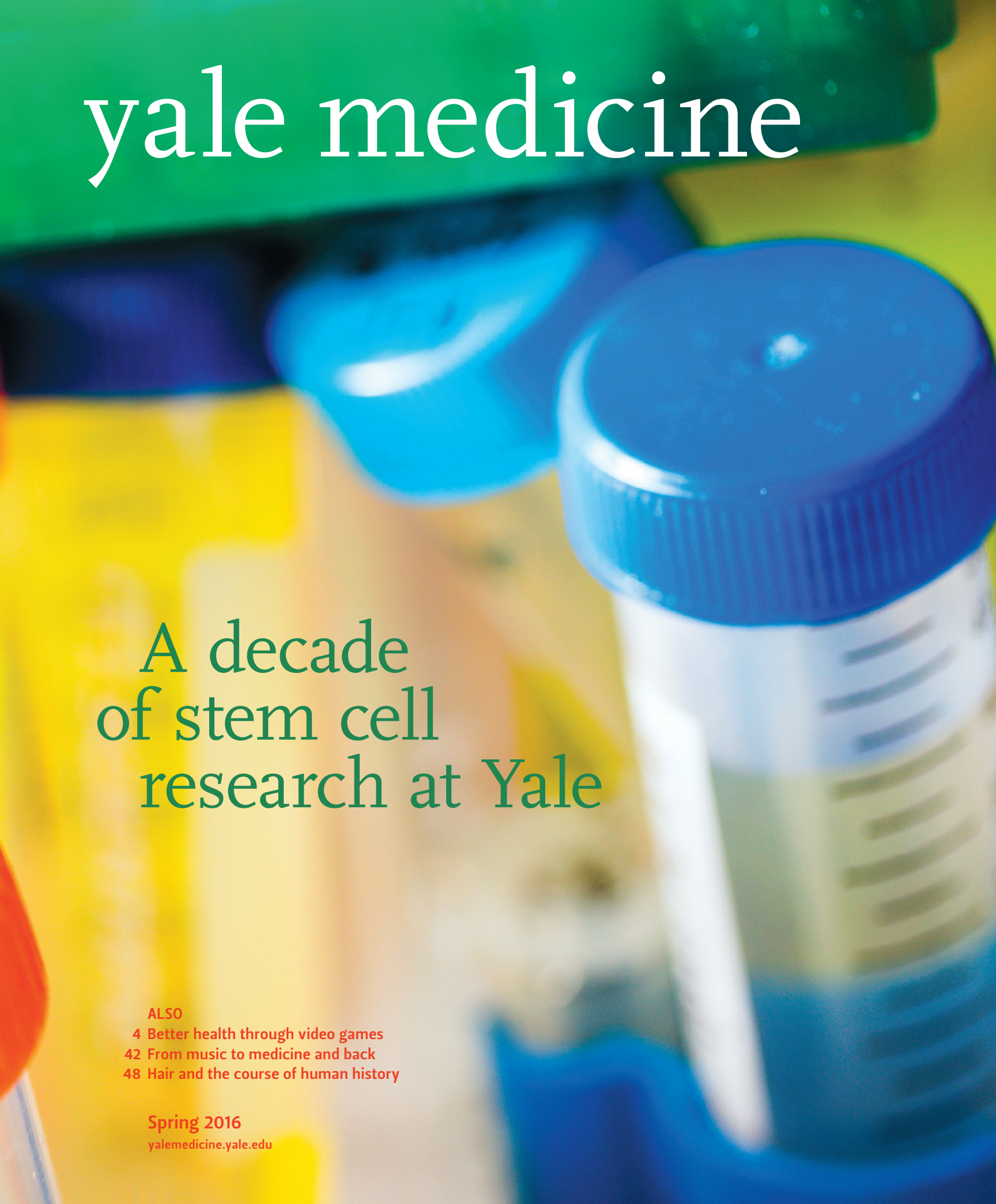
yale medicine



A decade of stem cell research at Yale

ALSO

Spring 2016
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Features

spring 2016 departments

from the editor

In recognition of 10 years of stem cell research at Yale, we have devoted this issue's feature section to the Yale Stem Cell Center. Elsewhere in the magazine, you'll find stories about ways in which our faculty, residents, and alumni are advancing medicine or exploring history.

Observing teenagers' obsession with video games prompted Lynn Fiellin, M.D. '96, HS '00, to wonder whether she could harness that fascination to impart messages about health behavior. Working with researchers, designers, educators, and community partners, she has developed a game that puts a virtual character into risky situations involving HIV, tobacco, and drug use.

By the time he got to medical school, Eliezer Sternberg, M.D., had already written two books about the mind. Now the first-year resident at Yale New Haven Hospital has written a third, about how behavior that might seem strange to most of us can make perfect sense to others. "Our brain is always trying to create a narrative of our lives," says Sternberg.

Hair, writes Kurt Stenn, M.D., a pathologist and dermatologist who spent 20 years on the School of Medicine faculty, has affected culture, psychology, and even global trade. When the European beaver population was decimated to meet the demand for beaver hats, European explorers and trappers crossed North America in search of the pelts. In his book, *Hair, A Human History*, Stenn starts by explaining why humans alone, of all primates, shed their body hair.

These and other stories await you in *Yale Medicine*. We hope you enjoy this issue.

John Curtis
Editor, Yale Medicine

SECOND OPINION
BY SIDNEY HARRIS

Send letters and news items to

Yale Medicine, 1 Church Street, Suite 300, New Haven, CT 06510 or email ymm@yale.edu. Please limit letters to 350 words and include a telephone number. Submissions may be edited for length.

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Yale SCHOOL OF MEDICINE

A decade of stem cell research at the School of Medicine

GERMAN BIOLOGISTS first named and described stem cells late in the 19th century. More than 100 years later, scientists continue to rely on these cells to unlock puzzles of the origins of human development and to advance clinical treatment for diseases that were once considered incurable. A decade ago, the Yale Stem Cell Center opened its doors to pursue that field of research.

Yale Medicine spoke with Dean Robert J. Alpern, M.D., Ensign Professor of Medicine, about the importance of human stem cell research and why much in the field remains to be explored.

Why did you decide to open the Yale Stem Cell Center in 2006? Stem cells represented a new area in biology with extraordinary potential to transform medicine. Understanding human embryonic stem cells has provided insights into many areas of biology, including development, tissue regeneration, and cancer. It is too early to know the full impact that understanding stem cells will have on medical care, but progress has been impressive.

Why is it important to study stem cells? Stem cells have enormous potential to replace damaged tissue. Research on stem cells provides insight into development and developmental anomalies. In addition, we are now learning that with many cancers, it is the stem cells that are the real culprits.

Which aspect of stem cell research do you see changing most rapidly in the next five years? There will be continuing progress on many fronts. We must perform high-quality research that leads to a thorough understanding of the biology of stem cells so that they can be used therapeutically with maximal efficacy and safety.

Stem cell research became politicized early on, partly due to the use of human embryos. Have we moved past the politics? If not, how can we? I am not sure that we have moved past the politics. There will always be ethical issues related to human embryonic stem cells and we must pay careful attention to these concerns. We should also keep dialogues open across a diverse group of individuals, from physicians to bioethicists to cell biologists, who contribute knowledge and guidance to the field.

ROBERT J. LISAK PHOTO

Better health through video games

NINETY-SEVEN PERCENT OF YOUNG AMERICANS—including the five children of Lynn E. Fiellin, M.D. '96, HS '00—play video games. According to the Entertainment Software Association, the industry's top trade group, 155 million Americans play video games with names like *Call of Duty*, *Grand Theft Auto*, and *Madden NFL 15*. What if, thought Fiellin, associate professor of medicine (general medicine) and in the Child Study Center, she could harness that fascination with video games to teach adolescents to avoid risky behaviors that could lead to HIV infection or drug addiction?

While there is a long-standing debate about the negative effects of video games (they're sedentary, they encourage obesity, they can be addictive), the use of games to promote health is growing. Studies have shown that video games can deliver health promotion and interventions, and pharmaceutical companies, nonprofits, foundations, and the National Institutes of Health are exploring these possibilities. With a grant from the National Institute of Child Health and Human Development, Fiellin has assembled a team of researchers, game designers, community partners, and educators to create *PlayForward: Elm City Stories*. The tablet-based game consists of 16 hours of play in which teens in after-school, school-based, and summer programs create a virtual character who faces risky scenarios—like taking a relative's prescription pills—to explore possible outcomes based on their actions and how those actions might affect their future. *Elm City Stories*, along with three other games designed to prevent tobacco and marijuana use, HIV infection in young women, and substance abuse in teens, emerged from the lab that Fiellin created in 2009. play-2PREVENT (p2P)

Now, Yale has launched the Center for Health & Learning Games, which will will house the p2P lab and partner with departments across the university and organizations nationwide to create and test additional games aimed at changing health behaviors and improving science, math, and other skills. The center will also offer training in game design in these areas. "While other schools have programs for developing games, this is the first I know of at a medical school and the first, I believe, that's trying to fuse best practices for learning games and games for behavior change, which are often found in separate silos," said Ben Sawyer, co-founder of the game consulting firm Digitalmill and a pioneer in the field of "serious" games—games designed for purposes other than entertainment. Marientina Gotsis, co-founder and director of the University of Southern California Creative Media & Behavioral Health Center, a research unit between the School of Cinematic Arts and the Keck School of Medicine, said that although some academic collaborations have produced games in health in the past eight years, none have led to the creation of formal centers or research units.

Although newly established, the center's work is well underway. Fiellin and deputy director Kimberly Hieftje, Ph.D., associate research scientist in medicine (general medicine), have established partnerships with pediatricians, emergency room physicians, obstetrician/gynecologists, and others. The center is collaborating with Yale's math department, educational games developer Yogome, and Amplify, an educational services company that is testing learning games in India in collaboration with The Global Education & Leadership Foundation. The center is also partnering with Peer Health Exchange, a national organization that teaches health education to high school students, to conduct implementation pilot studies to examine the integration of the game into their curriculum. In addition, Fiellin and her team will work with the Tobacco Centers of Regulatory Science (TCORS) at Yale and at USC, modifying their *PlayForward* game to collect data from teens on their attitudes, perceptions, and knowledge of e-cigarette and other tobacco product use.

The center grew out of Fiellin's conviction that there is a need both for games that foster learning and behavioral change and for research that shows that this approach works. It's not enough to develop a creative game with educational content, as Fiellin and her team found out when they created *Elm City Stories*. They hired a leading game design firm, Schell Games of Pittsburgh, Pa., to help them develop the game. While the partnership was successful from the start, both sides found it challenging to develop a game that would engage players and spark behavior changes that would lead to a reduced risk of HIV infection. So they drafted a series of game playbooks, guidebooks that incorporate established psychological theories into the gameplay. For example, minigames—games within the larger game—encourage players to consider their future goals and aspirations, learn to assess situations and think ahead, acquire knowledge (like debunking the myth that you can't get pregnant the first time you have sex), navigate peer relationships, and prioritize in order to maximize long-term benefits. "Our work is very much based in science," said Fiellin. "Just like any science project, you need a lab manual to help you get a good result." Now they use this approach for all of their games, which they then test in randomized controlled trials. "There have to be some data behind this," noted Fiellin. "You wouldn't want your child taking a medicine that hasn't been tested."

The Yale center will build and test prototypes and then present

Lynn Fiellin and a team of researchers, designers, community partners, and educators have created a video game that will help teens learn to navigate risky scenarios like drug use. Research shows, says Fiellin, that this approach can affect behavior.

JERRY DOMIAN PHOTO

ONLINE EXCLUSIVES

Since 2011, school faculty and administrators have tried to make things a little easier for young scientists with a Junior Principal Investigator Retreat that helps them build their organizational skills.

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them to game developers for final full development, in much the same way that biotech companies manufacture drugs and devices developed in academia. "It will be a research and prototyping factory rather than a full-fledged game factory," said Sawyer, who has worked with Fiellin since the beginning.

The center will also provide increased training around game design as a structured educational experience. The p2P lab, which will be incorporated into the center, has already worked with more than 25 interns and trainees, ranging from high school students to postdoctoral associates. These activities will be expanded, and discussions are underway to develop classes on the psychological constructs of games as well as other topics.

Using technology to improve access to care—especially with such hard-to-reach groups as adolescents is a powerful concept, according to Linda C. Mayes, M.D., Arnold Gesell Professor in the Child Study Center, who has worked with Fiellin on adapting games for children. Access to games that are well constructed and engaging may be better yet. "Playing a good game is like reading a good novel," said Hieftje. "It can have a lasting impact."

—Jill Max

»

Even irrational behavior has its logic

Schizophrenics who hear voices. An otherwise rational teacher who insists she was abducted by aliens. A woman with multiple personalities.

Most of us, including many physicians, would consider these people "crazy."

Eliezer J. Sternberg, M.D., a first-year neurology resident at Yale New Haven Hospital, begs to differ. Their behaviors may be strange, but they are not necessarily illogical, Sternberg wrote in his recently published book, *NeuroLogic: The Brain's Hidden Rationale Behind Our Irrational Behavior.*

"A lot of Oliver Sacks-type stories seem so crazy on the outside,"

Strange behaviors may not be illogical, says Eliezer Sternberg, a first-year neurology resident. His new book explains that a damaged brain may compensate in ways that seem logical to the patient, if not to the rest of the world.

WILLIAM K. SACCO PHOTO

he said. "But often, if you find out exactly what the defect is, exactly the brain problem, it's almost as if their behavior is a logical compensation for a really unfortunate circumstance."

Take schizophrenia. Hearing voices is the ultimate in irrationality, but schizophrenics don't recognize the voices in their heads as their own, Sternberg said. Faced with the irrational, their brains draw a logical, if false, conclusion: The voices are those of the FBI, or God, or aliens.

"How would your brain explain that to you?" Sternberg said. "If you are the kind of person who is paranoid about the government, then government paranoia might overtake you. That would make sense to you and give you closure."

Schizophrenia is just one of many neurological disorders or phenomena—both mundane and unusual—that Sternberg explains in his book. He tackles everything from why we forget to buy milk on the way home and whether visualizing golf improves your score to whether someone can be hypnotized to commit murder and why people believe in alien abductions. Along the way, Sternberg discusses such obscure and unusual disorders as Anton's syndrome, in which blind people do not realize they have gone blind. He explains how the damaged brain compensates in ways logical to the sufferer, if not to the rest of us.

A second theme is the mind's relentless striving to make sense of the world and maintain a sense of self. What appears delusional is the brain's way of compensating for a deficit or illness, he said. "Our brain is always trying to create a narrative of our lives and give us a story, give us a history, give us a purpose," Sternberg said.

