ANTARCTIC COLLAPSE? MEET THE GLACIER THAT MIGHT SINK THE WORLD'S COASTAL CITIES PAGE 40

SCIENTIFIC AMERICAN

HOW THE BRAIN READS FACES

Cracking the neural code

PLUS

GHOST FLOWERS
Resurrecting the genes of extinct plants PAGE 30

EXOPLANET NEXT DOOR
Venus can help in the hunt for extraterrestrial life PAGE 56

UNCONTACTED TRIBES
Can they be protected? PAGE 46

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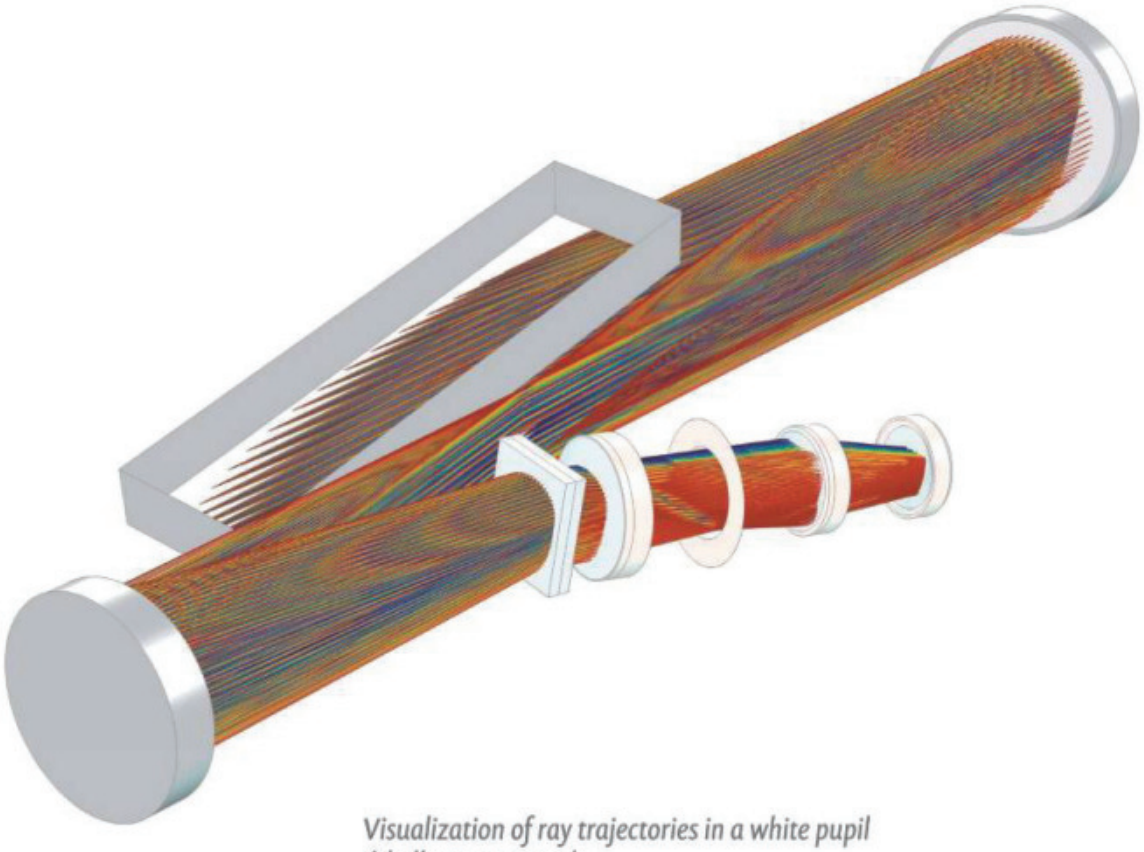
Looking beyond our solar system with ray tracing simulation...



Visualization of ray trajectories in a white pupil échelle spectrograph.

Astronomers detected an Earth-like planet 11 light-years away from our solar system. How? Through data from an échelle spectrograph called HARPS, which finds exoplanets by detecting tiny wobbles in the motion of stars. Engineers looking to further the search for Earth-mass exoplanets can use ray tracing simulation to improve the sensitivity of échelle spectrographs.

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SCIENTIFIC AMERICAN

ON THE COVER

Scientists have taken major steps toward understanding how the brain recognizes faces—one of the great challenges of neuroscience. Not only have they found sections of the cerebral cortex that perform this function, they have also decoded the computations that enable the brain to distinguish any given face.
Illustration by Maciej Frolow.

Photograph by Juan Arredondo

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SPECIAL REPORT

S1 Nature Outlook: Gene Therapy
A number of health issues that have proved difficult or impossible to remedy—sickle cell anemia, epilepsy, certain skin conditions—might be excellent targets for gene therapy. This report, from *Nature,* highlights the latest research.

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Mariette DiChristina is editor in chief of *Scientific American.*
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What's in a Face?

It's remarkable how often seemingly pedestrian things ultimately spark a sense of wonder when considered through the evidence-based view of research. Take the question of how we see faces, a ho-hum everyday occurrence that we easily do without conscious effort. Yet it is a feat full of puzzling intricacies that investigators are attempting to parse. How do the networks in the brain put various features into recognizable faces and, eventually, assemble a sensible picture of the world?

In this issue's cover story, "Face Values," neuroscientist and MacArthur Fellow Doris Y. Tsao describes her journey into this field of study. It began in her high school calculus course using differential equations to describe curves and continued in undergraduate studies—where she learned early experiments in how the primary visual cortex extracts edges from images—and graduate school. "I was captivated by the challenge of understanding vision and embarked on a quest," Tsao writes. Parsing these complex neural interactions begins on page 22.

Using our visual systems, we're also seeing—and welcoming—some new faces to *Scientific American,* as part of our ongoing refinement of editorial content. First of all, we've added some new advisers to our board below; their insights are invaluable to our science coverage. In addition, in recent months we've been joined by Claudia Wallis as the "Science of Health" columnist, as well as by climate scientist Kate Marvel, who writes "Hot Planet" on ScientificAmerican.com.

In this issue, technosociologist Zeynep Tufekci shares her expertise. Her monthly column, "The Intersection," on page 72, promises to cover critical issues that occur "where science and society meet." Her first essay, "Zombie Baby Monitors Attack," sheds light on "blatantly negligent security practices" that could undermine the Internet of Things. Also penning his first monthly installment is technology journalist Wade Roush. He will be writing "Ventures," covering "the business of innovation." In "Getting Out of Silicon Valley's Shadow," he discusses whether local economies need an economic injection from a so-called innovation district or technology cluster. The future awaits on page 19. SA

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Illustration by Nick Higgins

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October 2018

SHAPING UP SCIENCE

As a professor emeritus of genetics who spent many long hours writing grant proposals, I agree with "Rethink Funding," by John P. A. Ioannidis [State of the World's Science 2018]. The system is biased in favor of "politically savvy managers."

Yet Ioannidis does not address the overhead funds that line the coffers of universities. With state funding constantly dwindling, they rely on overhead more than ever. This is why academia favors big grant getters over innovative research. Reducing bloated academic administrations would be one modest way to solve the conundrum, but who is going to do that?

Paul F. Lurquin
Washington State University

There is a danger that new ideas will be held back if attention is directed too narrowly on the precision of scientific methods. Such ideas often arise from the use of imprecise approaches. For example, single case studies in medicine, surveys showing correlations in my own field of consumer behavior, and odd observations in astronomy can all lead to major advances because they pick up serendipitous findings that are hard to anticipate. The new ideas that are generated are usually tested by experiments, but such tests often provide limited stimulus for new thinking.

Robert East *Emeritus professor, Kingston University London*

"We must explicitly acknowledge, fund and motivate reproduction of study results."

Jose M. Soler
Autonomous University of Madrid

IOANNIDIS REPLIES: Lurquin points out the problem of large overheads, which have grown. Eliminating them is not easy, because one needs to find other sources for sustaining the infrastructure of research institutions. Unnecessary bureaucracy could be trimmed, of course.

East advocates the support of imprecise exploratory methods when they fuel new, exciting ideas. Such research is justifiable and necessary when we have no other better tools for initial discovery. But it needs to be recognized explicitly as being exploratory and thus often likely to be wrong and in need of careful subsequent validation with better methods.

REPLICATION TROUBLE

As an academic researcher, I was not too surprised to learn that a large fraction of results in even the best journals cannot be reproduced in "Make Research Reproducible," by Shannon Palus [State of the World's Science 2018]. As reported in both Palus's and Ioannidis's articles, researchers have many institutional pressures and personal motivations to publish flashy results and none to replicate those of others.

We must explicitly acknowledge, fund and motivate reproduction. It would help if journals had a section or associated publication accepting studies by independent authors seeking to reproduce works previously published by those journals. Their referees would not judge originality or interest but would value methodological rigor, clarity and, possibly, improvement or extension of the results.

Jose M. Soler
Autonomous University of Madrid

I think Palus's note that the original work discussed "appeared in a topflight journal," whereas "the replication effort can be found in a comparatively smaller one" is perhaps her most important observation.

What struck me was the high-handed way that some of these journals don't stand by their product. That cheapens the worth of the publication. If you publish a paper, the reputation of the publication is behind that study from a marketing POV. If the paper is later refuted by, or can't be replicated in, another study, you have a duty to publish the latter paper as well. This could be encouraged by an independent organization that simply records the number of times a counter paper was published in a different journal because the original publication refused it.

Neil Robertson *El Cerrito, Calif.*

LIMITED DECISIONS

It was fascinating to learn in "The Unsolvable Problem," by Toby S. Cubitt, David Pérez-García and Michael Wolf, that certain important questions in theoretical physics are undecidable by computation.

In discussing the primary example of such a question, the authors assert that determining the existence, or not, of an energy gap between the lowest energy state of a material and the next state up would depend on the material extending to infinity. Yet in that case, presumably the material itself will be forever unable to decide whether it is gapped or gapless because any causal influence between distant regions can travel only at the speed of light.

Tony Durham *Brighton, England*

THE AUTHORS REPLY: Strictly speaking, any undecidable problem must have an infinity somewhere. If you impose any limit, even the lifetime of the universe, then it is decidable, although in practice, that is not much better than if it were not.

In the case of the spectral gap problem, for any reasonably large, finite lattice size, the systems we construct will either be gapped or have an energy spectrum that is so dense, it becomes indistinguishable from gapless. In principle, if you limit how large the lattice can get (say, it needs to fit in your lab!), then the problem is decidable. But the undecidability of an idealized infinite lattice implies there is no better way to figure it out than taking a sample of material the size of your lab; a smaller sample will tell you nothing

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about the lab-sized one. Worse still, even if you determine whether the lab-sized sample is gapped or gapless, this could change just by adding a single extra atom.

It's important to emphasize that no materials anyone has encountered in reality display this perverse behavior. But we can look for simpler systems that exhibit similar physics, and we have made some progress on doing so in a follow-up paper.

Durham's scenario is somewhat similar to what we describe: In principle, given infinite time, the speed of light is no obstacle. A time limit would be qualitatively similar to imposing a finite size limit, equal to time multiplied by the speed of light.

DOWN UNDER DEVELOPMENT

In "Body Balance" [Advances], Maya Miller reports that developmental biologist Alberto Roselló-Díez and his colleagues found that when they suppressed growth of a limb in a mouse fetus, the surrounding cells communicated with the placenta, which slowed down the growth of the other three limbs to keep them symmetrical.

This mechanism for maintaining symmetry in development would, however, work only with placental mammals. How would marsupials manage this coordination?

David Weintraub *Edison, N.J.*

ROSELLÓ-DÍEZ REPLIES: It is worth noting that even though they lack a true placenta, marsupials do form a yolk-sac-derived placentalike structure. And whereas the most obvious mechanism we found involves the placenta, this does not mean it is the only one. It is possible that other organs with a key role in body growth, such as the liver, also participate in the systemic response triggered by a local injury. They could do so either in parallel to the placenta or at subsequent (postnatal) stages once the placenta is no longer present.

ERRATUM

"The Unsolvable Problem," by Toby S. Cubitt, David Pérez-García and Michael Wolf, should have worded a mathematical statement about deriving the number 1 from any whole number in this way: "If you take any whole number and divide it by 2 if it's even or multiply it by 3 and add 1 if it's odd, and then repeat the process, you always eventually reach the number 1."

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Call the Midwife … If You Can

For better birth outcomes, the U.S. should rethink maternity care

By the Editors

Despite the astronomical sums that the U.S. spends on maternity care, mortality rates for women and infants are significantly higher in America than in other wealthy countries. And because of a shortage of hospitals and ob-gyns, especially in rural areas, many women struggle to access proper care during pregnancy. Moreover, the rate of cesarean sections is exceedingly high at 32 percent—the World Health Organization considers the ideal rate to be around 10 percent—and 13 percent of women report feeling pressured by their providers to have the procedure.

Widespread adoption of midwife-directed care could alleviate all these problems. In many other developed countries, such as the U.K., France and Australia, midwifery is at least as common as care by obstetricians. In the U.S., certified midwives and nurse-midwives must hold a graduate degree from an institution accredited by the American College of Nurse-Midwives, and certified professional midwives must undergo at least two years of intensive training. This is designed to make midwives experts in normal physiological pregnancy and birth. Thus, for women with low-risk pregnancies who wish to deliver vaginally, it often makes sense to employ a midwife rather than a more costly surgeon. Yet only about 8 percent of U.S. births are attended by midwives.

The roots of America's aversion to midwifery go back to the late 1800s, when the advent of germ theory and anesthesia reduced much of the danger and discomfort associated with childbirth. The benefits of these technologies brought doctors to the forefront of maternity care and pushed midwives aside. Obstetricians helped to bar midwives from practicing in hospitals, which were now considered the safest birth settings. By the early 1960s midwifery was virtually obsolete.

It has made a comeback since then, with practitioners just as well trained as doctors to supervise uncomplicated deliveries. Studies show that midwife-attended births are as safe as physician-attended ones, and they are associated with lower rates of C-sections and other interventions that can be costly, risky and disruptive to the labor process. But midwifery still remains on the margins of maternity care in the U.S.

To bring it back into the mainstream, midwives must be fully integrated into the medical system. Some states currently refuse to recognize them as legitimate practitioners, and some severely limit what midwives are allowed to do, despite evidence that states with the most restrictive policies also have some of the highest rates of adverse birth outcomes, such as deaths of newborns. If midwives were allowed to work alongside other providers, patients would get the care advantages, and if difficulties arose, a woman whose home birth suddenly became complicated could be seamlessly transferred to a hospital.

Even when state laws are favorable, women who wish to work with midwives often face financial obstacles. Medicaid will cover all midwifery services, according to the Affordable Care Act, but the requirement does not extend to private insurers, many of whom lack in-network midwives or refuse to cover midwifery care at all. Half of planned nonhospital births are currently paid for by patients themselves, compared with just 3.4 percent of hospital births. Thus, a less expensive birth at home may paradoxically be out of reach for women who cannot afford to pay out of pocket. U.S. hospitals charge more than $13,000, on average, for an uncomplicated vaginal birth, whereas a similar midwife-attended birth outside of the hospital reduces that figure by at least half. Insurers would save money by embracing midwife-attended, nonhospital birth as a safe and inexpensive alternative.

A national shortage of birth centers further limits women's choices. These homelike settings are designed to support naturally laboring women with amenities such as warm baths and spacious beds and are consistently rated highly in surveys of patient satisfaction. Yet there are only around 350 existing freestanding birth centers in the entire nation, and nine states lack regulations for licensing such facilities. More government support for birth centers would help midwives meet a growing demand, which has already fueled an increase of 82 percent in centers since 2010.

Policy makers, providers and insurers all have good reasons to encourage a shift toward midwifery. The result will be more choices and better outcomes for mothers and babies. SA

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Illustration by Ramona Ring

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Howard M. Fillit is founding executive director and chief science officer at the Alzheimer's Drug Discovery Foundation in New York City.

New Strategy for Alzheimer's

We need better molecular biomarkers to create targeted drugs

By Howard M. Fillit

Alzheimer's disease is the sixth leading cause of death in the U.S., and unlike with cancer and heart disease, we lack the tools to effectively diagnose and treat it. In sharp contrast to other illnesses and despite many efforts, huge expense and hundreds of clinical trials, no new treatments have been approved in the past 16 years. The emphasis has been on drugs targeting beta-amyloid proteins, which clump into plaques in the brains of afflicted people. Unfortunately, these approaches have not yet yielded the results we hoped for.

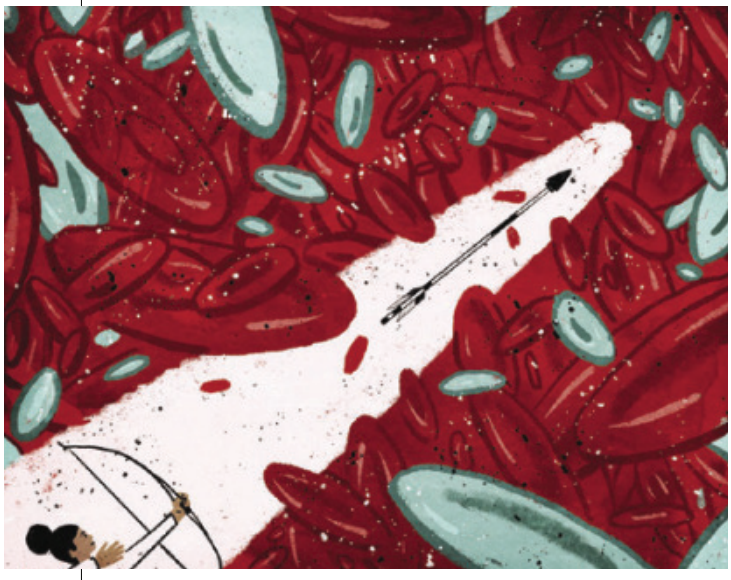
So now it is time to target novel pathways to tackle this incredibly complex disease. This has been a challenge because of the absence of affordable and noninvasive tests based on biomarkers that doctors can easily use in their offices. The alternatives have been expensive and invasive spinal taps or neuroimaging tests that can be performed only in a hospital or freestanding radiology office. New biomarkers are needed for specific molecular targets that can be used to subtype patients; for predicting the likelihood that they will acquire Alzheimer's; and possibly for providing a diagnosis even before symptoms are noticeable, enabling prevention. That is, they could do what currently available amyloid positron-emission tomography (PET) scans and cerebrospinal fluid tests do. Biomarkers can also be used to enroll patients in clinical trials directed to a specific target, such as beta-amyloid, and to measure how the body responds to a treatment—as was done most recently by Biogen with its anti-beta-amyloid monoclonal antibody. Ultimately biomarkers can determine which therapies would be most effective for an individual.

Such tools are already available for other diseases, including diabetes, hypertension, hyperlipidemia and cancer. In heart disease, for instance, serum cholesterol levels, which are measured after simply drawing blood with a needle stick, have long been used as a biomarker to identify patients at risk. The test is affordable and generally covered by employers or health insurance providers, including Medicare. If blood levels are high, drugs such as statins can be prescribed to lower cholesterol and with it the risk for heart disease. Doctors can also use cholesterol levels to see if a prescribed drug is working or needs an adjustment. LDL cholesterol is also recognized as a biomarker for heart disease risk by the Food and Drug Administration, so clinical trials can show that a drug lowers cholesterol and get approval for it.

Despite the existing tests for diagnostic and prognostic biomarkers, few patients in the U.S. have been tested with these confirmatory tests because of cost and access restrictions. And payers, including Medicare, will not cover amyloid PET scans, based on the perception that a definitive diagnosis has little clinical value.

But recent studies on the value of PET beta-amyloid brain scans, supported by the Centers for Medicare & Medicaid Services, have shown that practicing "dementia expert" doctors misdiagnose Alzheimer's in about 50 percent of cases and change their management and treatment of patients nearly 70 percent of the time when this test is used. An inexpensive blood test, covered by insurance, which can be performed in any clinical setting, would have a big impact on patients and their caregivers.

Recently the FDA issued guidelines recognizing the important role of biomarkers in demonstrating efficacy in clinical trials for Alzheimer's (especially early-stage ones). These new guidelines are a major step forward for fast-tracking drugs for the disease.



We need comparable tests—preferably blood tests—to help diagnose Alzheimer's and evaluate treatments. This will aid us in making clinical trials more rigorous, affordable and efficient, will accelerate drug development and will improve clinical care by providing access to accurate diagnoses. A new initiative called the Diagnostics Accelerator, under the auspices of the Alzheimer's Drug Discovery Foundation, aims to develop novel biomarkers from blood and accessible fluids and tissue. Such markers, specifically tied to Alzheimer's or other forms of dementia, will allow us to predict more accurately which treatment and prevention strategies will work in at-risk populations, as we can now do in cancer, heart disease and other diseases of aging. SA

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CAN A COMMUNITY INVIGORATE CANCER CARE?

A conversation with **ANDREW COOP,** global medicines lead, oncology business unit at AstraZeneca

Despite the advances in oncology research and care, cancer remains the world's second leading cause of death. But Andrew Coop hopes that his company might help to change that. Coop and the U.S. oncology team at AstraZeneca realize that bringing about meaningful change in cancer care is only possible when the entire community comes together. The company's YOUR Cancer program was designed to amplify and celebrate individuals and groups making a real difference in the oncology ecosystem — patients and caregivers, healthcare providers and researchers, advocates and policymakers and all those who are part of the oncology community.

How would you describe AstraZeneca's YOUR Cancer program?

YOUR Cancer is a new program designed to spotlight those at the forefront of cancer care. We recognize that any cancer diagnosis is devastating, but with this program we hope to reinforce the idea that it does not have to be one person's burden to bear. Our goal is to amplify the research, advocacy, policy, best practices, support initiatives and everything that's going on to improve the care of patients and their loved ones dealing with cancer. There are so many people who are touched by this disease but there's a tremendous community with experiences that can — and do — collectively make a difference. With YOUR Cancer, we hope to amplify and celebrate this collective effort.

What are the core pillars of the YOUR Cancer program?

There are four main pillars of this program. One, a digital hub, *www.YOURCancer.org*, where people can go to find community perspective and resources. We're inviting individuals and organizations to exchange ideas, get visibility for their work, and be part of this community. Two, an awards program designed to recognize unsung heroes of oncology — those individuals and organizations who are the true change agents in their communities. Three, a series of local roundtables to generate dialogue by bringing together policymakers, advocates and others to discuss important local issues in cancer care and come up with actionable solutions. And, four, a series of speaking engagements to profile key oncology leaders and raise important issues in cancer care.

Why is the YOUR Cancer program important to AstraZeneca?

There is an old proverb that if you want to go fast, you go alone, and if you want to go far, you go together. We want to go far at AstraZeneca. We've made a commitment to one day eliminate cancer as a cause of death, but we recognize that we can't do this alone. We're proud of our innovative portfolio and the work we do to take a molecule from our pipeline into the clinic where it can make a difference. But this is only one small part of bringing real change to patients and we realize that we need a village to do this. Through the YOUR Cancer program, we hope to offer our resources and platform to spotlight the oncology community as it works together to improve patient outcomes.

WE'VE MADE A COMMITMENT TO ONE DAY ELIMINATE CANCER AS A CAUSE OF DEATH, BUT WE RECOGNIZE THAT WE CAN'T DO THIS ALONE.

As part of the YOUR Cancer program, AstraZeneca developed the Cancer Community (C^2) Awards. How would you describe them?

We're excited about the C^2 awards because they're unique and meaningful. They celebrate members of the cancer community — whether it be individuals or organizations — who have an unstoppable drive to change cancer care. These awards also honor people who are working at the grassroots level — people who make an enormous difference to cancer patients and families but often fall outside the bounds of traditional awards programs. Each of the program's four awards recognizes contributions made toward eliminating cancer as a cause of death, whether by extending quality care to underserved communities, improving the patient experience, advancing precision medicine or just doing something flat-out inspiring to improve oncology care.

Each of the four winners will receive a $50,000 award that they can pay forward by donating it to a non-profit organization that serves the cancer community. The nature of these awards and paying it forward exemplifies the spirit of what we're looking to do in the YOUR Cancer program in general.

To learn more about the YOUR Cancer program and the C^2 awards, visit www.YOURcancer.org.

AstraZeneca

Introducing YOUR Cancer, an effort to spotlight the many individuals and organizations at the forefront of cancer care.

Cancer is personal, but never something you have to go through alone. It's a meal made in a neighbor's home or the friends that act like you're not sick at all. It's time with your favorite nurse and the doctors who are with you every step of the way. It's the policymakers who fight for funding and the researchers who try, fail, and try again to find the next breakthrough. It's the advocacy groups, associations, hospitals and all those working to make your cancer OUR cancer.

Join us in this movement to spotlight the work being done across the cancer community and help recognize those making a difference.

Visit www.YOURcancer.org to learn more.

YOUR cancer

A program by AstraZeneca

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www.YOURcancer.org

ADVANCES

Orcas can be rated on traits such as extraversion or dominance.

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INSIDE

GETTY IMAGES

ANIMAL COGNITION

Killer Personality

Despite evolving separately, orcas and chimpanzees have strikingly similar personality traits

Anybody who has taken an undergraduate psychology course or filled out one of those online tests is probably familiar with the "big five" personality traits: openness, conscientiousness, extraversion, agreeableness and neuroticism. For example, if you identify with the statement "I talk to a lot of different people at parties," you might score high on extraversion. An individual's personality is thought to be fairly stable by adulthood, and the idea that it can be measured by just a handful of factors goes back at least a century.

But humans are not the only species whose personalities can be quantified along these lines; caregivers in zoos, sanctuaries and other captive environments commonly assess the personalities of animals, based on months or years spent observing and interacting with them. The specifics vary among species (for example, newts can be scored for their libidinousness and zebra finches and rhesus macaques for boldness), but the underlying notion that personality can be described by a small set of factors remains the same. Now research suggests that animals as widely divergent as chimpanzees and killer whales have surprisingly similar personality profiles.

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Chimps share humans' "big five" personality traits, plus a sixth.

K & K AMMANN *Getty Images*

A team of researchers led by University of Edinburgh primatologist Drew Altschul amassed a quarter-century of chimp personality surveys. After passing data from 538 individual chimpanzees through a statistical model, Altschul and his team found that chimpanzee personality can be reduced to the same five traits applied to humans—plus a sixth known as dominance, which reflects the apes' "competitive prowess [and] social competence," they write. The results were published online last October in *eLife*.

That chimpanzees and humans have similar personality profiles makes some sense, given that the two species are so closely related. But what about our more distant cousins? Primatologist Yulán Úbeda of the University of Girona in Catalonia was recently busy preparing a lecture for staffers at the Loro Parque zoo in the Canary Islands. She decided to see if any personality research had been conducted with killer whales, one of the zoo's main attractions. "Not only were there no studies of personality in killer whales," but the only such cetacean studies she could find were limited to bottlenose dolphins, she says—and these did not utilize statistical techniques to reduce those personality metrics to a handful of factors. Úbeda asked trainers and researchers caring for 24 killer whales at three facilities in Spain and the U.S. to complete a survey originally designed to assess chimpanzee personality (though not the same survey Altschul used).

Killer whale personalities cluster into four traits, according to Úbeda's study, which was published last November in the *Journal of Comparative Psychology*. The first three are extraversion, dominance and carefulness; the fourth can be thought of as a combination of conscientiousness and agreeableness. When Úbeda compared these findings with the results of her own earlier research with chimpanzees, she found that the personality structures of the two species were quite similar (even though chimpanzee personality has six factors rather than four).

Given the differences in both habitat and neuroanatomy, not to mention the 94 million years that have passed since chimps and whales shared a common ancestor, Úbeda says she had not expected the two animals' personality traits to align so well with each other—or with those of humans. Still, "there's something about their social environment that has created this similarity in personality," says Justin Gregg, senior research associate at the Dolphin Communication Project, who was not involved in the study. Indeed, he explains, chimps and killer whales are both known for complex cognition, large brains relative to body size, and cultural learning—also features of our own species—and have similar societal structures as well.

Understanding personality is not just an intellectual exercise. For humans there is a well-established link between person-

BIOCHEMISTRY

Urine Trouble

Testing for caffeine in pee could help detect counterfeit samples

In a disturbing trend, scam artists are using commercially sold fake urine to fool doctors into prescribing pain medications such as hydrocodone—which can then be consumed or illegally sold. The synthetic pee lets patients pass tests intended to ensure they are not already taking opioid medications or drugs of abuse. Patrick Kyle, director of clinical chemistry and toxicology at the University of Mississippi Medical Center, says that "packaging materials and containers for some of these products are being left in the restrooms" at his hospital.

Hoping to address the situation, Kyle and his pathologist colleague Jaswinder Kaur have now shown how legal indulgences—including chocolate, coffee and cigarettes—can help distinguish real pee from fake.

Past approaches to spotting fake specimens have included testing urine's acidity and density and assessing concentration of a metabolic waste substance called creatinine. But some synthetic products now pass these evaluations, Kyle says.

The new method, described at the annual Society of Forensic Toxicologists (SOFT) meeting last October in Minneapolis, looks for four substances common in urine: caffeine and theobromine, both found in chocolate, tea and coffee; cotinine, produced as nicotine breaks down; and urobilin—degraded hemoglobin that gives urine its yellow color. The technique employs liquid chromatography to separate urine, just as water spilled on paper separates ink into different colors. The compounds then flow into mass spectrometers that identify them by their molecular weights.

The scientists studied the various substances in four different groups. One group of 100 urine samples came from people who had been observed providing them. A second set of 100 came from individuals seeking pain medication, who were not observed. A third came from 200 unobserved job applicants. And the final group consisted of 10 samples of commercially available synthetic urine. All samples provided by observed individuals were positive for at least one of the four test substances; three from the pain medica-

Illustrations by Thomas Fuchs

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ality and life span, and Altschul found a similar pattern for chimpanzees. "The core finding is that males who are higher in agreeableness will live longer than individuals who aren't as high," he says. Chimps have a reputation for aggression, but individuals that are "sympathetic, helpful, sensitive, protective and gentle" are likely to lead longer lives, he explains. Altschul is careful to point out, however, that this is ust a statistical correlation the underlying relation between personality and longevity in the apes is not yet known.

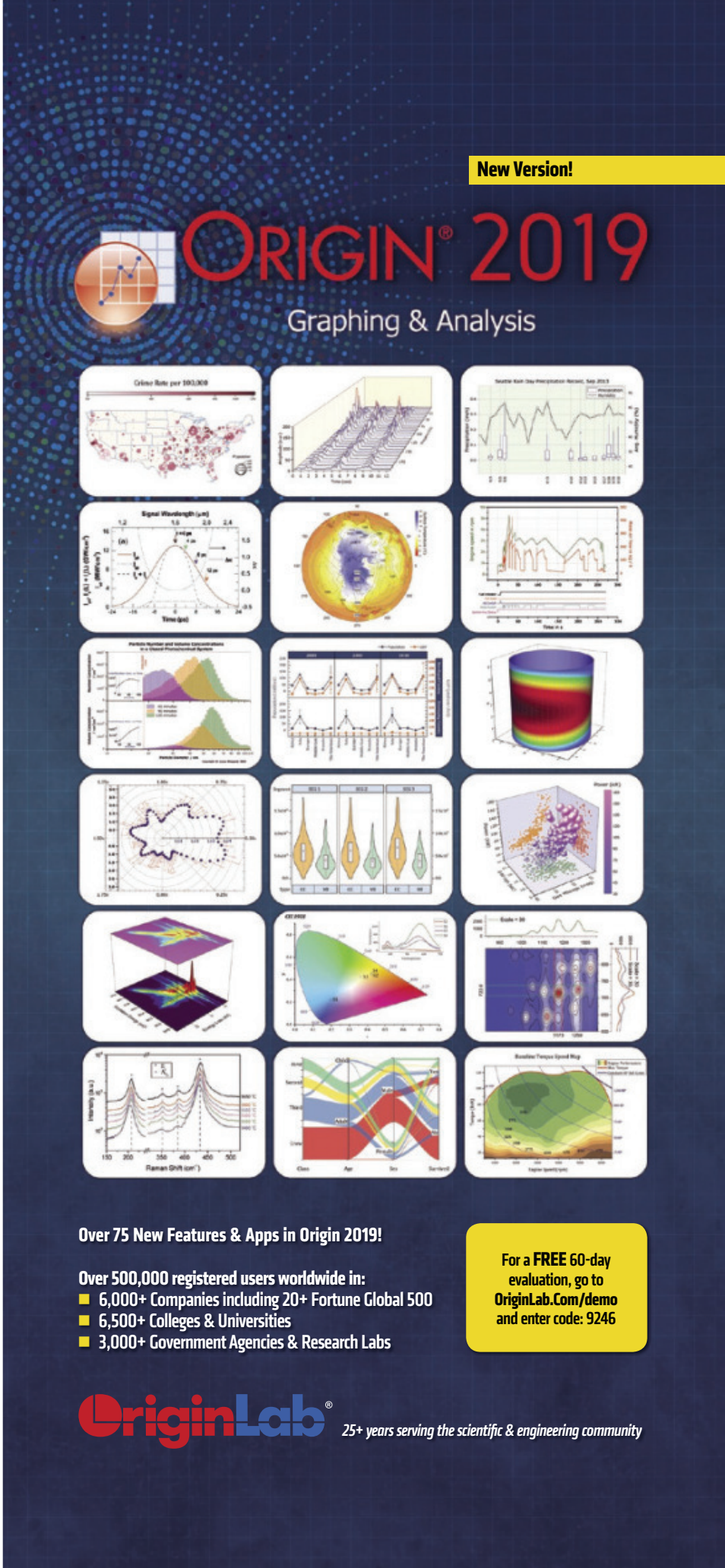
Duke University psychologist Paul Costa, who was not involved in Altschul's study, highlights the significance of human culture in increased life span, noting the potential role of captivity in explaining the chimp results. "The most important personality dimension related to longevity in humans is conscientiousness, and this was not related in this chimpanzee population," he says. The link in humans is most likely related to health behaviors. "People higher in conscientiousness exercise more, watch their diets, don't smoke and don't drink to excess," he explains. But in captivity, "even the most lackadaisical chimps are given a good diet and regular medical treatments," Costa adds, "whether they're conscientious or not."

—Jason G. Goldman

tion group and two from the job applicants lacked them. o synthetic urine samples contained any of the four substances. Negative results do not prove criminal activity—but they can indicate attempted deception, Kyle says. In such cases, he adds, "the clinic or the business should simply collect another specimen from the individual."

Michelle Peace of Virginia Commonwealth University, who is SOFT's president and was not involved in the study, notes that the test will not detect people passing off others' pee as their own. "If someone is carrying synthetic urine or somebody else's clean urine, you have to do observed collection," she says. Peace also warns that fake urine makers could easily add substances such as caffeine or theobromine to their products.

Some already do, Kyle says. He emphasizes that testing must therefore look for compounds naturally produced in our bodies (urobilin, in this case). Combining that with commonly consumed substances makes the test even more powerful—and is potentially more practical than watching people pee. *—Andy Extance*



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BIOMIMICRY

Crustacean Camera

e device mimics mantis shrimp's astounding vision

anti rim hold the title or the astest punch in the animal kingdom—po er ul enough to break seashells and a uarium glass. hey also boast some o the orld's most complex, extraordinary eyes. Human eyes have three kinds o light receptor cells, but these shrimp have a dozen, allo ing them to sense properties o light invisible to other animals.

ngineers at the niversity o llinois at rbana-Champaign have no made a camera that closely copies the crustacean's impressive visual system. he device, described last October in *Optica,* is a one-inch cube, and researchers say it could be made in bulk or apiece. hey believe it could ultimately be used to help cars detect hazards, to let military drones see camouflaged or shado ed targets, and to enable surgeons to per orm more accurately.

antis shrimp have t o visual superpo ers. For one, they can sense "polarized light, in hich all the aves undulate in the same plane (unpolarized light vibrates in every direction . ight bouncing off objects always contains a polarized component, and this property of light can reveal objects that otherwise blend into the background mantis shrimp use it to find prey in their blue-tinged ocean environs. hey can also detect an extensive span o light intensities kno n as dynamic range, hich lets them see very bright and dark areas at once.

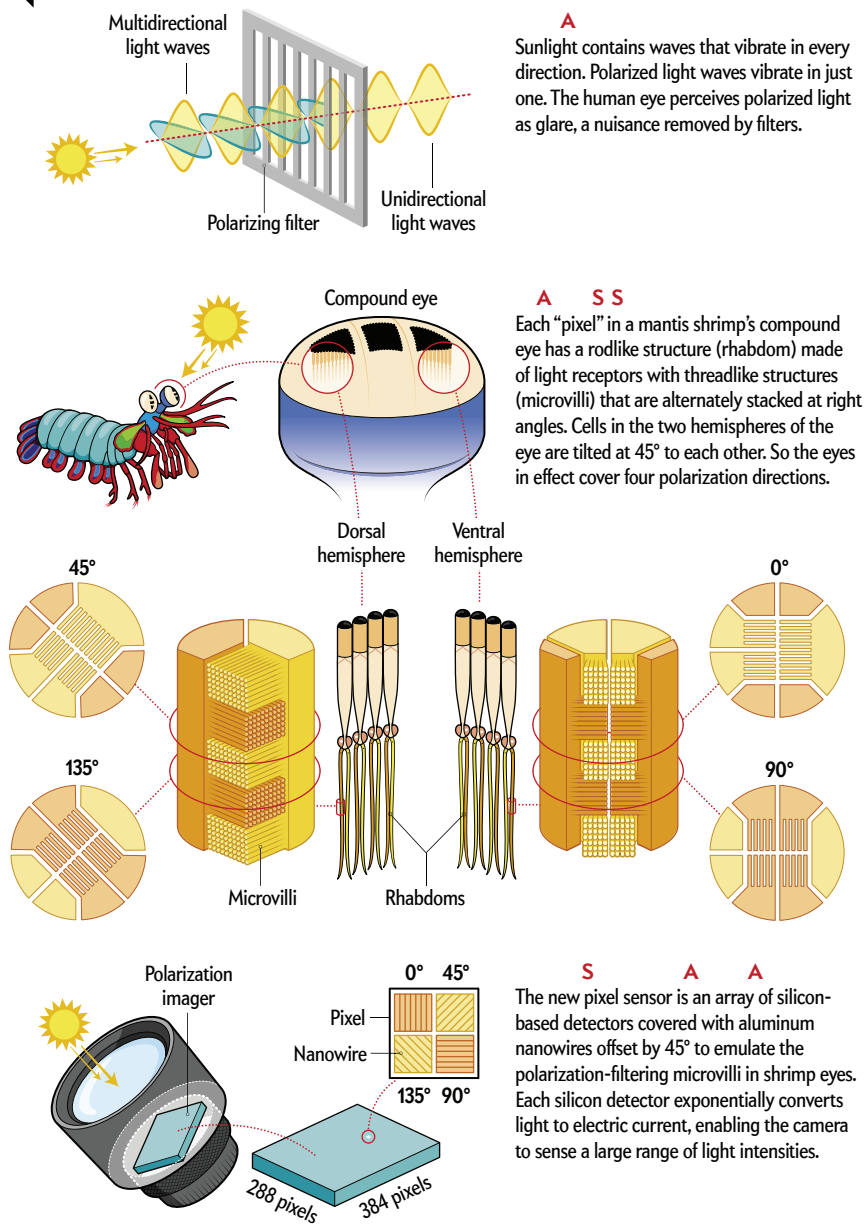
he ne camera emulates both abilities. lectrical and computer engineer iktor ruev and his colleagues made an array o tiny, silicon-based light detectors similar to those ound in commercial polarization cameras. But hereas conventional detectors produce an electric current that increases linearly ith light intensity, the ne detectors respond exponentially. his yields a dynamic range about , times higher than today's commercial cameras. he researchers also covered the detectors ith microscopic aluminum ires to imitate microvilli, the tubular structures in shrimp eyes that filter and sense polarized light.

For a real- orld test, the team drove around in a car mounted ith their ne camera and a standard one. Pictures rom the shrimp-eye camera had much higher contrast, especially in oggy and rainy conditions and in scenes ith a lot o light and shado s, ruev says.

he mantis shrimp is the only creature that can sense a ull spectrum o colors and polarization, says homas Cronin, a pro essor o biological sciences at the niversity o aryland, Baltimore County, ho as not involved in the study. his characteristic makes it ideal or a camera to emulate, he says "You ould get clear images of objects in a complicated background that are difficult to pick out ith other techni ues.

—Prachi Patel

How the Camera Mimics the Shrimp Eye



A
Sunlight contains waves that vibrate in every direction. Polarized light waves vibrate in just one. The human eye perceives polarized light as glare, a nuisance removed by filters.

A S S
Each "pixel" in a mantis shrimp's compound eye has a rodlike structure (rhabdom) made of light receptors with threadlike structures (microvilli) that are alternately stacked at right angles. Cells in the two hemispheres of the eye are tilted at 45° to each other. So the eyes in effect cover four polarization directions.

S A A
The new pixel sensor is an array of silicon-based detectors covered with aluminum nanowires offset by 45° to emulate the polarization-filtering microvilli in shrimp eyes. Each silicon detector exponentially converts light to electric current, enabling the camera to sense a large range of light intensities.

SOURCE: "BIOINSPIRED POLARIZATION IMAGER WITH HIGH DYNAMIC RANGE," BY MISSAEL GARCIA ET AL., IN *OPTICA*, VOL. 5, NO. 10; OCTOBER 20, 2018

Illustration by Brown Bird Design

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Cattle and zebras graze at a private wildlife conservancy in Kenya.

TONY KARUMBA Getty Images

CONSERVATION

Ghosts of Wildlife Past

ivestock and ildli e in Kenya can thrive together

en a nati na ar serve as oases in an increasingly human-cro ded orld, but they are not a conservation panacea. As in much o ast A rica, a striking t o thirds o the country's ildli e resides outside o national parks—and these animals are not elcome visitors or many lando ners, ho see them as competition or livestock. But in a rare in- in situation or humans and nature, researchers have no sho n that livestock and wildlife can benefit from each other's presence. A study published last October in *Nature Sustainability* ound that ildli e can boost bottom lines by providing opportunities or tourism, and livestock improve the uality o grass or all grazing species.

ecent history explains this symbiosis. Animals and savanna grasses evolved together or millennia—but Kenya's ildli e population dropped by about per- cent bet een and , according to a *PLOS ONE* study. With e er animals around to encourage ne gro th by removing old and dead grass stems, it seems livestock have stepped in to fill that ecological role.

" hink o livestock as the ghosts o ildli e past, says Felicia Keesing, a community ecologist at Bard College and lead author o the ne study. "Without the assist rom livestock, ildli e could keep going into a do n ard spiral.

Keesing and her colleagues ocused on aikipia, a heavily ranched region home to percent o Kenya's ildli e but no national parks. he researchers looked into common lando ner concerns about disease transmission and competition by surveying ticks, grass uality and animal numbers at 3 properties covering percent o aikipia. ome properties had only livestock or ildli e others ere integrated. o the team members' surprise, they ound only benefits in combining moderate numbers o cattle and ildli e. At mixed properties, livestock treated or ticks reduced the overall number o those pathogen-carrying parasites by 5 percent—and grass uality as higher than in livestock- or ildli e-only areas, hich tended to be overgrazed or undergrazed, respectively.

" o me, one o the most amazing things about this ork is that ildli e conservation and ranching can benefit each other over big spatial scales, says acob oheen, an animal ecologist at the niversity o Wyoming, ho as not involved in the study.

Keesing notes, though, that drought, poverty and politics can easily overpo er such solutions. In 2017 Laikipia suffered a series o violent raids by cattle herders rom other parts o drought-stricken Kenya. "People and ildli e in this region have figured out ways to coexist that can ork, Keesing says. "But the ecological, economic and social potential o this kind o management can be stressed by circumstances largely beyond their control.

—Rachel Nuwer

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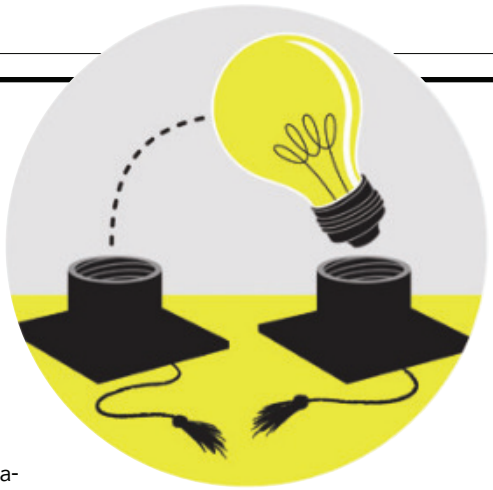
DATA SCIENCE

Idea Epidemic

An infectious disease model shows how science knowledge spreads



Like infectious diseases, ideas in the academic world are contagious. But why some travel far and wide while equally good ones remain in relative obscurity has been a mystery. Now a team of computer scientists has used an epidemiological model to simulate how ideas move from one academic institution to another. The model showed that ideas originating at prestigious institutions caused bigger "epidemics" than equally good ideas from less prominent places, explains Allison Morgan, a computer scientist at the University of Colorado Boulder and lead author of the new study.

"This implies that where an idea is born shapes how far it spreads, holding the quality of the idea constant," says senior author Aaron Clauset, also at Boulder.

Not only is this unfair—"it reveals a big weakness in how we're doing science," says Simon DeDeo, a professor of social and decision sciences at Carnegie Mellon University, who was not involved in the study. There are many highly trained people with good ideas who do not end up at top-tier institutions. "They are producing good ideas, and we know those ideas are getting lost," DeDeo says. "Our science, our scholarship, is not as good because of this."

The Colorado researchers analyzed an existing data set of computer science faculty hires in North America, as well as a database of publications by these hires. First they looked at how five big ideas in computer science spread to new institutions. They found that hiring a new faculty member accounted for this movement a little more than a third of the time—and in 81 percent of those cases, transmissions took place from higher- to lower-prestige universities. Then the team simulated the dissemination of ideas using an infectious disease model and found that the size of an idea "epidemic" (as measured by the number of institutions that published studies on an idea after it originated) depended on the prestige of the originating institution. The findings were published online last October in *EPJ Data Science*.

The researchers' model suggests that there "may be a number of quite good ideas that originate in the middle of the pack, in terms of universities," Clauset says. DeDeo agrees. There is a lot of good work coming out of less famous places, he says: "You can learn a huge amount from it, and you can learn things that other people don't know because they're not even paying attention." —*Viviane Callier*

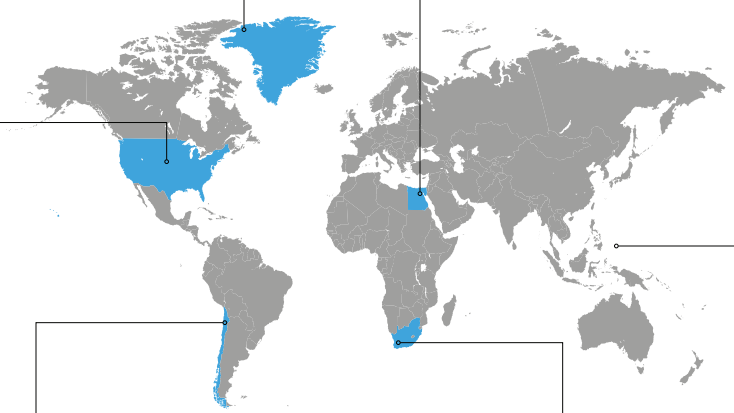
IN THE NEWS

Quick Hits

By Emiliano Rodríguez Mega

GREENLAND
Scientists spotted a 19-mile-wide crater hidden below Hiawatha Glacier in northwest Greenland. They believe it might represent a meteorite impact, but other experts say more evidence is needed to prove that the crater has an extraterrestrial origin.

EGYPT
An excavation near Cairo yielded dozens of mummified cats. Archaeologists also found two large mummified scarab beetles wrapped in linen and a rare collection of smaller scarab mummies.



U.S.
Rising e-cigarette use, or vaping, among teenagers has prompted the U.S. Food and Drug Administration to beef up efforts to combat youth smoking. The agency aims to ban menthol cigarettes, remove flavored cigars from the market and restrict the sale of vape flavors.

PALAU
The tiny Pacific archipelago became the first country to prohibit the use of sunscreens containing coral-toxic ingredients, including oxybenzone and octinoxate. The measure follows a similar legislative decision in Hawaii that takes effect in 2021.

CHILE
One of the driest places on earth, the Atacama Desert, is losing its microbial life because of unprecedented rains. Frequent rainfall for the past three years has caused the massive extinction of native bacterial species, research suggests.

SOUTH AFRICA
Students in Cape Town made bricks using urine from men's toilets, in a biochemical process involving bacteria, calcium and sand. The bricks offer a productive—and odorless—way to recycle human pee.

