STANFORD MEDICINE

Winter 2018

special report

OUT THERE
CHARTING MEDICINE'S UNKNOWNS

Frankenstein
Shelley's masterpiece still matters

Human organs from animals
Could this solve the donor shortage? Should it?

Brain balls
A boon for studying neurological disorders

The CRISPR conundrum
The power and risk of the revolutionary gene-editing tool

Heart transplant drama
Fifty years ago, the surgery was shocking

Ick!
A conversation with author Mary Roach

plus

In the heavens
A physician-astronaut sutures the International Space Station

New ideas for stroke recovery
Engineers, biologists and doctors focus on a win

STANFORD MEDICINE

Winter 2018

YOUNG BLOOD

TRACE OF HOPE FOR ALZHEIMER'S PATIENTS

Injections of blood plasma from young people show promise for helping Alzheimer's patients regain some ability to perform basic daily tasks that are crucial for independence, according to a small, early phase Stanford clinical trial. The improvement in functional ability was a surprise, says Sharon Sha, MD, a clinical associate professor of neurology and neurological sciences at Stanford and the trial's principal investigator. But she cautions that more study is needed, considering the trial included only 18 people and results were reported by patients or their caregivers. Participants didn't show improvements in either mood or cognition.

"Our enthusiasm concerning these findings needs to be tempered by the fact that this was a small trial," Sha says. "But these results certainly warrant further study."

Sha presented findings from the trial Nov. 4 at the 10th annual Clinical Trial on Alzheimer's Disease conference in Boston.

The trial tested the safety of plasma injections and a hypothesis based on findings by Tony Wyss-Coray, PhD, a Stanford professor of neurology and neurological sciences, that blood from young mice can rejuvenate brain tissue and improve cognitive performance in old mice.

Plasma infusions, which have been widely and safely used for other medical applications, were found safe. The researchers also found hints that people with Alzheimer's who received plasma from young people showed improvements in functional abilities — performing such basic daily life tasks as remembering to take medications, paying bills and preparing meals. The plasma used for the trial was from donors between ages 18 and 30.

The trial was conducted in two stages over six months with people with mild to moderate symptoms of Alzheimer's disease. During the first part of the trial, nine patients received infusions of plasma — the liquid, cell-free part of blood — and nine received a placebo of a saline solution. Participants and their caregivers didn't know which they received. During a second trial phase, people who had been receiving plasma were given the placebo and vice versa.

After each period of infusions, each participant took tests to assess mood, cognitive ability to do such things as memorize lists or recall recent events, and functional ability to perform life tasks.

Sha says participants who received plasma showed no significant changes in mood or cognitive ability, but showed statistically significant improvements on two of three different assessments of functional ability.

The trial was sponsored by Alkahest Inc., headquartered in San Carlos, California. Wyss-Coray is a co-founder of Alkahest but wasn't involved in the clinical study.

"I'm excited to see that giving repeated infusions of plasma to elderly people with Alzheimer's disease is safe and that we can move forward to larger studies," says Wyss-Coray, who is also a senior research career scientist at the Veterans Affairs Palo Alto Health Care System. "But I'm also realistic enough to know that it is very easy to cure diseases in small animals and a million times more difficult in humans." — BRUCE GOLDMAN

JASON HOLLEY

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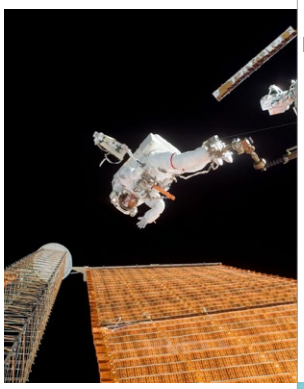

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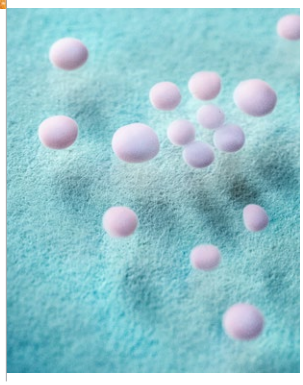

Balls of cells recapitulate brain regions
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DEPARTMENTS

COVER: MICHAEL WARAKSA

letter from the dean

Pitchforks and burning torches. Angry mobs and terrified villagers. These are the images that spring out of the flickering shadows when we talk about Frankenstein. Mary Shelley's iconic monster may seem like an odd starting point for an exploration of ethics in medicine. Indeed, the story of the lumbering brute is more often cited as a cautionary tale about science run amok; the very name of the scientist who created him has become synonymous with unnatural creations.

But as anesthesiologist Audrey Shafer, director of Stanford's Medicine and the Muse medical humanities program, writes in our cover story, there is much to learn from *Frankenstein; or, The Modern Prometheus*. Shelley was writing two centuries ago. The mechanized Industrial Revolution was exploding the social order and many feared where it might lead. Today, medical and scientific breakthroughs are turning last century's science fiction into our reality. For many, that's just as unsettling.

Yet in Shelley's novel, there is no torch-wielding mob. That image comes from the 1931 film starring Boris Karloff, who plays a stiff-legged, grunting beast. By comparison, Shelley's story describes an intelligent creature desperate for companionship and understanding. Indeed, it is through Victor Frankenstein's monster that readers are confronted with their humanity. It is through this nuanced, complex character that we feel compassion and a deep empathy.

At Stanford Medicine, empathy is vitally important to our vision of precision health, which brings together the high tech and the high touch, and recognizes the uniqueness of every individual. This winter, I'm working with the Rev. Professor Jane Shaw, Stanford's dean for religious life, to teach a new undergraduate seminar, Literature, Medicine and Empathy, that will explore the meaning of empathy, especially for those we deem "other."

It is important to note that Shelley's Dr. Frankenstein didn't create a monster. It was Frankenstein's lack of empathy, his own inhumanity, that transformed the creature into one. We fail the new generation of scientific and biomedical leaders when we fail to impress on them the importance of empathy. The good news is that this skill is eminently learnable. The sooner our young students and trainees start exercising these emotional muscles, the sooner they will appreciate the complex implications of their work.

We're living in the golden age of biomedicine. It is an exciting time. New frontiers are opening to us every day, yet without empathy and understanding, we risk becoming a modern Prometheus in our push toward scientific progress. But with a greater awareness of how the arts and humanities should inform our science, and how learning "soft skills" makes for better physicians and scientists, we can confidently push the limits of knowledge to create a better future for everyone.

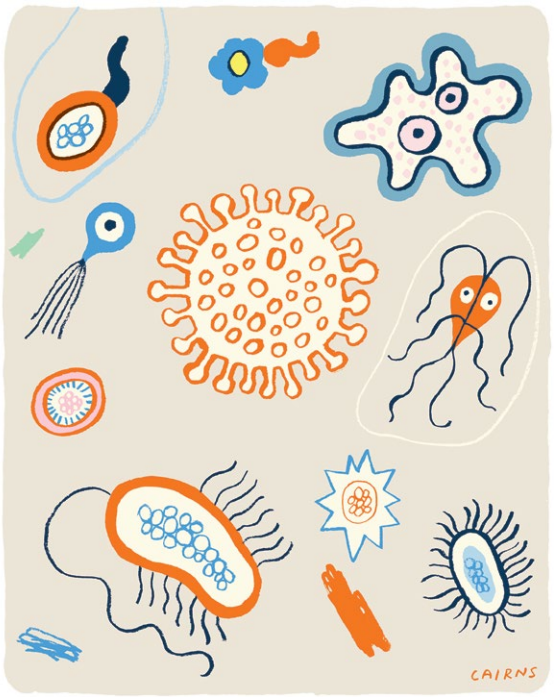
Sincerely,
Lloyd Minor, MD
Carl and Elizabeth Naumann Dean of the School of Medicine
Professor of Otolaryngology — Head & Neck Surgery

GLENN MATSUMURA

upfront

A QUICK LOOK AT THE LATEST DEVELOPMENTS FROM STANFORD MEDICINE

Mystery microbes



BRIAN CAIRNS

STANFORD SCIENTISTS DEVELOPING NONINVASIVE WAYS to detect organ-transplant rejection discovered something that gave them a new appreciation for the wide diversity of the human microbiome.

Traditionally, doctors detect rejection with a biopsy of the transplanted organ itself, a procedure that requires at least an afternoon spent recovering in the hospital. Stephen Quake, PhD, professor of bioengineering and of applied physics, and his team theorized that it might be possible to detect rejection through a less-invasive test: scanning blood samples for organ donors' DNA.

Over the course of several studies, the first of which was published in 2013, Quake and his colleagues collected samples from 156 heart, lung and bone marrow transplant recipients, as well as from 32 pregnant women. Those samples confirmed that blood analysis could detect levels of donor DNA, a sign of rejection, but they also provided data on bacteria, viruses and other microbes that make up a person's microbiome.

"We found the gamut," says Quake, senior author of a study published online Aug. 22 in the *Proceedings of the National Academy of Sciences*. "We found things that are related to things people have seen before, we found things that are divergent and we found things that are completely novel."

Of all the nonhuman DNA fragments the team collected, 99 percent of them failed to match anything in existing genetic databases the researchers examined. And when the team started characterizing the mystery DNA, they zeroed in on a host of viruses that had never been identified.

"There's all kinds of viruses that jump from other species into humans, a sort of spillover effect, and one of the dreams here is to discover new viruses that might ultimately become human pandemics," Quake says.

12%
of Americans have diabetes. Read about what's happening in a body that's on the road to diabetes at http://stan.md/2mCOig9.

Valve replacement insight

Mechanical heart valves are safer in certain cases than valves made of animal tissue, especially for replacing mitral valves, according to a Stanford study.

The study shows that replacements with mechanical mitral valves benefited patients until age 70, but the benefits of using mechanical aortic valves ended after age 55.

The revelation could have a major impact on future procedures, says Joseph Woo, MD, professor and chair of cardiothoracic surgery and senior author of the study published Nov. 8 in *The New England Journal of Medicine*.

upfront

Intensive-care inequities

THE QUALITY of neonatal intensive care in California is inconsistent across racial and ethnic groups, according to a Stanford examination of the care of more than 18,000 of the state's smallest babies at 134 hospitals.

"There's a long history of disparity in health care delivery, and our study shows that the NICU is really no different," says the study's senior author, Jochen Profit, MD, associate professor of pediatrics.

At some California hospitals, infants from vulnerable populations received worse care than white infants, while at others, they received better care. In general, the hospitals with the best outcomes for their patients also delivered better care to white infants. In addition, the study found that black and Hispanic infants were more likely than white infants to receive care in poor-quality NICUs.

The study, using data from the California Perinatal Quality Care Collaborative, was published Aug. 28 in *Pediatrics* and considered overall standards of care and whether they were met, overall quality of care at individual hospitals and health outcomes for the babies.

Addressing the disparities will require a nuanced approach, Profit says. "It's really important for NICUs to individualize care to the patient population they see," he says.

PEANUT BUTTER COOKIE? YES, PLEASE!

THERE'S NEW HOPE FOR KIDS who have multiple food allergies through a treatment that combines a drug with a food desensitization process, according to a study published Dec. 11 in *The Lancet Gastroenterology & Hepatology*.

The phase 2 clinical trial of 48 children ages 4 to 15 showed that most kids who received the antibody drug omalizumab while consuming gradually increasing doses of problematic foods could tolerate the foods at the end of the nine-month study, conducted at the Sean N. Parker Center for Allergy and Asthma Research at Stanford.

"This could be a very promising way to decrease the burden of living with food allergies," says senior author Sharon Chinthrajah, MD, a clinical assistant professor of medicine and pediatrics and director of the center's Clinical Translational Research Unit.

Ready, set, ...

MUSCLE STEM CELLS behave differently in the body than they do when they're removed for study, a revelation that Stanford researchers say could change their view of adult stem cell function.

Muscle stem cells are essential for healing. They exist mostly in a quiescent, or dormant, state in the body until a muscle injury requires them to jump into action. Until recently, scientists believed that very little of the everyday business of normal cells — producing RNA molecules and proteins — was going on in the dormant cells. But research by Thomas Rando, MD, PhD, professor of neurology and neurological sciences, and others has proven otherwise. While previous studies normally analyzed cells after they had been separated for hours from their native environment, Rando's team used a new technology to take a snapshot of the cells' activity while they were still in the body.

The researchers found that the cells are actually hotbeds of RNA production, but they also learned something new — that many of the RNA molecules are either degraded before they have a chance to make proteins or they are made into proteins that are then rapidly destroyed.

"It's possible that this is one way the cells stay ready to undergo a rapid transformation, either by blocking degradation of RNA or proteins or by swiftly initiating translation of already existing RNA transcripts," Rando says.

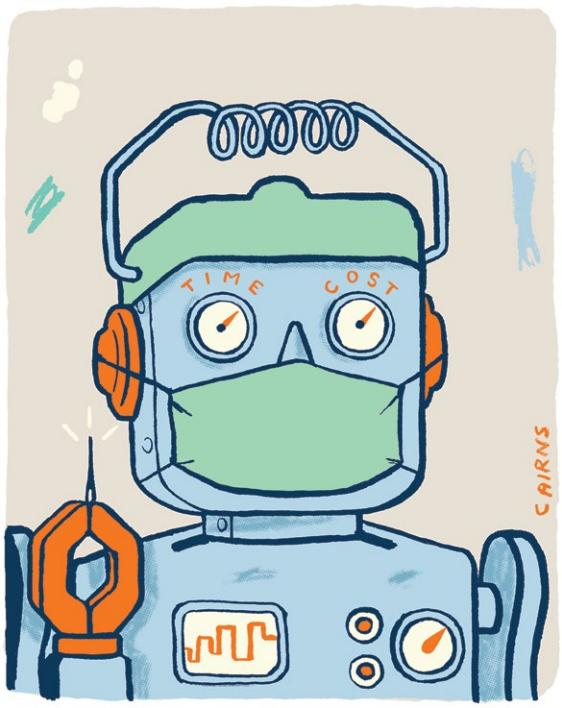
A study describing the research was published Nov. 14 in *Cell Reports*. Rando, the director of Stanford's Glenn Center for the Biology of Aging, is the senior author.

Robotics drawback

IT'S INTRIGUING TO CONSIDER how much more quickly we can accomplish things with help from robots, but a multiyear analysis shows that same efficiency might not be playing out yet in some operating rooms.

A Stanford study of thousands of laparoscopic kidney-removal surgeries from 2003 to 2015 showed that those performed with the help of robots resulted in surgeries that were slightly longer and more expensive.

"Although there was no statistical difference in outcome or length of hospital stay, the robotic-assisted surgeries cost more and had a higher probability of prolonged operative time," says Benjamin Chung, MD, associate professor of urology and senior author of a study published Oct. 24 in *JAMA*.



Researchers speculate that the discrepancy might be because extra time is needed to set up a robotic operating room or because a surgeon is early in the learning curve for using the technology, which was relatively new in 2003 when the study began.

But don't expect an end to the use of robots in operating rooms. While researchers say this particular surgery takes longer, the dexterity and high-tech magnification capabilities of robots can be invaluable to surgeons during procedures with a lot of delicate maneuvering and extensive internal suturing.

"There's a certain incentive" to use the latest technology in medicine, but benefits must be weighed against cost, Chung says. "Although robotic surgery has some advantages, are those advantages relevant enough in this type of case to justify an increase in cost?"

BRIAN CAIRNS

HALTING TUMOR GROWTH

CUTTING OFF THEIR SUPPLY of a particular signaling protein could stop some brain tumors from growing, say School of Medicine researchers.

The protein, neuroligin-3, helps healthy brains function. But the researchers showed in 2015 that the molecule also helps fuel the growth of certain aggressive brain tumors in mice.

The new research went further, showing that cancer cells from any form of these tumors, a particularly deadly group called high-grade gliomas, could not multiply when they were implanted into the brains of mice that were genetically engineered to lack neuroligin-3.

The research, published online Sept. 20 in *Nature*, could lead to new options for treating patients, says senior author Michelle Monje, MD, PhD, assistant professor of neurology, who notes that researchers are working toward a clinical trial.

"We have a really clear path forward for therapy," she says. "Any measurable extension of life and improvement of quality of life is a real win for these patients."

Cancer crushers

A VARIATION OF CD19 CAR T-CELL GENE THERAPY might help people with leukemia who have relapsed or failed to respond to the original therapy, according to a small study. Instead of seeking out CD19 molecules — often found on leukemia cells — and killing the cells, the new therapy targets CD22 molecules, aiming to benefit patients whose leukemia cells lack CD19.

The study's senior author, Crystal Mackall, MD, director of the Parker Institute for Cancer Immunotherapy at Stanford, says 11 of 15 trial patients went into temporary remission, with one still in remission 21 months later. The study was published Nov. 20 in *Nature Immunology*.

Now, Mackall and lead author Terry Fry, MD, a National Cancer Institute researcher, are testing a therapy recognizing both molecules.

Read more about cell therapy for relapsed leukemia patients at http://stan.md/2DCo2e2

why frankenstein matters

FRONTIERS IN SCIENCE, TECHNOLOGY AND MEDICINE

"Clear!" At some point during medical education and practice, every physician has heard or given this command. One person — such as a closely supervised medical student — pushes a button to deliver an electric shock and the patient's body jerks. The code team, in complex choreography, works to restore both the patient's cardiac rhythm and a pulse strong enough to perfuse vital organs.

By Audrey Shafer, MD

ILLUSTRATION BY MICHAEL WARAKSA

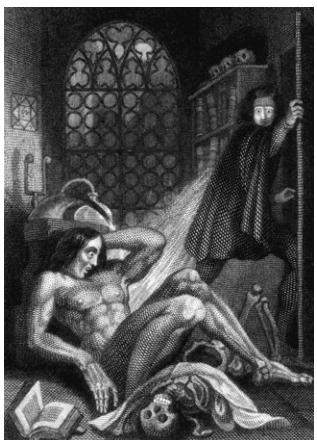
After a successful defibrillation effort, team members do not have time to dwell on the line crossed from death to life. It is even difficult to focus on the ultimate goal: to enable the patient to leave the hospital intact, perhaps to grasp a grandchild's — or grandparent's — hand while crossing the street to the park.

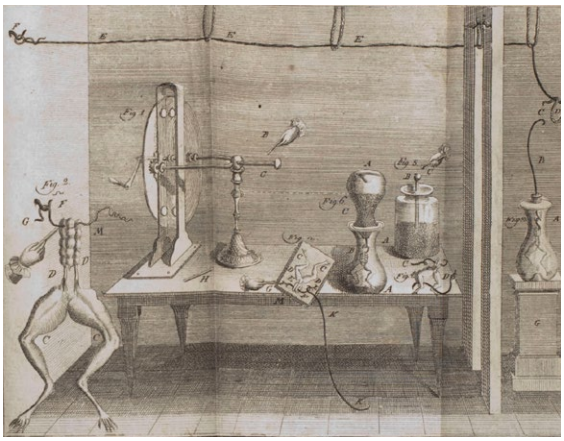
Despite these dramatic hospital scenes, many scientists, doctors and patients balk at any mention of the words Frankenstein and medicine in the same breath. Because, unlike the Victor Frankenstein of Mary Shelley's novel, the reanimators at a hospital code have not toiled alone in a garret; assembled body parts from slaughterhouses, dissecting rooms and charnel houses; or created an entirely new being. Nonetheless, in this bicentennial commemorative year of the book's publication, it is not only germane, but important to consider the impact of this story, including our reactions to it, on the state of scientific research today.