The 28-year-old Sternberg has been fascinated by the brain his entire life. *NeuroLogic* is not his first book. The Buffalo, N.Y., native had already written two volumes on the mind, the first when he was a 17-year-old high school junior, the second as an undergraduate at Brandeis University.

Driving him is the question of how a mere collection of cells—the human brain—can have consciousness and autonomy. "We are all made up of the same matter that everything else is," Sternberg said. "But human beings are the only collections of matter that reflect on their own existence. What is it that makes that possible?"

He wrote the first three chapters of what became *NeuroLogic* during a gap year he took from Tufts University School of Medicine to do research. Inspired by the popular economics book *Freakonomics*, Sternberg wanted to write a book for a general audience that didn't shortchange the science of the brain. To his surprise, several publishers loved his proposal. Once he had settled on a publisher, Sternberg finished the book in his last year and a half of medical school. How did he do it? By composing most of the book in 10- to 15-minute increments snatched from his studies. "I am good at doing a lot with a very little amount of time without losing momentum," he said.

The book was released in early January by Pantheon with a print run of 25,000 copies and has been reviewed in *The Washington Post*.

After completing his training, Sternberg, who dedicated his book to his wife, Sharona, and their 2-year-old son, Alex, wants to go into practice and do research. He also plans to write more books, possibly about epilepsy or comas.

Physicians should speak more often to a popular audience to prevent the spread of such dangerous misinformation as unfounded fears about childhood vaccines, Sternberg said. "People in medicine are really good at talking to each other but not as good at talking to the general public," he said. "I think that's a big problem, because some of the biggest speakers on medical issues have no medical training and say things that are really, really damaging."

—Christopher Hoffman

Treating psychosis early

For those who think the current U.S. mental health care system passes muster, Joel Roberts proposes this question: "Do we tell a patient with stage 2 cancer to wait and come back when it's stage 4?" When a mental illness led his college student son to the emergency

ONLINE EXCLUSIVES

On September 11, 2001, Melissa Thomas was a sophomore at West Point. Just over four years later she was at a forward operating base north of Baghdad. In January she told her story as part of a new lecture series, Student Voices.

Full stories and event photo galleries, as well as other online-only content, can be found on our home page at yalemedicine.yale.edu.

room, Roberts, of Fairfield County, Conn., researched treatment options across the country. Roberts, whose name has been changed to protect his family's privacy, found that most programs targeted patients in severe, prolonged crisis.

According to Vinod H. Srihari, M.D., associate professor of psychiatry, few people receive timely treatment after their first episode of psychosis. The reasons can include a combination of factors related to the patient or the family's awareness of a need for care, how to access professional care, and a lack of youth-oriented services.

Srihari wants to change these norms. "Patients may lack insight into their need for treatment, or, as is common to many youth, make poor choices around seeking help," he said. He believes that savvy marketing via mass and social media channels could help. Two teams at Yale and Harvard are testing this approach through a five-year clinical trial funded by the National Institutes of Health. The trial tests the ways in which patients are recruited: traditional referrals or a campaign that includes media messaging, professional outreach, and a rapid response to calls for help. In 2014, the trial's baseline year, both teams recruited via tried-and-true referrals from mostly traditional clinical settings.

Harvard Medical School's Prevention and Recovery in Early Psychosis clinic serves as

Vinod Srihari believes that patients with psychosis often don't receive the treatment they need early enough. A new program will help determine if a savvy marketing plan will help.

the trial's control and continues to recruit through referrals. At Yale, Srihari's team emphasizes early detection through advertising—he hired a New Haven-based marketing firm, Red Rock Branding, to pitch a local awareness campaign on psychosis, a mental disorder that includes hallucinations, paranoia, and delusions.

The opportunity pushed Red Rock's founder, Glen McDermott, and his team into uncharted territory. "Focusing on a small target population—100 of 400,000—that is confronting a confusing and sometimes scary set of experiences that are often stigmatized presents a communication challenge beyond the usual marketing strategy," McDermott said. The campaign, called Mindmap, targets women and men ages 16 to 35 in the New Haven area who may suffer from psychosis.

In February 2015, the Red Rock team launched mindmapct.org, a website with a quiz designed to assess symptoms of psychosis. Anyone who suspects they're at risk can call for a free screening by professionals at Yale's Specialized Treatment Early in Psychosis clinic. If they qualify, they can join the trial. McDermott collects metrics through the website, Facebook, and Twitter to determine how people arrive on the quiz page. When potential patients call for a phone assessment, the Yale team verifies which channel led them to the hotline. Recently Red Rock began hiring "Mindmap activists" to help refine and deliver the message, McDermott said. This cadre will share their own mental health journeys at events, write blog posts, and lead local workshops about psychosis.

Final results won't be available for some time, but Srihari has noted a correlation. Since the campaign's start, calls to the free screening hotline at Yale climbed to 150, a 65 percent increase over the baseline year. Of those evaluations, a total of 38 patients enrolled in treatment at STEP.

What excites Roberts, a volunteer advocate for Mindmap, is the campaign's potential to reduce the stigma of psychosis. Roberts wants to rewind back to that dark night on the psychiatric ward with his son. "I wish he could have heard from doctors and nurses that these symptoms are normal for your illness," he said. "What you are experiencing is normal, and you will get better."

—Kathleen Raven

round up

a collection of recent scientific findings

DID A KNOCK ON THE NOGGIN DRIVE HENRY VIII BONKERS?

In the last 10 years of his life, the English monarch suffered from memory lapses, fits of rage, uncontrollable impulses, headaches, insomnia, and perhaps even impotence. According to a paper published in the *Journal of Clinical Neuroscience*, these symptoms may have come from too much jousting. Yale researchers studied Henry VIII's letters and other sources of the time to document his medical history and events possibly related to his ailments. (He died in 1547.) Their findings support the notion that traumatic brain injuries from jousting may have caused the king's problems. Historians, said behavioral neurologist Arash Salardini, M.D., co-director of the Yale Memory Clinic and senior author of the study, point out that the king's behavior changed after a 1536 joust when a horse fell on him and knocked him out. "It is intriguing to think that modern European history may have changed forever because of a blow to the head," Salardini said.

GIRLS AT RISK OF AUTISM MORE SOCIALLY AWARE

Infant girls at risk of autism, a Yale School of Medicine study has found, are more socially aware than at-risk infant boys—they pay more attention to people and their faces. This increased awareness was linked to milder social impairments later on and may provide increased access to critical social experiences in early development. In the study, the first of its kind, 101 infants who have older siblings with autism and 61 infants with no risk of autism watched a video of a woman smiling and cooing while pointing to toys and making a sandwich. A team led by Katarzyna Chawarska, Ph.D., associate professor in the Yale Child Study Center and in the Department of Pediatrics, then tracked what the children looked at and for how long. Chawarska's lab hopes to discover why girls have this social advantage.

MAMMOTH ON THE MENU?

An anthropology professor's curiosity has debunked a myth about the main course at a 1951 dinner at the Explorers Club in New York. The dinner in the Grand Ballroom of the Roosevelt Hotel—which included Pacific spider crabs, green turtle soup, and bison steaks—boasted an entrée supposedly carved from the carcass of a 250,000-year-old woolly mammoth that had been preserved in glacial ice. Even some hungry explorers were skeptical—many thought it was an extinct giant ground sloth, *Megatherium*. By means of an explorer who missed the dinner, leftovers found their way to the Yale Peabody Museum of Natural History. Eric J. Sargis, anthropology professor and curator of mammalogy at the Peabody, along with Yale graduate students Matt Davis and Jessica Glass, and Gisella Caccone of the Yale Center for Genetic Analyses of Biodiversity, decided in 2014 to analyze the cooked meat's DNA through mitochondrial gene sequencing. The verdict? Neither mammoth nor sloth, but green sea turtle.

AGING RISK TAKERS STILL TAKE RISKS

People who take risks in their youth are more likely to continue taking risks when they're older, according to an analysis of more than 44,000 German citizens published in the *Journal of Personality and Social Psychology*. These findings, said Gregory R. Samanez-Larkin, Ph.D., assistant professor of psychology and a co-author of the paper, suggest that risk taking could be a personality trait that remains stable throughout adulthood. Samanez-Larkin and colleagues at the Max Planck Institute for Human Development in Germany and the University of Basel in Switzerland studied subjects ages 18 to 85 who participated for 10 years in a cross-national study. People's willingness to take risks, the study found, depends on both their age and the risky activity. The inclination to take financial risks remains steady until retirement age, while the willingness to trust people doesn't change with age.

CLOCKWISE FROM TOP: ISTOCK PHOTOS (3), INFANT PHOTO COURTESY OF KATARZYNA CHAWARSKA; OPPOSITE PAGE, WILLIAM K. SACCO PHOTO

A decade of stem cell research at Yale

ON THE SECOND FLOOR OF THE YALE STEM CELL CENTER is a machine that Haifan Lin, Ph.D., the center's director, likes to show to visitors. This $1 million metal box can do overnight what less than a decade ago would have taken hundreds of scientists years to accomplish—sequence a human genome. Already, Lin says, this 3-year-old machine is showing its age. Newer machines are even faster.

The machine is crucial to the work to which Lin has devoted his life, the study of stem cells. A decade ago, when the Yale Stem Cell Center was founded, this new field, "the ultimate frontier in biology and medicine," offered untold promise in any number of areas. Stem cells could reveal the secrets of how human bodies develop in the womb. Learning more about how stem cells differentiate and become bone, muscle, and other tissues could yield clues to controlling diseases. Stem cells have been used to test new drugs before they're tried out on patients. And stem cells could generate healthy new tissues and organs to treat disease without provoking an immune response.

Since its founding, the center's scientists have transplanted biomedically engineered lungs and tracheae made from stem cells into mice. They have sought cures for Parkinson's disease in stem cell research. They have studied links between stem cells and stroke. Scientists are trying to use stem cells to create retinal epithelial cells. Research into cancer stem cells could yield a treatment that would stop the disease at its source.

The potential of stem cells seems limitless, and the Yale Stem Cell Center is poised to pursue that promise.

ROBERT LISAK PHOTO

Haifan Lin believes that there is much to learn about the basic science of stem cells. When he launched the Yale Stem Cell Center a decade ago, he wanted to understand the development and biology of stem cells. "The inner working mechanisms of stem cells are still poorly understood," he says.

A chance to lead

Connecticut lawmakers' decision to fund stem cell research reverberates today

BY KATHLEEN RAVEN
PHOTOGRAPH BY ROBERT LISAK

On August 9, 2001, Milton Wallack listened on the radio as then-President George W. Bush announced plans to halt federal funding for certain areas of stem cell research. “I remember it all too well. I’ll never forget that date,” the co-founder of Connecticut Stem Cell Coalition said. A close relative had just been diagnosed with type 1 diabetes, a chronic condition in which the body’s immune system mistakenly attacks and destroys insulin-producing cells. Researchers thought stem cells could one day replace these lost cells.

Bush's mandate—which forced scientists to rely on just a few existing human embryonic stem (ES) cell lines—threatened scientific progress. Researchers prize human ES cells because they are easy to grow in the lab, and have the potential to become almost any cell in the body. Wallack, now a retired dentist in Branford, but always an activist, felt something had to be done.

He met with Yale's Diane Krause, M.D., Ph.D., professor of laboratory medicine, cell biology, and pathology, and Wesleyan University's Laura Grabel, Ph.D., the Lauren B. Dachs Professor of Science and Society, two researchers thinking of working with human ES cells in the state at the time. Gradually, Wallack's coalition expanded to include academics, lawyers, and politicians. In 2005, Wallack asked Paul Pescatello, J.D., Ph.D., then president and CEO of Connecticut United for Research Excellence, an organization formed to promote bioscience in the state, to become co-chair of the Connecticut Stem Cell Coalition. Their goal? Convince the state to provide funding for human embryonic stem cell research. Pescatello, who now leads the Connecticut Business & Industry Association's (CBIA) Connecticut Bioscience Growth Council (as well as the New England Biotech Association), agreed. "We wanted to make it clear that Connecticut would be a safe haven for stem cell research," said Pescatello, a lawyer who became a lobbyist for the biopharmaceutical industry after he lost his brother to glioblastoma.

Despite the controversy surrounding embryonic stem cell research, Pescatello believed that a bipartisan legislative coalition would support it. Working with business and economic development advocates, especially the lobbying team at the CBIA, Pescatello drafted the blueprint for what became Connecticut's stem cell statute. At the time, only California and New Jersey had plans to provide state funding for human ES cell research. Massachusetts' policymakers were debating the issue, but they faced pushback from the Roman Catholic Church, whose influence was decidedly less in Connecticut, Pescatello said. By 2005, Wallack and Pescatello along with their team were ready to take their legislation to the state capitol in Hartford. The proposed bill permitted human embryonic stem cell research and set aside state funding for it, but banned any activity related to human cloning.

PERFECT TIMING

Around the same time that Wallack and Pescatello's team of lobbyists were meeting with state lawmakers, newly appointed Dean Robert J. Alpern, M.D., Ensign Professor of Medicine, and Carolyn W. Slayman, Ph.D., Sterling Professor of Genetics, professor of cellular and molecular physiology, and deputy dean for academic and scientific affairs, asked a strategic planning committee where the School of Medicine should strengthen its research focus. "The medical school had faculty members—some of whom knew each other, some who didn't—who worked with stem cells," Slayman said. "But nobody would have looked from the outside and said, 'Yale is a powerhouse of stem cell research.' It just wasn't true at the time," she said. The committee recommended creating a stem cell center. In 2005, a search began for the new center's director.

Haifan Lin, Ph.D., then a professor at Duke University, stood out among potential candidates, Slayman recalled. While other medical schools had focused on disease-specific research, Lin suggested that the field had far more to learn about the basic biology of stem cells. "How can it be that at cell division (in stem cells), one daughter cell keeps all of its potential, while the other starts off on a process of differentiation?" Slayman said, her eyes widening at the memory of the tantalizing, yet incredibly basic science question that faced the burgeoning field at the time. Lin accepted the position.

Milton Wallack

"When we started this in 2004, people thought I was crazy and they said, 'You'll never get this done.'"

By late spring 2005, the Connecticut legislature's public health committee began reviewing the proposed stem cell legislation. That committee's co-chair, state senator and now U.S. Sen. Chris Murphy, became the bill's key champion, Pescatello said. Former Gov. M. Jodi Rell remembered very little resistance among lawmakers. "The bill was written and drafted about 20 times, then scientific leaders came in to make their case, and we decided this was the course we wanted to take," she said. "It was time to step out front." On June 15, 2005, Rell signed the act into law. The law earmarked $100 million in state funding for stem cell research, at a rate of $10 million per year through 2015. Gov. Dannel P. Malloy recently extended stem cell research funding for $10 million a year through 2018.

