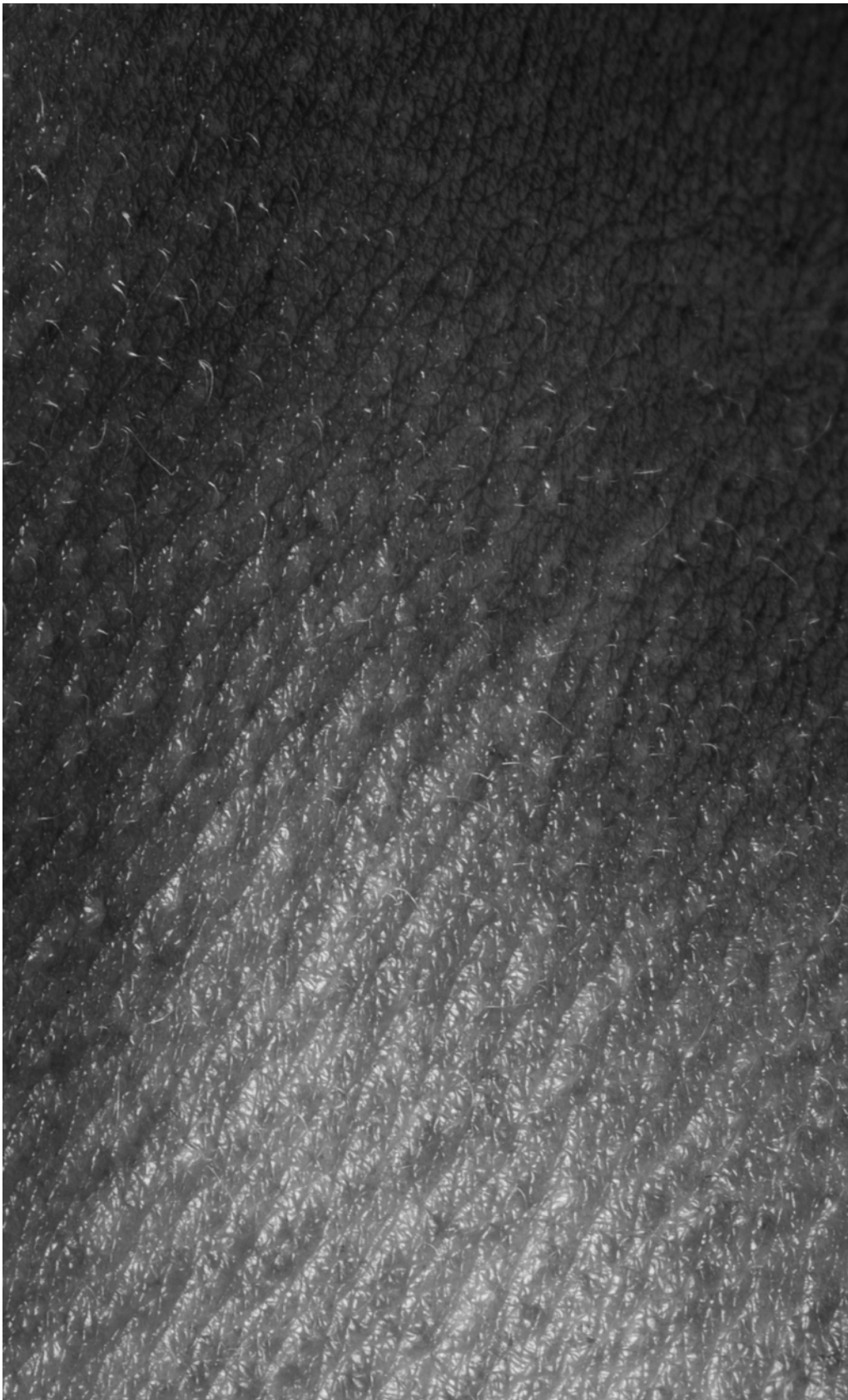
S T A N F O R D

M E D I C I N E

Summer 2015



special report

## SKIN DEEP
THE SCIENCE
OF THE BODY'S SURFACE



plus

# STANFORD MEDICINE

Summer 2015

# SCARSHIP ENTERPRISE

## TO BOLDLY EXPLORE NEW WAYS TO HEAL SCARS

Many people have scars from unfortunate past encounters with floors, doors and pavement. Most of the time these scars cause no lasting problems. But scars can be debilitating and even dangerous. • "The biomedical burden of scarring is enormous," says Michael Longaker, MD, co-director of Stanford's Institute for Stem Cell Biology and Regenerative Medicine. "About 80 million incisions a year in this country heal with a scar, and that's just on the skin alone. Internal scarring is responsible for many medical conditions, including liver cirrhosis, pulmonary fibrosis, intestinal adhesions and even the damage left behind after a heart attack."

Scars are comprised mainly of collagen, a fibrous protein secreted by a type of cell found in the skin called a fibroblast. Collagen is one of the main components of the extracellular matrix — a three-dimensional web that supports and stabilizes the cells in the skin.

Now Longaker and stem cell expert Irving Weissman, MD, and colleagues have identified the cell type in mice that is responsible for much of the development of a scar. They've shown that blocking this cell's activity with a small molecule can reduce the degree of scarring. Because a similar drug molecule is already approved for use in humans to treat type-2 diabetes, the researchers are hopeful that they can begin clinical trials in humans soon. The research was published recently in *Science*.

Interestingly, scars represent a kind of evolutionary compromise that emerged in the relatively recent past.

"We are the only species that heals with a pathological scar, called a keloid, which can overgrow the site of the original wound," says Longaker. "Humans are a tight-skinned species, and scarring is a late evolutionary event that probably arose in response to a need, as hunter-gatherers, to heal quickly to avoid infection or detection by predators. We've evolved for speedy repair."

Longaker and his colleagues found that a subset of fibroblast cells is responsible for much of the collagen deposition that leads to scarring. Inhibiting the activity of a protein on the surface of the cells significantly reduced the amount of scarring during wound healing in laboratory mice — from about 30 percent of the original wound area down to about 5 percent. Furthermore, the researchers showed the cells are also involved in the thickening and darkening of skin exposed to radiation therapy for cancer, as well as the spread of melanoma tumors in the animals.

Complete healing of wounds in which the activity of this protein was blocked required an additional six days compared with mice in which the protein remained active, but much of the repaired skin looked and appeared to function normally. In contrast, scarred skin is frequently less flexible and weaker than uninjured skin.

Longaker has been interested in how the skin heals for decades — ever since as a student he learned that human fetuses undergoing repair surgery in the womb heal without any scarring if the surgery takes place before the third trimester. Now he's excited to learn whether there's a way to recapture that long-lost ability as adults and at least reduce the degree of scarring during skin repair.

"I've been obsessed with scarring for 25 years," Longaker says. "Now we're bringing together the fields of wound healing and tumor development in remarkable new ways. It's incredibly exciting."

—KRISTA CONGER

MATTHEW BANDSUCH

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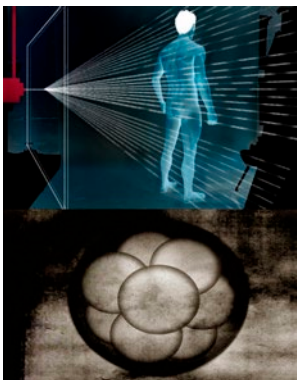
# STANFORD MEDICINE



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SPECIAL REPORT

## Skin deep

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DEPARTMENTS



COVER: MAX AGUILERA-HELLWEG

# letter from the dean

**Our bodies are in a constant state of renewal. The cells that compose the top layer of skin are consistently shed to make way for new, vibrant cells pushed up from below.** It is here, at the deepest layers of the skin — the dermis and hypodermis — where this routine cycle of transformation begins.

Medicine is not unlike the skin. It is in a constant state of renewal as older, less effective practices are shed to make way for fresh ideas, discoveries, innovations and technologies that transform the way we detect, treat and prevent all diseases.

Looking at our own skin, it appears static. When the skin is healthy and performing as intended, we do not see the cycle of transformation that happens at these subcutaneous levels. We aren't aware of the functioning that lies beneath the surface.

Medicine is no different. If the skin's surface is the care patients receive from our doctors, nurses and other providers in our clinics and hospitals, innovative and high-value care should rise naturally through the layers of our health delivery system. The underlying mechanisms and engines drive innovation and transformation and push them to the epidermis of medicine in the form of outstanding patient care.

At Stanford Medicine, we are uniquely poised to drive this cycle of renewal. Our basal layer — the bottom of the epidermis in which new cells are continuously produced — is our fundamental, or basic, research. Discoveries made here unlock the mysteries of biology and drive possibilities up through to the next layer, our translational research. Here, we make possibilities a reality, moving innovation from the lab to the patient's bedside.

Working collaboratively across disciplines, each scientific finding builds upon previous findings like the way new skin cells push aside the ones that came before them. When a major discovery breaks through the surface, it often makes headlines around the world, but the real amazing work is the step-by-step, cell-by-cell, advancement happening here every day.

This life cycle is not unique to academic medicine. We see this same pattern throughout health care, with the Affordable Care Act shifting the insurance landscape, as well as health-care startups rising to solve our toughest challenges and make care more efficient and convenient for patients.

Looking at the state of health care from above, as most of us do, it is easy to wonder if much is happening when we can't always see the change. We focus on the imperfections in the surface, such as the scrapes and wrinkles. But it is the unseen forces at work today that will shape how we stay healthy tomorrow.

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

GLENN MATSUMURA

# upfront

A QUICK LOOK AT THE LATEST DEVELOPMENTS FROM STANFORD MEDICINE

## Taming leukemia cells

AFTER A CHANCE OBSERVATION in the lab, Stanford scientists found a method that can force dangerous leukemia cells to mature into harmless immune cells called macrophages.

Ravi Majeti, MD, PhD, an assistant professor of medicine, and colleagues made the key observation after collecting cells from a patient with a type of B-cell acute lymphoblastic leukemia. The disease is a particularly aggressive form of leukemia, and any new treatment would be an exciting development.

The researchers were trying to keep the cells alive in a culture plate — "We were throwing everything at them to help them survive," says Majeti — when postdoctoral researcher Scott McClellan, MD, PhD, noticed that some of the cells were changing into what looked like macrophages. Then Majeti remembered an old research paper showing that early B-cell mouse progenitor cells could be forced to become macrophages when exposed to certain proteins.

