NEXT FRONTIERS

R. MOREL
20.12.2017

CHAMPIONS of SCIENCE

DEFEATING DISEASES WITH ENERGY

CURING CANCER WITH IMMUNOTHERAPY

ARE WE PREPARED FOR A PANDEMIC?

+ 10 START-UPS CHANGING HEALTHCARE

Johnson & Johnson INNOVATION

SCIENTIFIC AMERICAN CUSTOM MEDIA

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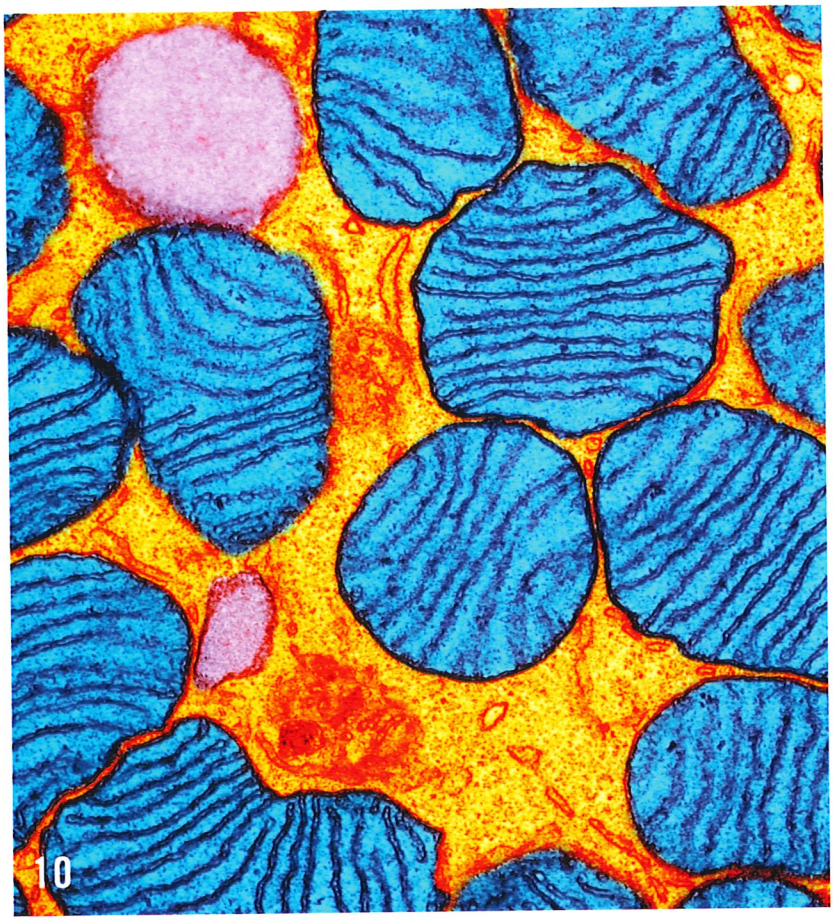

on the cover:
GLOW WELLNESS /GETTY IMAGES

NEXT **FRONTIERS**

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[LETTER FROM OUR PARTNER]

Exploring the Next Frontiers

Welcome to the inaugural issue of *Next Frontiers*, an exploration of what's new in the world of science, technology, engineering and novel white spaces. *Next Frontiers*, an evolution of the *PharmaFrontier*, features a broader array of content reflecting the vast panorama of innovation in multiple disciplines and across multiple geographies, and a new business model in the form of a partnership with Scientific American Custom Media.

The next frontiers in science and technology will impact our lives in imaginable and unimaginable ways, and provide unprecedented opportunities to help people live longer, healthier, happier lives. Yet, it can be hard to make the connection between novel but abstract innovations and the potential for significant impact on daily life. Also, we only tell part of the story — and often focus on late-stage research where the innovation is closer to the market and easier to relate. The leading edge of science and technology taking place in early stages at fledgling companies and universities as well as at unusual places, and the convergence across the fields are the untold stories yet to be fully mined.

That's why we at Johnson & Johnson Innovation believe science needs champions, and why we are partnering with Scientific American Custom Media to better tell the stories of science and the scientists who are forging next frontiers in research.

Inside the pages of our new publication, *Next Frontiers*, and at our new Champions of Science web portal, you will hear about the latest research at startup companies, new medical technologies, the latest on serious healthcare threats, and the number one most deadly class of diseases for children in the U.S. — and what researchers are doing about it.

Here we give a new voice to the most promising biomedicine, and to the people who are bringing it forward. And we hope to give new voice to you, our readers, as well. Join the conversation at the Scientific American Champions of Science hub (https://www.scientificamerican.com/champions-of-science/) and tell us what you're curious and passionate about in the world of scientific research.

Seema Kumar
Vice President
Innovation, Global Health,
and Policy Communication
Johnson & Johnson

[Q+A] From Car Care to Healthcare

William N. Hait (B.H.), global head, Johnson & Johnson External Innovation, talks to Scientific American Custom Media (SACM) about maintaining tomorrow's human bodies like we do today's vehicles.

SACM: ***You once said, "Imagine the human of the future will be more like our cars today." What did you mean?***

B.H.: When a car rolls off the assembly line, it comes equipped with numerous sensors that constantly monitor its health. If a component begins to drift out of spec, the check-engine light comes on and you take the car to the shop, where the data from the sensors are downloaded into a computer that recommends an adjustment before the car breaks down. Our cars enjoy a level of prevention and healthcare today that we should strive to achieve for humans in the future.

SACM: ***How does your car analogy relate to specific elements of healthcare?***

B.H.: At Johnson & Johnson, we strive to eliminate disease through prevention, disease interception and cures. Today, we are beginning to understand each individual's specs — that is, the diseases to which a person is susceptible. In the future, we too will be surrounded with sensors — wearables, implantables, et cetera — that continuously monitor our major components. And when we begin to go out of spec, our check engine light will come on and the data from our sensors will be downloaded into a computer that will recommend adjustments in diet, activities and medications before we break down with a disease.

SACM: ***Of these three concepts — prevention, interception and cure — where are we the closest and where do we have to the most work to do?***

B.H.: With some areas, such as infectious diseases, we have seen major advances in prevention and cures. In fact, the cure of Hepatitis C will intercept many cases of liver cancer. But many major killers, like lung cancer or Alzheimer's disease, represent huge unmet needs. These are complex illnesses where the causes are not always known. In addition, we must gain a clearer understanding of the individuals at greatest risk, so that prevention and interception will achieve the appropriate risk:benefit ratio.

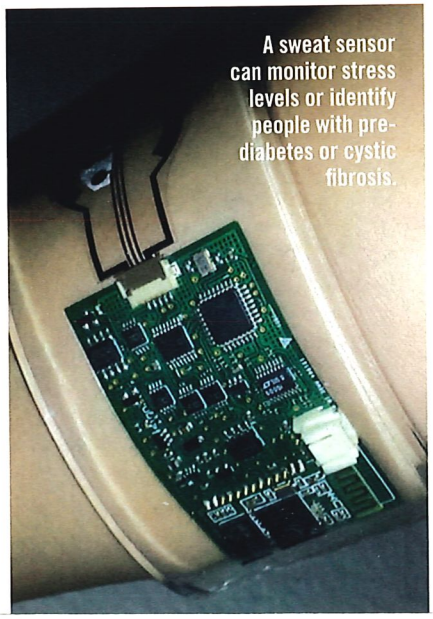
SACM: ***When do you think that your car analogy could turn into healthcare reality?***

B.H.: Monitors are not new. For example, implantable devices are available for patients with cardiac arrhythmias. These implantables not only monitor cardiac rate and rhythm, but can deliver a therapeutic shock to convert a serious arrhythmia back into a healthy state. Vaccines to prevent infectious diseases are in widespread use for an ever greater number of infectious agents. Statins intercept the disease-causing process of atherogenesis linked to hypercholesterolemia. The challenge is to apply this approach broadly. We need to increase our investment in prevention and interception, as we focus treatments on curing in addition to managing the morbidities of disease.

SWEAT-NOSIS

Anything in blood ends up in sweat, albeit at much lower levels. Stanford University biochemist Ronald Davis and pediatrician Carlos Milla, along with their team, built a wearable sweat detector from microprocessors and flexible sensors that could be used to detect and monitor a range of diseases.

Davis and Milla already showed that this sensor picks up some disease-related indications, such as high levels of chloride in the sweat of cystic fibrosis patients and high levels of glucose in the sweat of diabetics. The device, which is worn around the wrist, sends that data to a cellphone and then a server for analysis. Such sensors could help patients manage, or even avoid, a range of chronic illnesses. —NEIL SAVAGE



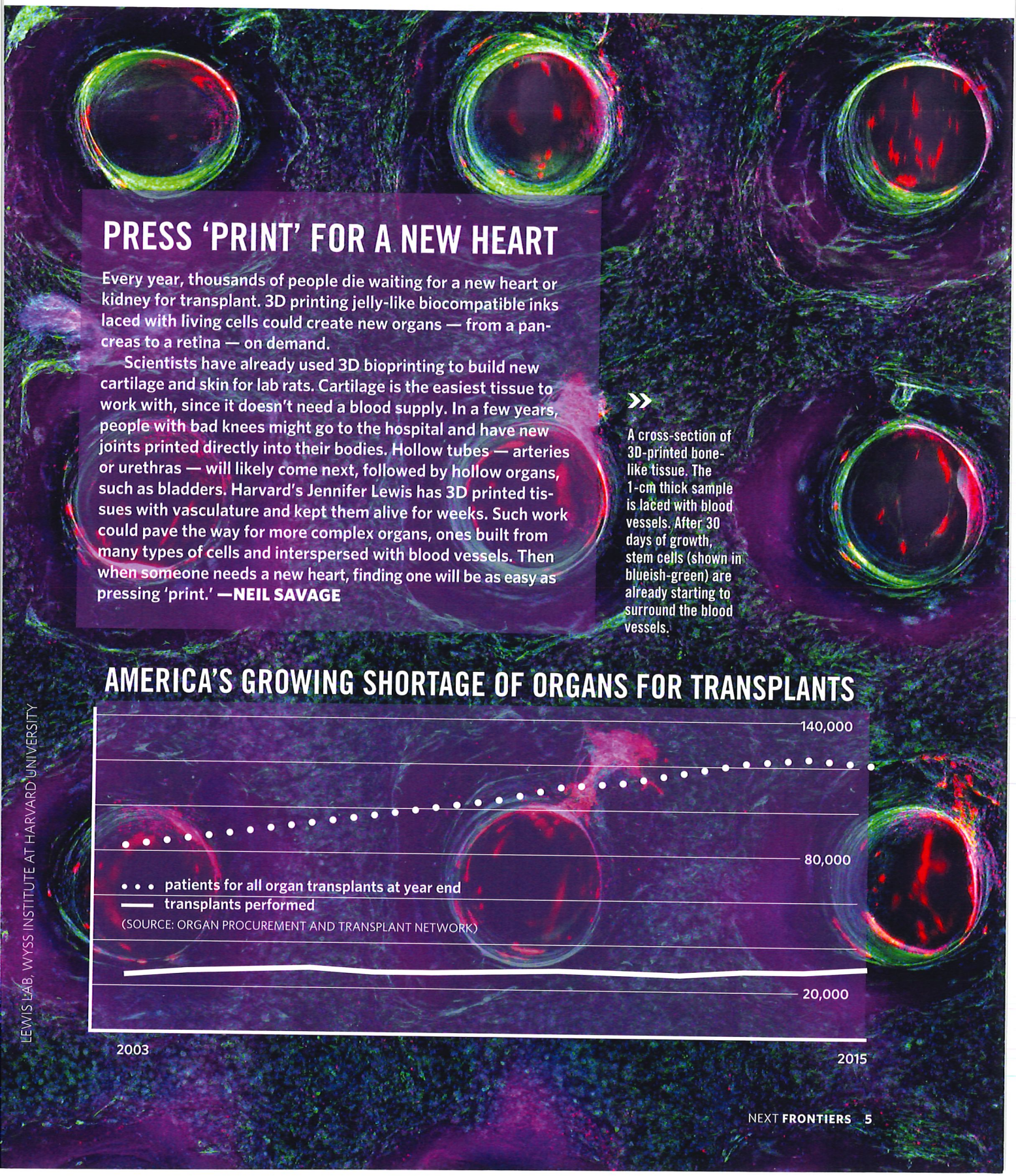
A sweat sensor can monitor stress levels or identify people with prediabetes or cystic fibrosis.