Shelley's *Frankenstein* has captured the imaginations of generations, even for those who have never read the tale written by a brilliant 18-year-old woman while on holiday with Lord Byron, Percy Bysshe Shelley and Dr. John Polidori amid extensive storms induced by volcanic ash during the so-called year without a summer. Mary Shelley (her name was Mary Wollstonecraft Godwin at the time) was intrigued by stories of science such as galvanism, which she would have heard through her father's scientist (then called natural philosopher) friends. With *Frankenstein*, Shelley wrote the first novel to forefront science as a means to create life, and as such, she wrote the first major work in the science fiction genre. Frankenstein, a flawed, obsessed student, feverishly reads extensive tomes and refines his experiments. After he succeeds in his labors, Frankenstein rejects his creation: He is revulsed by the sight of the "monster," whom he describes as hideous. This rejection of the monster leads to a cascade of calamities. The subtitle of the book, *The Modern Prometheus*, primes the reader for the theme of the dire consequences of "playing God."

Frankenstein is not only the first creation story to use scientific experimentation as its method, but it also presents a framework for narratively examining the morality and ethics of the experiment and experimenter. While artistic derivations, such as films and performances, and literary references have germinated from the book for the past 200 years, the current explosion of references to *Frankenstein* in relation to ethics, science and technology deserves scrutiny.

Science is, by its very nature, an exploration of new frontiers, a means to discover and test new ideas, and an impetus for paradigm shifts. Science is equated with progress and with advances in knowledge and understanding of





FRANKENSTEIN BY MARY SHELLEY, LEFT, WAS INFLUENCED BY SCIENTIFIC THEORIES OF THE AUTHOR'S TIME, INCLUDING GALVANISM — THE IDEA THAT ELECTRICITY COULD REANIMATE DEAD TISSUE. THE THEORY IS NAMED AFTER RESEARCHER LUIGI GALVANI, WHO PUBLISHED AN ILLUSTRATED REPORT, RIGHT, ON WHAT HE CALLED ANIMAL ELECTRICITY. AN ILLUSTRATION FROM THE NOVEL'S 1831 EDITION, CENTER, SHOWS THE MONSTER COMING TO LIFE.

CREDIT, FROM LEFT: RICHARD ROTHWELL, GL ARCHIVE/ALAMY; THEODORE VON HOLST, IANDAGNALL COMPUTING/ALAMY; LUIGI GALVANI, *DE VIRIBUS ELECTRICITATIS IN MOTU MUSCULARI COMMENTARIUS*

our world and ourselves. Although a basic tenet of science is to question, there is an underlying belief, embedded in words like "advances" and "progress," that science will better our lives.

Safeguards, protocols and institution approvals by committees educated in the horrible and numerous examples of unethical experiments done in the name of science are used to prevent a lone wolf like Victor Frankenstein from undertaking his garret experiments. Indeed, it is amusing to think of a mock Institutional Review Board approval process for a proposal he might put forward.

But these protections can go only so far. It is impossible to predict all of the consequences of our current and future scientific and technologic advances. We do not even need to speculate on the potential repercussions of, for example, the creation of a laboratory-designed self-replicating species, as we can look to unintended consequences of therapies such as the drug thalidomide, and controversies over certain gene therapies. This tension, this acknowledgment that unintended consequences occur, is unsettling.

The Stanford Medicine and the Muse Program

(http://medmuse.stanford.edu/) hosts a year of interdisciplinary discourse on the implications of *Frankenstein* in our time to encourage discussion and exchange across Stanford Medicine and beyond. Stanford Frankenstein@200 events, courses, and an archive, News of the Post Human, can be found at https://frankenstein.stanford.edu.

Science and technology have led to impressive improvements in health and health care. People I love are alive today because of cancer treatments unknown decades ago. We are incredibly grateful to the medical scientists who envisioned these drugs and who did the experiments to prove their effectiveness. As an anesthesiologist, I care for patients at vulnerable times in their lives; I use science and technology to render them unconscious — and to enable them to emerge from an anesthetized state.

But, as the frontiers are pushed further and further, the unintended consequences of how science and technology are used could affect who we are as humans, the viability of our planet and how society evolves. In terms of health, medicine and bioengineering, *Frankenstein* resonates far beyond defibrillation. These resonances include genetic engineering, tissue engineering, transplantation, transfusion, artificial intelligence, robotics, bioelectronics, virtual reality, cryonics, synthetic biology and neural networks. These fields are fascinating, worthy areas of exploration.

We, as physicians, health care providers, scientists and people who deeply value what life and health mean, cannot shy away from discussions of the potential implications of science, technology and the social contexts which give new capabilities and interventions even greater complexity. Not much is clear, but that makes the discussion more imperative. Even the call "Clear!" and the ritual removal of physical contact with a patient just about to receive a shock is not so "clear," as researchers scrutinize whether interruptions to chest compressions are necessary for occupational safety — that is, it may be deemed safe in the future for shocks and manual compressions to occur simultaneously.

We need to discuss the big questions surrounding what is human, and the implications of those questions. What do we think about the possibility of sentient nonhumans, enhanced beyond our limits, more sapient than Homo sapiens? Who or what will our great-grandchildren be competing against to gain entrance to medical school?

Studying and discussing works of art and imagination such as *Frankenstein*, and exchanging ideas and perspectives with those whose expertise lies outside the clinic and laboratory, such as artists, humanists and social scientists, can contribute not just to an awareness of our histories and cultures, but also can help us probe, examine and discover our understanding of what it means to be human. That much is clear. **SM**

— Audrey Shafer is a professor of anesthesiology, perioperative and pain medicine, and is director of the Medicine and the Muse program at Stanford. Contact her at ashafer@stanford.edu.

growing human organs

By Krista Conger

PHOTOGRAPHY BY TIMOTHY ARCHIBALD

A SLIGHT NOTE OF FRUSTRATION creeps into Hiromitsu Nakauchi's voice when he discusses his research. But it's not because the experiments aren't working, or that he's out of ideas, or that his ultimate goal is just too audacious.

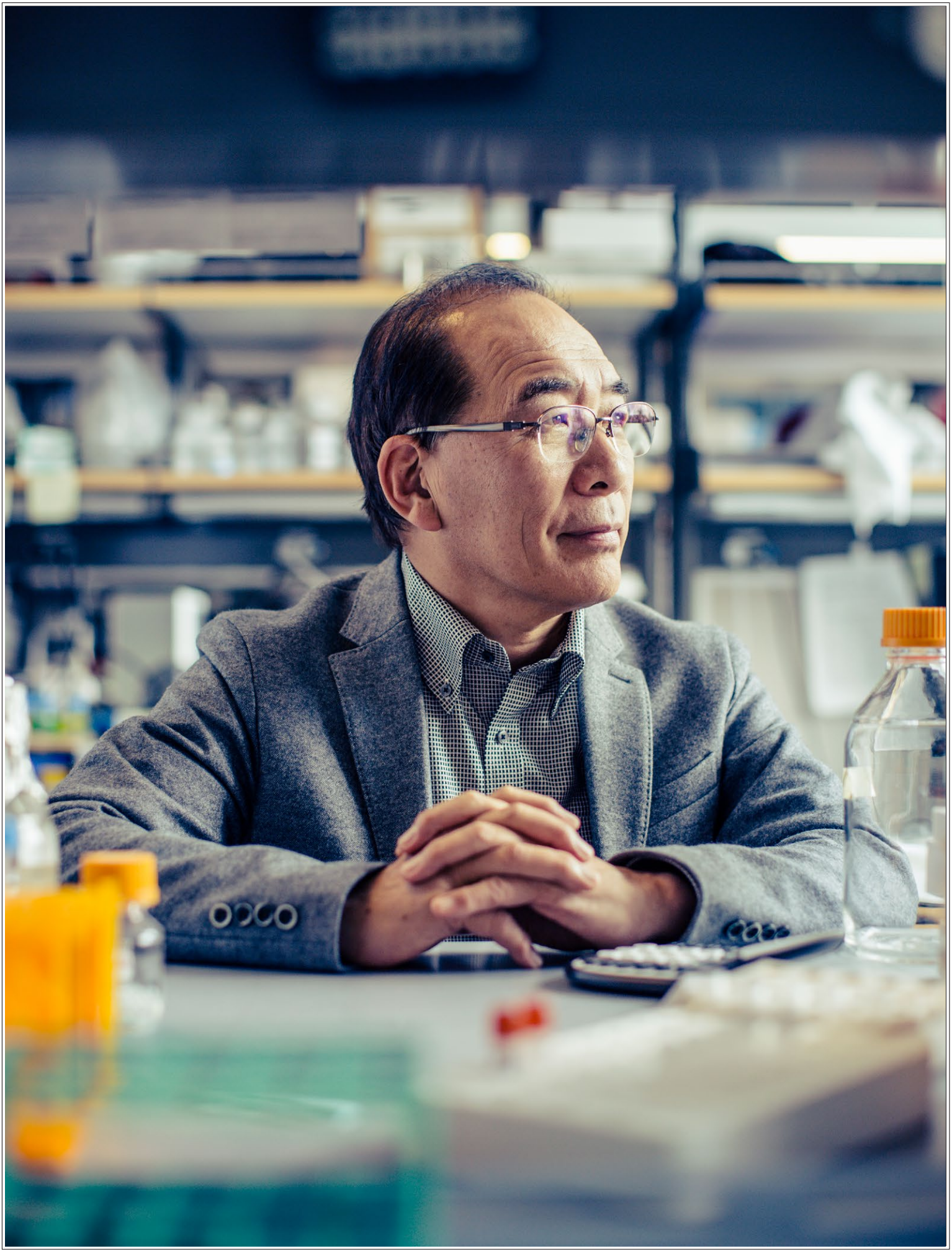
On the contrary, it just might work.

Nakauchi dreams of growing transplantable human organs in large animals like sheep or pigs. Recent advances in stem cell technology would ensure that each organ would be a genetic match for its recipient and would take only months to generate — alleviating the current desperate need for organ donors and subsequent lifelong immunosuppression.

"If we are able to generate human organs in animals we could help many, many people," says Nakauchi, MD, PhD, a professor of genetics at Stanford. "Furthermore, we could also use animal-grown human cells or tissue for toxicology studies or drug screening. Surgeons could practice surgery on intact human organs before operating on patients, and we could study aspects of early human development that have never before been accessible to researchers."

CAUTION SURROUNDS THE USE OF ANIMALS TO SOLVE DONOR SHORTAGES

STANFORD GENETICS PROFESSOR HIROMITSU NAKAUCHI, PICTURED IN HIS LAB, BELIEVES THERE ARE MANY BENEFITS TO GROWING HUMAN ORGANS IN LARGE ANIMALS.



So what's the problem?

Many people cite ongoing ethical concerns about creating sheep, pigs or primates sporting human cells. Could any of these "humanized" animals take on human attributes, intellect or consciousness? Could human cells find their way into an animal's reproductive system to create human eggs and sperm? What are our ethical obligations, if any, to these newly created human-animal chimeras?

Concerns like these prompted the Japanese government to ban the in-animal experiments necessary to determine whether Nakauchi's plan would work. As a result, Nakauchi, who at the time was the director of the Center for Stem Cell Biology and Regenerative Medicine at the University of Tokyo, uprooted his laboratory in early 2014 to come to Stanford, where federal laws about chimeric research and its funding were less restrictive.

But in September 2015 the U.S. National Institutes of Health abruptly announced a moratorium on funding studies in which developmentally flexible, or pluripotent, human stem cells are injected into early animal embryos — again impeding the very work to which Nakauchi has devoted his scientific career, and for which he had already moved across an ocean. Continuing the research without NIH support is legal, but it requires other sources of reliable, substantial funding.

"We can repeat experiments quite quickly in rats and mice," says Nakauchi. "But, although they mature fairly quickly, big animals are not easy to handle and they have specific breeding seasons around which we have to work. The research is very slow and expensive."

To the NIH, the timing of the funding moratorium made sense.

"We were seeing stem cell researchers beginning to pursue lines of inquiry that would eventually lead to the need to introduce human pluripotent stem cells into the early embryos of large vertebrates," says Carrie Wolinetz, PhD, the director of the NIH's Office of Science Policy. "Coupled with the rise of new gene-editing technologies, we felt it was the right time to take a deep breath and carefully consider the potential impact of such work from scientific, ethical and animal welfare angles."

In August 2016, the NIH asked for public comment on proposed changes to the funding guidelines that would allow some of this work to move forward, after a case-by-case review by a committee of experts. They received over 22,000 comments. Nearly all were against allowing the work to proceed. Many cited a reluctance to permit scientists to "play God" by pulling the developmental strings necessary to create human-animal chimeras.

"Although chimeras in general are quite common in biomedical research, I don't know that this was common knowledge to the general public," says Wolinetz. "Also, it seems that many commenters mistakenly believed that the proposed research involved human, rather than animal, embryos."

INTERSPECIES CONCERNS

Regardless of whether you're a philosopher, a biologist or a parent-to-be, the potential of a fertilized egg is staggering. Formerly dormant, the egg has now achieved pluripotency and can give rise to all the tissues of a growing embryo as well as the placenta. The resulting animal or human goes on to romp across the savannah, root in the dirt or govern a nation.

The early developmental dance is strictly choreographed. Fertilization is followed by cell division and, like clockwork, the egg becomes one cell, two cells, four cells, eight cells. Within about three or four days (in humans), the dividing cells have formed a solid spherical clump; after about five days a sphere of about 200 to 300 cells encloses a hollow, fluid-filled cavity called a blastocyst. After 17 days, the embryo enters a stage called gastrulation. During this mind-blowing, three-dimensional contortionist trick, a subset of cells on the surface of the blastocyst first dimple into and then burrow through the sphere to emerge on the other side, forming a tube that will become the digestive tract. (Say hello to your mouth and anus!)

Now the embryo has the structure necessary for the next, and possibly greatest, phase of development: the beginnings of organ formation. This is the stage of most interest for many regenerative medicine specialists seeking to grow human livers, pancreases or other organs in animals.

the earliest embryos of all species are difficult to distinguish from one another

NAKAUCHI CAME TO STANFORD TO CONTINUE RESEARCH THAT WAS BANNED IN JAPAN. THEN HE LOST MUCH OF HIS FUNDING SUPPORT.

The steps taken by the human embryo are shared among most mammals, with variations in timing. A cow, a sheep, a mouse or a rat start out the same, and, at the outset, the earliest embryos of all species are difficult to distinguish from one another.

That similarity is key to what Nakauchi and other regenerative medicine specialists are trying to achieve. If they can successfully integrate human pluripotent stem cells into the very early developmental stages of animal embryos, they could potentially generate biological chimeras composed of a mosaic of human and animal cells. But merging two species is tricky. The evolutionary distances between species can garble the transmission of developmental signaling pathways.

The eventual location and potential functional contributions of the human cells are also wild cards dependent in part on the timing of their introduction into the developing embryo. Those joining the developmental dance early in embryonic development can participate in more steps, and become more different types of tissues, than those cutting in later.

In 2010, Nakauchi successfully generated adult mouse-rat chimeras by injecting rat pluripotent stem cells into mouse blastocysts. Further experiments showed the viability of his dream of one species' organs developing in the bodies of another species: When mouse embryos unable to make their own pancreases were supplemented with rat pluripotent stem cells, the adult animals had a functioning pancreas comprised of rat cells.

Similarly, in March 2013, Nakauchi showed that pig pluripotent stem cells were able to grow a pancreas in a pig that had been genetically engineered to be unable to generate one of its own. The stage was set for similar experiments using human cells.

At the time, those experiments could not be conducted in Japan, despite Nakauchi's outspoken advocacy. Although there were signs of change (a national scientific advisory board recommended in June 2014 that the restrictions be lifted), Nakauchi was concerned that revising the guidelines

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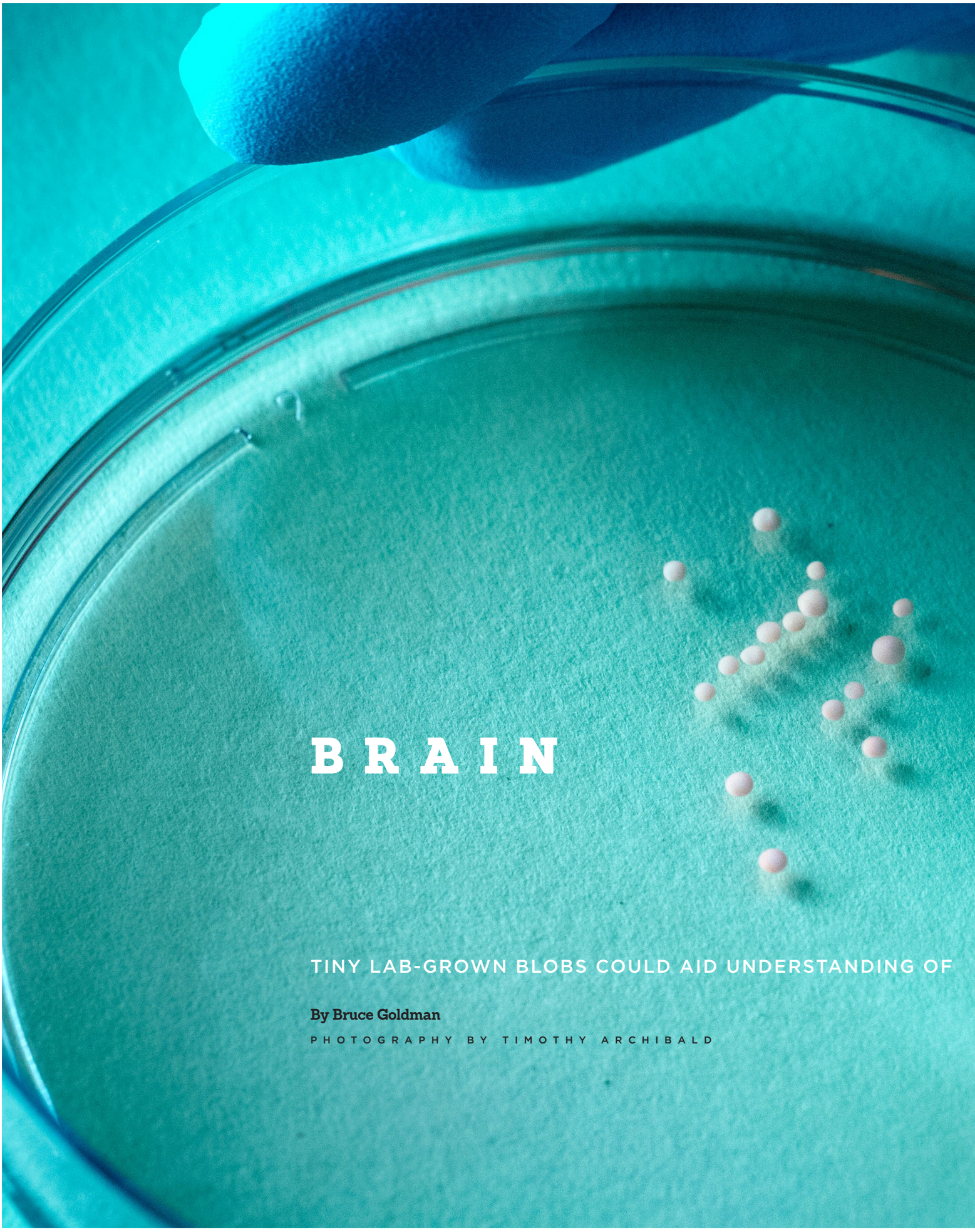


BRAIN

TINY LAB-GROWN BLOBS COULD AID UNDERSTANDING OF

By Bruce Goldman

PHOTOGRAPHY BY TIMOTHY ARCHIBALD

BALLS

NEUROLOGICAL DISEASE

A brain in a bottle, hmmm? And it's helping a Stanford neuroscientist do his research? C'mon. You're kidding, right?