PAUL BLOW

So the researchers conducted some experiments and saw that the methods also worked for human cells: They transformed the cancer cells into macrophages.

Since macrophages can engulf and digest cancer cells, the hope is that transforming cancer cells will not only neutralize them, but also turn them into cancer-fighting agents. "Because the macrophage cells came from the cancer cells, they will already carry with them the chemical signals that will identify the cancer cells, making an immune attack against the cancer more likely," says Majeti, lead author of a paper published in the *Proceedings of the National Academy of Sciences.*

About 8% of your DNA is made of sequences from viruses that infected your ancient ancestors. More at http://stan.md/1dcUC7Q.

### Hospitals rise

**"TOPPING OFF" CEREMONIES DURING the spring marked the end of the structural phase of construction for the new Stanford Hospital and the expansion of Lucile Packard Children's Hospital Stanford.**

**Scheduled to open to patients in 2018, the 824,000-square-foot Stanford Hospital will add 368 private rooms and double the size of the emergency department. The 521,000-square-foot addition to the children's hospital scheduled to open in 2017 nearly doubles the size of the existing facility, allowing for up to 361 beds on-site.**

# Kalanithi's words touch millions

STANFORD NEUROSURGEON PAUL KALANITHI, MD, DIED OF LUNG CANCER just a few weeks after his essay "Before I Go" was published in the spring issue of *Stanford Medicine* magazine, but he lived to see it appreciated by thousands. Since his death on March 9, his words have reached millions.

On Feb. 24, Longreads.com posted an excerpt on its blog and shared a link through Twitter; over the next week the essay on the magazine's website had more than 75,000 hits. Letters to Kalanithi poured in, thanking him for writing, asking permission to use the essay in classrooms and wishing him well. Tweets and blog posts encouraged others to read it: "This should be mandatory reading for humanity: time warps for young surgeon w/ metastatic cancer," tweeted Harvard physician Neel Shah, MD.

The essay has been republished by many media organizations, including *The Washington Post*, where it has had more than 4 million hits; *The Guardian* in England; and the *Huffington Post*'s German edition. *The Washington Post* distributed it on its wire service, resulting in republication throughout the world.

"The comments are among the most affirming I've seen on any of the articles on our site," wrote the *Post*'s senior editor for social issues, Sydney Trent, in an email to *Stanford Medicine*'s editor.

On Stanford websites, as of June 1 the essay had more than 500,000 hits, his obituary had been viewed a million times and the video had been viewed 300,000 times. You can see them at http://stanmed.stanford.edu/2015spring/before-i-go.html.

# A safer antibiotic

TREATMENT WITH AMINOGLYCOSIDES, the most commonly used class of antibiotics worldwide, is often a lifesaving necessity for many bacterial diseases, including pneumonia, peritonitis and sepsis. But an estimated 20-60 percent of patients who receive these antibiotics suffer partial or complete hearing loss.

Now, in a study published online in the *Journal of Clinical Investigation*, researchers led by Stanford otolaryngologists Anthony Ricci, PhD, and Alan Cheng, MD, report they have developed a modified version of an aminoglycoside that works effectively in mice without risking deafness or kidney damage, another common side effect.

"We targeted sites on the drug molecule that were not involved in the antimicrobial activity that kills off infection," Ricci says. The newly patented antibiotic is N1MS, which is derived from sisomicin, a type of aminoglycoside. N1MS cured urinary tract infection in mice just as well as the parent compound, but did not cause deafness, study results show.

The researchers hope to test versions of the modified antibiotic in humans soon.

PAUL BLOW

## HEALTHY APP-TITUDE

A FREE IPHONE APP, MYHEART COUNTS, IS ALLOWING USERS to contribute to a study of human heart health while learning about their own hearts.

The app, developed by Stanford researchers, takes advantage of the iPhone's built-in motion sensors to track participants' physical activity and to collect data during a 6-minute walk test. Once every three months, they're asked to report on one week's worth of activity and to update their risk-factor information.

Users can also enter data about their risk factors for heart disease and their readings from basic lab tests to get feedback on their chances of developing heart disease and to learn their "heart age."

Stanford researchers will analyze the data to learn how activity helps the heart. But they will also be looking at how well the app encourages users to exercise and eat well.

"We need to understand how to reach out to modify behavior long before we end up having to see someone for a heart attack or stroke," says Michael McConnell, MD, professor of cardiovascular medicine and principal investigator for the study. The app can be downloaded from Apple's App Store.

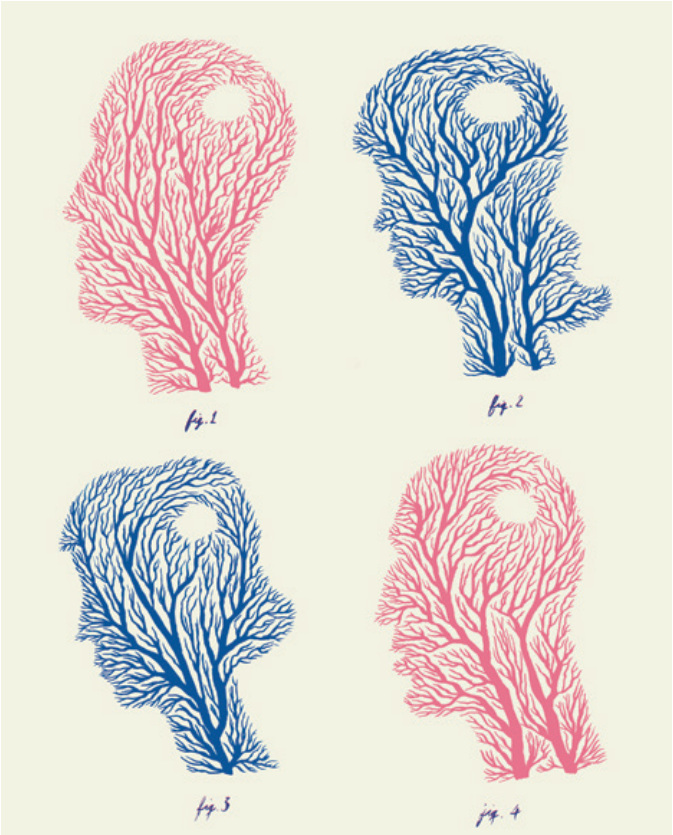
## My secret

**ABOUT A THIRD OF SEXUAL MINORITY medical students choose not to disclose their sexual identity or orientation during medical school, according to a study by Stanford researchers.**

**An online survey distributed to all medical students in the United States and Canada during the 2009-10 academic year found that of the 912 respondents who indicated they were sexual minorities, 269 (about 30 percent) reported that they concealed their sexual identity in medical school.**

**"Fear of discrimination was the most common theme — discrimination from peers, from your evaluators and faculty members, also from patients," says Matthew Mansh, lead author of the study and a fourth-year medical student.**

**The study results were published online in *Academic Medicine*.**



# Head shots

AN ANALYSIS OF THOUSANDS of brain scans shows similar gray-matter loss in the brains of people with diagnoses as different as schizophrenia, depression and addiction.

By studying whole-brain images from nearly 16,000 people gathered from 193 studies, Stanford researchers identified a common pattern in a spectrum of psychiatric disorders widely perceived to be distinct. The findings, published in *JAMA Psychiatry*, call into question a long-standing practice of distinguishing psychiatric disorders by symptoms rather than brain pathology.

"Researchers have tended to interpret their biological findings in terms of the one disorder they're focusing on," says Amit Etkin, MD, PhD, an assistant professor of psychiatry and behavioral sciences and the study's senior author.

Etkin and his team pooled data from the magnetic-resonance images of the brains of 7,381 patients with six diagnoses: schizophrenia, bipolar disorder, major depression, addiction, obsessive-compulsive disorder and anxiety disorders. Comparing the images with those from 8,511 healthy control subjects, the team found that gray-matter loss in three brain structures was similar among patients with different psychiatric conditions.

These structures — the left and right anterior insula and the dorsal anterior cingulate — are parts of a network in the brain whose components tend to fire in synchrony. This network is associated with higher-level functions such as concentrating in the face of distractions, multitasking or task-switching, planning and decision-making, and inhibition of counterproductive impulses.

Read more about this comparison of brain images from nearly 16,000 people at http://stan.md/1KVCABj.

## Silent X

**EARLY IN THE DEVELOPMENT OF female embryos, one X chromosome is shut down or silenced in each cell, ensuring that females, who have two X chromosomes, and males, who have only one, end up with roughly the same dosage of genes that occur on that chromosome.**

**Scientists have known about X inactivation for decades. Recently they learned that an RNA molecule called Xist is responsible. But it has been unclear exactly how Xist silences genes on the X chromosome.**

**In a study published in *Cell*, Stanford researchers have outlined the molecular steps of inactivation, showing that it occurs in an orderly fashion as early embryonic cells differentiate into more specialized tissues. They hope their findings will shed light on conditions in humans that are typically more severe in one gender than the other.**