DIGITALLY ENABLED MEDICAL DEVICES provide an increasing level of feedback on patients' health. This includes smart implants that, for example, detect pressure ulcers in hospital patients. In the near future, more patient data will be collected from orthopedic implants, heart implants and other devices that interact with the body.

PRESS 'PRINT' FOR A NEW HEART

Every year, thousands of people die waiting for a new heart or kidney for transplant. 3D printing jelly-like biocompatible inks laced with living cells could create new organs — from a pancreas to a retina — on demand.

Scientists have already used 3D bioprinting to build new cartilage and skin for lab rats. Cartilage is the easiest tissue to work with, since it doesn't need a blood supply. In a few years, people with bad knees might go to the hospital and have new joints printed directly into their bodies. Hollow tubes — arteries or urethras — will likely come next, followed by hollow organs, such as bladders. Harvard's Jennifer Lewis has 3D printed tissues with vasculature and kept them alive for weeks. Such work could pave the way for more complex organs, ones built from many types of cells and interspersed with blood vessels. Then when someone needs a new heart, finding one will be as easy as pressing 'print.' **—NEIL SAVAGE**



A cross-section of 3D-printed bone-like tissue. The 1-cm thick sample is laced with blood vessels. After 30 days of growth, stem cells (shown in blueish-green) are already starting to surround the blood vessels.

LEWIS LAB, WYSS INSTITUTE AT HARVARD UNIVERSITY

AMERICA'S GROWING SHORTAGE OF ORGANS FOR TRANSPLANTS

(SOURCE: ORGAN PROCUREMENT AND TRANSPLANT NETWORK)

A Treatment That's Easier to Stomach

BY MICHAEL EISENSTEIN

What if there were a cure for type 2 diabetes, but most patients couldn't benefit from it? This simple question inspired Ashish Nimgaonkar, a gastroenterologist at Johns Hopkins University, and his colleagues at the Center for Bioengineering Innovation and Design to found Glyscend, a biotechnology startup that is trying to develop an alternative to a costly and complicated diabetes treatment. Armed with funding from the World Without Disease QuickFire Challenge, which was sponsored by Johnson & Johnson Innovation and Janssen Research & Development, Glyscend is now accelerating toward clinical trials and, hopefully, an approved therapy.

3-5 BILLION PEOPLE lack access to the most basic and essential surgical care. This is changing with new medical technologies and tools — such as innovation in sterilization technologies, supply-chain improvements and education on new procedures for wound closure or hernia treatment — that enable lower-cost and safer procedures.

ALMOST 10% OF AMERICANS HAVE DIABETES.
-U.S. CENTERS FOR DISEASE CONTROL AND PREVENTION

Nimgaonkar first came to the idea of alternative diabetes treatments after reading reports of bariatric surgeries. In the morbidly obese, the surgeries seemed have a side effect of mitigating diabetes. "Patients who get surgery can go off their insulin and other diabetic medicines without having even lost an ounce of weight," he says. Evidence of this effect has grown to the point that some medical societies have moved to recommend bariatric surgeries to diabetic patients. Over the past year, a growing number of insurers have extended their coverage to include bariatric surgery for the treatment of diabetes, but many patients are either ineligible or reluctant to undergo this still-costly and highly-invasive procedure — assuming they even know about it. "Many doctors are not even aware that these endoscopic procedures and bariatric surgery are an option, so many patients don't even get referred," says Nimgaonkar.

"Many doctors are not even aware that these endoscopic procedures and bariatric surgery are an option, so many patients don't even get referred."

-ASHISH NIMGAONKAR

Current research suggests that the benefits of this procedure arise from reducing the interaction between digesting food and the intestinal wall. The details of this mechanism remain unclear, but could entail direct reduction of caloric intake, as well as altering the production of intestinal hormones that regulate insulin production and glucose regulation. Regardless, Glyscend aims to mimic the effect of a bariatric surgery with a pill that releases a polymer that forms a barrier within the intestine. Other companies have explored similar synthetic barrier-based approaches, including devices such as EndoBarrier — a flexible 'liner' manufactured by gi Dynamics that is delivered to the intestine via a non-surgical, endoscopic procedure. But a pill that can deliver equal or superior protection would be far more appealing to most patients.

Selecting the right material has been the central challenge. It has required extensive testing to identify patient-friendly materials that can reliably self-assemble into a robust barrier in the gut. "We made a long list of must-have and nice-to-have criteria that needed to be met," says Nimgaonkar. Initially, his group focused exclusively on materials with an established track record of human testing or clinical use. The researchers identified dozens of candidates which they winnowed down to a handful of polymers that appear to be safe and perform as intended in animal models. "We have shown significant reductions in blood glucose after administration of the polymers," Nimgaonkar says.

FIRING UP THE FUNDS

Initially, the company was scraping by with relatively modest funding from state and federal agencies, but, Glyscend received a big boost in 2016. As one of the three winners of the World Without Disease Challenge, the company netted $500,000 in funding — beating more than 470 rivals in a competition designed to reward innovative approaches to preventing and treating chronic disease.

"We were seeking cross-sector, technology-based solutions to a big unmet medical need, with a focus on lung cancer and diabetes," says Barry Springer, vice-president of strategy, innovation and research, Janssen BioTherapeutics. "We prioritized innovative, potentially transformative approaches." This award also establishes an open line of collaboration between the two companies, allowing Glyscend scientists to routinely connect with Johnson & Johnson's internal expertise in the metabolic disease space.

Still, much research lies ahead before Glyscend can even speculate on how well this will work or whether it will work at all. Glyscend is actively focused on developing new formulations with even better safety and efficacy characteristics, and it is developing a plan for clinical studies. "The next six months will be critical," says Nimgaonkar. "We are planning to see how well this polymer does in a relatively short clinical study early next year."

Springer has high hopes for Glyscend's future prospects: "I'm most excited about the potential to cure type 2 diabetes in a safe and noninvasive manner."

Building a World Without Alzheimer's

BY RENEE MORAD

Among the 10 leading causes of death, Alzheimer's disease (AD), which ranks as number six, is the only one that cannot be prevented, slowed or cured. While deaths from heart disease have decreased by 14% since 2000, deaths from AD have increased by 89% in the same timeframe, says the Alzheimer's Association. But Nicola Corbett, a research associate at the Hooper lab at the University of Manchester in the United Kingdom, is using induced pluripotent stem cells (iPSCs) to expose the cellular mechanisms behind AD. She envisions a future where Alzheimer's disease isn't "such a huge, unresolved problem" and dreams that one day her research will play a crucial role in turning AD from a death sentence into a manageable or perhaps even preventable disease.

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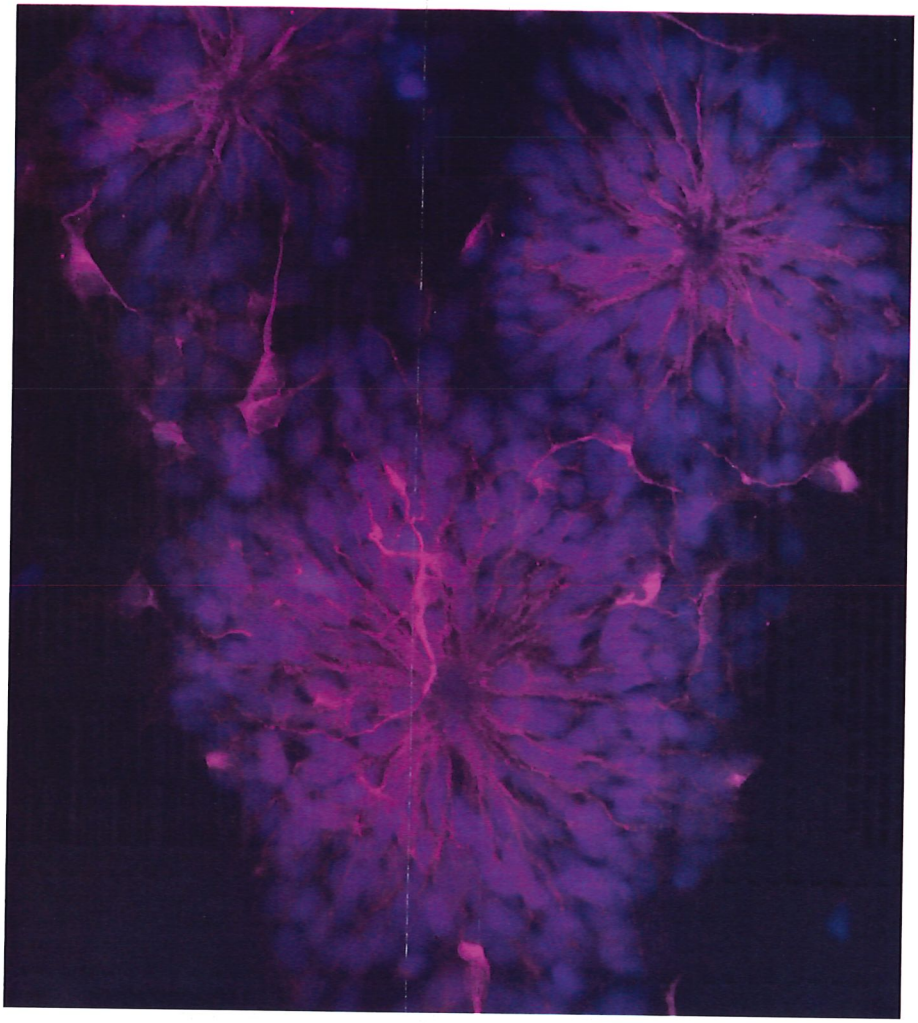


Nicola Corbett is chemically inducing stem cells into neurons to better understand Alzheimer's. Developing neurons are shown in purple.