LASTING IMPACT

In 2015, researchers at the Georgia Institute of Technology looked at how state funding had affected stem cell research in the few states that had set aside a large chunk of money in the mid-2000s. The team compared California, Connecticut, Maryland, and New York. "In both California and Connecticut, state funding programs appear to have contributed to over-performance in the field," they wrote in *Cell Stem Cell*. Connecticut especially seemed to reap benefits. Approximately 67 percent of human ES cell-related articles published by researchers in the state acknowledged state funding, according to the study.

Essentially no scientists were studying human embryonic stem cells in Connecticut in 2001, and now more than 150 researchers are working on such projects with state funding, Wallack said. At Yale, more than 30 labs work on human ES cell research today.

Both the medical school's stem cell core labs and the University of Connecticut-Wesleyan University Stem Cell Core have relied on state funding. While Yale's core labs provide embryonic stem cell culture, genomic analysis, and imaging services, the UConn core focuses on induced pluripotent stem (iPS) cell technology, said Marc Lalande, Ph.D., who has directed UConn's Stem Cell Institute in Farmington since its opening in 2007. The result has been close collaboration among the three universities in ways that complement one another, Lalande said. "Since this is a state fund, we have had a great collaboration. We have retreats once each semester," he said. "Diane and Haifan are good friends."

In March 2009, President Barack Obama, by executive order, lifted some of the restrictions on federal funding for human ES cells. One year later, UConn scientists contributed four brand-new human ES cell lines to the National Stem Cell Registry maintained by the National Institutes of Health for use by all stem cell researchers. Lalande pointed to the creation of ImStem, a stem cell therapy biotech company founded at UConn, and continued collaborations with Alexion, a biotech that was started by a Yale professor that moved its headquarters back to New Haven earlier this year.

Two years ago, the legislature approved a measure that moved the responsibility of distributing state stem cell research grants from the public health department to Connecticut Innovations, a quasi-public organization that serves as a state venture capital fund and lender. The Connecticut Stem Cell Program has been renamed the Regenerative Medicine Research Fund. This change reflects a broader trend in science, and does not take away the focus from stem cell research, Wallack said.

"When we started this in 2004, people thought I was crazy and they said, 'You'll never get this done,' " Wallack recalled. A self-described optimist who "always sees the glass 110 percent full," Wallack has already set his sights on a concern that weighs on all stem cell researchers who rely on state funding in Connecticut: how to secure the next round of funding after 2018. */yale medicine*

Kathleen Raven is an associate editor at Yale Medicine.

One stem cell or many?

Parkinson's disease once looked like a poster child for stem cell therapy. Researchers knew that the chronic illness started when cells that produced the neurotransmitter dopamine died. Without dopamine, such symptoms as muscle rigidity and tremors emerged. As early as 1990, a team in Sweden transplanted dopamine-producing cells from human fetuses into the brain of a male Parkinson's patient. Two months later, the patient's right arm appeared less rigid, and he could sleep through the night, the researchers wrote in the journal *Science*. Transplanted brain cells, the trial showed, could reverse some of Parkinson's hallmarks. Two more decades would pass before scientists found clues to suggest why the therapy worked. In the meantime, a reliable cell-based therapy for Parkinson's remains out of reach.

When D. Eugene Redmond Jr., M.D., professor of psychiatry and of neurosurgery, began researching Parkinson's in the 1980s, patients had only one main treatment option: a pill called levodopa, or l-dopa, which the brain converts to dopamine. The drawback? While effective early on, the drug eventually stops working, and can cause awful side effects like hallucinations. If a fresh supply of neuronal stem cells began replacing dopamine in a tiny midsection area of the brain, the symptoms could be eliminated and the disease could be considered cured, Redmond said.

Thirty-five years ago, Redmond started his lab on the Caribbean island of St. Kitts. Overrun with vervet monkeys, the island provided Redmond access to primates that can develop Parkinson's symptoms in ways that closely mimic symptoms in humans. The disease can be induced in monkeys by exposing them to the synthetic drug MPTP, a neurotoxin. It kills the dopamine-producing neuronal cells in the brain—humans exposed to the drug also develop Parkinson's symptoms. In 1985, Redmond injected fetal dopamine neurons directly into the monkeys' brains and they improved. This evidence helped support clinical trials in humans that would come later, including the Swedish study. Those neuronal cells, however, could not be grown in vitro, and the use of fetal tissue was and still is controversial.

Redmond and his lab members then tried multiple types of stem cells to see which could work as well as the fetal tissue grafts. Recently, they tried induced pluripotent stem (iPS) cells. These cells, derived from a monkey's skin cell, can be reprogrammed to become stem cells, then turned into dopamine neurons and injected back into the same monkey. Researchers want to use iPS cells as therapy in humans because the body is less likely to reject what it recognizes as its own tissue.

Some monkeys that received iPS cells got better, but not predictably or consistently. Redmond and colleagues wondered whether they'd missed a piece of the puzzle: Were they putting in the right type of dopamine neuron—the cell that they had been transplanting over the years? Or perhaps the transplanted cells were not receiving the correct signals—called growth factors—from surrounding cells.

Genetic sequencing technology could help answer these questions. Historically, A9 dopaminergic neurons, the ones predominantly lost in Parkinson's disease, have been grouped into a single cell class, said Montrell Demond Seay, Ph.D., associate research scientist in psychiatry, who works in Redmond's lab. "If your transplanted neuronal stem cell is not the one doing the real functional heavy lifting, then your replacement therapy will never work," Seay said. With the help of Sherman Weissman, M.D., Sterling Professor of Genetics, and Jennifer Yang, M.D., Ph.D., associate research scientist in genetics, Seay has sequenced about 200 neuronal stem cells from a single monkey. They extracted RNA from the A9 dopaminergic neurons and sent the material off for genetic sequencing. Next, a biostatistician will determine whether there are different A9 neuron cell types. Seay's goal is to sequence 1,000 neurons from five different monkeys. Seay hypothesizes that each A9 cell subtype is linked to a particular function, and therefore to different Parkinson's symptoms. In the future, cell transplants may include only specific subtypes for a more targeted therapy, he said.

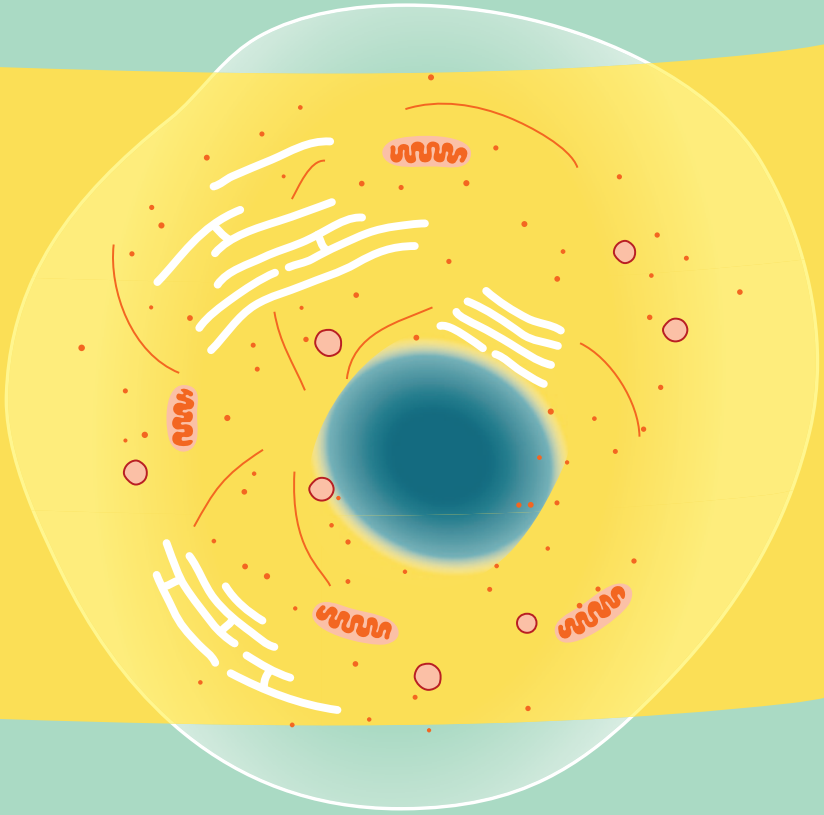
Redmond's lab is also trying to determine which growth factors will guide the organization of neuronal stem cells once they are transplanted. If developmental cues are absent when neurons are transplanted into adult brains, cells may not reach their designated target area. So far, Redmond and his team have tested glial cell line-derived neurotrophic factor (GDNF) as a possible instructional guide for stem cells in monkeys. The stem cells took root in the brains of 10 monkeys, they found, but after 11 months, only a small number of cells had differentiated into adult A9 dopaminergic neurons. To alleviate or cure Parkinson's, enough transplanted stem cells must survive to replace the original dopamine cells that have died and organize themselves within the right place.

Earlier this year, Redmond harvested eggs from the ovaries of 30 monkeys to use in another promising technique in stem cell research: somatic cell nuclear transfer. Redmond and his team will place the nucleus of a skin cell into an egg cell whose nucleus has been removed. The modified egg cell will receive an electric shock to make it divide and reproduce. Ideally, this single cell will form a blastocyst, which contains stem cells. After changing into the right type of A9 neurons, these cells could be implanted into the brain of the monkey that provided the skin cells. Since the cells would be immunologically matched to the donor, enough cells might survive, and the result would be a long-term cure. "A few human patients treated with fetal dopamine cells have recovered and stayed better for periods of 10 or 15 years. I think it's fair to say that there is proof of principle that this strategy will work," Redmond said. "Now we have to create exactly the right cell to do the job reliably and permanently."

—Kathleen Raven

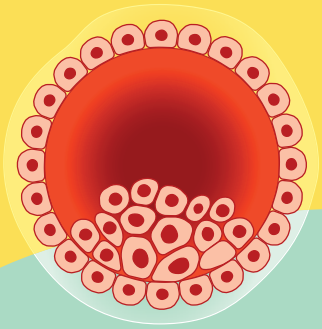
What are stem cells?

Every human being begins as an embryo consisting of a small bundle of stem cells—cells that are born as blank slates, and, when they receive the proper signals, turn into the skin, hair, muscle, blood, and other tissues that make up the human body. These toti- or pluripotent stem cells start with the ability to become any type of cell, but as the human body develops, they take on specific tasks that narrow their ability to differentiate. Five days after a fertilized egg gives rise to an embryo, the embryo's inner mass includes embryonic stem cells (ESCs), which can become any type of cell. As stem cells reach their adult or postnatal state, they are no longer toti- or pluripotent, but may still differentiate into several types of specialized cells.



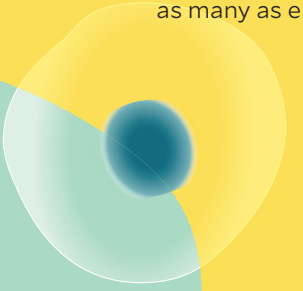
Embryonic stem cells

Embryonic stem cells are pluripotent—they can become any type of specialized cell and reproduce indefinitely. ESCs are created through fertilization but can also be created through somatic cell nuclear transfer: DNA from an adult cell, like a skin cell, is placed into an unfertilized egg whose own DNA has been removed. That new cell can become a blastocyst (a 5-day-old embryo), which then yields embryonic stem cells.



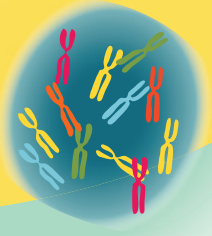
Adult stem cells

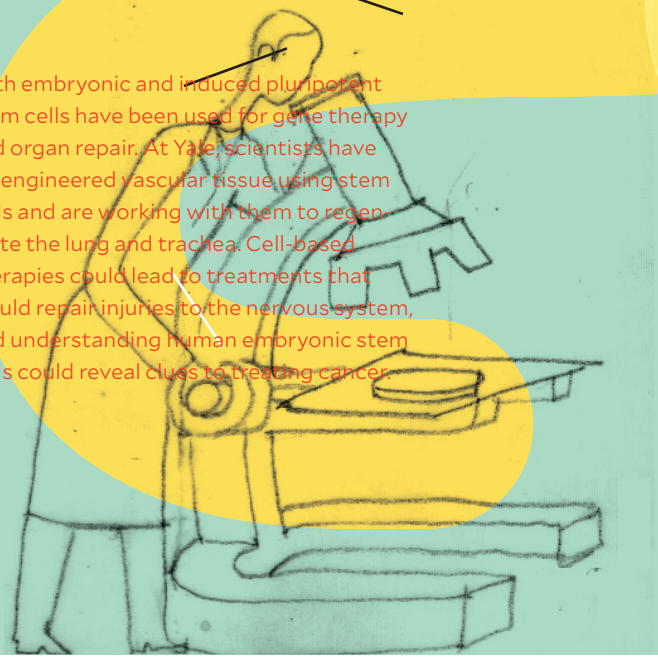
The term adult stem cells is a misnomer—everyone from newborns to the elderly has these postnatal cells, which are also called somatic stem cells. They reside in the brain, eye, muscle, skin, bone marrow, blood, and liver, self-renewing throughout an organism's lifetime and creating new cells to replace old ones. Natural adult stem cells are multipotent—able to turn themselves into several types of stem cells but not as many as embryonic stem cells.



