

Yale surgeons use engineered vessel to treat child's heart defect

For the first time in the U.S., a 'living graft' is implanted to treat congenital heart disorder

In August, a toddler born with only one functioning heart ventricle went under anesthesia at Yale so surgeons could repair the defect by attaching a new blood vessel to her heart.

Inserting artificial blood vessels, which are normally made of the same synthetic materials used for bypass surgeries, has become a relatively routine operation to help children with single-ventricle heart defects improve their circulation and live longer and healthier lives. But this child's operation, performed by Toshiharu Shinoka, M.D.,

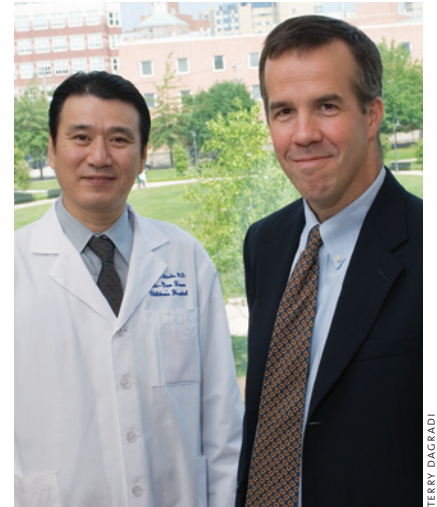
PH.D., associate professor of surgery and pediatrics and director of pediatric cardiovascular surgery at Yale-New Haven Hospital (YNHH), and Gary S. Kopf, M.D., professor of surgery, was very different. It was the first on U.S. soil to use a tissue-engineered blood vessel, or graft. Made of a biodegradable framework seeded with living cells, the graft is expected not merely to integrate into the child's heart, but to actually grow along with it.

"They're living vascular grafts. They respond to all the body's signals, so they're able to grow, repair, and remodel just like a regular blood vessel," says head researcher Christopher K. Breuer, M.D., associate professor of pediatric surgery and

pediatrics at the School of Medicine, of the small tube-shaped devices.

In the 1990s, Shinoka worked alongside Breuer at Children's Hospital Boston, where they bathed biodegradable scaffolds shaped like heart valves with blood vessel cells; the cells took, and the valves worked well in experiments with sheep. However, this method was impractical for clinical use, because forming usable tissue could take months.

Several years later, after having moved back to his native Japan, Shinoka devised a new technique using bone marrow cells, which yielded vessels in just hours, and over the ensuing years he implanted them into 25 Japanese children // **Heart** (page 7)



Toshiharu Shinoka and Christopher Breuer successfully implanted a tissue-engineered graft in a child with congenital heart disease.

Scientist joins a most distinguished fold

Pediatrician-turned-scientist wins the Lasker Award for research on molecular protein-folding machine

The elegant vaulted ceilings and leaded glass of the school's Medical Historical Library provided the proper setting for a September 12 reception that itself marked a milestone in Yale's medical history. Earlier that day, Arthur Horwich, M.D., Sterling Professor of Genetics and Pediatrics, learned that he was one of this year's recipients of the Albert Lasker Basic Medical Research Award, one of the most prestigious prizes in biomedicine, for his seminal work showing how proteins attain the myriad distinctive shapes required to properly perform their functions.

The library quickly filled with well-wishing colleagues and friends—they are one and the same, judging by the many mentions made that day of Horwich's modesty and good humor. As Dean Robert J. Alpern, M.D., noted in his remarks, we are accustomed to wondering why bad things happen to good people, but the recognition of Horwich's research with the Lasker Award shows that "really good things can happen to nice people": "I think everyone here knows that there's no one nicer than Art Horwich," said Alpern, "and probably no one more committed to their research."

Fittingly, Horwich shares the prize with yet another friend, Franz-Ulrich Hartl, M.D., DR.MED., of the Max Planck Institute of Biochemistry in Germany. For more than

two decades, Horwich and Hartl's transatlantic research collaboration has revealed and characterized the molecular machines that ensure that proteins fold properly, a process basic to life. The award was presented at a // **Award** (page 4)



Arthur Horwich (right) and Franz-Ulrich Hartl, co-recipients of this year's Albert Lasker Basic Medical Research Award, in Germany in 1991.

Yale's Class of 1961 comes together for research on cancer

When the 50th reunion of a Yale College class approaches, classmates traditionally team up to contribute to the Yale Alumni Fund, to provide an endowment for financial aid, or to meet other needs at their alma mater. But when it came time to think about how their class might mark its 50th, Edward H. Cantor, J.D., Vincent E. Teti, and John P. de Neufville, PH.D., of the Class of 1961 had a different idea—they wanted to raise money to combat cancer.

"It's a universal need and it's touched everyone, particularly in our age group," says Cantor, a retired lawyer from Orange, Conn., and all three men have indeed confronted cancer on a personal level. Both he and de Neufville, a member of the advisory board of Yale Cancer Center (YCC), recently lost their wives to the disease, and Teti, gift chairman for the class, has a family member currently fighting cancer. // **Class of '61** (page 7)

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After 50 years in his Yale lab searching for new and better cancer drugs, Alan Sartorelli is still hatching new and better ideas.

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5 Custom-made proteins, coming up!

Cross-campus collaboration yields a way to precisely place molecules on amino acids, a powerful new tool for researchers.

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Alan Sartorelli

Alan Sartorelli, seen here peering through a laboratory film, says he will follow his preclinical research on new cancer treatments wherever it takes him, and adopt virtually any technique to get an answer. "I'm a jack of all trades and a master of none," says Sartorelli, who joined the School of Medicine faculty in 1961 and served as director of Yale Cancer Center for nine years.

COURTESY OF PHILIP PENKETH

Jack of all trades

Cancer is relentless, so perseverance is essential in those who hope to vanquish it. Alan C. Sartorelli, Ph.D., is anything but a quitter. This October marks Sartorelli's 50th year on the Yale faculty, a half century in which he has continuously held multiple research grants in a hunt for new and better cancer treatments. On a recent afternoon it was business as usual: Sartorelli, who will be 80 years old in December, was applying final polish to a grant application bound for the National Institutes of Health.

The same tenaciousness has served Sartorelli well in his personal life. Born in hardscrabble Chelsea, Mass., across the Mystic River from Boston (and with the accent to prove it), Sartorelli took a restaurant job at age 12 and kept it all the way through his undergraduate years at the now-defunct New England College of Pharmacy, "about all I could afford at the time." He was a class officer during each of his four college years, and on nights and weekends eked out a living singing popular music at events around Boston. Even the indefatigable Sartorelli, now Alfred Gilman Professor of Pharmacology, scratches his head at how he got it all done, but says, "That's my way of functioning. I always do more than I can do. I try, at any rate."

Sartorelli obtained a laboratory assistantship at Middlebury College, in

Vermont, where he earned a master's degree in chemistry. He received a Ph.D. in Biochemical Oncology from the University of Wisconsin, and after a quirky three-year stint at a small cancer research foundation in Ardmore, Okla., he came to the School of Medicine in 1961.

As an assistant professor, "I didn't date very much. I just worked," says Sartorelli. But he did find time to develop an infatuation with the woman who would become his wife, the "gorgeous outside, but also inside" Alice Anderson, then registrar of the medical school.

Though she had declined a request for a date, Sartorelli's patience paid off one afternoon as he waited beneath the portico of Sterling Hall of Medicine for a rainstorm to taper off. "She came out with an umbrella, headed in the same direction, and she invited me under." It was a small umbrella, though, and water flowed off of it into his coat collar, pouring out the end of his pant leg "just like a drainpipe," Sartorelli recalls. "But I didn't care."

That waterlogged encounter led to a loving marriage that endured for 41 years, until Alice died in March, 2011.

Though he doesn't remember exactly why, "I knew I wanted to be a cancer researcher since I was six years of age," just about the time he got his first chemistry set, Sartorelli says.

That singular focus eventually brought him to the pinnacle of the profession. Sartorelli's CV needs many pages to embrace all the research papers and book chapters published, editorships and presidencies held, lectures given, and honors won. But, for him, no achievement matches his nine-year term as director of Yale Cancer Center. "I loved that job," he says. "It's exactly what I wanted to do."

Despite the disappointment of the FDA denying approval in 2009 at the Phase II stage to laromustine, a promising anti-cancer compound developed in his lab, Sartorelli has characteristically kept on. Members of his lab are now pinning their hopes on hypoxic cells, oxygen-deprived cells distinctive to tumors that Sartorelli believes are "a source of vulnerability for cancers." Because of hypoxic cells' metabolic anomalies, it is possible, he says, to create an inert "prodrug" specifically designed to home in on these cells that will transform into a potent cancer-killer once it enters them. This Trojan Horse strategy would spare normal tissue while delivering a killer blow to tumors on their own turf.