Corbett is opening up the possibility of studying the pathophysiology of Alzheimer's disease at the level of human cells.

ALZHEIMER'S DISEASE IS #6 AMONG LEADING CAUSES OF DEATH IN THE UNITED STATES.
-ALZHEIMER'S ASSOCIATION

"We don't really know where, or when, Alzheimer's even starts in the brain," Corbett says. She's studying the cellular biology of neurons derived from iPSCs, that were originally fibroblasts taken from patients with and without AD. By comparing these neurons, Corbett hopes to uncover the differences that arise in AD, and she's opening up the possibility of studying the pathophysiology of AD at the level of human cells.

Plenty of scientists have used iPSCs to make mature cells, including neurons, but Corbett aims to develop a cellular model of AD. Still, she admits that even the process of differentiating iPSCs into neurons is time-consuming and challenging — "some days, the cells just don't want to play ball," she says — but watching them turn into neurons is thrilling. "I always love looking down the microscope at them and finding new things," she says.

Once she gets this process working regularly, she can turn to building and applying her model system. With a regular supply of neurons from AD patients, Corbett will try to show that patient-derived iPSCs make a good disease model. If that works out, she can start to test potential treatments. This will mean looking for something that delays, or reverses, any differences between the diseased and healthy neurons.

Beyond battling AD in the lab, Corbett is a staunch supporter of scientists providing community service. For instance, she volunteers as a Dementia Friend, an England and Wales-based initiative focused on raising awareness about dementia and helping patients.

Others also want to help patients with AD. In November 2017, Microsoft founder Bill Gates announced a donation of $100 million of his own money to support AD research, and there's a lot of work to do. In thinking of the lack of medication for AD, Corbett says, "This is what neuroscientists, including myself, are working hard to change."

COURTESY OF NICOLA CORBETT

DEFEATING DISEASES WITH ENERGY

The cell's mitochondria generate 90% of a body's energy. Could scientists harness that power to fight disease and perhaps even aging?

BY RENEE MORAD

Scientists often refer to the mitochondria as the energy factories of the cell. For good reason. The intracellular organelles transform the food we eat and the air we breathe into an electric potential that drives processes like DNA replication or protein building. Individually, the impact of any given mitochondria is small. The potential energy within a cell is about 0.2 volts. But add all those cells up, and the potential energy within a human body is roughly equivalent to a lightning bolt.

Doug Wallace — director of the Center for Mitochondrial and Epigenomic Medicine at the Children's Hospital of Philadelphia Research Institute, and the 2017 winner of the Dr. Paul Janssen Award — has been studying mitochondria and their DNA for fifty years. More than anyone he understands the importance of mitochondria. "They generate more than 90% of cellular energy," he says. "Anything that generates that much energy can't be trivial."

And yet mitochondria, for all the energy they contribute, have been largely overlooked in medicine. "All the clinical subspecialties are based primarily around anatomy, and so you have neurologists, ophthalmologists, cardiologists, nephrologists, dermatologists and so on, but that model doesn't take into account mitochondria," says Wallace. "Since different organs rely on mitochondrial energy to different extents, partial mitochondrial defects result in organ-specific symptoms."

JGI / TOM GRILL / GETTY IMAGES

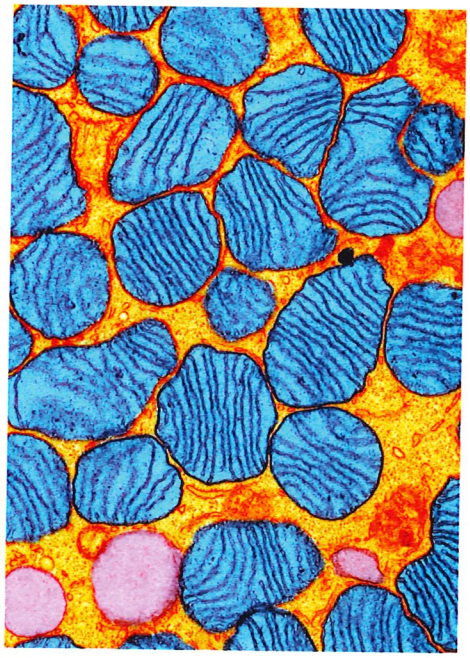
That's now changing. Led by Wallace, scientists are now digger deeper into the role mitochondrial disease might play in many of our most pervasive diseases and even into aging itself. The idea is nothing short of a paradigm shift, viewing energy broadly rather than organs specifically. And if Wallace is right, that idea could change millions of lives for the better.

MITOCHONDRIA GENERATE >90% OF A BODY'S ENERGY.
-DOUG WALLACE

In the past, scientists have frequently looked to nuclear DNA for answers about disease and aging, but Wallace believes mitochondrial DNA could be the missing link that can steer them toward new understandings about disease, and potentially, new therapies.

INSIDE MITOCHONDRIA

Most DNA, called nuclear DNA, is located in the nucleus of our cells, and contains two copies of each gene, of which there are more than 20,000. For each gene, one copy is inherited from the mother, and another is inherited from the father. But mitochondrial DNA, inherited exclusively from the mother, is much smaller and is located outside the nucleus, inside the mitochondrion. The mitochondria turn food's hydrogen and carbon and inhaled oxygen into carbon dioxide (CO_2), water and adenosine triphosphate, or ATP, which stores energy.



In 1980, Wallace discovered that mitochondrial DNA changes over time by sequential mutations. "Since almost everybody has a slightly different mitochondrial DNA that makes for different efficiencies in mitochondrial function, this creates a lot of energy diversity, which is good for adapting to changing environments. But it also means mitochondria are very important in susceptibility to disease," Wallace says.

"My belief is that mitochondrial dysfunction underlies the etiology of most common complex diseases, as well as aging," Wallace says. He explains that a person suffering from chronic headaches might see a neurologist, but there's also the possibility that "there's a systemic energy defect causing the headache. There's nothing wrong anatomically with the brain." Wallace believes the same can be said for problems with the heart, muscles, renal and endocrine systems.

A DEEPER UNDERSTANDING

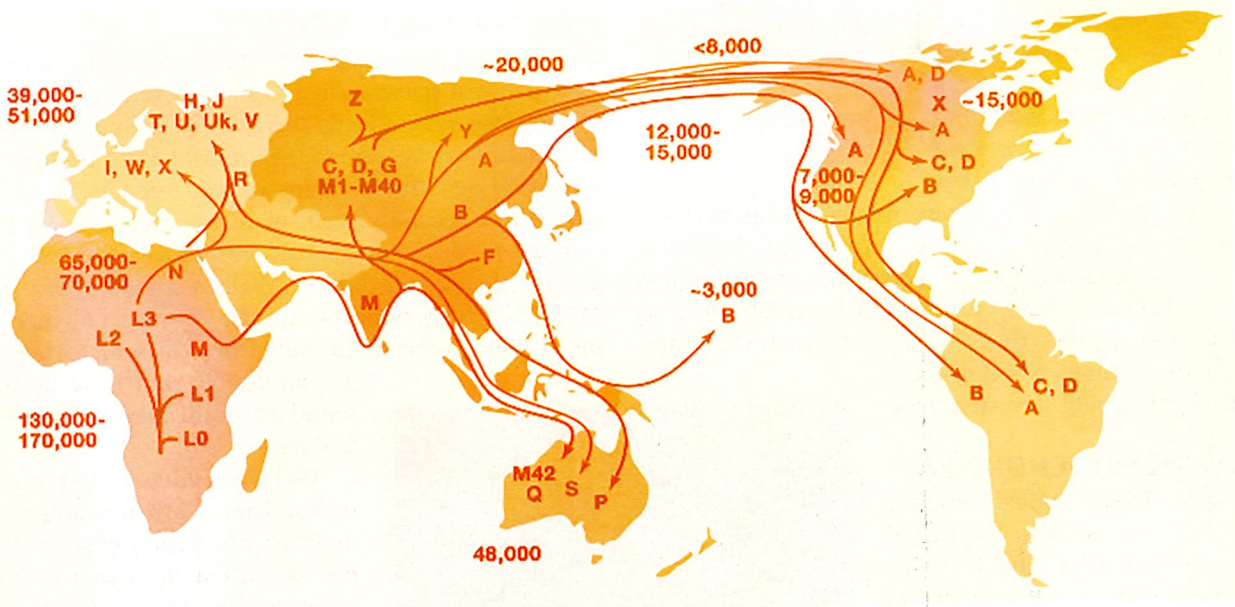
In 1988, Wallace found the first inherited mitochondrial-DNA disease, called Leber's hereditary optic neuropathy, which leads to vision loss. By the early 2000s, hundreds more mitochondrial-DNA diseases had been discovered. Many of these genetic disorders starve the body's cells of energy and come with symptoms such as seizures, respiratory problems and intellectual disabilities. Wallace's website called MITOMAP.org outlines all the known polymorphisms and pathogenic mutations, of which there are hundreds, that have been found in mitochondrial DNA to date.

Wallace believes that mitochondrial polymorphisms may be important for humans' predispositions to a variety of diseases. Recent studies suggest that mitochondrial DNA variations could lead to everything from autism, cancer and inflammation to neurodegenerative diseases. For example, one recent study, conducted by the Memorial Sloan Kettering Cancer Center and the Boston-based Cambridge Institute, suggests in many types of cancer, tumor cells have fewer copies of mitochondrial DNA than the cells that make up normal tissues. The researchers also discovered that the number of copies of mitochondrial DNA in certain tumors is related to the incidence of mutations that cause cells to become cancerous — a finding that could help direct new treatments for these tumors.

Mitochondrial DNA also plays a role in aging. "Over time, we accumulate more and more mitochondrial-DNA mutations that slowly erode our energetic capacity," Wallace says. "As people get older, this is why they often complain that they don't have the energy that they used to."

More important, their cells and organs don't have the energy they need to function and maintain them-

selves. Wallace believes this could lead to a number of age-related diseases, such as Alzheimer's and Parkinson's diseases. For large, energy-intensive organs — the brain uses 20% of the body's energy, for example — any change in energy output can have a profound effect on function.



Using mitochondrial DNA, Doug Wallace was able to retrace the migration of humans out of Africa.