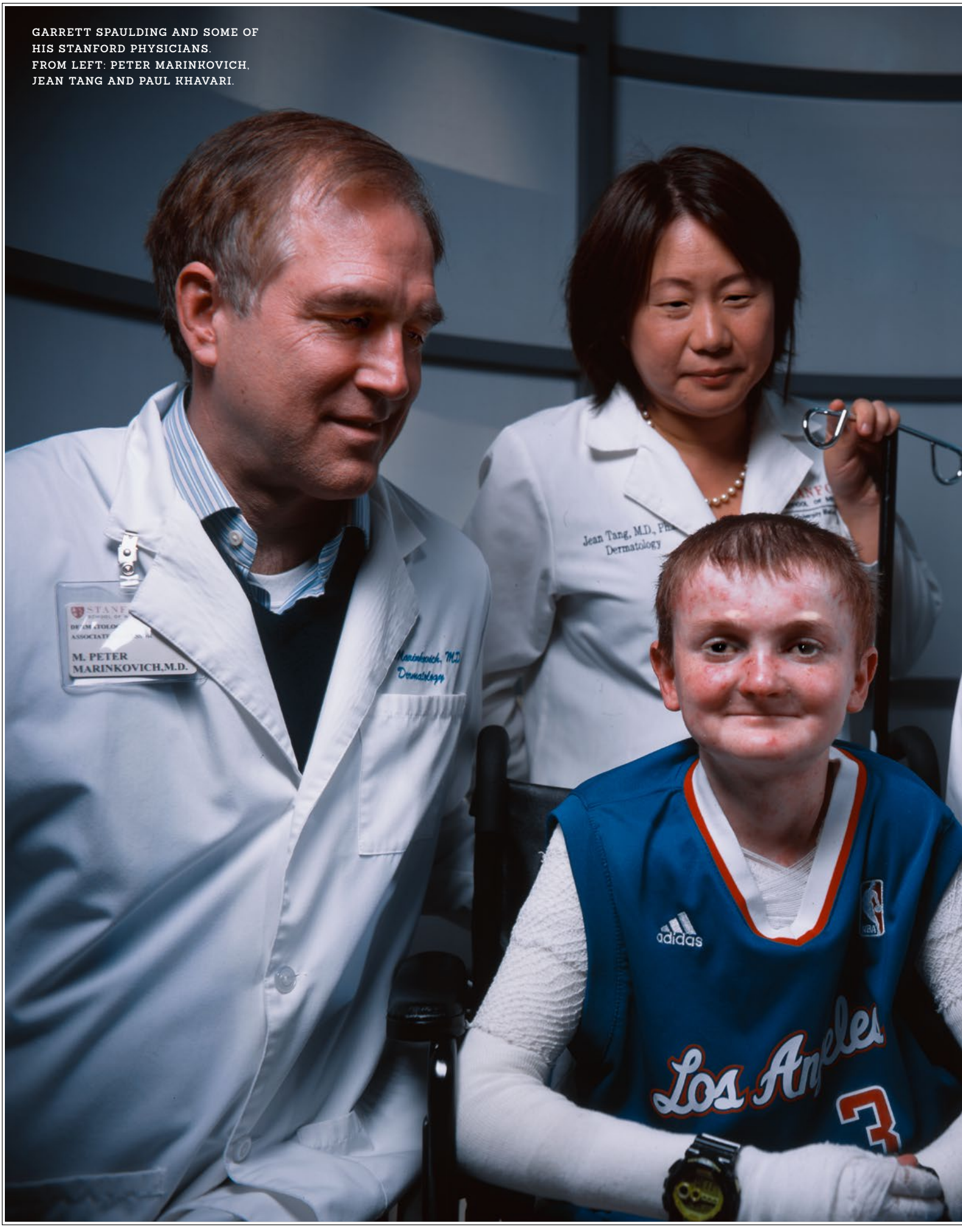
# below the surface

## THE INNER LIFE OF SKIN

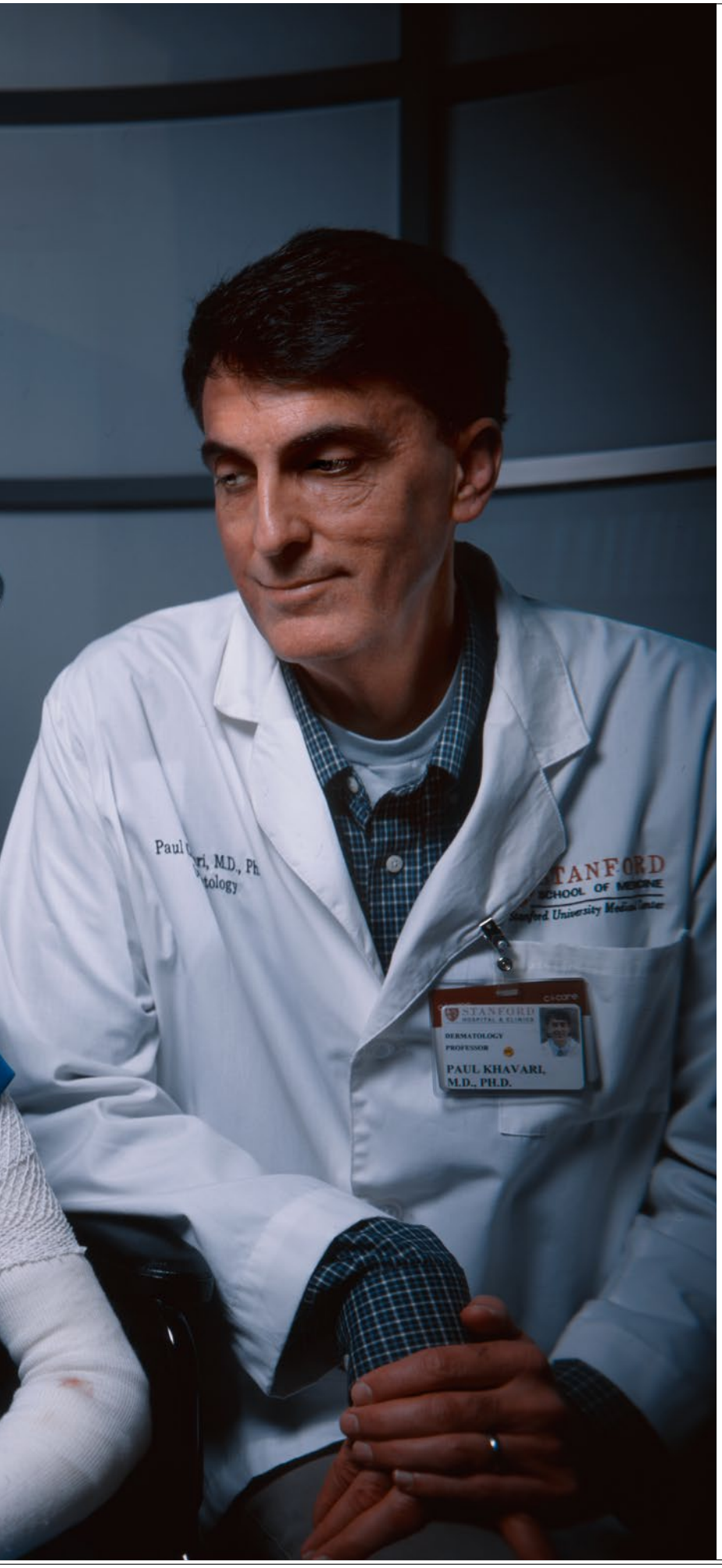
By definition, skin is superficial. It forms our surface. But skin is anything but one-dimensional.

Beyond its obvious roles of keeping our insides in and the outside out, skin has many less conspicuous duties: Its sweat glands help regulate temperature, its nerves provide the sense of touch, its deeper cells produce vitamin D, and its appearance advertises your age and health. • For those who can read skin's language, a close examination reveals clues about the whole body's health. A rash, for example, can indicate allergies; dark, velvety patches can point to diabetes; reddish, star-shaped patterns often mean liver disease; and deep folds in thickened palms suggest lung cancer. • When symptoms appear on the skin, they're easy to spot — and so are the successes (or failures) of attempts to heal them. This visibility is a boon to dermatologists, speeding their research into diseases and treatments. Among the most recent results are drugs that can cure skin cancers, experimental treatments for an agonizing blistering disease and insights into the genes that keep skin looking young. • And it's heartening to realize that many of their discoveries have implications not only for skin but also for our less accessible organs. • To get deeper into skin, read on.

PHOTOGRAPH BY MAX AGUILERA-HELLWEG




GARRETT SPAULDING AND SOME OF HIS STANFORD PHYSICIANS. FROM LEFT: PETER MARINKOVICH, JEAN TANG AND PAUL KHAVARI.






# THE BUTTERFLY EFFECT

## SKIN TOO FRAGILE TO TOUCH

Jan. 25, 1997, was part of dermatologist Paul Khavari's first weekend on call at Stanford. He remembers it clearly. Very early that Saturday morning, when it was still dark, he admitted a newborn from Gilroy with a horrifying constellation of symptoms.

"His whole body, his skin was blistered and falling off everywhere someone had touched him," Khavari remembers. "His parents were devastated, of course, at a time that was supposed to be one of the most joyful of their lives." • The baby had a severe form of a blistering skin disease called epidermolysis bullosa, and doctors like Khavari, now the chief

BY KRISTA CONGER
PHOTOGRAPHY BY
MAX AGUILERA-HELLWEG

# ‘If we could cure

**ONLY ONE CONDITION IN THIS FIELD, IT WOULD BE EB, HANDS DOWN.**

I don’t know any dermatologist who would answer differently. It’s hard for healthy people to realize just how important your skin is and how limited EB patients’ lives are.’

of dermatology at Stanford, knew that his life span would be measured in years of nearly unimaginable pain. As he and his colleagues gently outlined the disease to his parents, the baby’s father began to faint. Doctors rushed to support him.

“That was such a heart-wrenching evening,” the baby’s mother, Lorraine Montello, recalls. She and her husband had four other healthy kids and had expected an uneventful birth and recovery. Instead, their baby, Garrett Spaulding, was immediately transferred to Lucile Packard Children’s Hospital Stanford. They followed as soon as Montello was discharged. “It was a terribly stormy night,” recalls Montello. “Garrett had to be transported by ambulance because the weather was too rough to fly. We rushed into the room in the middle of the night to see a group of three very tall doctors standing over him. I thought, ‘This just doesn’t look good.’”

The doctors — the then-chair of the dermatology department, Al Lane, MD; the director of Stanford’s Blistering Disease Clinic, Peter Marinkovich, MD; and Khavari — were clustered around Garrett’s bed. They were some of the best-trained dermatologists in the country, but even they could offer no more than pain relief and bandaging to the wailing newborn.

“They were three giants, leaning over my tiny baby,” recalls Montello wryly, noting that each of the doctors stands well over 6 1/2 feet tall. “That was such an awful, horrible and depressing evening, but that provided a tiny bit of comic relief.”

Montello had no way of knowing at the time, but the trio of doctors were also well on their way to becoming giants in the study of epidermolysis bullosa, which affects only about 20 infants per 1 million births in the United States. (About two of those 20 have the same form of the condition as Garrett has.) Lane and Marinkovich had already devoted years of their lives to learning the molecular causes of EB, as it’s come to be called. And Khavari had just published a paper describing ways to apply then-nascent gene therapy techniques to correct genetic skin defects like EB.

The doctors’ single-minded devotion was the product of the previous decade of study at Stanford focusing on the rare disease, initiated by dermatologist Eugene Bauer, MD, in 1988. Now, nearly 30 years later, the Stanford team has launched the world’s first stem-cell-based clinical trial aimed at replacing the defective gene in patients’ skin cells with a working copy. The researchers have used sheets of corrected skin cells from four patients to cover some of their wounds; preliminary results will be announced this summer.