Asked about his hopes for the success of this latest venture, Sartorelli replies simply, "I think we're gonna do it." Then he gets back to work on the grant application.

Another side of 'Dr. Ruth' seen in session on resilience after trauma

Ruth Westheimer, Ed.D., is best known as "Dr. Ruth," the unabashed sex therapist who gained fame on radio and TV in the 1980s. But Westheimer's eventful, sometimes tragic early life taught her much about the importance of psychological strength in the face of hardship. In September, Westheimer contributed her hard-won wisdom to a session on "Resilience and Trauma" at the Yale Club of New York, sponsored by the Department of Psychiatry. Also featured were department Chair John H. Krystal, M.D., Robert McNeil Professor of Translational Research; William H. Sledge, M.D., George and Esther Gross Professor of Psychiatry; and Steven M. Southwick, M.D.,

professor of psychiatry and deputy director of the Clinical Neurosciences Division of the Department of Veterans Affairs National Center for Post-Traumatic Stress Disorder (PTSD).

Born Karola Ruth Siegel to Orthodox Jewish parents in Germany, Westheimer came of age as the Nazis were rising to power. After witnessing the abduction of her father, she was sent to a Swiss orphanage by her mother and grandmother, and later learned that both her parents had been murdered in the Holocaust.

Westheimer attributed her success in overcoming these challenges to solid social support, particularly that she received early in life; education;



Ruth Westheimer

an optimistic outlook; cognitive flexibility; coping skills; and pursuit of a worthwhile mission. These factors were echoed in research presented by Southwick, who has studied PTSD in ex-prisoners of war, Special Forces instructors, and civilians who have endured extremely traumatic events.

Westheimer's coping skills are exemplary, said her Yale hosts, calling her a "force of nature" who "embodies the idea of resilience and post-traumatic growth."

Cardiologist returns to Yale as new section chief



William Hellenbrand

The Department of Pediatrics has named William E. Hellenbrand, M.D., a pioneer in the development of catheterization devices and techniques for the treatment of heart disease

in children, as chief of the Section of Pediatric Cardiology.

With his new appointment, Hellenbrand rejoins the faculty of the School of Medicine, on which he served for 24 years.

Hellenbrand left Yale in 1999 to direct the catheterization lab at Morgan Stanley Children's Hospital of New York-Presbyterian, and became director of pediatric cardiology at the Columbia University College of Physicians and Surgeons in 2007.

Hellenbrand has led numerous clinical trials and published extensively on his innovations in cardiac catheterization.

In addition to serving as chief of pediatric cardiology at Yale-New Haven Children's Hospital, Hellenbrand will be involved in a new statewide program in congenital heart surgery in collaboration with Connecticut Children's Medical Center in Hartford.

After receiving his bachelor's degree from Brooklyn College of the City University of New York, and his medical degree from Downstate Medical Center of the State University of New York, Hellenbrand came to Yale, where he completed an internship and residency in pediatrics and a fellowship in pediatric cardiology. The last year of his residency was completed as a member of the United States Army at Walter Reed Army Medical Center in Washington, D.C.

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New recipe for natural Alzheimer's compound



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Preparations of a Chinese moss (above) have been sold as a dietary supplement to maintain memory and used to treat Alzheimer's disease in China since the 1990s. But huperzine A, the moss's active compound, can cost as much as \$1,000 per milligram—a typical dose—because the moss is rare and the chemical has been difficult to isolate.

That obstacle has been swept aside by Assistant Professor of Chemistry Seth Herzon, PH.D., and colleagues, who report the discovery of a new method to synthesize huperzine A in the August 25 issue of *Chemical Science*.

The process takes only eight steps and could lower the cost of the drug to fifty cents per milligram. Having a cheap and practical way to synthesize huperzine A paves the way for researchers who want to study its efficacy in treating Alzheimer's.

"We believe huperzine A has the potential to treat a range of neurologic disorders more effectively than the current options available," says Herzon. "And we now have a route to huperzine A that rivals nature's pathway."

Protecting the kidneys after heart surgery

Following cardiac surgery, many patients experience acute kidney injury (AKI), a complication that increases the risk of mortality. To evaluate kidney function and diagnose AKI, clinicians traditionally measure creatinine levels in a patient's bloodstream, but it may take up to three days for the concentration of this biomarker to peak.

New research published in two companion articles in the August 11 issue of the *Journal of the American Society of Nephrology* by a multidisciplinary group of Yale scientists suggests that measuring other biomarkers may be more effective.

The group, led by Chirag Parikh, M.D., PH.D., associate professor of medicine, collected samples from adult and pediatric patients undergoing cardiac surgery and measured the level of the proteins IL-18 and NGAL in urine, and NGAL in blood. These biomarkers identified AKI within six hours of surgery and one to two days earlier than creatinine. In addition, the IL-18 and plasma NGAL levels identified the adult patients who go on to develop severe kidney injury after cardiac surgery. Of the three biomarkers tested, urine IL-18 levels showed the strongest association (over a six-fold increase in risk) with severe AKI in both adults and children.

Seeing the good in biology's 'bad guys'

Though antioxidants may bring health benefits by curbing the damage caused by free radicals, research shows they are a double-edged sword

After healthy human cells convert nutrients into energy, there are some molecules left over. Some of these are useful and are integrated into the cell, but others are highly reactive and ready to wreak havoc. Called free radicals, these molecules have an unpaired electron in their atomic structure. To stabilize themselves, free radicals donate or steal an electron from whatever other molecule is close by, setting off a cascade of chemical reactions that can eventually damage DNA and other critical cellular components.

Luckily, cells can normally keep free radicals under control. But when exposed to damaging agents such as sunlight, cigarette smoke, pollution, or radiation, so many free radicals are formed in cells that normal control mechanisms



Sabrina Diano



Gerald Shadel



Tamas Horvath

can't get rid of all of them. Because of the potential damage they can do, such free radicals are considered bad guys in biology. Antioxidants, molecules that can block the formation of free radicals, have become popular ingredients in dietary supplements, hailed as a way to prevent diseases from cancer to Alzheimer's. But two new pieces of research by School of Medicine scientists show how important free radicals are to normal cell biology. And too many antioxidants, the papers suggest, can thwart important signaling pathways. It might be time to give the bad guys a break.

Over the past decade, scientists have shown that blocking a cell-signaling pathway called TOR extends the lifespan of yeast, roundworms, fruit flies, and mice. Gerald S. Shadel, PH.D., professor of pathology and genetics, suspected that mitochondria—the energy-generating powerhouse of cells—played a role in this longevity. After all, when mitochondria finalize the metabolism of glucose, they make reactive oxygen species (ROS), which are free radicals centered around oxygen atoms, and ROS are already known to affect aging.

"Reactive oxygen species in the mitochondria have been implicated in aging for many years," says Shadel. "These molecules are known to cause dysfunction of cells and tissues over time."

But when Shadel and members of his lab looked at a strain of yeast in which TOR signaling is reduced, he discovered something surprising. As the team reports in the June issue of *Cell Metabolism*, the lowered TOR signaling that increases this yeast strain's lifespan actually causes their mitochondria to produce a small burst of ROS. To see if these ROS molecules were necessary for the yeast's longevity or just a side effect, Shadel blocked ROS production in the yeast's mitochondria, and found that the yeast lived no longer than usual. But if mitochondrial ROS production was increased optimally, it was enough to extend the cells' lifespan on its own.

Shadel surmises that a small amount of ROS molecules prepares a cell to get rid of damaging ROS in the future—similar to the way a vaccine works. It's when a cell is bombarded with high numbers of ROS molecules at once that they cause damage. "The cell remembers these reactive oxygen species and mounts a response against them better next time," he says.

And lifespan isn't the only way that low levels of ROS may be helpful, according to another recent study led by Sabrina Diano, PH.D., associate professor of obstetrics, gynecology, and reproductive sciences and neurobiology.