GLOBALIZATION'S IMPACT

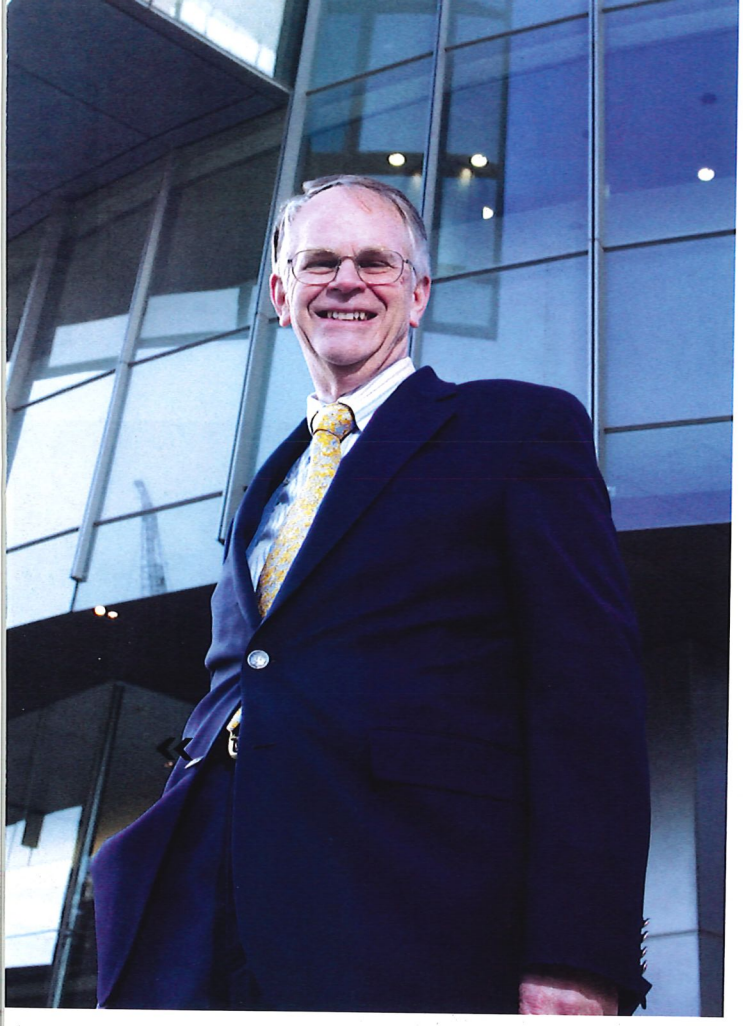
In the 1970s and '80s, Wallace pioneered the concept of maternal inheritance, and he used that pattern to identify the most recent common ancestor of all contemporary humans, the so-called Mitochondrial Eve (a term Wallace does not particularly like). In doing that work, Wallace noticed that human migrations were usually accompanied by mutations in mitochondrial DNA, which allowed our species to exploit new environments. That helped us as a species proliferate, but now it's presenting new challenges. For example, someone with mitochondria adapted to an active lifestyle, low-fat diet, and hot climate might be maladapted to a more the sedentary lifestyle and high-fat diets common in colder climates.

Wallace believes that globalization could have a profound effect on today's mitochondrial-DNA variants and that mitochondrial maladaptation could underpin many chronic diseases. In his view, human mitochondria today are often mismatched to their current climates and diets, which is why many chronic diseases like obesity, diabetes, autism and certain types of cancer and neurodegenerative diseases are on the rise.

"The caloric intake and climates of many individuals are no longer in sync with their genetic his-

AGAINST THE ODDS

Meredith Hardy's sons are living life to the fullest despite their devastating diagnosis. BY RENEE MORAD



Cellular energy, according to Doug Wallace, could be the key to future disease treatment.

tory," Wallace says. "It also explains why people with certain ancestral lineage might be more susceptible to certain types of diseases."

A MORE HOLISTIC APPROACH

In most genetic studies that have looked for associations between genes and diseases, investigators focus on variations in nuclear DNA, not mitochondrial DNA. And yet, after decades of research, it's evident that nuclear DNA might not contain all the answers scientists seek.

"We've completely ignored energy in Western medical philosophy," Wallace says. While Alzheimer's disease patients assume they need to see a neurologist, Wallace explains, nobody in the West is going to suggest a biochemist instead.

Wallace is confident that a more holistic approach to medicine and a greater emphasis on energy's role could bring forth new preventions and treatments for disease in the future. He's also certain that the significance of mitochondrial DNA should play a more prominent role: "You can't live without energy," he says.

About 18 months after her second child was born, Meredith Hardy had a painful realization. Her children were not normal. Her youngest son, Lachlan, almost died when he was three weeks old. She spent most of his infancy reviving him because he had a hard time breathing and sleeping at the same time. Her older son, Niels, started with acid reflux and chronic constipation. Then, he had frequent sinus infections, and his balance and speech were affected. He also had frequent vomiting and unexplained fevers.

After countless appointments and no diagnosis, Hardy and her family uprooted from Charlotte, North Carolina to Philadelphia to be close to the Children's Hospital of Philadelphia. She thought someone there might know what was happening to her boys.

Hardy's doctor at Children's Hospital of Philadelphia immediately suspected mitochondrial disease, which was ultimately confirmed by a muscle biopsy.

"We've helped more than 60 families so far with advice and by sharing our treatment plans." -MEREDITH HARDY

Mitochondrial disease is an inherited chronic illness that can be present at birth or developed later in life. It impacts an estimated one in 4,000 people and can cause debilitating physical, developmental and cognitive disabilities with symptoms ranging from poor growth and loss of muscle coordination to seizures, vision or hearing loss and organ failure.

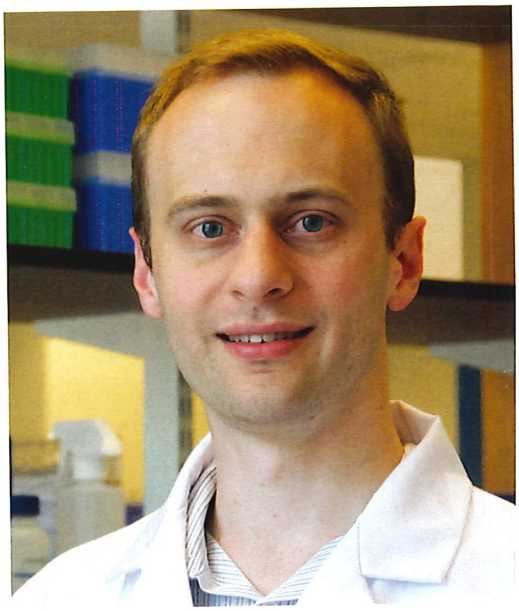
Today, the boys, now 13 and 11, are committed to a rigorous treatment plan, which includes immunoglobin therapy, steroids, seizure medication, a custom cocktail of supplements and two hours of intense interval exercise daily. They are thriving, and they represent hope for other families experiencing similar challenges. "We've helped more than 60 families so far with advice and by sharing our treatment plans," Hardy says.

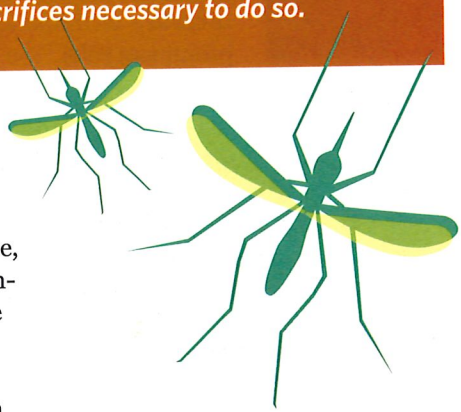
CHILDREN'S HOSPITAL OF PHILADELPHIA/ED CUNICELLI

[Q+A]

Defeating the Delivery of Disease

As the director of the Sculpting Evolution Group at the MIT Media Lab, Kevin Esvelt (K.E.) spends every day thinking about extinction. Esvelt is a biochemist, and he is developing a method to eradicate certain diseases before they eradicate us. Instead of tackling a disease after an infection, like most gene therapies would, Esvelt wants stop diseases before they strike. Using CRISPR/Cas9 gene editing and gene drive — a natural mechanism that preferentially pushes a gene from one generation to the next — Esvelt could, in theory, eliminate a disease by blocking the organisms that carries it (See Creating Complete Resistance with CRISPR/Cas9.) With CRISPR, Esvelt could, for example, block every mosquito in the world from carrying malaria. As beneficial as this sounds, it also makes many people nervous. Esvelt sat down with Elie Dolgin (E.D.) to discuss how to eliminate a disease and the sacrifices necessary to do so.





E.D. ***Can CRISPR actually eliminate diseases?***

K.E.: For any animals that serve as vectors or reservoirs of disease, we should be able to build organisms that are programmed to be immune to every virus known to infect them. So, this would mean things like malaria, which is spread by mosquitos, or Ebola, which has a reservoir in bats, or Lyme disease, which is carried primarily through the white-footed mouse.

E.D. ***What makes CRISPR unique in this kind of disease fighting?***

K.E.: CRISPR lets us harness a naturally occurring phenomenon called gene drive to spread genes of our choosing. This means that we could engineer an organism that would confer disease resistance to an entire species. Ideally, we'd want to start small and local, see how well it works, and only then scale up if it's warranted.

E.D. ***What determines if it's warranted?***

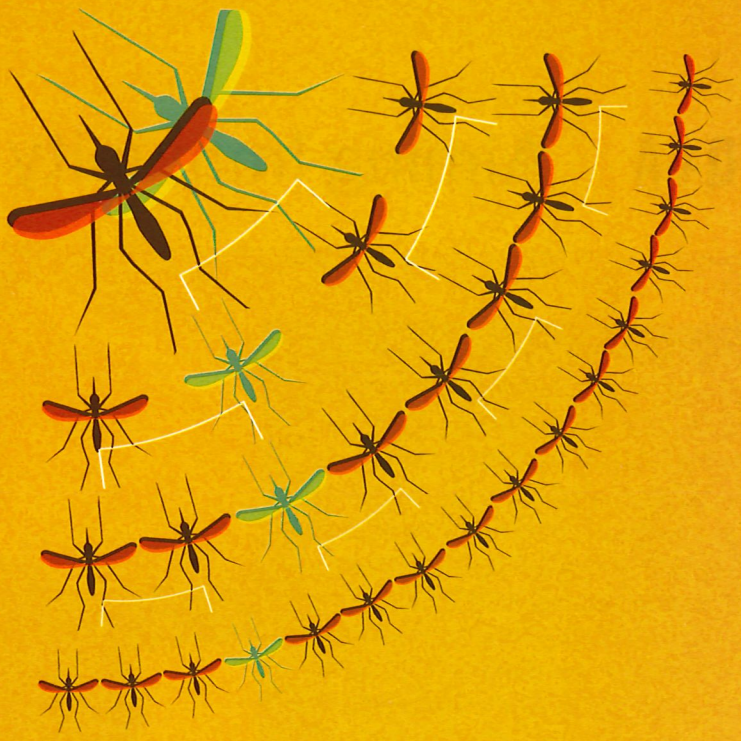
K.E.: It has to be a very big problem indeed for people to be willing to alter an entire species, which is spread across many different nations, all of which would have to agreed — and they would all have to agree to do it without the benefit of a field trial to show that it's safe and it works. Malaria is one of the only cases I can think of that fits the bill. A group called Target Malaria is working on this now, talking with lots of African countries at different levels, seeing if there can be a path to agreement.