For more details, visit www.ScientificAmerican.com/feb2019/advances

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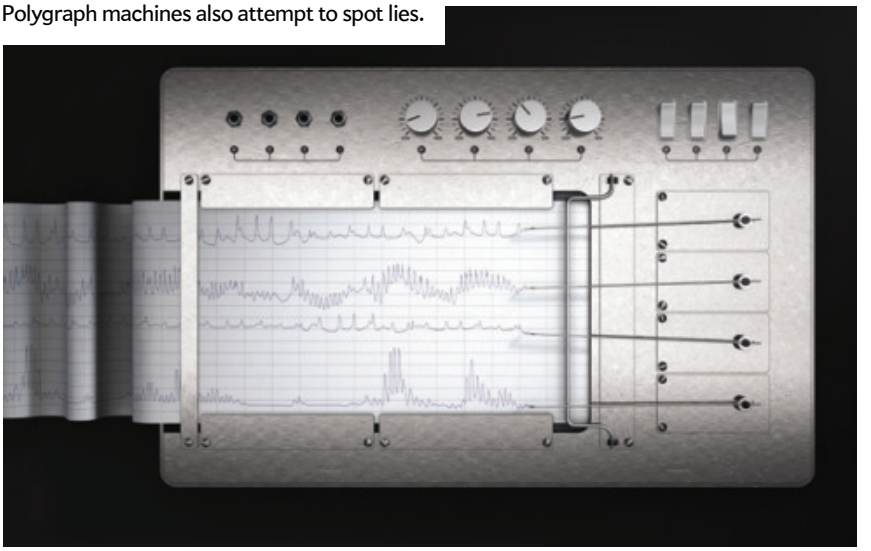
Polygraph machines also attempt to spot lies.



ALLAN SWART *Getty Images*

MACHINE LEARNING

Lie-Detector AI

Algorithm helps to identify fake police reports

S ain s ationa o ice or s recently welcomed a new member: an artificial-intelligence tool called VeriPol. It is the first text-based system for ferreting out phony robbery reports—and it is astoundingly accurate, researchers say.

When Miguel Camacho Collados worked as a police inspector in ranada several years ago, he became frustrated at how often his team had to deal with robbery complaints that turned out to be fake. "Many colleagues were wasting a lot of time investigating cases that had never occurred," says Camacho Collados, now at Spain's Ministry of nterior in Madrid. "It was a problem."

People fake robberies for various reasons. Some simply want to avoid telling family or friends they lost something valuable—but others do it to cash in on insurance claims, Camacho Collados says. Until recently, the only strategy for catching them was asking seasoned police officers to review suspicious reports, but this approach was not always effective. So Camacho Collados, who is also a trained mathematician, and other scientists designed an algorithm-based system that picks out false reports by scrutinizing the wording of statements.

The team trained eri ol on a total of 1,122 robbery reports the national police had closed—meaning either the thief had been convicted or the complainant had confessed to fabricating the crime. t then tested how accurately the algorithm classified a sample of 659 reports as true or false, compared with two human experts. VeriPol outperformed the cops by 15 and 20 percent, respectively. The results, published in June 2018 in *Knowledge-Based Systems,* have also helped researchers understand how people lie to the police. Fabricated reports, for example, tend to describe a specific modus operandi (the attacker usually wears a helmet or attacks from behind). They also use shorter sentences and lack information about the actual incident.

VeriPol is already being successfully deployed across Spain. A June 2017 pilot test in the cities of Murcia and Málaga helped to detect 25 and 39 false robberies in just one week—compared with only three and 12, respectively, for that month in the previous decade.

William Wang, a computer scientist at the University of California, Santa Barbara, who was not involved in the research, thinks VeriPol's success could be replicated in other countries—particularly where police departments are short-staffed. Camacho Collados hopes VeriPol will also be used to spot other often-staged crimes, such as home burglary or car theft. For now, he says, the message is clear: " eople are going to think more than once before filing a fake report."

—Emiliano Rodríguez Mega

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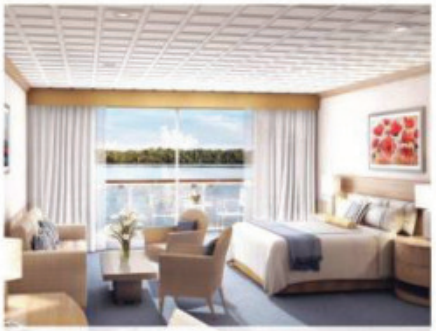

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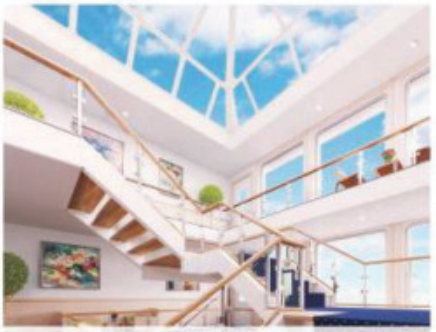

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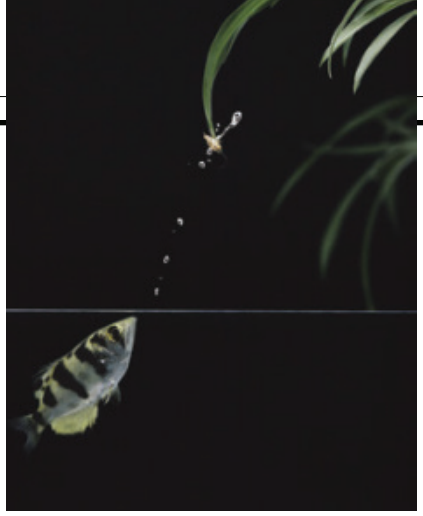
ANIMAL BEHAVIOR

Spitting Image

Archerfish can recognize human faces even from an angle

ni ersit of ford zoologist Cait Newport suspected the archerfish she was studying could recognize her. The tropical fish—known to spit jets of water at insect prey—would take aim at her when she walked into the laboratory.

Newport and her colleagues showed in 2016 that her fish could indeed remember human visages. She trained them to spew water at a head-on view of a specific computer-rendered face, which they picked out 77 to 89 percent of the time. But the researchers did not know what would happen if the fish encountered a familiar face from unfamiliar angles. Now, in a study described last November in *Animal Behaviour,* they have demonstrated that the fish can recognize the same face turned to the side by 30, 60 and 90 degrees—a nontrivial task.



Archerfish fires a water jet at its prey.

The experiments were intended to probe how fish perceive three-dimensional objects, and faces are particularly interesting examples. "They're complicated, they're quite difficult to [process] even for computers and people—and when you rotate them, they change in a really interesting way," Newport says.

For humans, face recognition happens in the cerebral cortex, the area of the mammalian brain responsible for higher cognition. Newport's research shows that an animal without a cortex can still distinguish a human face. "If fish are able to do these really complicated visual tasks with a really small brain, then maybe we can come up with different engineering solutions" for face-recognition technology, she says.

Fish are smarter than people give them credit for, says Vera Schluessel, a zoologist at the University of Bonn in Germany, who was not involved in the new study. "People always say that because something is older, it is more primitive. It's quite the opposite," Schluessel says. Archerfish might have different brain machinery from humans, but they are still able to extrapolate how objects might look from different angles—a crucial skill for hunting, navigating and spotting predators.

Schluessel's team and others have highlighted the visual capabilities of other fish: grey bamboo sharks can recognize shapes and navigate mazes from memory; the Ambon damselfish can see ultraviolet patterns invisible to humans on the faces of other fish; and angelfish can count. Now that we know some fish see us more clearly than we thought, maybe that should change how we see them. *—Megan Gannon*

G. I. BERNARD *Science Source*

BIOMECHANICS

Hop to It

Studying avian jumping helps scientists build better robots

icture a i eon perched on a telephone wire. Ready for takeoff, it raises its wings, springs into the air and flaps away, perhaps with the intention of leaving its calling card on your car's windshield. This series of actions is so commonplace that you probably do not pay it much attention. But University of Manchester biomechanical engineer Ben Parslew does. He is trying to design robots that can jump like birds.

Most conventional robots roll around on wheels, constraining mobility. There is a need for more agile robots that "can jump over obstacles or debris in cluttered environments," Parslew says. To design such a machine, he turned to nature: "Birds are really good jumpers," he notes.

The trouble is, when birds start to take off, they lean so far forward that, according to the rules of physics, they should tip over and fall onto their beaks. Yet that does not happen. Parslew and his team used computer modeling to discover how birds avoid this fate. They discovered that birds rotate their bodies slightly backward while accelerating into a jump. They also have flexible leg and toe joints, which prevent them from taking off briefly and immediately crashing into the ground. The results were published last October in *Royal Society Open Science.*

Parslew thinks engineers can use this information to design robots that can not only jump well but also launch into flight more efficiently. Most human-engineered flying machines require either long runways (think: airplanes) or flat, stable surfaces (think: helicopters or drones) for takeoff. Either way, they take a while to overcome gravity and gain elevation.

University of Southern California biomechanist Michael Habib, who was not involved in the study, says springs and levers enable more rapid acceleration than wheels and axles do. And many animals are masters of springs and levers. "A house cat will beat a Lamborghini Diablo off the line for the first 100 feet," he says. While the car has to rev up, the feline catapults itself into a run. The same principle underlies how birds initiate flight.

Australian diamond dove

"If you can understand how that works," Habib adds, "you can build a robot that's good at running around and good at flying, and it will also be good at taking off suddenly in all kinds of conditions and landing on a dime." Parslew is now designing such a robot, as an alternative to wheeled rovers for exploring other planets. *—Jason G. Goldman*

ALAMY

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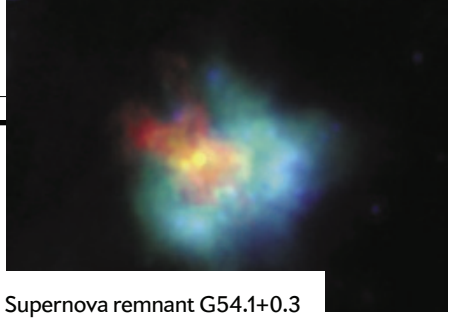

Supernova remnant G54.1+0.3

NASA, JPL-CALTECH, CXC, ESA/NRAO AND J. RHO *SETI Institute*

ASTROPHYSICS

Sand from Stardust

Silica may originate in exploding stars

Astronomers have long argued that the phrase "we are stardust" is more than poetic language. Now new evidence adds another stanza to this great cosmic verse.

Dust from silica—a common component of arth's core, sandy beaches, concrete, glass and even cell phones—has been detected within the remnants of two supernovae in the Milky ay galaxy. These observations, described last October in *Monthly Notices of the Royal Astronomical Society,* provide the first evidence that silica originated within exploding stars.

"This is a rich result in that something so common on arth has now been found to be created in the most violent explosions in the universe," says study co-author aley omez, an astronomer at Cardiff University in Wales. " t's an origin story."

Astronomers have long pondered how cosmic dust—whether it is composed of, say, silica, carbon or iron—is created. nitially they thought it formed when sunlike stars reached old age and threw off mighty winds, whose gases were thought to condense into solid dust grains just as snowflakes form in a chilly atmosphere. But when observers detected dust in galaxies so distant that they must have formed soon after the big bang—well before sunlike stars could have evolved—they knew there must be another source.

They started to suspect that dust appeared within supernovae explosions soon after the universe formed, but astronomers have only recently detected a handful of nearby supernovae remnants sprinkled with dust. And Mikako Matsuura, an astronomer who is also at Cardiff but was not involved in the study, says she is excited to see further evidence.

f the dust within these early-universe supernova remnants is also found to contain silica, the first planets might have looked similar to our own pale-blue dot. " t's really interesting to know we can make planets like arth so soon" in the universe's existence, omez says. " t doesn't take 1 billion years." —*Shannon Hall*

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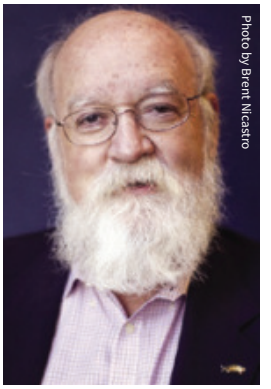

"If the topic comes up, acknowledge you're an atheist. No big deal. Now let's talk about something interesting."

— *Daniel C. Dennett*

Austin B. Fletcher Professor of Philosophy, Tufts University, FFRF Honorary Director

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The Promise of Virtual Reality

rom pain relief to mental health, is poised to reshape patient care

By Claudia Wallis

f ou sti t ink of virtual reality as the province of dystopian science fiction and geeky gamers, you had better think again. Faster than you can say "*Ready Player One,*" VR is starting to transform our world, and medicine may well be the first sector where the impact is profound. Behavioral neuroscientist Walter Greenleaf of Stanford University has been watching this field develop since the days when VR headsets cost $75,000 and were so heavy, he remembers counterbalancing them with a brick. Today some weigh about a pound and cost less than $200. Gaming and entertainment are driving current sales, but Greenleaf predicts that "the deepest and most significant market will be in clinical care and in improving health and wellness."

Even in the early days, when the user entered a laughably low-resolution world, VR showed great promise. By the mid-1990s research had shown it could distract patients from painful medical procedures and ease anxiety disorders. One initial success was SnowWorld, which immersed burn patients in a cool, frozen landscape where they could lob snowballs at cartoon penguins and snowmen, temporarily blocking out the real world where nurses were scrubbing wounds, stretching scar tissue and gingerly changing dressings. A 2011 study with 54 children in burn units found an up to 44 percent reduction in pain during VR sessions—with the bonus that these injured kids said they had "fun."

Claudia Wallis is an award-winning science journalist whose work has appeared in the *New York Times, Time, Fortune* and the *New Republic.* She was science editor at *Time* and managing editor of *Scientific American Mind.*

Another success came in the wake of 9/11. Psychologist JoAnn Difede of NewYork-Presbyterian/Weill Cornell Medical Center began using VR with World Trade Center survivors suffering from post-traumatic stress disorder (PTSD) and later with soldiers returning from Afghanistan and Iraq.

In Difede's laboratory, I saw the original 9/11 VR program with its scenes of lower Manhattan and the newer Bravemind system, which depicts Iraqi and Afghan locales. Developed with Department of Defense funding by Albert "Skip" Rizzo and Arno Hartholt, both at the University of Southern California, Bravemind is used to treat PTSD at about 100 U.S. sites. The approach is based on exposure therapy, in which patients mentally revisit the source of their trauma guided by a therapist who helps them form a more coherent, less intrusive memory. In VR, patients do not merely reimagine the scene, they are immersed in it.

Difede showed me how therapists can customize scenes in Bravemind to match a patient's experience. A keystroke can change the weather, add the sound of gunfire or the call to prayers. It can detonate a car bomb or ominously empty a marketplace. An optional menu of odors enables the patient to sniff gunpowder or spices through a metal tube. "What you do with exposure therapy is systematically go over the trauma," Difede explains. "We're teaching the brain to process and organize the memory so that it can be filed away and no longer intrudes constantly in the patient's life." The results, after nine to 12 gradually intensifying sessions, can be dramatic. One 2010 study with 20 patients found that 16 no longer met the criteria for PTSD after VR treatment.

Until recently, large-scale studies of VR have been missing in action. This is changing fast with the advent of cheaper, portable systems. Difede, Rizzo and three others just completed a randomized controlled trial with nearly 200 PTSD patients. Expected to be published this year, it may shed light on which patients do best with this high-tech therapy and which do not. In a study with her colleague, burn surgeon Abraham Houng, Difede is aiming to quantify the pain-distraction effects of a successor to SnowWorld called Bear Blast, a charming VR game in which patients toss balls at giggly cartoon bears. They will measure whether burn patients need lower doses of intravenous painkillers while playing.

Greenleaf counts at least 20 clinical arenas, ranging from surgical training to stroke rehabilitation to substance abuse where VR is being applied. It can, for example, help recovering addicts avoid relapses by practicing "refusal skills"—turning down drinks at a virtual bar or heroin at a virtual party. Brain imaging suggests that such scenes can evoke very real cravings, just as Bravemind can evoke the heart-racing panic of a PTSD episode. Researchers foresee a day when VR will help make mental health care cheaper and more accessible, including in rural areas.

In a compelling 2017 paper that reviews 25 years of work, Rizzo and co-author Sebastian Koenig ask whether clinical VR is finally "ready for primetime." If today's larger studies bear out previous findings, the answer seems to be an obvious "yes." SA

Illustration by Celia Krampien

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Wade Roush is host of Soonish, a podcast exploring how technology will shape the future.

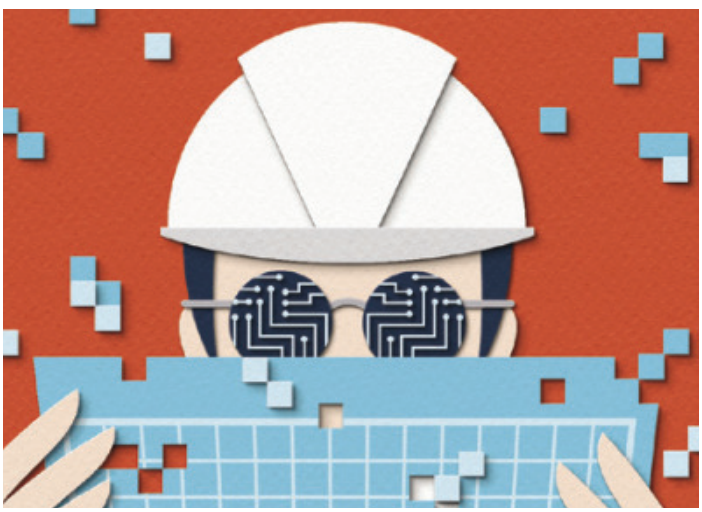
Getting Out of Silicon Valley's Shadow

You don't need programmers or venture capitalists for a thriving local economy

By Wade Roush

Let s sa ou re t e ma or of idd e a e, a (fictional) medium-sized city in Texas. The coal-fired electric power plant outside town just closed, and the steel mill in the next county over has gone bankrupt. Now voters expect you to do something about rising unemployment and the shrinking tax base. You might look at America's booming metropolitan areas, such as Boston, Seattle or Silicon Valley, and say what we need here is an "innovation district" or a "technology cluster."

Sounds great! But it's rarely the full answer.



You certainly wouldn't be the first public official to fall under technology's spell. After all, when high-growth companies flock to a specific location, jobs and higher incomes do tend to follow. Take the Kendall Square cluster, loosely defined as the area within a 10-minute walk of the subway station at the Massachusetts Institute of Technology. It's home to more than a dozen top biotech firms. Google, Microsoft, Amazon and Facebook all have research outposts here. And some 750 start-ups incubate at the Cambridge Innovation Center. It's all helped to give Cambridge the lowest unemployment rate in Massachusetts and a family income 59 percent above the national median.

Of course, the city is also home to high-paying institutions like Harvard University and M.I.T. But that, too, is part of the canonical definition of a cluster. Business scholars say it's hard to build a tech cluster without at least one research university to generate ideas and qualified employees.

And the ingredient list goes on. A base of older tech firms gives future start-up founders a place to train. Federal investment, which helped to put Silicon Valley's semiconductor industry on the map, is a huge boost. Finally, you need local venture capitalists willing to invest in high-risk enterprises.

Put it all together, and you get what I think of as the proximity effect—a self-sustaining churn of people, inspiration, investment, intellectual property and profit. It's no wonder that dozens of U.S. cities, both large (San Diego, St. Louis) and medium-sized (Columbus, Chattanooga), are investing in innovation districts. But there's a problem: it can take decades of planning to assemble all the components of a cluster, and you can't invest in just one element while ignoring the others.

Floridians paid a lot to learn that lesson. Between 2003 and 2008 then governors Jeb Bush and Charlie Crist arranged hundreds of millions of dollars in subsidies to bring biotech laboratories such as the Max Planck Florida Institute for Neuroscience to the Palm Beach County area. The private-sector spin-offs Bush and Crist had promised never emerged, and between 2007 and 2012 the state's spending spree had brought fewer than 1,000 new jobs to Florida. "We didn't have the infrastructure that was needed to develop the industry at a rapid pace," the president of the Business Development Board of Palm Beach County told reporters.

Fortunately, cities don't need to follow the classic cluster model. There's new evidence that regions can develop fast-growing business scenes even if some of the traditional cluster ingredients are sparse or missing. The Detroit area, for example, is home to only a handful of venture firms. But it's developing a distinctive mix of start-ups focused on what Detroit does best: manufacturing, robotics and next-generation transportation technologies, with a dose of software. Ted Serbinski, managing director of Detroit's Techstars Mobility incubator, has called it "the intersection of steel and bits."

In fact, quite a few of the metro areas that show the strongest start-up growth lately fall outside the traditional cluster definition. In the Ewing Marion Kauffman Foundation's 2017 rankings of start-up growth, the Columbus, Nashville and Atlanta metropolitan areas placed third, fourth and fifth, respectively. All have strong universities. But none has a major tech-industry legacy or a substantial venture-capital community.

As mayor of Middlevale, you're not going to build a research university from scratch or lure a flock of venture firms to town. But you can focus on the skills your citizens already have and look for ways to match those with the more digital, distributed, globalized economy of the 21st century. Admire the clusters—and then go your own way. SA

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Illustration by Zara Picken

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THE REMARKABLE SENSE OF ANTISENSE

A conversation with **DR. STANLEY CROOKE,** founder, chairman and chief executive officer of Ionis Pharmaceuticals

In 1989, Stanley Crooke, MD, PhD, took a chance on a little-known technology called antisense — a new way to find and validate drug targets by enhancing the human immune response and preventing production of proteins known to cause disease. As a physician and pharmacologist, Dr. Crooke recognized its potential to bring relief to patients with few options, and built a company, Ionis Pharmaceuticals, to do just that. After 30 years, Dr. Crooke's bet has paid off, with two recently approved first-in-class drugs and an advanced antisense technology platform that promises to boost the efficacy, safety and scope of treatments in major areas of medical need. With an advancing and growing pipeline of more than 45 investigational therapies, Ionis stands ready to lead the future of medicine.

You've said the biggest myth in medicine is that developing a new drug is easy. Why is it so hard?
Pharmaceuticals are a unique business because the compounds we test fail to make it to patients 99 percent of the time. It's remarkable they work at all. Researchers must investigate millions of possible combinations of proteins and molecules that will bind to the cell structure and safely deliver a prophylactic effect to the patient. Even though the basic science behind medicine is steadily improving, the extensive resources and regulatory commitments required to innovate are making it even harder to produce those breakthrough therapies society expects from our industry.

What motivated you to found Ionis, and how did it shape the company's distinctive approach to drug discovery?
I founded the company in 1989, after holding senior R&D positions at several major big pharma companies. There I experienced the productivity constraints that, even then, were making R&D investment increasingly untenable. I decided to pursue my research interest in a novel treatment pathway called antisense technology. I became convinced that antisense had commercial potential through its impact on the binding properties of ribonucleic acid (RNA), which controls the synthesis of proteins and enhances immune response, making it superior to the conventional small molecule platform used in identifying drug targets. At the start, I told investors that it would take 20 years and $2 billion before I knew, and there would be many setbacks along the way, but I thought it was worth it.

Is the full potential of Ionis' antisense technology within reach?
My hunch was that RNA-focused antisense would make drug timelines faster, more precise, predictably safe, and applicable to conditions previously thought "undruggable." We had a few early wins: *Vitravene*, for CMV retinitis in immunocompromised patients; and *Kynamro*, for homozygous familial hypercholesterolemia (FH). But full confirmation had to wait for SPINRAZA®*, our first-in-class antisense therapy for spinal muscular atrophy (SMA). After approval it was launched in 2017 by our strategic partner Biogen. Today, antisense RNA-targeted technology forms the base of our R&D pipeline of some 45 drugs, 11 of which we expect to enter Phase-III within the next 12 to 18 months. In that pipeline we cover treatments from Parkinson's disease to ALS, dyslipidemia and NASH, hypertension, cancer, blood disorders like thalassemia, and other rare conditions, including Huntington's disease. The richness reflects that early commitment we made to go places where others have not, and to work the science in ways that have never been tried before. Our reach is high: the Ionis R&D model requires all pipeline candidates be positioned for first-in-class status after regulatory approval.

OUR CULTURE IS BUILT ON OPEN SCIENCE AND AN ABSOLUTE AVERSION TO THE WORD "NO."

The Ionis mission statement starts by saying "sick people depend on us." What does this mean in practice?
I discovered early in my career you can do more good with a single drug than as an individual researcher or physician. Everyone at Ionis must believe that what they do is grounded in an awareness that there are sick people waiting on our research. If you come to work every day thinking about the patient and you reward the curiosity implicit in doing good science, silos will fall and creativity will flourish. Our culture is built on open science and an absolute aversion to the word "no." A desperate patient with few options for treatment should never hear that word. Once you've brought hope to patients, you just want to do it again, and again.

For more information, visit www.ionispharma.com.

*SPINRAZA® is marketed by Biogen.

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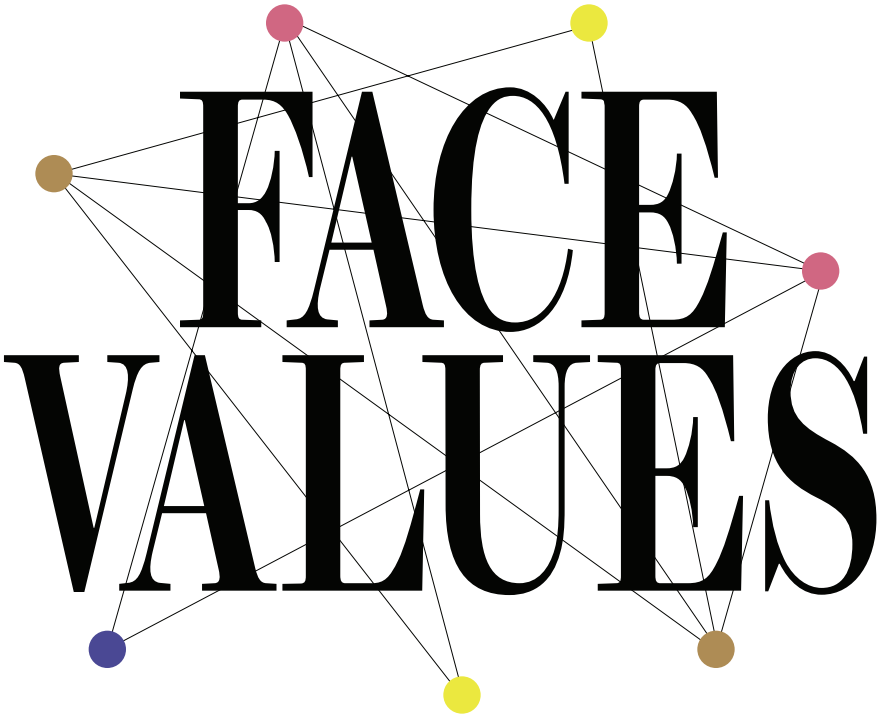

FACE VALUES

Brain regions that process faces reveal deep insights into the neural mechanisms of vision

By Doris Y. Tsao

WHEN I WAS IN HIGH SCHOOL, I LEARNED ONE DAY ABOUT THE DENSITY OF CURVES in an introductory course on calculus. A simple pair of differential equations, which model the interactions of predators and prey, can give rise to an infinite number of closed curves—picture concentric circles, one nested within another, like a bull's-eye. What is more, the density of these curves varies depending on their location.

This last fact seemed so strange to me. I could easily imagine a finite set of curves coming close together or pulling apart. But how could an infinity of curves be denser in one region and less dense in another? I soon learned that there are different types of infinity, which have paradoxical qualities, like Hilbert's Hotel (where the rooms are always fully booked but new guests can always be accommodated) and the Banach-Tarski apple (which can be split into five pieces and rearranged to make two apples of equal volume as the original). I spent hours poring over these mathematical proofs. Ultimately they struck me as symbolic magic of no real consequence, but the seed of interest had taken root.

Illustration by Brian Stauffer

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Doris Y. Tsao is a professor of biology at the California Institute of Technology and an investigator of the Howard Hughes Medical Institute. She is also director of the Tianqiao and Chrissy Chen Center for Systems Neuroscience at Caltech. In October she was named a MacArthur Fellow.

IN BRIEF

Understanding vision remains one of the grand challenges that neuroscientists confront. **One key aspect** of this problem relates to the way the brain identifies faces, the most important social emblem. **Neurons** in defined sections of the cerebral cortex, called face patches, are dedicated to recognizing faces. **Uncovering** the organization of the face-patch system served as a prelude to deducing the underlying computations that the brain makes to identify faces. **This neural code** may serve as a Rosetta stone for representing other objects besides faces.

Later, as an undergraduate at the California Institute of Technology, I learned about the experiments of David Hubel and Torsten Wiesel and their landmark discovery of how a region in the brain called the primary visual cortex extracts edges from the images relayed from the eyes. I realized that what had actually mystified me back in high school was the act of trying to *imagine* different densities of infinity. Unlike the mathematical tricks I had studied in high school, the edges that Hubel and Wiesel described are processed by neurons, so they actually exist in the brain. I came to recognize that visual neuroscience was a way to understand how this neural activity gives rise to the conscious perception of a curve.

The sense of excitement this realization triggered is hard to describe. I believe at each stage in life one has a duty. And the duty of a college student is to dream, to find the thing that captures one's heart and seems worth devoting a whole life to. Indeed, this is the single most important step in science—to find the right problem. I was captivated by the challenge of understanding vision and embarked on a quest to learn how patterns of electrical activity in the brain are able to encode perceptions of visual objects—not just lines and curves but even objects as hard to define as faces. Accomplishing this objective required pinpointing the specific brain regions dedicated to facial recognition and deciphering their underlying neural code—the means by which a pattern of electrical impulses allows us to identify people around us.

The journey of discovery began in graduate school at Harvard University, where I studied stereopsis, the mechanism by which depth perception arises from differences between the images in the two eyes. One day I came across a paper by neuroscientist Nancy Kanwisher, now at the Massachusetts Institute of Technology, and her colleagues, reporting the discovery of an area in the human brain that responded much more strongly to pictures of faces than to images of any other object when a person was inside a functional magnetic resonance imaging (fMRI) brain scanner. The paper seemed bizarre. I was used to the brain being made of parts with names like basal ganglia and orbitofrontal cortex that had some vague purpose one could only begin to fathom. The concept of an area specifically devoted to processing faces seemed all too comprehensible and therefore impossible. Anyone could make a reasonable conjecture about the function of a face area—it should probably represent all the different faces that we know and something about their expression and gender.

As a graduate student, I had used fMRI on monkeys to identify areas activated by the perception of three-dimensionality in images. I decided to show pictures of faces and other objects to a monkey. When I compared activation in the monkey's brain to faces with activation to other objects, I found several areas that lit up selectively to faces in the temporal lobe (the area underneath the temple)—specifically in a region called the inferotemporal (IT) cortex. Charles Gross, a pioneer in the field of object vision, had discovered face-selective neurons in the IT cortex of macaques in the early 1970s. But he had reported that these cells were randomly scattered throughout the IT cortex. Our fMRI results provided the first indication that face cells might be concentrated into defined regions.

FACE PATCHES

AFTER PUBLISHING MY WORK, I was invited to give a talk describing the fMRI study for a faculty position at Caltech, but I was not offered the job. Many people were skeptical of the value of fMRI, which measures local blood flow, the brain's plumbing. They argued that showing increased blood flow to a brain area when a subject is looking at faces falls far short of clarifying what neurons in the area are actually encoding because the relation between blood flow and electrical activity is unclear. Perhaps by chance these face patches simply contained a slightly larger number of neurons responsive to faces, like icebergs randomly clustered at sea.

Because I had done the imaging experiment in a monkey, I could directly address this concern by inserting an electrode into an fMRI-identified face area and asking, What images drive single neurons in this region most strongly? I performed this experiment together with Winrich Freiwald, then a postdoctoral fellow in Margaret Livingstone's laboratory at Harvard, where I was a graduate student. We presented faces and other objects to a monkey while amplifying the electrical activity of individual neurons recorded by the electrode. To monitor responses in real time, the neurons' electrical signals were converted to an audio signal that we could hear with a loudspeaker in the lab.

This experiment revealed an astonishing result: almost every single cell in the area identified through fMRI was dedicated to processing faces. I can recall the excitement of our first recording, hearing the "pop" of cell after cell responding strongly to faces and very little to other objects. We sensed we were on to something important, a piece of cortex that could reveal the brain's high-level code for visual objects. Marge remarked on the face patches: "You've found a golden egg."

I also remember feeling surprised during that first experiment. I had expected the face area would contain cells that responded selectively to specific individuals, analogous to orientation-selective cells in the primary visual cortex that each respond to a specific edge orientation. In fact, a number of well-publicized studies had suggested that single neurons can be remarkably selective for the faces of familiar people—responding, say, only to Jennifer Aniston. Contrary to my expectation, each cell seemed to fire vigorously to almost any face.

I plugged madly away at Photoshop during these early experiments and found that the cells responded not just to faces of humans and monkeys but even to highly simplified cartoon faces.

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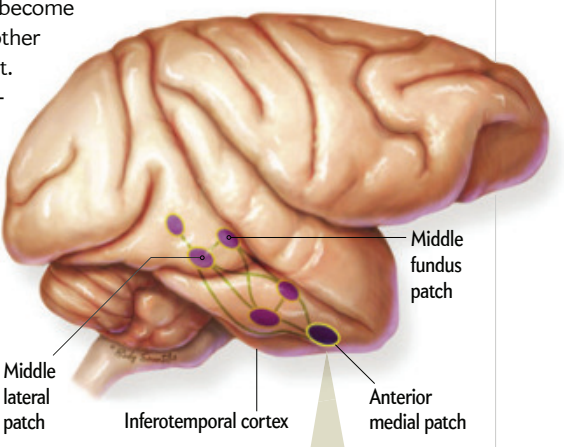
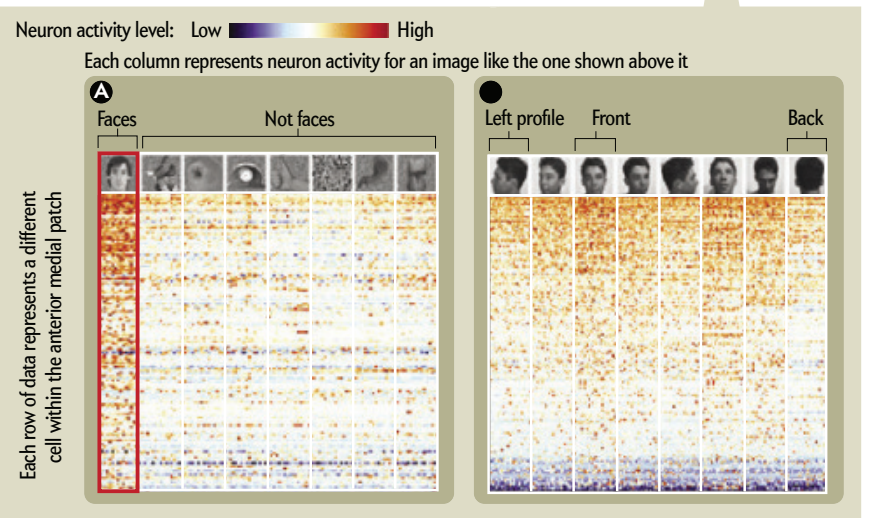
Observing this phenomenon, I decided to create cartoon faces with 19 different features that seemed pertinent to defining the identity of a face, including inter-eye distance, face aspect ratio and mouth height, among other characteristics. We then went on to alter these values—the inter-eye distance, for instance, varied from being almost cyclopean to just inside the face boundary. Individual cells responded to most faces but interestingly did not always exhibit the exact same rate of firing to all faces. Instead there was a systematic variation in their response: when we plotted the firing of cells for the different cartoon features, we found a pattern in which there was a minimal response to one feature extreme—the smallest inter-eye distance, for instance—and a maximal response to the opposite extreme—the largest eye separation—with intermediate responses to feature values in the middle. The response as a function of the value for each feature looked like a ramp, a line slanted up or down.

Once again, I was invited to give a job talk at Caltech. Returning, I had more to offer than just fMRI images. With the addition of the new results from single-cell recordings, it was clear to everyone that these face patches were real and likely played an important role in facial recognition. Furthermore, understanding their underlying neural processes seemed like an effective way to gain traction on the general problem of how the brain represents visual objects. This time I was offered the job.

Where Are the Face Detectors?

A set of six nodes in the inferotemporal (IT) cortex of both brain hemispheres specializes in identifying faces. These "face patches" function as an assembly line: in the middle lateral and middle fundus patches, one neuron might become active when faces look straight ahead; another might turn on for a face looking to the right. At the end of the assembly line, in the anterior medial patch, varying views are stitched together. Neurons in this patch are active in response to the face of a specific individual, no matter if the view is from the front or side. Responses from a face patch of one monkey are generated for faces but not objects (*red areas in* A) and for the same individual, such as the dark-haired man, from varying angles (*red areas in* B).





CONTRAST IS KEY

AT CALTECH, my colleagues and I dug deeper into the question of how these cells detect faces. We took inspiration from a paper by Pawan Sinha, a vision and computational neuroscientist at M.I.T., that suggested faces could be discerned by checking for specific contrast relations between different regions of the face—whether the forehead region is brighter than the mouth region, for example. Sinha suggested a clever way to determine *which* contrast relations can be used to recognize a face: they should be the ones that are immune to changes in lighting. For example, left-eye-darker-than-nose is a useful feature for detecting a face because it does not matter if a face is photographed with lighting from above, left, right or below: the left eye is *always* darker than the nose (check for yourself).

From a theoretical standpoint, this idea provides a simple, elegant computational mechanism for facial recognition, and we wondered whether face cells might be using it. When we measured the response of cells to faces in which different regions varied in brightness, we found that cells often had a significant preference for a particular contrast feature in an image.

To our astonishment, almost all the cells were wholly consistent in their contrast preferences—just a single cell was found that preferred the opposite polarity. Moreover, the preferred features were precisely those identified by Sinha as being invulnerable to lighting changes. The experiment thus confirmed that face cells use contrast relations to detect faces.

More broadly, the result confirmed that these cells truly were face cells. At talks, skeptics would ask, how do you know? You can't test every possible stimulus. How

FROM "FUNCTIONAL COMPARTMENTALIZATION AND VIEWPOINT GENERALIZATION WITHIN THE MACAQUE FACE-PROCESSING SYSTEM," BY WINRICH A. FREIWALD AND DORIS Y. TSAO, IN *SCIENCE*, VOL. 330; NOVEMBER 5, 2010 (*data grids* and *photo insets*)

Illustration by Body Scientific (brain)

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can you be sure it's a face cell and not a pomegranate cell or a lawn mower cell? This result nailed it for me. The precise match between the way cells reacted to changes in contrast between different parts of the face and Sinha's computational prediction was uncanny.

Our initial experiments had revealed two nearby cortical patches that lit up to faces. But after further scanning (with the help of a contrast agent that increased severalfold the robustness of the signal), it became clear that there are actually six face patches in each of the brain's two hemispheres (making a dozen golden eggs total). They are distributed along the entire length of the temporal lobe. These six patches, moreover, are not randomly scattered throughout the IT cortex. They are located in similar locations across hemispheres in each animal. Moreover, work by our group and others has found that a similar pattern of multiple face patches spanning the IT cortex exists in humans and other primates such as marmosets.

This observation of a stereotyped pattern suggested that the patches might constitute a kind of assembly line for processing faces. If so, one would expect the six patches to be connected to one another and each patch to serve a distinct function.

To explore the neural connections among patches, we electrically stimulated different patches with tiny amounts of current—a technique called microstimulation—while the monkey was inside an fMRI scanner. The goal was to find out what other parts of the brain light up when a particular face patch is stimulated. We discovered that whenever we stimulated one face patch, the other patches would light up but not the surrounding cortex, indicating that, indeed, the face patches are strongly interconnected. Furthermore, we found that each patch performs a different function. We presented pictures of 25 people, each at eight different head orientations, to monkeys and recorded responses from cells in three regions: the middle lateral and middle fundus patches (ML/MF), the anterior lateral patch (AL) and the anterior medial patch (AM).

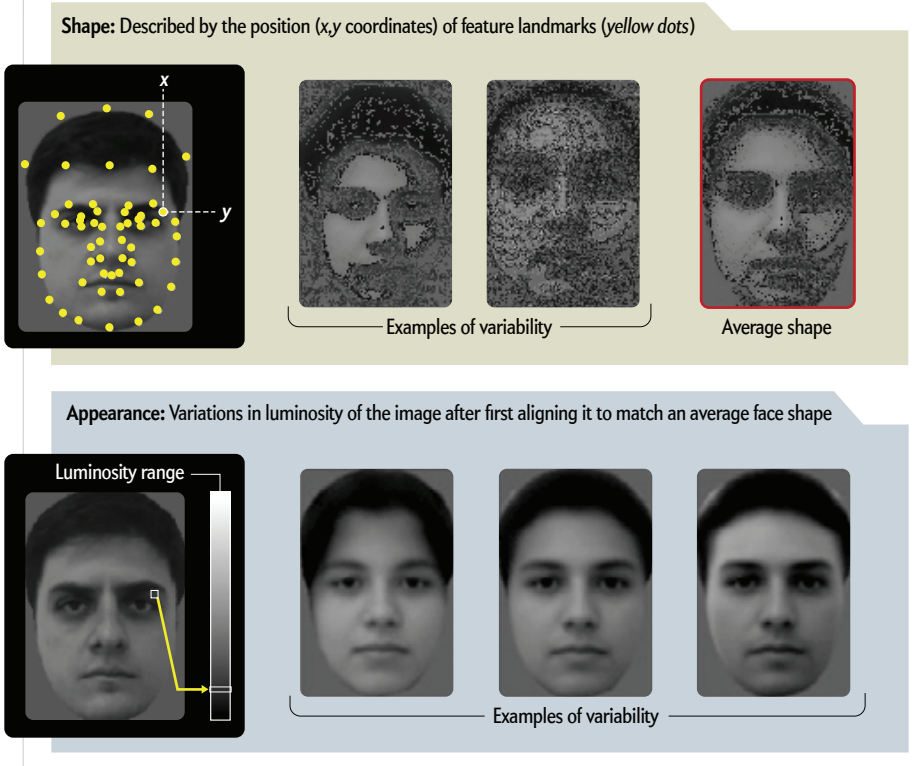
We found striking differences among these three regions. In ML/MF, cells responded selectively to specific views. For example, one cell might prefer faces looking straight ahead, whereas another might opt for faces looking to the left. In AL, cells were less view-specific. One class of cells responded to faces looking up, down and straight ahead; another responded to faces looking to the left or right. In AM, cells responded to specific individuals regardless of whether the view of the face was frontal or in profile. Thus, at the end of the network in AM, view-specific representations were successfully stitched into a view-invariant one.

Apparently face patches do act as an assembly line to solve one of the big challenges of vision: how to recognize things around us despite changes in the way they look. A car can have any make and color, appear at any viewing angle and distance, and be partially obscured by closer objects such as trees or other cars. Recognizing an object despite these visual transformations is called the invariance problem, and it became clear to us that a major function of the face-patch network is to overcome this impediment.

Given the great sensitivity of cells in face patches to changes in facial identity, one might expect

Shape + Appearance = Face

Identifying the face patches was only a first step. It then became necessary to explore what happens in the neurons within each patch, setting off a search for the brain's coding scheme for faces. To derive quantitative measures for faces, the Tsao laboratory came up with 25 features for shape and 25 for appearance that could be used by each neuron in a face patch—a 50-dimensional face space. The shape features can be thought of as those defining the skeleton—how wide the head is or the distance between the eyes. The appearance features specify the face's surface texture (complexion, eye or hair color, and so on).



FROM "THE CODE FOR FACIAL IDENTITY IN THE PRIMATE BRAIN," BY LE CHANG AND DORIS Y. TSAO, IN *CELL*, VOL. 169, NO. 6; JUNE 1, 2017 (*face images*)

Graphics by Jen Christiansen

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that altering these cells' responses should modify an animal's perception of facial identity. Neuroscientists Josef Parvizi and Kalanit Grill-Spector of Stanford University had electrically stimulated a face-patch area in human subjects who had electrodes implanted in their brains for the purpose of identifying the source of epileptic seizures and found that stimulation distorted the subjects' perception of a face.

We wondered whether we would find the same effect in monkeys when we stimulated their face patches. Would doing so alter the perception only of faces, or would it affect that of other objects as well? The boundary between a face and a nonface object is fluid—one can see a face in a cloud or an electrical outlet if prompted. We wanted to use electrical microstimulation as a tool to delineate precisely what constitutes a face for a face patch. We trained monkeys to report whether two sequentially presented faces were the same or different. Consistent with the earlier results in humans, we found that microstimulation of face patches strongly distorted perception so that the animal would always signal two identical faces as being different.

Interestingly, microstimulation had no effect on the perception of many nonface objects, but it did significantly affect responses to a few objects whose shape is consistent with a face—apples, for one. But why does this stimulation influence the perception of an apple?

One possibility is that the face patches are typically used to represent not just faces but also other round objects like apples. Another hypothesis is that face patches are not normally used to represent these objects, but stimulation induces an apple to appear facelike. It remains unclear whether face patches are useful for detecting any nonface objects.

CRACKING THE CODE

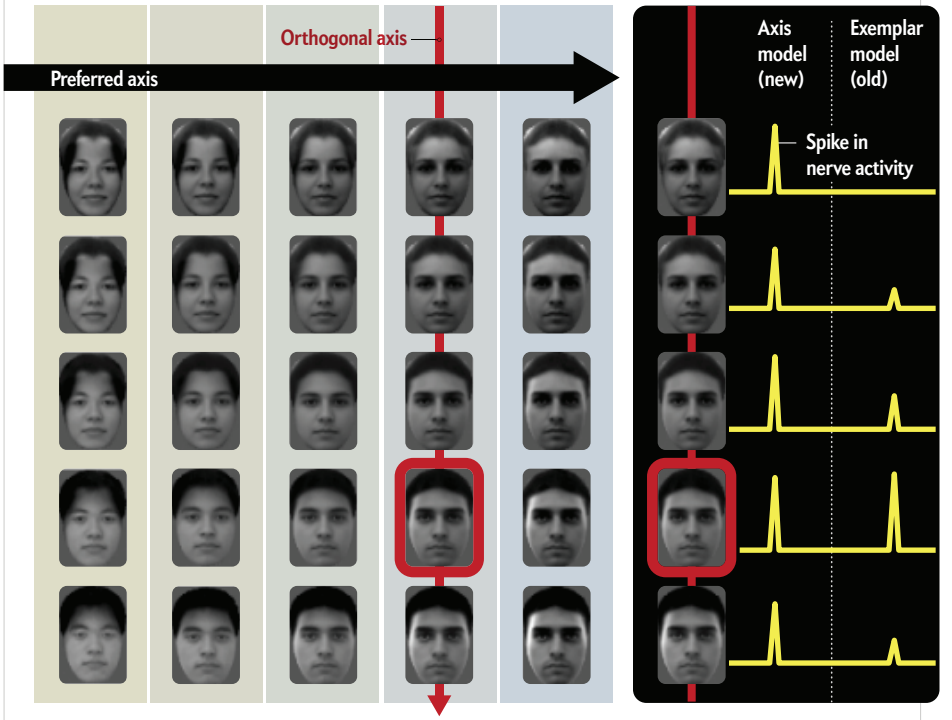
UNCOVERING the organization of the face-patch system and properties of the cells within was a major accomplishment. But my dream when we first began recording from face patches was to achieve something more. I had intuited that these cells would allow us to crack the neural code for facial identity. That means understanding how individual neurons process faces at a level of detail that would let us predict a cell's response to any given face or decode the identity of an arbitrary face based only on neural activity.

The central challenge was to figure out a way to describe faces quantitatively with high precision. Le Chang, then a postdoc in my lab, had the brilliant insight to adopt a technique from the field of computer vision called the active appearance model. In this approach, a face has two sets of descriptors, one for shape and another for appearance. Think of the shape features as those defined by the skeleton—how wide the head is or the distance between the eyes. The appearance features define the surface texture of the face (complexion, eye or hair color, and so on).

To generate these shape and appearance descriptors for faces, we started with a large database of face images. For each face, we placed a set of markers on key features. The spatial locations of these markers described the shape of the face. From these varied shapes, we calculated an average face. We then morphed each face image in the database so its key features exactly matched that of the average face.