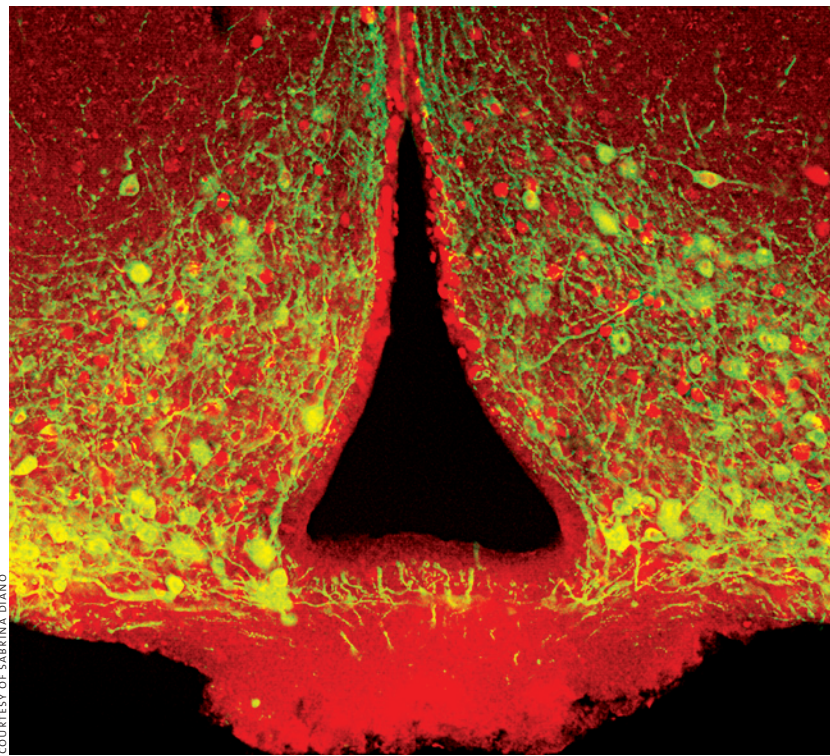
While researching neurons in the brain that regulate eating, Diano and senior author Tamas L. Horvath, D.V.M.,

PH.D., the Jean and David W. Wallace Professor of Biomedical Research, discovered that ROS molecules play a vital role in controlling hunger. "When these neurons were active, and the mice would stop eating, the ROS levels were higher," says Diano. "It was just an incidental observation, but we decided to look at it more closely."

ROS molecules are produced when the body metabolizes food, so it makes sense that they might be involved in feeding, but Diano, Horvath, and colleagues discovered that they play a vital role. When there are no ROS molecules around a particular set of neurons in the brain, the group found, these neurons send a hunger signal to the rest of the body. But when these neurons are exposed to ROS, they send a satiety signal that tells the body it's time to stop eating.

"When you eat a large meal, it's actually very important to get a surge of reactive oxygen species," says Horvath. "That's the signal to stop eating."

// Free radicals (page 8)



COURTESY OF SABRINA DIANO

In a fluorescence micrograph of a section of a mouse's brain, POMC neurons are labeled green, and a protein associated with overall neural activity is labeled red. When obese mice on a high-fat diet were treated with a compound that allowed levels of radical oxygen species in POMC neurons to rise, the neurons' activity increased (yellow) and the mice ate significantly less.

The world is 'Closer to Free'

Yale Cancer Center and Smilow Cancer Hospital at Yale-New Haven have joined forces to create Closer to Free—a fund that provides essential financial resources for breakthrough cancer research and compassionate patient care by combining the gifts of many donors. This support is critical to ensure that new research can be pursued without delay, that promising treatments are aggressively developed, and that patient care is continuously enhanced. The generous support of Closer to Free donors accelerates our ongoing work and helps to launch important new research projects and patient programs at Yale and Smilow.

There are many opportunities for members of the community, patients and their families, cancer survivors, and others passionate about cancer research and patient care to become involved in the mission of Closer to Free. Individual contributions as well as organized efforts to raise funds through events all can have an impact.

For more information on how you can help, visit the website at givecloserstofree.org or contact Jancy Houck, assistant vice president for development and director of medical development at (203) 436-8560.

closer to free

OUT & ABOUT

August 6 Friends, staff, and volunteers celebrated the **HAVEN Free Clinic's 5th Anniversary**. Founded by Yale students in the health professions, HAVEN provides care to uninsured patients at the Fair Haven Community Health Center (FHCHC), which marks its 40th anniversary this year. **1.** (Front, from left) volunteers **Nyasha George** '12 and **Jing Chen** '12; FHCHC Executive Director **Katrina Clark**, M.P.H.; board member **Peter Zhao** '14; and volunteer **Casey Watts**, of the Yale College Class of 2012. (Back, from left) Attending nurse **Elizabeth Magenheimer**, APRN, assistant clinical professor at the School of Nursing; attending physician **Steven Wolfson**, M.D., associate clinical professor of internal medicine; **Laurie Bridger**, M.D., assistant clinical professor of internal medicine and HAVEN medical director; and attending physician **Nancy R. Angoff**, M.D., M.P.H., M.Ed., associate dean of student affairs and associate professor of internal medicine. **2.** Congresswoman **Rosa L. DeLauro** (D-CT). **3.** Angoff and Chen.



HAROLD SHAPIRO (3)

August 18, 2011 The School of Medicine formally welcomed the 101 members of the Class of 2015 at the **White Coat Ceremony**, an annual ritual in which new students receive physician's jackets. **1. David A. Hafler**, M.D., Gilbert H. Glaser, M.D., Professor, chair of the Department of Neurology, and professor of immunobiology, gave this year's keynote speech. **2. Forrester A. Lee**, M.D., assistant dean for multicultural affairs and professor of medicine (left) and **Laura R. Ment**, M.D., professor of pediatrics and neurology and associate dean for admissions (not visible), help **Michael Chang** with his jacket. **3.** (From left) **Frank Gruskay**, M.D. '54, with grandson and first-year student **Jordan Gruskay**, son **Jeffrey Gruskay**, M.D. '81 and associate clinical professor of pediatrics, and Dean and Ensign Professor of Medicine **Robert J. Alpern**, M.D. **4.** (From left) **Ben Albright**, **Pretpaul Bagi**, **Aditi Balakrishna**, **Zeb Balsen**, **Jessica Becker**, **Dipankan Bhattacharya**, **Xiao (Mark) Bi**, **Sean Bickerton**, and **Remy Bizimungu**. **5. Aileen Morrison** (left) with her mother, **Lai Kuen (Phinney) Morrison**.



TERRY DAGRADI (5)

September 17 **Yale Tomorrow**, Yale University's five-year comprehensive fundraising campaign, which raised a record \$3.886 billion, formally concluded with a celebration on campus. **1. James Kim**, a graduate student at the School of Music, gave a solo cello performance at Yale's Sprague Hall. **2.** Guests attended dinner in the Commons at Woolsey Hall. **3.** The work of Yale faculty, such as **Thomas J. Lynch**, M.D., Richard Sackler and Jonathan Sackler Professor of Medicine, director of Yale Cancer Center, and physician-in-chief at Smilow Cancer Hospital (on screen), was highlighted during an evening of performances.



MICHAEL MARSLAND (3)

// **Award** (from page 1) ceremony in New York City on September 23.

It could be said that Horwich's path to the Lasker began when he decided to specialize in pediatrics after receiving his M.D. at Brown University, because the discoveries that decisively steered his scientific career at Yale were made while he was attempting to decipher the causes of X-linked inherited lethal ammonia intoxication, a deadly genetic disease of infancy caused by the absence of a protein known as OTC.

For OTC molecules to perform their crucial enzymatic function in the cell after they are synthesized, they must unfold, cross through the walls of compartments called mitochondria, and promptly refold into the proper three-dimensional shape.

In work that won a Nobel Prize in 1972, biochemist Christian Anfinsen, PH.D., had shown that unfolded proteins contain sufficient information in themselves to assume a proper shape. But in 1987, experiments with OTC in yeast cells prompted Horwich and his student Ming Cheng to contemplate the then-heretical notion that there might also be molecular machines that assist proteins in folding.

Horwich and Cheng had identified a mutant yeast strain in which OTC

molecules remained unfolded in the mitochondria and had stuck together in clumps (this sort of protein aggregation is a hallmark of neurodegenerative conditions such as Alzheimer's disease) and they enlisted Hartl's help to understand the finding. The scientists soon concluded that a defective ring-shaped protein, now known as Hsp60, was the cause.

Horwich continued his research, shifting his focus to a bacterial relative of Hsp60 called GroEL. By 1993, through collaborative work with the late Yale X-ray crystallographer Paul B Sigler, PH.D., and numerous other colleagues, the atomic structure of GroEL—a "beautiful work of nature," in Horwich's words—had been revealed.

GroEL was eventually understood to be part of a pinecone-shaped complex, dubbed a "chaperonin" for its helping role, in which two stacked rings form a cylindrical chamber that can be covered by a cap, called GroES (see illustration at right).

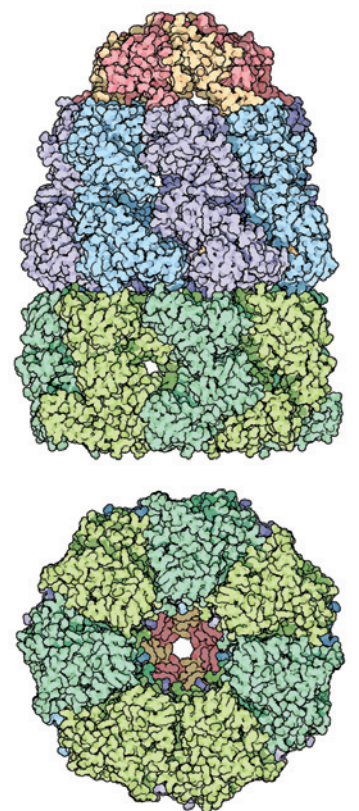
In further experiments, the purpose of those parts was clarified, and the several steps of GroEL/GroES-assisted protein folding were described down to the second.