If the treatment is deemed safe, the physicians will move to a larger trial in the hopes that one day no child will have to suffer like Garrett.

“Of all the skin conditions we see in dermatology, EB is the most completely debilitating and awful,” says Jean Tang, MD, PhD, an associate professor of dermatology and who, along with Marinkovich, directs the phase-1 clinical trial. “If we could cure only one condition in this field, it would be EB, hands down. I don’t know any dermatologist who would answer differently. It’s hard for healthy people to realize just how important your skin is and how limited EB patients’ lives are.”

**PATIENTS WITH SEVERE FORMS** of EB experience the equivalent of third-degree burns, as their skin blisters and sloughs off at the slightest friction. A parent’s touch. A friendly handshake. A step in a snug sneaker. In some circles they’re known as the “butterfly children” to compare the fragility of their skin to that of a butterfly’s wing. In the Netherlands, at least two infants with the most severe forms of the disorder have been euthanized to end what’s described as unbearable, unrelenting pain.

There is no cure.

The condition demands extensive bandaging, from head to toe, in a regimen that can take hours every morning and evening. Infection of the open wounds is common, and fingers and toes frequently fuse together as a result of the


ZURAB SIPRASHVILI GROWS GENETICALLY ENGINEERED SKIN. SHEETS HE GREW IN THIS LABORATORY HAVE BEEN USED IN STANFORD'S EXPERIMENTAL TREATMENTS FOR EB.

PAUL MARTINEZ HAS AN EXPERIMENTAL SKIN GRAFT ON HIS LEFT HAND.

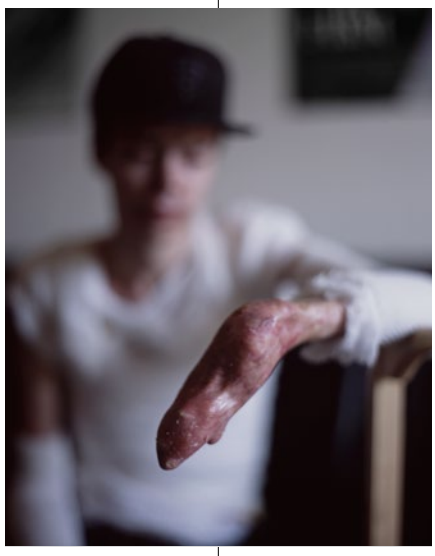
# ‘It’s been a

**DECADES-LONG JOURNEY.’ THE ONGOING CLINICAL TRIAL FOCUSES**

on replacing the defective gene in stem cells in the skin that develop into keratinocytes — the cells that overlap like shingles to form a protective barrier against the outside world.

constant scarring and healing between the digits. Because the condition can also affect internal organs and the gastrointestinal tract, patients struggle to maintain adequate nutrition and often experience organ and dental problems.

Garrett Spaulding is now 18. Montello, who underwent a crash course in the disease after his birth, has served for the past decade as coordinator for Stanford’s EB clinic. She spends about five hours every other day replacing the gauze that covers much of Spaulding’s body. “A large percentage of his body is covered with deep, open wounds,” she says. She often has to take breaks from the bandaging because of the excruciating pain it causes him. “When he was younger he’d say, ‘Mom, I hate you, I want to die’ — and he meant it,” she recalls.



“The amount of suffering is astronomical,” says Khavari. “It’s intimidating. I remember thinking, that night in 1997, ‘We need to be able to do more for these children.’”

In the intervening years, Khavari and his colleagues have dedicated themselves to understanding the disease and finding new ways to treat it.

“It’s been a decades-long journey,” says Khavari, but they haven’t wavered. The ongoing clinical trial focuses on replacing the defective gene in stem cells in the skin that develop into keratinocytes — the cells that overlap like shingles to form a protective barrier against the outside world. Healthy keratinocytes produce a protein called type-7 collagen that is essential to hold skin layers together. People with Spaulding’s form of EB have a mutation in the gene that encodes this protein. The researchers correct the gene in naturally occurring stem cells from the patients and allow them to grow into thin sheets of skin to patch onto the patient’s wounds, a process known as grafting.

In addition, the group is pursuing at least two other approaches to combat the disease. One, called therapeutic reprogramming, is similar to the current trial but would rely on stem cells created in a laboratory. Another, called protein therapy, would directly deliver the missing collagen protein to the surface of the skin.

By covering all the bases, the researchers hope to find at least one approach, or perhaps a combination of techniques, that can help people like Spaulding.

“We are at a unique moment in history,” says Anthony Oro, MD, PhD, a professor of dermatology at Stanford and a member of the EB team. “We have access to stem cell biology, gene-editing tools and bioengineering and transplant biology. We’re hoping that this will all crystalize in better ways to treat these kids.”

Khavari sums up the dedication of the group more simply: “We want to make these children well.”

**THE SKIN IS THE LARGEST ORGAN** in the body. In an adult human, the skin totals about 1.5 to 2 square meters, or roughly the area of a nice-sized throw blanket. It serves as an essential barrier between the messy gloop and rippling red cords of our innards and muscles and a world teeming with dangers — infectious microbes, toxic substances and even the hot and cold air around us that would quickly desiccate us into shriveled husks if we were left unprotected. It allows us to feel changes in temperature and pressure, and, yes, even pain. One square centimeter of human skin contains 200 pain receptors, all primed to trans-

mit pain signals in the most efficient, speedy way possible to encourage us to lift our hand off that burner, or to recoil from the knife that has only begun to break the skin. In EB patients, those receptors are firing almost nonstop.

"We don't know what it is like to not be in pain," says Paul Martinez, a 32-year-old man with EB from Stockton, California. Martinez is a participant in Stanford's current clinical trial. "It's just normal for us."

The top layer of the skin, the epidermis, is made up primarily of keratinocytes. These flat, irregularly shaped cells create an impervious sheet locking out water and bacteria. Under the epidermis, which can range from 0.2 to 4 millimeters in thickness, are two fibrous sheets collectively called the basement membrane. Like the bologna in a sandwich, the basement membrane separates the epidermis from the dermis, which consists of connective tissue housing hair follicles, sweat glands and blood vessels.

The basement membrane is the culprit in EB. People with Spaulding's form of EB have mutations in the gene for type-7 collagen — one of the most important proteins you've never heard of. Like rebar used to stabilize layers of concrete in building, or toothpicks holding together that slippery sandwich, type-7 collagen connects and anchors the dermis to the epidermis to allow them to move smoothly together in response to pressure or friction. In its absence, the layers slide past one another, causing damage and blistering at the slightest friction or pressure. Often the blisters grow and migrate across the skin and eventually pop, sloughing off skin and leaving an open, weeping wound that heals slowly if at all.

This cycle of blistering and healing often eventually causes the toes and fingers of patients to fuse together and curl inward, leading to a condition called "mitten hand" that resembles a ball of flesh with no digits. Surgery can sometimes free the hand, but the condition inevitably recurs.

In decades past, children with EB died within a few years from massive infection or fluid loss from their wounds. They are often severely underweight, as their bodies frantically divert calories to skin healing, rather than using them for growth or weight gain. As bandaging techniques and antibiotic therapies have improved, children are living into their 20s, only to face another challenge: The constant rounds of regeneration drastically increase the chances of developing a skin cancer known as squamous cell carcinoma. Although this type of cancer is often curable in healthy people, it recurs repeatedly at multiple sites across the body in people with EB. The cancer, combined with frequent difficulties with nutrition as patients struggle to eat with painful sores in their mouths and throughout their digestive system, as well as other organ problems, means that few with EB live past the age of 30.

In this context, Martinez is an old man.

Despite the severity of EB, there are some hopeful aspects of the disease. Although type-7 collagen is a large, unwieldy gene, it's the only culprit in the form of EB that Spaulding and Martinez have. The fact that it affects the skin also means the damage is relatively accessible to physicians and any changes can, for the most part, be monitored visually.

"The skin is a very accessible organ," says Zurab Siprashvili, PhD, a senior scientist in Khavari's laboratory. "Compared with the liver or heart, it is easy to study. But it turns out that it is also very complex. It protects us from sun damage, the weather, and it has to constantly renew itself. Adult stem cells on the base of the epidermis divide to renew themselves and create new keratinocytes to migrate to the surface to replace those that are damaged or shed."

If doctors deliver the missing gene, or even the protein it encodes, to those stem cells, it may help tie the epidermis and dermis together to prevent the blistering, skin loss and possibly even cancer. (Simply delivering it to mature keratinocytes

'The skin is a **VERY ACCESSIBLE ORGAN. COMPARED WITH THE LIVER OR HEART,** it is easy to study. But it turns out that it is also very complex. It protects us from sun damage, the weather, and it has to constantly renew itself.'

is not enough because of the continual sloughing of the mature cells that occurs even in healthy skin.) But it's been a journey of 20-plus years to move from concept to human trials.

"For us, it's not enough to simply understand the molecular biology of the disease," says Khavari. The team has had to move through a labyrinth of not just scientific challenges, but also the necessary regulatory approvals, from the institutional review boards that approve research involving human subjects to the Food and Drug Administration. They found themselves balancing their desire for speed with the need to cross every "t" and dot every "i" to ensure they would not inadvertently do more harm than good to the people they were trying so desperately to help.

**EPIDERMOLYSIS BULLOSA WAS** first discovered in the late 1800s. It's a member of a family of conditions called blistering diseases. EB occurs in three forms: simplex, junctional and dystrophic. Each of the three is caused by mutations affecting essential basement membrane components: the proteins keratin, laminin or collagen.

Junctional dystrophic EB is the most severe form of the disorder; these children lack laminin-332 and rarely live past 5 years of age. Recessive dystrophic EB, the form that Spaulding and Martinez have, is the next most severe. People with EB simplex can live relatively normal lives, although their skin blisters frequently, often on the hands and feet.

Stanford's push to find a treatment or cure for EB can be traced back to 1988, when Bauer came to Stanford from Washington University in St. Louis. After completing an internship in dermatology Bauer became a postdoctoral scholar in Arthur Eisen's laboratory at Washington University where he studied tadpole metamorphosis — how the animal loses its tail and grows legs to become an adult frog.