The Face Code, at Last

Having 50 coordinates that describe shape and appearance allows for a description of neurons' firing in response to a particular face—a description that functions as a code that can be visualized geometrically. In this code, each face cell receives inputs for a face in the form of the 50 coordinates, or dimensions. The neuron then fires with a particular intensity in response to a certain face (*red outlines*), along what is called the preferred axis. The intensity increases steadily (monotonically) along the preferred axis. Furthermore the response is the same for every face on an axis at right angles to the preferred axis, even though those faces may look very different. This axis model of facial coding differs from a previous exemplar model that suggests that each neuron fires with maximum intensity to a single most preferred face.



FROM "THE CODE FOR FACIAL IDENTITY IN THE PRIMATE BRAIN," BY LE CHANG AND DORIS Y. TSAO, IN *CELL*, VOL. 169, NO. 6; JUNE 1, 2017 (*face grid*)

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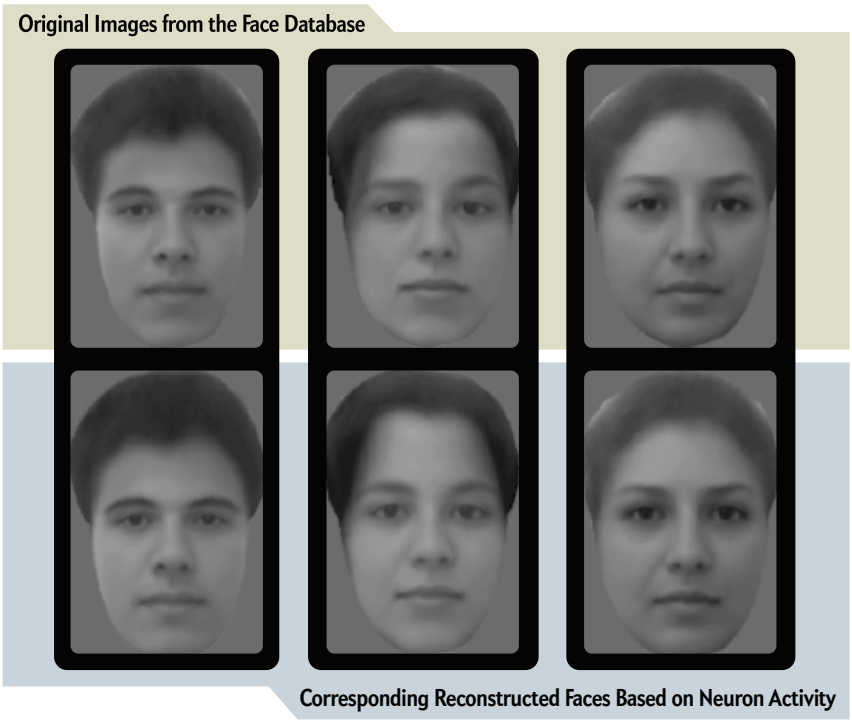
Pictures Worth 205 Neurons

For a given face, we can predict how a cell will respond by taking a weighted sum of all 50 face coordinates. To predict what face the monkey saw from neuronal activity, this entire process can be reversed: By knowing the response of 205 face cells, it is possible to predict the 50 coordinates defining the exact facial features—and make a highly accurate reconstruction of a given face.



The resulting images constituted the appearance of the faces independent of shape.

We then performed principal components analysis independently on the shape and appearance descriptors across the entire set of faces. This is a mathematical technique that finds the dimensions that vary the most in a complex data set.

By taking the top 25 principal components for shape and the top 25 for appearance, we created a 50-dimensional face space. This space is similar to our familiar 3-D space, but each point represents a face rather than a spatial location, and it comprises much more than just three dimensions. For 3-D space, any point can be described by three coordinates (x,y,z). For a 50-D face space, any point can be described by 50 coordinates.

In our experiment, we randomly drew 2,000 faces and presented them to a monkey while recording cells from two face patches. We found that almost every cell showed graded responses—resembling a ramp slanting up or down—to a subset of the 50 features, consistent with my earlier experiments with cartoon faces. But we had a new insight about why this is important. If a face cell has ramp-shaped tuning to different features, its response can be roughly approximated by a simple weighted sum of the facial features, with weights determined by the slopes of the ramp-shaped tuning functions. In other words:

response of face cells = weight matrix × 50 face features

We can then simply invert this equation to convert it to a form that lets us *predict* the face being shown from face cell responses:

50 face features = (1/weight matrix) × response of face cells

At first, this equation seemed impossibly simple to us. To test it, we used responses to all but one of the 2,000 faces to learn the weight matrix and then tried to predict the 50 face features of the excluded face. Astonishingly, the prediction turned out to be almost indistinguishable from the actual face.

A WIN-WIN BET

AT A MEETING in Ascona, Switzerland, I presented our findings on how we could reconstruct faces using neural activity. After my talk, Rodrigo Quian Quiroga, who discovered the famous Jennifer Aniston cell in the human medial temporal lobe in 2005 and is now at the University of Leicester in England, asked me how my cells related to his concept that single neurons react to the faces of specific people. The Jennifer Aniston cell, also known as a grandmother cell, is a putative type of neuron that switches on in response to the face of a recognizable person—a celebrity or a close relative.

I told Rodrigo I thought our cells could be the building blocks for his cells, without thinking very deeply about how this would work. That night, sleepless from jet lag, I recognized a major difference between our face cells and his. I had described in my talk how our face cells computed their response to weighted sums of different face features. In the middle of the night, I realized this computation is the same as a mathematical operation known as the dot product, whose geometric representation is the projection of a vector onto an axis (like the sun projecting the shadow of a flagpole onto the ground).

Remembering my high school linear algebra, I realized this implied that we should be able to construct a large "null space" of faces for each cell—a series of faces of varying identity that lie on an axis

DORIS Y. TSAO (*face images*)

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perpendicular to the axis of projection. Moreover, all these faces would cause the cell to fire in exactly the same way.

And this, in turn, would suggest cells in face patches are fundamentally different from grandmother cells. It would demolish the vague intuition everyone shared about face cells—that they should be tuned to specific faces.

I was the first person in the meeting's breakfast hall at 5 A.M. the next morning and hoped to find Rodrigo so I could tell him about this counterintuitive prediction. Amazingly, when he finally showed up, he told me he had the exact same idea. So we made a bet, and Rodrigo allowed the terms to be framed in a way that would be win-win for me. If each cell really turned out to have the same response to different faces, then I would send Rodrigo an expensive bottle of wine. If on the other hand, the prediction did not pan out, he would send me solace wine.

In search of an answer back in our lab at Caltech, Le Chang first mapped the preferred axis for a given cell using responses to the 2,000 faces. Then he generated, while still recording from the same cell, a range of faces that could all be placed on an axis perpendicular to the cell's preferred axis. Remarkably, all these faces elicited exactly the same response in the cell. The next week Rodrigo received an exquisite bottle of Cabernet.

The finding proved that face cells are not encoding the identities of specific individuals in the IT cortex. Instead they are performing an axis projection, a much more abstract computation.

An analogy can be made to color. Colors can be coded by specific names, such as periwinkle, celandine and azure. Alternatively, one can code colors by particular combinations of three simple numbers that represent the amount of red, green and blue that make up that color. In the latter scheme, a color cell performing a projection onto the red axis would fire electrical impulses, or spikes, proportional to the amount of red in any color. Such a cell would fire at the same intensity for a brown or yellow color containing the same amount of red mixed in with other colors. Face cells use the same scheme, but instead of just three axes, there are 50. And instead of each axis coding the amount of red, green or blue, each axis codes the amount of deviation of the shape or appearance of any given face from an average face.

It would seem then that the Jennifer Aniston cells do not exist, at least not in the IT cortex. But single neurons responding selectively to specific familiar individuals may still be at work in a part of the brain that processes the output of face cells. Memory storage regions—the hippocampus and surrounding areas—may contain cells that help a person recognize someone from past experience, akin to the famed grandmother cells.

Facial recognition in the IT cortex thus rests on a set of about 50 numbers in total that represent the measurement of a face along a set of axes. And the discovery of this extremely simple code for face identity has major implications for our understanding of visual object representation. It is possible that all of the IT cortex might be organized along the same principles governing the face-patch system, with clusters of neurons encoding different sets of axes to represent an object. We are now conducting experiments to test this idea.

NEURAL ROSETTA STONE

IF YOU EVER GO to the British Museum, you will see an amazing artifact, the Rosetta stone, on which the same decree of Memphis is engraved in three different languages: Egyptian hieroglyphics, Demotic and Ancient Greek. Because philologists knew Ancient Greek, they could use the Rosetta stone to help decipher Egyptian hieroglyphics and Demotic. Similarly, faces, face patches and the IT cortex form a neural Rosetta stone—one that is still being deciphered. By showing pictures of faces to monkeys, we discovered face patches and learned how cells within these patches detect and identify faces. In turn, understanding coding principles in the face-patch network may one day lead to insight into the organization of the entire IT cortex, revealing the secret to how object identity more generally is encoded. Perhaps the IT cortex contains additional networks specialized for processing other types of objects—a whirring factory with multiple assembly lines.

I also hope that knowing the code for facial identity can help fulfill my college dream of discovering how we imagine curves. Now that we understand face patches, we can begin to train animals to imagine faces and explore how neural activity is shaped by the purely internal act of imagination. Lots of new questions arise. Does imagination reactivate the code for the imagined face in the face patches? Does it bring back even earlier representations of contours and shading that provide inputs to the face-patch system? We now have the tools to probe these questions and better understand how the brain sees objects, imagined or real.

Because almost all the brain's core behaviors—consciousness, visual memory, decision-making, language—require object interactions, a deep understanding of object perception will help us gain insight into the entire brain, not just the visual cortex. We are only starting to solve the enigma of the face. SA

MORE TO EXPLORE

The Code for Facial Identity in the Primate Brain. Le Chang and Doris Y. Tsao in *Cell,* Vol. 169, No. 6, pages 1013–1028; June 1, 2017.
How Do We Recognize a Face? Rodrigo Quian Quiroga in *Cell*, Vol. 169, No. 6, pages 975–977; June 1, 2017.

FROM OUR ARCHIVES

The Face as Entryway to the Self. Christof Koch; Consciousness Redux, *Scientific American Mind,* January/February 2015.

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| GHOST | FLOWERS |

The genes of Hawaiian plants, extinct for more than a century, have been brought back from the dead. Today we can smell their scents

By Rowan Jacobsen

Photographs by Floto + Warner

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BACK FROM THE BRINK: The Wynberg conebush (*left*) went extinct in 1806, and Maui's mountain hibiscus (*right*) followed in 1912. But their DNA has been recovered, and some rejuvenated scent genes are once again producing fragrances. The hibiscus, sniffed by people for the first time in more than a century, evokes bark and juniper, with hints of citrus and thyme.

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Journalist **Rowan Jacobsen** is author of several books, such as *Shadows on the Gulf* (Bloomsbury, 2011) and *The Essential Oyster* (Bloomsbury, 2016), and many magazine articles. He was a 2017–18 Knight Science Journalism Fellow at the Massachusetts Institute of Technology.

IN 1912, ON THE ANCIENT LAVA FIELDS OF HALEAKALĀ ON THE HAWAIIAN ISLAND OF MAUI, A SINGLE tree stood near death. Fifteen feet tall, its bark encrusted with lichens, it was down to its last flower.

The Hawaiians called this tree *hau kuahiwi,* the mountain hibiscus. Unlike the more familiar Hawaiian hibiscus, which grows in moist valleys and opens wide in a welcoming *aloha,* the mountain hibiscus grew only on the dry, well-drained lava fields of Hawaii's volcanoes. The plant unfolded only two of its five hibiscuslike petals, keeping the rest closed in a demure, curved tube designed for Maui's honeycreepers—nectar-eating songbirds with curved bills that were its favored pollinators.

IN BRIEF

Dead is dead, went the dogma of extinction, for when the last of a species vanishes, it is gone from the world forever. **But genes of the dead** can be resurrected, a group of scientists has shown, by recovering DNA and making it function again. **Scent genes** from long-gone flowers have been recovered in this way, and researchers have smelled their products.

But this tree had not reproduced in years. Most honeycreepers had disappeared as the 19th century gave way to the 20th. The lava fields of Haleakalā had been turned into cattle ranches. Cows rubbed its trunk raw. Rats ate its seeds.

Up the slope came a botanist, dressed in Rough Rider cavalry hat and khakis, a collector's bag over his shoulder. His name was Gerrit Wilder, and he was on the original expedition that identified this tree in 1910. Because of that, the tree was named for him, *Hibiscadelphus wilderianus.* It was the only member of its species ever found. Its sickly state was why Wilder had returned. He plucked the last flower, along with some twigs and leaves, and nestled them into his bag. Then he turned and made his way slowly down the slope.

Not long after that, the tree succumbed to the cattle and the rats and dropped its final leaves. *H. wilderianus* was extinct. And that should have been that. Extinction is supposed to be forever.

Recent breakthroughs in DNA sequencing, however, have made it increasingly easy to read the genes of long-dead organisms and "reboot" those DNA stretches. Serious efforts are underway to use such tech to revive the passenger pigeon and the woolly mammoth. Both projects depend on bioengineering advances that are still years away. Yet in 2018, in an eighth-floor laboratory built above the burgeoning Seaport District in Boston, a crucial part of this long-dead mountain hibiscus came back to life.

A collection of gene engineers, working for a company called Ginkgo Bioworks, was able to re-create the scent genes from the flower. They rebuilt the genetic material that had produced the flowers' distinctive odor, got it working again in another life-form—a yeast—and human noses smelled something that had vanished from the planet more than a century ago. Like Odysseus raising the dead in Hades and plying them for information, some kind of communication took place between the living and the deceased. There were no flowers, no petals, but these were the actual DNA sequences of the plant telling cells to churn out molecules as they used to do on Maui, and those molecules were grabbed in people's noses, sending signals to their brains. It was the most tangible sign yet that the hard membrane of extinction is beginning to soften. This newfound porosity forces a strange question: Can we reboot enough genes to say that something isn't quite dead anymore?

SCENT OF LIFE

THE RESURRECTION PROJECT BEGAN, oddly enough, at the 2014 annual convention of the International Federation of Essential Oils and Aroma Trades in Rome, where Jason Kelly, Ginkgo's CEO, was looking to drum up business. Kelly and his Ginkgo co-founders graduated in 2008 from the Massachusetts Institute of Tech-

RECOVERED GENES: Researchers found fragmented DNA in extinct plant specimens at the Harvard Herbaria. They spliced the DNA together into scent genes for the Wynberg conebush (*Leucadendron grandiflorum* Salisb.) (*1*); the mountain hibiscus (*Hibiscadelphus wilderianus* Rock) (*2*); and the Falls-of-the-Ohio scurfpea (*Orbexilum stipulatum* [Torr. & A. Gray] Rydb.) (*3*). These three produced fragrant compounds. A myrtle, *Myrcia skeldingii* Proctor (*4*), yielded a gene that did not make a scent molecule.

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SPECIMENS PHOTOGRAPHED AT HERBARIUM OF ARNOLD ARBORETUM AND GRAY HERBARIUM OF HARVARD UNIVERSITY

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nology with some of the first Ph.D.s in synthetic biology awarded for that specialization. His firm is also highly specialized: if another company needs a new microbe to produce some valuable molecule—for fuel, fiber, fragrance, pharmaceutical, whatever—Ginkgo will design and test hundreds of prototypes in its biofoundries and hand over the top performers.

Many of Ginkgo's best clients are in the flavors and fragrances industry, where raw ingredients can be astronomically expensive. All those fragrance molecules are produced by enzymes in the plant cells, and the blueprint for those enzymes is coded in DNA by a gene. Like software, this code can run on any compatible platform, and life is surprisingly platform-agnostic. All living things use the same four-letter language of DNA—components labeled A, T, C and G—and yeast and plants run many of the same genes. By inserting fragrance genes into specially engineered strains of brewer's yeast, Ginkgo brews scent molecules in a flask, just like making beer.

At the trade show, Kelly met a consultant for Givaudan, the Swiss perfume giant, who told Kelly about Givaudan's Scent Trek program, which dispatched explorers into the world's rain forests to capture the air around rare flowers so the scents could be identified. Kelly was intrigued. If Ginkgo could get samples of these plants, the company could sequence the genes and synthesize the enzymes that made the smells. But as the two brainstormed, Kelly had a much crazier idea. What if he was able to go beyond obscure plants and bring back the scent of flowers that no longer even existed?

"The planet has spent hundreds of millions of years evolving DNA. And we just have to let it go away? For a biological designer, it's frustrating."
—Jason Kelly, Ginkgo Bioworks

This would be the first step, he thought, in reversing a tremendous biological waste. "The planet has spent three billion years trying out different DNA sequences through this process we call evolution," Kelly says, "and that's what we have today. But along the way, a lot got lost for some random reason—a meteor or whatever—and some of that stuff was incredible. The planet spent hundreds of millions of years evolving DNA. And we just have to let it go away? For a biological designer, it's frustrating to imagine losing all that great code."

Kelly's original plan riffed on *Jurassic Park:* Recover an Ice Age flower from the Arctic permafrost, sequence its genes and synthesize the ones responsible for fragrance, then put them in yeast cells. When the genes instructed the cells to make the fragrant molecules, Kelly could brew up a little Extinction N° 5.

It was a long shot. Although a handful of ancient genes had been reconstructed in labs, most simply sat there, never being asked to produce a protein and thus rejoin our world. Even if Ginkgo was able to rebuild old genes, those genes might not function in new yeast. Kelly also worried about tying up precious resources. Everyone at his company was already overworked. The last thing they needed was to get sucked into a Jurassic lark.

But the project found a champion in Christina Agapakis, Ginkgo's creative director. Agapakis earned her Ph.D. in synthetic biology at Harvard University, and she worked on optimizing bacteria to produce hydrogen fuel and created art based on the shapes of antibodies. Warm and witty, she was drawn to research that probed the borderlands between natural and unnatural and opened up interesting conversations about genetically modified organisms. A perfume of extinct florals that people could smell while meditating on these lost species was right up her alley. She dubbed the venture "Project Cretaceous," after the period when flowers first came into existence. She began by contacting experts in Ice Age excavations, who told her it was impossible to sequence a full genome out of the gunky specks of plant that emerge from the permafrost. The Ice Age was a dead end.

Before giving up, Agapakis did what any good Millennial would do: she googled "extinct plant DNA sequencing." Far down the list of results, she found an obscure paper from the *Biological Journal of the Linnean Society* on museomics, a new technique for extracting DNA from museum-preserved plants and animals. So she did not need permafrost after all. She just needed an herbarium.

The realization made the Harvard grad smile. She knew just where to find one of those.

THE DNA SEARCH

THE HARVARD HERBARIA, which date back to 1842, anchor one brick-lined end of a street named Divinity Avenue, and their numerous floors are filled with formaldehyde-scented cabinets holding more than five million samples. They do not embrace change enthusiastically, so when Agapakis pitched her plan in 2016, the curator was skeptical. Do *what* with their plants? The herbaria were not in the business of giving away their collection to for-profit entities. Besides, they had no searchable database for their holdings, so they had no idea if they had any extinct plants or not.

It took Agapakis months of negotiations to reach an agreement. The deal was sealed when she offered to provide genomes of any extinct plants she found to the research community. Even so, she had to find the plants on her own, with no help from herbaria staff, and if she did find what she was looking for she could not take more than a pinky-nail-sized fragment of extraneous material.

Agapakis and Dawn Thompson, Ginkgo's head of Next Generation Sequencing, printed out the IUCN Red List of 116 modern plant extinctions and began their quest. The collection was arranged by plant family first and geography second, so the only way to find a sample was to go to the corresponding floor of the herbaria, find the aisle for the right family and then search in all the folders for the particular country or area. The aisles were endless, the cabinets seemingly filled with everything but the plants they were looking for. Then, in the Hawaii room, Agapakis cranked a big wheel to roll the creaking cabinets apart, opened the doors, paged through the folders, opened one, and gazed down at three long twigs holding an array of broad, beautiful leaves and a single pressed flower bud. "Flora of the Hawaiian Islands" read the attached card. "*Hibiscadelphus wilderianus.*" Agapakis felt an

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Road to Resurrection

Bringing genes back from the dead is not simply a matter of finding ancient DNA. The genetic material has to be refashioned into a working gene that can instruct a cell to make molecules. The gene—in this case from an extinct Hawaiian plant called a mountain hibiscus—then has to be placed into a new, living host. Synthetic biologists at Ginkgo Bioworks inserted the gene into yeast, where it actually made fragrant compounds.

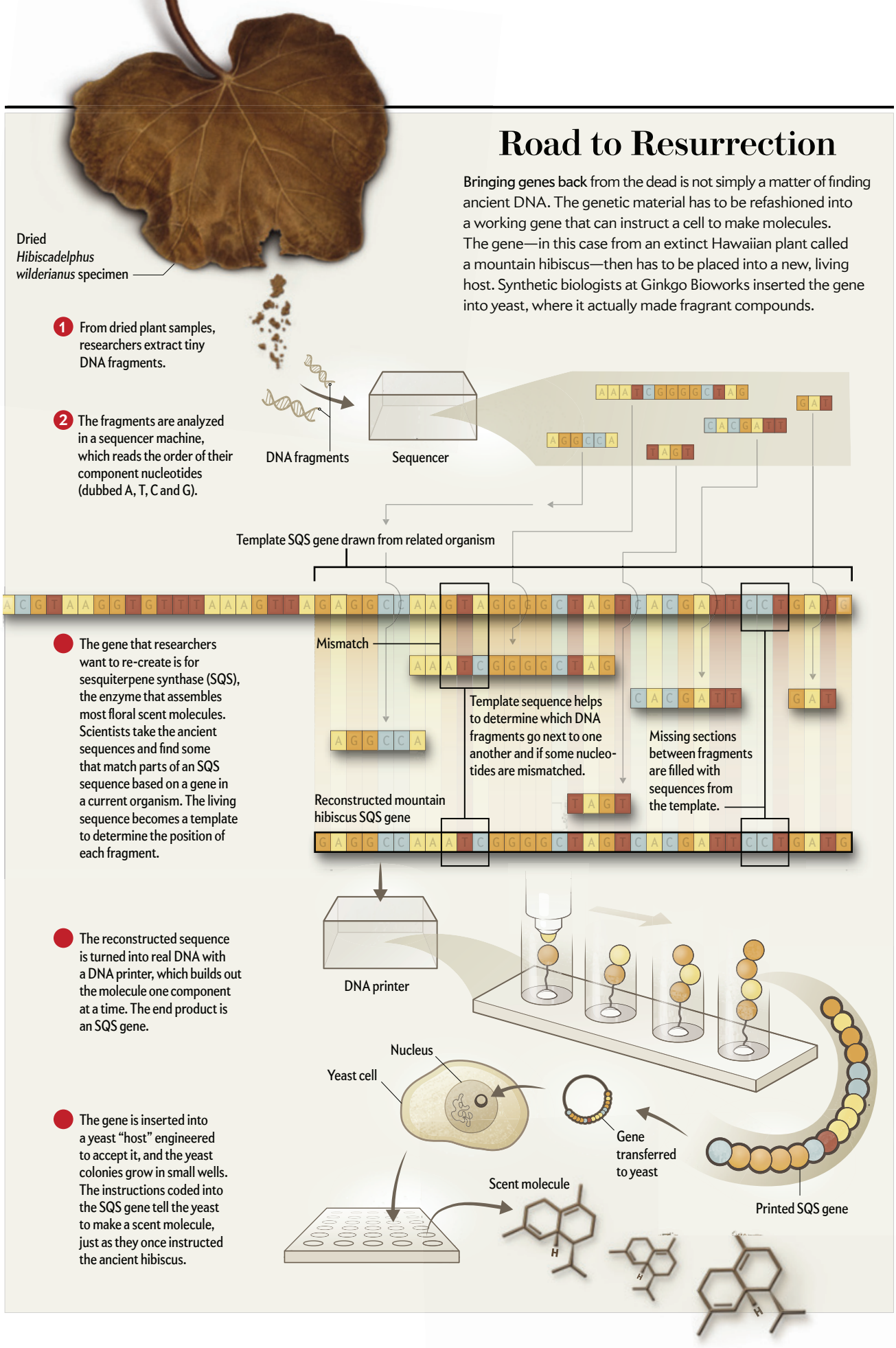

Illustration by Rebecca Konte

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DE-EXTINCTION ROOM: At Ginkgo Bioworks in Boston, a laboratory (*1*) is set up to engineer yeast to produce nonyeast molecules—such as scent compounds of extinct plants. An engineer there (*2*) prepares cells so their genetic code can be analyzed. Finally, Christina Agapakis, who directed the restoration project (*3*), sniffs mixtures of different compounds that originated from the recovered DNA of the extinct mountain hibiscus.

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electric thrill. It was Wilder's extinct tree, right in front of her.

In the end, the scientists found 20 of the plants on their list in the herbaria, 14 of which had enough material to spare. Under the baleful eye of the curator, they snapped off the least important bits and placed them in plastic baggies.

Then it was time for the hard part. DNA degrades after an organism dies. Ginkgo was going to have to find needles of DNA in haystacks of cellulose. And the team had only enough material for a few attempts. The researchers decided to practice on an oak leaf scavenged from the streets of Boston. Even that did not go well. Despite their state-of-the-art sequencing equipment, they struggled to extract DNA from the samples. The ancient samples did not produce anything.

With pressure mounting to yield the sequencing machine to paying projects, Agapakis and Thompson had a sobering conversation. If they kept trying, they were going to run out of plant material, and there was no way they were getting more. They decided to put Project Cretaceous on hold until they found a more effective way of doing it.

Months later, at a conference, Kelly met Beth Shapiro, co-director of the Paleogenomics Lab at the University of California, Santa Cruz. This is the place you go if you want to de-extinct a mammoth or a passenger pigeon. Every year it gets better and better at extracting tiny amounts of DNA from iffy old material. In 2016 the lab was able to identify 0.01 to 0.05 percent mammoth DNA—a mere whiff of pachyderm—in 5,650-year-old lake sediments from an island in the Bering Strait. Send us your flowers, Shapiro said.

Thompson overnighted her plastic baggies of leaf matter to Josh Kapp, a grad student in the Paleogenomics Lab. Kapp did not like what he saw. He pulverized each sample into powder to maximize the surface area, but the plants did not powder as nicely as the bone he was used to. But after many filtration steps and some creative applications of chemicals that bind to DNA fragments, Kapp ended up with 14 microtubes holding the secrets of lost plants, which he packed in dry ice and sent back to Ginkgo. When Thompson ran the samples through her sequencing machine in Boston, she was thrilled to see numerous short reads come through: millions of fragments of genetic code, each just 40 or 50 letters long.

RECONSTRUCTION IN ACTION

BUT DID ANY OF THOSE fragments belong to a scent gene, and could they be put back together? Ginkgo was looking for genes, typically about 1,700 letters long, that made enzymes called sesquiterpene synthases (SQSs); these are the enzymes that stitch together most good floral scent molecules. A typical flower might have several of these genes. With all the tiny fragments they had recovered, it was as if the Ginkgo researchers had a book for each plant—the extinct plant genome—all chopped up into random 50-letter chunks and mixed together, and they needed to reassemble a few 1,700-letter passages in just the right way.

If the scientists had copies of the original books to use as a template or even a few chapters, they could figure out where the fragments went. Here evolution came to the rescue. It never invents anything from scratch. New species evolve from older species, tweaking or repurposing the original genes. So most SQS genes in modern plants share a lot of DNA code with closely related ancestors. Jue Wang, a computational biologist then working at Ginkgo, was tasked with this book-reassembly problem. He realized those modern SQSs could serve as the template. It was like trying to reconstruct a lost version of the Bible using the King James and New International versions as guides. The wording would not exactly match, but they would be a decent guide to what went where.

Bit by bit, Wang built his genes on the scaffolding modern relatives provided, relying on sequence overlaps for placement. He filled in any missing letters of DNA from the modern templates. If his fragmented Bible read "In th_ beg_ _ning was the W_ _ d," he could look to the King James and be pretty confident which letters were missing.

Ultimately Wang was able to reconstruct 2,738 versions of genes from the extinct flowers. Undoubtedly these strings of biological letters had a few typos. Would that ruin their functions? Occasionally a single wrong letter of DNA will break a gene catastrophically, as in sickle cell anemia. But often minor changes do not affect the end product. In fact, sometimes genes with significantly different forms will function similarly. In Biblical terms, "In the beginning was the Word" (King James) and "The Word was first" (The Message) do not match letter by letter, but both get the job done. Wang thought most of his letter strings would be too glitchy. He just hoped a few would work as instructions for a real cell.

For that to happen, these genes, which existed solely in Wang's computer, had to be converted into physical DNA. That is a fairly straightforward job, done with a DNA printer that resembles a 3-D printer but shoots out As, Cs, Gs and Ts, which bind together chemically into a classic double helix. Although this is often called synthetic DNA, it is just as real as any other DNA. Molecules are molecules.

Then it was up to the yeast, each of the 2,000-odd genes going into a colony bred to accept new DNA and make molecules according to its instructions. For several days the colonies frothed like beer brewing in their tiny containers. Scott Marr, a molecular microbiologist at Ginkgo, watched, wondering what they had made. When the fermentation subsided, Marr ran a sample of each colony through a mass spectrometer, a kind of artificial nose that was capable of detecting and identifying the minuscule amount of molecules being produced in each strain. Each mass shows up as a differently sized peak on a graph. It was Marr's job to read the pattern of peaks like a fingerprint.

He wrote programs to eliminate all the regular products of yeast metabolism in the machine's readout, so only nonyeast SQS products—scent-making sesquiterpenes—would show up. Mindful of the long odds and the likelihood of typos in the Ginkgo translations, Marr crossed his fingers and ran the samples. The readouts showed nothing. Then more nothing. It looked like the scientists had pieced together book passages with too many letter mistakes, paragraphs that no cell could read.

And then there it was: a peak. After a while, there was another and another. Marr let out a pent-up breath and began to match the molecular fingerprints to his database of terpenes. Then he broke the good news to the Project Cretaceous team: dozens of the flower-yeast chimeras were alive.

Agapakis sat at a table, listening to Marr's report and taking it all in. It had been three years since the initial crazy idea. Many times she and her colleagues had nearly abandoned it. And now they had molecules. Real molecules! Made by genes that had not existed in a century!

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PROJECT CRETACEOUS: In the Ginkgo effort, which the researchers whimsically named for the Cretaceous period, they re-created genes for scent molecules from 14 extinct (or nearly so) plants. These eight yielded promising DNA sequences but did not churn out scent compounds when placed in designer yeast: *Erica pyramidalis* Sol. (*1*), *Crassula subulata* var. *subulata* L. (*2*), *Nesiota elliptica* (Roxb.) Hook. f. (*3*), *Pradosia glaziovii* (Pierre) T. D. Penn. (*4*), *Macrostylis villosa* (Thunb.) Sond. (*5*), *Shorea cuspidata* P. S. Ashton (*6*), *Stenocarpus dumbeensis* Guillaumin (*7*) and *Thamnea depressa* Oliv. (*8*).

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BACK IN THE REAL WORLD

GINKGO'S YEAST was able to get genes from three different extinct plants to produce sesquiterpenes. Although the microscopic amounts were far too small to smell directly, the scientists had some inklings of what the eventual floral nature might be, based on the smells of modern counterparts. One of the plants, the Falls-of-the-Ohio scurfpea—a legume that made the fatal mistake of growing only on a few rocky islets in the Ohio River that were drowned by dams in the 1920s—produced a handful of sesquiterpenes that, if some 21st-century relatives were any guide, would have woody, peppery, balsamic scents.

The Wynberg conebush—a five-foot-tall flower with white petals and a yellow head that grew in the granite hills above Cape Town until 1806, when it disappeared forever underneath South Africa's expanding vineyards—produced an astonishing 21 sesquiterpenes, many of which are associated with tantalizing scents: jasmine, lemongrass, cannabis, chamomile, turmeric, ginger, hops. That awkward mix sounded like a good match for a flower that had been noted for its "strong and disagreeable smell."

Eleven sesquiterpenes came from *H. wilderianus,* the mountain hibiscus, which had last released its essence to the world in 1912, as Gerrit Wilder picked that final flower and descended Haleakalā, never expecting that anyone would smell the *hau kuahiwi* again. From there, the genes' unlikely journey along Resurrection Road had taken them to the College of Hawaii's herbarium, where the plant was dried and pressed and eventually shared with the Harvard Herbaria. There it waited for decades for Agapakis to open its manila folder and break off a piece of the corpse. The genes were liquefied in Santa Cruz, digitized in Boston, then reanimated in the tender embrace of an organism completely unlike the one that hosted their last appearance on planet Earth. The genes had crossed time and space and outward form, but their information held.

And then it was time to smell them. The Project Cretaceous team picked the *Hibiscadelphus* to go first because its allure was captivating, much as it had been for many a honeycreeper for millennia. On a bright August day in a crisp white conference room, the group gathered to sample a variety of formulations—created for the company by Berlin-based scent artist Sissel Tolaas—that blended the Hawaiian molecules in different combinations and concentrations. One of the molecules, juniper camphor, was a pricey ingredient in fragrant oils. *Hibiscadelphus* had expensive tastes.

They dipped paper fragrance test strips into 11 elfin bottles, held them a few inches from their noses and sniffed gently. Team members grinned at one another as if they could not quite believe they were here. "First resurrected fragrance!" Kelly announced. Agapakis's reaction was more visceral. "I feel overwhelmed," she said. "I couldn't imagine what this was going to smell like."

Some samples had flashes of citrus or thyme. All had a woody core of bark and juniper that must have been the essence of *hau kuahiwi*. "I like the lightness," Agapakis said, eyes closed as she inhaled. "It feels ethereal."

Lurking in the background of several samples was a smoky hint of sulfurous dirt. Kelly's eyes twinkled as he held one under his nose. "This is pretty magical, to be honest," he said. "I hope it captures people's imagination and gets them to think about what we've lost."

The scent—and the thoughts it inspires—is an important milestone, says Stanford University bioengineer Megan Palmer, a board member of Revive & Restore, a nonprofit that is supporting the passenger pigeon and woolly mammoth resurrection projects. "We can't know exactly what these flowers smelled like," she says, "but we can get molecular hints that we interpret through what we know about the species we see in the world today." As scientific advances, she adds, "these techniques can help us make smarter guesses at how extinct species functioned. They may even allow more ambitious projects to restore those functions and the species that gave rise to them."

Because of this work, we are a tiny bit closer to coaxing saber-toothed tiger musk or Neandertal hemoglobin out of cells. And as more of these freelance genes return to function in new forms, they make us begin to question our old emphasis on species. The traditional genetic container may not limit the life of its contents. Sitting in that Boston conference room, it seemed clear that one of the most opportune moments in DNA's four-billion-year career had begun. This novel environment of bioengineering labs and digital databases and DNA printers was giving genes a newfound freedom to flow, new ways to replicate, new habitats to populate, new organisms to seduce. The original form may go extinct, but many functions can return, and at some point—nobody really knows what that is—that resurrection may get an organism to the point of "no longer dead."

Because of this work with ancient flowers, we are a tiny bit closer to coaxing saber-toothed tiger musk or Neandertal hemoglobin out of cells.

As the essential oils saturated the air, the room became an unlikely tropical oasis, a hint of smoke in the distance, and it was easy to imagine the sun-baked lava fields of Haleakalā in the ancient past, a forest of mountain hibiscus all around, bright red honeycreepers flitting from blossom to blossom. That world will never come again, but some of the countless genes from primordial Hawaii and other lost landscapes may do just that. They are pressing against the membrane of extinction at this very moment, probing, hungry for any chance to get back in the action. SA

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FROM OUR ARCHIVES

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ENVIRONMENT

Rapid glacier retreat could put coastlines underwater sooner than anticipated

Is Antarctica Collapsing?

By Richard B. Alley

Illustration By Peter Horvath

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Richard B. Alley is a professor of geosciences at Pennsylvania State University. He has spent more than 40 years studying ice sheets and has advised the U.S. government on a variety of climate issues.

GLACIERS ARE MELTING. SEAS ARE rising. We already know ocean water will move inland along the Eastern Seaboard, the Gulf of Mexico and coastlines around the world. What scientists are urgently trying to figure out is whether the inundation will be much worse than anticipated—many feet instead of a few. The big question is: Are we entering an era of even faster ice melt? If so, how much and how fast? The answer depends greatly on how the gigantic Thwaites Glacier in West Antarctica responds to human decisions. It will determine whether the stingrays cruising seaside streets are sports cars or stealthy creatures with long, ominous tails.

IN BRIEF

Big glaciers on Greenland, such as Jakobshavn, are flowing quickly into the ocean, raising sea level slightly. **The much larger Thwaites Glacier** in West Antarctica has begun flowing faster, too. The key factor determining its fate is whether it will retreat into the great Bentley Subglacial Trench behind it. **If it does retreat,** that would create very high ice cliffs that would break off into the ocean. If Thwaites starts to crumble, it could raise sea level by as much as 11 feet in just a few decades.

Global warming is melting glaciers up in mountainous areas and expanding ocean water, while shrinking ice at both poles. Averaged over the planet's oceans for the past 25 years, sea level has risen just over a tenth of an inch per year, or about a foot per century. Melting the rest of the globe's mountain glaciers would raise the sea a little more than another foot. But the enormous ice sheets on land in the Arctic and Antarctic hold more than 200 feet of sea-level rise; a small change to them can create big changes to our coasts. Ice cliffs many miles long and thousands of feet high could steadily break off and disappear, raising seas significantly.

Well-reasoned projections for additional sea-level rise this century have remained modest—maybe two feet for moderate warming and less than four feet even with strong warming. Scientists have solid evidence that long-term, sustained heating will add a lot to that over ensuing centuries. But the world might be entering an era of even more rapid ice melt if the front edges of the ice sheets retreat.

To learn whether this could happen, we look for clues from changes underway today, aided by insights gained about Earth's past and from the physics of ice. Many of the clues have come from dramatic changes that started about two decades ago on Jakobshavn Glacier, an important piece of the Greenland Ice Sheet. Glaciers spread under their own weight toward the sea, where the front edges melt or fall off, to be replaced by ice flowing from behind. When the loss is faster than the flow from behind, the leading edge retreats backward, shrinking the ice sheet on land and raising sea level.

During the 1980s Jakobshavn was among the fastest-moving glaciers known, racing toward Baffin Bay, even though it was being held back by an ice shelf—an extension of the ice floating on top of the sea. In the 1990s ocean warming of about 1.8 degrees Fahrenheit (one degree Celsius) dismantled the ice shelf, and the glacier on land behind it responded by more than doubling its speed toward the shore. Today Jakobshavn is retreating and thinning extensively and is one of the largest single contributors to global sea-level rise. Geologic records in rocks there show that comparable events have occurred in the past. Our current observations reveal similar actions transforming other Greenland glaciers.

If Thwaites, far larger, unzips the way Jakobshavn did, it and adjacent ice could crumble, perhaps in as little as a few decades, raising sea level 11 feet. So are we risking catastrophic sea-level rise in the near future? Or is the risk overhyped? How will we know how Thwaites will behave? Data are coming in right now.

WAFFLES ON THE COAST

CALCULATING THWAITES'S THREAT is complex. To make sense of it, let's begin with breakfast. If you pour batter on a waffle iron, your mound will spread across the iron's crosshatched grid. Physically, the weight of the batter pushes the mound outward against the friction on the grid below it. This spreading slows as cooking stiffens the batter—or if you hold the batter back with your spatula.

Glacial ice sheets are like big waffles, up to two miles thick and a continent wide. Snow falls on top and is squeezed into ice under the weight of subsequent snowfalls. These huge ice mounds are strong—I have landed on them in heavy ski-equipped military transport planes—but they still spread. Their temperature is often within a few degrees of the melting point, making the ice soft enough to slowly flow from the high, central region toward the edges, where it more readily melts and breaks off. Thicker or steeper mounds such as those on Greenland and Antarctica spread faster.

Left to itself, an ice sheet grows until it is thick and steep enough for the spreading, melting and breaking to balance the ongoing, additional snowfall. The mound can stay at one size for a long time. But that is not the case on our warming planet. The moisture in the snow that falls on Greenland and Antarctica each year, which almost entirely comes from the sea, is equal to a layer of water evaporated from all oceans, just over a quarter of an inch deep. The ice sheets are now returning about 15 percent more than this amount to the oceans, by meltwater runoff or icebergs that "calve" off, raising sea level a little. If melting remains greater than snowfall for long enough, an ice sheet can disappear. But that could take almost 100,000 years at recent rates. If warming rises, however, the melting quickens. That is the case we are facing globally.

PRECEDING PAGE: GETTY IMAGES (*hand, water, buildings*)

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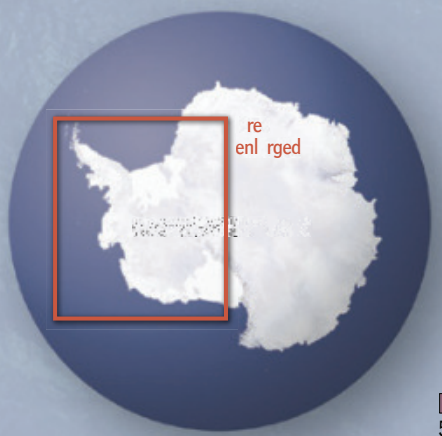
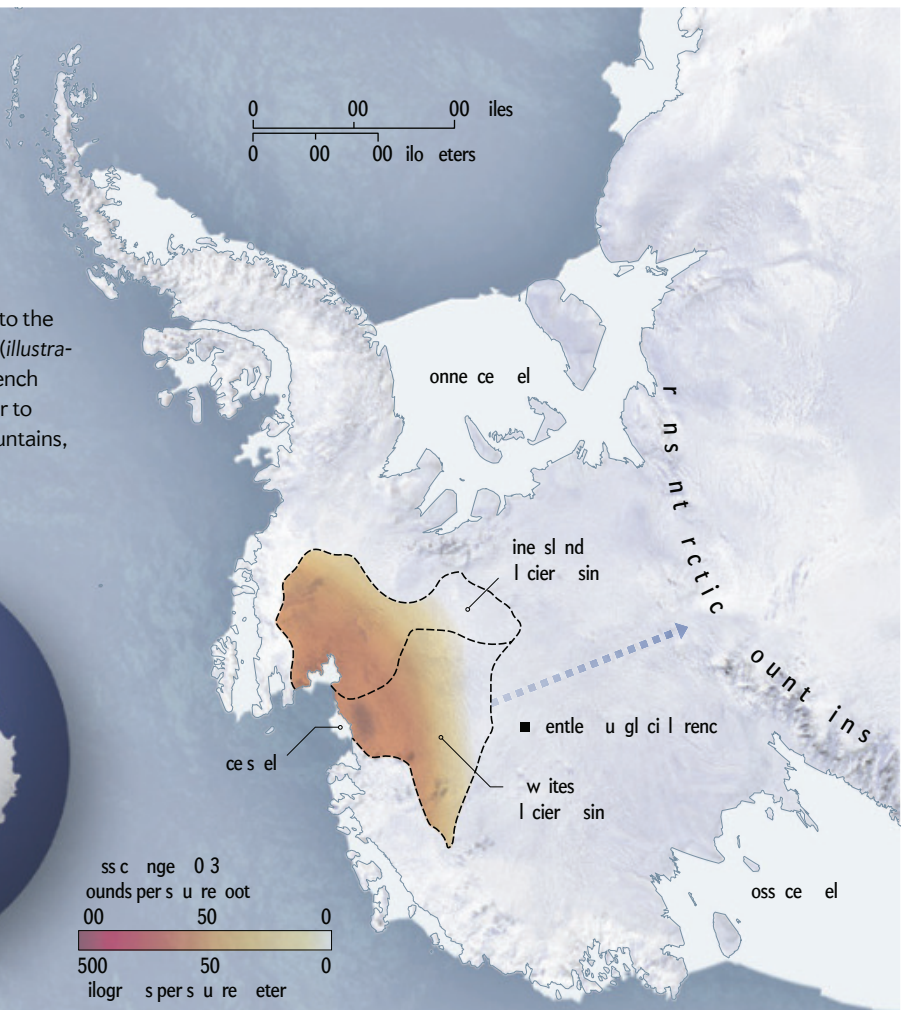
Raising the Global Sea

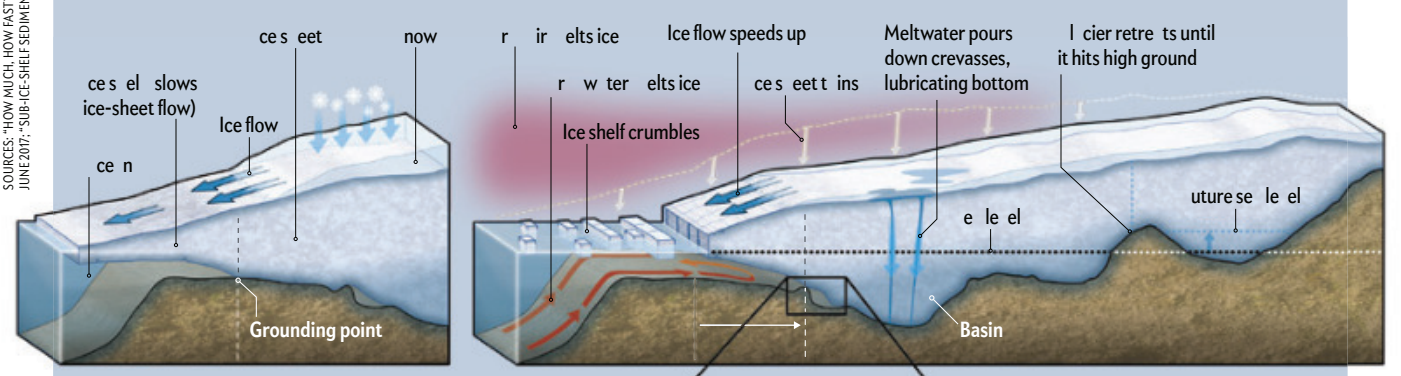
Small glaciers drain parts of West Antarctica and can raise sea level a little if they melt. But the truly vast glaciers such as Pine Island and Thwaites pose a much larger threat (*main map*). Thwaites is starting to thin; ice flows into the sea as the leading edge recedes inland (*illustrations*). The broad Bentley Subglacial Trench behind Thwaites could allow the glacier to retreat as far as the Transantarctic Mountains, which would raise sea level by 11 feet.





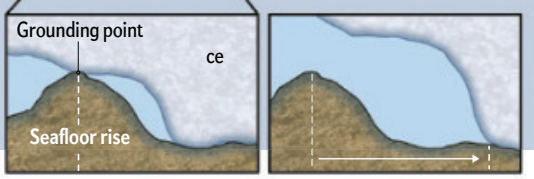
How to Unzip an Ice Sheet

New snow adds to an ice sheet, but the ice also flows under its own weight into the sea and melts (*short illustration*). Ice sheets in West Antarctica are losing slightly more mass than they gain, raising sea level. An ice shelf floating on the ocean at the front edge of the sheet slows the flow, but if warm air and water disintegrate the shelf, the sheet's flow quickens, and the sheet gets t inner *long illustration*). The front edge recedes, and the grounding point where the ice contacts the seafloor recedes with it. If a deep basin exists behind that point, the retreat will continue unimpeded, raising sea level significantly, until the ice reaches the next high ground inland or gets hung up on a seafloor bump (*inset*).



Jumping the Bump

A receding ice sheet can catch on a seafloor rise, or bump, creating friction and blocking warm water from melting the underside. If the retreat clears the bump, friction drops, and the water has open access.



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Map by Mapping Specialists, Illustration by Ben Gililand

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TERRIBLE BEAUTY

AN ICE SHEET'S FLOW depends on how strong the mound is, how well lubricated it is underneath on land, and whether or not it is held back by a spatula—an attached, floating ice shelf. General atmospheric warming can soften ice and thaw the places where the ice bottom is frozen to the rock below, allowing the ice to slide faster toward the sea. But the heat takes a long time to be conducted through two-mile piles. The big ice sheets have not finished warming from the rising air temperatures that ended the most recent ice age more than 10,000 years ago!

A speedier way to warm the ice and its bed is for water melting on top to pour down into crevasses. In some places on the flanks of Greenland's ice, meltwater in summer collects in large hollows on the surface, forming big, beautiful blue lakes. The water, being denser than ice, tends to wedge open crevasses that can reach the bed at the bottom and drain the lake. An expanding lake can break through half a mile of ice or more, creating a flow of water greater than Niagara Falls. In an hour, that can warm the bed as much as would have occurred over 10,000 years.

This process is important, and we are studying it eagerly. But it is not the greatest worry for people on Earth's coasts, because the bumpy bed can also keep the ice from speeding toward the sea.

The same mechanism presents a stronger threat if it happens on an ice shelf. In very cold places, the ice flowing into the ocean remains attached but floating. These ice shelves almost always occur in protected bays or fjords. The motion of ice shelves is slowed by friction along the shorelines around them and perhaps with upward protrusions from the seafloor, where the ice locally runs aground. The shelf slows the flow of the nonfloating ice on land toward the sea.