In brief, an unfolded or poorly folded protein enters the GroEL chamber,

which is then capped by GroES. This provides an opportunity for the protein to fold in isolation, protected from sticking to other proteins. After about 10 seconds the GroES cap springs off. If the protein is properly folded, it goes on to do its job; if not, it may reenter GroEL several times for additional folding attempts.

Ultimately, these findings build on Anfinsen's work, which was done in a cell-free system, rather than overturn it. Proteins indeed contain all the information they need to properly fold, but in the cell's crowded confines chaperonins assist the process greatly by providing a vital check on protein aggregation.

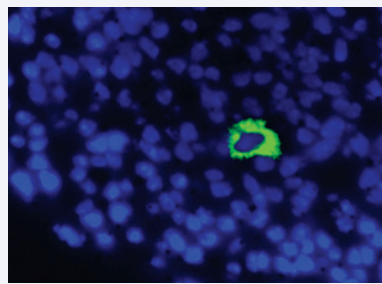
Understanding the workings of the GroEL/GroES complex has major implications for medicine, as eloquently expressed on the Lasker Foundation's website: "When proteins aggregate, illnesses such as Alzheimer's disease, Huntington's disease, and amyotrophic lateral sclerosis can arise, and adjusting chaperone activity might provide therapeutic benefit . . . Across the tree of life, the folding machines isolate young proteins and create a transformative moment. Then the devices send forth the mature protein molecules to join the hustle and bustle that makes cells what they are."



Artist David Goodsell's rendering of the atomic structure of the GroEL/GroES complex studied by Arthur Horwich. (Top) GroEL's double rings, in shades of green, blue, and purple, are capped by GroES, shown in red and orange. (Bottom) A view through the GroEL rings toward the GroES cap shows the protein-folding chamber formed by the complex.

DAVID GOODSSELL (RCSB PDB MAY 2002. MOLECULE OF THE MONTH WWW.PDB.ORG)

Uterine cells may be a new diabetes remedy



COURTESY OF HUGH TAYLOR

When type 1 diabetes destroys the insulin-producing islet cells of the pancreas, the only cure—apart from a lifetime of insulin injections—would be implanting new islet cells. Scientists have harvested these cells from cadavers, grown them from bone marrow, and coaxed umbilical cord cells to turn into islet cells with some success. Now they have a new source: the uterus.

Stem cells in the lining of the uterus generate new tissue each month as part of the menstrual cycle. But they can also form other cell types. A team led by Hugh S. Taylor, M.D., professor of obstetrics, gynecology, and reproductive sciences, reported online August 30 in *Molecular Therapy* that they bathed uterine stem cells in a mix of nutrients that turned them into pancreatic islet cells. Within three weeks the cells began to produce insulin (green in photo), and when they were implanted into mice with type 1 diabetes, the disease vanished within five weeks.

Taylor's group is now determining how long the treatment lasts, and how changing the nutrient bath or increasing the dose of injected cells could make the technique more effective.

Adding antipsychotics does little for PTSD

Treatment for post-traumatic stress disorder (PTSD), a severe anxiety disorder that can follow traumatic events, commonly includes antidepressant medications. However, many PTSD sufferers do not get relief from these drugs. In such cases, anti-psychotics such as risperidone, usually used to treat schizophrenia and bipolar disorder, are often added to the patient's drug regimen.

"There is not a lot of evidence to guide psychiatrists caring for patients with treatment-resistant PTSD," says John H. Krystal, M.D., Robert L. McNeil Jr. Professor of Translational Research, chair of the Department of Psychiatry, and director of the Clinical Neuroscience Division of the Department of Veterans Affairs National Center for PTSD. A new study by the (VA) and a Yale team led by Krystal, the first focused on antidepressant-resistant PTSD symptoms, indicates that risperidone is ineffective as an adjunct treatment.

In the six-month study, published August 3 in *JAMA*, 247 subjects with PTSD received either risperidone or a placebo in addition to their existing treatments. Standard measures showed no significant reduction in PTSD symptoms in the group of veterans receiving risperidone, highlighting the need for further research in this area.

New hope for old brains seen in study of memory

A neurobiologist's findings on the mechanisms of age-related cognitive decline will guide future research and may lead to new treatments

The prefrontal cortex (PFC)—the front part of the brain, just behind the forehead—is the site of a dizzying array of important neurological functions. One is working memory, the short-term memory we rely on when performing simple tasks like remembering where we left our car in a parking lot. Networks of neurons in the PFC fire persistently to keep information like this in mind while we go about our business. But like other functions of the PFC, working memory declines with age: we become increasingly forgetful and distractible, and complex tasks can pose new difficulties.

Recent work by a team of School of Medicine scientists in the lab of Amy F.T. Arnsten, PH.D., professor of neurobiology and psychology, offers new insights into age-related decline in working memory and suggests that certain drugs may lessen or reverse some of this drop-off.

Arnsten, a member of Yale's Kavli Institute for Neuroscience, and colleagues had previously shown that elevated activity of cyclic AMP (cAMP), a chemical messenger inside cells, reduces neuronal firing in the brains of fatigued or stressed young animals by opening tiny pores in neurons known as potassium channels: when the channels open near neural connections, networks disconnect and the function of the PFC is impaired. Now, in the aging brain under normal conditions, Arnsten's team has discovered these same physiological changes—which may increase vulnerability for age-related neurodegenerative diseases—as well as a potential way to reverse the changes.

In the new research, published July 27 in *Nature*, Arnsten's team—including Min Wang, PH.D., research scientist in the Department of Neurobiology and lead author of the study; James A. Mazer, PH.D., associate professor of neurobiology and psychology; and Daeyeol Lee, PH.D., associate professor of neurobiology and psychology, and member of the Kavli Institute—measured the function of PFC neurons in animals of different age groups to gauge the animals' ability to remember spatial locations over a period of time.

The team found a marked reduction in the firing rate of working-memory cells in the PFC of middle-aged and elderly animals. But by using drugs that inhibit cAMP signaling, or that block the potassium channels regulated by cAMP, the scientists were able to significantly restore the firing of these neurons and enhance the animals' ability to perform the task. The findings suggest that compensating



TERRY DAGRADI

Amy Arnsten's work on the brain's prefrontal cortex has shed new light on the causes of cognitive decline as we age. Her recent research on working memory (our ability to keep pieces of information in mind while we execute short-term tasks) suggests that memory may be preserved or enhanced in the elderly with drugs that compensate for age-related changes in brain function.

for neural changes at the molecular level may aid in combating age-related deterioration of working memory.

One of the substances that enhanced neuronal firing by dampening cAMP signaling, guanfacine, is already approved for treating hypertension in adults and attention-deficit hyperactivity disorder in children, and it may now prove useful in the elderly. The School of Medicine is now enrolling elderly subjects who do not have Alzheimer's disease or other forms of dementia in a clinical trial to test guanfacine's ability to improve working memory and the ability to manage complex decisions and tasks.

"Age-related cognitive deficits can have a serious impact on our lives in the information age, as people often need higher cognitive functions to meet even basic needs, such as paying bills or accessing medical care," says Arnsten. "These abilities are critical for maintaining demanding careers and being able to live independently as we grow older."

Cellular toolkit opens up a world of possibilities

Cells are like novels: they're made up of words and sentences, each spelled out in combinations of letters. All of cell biology is dictated by the letters of the genetic code, which determine the amino acid sequences of the proteins that carry out distinct tasks. Now, Yale scientists have shaken up the alphabet of life, adding a new letter to its mix.

"I really believe that the genetic code can evolve and expand," says Dieter Söll, PH.D., Sterling Professor of Molecular Biophysics and Biochemistry and professor of chemistry, senior author of a paper on the new work. "This is proof that we can make that happen."

Genes are made up of four different nucleotides. Each triplet of nucleotides—called a codon—codes for one building block of a protein, called an amino acid. Since there are 64 possible DNA triplets in this genetic code, but only 22 standard amino acids, many codons are redundant.

Once a protein is assembled from a string of amino acids, other molecules

can attach to these amino acids, altering the protein's function. One example is phosphorylation, the addition of a phosphate molecule. When the amino acid serine is phosphorylated, the resulting compound is called phosphoserine. Many human diseases, including cancer, involve faulty phosphorylation, but it has been a struggle for scientists to find out more because they don't know how cells add phosphate molecules in the first place.

"We don't have tools that enable us to take a protein and phosphorylate certain serines in a controlled and precise way," says Söll's collaborator Jesse Rinehart, PH.D., assistant professor of cellular and molecular physiology at the



TERRY DAGRADI

Dieter Söll (left) and Jesse Rinehart have found a way to tweak the genetic code to gain precise control over the phosphorylation of proteins. The technique will make it possible for scientists to tackle a range of previously intractable questions about normal biology and the biology of disease.