Exaggerating, maybe. Kidding, no. And we're not talking about computers. A Stanford neuroscientist is growing brainlike blobs in dishes, and they're helping him learn a whole lot about his favorite subject.

A brain is a complicated thing — the most complicated thing in the universe, some say — with close to 90 billion nerve cells, or neurons, and some 150 trillion individual neuron-to-neuron connections, called synapses. So, not such an easy entity for researchers to wrap their heads around.

Get out your 3-D glasses, because what follows reads like science fiction: Suppose you hope to learn what goes wrong during early brain development. One could learn a great deal about an individual's neurodevelopmental condition by studying that person's

neurons close up, at the molecular, cellular and circuit levels. But how? You can't exactly scoop a chunk out of someone's living brain. And dead ones don't tell you nearly enough.

Is there a workaround?

A team led by Sergiu Pasca, MD, assistant professor of psychiatry and behavioral sciences, has found one — a technique that reliably and selectively produces pinhead-sized replicas of specific, different human brain parts in laboratory dishware. While researchers had previously developed other ways to culture cells to form brain organoids — minute clumps of tissue enriched for brain cells — these organoids also contained stray cells from other parts of the body, and they lacked the structural organization that characterizes components of a real brain.

PASCA'S METHOD IS NOTABLE because the clumps he's growing contain only cells that are supposed to be in the brain, and because, rather amazingly, the clumps' structures actually recapitulate those of distinct brain regions. His technical term for these little brain balls is brain-region-specific spheroids.

Pasca published his method for creating the brain balls in 2015 and knows of a dozen laboratories around the world that have successfully created them since then. Based on the hundreds of questions he has received about the protocol, he assumes there are many more.

The spheroids enable researchers to zero in on the pathological mechanisms that disrupt fetal brain development in autism, epilepsy and other neurodevelopmental disorders. They can also help neuroscientists understand the causes of faulty brain development in prematurely delivered babies.

"This is our doorway into personalized psychiatry," says Pasca.

A brain ball is not a brain. The constructs are, at present, devoid of some important cell types found in a real human brain. They receive no sensory inputs from the outside world, and they can't initiate muscular contractions. They also lack blood vessels, whose absence means a brain ball has to get its nutrients only at its surface, limiting its size. Scientists are far from being able to grow a brain in a bottle.

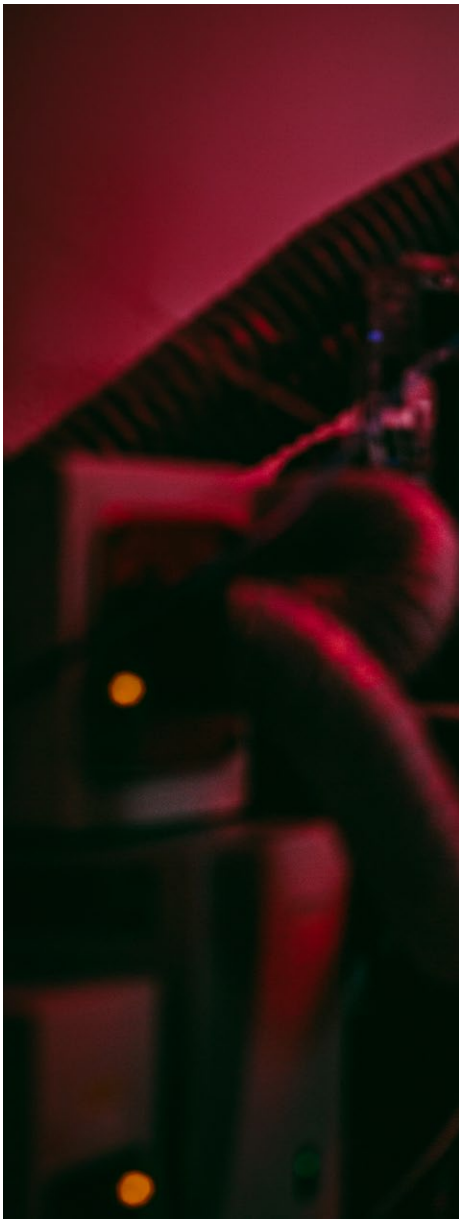
But as researchers learn to create more complex brain organoids and consider transplanting them into animals, ethical quandaries will multiply.

Pasca's interest in research all started with chemistry experiments in his childhood home in Transylvania, a fabled region of Romania where he was born in 1982. He set up a chemistry lab in his parents' basement at age 11 and promptly presented them with his first product: a crater in their backyard. His mastery of the subject improved, and in his final year in high school he won a national chemistry competition and a free ride to a nearby medical school. There, he met the woman who is now his wife, Anca, in a microbiology class. She was from Transylvania, too.

"I was born 30 miles from Dracula's castle," says Anca Pasca, MD, a clinical fellow in neonatology in Stanford's Department of Pediatrics.

Sergiu Pasca realized early in his medical training that his primary interest was research. But the school he was attending was so resource-poor that his biochemistry professor had to tap her own salary to fund his project: analyzing numerous substances in the blood of children with autism in search of a biochemical signature.

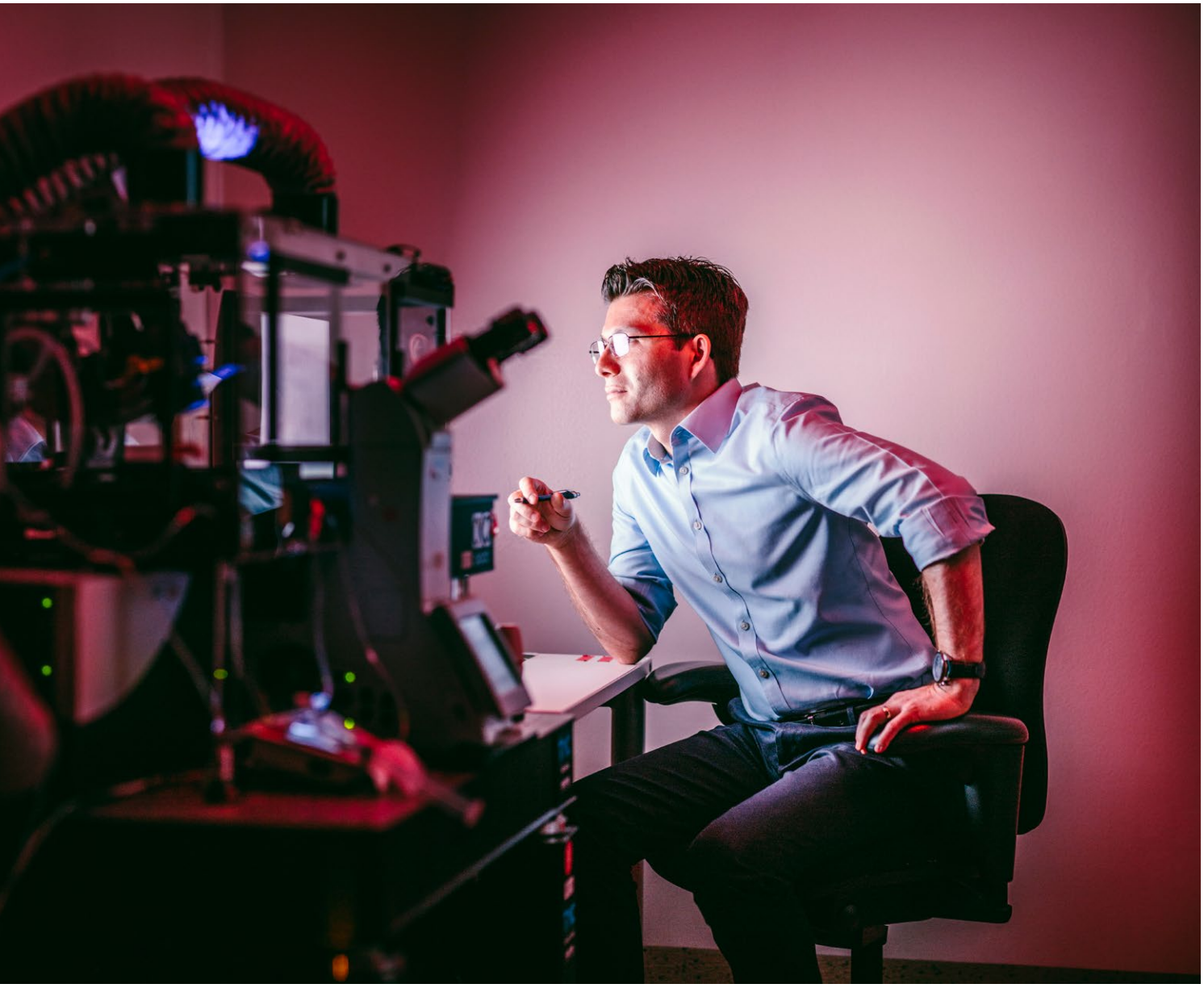
"I needed blood," recalls Pasca, "so I would approach parents outside of a treatment center and ask them if I could get samples from their kids. You might expect the parents to be a little suspicious — after all, this was Transylvania — but instead these people would cry and hug me and thank me for working on this disease."



'THIS IS OUR DOORWAY INTO PERSONALIZED PSYCHIATRY,' PASCA SAYS OF RESEARCH THAT CAN HOME IN ON MECHANISMS THAT DISRUPT FETAL BRAIN DEVELOPMENT.

Eventually, Pasca decided that "blood is pretty far from the brain." He wanted to study autism up close, at the level of the neuron. And he knew exactly where, and with whom, he wanted to study it.

He came to Stanford in 2009 to pursue a postdoctoral fellowship in the lab of Ricardo Dolmetsch, PhD, then an assis-



SERGIU PASCA USES THIS IMAGING SYSTEM TO OBSERVE THE 3-D BRAIN CULTURES HE AND HIS TEAM CREATE TO STUDY BRAIN DEVELOPMENT.

tant professor of neurobiology and now global head of neuroscience at Novartis Institutes for Biomedical Research in Cambridge, Massachusetts. Dolmetsch had redirected his research to autism spectrum disorder after his son was diagnosed with it.

"Coming from an unknown medical school in Romania, without any molecular biology experience, and barely able to speak English, I thought I had no shot at joining such a successful lab," Pasca says. "But Ricardo was looking for somebody with an interest in autism, and he gave me a chance."

When Pasca started his postdoc in 2009, researchers were exploring ways to grow specific cell types from induced pluripotent stem cells, which had recently been discovered. Like embryonic stem cells, induced pluripotent stem cells (known as iPS cells) are capable of differentiating into virtually all the body's different cell types. But unlike embryonic stem cells, iPS cells can be obtained, with relatively routine laboratory procedures, from any person's skin. Dolmetsch wanted to generate neurons derived from the skin of a patient with a rare form of autism called Timothy syndrome that is caused by a genetic mutation. Pasca signed on.

In 2011, Dolmetsch and Pasca succeeded, which allowed them to pinpoint a mutation-induced physiological malfunction responsible for the symptoms of the disorder. Theirs was the first model of autism built from neurons that mirrored those in the brains of patients.

THE SCIENTISTS HOPED TO MONITOR THESE NEURONS' DEVELOPMENT OVER A LONGER TERM. "But the two-dimensional cultures we were using were too constrained," says Pasca. "The cells didn't act quite as they would in a human brain. Most 2-D cultures disintegrate after 100 days or so. But neurogenesis in the human cortex is complete only by 26 weeks of gestation, and astrocytes, brain cells that are absolutely essential for making working synapses between neurons, don't even start getting made until late in gestation."

Pasca resolved to improve the culture situation. That summer, he began noodling around with what he calls a "Saturday experiment" of trying to perfect a three-dimensional environment for culturing brain cells. By coating the bottom of the dish with a nontoxic repellent, he coerced neural progenitor cells to float freely in their nutrient broth, rather than hug the bottom of the dish as is their wont.

Thus suspended, the cells proliferated, differentiated and clustered into tiny balls. These almost perfectly round clusters of cells continued to grow, differentiating further and eventually approaching one-sixth of an inch in diameter and perhaps a million cells apiece, forming brain-region-specific spheroids.

"The 3-D experiments were more of a game in the beginning," Pasca says. "They started as an exploration of how much self-organization one can see in a dish after coaxing stem cells toward a neural fate. I was new to developmental neurobiology and fascinated by how cells assemble to form such complex structures as the mammalian central nervous system."

Anca Pasca, who was doing her pediatrics residency at Stanford during that time, would often come to the lab to do experiments on her own.

"After we moved here in 2009, Sergiu began spending a lot of time in the lab," says Pasca. "We had no friends and no family here, and I was getting bored staying home studying for my medical boards. We started wondering, what if we let these neural progenitor cells just float, suspended, in the dish instead of letting them attach?"

"She thought this could be a big thing," says Sergiu Pasca, "and she continued to work on optimizing the culture medium and characterizing the little spheres."

Initially, Pasca and his colleagues produced brain balls by seeding their 3-D cultures with neural progenitor cells they

PASCA'S SUSPENDED PROGENITOR CELLS PROLIFERATE, DIFFERENTIATE, CLUSTER AND GROW INTO NEURAL SPHEROIDS THAT ARE ONE-SIXTH OF AN INCH IN DIAMETER.

generated from iPS cells grown in standard 2-D cultures. (Pasca now refers to this as the "2.5-D" method.) But eventually they learned how to proceed entirely in three dimensions, starting with actual iPS cells they then guided, in 3-D culture, through the neural-progenitor phase and then all the way to full-fledged, all-brain-and-only-brain brain-ball status.

Pasca's brain balls can remain viable for up to two years or longer in culture — a record duration, long enough not only for the neurons they contain to mature thoroughly, but for their resident neural progenitor cells to spawn viable astrocytes, too. That, in turn, makes it possible for the neurons to form functioning synapses and complex circuits.

BY MID-2014, PASCA had an assistant professorship in a tenure-track job and his own lab at Stanford. He also had multiple rounds of culture-medium optimization and brain ball characterization under his belt.

The neurons in the brain balls acted, for all practical purposes, like the ones in a living brain. Their synapses were in working order, allowing neurons to form complex circuits through which they could talk to one another. These circuits closely approximated the real architecture of the brain region they'd been coaxed to mimic.

> **'WE STARTED WONDERING, WHAT IF WE LET THESE NEURAL PROGENITOR CELLS JUST FLOAT, SUSPENDED, IN THE DISH INSTEAD OF LETTING THEM ATTACH?'**

"I found myself wondering why people hadn't tried this before," says Pasca. In fact, others have used 3-D tactics to produce cultures enriched for brain cells, but they contained haphazard combinations of cells from other tissues. They also lacked the Pasca brain balls' astounding brain-region mimicry.

The key missing ingredient: patience. While others simply allowed their cell cultures to grow in a dish in a hands-off, nondirected fashion, the Pascas and their lab mates coaxed and coached their brain balls along desired developmental pathways by applying various combinations of small-molecule nutrients, trial-and-error style, iteration after iteration.

The Pasca group published its findings in a paper in *Nature Methods* in May 2015. One of the most amazing things about their brain balls was that, with not much chemical guidance, they tended to take on a default structure that's a facsimile of the most evolutionarily advanced part of the brain: the human cerebral cortex, with all six layers you find in a living human brain.

The types and amounts of various proteins that each layer's neurons were manufacturing mirrored those of the equivalent layer in an actual human cortex. And those neurons were alive and kicking: They sported ship-shape synapses, displayed spontaneous activity, fired in networked synchrony and were surrounded, as in real life, by their BFFs: happy, healthy astrocytes. (Astrocytes always pop up spontaneously in brain balls if you culture them long enough.)

"It's amazing that these cells already self-organize and know what they need to do," Pasca marvels.

The iPS cells Pasca's team uses as starter seeds for brain balls are generated from skin cells, so researchers can produce brain balls whose cells are genetically identical to the brain cells in the person whose skin is used. That makes brain balls powerful tools for studying any neurological disorder with a genetic component.

"Early on, I didn't really believe this was going to work," he says. "But Anca continued to help me optimize the protocols for the culture system until it did."

Anca Pasca was a lead author of her husband's 2015 paper, and he credits her for much of the hands-on work that helped to turn those "Saturday experiments" to a front-burner project. Her co-lead author, Steven Sloan, PhD, is an MD student who did his graduate work in the laboratory of the late Ben Barres, MD, PhD. On acquiring his PhD, Sloan has continued his research in the Pasca lab.

Throughout his postdoc period and beyond, Sergiu Pasca also was encouraged in his 3-D culture push by Barres, whom he calls his "second mentor." Barres, who died in December 2017, was a professor of neurobiology, of developmental biology and of neurology and neurological sciences. Much of what's known about astrocytes stems from Barres' decades of research.

The two notoriously late-night workers would engage in conversational collisions in the hallway or stop into each other's adjacent offices when they saw the light on. Later, when Pasca moved his lab to a new location, they would often exchange emails or text messages until early morning.

"He really believed this could be done when nobody else did," Pasca says. Barres also gave him an ultimatum: "He'd warn me that if my cultures weren't producing astrocytes, they were crap."

"Sergiu has accomplished something quite magnificent," said Barres in an interview before his death. "The power and promise of this method is extraordinary. You can watch all kinds of brain diseases developing in a dish."

A brain ball isn't limited by fate to become a little cortex Mini-Me. With the right factors supplied at the right time, each can take on (neuroanatomically speaking) a personality of its own. This means researchers can make brain balls that

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CRISPR is a revolutionary gene-editing tool, but it's not without risk

target, delete, repair

ONCE A MONTH, DAVID SANCHEZ, 15, comes to Lucile Packard Children's Hospital Stanford for an infusion of donor red blood cells. David was born with sickle-cell disease, an inherited disorder caused by a mutation in one gene among the roughly 20,000 in our DNA.

David's monthly infusions offer only temporary relief from the debilitating and potentially deadly complications of his disease. But what if his genetic disease — and thousands of others — could be cured by simply fixing the mutation? Researchers are betting they can with CRISPR, a powerful technology that allows scientists to quickly target, delete and repair any mutated sequence of DNA in any gene.

Other gene-editing tools have emerged in recent years, but none seems to match the precision, low cost and usability of CRISPR, which is rapidly transforming genetic research and has entered testing as a medical treatment.

"It's no exaggeration to say that CRISPR has been revolutionary," says Mark Mercola, PhD, a professor of cardiovascular medicine and a member of the Stanford Cardiovascular Institute. "With CRISPR, we can do genetic experiments that would have been unimaginable just a few years ago, not just on inherited disorders but also on genes that contribute to acquired diseases, including AIDS, cancer and heart diseases."

by Mark Shwartz

ILLUSTRATION BY JASON HOLLEY
PHOTOGRAPHY BY TIMOTHY ARCHIBALD

CRISPR was introduced to the world in 2012, and the technology has since generated a tsunami of research. Barely a week goes by without news of another CRISPR "breakthrough." But the rapid pace of discovery has raised questions about the regulation and oversight of this gene-altering tool.

Some fear that CRISPR will be used to create designer babies with desirable physical traits and talents. Others are concerned about ongoing experiments to alter the DNA of disease-spreading insects and to genetically enhance crops and livestock, in part because of unintended impacts on the environment. Laboratories have already used CRISPR to engineer bigger tomatoes, longer-lasting mushrooms and leaner pigs for CRISPR bacon — items that may one day appear on your grocery shelf.

"When it comes to experiments on animals, plants and microbes, two things worry me," says Stanford bioethicist Hank Greely, JD, a professor of law. "One is the intentional misuse of CRISPR. The other is that people with good intentions will inadvertently cause harm.

"But for treating classic genetic diseases like sickle cell, I think CRISPR will be transformative," he adds, "and that's a great thing."

'For treating classic genetic diseases like sickle cell, I think CRISPR will be transformative, and that's a great thing.'