Induced pluripotent stem cell

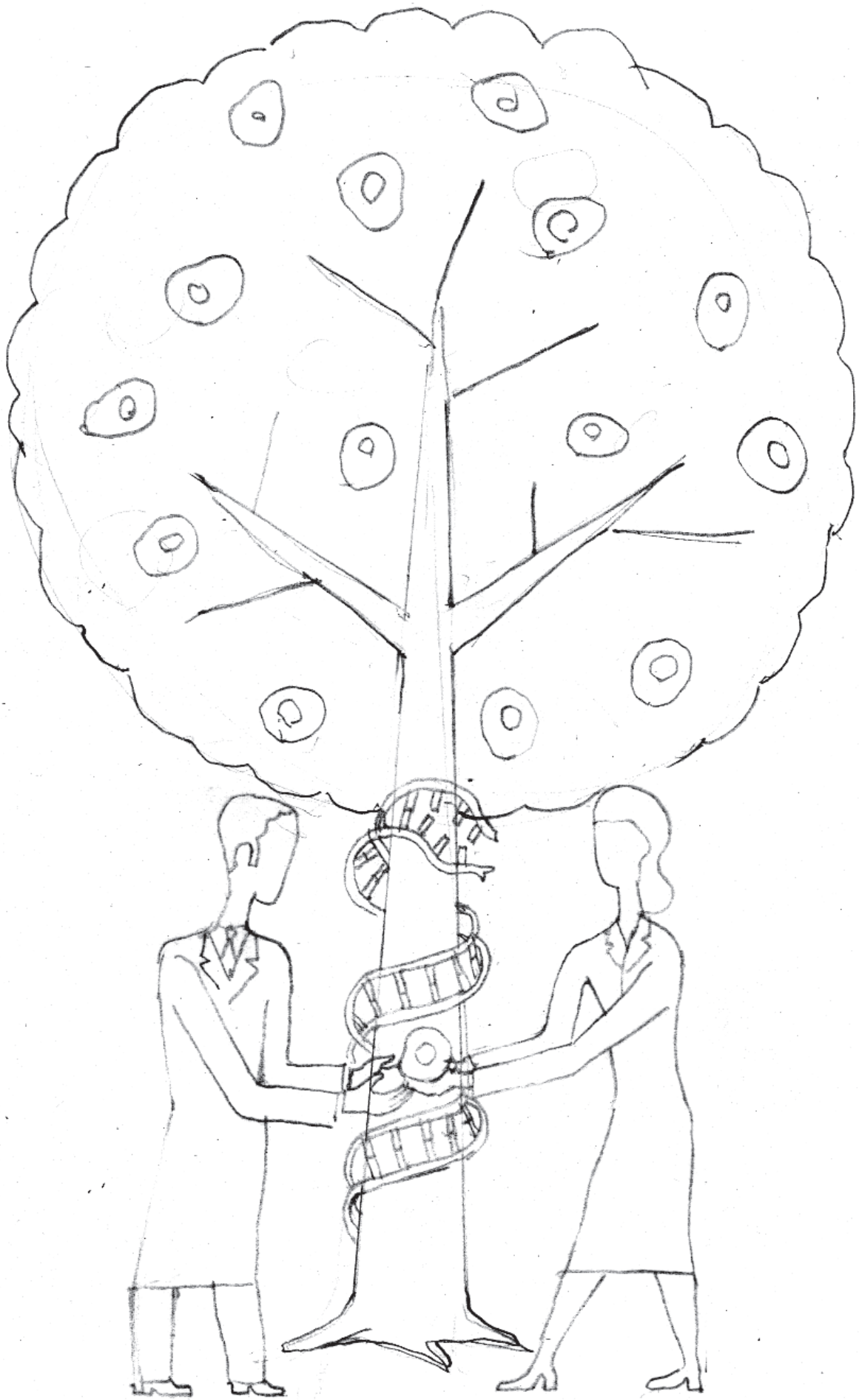
Scientists have learned to tweak adult stem cells, reprogramming them in the lab to make them similar to ESCs in their ability to differentiate. Induced pluripotent stem cell lines are adult stem cells that have been "walked backward" and are as pluripotent as ESCs but don't require the destruction of an embryo.





Both embryonic and induced pluripotent stem cells have been used for gene therapy and organ repair. At Yale, scientists have bioengineered vascular tissue using stem cells and are working with them to regenerate the lung and trachea. Cell-based therapies could lead to treatments that would repair injuries to the nervous system, and understanding human embryonic stem cells could reveal clues to treating cancer.

PHOTO/ILLUSTRATION CREDIT



Religion, politics, morality, and stem cells

Priests, presidents, and scientists have debated for years the medical benefits and moral dilemmas posed by stem cell research, with no clear consensus.

BY JENNY BLAIR
ILLUSTRATION BY OTTO STEININGER

It was standing room only in the auditorium in the Anlyan Center on April 3, 2003, when actor Christopher Reeve came to speak about stem cells. Famous for playing Superman on the screen, he lost the use of all four limbs after a horseback-riding accident in 1995, and had become an activist supporting human embryonic stem cell (ESC) research. In his talk at Yale, Reeve decried barriers to the ESC research that he believed had the potential to cure his condition.

"It's morally irresponsible not to allow research to go ahead on all these fronts, with very strict ethical guidelines," said Reeve. He would not live to see this area of research bear fruit. In October 2004, he died of cardiac arrest.

Not everyone agreed with Reeve, however. Ethical, political, and religious concerns have plagued stem cell research since at least 1998, when researchers in Wisconsin derived the first human ESC line. This area of science may not only involve the destruction of human embryos to harvest or test stem cells, but it also raises concerns about such issues as human-animal chimeras, cloning, and donor payment or consent. Yet stem cells hold promise for treating patients with amyotrophic lateral sclerosis, diabetes, spinal injuries like Reeve's, or other devastating conditions. The result: years of passionate debate that has reached no consensus, leading to a patchwork ethical and legal status for the cells. In the United States, state stem cell laws range from outright bans to encouragement and funding. Federal law permits the research, yet does not fund experiments that involve embryo creation or destruction. Promising though it is, human embryonic stem cell research in this country has proceeded in fits and starts.

PROTECTING THE EMBRYO & EGG DONOR

The year that Reeve spoke, stem cell research in the United States was sputtering. Two years earlier, President George W. Bush had announced that due to concerns over embryo destruction, federal funds could fund research only on existing lines.

Though the term stem cell includes ESCs as well as other types of stem cells, including adult stem cells found in fully formed organs, concerns about embryo destruction have dominated the ethical conversation since stem cells first appeared in labs, recapitulating arguments about the personhood and moral status of the embryo. Is the common practice of retrieving stem cells from an excess fertility clinic embryo justifiable, though that embryo be destroyed in the process? Some say yes, if the knowledge gained could save lives.

Others, like Daniel Sulmasy, M.D., Ph.D., a University of Chicago ethicist and former Franciscan friar who served on New York State's stem cell ethics board from 2007 to 2009, say human rights begin at conception. That view makes embryonic destruction unethical and proposes a moral distinction between letting embryos die naturally and destroying them in the lab.

The creation of new embryos—a practice that made headlines in 2014 when Oregon researchers announced that they had created patient-specific ESCs via "therapeutic cloning" with human eggs—also troubles Sulmasy. Anyone who believes human life merits respect from conception to natural death, he says, should oppose the creation of new members of humanity just to use those lives. In this view, he says, "No good end could justify that means."

Since the 1973 *Roe v. Wade* decision that legalized abortion, such embryo-centered ideas have influenced federal policy. A two-year moratorium on funding embryo research followed that Supreme Court case; even after the moratorium was lifted, no federal funds were forthcoming. In 1979, an Ethics Advisory Board, born of the newly established congressional National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, approved experimentation on embryos up to 14 days postconception, when the primitive nervous system arises. But despite that recommendation, Congress soon blocked federal funding for such research. The 1995 Dickey-Wicker Amendment banned the use of federal funds for creating or destroying human embryos, a ban that remains in effect today. In August 2000, the Clinton administration published guidelines that would have allowed scientists to use federal funds to buy cells extracted from unused frozen embryos. A year later, before funding was dispersed, President Bush overturned these guidelines with his landmark announcement. It pleased no one.

"Neither side liked Bush's attempt at a compromise solution," says Stephen Latham, J.D., Ph.D., director of Yale's Interdisciplinary Center for Bioethics, who formerly served on Connecticut's State Stem Cell Research Advisory Committee and who is now a member of Yale's Embryonic Stem Cell Research Oversight Committtee (ESCRO). Those opposed to embryonic destruction thought the government's hands were unclean, Latham recalls. Those who supported ESC research pointed out that the existing stem cell lines were of poor quality. Advocates and patients like Reeve seethed, and scientists, urged on by the president's Council on Bioethics, changed gears and sought non-destructive ways to obtain useful stem cells.

Although the federal government would provide no funding for the research, it did not ban it. Some states, like Arkansas, Indiana, and the Dakotas, did ban the research, while others, like California and

Connecticut, established funding and advisory committees. "We had this very sharp debate, but nobody ever said 'Let's make this illegal,' " Latham says.

Money figures, too, into donor ethics. Sulmasy and others worry that stem cell research or therapy could lead to coercive payments to economically disadvantaged women for their eggs—a concern that becomes more relevant in the wake of the 2014 therapeutic cloning achievement, which could lead to any number of patient-specific ESC therapies. The National Academies of Science disapprove of paying egg donors, though the ethics board in New York State decided (after Sulmasy left) to approve such payment from public research funds.

STEM CELLS WITHOUT EMBRYOS

In 2007, there came a long-awaited game-changer: stem cells that didn't require embryo destruction. Scientists in the United States and Japan had walked human adult skin cells back into an embryo-like state, creating induced pluripotent stem cells (iPS cells), a momentous discovery that changed the field. Nine years later, Latham says, researchers are doing more work with iPS cells, which are cheaper and easier to procure than ESCs.

Alas, iPS cells didn't do away with the ethical issues. For instance, iPS experiments may make use of ESCs as gold-standard comparisons, which means embryo destruction.

Another line of research attempts to derive sperm and eggs from iPS cells. In 2012, a Japanese group achieved this science fiction-like result in mice, announcing that it had created functional sperm from mouse skin cells; the new sperm successfully fertilized an egg, which in turn gave rise to healthy offspring. Needless to say, the prospect of doing such a thing in humans is unsettling.

Then too, iPS researchers soon faced new consent issues. A major regulatory shift came in 2009, when President Barack Obama revoked the Bush ban by executive order, reintroducing federal funding for the study of stem cells derived from excess IVF embryos (though not for their derivation). Stem cell research advocates praised the step. The Obama order, however, included strict criteria relating to informed consent. Were biological parents of donated embryos fully aware of what might become of their donation?

"Some of the lines that Bush's NIH was willing to fund turned out not to have good consent behind them," Latham says. New guidelines eventually banned funding for research on older cell lines derived from lab-created embryos, admitting only those derived from fertility clinic extras.

Early iPS cells derived from commercially available cell lines, too, are likely to have been done without donor consent—as with Henrietta Lacks, whose famously immortal cervical cancer cells became a cornerstone of modern biomedical research, though she never consented to their dispersal before her death in 1951.

"There are ethical concerns about derivation of iPS cells," says Sandra Alfano, Pharm.D., a co-chair of the Yale ESCRO since its founding in 2006. "This idea of review of provenance and whether there was adequate informed consent, that's probably the biggest part of the job for ESCRO currently."

Maurice J. Mahoney, M.D., J.D., the other co-chair, adds, "We now insist that people be asked, 'Is it all right that a cell line that came from your body ends up around the world, in many laboratories, and may be sold, may end up in animal species, which means that animal research is going on with cells from your body?' ... We push those issues now."

These days, according to Latham, the ESCRO gives extra attention mainly to research proposals that involve mixing human ESCs with animal embryos in such a way that the animal's nervous tissue or its sex cells could be affected. This addresses unlikely but nonetheless prevalent public concerns that a mouse could be neurologically humanized in a way that could increase its suffering, or that one with altered gametes might escape, reproduce, and cause an unpredictable environmental effect.

NO ESCAPING THE ETHICAL QUESTIONS

Yale's ESCRO observes its 10th anniversary this June, well into the era of stem cell clinical trials. Dozens are now underway, thorny issues notwithstanding. For any discussion of ethical restrictions on stem cell research must also take into account the human cost of such restrictions—something Reeve made clear in his talk at Yale. Millions could die, he said, while scientists look for a way to avoid the ESC moral quandary.

"To say that we should just work on adult stem cells because we'll get there [eventually], that's not fair to the people who are suffering from diseases like ALS," Reeve said. "We're going to lose valuable time." */yale medicine*

Jenny Blair, M.D. '04, is a frequent contributor to Yale Medicine.

Hair, mice, and how cells regenerate

The human body loses billions of cells every day, but its self-renewing supply of stem cells, which can become any type of tissue, continuously replace those lost cells. Researchers, however, understand little about how this regeneration is sustained. Valentina Greco, Ph.D., associate professor of genetics, of cell biology and of dermatology, and principal investigator at Greco Lab, wants to get to the bottom of it.

What enables normal tissue, which can harbor mutated cells, to continue to regenerate as healthy tissue and not become cancerous? Greco looks for the answer in hair follicle stem cells in their niche—the microenvironment in which stem cells live. She studies them in the skin of live healthy mice.

Greco and her colleagues Ann Haberman, Ph.D., assistant professor of laboratory medicine and of immunobiology, and David Gonzalez, M.H.S., a research associate at Yale's In Vivo Imaging Facility, adapted two-photon fluorescence microscopy to visualize cells in live mice. Greco can tag the cells she wants to follow in fluorescent transgenic mice, and track them throughout their life cycle. Observing these cells in their natural environment, Greco hopes to identify the choices and behaviors of stem cells that sustain normal tissue function even when mutations are present.

A better understanding of normal cell regeneration could help researchers predict when something will go wrong. "We could capture the initiation of cancer and understand how it emerges from normal tissue growth," Greco said. "This has tremendous potential for cancer prevention."

—Sonya Collins

As an anesthesiology resident in Boston, Laura Niklason watched as cardiac surgeons sought usable veins for bypass surgery. That's when she began working on creating new blood vessels in the lab. Now, her work in tissue engineering has moved on to the lung and trachea.

Organ in a bottle

Laura Niklason works to engineer organs as replacements for those that fail.

BY ASHLEY P. TAYLOR
PHOTOGRAPHS BY ROBERT LISAK

On the windowsill of Laura Niklason's office is an unusual knickknack: a clear glass jar like a jug turned on its side with two cork-shaped stoppers along its top, thin protrusions on both ends, and, inside, a paper sailboat. A ship in a bottle. The boat, stuck in there, Niklason says, by a stir-crazy grad student late one night in the lab, is no miniature yacht. But inside bottles like these, called bioreactors, Niklason, Ph.D., M.D., the Nicholas Greene Professor of Anesthesiology and Biomedical Engineering, builds structures that trump the trickiest marine art project: blood vessels, windpipes, and lungs.

Niklason first had the idea to build organs in the lab when, during her time as an anesthesiology resident in Boston, she watched cardiac surgeons struggle to find transplantable veins for bypass operations: "We ought to be able to grow a new one," Niklason remembers thinking. She also has a doctorate in biophysics, and was a postdoc in the lab of chemical engineer and biomedical engineering guru Robert Langer, Ph.D., at the Massachusetts Institute of Technology. It was there that she grew her first blood vessels.

She continued her vascular engineering research at Duke University and founded a company, Humacyte, to build replacement tissues for clinical use. It is now testing engineered vessels for use in hemodialysis patients. Since coming to Yale in 2006, Niklason has expanded her tissue engineering work to the lung and trachea. She has also been collaborating with the core labs of the Yale Stem Cell Center, where she has a secondary appointment. Stem cell technology touches every area of her research. Eventually, she hopes to use stem cells, which can differentiate into many tissue types, as the cellular materials for all of her engineered organs.