// Genetic code (page 6)

// **Genetic code** (from page 5) School of Medicine. “And that’s really limited our ability to study phosphorylation.”

Söll and Rinehart had an idea: what if they made a protein from scratch that had phosphoserine as one of the starting amino acids, rather than trying to add phosphate to serines later? “What we really wanted to do,” says Rinehart, “was to bypass the cell’s normal machinery, and produce proteins in a new way, using a new code.” The researchers didn’t want every serine to be a phosphoserine, but they wanted to mimic the pattern

of phosphorylation found naturally in cells. Molecules called tRNA, the major research focus of Söll’s lab, match up codons with the appropriate amino acids. As described in the August 26 issue of *Science*, Rinehart and Söll created a new tRNA that matched phosphoserine to a rare codon that usually signals the end of a protein-coding message. “We made room for a new amino acid. This allows us to have control over where phosphoserine occurs,” says Rinehart.

Next, Söll and Rinehart engineered a mammalian gene that had

the special codon in every place that they wanted a phosphoserine, then added the gene, the new tRNA, and some additional enzymes to a bacterial cell. The result: the bacterium churned out copies of the protein that had phosphoserine integrated into all the right spots.

Some proteins are activated by phosphorylation and others are shut off. By comparing proteins made with their new tool to those made with typical sequences, Söll and Rinehart will be able to precisely determine phosphorylation’s effects.

Phosphoserines aren’t the only modified amino acid, and Söll envisions using the new method to add phosphate and other molecules, such as acetyl and methyl groups, onto other amino acids. “There are lots of ways that we can expand this tool-kit,” says Söll.

“You could say this is just a curiosity—we’ve done something that no one else has done before,” says Rinehart. “But in this case, it is more than that. There is a vast amount of medically important work that can be done now on phosphorylation.”

Grants and contracts awarded to Yale School of Medicine

November 2010 – February 2011

Jacqueline Barker, NIH, *Role of Corticostriatal Dopamine Signaling in Response Strategy Selection*, 1 year, \$82,760 • **Hilary Blumberg**, NIH, *Genetic Influences on Functional Connectivity in Bipolar Disorder*, 5 years, \$4,012,300
Hal Blumenfeld, NIH, *Remote Effects of Focal Hippocampal Seizures on Neocortical Function*, 4 years, \$1,438,329 • **Clifford W. Bogue**, NIH, *Developmental Adaptation: Child Health Research Center*, 4.8 years, \$2,223,688 • **Judson Brewer**, NIH, *Brain Changes with Mindfulness Training in Smokers Using fMRI*, 1 year, \$196,350
Kathleen M. Carroll, NIH, *Computer Based Training in Cognitive Behavioral Therapy: Web-based Delivery of CBT4CBT*, 5 years, \$2,716,073
Richard Carson, Department of Veterans Affairs, *PET Scans on Non-Human Primates*, 8 months, \$78,960 • **Brenda Cartmel**, NIH, *The Genetics of Tanning Addiction*, 2 years, \$422,853 • **Chiswili Chabu**, NIH, *Live Analysis of Tumor Interaction with Host Immune Cells*, 2 years, \$102,628 • **Yoonsang Cho**, NIH, *Therapeutic Application of Small Molecule MIF Inhibitors in Rheumatoid Arthritis*, 5 years, \$651,510
Rituparna Das, NIH, *Role of Macrophage Migration Inhibitory Factor (MIF) in Pathogenesis of Tuberculosis*, 1 year, \$61,790 • **Patrick G. Gallagher**, NIH, *Barrier Insulators in Erythropoiesis*, 3.9 years, \$1,776,934 • **Andrew Goodman**, NIH, *Corrinoid Response of the Human Gut Microbiota*, 4.5 years, \$625,805 • **Yongtao Guan**, NIH, *Statistical Methods for Understanding Heterogeneity in Cocaine Relapse*, 3 years, \$1,193,463
Ann Haberman, NIH, *Yale Microscopy Workshop and Symposium*, 1 year, \$5,000 • **Michael Hughes**, NIH, *Profiling the Circadian Transcriptome of Drosophila Nervous System Using RNA Sequencing*, 2 years, \$111,484 • **Akiko Iwasaki**, NIH, *Antiviral CTL Mobilization to the Genital Mucosa*, 5 years, \$1,745,940 • **Sven-Eric Jordt**, NIH, *Counter Irritation by Menthol: Molecular Targets and Role in Airway Disease*, 4 years, \$1,432,211 • **Kenneth Kidd**, Department of Justice, *Further Development of SNP Panels for Forensics*, 2 years, \$1,351,352 • **Steven H. Kleinstein**, NIH, *Computational Tools for Analysis of B Cell Somatic Hypermutation*, 2 years, \$255,632
Michael Koelle, NIH, *G Protein Signaling in the C. elegans Nervous System*, 5 years, \$2,671,918
Michael Nitabach, NIH, *Transgenic Tethered Peptides*, 4 years, \$1,668,075 • **Daniel Pelletier**, NIH, *Molecular and Genetic Predictors of Disability Progression in MS*, 3.7 years, \$1,159,483
Matthew Phillips, NIH, *Center-Surround Functional Organization and Respiratory Modulation of Lateral Inhibition in the Mammalian Olfactory Bulb*, 2 years, \$82,760 • **Christopher Pittenger**, NIH, *5-HT_{1B} Receptor Function in OCD: an Examination Using PET Imaging and Pre-pulse*, 2 years, \$388,891 • **Jordan S. Pober**, NIH, *Presentation of Alloantigen by Human Vascular Cells*, 5 years, \$2,704,041 • **Matthew Rodeheffer**, NIH, *Cellular and Molecular Mechanisms of White Adipose Tissue Mass Regulation in Development and Disease*, 5 years, \$2,078,475

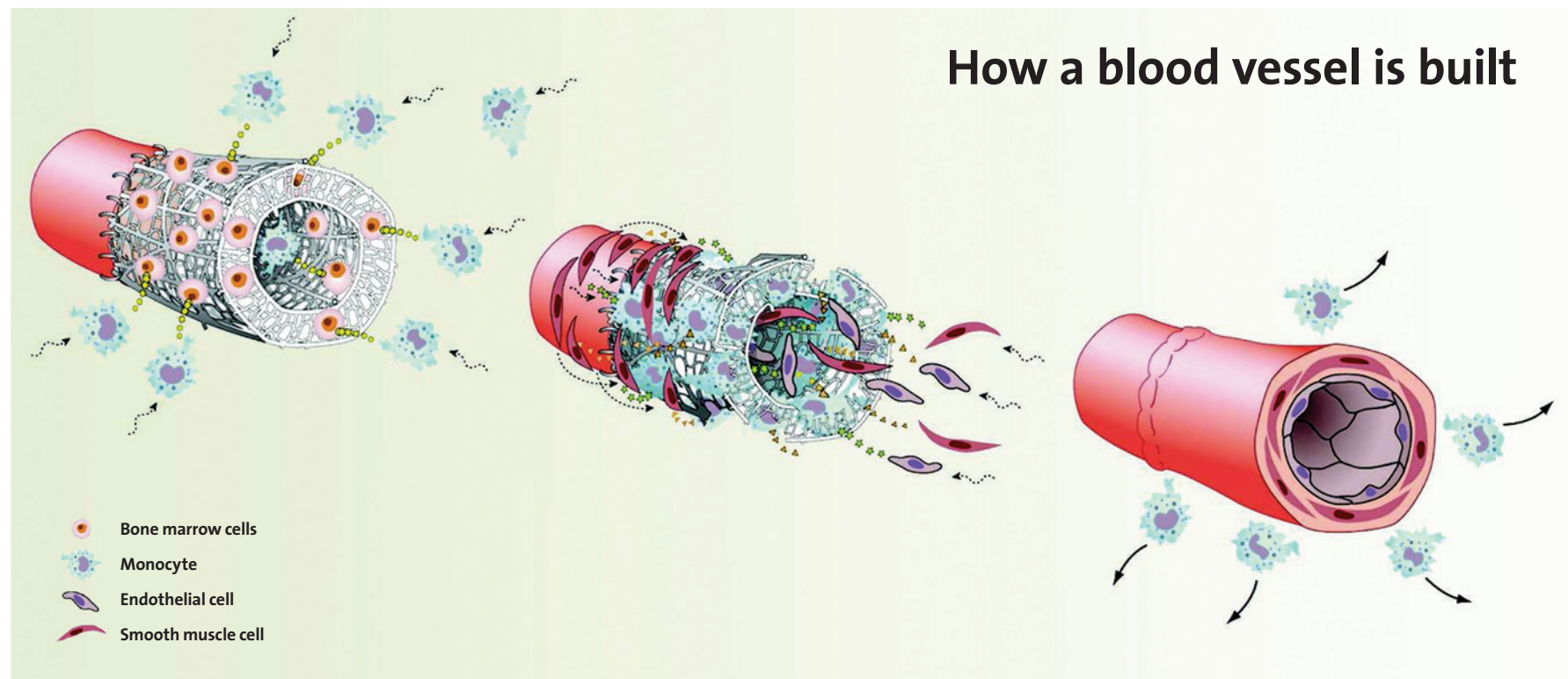
Diego Rodriguez Gil, NIH, *Axon Guidance in the Olfactory System*, 3 years, \$496,500 • **Emre Seli**, NIH, *Regulation of Maternal mRNA Translation in Early Mammalian Development*, 4.9 years, \$2,006,688 • **Michael Warren**, NIH, *Integrin Signaling through Arg Kinase Regulates Synapse and Dendrite Stabilization*, 3 years, \$93,606
Edward White, NIH, *Online Respondent-Driven Sampling and Data Collection for Men Who Have Sex with Men*, 2 years, \$467,895 • **Shari Wiseman**, NIH, *Regulated Degradation of EF2K: Linking Neuronal Protein Synthesis and Turnover*, 1 year, \$70,800 • **Caroline Zeiss**, NIH, *Complex Mouse Models of Age-Related Macular Degeneration*, 3 years, \$385,334