LIVING DAY TO DAY

OUR GENES ARE ENCODED with instructions for making proteins. The "letters" in that genetic code are four chemical building blocks — adenosine, cytosine, guanine and thymine, known simply as A, C, G and T.

The DNA double helix in humans consists of 6 billion of these building blocks arranged in a specific order, but a single error in that sequence can be deadly. Scientists have identified more than 10,000 inherited diseases caused by a single defective gene, many incurable, like cystic fibrosis, hemophilia, muscular dystrophy and Tay-Sachs.

In sickle-cell disease, for example, one building block — an A — is mistakenly converted to T in a gene that makes hemoglobin, the protein in red blood cells that delivers oxygen from the lungs to the rest of the body.

"It's like having one typo in a book containing 6 billion letters," says Matthew Porteus, MD, PhD, an associate professor of pediatrics at Stanford, and a scientific co-founder and advisory board member of CRISPR Therapeutics, a company that uses CRISPR technology. "We spent six years trying to repair that one mutation using older gene-editing technologies, but with CRISPR, we finally had a tool that was much easier to use and far more efficient."

Hemoglobin helps red blood cells maintain a smooth, round shape, which allows them to move freely through blood vessels. But in sickle-cell disease, the damaged gene produces stiff, sticky red blood cells that collapse into a sickle shape after delivering oxygen. The sickled cells often clump together, causing excruciating pain and blocking the flow of oxygen-rich, normal red blood cells to vital organs.

For David Sanchez, prolonged blockages have led to chronic kidney disease and permanent damage to his spleen. By age 10, he had been admitted to Packard Children's Hospital twice with acute chest syndrome, a potentially fatal condition that occurs when sickled cells block the flow of oxygen to the lungs.

"The hospital is my second home. I always have good doctors here," says David, who has also experienced back pain so severe he could barely walk.

"He's been poked and poked since infancy," says Dolores Sanchez, David's grandmother and legal guardian. "We live day by day and try to give him the best quality of life. Just let him be a child."

Sickle-cell disease affects about 100,000 people in the United States, primarily African Americans, and millions more worldwide. About 15 percent of patients can be cured with a bone-marrow transplant from a healthy sibling.

"Even with the best care, patients in the U.S. typically die in their mid-40s. In low-income countries where medical care is poor, many children die before age 5," says Porteus.

But for David and millions of others, the most promising approach may be genetic engineering. Next year, Porteus hopes to launch Stanford's first clinical trial of CRISPR. The goal: correct the genetic typo that causes sickle-cell disease so that patients like David can live long, healthy lives.

GIFT FROM MOTHER NATURE

THE CRISPR REVOLUTION SWEEPING through laboratories around the world has humble roots that go back billions of years.

"CRISPR is a gift from Mother Nature," says Stanley Qi, PhD, an assistant professor of bioengineering and of chemical and systems biology, and the scientific co-founder of Refuge

DAVID SANCHEZ, AT HOME WITH HIS GRANDMOTHER DOLORES SANCHEZ

Biotechnologies Inc., which uses CRISPR technology. "It was first observed in 1987, when researchers in Japan noticed a weird, repeating sequence in the DNA of *E. coli* bacteria."

Later studies found repeating segments of DNA in other microbial species. These mysterious repeats consisted of a short sequence of genetic code and a similar sequence in reverse. This peculiar palindrome pattern was dubbed CRISPR — "clustered regularly interspaced short palindromic repeats."

Further research led to the discovery of CRISPR-associated (Cas) genes, which produce Cas enzymes that can slice through DNA. Scientists eventually realized that bacteria have been using CRISPR-Cas complexes for billions of years to attack and destroy enemy viruses, and that this ancient bacterial immune system could be adapted for use in genetic engineering.

In 2012, UC-Berkeley professor Jennifer Doudna, PhD, and colleagues showed how CRISPR and the enzyme Cas9 could be quickly engineered to find and cut specific sequences of DNA in a test tube. The following year, separate studies by Doudna and others — including an MIT team led by Stanford alumnus Feng Zhang, PhD — demonstrated that CRISPR-Cas9 could be programmed to edit human DNA.

"These landmark studies demonstrated the power of CRISPR-Cas9 to target and delete any sequence of DNA in the human genome," says Qi, a former PhD student in Doudna's lab. "It's a simple process. To fix a damaged gene, you begin by designing an RNA molecule that matches the mutated DNA sequence in that gene. You then combine the RNA with a Cas9 enzyme, which can cut through DNA like a sharp scissors. The RNA acts like a very fast GPS — it guides the Cas9 enzyme to the mutated DNA sequence. The enzyme then binds to the sequence and deletes it."

The final repair can be done using a benign virus that's engineered to deliver and insert the correct DNA sequence into the edited gene. The result is a normal gene free of the disease-causing mutation.

Older gene-editing tools use proteins instead of RNA to target damaged genes. But it can take months to design a single, customized protein at a cost of more than $1,000. With CRISPR, scientists can create a short RNA template in just a few days using free software and a DNA starter kit that costs $65 plus shipping. Unlike protein-based technologies, the RNA in CRISPR can be reprogrammed to target multiple genes.

CLINICAL TRIAL

THE PROPOSED STANFORD clinical trial will focus on the stem cells in our bone marrow that produce red blood cells.

People with sickle-cell disease have two defective hemoglobin genes in their stem cells, one from each parent. Together, the two defective genes are what cause red blood cells, which are normally disc-shaped and flexible, to become stiff and sticky as they mature.

People who inherit one defective gene and one normal gene have what is known as sickle-cell trait, a condition that affects about 3 million Americans. Most of their red blood cells are normal, allowing them to lead healthy lives free of sickle-cell disease. However, the abnormal hemoglobin gene in their DNA can be passed on to their children.

In his trial, Porteus plans to repair and replace defective blood stem cells in patients with sickle-cell disease. The idea is to transform the patients into healthy people with sickle-cell trait by converting their defective stem cells with two abnormal hemoglobin genes into stem cells with just a single abnormal gene.

CRISPR's job will be to remove the mutated DNA sequence from one of the genes.

"Our first step will be to design CRISPR-Cas9 to locate and delete the DNA mutation," says Porteus. "But that won't fix anything. We also have to engineer a virus to deliver the correct sequence of normal DNA."

Once the gene has been repaired, the newly modified stem cells with sickle-cell trait will be injected back into the patient's bloodstream. Ideally, some will find their way into the bone marrow and start cranking out millions of healthy red blood cells.

"We'll probably have to use chemotherapy to create a space in the patient's bone marrow for the corrected stem cells to be taken up," says Porteus.

"The repaired stem cells could create enough normal red blood cells for the patient to be symptom-free for life," he adds. "That's the ultimate goal."

'The repaired stem cells could create enough normal red blood cells for the patient to be symptom-free for life. That's the ultimate goal.'

70 PERCENT THRESHOLD

THE CRISPR PROCESS DOESN'T have to be perfect to be effective, says Porteus. That's because symptoms of the disease occur only if the proportion of sickled cells in the bloodstream is above 30 percent. If at least 70 percent of the red blood cells are healthy, the patient is symptom-free.

"Having 20 percent corrected stem cells in the bone marrow will probably be sufficient for most patients to get above the 70 percent threshold," explains Porteus. "That's because healthy red blood cells live about five times longer than diseased cells and quickly outnumber them."

Monitoring the modified stem cells to make sure they are producing enough healthy red blood cells will be crucial, he adds.

"The proof will come when we follow the patients over time and see whether they have any symptoms of the disease," says Porteus. "They could remain symptom-free, or they might need additional treatments. Some things we'll know in a month, others in 10 years."

MATTHEW PORTEUS IS PLANNING A CLINICAL TRIAL OF CRISPR AT STANFORD TO TREAT SICKLE-CELL DISEASE.

Patients like David are well aware of the 70 percent target. Every Monday he undergoes a blood test at a hospital clinic to measure his sickle-cell count. The results determine how much healthy donor blood he will receive at his next infusion, which is part of a three-hour procedure known as apheresis, where David's diseased red blood cells are removed and replaced with normal donor cells.

But the benefits of the infusion last only about a month, during which time his defective stem cells continue to function, producing more diseased red blood cells.

Prior to his infusion last November, David's count had risen to 24 percent, slightly below the level that triggers new symptoms. But after the infusion, the proportion of sickled cells dropped to just 12 percent.

Staying above the 70 percent threshold has reduced many of David's symptoms. But last spring, intense headaches forced him to withdraw from school. He was diagnosed with moyamoya disease, a potentially lethal condition caused by blockage in the arteries to his brain. He had surgery at Packard Children's to bypass the blocked arteries and restore blood flow.

"The brain surgery saved his life," says Jennifer Andrews, MD, MSc, David's primary doctor, a clinical associate professor of pathology and of pediatrics. "Without it, he could have had a major stroke."

His grandmother recalls the day of the procedure: "Before he went into surgery I said, 'Baby, aren't you scared?'" she says. "He said, 'No, Nana, would you rather take care of me like I am now, or after I have a stroke?' He's a very compassionate child."

David recovered from the surgery and has enrolled as a freshman in an online high school that lets him study at his own pace. That way he doesn't have to worry about missing class because of lengthy medical procedures or when symptoms recur.

If the CRISPR clinical trial at Stanford is successful, monthly infusions of donor red blood cells for people with sickle-cell disease could be a thing of the past.

"I think it's great that people are working with CRISPR to cure sickle cell and other diseases," says David. "It's really cool that they could come up with something like this. So many people have lives that could be so much better."

DESIGNER BABIES

Clinical trials of CRISPR like the one Porteus is proposing have broad public support, in part because using CRISPR in adults and children would alter their DNA, but not that of their offspring.

Editing human embryos to repair disease-causing genes is far more controversial. One concern is that CRISPR occasionally targets and removes the wrong gene. One off-target event could have serious consequences for newborns and their descendants.

"The idea of editing human embryos makes a lot of people queasy, and it should," says Mercola. "CRISPR isn't perfect, and when you alter embryonic DNA, the results are passed from one generation to the next."

Public anxiety was heightened in 2015 when scientists in China used CRISPR to edit human embryos for the first time. Although the experimental embryos were not viable, some worried that fertility clinics would start using CRISPR to genetically engineer children with traits parents might want, like making them stronger, taller or smarter.

"People are most worried about enhancement, using CRISPR to give babies superpowers," says Greely. "But we don't know now any genes that give people superpowers. For practical and regulatory reasons, we're not going to be CRISPRing embryos and making designer babies any time soon."

Greely also sees little justification for using CRISPR in embryos to prevent disease.

"Very few people will need to do gene editing to have

healthy babies," he argues. "Almost every genetic disease can be avoided using preimplantation genetic diagnosis. Rather than changing genes in an embryo, you just select an embryo that doesn't have the dangerous genes. PGD has been around for almost 30 years. It's safe and effective."

In a 2017 report, the National Academy of Sciences recommended that, for now, CRISPR and other gene-editing tools be permitted only in human clinical trials aimed at curing and preventing serious diseases, not enhancing babies.

PROCEED WITH CAUTION

Sickle-cell disease seems well-suited for CRISPR gene therapy because it targets a specific type of cell, according to the 2017 NAS report. Other inherited diseases such as cystic fibrosis and muscular dystrophy may be more difficult to treat because they affect different cell types in different organs. Despite these challenges, a number of labs are using CRISPR to find cures for these and other genetic diseases in adults and children.

"For what we're doing, CRISPR has made things easier," says Porteus, who served on the NAS report committee. "The momentum for developing new gene therapies is incredible. We want to move fast because the patients deserve that, but we want to move carefully. We don't want to do something that causes a huge setback."

Gene therapy did suffer a major setback in 1999 when an 18-year-old man with an inherited liver disease died during a clinical trial at the University of Pennsylvania. Researchers had injected what was thought to be a harmless virus carrying a modified gene into the man's liver. But the virus ran amok, triggering a severe immune response, and the young man died four days later.

Before then, gene therapy had been considered a promising, breakthrough treatment for many diseases, but the clinical-trial death stopped other researchers in their tracks.

Fast forward to 2016, when a different group from the University of Pennsylvania asked a federal panel to greenlight the first-ever clinical trial using CRISPR. The trial was designed to genetically alter immune cells in cancer patients, then reinject the modified cells to see if they improve the immune system's ability to fight off the disease.

Hearings were held before the Recombinant DNA Advisory Committee, a panel of experts that advises the director of the National Institutes of Health on whether to approve federally funded gene-transfer trials.

"There was a lot of trepidation at the hearings, in part because the cancer protocol is so complex," says Stanford bioethicist Mildred Cho, PhD, who is a member of the advisory committee. "It requires manipulating lots of different systems at the same time, especially the immune system, which is not fully predictable."

Unresolved questions about the 1999 fatality persisted throughout the hearings, but the committee ultimately recommended that the clinical trial proceed using CRISPR.

"In the 1999 case, a genetically altered virus was infused directly into the patient's liver, so there was little control on where it spread through the bloodstream," says Cho, a professor of pediatrics and of medicine. "But most CRISPR protocols are *ex vivo* — they take the cells out of the body, manipulate them and then put them back. That, at least, allows for some kind of risk assessment to see if there are any off-target gene modifications, or if they've turned the immune cells into cancer cells by accident."

Even if CRISPR proves successful, Cho worries that for many patients, the financial cost will be prohibitive.

"Gene therapy is not the same as taking a pill from the pharmacy," she says. "It's more like getting an organ transplant. It's a very complex procedure. Cancer immunotherapy already costs in the hundreds of thousands of dollars per year. There's no way that gene-edited treatments are going to be any less expensive."

RUNAWAY EVOLUTION

Cho is also concerned about using CRISPR to control entire populations of disease-spreading animals, like mosquitoes that carry malaria and mice that transmit Lyme disease. Researchers are exploring ways of altering the DNA in these and other fast-breeding species so that future generations cannot spread disease.

But attempts to manipulate nature, though well-meaning, sometimes backfire.

"We don't have the ability to control runaway evolutionary changes to wild populations," says Cho. "There's no regulatory framework to test mosquitoes and other modified organisms. Once they're released in the wild, it's hard to reverse any inadvertent effects."

CRISPR also makes it easier for people with bad intentions to do harm, adds Greely.

"Smallpox has been eradicated in the wild," he says. "But if you want to make a biological weapon, you can use CRISPR to turn ordinary cowpox virus into smallpox."

What's needed, Greely says, are well-thought-out, well-enforced federal regulations that make it difficult for CRISPR to be misused accidentally or intentionally.

"The Obama administration listed gene editing as one of the four biggest threats to the country," he says. "It might be

The power of CRISPR

IT'S NOT JUST FOR GENE THERAPY

Researchers around the world have quickly adopted the new gene-editing tool known as CRISPR to solve mysteries about the human body. At Stanford, scientists are refining the tool itself and putting it to work.

How hearts develop

"My lab focuses on discovering new drug targets to fight heart disease," says Mark Mercola, PhD, a professor of cardiovascular medicine. "One of our biggest unsolved problems is figuring out which genes and proteins are involved in embryonic heart development."

In 2015, Mercola's team found evidence that a family of proteins called Id plays a key role in transforming human embryonic stem cells into heart muscle cells. But not everyone was convinced.

"We submitted our paper to the journal *Genes & Development*, but the editors told us we were wrong," he recalls. "They wouldn't even send the paper out for review."

The editors pointed to a 2004 Cornell University study, where researchers knocked out the genes that make Id proteins in mouse embryos, yet the embryos developed tiny, beating hearts. The results seemed to prove that heart muscle cells can develop even after the Id proteins have been removed.

It would take more than a decade, and the discovery of CRISPR, for the full story to be told.

"There are actually four different Id genes, but the Cornell group only knocked out three of them," says Mercola. "It required years of breeding generations of mice. Back then, a quadruple Id knockout would have been unthinkable. But with CRISPR, why not?"

Armed with CRISPR, Mercola and his co-workers returned to the lab and simultaneously knocked out all four Id genes in the embryos of mice.

The results were dramatic: The quadruple knockout produced heartless embryos, confirming that Id is essential for early heart formation. The entire experiment took months to complete instead of years.

"Five years ago, the idea of doing a quadruple knockout would have been crazy, but with CRISPR you don't even do any breeding," Mercola says.

He and his colleagues submitted their results to *Genes & Development* in 2017, and the study was published that year.

Gene toggler and chromosome bender

Stanley Qi, PhD, has invented an alternative version of CRISPR that lets scientists control a gene without destroying it. He calls the reversible system CRISPRa/i, shorthand for CRISPR activation and interference. In a few short years, it's become a standard research tool in biomedicine.

"CRISPRa/i allows you to turn specific genes on and off repeatedly," says Qi, an assistant professor of bioengineering and of chemical and systems biology. "You can simultaneously activate or repress a whole set of genes and see how different genes interact and affect the course of complex diseases, like cancers and Alzheimer's."

Kevin Wang, MD, PhD, an assistant professor of dermatology, is using a similar technique to study how the three-dimensional configuration of DNA — its various loops and curls — affects a gene's function. His invention is the first technology capable of reversibly creating artificial loops in mammalian chromosomes to modulate gene expression.

Wang predicts that many new applications will emerge as CRISPR matures.

"CRISPR is kind of like Legos," he says. "You can add anything you want to it."

ISIS or North Korea. I guarantee that there are people in Washington, D.C., very worried about this."

CRISPR MODEL T

STILL, THE PROMISE THAT CRISPR offers keeps researchers focused on the future.

Beyond treating individual patients, the most important application of CRISPR may lie in the discovery of new drugs for dozens of intractable diseases, says Mercola. "We're just scratching the surface in the drug-target space," he says. "For me, that's where this field is going. CRISPR is a great example of how basic research can lead to something of tremendous utility in a record amount of time."

At Stanford, recruitment of participants for the sickle-cell clinical trial could begin early next year. But more work is needed to demonstrate that stem cells altered with CRISPR are ready to be tested in people. Last year, Porteus received a $5.2 million grant from the California Institute for Regenerative Medicine to fund that additional research.

Donated human stem cells are now being processed at the Stanford Laboratory for Cell and Gene Management, a large facility dedicated to making biological materials that meet the rigorous federal standards for clinical trials, including a high level of sterility and a strict protocol for chain of custody.

"Before the lab opened in 2016, there was no way for us to conduct an entire clinical trial at Stanford," says Porteus. "We'd have to send the stem cells to a company off campus for processing. But the new lab demonstrates a major commitment by Stanford to be at the forefront of gene therapy just as this promising field is emerging."

Greely compares the invention of CRISPR today to the rollout of the Ford Model T a century ago.