"One of the enzymes in this process was a protein called matrix metalloproteinase 1, or MMP1," says Bauer. MMP1 degrades matrix proteins in the space between cells to allow the drastic tissue remodeling necessary to switch from wriggling to hopping. Although the role of type-7 collagen hadn't yet been identified in EB, Bauer, who had continued to see the occasional dermatology patient during his postdoc years, began to wonder whether MMP1 could be responsible for the blistering seen in skin diseases like epidermolysis bullosa.

"You might say I moved from tadpoles to humans," says Bauer. "I transferred back to the clinic in the early '70s and began to focus my research increasingly on patients with epidermolysis bullosa." He also developed a close relationship with Lynn and Gary Anderson, whose two children, Chuck and Christine, died from EB: Chuck, at 27, in 1988 and Christine, at 14, in 1993.

The Andersons launched the Los Angeles-based EB Medical Research Foundation in 1991 to raise funds to combat the disease. To date, the organization has raised over $5 million for EB research. "I cared for both Chuck and Christine and I consider Lynn and Gary to be personal friends," says Bauer. "When you get to know patients and their families who are at first intimately affected, and then intimately committed and involved in the research effort, there's a real potency and urgency brought to the table."

That urgency translated into a cascade of research findings that led to the current clinical trial.

In the late 1980s, Robert Burgeson, PhD, and his research group at Shriner's Hospital in Portland, Oregon, discovered type-7 collagen and helped show that patients with recessive dystrophic EB lacked this protein. In 1988, Bauer kept the ball rolling when he moved from St. Louis to Stanford to serve as the chair of dermatology.

"From 1988 to the early '90s, we focused on identifying the mutations in the type-7 collagen gene that caused the disease, in the hopes that we could supply protein corrective therapy as had been done in other diseases," says Bauer. "In the early to mid-1990s we were investigating whether it was possible to insert genes into cells, and turn them off and on. All these things were, of course, very rudimentary compared with what we are doing now."

Khavari joined the team in 1993 after earning a PhD in the Stanford laboratory of Gerald Crabtree, PhD.

"Paul's fundamental knowledge and skills in molecular biology techniques took our efforts to an entirely different level," says Bauer.

Marinkovich, in turn, joined the team in 1995 after completing his fellowship training in the Burgeson laboratory. There, he had helped discover the laminin-332 protein and showed that it is defective or non-functional in children with the junctional dystrophic form of the disease. He'd also learned how this laminin works together with type-7 collagen to keep skin from blistering.

"Understanding how these proteins work together, and how this interaction is disrupted in EB, was key to our subsequent therapeutic studies," says Marinkovich.

In 1995, Bauer became dean of the medical school and transferred his grants and the chairmanship of the department to Lane. But work continued apace.

"In 1996, a year before Garrett was born, we used gene therapy to correct a different genetic mutation in human skin cells and grow the then-normal skin on the backs of laboratory mice," says Khavari. "This was the first time that the idea of correcting mutations in skin cells was shown to be possible."

During this time, the doctors were often reminded of the awful toll of the disease. Khavari recalls a Halloween party for patients and staff hosted at Lane's house about 10 years ago. "One child came in costume as a mummy, covered in bandages. During the evening, some of the blood from his wounds began to seep through the gauze, and those who didn't know this child had EB were remarking about how realistic the bloodstains were. It's impossible for me to imagine what it's like to be the parent of that child."

As Garrett grew, Montello developed what she called a "patch-and-go" philosophy, determined to give her son as normal a life as possible. When he turned 8 he got a bike for Christmas and rode it with abandon, disregarding his many bandages. "He's such a fighter, and has developed such a positive attitude," says Montello. "When he learned that kids with EB were sometimes called 'butterfly kids' he didn't like it. He thought it was kind of girly. He said, 'Can you call me a dragonfly kid instead?' And that describes him perfectly. He is a bit of a dragon."

Many EB children and their families adopt similar approaches.

"There's something about these patients and family members that is very unique," says Tang. "They seem to have a unique ability to accept the condition, and move on to what needs to happen to live the best life possible. It's sad, but also so inspirational. What is it about the human spirit that keeps them going?"

Many of today's gene therapy approaches rely on a class of viruses called retroviruses. In the normal course of their reproductive cycle, these viruses infect cells and insert their genetic material directly into those cells' DNA until they're ready to spread further. When using retroviruses for gene therapy, researchers remove disease-causing genes and sneak in an additional one — a gene that makes a missing or malfunctioning protein. Once the viruses insert the gene into the DNA of the patient's cells, the cells can begin to make the missing protein.

Preparations for the current clinical trial began in earnest in 2003. In the first four years, the researchers conducted laboratory and animal studies to show the approach was technically feasible. From 2007 to 2010, they designed a virus capable of inserting the corrected type-7 collagen gene into a target cell's genome so it could direct the creation of a functional version of the protein. This was hard in part because the gene is large and difficult to fit into the viral envelope.

Once the virus was made, the researchers had to find a way to manufacture it for use in humans. This required what the FDA has designated as "Current Good Manufacturing Practices," or CGMP. Because Stanford did not have a CGMP facility, the researchers partnered with colleagues at Indiana University to use theirs. (Stanford is in the process of opening its own CGMP facility later this year.) They also had to overcome an alphabet soup of regulatory hurdles before a single patient could be treated.

"Fundamentally, the Stanford group has done something that no other EB research group in the world has yet done," says Bauer, who is now the Lucy Becker Professor in Medicine, Emeritus. "It's a wholly professional and rigorous approach by a spectacular group of people all focused on a single endpoint: to help patients with terrible lives. I'm very proud of them."

In 2010, the team began to enroll five patients for the first trial. All of these first patients are adults, willing and able to give informed consent for their participation. (Trials involving children are subject to more stringent requirements.) Any future phases of the trial will likely include minors.

"Once we learn whether the treatment is safe, we'd like to include children as quickly as possible, in an attempt to improve their quality of life and prevent ongoing damage caused by scarring," says Khavari.

**THE RESEARCHERS NEED ROUGHLY 28 DAYS** to prepare for the experimental skin grafting. It's conducted primarily in a specialized clean room on the second floor of the Lorry I. Lokey Stem Cell Research Building. The dimly lit room is small, with carefully controlled airflow and filters to remove any contaminants. Steps sound sticky as scientists walk over an adhesive mat to clean their shoes.

"The incubator is there," says Siprashvili, indicating a portion of the room blocked off from the door by a transparent plastic curtain hanging down in flaps like the panels covering a car wash entrance. The tan metal box is about the size of a refrigerator, with two doors. It's an unprepossessing repository of the hopes, dreams and years of hard work of patients and clinicians. Currently it shelters the genetically corrected cells of the fifth (and last) participant in the phase-1 clinical trial.

Once, the cells of the patient didn't make type-7 collagen. Now they do.

Siprashvili supervises the care and feeding of the tiny plugs of skin cells obtained from the participants. Each of the subjects has recessive dystrophic EB. Four have now received grafts made of sheets of their own corrected skin cells, and researchers are preparing the skin grafts for the fifth. And then the researchers will watch, and wait.

Phase-1 clinical trials are meant to assess the safety of a particular intervention, not its efficacy. The patients will return for monitoring, at first on a monthly basis. Then if no adverse effects are seen (a loss of the skin graft, a propensity of the graft to migrate or to become cancerous, for example),

‘I don’t know

**HOW, OR WHETHER, MY PARTICIPATION IN THIS TRIAL WILL**

benefit me, personally. I’m 32 years old, which is quite old for this disease. I’m lucky to be alive. I didn’t do this for myself; I did it for the children. I don’t want anyone to go through this. We have to stop this.’

the researchers will move on to a phase-2 trial, which they hope will include children. A phase-2 trial includes a larger number of patients and tests the effectiveness of a treatment along with its safety.

“This itself has been a 10-year process to get to this stage,” says Siprashvili. “We had to first create and outfit this room. And then we had to learn how to reliably and safely not only grow the cells from the patients, but also to design a virus to safely carry the corrected collagen gene into the cells.”

In layman’s terms, the process goes something like this: Collect two, 8-millimeter-square skin biopsies from patients; isolate the keratinocytes, which will contain epidermal stem cells as well; infect the cells with the genetically engineered virus carrying the corrected type-7 collagen gene; grow the cells over a period of about three weeks into eight thin sheets (each roughly the size of a playing card); conduct a series of tests on the cells to ensure their purity and safety; and then carefully, oh so carefully (!), hand-carry the newly minted skin in a small, air-tight box to the operating room where the patient waits under general anesthesia.

“Once the sheets of cells are grown, they have about a 24-hour half-life during which they must be grafted,” says Siprashvili. “As far as a production process for a biological product for use in humans, this is one of the most complex and difficult in the world.”

Each patient gets six grafts — five over previously existing wounds and one on a wound created deliberately during the grafting process. The patient spends a few days in the hospital, moving as little as possible to avoid disturbing the grafts before they’ve adhered to the underlying tissue.

A key part of the study is confirming that type-7 collagen is correctly incorporated into the anchoring fibrils that hold the skin layers together, and that the protein is fully functional.

“In terms of therapy, understanding the type-7 collagen protein has been just as critical as understanding the type-7 collagen gene,” says Marinkovich.

The first patient received the grafts in November 2013. Martinez, a long-standing patient of Marinkovich’s, was the third patient to participate in the trial. He received his grafts on Dec. 1, 2014: one graft on the top of his left hand, two on the top and side of his right hand, two on the side of his left foot, and one near his right heel.

“I don’t know how, or whether, my participation in this trial will benefit me, personally,” says Martinez, who lives alone but requires daily care. Unlike many EB patients, Martinez finished high school and went on to complete a degree in business marketing at a community college. But as the years pass, the disease is taking its toll. His hands are fused, and he no longer holds a job.

“I’m 32 years old, which is quite old for this disease,” says Martinez. “I’m lucky to be alive. I didn’t do this for myself; I did it for the children. I don’t want anyone to go through this. We have to stop this.”

It’s too early to tell whether the skin grafts will help any of the first participants. That’s not even the point of the trial. But physicians and patients are hopeful that grafting even small patches of tissue will make a difference in the recipients’ quality of life — perhaps by preventing blistering on especially vulnerable areas of the body, or slowing or stopping the development of mitten hand, or even helping chronic wounds heal at last.

“We need to not let ‘perfect’ be the enemy of ‘good enough,’” says Tang. “Even just preserving their hand and finger function would be a tremendous step forward.”