E.D. ***And for other diseases like Lyme?***

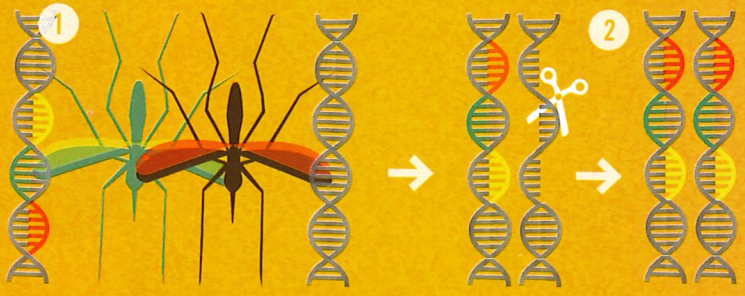
K.E.: Here's the thing: Technically we could do it, but socially and diplomatically we can't. So, what we need is a version of gene drive that can still amplify but is self-exhausting. Then every town could decide for itself whether it wanted this kind of local version of gene drive in their backyard. We're still working on that system, but I'm not really worried about technical hurdles. The question is whether the technical solutions like this will be sufficient to solve the social and diplomatic problems.

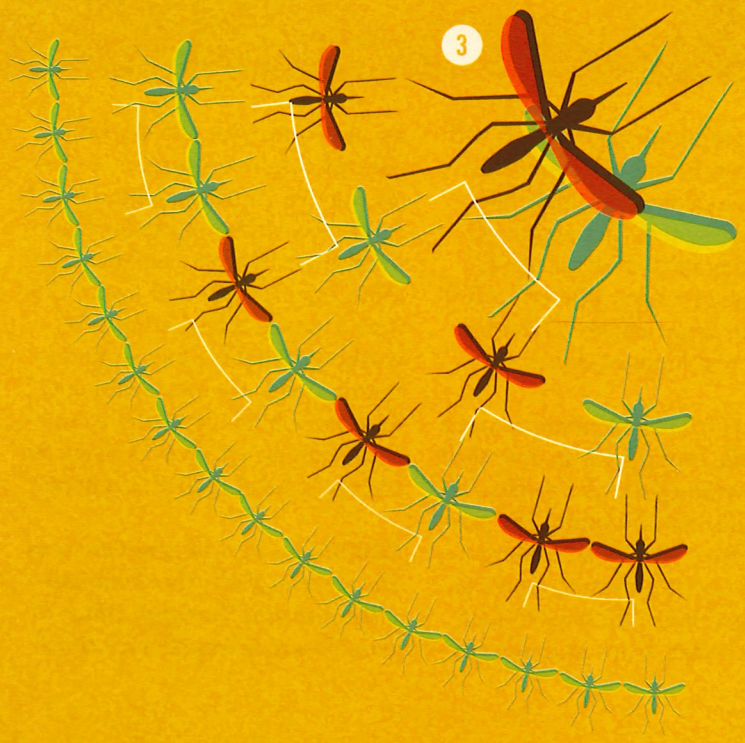
CREATING OVERALL RESISTANCE WITH CRISPR/CAS9

In a traditional attempt to fight malaria, a resistance gene, which prevents the insect from carrying the disease, is engineered into one chromosome of a mosquito. When that mosquito (*green*) mates with an ordinary mosquito (*brown*), only half of the offspring get the resistance gene. Consequently, the mosquitoes carrying the resistance gene dwindle — or even disappear — over just a few generations of mating with ordinary mosquitoes.



1. Instead, Esvelt and his colleagues make mosquitoes with a resistance gene embedded in a CRISPR/Cas9 system, which is designed to insert that gene in other chromosomes. In each chromosome, these mosquitoes carry the resistance gene (*green*), the genes for the Cas9 enzyme (*yellow*) and guide RNAs (*red*). When a mosquito with the resistance complex mates with an ordinary one (*brown*), the offspring gets one resistance-complex chromosome and one wild type.

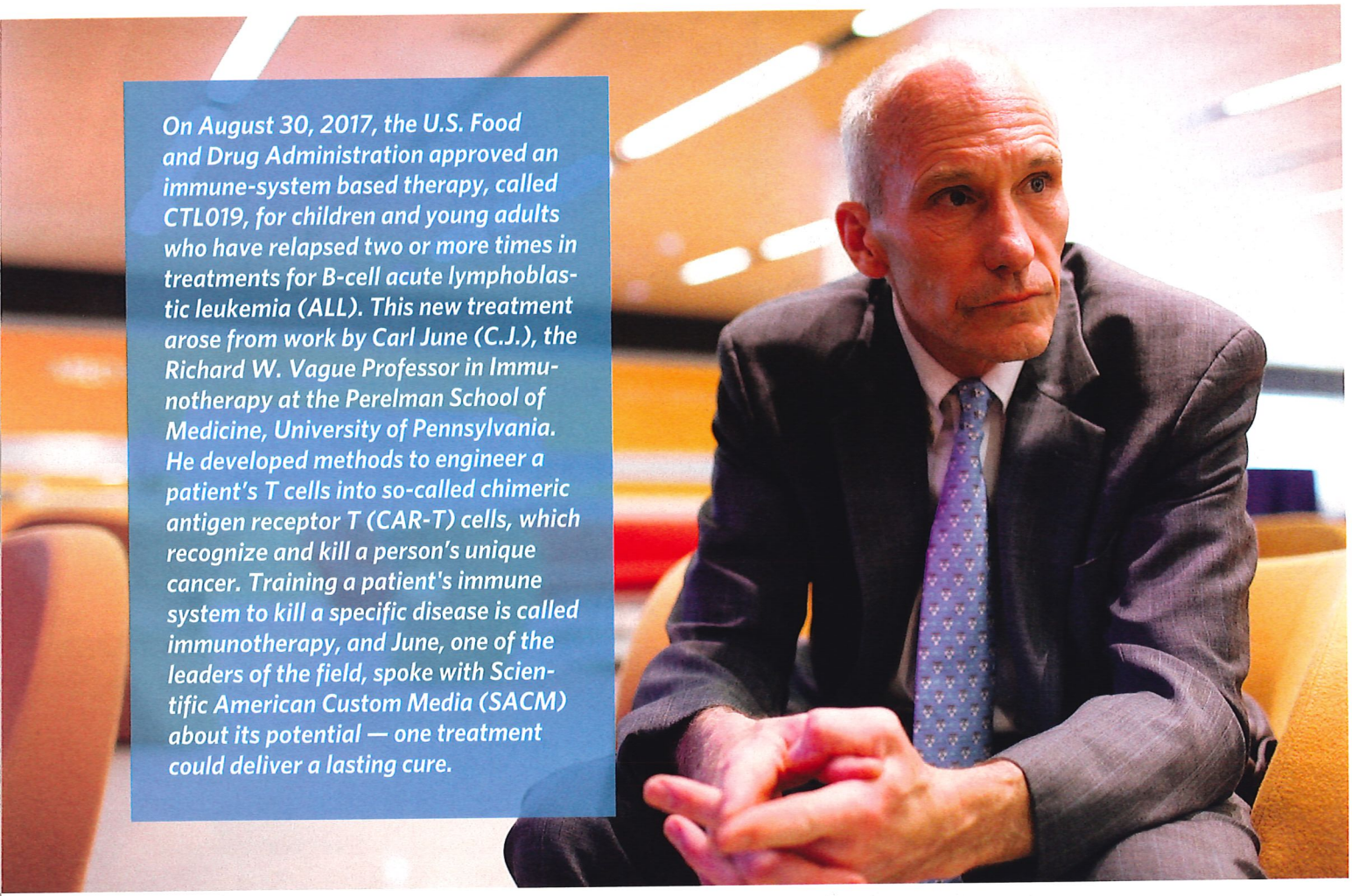




2. Then, the guide RNAs direct Cas9 to cut out the pieces of the wild-type chromosome that align with the CRISPR/Cas9 system. In repairing the break in the chromosome, the resistance complex is used as a template — adding the genes for the Cas9 enzyme and guide RNAs, plus the resistance gene to the wild-type chromosome.

3. This process gets repeated every time a resistant mosquito mates with an ordinary one, and soon the entire population carries the resistance gene. This would eliminate the carrier mechanism of malaria, and the disease along with it.

[Q+A] Aiming Immunity at Cancer



On August 30, 2017, the U.S. Food and Drug Administration approved an immune-system based therapy, called CTL019, for children and young adults who have relapsed two or more times in treatments for B-cell acute lymphoblastic leukemia (ALL). This new treatment arose from work by Carl June (C.J.), the Richard W. Vague Professor in Immunotherapy at the Perelman School of Medicine, University of Pennsylvania. He developed methods to engineer a patient's T cells into so-called chimeric antigen receptor T (CAR-T) cells, which recognize and kill a person's unique cancer. Training a patient's immune system to kill a specific disease is called immunotherapy, and June, one of the leaders of the field, spoke with Scientific American Custom Media (SACM) about its potential — one treatment could deliver a lasting cure.

SACM: ***What is the key feature of immunotherapy?***
C.J.: A single treatment of cellular immunotherapy gives a person cancer-fighting CAR-T cells that can last a lifetime. That is very different than most of the other cancer therapies, which are often given over and over.