Non-federal

Amy Ahasic, American Heart Association, *Genotype-Phenotype Variations in Adipokines and Related Metabolic Pathways in ARDS Susceptibility and Survival*, 4.7 years, \$576,462 • **Serap Aksoy**, Monell (Ambrose) Foundation, *New Strategies for African Trypanosomiasis Control*, 2 years, \$100,000 • **Amy F.T. Arnsten**, Eli Lilly and Company, *mGluR2 vs. mGluR3 Mechanisms in Primate Dorsolateral Prefrontal Cortex: Immunoelectronic Microscopy*, 1 year, \$49,857 • **Marc Auerbach**, R Baby Foundation, *A Multi-Centered Network Using Simulation-Based Interventions to Improve Pediatric Emergency Care Patient Outcomes*, 1 year, \$150,000 • **Valeria Benavides**, Endocrine Fellows Foundation, *Teratogenic Potential of Antithyroid Drugs*, 1 year, \$7,500
Linda Bockenstedt, L2 Diagnostics, LLC, *T Cell Quantikine Assay for Diagnosis of Disseminated Lyme Borreliosis*, 1 year, \$125,033
Carmen Booth, Baxter Bioscience (division of Baxter Healthcare Corporation), *Hemophilia A in Wag/RijYcb Rats*, 1 year, \$91,671 • **Martina Brueckner**, New England Research Institutes, *Congenital Heart Disease Genetic Network Study*, 1 year, \$50,000 • **Irina Buhimschi**, Bill and Melinda Gates Foundation, *Reducing Deaths from Preeclampsia Through the Congo Red Dot Test*, 1.5 years, \$127,000 • **Sreeranga Chandra**, William N. & Bernice E. Bumpus Foundation, *Synaptic Vesicle Endocytosis Deficits: A Common New Mechanism in Parkinson’s Disease*, 6 months, \$100,000 • **Pamela Chang**, Cancer Research Institute, Inc., *Characterization of Basophils that Initiate Th2 Responses to Protease Allergens*, 3 years, \$23,250 • **Yung-Chi Cheng**, National Foundation for Cancer Research, *National Foundation for Cancer Research*, 3 years, \$225,000 • **Chiayu Chiu**, Epilepsy Foundation of America, *Somatostatin Interneuron Modulation of Dentate Glutamatergic Transmission*, 1 year, \$45,000 • **Judy Cho**, PSC Partners Seeking a Cure, *Identification of Genetic Profiles Unique to PSC-IBD*, 2 years, \$40,000 • **Hyung Chun**, Gilead Sciences, *Defining the Apelin-enos Axis in Pulmonary Arterial Hypertension*, 2 years, \$130,000 • **Gary W. Cline**, Juvenile Diabetes Research Foundation International, *Imaging Beta-Cell Mass in Healthy and T1DM with ¹⁸F-FPEB*

and B/I Infusion, 1.9 years, \$468,089 • **Kevin Collins**, American Heart Association, *Molecular Basis of Ether-à-go-go Related Gene (ERG) Potassium Channel Regulation*, 2 years, \$94,000
Joseph Craft, Alliance for Lupus Research, *Follicular Helper T Cell in Lupus: Characterization and Therapeutic Targets*, 2 years, \$385,444 • **Henk De Feyter**, American Institute for Cancer Research, *Dietary Manipulation of Glucose and Glutamine Metabolism*, 2 years, \$75,282 • **Robin de Graaf**, Resonance Research, Inc., *Fully Compensated Dynamic Shim System for in vivo MRI and MRS*, 1 year, \$188,965 • **Michael P. DiGiovanna**, Pfizer Inc., U.S. Pharmaceuticals Group, *Combination Targeting of IGF-1 Receptor and HER2 in Breast Cancer*, 1.8 years, \$126,051
Annarita Di Lorenzo, American Heart Association, *Role of Nitric Oxide (NO) in Regulating VEGF-Cadherin Biological Functions*, 4 years, \$308,000
John Forrest, Doris Duke Charitable Foundation, *Doris Duke Clinical Research Fellowship for Medical Students*, 3.5 years, \$600,000; Doris Duke Charitable Foundation, *One Year Child Abuse and Maltreatment Research Fellowships*, 1.5 years, \$97,200 • **Liana Fraenkel**, Arthritis Foundation, *Measuring Patients’ Risk Perceptions in Real Time*, 2 years, \$200,000 • **Stanley Frencher**, Foundation for Informed Medical Decision Making, *Prostate Education Project (“PEP Talk”): Cutting Through the Uncertainty of Prostate Cancer for Black Men Using Barbershop Outreach*, 1 year, \$100,000 • **Joel E. Gelernter**, Virginia Commonwealth University, *Stress Induced Drinking in OEF/OIF Veterans: The Role of Combat History and PTSD*, 6 months, \$35,802
Valentina Greco, American Skin Association, *Stem Cell Niche Dynamics during Hair Follicle Regeneration*, 1 year, \$60,000 • **Kevan Herold**, University of California, San Francisco, *JDRF Collaborative Center for Cell Therapy*, 1 year, \$120,367
Samuel M. Huber, Crohn’s & Colitis Foundation of America, *Analysis of the Role of IL-22BP in Intestinal Inflammation and Colon Cancer*, 2 years, \$99,940 • **Jeannette R. Ickovics**, Kresge Foundation, *Community Intervention for Health: A Comprehensive Multi-Sector Approach to Improve Community Health*, 3 years, \$750,000
Melinda Irwin, American Institute for Cancer Research, *Telephone vs. In-person Counseling for Weight Loss in Women with Breast Cancer*, 2 years, \$164,494 • **Suk-Won Jin**, American Heart Association, *Vascular Lumen Formation during Vertebrate Embryo Development*, 1.6 years, \$154,000 • **Beth Jones**, Griffin Hospital, *Physician Training Award in Preventive Medicine*, 3 years, \$19,734 • **Leonard Kaczmarek**, FRAXA Research Foundation, *FMRP Regulation of Slack Isoforms in a Mouse Model of Fragile X Syndrome*, 4 months, \$16,688 • **Arie Kaffman**, Charles A. Dana Foundation, Inc., *Early Life Stress Programs Synaptic Development by Regulating a Novel Innate Immune Pathway in the Developing Mammalian Brain*, 2 years, \$200,000
Harlan Krumholz, Patrick and Catherine Weldon Donaghue Medical Research Foundation, *Hospitalomics*, 4 years, \$933,955 • **Gary Kupfer**, St. Baldrick’s Foundation, *Deep Exomic Sequencing for Familial Cancer Syndromes*, 1 year, \$50,000
Dan Landau, Dana Farber Cancer Institute, *Fellowship Support with Dana-Farber Cancer Institute Grant Agreement*, 2.6 years, \$173,941
Judith Lichtman, University of Medicine and Dentistry of New Jersey, *Carotid Revasculariza-*