MELTWATER pours into the Greenland ice sheet, hastening its slump toward the sea—a sign of things to come in Antarctica.

Warming air can create lakes on top of the ice shelves. When the lakes break through crevasses, a shelf can fall apart. For example, the Larsen B Ice Shelf in the Antarctic Peninsula, north of Thwaites, disintegrated almost completely in a mere five weeks in 2002, with icebergs breaking off and toppling like dominoes. That did not immediately raise sea level—the shelf was floating already—but the loss of the shelf allowed the ice sheet on land behind it to flow faster into the ocean—like pulling a spatula away, allowing the batter to run. The ice flowed as much as six to eight times quicker than it had been moving earlier. Fortunately, there was not a lot of ice behind the Larsen B Ice Shelf in the narrow Antarctic Peninsula, so it has raised sea level only a little. But the event put society on notice that ice shelves can disintegrate quickly, releasing the glaciers they had been holding back. Ice shelves can also be melted from below by warming seawater, as happened to Jakobshavn.

When shelves are lost, icebergs calve directly from ice-sheet cliffs that face the sea. Although this delights passengers on cruise ships in Alaska and elsewhere, it speeds up the ice sheet's demise. At Jakobshavn today, the icebergs calve from a cliff that towers more than 300 feet above the ocean's edge—a 30-story building—and extends about nine times that much below the water. As these icebergs roll over, they make splashes 50 stories high and earthquakes that can be monitored from the U.S.

So far ice-shelf loss and ice-cliff calving are contributing moderately to sea-level rise. But at Thwaites, this process could make the rise much more dramatic because a geologic accident has placed the glacier near a "tipping point" into the great Bentley Subglacial Trench.

JUMP THE BUMP

ON AN AUTUMN MORNING in 1956, Charles Bentley (who years later would be my Ph.D. adviser) defended his thesis at Columbia University. The next day he hopped a train to Panama, then caught a ship heading south, to be part of the International Geophysical Year research project that would analyze planet Earth. He spent two years in West Antarctica before returning to find that he had not graduated yet, because his thesis fee had not been paid. In the meantime, he and his team traversed more than 3,000 miles of ice, to and from the Byrd Station research base and across vast reaches of West Antarctica. (Bentley died at age 87 in 2017.)

Of the many measurements and discoveries they made, the most important for our story involved the ice thickness. They set off small explosions on the surface and used seismometers to listen to sound traveling through the ice sheet and bouncing back off the bed. These data showed that West Antarctica was not a thin drape of ice overlying a high continent, as some had expected. Instead Bentley and his team found very thick ice, and they discovered the Bentley Subglacial Trench. There the bed plunges more than a mile and a half below sea level—Earth's deepest place not under an ocean. And the ice filling it extends more than a mile above sea level.

Bentley and glaciologists who followed him had found a tipping point. The great trench and adjacent basins underlie the vast center of the West Antarctic Ice Sheet. If the front edge of Thwaites retreated from the coast back into the trench, it could make an ice face thousands of feet high, extending from far above the trench to deep down into it. Such a cliff—much bigger than at Jakobshavn or anywhere else on Earth—could break fast, making incredibly tall icebergs that would roll over and float away through the trench outlet to the ocean, raising sea level a lot.

Decades of additional research have established just how important this mechanism is. John Anderson, who recently retired after 43 years at Rice University, and many of his graduate students tirelessly mapped the continental shelf under the ocean around Antarctica, using side-scan sonar and other tools. During ice ages, Antarctic ice spread many miles farther in all directions and withdrew as ice ages ended. The seafloor around Antarctica today was the bed under the ice sheet in the past. Telltale imprints left in seafloor sediments give us accurate stories about ice sheets.

One story is that as expanding ice sheets push forward into the

KONRAD STEFFEN, CIRES AND UNIVERSITY OF COLORADO

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sea, they drag sediment with them. The ice stabilizes when it reaches a local high in the seafloor and then builds the seafloor higher there by piling the sediment into raised moraine shoals—long, stony walls that grow where the ice ends. Ice can sit in such a position for hundreds or thousands of years, rebuffing weak efforts to dislodge it. But if enough warming occurs, the ice retreats back down the sloping bed into the valley behind the shoal. The ice rarely stabilizes again until it reaches the next high ridge, often far behind it. Meanwhile icebergs float over the abandoned moraine shoal, which is still below sea level, and out into the ocean.

This is now happening in many places around Antarctica and Greenland. Jakobshavn Glacier has "jumped the bump" of a former moraine shoal and is retreating back through its valley-shaped fjord, "unzipping" a path into the greater ice sheet. When the first European explorers visited the area that is now Glacier Bay in Alaska, it was filled with a vast glacier ending on a large moraine shoal. Since then, the ice has retreated from that ridge, or bump, more than 60 miles inland to get to the next high ground, which today is the current shoreline of the beautiful bay.

Fortunately, most such retreats have only a limited effect on global sea level. Even a big Glacier Bay–sized glacier is small compared with the world ocean. Jakobshavn is just one of dozens of major drainages around Greenland's ice sheet, but they do not quickly destabilize their neighbors in adjacent fjords, and they end not too far inland where the bed rises again. Similarly, Antarctica is drained by a great number of glaciers flowing down into their own waffle-iron valleys. With enough warming, many of them might retreat in unison, but each by itself is not a huge influence on the global sea.

The Bentley trench in West Antarctica and a few other deep regions in East Antarctica, including the Wilkes and Aurora basins, present a different story. Retreat through one of these to the next high ground would have global importance. Models point to Thwaites Glacier as the most likely path into the Bentley trench and connecting basins. If it started unzipping into the interior as Jakobshavn has, the melting could potentially raise sea level 11 feet before it stabilizes on high ground on the other side of the trench. The East Antarctic basins by themselves could raise sea level more than Thwaites would, but they require more warming to cause those glaciers to jump their bumps.

Note that there is nothing bizarre about this scenario. With sufficient warming, ice retreats, usually to the next high ground. This has been observed over and over in the past and present. If Thwaites becomes warm enough to start acting like ice in Greenland and Alaska, then it should retreat.

A FRACTURED FUTURE?

HOW FAST COULD THWAITES GO? How much warming can we cause before it goes there?

My colleagues David Pollard of Pennsylvania State University and Robert M. DeConto of the University of Massachusetts Amherst programmed an ice-flow model that uses the relevant physics and can be run fast enough on advanced computers to study big changes in ice sheets over long times. I helped them a little with the physics of calving from high cliffs after ice shelves break off, especially if surface meltwater wedges open crevasses.

Pollard and DeConto optimized this model to match data from the geologic past and to assess the impacts of different amounts of human-caused warming. They determined that we probably have a few decades even under fast warming before the collapse of Thwaites is triggered by loss of its shelf and meltwater widening crevasses. Thwaites then would take a century or so to collapse completely. They did not know how fast the ice could break, though, so they set a top rate equal to what Jakobshavn had done in Greenland. (It has already exceeded that rate briefly.) And because Thwaites is thicker, it could make much higher cliffs than Jakobshavn. Higher cliffs tend to break faster (one reason highway engineers leave slopes rather than cliffs). So we could be underestimating the worst-case scenario, but we really do not know.

This is a good model, but it surely is not the last word from Pollard and DeConto or others. Some hope remains that Thwaites could stabilize on a deeper ridge on the downslope of the trench, behind its current position, before retreating still more, for example. Or icebergs could break off and pile up for a while behind the current ridge where the ice now starts to float, helping to reform a shelf that could lessen the ice loss.

To address these and other questions, the National Science Foundation and the British Antarctic Survey, together with other international collaborators, have launched a major effort to learn even more about Thwaites's history, how the glacier is flowing, and what the seafloor surface is that it is flowing over, which will help all of us involved to better predict its future. The data are almost guaranteed to reduce uncertainties and to be fascinating.

Some questions may remain difficult to answer. Think of all the ceramic coffee cups you have seen dropped on a hard floor. Some bounce, some crack, some chip, some break into a million pieces. The physical processes of these fractures are well known and readily calculated, and the behavior averaged across many dropped cups is predictable. But you would not want to bet your career, or anything else important, predicting the fate of the next cup that hits the floor.

The future of Thwaites depends a lot on fractures. Will the ice shelf fracture from the ice that now feeds it, causing the ice sheet to jump the bump and retreat into the deep basins? Will huge icebergs break off rapidly if ice-shelf loss produces a cliff along the sheet's face that is higher than any now on Earth, driving retreat faster than any we have seen? Meltwater is important, but how much of the water will run off in rivers to the sea, and how much will percolate into snow and refreeze? How fast will the air warm? I suspect that coffee cups are easy to predict in comparison.

If the world can muster the effort, slowing and stopping warming from greenhouse gas emissions will slow sea-level rise, easing the mounting costs of coastal damage. But if Thwaites is poised to retreat briskly, preventing warming by limiting the damage incurred by human activity could be vastly more valuable. SA

MORE TO EXPLORE

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CECILIA GUIDO patrols a stretch of the Caquetá River in Colombia with her son, Luis Eduardo Marin, and granddaughter, Nayda Guido, as part of their community's efforts to protect the Curare–Los Ingleses Indigenous Reserve and the uncontacted people who live there.

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GUARDIANS *of the* TIGER PEOPLE

As anthropologists debate how best to protect uncontacted tribes, indigenous groups in Colombia are working to shield their isolated neighbors from the march of modernity

By Adam Piore

Photographs by Juan Arredondo

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Adam Piore is a freelance journalist. His last article for *Scientific American* examined the movement to bring evolution back to the classroom.

JHONATTAN ANDRES PEREA SQUINTS THROUGH the blinding Amazonian sunlight into a wall of jungle. He steers the tiny motor powering his wood longboat through a tributary of Colombia's mighty Caquetá River and putters up to a muddy bank. Hopping onto a barely discernible path, the twentysomething member of the Carijona tribe beckons five others, including me, to follow. Then he disappears into the green, amid a cacophony of unseen birds, monkeys and insects. The vegetation is so dense and the dark, musty path so twisting that for a few moments, it seems to those of us behind Perea that the jungle has swallowed our young guide whole. Until we emerge from the trees a few minutes later to find him standing before a shimmering salt lake. Perea is gazing intently into the distance. "This is as far as we are allowed to go," he says. "There's a swampland beyond this. According to legend, that swampland divides us physically and spiritually." Then he points solemnly across the lake. "That way," he says. Somewhere out there. "That is where they are."

1

"They" are the mysterious tribespeople who reside as close as six miles from the invisible boundary that marks the beginning of their territory here in the Curare–Los Ingleses Indigenous Reserve in southeastern Colombia. Unlike the Carijona and the other tribes that live on the periphery of this territory, which extends into the neighboring Río Puré National Natural Park and other areas, this enigmatic group has had virtually no exposure to modern civilization. Indeed, it has actively sought to avoid any contact with the outside world. Its members survive much as they have for millennia, naked in the jungle, hunting with poison-tipped arrows and blow darts, using stone axes to fell trees and bamboo knives to cut their food.

Some of Perea's tribe call these men and women "our brothers living in a natural state." Other locals call them the "Tiger People." (There are no tigers in South America, but the word *tigre* is sometimes used to refer to local jaguars.) It is a nickname passed down through the generations from a time before the missionaries, the rubber barons and all the trappings of the modern Western world reached this remote area. The legends tell of a clan of fierce warriors who painted stripes on their bodies, pierced their noses and ate their enemies before fleeing down a Caquetá tributary called the Bernardo River into the wilderness around the 19th century to escape the white man. The Carijona and the 14 other tribes that inhabit the lands that border the territory of the uncontacted group regard their isolated neighbors with a mixture of awe and fear; they envy the purity of the tribe's culture and believe its shamans to be so close to nature that they can control the elements.

Nobody knows how many of these secluded people now reside in this jungle sanctuary—estimates range from 50 to 500. But encroachment by outsiders would threaten their way of life—in fact, their very existence. Perea and his peers are working to prevent intrusion. I have come to Curare to see how they are helping their uncontacted neighbors maintain their solitude in an increasingly connected world.

Anthropologists, activists and government officials have long debated how best to protect such uncontacted tribes in the Amazon and elsewhere. Because they have been living in isolation, they have little or no immunity to diseases common among

IN BRIEF

An estimated 100 tribes around the world live in isolation. Contact with outsiders can be disastrous, often exposing them to deadly pathogens.

Scholars and policy makers have long debated how to protect these uncontacted groups. In Colombia, indigenous people are defending their neighbors.

Their work could pave the way for safeguarding perhaps as many as 17 other uncontacted tribes that are thought to live in the Colombian Amazon.

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LONGHOUSE, or *maloca*, in Curare serves as a gathering place for the local communities to discuss efforts to protect their isolated neighbors (*2*). Those efforts include manning several control posts strategically located along the border of the protected lands (*1*).

denizens of the industrial world. Encounters with outsiders—all of whom carry potentially deadly pathogens—could thus wipe out these communities. Many experts contend that keeping visitors away is the only way to safeguard them from disease. Perhaps more important, many of these tribes are aware of a larger world and have chosen to remain isolated. "No contact," in this view, is thus a matter of human rights. Others counter that contact is inevitable and that preparing the tribes for that eventuality is the most prudent course of action. The march of modernity stops for no one. And without regular contact, it is impossible to protect the tribes from armed, evil actors who covet virgin timber, gold and other natural resources often hidden in their lands.

In 2012 Perea's tribe and the other communities of Curare, along with groups in other nearby areas, launched an aggressive effort to patrol the borders and protect the lands of their uncontacted counterparts from incursions of loggers, hunters, gold miners, missionaries, smugglers, drug dealers and communist insurgents. Recently their mission has taken on added urgency. For decades Colombia's civil war stalled development in the Amazon, and the presence of insurgent camps, right-

Living in Solitude

Deep in the Colombian Amazon, tribespeople have been found living in isolation from the outside world. Their territory encompasses part of the Curare–Los Ingleses Indigenous Reserve and neighboring areas, including a large portion of the Río Puré National Natural Park. Other tribes are working to protect the uncontacted group.

Map by Mapping Specialists

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wing paramilitaries and drug labs hidden within its jungles rendered them too dangerous to many of the forces most likely to try and exploit them. In November 2016, however, the government and the insurgents signed a peace accord. Stability could bring economic boom times—and, many fear, the kinds of development pressures that have jeopardized efforts to protect isolated tribes in neighboring countries. The peace accords have also spawned an array of more immediate perils in the form of new splinter groups and hard-line rebel holdovers that are looking to set up novel routes through the vast unexplored interior and fund their efforts with clandestine drug facilities and illegal mining.

Now the race is on to implement a nationwide policy hammered out among nongovernmental organizations (NGOs), Colombia's indigenous leaders and its Ministry of Interior and signed by the nation's outgoing president Juan Manuel Santos and his cabinet ministers last summer. The new protocols guarantee the rights of isolated peoples to self-determination and spell out the procedures for defending these rights for new groups identified across the country. Although the Tiger People are the only uncontacted tribe whose presence has so far been confirmed, evidence suggests that as many as 17 other tribes may be living in isolation elsewhere in the Colombian Amazon.

As international NGOs gather the proof they need to demonstrate the presence of new tribes deserving of federal protection, the efforts of Perea and others in Curare are serving as an important model that is showing doubters that such security is even possible.

1

THE NGO SURVIVAL INTERNATIONAL estimates there are more than 100 uncontacted tribes around the world, groups it defines as "tribal peoples who have no peaceful contact with anyone in the mainstream or dominant society." In Colombia, as in the rest of the Amazon, most live in isolation by choice. Many originally fled the colonists of the 18th to early 20th centuries, rubber barons who brutalized and enslaved indigenous workers and missionaries who attempted to "civilize" and convert natives by forbidding the practice of long-held traditions.

More recent "first contacts" have proved catastrophic in other ways. The most common contacts in recent decades have occurred across Colombia's border in Brazil, home to the largest tracts of virgin rain forest. Throughout the 20th century, the Brazilian government sought to open up the region, sending a core of explorers into the wilderness to establish small airstrip outposts in the jungle and later cutting new roads, allowing civilization to creep ever deeper into the interior. To contact the tribes living there, first the nation's Indian Protection Service and later the National Indian Foundation (FUNAI) sent scouts known as *sertanistas* ahead of the explorers, with the mission of luring natives out and assimilating them into society.

Those initial encounters provided a catalog of the devastation that would later be visited on other native peoples across the rest of the Amazon. Lacking immunity to many modern diseases, many villages have lost 50 to 90 percent of their populations in the wake of contact. The survivors have often ended up in squalid jungle settlements or on the streets, alienated from traditions and community, living as alcoholics or prostitutes and losing any semblance of self-sufficiency.

In the early 1960s a pair of famed *sertanistas,* the brothers Cláudio and Orlando Villas-Bôas, succeeded in leading efforts to create a vast reserve, known as the Xingu National Park, the first in a mosaic of closed sanctuaries where indigenous peoples could, in theory, live unmolested. Xingu would become a model for other such indigenous reserves across the Amazon, including Curare. Even so, in the years that followed, first contacts often continued to prove calamitous, with disease devastating tribes even before relocation could be considered. Colombia saw its own share of tragic tales, perhaps most famously that of the Nukak-Maku, a hunter-gatherer tribe that was ravaged by disease after official contact was established in 1988 and is fighting extinction today.

In Brazil, by the 1980s, the ill effects of contact had come to seem so inevitable that some *sertanistas,* led by a dynamic Villas-Bôas protégé named Sydney Possuelo, had begun to equate contact with genocide and to advocate for a radical strategy. In 1988 Possuelo won support for a new "no contact" approach: mapping indigenous lands and keeping out loggers, miners and other interlopers—and thus, many believe, saving countless lives. Brazil's no-contact policy has since remained the standard for how to approach indigenous rights in nations across the region, favored by indigenous groups and NGOs alike. It was used as a model by Peru and officially incorporated into its national policy in 2006.

Even so, ever since, the hands-off approach has been under virtually constant attack from would-be colonists and powerful mining, ranching and timber interests, who have long sought

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SHAMANS Moises Nilmore Yakuna (*red shirt*) and Alfonso Matapí (*blue striped shirt*) join the annual meeting of the Curare communities to review their protection plans for the uncontacted tribespeople (*1*). Daniel Aristizabal of the Amazon Conservation Team (*center*) and members of the Río Puré National Natural Park team work on the meeting minutes (*2*).

access to protected lands—sometimes with success. In 2006 Possuelo was fired from his post after criticizing the head of FUNAI for stating publicly that native peoples had too much land.

More recently, some anthropologists have begun to suggest that the no-contact policy is ill conceived in the face of ruthless groups that operate outside of the law in the jungle. In a controversial editorial published in 2015 in *Science,* Robert S. Walker of the University of Missouri and Kim R. Hill of Arizona State University argued that miners, loggers and hunters routinely penetrate into protected territories, exposing the tribespeople there to deadly pathogens and committing atrocities with virtual impunity. The safest, most humane approach to safeguarding isolated tribes, in their view, was "controlled contact."

Hill says the essay was the culmination of decades of work in the field and repeated encounters with tribes that spoke of starvation, brutality and an unsettled life on the run. He spoke out, he says, because these stories long ago burst his early idealism, and he is convinced that the epidemiological challenges can be managed with better planning. "All of the isolated tribes in the world are pretty much under the control of pathetically inept and corrupt Third World governments that are doing a piss-poor job of protecting them," he explains. "So that protection is really an illusion. By keeping the tribes away from transparent information collecting, we have no idea what's really happening to them. And I think all kinds of horrific things are happening and stay hidden, specifically because we can't talk to them and ask them what's going on."

Despite Hill's stated intentions, the *Science* editorial sparked widespread outrage from indigenous-rights groups, NGOs and others, prompting angry letters—even death threats. (Walker declined to comment for this article, saying he no longer speaks publicly about the issue.)

"Even if you could [make] safe, controlled contact, which I don't think you can, what then happens?" demands Fiona Watson, director of advocacy and research for Survival International, the organization that has been perhaps the most vocal critic of Hill's and Walker's argument. "When you look at cases where tribes have been contacted recently, it's not making their life any better. In fact, you could argue it's making it worse. Now they are surrounded; their lands are being invaded; they're much more exposed to disease."

Many of Hill's colleagues, meanwhile, remain torn. Stephen Beckerman, a cultural anthropologist at Pennsylvania State University, notes that "everyone can agree that the most important thing is to keep them alive." But he says no existing approach is ideal. "Every cell in my body emotionally screams, 'Leave them the hell alone!' " says Beckerman, whose fieldwork focuses on the Barí tribe of Venezuela and Colombia and the Waorani of Ecuador. "And every day of experience I have had in the tropical forest working there, reading about it, talking to other people who have worked there, says, 'That's not going to happen.' "

FOR A FIRST-TIME VISITOR, the trip to Curare can seem like a journey to the end of the earth. To get there, I caught a plane to Bogotá, where I met Daniel Aristizabal, a skinny thirtysomething Colombian with a dark ponytail, a worn, white T-shirt and faded cargo pants. Aristizabal works for the Amazon Conservation Team (ACT), an American NGO. Together we flew to Leticia in Colombia's extreme south, then boarded a beat-up World War II–era cargo plane bound for the remote frontier town of La Pedrera, a dusty outpost deep in the Amazon built around an airstrip. Cruising at 15,000 feet and surrounded by pallets of eggs, powdered milk and sacks of flour, I gazed through a small window. Below, hundreds of miles of thick primary jungle unfolded, broken only by the many long, powerful tributaries of the Amazon River curling through the green in an endless succession of brown curves. I did not see a single settlement the entire 200-mile trip. In La Pedrera we stepped onto a rickety, wood longboat and headed upriver. Five hours later—four full days after setting out from New York City—I finally arrived at my destination.

The people here live in jungle settlements along the river with no running water or electricity aside from a few rarely used generators. They obtain most of their food through hunting, fishing and the cultivation of traditional crops. There are no roads, just jungle paths and dugout canoes. La Pedrera is the nearest town, with a hotel and restaurant. The tribespeople like to say they are poor in money and material possessions but rich in land and natural resources.

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Yet as remote as Curare is, life here in the borderland is nonetheless shot through with elements of modernity. Many of the children attend a boarding school across the river from La Pedrera that was run by Catholic priests until last year, when the government took it over. Tribespeople regularly travel to La Pedrera for modern health care and to more distant cities such as Leticia and even Bogotá when they have a serious illness or a broken bone. Many wear modern clothing and use machetes, flashlights and steel pots purchased in towns such as La Pedrera and have been exposed to television. It is a testament to the determination of the uncontacted tribespeople and their self-appointed guardians that these influences have not reached the interior.

The indigenous people in Curare and Río Puré have known for generations of the presence of their mysterious brethren in the interior, believed by scholars to be members of two related tribes called the Yuri and Passé. But it was the arrival of a Colombian environmentalist named Roberto Franco and ACT in the early 2000s that would thrust them into the center of Colombia's dialogue over how to defend its most isolated peoples.

Franco, the author of numerous books on the history of the Amazon, was for years one of the leading Colombian proponents of the idea that the best way to protect the rain forests was to uphold the land rights of the nation's indigenous tribes, whose cultures were based on living in harmony with their surroundings. He had also worked as an anthropological consultant to government agencies, had seen the ravages of first contact firsthand and had come to believe that "self-isolation" was a human-rights issue. Intent on finding a way to shield the nation's most vulnerable groups, Franco began collecting scraps of information about isolated peoples during his expeditions through the Amazon in the 1980s. He scoured the historical literature for clues, pored over maps and conducted interviews—even meeting with former rebel commanders and drug traffickers who had come across uncontacted tribespeople in their travels through the bush.

To win official government protection, however, Franco needed concrete proof of the existence of these tribes. In 2007 ACT agreed to support his efforts to get it. By then Franco had already decided that Curare and Río Puré were the most promising places to start. In the late 1960s a rubber tapper and fur trader named Julian Gil came across a well-worn path deep in the jungle, far from any settlement, and followed it to a vast longhouse, or *maloca,* where he discovered scores of tribesmen in the middle of a celebration. They wore nothing but tiny pouches covering their privates and sticks as thick as pencils through piercings in their ears and noses. They had painted their bodies in stripes. But the tribe wanted nothing to do with the visitors, and the meeting turned violent, resulting in the disappearance of Gil and the deaths of a number of tribesmen. The Colombian military took several tribe members prisoner, prompting a worldwide outcry. The military subsequently freed the prisoners and vowed to leave the tribe in peace.

These people are believed to have been members of the Yuri and Passé tribes, groups that began fleeing white slavers hundreds of years ago, settled in the area and were thought to have gone extinct. But in 2010 Franco and a small crew flew over the most likely habitation zones in Curare and Río Puré in a single-engine Cessna. On the first day they spotted a longhouse surrounded by fruit trees—and snapped photographs of an indigenous tribeswoman, her face and body painted, who could clearly be seen gazing up at the plane. The footage, along with the identification of four other *malocas,* was enough to get the government and the nation's indigenous groups to agree to begin the process of hammering out protections for the nation's isolated peoples.

In 2014 Franco was flying home from another community farther north when his aircraft went down, killing all 10 people onboard—including Daniel Matapí, another ACT staff member. It was a devastating blow for ACT and for Aristizabal, then a young Ministry of Interior official, whose graduate thesis focused on preserving the privacy of isolated tribes. Aristizabal had been closely collaborating with Franco to develop new laws to that end. After Franco's untimely death, Aristizabal agreed to join ACT and continue his legacy.

A CENTRAL TENET of that legacy has been partnering with the indigenous groups in Curare to support their protection efforts. While I was in Curare, the communities were holding their annual meeting to review those efforts and plan for the year ahead. Aristizabal and I made our way to an enormous *maloca* with a 30-foot-high thatched-palm roof to join them.

Once inside, Aristizabal and I were greeted like old friends. In the center of the structure, eight male community elders dressed in soccer shirts and T-shirts were clustered together on their ritual wood benches. As they chatted and laughed, they passed around tall, cylindrical Tupperware containers of *mambe,* a mixture of coca leaves and ash, copious amounts of which they shoveled into the space between their lips and gums with metal spoons. Around them, children chased one another, tripping and laughing, as their parents watched from long planks arrayed between the pillars holding up the structure. Others reclined in hammocks slung to the far walls.

> e t n er in an rain
> ere a me a e fr m t e i er
> e e a in ea e a ne
> —*Alfonso Matapí, shaman*

Over the next three nights, various tribal figures would step across the hard-packed earth to the front of the *maloca* to deliver reports on a wide range of activities, conducted over the previous year, aimed at securing the reserve and its inhabitants. The proceedings were unhurried and deliberate, offering ample opportunity to reflect on the challenges facing both the uncontacted peoples and their guardians.

Some participants spoke about preserving the cultural traditions of the tribes that do have contact with the world beyond. One young tribesman described his efforts to make story books for the smallest children detailing the traditional legends that would help explain the importance of the protection of sacred places and the reserve management plan. "As you know, the sto-

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MEMBERS of the indigenous communities in and around the Curare reserve balance their protection efforts with the tasks of everyday life: tending cooking fires (*1*), making cassava meal (*2*) and preparing *mambe,* a mixture of coca leaves and ash (*3*).

ries of the elders are very, very long. For example, the origins of animals and the origin of crops," he noted. "So we listened to all the stories, and part of the challenge was to summarize them." The report was followed by a chorus of low, deep-throated mmhmms from the elders and the rest of the *maloca,* a traditional way of showing their appreciation or support for a point.

Other speakers raised the issue of sustainability of the reserve's flora and fauna. When a tribal elder reported on the results of an investigation into the illegal killing of a pregnant tapir in an area where the tribe had restricted hunting, an angry debate broke out over how large a fine or how much volunteer work to impose on the guilty parties as a penalty.

Eventually the topic turned to the battle to keep interlopers out of the reserve. Even without development, the threats to the location and the isolated tribespeople that live there are many. In 2015, before the peace accords, Colombian authorities intercepted two American evangelical missionaries south of Río Puré who were attempting to contact and convert the isolated tribes to Christianity, seemingly indifferent to the danger that contact might pose to their targets—and to themselves.

From the east, illegal gold-mining barges, crossing in from Brazil, are a constant concern. Drug traffickers and bandits, meanwhile, have made intermittent appearances in some areas of Curare itself—and some fear their presence might actually increase as the insurgent demobilization progresses. In 2016 members of a dissident faction of the Revolutionary Armed Forces of Colombia (FARC), unhappy with the peace accords, entered the reserve. Toting their weapons and slogans, they convinced the teenage son of a Curare community elder to run away with them.

To monitor these threats and help respond to them, ACT staffers supplement the tribal on-the-ground patrols with modern technology. From offices in Bogotá and Virginia, ACT staffers comb through reams of satellite imagery, searching for signs of illegal barges and deforestation while looking for isolated tribal dwellings. (The images are provided free of charge by U.S. commercial satellite provider DigitalGlobe, and the quality and resolution improve by the year: it is now at 30 centimeters, clear enough to examine a banana leaf from space.)

ACT staffers also confer regularly with partners in the Na-

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tional Natural Parks of Colombia, take reports from neighbors who border the indigenous lands and, when necessary, call on allies in the Ministry of Interior and Ministry of National Defense to act as their muscle. It was the Ministry of Interior that issued a formal warning to the American missionaries, who were deterred the following year. Previously, the Colombian military conducted flyovers at the border to scare away would-be prospectors in Brazil. And in 2017 the military bombed a pair of illegal mining barges to the north, after ACT notified them of the presence upriver.

But the heart of protection plans remains the efforts of the indigenous communities themselves to police their lands, provide eyes on the ground and, when possible, shield their vulnerable neighbors from outsiders. In 2012 the communities incorporated the untouchable zone into a detailed reserve management plan and established two ACT-funded "control posts"—three others are run by the National Natural Parks of Colombia and are placed at strategically located bends in the river on the border of the protected territories. The locals and the park rangers are not armed during these patrols. Instead they rely on human connection, politely explaining the protected zone, refusing bribes and then retreating if they sense any danger. Often this simple approach is enough. For now, there are plenty of other places to mine and fish. But the danger of violence is always a concern.

The recent missionary incursion is an indication of a key liability. With limited funding, the guards are stretched thin, leaving parts of the borderland vulnerable to penetration by stealthy interlopers. At the meeting tribesmen complained that the loss of support from another NGO had forced them to reduce the number of guards at the post.

CHILDREN from the indigenous community of Borikada in Curare play on jungle vines.

Perhaps the most vulnerable control post is in on the southern end of the isolated peoples' territories, just across the border from Brazil, where illegal gold-mining barges proliferate. The post, known as Puerto Franco, is so remote, the situation so dangerous, that guards are required to make radio contact several times a day and are taught to use code words to convey if they are in trouble. In case of an attack from gold miners, ACT has built an emergency shelter with supplies and a spare radio in a secret location nearby.

For the tribespeople themselves, an essential element is the involvement of their shamans, their spiritual guides and the keepers of traditional tribal knowledge. Sitting on a bench in the longhouse one afternoon during my visit, local shaman Moises Nilmore Yakuna, age 55, removed a small pouch from around his neck. He shook out a fine, black powder into his palm and explained how he uses the powerful snuff, made from tobacco and other ingredients from the jungle, to "open up" his mind and reach the tribespeople using his thoughts. By performing traditional rituals, including dances, he and the other tribal shamans have built a protective wall with the spirits to keep miners, loggers and drug traffickers out of the forbidden territories. "Through our spiritual work with our thoughts, we give them space, so they can live in peace," he told me.

It is a job that is so important the locals have brought in outside help. They did so in 2016, a few months after Franco's death, when a guard at one of the control posts mysteriously fell ill and died. That incident, along with a series of unexplained thunderstorms on otherwise sunny days, prompted the elders to send

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for a shaman from a community three days upriver in a neighboring national park.

The shaman, Alfonso Matapí, age 78, says that when he arrived, he quickly realized that the locals were out of sync with the natural elements of the jungle and had angered the far more powerful medicine men of the Tiger People. Franco's plane, he opines, "came down not because of a malfunction but because the tribes didn't want the flights. There were many flights. And they made his plane crash." (The others onboard were innocent victims.) The guard perished because he entered forbidden lands near the sacred salt lake; the animals that rely on the lake fought back. "The thunder, wind and rain were [a message from the Tiger People] saying, 'Leave us alone,'" Matapí explains. "So I try to send them thoughts saying, 'Don't worry, we're going to leave you alone. Don't worry, we're not going to bother you.'"

IT IS POSSIBLE, of course, that the isolated tribes will initiate contact with their neighbors in the borderland. To help prepare the residents of Curare for such an event, ACT and community members have consulted with groups and individuals who have experience with uncontacted tribes. Among them is Luis Felipe Torres, an anthropologist, who led a Ministry of Culture team in Peru from 2012 to 2017 that oversaw a high-profile case of contact.

> "It is very difficult to protect me ne fr m c ntact f re er t t at e n t mean t at e n t re ect t eir e ire t a i c ntact"
>
> —*Daniel Aristizabal, Amazon Conservation Team*

In recent years different bands consisting of several members of the Mashco Piro tribe began to emerge with increasing frequency from the jungles in the Madre de Dios region of southern Peru and attempt to trade with the locals. Their contacts have continued intermittently ever since. Though mostly peaceful, misunderstandings have resulted in the deaths of at least two villagers in 2011 and 2015—they were both shot with arrows—which prompted the government to send in Torres and his team to manage the situation.

Often, Torres notes, the emerging isolated peoples are eager to exchange goods and food and may misinterpret the efforts of the locals to shield them from potentially contaminated items as a hostile gesture. That is likely what led to the two deaths in Peru. Torres has helped Aristizabal arrange mutual visits between those living in Madre de Dios and the locals in Curare so that the Colombians can learn from their counterparts.

Colombia's new policy on isolated tribes assigns responsibilities to a wide array of government agencies once the presence of a previously unknown isolated tribe is suspected. And it increases the land rights and protections conferred on isolated tribes as confirmation of their existence moves from suspected to confirmed. The document also requires contingency planning in case of first contact and creates a national committee for coordination that would include indigenous leaders and representatives from the national land agency treasury, ministries of environment, health and interior, and armed services, among others.

For his part, Aristizabal is under no illusions as to the size of the challenges that he faces. If anyone needed a reminder, certain events of late have provided plenty. Recently a dissident FARC faction was back in the area. One group found the wife of a prominent local leader and village elder whom I met during my visit and threatened to kill him and his family if he did not stop speaking out about indigenous land rights. Yet Aristizabal remains firm in his belief that shielding isolated tribes from contact is the best thing to do. "Of course, it is very difficult to protect someone from contact forever," he says. "But that doesn't mean that we shouldn't respect their desire to avoid contact. Why should we make the decision for them?"

In recent months ACT has continued to try to gather the proof it needs to expand its efforts to other tribes. Not long ago it had a potential breakthrough in the region up the Caquetá where Franco perished. For five years ACT members had been combing through high-resolution photographs, searching for evidence of the isolated, indigenous community believed to live in Chiribiquete National Park. One day in January 2017 Brian Hettler, a staffer at ACT's Virginia office, received some of the clearest photographs he had ever seen of the area, which was often obscured by clouds.

That day, the ubiquitous clouds had miraculously lifted, revealing tabletop mountains studded with emerald green triple-canopy jungle and rugged cliffs that are home to some of the greatest concentrations of pre-Columbian cave paintings in the world. It did not take long for Hettler to spot a patch of white in the impenetrable wall of green and, within it, what appeared to be the telltale faded-brown color of a man-made dried-thatch roof.

Hettler believes he has found evidence of another isolated settlement. ACT is already at work with the other indigenous tribes that live in the area to develop protection plans. Now that the Colombian government has embraced the ACT vision, if the presence of the tribe is further confirmed, perhaps it will be possible to help that tribe continue living in its present state. Perhaps there, too, for a time the relentless tide of modernity can be held at bay. SA

MORE TO EXPLORE

Colombian Government Approves Decree for the Protection of Isolated Indigenous Groups. Amazon Conservation Team. Published online July 18, 2018. a a on tea org colo ian-govern ent-a roves-ground reaking-co unit -led- national- u lic- olic - or-t e- rotection-o -isolated-indigenous-grou s

FROM OUR ARCHIVES

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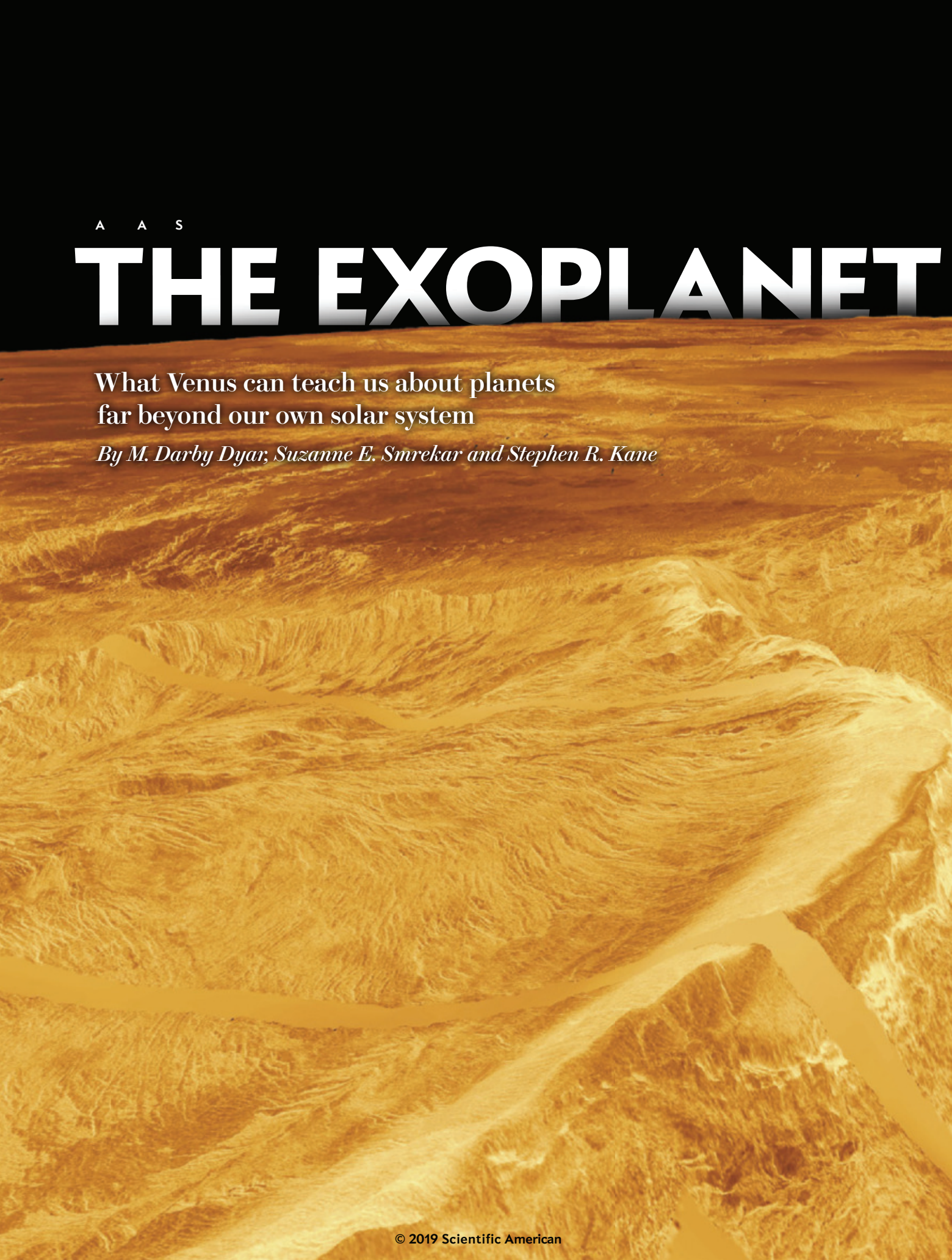
A A S

THE EXOPLANET

What Venus can teach us about planets far beyond our own solar system

By M. Darby Dyar, Suzanne E. Smrekar and Stephen R. Kane



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NEXT DOOR

A A A A fr m t e a e an
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M. Darby Dyar is a mineral spectroscopist who studies extraterrestrial minerals and glasses from the moon, Mars, comets and asteroids. She is a senior scientist at the Planetary Science Institute and Kennedy-Schelkunoff Professor of Astronomy at Mount Holyoke College.

Suzanne E. Smrekar studies the different evolutionary paths for rocky planets, with occasional fieldwork at volcanoes. She is a senior research scientist and deputy principal investigator of the InSight Mission at NASA's Jet Propulsion Laboratory, where the mountain biking is awesome.

Stephen R. Kane is a planetary astrophysicist who has discovered hundreds of exoplanets and studies their potential for habitability. He is an associate professor in the department of earth sciences at the University of California, Riverside.

IN 1982 ALL ANYONE COULD TALK ABOUT IN THE PLANETARY SCIENCE DEPARTMENT AT THE Massachusetts Institute of Technology was the cancellation of NASA's latest flagship mission, the Venus Orbital Imaging Radar (VOIR). One of us (Dyar) was a graduate student there at the time. (The other two were still in college and elementary school.) Graduate students wept openly in the hallways, and veteran faculty shook their heads. The newly elected Reagan administration had enacted sweeping cuts to space exploration, and VOIR was one of the casualties.

Shortly afterward, though, scientists cobbled together plans for a bargain-priced spacecraft ($680 million) made of leftover hardware and, miraculously, saved the mission. In 1989 the Magellan orbiter launched on a reconnaissance mission to Venus, and by 1990 it was in orbit. Over the next five years the orbiter returned near-global radar images, gravity data and a topographic map of the second planet from the sun. It was the latest in a long line of Soviet and U.S. missions to our neighboring planet, but when Magellan plunged to Venus's surface in 1994, NASA's support for Venus spacecraft died with it. Since then, scientists have submitted more than 25 proposals for return missions to Venus, and although some of those received high rankings from review boards, none were approved. Decades-old data gathered by Magellan remain the foundation of Venus geoscience to this day.

But planetary scientists never give up, and we have made progress in uncovering the secrets of this world nonetheless. Since Magellan, the European and Japanese space agencies have sent successful missions to Venus, leading to breakthroughs in understanding its atmosphere. Meanwhile scientists have been busy rewriting the textbooks on our sister planet by performing new analyses of Magellan data. We now think that volcanoes are rampant on Venus, and we have even found hints of the start of plate tectonics, which scientists think is critical for a planet's habitability. New theoretical models also suggest Venus may have had liquid water on its surface until relatively late in its history—meaning that it may have been hospitable to life much longer than we once thought.

IN BRIEF

Venus and Earth started out much the same, but at some point, the planets diverged. Earth went on to host oceans and an atmosphere.

Venus's surface, meanwhile, became inhospitable to life. Yet our neighboring planet still has active volcanism and hints of nascent plate tectonics.

Learning why Venus evolved the way it did could illuminate the possibilities for life on the many Venus-like exoplanets out there. A new mission to Venus is needed.

PRECEDING PAGES: NASA AND JPL

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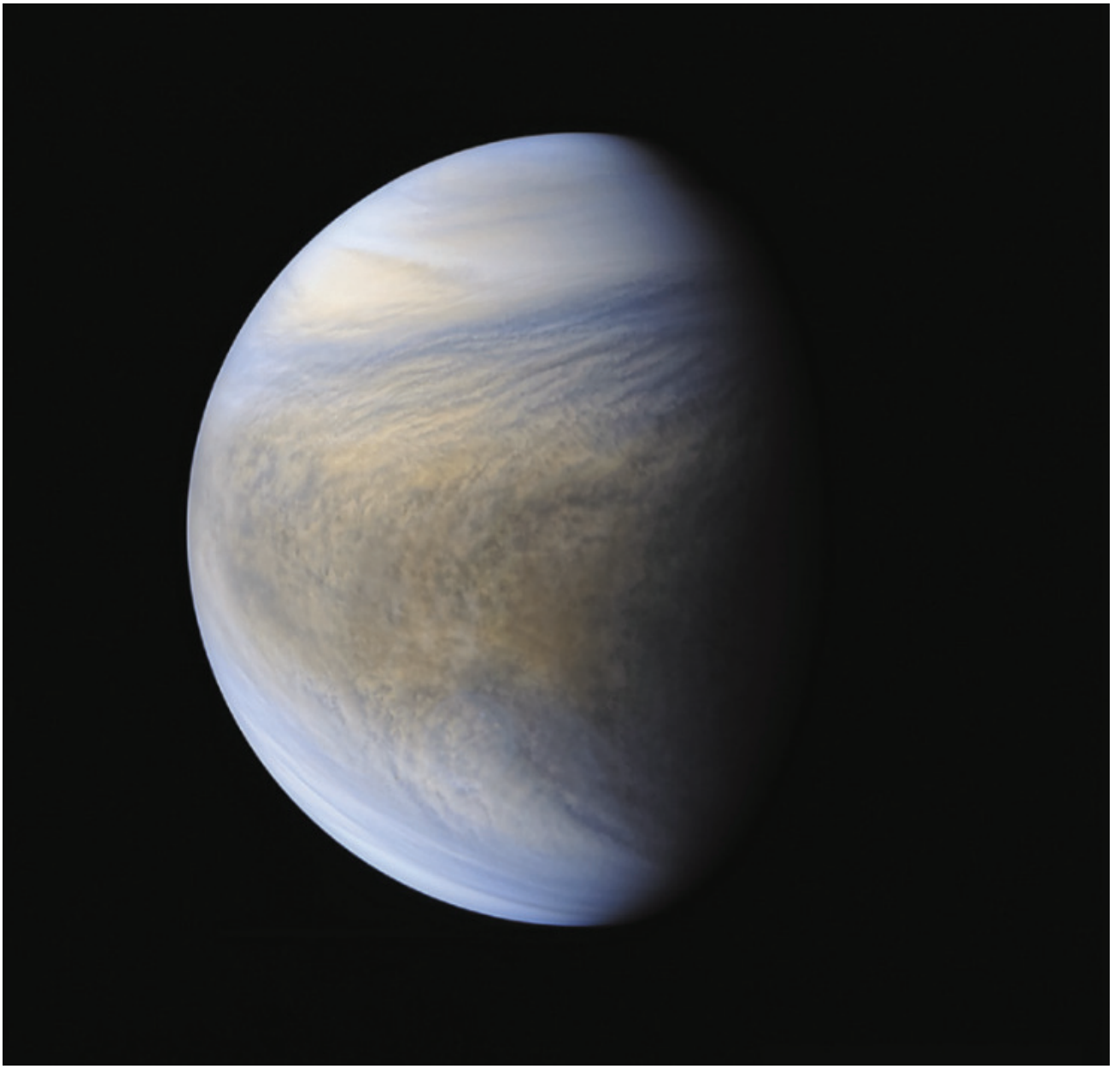

JAXA, ISAS, DARTS AND DAMIA BOUIC

VENUS'S ATMOSPHERE, as seen in this composite image from data taken by Japan's Akatsuki spacecraft, contains thick clouds of sulfuric acid.

All of this coincides with another stunning development in astronomy: the discovery of thousands of exoplanets in other solar systems, many of them roughly the same size and distance from their stars as Venus. Anything we learn about the planet next door could teach us about these distant, inaccessible worlds. In particular, if we can figure out whether and when Venus may have had the conditions to host life, we will know more about the likelihood of finding living beings on the plethora of Venus-like bodies throughout the Milky Way.

A A A

MOST OF THE EXOPLANETS discovered so far were found using the transit method, in which astronomers watch stars for telltale brightness fluctuations that occur as orbiting worlds pass in front of them. With this technique, we can measure a distant planet's size, but size tells us only so much. After all, if an extraterrestrial observer were to look at our solar system using the transit method, Venus and Earth would appear almost identical. Yet Venus is forbidding to life, whereas Earth has been continually habitable for the past four billion years.

We can further differentiate between similarly sized planets by measuring their distances from their stars. The "habitable zone" is the region around a star where a rocky planet could have liquid water on its surface. Earth, obviously, is in this zone. Venus, we think, used to be in this zone—for quite a while, in fact. Yet the

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boundaries of the habitable zone move outward with time as the sun's luminosity increases with age. Venus is now outside this range and occupies what we call the "Venus zone," where surface conditions are so hot that a planet is likely to have a runaway greenhouse atmosphere that would boil its oceans away.

Venus and Earth formed under very similar conditions—including those that gave Earth its oceans. Comet impacts probably brought ice to the surface of both planets. The solar wind (charged particles gushing off the sun) most likely implanted a thin layer of hydrogen ions on the surfaces of both. And when Venus and Earth were protoplanets building up from the primordial dust disk that circled the sun, both collected hydrogen and other volatiles, chemicals that can easily boil away. Simulations of early Venus show that the planet's surface may have had liquid water earlier than Earth and that water might have been there until about a billion years ago.