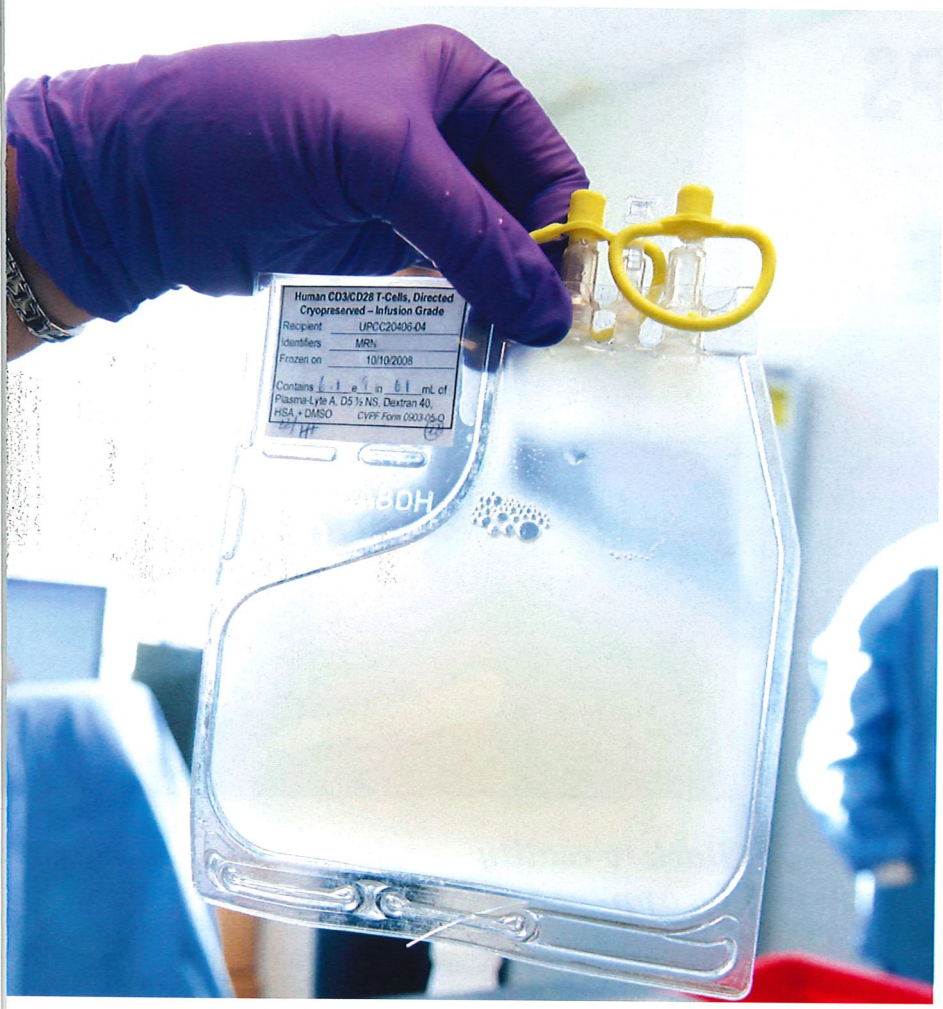
SACM: ***Can immunotherapy only fight ALL?***
C.J.: I think immunotherapy is eventually going to treat all cancers. Rather than directly targeting the cancer, immunotherapy targets the immune system, and then the immune system deals with the cancer. In a way, it's more like a device-independent thing, like a software system. In the past, all cancer therapies were specific for each kind of cancer. But the CAR-T cell approaches can be very similar for different kinds of cancer.

SACM: ***With the immune system doing the heavy lifting, does that reduce side-effects for patients?***
C.J.: With chemotherapy, the primary effects have been off-target—loss of appetite, nausea, vomiting, all those things. Those don't help you get better. Now, immunotherapy does have side-effects, but in general, they're on-target: It's an over-active immune system, which can lead to different kinds of autoimmunity, and that can affect the joints or colon or other areas. But it also means the treatment is working. What we have found is that patients are more willing to have those kinds of side-effects because they accept that it's a sign the therapy is helping them get better.

SACM: ***You've had great success in treating pediatric leukemia with immunotherapy. What is your latest advance with that?***

ANDREW RENNEISEN / PHILADELPHIA INQUIRER

EARLY DETECTION will transform the standard of cancer care. Diagnostic tools — from breathalyzer-type technologies to tumor-analysis algorithms — will identify tumors very early, when treatment is most likely to succeed.



«
A patient's T cells get turned into personalized cancer medicine.

C.J.: When we used CAR-T therapy with children and young adults with ALL, more than 90% of them went into remission. Whenever you start something at a single center like we did in Philadelphia, you don't know initially if you just got lucky and happened to pick people who are going to do well. But a global clinical trial carried out by Novartis — using our immunotherapy method for pediatric leukemia — got the same results in an international trial: remission in approximately 90% of the children treated. So, now we know that our initial results weren't a fluke, and that's very gratifying. Because the first patients we treated as still in remission, we also now know that it's durable for at least five years. So, we now believe that some patients are cured.

"A single treatment of cellular immunotherapy gives a person cancer-fighting CAR-T cells that can last a lifetime."-CARL JUNE

SACM: ***Although you've focused on pediatric leukemia, what other cancers could be treated with immunotherapy?***
C.J.: Today, the number one cause of cancer death in kids is brain cancer. So, the next big medical need is learning how to treat that and other solid tumors. That's what we're working on now.

SACM: ***With patients cancer-free for five years, are you starting to feel confident that it's a permanent repair?***
C.J.: Leukemia starts in the bone marrow, and with next-generation sequencing we can find a single leukemic cell in a million cells. Most of our patients start with 90% of their bone marrow being cancer cells. After treatment they have less than one cancerous cell in a million bone-marrow cells. It's a huge reduction. We don't know that there's not some sanctuary where there's some cancer cell hiding out in a patient, but they are clinically well. Only time will tell if the cancer is eradicated or not.

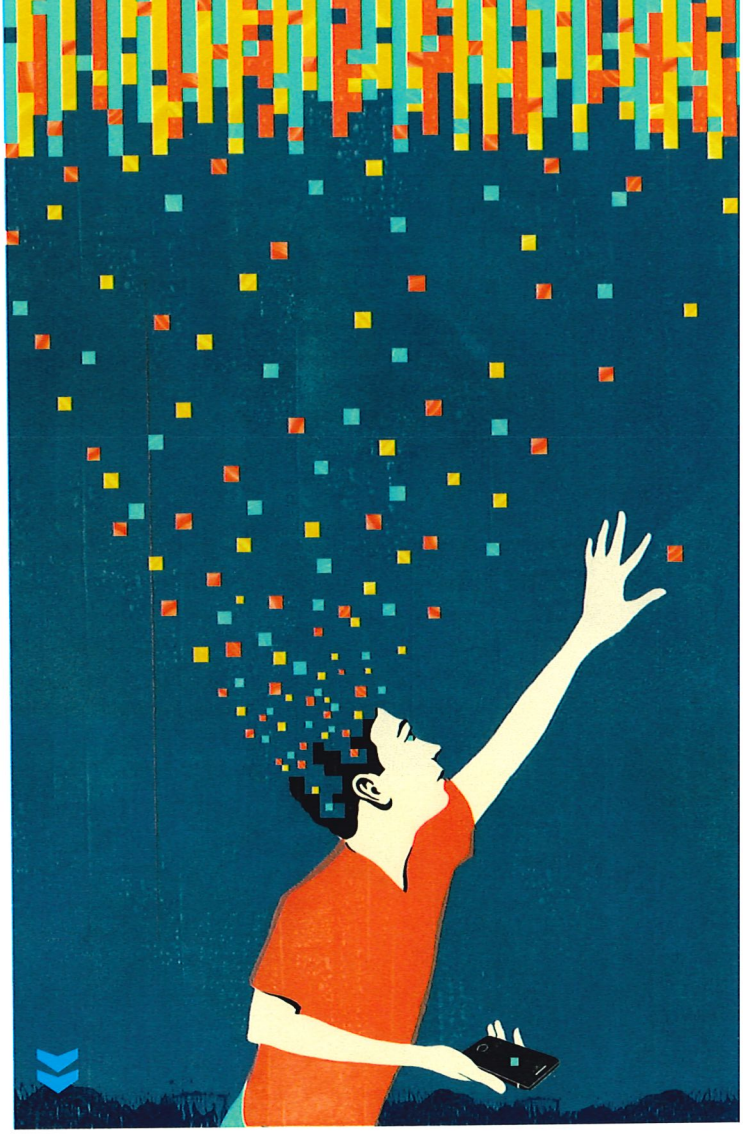
SACM: ***And there's no tune-up or anything after the first treatment?***
C.J.: Nothing. That's what's so nice about it. It's just a complete change in medical-care delivery.

COURTESY OF PENN MEDICINE

Johnson & Johnson INNOVATION | JLABS

10 START-UPS CHANGING HEALTHCARE

Better healthcare relies on turning good ideas into real-world solutions. Johnson & Johnson developed JLABS to help emerging companies transform scientific discoveries into tomorrow's healthcare products. Among the dozens of companies JLABS supports, here are 10 that promise crucial improvements.



Discovering disease-fighting proteins

A drug's effect depends on its target. More than half of all prescribed drugs, including antihistamines and opiates, target a family of hundreds of proteins known as the G-protein coupled receptors (GPCRs). These molecules help cells talk to each other, and play key roles in cardiovascular, gastrointestinal, hormonal and neurological disorders. However, current drugs only target a few dozen of these GPCRs.

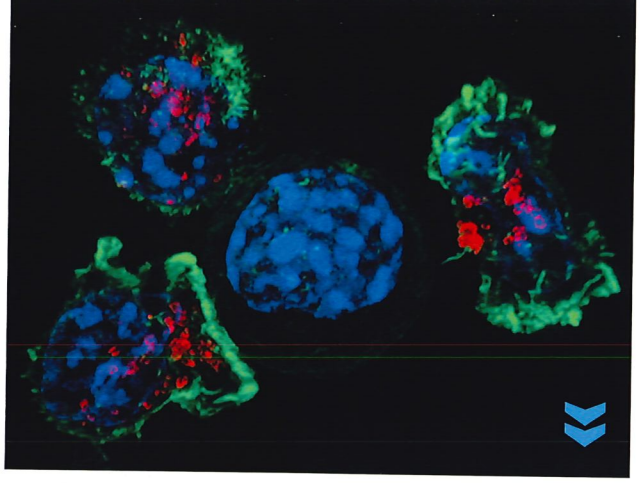
To find new drugs that activate or deactivate GPCRs, Ab Initio Biotherapeutics works primarily with large, diverse sets of antibodies to determine which variants best interact with a target or exhibit a desired function. The companies scientists then create more variants that resemble the most successful proteins, says Ab Initio's co-founder, CEO and president, Kenneth Lin.

To find new drugs Ab Initio Biotherapeutics works primarily with large, diverse sets of antibodies.