Still, Martinez feels that for him, for now, the results have been positive. His grafted skin has not blistered and appears relatively normal.

**WEB EXTRA**

Living with the world’s worst skin disease:

http://stan.md/1LuvuEX

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# wither youth

## WHY DOES SKIN GROW OLD?

Beauty is only skin deep, right?
So no wonder people care so much
about how their skin looks.
Over $140 billion a year is spent globally on cosmetics.
In 2011 there were 4.1 million Botox procedures

in the United States, 718,000 chemical peels, more than a half-million laser skin procedures, 672,000 microdermabrasions (a kind of ultra-gentle sandblasting of the skin), 153,000 eyelid surgeries and a bunch of face-lifts. You get the idea. • Whatever skin may lack in depth, it makes up for it by covering a lot of territory. A typical person's skin is stretched over 20 or 22 square feet of surface area, about the size of a standard doorway. Your skin is the largest organ in your body, weighing about 8 pounds. It buffers you against the elements and insults of the outside world, locks out toxins and pathogens, locks in body fluids, senses the tactile environment, regulates body temperature via sweating, makes vitamin D — and just plain keeps you structurally intact by enveloping your fat, organs and bones. • Dermatologist Anne Chang, MD, is working hard to break down the wall between aesthetic dermatology (the dermatology of appearance) and geriatric dermatology (the dermatology of aging). Her research into the underlying causes of skin aging holds implications not just for slowing or reversing the superficial effects of that aging process but also, quite possibly, for staving off a host of age-related skin diseases including skin cancer. • Our skin reveals a lot about us to ourselves and to others. It reflects our mood — it flushes when we're embarrassed; it turns livid with rage. It also provides a clue about our age.

**BY BRUCE GOLDMAN**

PHOTOGRAPHY BY MAX AGUILERA-HELLWEG

DERMATOLOGIST ANNE CHANG IS DISCOVERING CLUES TO KEEPING SKIN YOUTHFUL AND HEALTHY.

As we get older our skin does, too. It gets thinner, less elastic, subject to discoloration. Cells that produce collagen, a key structural element in skin, make less of it and replicate less often.

The terrain of aging skin grows all too familiar with the passing years: bags under the eyes, crow's feet, jowls, tiny tangles of blood vessels, ever more pronounced pores and pits and pigmentation irregularities. Then there are wrinkles — long, deep "frown lines" radiating upward from the inside edges of the eyebrows and "laugh lines" that trace a furrow from our nostrils to the edges of our lips in our 40s, and finer lines that start crisscrossing our faces in our 50s. Sagging skin gets more prominent in our later years as we lose bone and fat.

And it's all right there on the very outside of us, where everyone else can see it.

That's just fine with Anne Chang. "One of the nice things about skin is that it's amenable to direct inspection," she says. "You can look at it. That makes it a great proving ground for evidence-based medicine." It's also a plus when it comes to following doctor's orders. "Patients care about skin because they can see it. So they're motivated to try to improve their condition. When they see things working, that's positive feedback for them to continue doing what they're supposed to be doing."

Skin can tell you about what's going on inside of you, too. "Lots of diseases have cutaneous manifestations," Chang says. Sometimes itchy skin means liver or kidney trouble. Dry skin can signify thyroid trouble. Scaling of the hands and feet, blistering, or rashes around the mouth can be signs of cancer in an internal organ.

Aging puts skin at an ever higher risk of problems in its own right. In particular, the incidence of three different types of skin cancer — basal cell carcinoma, squamous cell carcinoma and melanoma — increases with age. Rates of melanoma, by far the most deadly of the trio, rise dramatically after age 50. So slowing the aging process in skin is not merely a cosmetic concern. It's a health issue.

Chang says, "We've been asking, can you turn back time? Can aging effects be reversed? Can you rejuvenate skin, make it young again?" Some 40 million American baby boomers age 65 and older, and probably a fair number of people younger than that, would like to know, too.

'Lots of diseases HAVE CUTANEOUS MANIFESTATIONS.' SOMETIMES ITCHY SKIN MEANS LIVER OR KIDNEY TROUBLE. DRY SKIN CAN SIGNIFY THYROID TROUBLE. SCALING OF THE HANDS AND FEET, BLISTERING, OR RASHES AROUND THE MOUTH CAN BE SIGNS OF CANCER IN AN INTERNAL ORGAN.

## SAME OL', SAME OL'

The standard bromides for keeping your skin young are about the same as the ones for staying healthy in general: Eat a good diet. Quit smoking. Avoid pollution. Manage stress. Get some sleep.

There is one special arrow of advice aimed directly at your skin: Stay out of the sun. If you're going to get exposed, wear sunblock or sun-protective clothing.

Unquestionably, different histories of exposure to sunlight, pollution, smoking and nutrients lead to different outcomes. Then again, says Chang, stick a fair-skinned, redheaded person in strong sunlight for 20 minutes and they'll burn. Put a dark-skinned person in the sun for the same amount of time, and the consequences will be less severe.

Although that's a no-brainer, Chang says our responses to all kinds of exposures are in no small part conditioned by underlying genetic predispositions. "We're bombarded with marketing that says you can improve your skin if you buy this or that. But there's more to the story than just external treatments or therapies," she says. Genes are a big part of it. "But nobody's ever found what those genes are that keep our skin healthy."

Well, that's no longer quite true, thanks to Chang herself.

## OUR BIRTHDAY SUIT

What is this thing called skin, which we wear day and night from the time we come out of the womb until the day we die?

Skin is a highly organized organ consisting of two layers: an outer one called the epidermis and an underlying one called the dermis.

The epidermis is itself a multilayered tissue, and an active one. At its base are stem cells that can generate daughter cells that gradually get pushed upward through several epidermal

layers, during which migration they lose moisture content. By the time they reach the surface, they've flattened and coalesced into a tough, waterproof coat of dead cells called the stratum corneum. A person sheds 40,000 of these dead skin cells (called squamous cells) each minute of the day. Successive layers below the stratum corneum host various cell types including squamous cells and melanocytes, which make a dark pigment that protects against ultraviolet light. In the deepest layer of the epidermis, the stratum basale, new squamous cells are formed.

Below the epidermis lies the dermis, which contains collagen-producing fibroblasts, lymph and blood vessels, touch receptors, immune cells, sweat glands and sebaceous glands, which produce an oily substance called sebum that keeps skin moist.

What all cell types have in common is that their molecular contents are prone to damage by a ubiquitous chemical reaction called oxidation that can produce electron-rich chunks of broken molecules that, Chang says, rattle around like little firecrackers and cause damage, breaking some molecules apart and smooshing others together. Either way, it can be bad for a cell. Among the agents triggering oxidation are not only oxygen, as one might surmise, but sunlight, air pollution, cigarette smoke and the plain old everyday process of converting the food we eat into the energy and chemicals that all the cells in our body use. Get used to it. There's no way around it.

A major internal source of oxidant chemicals as well as other cell-irritating substances is inflammation, a crucial part of the immune response that tends to slip into overdrive as we grow older. A few years ago, Chang spearheaded a study that measured 46 middle-aged Japanese women's blood levels of metabolites called isoprostanes, produced from the breakdown of inflammatory substances called prostaglandins. Because they circulate in the blood, isoprostane levels are an accessible proxy for systemic inflammation. And sure enough, the women with the "oldest" skin for their age had the highest isoprostane levels in their blood, which strongly suggests an inflammatory component to skin aging. Prostaglandins are manufactured by an enzyme that is blocked by aspirin, ibuprofen and other so-called NSAIDs (for "nonsteroidal anti-inflammatory drugs"). Chang hopes to test such a drug for its anti-aging effects on skin.

To find out what the underlying genetic drivers of the aging process in skin might be, Chang launched a study in collaboration with Nir Barzilai, MD, professor of medicine and director of the Institute for Aging Research at Albert Einstein College of Medicine in the Bronx, who has assembled a cohort of some 600 centenarian Ashkenazi Jews (technically, they're between ages 95 and 112) along with their children and children's spouses, in order to explore the molecular wellsprings of longevity.

A requirement for participation in Barzilai's ongoing project is that all four of a potential subject's grandparents have to have been Ashkenazis: descended from a "founder group" of some 30,000 northern and eastern Europe-dwelling Jews in the 17th century who had survived plagues and pogroms over several centuries. Having until recently married almost strictly among themselves for the entirety of their long European residency, Ashkenazi Jews have remarkably homogeneous genetic backgrounds. This makes them ideal for studying whatever genetic differences do crop up among them, including differences in genes associated with aging, according to Barzilai. "We want to know why some people age quickly and others age slowly," he says.

A key first step toward figuring that out is finding genes that, when they don't work right, leave the skin more vulnerable to the ravages of the environment. This, in turn, could lead to better understanding of the aging process in skin and — via hard work, luck, or both — drugs and procedures that stave off superficial effects of aging as well as life-threatening, age-related skin diseases.

The fact that so many of Barzilai's subjects are very old was hugely beneficial for Chang's purposes. The older you get and the longer your skin is exposed to internal and external factors influencing its aging, the easier it gets to spot the signs of aging written on the skin and to differentiate those whose skin is aging slowly from those whose skin is not.

"One of our centenarians was 48 years older than you

The older you get

AND THE LONGER YOUR SKIN IS EXPOSED TO INTERNAL AND EXTERNAL FACTORS INFLUENCING ITS AGING, THE EASIER IT GETS TO SPOT THE SIGNS OF AGING WRITTEN ON THE SKIN AND TO DIFFERENTIATE THOSE WHOSE SKIN IS AGING SLOWLY FROM THOSE WHOSE SKIN IS NOT.

would expect her skin to look based strictly on chronological age," Barzilai says.

His New York-based team shipped photographs of a number of Ashkenazi subjects of various ages to Chang's lab at Stanford, where her team classified individuals according to standard dermatological measures of skin aging such as relative abundance of wrinkles and sagging.

Then they separated the subjects into two groups: 218 whose skin was aging the most slowly relative to their actual age, and the 210 other participants with more rapidly aging skin. Chang and her associates obtained blood cells from the subjects, analyzed the DNA, and compared the largely similar genomes of the two groups, keeping their eye out for tiny gene variants that were over- or under-represented in one group or the other.