We have never had better reasons to send a new major mission to the oft-ignored second planet from the sun.

The fact remains, though, that Venus is now forbiddingly inhospitable. What happened? Does Venus represent the end state for all habitable planets, or is it merely one of many ways that planets of this size can turn out? These are some of the major questions we want to go back to Venus to answer.

S S A

OUR KNOWLEDGE OF VENUS is limited in part by the immense difficulty of seeing through the planet's thick, noxious atmosphere. High up, clouds of sulfuric acid shroud the world. On the ground, the air pressure is comparable to the water pressure 3,000 feet below the surface of Earth's oceans. The atmosphere there is so dense that its main constituent, carbon dioxide, acts as a supercritical fluid, with properties midway between a gas and a liquid.

Scientists think this atmosphere was once Earth-like. Unlike our world, though, Venus now lacks a magnetic field to repel the solar wind. We think that over the eons, the solar wind eliminated the planet's water by dissociating it into hydrogen and oxygen ions and carrying them off into space. Without surface water to dissolve the carbon dioxide and other gases constantly escaping from the interior, these chemicals accumulated in the atmosphere. Because of the greenhouse effect of this atmosphere, surface temperatures on Venus are nearly 800 degrees Fahrenheit higher than on Earth—hot enough to make rocks glow.

The only data we have from the surface of Venus were collected by the four Soviet Venera landers that touched down in the 1970s and 1980s. These probes survived for only a few minutes on the planet's brutal surface, but in that brief time they gathered and sent back rough measurements of the chemical composition there. Beyond those readings, our knowledge of the surface mineralogy rests solely on controversial interpretations of radar measurements made by Magellan and our limited knowledge of probable chemical reactions between the planet's rocks and atmospheric gases under Venusian conditions.

Recently, though, researchers found that it is possible to map the minerals on Venus from orbit by looking through several "windows" in the electromagnetic spectrum where visible light escapes absorption by carbon dioxide in the atmosphere. Serendipitously, these windows coincide with critical regions for identifying the typical planetary minerals olivine and pyroxene, offering hope that we could finally determine the basic ingredients of Venus. Europe's Venus Express spacecraft, which orbited Venus from 2006 to 2014, used one of these windows to produce the first map of heat radiating from the planet's surface over much of the southern hemisphere. This map includes spectral features—peaks and dips in light and heat—that can identify minerals on the ground.

The map also identifies many hotspots—areas emitting so much heat that the most likely explanation is recent volcanism. This is an exciting find because it shows that unlike the moon, which has long been silent, and Mars, where modern volcanism has been isolated at best, Venus is still active—and that discovery has implications for the planet's suitability for life.

A S

ON EARTH, volcanism is usually associated with plate tectonics—the shifting and sliding of large pieces of crust responsible for most of the geologic features on our planet. Plate tectonics is also behind the long-term climate cycles, occurring over periods of around 100 million years, that enabled life to arise on Earth. Plate tectonics formed new crust at Earth's mid-ocean ridges and allowed layers of its crust to sink into the mantle—two processes that enabled our planet to lose its internal heat and cool to a point where life could arise. Tectonics also released volatile chemicals such as water, carbon dioxide and sulfur dioxide from deep within Earth out into the atmosphere and cycled volatiles back into the mantle when plates slipped underneath other plates.

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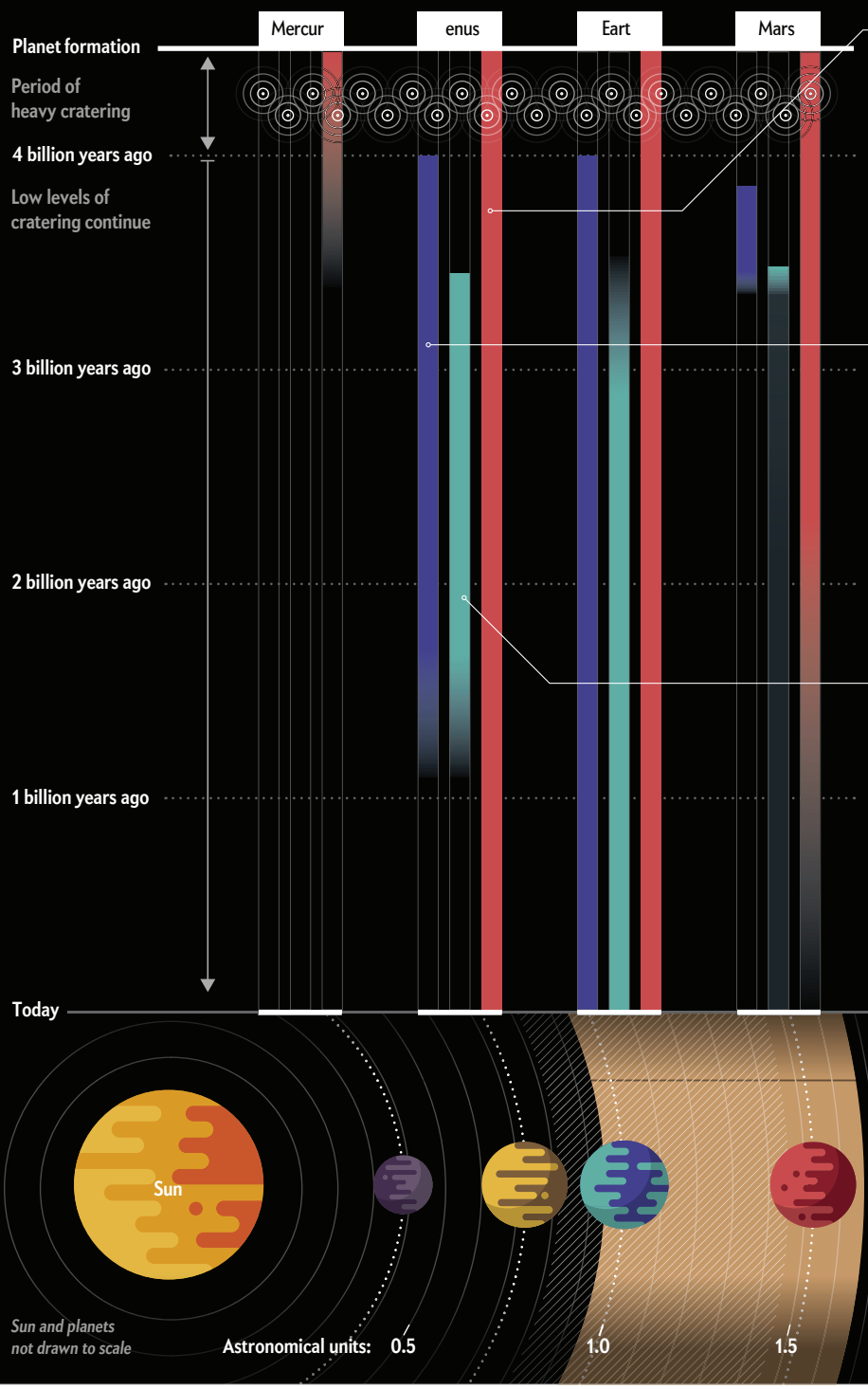
Planetary Comparisons

at ma e a anet a ita e This is one of the biggest questions in astronomy. Earth and Venus started out quite similar, but one is now a bastion of life and the other an inhospitable wasteland. By studying the development of volcanism, plate tectonics and other conditions on Venus, scientists hope to understand why the planet evolved as it did and whether it can teach us about the prospects for life on the many Venus-like exoplanets throughout the Milky Way.



VOLCANIC/ TECTONIC ACTIVITY

Volcanism and the related process of shifting planetary plates called plate tectonics play a large role in the habitability of Earth. They help sustain our planet's atmosphere and oceans and provide the continents needed to support life. Venus is the only other inner planet with signs of both phenomena today.

LIQUID SURFACE WATER PRESENT

Water, the key ingredient for life, was present inside the building blocks of planets and was released to the surface via volcanism, with lesser contributions from cometary impacts. Aside from Earth, Venus most likely held onto its oceans the longest.

CONDITIONS FAVORABLE TO DNA-BASED LIFE

Scientists can only speculate on when and how long each planet had the necessary ingredients to host life. But researchers have reason to believe Venus became a habitable world before Earth and spent more than a billion years with the conditions needed for life.

HABITABLE ZONE

This region is the area around a star where planets could sustain liquid water and thus potential life. Because the sun has grown more luminous over time, the boundaries of the habitable zone in the solar system have shifted outward.

Habitable Zone
1 billion years ago
Today

Graphic by Tiffany Farrant-Gonzalez

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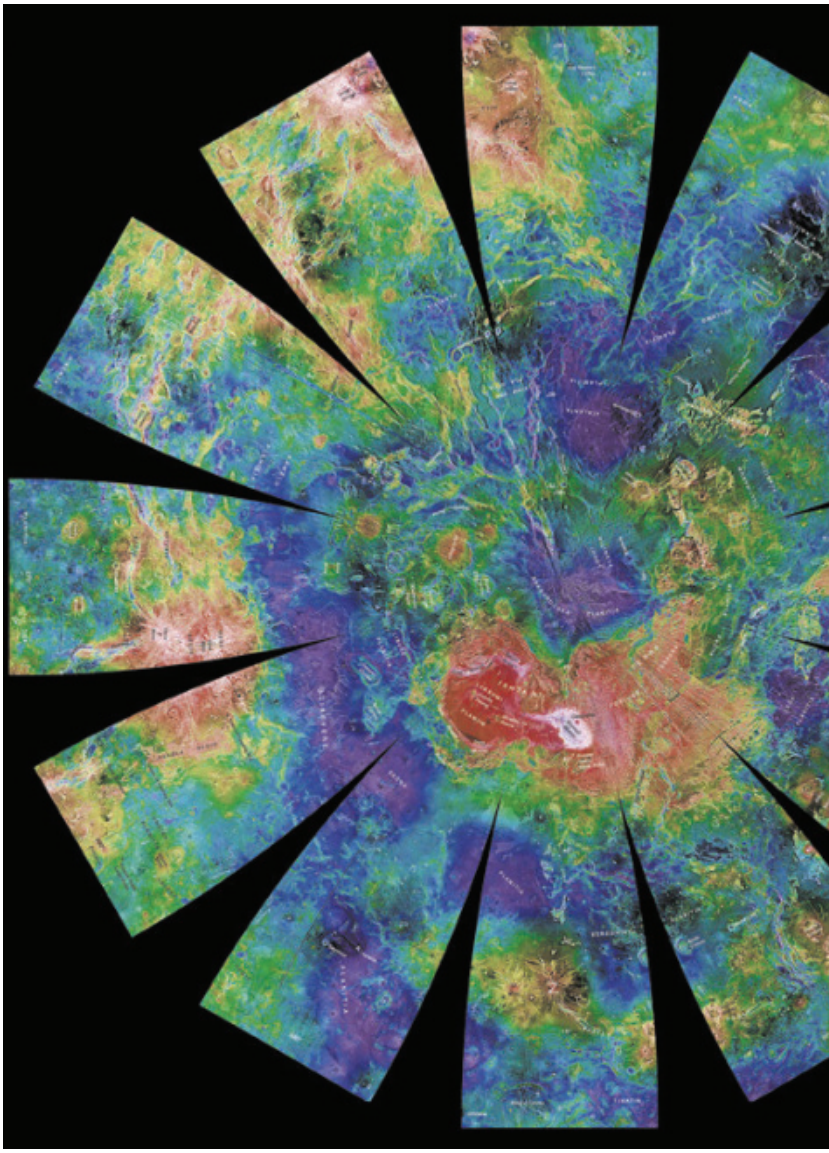
Without volcanism, there would be little surface water and no place for the origins of life. This cycling of volatiles helps to sustain Earth's atmosphere, which was crucial for the emergence of life. Similarly, continents, which provide a buoyant, stable platform above sea level for marine life to evolve onto land, are a product of plate tectonics. For these and many other reasons, understanding whether Venus has plate tectonics—and why or why not—is key.

On Earth, limited data suggest that plate tectonics began as early as four billion years ago, leaving little record. We do not really know how a planet transitions from a basalt-covered world, possibly with oceans, to an intricate system of moving plates with complex features. One leading hypothesis is that blobs of material from deep inside Earth called plumes burst onto the surface, initiating subduction—the act of one plate sliding under another. The hot plume weakens the lithosphere (which includes the crust and upper mantle) and pushes up, causing the surface to crack, or "rift." Pressure from the plume head can create violent volcanism, as observed on both Earth and Venus. The load on the cracked lithosphere can cause this layer to sink and prompt subduction, whereby one layer of the lithosphere slides under another. If this process happens often enough, the subducting plates link up, and plate tectonics begins.

This may be happening on present-day Venus. The lithosphere on Venus now is warm and thin—much like Earth's was back when plate tectonics started up. And some data show compelling similarities between features on Venus and terrestrial subduction zones. One example is Artemis Corona, a circular formation near the equator on Venus that is similar in scale and shape to the Aleutian trench that lies under the ocean along the coast of Alaska. Scientists have theorized that such Venusian features represent spots where plumes from the mantle are rising up to the surface and pushing the crust apart.

Furthermore, recent laboratory experiments and computer simulations suggest that these plumes are inducing subduction where they crack through the top layer of crust. In particular, the experiments explain why subduction seems to take place around only part of the circle: as the brittle lithosphere rips apart in the center, it splits into segments, just as paper rips into different wedges when poked with a pencil. As the lithosphere sinks, it continues to tear, forming segments. If these segments were to join, we would be seeing the initiation of plate tectonics on Venus.

Existing images of these features are too low in resolution for us to know for sure what we are seeing. But it appears that plate tectonics on Venus is in the early stages of development. The Magellan observations show no evidence of interconnected plates—rather we see isolated spots where subduction is beginning, in each case around one of these circular regions where plumes appear to be rising up. Two questions follow: Why did plate tectonics not develop sooner, and what course will it take now? As Venus cools more fully over time, the faults that are now opening may endure, allowing the planet to undergo the same transition to plate tectonics experienced on Earth. If we can watch the beginning of plate tectonics unfold on Venus, then this process and its accompanying atmospheric stabilization may be common on exoplanets on the path to habitability themselves.



GLOBAL MAPS of Venus from Magellan and Venera spacecraft data show diverse features, including the circular Artemis Corona (*box*), that could be indications of plate tectonics.

NASA, JPL AND USGS

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WE HAVE NEVER HAD BETTER REASONS to send a new major mission to the oft-ignored second planet from the sun. With high-resolution global imaging and spectra, we can answer compelling questions about volcanism and possible plate tectonics at Venus. Is the process truly occurring now? How do the surface activities relate to what is happening in the planet's interior?

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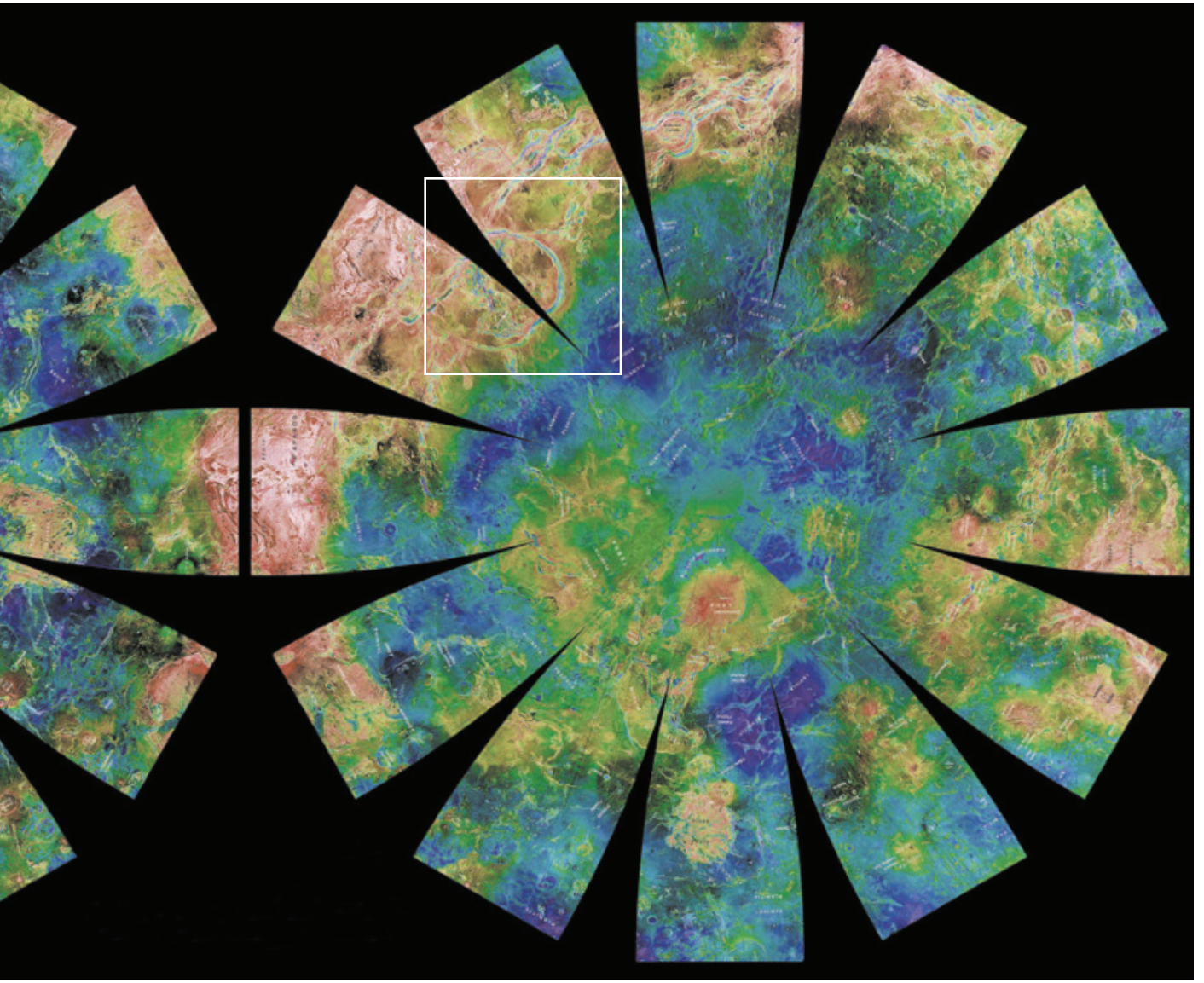

How do the conditions on Venus, such as its temperature, affect this tectonic activity? And are some surface features we see, such as the crinkles scientists call tesserae, remnants of a past, wet epoch?

In 2019 NASA will solicit proposals for the next group of its smallest class of space probes, called Discovery missions. Another of us (Smrekar) and Dyar are leading one proposed mission called VERITAS (Venus Emissivity, Radio Science, InSAR, Topography, and Spectroscopy), which would map the surface in much greater detail than ever before. It would carry several instruments, including an imaging camera and spectrometer, to provide orders-of-magnitude-level improvements in topography resolution and the first-of-its-kind global composition map of the planet. Other Venus mission proposals are also in the works, and we should find out the final results in 2021.

Nearly 30 years after Magellan arrived at Venus, the generation of scientists who launched Magellan is growing old and retiring. A mission to Venus now would allow researchers to pass the torch to a new generation who can bring us closer to understanding why our planetary sister evolved so differently from Earth. Perhaps we may even discover what conditions are necessary for the emergence of life. SA

MORE TO EXPLORE

Was Venus the First Habitable World of Our Solar System? M. J. Way et al. in *Geophysical Research Letters,* Vol. 43, No. 16, pages 8376–8383; August 28, 2016.

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Global Climate Change on Venus. Mark A. Bullock and David H. Grinspoon; March 1999.

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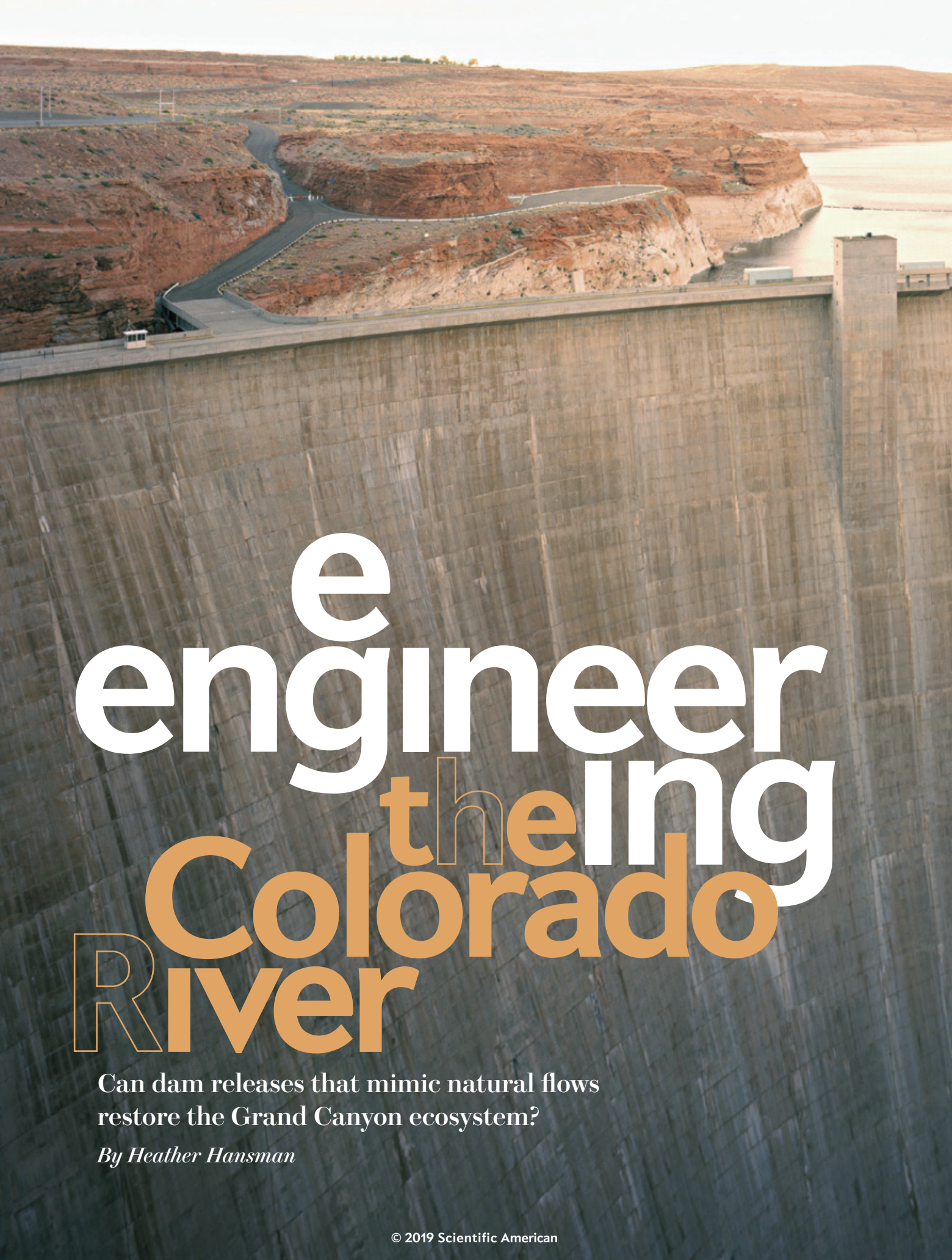

e engineer ing the Colorado River

Can dam releases that mimic natural flows restore the Grand Canyon ecosystem?

By Heather Hansman

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A A in Arizona creates hydropower by controlling releases from Lake Powell, the second largest reservoir in the U.S.

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ON WEEKDAY EVENINGS, MILLIONS of workers return to their homes across the American Southwest and turn on their air conditioners, microwaves and televisions. From Tucson to Burbank, power needs surge. Meeting this demand begins at 5 or 6 A.M. inside the Glen Canyon Dam, the chip of concrete that plugs the Colorado River just above the Grand Canyon. At noon, an average peak of 14,000 cubic feet of water per second is churned through eight turbines, then released.

Heather Hansman is a freelance writer who lives in Seattle. *Downriver,* her book about the Green River, climate change and water in the West, comes out this spring from the University of Chicago Press.

Artificial tides oscillate downstream where the canyon gorge is steep and narrow for more than 200 miles, sloughing the sandstone banks and sluicing fish out of eddies. These flows are calculated and controlled at all times by the U.S. Bureau of Reclamation, sometimes doubling in volume as the water moves downstream. Raft guides who lead trips down the Colorado know to stake their boats high and leave lots of rope for them to float, so that they do not get stranded in the morning as the levels go down overnight. The river, they know, is constantly changing.

If you were boating or fishing on the Colorado in the summer of 2018, however, you might have noticed that days passed without any tides at all. In a rare opportunity for scientists who are trying to better understand the river ecosystem, the Bureau of Reclamation was releasing steady flows of 8,000 cubic feet per second through summer weekends. Aquatic ecologist Ted Kennedy and his team at the Grand Canyon Monitoring and Research Center (GCMRC) wanted to see if holding the river at a consistent level would aid the struggling native bug population, 85 percent of which lay their eggs in the intertidal zone. Those eggs can get wet, but they cannot get dry; eggs laid at high tides desiccate within an hour of the water dropping.

Bugs might seem like a lowly thing to focus on. But they form the basis of a complex food web. When their numbers drop, that reduction affects species, such as bats and endangered humpback chub, that feed on them. In a national park held up as an iconic wild, Kennedy and his group are trying to figure out why, according to their research published in 2016 in *BioScience,* the Grand Canyon section of the Colorado has one of the lowest insect diversities in the country. "There are more bugs in the Detroit River," says Jeff Muehlbauer, a biologist in Kennedy's laboratory.

Last summer the researchers were testing whether adjusting dam releases so that the Colorado runs closer to its natural course might help insect populations recover. In those tests, they artificially created the kind of flow patterns that allowed life to flourish before the dam went in—without removing the dam itself.

Nearly 40 million people depend on the Colorado for the necessities of daily life, including electricity, tap water and the irrigation of 10 percent of land used for U.S. food production. Ever since Glen Canyon Dam opened in 1963, the river has been engineered to accommodate these demands. Doing so changed the ecosystem balance, which was dependent on ingredients such as sediment, snowmelt and seasonal flows. For more than 30 years researchers have been trying to figure out how to help the ecosystem coexist with human needs, and they are finally beginning to test some solutions. By working out an experimental flow schedule that minimally impacted power generation, the 2018 bug tests marked one of the first times that dam operations were adjusted for species health in the Grand Canyon.

Meanwhile, though, the river is dwindling. The Colorado River Basin has been in a drought for almost two decades; 2018 was the third-driest year ever recorded. Since 2000 ambient temperatures in the basin have been 1.6 degrees Fahrenheit warmer than 20th-century averages, and researchers predict they will reach up to 9.5 degrees F hotter still by 2100. The effects of climate change could decrease river flow by as much as half by the end of the century. With earlier snowmelt and more evaporation, the Bureau of Reclamation has predicted that it may have to cut the amount of water it sends downstream for the first time—as soon as 2020. That will stress every part of the system, from hydropower and city water supplies to native fish populations. It will also mean less room for experimental flows, a tool the scientists think is critical for understanding how to protect the canyon.

IN BRIEF

Nearly 40 million people rely on the Colorado River for water and power, and its flow is engineered to maximize those resources. But the ever changing releases from the Glen Canyon Dam have harmed the Grand Canyon ecosystem.

In 2018 researchers tested consistent dam releases that allowed the river to run more "naturally." They are trying to understand how to bring back native insect populations—and restore ecosystem health—without disrupting energy production.

But as the result of climate change, decreased snowfall and increased evaporation mean there is less water available for experimental flows. As new research informs management of the Colorado River, the western U.S. is preparing for water cutbacks.

PRECEDING PAGES: MICHAEL HALL *Getty Images*

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The insect research is a meaningful step toward sustaining the river for habitat as well as for humans. It also runs straight into a core conflict between science and Colorado River policy: scientists want the flexibility to experiment, whereas power and water managers want stability. As the Colorado dries up, this conflict will intensify. And yet if Kennedy and others can show that changing the flow can bring back insect populations, it could make ecosystem health a bigger priority for those who manage the most used river in the West.

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AS SOON AS THE PENSTOCKS CLOSED on the Glen Canyon Dam in 1966, it became clear that the fragile, federally protected downstream ecosystem of the Grand Canyon National Park was unexpectedly altered. Inconsistent, sediment-depleted flows scoured sandbars, a significant habitat structure for native plants such as coyote willow and arrowweed. The clear, 48-degree water, released from the depths of Lake Powell, stressed endangered fish, which were adapted to silty, 80-degree flows. Very little was known about the interconnectedness of such elements before the dam was constructed, so these changes came about without forethought for the consequences.

It was not until 1989, after scientific evidence from an initial 1982 assessment and under pressure from both the public and agencies such as the National Park Service, that the secretary of the interior asked for the first environmental impact statement on the dam. The results, finalized in 1995, confirmed that endangered species and valuable resources were being affected, but the Department of the Interior did not have enough data to quantify how much things were changing. Information found during that investigation sparked the 1992 Grand Canyon Protection Act, which required the Bureau of Reclamation to maintain both hydropower and natural habitat while managing the dam.

To uphold the act, in 1996 the Bureau of Reclamation formed a federal advisory committee to guide dam operations. Called the Adaptive Management Program (AMP), it is made up of 25 stakeholders who represent groups that have legal rights to the water or depend on the canyon economically. They include the Hualapai Tribe, whose reservation runs 108 miles along the river and the Grand Canyon; Western Area Power, which provides power to customers in 15 states; and the tourism industry, which brings $938 million to the local economy. Adaptive management, a term coined by fish biologists in Canada in the 1970s, is the practice of changing management decisions based on ongoing research. In other words, it is learning by doing. The Glen Canyon AMP was the first time that adaptive management had been applied to a federal project with so many stakeholders.

Exactly how the dam, drought and other variables stress the Colorado River ecosystem had long been poorly understood. Shifts in water temperature, flood timing, sediment suspension, chemical composition and species diversity all respond to one another. “You can’t pull one string and not expect it to change,” Kennedy says. So, in 1995, as part of the AMP, the U.S. Geological Survey created the Grand Canyon Monitoring and Research Center to investigate those impacts and serve as the sole science voice among its powerful group.

Under the aegis of the USGS, the geologists, hydrologists, biologists, ecologists and other scientists of the GCMRC monitor the river and advise the AMP. During the past two decades the researchers have built a longitudinal data set to establish a baseline of life in the canyon. They devised experiments to explore declining fish populations and disappearing sandbars—all, ideally, without cutting into the needs of the other stakeholders. “Nobody had done ecosystem science and looked at the management of a dam before,” says Dave Wegner, a former Bureau of Reclamation ecologist who set up the GCMRC at its outset. “We were making it up as we went.”

It is easier to flexibly manage an ecosystem in the single-species fisheries where adaptive management was first conceived. In a nonlinear system as complex as the Colorado River, this iterative strategy is also a tension point—especially when any tweaks require consensus among 25 competing values. “We change something we can control, and then two things we can’t control very quickly change,” says geologist Ted Melis, deputy director of the Southwest Biological Science Center, which oversees the GCMRC. For instance, the GCMRC is currently trying to unpack a 1,000 percent increase in populations of predatory, nonnative brown trout since 2012. The spike happened around the same time as experimental high flows that were designed to build sandbars. But that is the point of adaptive management, Melis says: learning from the ecosystem shifts and responding to them.

LOOK TO THE BUGS

IN NOVEMBER 2017, several months before the weekend bug flow experiment began in the Grand Canyon, I joined Muehlbauer and David Goodenough, another researcher in Kennedy’s lab, to collect monthly samples of insect populations on the shore and in the river. If the GCMRC scientists can understand what is triggering the bug die-offs, they can explicitly show how factors such as flow and food webs are related—and why they must be considered in any management strategy for a rapidly changing future.

Kennedy has been studying Grand Canyon insects since 2002. He thinks that hydropeaking—that is, spiking flows up and down for power needs—is part of why scientists see minimal numbers of

Map by Mapping Specialists

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midges and almost no mayflies, stone flies or caddis flies, all of which are prevalent on other western rivers and were likely once abundant on the Colorado. His team modeled how insect egg-laying cycles responded to hydropeaking, and in 2016 the researchers released a paper hypothesizing that limiting the artificial tides created by dam releases—for even just two days in a row—would give bugs enough time to reproduce. Now Kennedy and his team are racing to test whether adjusting the flow toward a more natural state will restore and protect the Grand Canyon ecosystem in an increasingly drought-strapped, human-impacted river.

It is only recently that such an experiment could take place. In 2016, because both science and statutory responsibilities (such as additions to the endangered species list) had changed, the Bureau of Reclamation and the National Park Service revised the original environmental impact statement to allow for a broader range of experimental flows. The 2018 bug flow is the first test the GCMRC has tried within the new legal framework. It is timely work in the context of a global problem: a 2017 paper in *PLOS ONE* found that in Germany, flying insect populations have plummeted by 75 percent since 1990. The authors, led by Caspar A. Hallmann of Radboud University in the Netherlands, warned this drop would have cascading impacts on pollination and nutrient cycles across Europe—a scenario already playing out on the Colorado.

On a chilly November dawn, the researchers and I left the GCMRC offices in Flagstaff, Ariz., and drove down to the Lees Ferry boat ramp, which is 16 miles below the Glen Canyon Dam. In a jet boat named *Quicksilver,* we zipped up the black glass of the river toward the dam, then turned downstream into the throat of the Grand Canyon. Muehlbauer and Goodenough set four sticky traps—back-to-back petri dishes lined with adhesive and glued to aluminum stakes—at monitoring points approximately every mile to catch adult invertebrates. We passed through 21 miles of the canyon, taking drag samples of what is suspended in the water column to see how bug density and species diversity changed the farther we got from the dam.

There were almost no bugs on the river. None in our teeth or our eyes as we motored downstream. Nothing biting when we pulled up in tamarisk bushes to collect the sticky traps. When Muehlbauer pulled a sample stake and looked inside the petri dish, he was underwhelmed. "Oh, my God, David," he said, rolling his eyes at Goodenough. "We caught … midges!"

Later, they sorted through the samples in the lab, pulling out chironomine bodies with tweezers and tallying the different species, painstakingly adding to a 22-year record of the individual bug totals along the river. Kennedy hopes the data from the controlled flows during the summer of 2018 will reveal how the physical processes of dam releases impact the bugs. The researchers are worried that climate change, among other factors, is altering conditions faster than they can study them. But if the GCMRC can show that engineering the river to run more naturally makes the entire ecosystem more sustainable, it will emphasize the riskiness of new projects that threaten to divert even more water from the Colorado.

Take the Lake Powell Pipeline, for example. It would remove 86,249 acre-feet of water every year from Lake Powell—the man-made reservoir behind the Glen Canyon Dam—and divert it to two growing counties in southern Utah. The pipeline was first proposed in 2006 by the Utah Division of Water Resources, and in September 2018 the Federal Energy Regulatory Commission agreed to license the hydroelectric part of the project. As expanding communities try to claim every drop of water they are legally allotted, Kennedy is looking at how bugs are tied to the rest of the river system—and demonstrating how the AMP can manage for both in the face of less water coming downstream.

A HOTTER, DRIER FUTURE

GIVING SCIENTISTS A VOICE in water management has led to new insights about how the Colorado River reservoirs are suffering from climate change. Much of the news is alarming. A 2017 study, published in *Water Resources Research,* by climate scientists Brad Udall of Colorado State University and Jonathan Overpeck, then at the University of Arizona, found that average Colorado River flows in the 21st century were 19 percent lower than in the 20th. They predicted flows could drop by up to 55 percent by 2100 as a result of the effects of global warming. "If you've been paying attention, especially in the past two or three years, you should be frightened right now," Udall says, referring to how soon there might not be enough water to meet legal and environmental needs. In the Bureau of Reclamation's yearly water tally, which ends in September, the amount of water that flowed into the Colorado River Basin in 2018 was only 43 percent of the historical average.

The scientists want to present reasons for amending flows in the name of nature before it is too late to avoid ecosystem collapse.

There is also problematic math at Lake Powell. Because the Colorado's water is allocated down to virtually the last drop, the lake level is crucial to a 1922 legal compact that guarantees 8.23 million acre-feet of water will flow past Lees Ferry every year. The Bureau of Reclamation built reservoirs—including Powell—starting in the 1950s. But these storage systems only work if they are replenished. Lake Powell is considered "full" at 3,700 feet above sea level; the last time that happened was 1986. In 2002, the driest year on record, only 3.8 million acre-feet flowed into Powell from upstream on the Colorado. Because Lake Powell's entire purpose is to keep the downstream water supply consistent even when it does not rain or snow, the legally obligated 8.23 million acre-feet still went out.

This logic, however, is fundamentally flawed. The compact water was allocated based on calculations done by the Bureau of Reclamation in the early 1900s, the wettest recorded period in measured history, which concluded that 18 million acre-feet of water flowed through the river basin every year. Data collected from USGS river gauges installed at Lees Ferry in 1922 have showed that average yearly flows are actually 14.8 million. Because the compact is federal law, the 8.23 million acre-feet of downstream obligations still stand. Water managers call this a

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CLIMATE CHANGE is accelerating a nearly 20-year drought at Lake Powell; the first ever cutbacks to downstream water allotments could occur as soon as 2020.

ADRIA PHOTOGRAPHY *Getty Images*

structural deficit, and it means that if every state claims its entire share—a near-future scenario thanks to projects like the Lake Powell Pipeline—there will not be enough to go around.

The accelerating drought has become so threatening that in 2018, seven "basin states" drafted contingency plans. Each state outlined how much of its allocated compact water it would leave in reservoirs if Lake Powell's level hit 3,525 feet above sea level—just high enough to comfortably maintain power production at the dam. (In November 2018 Powell was at 3,588 feet.) Although interim guidelines came out in 2007, this official step marked the first time since the compact was signed nearly 100 years ago that the basin states made a legally enforceable plan for a drier future. Finally, policy is starting to reflect science.

This shrinking volume of water also makes experimentation more difficult to pull off. "Everything we do within the Adaptive Management Program has to work within the annual volume of release," says Katrina Grantz, former Upper Colorado region chief of the AMP. The GCMRC researchers have considered any reasonable options that would increase the supply. One long-standing and controversial idea is to remove the Glen Canyon Dam altogether, then store the reservoir's water in Lake Mead to minimize evaporation. But so far neither science nor policy supports removal. A 2016 white paper by John C. Schmidt, a geomorphologist at Utah State University and a former head of the GCMRC, found that any water savings from consolidating reservoirs would be less than 1 percent of the average inflow. It is impossible to untangle the human uses of the river without upending life in the Southwest, Schmidt explains. "Sometimes we are agreeing to compromise the environmental health of the rivers to provide utilitarian benefits," he says.

RACING TO ADAPT

AS AN IMPENDING WATER CRISIS DAWNS, the GCMRC scientists are trying to experiment as much as possible. They want to present concrete reasons for amending flows in the name of nature before it is too late to avoid ecosystem collapse. In Kennedy's "encouraging" preliminary results from the bug flows, he says his team saw more than twice as much larval emergence in May 2018 as it has in any month it has monitored over the past seven years. On these "bug flow weekends," the researchers found millions of rinds of spaghettilike midge egg casings on the banks. The Arizona Game and Fish Department's creel survey reported that fishing catch rates were up, and anecdotally, river runners and fly-fishing guides complained that it was buggier than usual. "These findings are a powerful reminder that flows really do matter," Kennedy says.

This success represents a promising step toward increased experimentation and variable flows on the Colorado River. Kennedy hopes it convinces the AMP to green-light another year or two of bug flows. But it could have wider implications, too. The AMP is starting to become a global model for managing dam operations while balancing the competing demands of ecosystems, energy and irrigation. Over the past 20 years, Melis says, hydrologists and engineers from planned dams in the Brazilian Amazon—as well as researchers from Japan, China, Canada and other Bureau of Reclamation projects in the U.S.—have come to Arizona to learn from and share information with the AMP.

The collaborative, long-term thinking of adaptive management can seem idealistic. Melis refers to a "potpourri" of resources the scientists must consider as they try to find the connections that will restore ecosystem health. But in the changed and changing Colorado River system, there is plenty that still feels wild, even if it will take precise management to keep it seemingly so.

When Muehlbauer, Goodenough and I came back to the boat launch after a day of collecting bug samples, the late November sun was casting shadows on the canyon walls. The temperature was rapidly dropping. We were the only humans around as bats circled and clicked in the coming dark. But far down the grid, people across the Southwest were coming home from work and turning on their lights. The river had come up to meet them. SA

MORE TO EXPLORE

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FROM OUR ARCHIVES

Change of State. Dan Baum; August 2015.

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Leading the way at Albert Einstein College of Medicine (clockwise from left): Trudy Schlachter; Ana Maria Cuervo, M.D., Ph.D., Robert and Renée Belfer Chair for the Study of Neurodegenerative Diseases; Terri Goldberg; and Chinazo O. Cunningham, M.D., M.S., Professor, Department of Medicine

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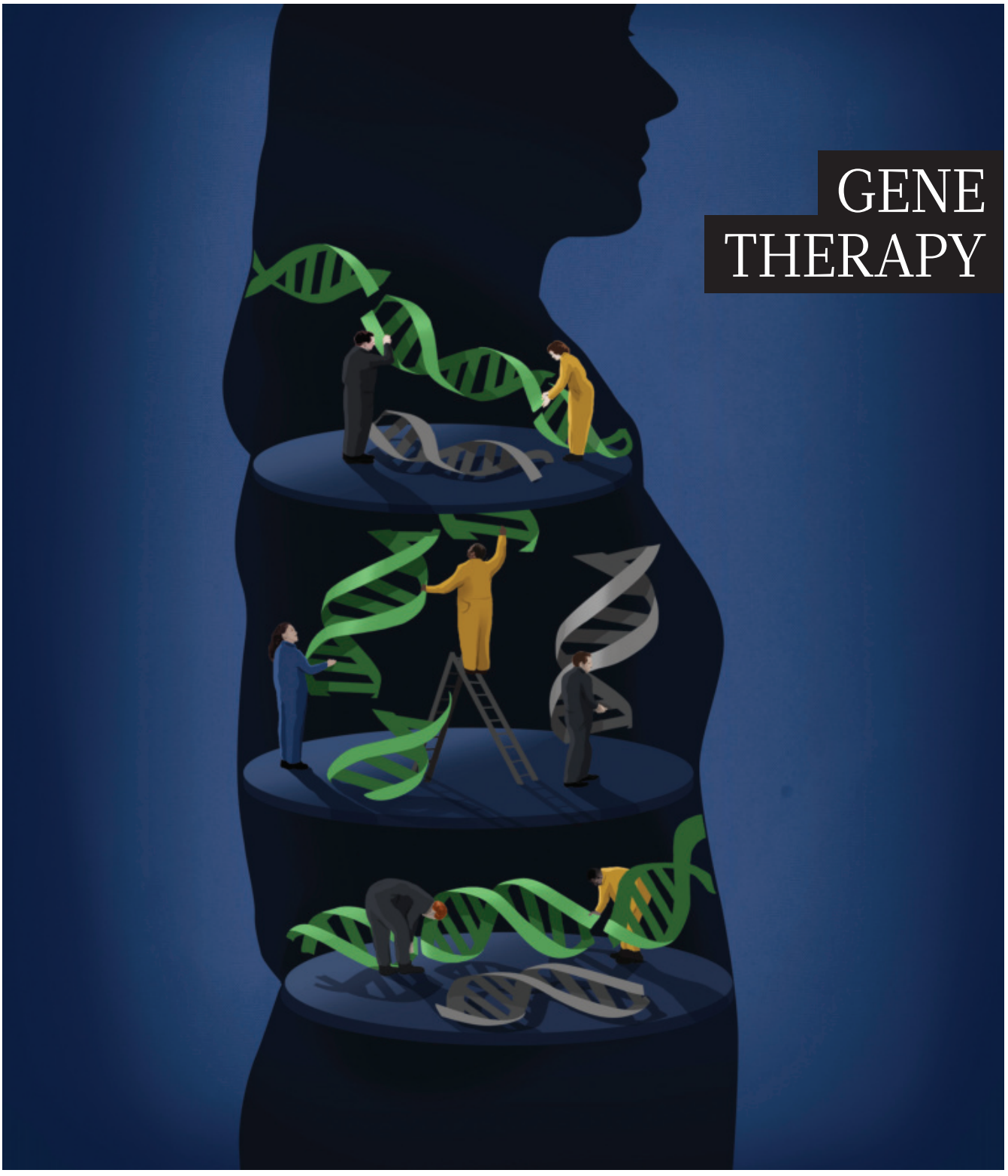

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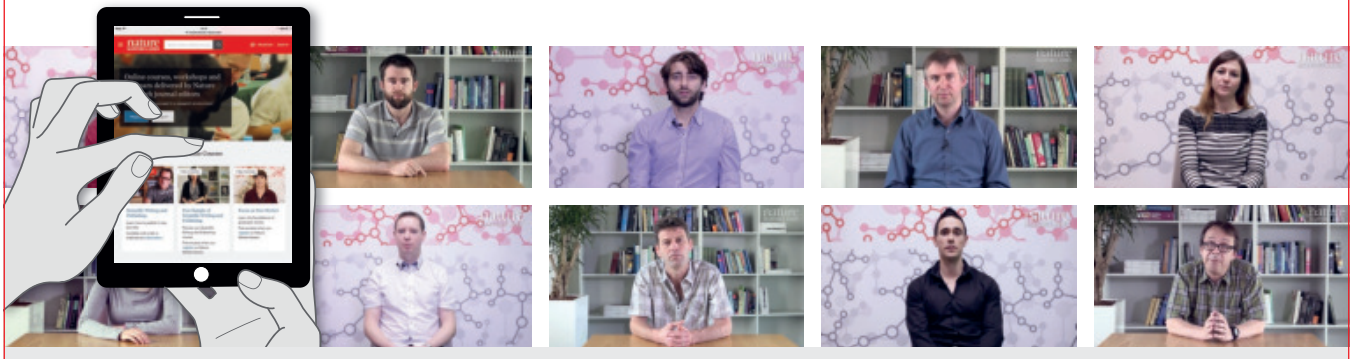

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Pharmaceuticals cannot always fix a malfunctioning human body. Sometimes the only way to treat what ails a person is to tinker with their genes: the blueprints for how biological systems are built and how they operate. Some researchers are using gene-editing techniques such as CRISPR to precisely alter DNA sequences. Others are genetically modifying immune cells to imbue them with the ability to fight cancer. And in the past couple of years, there has been a rapid acceleration in the development of a wide range of treatments in which disease-causing genes are replaced in their entirety.

This Outlook therefore focuses on the rich assortment of research in which new genes are introduced into a person, usually by means of a viral vector (see page S16). Successful animal experiments indicate that human genetic disorders could one day be repaired in the womb, so that a baby might enter the world disease-free (S4). And a number of health issues that have proved difficult or impossible to remedy — such as sickle-cell disease (S10), epilepsy (S8) and certain intractable skin conditions (S12) — might be excellent targets for gene therapy.

But gene therapy need not be limited to diseases that originate from genetic abnormalities. It might be possible to treat some viral infections with DNA, by using it to prompt the body into creating just the right monoclonal antibodies to ward off invading pathogens (S14).

Gene therapy remains an expensive medical path, however. Moving it out of the laboratory and into the clinic will require innovative pricing schemes (S21) and regulatory policies (S18). Along the way, clinicians, patients and policymakers will grapple with tricky ethical questions (S7).

We are pleased to acknowledge the financial support of Pfizer Inc. in producing this Outlook. As always, *Nature* has sole responsibility for all editorial content.

Herb Brody
Chief supplements editor

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NEONATOLOGY

The fix is *in utero*

Some genetic diseases cause damage even before a child is born. The answer to these devastating conditions could lie in gene therapy delivered while the baby is still in the womb.

JOHN FEDELE/GETTY

Hereditary disorders that are discovered during prenatal scans could one day be cured before birth.

BY SARAH DEWEERDT

In July, an international team of researchers reported that they had used gene therapy to correct a fatal brain disorder in mice — before the mice were even born[1].

The mice had a defect in a gene known as *GBA*, which encodes an enzyme responsible for breaking down a fatty molecule called glucocerebroside. Without the enzyme, glucocerebroside builds up in the brain, causing irreversible brain damage. The mice typically die within about 14 days of birth.

The mice model a condition in humans called acute neuronopathic Gaucher's disease. Children born with this genetic mutation rarely live past the age of two.