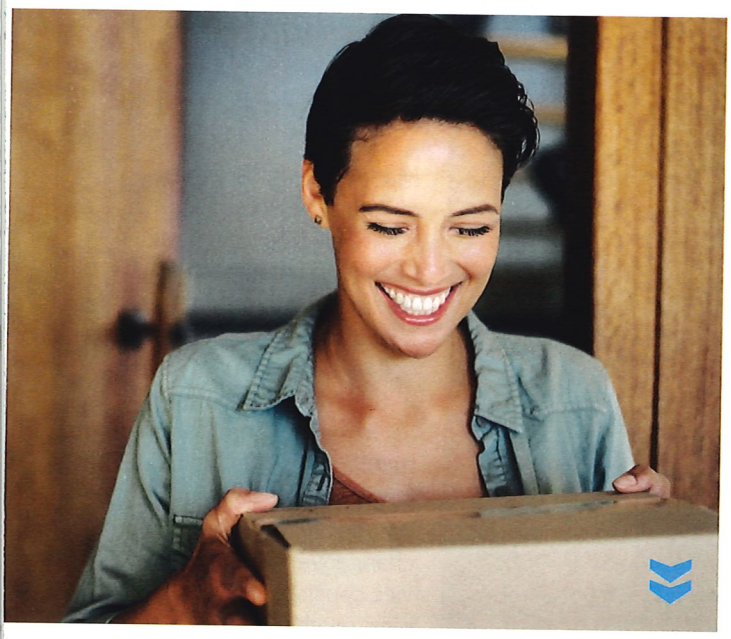
In 2016, the San Francisco-based firm partnered with Pfizer to help it engineer antibodies that could activate an undisclosed GPCR. According to Lin, Ab Initio is also working on a therapy targeting MC4R, a GPCR strongly linked with appetite.

Back to reality by app

The Toronto-based digital health-innovation company App for Independence, or A4i, is developing clinically-proven mobile interventions to help patients with schizophrenia and psychosis, and their caregivers, better manage symptoms. A4i is a joint venture between The Center for Addiction and Mental Health in Canada and digital health solution-provider MEMOTEXT. This company developed an app from evidence-based content that helps patients prepare for everyday tasks. It can be set up to provide reminders and a feed with evidence-based and peer-to-peer support. Users can also give it access to a device's microphone to use an ambient sound recorder, which is designed to help individuals understand if sounds are real or hallucinations. As explained by Amos Adler, CEO of A4i, "If we can succeed in automating some risk identification and creating relevance for patients with our personalization algorithms and machine learning, then we can succeed in creating engaging support for patients beyond the walls of the provider setting."



T cells (*green*) can be tailored to find, surround and attack a patient's cancer cells (*center*).



Reproductive Health Reports by Mail

Roughly one million sexually transmitted infections are exchanged each day. If untreated, they can lead to cervical cancer, pelvic inflammatory disease and infertility. However, people are often reluctant to ask their doctors to test for such infections, so Eve Medical in Toronto developed a kit for women to screen themselves.

"It started when I found out that several of my friends had been avoiding their screening tests for years, and I realized a lot of them were seeing this as a necessary evil instead of something positive they were doing to take care of their health," says Jessica Ching, Eve Medical co-founder and CEO.

Women can order Eve Medical's kit online — deliverable anywhere in Canada, and soon to more areas — to collect samples themselves. They send samples to a lab in a pre-paid box and can read their results on the company's site. Counseling sessions with licensed physicians are available after women get their results. Currently Eve Medical screens for human papillomavirus (HPV), chlamydia and gonorrhea.

A CAR-T of cancer therapies

Instead of treating cancer, chimeric antigen receptor T (CAR-T) cells might create cures. These reprogrammed immune cells hunt down and kill cancer cells that have evaded a patient's immune system. But CAR-T therapies pose some risks. Earlier this year, Juno Therapeutics cancelled an experimental CAR-T therapy following the deaths of five patients from severe brain swelling.

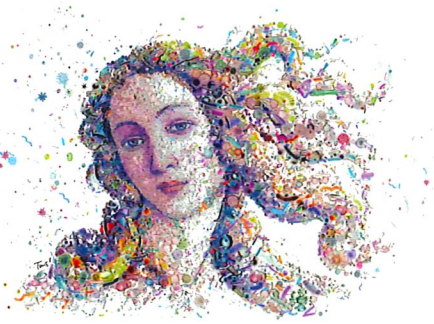
San Francisco-based Chimera Bioengineering is developing gene sequences that, when plugged into CAR-T cells, can help scientists control the immunological response with specific drugs. For example, they can boost the number of CAR proteins to make T cells more likely to bind to diseased cells than healthy ones, or decrease the number of CAR proteins to reduce the T cells' potentially dangerous inflammatory responses. "It's like a remote control for your TV, but instead of an electromagnetic signal, the drug is the controlling signal," says Ben Wang, co-founder of Chimera Bioengineering.

Acne and antibiotics

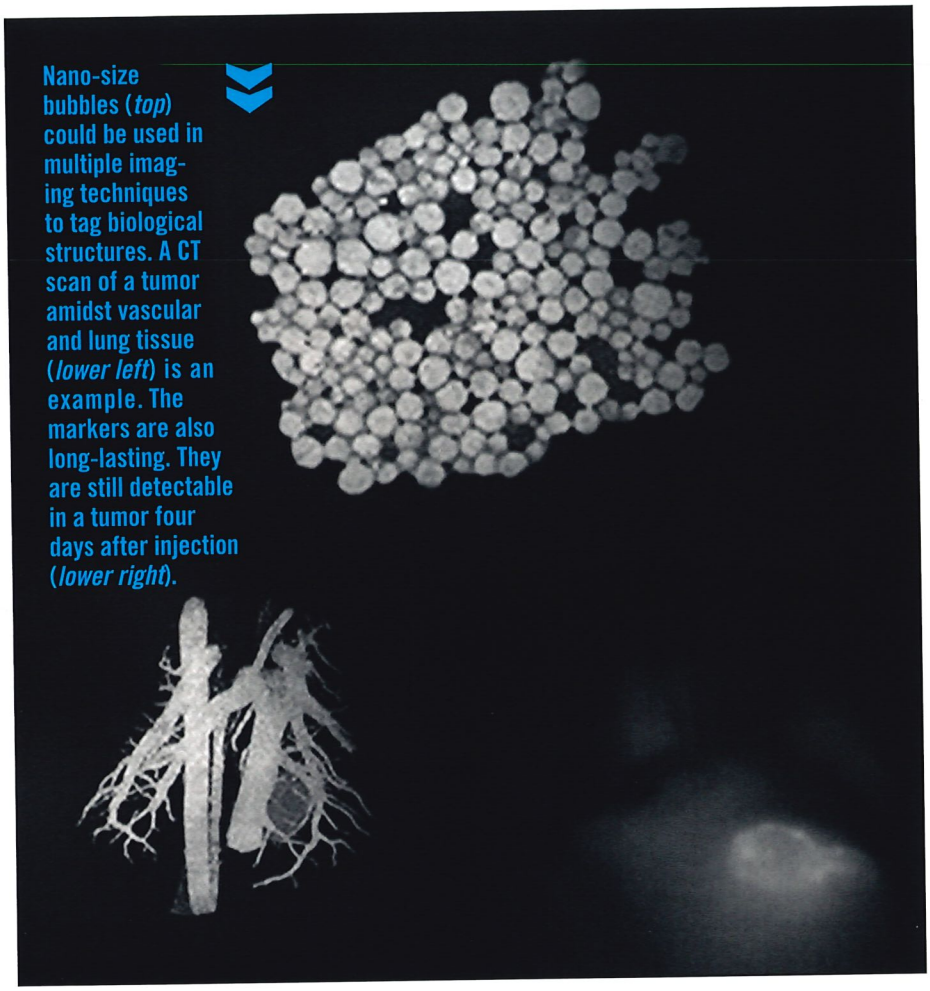
Your face is covered in bacteria, and much of it is *Propionibacterium acnes*. Most strains are linked with healthy skin, but certain ones are linked with acne. For decades, doctors have taken a scorched-earth approach to acne, prescribing antibiotics that killed all forms of *P. acnes*, good or bad. As a result, up to 70% of these microbes are now resistant to conventional antibiotics. "Dermatologists, despite being 1% of the medical force, prescribe upwards of 8% of antibiotics nationally annually," says Naked Biome CEO and co-founder, Emma Taylor.

Naked Biome is developing a probiotic therapy for acne. Instead of killing *P. acnes*, the San Francisco-based firm would have patients flood their faces with live, healthy strains of the bacterium, ensuring the good bacteria will outcompete the bad, Taylor says.

Hopefully, this will treat and prevent acne and other skin diseases and reduce antibiotic use. Naked Biome is entering clinical trials to see if its approach is safe and effective.



TOP: NIH CENTER: YURI ARCURS / GETTY IMAGES



Nano-size bubbles (*top*) could be used in multiple imaging techniques to tag biological structures. A CT scan of a tumor amidst vascular and lung tissue (*lower left*) is an example. The markers are also long-lasting. They are still detectable in a tumor four days after injection (*lower right*).

Lighting up tumors

Operating rooms increasingly rely on imaging technologies to help guide surgeries, both before and during a procedure. However, existing imaging agents work for only for a few minutes at a time, and they usually they are only suitable for one kind of imaging. Multiple injections with imaging agents can increase the risk of kidney damage.

NanoVista has developed a way to combine multiple imaging agents in bubbles of fatty molecules each about 100 nanometers, or billionths of a meter, wide. The Toronto-based firm's first product works with multiple imaging technologies, remains effective for up to two weeks and was successfully tested on 10 different human and animal tumor types. NanoVista's bubbles are designed to be injected a week before surgery to help plan tumor removals. These will also visibly fluoresce during operations to help surgeons completely remove cancers, says NanoVista co-founder, Jinzi Zheng.

Morphing in medical packaging

Manufacturing lines rely on molds and dies to press out items. The downtime needed to change them for different products can cost manufacturers millions of dollars annually.

PinPress is developing a shapeshifting tool that can essentially serve as a thousand molds in one, significantly reducing changeover time. Their device consists of a block of pins, much like old pin-art desktop toys. A magnetic actuator individually moves pins up and down, and fluids fill the cavity under the pins to lock the block's shape in place. An elastic rubber-like skin can be placed on these pins to smooth the surface and cover the space between the pins, says PinPress co-founder and CEO, Asif Khan.

Currently, the pins are roughly seven millimeters wide, but the company hopes to shrink them to less than a millimeter to help make products with finer details, Khan says. The Port Hope, Ontario-based firm is now working on blister packages for pills and tablets.

BIOLOGICAL PROCESSES, such as tumor activity, often can't be seen with a simple visual inspection. Scientists are going beyond visible light and integrating the near-infrared spectrum into screenings, and this can show biological activity.

Pumping up a failing heart

One in five U.S. adults will develop heart failure, according to the American Heart Association. When drugs can no longer help patients with advanced heart failure, one recourse is left ventricular assist devices, which help circulate blood using mechanical pumps connected to the heart by tubes. However, implanting these bulky machines involves invasive, risky surgeries — 60% of patients experience severe complication, and 10% die soon after surgery.

One in five U.S. adults will develop heart failure.

Procyrion, a Houston-based company, is developing Aortix, a heart pump thinner than a pencil and less than 6.5 centimeters long. Aortix can be delivered into the aorta in a minimally invasive manner by inserting a catheter into a large artery near the surface of the groin.