They found three genes in which the presence of particular variants was associated with a differential likelihood of people's skin being old or young for their age. None of these genes had previously been implicated as aging-related. In fact, not all that much is known about any of them. One seems to be involved in immune function. A second gene has been tied to a condition called premature ovarian insufficiency, an arguably aging-related condition in which women run out of ova before reaching the typical age of menopause onset. And the third gene appears to be associated with the ability of fibroblasts — collagen-producing cells — to dodge their suicidal response to certain stresses. "These genes are not associated with longevity per se," says Barzilai. "They don't come up when we look at very long-lived people versus those who die young."

"It turns out centenarians don't necessarily have better skin-aging genes than younger groups," says Chang. "There's a different set of genes for skin aging. Skin youthfulness, cardiac health, glucose metabolism — these don't necessarily all go together."

Chang wants to do further experiments along these lines using skin samples from individuals with and without these gene variants. "Looking at blood is like looking at a fossil," she says. "You're guessing about what's going on in skin based on indirect evidence." Using skin rather than blood will allow Chang to directly explore what these genes' protein products are doing inside skin cells.

## SERENDIPITY

In March 2009, Chang attended a gala event celebrating the Department of Dermatology's 50th anniversary. So did a large number of physicians who had completed their residencies in the department before moving on to institutions far and wide. Among them was Patrick Bitter, MD, an alumnus of Stanford's medical school who completed his dermatological residency here in 1986. Now in private practice, Bitter is the co-inventor of a commercially available procedure called broadband light therapy, or BBL. (About $215 million was spent on BBL treatments in the United States in 2009.) Approved by the Food and Drug Administration for ridding skin of redness, discoloration and unwanted hair, BBL employs a hand-held device that directs high-intensity light in the visible and infrared frequencies at the area of skin needing treatment.

Bitter was well aware that BBL works — it's used millions of times a year in the United States with reliable cosmetic success — but was wondering if anybody there might be able to help him figure out exactly how. Above all, he wished to know whether the treatment was purely superficial and short term, or whether the visible results reflected an underlying rejuvenation process.

All experts acknowledge that ultraviolet light is rough on skin. But what about the rest of the rainbow? Might visible and infrared light's effects be not only benign but beneficial?

In 2007, Stanford dermatology professor Howard Chang, MD, PhD, and some colleagues blocked the action of a protein complex called NF-kappa-B in the epidermis of mice. NF-kappa-B is a molecular "master switch" that, when activated, causes wholesale shifts in which genes in a cell are turned on and which are dormant. Chang and his associates found that blocking it rendered old mice's skin more youthful looking.

Bitter had heard a talk Howard Chang had given about his experiments with mice and was curious about whether BBL might be exerting an anti-aging effect on human skin by, for example, blocking NF-kappa-B there. But how to bridge this gap between clinical practice and basic science? Anne Chang had already proposed to explore the phenomenon in humans, and was looking for ways to study that question.

Another collaboration was born. In 2013 Anne Chang was the lead author of a paper on which Bitter was the second author and Howard Chang was the senior author. In that study, the researchers got skin biopsies from the forearms of five older women with moderate to severe photoaging damage and five younger women with no signs of photoaging on their arms, then used a laboratory technique to estimate the activity levels of each of the 22,000 or so genes in the cells making up every woman's biopsy sample. After the older women had undergone a course of BBL treatment, the investigators again took biopsy samples from them.

They found almost 2,300 genes whose output differed significantly in old versus young women. More striking,

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# SURVIVING MELANOMA

## NEW HOPE FOR BEATING SKIN CANCER'S DEADLIEST FORM

**By Sarah C.P. Williams**

ILLUSTRATION BY MATTHEW BANDSUCH

It starts as a tiny dark spot on your calf or the crook of your neck or your back. It's probably blotchy, like a Rorschach test, and if a doctor notices it, she is likely to take a second look. "I'd like to examine this one more closely," she might say about the mark on your skin that you'd perhaps never even noticed. And it's often good news to hear a doctor say that, because if you catch this little mass of dark, feisty cells before they spread, the inkblot can't seep into your body and stain your liver or bones or brain with cancer. • While relatively rare, with 21 new cases per 100,000 people in the United States each year, melanomas are the most dangerous form of skin cancer that humans develop. They begin when melanocytes, cells that produce and contain the pigment melanin and dictate the tone of a person's skin, mutate and start dividing too quickly, forming these telltale blotches. But once a melanoma has advanced from being an isolated group of cells on the skin and has sent scouts to other parts of the body, it's notoriously hard to treat, despite its small size. • "Gram for gram, melanoma is the most deadly form of skin cancer," says Stanford dermatologist and melanoma program director Susan Swetter, MD. "Differences in survival drop dramatically with only a few millimeters of increased tumor thickness on the skin." • Over the past five years, however, a new generation of melanoma drugs has emerged that may change the cancer's deadly reputation. At Stanford and around the country, basic researchers are revealing weak spots in melanoma cells that treatments

can target, and physicians like Swetter are shepherding these new approaches through trials and into their clinics, extending patients' lives.

"This is absolutely the most exciting time in my career for treating melanoma," says Paul Khavari, MD, PhD, the chair of dermatology at Stanford.

At the same time, scientists are learning more about what makes people more prone to developing melanoma and — time and time again — placing the majority of the blame squarely on exposure to ultraviolet radiation, mainly the sun and artificial sources of ultraviolet light, such as tanning beds. Fortunately, regulations on tanning beds are tightening, public health initiatives on the dangers of tanning are ramping up, and compounds are being discovered that lessen the damage ultraviolet radiation can wreak on cells. For the first time in recent memory, scientists are hopeful that both the incidence and mortality of melanoma could soon start declining, after steadily increasing for the past four decades.

## LIVING LONGER

When they're taught how to recognize potential melanomas among the constellation of dots on patients' bodies, medical students are often told to think of the cancers as the "ugly ducklings" of skin spots. While small, regularly brown moles rarely pose a threat, spots that are asymmetric with uneven borders and various colors are more alarming.

For Trista McNeill, a director at eBay and an active runner and swimmer, concerning-looking moles were nothing new: She has fair, freckled skin; spent her childhood outside (often without sunscreen); and had two moles removed from her face as a teenager. But in 2007, when she was 37, an odd-looking spot on her skin started bleeding. In cases like McNeill's, a biopsy of the suspicious spot sent off to the lab will reveal whether it's cancer. If it is melanoma, its thickness, some microscopic features, and, mostly, whether it's begun to spread to draining lymph nodes will dictate what happens next. The earliest stages of melanoma, when confined to the skin, as McNeill's was in 2007, are straightforward to treat: Simply removing the cells from where they've nestled into the skin and checking the region's lymph nodes to see if melanoma has spread is usually enough. And about 84 percent of melanomas are diagnosed when they're still in this contained stage, according to the National Cancer Institute.

For some patients, though, the story doesn't end here. Take McNeill: She had occasional skin checks to ensure her melanoma wasn't reemerging. She went scuba diving in Mexico, the Philippines and Palau, diligently slathering sunscreen all over herself before each dive to prevent another episode of cancer. Nothing ever appeared. But in early 2014, nearly seven years after her initial diagnosis, McNeill — while attending the South by Southwest art and technology conference in Austin, Texas — felt an ache in her side. "It started hurting so badly that I thought I must have a gallstone or something," she recalls. In an emergency room in Austin, scans revealed that her liver and lungs were dotted with melanoma. "It was completely shocking," McNeill says. "It had been seven whole years, so I thought I was pretty much in the clear."

Once melanoma has moved to other organs, at which point it is termed metastatic, the news is often dire for patients — or at least it was. "Metastatic melanoma has been known as the chemotherapy-resistant cancer, and we previously had extremely ineffective therapies for advanced disease," says Swetter. "To see a cure in patients whose melanoma had spread was extremely rare, until now."

For the latter part of the 20th century, metastatic melanoma was most often treated with the chemotherapeutic drug dacarbazine. But dacarbazine works in only about 15 percent of patients, and it shrinks their tumors only temporarily. Among those people with the most advanced melanomas who were treated with the drug, only 2 percent were alive six years later, a 1984 study found.

In 1998, the Food and Drug Administration approved interleukin-2, which treats metastatic melanoma by revving up the activity of the patient's immune system to fight tumors. But, once again, the drug works for only a select few: Trials conducted before the drug was approved found that less than 7 percent of patients went into remission after taking IL-2. And it carries with it a host of serious side effects.

But just after the turn of the millennium, some of the first large, genetic studies of melanoma started to be published. About half of all skin melanomas, researchers found, had mutations in a gene called BRAF. The protein encoded by the mutated gene makes cells divide too quickly and prevents them from dying. If they could block that protein, scientists realized, they might be able to put the brakes on melanomas. At the same time, other research teams started to learn more effective ways of harnessing the power of the immune system to fight cancers like melanoma.

Over the past five years, that research has paid off. In 2011, the FDA approved ipilimumab, an immune drug, and vemurarenib, which blocks mutated BRAF, for use in metastatic melanoma. In 2013, the regulatory agency approved two more drugs targeting pathways related to BRAF: dabrafenib and trametinib. Then, in September 2014, another immune-based melanoma treatment won approval: pembro-

lizumab, followed by nivolumab in March 2015.

For McNeill, the timing of her metastatic disease couldn't have been better. "If you have to have melanoma, now's the best time," one doctor told her. Back at Stanford, after her emergency room diagnosis in Texas, McNeill saw not only Swetter, but a team of doctors from multiple disciplines, including medical oncology to guide drug selection and coax her tumors to shrink, and surgery to remove her ovaries when they became affected by the cancer. But things kept looking worse: In June, only a few months after her cancer had returned, she started having trouble controlling one of her feet. An MRI revealed that the melanoma had spread to her brain and was affecting her motor cortex — the part of the brain that oversees the movement of the rest of the body.

"I realized at that point that I had a formidable foe and that I still had a lot of fighting to do," says McNeill. Radiation oncology was added to the list of departments teaming up on her case; they gave her a 15-day course of whole-brain radiation. Luckily, the tumor began to shrink. That's when McNeill started to get good news. Genetic testing revealed that her melanoma cells had mutations in BRAF and expressed PD-L1, a protein involved in the immune system. Knowing this helped her doctors choose the right drugs to attack her tumors. She was started on two of the targeted therapies that have been approved only since 2013: dabrafenib and trametinib.