In the study, researchers injected a virus bearing an intact copy of the *GBA* gene into the brains of fetal mice about mid-way through gestation. The treated mice were born normally, and lived for at least 18 weeks with little evidence of brain pathology. "You're talking about prolonging life significantly," says Jerry Chan, a fetal-medicine specialist at Duke-NUS Medical School in Singapore and an author of the study.

The researchers also administered the gene therapy to healthy macaque fetuses, and showed that it could transform brain tissue without serious side effects in an animal model that more closely approximates the body size and pregnancy physiology of humans.

"What we were trying to do is show the best possible experiments that would justify, if there ever was, a path to human clinical translation," says study leader Simon Waddington, a gene-therapy researcher at University College London.

Other researchers in the small field of prenatal gene therapy see the research as a leap forward, and say it provides the strongest evidence yet that the approach could be feasible in humans. "The combination of those two aspects of the study made it very, very exciting," says Bill Peranteau, a fetal surgeon at the Children's Hospital of Philadelphia in Pennsylvania.

The technical challenges, safety concerns and ethical issues of prenatal gene therapy are substantial. But this approach is more than just hotshot medicine. It could be the best way to treat a select group of devastating genetic diseases — and perhaps the only way to achieve a lasting cure.

EARLY ADVANTAGES

Acute neuronopathic Gaucher's disease is one of the best candidates for treatment with prenatal gene therapy. That's because the build-up of glucocerebroside begins in the fetus. In the absence of any intervention, irreversible brain damage can occur even before birth. "The

main advantage is preventing the damage from occurring in the first place," Waddington says.

With other genetic diseases, the effects might not begin until sometime in infancy or early childhood. But even then, prenatal gene therapy might be more effective or efficient than waiting until after birth. "You are trying to take advantage of the normal developmental properties of the fetus to increase the efficiency and the likelihood of success of the treatment," says Peranteau, who is working on animal studies of prenatal gene therapy for metabolic diseases affecting the liver.

Before birth, the blood–brain barrier that prevents many molecules from crossing from the bloodstream into brain tissue is immature, a situation that eases delivery of genes to the central nervous system. In a 2011 paper[2], Waddington and his colleagues showed that a gene-therapy vector called AAV2/9 reaches nerve cells in the brain much more reliably in fetal mice than in those already born.

Another advantage of prenatal intervention is that the immune system is still immature. Therefore, the packaging used to deliver gene therapy — whether a virus or another type of vector — might be less likely to cause an adverse reaction. Also, the body develops immune tolerance to the vector, so if a gene therapy 'booster shot' needs to be administered later in life, it is more likely to succeed. The immune system will also accept the normal protein encoded by the gene therapy, rather than destroying it — as has sometimes been seen with postnatal gene therapy and protein-replacement therapies.

In addition, rapid fetal growth and development means more bang for the gene-therapy buck. At any given time, a large proportion of cells in the fetus is actively dividing. That yields a greater likelihood of the vector integrating into the genome. The population of corrected cells will continue to expand throughout gestation. Furthermore, to effect a cure, it is important to get replacement genes into stem cells or progenitor cells — and these long-lived cells are more abundant and more accessible before birth.

Finally, a 20-week fetus weighs roughly 300 grams, whereas a newborn tips the scales at around 3.5 kilograms. That small size translates directly into a higher therapeutic effect from a given dose of treatment. That's a big advantage because gene-therapy products can be expensive and laborious to produce.

A RISKY BUSINESS

But the fetal time period also poses unique challenges. Any prenatal intervention is complex because it affects two people — the mother and the fetus. "You've always got to take both into consideration, and you've also got to think about the future children of the mother herself," says Anna David, a fetal-medicine specialist and gene-therapy researcher at University College London.

Generally, the delivery of prenatal gene therapy is fairly straightforward. It involves injecting the treatment into an umbilical blood vessel, the amniotic fluid or occasionally directly into fetal tissue — often with the guidance of an ultrasound probe. The techniques are similar to well-established methods used in amniocentesis, chorionic-villus sampling or umbilical-vein blood transfusion.

"The procedures themselves are relatively safe," says David. Still, they do come with a small risk of infection, preterm labour and loss of the pregnancy. All in all, she says, "it's going to be a lot safer, probably, to treat it after the baby is born when you've got the baby and you're not risking the mother".

Then there are the usual risks involved in gene therapy, such as the potential for the vector to provoke an immune reaction in the patient, or incorporate into the genome in a location where it could trigger cancer. Some of these risks are magnified in the prenatal setting. For example, if the gene therapy gets into the mother's bloodstream, it could cause a dangerous immune reaction in her body or even be incorporated into her cells.

In the fetus, especially if given early in development, the gene therapy could alter germ cells that will eventually develop into eggs and sperm, causing changes that could be passed down to eventual offspring — a possibility that many scientists consider ethically problematic. The therapy might also disrupt normal body-system development by triggering the expression of genes in an inappropriate place or at an inappropriate time. That could potentially cause lasting effects, such as organ malformation.

Parents facing an *in utero* diagnosis of a serious genetic condition must often decide whether to raise a child with a lifelong disability or terminate the pregnancy. The appeal of prenatal gene therapy is that it offers a potential third path. But these treatments also raise the stakes: what if the gene therapy doesn't work, leaving parents with a seriously ill child they weren't prepared for and would not have chosen to raise? Similarly, a gene therapy that is only partially effective could turn a disease that previously would have been fatal in infancy into one that results in long-term disability — so it could actually increase suffering for the patient and family.

As a result of such concerns, researchers are cautious about the prospect of attempting prenatal gene therapy in humans. "If there is an adequate treatment for something after birth, that is the way to go," Peranteau says.

ORIGIN STORY

Even so, scientists have been thinking about prenatal gene therapy for nearly as long as they have been working on postnatal gene therapy. The first proof-of-concept studies[3] in animal models, showing that a gene could be introduced into an organism before birth, were published in 1995 — just a couple of years after the first human gene-therapy trial.

Often, scientists have looked to the prenatal window not just for the opportunity to treat diseases that begin before birth, but as a way around some of the difficulties of postnatal gene therapy. Charles Coutelle at Imperial College London, says that what prompted him to enter the field in the mid-1990s was, "to be quite frank, frustration with the efficiency of gene therapy at the time".

Coutelle had been involved in one of the first human trials of gene therapy for cystic fibrosis, a genetic disorder that affects the lung and other organ systems. It was difficult to deliver gene therapy to the lungs of people with cystic fibrosis because even in young children, the airways were full of viscous mucus and scar tissue; immune-system dysfunction also presented a hurdle. Coutelle thought it might be easier to correct cystic fibrosis *in utero*, when amniotic fluid moves freely in and out of the lungs.

"You are trying to take advantage of the normal developmental properties of the fetus."

Coutelle and his team spent several years perfecting fetal transfer techniques in mouse models, as well as working out which vectors would be best to use prenatally against cystic fibrosis or other serious diseases. The first big success — and an achievement that remains significant today — came in 2004. That year, a group including Coutelle and Waddington corrected the bleeding disorder haemophilia B in prenatal mice by injecting them with a virus bearing an intact copy of factor IX, a protein involved in blood clotting[4].

But the team soon had to switch gears. One vector used in the haemophilia work yielded only a temporary cure; another produced more lasting results but led to an increased risk of liver tumours. More importantly, the development of postnatal gene therapy for haemophilia had taken a sudden leap forward. "Once you have an established postnatal gene therapy there's no point in doing it prenatally. Or you have to have good reasons for doing it," Coutelle says.

A SURFEIT OF TARGETS

Waddington decided to look for a more challenging target disease that causes more severe effects earlier on, which led him to Gaucher's disease. But that is just one of a fairly broad array of metabolic disorders, including Tay–Sachs disease, Niemann–Pick disease and mucopolysaccharidosis, that cause *in utero* damage and could therefore be good targets for prenatal gene therapy.

Other researchers argue that haemophilia remains a good prenatal target. Researchers led by Graça Almeida-Porada and Christopher Porada at Wake Forest University in Winston-Salem, North Carolina, are working with a sheep model of haemophilia A. This form of haemophilia accounts for about 80% of haemophilia cases in humans, but has proven

much more difficult to address with postnatal gene therapy than has haemophilia B.

One major issue is that the protein involved in haemophilia A — factor VIII — is highly immunogenic. Many people with a severe form of haemophilia A develop antibodies against factor VIII, which makes replacement therapy more costly and complicated, says Almeida-Porada. "The goal of going prior to birth is that you would induce tolerance to the protein — these patients would never develop an immune response," she explains. The team aims to cure haemophilia A in fetal sheep by collecting stem cells from the amniotic fluid, correcting the factor VIII gene and infusing the cells back into the fetus.

Studies of prenatal gene therapy in animal models are a dance between practicality and possibility. They depend on the availability of animal models for a given disease, and are shaped by the pace of advances in postnatal therapy or other experimental treatments, such as *in utero* stem-cell therapy or bone-marrow transplantation.

In June, researchers at Yale University in New Haven, Connecticut, reported that they had corrected the inherited blood disorder β-thalassaemia in fetal mice[5]. The disease is caused by mutations in the β-globin gene, which encodes a subunit of haemoglobin, the oxygen-carrying protein found in red blood cells. In β-thalassaemia, haemoglobin is less able to carry oxygen, leading to fatigue, growth stunting and damage to organs.

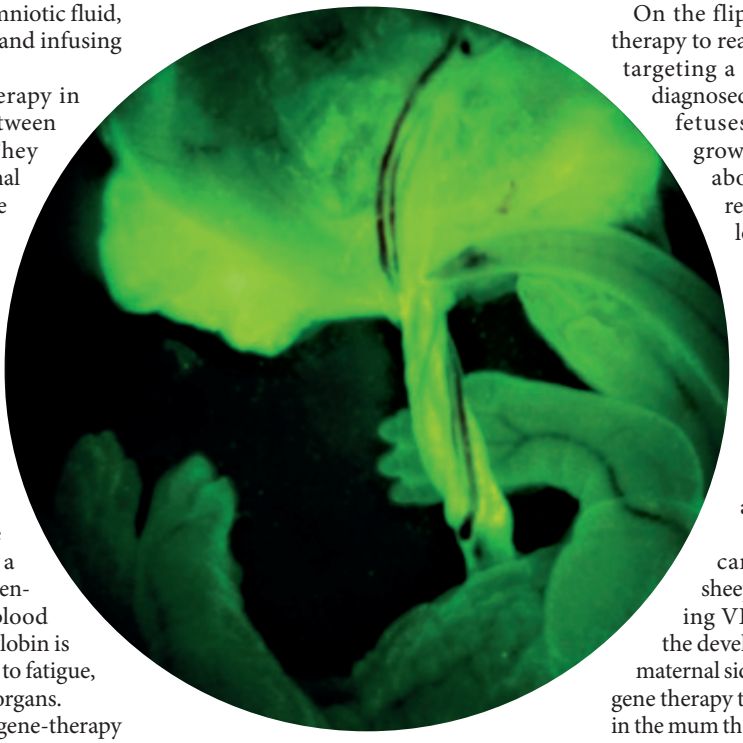
In the study, researchers used gene-therapy delivery vehicles called peptide nucleic acids (PNAs). PNAs are particles consisting of a biocompatible polymer surrounding an intact copy of the β-globin gene. "*In utero* injection of these molecules with a single injection was effective to achieve a phenotypic correction in the mice after birth," says study author Peter Glazer, a radiation oncologist and geneticist at Yale.

The PNAs make use of a cell's own DNA-repair mechanisms to incorporate the correct copy of the β-globin gene into the genome, potentially sidestepping some of the safety issues associated with gene-therapy delivery by viruses. And, crucially, the approach might be more effective prenatally than it is after birth. "In the developing fetus, the cells are more amenable to gene editing," Glazer says. "The DNA-repair capacity of the cells is revved up" because cells are dividing so rapidly, his team's data suggest.

Glazer envisions PNA-based gene therapy for thalassaemia or sickle-cell disease (another inherited blood disorder) being tried first in children, then infants and finally *in utero*. But how quickly this might happen is not clear. "For thalassaemia, a stem-cell approach is probably going to reach clinical practice much faster," says Chan. The safety of stem-cell or bone-marrow transplantation is better established than that of gene therapy, he says.

A BOON FOR RESEARCH

But even if prenatal gene therapy doesn't reach the clinic, it could still be useful as a research tool. That's already the case with cystic fibrosis, says Marianne Carlon, a gene-therapy researcher at the Catholic University of Leuven in Belgium.



ADELE RICCIARDI/DAVID STITELMAN LAB/YALE

Fluorescent nanoparticles reveal a mouse fetus, umbilical cord and placenta.

Carlon and her colleagues have found that gene-therapy vectors can distribute more evenly through the lungs of fetal pigs than through the lungs of newborn pigs. The question is whether such even distribution is necessary or whether just reaching the large- and medium-sized airways is sufficient to prevent the lung damage in cystic fibrosis. *In utero* studies in animal models could also help to resolve questions about which cell types in the airways need to be targeted for gene therapy to be effective in cystic fibrosis.

"We would rather start in a neonatal setting" for attempting gene therapy on cystic fibrosis, Carlon says. Then, she adds, it would make sense to "move towards a fetal setting if you really see that you have difficulties targeting the right cell".

One reason that prenatal gene therapy for cystic fibrosis is not likely to be practical is that *in utero* screening for the disease is not widespread. As a result, the diagnosis is rarely made until after birth. "Without a prenatal diagnosis there is no prenatal gene therapy," Coutelle says.

Clinicians would need to be able not only to detect a disease before birth, but also to confidently predict that its severity would be sufficient to warrant gene therapy. These are complex questions that aren't fully resolved for all the prenatal target disorders. However, if there is no prenatal treatment for a disease, there might be little point in identifying it *in utero*.

Waddington's attitude is simply to bypass this catch-22 situation. "We'll develop the cures, and then that justifies doing the diagnoses," he says.

On the flip side, the first prenatal gene therapy to reach human trials might be one targeting a condition that is exclusively diagnosed *in utero* because it only affects fetuses before birth. Intrauterine growth restriction (IUGR) affects about 3% of all pregnancies and results in babies with dangerously low birth weight.

Unlike other prenatal gene therapy targets, IUGR is not a single-gene disorder. It occurs when, for unknown reasons, the normal remodelling of uterine arteries during pregnancy does not occur. That leaves the placenta and developing fetus starved of blood and nutrients.

David has shown that IUGR can be alleviated — at least in sheep — by delivering a gene encoding VEGF, a protein that stimulates the development of blood vessels, to the maternal side of the placenta[6]. "We're giving gene therapy to the mum, to treat a condition in the mum that causes a problem in the fetus," David says.

VEGF is expressed for only about a week, but that's long enough to trigger expansion of the placental vasculature. A similar approach has been used to stimulate the growth of blood vessels in the heart and neck, so the therapy, known as therapeutic angiogenesis, is well established postnatally. David has applied for regulatory and ethical approval to conduct a trial of the therapy in pregnant women.

"It's a major cause of cardiovascular disease and diabetes later in life," David says, referring to IUGR. "There's no treatment. And women want it, when you ask them. They're desperate to have a treatment." ■

Sarah DeWeerdt *is a science journalist in Seattle, Washington.*

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PERSPECTIVE

A genetically augmented future

Gene therapy could one day be used for bodily enhancement, creating an ethical minefield for physicians, says **Ellen Wright Clayton**.

The year is 2030. Gene therapy to insert the DNA sequence for dystrophin has been approved by regulators and is commonly used in children with Duchenne muscular dystrophy (DMD), a disorder linked to the X chromosome. Evidence shows that the intervention increases muscle mass in anyone who receives it. The treatment is widely available, but very expensive.

Alex, a slender adolescent, walks into a physician's office, accompanied by well-to-do parents. Alex does not have DMD, but wants to be stronger. Exercise is not providing enough benefits, and anabolic steroids have too many side effects. Alex is adamant about wanting dystrophin gene therapy and accurately cites its risks and benefits. Alex's parents are willing to pay for the treatment.

The cure for DMD described previously represents a cherished goal for gene therapy, and there is a lot of public support for fixing such heritable disorders in this way[1]. Yet Alex's request raises a host of questions.

We do not know why Alex wants to be stronger. Alex could have a milder form of muscular dystrophy or, if female, could be a carrier who experiences milder symptoms of DMD[2]. Alex might have some other cause of muscle weakness — or might want to be stronger for the sake of appearance, or to be more competitive in athletics. As is the case for many medical interventions, the potential uses of this therapy go beyond the specific disease for which it was developed. Possible applications range from treating milder disease to improving human characteristics — a continuum that could lack clear boundaries.

Let's assume that Alex does not have a diagnosed physical problem and wants the therapy simply to become stronger. The main debate about using medical interventions for such bodily enhancements focuses on the extent to which they give individuals an advantage over other people. A 2017 report by the US National Academies on gene editing in humans captures the debate well[1]. The authors summarize surveys that show that most people disapprove of using gene therapy to improve a person's physical and intellectual characteristics. The public tends to honour narratives of success based on personal diligence, or even accident of birth, over traits that can be purchased. This preference touches on a larger issue: the extent to which uses of gene therapy would exacerbate social inequality. If there is a widespread perception that this would be the result, society might try to limit its use to the few people who genuinely need it to treat their disease. Or there might be an effort to make such therapies available to all who want them.

Back to Alex in the world of 2030. Assuming that the US Food and Drug Administration's regulations are still the same, physicians would be free to use the approved DMD intervention for any purpose. After all, many medicines are legally prescribed for reasons that have nothing to do with their original indication. So what should happen? How hard should a physician try to understand the source of Alex's desire to be stronger?

Alex's wish might be a product of the social and cultural environment. The request might reflect issues with self-image. The desire to be stronger could reveal a psychological problem that needs to be resolved. Or a physician could conclude that Alex is suffering, thereby making the case for gene therapy more compelling. For example, medical and surgical interventions are sometimes prescribed to prevent or relieve psychological distress in children or young people who are abnormally short[3] or who have potentially stigmatizing physical features[4]. It is important to ensure that Alex understands and agrees to the therapy, but in the end, it can be hard to ascertain the source of a person's desire for a given treatment — especially if the person is an adolescent.

Are Alex's parents wrong to support their child's desire? Perhaps they are putting undue pressure on Alex. Perhaps they want to alleviate Alex's distress. Perhaps they are just indulgent. Society's default position is that parents should have the last say in such matters because they are assumed to care more for their children than does anyone else. Parents have a responsibility for shaping their children's future, creating opportunities and drilling into them all sorts of values. Parents are largely free to pursue their vision for their children's lives, unless those actions are illegal or constitute abuse or neglect.

CONCERNS ABOUT EQUITY SHOULD LEAD SOCIETY TO DEVELOP GUIDELINES FOR GENE THERAPY TO AVOID A NIGHTMARE FUTURE.

So what is the physician to do? Assuming that gene therapy for enhancement has not been outlawed, he or she can and should turn to medical ethics and the goals of medicine[5] for guidance. Respect for persons — a fundamental principle of medical ethics — would direct the physician to attempt to discover more about what is driving the patient and their parents' wishes, and to ensure that they understand what is at stake and that their expectations are realistic[6]. If the decision to proceed was made to relieve suffering, and with the adolescent's informed assent and the parents' permission, pursuing the goals of medicine would lead the physician to use the therapy to confer only traits within the normal range of human characteristics.

Ultimately, the ethics of enhancement are intertwined with views of fairness. Concerns about equity should lead society to develop guidelines for gene therapy to avoid a nightmare future in which a group of privileged people becomes stronger, smarter and more beautiful than the rest. But because drawing lines between treatment and enhancement is difficult, the more likely and more unsettling scenario is that physicians will be left to rely on their own ethical commitments to decide when to use gene therapy. ■

Ellen Wright Clayton *studies medical ethics and health policy at Vanderbilt University Medical Center in Nashville, Tennessee.*
e-mail: ellen.clayton@vanderbilt.edu

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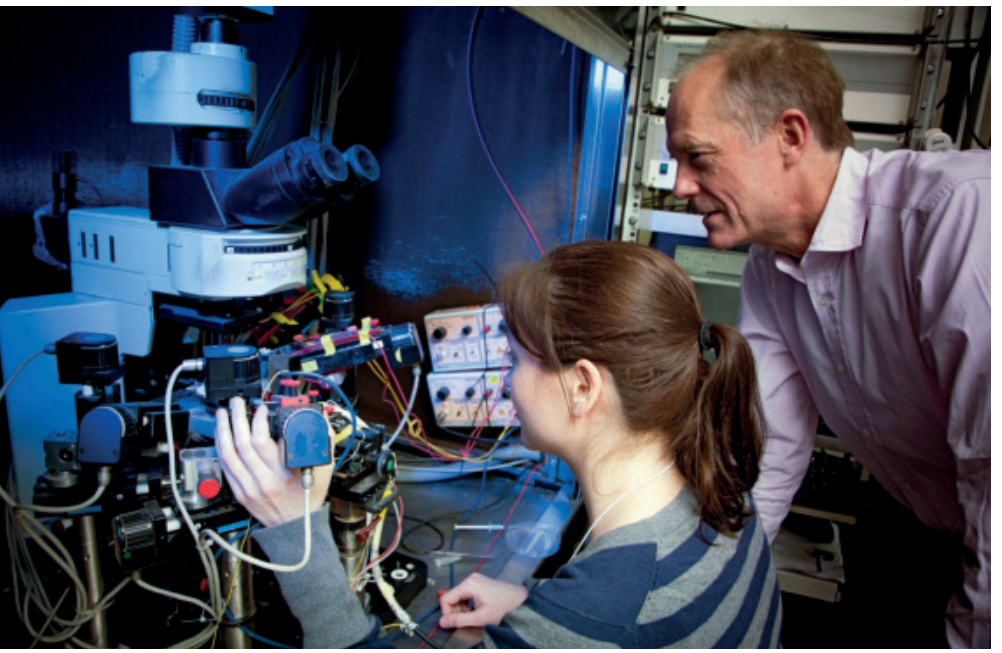


DAVID BISHOP/UCL HEALTH CREATIVES

Elizabeth Nicholson and Dimitri Kullmann at University College London.

NEUROLOGY

Repairs for a runaway brain

Gene therapy could damp down epilepsy seizures in people for whom current drugs are ineffective.

BY LIAM DREW

The seizures of around one-third of people with epilepsy are resistant to available medicines — a statistic that haunts neurology. It has been this way for decades. The medicines have got better by becoming safer and causing fewer side effects. But still there are people for whom the drugs simply don't work — and for them, epilepsy can be ruinous.

"There's stigma; they can't drive; they have difficulty holding down jobs; they have difficulty maintaining relationships," says Dimitri Kullmann, a neurologist and neuroscientist at University College London (UCL).

Currently, the main hope for people with severe drug-resistant epilepsy is surgery. Someone whose seizures arise from a well-defined region of the brain might be offered an operation to remove that region. This is a drastic procedure, but not especially rare; it is carried out about 500 times every year in the United States.

Kullmann is hoping that gene therapy can make such surgery unnecessary. His group and others are investigating the potential benefits of introducing different genes into the brains of people with epilepsy, each one selected to quell the rampage of electrical activity that causes epileptic seizures. The most advanced projects are now being readied for clinical trials.

EXCITATION AND INHIBITION

Epilepsy comes in many forms. It is defined by the repeated occurrence of seizures — but these seizures can vary in their nature, intensity and frequency. And the disorder can arise from numerous causes, progress in different ways and affect distinct parts of the brain.

Crucially, epilepsy can either be focal, with seizures beginning in a specific brain region, or generalized, with seizures developing across wide spans of the brain. Focal epilepsy is more common, and it can be further subcategorized according to whether the seizures remain focal or spread to become generalized. There is also variation in the size of the seizure-generating focus and whether it is discrete, and therefore potentially removable, or enmeshed with vital brain tissue, and thus inoperable.

Brains essentially work by relaying electrical signals from neuron to neuron through the release of chemical neurotransmitters. Excitatory neurons release neurotransmitters that electrically stimulate neighbouring cells, whereas inhibitory neurons release neurotransmitters that suppress electrical activity. A seizure is a period of runaway electrical activity during which the normal balance between excitation and inhibition is lost. Current anti-seizure drugs either dampen excitatory mechanisms or boost inhibitory ones. But they do so indiscriminately, producing wide-ranging side effects by affecting neural circuits throughout the nervous system.

Current gene-therapy strategies, by contrast, use harmless viruses to introduce one or two therapeutic genes into the defined volume of tissue from which focal epilepsy emanates. "It is more personal, more targeted, and probably has fewer side effects because we treat the tissue that needs to be treated, instead of treating the whole body," says Merab Kokaia, a neuroscientist working on this approach at Lund University in Sweden. The strategies in development target focal epilepsy, but treating generalized epilepsy is a longer-term possibility.

RESTORING BALANCE

The brains of people with epilepsy contain increased amounts of neuropeptide Y (NPY), a chemical that certain neurons release when they are especially active. NPY acts on five receptors, Y1 to Y5, some of which are excitatory and some inhibitory. The levels of some of these receptors are also altered in epilepsy: notably, levels of Y2, which strongly inhibits neurotransmitter release, are higher. Overall, the accumulation of NPY and the altered levels of its receptors seem to represent an adaptive response — an intrinsic bid to hold back runaway brain activity.

In 2004, investigators used a viral vector to deliver the *NPY* gene into the brains of rats that had been manipulated to display a form of epileptic activity[1]. The resulting overexpression of NPY caused a reduction in seizure frequency. Other animal experiments also showed that overexpressing the neuropeptide galanin likewise suppressed seizures.

Kokaia, who was already working on NPY and epilepsy at the time, became interested in the therapeutic potential of this approach and started experimenting with introducing genes for neuropeptides, their receptors or both. He found that overexpressing NPY alone decreased seizure frequency, but simultaneously overexpressing it with the inhibitory Y2 receptor dramatically heightened the anti-seizure effect[2]. "What we are trying to do is boost the natural response of the brain by gene therapy," says Kokaia.

In 2015, Kokaia co-founded CombiGene in Lund, Sweden, to commercially develop this technique. In the past two years, CombiGene has confirmed the anti-seizure effects of the NPY–Y2 combination therapy, now called CG01, in further rodent models of epilepsy. And the company has successfully introduced the NPY and Y2 genes into brain tissue that was surgically removed from people with epilepsy.

Experiments using such tissue also ended

ESTHER KROOK-MAGNUSON

interest in the second neuropeptide, galanin. Whereas NPY suppressed neurotransmission in human tissue, galanin did nothing — human neurons lack functional receptors for it.

Kullmann's move into the epilepsy field was serendipitous. His group was investigating the voltage-gated potassium channel Kv1.1 — a type of ion channel that electrically quiets neurons — as part of work on an entirely different neurological condition, episodic ataxia. The group made a virus that transferred the Kv1.1 gene into neurons. Because a neighbouring laboratory was routinely using rodent models of epilepsy, Kullmann and colleagues thought it might be worth testing Kv1.1 in these animals. The effect, published in 2012, was a dramatic reduction in seizure frequency[3]. After seeing this effect in three separate animal models, Kullmann and UCL colleague Stephanie Schorge developed a viral vector that introduces a modified Kv1.1 gene specifically into excitatory neurons, and does not integrate the gene into the cell's genome.

In principle, CG01 or Kv1.1 could provide long-term suppression of epileptic seizures following a single injection, with the genes continually generating products that calm the neurons in which they are expressed.

TRIGGERED ACTIVATION

Several alternative approaches are mainly based on converting widely used basic-research technologies into clinical tools. These approaches are more complicated, but hold potential advantages over CG01 or Kv1.1.

Opsins, for example, are membrane proteins that are activated by light, and the genes encoding them have been isolated from microorganisms. When illuminated, some types excite neurons, whereas others inhibit them. The big appeal of opsins is that they could remain inert in neurons when brain function is normal and only be called into action when needed.

Esther Krook-Magnuson, a neuroscientist at the University of Minnesota in Minneapolis, has shown that opsins can control seizures in rats[4]. Her team introduced inhibitory opsins into the rats' epileptic foci, then implanted seizure-detecting electrodes into their brains, along with fibre optics that light up to activate the opsins. An algorithm switched on the light when it detected the first signs of epileptic activity, quashing seizures early. Krook-Magnuson notes that implanting electrodes and light sources into humans would be less invasive than the current option of removing an area of brain.

However, this system requires a reliable seizure-detection method, an effective light-delivery technique and a way to get the right amount of virus into the right neurons. All three components will have to be optimized before the system has a chance of reaching the clinic.

The need to develop more than one technology can put off potential investors, says Kullmann. He has first-hand experience of this from trying to transform another research tool — DREADDs (designer receptors exclusively activated by designer drugs) — into a therapy. DREADDs are genetically engineered receptors that, like opsins, sit silently in neurons unless they are activated by a stimulus, but in this case, the stimulus is a drug rather than light.

Both Kullmann and Kokaia have found that inhibitory DREADDs can suppress seizures when the genes encoding them are inserted into the seizure foci of epileptic animals using viral vectors. If the therapy were translated to humans, people might take the activating drug regularly in a similar way to current epilepsy medicines — but with the advantage that the DREADDs would not inhibit brain tissue outside the region where the DREADD is situated. Alternatively, people might receive the drug automatically through an implanted, seizure-activated drug-delivery system, or simply take the drug when they feel the first indications of a seizure.

Kullmann is also exploring an ion channel that was originally identified in nematode worms. In nematodes, the glutamate-gated chloride (GluCl) channel is inhibitory and is activated by the neurotransmitter glutamate. But in mammals, glutamate is the main excitatory neurotransmitter that is responsible for driving excess activity during seizures, and none of its receptors is inhibitory.

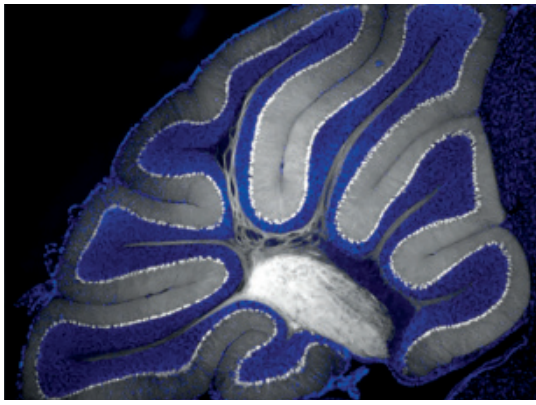
Kullmann and his colleague Andreas Lieb were interested in using an engineered version of the GluCl channel that is activated by a drug, but then they learnt that mutations in GluCl can change its glutamate sensitivity. If they picked a mutated channel that was insensitive to normal levels of glutamate, but activated by the high levels of glutamate that occur during seizures, they might have an appealing gene-therapy agent: an inhibitory ion channel that is ordinarily inactive but called into action during seizures. Early findings are encouraging: in two rat models, GluCl decreases seizure frequency[5].

PRIMED FOR CLINICAL TRIALS

In January, CombiGene partnered with the London-based incubator Cell and Gene Therapy Catapult to develop manufacturing processes for CG01 in preparation for clinical trials. And in April, Kullmann and Schorge received nearly £2 million (US$2.5 million) from the UK Medical Research Council to move the modified Kv1.1 virus towards the clinic.

Several technical hurdles remain, including scaling up the drug-delivery system: a human brain is around 700 times larger than the rat brains in which the viral vectors have been tested. But a major advantage of using NPY, Y2 and Kv1.1 is that they are derived from human genes — and therefore unlikely to evoke an immune response. By contrast, microbial opsins and GluCl from nematodes carry the risk of rejection by the immune system.

The hope is that gene-therapy treatments will be applicable to all drug-resistant focal epilepsies, including in people whose larger or awkwardly located foci make them ineligible for surgery, says CombiGene chief executive Jan Nilsson. And, more speculatively, if it is successful, gene therapy could potentially be adopted by some people instead of conventional drugs.



Brain cells could be manipulated using light.

But for the time being, CombiGene and Kullmann's team are planning safety and tolerability trials that will involve only people with drug-resistant epilepsy who are awaiting surgery. This is not because people in this group are the sole intended recipients of gene therapy — rather, they present a unique opportunity.

"What we are trying to do is boost the natural response of the brain by gene therapy."

The virus is likely to be given during presurgical investigations of the seizure locus, then allowed to enter neurons and deposit its genetic cargo while the patient spends weeks to months awaiting surgery. In phase I trials, surgeons will then almost certainly remove the focus. This procedure will allow researchers to carefully examine whether the gene delivery worked, and will also provide a fail-safe mechanism for excising genetically modified tissue should any safety issues arise.

The alternative is that people could opt out of surgery. If gene therapy is to be approved for epilepsy, numerous larger, more stringently controlled trials specifically designed to look at anti-seizure effects will be needed. But Kullmann allows himself to imagine a best-case scenario with the first exploratory trial. Someone who has stopped having seizures after the gene transfer, he says, might simply elect not to have surgery — entering a realm where their seizures are quelled not by conventional medication, but by DNA. ■

Liam Drew *is a freelance science writer in London.*

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STEVE BABULJAK/UCSF

Six-year-old twins Tylee and Taleeke both have sickle-cell disease.

BLOOD DISEASE

Medicine is in the blood

Sickle-cell disease is an ideal target for gene therapy, but economic and social barriers to treatment are rife.

BY ANNA NOWOGRODZKI

Elliott Vichinsky estimates that at least 30% of his adult patients with sickle-cell disease die from preventable causes. Red blood cells are supposed to be shaped like concave discs, but in people with sickle-cell disease, a mutation in a single gene collapses them into a crescent shape. The pointy sickles catch on each other and clog blood vessels. They cut off oxygen to limbs. They cause kidney failure, hypertension, lung problems and strokes — along with bouts of excruciating pain.

These are common and treatable complications, so why the high death rate? Vichinsky attributes it to a lack of infrastructure, such as care centres, to properly monitor adults with sickle-cell disease. This is partly because the disease mainly affects low-income minorities and people in developing countries. "If they were tracked before," says Vichinsky, "they would not be dead."

Gene therapy might offer a cure for sickle-cell disease, and clinical trials are already under way. "In the long run I think it will be able to cure the disease," says Vichinsky, a haematologist and oncologist at the University of California, San Francisco (UCSF) Benioff Children's Hospital in Oakland. The approach is promising because just a single gene needs correcting: the one for the β-globin subunit of haemoglobin, the body's oxygen ferry. But Vichinsky is concerned that the same problems that make current care ineffective will also plague this gene-therapy treatment. As his patients attest, sickle-cell care is often inadequate for reasons that have little to do with scientific advancement and lots to do with economics and racism.

For people with sickle-cell disease in the United States, paying for the treatment could be a challenge: it involves such hefty upfront costs that insurers might not be able to cover the treatment, even if it saves them money in the long term.

The only current cure for sickle-cell disease is a bone-marrow transplant from a matched healthy donor. The stem cells that serve as blood-cell factories — haematopoetic stem cells — are removed from the donor's bone marrow or blood, then infused into the recipient. If the transplant works, the donor's stem cells churn out non-sickle-shaped red blood cells, curing the disease. Donors can be a sibling or someone unrelated with the same bone-marrow type, but less than one-third of people with sickle-cell disease can find a matched donor.

Gene therapy could provide a cure for many more people because it doesn't rely on a donor: instead, stem cells are harvested from the patient's own bone marrow. As a further benefit, gene therapy avoids conflict between the donor's and recipient's cells. After a bone-marrow transplant, doctors have to suppress the recipient's immune system to prevent it from attacking the transplant, which leaves the patient vulnerable to infection. Even then, the donor cells might attack the recipient's cells, resulting in graft-versus-host disease — the leading cause of death after a bone-marrow transplant. Gene therapy eliminates this concern.

GENE THERAPY ON TRIAL

Mark Walters, a paediatrician at UCSF Benioff, is working on two gene-therapy clinical trials. One by Bluebird Bio in Cambridge, Massachusetts, is in phase I/II, and one by Bioverativ in Waltham, Massachusetts, will start soon.

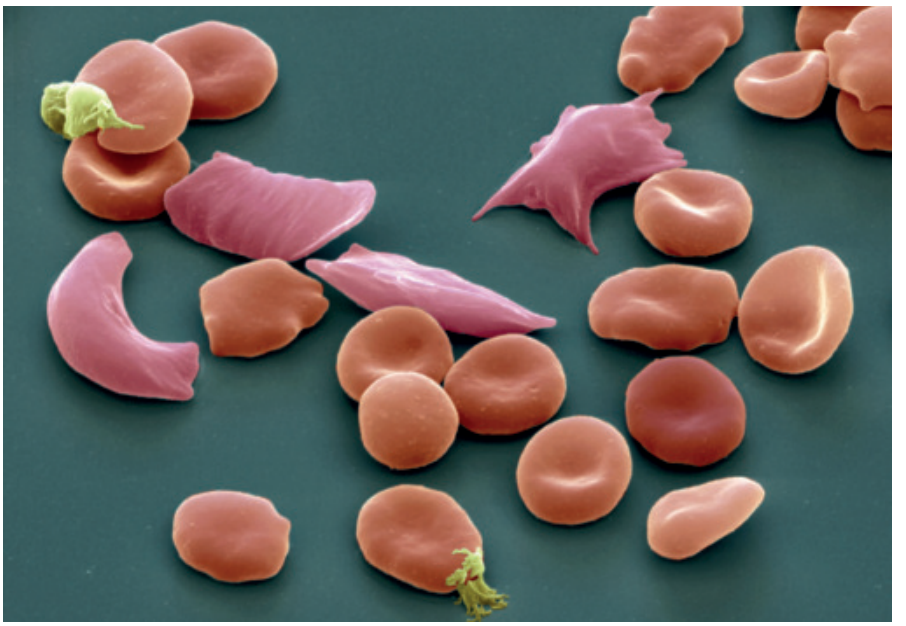
For the Bluebird Bio trial, Walters has enrolled two people so far, and plans to enrol four or five in all at his institution — a total of 50 people will be recruited across the United States. The trial is using the gene-therapy drug LentiGlobin BB305 to insert a healthy version of the β-globin gene into people's blood stem cells. With the gene, the stem cells will make normal red blood cells instead of sickle-shaped ones.

Stem cells are harvested from each person in the trial, and they receive blood transfusions every 3–4 weeks to reduce the percentage of sickle cells in their blood, says Walters. "We don't want patients having complications in the middle of the trial or leading up to it."

It takes about a month for the new gene to be inserted into the patients' stem cells. After being collected up, the cells are shipped overnight by plane to a central manufacturing location, where they spend several days just multiplying. Then scientists put the β-globin gene into the stem cells using LentiGlobin BB305, a vector made from a virus. After quality-control testing, the improved stem cells are frozen and shipped back to UCSF Benioff.

In the meantime, the patients receive four days of intensive chemotherapy to wipe out any remaining stem cells with the old, problematic version of the gene. The improved stem cells

EYE OF SCIENCE/SPL



Normal red blood cells (red) compared with the elongated blood cells in sickle-cell disease (pink).

are then reinfused into the person around a day later, and their immune system regains its strength slowly. "It takes about three months to completely recover," says Walters.

A COSTLY ENDEAVOUR

The clinical trials will demonstrate whether gene therapy is effective at curing sickle-cell disease. But even if it is, the cost of treatment is likely to be very high. For example, voretigene neparvovec (Luxturna), a gene therapy for degenerative blindness, costs US$425,000 per eye. "We're looking upwards of $500,000 to $700,000" for sickle-cell gene therapy, spread over multiple years, says Stephanie Farnia, director of health policy and strategic relations at the American Society for Blood and Marrow Transplantation in Chicago, Illinois. And this is a disease for which more than 50% of patients in the United States rely on government health insurance such as Medicare and Medicaid.

In the long term, an expensive cure for sickle-cell disease would probably be cheaper than — and much more preferable to — dealing with 30–40 years of the disease's chronic, long-term effects. But even if the pharmaceutical company spreads the cost to insurers over 5–7 years, Farnia says, insurers, particularly government-funded ones, will probably not have sufficient capital to pay for everyone who wants the treatment. "The really tough part is these budgets do not have a lot of room in them for additional costs," Farnia says. It's like trying to pay for an entire 30-year mortgage in just five years, she says. "You're going to save a lot more money down the road, but can you come up with the money to do that?"

For a possible preview, Farnia suggests looking to chimeric antigen receptor T-cell (CAR-T) therapy — a type of immunotherapy that has shown promising results in treating certain types of cancer. US medical centres and hospitals are paying for CAR-T therapy up front to treat their patients, before knowing whether insurers will reimburse them for it. "And they have to hope they can figure out with payers that they get reimbursed for enough of that," Farnia says.

CHALLENGES AHEAD

There are other concerns with gene therapy as well. For one, more long-term monitoring is needed. The added gene slips in at random places in each stem cell's genome, so it has thousands of opportunities to land in the middle of another important gene. It could theoretically wind up in a gene that suppresses cancer. No one has yet observed a leukaemia caused by delivering treatments with the family of viral vectors that LentiGlobin BB305 belongs to, Walters says, but a stem cell is long-lived. "If you treat a child, it's going to be a source of blood for the next 50–60 years." No patients have been monitored for anywhere near that long after gene therapy.

Although gene therapy opens up bone-marrow transplants to more people than the one-third who have a suitable bone-marrow donor, it doesn't open it up to everyone. "It's still an intensive procedure," says Walters, particularly the high dose of chemotherapy that people receive before the stem cells are returned to their bodies. "Not everybody is well enough to go through it."

Recruiting for clinical trials might also be a problem. Current trials involve small numbers of people with sickle-cell disease, but if the treatments work, future trials will require many more participants. In the United States, sickle-cell disease is more common among black and Hispanic populations, and there is an ugly history of non-consensual medical research on black people, causing some to be wary of participating in clinical trials. And racial bias also gets in the way of treating the disease. "The hallmark of sickle-cell disease is pain, and it's excruciating pain. It's like putting a tourniquet on and depriving a limb of oxygen," says Walters. And unfortunately, doctors have been shown by multiple studies to be less likely to believe black people's claims to be in pain than white people's (see, for example, K. M. Hoffman *et al. Proc. Natl Acad. Sci. USA* **113**, 4296–4301; 2016).

> ***"Sickle-cell disease represents the best and worst of health care in the United States."***

Sickle-cell disease is a chronic condition. Management of chronic diseases isn't typically groundbreaking, and even among chronic diseases, sickle cell is typically neglected. "It's not received the attention or the national funding that it maybe should have received, because it's not as politically connected," says Walters.

Vichinsky argues that gene therapy should be part of a multidisciplinary programme that includes basic care, not a substitute for basic care. "We shouldn't push them into gene therapy just because there's no basic care available," he says. The US Centers for Disease Control and Prevention list 175 providers of paediatric care for sickle-cell disease in the United States, but only 44 providers of adult care. Vichinsky started his own adult programme because he had nowhere else to transfer his young patients when they became adults. "It has to do I think with money and ethnicity," he says.

Basic care for sickle-cell disease should be modelled on current programmes for cystic fibrosis or childhood cancer, says Vichinsky. He advocates that sickle-cell-disease medical centres should include multidisciplinary teams to monitor people for the degenerative effects of sickle cells across many different organ systems, such as the lungs, heart, kidneys, spleen and brain. That way, doctors could detect early warning signs of problems such as renal failure and hypertension.

He is optimistic, however, that sickle-cell gene therapy might act "as a kind of door opener to the field of gene therapy". There are a handful of gene-therapy drugs on the market, but sickle-cell disease's role as an early gene-therapy target, and the promise of that therapy, might attract interest in how best to care for people with this disease, and propel standards of care forward.

"Sickle-cell disease represents the best and worst of health care in the United States," Vichinsky says. Technologically advanced gene therapy is a hot research area, but not yet proven to work. Mundane chronic illness care is neglected, but it would save lives. "Most adults don't have access to multidisciplinary services," says Vichinsky. "I believe to some extent that gene therapy will actually stimulate the medical and scientific community to bring that to sickle cell." ■

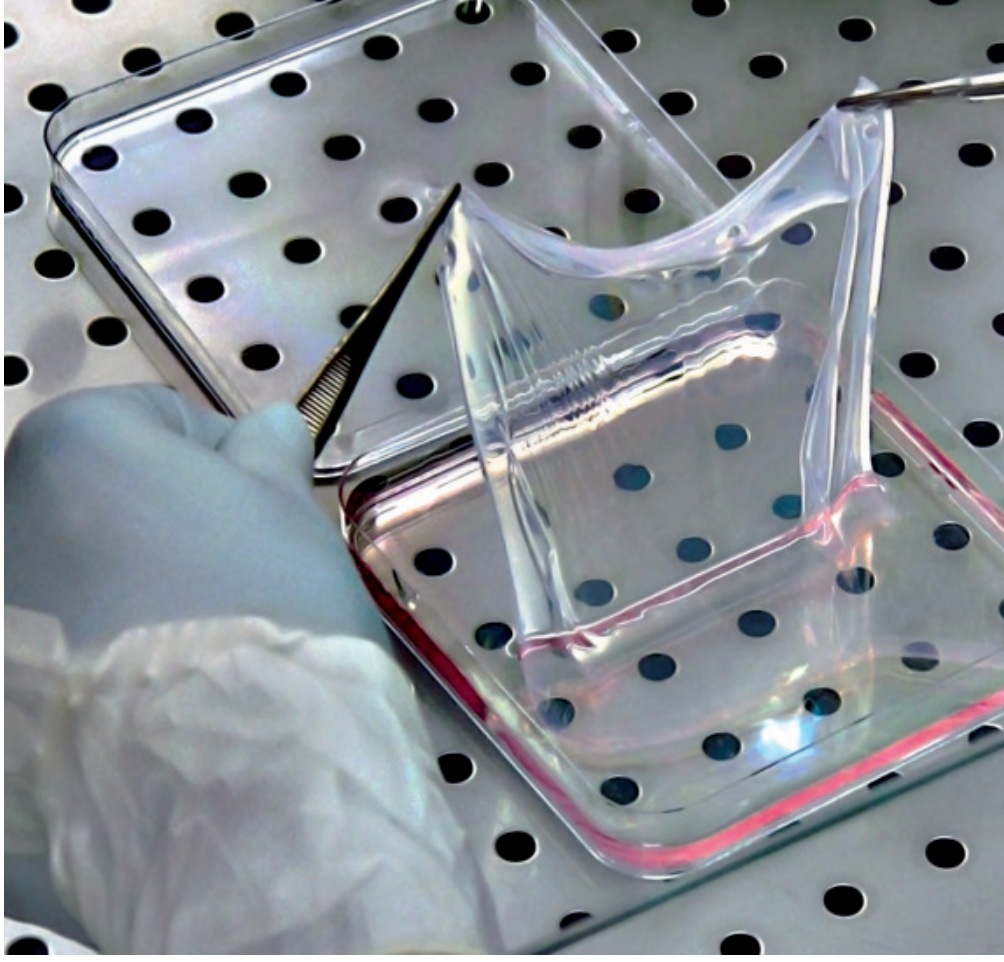
Anna Nowogrodzki *is a science writer based in Boston, Massachusetts.*

DERMATOLOGY

Under the skin

The largest organ in the body is a prime target for gene therapy.

BY KAT ARNEY



CMR UNIMORE

It's not often that a figure in a scientific paper can make you wince with pain. But it's impossible to look at figure 1a in Michele De Luca's 2017 *Nature* paper and not feel a sympathetic twinge at the sight of a young boy, Hassan, covered from head to toe with red-raw wounds[1].

The son of Syrian refugees who fled to Germany, Hassan was born with junctional epidermolysis bullosa (JEB) — a condition caused by a genetic fault in one of three genes (*LAMA3*, *LAMB3* and *LAMC2*) encoding subunits of the laminin-332 protein, which binds the surface of the skin to the underlying layers. Affected children rapidly develop large, painful blisters over their skin and internal mucous membranes, which can easily become infected.

By 2015, when Hassan was seven, his skin was almost entirely destroyed and he was suffering from severe bacterial infections. Doctors at Ruhr University in Bochum, Germany, could offer only palliative care to relieve his suffering. But Hassan's father enquired about experimental treatments, and the doctors got in touch with De Luca at the University of Modena and Reggio Emilia, Italy, who was working on a radical skin therapy.

De Luca's research builds on the life-saving work of cell biologist Howard Green at the Massachusetts Institute of Technology in Cambridge. Green was the first to discover that sheets of skin cells could be grown in the laboratory, creating personalized skin grafts that avoid the problems of immune rejection. De Luca worked with Green at Harvard Medical School in Boston, Massachusetts, in the 1980s, and he later decided to develop Green's approach for treating genetic skin conditions by genetically modifying the skin cells to fix the disease-causing mutation.

"We've been using epidermal skin-cell cultures for many years to treat hundreds of patients, carrying out a lot of work on basic stem-cell biology as well as gaining clinical experience, so it was obvious to try and genetically modify these cells for treating rare skin diseases like JEB," De Luca says.