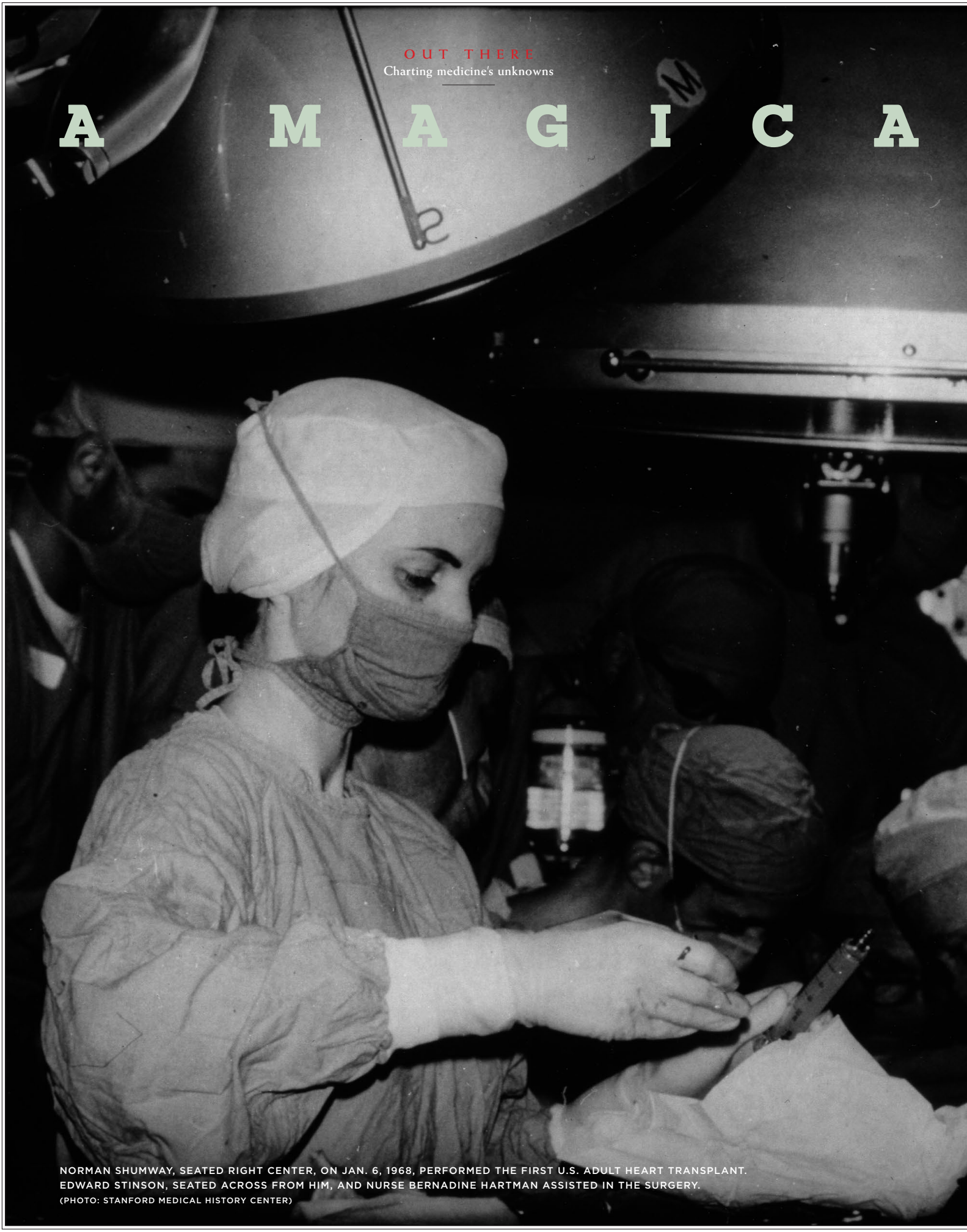
"The Model T was cheap and reliable, and before long everybody had a car and the world changed," he says. "CRISPR has made gene editing cheap, easy and accessible, and therefore more common. I think it's going to change the world. Exactly how beats me." SM

— Contact Mark Shwartz at medmag@stanford.edu

OUT THERE

Charting medicine's unknowns

AMAGICA

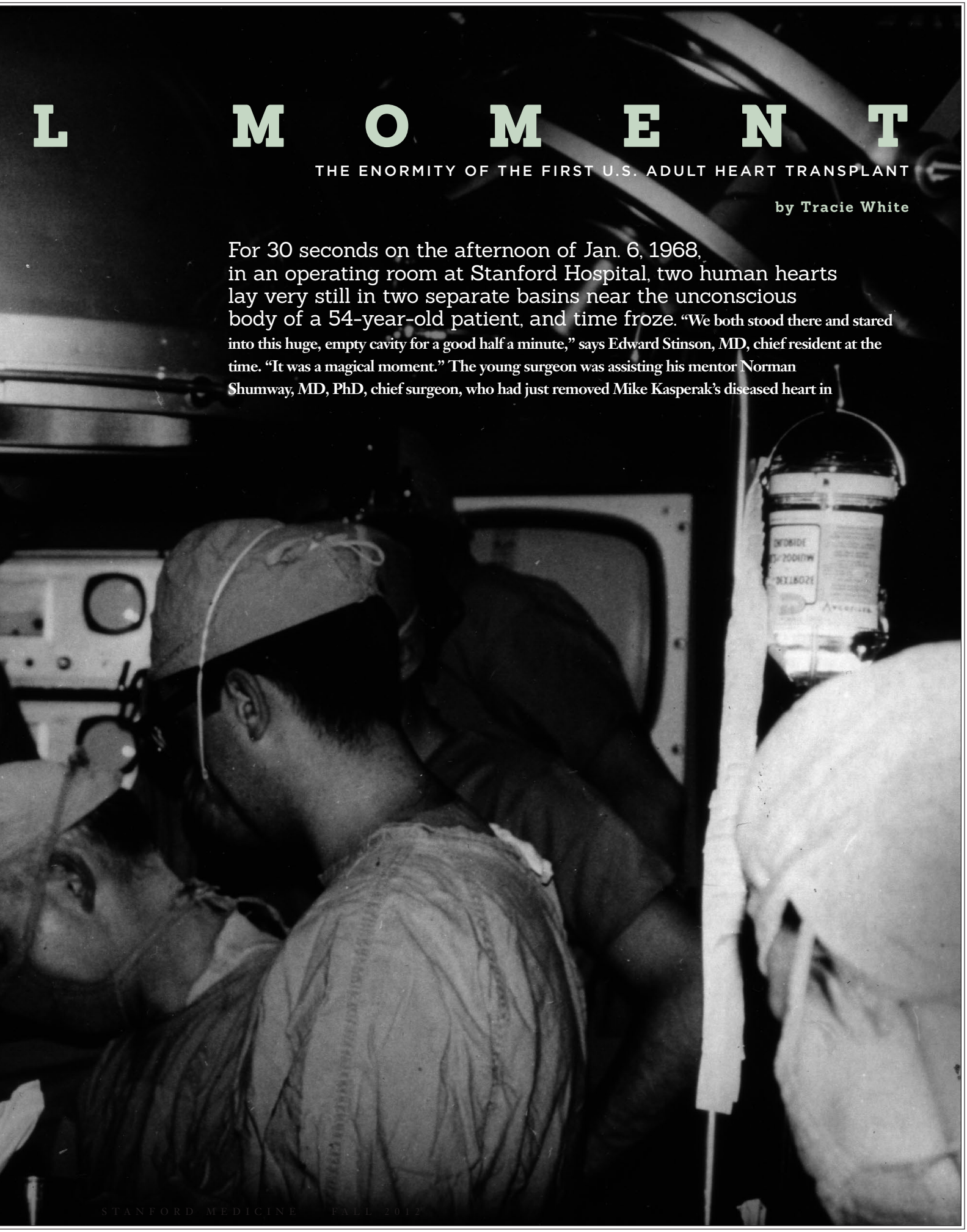


NORMAN SHUMWAY, SEATED RIGHT CENTER, ON JAN. 6, 1968, PERFORMED THE FIRST U.S. ADULT HEART TRANSPLANT. EDWARD STINSON, SEATED ACROSS FROM HIM, AND NURSE BERNADINE HARTMAN ASSISTED IN THE SURGERY.
(PHOTO: STANFORD MEDICAL HISTORY CENTER)

L M O M E N T

THE ENORMITY OF THE FIRST U.S. ADULT HEART TRANSPLANT

by Tracie White



For 30 seconds on the afternoon of Jan. 6, 1968, in an operating room at Stanford Hospital, two human hearts lay very still in two separate basins near the unconscious body of a 54-year-old patient, and time froze. "We both stood there and stared into this huge, empty cavity for a good half a minute," says Edward Stinson, MD, chief resident at the time. "It was a magical moment." The young surgeon was assisting his mentor Norman Shumway, MD, PhD, chief surgeon, who had just removed Mike Kasperak's diseased heart in

an effort to save the retired steelworker's life. It was the first attempted heart transplant of an adult in the United States.

"Do you think this is really legal?" Stinson asked Shumway.

"I guess we'll see," Shumway said.

One of the two hearts, diseased beyond repair, would never beat again. But the other, if transplanted into Kasperak's chest within the next hour or two, could start up again and save his life. It was an outrageous act that was being followed with bated breath by the world as a frenzied press corps, camped out in the hallways of the hospital's basement, issued moment-by-moment reports.

"I just remember thinking the future was going to be different if they can transplant a heart," Tom Brokaw, the anchor and managing editor of *NBC Nightly News* for 22 years, says in a recent interview. On that day, he was one of the reporters at the hospital, waiting for the news to break.

That surgery, 50 years ago, captured a moment in history when transplantation of a human heart was so hard to fathom, so bizarre, it was considered shocking, almost indecent. The heart, more than any other organ, holds a unique place in the public imagination, seen as the seat of the soul, the symbol of love and compassion. So, what happens if it's cut out and replaced with a stranger's? Does a man become a woman if transplanted with a woman's heart? Was it even legal? These types of questions hung over the surgery, as Shumway and Stinson paused for a moment to consider the enormity of their actions.

Today in the United States, death is defined by law as the cessation of electrical activity in the brain — although this definition is not without controversy. In 1968, the legal moment of death was murkier. Was it when the brain stopped working or when the heart stopped beating? For those pioneering surgeons and cardiologists, using the still-beating heart of a brain-dead donor was just common sense if it gave a dying patient a second chance at life. Sick hearts must be replaced with healthy hearts to save lives.

On that cold, bright winter day in 1968, the spell broke and the surgeons got back to work. There was no turning back.

RACE TO TRANSPLANT

In the race to be the first to transplant the human heart — and a race it was — Shumway, a tall, lanky country boy from Michigan, was considered the leader of the pack. His decades-long research working with Richard Lower, MD, in dogs in the laboratory, ultimately led to what remains the standard surgical technique for heart transplantation.

The researchers' first big success occurred in 1959, when Shumway and Lower — a surgical resident who later joined the faculty of the Stanford School of Medicine — successfully performed the first dog heart transplantation. Shumway, along with a gang of rotating residents, continued studies in the lab for eight more years and in the process developed a method of preserving the donor heart by placing it in a solution of ice-cold saltwater to reduce its metabolism. They learned about the transplant rejection response, which would become the key stumbling block to successful heart transplants.

Then, on Nov. 20, 1967, Shumway and his team announced that Stanford was finally ready to conduct the first human heart transplant, and the wait for a suitable patient and a donor began. A potential patient had been identified in October, but died before a donor could be found. Two weeks after Shumway's announcement, on Dec. 3, 1967, South African surgeon Christiaan Barnard, MD, surprised not only Shumway, but also the entire world, by giving Louis Washkansky, a grocer dying of heart disease, a new heart. Using Shumway's simple surgical technique, Barnard forever cemented himself into the annals of history as the first to transplant an adult human heart. Washkansky lived 18 days.

IT WAS AN OUTRAGEOUS ACT THAT WAS BEING FOLLOWED WITH BATED BREATH BY THE WORLD.

SHUMWAY'S FIRST

It was a shock to the Stanford program. Everyone had expected Shumway to be the first. In fact, Shumway's first human heart transplant would be the world's fourth. On Dec. 6, 1967, in New York, the first pediatric heart transplant was performed. The infant's heart stopped beating after seven hours. Barnard performed a second transplant on Jan. 2, 1968.

Not until Jan. 5, 1968, were both a donor and a transplant recipient found at Stanford.

At 2 p.m. Jan. 5, Kasperak had a massive heart attack at his home in East Palo Alto. He'd been living with heart disease for several years, and the prognosis wasn't good.

"He had been referred to me," says Don Harrison, MD, a Stanford cardiologist. "He had end-stage heart disease and was not going to live very long. I remember talking to his wife about this transplant surgery. I explained to her that this was a new procedure that had only been done once

HEART RECIPIENT MIKE KASPERAK, LEFT, AND HIS WIFE, FERNE. SURGEON NORMAN SHUMWAY AND CARDIOLOGIST ED HARRISON SPEAK TO THE MEDIA, BELOW, AFTER THE HISTORIC SURGERY.

in the world before. I had to explain to her that her husband was terminally ill, and there was nothing we could do." According to news reports, Kasperak asked his wife, Ferne, if he should go ahead with the operation.

"Go ahead," she said. "I want you alive with me."

Just four hours after Kasperak's heart attack and 7 miles west of his home, another tragedy occurred. Virginia-Mae White, a 43-year-old housewife and mother of two from Mountain View, suffered a brain hemorrhage that left her in a coma at nearby El Camino Hospital. Physicians had confirmed that she was brain-dead by the time they placed her on a respirator, which pumped air in and out of her lungs and kept her heart beating.

Part of the pathos surrounding the drama of each of the 2,000 heart transplants routinely done each year in the United States comes from the reality that for one person to live, another must die. Today, more than 4,000 people in the United States are waiting for a donor heart at any given time. Each case evokes the same emotional quandary that Shumway felt when he picked up the phone just before noon Jan. 6, 1968, to call Bill White, Virginia's husband, to ask him for his wife's heart.

The couple lived in a modest home and had two children, an 18-year-old daughter and a 12-year-old son. They had recently celebrated their 25th wedding anniversary. Shumway was typically light-hearted and quick-witted. In his lab, the professor of cardiothoracic surgery was upbeat, confident, somewhat irreverent and brilliant. His team members loved him. For him, as for anyone, this wasn't going to be an easy conversation.

In his book *Every Second Counts: The Race to Transplant the First Human Heart*, author Donald McRae describes the conversation between Shumway and Bill White that day:

"Once Shumway had explained the mechanics of transplantation and discussed the concept of brain death, White revealed that his wife had been fascinated by the South African transplant. She and Bill had recently talked to friends about Edward Darvall — who had allowed his daughter's heart to be used for the Washkansky transplant. 'How marvelous,' Virginia White said, 'to give someone else a chance to live.'

"White needed only 30 minutes to discuss the transplant with his children. His answer to Shumway was decisive. They wanted him to proceed."

"Knowing that she is helping another is easing our grief," Bill White said later in news reports. "I've got two of the proudest children you ever knew."

It was time to round up the surgical team.

BRINGING THE DONOR TO STANFORD

That afternoon, Stinson was sent to pick up Virginia White at El Camino Hospital in an ambulance and deliver her, with her heart still beating, to Stanford Hospital at 3:30 p.m. Shumway received a neurologist's confirmation of brain death to proceed, and the surgery began.

Two surgical teams were set up in two adjoining rooms on the second floor of the east wing of the hospital. Stinson removed White's heart in Room 12, then walked it over in a basin filled with cold saltwater to Room 13, where Shumway was waiting.

Kasperak was connected to a heart-lung machine that kept his blood circulating while Shumway cut out his diseased heart.

White's heart, just a third the size of Kasperak's, which was swollen by disease, was then lifted out of its basin and placed inside the empty chest cavity. Shumway sutured White's heart into Kasperak's chest, connecting the major heart vessels — the vena cava, the aorta, the pulmonary artery — and the left atrium.

In all, the surgery took about 3½ hours. White's heart had been motionless for two hours. Now, there was nothing to do but wait and see if it would beat again.

It generally takes about 20 or 30 minutes for a transplanted heart to begin to beat after surgery. The surgeon triggers the electrical system of the heart with a single shock from a defibrillator, then waits for it to "pink up" as blood flows back into it. The recipient remains attached to the heart-lung machine until the heart starts to beat effectively again and can take over to keep the blood circulating.

"The excitement was palpable," Harrison says. Ten, 20 minutes passed. At 25 minutes, the new heart faintly pulsed and then grew stronger. "We were all elated."

LEFT: AP NEWSWIRE; RIGHT: STANFORD MEDICAL HISTORY CENTER

'A THREE-RING CIRCUS'

Downstairs, all hell broke loose. Fifty or so journalists had arrived even before surgery began, according to an article in S*tanford Report* by Spyros Andreopoulos, director of the medical center's news office at the time. He had converted two classrooms into an impromptu press room.

"The tip actually came from a reporter from the *San Jose Mercury News* who was at a wedding reception with members of the transplant team," Andreopoulos wrote. "When they received an emergency call from the hospital, he deduced that the transplant operation was imminent." The news spread fast. Television reports aired that night.

"My friends and I were on the phone that night saying, 'Oh my gracious, did you hear they did the transplant?'" says Joan Miller, RN, who was at home after finishing her shift on the third floor of the hospital, just above the surgical rooms.

"When I arrived at work it was chaos. It was like a three-ring circus. People were everywhere. It was just great fun and exciting. On break, we'd race down to the basement to see it all — the cameras, the equipment, the news anchors."

By the time the operation was complete and Kasperak was moved on a gurney down the hall to the intensive care unit, reporters were literally scaling the hospital walls trying to snap photos of him through the window of his room.

"I remember thinking they were going to break their necks!" says Stinson, who saw them climbing when he stepped outside. Kasperak's nurses, though, were quick to close the curtains, preventing any photos, and the defeated reporters climbed back down.

The next morning, Shumway, with Harrison by his side, stood with arms folded over a wrinkled, white lab coat and faced the crowd of several hundred reporters at a news conference held in one of the medical school's amphitheaters.

"We have reached first base, so to speak, but our work is just beginning," Shumway said, cameras clicking. "The heart transplant patient, Mike Kasperak, awakened in satisfactory condition." Harrison, the patient's cardiologist, presented diagrams of cardiac functioning measurements collected through the night showing that the heart was functioning well.

AFTER THE TRANSPLANT, ED STINSON KEPT VIGIL OVER THE PATIENT. HE REFLECTS ON THE SURGERY IN THIS VIDEO: http://stan.md/2DXwNi2.

Shumway, known to be shy of the media, would later turn down offers to appear on *Face the Nation*, *Meet the Press* and the *Today* show, but that morning he appeared calm and in high spirits.

"Shumway looked just a little bit like a guy who had just got off the gridiron," Brokaw says. "Exhausted, but pleased with himself. He looked the part — handsome, white jacket, just a built-in charisma. Here was this monumental moment, and he handled it with such modesty."

During the next few weeks, Stinson, who later joined the School of Medicine faculty, led the fight to keep Kasperak alive. The first five nights post-surgery, Stinson remained sleepless by his patient's side. Meanwhile, the Stanford press office issued daily bulletins on Kasperak's condition.

"The patient, Mike Kasperak, 54 years old, was reported to be awake and alert," the *New York Times* reported three days after surgery. "He was allowed a first visit with his wife yesterday evening and slept during the night." Two days later, it followed up with: "Mr. Kasperak managed to scribble an 'I love you' note and hand it to his wife."

For the first few days post-surgery, Kasperak's condition remained hopeful, but then he slipped into a semi-comatose state. Extensive bleeding of the stomach led to worries that his liver and kidneys had been too severely damaged by years of heart disease to keep him alive.

"In retrospect, he was too ill at the time of surgery," Stinson says. "His lungs, liver, kidneys, GI tract weren't functioning well. His body didn't tolerate the stress of the operation well." Fifteen days after the surgery, Kasperak died of severe hemorrhaging. Stinson, making certain he was given enough morphine that he was never in pain, was there by his side.

In the aftermath of the Stanford transplant, the world hit near-hysteria in its fascination with heart transplants. Nearly 100 medical institutions jumped in to attempt the operation. The surgery itself proved fairly simple, but the inability to prevent recipients' bodies from rejecting foreign hearts quickly led to alarming death rates. Sensationalized accounts of these operations appeared in newspapers like the *National Enquirer*. One paper ran with this headline: "Docs give her

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TIMOTHY ARCHIBALD

what happened next

STANFORD'S HEART TRANSPLANT BREAKTHROUGH PRECIPITATED YEARS OF PROTOCOL ADVANCES

The first successful adult heart transplant in the United States, performed 50 years ago at Stanford Hospital by Norman Shumway, MD, PhD, ultimately led to the success of the procedure around the world today.