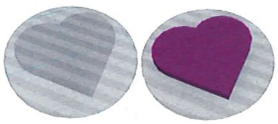
The company has completed animal testing with prototypes and has moved on to human trials. It hopes to have Aortix ready for the market by 2020, says Procyrion CEO, Ben Hertzog.

An app to engage patients

Self Care Catalysts in Toronto has developed a mobile- and web-based app that patients can use to share relevant medical information, such as symptoms, medications and moods. They can also supply health data from their smartwatches and other wearable devices, and interact with their peers on the app's social network for support.

The company plans to capture everything that happens to patients "outside the clinic in the real world in real-time," says the company's founder and CEO Grace Castillo-Soyao. Much remains unknown about patients' experiences and decisions between visits to doctors or researchers, she notes. Doctors and researchers can look at anonymized, aggregated data from patients to monitor, say, how well drugs or behavioral intervention programs are working, Castillo-Soyao explains.

By engaging with patients, doctors and researchers can also hopefully keep patients in clinical trials. As Castillo-Soyao points out, "One of the most expensive problems in clinical trials is retaining patients. By engaging patients, we can help retain them."



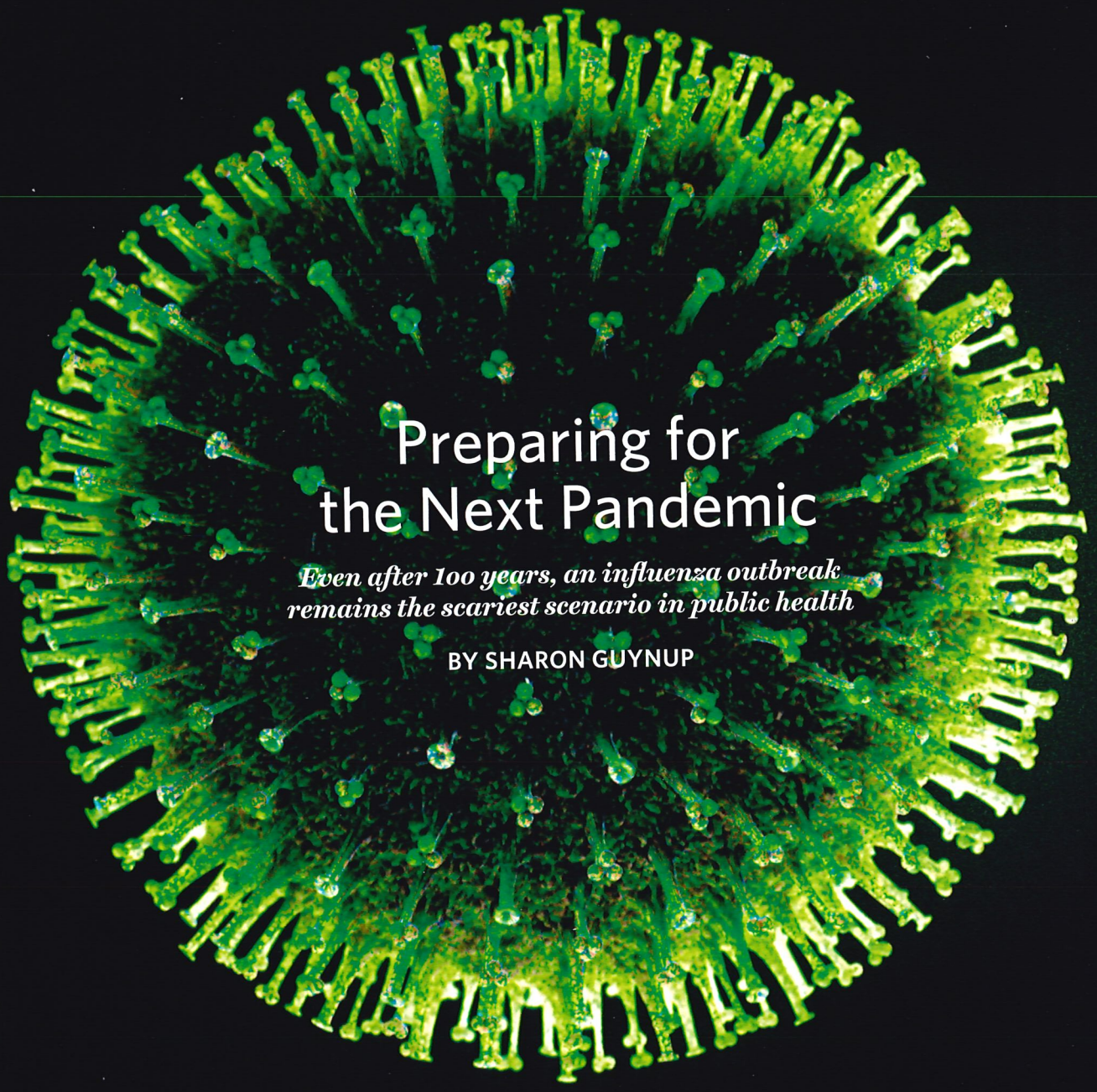
A bright spot in fighting skin cancer

Sunscreen can only help prevent skin cancer if it's continually on the skin. Suncayr has developed a system that lets people know when to reapply.

The Kitchener, Ontario-based firm engineered a transparent ink that changes color when exposed to ultraviolet rays and incorporated it into stickers called SPOTs. People stick the SPOTs on their skin. When the SPOTs change color, it's time to reapply. "You can use one SPOT all day long, even if you're swimming or sweating" says Andrew Martinko, co-founder of Suncayr.

All the ingredients in each SPOT are already approved by the U.S. Food and Drug Administration and in use in cosmetic products. Martinko says that Suncayr will sell SPOTs in Australia in 2017 and launch in North America in 2018.

Written and reported by Charles Q. Choi and Renee Morad.



Preparing for the Next Pandemic

Even after 100 years, an influenza outbreak remains the scariest scenario in public health

BY SHARON GUYNUP

In 1918, the Spanish flu infected about one-third of the world's population and killed some 50 million people. Some died within hours of the first symptoms.

Nearly 100 years later, the threat of influenza still looms. "A highly virulent strain similar to 1918 could have a similar impact today," says John Brownstein, a public health surveillance expert and professor at Harvard University.

Scientists have worked for decades to speed threat detection, improve preventative vaccines, and reduce response time during an outbreak, but the question persists: A century after the Spanish flu, how far have we come in our ability to prevent and fight infectious and newly-emerging diseases?

250,000–500,000 PEOPLE DIE A YEAR FROM INFLUENZA.
-WORLD HEALTH ORGANIZATION

UNIVERSAL CHALLENGE

Though medical knowledge, technology and communication has come a long way in the past 100 years, Brownstein says that, "vaccines are still our main weapon."

Recently, the U.S. government and the private sector have focused specifically on expanding the nation's vaccine supply and improving effectiveness. Advances include vaccines targeted for people 65 and older who are among those at greatest risk — and a 'quadrivalent' vaccine that protects against four flu strains. Some researchers are trying to create the holy grail: a universal vaccine. It would offer broad immunity against all influenza infections rather than targeting the constantly-changing surface antigens of a virus, as current vaccines do. That appears to be years away.

In the meantime, Brownstein says, "We face this onslaught of misinformation" about vaccines and their potential side effects. Those misconceptions are mostly associated with the measles, mumps and rubella vaccine, but hesitancy extends to other vaccines as well. To combat this, Brownstein says the public health community needs "to report fact-based discussions in public health."

"If you want to look into your crystal ball, flu remains our number one global infectious disease threat."

-PAUL BIDDINGER

DETECTION AHEAD OF RUNAWAY INFECTION

Beyond preventing outbreaks in the first place, rapidly detecting them is the next best thing, says Paul Biddinger, vice chair for emergency preparedness at Massachusetts General Hospital: "It gives you an opportunity to intervene." As global travel and trade continue to increase, so too will the need for accurate and rapid threat detection.

As it stands, the first reliable testing in the U.S. for an emerging flu strain happens at the Centers for Disease Control and Prevention (CDC) in Atlanta. Only once an outbreak is well underway are these tests distributed to state labs and then hospitals.

For example, during the 2009 swine flu epidemic, it took three weeks for the diagnostic to be developed, manufactured and distributed. Biddinger notes, "By the time many are diagnosed, they've been in the community — or the hospital — potentially infecting others."

While current 'rapid influenza diagnostic tests' can be administered anywhere and give results in 15 minutes, false negatives are common — and they don't distinguish between seasonal flu and the more virulent influenza A viruses. More sensitive tests are needed.

SOUPED-UP SURVEILLANCE

When a threat is detected, it should be met with a robust public health response. If not, a few infections could blossom into an epidemic. To fashion that response, says Stephen Redd, director of the CDC Office of Public Health Preparedness and Response, scientists first need to understand the enemy: how a virus is transmitted. They can then determine the level of quarantine necessary for patients in hospitals, whether to move stockpiled anti-viral drugs to state health departments — and whether to close schools to limit transmission.

Those who have developed solid emergency plans will fare best, says Daniel Kollek, director of the Centre for Excellence in Emergency Preparedness at McMaster University. Those communities will have identified clinics, schools, universities and other public spaces to care for patients and set up home-care strategies. A plan will be in place for highly contagious pathogens, like Ebola, which require medical teams to wear protective clothing. That, Kollek notes, is problematic, since protective gear is not widely available and requires intensive training to use without self-contaminating.

But planning is not enough. "You need full-scale drills," Biddinger says. "Places that have not practiced will not be ready," because "response to disasters has so much commonality that you don't practice the disaster, you practice the response."

There have been some big leaps forward in data-sharing across the United States and internationally that have saved lives. Within weeks of the emergence of SARS in Hong Kong, for example, researchers determined that only those with active symptoms were contagious. "That allowed global public health agencies to shut down a rapidly-spreading epidemic," says Biddinger, which he calls "unprecedented."

However, influenza is harder to control than emerging diseases like Ebola since it can be transmitted before a patient even shows symptoms. "If you want to look into your crystal ball," Biddinger says, "flu remains our number one global infectious disease threat."

IAN CUMING/GETTY IMAGES

THE CHAMPIONS OF SCIENCE

"WHAT'S NEW?"

QUICKFIRE CHALLENGE:

THE LAB COAT OF THE FUTURE

"I find it amazing that the white lab coat hasn't substantially changed for over a century, while at the same time, science, technology and fashion have gone through amazing transformations. I'm very excited to be part of the Challenge to get people thinking and talking about the role that science, technology and innovation play in our lives."

—DAYMOND JOHN

World-renowned entrepreneur and Shark on ABC's four-time Emmy Award winning series, Shark Tank

CAN YOU ENVISION THE LAB COAT OF THE FUTURE? Learn more about the challenge and submit your idea for a chance to win $50,000 in grants at: jlabs.jnjinnovation.com/quickfire-challenges/labcoat-future.

CHAMPIONSOFSCIENCE
A DR. PAUL JANSSEN PROJECT

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