The idea of growing genetically modified skin for therapeutic use was first proposed in 1994 by dermatologist Gerald Krueger at the University of Utah in Salt Lake City[2], and De Luca and his team reported the results[3] from an initial small clinical trial of genetically modified skin grafting back in 2006.

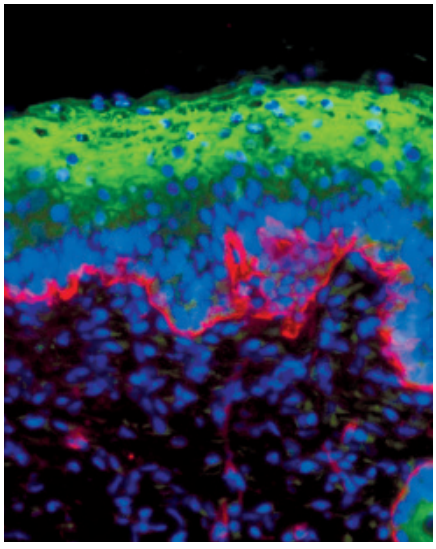
The recipient was a 36-year-old man with JEB caused by a *LAMB3* mutation. He was treated with nine small patches of skin that were grown from his own epidermal cells and modified with a viral vector expressing the missing gene. The grafts remained stable and healthy for more than a year, proving that the technique had the potential to provide long-term correction of the condition.

UNSCHEDULED INTERRUPTION

Despite this early success, De Luca's clinical work ground to a halt for nearly a decade owing to European Union legislation governing cell and gene therapies. "The regulations regarded our grafts as medical products, so they had to go through the same regulatory process," he sighs. "We had to stop all our activities, build up a compliant manufacturing facility and register the therapy — it was only in 2015 that we were finally able to start our trials again."

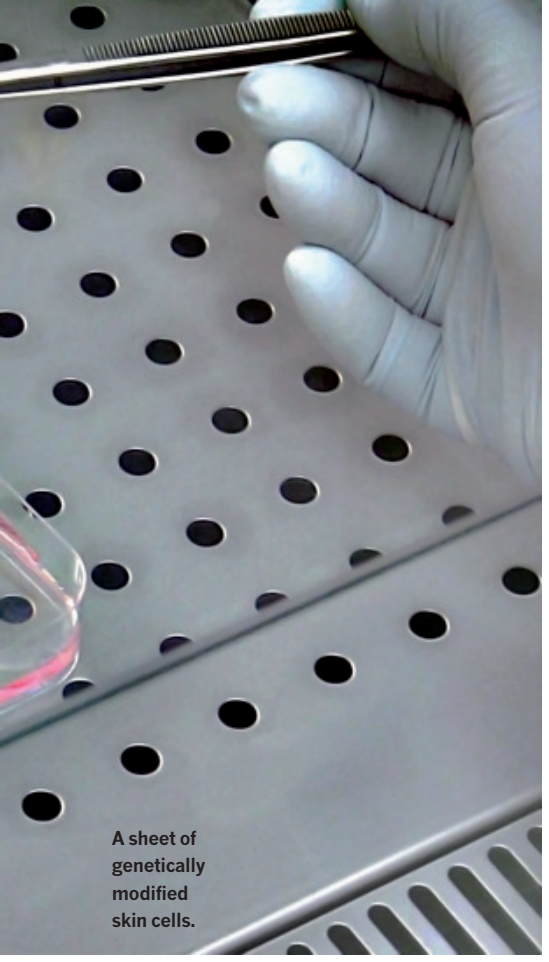
Luckily, this was just in time for Hassan. De Luca's team took a tiny unblistered skin sample from the child's groin, then carefully cultured the epidermal stem cells and modified them with a viral vector carrying a functional version of *LAMB3*. The next challenge was growing enough 12-centimetre-square sheets of modified cells for Ruhr University plastic surgeon Tobias Hirsch to wrap around the child's fragile body.

After two major operations to replace the skin on Hassan's limbs and torso, followed by some smaller procedures, around 80% of the entire epidermis had been replaced, making it the largest genetically modified graft performed to date. By the time the results were published in 2017, Hassan was like a different child, his raw blisters replaced with smooth, perfectly functional skin.



XIAOYANG WU/CYNTHIA LI

A skin graft with fluorescent staining.



A sheet of genetically modified skin cells.

RUHR-UNIVERSITY BOCHUM

As well as detailing Hassan's progress, the paper[1] reveals why the treatment was a success. The skin is made up of many different types of cells, some that are short-lived and others that are much more persistent. The researchers showed that long-term grafting was only possible if the genetically modified cells were holoclones — a relatively rare type of immortal cell that can self-renew indefinitely. By adjusting the culture conditions, De Luca and his team were able to encourage the growth of holoclones, greatly increasing the chance that the resulting grafts would work.

"After three years, his skin is stable with no blistering, and it should last a lifetime," says De Luca. "There are still some areas of blistering that weren't covered with the grafts, and there are other tissues like the mouth mucosa that we couldn't treat, but although we didn't completely cure the disease, we still fixed 80% of his skin."

FROM GRAFTS TO PATCHES

Over at the University of Chicago in Illinois, Xiaoyang Wu is generating genetically modified skin with a different purpose in mind. In 2017, he and his team showed that genetically modified skin grafts could be used as living 'drug patches' in mice[4], akin to plastic nicotine or hormone patches.

Using the gene-editing technique CRISPR–Cas9, the researchers modified epidermal stem cells with a version of the gene encoding GLP1 — a hormone that controls blood sugar levels and suppresses appetite — which could be switched on by the antibiotic doxycycline. They then grew the cells into small skin grafts and transplanted them onto the backs of mice.

The researchers found that the engineered skin grafts could successfully secrete GLP1 into the animals' blood in response to the drug, slowing weight gain and preventing diabetes in mice kept on a high-fat diet.

Wu's team has now used this technique to create similar patches of CRISPR-modified skin cells that produce a tweaked version of an enzyme called BChE, which breaks down cocaine[5]. Wu's version metabolizes the drug more than 4,000 times faster than the naturally occurring form, rapidly clearing it from the body and quickly killing the 'high'.

When tested in mice, the skin patch stopped the animals from becoming addicted to cocaine and prevented them from overdosing, pointing towards a potentially promising treatment for people with drug addictions. Wu and his team are also working on skin patches that could serve as long-term living biosensors — for example, engineering cells that change colour or fluoresce in response to blood glucose levels.

"Many researchers are focusing on gene therapy for internal organs like the liver, but the skin is much easier — we can culture the cells indefinitely and do the editing outside the body," Wu explains. "We can also very carefully choose the correct clones to grow up into patches, with no off-target effects or rogue genetic changes."

But human trials are likely to be some years off. "Right now we are still at the proof-of-concept stage," Wu says. "Once the technology is more established and we are confident in the procedure, we can think about moving into clinical trials to treat diseases."

Although De Luca finds this idea intriguing, he is more focused on making genetically modified skin replacement a viable treatment for the thousands of children born every year with genetic skin disorders. He is currently running two clinical trials for people with different forms of JEB, but is keen to expand into other forms of epidermolysis bullosa, which can be caused by a fault in any one of at least 18 different genes and affects around 1 in every 20,000 children born in the United States. And it's by focusing on the youngest patients, who have the most to gain from early intervention, that De Luca hopes to make the biggest difference.

"If we treat these children as soon as we can, we will prevent the formation of skin lesions rather than having to cure them — and, obviously, we need to grow less skin to cover them," he says. "If you asked me 30 years ago if it was realistic to replace the whole skin with transgenic epidermis, I would have said no, but we have done it. The final aim of my career is to make this gene therapy a real treatment for children — not a clinical trial or a demonstration of what we might do, but something that is used to treat everyone who needs it."

"After three years, his skin is stable with no blistering, and it should last a lifetime."

Three years on from his record-breaking skin replacement, Hassan is living testament to this possibility, regularly visiting the team in Modena for check-ups.

"When he was in hospital he weighed just 17 kilos and was dying, but now he is growing up," De Luca says proudly. "I last saw him two weeks ago and he is like a mascot for the institute — there is a big celebration every time we see him, and everyone who was involved in his treatment wants to give him a hug." ■

Kat Arney *is a science writer and broadcaster living near London.*

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Around 80% of Hassan's skin was replaced with genetically modified skin grafts.

SAM FALCONER

IMMUNOLOGY

A genetic shortcut

Gene therapies that turn the body into a designer antibody factory could bypass drawbacks of expensive treatments.

BY AMANDA KEENER

Outbreaks of infectious disease are becoming more common in many parts of the world. Between 1980 and 2010, the number of outbreaks reported worldwide more than tripled every five years. Unexpected outbreaks caused by viruses such as Ebola and Zika have led researchers to seek faster and cheaper strategies for addressing pathogenic agents they know little about. These strategies include using laboratory-made, monoclonal antibodies that can immediately bind to and neutralize specific viruses or bacteria in a person who has been infected, but also protect, for a time, anyone who is likely to be exposed to a particular pathogenic species.

But monoclonal antibodies are expensive to produce, must be stored in the cold and often require repeated administration by injection to work. That's not to mention the one to two years it takes to grow the cells that produce such antibodies and to purify and test the resulting proteins. "There's a short window of opportunity one has to halt an emerging infectious-disease breakout, and making antibodies takes time," says Neal Padte, chief operating officer at biotechnology company Renbio in New York City.

Padte belongs to a growing group of researchers who want to skip those steps by simply giving the body the genetic information it needs to make the antibodies. This can be achieved by delivering the DNA that encodes those antibodies to the cell nucleus — a process called antibody gene transfer. It's similar to the idea behind DNA vaccines, which deliver DNA that encodes vaccine components to cells. The approaches differ in that DNA vaccines are designed to trigger the immune system to make its own antibodies, whereas antibody gene transfer aims to introduce antibodies without inciting such an immune response.

Taking notes from the fields of DNA vaccines and gene therapy, researchers are working to bring treatments based on antibody gene transfer into clinical trials, using infectious diseases as a proving ground. The approach also holds promise for tackling non-infectious conditions such as cancer. "Wherever antibodies work, we believe this technology can work in the same way," Padte says.

Antibody gene transfer has to overcome the same hurdles relating to safety and delivery as does any other gene therapy, as well as more-specific challenges such as getting cells that don't normally make antibodies to produce them in large quantities. "We know it works [in mouse models]. You can do it for another thousand disease indications and it will work every time," says Kevin Hollevoet, an immunologist at the University of Leuven in Belgium. The big question, he says, is whether the approach can be applied to people.

PICK-YOUR-OWN ANTIBODIES

David Weiner, director of the Vaccine and Immunotherapy Center at the Wistar Institute in Philadelphia, Pennsylvania, has devoted almost three decades to developing and refining DNA-vaccine technology. But about eight years ago, Weiner realized that his work could make an impact in a very different field. His then-teenage daughter was diagnosed with severe Crohn's disease, and the only treatment that worked for her was a monoclonal-antibody drug that had to be injected several times a month. Weiner took notice of the fast growth of therapies based on monoclonal antibodies, which include anti-inflammatory drugs such as adalimumab (Humira) and checkpoint inhibitors such as pembrolizumab (Keytruda). "It's one of the most important fields in biotech," Weiner says.

The drugs that the field produces are also among the most expensive. Costing up to US$100,000 per year of treatment, monoclonal-antibody therapies are out of reach for most of the world's population. Weiner thinks that gene therapy could make such drugs more accessible. It costs much less to make DNA in the lab than to produce monoclonal antibodies. The approach would also require fewer doses because lab-made DNA can last for weeks to months in the cell nucleus, while continuously instructing the cell to churn out antibodies.

Since 2013, Inovio Pharmaceuticals in Plymouth Meeting, Pennsylvania, a company co-founded by Weiner, together with Weiner and his team at Wistar, has been developing a number of DNA-encoded monoclonal antibodies. It started by creating antibodies to tackle viral infectious diseases such as chikungunya and dengue fever and has now broadened its scope to develop such antibodies against antibiotic-resistant pneumonia and two proteins found at elevated levels in tumours of the prostate gland. They are now working on DNA-encoded monoclonal antibodies that mimic antibodies against the Ebola virus from

CAROLINE SINNO PHOTOGRAPHY

the blood of people who survived infection.

Inovio is not alone. Several groups of researchers have produced monoclonal antibodies in mice that can protect the animals from infection and attack tumours. For example, Padte and his collaborators in the United States and China delivered genes that encode the three antibodies that comprise the anti-Ebola-virus vaccine ZMapp, as well as three anti-influenza antibodies, into mice[1]. The antibodies protected the animals from both Ebola and influenza.

This ability to pick and choose the most effective antibodies for a disease is especially attractive to researchers who study a special class of antibody that can neutralize multiple strains of HIV. Up to one-third of people with the virus make these antibodies. That could be down to genetic differences between individuals; it might also relate to the strain of HIV encountered. "What you can do with antibody gene transfer is just take the successful antibodies that came out of these unusual pairings of people and viruses and give them to a broad audience," says Alejandro Balazs, who studies immunity against HIV at the Ragon Institute of MGH, MIT and Harvard in Cambridge, Massachusetts. That way, he says, "You are taking the black box of the immune response out of the equation."

The US National Institute of Allergy and Infectious Diseases in Bethesda, Maryland, is testing the delivery of a gene that encodes one such neutralizing antibody, on which Balazs has worked for more than ten years. The trial will evaluate the therapy's safety in people with HIV. If it goes well, Balazs says, there might be opportunities to check whether the participants' bodies are converting the gene into the desired antibody. A separate trial, run by the International AIDS Vaccine Initiative in New York City, is testing the safety of another gene encoding an HIV-neutralizing antibody in a cohort of healthy men. The outcomes of both HIV trials will signpost how well antibody gene transfer works in humans. "A lot of people are looking at this very closely," Balazs says.

IT'S ALL IN THE DELIVERY

There are many ways of delivering genes to cells. Few have been tested in people, however, and none has been assessed for inducing antibody production. The HIV trials use a virus called adeno-associated virus (AAV) to carry genes encoding HIV-targeting antibodies into the muscle cells of participants. AAV has a knack for getting foreign DNA into human cells, says Ronald Crystal, who works on gene therapy at Weill Cornell Medicine in New York City. "That's what they live for."

AAV is also well suited to inserting antibody genes into hard-to-reach organs such as the brain. Crystal and his collaborators used the AAV approach to deliver an antibody that reduced levels of tau, a protein implicated in Alzheimer's disease, into the brains of mice with another type of dementia[2].

But AAV, as well as other viruses used in antibody gene transfer, has downsides. It can incite an immune response. And because the virus is grown inside cells, production can be time-consuming and costly. Approaches that leave out viruses, such as Weiner's DNA-encoded monoclonal antibodies, avoid those limitations. But without a virus to transfer the DNA, cells have to be coaxed into accepting foreign genes, usually by a process called electroporation, in which an electric current is used to create tiny, temporary holes in cells through which DNA can pass.

Neal Padte (left) is building DNA constructs that could enable the body to produce tailored antibodies.

Scancell, a cancer-immunotherapy company in Oxford, UK, has used electroporation to transfer a gene encoding a lab-designed antibody that primes immune cells called T cells to target tumours in people with melanoma. In 2017, the company reported that the treatment safely induced an immune response against the cancer.

For an even simpler approach to delivering antibody genes, others are turning to messenger RNA — the molecule that conveys information stored in DNA to the cellular machinery that makes proteins. For reasons not fully understood, mRNA can make its way into muscle cells without the need for electroporation.

In 2017, Drew Weissman at the University of Pennsylvania in Philadelphia and his collaborators injected an mRNA sequence for an HIV-neutralizing antibody into mice, protecting the animals from infection with HIV[3]. The biopharmaceutical company CureVac in Tübingen, Germany, and its collaborators reported success with mRNA-encoded antibodies against viral proteins involved in influenza and rabies, as well as the mRNA-encoded monoclonal-antibody drug rituximab, which is used to treat non-Hodgkin's lymphoma[4]. And BioNTech in Mainz, Germany, is experimenting with mRNA as a means of introducing T-cell activating antibodies for cancer immunotherapy[5].

THE HUMAN PROBLEM

As antibody gene transfer enters clinical testing for infectious diseases and cancer, some researchers are starting to consider how to make it work for chronic conditions such as arthritis. This is more challenging because people with such disorders often have to switch between monoclonal antibodies to find the one that works best. A therapy that enables the body to produce antibodies for up to years at a time, as can be the case with AAV-delivered genes, would remove that option. "There is the risk that you can't shut it off," says Crystal.

Balazs and other researchers are working on 'off switches' in the form of complementary gene therapies or drugs. But for now, Balazs says, it is still unclear whether approaches that have been successful in mice will work in humans. "We're asking this one site of muscle to pump out enough antibodies to distribute to the entire body," says Hollevoet, who is studying sheep to get a better sense of how much antibody the human body might produce.

For the antibodies that have been tested only in animals, it's impossible to know the concentration in blood that will be needed to treat a given disease. "That's why these first clinical trials are going to be so important," says Balazs. Then researchers can deal with next-level features such as off switches. The mission is straightforward, he says: "Let's just see if we can make the thing turn on." ■

Amanda Keener *is a freelance science writer in Littleton, Colorado.*

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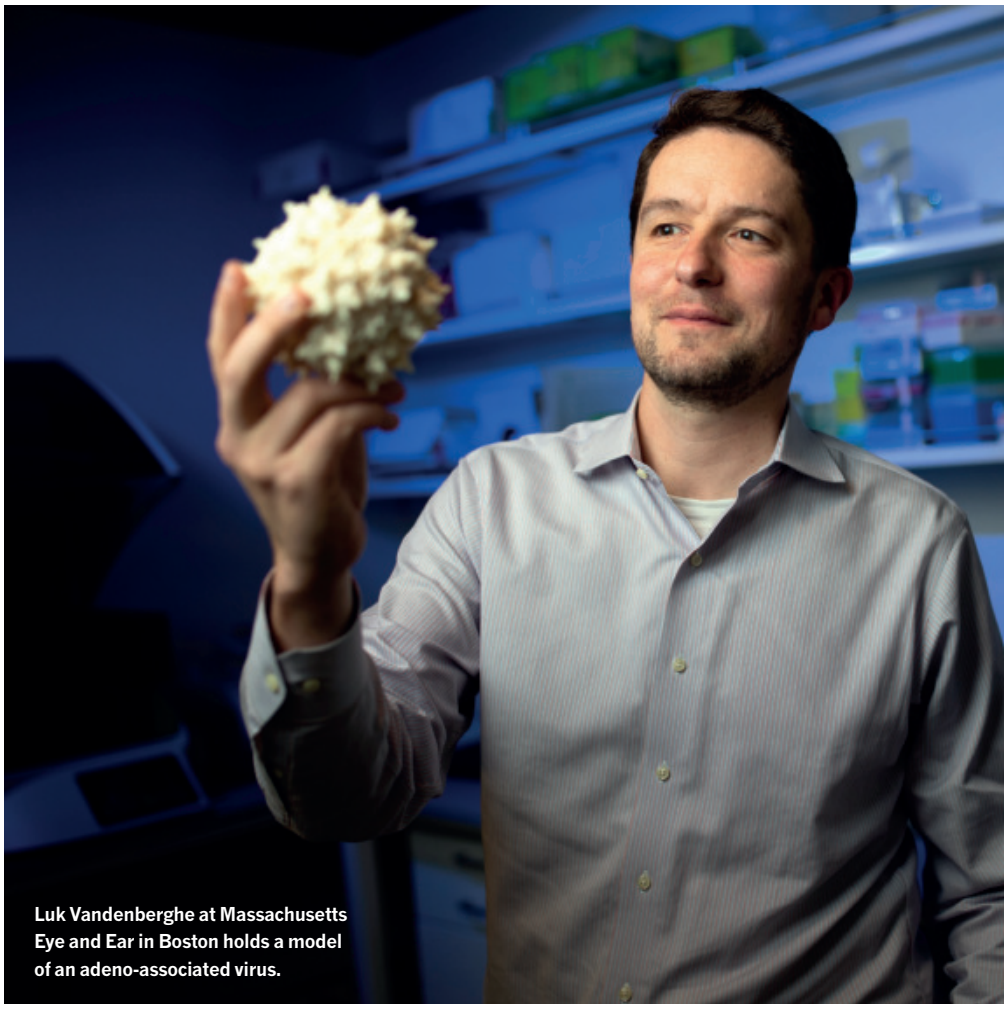
THERAPEUTICS

Special delivery

By tweaking a virus's shell, Luk Vandenberghe thinks he can transport genes into cells much more efficiently and cost-effectively.

BY NEIL SAVAGE



Luk Vandenberghe at Massachusetts Eye and Ear in Boston holds a model of an adeno-associated virus.

ARAM BOGHOSIAN/MASSACHUSETTS EYE AND EAR

Luk Vandenberghe walks over to a shelf in his office and picks up two fist-sized objects. One is a more complicated version of a Rubik's Cube, with 20 individually coloured sides instead of the standard 6. The other is an off-white glob of hard plastic produced by a 3D printer. It's studded with bumps, dimples and repeating triads of vaguely pyramid-like shapes, 20 in all.

Both are models of an adeno-associated virus (AAV), a favourite vector among clinicians for delivering genes to cells. Vandenberghe, a bioengineer who directs the Grousbeck Gene Therapy Center at Massachusetts Eye and Ear in Boston, is trying to work out what effect all those tiny structures have on the behaviour of the virus. His aim is to manipulate them to improve the vector's ability to deliver genes without, in essence, messing up the colour pattern on the Rubik's Cube — or in this case, the icosahedron.

Vandenberghe completed his doctorate on the structural basis of AAVs in 2007 at the Catholic University of Leuven in Belgium, and later went on to become an associate professor at Harvard University in Cambridge, Massachusetts. Through a mix of computational modelling and DNA synthesis, he has been trying to solve the problems that arise from using natural AAVs for gene therapy, and has founded three companies to bring his technologies to market. One of them is using an unusual non-profit approach to tackle the economics of developing gene therapy for extremely rare diseases.

Naturally occurring AAVs have become a workhorse of gene therapy. They infect human cells without causing illness, and different variations of the virus target different cell types — so selecting the right virus is essential for getting replacement genes to cells where they are needed. Vandenberghe and his colleagues have so far identified more than 140 natural variations of the virus[1].

But scientists would like to fine-tune AAVs to improve their specificity and the efficiency with which they penetrate tissue. The goal of AAV research over the past two decades has been treatments that use lower doses and do not affect off-target tissues.

Researchers are also trying to solve another problem. Because the viruses circulate in the wild, many people have been exposed to them and have developed immunity. That puts therapies that rely on AAVs out of reach for many patients. Estimates for the number of people with immunity vary widely, Vandenberghe says, from 20–90%. Some of that variation is due to geography; the viruses are more prevalent in Africa, for instance, than in the United States.

Bioengineers think they can achieve large changes in the function of AAVs by altering the capsid — the protein shell of the virus. For instance, capsid differences are the reason why one naturally occurring AAV targets liver cells with up to 100 times the efficiency of another. "Unfortunately, we still don't know exactly what it is that makes one virus go to the liver 100-fold better than the other," Vandenberghe says. Scientists also don't fully understand how a change in one part of the virus might affect the structure in another part, in much the same way that moving a red square on a Rubik's Cube might put a green square on another face out of place. "What we're trying to do is exactly solve that Rubik's Cube dilemma," says Vandenberghe. "That's not trivial on a cube, and it is certainly not trivial on an icosahedron."

LEARNING FROM HISTORY

To learn more about how structure affects function, Vandenberghe and his team decided to reconstruct the evolutionary history of AAVs. In 2015, he and his colleagues fed the protein sequences of 75 AAV variants isolated from human and non-human primate tissues into an evolutionary computer simulation and reconstructed the sequences of nine possible ancestors of modern AAVs[2], the oldest of which they named Anc80. Vandenberghe is not claiming these are the actual forms of previous generations of viruses, but that isn't the point, he says. "We didn't quite care. What we really wanted to do was find inroads into this structural problem that we had."

On the basis of the sequences, the researchers synthesized the ancestral viruses and examined their characteristics — and Anc80 proved to be especially interesting. When injected into mice, the virus was able to penetrate all of the hair cells in the inner ear and most of the hair cells in the outer ear, something no previous virus had accomplished. In 2017, Vandenberghe and his colleagues used Anc80 in mice to treat a genetic

disorder called Usher syndrome that causes deafness and visual impairment[3]. Excited by the potential of such a vector, Vandenberghe and his colleagues founded a company, Akouos, in Boston to develop treatments for hearing loss. In August, the start-up secured US$50 million in a first round of investment.

Vandenberghe's team is also collaborating with Selecta Biosciences in Watertown, Massachusetts, which wants to develop gene therapies using Anc80. Vivet Therapeutics in Paris is licensing the vector for use in developing treatments for inherited liver disease. And Lonza in Basel, Switzerland, is licensing the technique for making the virus so it can manufacture the vector for drug-makers. Back in 2011, before the Anc80 work, Vandenberghe also co-founded GenSight Biologics in Paris to develop treatments for rare inherited retinal diseases; the company currently has two drugs in clinical trials.

Creating better vectors is the key to expanding gene therapy, says Eric Kelsic, a systems biologist in the laboratory of molecular engineer George Church at Harvard University. Kelsic is taking a data-driven approach to capsid engineering. He selects an amino acid from the protein sequence of an AAV and systematically switches it with each of the other 19 amino acids in existence in turn to see what changes. Then he moves on to the next amino acid in the sequence and repeats the process. "With this approach, we know what the effect is for every possible individual change," he says. Using machine learning, he predicts what will happen when single-amino-acid changes are combined, then synthesizes promising sequences and tests the AAVs in mice or non-human primates.

Kelsic and Church have founded a company, Dyno Therapeutics in Cambridge, Massachusetts, to create vectors this way. Kelsic predicts that even for tissues such as the brain that can already be targeted with AAVs, more-efficient viruses will lead to improved therapies. The greater achievement, however, will be the ability to target organs that are currently hard to treat, such as the lung and kidney. "As we improve delivery further it will enable new therapies which just aren't possible today," he says.

A DIFFERENT BUSINESS MODEL

The companies that these researchers have founded follow the standard for-profit model used by most biotechnology start-ups. But Vandenberghe is taking a different approach with Odylia Therapeutics, a not-for-profit company he founded in February. Odylia aims to develop therapies for what Vandenberghe calls "ultra-rare" genetic causes of blindness, which he defines as those that affect 3,000 or fewer people in the United States. The firm is supported financially by Massachusetts Eye and Ear and the Usher 2020 Foundation in Atlanta, Georgia, a charity focused on curing the sight loss caused by Usher syndrome. One of the charity's founders, Scott Dorfman, who has two children with Usher syndrome, is chief executive of Odylia.

So far there is only one available gene therapy for blindness. In late 2017, the US Food and Drug Administration (FDA) approved voretigene neparvovec (Luxturna) for the treatment of eye disease caused by a mutation in the *RPE65* gene, which normally produces a protein in the thin layer of cells at the back of the eye. As a proof of concept, the treatment shows that gene therapy can be used to cure eye disease. But mutations in more than 200 genes have been linked to hereditary eye diseases, and Vandenberghe says that there is little appetite in the pharmaceutical industry for developing individual therapies to correct many of the other genes.

"As we improve delivery further it will enable new therapies which just aren't possible today."

It can cost millions of dollars to develop a drug and take it through clinical trials, and if a disease is rare, it may not make economic sense for companies to pursue a treatment for it. That is a particular issue in gene therapy, in which people are often cured with a single dose rather than a life-long drug regimen. The doses required for eye diseases are tiny because the retina is a relatively small organ, and some retinal diseases are so rare that it's possible that a single batch of the drug could treat the entire patient population in the United States, Vandenberghe says.

A WIDER CONCERN

The question of how to develop gene therapies for rare diseases is of great concern to the US National Institutes of Health, says P. J. Brooks, program director at the institute's Office of Rare Diseases Research in Bethesda, Maryland. "When people discuss business models around treatments for rare diseases, the basic assumption is that there is a business model," he says. "But for some of these diseases where there's a very small patient population, there may not be one." Brooks says Odylia is the first company he has heard of to try this non-profit approach.

The idea, Vandenberghe says, is to find economies of scale by sharing resources and scientific and commercial expertise across the development of a range of drugs that are similar to one another. If the same group of people develops the drugs, designs the clinical trials and produces the materials, there should be less duplication of effort, he notes. Vandenberghe also hopes that after creating two or three successful treatments, the company will be able to provide data to convince the FDA that there are enough similarities between the drugs to enable them to use experience with one drug to help establish the safety and efficacy of another. It is also possible that Odylia will take development of a drug far enough in this model that a for-profit company will decide to buy it and complete the work, providing funding for Odylia while reducing the pharmaceutical company's costs and risks.

If Odylia does bring a drug to market, it will probably be sold at cost, Vandenberghe says. That could still be expensive, but possibly less so than if it had been developed the usual way. There is also a chance that if a drug candidate gets through phase I and II clinical trials, the FDA could allow it to be provided on a compassionate-use basis without a final clinical trial, or that most patients could be treated as part of an open-ended trial.

If the model is successful, it could be extended to other rare, single-gene disorders and perhaps provide insights for developing gene therapies for more common conditions. "Maybe this is one of those areas where industry can acknowledge that this is indeed non-competitive," Vandenberghe says. Ideally, he says, that would set up a happy scenario. "We can all come together around some of these common goals, apply them to ultra-rare diseases, and then take those lessons to the more commercial world afterwards." ■

Neil Savage *is a science and technology journalist in Lowell, Massachusetts.*

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REGULATING A REVOLUTION

Health authorities wade into the flood of gene therapies.

BY ERIC BENDER

SAM FALCONER

For rare genetic diseases that affect the young, such as a neurodegenerative condition called spinal muscular atrophy, gene therapies bring much-needed hope — a chance for the child to live a relatively normal life. But they also raise serious fears about their efficacy and the potential risks that accompany irreversible one-off treatments.

The responsibility for balancing these hopes and fears lies with the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA). Their credentials as gatekeepers to the therapies will soon be tested by a flood of clinical trials. This year the FDA expects to receive about 250 applications to start clinical trials for novel cell and gene therapies, says FDA commissioner Scott Gottlieb.

Faced with rapid advances in biological understanding and therapeutic delivery technologies, the two regulatory agencies are establishing new guidelines for clinical trials and are preparing to make tough decisions about which drugs to approve for marketing. But drawing on their experience with hundreds of earlier studies, the agencies are confident that they can assess gene therapies as effectively as they do any other novel therapeutics.

STANDARDIZING SAFETY

Gene therapy has long been haunted by a very small number of deaths, originally in a 1999 US clinical trial and then in a European study a few years later. However, a series of successful clinical trials over the past decade has created sufficient confidence to move forward with these treatments.

One milestone, in December 2017, was the first FDA approval of an *in vivo* gene-therapy product, for Luxturna from Spark Therapeutics, based in Philadelphia, Pennsylvania. Luxturna treats a rare, inherited eye condition caused by mutations to a gene called *RPE65* that can cause blindness.

Another was the announcement in August 2018 that gene therapies no longer need to be reviewed before clinical studies can begin by a US National Institutes of Health (NIH) advisory committee on recombinant DNA that was created at the dawn of genetic medicine. "There is no longer sufficient evidence to claim that the risks of gene therapy are entirely unique and unpredictable — or that the field still requires special oversight that falls outside our existing framework for ensuring safety," wrote Gottlieb and NIH director Francis Collins in a paper published earlier this year (F. S. Collins & S. Gottlieb *N. Engl. J. Med.* **379**, 1393–1395; 2018).

Even so, such a new class of medicines still poses serious risks. "It's not that people say: 'Oh, it's all safe, don't worry'," says Katherine High, a haematologist and president of Spark. "It's that now we really have some parameters inside which we can work."

She points out, for example, that previous trials have gathered plenty of evidence about therapies such as Luxturna that are delivered by adeno-associated viruses (AAV), especially for systemic administration or for commonly targeted tissues such as the eye. Such AAV therapies often create a short-term immune response in the liver, but this problem can generally be treated by using steroids. "For other target tissues, or for doses that are higher than people have used to date, you may need additional information," High says. "There actually are a wealth of approaches to overcome immune response, and it's a matter of doing the clinical investigations and finding answers."

Barry Byrne, director of the Powell Gene Therapy Center at the University of Florida in Gainesville, says it is far too soon to declare today's gene therapies safe. "There's very limited experience," he cautions, "and there's much more work to be done to understand how these might be used in a variety of conditions."

There are many unanswered questions, such as what happens if a patient who receives a gene therapy delivered by AAV has previously been exposed to some form of the virus, or if proteins created by gene therapies provoke a reaction because the immune system has not been trained to recognize them as 'self', Byrne adds. But he believes that strategies are emerging to avoid or control such immune problems.

> "YOU CANNOT HAVE TWO STANDARDS FOR SAFETY."

New forms of gene-therapy delivery and mechanisms of action sometimes do not perform as expected when they enter clinical studies. In September 2018, Sangamo Therapeutics, based in Richmond, California, reported the initial results of the first trial of gene editing inside the body, for a therapy to treat a rare metabolic disease called Hunter syndrome. The disease, which primarily affects males, causes a host of serious symptoms, and treatment currently requires weekly injections of enzymes. But the initial Sangamo trials failed to demonstrate clinical benefit, and they are now continuing with higher doses.

The regulatory agencies are seeking to provide more guidance on such emerging gene-editing therapies. The EMA and the FDA are working together "to avoid digressions between the two of us", says Hans-Georg Eichler, senior medical officer at the EMA. "In gene therapy in general, we like to believe that we know what the major risks are, but you can never know," Eichler says. "Tomorrow, something totally new could come out of the blue. But that doesn't say that gene therapy shouldn't be made available to patients."

BETTER BY DESIGN

Given the novelty and the potential risks and rewards of gene therapies, their sponsors tend to start working with regulatory agencies early in development — often, very early. "Ideally, you talk with the agencies when you are designing your preclinical development," says Anne-Virginie Eggimann, vice-president for regulation at biotech company Bluebird Bio in Cambridge, Massachusetts. "You can have a general discussion with them on designing that programme, as well as how you see your first-in-human clinical trial." In October, Bluebird Bio submitted a marketing application to the EMA for its LentiGlobin gene therapy, which is designed to treat a rare blood disease called transfusion-dependent β-thalassaemia.

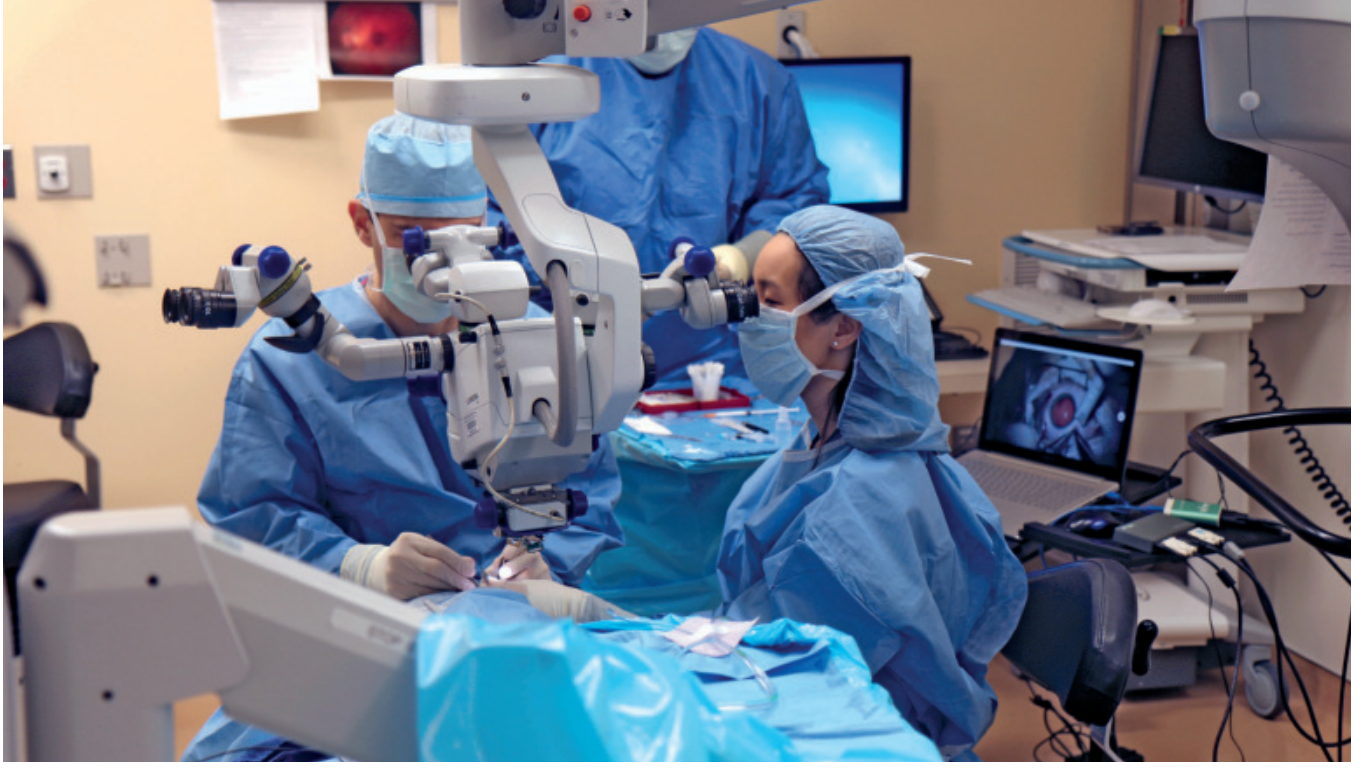
Like LentiGlobin, about 70% of the investigational new drug (IND) applications for gene therapy submitted to the FDA are for rare diseases. Most of these conditions first appear in childhood, and most of those have devastating results. But running a normal clinical trial, which includes large numbers of subjects and a control arm, is often impossible.

"We know that in these situations you have to exercise some flexibility, and that is exactly what we usually discuss with the companies when they come early," says Eichler. "We negotiate and see how can we get the best that is doable in the circumstances."

Given the devastating nature of many rare inherited diseases that strike children, parents often press for accelerated clinical tests. But developers emphasize that lowering safety standards is not an option. "I really understand the urgency of parents whose child has a serious illness," says High. "On the other hand, this is a field where you cannot have two standards for safety."

Trial sponsors and regulatory agencies also worry about how candidate products are manufactured, and how the products might be affected by changes in the manufacturing process over time. Making gene therapies is a highly complex process using biological materials, and extremely high quality must be assured at every step. Most academic labs and biotech startups lack the expertise and the equipment to pull off this feat well enough to produce commercial-grade therapies at a commercial scale. Few biomanufacturing facilities currently provide such services, and these operations are overloaded by the number of therapies now heading towards clinical trials. The difficulties are compounded by the need, as trials progress, to improve the manufacturing processes while keeping the product consistent enough to keep regulators happy.

"Manufacturing is something we will have to think about differently, so we can get it right the first time," says Peter Marks, director of the FDA's Center for Biologics Evaluation and



ED SHIPMAN/MASSACHUSETTS EYE AND EAR

Surgeons use Luxturna, the first *in vivo* gene therapy to be approved by the US Food and Drug Administration, to treat a boy with a genetic eye condition.

Research in Silver Spring, Maryland, which oversees gene therapies.

"Quite often people develop things on the lab bench at a very small scale, and they need to scale up and scale out their thinking," says Jacqueline Barry, chief clinical officer for the Cell and Gene Therapy Catapult, a UK government commercial incubator. "We try to work with them very early on about moving to a good manufacturing process and gathering data that will support the evolution of the product between clinical-trial phases without having to go back and redo studies."

Gene therapies also require follow-up for patients that extends for years after product approval because the long-term effects of these one-time treatments are simply not known. "Clinicians must come to grips with that idea," says Eichler. "As we treat, we must ascertain that the patient experience — good or bad — must somehow be fed back to decision-makers and contribute to long-term knowledge generation."

SEEKING APPROVAL

Europe and the United States have very different legal and regulatory regimes for approving gene therapies. The main difference is that the FDA oversees clinical trials, whereas the EMA does not. To run a clinical trial in any of the 28 members of the European Union, "you have to get approval from a competent authority and from the ethics committee in that member state," says Barry. You also have to get approval for using a genetically modified organism (GMO). However, "the clinical-trial directive and the GMO directive are translated slightly differently in each country," she points out.

Moreover, participation in decisions is structured differently in Europe and the United States, says Eggimann. At the EMA, committee members from various states meet to make decisions about marketing approval. At the FDA, reviewers within the appropriate division follow the drug candidate throughout its entire life cycle.

But the two agencies take similar data-driven approaches to assessing drug safety and efficacy, often actively working together in the process. Several times a year, for example, they hold teleconferences on gene therapies. "We all know there are so many uncertainties in this field, and so many new developments that we want to keep each other abreast of," says Eichler.

> "I DON'T SEE THE AGENCIES AS A BARRIER AT ALL."

Both agencies released major updates to their gene-therapy guidelines in 2018. The FDA, for example, offered its first draft recommendations by class of illness, starting with haemophilia, retinal disorders and rare diseases. It also added draft frameworks for certain manufacturing processes and requirements for long-term patient follow-up. The EMA also completely overhauled its frameworks for gene therapies. For instance, it reworked its guidance on the design, manufacture, characterization and testing of delivery mechanisms.

"As the field gains more and more experience, the broad outlines of what needs to be submitted to initiate clinical studies have come more clearly into focus," says High. "You find that reflected in the guidance documents that the FDA and the EMA provide."

Gene-therapy developers worry that the agencies lack enough experts to deal with the incoming wave of trials for cell and gene therapies, which the FDA estimates will reach 1,000 a year by 2021. "They don't have enough people to handle that kind of workload," says High.

"For the FDA, the issue is always around the budget, and being able to have the appropriate technology and people to deliver on their commitments," says Peter Saltonstall, president of the National Organization for Rare Disorders based in Danbury, Connecticut.

It is still early days for gene therapies, but so far, developers generally give both agencies high marks as partners. "I don't see the agencies as a barrier at all," says Byrne. "They have so many mechanisms for interacting with sponsors now, and they've always approached sponsors as collaborators in bringing these agents forward."

Eggimann agrees. "The regulators have been very supportive of innovation and gene therapy in general, and they are very eager to learn," she says. "Our challenge comes from the novelty of the science, not so much from the regulatory aspects."

Meanwhile, the therapies keep moving forward. Among them is AVXS-101, a gene therapy from AveXis based in Bannockburn, Illinois. AVXS-101 has raised high hopes in early clinical trials for the treatment of spinal muscular atrophy, that devastating neurodegenerative condition that affects children. In October 2018, AveXis applied to both the FDA and the EMA for marketing approval — yet another bridge that gene therapy is crossing on its journey from the lab to the clinic. ■

Eric Bender *is a science journalist based in Newton, Massachusetts.*

PERSPECTIVE

Access and affordability for all

The hope of gene therapy could be crushed by its financial burden unless there are more rational ways of paying for it, says **Michael Sherman**.

Gene therapy offers the possibility of a cure for previously untreatable diseases. But although the science and technology behind it are awe-inspiring, the costs can be daunting. Treatments are likely to have a price tag in the neighbourhood of US$1 million or more — a cost that is ultimately borne by all individuals, not just patients, through taxes and insurance premiums.

In the United States, which lacks government-administered provision of universal health care, there is a strong expectation that health insurers will pay for therapies that have been approved by the US Food and Drug Administration (FDA), particularly if a treatment is the only effective one for a given malady. In cases in which the efficacy data and value proposition are questionable, FDA approval can create enormous pressure to provide coverage.

Some stakeholders — including pharmaceutical companies and government policymakers — have been squeamish about introducing measures of cost effectiveness into the decision-making process because of concerns that such an approach could lead to putting a price on life and, ultimately, the rationing of care. Unfortunately, this has had an unintended consequence: it has led to a system that has no mechanism for imposing price ceilings. Many individuals in the United States see substantial cost increases for their medications year after year.

One possibility would be for the FDA to consider a pathway in which it expedites approval for a treatment in the absence of sufficient high-quality data, particularly for rare diseases that have no effective treatment, in return for the drug maker agreeing to a so-called value-based agreement that would tie reimbursement to the success of the drug. When treatment works, the manufacturer would receive full payment. When the patient shows a limited response to treatment, there would be a partial payment. And when the treatment fails altogether, no payment would be made.

I work for the health insurer Harvard Pilgrim Health Care in Wellesley, Massachusetts, and in January my company entered into a value-based agreement with Spark Therapeutics in Philadelphia, Pennsylvania, for the gene therapy voretigene neparvovec (Luxturna), a treatment for a form of hereditary blindness. This agreement is already driving considerable discussion between payers and pharmaceutical companies that have upcoming gene therapies and other high-cost, innovative treatments. Other firms have forged similar deals. For example, in 2016, the pharmaceutical company Novartis in Basel, Switzerland, signed a deal with several insurers, including Cigna in Bloomfield, Connecticut, and Harvard Pilgrim, for its combination drug sacubitril–valsartan, a treatment for heart failure. In the event that people receiving the drug fail to show a reduced rate of hospitalization for heart failure in clinical trials, the drug cost will be reduced. Collaborative deals such as this give hope that stakeholders will work together to ensure that all who might benefit have access to cutting-edge medical advances.

Gene therapy, which offers the potential of extremely effective but extremely expensive treatments, is a good candidate for value-based agreements. Take, for example, the high-cost biological drug eteplirsen, which targets the gene responsible for Duchenne muscular dystrophy (DMD). The FDA expedited approval of the drug in 2016 because DMD was a fatal, progressive disease with insufficient treatment options. Approval was granted despite the FDA's advisory committee voting against it and despite slim evidence of efficacy — the pivotal trial, which enrolled just 12 boys, showed very small changes in the surrogate measure used as an outcome.

The agency's decision sent shock waves through the US insurance industry and led to variability in coverage policies. Many companies agreed to pay for the drug, which costs around $300,000 per year, but others initially declined to do so.

In this case, a value-based agreement could have set out a multi-year payment model that would terminate if the effectiveness of the drug failed to persist over the long term. And because such a deal would enable broad access to the therapy, it would in turn generate robust real-world evidence of the treatment's efficacy. Such data could then be used to gain conventional FDA approval. Sarepta Therapeutics in Cambridge, Massachusetts, the company that developed eteplirsen, chose not to enter into value-based agreements for that drug, but it is collaborating with a partner to develop a one-time DMD gene therapy that is expected to be much more expensive. That therapy might present an opportunity to enter into an innovative financing agreement to promote access.

TREATMENTS ARE LIKELY TO HAVE A PRICE TAG IN THE NEIGHBOURHOOD OF US$1 MILLION OR MORE.

Some pharmaceutical companies oppose value-based pricing, questioning whether the approach maximizes shareholder value. It is fair to acknowledge that any solution to improve access to health-care advances should provide a reasonable return to the companies that develop such innovations. It is also appropriate to ask whether treatments for rare conditions should be priced higher to ensure that companies will pursue the development of drugs that will always have a limited market.

Whether or not we choose to acknowledge it, there is a limit to the portion of a country's gross domestic product that can be spent on health care. To balance access and affordability over the long term and ensure that our loved ones can receive the next generation of innovative therapies, payers, pharmaceutical companies and regulatory agencies need to collaborate in a way that benefits all stakeholders. Value-based agreements from the past few years provide a model that could be applied to upcoming gene therapies and other high-cost, innovative treatments. A spirit of collaboration among industry players could ensure that everyone who needs an innovative, expensive treatment can have access to it. ■

Michael Sherman *is senior vice president and chief medical officer at Harvard Pilgrim Health Care in Wellesley, Massachusetts, and a faculty member at Harvard Medical School in Boston, Massachusetts. e-mail: michael_sherman@harvardpilgrim.org*

nature

www.nature.com/collections/gene-therapy-outlook

No Beast So Fierce: The Terrifying True Story of the Champawat Tiger, the Deadliest Animal in History

by Dane Huckelbridge.
William Morrow, 2019 ($26.99)

TIGERS evolved to be fierce fighters, but they rarely attack humans.

Sometime around the beginning of the 20th century, a Bengal tiger emerged regularly out of the forests of the Himalayan foothills to stalk its preferred prey: humans. This tiger came to be known as the Man-Eater of Champawat and, over the course of a decade, killed an estimated 436 people—highly unusual and terrifying behavior for its kind. History writer Huckelbridge chronicles the conditions that created such a beast—including hunting territory diminished through ecological mismanagement, loss of its normal prey species and the degradation of its natural habitat—and the riveting story of the legendary hunter, Jim Corbett, who was commissioned by the British government to exterminate the animal. It is a haunting tale and a cautionary one, too; similar bad ecological practices stalk our relationships with apex predators of today. "We're still negotiating," he writes, "how to best live alongside them."

