versions like suits,” according to Sestan. They can do so because an mRNA sequence can be spliced in different configurations, meaning a single gene can create different versions of a protein.

While mRNA expression significantly differed between brain regions and across developmental periods, it varied less by ethnicity or sex. Even so, expression of 159 genes differed between males and females. Most of these sex-based expression differences appeared before birth and vanished by adulthood, but Sestan says they “may offer some insight into why there is a difference in incidence,

prevalence, and severity of brain disorders between sexes.”

Though this study excluded tissue from people with overt medical or large-scale genetic abnormalities, some of the same sex-biased genes observed in the work by Sestan and colleagues have been fingered by other researchers as increasing the risk of psychiatric and neurological disorders. They include genes suspected of contributing to schizophrenia and autism, two disorders that may start brewing early in development and affect males and females differently.

Sestan and colleagues also found 29 groups of genes that were expressed together in certain brain regions during specific developmental periods. They were able to tie some of these gene expression networks to particular biological processes, yielding clues to what the genes do. Furthermore, some of the genes at the hub of these networks have been implicated in schizophrenia, mood disorders, Rett syndrome, and intellectual disability. Now, researchers who study such disorders can look to these co-expressed genes for causal leads.

Sestan and his collaborators hope that their study will help scientists who study these conditions and others. To that end, they have made their data set publicly available. After all, as Sestan well knows, it will take a village of scientific sleuths to solve the mysteries of our most complex organ.



Sterling Professor of Genetics and Pediatrics Arthur Horwich, M.D. (third from left), is a co-recipient of the 2011 Albert Lasker Basic Medical Research Award for his seminal work on the mechanisms of cellular protein folding (see *Medicine@Yale*, September/October 2011). The recipients were honored at a ceremony in New York City on September 23. (From left) Franz-Ulrich Hartl, M.D., DR.MED., of the Max Planck Institute of Biochemistry in Germany, Horwich’s longtime collaborator and co-recipient; Tu Youyou, of the China Academy of Chinese Medical Sciences, recipient of the Lasker-DeBakey Clinical Medical Research Award; Horwich; and John I. Gallin, M.D., representing the Clinical Center of the National Institutes of Health, recipient of the Lasker-Bloomberg Public Service Award.