"She's an amazing inventor," says Haifan Lin, Ph.D., the Eugene Higgins Professor of Cell Biology; professor of genetics; and of obstetrics, gynecology, and reproductive sciences; and director of the Yale Stem Cell Center. "She's a modern Renaissance woman."

A BIOREACTOR

Niklason's initial framework for engineering a replacement artery was to take blood vessel cells from a patient or animal, culture them on a tube-shaped biodegradable scaffold, and then implant the engineered vessels into the same patient or animal. To avoid immune rejection, the idea was to "make an engineered artery just for that patient or just for that animal." In the Langer lab, her attempts to grow an artery this way failed for two years—until she started pumping nutrient-rich liquid (called medium) through the vessel as it developed within the bioreactor, causing it to expand and contract as blood vessels do in the body. To set up a blood-vessel bioreactor like the one in Niklason's office, a researcher takes a silicone tube, sews a scaffold of biodegradable mesh around it, and threads it between the glass container's protruding ends. The researcher then pipettes a solution of cells onto that scaffold. As the cells grow around the tube, medium courses through it, strengthening the developing vessel. Other tubes for providing nutrients and gas exchange enter the bioreactor through the stoppers on top, and the whole thing is filled with medium and kept in an incubator to control the temperature and atmosphere. Making a blood vessel this way takes about two months. Near the end of the growth period, the silicone tubing is removed, and the vessel is suitable for implantation into the body. In 1999, Niklason reported in *Science* that by using this method, she had successfully implanted pigs with engineered arteries made from their own cells.

At Duke, Niklason tried the same approach using vascular cells isolated from elderly patients, but ran into problems. Because the patients' cells were old, they had limited lifespans—they stopped dividing and became difficult to grow. Additionally, the tissues they spawned were not as sturdy as those derived from younger cells. Niklason tried using gene therapy to trigger a lifespan-increasing enzyme, with limited success. "The cells lived longer, but they didn't make tissues that were mechanically more robust."

Once at Yale, Niklason tried a new approach: differentiating stem cells into smooth muscle cells (SMCs), a major component of blood vessels, and using them to create arteries. These newly differentiated human cells, unlike those from elderly patients, would be young enough to work. In 2008, her lab reported that it had created an engineered artery by differentiating bone marrow-derived stem cells into SMCs and then coaxing the cells to form a blood vessel as before.

Now her team is building arteries and other tissues with induced pluripotent stem cells (iPSCs). These cells are created by taking such differentiated cells as skin cells and treating them with certain factors that convert them into stem cells. Since a skin biopsy is an easier and less painful procedure than bone-marrow isolation, this method has clinical advantages. Eventually, Niklason hopes, a doctor could take cells from a skin biopsy, create patient-specific iPSCs, and then differentiate those iPSCs into the tissue types needed to make personalized replacement organs.

The technology is a few steps behind this vision, however. "We can differentiate the cells from stem cells; we can make smooth muscle cells fairly well," says Niklason, "but not well enough such that they create arteries that are implantable and strong enough to function long term."

Laura Niklason

> "Stem cell science has just exploded in terms of what we know over the last 20 years. The building blocks and the tools that we have at hand now are just so vastly different from what they were even 10 years ago."

Down another avenue of research, however, Niklason realized that personalized organs weren't always the best choice. Beyond the problem of old cells, which stem cell technologies could circumvent, there were the constraints of time. If you need a new blood vessel, Niklason says, "you probably don't have the luxury of sitting around three or four months and waiting for me to grow you a new artery. We started racking our brains about how to solve this problem in such a way that we could make a universal artery." Her solution was something called decellularization.

Our cells secrete proteins that form the scaffold on which they live and move—the extracellular matrix. Wash away the cells, and the scaffold remains; this washing step is decellularization. Niklason washed away the cells of her engineered blood vessels and implanted those decellularized arteries into animal models. The decellularized vessels, she found, worked as well as transplanted native blood vessels—and with no immune rejection. "I can take this tissue, and I can implant it into any human, and it won't be rejected by the body because we've washed away the stuff that came from somebody else." Furthermore, the vessels didn't stay decellularized forever. Taking cues from the extracellular matrix, "cells from the patient infiltrate into this tissue and turn it into a living tissue over time."

The hemodialysis graft that Niklason's company is currently testing is one such decellularized blood vessel. Hemodialysis grafts create a conduit between a vein and an artery in the arm into which large-bore needles can be inserted to transport blood to and from the dialysis machine. Such grafts are made with either a patient's own vein from elsewhere in the body or from plastic, and they often fail. Phase III trials comparing Humacyte's decellularized grafts to their plastic equivalents are slated to begin this year. "My hope is that we'll be able to grow thousands of these tissues that can then go out to hospitals and be implanted into any patient who needs a replacement blood vessel of this type," Niklason says.

Niklason is also using decellularization to engineer tracheae (windpipes). Unlike blood vessels, which are flexible, the trachea—supported by rings of cartilage surrounding the airway—is designed to resist collapse. In Niklason's engineered windpipes, which she has tested in rats and primates, that function is served by a metal stent on which the tracheal cells are grown. "We've got a stent-tissue composite," she says.

The cells that Niklason cultures in order to make decellularized blood vessels or tracheae for patients come from organ donors, but Niklason would like to use stem cells instead. She envisions a "bank" of stem cells that could be differentiated into various cell types as needed. "If we had an infinite cell bank, that would be wonderful in terms of the reproducibility of the vessels that we make," says Niklason.

MORE COMPLEX TISSUES

The decellularization strategy worked with blood vessels and tracheae, Niklason says, because many of their functions come from their physical architecture, which remains when you strip away the cells. That is not the case with such complex tissues as the kidney, heart,

and lung, Niklason says. "Their function is derived from the cells that are there. ... So if you strip the cells away you have no organ function."

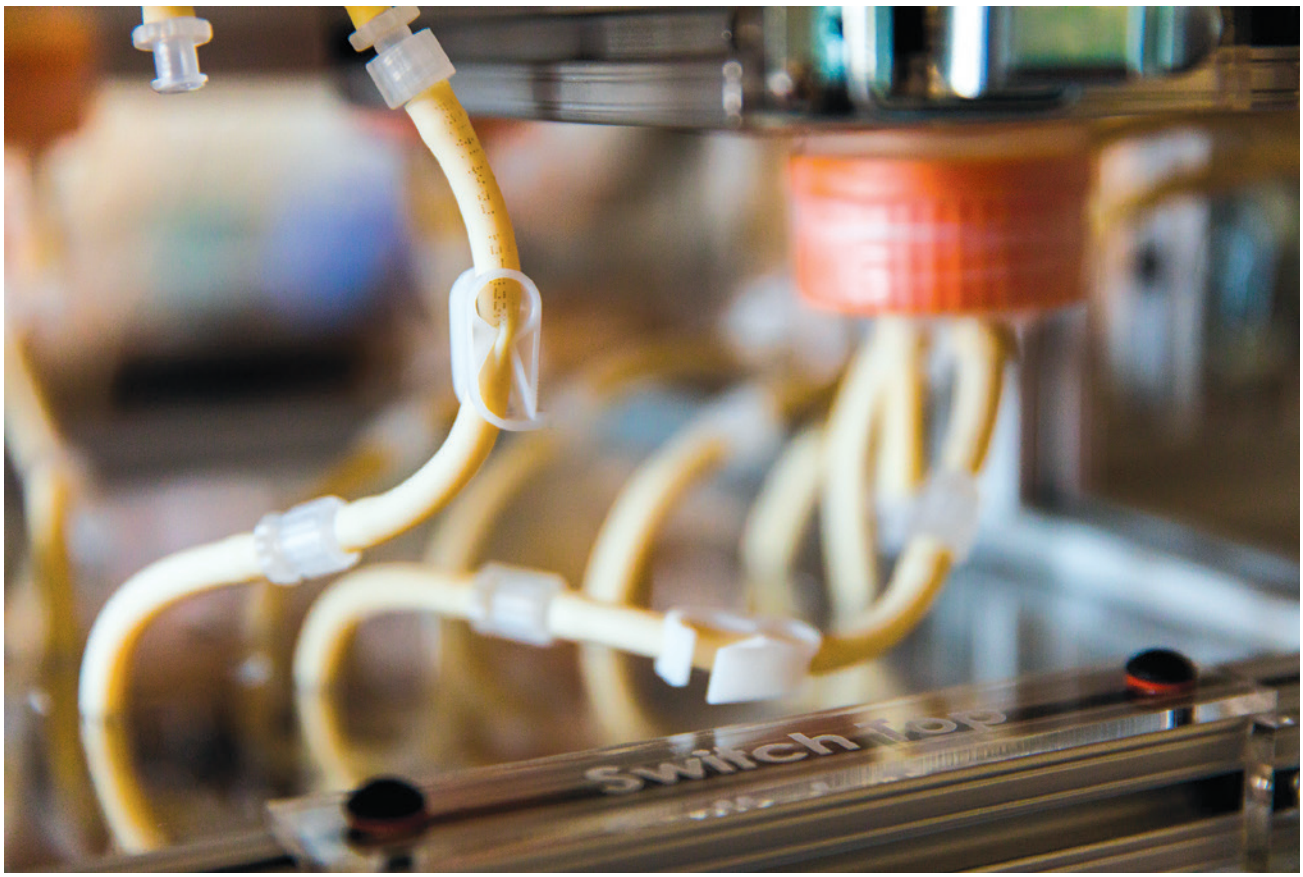
It is for engineering and transplanting one such complex organ, lungs, into rats that Niklason is perhaps best known. For that project, reported in a 2010 *Science* paper, she also used the technique of decellularization, but this time for a different purpose. Instead of trying to engineer the many branching airways and air sacs of the lung, she decided to take a donor lung, wash away the cells, and use it as a scaffold on which to regrow the recipient's own lung cells in a bioreactor that both pumped fluid through the lung's vascular system and used another pump to make the lung "breathe." Then, the recipients were rodents, but the goal is, of course, to build customized lungs for patients.

To reach that goal, the Niklason lab is counting on iPSCs. The lung contains many "flavors of epithelium," she says, and growing enough of those various cell types from lung tissue biopsies is difficult. Instead, she and her team are developing tools to differentiate them from iPSCs.

It helps that her lab is right above the stem cell core, the labs that specialize in producing human embryonic stem cells and iPSCs. "We work with them constantly," says Niklason. As Niklason's engineering approaches turn more and more toward iPSCs, that collaboration is bound to continue.

"Stem cell science has just exploded in terms of what we know over the last 20 years," says Niklason. "The building blocks and the tools that we have at hand now are just so vastly different from what they were even 10 years ago." Then, scientists had just figured out how to create iPSCs from mouse tissue. Now, Niklason is using them to develop personalized engineered organs. "It's a very exciting time to be working in this area, and I feel very fortunate." */yale medicine*

Ashley P. Taylor is a freelance writer in Brooklyn, N.Y.



Embryonic stem cells and diseases of the retina

BY SONYA COLLINS
ILLUSTRATION BY OTTO STEININGER

Seeing begins with photoreceptors, the cells that convert light into signals that the brain translates into the images that we see. Those photoreceptors' lives depend on a layer of cells at the back of the eye called the retinal pigment epithelium (RPE). "You can think of RPE as a nurse that keeps photoreceptors happy and functioning. If RPE gets sick and dies, photoreceptors get sick and die," said Lawrence Rizzolo, Ph.D., professor of surgery (gross anatomy) who also runs a lab in Yale's Stem Cell Center. "It happens the other way, too. If photoreceptors die, RPE—not having photoreceptors to interact with—dies, too."

As part of their day-to-day operations, photoreceptors shed some of their light-capturing membranes and acquire new ones. RPE eats the discarded membranes, clearing them from the eye. "If that doesn't happen, you get all this debris in the retina that isn't degraded, and retinal diseases occur," Rizzolo said. Those diseases are some of the leading causes of blindness, including macular degeneration, diabetic retinopathy, and retinitis pigmentosa.

RPE's critical role in maintaining the health of photoreceptors makes this layer of cells a potential target for treatment of these blinding diseases of the retina. Researchers in Rizzolo's lab are using human embryonic stem cells to bioengineer RPE and retinal progenitor cells (RPCs). They hope one day to implant the cells and restore sight to people with certain types of vision loss.

Animal studies have shown that implanting stem cell-derived RPE in the eye in the early stages of disease could replace host RPE and slow vision loss. But later in the disease, the procedure does not yield the same benefits. In order for RPE transplant to gain traction as a treatment option, Rizzolo says, it needs to be available to patients who have begun to lose some vision and are willing to take the risk of surgery. "Suppose you see okay now, and you'll probably see okay for another 10 years, but then I told you things are going to get worse, and if this procedure works, we'll slow that down—but if it doesn't work, you could go blind tomorrow because, after all, it is still surgery and a difficult one."

That's not the only challenge for Rizzolo and other researchers. As embryonic stem cells differentiate to become RPE cells, they need RPCs nearby to shepherd them through the process and vice versa. For full function of both tissues, they need to co-differentiate.

To address this problem, Rizzolo is growing RPE cells on a matrix alongside retinal progenitor cells. He and other researchers still need to find a way to grow this retinal tissue in a flat sheet that mimics a normal human retina. "When you grow retinal progenitor

cells, they grow as tiny spheres that don't undo themselves when you transplant them," said Rizzolo. Because these light-sensitive cells, which don't work without physical contact with RPE, are trapped inside those tiny spheres, RPE cannot keep them alive.