THE OPERATION, WHICH TOOK PLACE JAN. 6, 1968, sparked a flurry of heart transplantations worldwide, but most institutions and cardiac surgeons quickly stopped because of the high rate of post-surgical deaths.

However, Shumway and his team at Stanford persisted.

"Norman Shumway not only introduced a lifesaving procedure but also made sure that the operation became widespread practice," says Lloyd Minor, MD, dean of the School of Medicine. "We are honored to celebrate the anniversary of this unforgettable moment in Stanford Medicine's history, and to recognize Dr. Shumway's radical innovation and perseverance."

Dream finally realized

The operation was the culmination of a decade of research during which Shumway and colleagues perfected the surgical technique still in use around the world today. Through studies in dogs, they worked out the surgery, developed the method of preserving the donor heart in cold saltwater, and gained insights for overcoming the key stumbling block to survival after heart transplantation — donor heart rejection.

In the years following that first transplant, Stanford's program — working under the auspices of the National Institutes of Health Program Project Grant for Cardiac Transplantation — made further advances that greatly improved patient survival rates, writes Joseph Woo, MD, current chair of cardiothoracic surgery, in a 2015 article for the journal *Seminars in Thoracic and Cardiovascular Surgery.*

"These included refinements in immunosuppression, management of complications such as infection and lymphoma, distant heart procurement, patient and donor selection criteria, and the diagnosis of rejection by biopsy," Woo writes.

In 1972, assistant professor of cardiovascular surgery Edward Stinson, MD, who assisted in the first transplant, and visiting scientist Philip Caves, MD, performed the first cardiac biopsy on a transplant patient, which provided a noninvasive method of measuring the potential for rejection of a donor heart. By 1980, Stanford had also advanced the use of the immunosuppressive drug cyclosporine, an essential breakthrough for preventing donor heart rejection.

Using these improvements, in 1981, Bruce Reitz, MD, who succeeded Shumway as chair of the department and is now a professor emeritus of cardiothoracic surgery, performed the world's first heart-lung transplant at Stanford.

Mechanical heart advances

DURING THE 1980s, Stanford went on to advance the field of mechanical heart support. Stanford researchers developed a left ventricular assist device, or LVAD, which made history in 1984 when Phil Oyer, MD, PhD, Stanford professor of cardiothoracic surgery, implanted the device for the first time to keep a gravely ill heart patient alive mechanically for eight days until a heart was available for transplantation — a procedure called "bridge to transplant."

"Although a few other types of LVADs had been implanted elsewhere by that time, this was the first patient in the world who survived both the LVAD implant and heart transplant operation to be discharged from the hospital and, in fact, lived an active life for more than 23 years," Oyer says.

Surgery improved

IN 1995, REITZ performed the first Heartport procedure, using a device that allows for heart surgery via small incisions between the patient's ribs, eliminating the need for cutting the breastbone. And in 2004, Lucile Packard Children's Hospital became one of the first U.S. hospitals to use the Berlin Heart, an external heart pump, keeping a 3-month-old child alive for 55 days until a transplant could be done.

Since that first heart transplant in 1968, the total number of heart transplants performed at Stanford had reached 1,933 as of December 2017. More than 60,000 successful heart transplants have been performed around the world.

Today, 80 percent of patients who receive a heart transplant survive the first year. - TRACIE WHITE

A CONVERSATION WITH AUTHOR MARY ROACH

Exploring our miraculous icky parts

Mary Roach calls herself the bottom feeder of nonfiction. *The New York Times* best-selling author delves into the crevices and alleys of life and the human body where few other authors explore. She plows through areas that make a reader wonder: What's she thinking, and why does she want to go there?

Roach says, "I'm not, by trade or character, a spotlight operator. I'm the goober with a flashlight, stumbling into corners and crannies, not looking for anything specific but knowing when I've found it." From talking to U.S. military special operations teams in Djibouti about diarrhea (in her most recent book, *Grunt: The Curious Science of Humans at War*) to detailing the human body as it decomposes (in *Stiff: The Curious Lives of Human Cadavers*), Roach's motto seems to be: Who wants to write — or read — a boring science book?

For this special issue of *Stanford Medicine* on pushing the limits in biomedicine, Executive Editor Paul Costello spoke with Roach, a writer whose career not only exemplifies that notion but also encapsulates it.

COSTELLO What makes you so curious about areas of the human body where no one else ventures?

ROACH Well, part of it *is* no one else ventures there. The stuff that other people leave alone, I'm like, "I'll take that." Everybody has a certain amount of where they're both drawn to something and repelled by it. And I'll find a way, as a writer, to take them by the hand and say, "OK, yeah, this is a little repellent, a little grotesque, but come with me."

COSTELLO Is the taboo also appealing?

ROACH When *Grunt* came out, the most common questions I was asked in interviews were about the flies and the maggots or the penis transplantation, the cadaver run-through. Those are the things people zeroed in on and they're fairly gross, taboo and unsettling. Part of it is tapping into something most people are curious about. I don't know that I'm special in the way that I'm able to bypass the normal feelings of revulsion.

COSTELLO Your first book, *Stiff*, was about cadavers. Doesn't sound like a best-seller.

ROACH *Stiff* really got rolling through word of mouth because it was the combination of this topic, this seemingly dark world of cadaver research, but the tone of the book was humorous. People tended to talk to other people about it: "I'm reading this book. It sounds kind of gross, but it's actually funny and kind of uplifting."

COSTELLO I'm guessing you're really trying to get readers to look at something they may find disturbing or gross and flip it around, making it endlessly human and thereby understood?

ROACH Absolutely. I think that people come to these topics thinking, "Oh, this is going to be disgusting and disturbing." Sometimes I use humor, and sometimes I'm just very straightforward. There's something about the straightforwardness of the writing that encourages people to step in.

Once they're in, they start to learn all these things. They come away saying, "I thought this would just be gross, but it was really interesting and I learned a lot." Anytime anybody learns a lot, particularly something about the human gut, like the colon, the rectum, the anal sphincter, this is a miraculous thing.

You hear a lot about the brain and the heart. People have a sense that these are miraculous, but not so much the nether regions or the inside of the nose, the nostrils, the tongue. The icky parts are just as miraculous, and people tend to overlook them. I'm the plumber.

COSTELLO Has any exploration changed the way you experience things or look at your body?

ROACH If you hold food or wine in your mouth and exhale through your nose, you're sniffing in reverse. It's called retronasal olfaction. You're getting this whole other sensation. You're experiencing all these vapors as they're warmed and released in your mouth. People think, "Oh, you smell the aromas outside the body and on the plate or in the glass." But you smell the aromas from inside your mouth, too. That changed how I experience my meals.

> They come away saying, 'I thought this would just be gross, but it was really interesting and I learned a lot.'

COSTELLO Before *Grunt*, I never considered diarrhea to be a national security threat.

ROACH Especially when you consider that the people who are the farthest out in the boonies, the farthest away from clean food and water are special operations teams.

They're out in some far-off village eating goat that's marginally cooked and not refrigerated, and water that may not have been treated. These people are doing the really high-risk operations, and they get hit at a tremendously high rate with really debilitating food poisoning.

COSTELLO I found it especially funny that one of the guys from special ops asked: "Why are you here? What's this again?"

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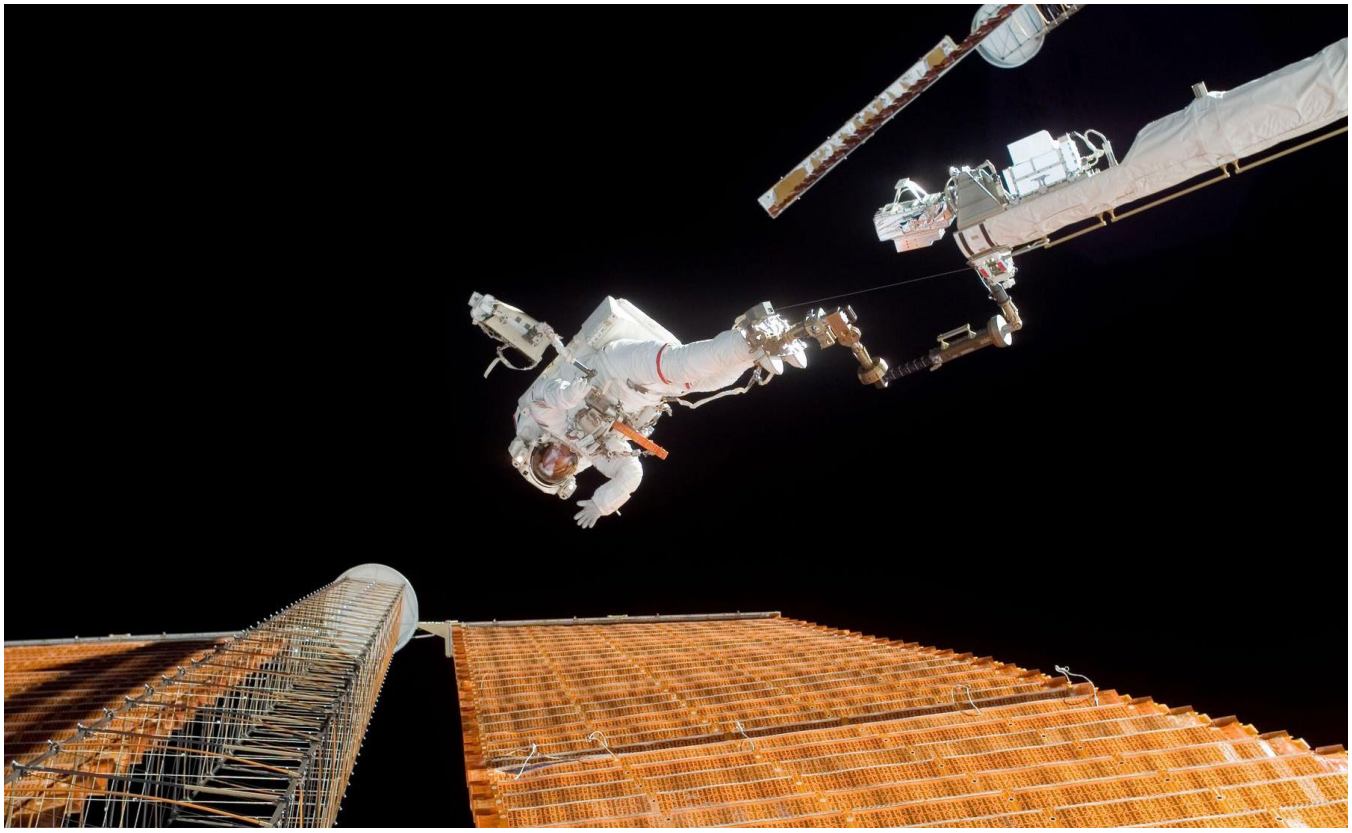
TIMOTHY ARCHIBALD

plus

EXPLORING THE REALMS OF MEDICINE AND HEALING



SCOTT PARAZYNSKI DURING A SPACEWALK TO REPAIR A SOLAR WING ON THE INTERNATIONAL SPACE STATION.

DOUGLAS WHEELOCK, COURTESY OF NASA

Operating in zero gravity

A PHYSICIAN-ASTRONAUT IN SPACE

THE YEAR WAS 2007 AND SCOTT PARAZYNSKI, MD, was on the International Space Station. He and the rest of the space shuttle Discovery's crew had delivered a new module for the station and were readying for their next mission: to reposition the solar arrays — the station's massive wings. But there was a hitch. An array on one of the wings ripped while being unfurled, forcing the astronauts to change their plans.

Parazynski, an alumnus of Stanford University and the School of Medicine, had been 22 months into a residency in emergency medicine when he joined NASA. He didn't get to finish his medical training, but he put his suturing skills to work while dangling from a "space cherry picker," reinforcing the damaged wing with straps that worked like cuff links.

In his 2017 memoir, *The Sky Below*, co-authored with Susy Flory and published by Little A, Parazynski describes floating out of the hatch, moving down a long space station truss to reach the robotic arm, the Canadarm2. There, Douglas

"Wheels" Wheelock helped secure his boots in the foot restraint, which (he hoped) would hold him fast on his ride out to the damaged portion of the array. On the tool carrier built into the front of his suit, Parazynski had a pin puller to tug the solar panel toward him, a cutter for clipping cables, and his "hockey stick" — an L-shaped tool he could use to push the panel away. Wheelock remained perched at the end of the truss to monitor Parazynski and the arm. Engineers had warned that direct contact with the panels would send them into wavelike patterns, between 5 and 6 feet in and out, which would hamper their progress.

Inside the station, Stephanie Wilson and Daniel Tani controlled the robotic arm, and Paolo Nespoli issued safety warnings. Commander Pamela "Pambo" Melroy called directions to Parazynski and confirmed his movements, which he called back to her and to Mission Control in Houston. From Houston, the lead space station flight director, Derek Hassman, led the repair effort; lead spacewalk officer, Dina Contella, oversaw the extravehicular activity, known as an EVA; robotics officer Sarmad Aziz monitored the robotics team; and astronaut Steve "Swanny" Swanson was the primary capsule communicator.

"It is definitely a dream team, and this is the gold medal round," writes Parazynski, who describes the mission in the following excerpt.

EXCERPT

OUR GOAL IS TO CARRY out the full repairs, including a major ride on the robotic arm to the repair site and back, within 6½ or seven hours. I don't care about the lack of food or bathroom breaks — I'm fully equipped to manage the latter — but if we attempt to stay much longer, the EVA suit will be close to draining the tanks to empty. In terms of consumables like oxygen, CO_2 scrubbing and battery power, no one wants to cut it too close.

My feet are now locked into the foot restraint on the boom, which in turn is attached to Canadarm2 … and the arm starts moving slowly. The views are staggering, unlike anything any other human being has ever seen before.

I am positioned on top of a space cherry picker, well above the ISS and Discovery and our pale blue dot of a home planet. There's no way to do this experience justice; all I can mutter is a markedly uninspired, "Wow, that is the most incredible sight I've ever seen!"

I continue flying out toward the end of the solar array, Steph and Dan taking good care of me, but I feel like a tiny worm dangling on the end of a fishing line cast out in slow motion. I am minuscule against the great blackness of space.

There's no way to do this experience justice; all I can mutter is a markedly uninspired, 'Wow, this is the most incredible sight I've ever seen!'

I have some prep work to do on this utterly unique commute to work, but I do notice Wheels making good progress out to the tip of the station, backdropped by an orbital sunset. The sky is below, with the Earth's atmosphere so thin, a beautiful blue skin around the pulsing, glowing blue, green and rich brown beauty of the planet. Clouds of every color and shape and configuration float inside the bluish atmospheric bubble, sometimes pierced by brilliant streaks of lightning.

I look for edges of continents, and for places I've traveled to and places I still want to go. I see Everest rearing her magnificent, snowy head above her sisters, the great chain of the Himalayas. I smile. Maybe someday I'll go there and climb it, and possibly even see the space station fly overhead.

Paolo suddenly interrupts my sightseeing, wanting to run through the cautions and warnings involved in working on the solar panel. He begins rattling off a litany of "no touch" zones, along with a dire warning that I may actually experience current arcing from the damaged panel to my spacesuit. I thank him for his important words of counsel and he replies, "Wait, I'm only halfway done!"

I bend back at my knees as far as they'll take me, since the robotic maneuver has mostly kept the ISS at my back, out of my field of view. I finally see our destination and my heart begins to race. Reverie interrupted, it's time to work.

I go into my hyperfocused state and survey the damage. "The steel metal braid wire is frayed and tangled in front of me, like a hairball." It looked like the size of a ping-pong ball. "There's several strands of wires all grouped together there," I report.

"I'm sure that's causing shudders on the ground somewhere," says Pambo.

"You have some surgery to do, Dr. Parazynski," she adds.

"I think so." Her voice makes me feel safe. I know she's crouched up in the window with a set of binoculars, tracking my every move.

But wait. I can't quite reach the site.

The arm is stretched out as far as it can go and I can practically feel everyone listening, holding their collective breath. Now it is up to Wheels and me, Stephanie and Dan on the arm, and the rest of the watchful crew inside Discovery, ISS and Mission Control, to get the job done. I ask the robotic arm crew if they can reorient me to allow me another couple feet of reach. Dan replies that he can do so, but it will take some time to pull me back and reorient the arm to make another pass. On the ground, Sarmad confirms, "I can't

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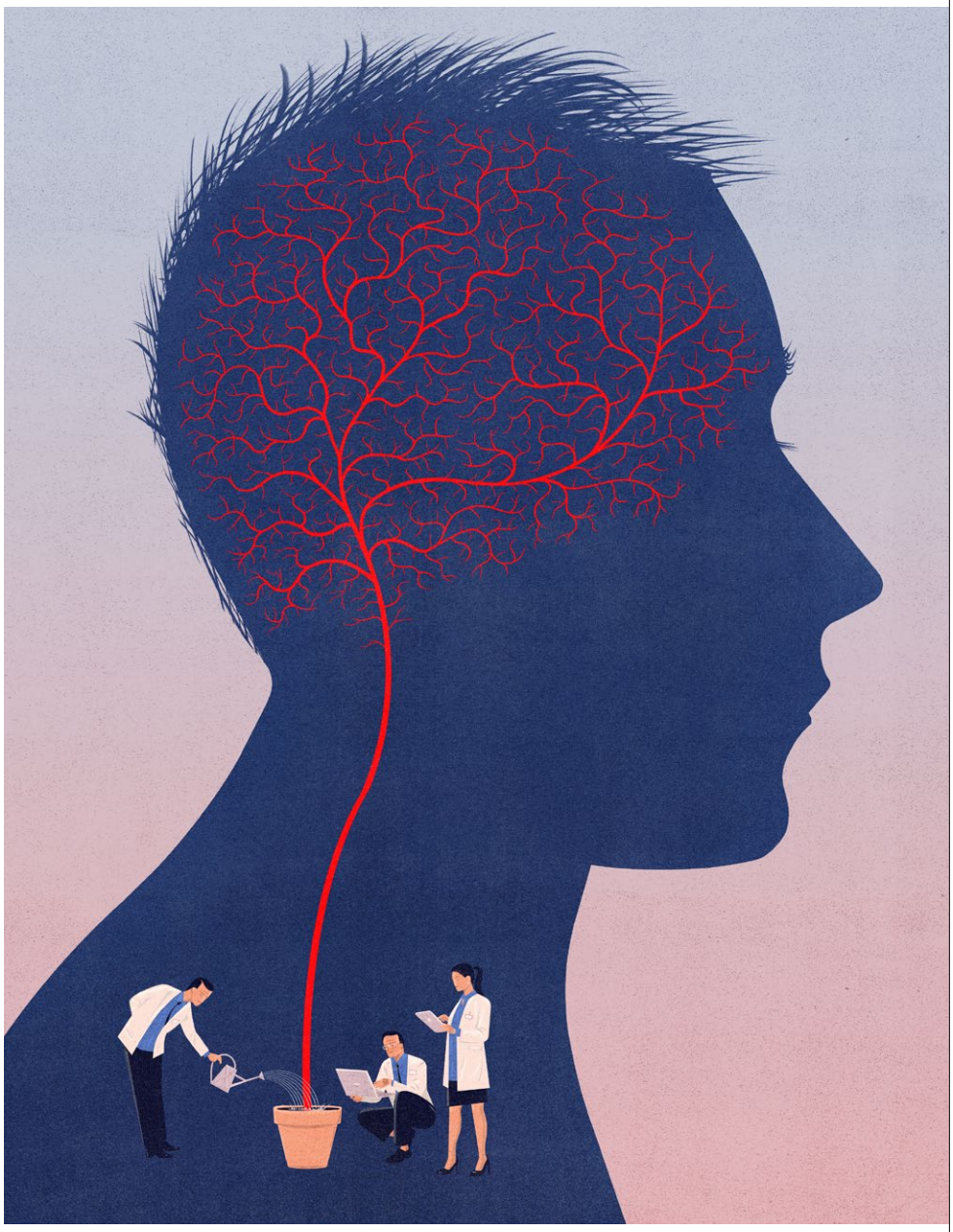
plus

Recovering from stroke

ENGINEERS, BIOLOGISTS AND DOCTORS FOCUS ON A WIN

By Nathan Collins

ILLUSTRATION BY FRANCESCO BONGIONI



DAVID WILSON DOESN'T REMEMBER those moments all that well, but his wife will never forget. Wilson had come out of surgery to remove his thyroid — doctors found a malignant tumor — but three hours later he was still having trouble speaking and moving. Perhaps, Janet Wilson thought, it was just taking a long time for the anesthesia to wear off, but she was ill at ease. As the hours went by, David Wilson's condition worsened, and unease turned to dread.