tion Endarterectomy vs. Stenting Trial (CREST): Long Term Follow-up, 5 years, \$145,408 • **Nita J. Mahle**, Harry J. Lloyd Charitable Trust, *A Preclinical Study of p45-SHER3: A Putative Metastasis Factor in Melanoma*, 1 year, \$75,000 • **Robert Makuch**, IMD Marketing Consulting Co., Ltd, *Yale University: Drug Registration Program Training*, 2 months, \$64,800 • **Carolyn Mazure**, The Grace J. Fippinger Foundation, *Pilot Project Program: Gender Differences in Cardiovascular Health*, 1 year, \$7,573 • **Ira Milosevic**, Epilepsy Foundation of America, *Impaired Synaptic Vesicle Cycling and Epilepsy*, 1 year, \$45,000 • **Deepak Narayan**, Breast Cancer Alliance, Inc., *Autologous Breast Reconstruction Utilizing Acellularized Cadaver Dermis and Adipose-Derived Pericytes*, 1 year, \$100,000 • **Don Nguyen**, Uniting Against Lung Cancer, *Identifying in vivo Mechanisms of Therapeutic Resistance by Brain Metastasis from Lung Cancer*, 2 years, \$99,998 • **Marcella Nunez-Smith**, Connecticut Health Foundation, *Website Design, Development and Maintenance*, 1 year, \$23,000 • **Kevin C. O’Connor**, Nancy Davis Foundation for Multiple Sclerosis, *Antigen-Antibody Complex in MS*, 2 years, \$150,000 • **Elaine O’Keefe**, Connecticut Association of Directors of Health, *Measuring Quality in Local Public Health Emergency Preparedness: The H1N1 Experience*, 2 years, \$8,561 • **John Persing**, American Society of Maxillofacial Surgeons, *Assessing Neurocognitive Outcomes in Plagiocephaly Using Event-Related Potentials*, 1 year, \$8,000 • **Katerina Politi**, Uniting Against Lung Cancer, *Uncovering New Mechanisms of Resistance to Targeted Therapies using Mouse Models of EGFR Mutant Lung Adenocarcinoma*, 2 years, \$100,000 • **William Rosenblatt**, Society for Airway Management, *Use of Expiratory Ventilatory Assistance during Transtracheal Jet Ventilation*, 1 year, \$5,774 • **Nicola Santoro**, American Heart Association, *The Role of Hepatic De Novo Lipogenesis (DNL) in the Pathogenesis of Hepatic Steatosis in Obese Children and Adolescents*, 2 years, \$110,000 • **David G. Schatz**, U.S.-Israel Binational Science Foundation, *Regulation of V(D)J Recombination by a RAG-1-MDC1 Interaction*, 4 years, \$28,000 • **Hao Shi**, Muscular Dystrophy Association, *Role of MKP-5 in Duchenne Muscular Dystrophy*, 3 years, \$180,000 • **Mark Shlomchik**, Lupus Research Institute, Inc., *Generation of SmD-Specific TCT Transgenic Mice*, 3.1 years, \$300,000 • **Gerald I. Shulman**, The Danish Agency for Science, Technology and Innovation, *Unraveling the Paradox of Selective Hepatic Insulin in Type 2 Diabetes*, 1 year, \$6,877
Frederick J. Sigworth, University of Washington, Seattle, *Structures of Membrane Proteins in Membranes: Cryo-EM Study of HCN Channels*, 4.7 years, \$12,394 • **Matthew W. State**, Simons Foundation, *Whole Exome Sequencing of Simons Simplex Trios*, 1 year, \$2,763,523 • **Mario Strazabosco**, *Partners Seeking a Cure*, *Pathogenesis of PSC: Role of TGR5 in the Regulation of the Innate Immune Response in the Biliary Epithelium*, 2 years, \$40,000 • **Diana Vesely**, Arthritis Foundation, *Langerhans Cells: Induction of T Regulatory Cells and Lyme Arthritis*, 1 year, \$50,000
Xiao-Jing Wang, The Swartz Foundation, *Swartz Initiative in Theoretical Neurobiology at Yale: Postdoctoral Support*, 1 year, \$55,000
Stephen Waxman, Paralyzed Veterans of America, *Role of Glial Scarring after Injury to the Central Nervous System*, 2 years, \$241,391



COURTESY OF THE NATIONAL ACADEMY OF SCIENCES

with single-ventricle defects. After six or more years of follow-up, all the children who received these grafts in Japan are doing well.

In 2007 Shinoka came Yale, which he calls “an ideal place for me to work,” to continue refining the technique with Breuer. After four years of testing their tissue-engineered blood vessels in the lab, the two surgeons set out to obtain the FDA approval that led to the September operation at YNHH.

“By seeding these cells onto the scaffold,” Breuer says, “we can actually induce the body to regenerate a blood vessel or grow a blood vessel, just like a salamander can regrow its tail or a starfish can regrow one of its arms.”

Unlike synthetic grafts, which must be either deliberately oversized to accommodate a child’s growth or replaced in risky repeat operations as a child develops, the tissue-engineered vessels seem to grow right along with the child. As the scaffolds dissolve and are replaced by collagen, the grafts

develop the same cell layers seen in natural veins. Breuer and Shinoka presumed that stem cells in the bone marrow they used must be the source of those cell layers, but “we began to study how these grafts actually formed,” says Breuer, “and we surprised ourselves.”

In the lab they noticed that almost all bone-marrow cells had disappeared from the graft after a week. Yet during those crucial first few days, they learned, the stem cells were using molecules normally seen in inflammation to signal cells to leave nearby blood vessels and start building a new vessel around the scaffold (see illustration). What the surgeons were witnessing was, in essence, vein regeneration.

Breuer, who directs the medical school’s tissue engineering program, first became interested in tissue engineering trying to create an intestinal graft that could be transplanted into babies who had lost portions of their bowel to the lethal disease necrotizing enterocolitis. Though surgeons can

save some of these babies by removing portions of dead bowel, many do not survive, and he hoped to be able to engineer replacement tissue that could save their lives. But a year’s worth of bowel experiments led nowhere, Breuer says, so he turned his attention instead to blood vessels and heart valves, which are structurally simpler tissues. Within a year he was able to prove it was feasible to tissue-engineer a blood vessel.

When he came to Yale in 2003 after fulfilling a military service obligation in Afghanistan, where he says he found a “very fertile environment” in which to resume his research.

The child treated in August is doing well, and Shinoka and Breuer now aim to implant the grafts in six more children, carefully documenting the grafts’ growth using MRIs, and monitoring the children for complications. As they decipher how the signaling molecules that are sent out by bone-marrow cells help to form the grafts, they hope one day to be able to skip

Pediatric surgeons Christopher Breuer and Toshiharu Shinoka seed biodegradable tubular scaffolds with bone marrow cells to engineer new blood vessels for children. The bone marrow cells disappear quickly, but first stimulate an inflammatory response that attracts immune cells to the graft (left). In turn, the immune cells attract epithelial and smooth muscle cells to the dissolving graft (middle) that eventually form the new vessel (right).

the bone-marrow step entirely, creating an “off-the-shelf” graft.

While they cautiously designed the current graft to be used in a low-pressure area of the heart, they hope to engineer arteries and valves that can withstand higher blood pressures and turbulence. Such grafts could improve on existing technology for dialysis catheters or cardiac bypass operations. But they could be lifesaving in more difficult-to-treat forms of congenital heart disease by preventing the need for dangerous replacement surgeries in growing children. “That,” says Breuer, “is where our work could potentially have the biggest impact.”

// Class of ’61 (from page 1) After an initial meeting in early 2011, the alumni and their wives decided to devote themselves to raising funds for a 50th reunion gift to YCC. In the following months, before their June reunion, they began soliciting the roughly 850 classmates they were able to reach.

“Astoundingly,” says Cantor, “we got donations from 116 class members in a very short period of time.” Of these 116, nine were widows of class members, some of whom had died after fighting cancer, Cantor says. In the end, the class’s unique effort raised about \$1.2 million for YCC.

A general fundraising effort had already begun under Teti’s leadership by the time the YCC idea was born, but when Cantor told classmates who had already made pledges about the new plan, a number increased their pledges. “There are people who doubled their pledges,” Cantor says. “There are people who have a history of giving a hundred dollars to Yale who gave five thousand for this initiative.”

Cantor wasn’t surprised that his class embraced this unique idea,

because the class itself is special, he says. Yale College classes typically gather once or twice every five years, but the Class of 1961 gathers somewhere in the U.S. twice each year. “As a result we’ve developed incredibly warm feelings for each other as a class. I experienced that during my wife’s illness, and in the way my classmates and their spouses reached out to me [after her passing on July 7],” Cantor says. “We are our own community of support.”

The money raised by the class now comprise two separate funds: the Class of 1961 Yale Cancer Center Initiative, and a smaller endowment—about \$175,000 at present—called the Cantor-Smith Cancer Research Fund, named by classmates in honor of Cantor and classmate DeForest W. “Frosty” Smith, for their long-standing commitment to their class and to Yale.

And the campaign is not over, says Cantor. “Even though campaigns usually stop at the time of a reunion,” he says, “this one can’t stop. It has too much momentum, and it’s too important. We’re going to continue to run with it.”



Edward Cantor of the Yale College Class of 1961 (left) is one of the leaders of an effort to raise money for cancer research at Yale to mark the class’s 50th reunion. Two new endowments, funded with more than \$1 million in contributions from the class, will fund research at Yale Cancer Center (YCC) under the leadership of YCC Director Thomas Lynch (right).