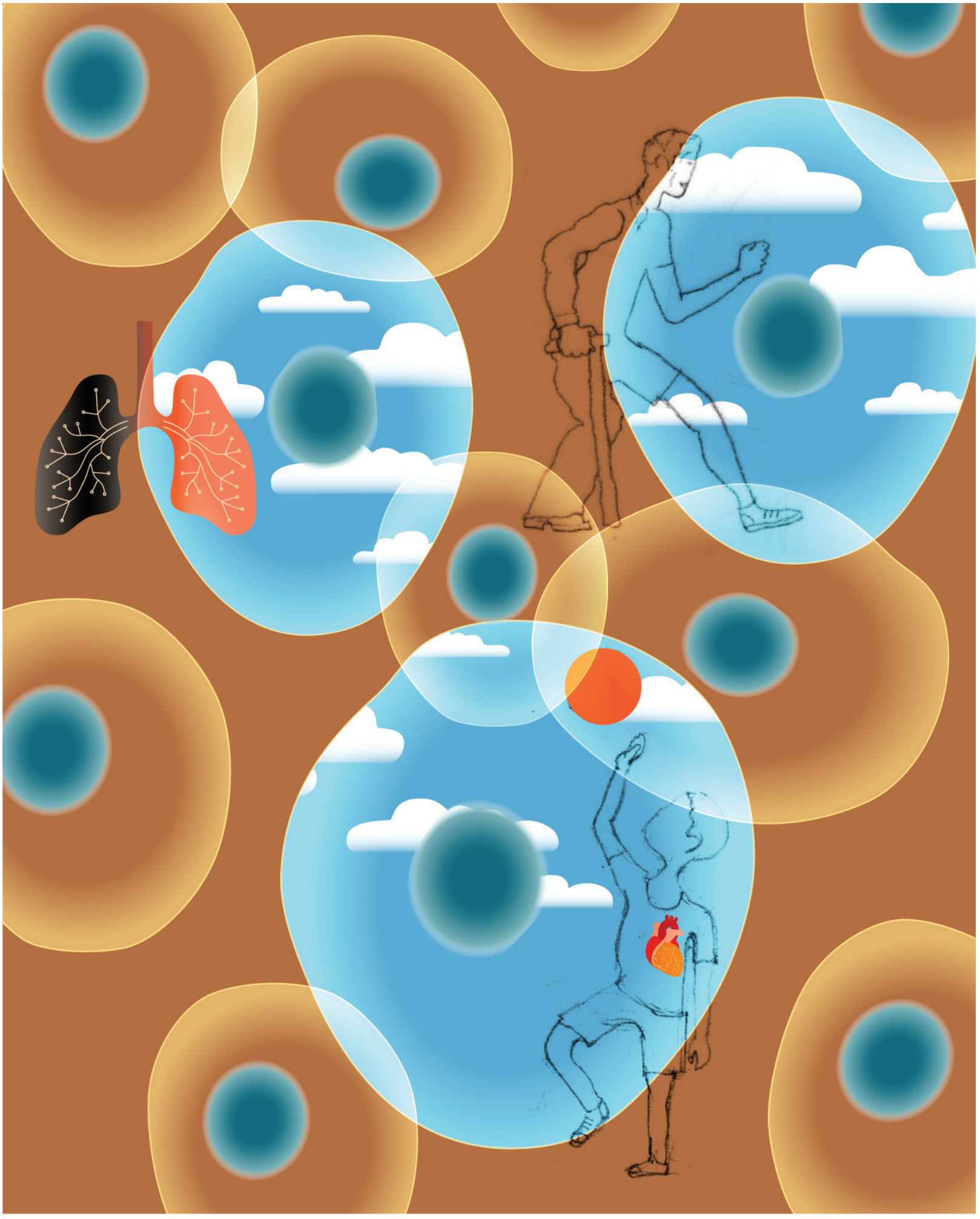
Rizzolo and his team have developed a gelatin-based scaffold in which to suspend RPCs and present them to RPE as a flat sheet. So far, the scaffold has allowed his team to produce flat, sheet-like retinal tissue.

The question now is, if researchers implant the retinal cells later in the progress of the disease, will they still slow it down or better yet, reverse it? "Those experiments are in progress," Rizzolo says.

Rizzolo's team and physicians at the Yale Eye Center will try the procedure on a live pig who underwent retinal laser burns that simulate macular degeneration. After surgery, the pig will undergo tests to reveal whether its eyes have resumed normal communication with the brain.

"If the signal gets to the visual cortex in the back of the brain, this will tell me that not only did I reinstate circuits in the retina, but those circuits are sending information to other parts of the brain." *yale medicine*

Sonya Collins is a freelance writer in Atlanta, Ga.



From spare parts to delaying old age—the promise and future of stem cell research

BY BRUCE FELLMAN
ILLUSTRATION BY OTTO STEININGER

Since their first therapeutic human use in 1957, when Seattle physician and future Nobel laureate E. Donnall Thomas, M.D., attempted a bone marrow transplant to treat leukemia, stem cells—those miraculous collections of cytoplasm and nuclei capable of an astonishing amount of cellular transformation—have offered to medical researchers, doctors, and the public alike the prospect of curing intractable diseases and crafting a storehouse of spare parts to remedy all manner of tissue damage.

In 2006, buoyed by a combination of $10 million from the State of Connecticut and $80 million in university funds, Yale created its own Stem Cell Center (YSCC) at the School of Medicine and recruited Haifan Lin, Ph.D., a rising superstar in the research community, to lead the fledgling effort.

"Ten years ago, we began the center with a vision for what we might be able to do with stem cells, both in terms of medical applications and helping resolve the mystery of life," says Lin. "I'm happy to tell you that quite a lot has been achieved on both fronts."

More than 89 research groups from 23 departments are gathered under the YSCC umbrella, and their interests run the gamut from deciphering the fundamentals of stem cell biology to developing the best ways of using the cells to treat some of the worst human scourges, cancer and heart disease among them. Working with the highest of high-tech tools in laboratories dedicated to genomics as well as to growing, imaging, and manipulating what Lin calls "the mother of all cells," scientists here are beginning to see these investments pay off. They now have the ability to make custom-tailored tissues and organs that, because they're made from an individual's own stem cells, are transplantable with much less risk of the body's immune system attacking them and causing rejection.

"YSCC researchers have pioneered this approach to repair children's broken hearts," says Lin, highlighting work by Christopher K. Breuer, M.D., and Toshiharu Shinoka, M.D., who developed techniques in which stem cells harvested from the bone marrow of children born with heart ventricular or atrial defects could be reprogrammed to transform into new, fully functional blood vessels that were then used to repair the heart defects. (The two doctors now head the Tissue Engineering Program at Nationwide Children's Hospital in Columbus, Ohio.)

THIS ISN'T SCIENCE FICTION ANYMORE

The first successful operation using such stem cell-engineered cardiac tissues took place five years ago at Yale-New Haven Hospital, and offshoots of the techniques are under investigation to develop other replacement parts, from sections of the brain to new lungs. "This isn't science fiction anymore," says Lin, noting that 400,000 people die each year from lung disease because, to a large degree, "there aren't enough donors."

Much of this progress, however, would never have been possible were it not for a fundamental breakthrough announced at the time the YSCC opened for business. In 2006, Japanese researchers demonstrated that such ordinary adult mouse cells as skin cells could be reprogrammed to become nearly as malleable as embryonic stem cells, and the same possibility was shown in human adult cells the following year. This discovery allowed researchers to work with stem cells that had not come from aborted fetuses, thereby avoiding the fierce ethical and moral debates. The ability to now use induced pluripotent stem cells—iPSCs, for short—however, has given Yale scientists an almost limitless supply of raw material for applied and equally critical basic investigations.

REPROGRAMMING ADULT CELLS

The ability to reprogram an adult cell so that it functions like an embryonic one is "incredibly cool," says Diane S. Krause, M.D., Ph.D., the YSCC's associate director who works with bone marrow-derived stem cells to understand their involvement in the development of certain kinds of leukemia and how such cells might be used in therapies against cancer.

Krause, a professor of laboratory medicine, cell biology, and pathology, explains that while iPSCs have yet to make a jump into a hospital setting, there are at least a couple of scenarios—gene therapy and organ repair—on the horizon. In advanced cases of sickle-cell anemia, for example, doctors attempt to treat the condition with a bone marrow transplant that comes from a close relative of the sufferer. A cure is possible, says Krause, "but the patient is also very much at risk for graft-versus-host disease, which is serious and can be fatal. So what if you could take the patient's own stem cells, correct the genetic defect that we know causes the disease, then induce them to make fixed copies that we could now transplant back? With such an autologous transplant, there would be little risk of graft-versus-host disease."

In the case of a heart attack, adult stem cells from the organ could be induced to become, say, muscle cells that can be transplanted to regenerate new functional cardiac tissue instead of the scarring that now typically results when an infarct leads to oxygen deprivation and tissue death.

Another area in which stem cells could prove important involves the liver, particularly in the case

of accidental or deliberate acetaminophen overdoses, which can kill enough cells to prove fatal. "The liver is actually really good at regenerating," says Krause, "but there are some patients who have a transient problem with liver regeneration, and if they could just get enough cells to function until their own liver restores itself, they would be able to survive long term."

An autologous transplant of iPSCs reprogrammed to become liver stem cells could, in theory at least, keep a patient alive long enough to enable the damaged organ to regain its functionality. All this, of course, is a promise for the future. "We know perfectly well that we can use iPSCs to treat acute liver failure," says Krause. "But we don't know how to make the cells become functional lymphocytes, how to get enough of them, and how to make sure they're safe."

THE IMPORTANCE OF BASIC RESEARCH

That, says Lin, is where fundamental research comes in. "We realized early on that we didn't fully understand the inner workings of stem cells, and without the knowledge of the molecules that make them tick and make them quiet, we would never be able to harness their power and come up with rationally designed therapies," says Lin. "We'd just be guessing."

Lin received his bachelor's degree at Fudan University in 1982 in his native China, and a doctorate at Cornell in 1990. Starting in 1994 at the Duke University Medical School, Lin focused on a bold but risky research area: the vast stretch of the genome known as "junk DNA." A small percentage of the human genome—some 26,000 genes—is known to make messenger RNA molecules that help code for proteins, says the researcher. "The rest was considered useless," Lin explained, "but that turned out to be more because of technological limitations than reality. We just weren't able to find where the genes were and how they might affect development in model species and in humans, so we dismissed them as unimportant."

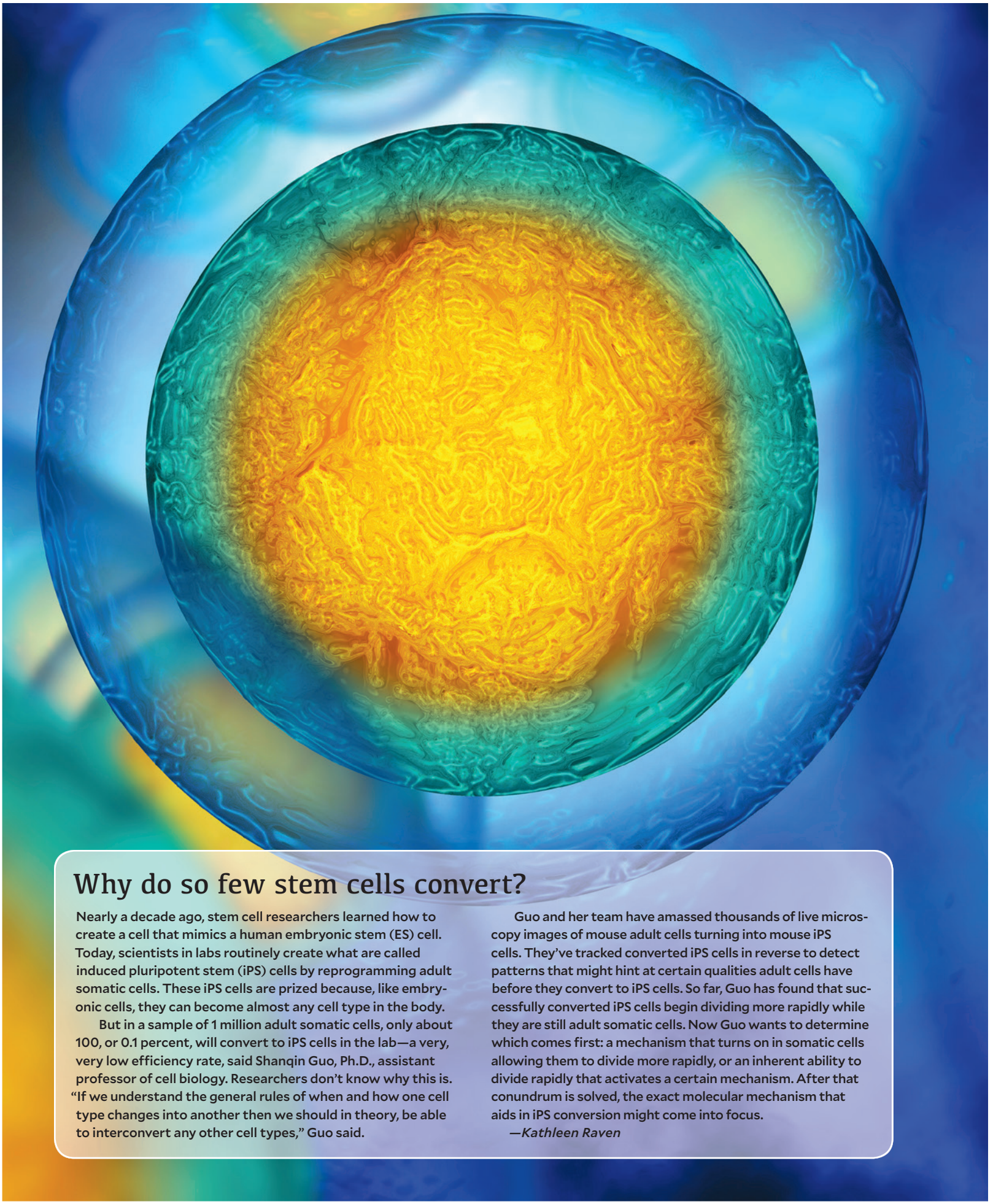
With improvements in molecular tools, including such revolutionary technologies as DNA deep sequencing, a gene-editing method known as CRISPR, and others being used and developed in the YSCC core laboratories, Lin and others discovered that this viewpoint was akin to saying that since most humans lived in cities, the countryside no longer mattered. It turned out that this so-called noncoding stretch of the genome mattered plenty. "Junk DNA is making millions of little RNAs that are very important for determining the fate of stem cells—for turning them on and off at the right time," Lin explains.

Learn to hit the start button effectively, and the result can be a supply of spare parts. Learn to hit the stop button, and the result might be the medical equivalent of the Holy Grail: an effective cure for cancer. "Studying stem cells is not only important in regenerative medicine," says Lin. "We believe that the fundamental insights we're discovering will turn out to be crucial in creating a kind of personalized medicine that can treat malignancies."

Current cancer treatment, of course, is brutal, since it can't discriminate between actively dividing normal cells and their out-of-control counterparts. But Lin is working with some of his fundamental RNA insights on stem cell reprogramming and control to find medications and techniques to better diagnose and conquer breast cancer. Preliminary results from his lab suggest that the rogue cells responsible for metastatic disease can be stopped from migrating, and over the next decade, Lin feels that such studies may lead to the rational design of "very targeted, much less harmful" therapies.