"I knew I had a problem," David Wilson says. "I didn't know what it was."

Looking at him now, one wouldn't necessarily know that Wilson suffered a massive stroke that day. At 63, he's slim, energetic and quick with a joke. He drives a yellow Corvette, plays golf, reads Dickens and plays Magic, The Gathering, a hobby he picked up from his son. That he uses a small hiking pole when he walks could easily be the result of an old football injury, not because five years ago he found himself unable to walk, speak, read, write or take care of his most basic needs. Even after six months of rehabilitation, "I was in a wheelchair and my speech was really bad," Wilson says.

"For 2½ years, she had to do everything for me," he says, looking to his wife.

Every year, roughly 795,000 Americans have a stroke — a life-threatening event resulting from poor blood flow in the brain, often caused by a blood clot or other obstruction that blocks a blood vessel, as happened to Wilson. Despite advances in immediate treatments that greatly reduce long-term brain damage for many patients, 17 million Americans have stroke-related disabilities. Besides physical limitations, many have short-term memory loss, complicating their mental and physical recovery, and will lose long-term memories sooner than the norm.

Wilson's recovery, he and his wife say, benefited greatly from his access to faculty, therapists and research at Stanford and elsewhere. And they believe that most, if not all, stroke survivors who have the same access to care Wilson had could see similar improvements. Still, many don't — in part because doctors don't have good data on what treatments work, let alone which treatments work best for which patients.

"The first thing that family members, or patients, if they can talk, ask the doctor is 'Am I going to get better? How much better am I going to get?'" says Marion Buckwalter, MD, PhD, an associate professor of neurology and neurosurgery and a member of Stanford Bio-X and the Stanford Neurosciences Institute.

"The answers right now are, No. 1, I can make an educated guess about how much better you're going to get, but I might not be that good at it, and No. 2, maybe rehab will help you get better, but there's not a lot of data to show that it actually helps," Buckwalter says.

"And there's really not a lot else," she says — no drugs and no proven therapies to make stroke survivors' lives more livable.

Yet like the Wilsons, Buckwalter and her colleague (and Wilson's doctor) Maarten Lansberg, MD, PhD, an associate professor of neurology and a member of Bio-X and the Neurosciences Institute, are hopeful — even a bit upbeat — about stroke recovery. In 2015, the pair launched what is now the Stanford Stroke Recovery Program to remove barriers between engineering, medicine and basic science researchers to improve long-term stroke recovery. The researchers' ideas are mostly in their infancy, and may sound a bit wacky — injectable, drug-delivering gels, magnetic pulses fired into the brain, even robotic ankles — but, Buckwalter and Lansberg say, the future could be bright.

THE REALITY OF REHABILITATION

IT COULD USE SOME BRIGHTENING. Stroke remains the fifth-leading cause of death in the United States and a leading cause of disability, according to the American Stroke Association. Until the 1950s, researchers understood little about strokes. But doctors now know that high blood pressure and smoking increase the risk of strokes, and aspirin can help prevent them. In 1996, the Food and Drug Administration approved a drug that dissolves the blood clots that cause five-sixths of strokes, and there are now surgical techniques to break up or remove clots before too much damage is done.

Rehabilitation, however, has lagged and mostly involves relearning and practicing basic skills — how to walk, how to form sentences or just how to pick up a bowl with two hands. What's more, most stroke patients don't have the benefit of adaptable young brains.

Efforts to do better are complicated because the brain is very complex, Lansberg says. Preventing stroke and treating it as it's happening are problems of plumbing — thinning blood and dissolving and otherwise breaking up clots. But stroke recovery is a neuroscience problem.

> Preventing and treating stroke are problems of plumbing — thinning blood and dissolving or breaking up clots. -But recovery is a neuroscience problem.

That observation, Lansberg says, motivated him and Buckwalter to create their recovery program's predecessor, the Stroke Collaborative Action Network, in 2015 with help from a Stanford Neurosciences Institute Big Ideas grant. "We felt this was a big unmet need. Essentially, we do not have effective therapies," Lansberg says.

Lansberg and Buckwalter are looking at how to prevent dementia, which affects about 40 percent of patients in the first 10 years after a stroke. Buckwalter's lab recently showed in mice that stroke triggers something similar to an autoimmune disease in the brain, leading to dementia. What's exciting, Buckwalter says, is that in mice, the disease can be treated with a version of an FDA-approved drug, suggesting doctors may already have a tool to fight dementia. "Right now, we are doing studies in patients to determine if there are biomarkers in humans that show us that the same or a similar process is causing dementia" in stroke patients, Buckwalter says. (Wilson is a participant in Lansberg and Buckwalter's study.)

But that research is just the tip of the iceberg.

STICKY GELS FOR A STICKY PROBLEM

SARAH HEILSHORN, PHD, an associate professor of materials science and engineering, is not who you might expect to study stroke recovery, but she was interested in finding ways to treat Alzheimer's and other neurodegenerative diseases using an unusual approach: injectable gels that could deliver powerful, localized doses of drugs capable of rebuilding damaged brain tissues. She's working with Paul George, MD, PhD, an assistant professor of neurology, whose research in rats uncovered a protein produced by immature nerve cells that helps restore function of the nerve cells in the area surrounding the stroke site.

If something similar happens in humans, a drug that is based on those proteins might form the basis of a stroke treatment. The challenge would be delivering the drug: Usually, proteins either dissipate throughout the bloodstream or are eaten up by enzymes. To counter this, doctors could inject a single high dose or use multiple smaller injections. Neither strategy is great — a single high dose leads the drug concentration to spike too high, then rapidly fall too low. Also, Heilshorn says, "no one wants multiple injections to the brain."

Heilshorn's injectable gels, which are being tested in rats, could solve the problem in an elegant way, she says. They are engineered to hold on to the proteins, preventing them from diffus-

ing or being eaten up. The gels are also biodegradable, so, ideally all that's left after treatment is a healthier brain.

THE NEUROSCIENCE OF THE INDIVIDUAL

AMIT ETKIN, MD, PHD, AN ASSOCIATE PROFESSOR of psychiatry and behavioral sciences, is hoping to heal the brain in an entirely different way: stimulating it with beams of magnetic energy. Transcranial magnetic stimulation has the potential to rehabilitate stroke-damaged brains, Etkin says, tailored to the way a stroke has impacted each patient's brain.

The idea to use TMS in stroke patients came from frustration with conventional approaches to diagnosing, treating and simply understanding such psychiatric diseases as major depression. The problem, Etkin says, is that conventional methods uncover correlations, not causation. Researchers studying depression, for example, often look for correlations between specific behaviors associated with depression and brain activity as measured by an fMRI brain scanner. Similarly, stroke studies might look for correlations between aphasia, the language disorder that leaves David Wilson occasionally looking to his wife for the right words, and damage to a particular part of the brain.

But Etkin wants to understand causation. For instance: How does damage to one part of the brain change the circuits responsible for movement or speech? Using a combination of TMS and electrical recordings taken from a person's scalp, the team injects energy into one part of the brain, then follows it through brain circuits, revealing "the causal influence of one brain region on other brain regions," Etkin says. His team has tested its technique in about 20 stroke patients, creating a separate map of each person's brain — a "neuroscience of the individual," Etkin says.

TMS also may be able to reshape the connections between the neurons that make up those circuits — again, tailored to each patient. TMS temporarily improved aphasia in one of Etkin and Lansberg's patients, and there are signs that continuing the treatment over several days could provide more lasting relief.

Beyond TMS, stimulation itself — maybe even just poking the brain with a needle — could be the key to rebuilding it, says Gary Steinberg, MD, PhD, the Bernard and Ronni Lacroute-William Randolph Hearst Professor of Neurosurgery and the Neurosciences. In rodents, Steinberg has shown that injecting stem cells into the area immediately around a stroke site can help resurrect damaged, although not destroyed, neural function. Recently, he has applied optogenetics, which uses light to activate specific genetically modified neurons, to rebuild neural circuits in mice that have had strokes. Others have used electrical stimulation to similar effect.

It's not clear why stimulation seems to work, Steinberg says, but possibly it helps restore a balance between the left and right brain hemispheres upset by stroke. Or, it may simply help rebuild connections between individual neurons.

"We need to figure out mechanisms," he says, but "I'm an advocate of using every form of energy" to explore stimulating the brain.

ROBOTS TO THE RESCUE?

THE FLIP SIDE OF THE promise of new techniques is that injectable gels and brain stimulation may not be widely available to patients within the next few years. Meanwhile, tens of millions of patients need help now just to walk around.

Enter Steven Collins, PhD, an associate professor of mechanical engineering, and his robotic ankles. The devices, which look like an exoskeleton around the ankle, help patients with gait abnormalities — for example, a limp resulting from damage to the muscle-control center on one side of the brain — by giving a small mechanical kick to the affected leg.

Collins does not view his ankles as a path toward rehabilitation, despite widespread interest. "People have been trying to develop robotic devices to replace clinicians or augment therapy, but they have not been successful, and there have been a couple notable failures." In one test of a robotic exoskeleton intended to help stroke survivors move their legs in a more natural way during treadmill rehabilitation, patients mostly let the robots guide the walking, rather than engaging their own muscles and the brain circuits responsible for activating them. "In the near term, the more obvious application of robotic devices is for gait assistance" to help people walk better, Collins says.

But even robotic assistance has problems, Collins says. Often, engineers invest time and money into building lightweight, compact devices designed to help people, only to discover they don't work. And, Collins says, most engineers don't involve patients in the design process.

The solution is twofold. First, Collins and his team have built an "emulator" that helps engineers tailor a device's specifications to patients before sinking resources into creating mobile, wearable designs. The emulator is a robotic device worn on a patient's ankle, similar to what one would wear in the real world, except connected to powerful off-board computers, motors and other devices in the lab. The second idea, "human-in-the-loop optimization," is to have patients participate in the design process.

Those ideas allow researchers, and eventually doctors, to try variations to see which design works best for a patient before trying to make the ankle lightweight and compact. "We measure your performance in real time while you're using the device," Collins says, and "we systematically vary the device characteristics for control so as to maximize your performance."

Collins and his team reported last year in *Science* the results of an experiment that showed robotic ankles designed using the emulator cut the energy expended on walking by an average of 24 percent in 11 healthy adults. Working with Lansberg, Collins plans to begin studies in stroke patients this year.

AN ADVENTUROUS OUTLOOK

COLLINS' STUDY and others at Stanford illustrate principles that Janet and David Wilson believe are essential to Wilson's recovery: tailoring stroke therapies and treatments to individual patients, and trying something new when one approach isn't working.

For Buckwalter, they also illustrate an important Stroke Recovery Program aim:

connecting researchers directly to patients. "The barrier's basically dropped for someone who's in engineering or another field and might normally not have any contact with stroke patients or might not know how to do clinical research," she says. "There's an entrepreneurial and adventurous, innovative outlook that people have here. We'd like to tap into that spirit and try to move things forward with rehabilitation."

Lansberg agrees. "I lived through this period where it seemed tough to get anything done for acute stroke. It seemed pretty insurmountable not too long ago," yet dramatic progress has been made in the past 20 years. "So I've seen how if you bring the right technology together with the right clinical teams, you can make very rapid progress." SM

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FEATURE

Animal-grown human organs

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could take a year or more — time he thought he couldn't afford to lose. His instincts, at least on this matter, were correct. As of January 2018, the restrictions in Japan have not changed. The United States, he believed, would support his research.

CHIMERA MYTHOLOGY

The idea of chimeras has captured human imagination since Greek mythology introduced the Chimera — sometimes conceived as a fire-breathing dragon-goat-lion. Often the stuff of monsters or fables, they invoke a knee-jerk negative response in many people. Biologically, chimeras are organisms made up of a mosaic of cells that contain two or more distinct genomes. This can occur naturally when fetal or maternal cells cross the placenta during pregnancy to take up residence in the baby or the mother, or after medical procedures such as organ transplantation or blood transfusion. The term interspecies chimera is used when the genomes come from different species.

Many people are taken aback when first introduced to the idea of deliberately creating interspecies chimeric animals with human cells. But interspecies chimeras, whether naturally occurring or scientifically generated, have been around for a long time. Thousands of people are walking around with heart valves from pigs after their own have failed. Conversely, "humanized" mice genetically engineered to lack their own blood and immune system can develop a human immune system when researchers introduce human hematopoietic stem cells. Mice are also commonly used to test the responses of implanted human tumor cells to various drugs or growth conditions.

But introducing pluripotent human stem cells into an early animal embryo, as Nakauchi proposes, is somewhat different than these examples. These cells have the capacity to become nearly any tissue in the body, and, when injected into a developing embryo, they have the opportunity and the means to do so.

NIH FUNDING BLOCKED

In 2014, Nakauchi arrived at Stanford eager to continue his experiments with large animals with the expectation of receiving NIH funding to advance his research. In the interim his move was supported by a $6 million research leadership grant from the California Institute for Regenerative Medicine. The award was designed to help bring stem cell researchers from outside California to the state, and to allow them to pursue high-risk, high-reward research. The recruitment marked a return to Stanford for Nakauchi, who studied immune-cell genes as a postdoctoral scholar in the laboratory of the late Stanford geneticist Leonard Herzenberg, PhD.

But the 2015 NIH funding ban was implemented before Nakauchi was able to receive a grant from the agency. Shortly after the funding moratorium, seven Stanford faculty members, including Nakauchi and cardiologist and stem cell researcher Sean Wu, MD, PhD, authored a letter in *Science* magazine describing the detrimental effects of the ban.

Nakauchi is using the funding from CIRM as a stopgap measure to continue his preliminary studies of human pluripotent stem cells in pigs and sheep. He also continued his groundbreaking research in mice and rats. In early 2017 he showed that islet cells from mouse pancreases grown in rats could reverse diabetes in mice, normalizing their blood glucose levels for over a year without the need for ongoing immunosuppression.

In August 2016, the NIH published proposed changes to the funding guidelines after extensive consultations with experts, including Nakauchi and Hank Greely, JD, a Stanford law professor who works on bioethics.

Prior to the 2015 funding moratorium, the guidelines prohibited the funding of any research in which human pluripotent stem cells would be introduced into primate blastocysts. They also prohibited funding the breeding of animals whose reproductive systems might have incorporated pluripotent human cells.

The suggested changes broaden the funding restrictions to include injecting human pluripotent stem cells into primate embryos at any early developmental stage up to and including the blastocyst stage, and expand the breeding restriction to include any instance in which any type of human cells (not only those that are pluripotent) may contribute to the production of egg or sperm cells. They also proposed the creation of a new NIH steering committee of federally employed, scientific experts to review research proposals in which human pluripotent cells are introduced into any vertebrate embryo prior to the end of gastrulation.

Some scientists were encouraged by the agency's move.

"Their statement made it sound that NIH is opening to the possibility that people can do this kind of work," says Wu. But the wheels of change move slowly, and more than a year later no new guidelines have been issued.

"What I find so frustrating," says Greely, "is that NIH did have that conversation with scientists, held workshops, gathered expert opinion on both the science and ethics sides, and reached a conclusion, but then just stopped."

For now, any work that involves the injection of human pluripotent stem cells into an early animal embryo is ineligible for NIH funding.

When asked about the delay, Wolinetz

says, "I do understand scientists' frustration. We do see value in this research, it's just a matter of making sure the appropriate guidance is in place," she says. "We are still in the policy development process, and I don't really know when we will finalize new guidelines or what the final policy will look like. It is still in limbo."

AS HE WAITS, NAKAUCHI CONTINUES TO DREAM. He's experimenting with ways to introduce what are known as committed progenitor cells — cells that are already a few steps along a pathway of specialization toward specific organs or tissues. These cells have closed many of the developmental doors that are accessible to pluripotent stem cells and should be unable to distribute themselves willy-nilly throughout a developing embryo. Not only would these committed progenitor cells circumvent the NIH ban, they also might be more efficient at generating specific organs and lead to more healthy, more viable embryos.

"We are trying to ensure that the human cells contribute only to the generation of certain organs," says Nakauchi. "With our new, targeted organ generation, we don't need to worry about human cells integrating where we don't want them, so there should be many fewer ethical concerns."

He also envisions the possibility of tinkering with molecules on the surface of the human cells that our immune systems use to recognize self from nonself in ways that would render immunologically invisible, or "universal" organs that could be accepted by any ailing patient. Or how about a cow with human blood for transfusions? The lack of funds, however, has slowed the research. "This is a really expensive project," he says of the large-animal studies. "Eventually we need to get more funding."

For better or for worse, more funding may require better education of the public.

"Chimeras are very important research tools and disease models, but the creation of animal-human chimeras often comes across with a big ick factor. In some ways the onus is on us to communicate to the public what this research entails," says the NIH's Wolinetz.

"Advances in technology are making the ethical issues both easier and harder," says Greely, who points out that some scientists are eager to study human brain cells in animals as a way to learn more about diseases such as Alzheimer's or Parkinson's, or other conditions such as autism or depression. Although these experiments will likely reignite the national discussion of what it means to be human and what our moral obligations to such research animals may be, human consciousness doesn't reside in our pancreases or livers or hearts.

"Thoughtful discussion is always important," says Greely. "But evidence is mounting that it may well be possible to transplant human stem cells into nonhuman animals to create organs in ways about which few people would have ethical concerns."

Nakauchi is more blunt.

"More than 116,000 patients are on the waiting list and 20 people die each day in the United States alone due to a lack of donor organs," says Nakauchi. "Animal-grown organs could transform the lives of thousands of people facing organ failure. I don't understand why there continues to be resistance. We could help so many people." SM

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FEATURE

Brain balls

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mimic two different brain regions containing different kinds of neurons, fuse the balls together and see how they talk to each other.

Pasca's group has done just that, showing in an April 2017 paper in *Nature* that when two brain balls representing different brain regions are brought into contact, they can fuse and forge complex neuronal connections.

WHEN A BRAIN BALL MEETS A BRAIN BALL

In real brains, excitatory neurons secrete a substance whose arrival at one of its receptors on the next neuron in a relay increases the likelihood of that next neuron firing off an impulse. During fetal development, the cerebral cortex's excitatory neurons are eventually joined by inhibitory neurons that originate in an underlying region of the developing forebrain. Those inhibitory cells migrate several millimeters to the cortex, where they interlace with excitatory cells to form circuits that drive the brain's advanced cognitive activities — and in which an excitation-to-inhibition imbalance can lead to epilepsy and has been suspected to play a role in autism. But no one had been able to watch this happen to human cells in real time in a dish, or anywhere else.

In the study, Pasca's team cultured two separate batches of human brain balls generated from a healthy subject's skin. They bathed one batch in a medium that fostered cerebral cortexlike brain balls containing excitatory neurons. They placed the other batch in dishes whose nutrient broth steered balls toward resembling the underlying brain region where inhibitory neurons originate. Then, the investigators juxtaposed the two distinct brain ball types in the same dish.