The Discrete Charm of the Machine: Why the World Became Digital

by Ken Steiglitz.
Princeton University Press, 2019 ($27.95)

Digital technology has such a firm hold on modern life that it is hard to remember how recently we lived without it. Computer scientist Steiglitz examines the global transformation from analog to digital and the ways it changed how we calculate, communicate and entertain ourselves. He describes the nuts and bolts of taking something analog, such as waves traveling through the air that make sound, and converting them into 0s and 1s, all in witty and cogent language. In addition to celebrating the gains of the digital revolution, Steiglitz questions what we may have lost. Noting that the human brain uses both analog and digital mechanisms, he asks, "Is there some 'magic' that remains hidden in the analog world, beyond the reach of the digital computer?" *—Clara Moskowitz*

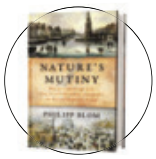
Good to Go: What the Athlete in All of Us Can Learn from the Strange Science of Recovery

by Christie Aschwanden.
W. W. Norton, 2018 ($27.95)

After a long run, journalist Aschwanden went to relieve her sore legs with nitrogen gas. Standing naked in a steel chamber and receiving a blast of frigid air, she felt a rush of adrenaline. "I was ready to kick some ass…," she writes. "I was sold." But the truth, she finds out, is that no scientist can confirm the benefits of this kind of cryotherapy. A lifetime racer and former cross-country skier, Aschwanden provides an amusing and exhaustive takedown of the recovery products and trends that fitness enthusiasts have transformed into a multibillion-dollar industry, from sweating at infrared saunas to hydrating with sports drinks. Her findings debunk many ideas about what does help the body recover—and what does not. *—Emiliano Rodríguez Mega*

Nature's Mutiny: How the Little Ice Age of the Long Seventeenth Century Transformed the West and Shaped the Present

by Philipp Blom. Liveright, 2019 ($27.95)



For reasons still being explored, Earth plunged into the Little Ice Age from the late 16th to the early 19th century. Across the Western world, failed harvests led to famine and social unrest. Using first-person accounts, history writer Blom shows how the climatic upheaval helped to usher in economic and scientific changes. The Little Ice Age spurred agricultural innovations while causing considerable human suffering and growing inequality. For example, displaced by new farming practices, landless peasants fled to city slums, where disease spread easily. The book gives context to the current human-driven climate crisis, which is catalyzing similar shifts and underscores that our choices dictate how global warming impacts human life. *—Andrea Thompson*

ANUP SHAH *Getty Images*

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Zombie Baby Monitors Attack

It's a malware-eat-malware world

By Zeynep Tufekci

a a man e ice come with chips and are connected to the Internet—the so-called Internet of Things. The smart fridge that alerts you when milk is low or adds it to the shopping list—maybe even orders it from the grocery app! The air conditioner that anticipates when you want the house cooler for a run on the treadmill but turns itself down when you're out at the movies. A baby monitor that tells you when it's time to stock up on teething gel: the little one has been tossing and turning a little too much.

It sounds useful and wondrous. It's quite possible, however, that your Internet-connected baby monitor instead spent last night teaming up with millions of other devices—cameras, printers, routers, speakers, air conditioners, DVRs, and more—to censor journalists; take down music, social media, or movie sites such as Twitter or Netflix; sabotage open-source software projects; knock almost a million German houses off-line; or bring down cell-phone communications in Liberia. With all this extra stealth activity, it's also running up your electricity bill.

Wait … what? The problem is painfully simple and terribly thorny, and it is as much about globalization, law and liability as it is about technology. Most of our gizmos rely on generic hardware, much of it produced in China, used in consumer products worldwide. To do their work, these devices run software and have user profiles that can be logged into to configure them. Unfortunately, a sizable number of manufacturers have chosen to allow simple and already widely known passwords like "password," "pass," "1234," "admin," "default" or "guest" to access the device.

In a simple but devastating attack, someone put together a list of 61 such user name/password combinations and wrote a program that scans the Internet for products that use them. Once in, the software promptly installs itself and, in a devious twist, scans the device for other well-known malware and erases it, so that it can be the sole parasite. The malicious program, dubbed Mirai, then chains millions of these vulnerable devices together into a botnet—a network of infected computers. When giant hordes of zombie baby monitors, printers and cameras simultaneously ping their victim, the targeted site becomes overwhelmed and thus inaccessible unless it employs expensive protections.

To make things worse, the authors of Mirai released the source code shortly after their debut censorship attack on the Web site of Brian Krebs, an Internet security investigative journalist. Now even people with rudimentary levels of coding skill can assemble their own giant zombie botnets. There are also "peeping Tom" sites that randomly scan for, and easily find, cameras with these simple, known passwords and stream their feed to the world.

What's the fix? You might have noticed that phones or laptops occasionally need software updates. These introduce new features, but they also often patch bugs and fix software vulnerabilities. Alas, most devices vulnerable to Mirai were also shipped with no feasible or easy way to update or fix them.

I babysat various computer networks to pay for college, and the passwords that Mirai uses would be the same combinations I'd try when faced with a device with an unknown login. That this is still true so many years later points to the actual problem: nobody is minding the store. Indeed, why bother? For manufacturers of chips or devices, there is often little to no downside to shoddy security.

There is no authority with teeth and no clear law outlining liability from harm caused by such blatantly negligent security practices. The original authors of Mirai appear to be U.S. college students who eventually pled guilty after being caught, but that's mostly irrelevant. As long as there are large numbers of devices with the "admin/admin" username/password combination, someone would have done this eventually. The bad news is that there is no real solution to Mirai except waiting for existing vulnerable devices to degrade. The good news is that if a few device makers who shipped "admin/admin" gadgets were forced to pay hefty fines or if parents of a hacked baby monitor could sue manufacturers or sellers, security would probably improve rapidly.

The Internet of Things promised us great wonders, but I'd like them to be less exciting. It's time to make baby monitors boring again—and go back to worrying about the little one's teething rather than his or her security camera joining a zombie botnet and wreaking havoc across the globe. SA

Zeynep Tufekci is an associate professor at the University of North Carolina, whose research revolves around how technology, science and society interact.

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Illustration by Jay Bendt

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DISCOVERED!

LARGEST HOARD IN DECADES!

Unopened Bags of Wild West Silver Dollars

In the Wild West, the Morgan Silver Dollar was king. A cowboy could walk into a saloon, slap down one of these dusty coins and purchase a decent bottle of brandy.

Today, the Morgan is still king. Struck in 90% pure American silver, it's the most widely coveted vintage Silver Dollar in the world, with collectors spending thousands of dollars on high-grade, low-mintage coins.

Finding a fresh bag of Morgan Silver Dollars is nearly unheard of today. For such a relic to exist, someone would have had to purchase a bag, and then miraculously leave it unopened for at least 50 years.

Incredibly, that's exactly what happened. Read on to find out more!

Actual size is 38.1 mm

The New York Bank Hoard—Last of the Great Treasury Hoard

In 1962, the U.S. Treasury opened its vaults and released thousands of "fresh" Morgan Silver Dollars to the public at face value. It's one of the greatest events in numismatic history.

During this historic sale, a Wall Street employee bought 16 bags—a total of 16,000 coins—placed them into a bank vault, and walked away. For one of the first times in history, a modern find of unopened bags of Morgans could actually be traced back to, and certified as coming from, the Great Treasury Hoard.

Recently, the family of the Wall Street employee brought in experts to carefully open the bags and examine their contents. Once they picked their jaws up on the ground, they estimated the hoard's value—a hoard of "fresh" coins more than 130 years old—to be between $1 and $1.5 million!

Hold Wild West History In Your Hands

Each Wild West Silver Dollar from this historic find has been certified by respected third-party grading service NGC and sealed in a protective display holder with an exclusive label identifying it as "New York Bank Hoard from U.S. Treasury Bag." Secure yours today and you'll be able to hold real, certified Wild West history in your hands!

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Much of this historic hoard has already been snatched up into world-class collections around the world. This may be your only chance to secure one of these coins, still in its original Brilliant Uncirculated (BU) condition after more than 130 years, for the amazing low price of just $99 per coin.

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Steve Mirsky has been writing the Anti Gravity column since a typical tectonic plate was about 36 inches from its current location. He also hosts the *Scientific American* podcast Science Talk.

What the Deuce

A number of studies about number two

By Steve Mirsky

ere een a t f cra in the news lately, and for a change I mean that literally. Let's start with the study presented last November 18 at the annual meeting of the American Physical Society's Division of Fluid Dynamics entitled "How Do Wombats Make Cubed Poo?" Yes, wombats produce dicelike discharges. The marsupial's unique ability attracted the attention of researchers who looked at the innards recovered from two wombats lost in the everyday carnage of roadways around the world.

"In the final 8 percent of the intestine," the dung detectives wrote, "feces changed from a liquid-like state into a solid state composed of separated cubes of length 2 cm. This shape change was due to the azimuthally varying elastic properties of the intestinal wall." After that inspection, they emptied the intestines and inflated them, presumably not by mouth.

"We found," they wrote, "that the local strain varies from 20 percent at the cube's corners to 75 percent at its edges. Thus, the intestine stretches preferentially at the walls to facilitate cube formation. This study addresses the long-standing mystery of cubic scat formation and provides insight into new manufacturing techniques for non-axisymmetric structures using soft tissues." At long last, 3M meets BM.

Back in March 2018, Israeli researchers published a study in the journal *Applied Energy* stating that poultry expulsions could be pressure-cooked into a burnable powder that might replace some coal in electricity production. Or even be pressed into briquettes for cooking. Just before Thanksgiving, NPR did a story about this research and pointed out that someone could theoretically collect a turkey's droppings over its lifetime, turn that mess into fuel and then use it to cook the very same turkey. Perhaps selective breeding could even get the hapless bird to go pluck itself.

In the December 20th edition of the *Journal of Cleaner Production,* the same Israeli group published a similar study with human excreta. To quote: "It is postulated that hydrothermal carbonization of human excreta could potentially serve as a sustainable sanitation technology." Perhaps your future energy-efficient home will be able to connect the toilet directly to the furnace.

Last November, Tech Insider dredged up and tweeted video related to a story first reported in 2015 about Antarctica's Gentoo penguins getting together to relieve themselves en masse. Their warm guano helps to melt the snow and ice. Having thus cleared the field, the birds can build nests on beaches or small patches of vegetation.

In the same month the news site Crosscut ran a piece about the University of Washington's Conservation Canines program. Reporter Hannah Weinberger wrote that "a rotating cast of 17 lucky dogs … [are] taught to approach scent detection as a game, where they are rewarded for learning how to track the scents of dozens of species' feces."

The samples that the dogs then locate in the field give researchers valuable information about local animal populations—more data than could be generated by camera traps or hair snares. So what's it like to sniff out scat for a living? One dog allegedly described it as "rough."

Also in November the *Journal of Paediatrics and Child Health* ran a study entitled "Everything Is Awesome: Don't Forget the Lego." Six pediatric health care professionals swallowed a plastic Lego minifigure head, representing the myriad small objects little kids swallow, and then pawed through their own stool to see how long it took for the head to emerge. The time between ingestion and elimination was dubbed the Found and Retrieved Time (FART), which averaged 1.71 days.

The authors noted that "it is likely that objects would pass faster in a more immature gut." Therefore, they "advocate that no parent should be expected to search through their child's faeces to prove object retrieval." In other words, trust the process—these things have a way of working themselves out. SA

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Illustration by Matt Collins

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FEBRUARY

1969 Evolution Wars

"At the end of his *Descent of Man and Selection in Relation to Sex* (1871), Charles Darwin wrote: 'The main conclusion arrived at in this work, namely that man is descended from some lowly organized form, will, I regret to think, be highly distasteful to many.' Half a century later his prediction was fully realized in the U.S., where many Americans waged what is sometimes called the 'monkey war.' Fundamentalists-Christians of various denominations who believed that evolution contradicted the Bible sought to check the spread of evolutionary thought by making it a crime to teach it. Not until November 12 of last year [1968], when the U.S. Supreme Court ruled that a law barring the teaching of evolution in public schools and colleges was unconstitutional, could it be said that the monkey war had come to an end. The best-known battle in this ideological conflict was fought in 1925, when John Thomas Scopes was tried in Dayton, Tenn., for teaching evolution.
—L. Sprague de Camp"

De Camp is now best known as a science-fiction writer.

Wankel Rotary Engine

"The reciprocating-piston internal-combustion engine has been so successful that one is seldom aware that a small army of inventors is determined to see it replaced by some kind of 'rotary' engine. In the piston engine the conversion of linear reciprocating motion to rotary motion, by means of the connecting rod–crankshaft arrangement, is inherently wasteful of the energy supplied by the combustion process. There are 30 to 40 such rotary engines, all 'ideal' to a greater or lesser extent (such as the one conceived by Felix Wankel in 1956). There still appear to be problems, however, of providing adequate sealing and lubrication; such problems are characteristic of virtually all the rotary engines."

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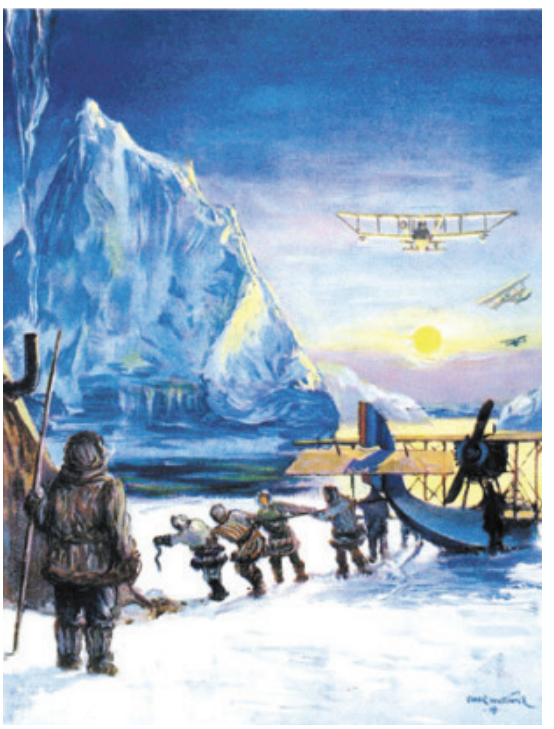
1919 Molasses Disaster

What is there in molasses that would make it explode, particularly in winter time when the sticky syrup is proverbially slow? Two weeks ago a large tank of molasses exploded in Boston, killing a dozen persons and injuring 50 more, and no completely satisfactory explanation of the disaster is obtainable. The tank was a huge cylindrical structure with a capacity of two million gallons. Without an instant's warning the top was blown into the air and the sides were burst apart. Wreckage was scattered in all directions while a deluge of molasses spread over the ruins and into the street, suffocating many of the injured."

We also published (online) an article on August 1, 2013, by Ferris Jabr: "The Science of the Great Molasses Flood."



1919 Our cover image for the first issue in February showcases big plans for polar exploration by airplane.

Barbed-Wire Disease

"We welcome a little pamphlet by Dr. A. L. Vischer, of Basle, devoted to the study of prisoners of war, and especially what was called the 'barbed-wire disease.' Four to five million men have been kept in confinement in enemy countries, and many of them will return with impaired mentality to their homes. Dr. Vischer draws a picture of a mentality characteristic of prisoners of war, to which the majority fall victim within two or three months and from which few escape completely. The factors in its causation he considers to be loss of liberty for an unknown period in close company with many others. The result is a continual longing with entire inability to perform. The factor of loneliness in the midst of company he illustrates from writings emanating from various camps."

1869 A Dangerous Procedure

"The *Medical Record* gives an account of a successful operation for the transfusion of blood recently performed by Dr. Enrico Albanese at the hospital of Palermo, Sicily. A youth aged seventeen, Giuseppe Ginazzo, of Cinisi, was received with an extensive ulceration of the leg, which in the end rendered amputation necessary. In this emergency Dr. Albanese had recourse to the transfusion of blood as the only remedy that had not yet been tried. Two assistants of the hospital offered to have their veins opened for the purpose, and thus at two different intervals, 220 grams of blood were introduced into the patient's system. After the first time he recovered the faculty of speech, and stated that before he could neither see nor hear, but felt as if he were flying in the air. He is now in a fair state of recovery."

The ABO blood types were not discovered until 1900–1901.

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Realizing the promise of gene therapy through collaboration and partnering: Pfizer's view

AUTHORS
Anna P. Tretiakova, John E. Murphy, Michael Binks, Paul Mensah, Joseph Rabinowitz, Douglas M. McCarty, Katherine Beaverson, Molly MacLeod, Gregory LaRosa, and Seng H. Cheng

AFFILIATION
Pfizer, Inc. 235 E 42nd St, New York, NY, USA, 10017

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Gene therapy is a promising approach to altering the genetic composition of cells as a way to correct disease-causing mutations or to express proteins or RNA molecules that confer a therapeutic benefit. The concept of gene therapy is straightforward: deliver nucleic acids to target cells to alter their function in a beneficial manner. Moving from concept to reality, however, is a complex process comprised of multiple steps and components, including systems for getting nucleic acids into target cells, DNA regulatory elements that control the amount, location and duration of gene expression, and production of proteins with appropriate activity to alter cellular function in the desired manner. Pfizer is currently focusing on diseases that have single-gene defects, such as certain neuromuscular and hematologic diseases, and we have a robust pipeline of potential gene therapy treatments in preclinical and clinical development. Our current portfolio includes a phase 1b clinical trial for Duchenne muscular dystrophy (DMD), a pivotal phase 3 program in hemophilia B as part of a collaboration with Spark Therapeutics, and an ongoing phase 1/2 trial in hemophilia A in collaboration with Sangamo Therapeutics, Inc.

Given the multiple elements required for successful gene therapy development, collaboration among industry, academia, regulatory, clinician and patient communities is essential. Such partnerships ensure that the necessary expertise is harnessed to achieve maximum benefit: gene therapy products that are clinically beneficial, meaningful to patients and commercially accessible.

Although the clinical utility of *ex vivo* gene therapy has been validated with multiple approved products (for example, Strimvelis, KYMRIAH and YESCARTA), the delivery of genes to cells *in vivo* has been more challenging. One factor that contributes to the challenge is the immune responses that patients may have to viral vectors or to transgene products that were not previously present in the patient's body. Another challenge lies in the limited access that gene therapies may have to the surface of target cells *in vivo* as compared with cultured cells. As a result, gene therapy clinical trials conducted by other pharmaceutical companies over the past 20 years in diverse indications including cystic fibrosis and age-related macular degeneration have failed to advance successfully through clinical drug development.

However, advances in vector engineering, transgene optimization and the combinatorial use of regulatory elements over the past several years have addressed some of the challenges of *in vivo* gene therapy, and Pfizer believes that gene therapy for single-gene disorders is at a pivotal period in its evolution. In some ways, the field is following a trajectory similar to the development of biologic therapies, which have become common, and critical components of treatment regimens for many serious medical conditions, including cancers, neurologic disorders, diabetes and autoimmune diseases. Innovations in vector design and an enhanced

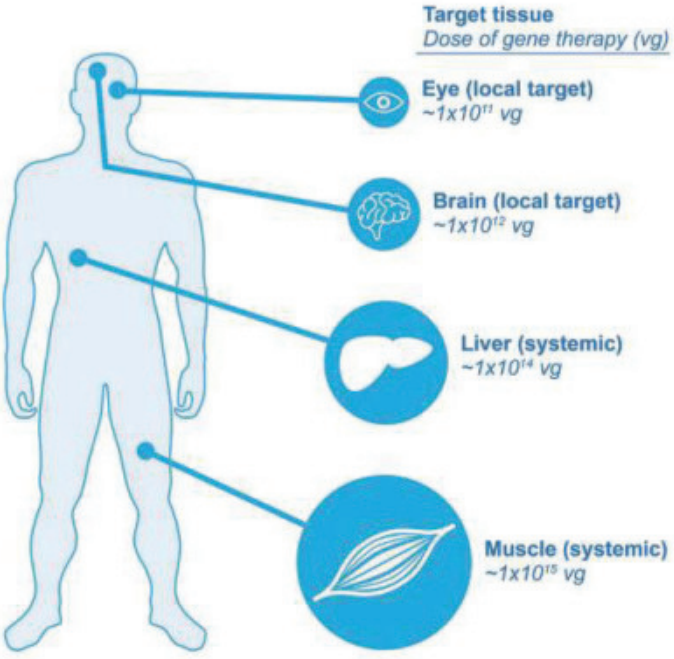

Figure 1: Target size impacts dose. In gene therapy, large target tissues have many cells that need to receive the therapeutic gene, and therefore need to receive a large dose (vector genomes, or vg) of a gene therapy product. For example, gene therapy that is administered as an intravascular injection to provide systemic exposure to multiple organs would need to be given in a large dose. This is in contrast to gene therapy that is administered to a local area of a smaller organ such as the eye, which would require a smaller dose for a smaller number of cells.

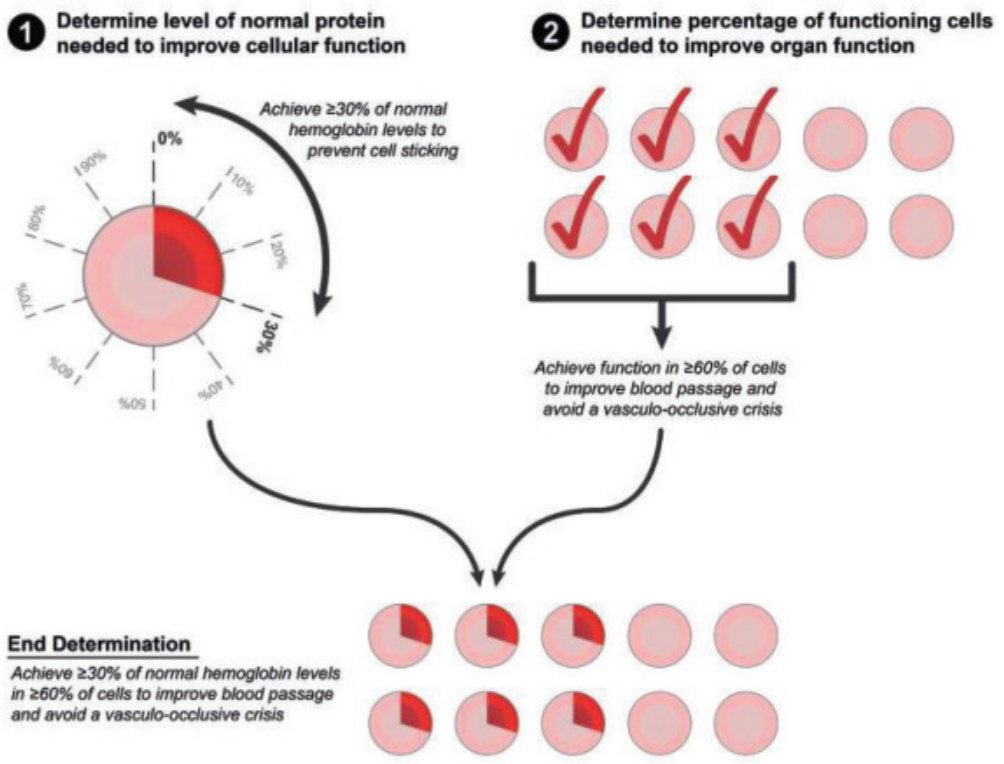

Figure 2: Two components to correcting a disease: Cellular function and tissue or organ function. When considering how to treat a single-gene disease with gene therapy, there are two underlying questions. First: how much protein does the therapeutic gene need to produce in order to improve cellular function? In the example of sickle cell anemia, studies have shown that a red blood cell becomes less sticky if at least 30% of the cell's hemoglobin is not of the sickle variant. Second: how many functional cells does a tissue or organ need to work properly? Transfusion and transplant studies have shown that if at least 60–70% of red blood cells are normal, this is sufficient to improve blood passage and avoid a vasculo-occlusive crisis in patients with sickle cell anemia. Taken together, the answers to these questions provide evidence-based goals when designing a treatment and, in the above example, suggest that sickle cell anemia can theoretically be corrected when at least 60–70% of red blood cells have at least 30% non-sickling hemoglobin[8].

understanding of the biology of certain diseases have enabled the development of novel gene therapy approaches, and numerous late-stage trials of next-generation product candidates, including from Pfizer, are ongoing. Data from these trials will hopefully advance our current understanding of the potential for gene therapy as a therapeutic option, while laying the foundation for future improvements.

The unmet needs of patients with single-gene disorders fall largely in two domains. One area of unmet need is found among patients with diseases for which therapy exists but may only be palliative or associated with high treatment burdens. For example, individuals with hemophilia B are able to address bleeding episodes through frequent intravenous blood transfusions and may be able to achieve disease management with recombinant Factor IX protein therapy. However, gene therapy may improve the quality of life for people with hemophilia B by reducing or eliminating the need for frequent dosing and by ensuring a stable level of Factor IX expression, thus avoiding the peaks and troughs associated with intravenous administration of Factor IX protein. The other type of unmet need is found among individuals with rare, single-gene disorders for which no treatments exist for the majority of patients. Examples in this category include debilitating, progressive disorders, such as DMD, spinal muscular atrophy and Friedreich's ataxia.

The recent technological advances made in gene therapy have opened up the potential to address a broad array of challenges, and Pfizer is pursuing potential solutions in both areas of unmet need. However, achieving the goal of such gene therapies requires not only novel technology, but innovative approaches to solving the technical challenges inherent to the research and development process: translational science, robust and scalable manufacturing, and a collaborative model that takes into account the need to move forward all of these components in tandem. Herein we present Pfizer's perspective on some of the ways in which companies can organize and collaborate in order to work towards realizing the full promise of gene therapy.

TRANSLATING DISEASE BIOLOGY TO THERAPEUTIC STRATEGIES

Focus on understanding disease biology

Although most conditions targeted by gene therapy result from alterations in the activity of a single gene, the effects of these alterations can vary among different cell types and tissues and at various points in a patient's age or developmental stage. Consequently, safe and effective development of gene therapies requires clear insights into disease biology across various cells, tissues and patient demographics. This includes understanding which cell types and tissues need to be targeted and determining if those targets change over time or as a factor of disease progression. While target cell types that undergo frequent cell division require integrating vectors or gene editing strategies for effective treatment, non-dividing target cells can be treated with vectors that remain episomal. Establishing benchmarks for expression of the delivered gene, with respect to both the number of expressing cells and the overall level of expression (**Fig. 1**), is important for informing decisions about optimizing transduction and designing expression cassettes that confer clinically therapeutic levels and localization of the expressed protein. Some diseases, such as DMD, require protein expression predominantly within specific cell types (for example, skeletal and heart muscle). Other diseases, such as hemophilia, may have less stringent requirements for where the protein is expressed as long as it is secreted and at a level that restores correct biologic activity. Access to the tissues to be targeted in a specific disease also plays an important part in vector selection and design, and dosing strategies (**Fig. 2**). For example, in many ongoing clinical studies

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that use an adeno-associated virus (AAV) vector to deliver a gene, localized injection of AAV is being used as a dosing strategy to address tissue accessibility.

Hemophilia and DMD, two indications for which Pfizer has potential therapeutics being evaluated in the clinic, provide examples of the role that disease biology plays in gene therapy development. Hemophilia is an indication with a relatively wide therapeutic window with respect to expression levels and relatively straightforward tissue targeting requirements. This is because delivery of Factor VIII (for hemophilia A) or Factor IX (for hemophilia B) coding sequences to liver cells is expected to sufficiently restore blood clotting activity to significantly reduce the bleeding episodes seen in hemophilia. On the other end of the therapeutic range, healthy individuals show levels of Factor VIII or IX up to 150%[1], thus overexpression of the clotting factor is not a concern. The ability to detect Factor VIII or IX activity in the plasma also provides an easily measurable biomarker that is directly related to disease severity and treatment effect. In contrast, DMD represents an indication with additional challenges in effectively transducing a sufficient number of muscle cells and achieving high enough levels of protein expression within those cells to achieve clinically relevant benefit. This is due to the large mass and broad distribution of the muscle tissues that are affected by the disease. The difficulty in accessing muscle cell samples and measuring intracellular dystrophin also complicates obtaining a biomarker of effect.

Freidreich's ataxia exemplifies how disease biology may complicate therapy for a single disease because it affects both the central nervous system and cardiac function. Clinically relevant transduction rates and expression levels may vary among different tissue types and it may be challenging to develop a single gene therapy, or routes of administration, optimized for multiple anatomic compartments.

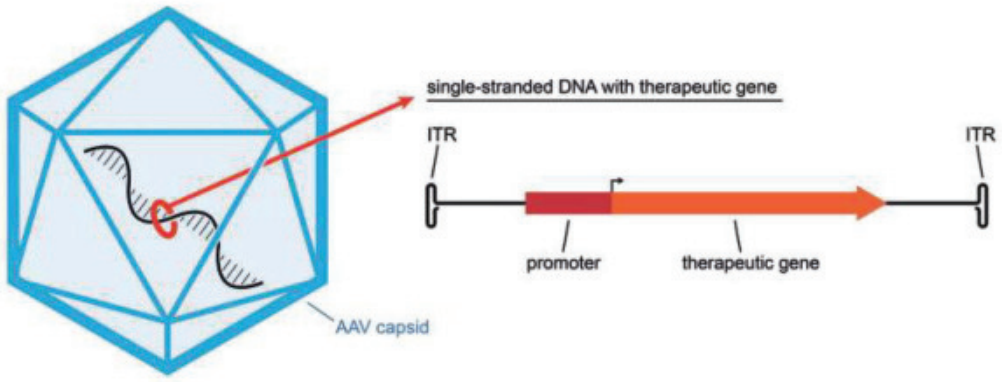

Figure 3: Adeno-Associated Virus (AAV) Gene Therapy Vector. AAV is a small non-enveloped virus that is used to deliver genes to cells in gene therapy. The virus has a linear single strand of DNA inside a protein capsid, and the DNA has two native genes that are used for virus replication. To create a vector for gene therapy, the native genes are replaced with a transcriptional cassette that contains a therapeutic gene and a promoter to direct expression of the therapeutic gene in specific cell types. The cassette also has an inverted terminal repeat (ITR) on each end. After an AAV vector delivers a gene into the nucleus of a cell, and the single-stranded DNA is converted into a double strand, the ITRs are used to convert the linear DNA into a circle, called an episome.

Optimizing vector design and engineering

Given the prominent role that disease biology plays in defining the requirements for potential gene therapies in specific diseases, it is unlikely that a single vector or expression system will be applicable to all indications that could be treated with this therapeutic modality. Thus Pfizer scientists believe it will likely be important to develop a suite of recombinant adeno-associated virus (rAAV)-based vector systems that can be deployed based on the desired product profile. AAV is one of the most actively employed vectors for *in vivo* gene therapies because of its versatility in targeted applications and its safety profile compared to other viruses. Compared to the wild-type AAV, which consists of a capsid shell encasing a single-stranded DNA, the rAAV used in gene therapy lacks components of its own viral DNA but retains the ability to deliver exogenous DNA (that is, an engineered transgene expression cassette) for therapeutic purposes into the nucleus of target cells. Capsid and transgene cassette engineering will therefore play a vital part in developing gene therapies that are optimized for safety and efficacy within specific indications (**Fig. 3**).

Capsid engineering has been used to improve delivery to and transduction of specific tissues, which is necessary for clinically meaningful protein expression. Naturally occurring AAV variants have different tissue tropisms owing to subtle differences in binding preferences of cell surface receptors, and those variants can be of use in targeting specific tissues. Additionally, engineering capsids to develop novel AAV variants, such as through peptide ligand insertion or directed evolution through capsid shuffling, may have further benefits for cell or tissue specificity.

Capsid engineering may also be employed to reduce anti-capsid immune responses that can interfere with transduction activity. AAV is less immunogenic compared with other viruses, primarily because it is unable to replicate or infect without the presence of a helper virus (such as an adenovirus). However, many people have already been exposed to some variant of AAV and may have a pre-existing adaptive immune response to that variant. The concern with such pre-existing immunogenicity is that circulating neutralizing antibodies (NAbs) and T cells may reduce clinical efficacy of AAV vectors. Approaches to overcoming this challenge may include selecting a vector that either has not previously circulated or that does not elicit a clinically significant adaptive immune response, as well as engineering AAV to modify particular antigenic domains on the capsid shell. In any of these cases, performing neutralization assays with living cells to quantify the expected immune response of a given capsid will be helpful in the selection of the vector.

Because a single-stranded transgene delivered to the nucleus of the target cell(s) needs to be converted to a double-stranded molecule to be expressed, this can be a rate limiting step in gene expression[2,3]. One established approach to overcoming this is to develop a self-complementary transgene

to bypass the need for single- to double-stranded conversion. An example of such so-called transgene-cassette engineering is the approach that AveXis (now Novartis) took with the human SMN transgene for the treatment of spinal muscular atrophy (SMA), the leading genetic disease associated with infant mortality (www.avexis.com)[4]. This transgene is under the transcriptional control of the cytomegalovirus enhanced chicken beta-actin hybrid (CB) promoter (NCT03306277)[4]. A pivotal phase 3 trial of this optimized sequence delivered with an AAV9 vector, the same vector Pfizer is using in its DMD clinical trial, is currently ongoing (www.avexis.com; NCT03306277)[4].

The use of naturally occurring gene variants offers another approach to optimizing protein activity[5]. For example, Spark and Pfizer's fidanacogene elaparvovec comprises a naturally occurring variant of Factor IX that has been shown to increase clotting activity eight-fold compared with wild-type Factor IX[5]. Spark has further optimized the codon usage within this Factor IX variant to increase the expressed protein's stability and activity and to reduce its immunogenicity (www.sparktx.com)[6].

Another key component of vector engineering is the development of expression constructs that can fit within the size constraints of particular vector systems. For example, the payload capacity of most AAV vectors is less than 5 kb of sequence, which must comprise coding sequences as well as regulatory elements. DMD results from a loss of functional dystrophin protein. The DMD gene is one of the largest human genes, comprising 2.3 mb of DNA. The full dystrophin cDNA is 14 kb long and cannot be accommodated within an AAV vector. PF-06939926, Pfizer's phase 1 investigational candidate for the treatment of DMD, utilizes a shortened version of the human dystrophin cDNA that has been engineered to provide essential protein function under the control of a human muscle-specific promoter that comprises less than 5 kb of DNA sequence (mini-dystrophin). Similarly, full-length cDNA for Factor VIII is approximately 7 kb of sequence, therefore a fully functional B-domain deleted version that can fit into AAV is being used in all current gene therapy trials.

ROBUST, SCALABLE AND REPRODUCIBLE MANUFACTURING

At Pfizer, we believe that transforming gene therapy from a promising approach to a commercially viable therapeutic modality requires the development of robust, scalable and reproducible manufacturing processes. Consequently, the feasibility of commercial-scale manufacturing of a particular gene therapy candidate must be evaluated at the earliest stages of the development pathway. Manufacturing processes that are being developed by Pfizer also need to balance the goal of establishing a consistent manufacturing approach with the unique vector design requirements for individual disease indications.

One approach that we are exploring at Pfizer is to build internal manufacturing capabilities. This has the potential to provide Pfizer with direct control over process development and flexibility to implement process improvements and to address the parameters of particular gene therapy products.

Another key gene therapy manufacturing asset for Pfizer and other companies pursuing gene therapies is in-house plasmid production capabilities. The availability of high-quality plasmids can often be rate limiting for programs in development. The importance of plasmid quality is highlighted by the potential for the United States Food and Drug Administration (FDA) to place a clinical hold on a gene therapy trial if there is contamination of the plasmid used to manufacture clinical trial material.

Finally, development of robust, scalable manufacturing also requires constant innovation. The desire to innovate proprietary technology, which can be time and cost-intensive, needs to be considered alongside the importance of moving optimized new products toward patients as quickly as possible. Consequently, Pfizer's strategy regarding a given manufacturing technology takes into account its potential clinical value, commercial viability, development time and cost calculations and the company's commitment to improving patient care and outcomes today and in the future.

MULTIPLE APPROACHES TO COLLABORATION

To ensure that translational biology and scalable manufacturing processes advance in tandem to support commercially viable products, Pfizer engages with partners throughout the clinical, research, regulatory, academic and advocacy communities and with smaller, gene therapy-focused biotechnology companies. This is particularly true with respect to rare diseases, for which there are often just a handful of clinicians and researchers with sufficient relevant expertise and hands-on patient experience.

A recent example of the partnership-focused gene therapy ecosystem comes from Spark Therapeutics, Pfizer's partner for hemophilia B gene therapy. Apart from Spark's hemophilia B collaboration with Pfizer, their LUXTURNA gene therapy for confirmed biallelic *RPE65* mutation-associated retinal dystrophy resulted from 25 years of research by Jean Bennett, PhD, and Al Maguire, MD, at Penn Medicine's Center for Advanced Retinal and Ocular Therapeutics group in collaboration with the Children's Hospital of Philadelphia (CHOP) in the United States (www.pennmedicine.org). The 2013 spinoff of Spark from CHOP enabled the company to develop its landmark gene therapy trial that led to its 2017 FDA approval (sparktx.com; www.blindness.org)[7]. Similarly, research from the network of academics and clinicians at the Nationwide Children's Hospital's Center for Gene Therapy in Columbus, Ohio in the US has led to the spinoff of several companies with gene therapies in clinical trials, including AveXis.

Seamless integration of technological expertise and resources across key communities should enable an informed development process that can reduce the time and cost needed to develop therapies that truly address patients' clinical needs and quality of life concerns.

Consortia participation

Another way in which Pfizer collaborates with other key gene therapy communities is through participation in a variety of consortia. Pfizer has participated in many consortia, including public–private partnerships such the Innovative Medicines Initiative (IMI), a European Union initiative that seeks to address specific, yet widespread healthcare challenges by facilitating the sharing of knowledge and resources among cross-disciplinary partners. We believe there is a significant opportunity to leverage this

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collaborative model for gene therapy, such as through IMI's 'Think Big' initiative for advanced therapy medicinal products (ATMPs). This collaborative approach encourages the development of solutions to challenges associated with this therapeutic paradigm.

Engagement with patient advocacy organizations and patient communities

Individuals with rare diseases and the advocacy organizations that represent them have expertise in the 'lived experience' of their disease. They are often experts in the science and biology of their diseases and are focused on building their capabilities to engage with the medical and pharmaceutical industry communities in the drug development process. They can provide invaluable insights about the burden of disease and the impact of current therapies on their lives. These insights are critical in establishing a true patient-centric approach that values benefit, meaningfulness and access. This is particularly true with emerging technologies such as gene therapy, where uncertainty is a variable that must also be factored into any risk-benefit equation and patient choice. Patient advocacy associations can be quite impactful in educating regulators about risk-benefit profiles that the patient community views as acceptable, motivating patients and providers to participate in clinical trials and enabling scientific advancement through collaborations with academia and industry.

Opportunities for collaboration with patient and advocacy groups may differ from one community to another based on the unmet need and priorities. For patient communities in which gene therapy is advancing through clinical development and for whom there is historical clinical research experience (for example, DMD), opportunities for collaboration with industry may focus on community education, community engagement to optimize development programs, and/or creating shared expectations on what gene therapy can and cannot achieve for disease management. Pfizer works closely with several advocacy groups within the DMD community on coalition-model efforts to solve for common challenges in drug development, including the Collaborative Trajectory Analysis Project (cTAP: http://ctap-duchenne.org), the Duchenne Regulatory Science Consortia (D-RSC: https://c-path.org/programs/d-rsc) and Project HERCULES (HEalth Research Collaboration United in Leading Evidence Synthesis: http://hercules.duchenneuk.org). Pfizer is also advancing with Parent Project Muscular Dystrophy (www.parentprojectmd.org) important patient preference research seeking to obtain quantitative evidence on patient and caregiver views on benefit and risk of emerging therapies including gene therapy.

For patient communities where gene therapy may be in earlier pre-clinical or even discovery phases, opportunities for collaboration with industry may focus more on transparency about the research agenda, optimizing access to scientific thought-leadership and data, and advancing the science through de-risking strategies, such as cost-sharing and consortia.

Harmonizing strategies for drug approval and market access

Pfizer has been a part of ongoing conversations with regulators and payors that we believe are essential for harmonizing approaches for drug approvals and market access. A clear regulatory pathway and a regulatory environment that values gene therapy as a potentially life-changing treatment modality are critical for the success of the field as a whole. Regulatory agencies, especially the FDA under commissioner Scott Gottlieb, have recognized these needs and have recently drafted guidance for pre-clinical, clinical and chemistry, manufacturing and controls expectations.

Following the issuance of the draft guidance, Gottlieb made clear the need for both consistency and flexibility in harmonizing gene therapy regulatory guidelines (www.fda.gov). Consistent and clear regulatory expectations will be critical for enabling gene therapy as a robust therapeutic class with commercially viable timelines and development costs rather than as a collection of one-off products that each require a new, expensive and time-consuming regulatory process. This is of particular importance for the development of gene therapies for small patient populations to ensure economic viability. And as regulatory agencies seek to exercise flexibility to facilitate gene therapy development, there also remains a lack of consistency in where to offer such flexibility, which creates a challenge for global development. Companies such as Pfizer that are pursuing a global plan for product development will be well positioned to help drive common experience and shared learning among regulatory agencies.

PFIZER'S AIMS FOR FUTURE INNOVATION

After decades of development, Pfizer believes that gene therapy for single gene disorders is on the cusp of becoming a robust therapeutic modality in a variety of disease indications, and it is a major focus of our efforts in rare disease. Additional advances in vector engineering, disease modelling and both clinical and commercial-scale manufacturing are essential to ensure that the full potential of this approach is realized for as many patients as possible. We hope that our continued innovation and collaborations with academia, industry and patients will allow us, and others in the field, to transform gene therapy from an interesting scientific concept into a broad portfolio of commercial products that improve patient care and outcomes.

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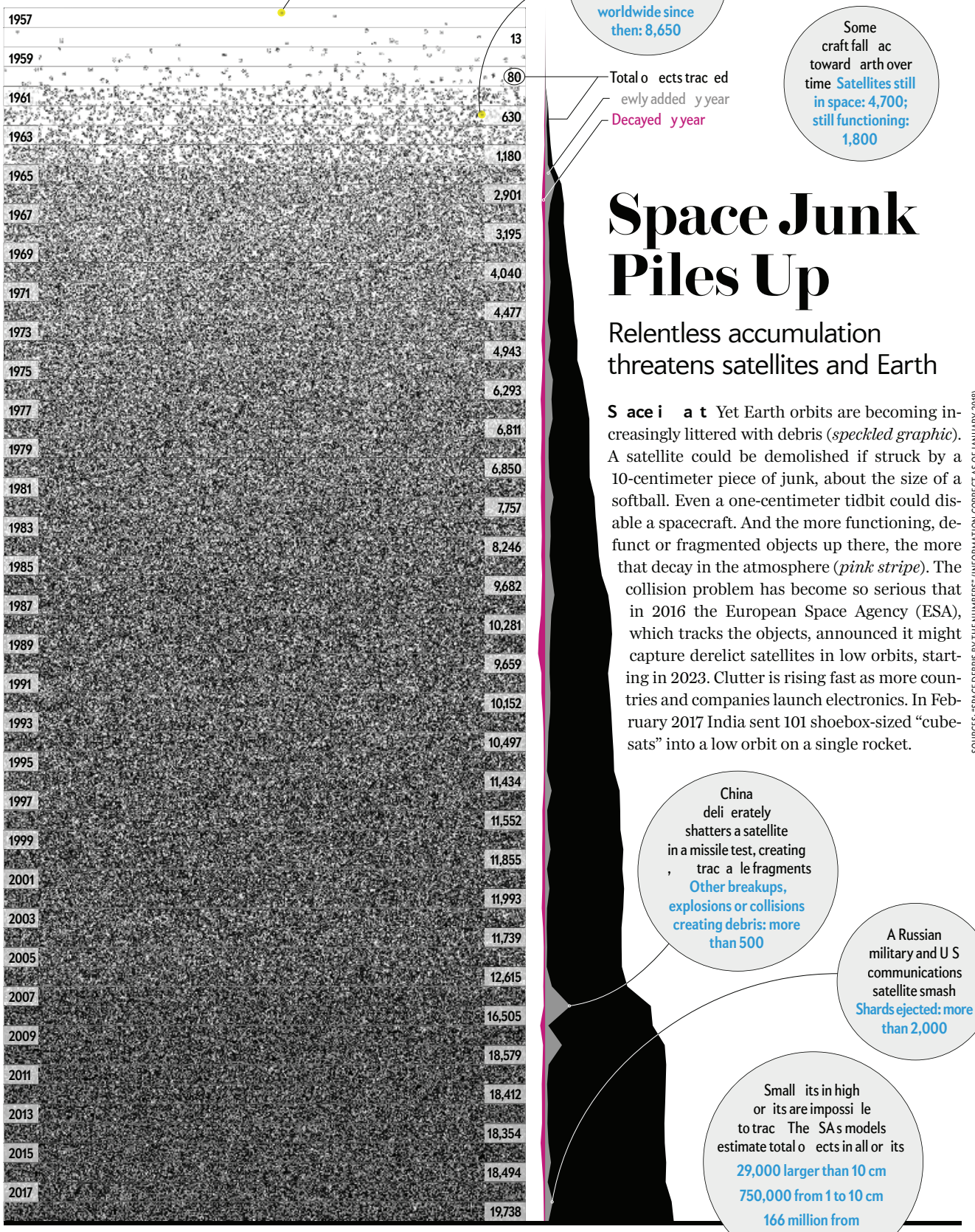
SOURCES: "SPACE DEBRIS BY THE NUMBERS" (INFORMATION CORRECT AS OF JANUARY 2018), EUROPEAN SPACE AGENCY *www.esa.int; SPACE DEBRIS: THE ESA APPROACH*, ESA BR-336. EUROPEAN SPACE AGENCY, MARCH 2017; ESA SPACE DEBRIS OFFICE *discosweb.esoc.esa.int (raw data)*



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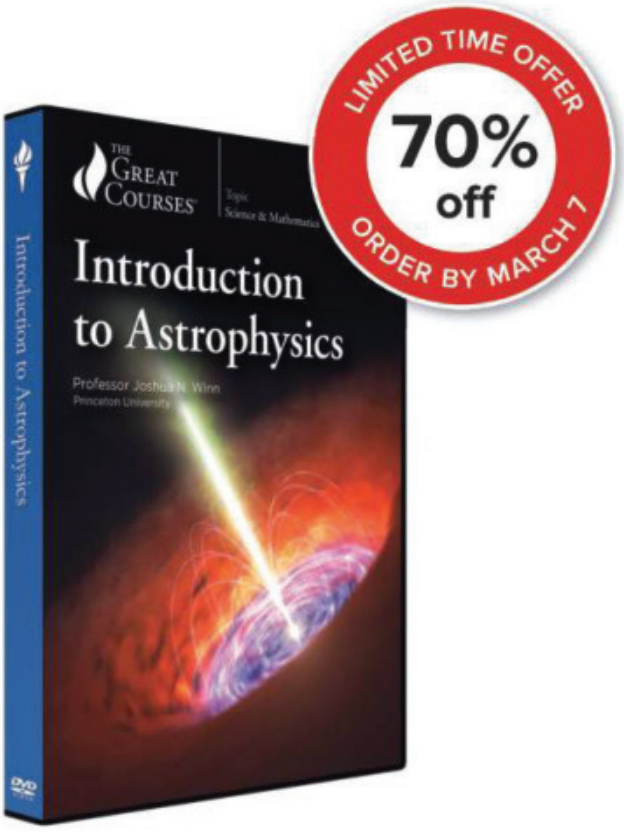

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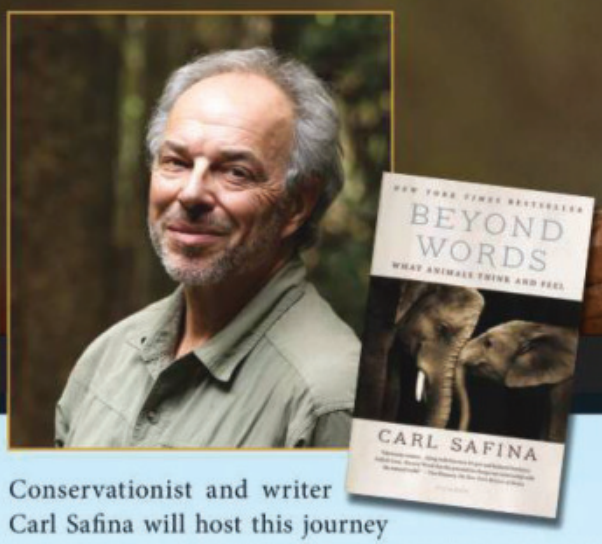

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