HAROLD SHAPIRO

Both funds will be used at the discretion of YCC Director Thomas J. Lynch Jr., M.D., the Richard Sackler and Jonathan Sackler Professor of Medicine and physician-in-chief at Smilow Cancer Hospital. An authority on lung cancer, Lynch is a pioneer in “personalized” cancer therapies, in which individual patients’ treatments are customized for maximum effectiveness by analyzing small differences in their genomes or in the genetic makeup of their tumors.

“Donors to the Class of 1961 Yale Cancer Center Initiative and the Cantor-Smith Cancer Research Endowment are playing a pivotal role in our research enterprise,” says Lynch. “Their generosity allows me to make meaningful investments in translational cancer research projects led by our exceptional faculty. That the Class intends to continue their support of Yale Cancer Center over time means each year we will conduct more research that leads to cures.”

Expert on immune responses to viruses wins the Eli Lilly Award

Akiko Iwasaki, PH.D., professor of immunobiology and of molecular, cellular, and developmental biology, is the recipient of the 2012 Eli Lilly and Company Research Award. The oldest and most prestigious prize of the American Society for Microbiology (ASM), the award honors “fundamental research of unusual merit in microbiology or immunology by an individual on the threshold of his or her career,” according to the ASM website. The award, given continually since 1936, will be presented in June 2012 at the ASM General Meeting in San Francisco, where Iwasaki will deliver the Eli Lilly Award Lecture.

Iwasaki’s widely published research focuses on the mechanisms of virus recognition and their link to adaptive immunity, particularly at mucosal surfaces, with an aim toward

understanding how immunity is created and maintained at mucosal surfaces. Iwasaki has conducted extensive research on immune responses to herpes simplex viruses in the genital tract and influenza infection in the lung. Recently, her team has analyzed the ways in which autophagy—a catabolic process in which cells degrade their own components—mediates immune responses to viruses. Her lab’s goal is to use the knowledge gained through research to design vaccines or microbicides to prevent viral and bacterial infection.

Iwasaki’s past honors include the Wyeth-Lederle Vaccines Young Investigator Award in Vaccine Development, the Burroughs Wellcome Fund Investigator in Pathogenesis in Infectious Diseases, and the BD Biosciences Investigator Award from the American Association of Immunologists.

Iwasaki received her doctorate from the University of Toronto in 1998, and joined the School of Medicine’s faculty in 2000.



Akiko Iwasaki

Chair of Department of Surgery to be next president of society of endocrine surgeons

Robert Udelsman, M.D., M.B.A., chair and William H. Carmalt Professor of Surgery and surgeon-in-chief at Yale-New Haven Hospital, is the president-elect of the International Association of Endocrine Surgeons, a global society of more than 400 surgical specialists.

Udelsman’s innovations have made Yale one of the world’s premier centers for the surgical treatment of primary hyperparathyroidism (PHP), an uncommon disease in which one of the parathyroid glands in the neck enlarges and produces too much hormone. Too much parathyroid hormone (PTH) causes bone loss, kidney stones, and other health problems.

Surgery for PHP usually requires general anesthesia and a hospital stay of several days. In Udelsman’s approach, now adopted by other

endocrine surgeons at Yale, the patient receives local anesthesia and only a small incision is made. Because PTH levels must drop sufficiently for surgeons to be confident that the treatment will be successful, at Yale a lab technician stationed in the operating room checks hormone levels immediately, rather than sending a blood sample to another part of the hospital. The entire procedure typically takes half an hour, and the patient returns home the same day.

Udelsman, who joined the Yale faculty in 2001, received his M.D. from the George Washington University School of Medicine and Health Sciences in 1981 and completed his surgical residency at The Johns Hopkins Hospital, where he was chief resident. He also completed fellowships in surgical oncology at the National Cancer Institute, in endocrinology at the National Institute of Child Health and Human Development, and in gastrointestinal surgery at The Johns Hopkins Hospital.



Robert Udelsman

// Free radicals (from page 3) In their most recent work, published in the August issue of *Nature Medicine*, the Diano and Horvath team show how this pathway goes awry in animals that overeat. These animals’ bodies, the researchers found, start to generate cellular organelles called peroxisomes that eliminate ROS from cells, so the ROS molecules no longer build up enough to signal satiety. “The body adapts and you can no longer feel satiety anymore,” Horvath says.

But fortunately this effect is reversible. When the scientists blocked peroxisome function in mice on a high-fat, high-carbohydrate, “junk food” diet and simultaneously increased the

amount of ROS in the neurons, “the neurons became active again, and the animals stopped eating,” says Diano.

The new research suggests that perhaps we shouldn’t rush to rid our bodies of free radicals. Sometimes they’re necessary, and Shadel says the next step is to devise new ways to keep free radicals in balance without losing their benefits. “Yes, there are many diseases caused by reactive oxygen species, and in those circumstances, antioxidants are beneficial,” he says. “But now we’re seeing other cases where they can be detrimental. There’s a sweet spot to hit where you’re eliminating stress but not normal signaling.”

Four School of Medicine scientists receive NIH Director’s Awards

Four School of Medicine faculty members have been named recipients of this year’s National Institutes of Health (NIH) Director’s Awards.

Megan C. King, PH.D., assistant professor of cell biology, and Christian D. Schlieker, PH.D., assistant professor of molecular biophysics and biochemistry, are recipients of New Innovator Awards, each worth \$1.5 million for five years. James F. Leckman, M.D., Neison Harris

protein folding, particularly in instances when mutations of proteins in the membrane of a cell’s nucleus cause diseases like the progeria syndromes, in which children experience symptoms of rapid aging. Schlieker and members of his lab study how these proteins are repaired or degraded in the nuclear envelope. Understanding this process may one day lead to new treatments for viral infections as well as the



Megan King



Christian Schlieker



James Leckman



Bruce Wexler

Professor of Child Psychiatry, and professor of psychiatry, psychology, and pediatrics, and Bruce E. Wexler, M.D., senior research scientist and professor emeritus of psychiatry, are joint recipients of a Transformative Research Award, worth approximately \$4 million over four years.

New Innovator Awards are meant to support “exceptionally creative new investigators who propose highly innovative projects that have the potential for unusually high impact.” In comparison with traditional NIH grants, the New Innovator Awards are designed to support research projects that are at an early stage and may lack the preliminary data usually required for the mainstays of NIH funding known as R01 grants.

King, whose project is titled “The Role of Nuclear Architecture in Adaptation,” studies the interface between the nucleus and cytoskeleton in cells, and the ways in which structural elements of the cell nucleus influence genome stability. In times of stress, greater flexibility of genetic mechanisms may promote adaptation.

King is studying how nuclear compartmentalization influences the balance of genome stability and adaptability through mechanisms such as DNA repair. Understanding these processes may help determine how some organisms become pathogenic, and may lead to new ways to fight infectious disease.

King was also named one of fifteen Searle Scholars for 2011 by the Searle Funds at the Chicago Community Trust, which supports the research of promising young scientists in the chemical and biological sciences who have recently been named assistant professors on a tenure-track appointment.

Schlieker’s project is called “Deciphering Novel Protein Quality Control Pathways in the Nuclear Periphery.” A biochemist, Schlieker focuses on the mechanisms of

wide assortment of musculoskeletal and neuronal disorders collectively called nuclear envelopopathies.

The Transformative Research Award initiative was created “to support exceptionally innovative and/or unconventional research projects that have the potential to create or overturn fundamental paradigms,” and typically supports risky work with little preliminary data that may not fare well in standard grant applications.

Leckman and Wexler’s project, “Integrated Brain, Body, And Social Intervention for ADHD,” explores an innovative and non-pharmacologic treatment for attention-deficit hyperactivity disorder (ADHD) that emphasizes a combination of cognitive and physical exercises designed to “cross-train” the brain. The physical component of the intervention was developed by Jinxia Dong, PH.D., professor of Physical Education and Sport Sciences at Peking University and a former national gymnast. The grant will fund a trial of the new treatment program in schools in both Hamden, Conn., and Beijing, China.

Leckman served as director of research at the School of Medicine’s Child Study Center for 25 years. He studies Tourette syndrome, ADHD, obsessive-compulsive disorder, and autism. In 2007, the Brain and Behavior Research Foundation (formerly NARSAD) awarded him the Ruane Prize for Outstanding Achievement in Child and Adolescent Psychiatric Research for his work on the causes, pathophysiology, treatment, and prevention of severe child psychiatric illness.

Wexler has been a pioneer in the effort to harness neuroplasticity in new treatments for the incapacitating cognitive deficits associated with major mental illnesses. Yale has applied for multiple patents for the computerized cognitive exercises he has developed to engage and promote development of under-functioning neural systems.