So, what happened in the petri dish when excitatory and inhibitory brain balls touched? Within a few days, the balls fused, and the researchers could watch inhibitory neurons from one migrating into the other, excitatory-neuron-rich one.

On reaching their destination, the inhibitory neurons sprouted dendrites — the foliagelike "tails" that neurons use for receiving inputs from other neurons — and hooked up with the excitatory neurons. The two neuronal types formed functional, mutually signaling circuits.

Then the investigators generated both types of brain balls from skin samples of patients with the autism-related Timothy syndrome, fused them and watched. What they saw was this: The inhibitory neurons appeared to develop normally at first, but migrated in a markedly inefficient way. Pasca's team showed that two different drugs could restore normal migration and, ultimately, normal signaling properties to the Timothy-syndrome-derived inhibitory neurons.

RUNNING WITH THE SPHEROIDS

Anca Pasca has taken a two-year sabbatical from her clinical work to concentrate on using the brain balls to study hypoxia, an oxygen deficiency in the brains of babies born before their lungs have matured sufficiently.

"Technology now allows us to save babies as early as 22 to 23 weeks of ges-

tation," she says. "But up to 90 percent of these saved preemies will wind up with significant neurodevelopmental impairment. We see a lot of hypoxia in the NICU [neonatal intensive care unit]. We think it's one of the most important causes for abnormal brain development ranging from mild learning deficiencies to cerebral palsy."

"Thanks to three-dimensional culture, we now have a way of mimicking developing brains' hypoxia exposure in a dish and I can study them. Once I understand what's happening to them, the next step is to come up with a drug to prevent this from happening."

Pasca's brain-ball-generating method has been reproduced, and put to work, in numerous other labs, and not just to study early development. "Pasca's technique has become the standard method for generating neural spheroids in three dimensions," says Boston University School of Medicine research associate professor Weiming Xia, PhD.

In a study published in 2016 in *PLOS One*, Xia and his colleagues compared brain balls à la Pasca with old-hat 2-D neuronal cultures as vehicles for screening a couple of experimental drugs targeting Alzheimer's disease. The scientists found that the drugs — both of which work by reducing the production of a substance called A-beta that aggregates into gummy plaques characteristic of the disorder — showed less potency in brain balls than in 2-D neuronal cultures. That means a lot of expensive follow-up after a positive result using the 2-D assay could turn out to be a waste of time.

The reason for the drugs' reduced efficacy in brain balls, Xia says, is that they had a hard time getting inside the brain balls. Because brain balls approximate the brain far more closely than flat sheets of neurons at the bottom of a petri dish, they probably provide more meaningful results, he says, and could help steer research to drugs that do find ways to penetrate and permeate the spheroids.

And in Pasca's lab, the team has made brain balls resembling other important brain regions such as the midbrain structure called the striatum, a key component for facilitating movement and the brain's reward system. The hope is to fuse the striatal balls with cortical balls and try to generate, in a dish, a nerve tract running between the striatum and the cortex that's involved in movement disorders such as Parkinson's and Huntington's diseases as well as psychiatric conditions such as obsessive-compulsive and attention-deficit hyperactivity disorders. And they're trying to replicate the spinal cord and a deep-brain structure called the thalamus — a relay station for sensory inputs.

Thalamic brain balls will be particularly useful to John Huguenard, PhD, professor of neurobiology and of neurosurgery and one of the co-authors of Pasca's 2015 paper, who is particularly interested in the circuits by which the thalamus communicates with the cortex, and vice versa.

"Genetic variants are estimated to account for up to 50 percent of seizure susceptibility," says Huguenard. If Pasca's brain ball-fusion results in the recapitulation of the nerve tracts connecting the two regions, Huguenard can study at close range the effects of genetic insults that induce a predisposition to epilepsy in a developing brain.

PUSHING THE BOUNDARIES

These balls of cells floating in a petri dish lack some crucial features of functioning brains — sensory input, for example, and connections to muscles, the immune system and a circulatory system. But Pasca thinks some of these problems will find solutions. Transplanting human brain balls into rodent brains could result in their tapping into the animals' circulatory systems.

He hopes to implant such fusion products, or just single brain balls, into a mouse, placing a patient-derived construct on one side of the mouse's brain and another one derived from a healthy person on the other, then comparing how the two different brain balls operate in that living environment.

Pasca acknowledges the need for caution. "This type of transplant experiment requires approval like all of our experiments, but we are also actively engaged in conversations with ethicists and other scientists in the field about the best way to move forward." He's part of a group working with the National Institutes of Health to create guidelines for the quickly advancing field.

Where would he draw the line? "Primates. I would not want to transplant human brain cells into a nonhuman primate without a strong rationale."

And interest continues to build. Pasca organized a December 2017 inaugural meeting focusing on three-dimensional modeling of the human brain. The meeting, held at Cold Spring Harbor Laboratory in New York, drew 130 participants from around the world, and he's co-chairing a weeklong course in Italy this summer. Stanford has licensed the technology to a Vancouver-based company, STEMCELL Technologies, which plans to release brain ball culture kits that could speed researchers' adoption of Pasca's advance.

Meanwhile, Pasca's lab now boasts almost as many different cultures as the United Nations. "We have hundreds of iPS cell lines obtained from patients with various psychiatric disorders," he says. While planetary peace may be a distant development, learning how a living brain develops is a dream that's rapidly coming true. **SM**

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FEATURE

Miracle moment

CONTINUED FROM PAGE 32

a man's heart — now she puffs stogies and rants and raves at TV wrestlers."

At the same time, lawsuits against heart surgeons became something of a fad worldwide, with defense attorneys claiming their clients were not guilty of murder despite having, for example, shot a victim in the head. It was the surgeons, who removed the victims' hearts, who were guilty of the murder, they argued.

The Santa Clara County coroner threatened to bring murder charges against Shumway after his first transplant, but the district attorney refused. Shumway did testify in the 1974 murder trial in Oakland of Andrew Lyons, who had shot one of Shumway's transplant donors in the head.

"I'm saying anyone who is brain-dead is dead," Shumway testified, according to a story in the *New York*

Times. Lyons was found guilty.

Not until 1976 would the issue of cause of death be resolved in California, with the establishment of a state law on brain death that made it clear doctors could legally remove a beating heart from the body of a brain-dead patient.

In 1970, on the third anniversary of Barnard's first transplant, exhausted by this near madness and frightened by the soaring death rates, the medical establishment, led by the American Heart Association, called for a moratorium on heart transplants. All major institutions complied, except for one: Stanford.

A 1971 *Life* magazine cover story, "A new report on an era of medical failure: The tragic record of heart transplants," reported the numbers: of the 166 heart transplants performed, only 23 recipients were still alive, giving the procedure an overall mortality rate of 85 percent.

"Shumway had been the man who American medicine thought would usher in the era of transplanted hearts," the magazine reported. "Instead he became the principal surgeon to survive it. Mercifully, the race was no longer a race. The spectators had gone home; all the runners save one had dropped out. He could afford to take all the time he needed to reach the finish line."

REFINING THE WORK

"We just ignored it all," says John Schroeder, MD, a professor of cardiovascular medicine who in 1968 was a member of the Shumway team as a cardiology resident. He helped write the grant proposals that kept Stanford's research program alive following Kasperak's transplant.

Returning to the laboratory, the Stanford physician-scientists continued to methodically publish scientific papers and conduct heart transplants, slowly establishing new protocols for the selection of patients and for measuring and treating rejection that would lead to the success of heart transplantation.

Today, Stanford Medicine's reputation is firmly established as the research center responsible for leading to the thousands of successful transplants carried out annually around the world. But that first surgery remains a magical moment, for Stinson at least, and an essential one, along the journey toward making heart transplantation a standard operation.

"We learned a lesson," Stinson says. "Patient selection would be key to the success of this operation. Mr. Kasperak was just too sick to survive. At the time of his death, the heart was probably the only functioning organ he had." Shumway, who died of cancer in 2006, for many years kept a slogan hanging on his wall that said: "Where there is death, there is hope."

The year following Mike Kasperak's death, Ferne Kasperak was asked by a reporter at the *Palo Alto Times* about the decision that led to her husband undergoing the first adult heart transplant in the United States.

"He had 15 days extra that I don't think he would have had," she reportedly said. "I have no regrets, and I don't think Mike did either." SM

— Contact Tracie White at traciew@stanford.edu

FEATURE

A conversation with Mary Roach

CONTINUED FROM PAGE 35

ROACH It was one of the stranger reporting challenges for me because on this base in Djibouti the special operations guys are off in a restricted zone. I don't have the clearance to go in there. The only time they come out, my only opportunity to talk to them about diarrhea, is at mealtime when they sit down at this table. They come in. They're often by themselves. They eat their food, then they leave. I had to march up to this man. He thought I was with the Naval Criminal Investigation Service. He thought he was in trouble for something.

I kept saying, "No. Actually, I've traveled all the way to Djibouti to talk to you about diarrhea."

COSTELLO Why do people let you in their front door?

ROACH I expected military public affairs people to be wary, squirrely, turning me down all the time. In fact, they were the opposite when they heard that I was reporting on science and medicine, the military science that goes toward keeping people alive and putting them back together, rather than the weapons side of it.

That was not a threat to them. The approval was hung up for a while and I wrote to this woman. I said, "So, is there anything I can do? Do people have a problem with my approach or something I've written in the past?"

She said, "We don't care about you. We're concerned with *Zero Dark Thirty*. We're concerned with special operations people writing memoirs and revealing things that are classified. We're fine with you coming here and reporting about people who are repairing genitalia that are damaged in an IED explosion. We are fine with you writing about the problem of food poisoning out in Somalia or Djibouti."

COSTELLO Are you ever traumatized or shocked by what you're looking at?

ROACH Traumatized? No. I think the hardest part of *Grunt*, was sitting down with a man who'd stepped on an IED and lost part of both legs and part of his penis. Asking him to tell me that story, what was that like, re-creating that moment from the time he stepped on it clear through to when he made it back to the base. I'd never really spoken to someone who'd been through that.

I was really awed by him, and his courage, and what a decent person he was, and what an awful thing he'd been through.

COSTELLO In the intro to *Grunt*, you wrote: "I'm interested in the part that no one makes movies about, not the killing but the keeping alive."

ROACH In its subtle way, it's an antiwar book. I don't hammer home any particular political point. … It was interesting to me to speak to these people and to come away with a far more nuanced sense of what it means to be in the military. There is no one military type. These people were extraordinary and very committed and very caring.

They're folks who signed up for the military and spent their whole careers in it, but they're not fans of battle or war.

WEB EXTRA

Hear the conversation at http://stan.md/2EBaMH6

COSTELLO Is there something you're also trying to convey to the healers?

ROACH Yes. *Thank you* really is the message. Not just to military medical personnel I wrote about in *Grunt*, but also to NASA support teams reflected in *Packing for Mars* — the astronaut book. Whether it's an astronaut, or a soldier, or a Marine, those stories of saving human lives and, even more so, just healing people and putting them back together. That story doesn't get told enough, and I think that those people deserve a lot of recognition and gratitude.

COSTELLO What are the elements of storytelling and narrative for research scientists who want to tell their story?

ROACH The challenge for most research scientists, I think, is that the things they're excited about and fascinated by are so dialed down, and specific, and complicated compared with what sparks the curiosity and interest of the average person who doesn't have a background in bioscience.

I think they're so far away from someone like me discovering, "Oh, this is how a bladder works. Stretch receptors, wow, that's cool." … So I'm the interpreter between the two.

COSTELLO So who are Mary Roach readers? Can you define them?

ROACH You know that scene in *Being John Malkovich* where he's in that restaurant and everybody looks like John Malkovich? That's how I picture it. Thousands of Mary Roaches. **SM**

This interview was condensed and edited by Paul Costello

FEATURE

Operating in zero gravity

CONTINUED FROM PAGE 37

give him any more." Meanwhile, Swanny calls up and informs us that we're already running short on time, with about an hour and a half before we have to wrap it up.

We haven't even begun the actual repair and we're already short on time. *Dammit!* But I stretch, my long arms extending out fully, and with the pin puller tool I can just barely reach the panel. I pull it gently toward me.

Wheels is watching below. "Looking good, Spike."

Finally, I truly get to work. First, we have to cut the hairball out, allowing the cable to retract toward Wheels, with him controlling it with his modified Vise-Grip.

For the next bit, I need to be even closer, close enough to push a cuff link tab into a hole that had been used to keep the solar panel aligned during its launch. I'm juggling my three tools, using the pin puller to pull in the wing, maneuvering the cuff link into and through the hole with the taped-up wire following it in, and using the hockey stick to keep the wing from getting in contact with my suit. I could really use an extra hand, but that's not gonna happen.

"Heads up!" It's Wheels, and I tell him I see the wave coming. I hear Pam breathe in hard as I lean back a bit and grapple with the hockey stick, using it to push the billowing wing away from me. Then I quickly get back to work.

After that, with the technique and the pattern established, it's just a delicate suture job and time flows as I concentrate on the tools, the wing and the work.

Finally, it's done. Hairball removed. Five sutures in, five homemade cuff links and wires holding it together, spanning two rips. Over six hours have gone by, and we still need to deploy the panel and get home. I stow my tools, stop for a moment and breathe. I straighten up and try to give my body a quick break, consciously relaxing clenched, tired muscles. I open and close my hands, fighting the pressurized gloves.

"Discovery, Houston," Swanny says from the ground. "We are happy with the current config, and we are ready for you to back off and get ready for the deploy." Wheels and I monitor the slow, segmented extension of the balky panel, and soon realize that it's all going to work.

It's a triumphant moment when we hear the panel is fully extended, cheers audible on the communication loop from Mission Control. Our work here is done. And somehow I know it's the best day on the job I will ever have.

"All right," I say, trying not to sound too excited. As if this is just another day in the training pool. "That's how you do it!"

"Excellent," says Pam. Her voice is guarded, though. She still has to get me back inside. "You know there aren't many people in the office who could do what you just did there."

"I hope they don't have to!" I say. Relief washes over me. "That was a beautiful day in space right there."

As I fly back toward the airlock, my stomach growls and my beat-up knuckles sting with blisters. I'm exhausted but overjoyed. As I fly through space this one last time, I'm grateful. I can't believe we all did it. And I can't believe I got to be a part of it. I look once again, drunk with the beauty of the Earth and the thin blue line below.

I think of the team, the hundreds of brilliant and hard-working people who came together for this, one of NASA's finest moments. We did it. **SM**

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TINY HEART REPAIRS

BABIES WITH RARE GENETIC DISORDERS HAVE A CHANCE FOR LONGER LIVES

It was once unusual for children with Down syndrome to have surgery to repair heart defects that are associated with the disorder. "Back in 1975, folks would've said there's nothing we can do to help those babies. But now people have proven if you do heart surgery early, patients with Down syndrome can live to adulthood and be active members of their community. The difference it makes for them is tremendous," says Stanford pediatric cardiologist Thomas Collins, MD.

Collins believes new research might also change attitudes about performing surgery for others who, like Down syndrome babies, are born with a third copy of a chromosome — in this case, babies with trisomy 13 or trisomy 18.

Pediatric cardiologist Thomas Collins hopes research on the benefits of early heart surgery can improve options for babies with a third copy of chromosomes 13 or 18.

In a recent study published in *Pediatrics*, Collins and colleagues from the University of Arkansas for Medical Sciences showed that heart surgery can more than double the life spans of babies with trisomy 13, also called Patau syndrome, or trisomy 18, also called Edwards syndrome.

Birth defects and disabilities are far more severe in Patau and Edwards syndrome babies than they are in Down syndrome babies, who can live for many decades. Many Patau and Edwards syndrome babies die within hours or days of birth and most don't live past a year old.

Their heart conditions are often treated with standard medical care — blood pressure medication, ventilators and intravenous fluids. Surgery is rarely an option. "The thought has been it doesn't make sense to undertake a major heart surgery if the patient's death within a few months is a near certainty," Collins says.

Extending the lives of these babies means they still might not live past the age of 2, but even that improvement gives parents more time with their children and more options for care, Collins points out. It also gives specialists more time to develop treatments for other health issues, such as breathing difficulties.

For their study, researchers used data on nearly 1,600 trisomy 13 and 18 patients from 44 children's hospitals across the United States between 2004 and 2015. They found that heart surgery increased survival and hospital discharge on average from 33 percent to about 67 percent and that the benefit lasted through two years of follow-up, Collins says. "Especially for trisomy 18, the number of babies that survive more than doubles after surgery," he says.

Most infants in the study were admitted at less than a day old, and 51 percent of infants in the study who had congenital heart defects died in the hospital or were discharged to hospice.

Collins says he hopes the research will change how doctors approach treating Patau and Edwards syndrome babies once heart issues are addressed. He says he plans to study more than 3,000 trisomy 13 and 18 patients to determine how their collective health problems fit together, with a goal toward creating a guideline for treatment priorities.

"Surgery gives parents the option to say, 'We're going to do everything we can for our baby,'" Collins says. "And, now we've shown that heart surgeries could allow parents to take their babies home from the hospital, and have them for two years or beyond, as opposed to two weeks." — AYLIN WOODWARD

TIMOTHY ARCHIBALD

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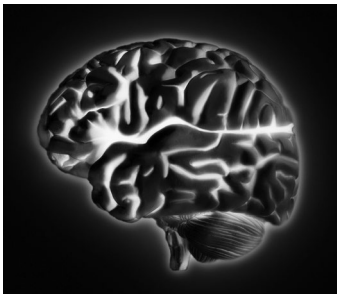
Zapping bad impulses

IMPLANTABLE BRAIN DEVICES COULD DETECT AND SQUELCH DESTRUCTIVE URGES

Stanford researchers have identified a pattern of electrical activity that occurs deep in mouse brains just before they do something destructively impulsive. The knowledge, gathered by studying mice in a regimen that turned them into binge eaters, helped researchers discover that small electrical "zaps" to that area of the brain just before the behavior can halt it.

"Impulses are normal and absolutely necessary for survival," says Casey Halpern, MD, assistant professor of neurosurgery. "They convert our feelings about what's rewarding into concrete action to obtain food, sex, sleep and defenses against rivals or predators."

But impulses can run amok, resulting in addictive or dangerous behavior.



"Imagine if you could predict and prevent a suicide attempt, a heroin injection, a burst of binge eating or alcohol intake, or a sudden bout of uncontrolled rage," says Halpern, senior author of a paper on the findings, published Dec.18 in the *Proceedings of the National Academy of Sciences*.

It's worth noting the heightened brain activity didn't occur when mice acted on routine impulses, such as seeking out a buddy for ordinary interactions. It occurred only when they started binge-eating high-fat food they'd been hypersensitized to obsessively desire.

Halpern said the research could lead to noninvasive ways to treat addiction, and to development of an implantable device to monitor the area of the brain that helps generate pleasure-seeking impulses. When signals preceding bursts of impulsivity are detected, the device could deliver small electricity zaps to stop impulses.

Deep-brain stimulation has Food and Drug Administration approval to treat Parkinson's disease and essential tremor and is in clinical trials for such brain disorders as depression and obsessive-compulsive disorder. Most devices fire at preprogrammed rates, but Halpern says new technology might enable charges to be timed to signals.

Researchers found the signature pattern in one person with obsessive compulsive behavior who consented to monitoring during a task-for-cash reward test. "The fact that we saw a similar signal prior to two different behaviors, both intended to obtain rewards — food in the case of mice, money in the case of the human subject — to which the individuals had become hypersensitized by their repeated exposure suggests that this signal may be common to many impulsive behaviors, making them amenable to treatment along similar lines," says Halpern.

— BRUCE GOLDMAN

TETRA IMAGES