Stem cell research may point to something even more astounding. "We are on the verge of learning how to protect the genome from being damaged, and this might enable us to figure out how to extend a healthy life for a longer time," says Lin, suggesting that "old age" may, sometime in the not-too-distant future, need to be redefined. "We're very excited about the progress we've made and the prospects of what's to come. The whole field is undergoing evolutionary change, and Yale is an integral part of it." */yale medicine*

Bruce Fellman is a freelance writer in North Stonington, Conn.



Why do so few stem cells convert?

Nearly a decade ago, stem cell researchers learned how to create a cell that mimics a human embryonic stem (ES) cell. Today, scientists in labs routinely create what are called induced pluripotent stem (iPS) cells by reprogramming adult somatic cells. These iPS cells are prized because, like embryonic cells, they can become almost any cell type in the body.

But in a sample of 1 million adult somatic cells, only about 100, or 0.1 percent, will convert to iPS cells in the lab—a very, very low efficiency rate, said Shanqin Guo, Ph.D., assistant professor of cell biology. Researchers don't know why this is. "If we understand the general rules of when and how one cell type changes into another then we should in theory, be able to interconvert any other cell types," Guo said.

Guo and her team have amassed thousands of live microscopy images of mouse adult cells turning into mouse iPS cells. They've tracked converted iPS cells in reverse to detect patterns that might hint at certain qualities adult cells have before they convert to iPS cells. So far, Guo has found that successfully converted iPS cells begin dividing more rapidly while they are still adult somatic cells. Now Guo wants to determine which comes first: a mechanism that turns on in somatic cells allowing them to divide more rapidly, or an inherent ability to divide rapidly that activates a certain mechanism. After that conundrum is solved, the exact molecular mechanism that aids in iPS conversion might come into focus.

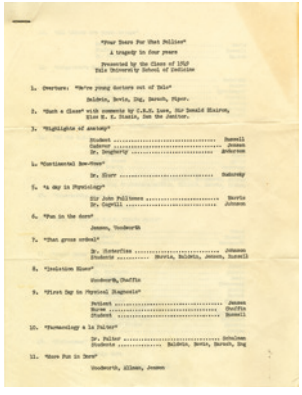
—Kathleen Raven

Longest-running show on Cedar Street ends after more than 60 years

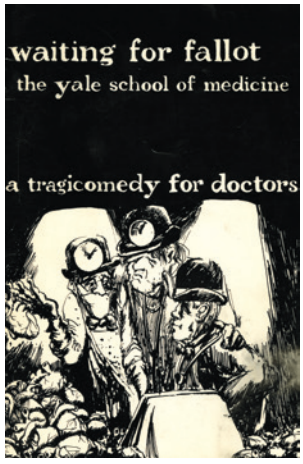
Student spoof of life at Yale Med will re-emerge as a Fourth-Year Show

By John Curtis

In 1949, William G. Anlyan, then a fourth-year med student, encouraged his classmates to poke fun at their professors and deans in a song and dance review called the "Four Years for What Follies." Anlyan wrote the script, directed the show, and provided piano accompaniment. It was an outgrowth of the vocal quartet (The Forceps, featuring Bi, Tri, Quadri, and Contra) he had formed previously. For the next few years most fourth-year classes maintained the new tradition, though some were too caught up in their coursework for such frivolity. By the 1960s—the exact date is unclear—the scattering of fourth-years to clinical clerkship sites across Connecticut had made it difficult to produce a show. A second-year show marking the end of a pathology course took over as the main student production.



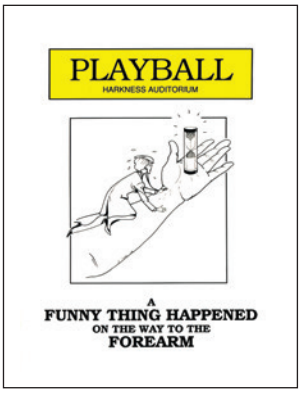
Class of 1949



Class of 1980

That show endured until Saturday, Feb. 20, of this year, when the curtain fell on the longest-running production on Cedar Street. The introduction of a new curriculum, which will have second-year students on clinical rotations at a time when the frenzy of producing the show kept them out of class for weeks in February, made this year's show the last second-year production. It is hoped that fourth-year students will carry on the tradition.

As they prepared this farewell show, members of the Class of 2018 felt an obligation to honor the tradition and those who have made it such a success over the years. "It influenced our whole plot," said Robin Wu, one of the show's co-directors, with Max Farina and Tejas Sathe. "It was important to acknowledge the tradition of the show," added Farina.



Class of 1990

This year's show, "Remediation," paid tribute to past shows through the travails of four stereotypical medical students (the nerdy scientist, the do-gooder, the legacy admit, and the shallow frat boy), all of whom had failed a qualifier in the history of medicine. Each incorrect response to the question, "What was the most important day in the history of the Yale School of Medicine?" sends them on a trip through history. Unbeknownst to them, Lawrence Rizzolo, Ph.D., one of their anatomy professors, has rigged their computer as a time machine. Their first stop takes them to medieval times, and an encounter with an early incarnation of Auguste H. Fortin VI, M.D., M.P.H., associate professor of medicine. "Medicine?" the medieval Fortin asks.

Class of 1996

"Medicine is just conjecture and fraud. We are a highly respected institution: The Yale School of Magic!!"

The students continue through key moments of the 20th century, including the birth of modern neurosurgery, rock and roll, the civil rights movement, and the admission of the first African-American woman to the medical school.

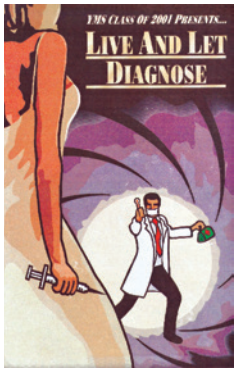
The climactic scene, based on *Star Wars*, pits Sam (played by Alyssa Mitson-Salazar) against "Darth Alpern" (played by Daniel Barson) in a "Doc Off" duel for the soul of the medical school. "Between the consulting gigs and all the talk of RVUs, it's become so clear that medicine has become such a business," Sam tells Darth Alpern. "And it seems that you're doing a great job running that business. But can we still call this doctoring?"

In the end, Darth Alpern promises to hold a Town Hall on the subject and the students find their way back to Cedar Street. And the elusive answer to the question, What was the most important day in the history of the Yale School of Medicine?

"Where would Yale Med be today without *every day*?" asks Sam. "Without every moment? Without … ."

On a screen in the background, a computer taps out the letters T-O-D-A-Y.

Class of 2000



Class of 2001

OPPOSITE PAGE Producers of the first student show, 1949's fourth-year production, "Four Years for What Follies," typed their program on stationery. Over time, the playbills became more polished and the show titles were not averse to puns and plays on other titles. The Class of 1982 evoked Samuel Beckett with "Waiting for Fallot," a reference to a congenital heart defect. The popular Broadway musical comedy, *A Funny Thing Happened on the Way to the Forum*, inspired the Class of 1990. When the Class of 1996 produced their show, their playbill was designed to look like *TV Guide* and asked "Docs on T.V.? See p.2." At the time, eight popular television shows, including *ER*, *Northern Exposure*, and *Dr. Quinn, Medicine Woman*, featured physicians.

ABOVE, PROGRAMS The Class of 2000 took their title from a popular TV show of the 1990s, calling their production "The Rx Files." The plot had Agents Mulder and Scully searching for the missing Cushing brain registry. James Bond was the inspiration for the Class of 2001's "Live and Let Diagnose," whose plot lines included human clones and Y-agra, a drug that compels medical students to attend class.

ABOVE, PHOTOS This spring, the Class of 2018 presented the last second-year show, "Remediation." The plot had students traveling through time to milestones in the medical school's history. Sophie Chung (top) played Harvey Cushing, M.D., in a scene called "Phantom of the Operating Room." No second-year show would be complete without a joke about the digital rectal exam (bottom). A hapless patient, played by Dharshan Anandasivam, assumes the position as Sam, played by Alyssa Mitson-Salazar, prepares to administer the exam during a "Doc Off" with "Darth Alpern."

JOHN CURTIS PHOTOS, PROGRAMS COURTESY OF THE CUSHING/WHITNEY MEDICAL LIBRARY

From music to medicine and back

A LIFELONG LOVE OF JAZZ and a desire to care for society's most vulnerable children have sustained Eli Newberger throughout his career.

One night last December, Scullers Jazz Club in Cambridge, Mass., was packed with national experts on child abuse, Peace Corps veterans, and book group buddies, all there to honor Eli Newberger, M.D. '66, HS '67, M.P.H., who sat in perhaps his favorite spot on Earth—on stage, cradling his beloved tuba.

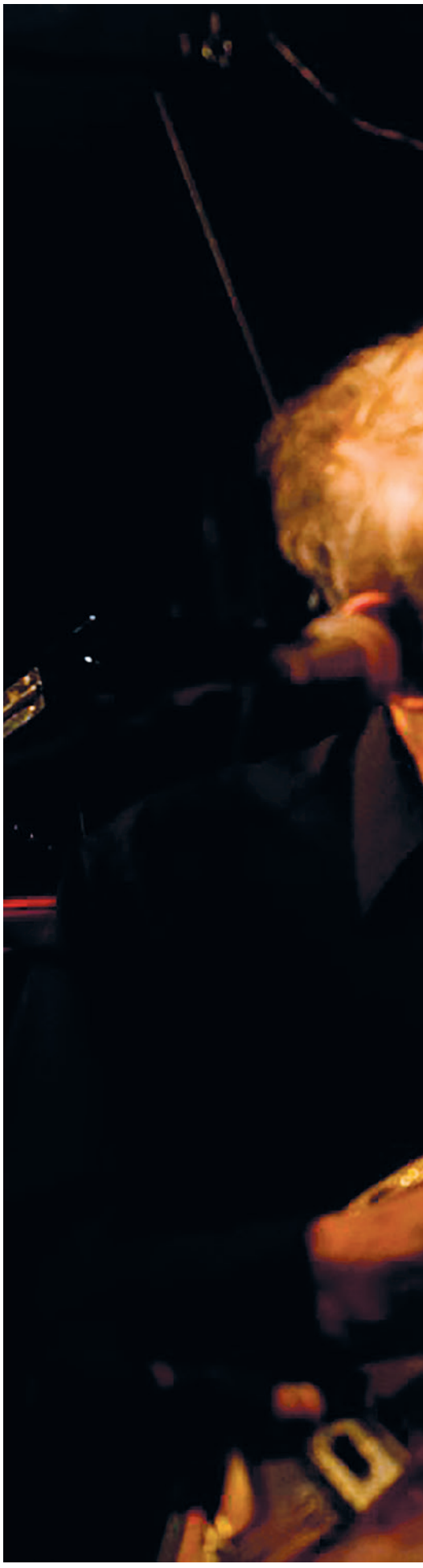
Newberger, a renowned child abuse expert as well as a fixture in Boston's jazz scene, was turning 75 the day after Christmas. The club added a second show to accommodate fans of his medicine and his music.

Kicking off an all-Gershwin set with his group, Eli & the Hot Six, Newberger told the crowd: "The amygdala in the brain is the center for our sensation of stress. It sets off a cascade of hormones and messages. This is also where music enters our brain." Not your typical stage patter.

But then, Newberger's not your typical musician or pediatrician. Both pursuits have been important to him throughout his life: In addition to establishing himself as an expert on child abuse, he has released more than 40 acclaimed jazz albums. As a pediatrician, he's testified in prominent cases of child and sexual abuse.

His path began at Yale College, where he started in physics before switching to music theory and taking pre-med courses on the side. By the time he graduated in 1962, he'd decided to apply to medical school and do music—he's played the tuba since he was 10—on the side. He graduated, married Carolyn Moore, a flautist from Sarah Lawrence, and the couple played with the New Haven Symphony Orchestra while he attended medical school. The two would continue to work together—for 30 years, the couple collaborated at Boston Children's Hospital, where he was a physician chief and she was director of research and training in the Family Development Program.

After receiving his medical degree, Newberger completed an internship in internal medicine at Yale-New Haven Hospital. But the Vietnam War was raging, and male doctors were required



Throughout his life and career, music has sustained Eli Newberger and helped him relieve the stress of his work as a pediatrician who has offered his expertise in child and sexual abuse in high-profile criminal trials. He relaxes by playing the tuba in his jazz band, Eli & the Hot Six.

ERIK JACOBS PHOTO

ONLINE EXCLUSIVES

As a high school student, Sudhakar Nuti came to Yale to learn anatomy from medical students. Last fall, he became the first graduate of the Anatomy Teaching Program to enter Yale as a medical student.

Mary Bassett, M.D., M.P.H., New York City's new health commissioner, talks about health inequities on the Department of Internal Medicine's Global Health Day.

Full stories and event photo galleries, as well as other online-only content, can be found on our home page at yalemedicine.yale.edu.

to register for the draft. The Newbergers opposed the war, so he applied to become a doctor in the Peace Corps. In 1967, the couple moved to Upper Volta in West Africa—now Burkina Faso—with their 1-month-old daughter.

Newberger's stint in Africa included working with impoverished mothers and children, and led him to an interest in pediatrics and a residency at Boston Children's Hospital. As a resident, he alerted the physician-in-chief about "a worrying pattern of rehospitalizations" of young patients who had been reported to child protective services. Mandated reporting laws for suspected child abuse were new, and the hospital staff wasn't yet well trained in recognizing such abuse. Newberger was asked to find out what other hospitals were doing.

He was just 29 years old when he was asked to start a child abuse unit at Children's Hospital. He had no experience in the field, but Newberger's multidisciplinary team of doctors, nurses, and social workers would become a national model.

In Boston, Newberger is best known as the key prosecution witness in the trial of Louise Woodward, the British nanny convicted of second-degree murder in the death of 8-month-old Matthew Eappen in 1997. Newberger testified that Matthew was the victim of violent prolonged shaking, and that a blood clot on his brain and a fractured skull indicated that he had also been slammed against a hard surface. Newberger also offered his expertise on the effects of abuse on children and their families during the sex abuse crisis in the Archdiocese of Boston.

Today, the Newbergers are semi-retired from the health care field, but perform with Eli & the Hot Six, in which Carolyn plays the washboard. They have a second home in the Berkshires, where he writes music reviews for the online site *The Berkshire Edge*, and Carolyn, a gifted artist, illustrates them. The booklet that accompanies the Hot Six's new CD, "Contemporary Classic Jazz," features Carolyn's real-time sketches of the performers.

The nexus of medicine and music has sustained Newberger throughout his career. Starting in 1971, he and his band had a regular Thursday night gig at a suburban Boston pub. It was the same year he started his Thursday outpatient clinic, and he'd go directly from the hospital to the pub. "I had 30 years of stress overload that was compensated by performing jazz," he said. "The positive sensations in experiencing music are processed in the same midbrain organs as those that bring us to hyperalert in the face of severe danger. The music enabled me to do what's most challenging—and for many physicians in child abuse work—vexatious, caring for the victims and their families, offending and unprotecting parents included."

—Bella English

Bella English is a reporter for *The Boston Globe*, where a version of this article first appeared.

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Pearls of wisdom from years on the wards

In the fall of 1960, Lewis Landsberg, M.D. '64, HS '70, first set eyes on the legendary Paul Beeson, M.D., at a Saturday morning medical ground rounds. As Beeson entered Fitkin Amphitheatre, the renowned chair of internal medicine at Yale took his usual seat in the first row on the right-hand side of the lecture hall. Then the learning began with the clinical presentation of real patients, who were frequently in attendance. It didn't take but a couple of months for Landsberg, then a first-year medical student, to realize that he was no longer interested in a career in psychiatry.

"Internal medicine at Yale was exciting and compelling," said Landsberg about his choice of specialty. "Intellectually challenging, it was an area of medicine I wanted to pursue." And indeed he did—becoming a leader in his field and reaching the highest ranks of academic medicine.

Landsberg's leadership roles took him from Yale to Harvard and finally Northwestern, where he served as dean of the medical school. During almost half a century of experience as a clinician and teacher, Landsberg distilled his knowledge into aphorisms to teach budding physicians the art and science of caring for ill patients. He often offered his "pearls" of clinical wisdom on rounds and during morning

report, but he never wrote them down—until recently.

Prompted by colleagues and students, Landsberg spent a little over a year recalling from memory the many "pithy statements of fact" now featured in the new book *On Rounds: 1000 Internal Medicine Pearls—Clinical Aphorisms and Related Pathophysiology* (Wolters Kluwer, 2016). The pocket-sized book presents the pearls by organ system for easy reference, featuring information Landsberg deemed most critical to developing mature clinical judgment. For example, a favorite Landsberg aphorism, "Never let a single laboratory result dissuade you from a diagnosis strongly suggested by the weight of the clinical findings," reminds inexperienced-to-seasoned clinicians not to rely solely on the numbers.

The book also includes a few faux pearls to keep readers on their toes. For example, a widely held belief is that antibiotics should be avoided in cases of *Salmonella* enteritis because treatment may result in a prolonged carrier state. Not true, according to Landsberg. "The point is to be aware," he said. "Not everything people tell you is correct."

A master clinician in his own right, Landsberg learned from the very best. A member of Beeson's last internship group, known as the Iron 'Terns, the native New Yorker went on to become chief resident in medicine at Yale-New Haven Hospital under the mentorship of Philip K. Bondy, M.D. Landsberg then completed a research fellowship at the National Institutes of Health in the laboratory of Nobel laureate Julius Axelrod, Ph.D., before returning to Yale as a junior faculty member. In 1972, former Yale professor Franklin H. Epstein, M.D., moved on to Harvard Medical School and lured Landsberg away from his alma mater. During his 18-year tenure at Harvard, Landsberg served as chief of the Division of Endocrinology and Metabolism. Leaving Boston for Chicago in 1990, he became chair of internal medicine at Northwestern and a decade later, dean.

In 2007, Landsberg stepped down from the top spot to launch the Northwestern Comprehensive Center on Obesity. Running the center has given him the opportunity to tackle the problem of obesity with novel clinical approaches and advancements in research, including his own. He has long conducted studies in the areas of catecholamines, dietary intake and the sympathetic nervous system, and obesity and hypertension. It also has afforded him the time to return to teaching medical students and residents—and sharing his pearls.

Landsberg dedicated his book in part to his intern group at Yale, "whose friendship has been a lifelong treasure." He also acknowledged some of the many mentors who helped shaped his career, including Yale professors Beeson, Bondy, and Epstein. Additionally, he thanked his son Judd, a 1996 graduate of Yale's medical school, for "many fruitful discussions" as the book came together.

Over the course of more than 50 years as a clinician, Lewis Landsberg has distilled his knowledge into aphorisms that he shared with younger doctors. Now he has published his pearls of wisdom in a book.

Released last September, the book has already started reaching its target audience. At Northwestern, the Department of Medicine distributed it to residents and faculty members. Internal medicine residency program director Aashish Didwania, M.D., describes it as "extremely accessible and clinically relevant," and containing pearls not easily found in textbooks. Chief medical resident Natasha Nichols, M.D., often uses Landsberg's book after a heavy call day to look for teaching points to discuss on rounds.

While he doesn't carry the book in his white coat, second-year resident Andrew Davis, M.D., appreciates having Landsberg's tried-and-true observations close at hand. "The book taps into how a master clinician thinks, which is one quality that makes it unique."

—Cheryl SooHoo

JIM ZIV PHOTO

How Haifan Lin pushes the envelope on stem cell research

WHEN HAIFAN LIN, PH.D., the Eugene Higgins Professor of Cell Biology and founding director of the Yale Stem Cell Center, arrived in New Haven in 2006, Dean Robert J. Alpern, M.D., Ensign Professor of Medicine, gave him a straightforward albeit Herculean mission: Build a top-notch stem cell research center. Lin took note of School of Medicine researchers whose experiments had already delved deep into stem cells, and asked them to join the center as affiliates.

Over the next decade, Lin established training platforms and programs to help more than 40 labs launch research projects on human embryonic stem cells and induced pluripotent stem cells (iPSCs). He also recruited a handful of fast-rising stars to the center and recruited others to Yale. Now, Yale's 91 stem cell researchers collaborate, troubleshoot, and problem solve across the campus—not just within the brick walls of the center on Amistad Street. The center acts as a hub rather than a hierarchy, and that has encouraged spontaneity and creativity within research experiments, Lin said.

As Lin recalled the center's contributions to stem cell science, he highlighted its breakthroughs in basic biology and innovations in translational science. In 2010, *Time* magazine featured lab-grown lungs created by Laura Niklason, Ph.D., M.D., the Nicholas Greene Professor of Anesthesiology and Biomedical Engineering, as No. 12 out of 50 important inventions that year. (Apple's iPad was No. 34 that year.) For Lin, who began researching stem cells in fruit flies as a postdoc at the Department of Embryology at the Carnegie Institution for Science in Baltimore Md., in the 1990s, the field has advanced at warp speed. "Using stem cells to cure diseases is not a promise of tomorrow, it has begun as a reality of today," he said.

To nominate a subject for Q&A, contact
Yale Medicine, 1 Church Street, Suite 300, New Haven, CT 06510 or email ymm@yale.edu

What aspect of stem cell basic science research excites you most right now? We are exploring new territory within the molecular mechanisms that govern stem cell division. For example, Andrew Zhuo Xiao, Ph.D., assistant professor of genetics, recently discovered a new modification of the DNA structure as a mechanism of gene regulation. DNA carries genetic information, but there are molecules modifying DNA to determine which genes are active or inactive. Xiao found this new kind of modification to be important for embryonic stem cells. He also discovered a specific protein responsible for regulating this modification of DNA. If a stem cell lacks the modification, then its fate will change. Researchers didn't know this form of gene regulation existed in stem cells or any mammalian cells. This is one example of how we are pushing the envelope of knowledge not only on stem cells, but also on basic biology.

Tell us about your own research. In one area of my research, I focus on understanding a new class of genes that produce tiny RNAs instead of proteins. In my lab, we have cloned over 10 million tiny RNAs, a number that is about 400 times more than the total known number of genes. Imagine that the nucleotides that make up a gene are beads on a necklace. Most genes make RNAs that are 1,000 beads (nucleotides) or longer. But these genes make tiny RNAs that have only 24 to 31. These genes are located in the part of the genome that used to be called junk DNA. People thought they had no purpose, but I believed they existed for a reason. The latest research from my lab suggests that these RNA-making genes could be closely related to cancer. Normally, these genes are expressed only in reproductive cells (egg or sperm). But we found that regular cells in the body, called somatic cells, become cancerous when some of these genes are expressed. We have preliminary evidence to show that if you remove the expression of these genes, then it may be possible to slow down cancer development.

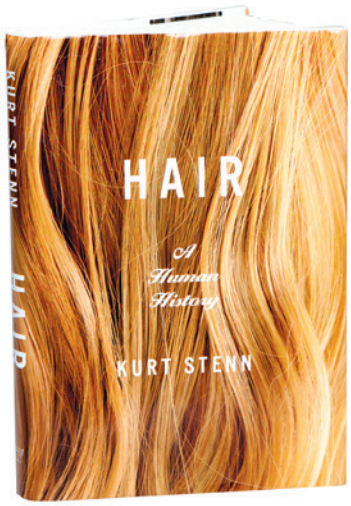
Many universities and colleges have stem cell research centers. How is Yale's different? Many stem cell centers are heavily focused on the translational side. This strategy has its reasons and strengths. However, we started by exploring the basic science to better understand what is going on behind the development and biology of stem cells because the inner working mechanisms of stem cells are still poorly understood. Our strategy is to start by discovering more about the fundamental principles and theories around stem cells, and then apply this new knowledge to translational and clinical research.

Bone marrow transplants were for a long time the only stem cell therapy approved by the Food and Drug Administration. Why don't we have more approved therapies? Several other stem cell–related therapies have recently been approved by the FDA for clinical trial. For example, Yale-New Haven Hospital has the first FDA-approved clinical trial for a bone marrow cell-based therapy for congenital heart defects, which has been very successful. These new approvals reflect the rapid progress of the field. We are still working on the best and most reliable methods for growing millions of stem cells outside the body for therapeutic purposes. A stem cell transplant requires many cells—just isolating the cells is not enough. We also need to find a way to amplify stem cells without changing their properties.

Why was Shinya Yamanaka's discovery of induced pluripotent stem (iPS) cells in Japan in 2006 so important? It offered three huge advantages. The first is ethical. Even a person who favors a conservative approach to stem cell research does not have a problem turning his or her own ordinary cells, such as skin cells, into stem cells for treatment. The second advantage is that iPS cells from a person's body can become various types of tissue cells that will be recognized by our immune system as our own cells, and so you do not have to worry about our bodies rejecting them after transplantation. The third is that we can now obtain all types of cells from our iPS cells instead of directly from our body, which is often impossible. This way we can study the causes of diseases in our tissue cells and try out different treatments without using or hurting our bodies.

Stem cells exist throughout the human body in all organs and tissue, but are rare and difficult to find. Why is that? Because they are the most important cells, so they exist in extremely small numbers and often hide in the most protected locales. Like on a battlefield, the soldiers, or regular cells, are on the frontline. But the commander, or stem cell, is hiding, usually toward the back, in a fortified shelter. That's why we've had to use special methods in the lab to identify stem cells.

TERRY DAGRADI PHOTO



Hair and the course of human history

By Cathy Shufro

The hair on our heads is just the departure point for this wide-ranging book by Kurt Stenn, M.D. The former Yale pathologist and dermatologist moves from the evolution of human hair to hair's effects on culture, psychology, and global trade. By the end of *Hair: A Human History*, a reader might even be convinced that hair makes the world go 'round.

Stenn begins by explaining why we, of all primates, lost most of our body hair: Our ancestors became naked apes to cool their growing and temperature-sensitive brains, which would suffer a meltdown (that is, brain death) at 107 degrees Fahrenheit. Just 10 or 20 minutes of walking, scientists have estimated, would have felled upright fur-covered hominids with heatstroke.

Unlike animal hair, which grows on a fixed cycle and sheds twice a year, human hair follicles stagger their growth. Moreover, each type of human hair abides by its own calendar. A scalp hair shaft will grow for two to six years, allowing humans to wear hair cascading down their backs or in coronas around their heads. Eyelashes remain short because they grow for just 30 days.

Another mammal's hair—sheep's wool—shaped Western culture. English herders raised the best wool, and competed with Flanders to turn it into cloth for the world. The wool trade created the fortunes of such bankers as the Florentines, whose patronage of Michelangelo gave us the Sistine Chapel's painted ceiling. The descendant of an English wool merchant named John Barton placed a sign in the window of his "fair stone house" that exulted, "I thank God and ever shall/It is the sheepe hath payed for all."

The hair of the beaver also changed the course of history. By the 16th century, beaver-felt hats were all the rage in Europe. Hatters who used toxic mercury in the felting process developed dementia—thus, the expression "mad as a hatter." Nonetheless, "everyone who was anyone" wanted a beaver hat, Stenn writes. When the fashion killed off beavers in European forests, traders sailed to North America, where Native Americans bartered pelts for pots, guns, rum, and metal beaver traps. By about 1840, the trade had ravaged the North American beaver population as well.

Animal hair does more than keep us warm and stylish. Bow makers, called archetiers, use horsehair and rosin to create the ribbon on a violin or cello bow. (Stallions from cold climates provide the best bow hair.) Percussionists strike drums using hammers cushioned with sheep's wool felt. Paint brushes contain hair from pigs, squirrels, badgers, and cows.

Research into hair could help solve fundamental scientific problems, Stenn says. For instance, scientists do not fully understand what causes stem cells in the mid-follicle to differentiate into hair shaft cells. "If we understood the hair follicle," says Stenn, "we would probably get a good understanding of the regeneration process of the lung and the kidney and the eye. Biology is so conserved that the law of one organ system is very related to the law of another system."

During two years of research, Stenn visited wigmakers in Japan, studied the anthropology of hair in Paris, learned about furs in Montreal, and toured a wool museum in Wales. Stenn, on the faculty at the School of Medicine from 1971 to 1991 and the former director of skin biology at Johnson & Johnson, now writes full time. Next, he plans an illustrated children's book on hair. "I'll still keep the science in," says Stenn. He may use dogs and cats to demonstrate that fur is directional. "You don't pet your cat from tail to head."

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TERRY DAGRADI PHOTO; OPPOSITE PAGE, ROBERT LISAK PHOTO

Dancing for Donation

ELEVEN COUPLES, including physicians, transplant nurses, an organ recipient, and donor advocates, danced away the night of March 18 at the Aria Banquet Facility in Prospect to raise awareness of organ donation in a time of organ shortages. More than 500 people at the Dancing for Donation Gala, sponsored by Donate Life Connecticut, watched dancers including Yale's own Joyce Alpert, Manuel Rodriguez and Patricia Aguayo, Bill and Christy Asch, Gary and Deborah Desir (in photo), and Frank and Margaret Bia, perform ballroom routines. Donations made on behalf of the teams raised more than $45,000. The event's grand champions, Rodriguez and Aguayo, raised more than $10,000. The Desirs won first place in talent, and the Bias took second place.

—John Curtis