"In the past, the median survival for stage-4 disease has been six to nine months," Swetter says. "Now, I have patients who are four or five years out with advanced melanoma on the newer targeted drugs and immunotherapies and still in complete remission." At least 40 percent of her patients are surviving for the first few years after a stage-4 melanoma diagnosis, she estimates. There's still room for improvement, though, and luckily, there are a growing number of clinicians turning their attention toward developing next-generation drugs for melanoma.

"After decades of treatment failures, melanoma has become a cancer that's being actively studied again," Swetter says. "Prior to the last decade, researchers and clinicians alike became discouraged with the dismal response to treatment for advanced disease, and fortunately for patients this has changed."

### DRIVEN BY BASIC RESEARCH

Research in a Stanford basic biology lab has provided a better understanding of why melanoma is so good at evading most treatments. In 2010, Irving Weissman, MD, the director of Stanford's Institute for Stem Cell Biology and Regenerative Medicine, discovered that a subset of melanoma cells have a protein called CD271 jutting out of their surface.

To study these CD271-studded cells further, Weissman's research group turned to samples from patients' melanomas, rather than mice with the cancer. "Almost everybody uses a line of mice prone to melanoma that's been bred for so many generations it doesn't resemble anything you see in humans," he explained.

Weissman and postdoctoral scholar Alex Boiko, PhD, took the CD271-studded cells from human melanoma biopsies performed at Stanford (depending on the patient, 2-40 percent of the total melanoma cells carried CD271) and implanted them in immune-deficient mice. Almost three-quarters of the CD271-carrying cells took root in the rodents, causing melanoma. But less than one in 10 of the non-CD271-containing cells could do the same. CD271, Boiko and Weissman concluded, was a marker for cancer stem cells — cells that are able to give rise to a new tumor.

But that wasn't all Weissman and his colleagues found about the newly identified melanoma stem cells. They went on to show why cells with CD271 escaped most existing melanoma treatments: They lacked a number of markers that other tumor cells have. In fact, Weissman found, they

MELANOMA HAS BECOME A CANCER that's actively studied again. 'Prior to the last decade, researchers and clinicians alike became discouraged with the dismal response to treatment for advanced disease, and fortunately for patients this has changed.'

# NEW INSIGHTS ON A SKIN CANCER DRUG

## AN EXPLANATION FOR RESISTANCE

FIVE YEARS AGO, WINNIE BAZURTO WAS ON THE VERGE OF LOSING vision in her right eye because of a fast-growing tumor on her lower eyelid. Normally, the type of cancer she had, basal cell carcinoma, would have been treated with surgery or radiation. But because of her age, Bazurto, nearly 100 at the time, was a special case. She got what was then a special treatment: a new skin cancer drug. *[Read more of Bazurto's story in our Summer 2013 issue.]*

The drug, vismodegib, was the first drug approved by the U.S. Food and Drug Administration to treat advanced basal cell carcinoma, the most commonly diagnosed cancer in the United States.

Cancer, however, works hard to stay alive, to find ways to return. Though the drug is holding Bazurto's cancer in check, in about 20 percent of patients it recurs in a few months. Now a team of Stanford researchers has identified exactly how the cancer gets past vismodegib's ability to block what they knew to be the key enabler of the cancer's growth — untimely activation of the Hedgehog molecular signaling pathway.

Like other signaling pathways (hundreds of which exist in living organisms), the Hedgehog pathway is a cascade of protein interactions, with one protein activating the next, in a chain reaction of sorts. Vismodegib, sold under the brand name Erivedge, binds to and inactivates a protein called Smoothened, one of the Hedgehog pathway's first steps.

Recognition of the importance of the Hedgehog signaling pathway dates back to the 1970s, when scientists studying the biology of development from single egg to complex organism discovered its role in determining the body plan of the fruit fly. In humans, the pathway is also important for normal development. In 1996, a team of Stanford and UC-San Francisco scientists made the connection between this signaling pathway and cancer: They found malfunctions in the pathway could cause basal cell carcinoma.

The latest round of discoveries at Stanford found a pattern in how Smoothened proteins were mutating to develop resistance to vismodegib. They also found that they could use another class of drugs called Gli inhibitors to block the Smoothened mutation downstream.

This new entry in the encyclopedia of Hedgehog signaling pathway behavior is a big step in genomics-driven medicine, says Stanford vismodegib researcher and Bazurto's dermatologist, Jean Tang, MD, PhD. The same pathway is central to the development of other cancers, including some of its most lethal forms: non-small cell lung cancer, ovarian cancer, certain types of leukemia, the bone marrow disorder myelodysplastic syndrome and the most common malignant brain cancer — medulloblastoma.

Now, these researchers are building a database of skin cancer biopsies to build a profile of each patient's cancer, identifying which mutations are its engines and which currently available drugs can counteract them.

Bazurto will be 104 years old this August. She's a bit frail, of course, but one problem she doesn't have is poor vision. Watching football and baseball on television is one of her great joys, she says. And she's still at it. — SARA WYKES

lacked the proteins that most classic immune therapies were designed to seek out and destroy. The observation explained why these therapies hadn't been hugely successful. While immunotherapies might eliminate some melanoma cells, they missed targeting the cells with CD271 — the very cells that can best spread a cancer.

But in the process of his research, Weissman also found a marker — a protein called CD47 — that all tumor cells appear to have, including the stem cells. Now, his group is developing a drug that blocks CD47, making the tumor cells suddenly susceptible to attacks from certain immune system cells, known as macrophages. Macrophages eat the tumor cells and present the digested materials to killer T cells, which go on to attack not only tumor cells that lack CD271 but also those that carry it. This "cross-presentation" to killer T cells should activate more effective immune responses, Weissman says. He hopes to test it as a treatment in melanoma patients some day soon.

And while immune approaches like Weissman's progress, research continues on the genetics underlying melanomas, aiming to find genes outside of the BRAF pathway that cause the other half of the melanomas. In his lab, Khavari is developing new strains of mice that have the same genetic mutations that can cause melanoma in humans.

"In cancer sequencing, there have been a huge number of genes discovered, but people don't know which of those are really driving the tumors," Khavari says. By mutating the same genes in mice, his research team can investigate their biological consequences and — they hope — find more targets for drugs that block melanoma's formation, growth and spread.

### THE END OF THE BRONZE AGE?

While the newest melanoma drugs aim to decrease the mortality rate attributed to metastatic melanoma, most researchers agree that there's another, more powerful way to lower the number of people who die from the disease: keep people from getting it in the first place.

"Despite all the encouraging research in therapies, what would make the most impact on improving survival is better prevention," says Swetter.

In 1903, a German medical company accidentally discovered that ultraviolet lamps tanned people's skin and started manufacturing tanning beds. Slow to catch on at first, tanning beds didn't reach the United States until the late 1970s. At that point — thanks to a few celebrities with bronzed looks and an already growing trend of tanning outdoors — tanning beds rapidly took off. By the 1980s, indoor tanning was widespread in the United States and Europe; it offered a new, easy way to get that coveted tan, even in mid-winter. But in the mid-1990s, data started building up that the more time people spent in tanning beds — or in the sun without sunscreen — the more likely they were to develop melanoma, as well as other forms of skin cancer. The natural or artificial UV rays that darken skin also cause mutations in the DNA of skin cells. And the more mutations accumulate, the more likely one will affect BRAF or another melanoma-linked gene, flipping a cell from healthy to cancerous. Tanning beds accelerate this process because they provide a more concentrated dose of UV rays — around 15 times stronger than those from the sun.

Tanning in a UV bed a single time increases a person's risk of developing melanoma by 20 percent, a 2012 study in the *British Medical Journal* reported. If indoor tanning starts in young adulthood — before age 35 — or if a person has had more than five sunburns, that risk is at least doubled, studies have found. While most cases of melanoma are in light-skinned Caucasians, dark-skinned people can also get the cancer; they also have increased odds the more times they sunburn and the more time they spend in tanning beds. In all, researchers estimated in 2011 that about 86 percent of melanomas in fair-complexioned individuals are due to ultraviolet exposure.

Yet despite the evidence that tanning significantly boosts melanoma risk, tanning salons stay in business and beachgoers continue forgoing sunscreen to darken their skin. The American Academy of Dermatology reports that more than a million people a day visit tanning salons in the United States, and nearly 30 million people tan indoors a year. More than 70 percent of these are Caucasian females, mostly under the age of 30. And the rates of melanoma in the United States reflect these numbers: While rates of the cancer in women decreased from 1978 to 1987, then remained steady for five years, they've been climbing ever since. Much of that rise has been attributed to the increased use of tanning beds beginning in the 1980s.

So what can be done to stop these climbing rates? Queensland — an Australian state with the highest rates of melanoma in the world — launched massive public health campaigns beginning in the 1980s aimed at educating the public on the risks of sun exposure and tanning, as well as how to recognize early melanoma, Swetter says. Since then, they've seen the rates of melanoma in Queensland start to drop.

In the United States, word is starting to get out — 11 states have now banned tanning beds for minors (with more considering similar legislation), and the FDA has upped its regulation of the devices. But with 55 percent of current college students having tanned indoors at least once, more education is needed. Swetter has been involved in studies that probe what makes people less likely to tan: Using sunless tanning lotions that artificially darken your skin helps avoid harmful ultraviolet radiation, and educating tanning salon workers in cancer risks makes it more likely they'll tell their patrons about these risks.

"But it's really difficult to change tanning behaviors," is how Swetter sums up much of the data.

Catching melanoma early, though, is another matter. Swetter's research has found that if someone routinely has skin exams — either using a mirror (or a partner) at home to examine moles on the back or hard-to-see areas, or visiting a doctor's office — they're more than three times as likely to be diagnosed with an early, curable melanoma than a more advanced form of the cancer. Indeed, when a region in Germany launched a statewide skin-cancer-screening program in the mid-2000s, its death rates from melanoma were nearly 50 percent lower five years later. Routine skin exams, Swetter

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'IN CANCER SEQUENCING, THERE have been a huge number of genes discovered.' By mutating the same genes in mice, Paul Khavari's team is investigating their biological consequences.

# new lungs, new life

## A TRANSPLANT SURVIVOR'S STRUGGLE TO KEEP HER SMILE

Cassie Stockton reclines on a doctor's exam chair, preparing for yet another medical procedure. The 21-year-old community college student, who hopes to become an ultrasound technician, is a patient at Stanford's Laser and Aesthetic Dermatology Clinic. A tiny woman, with white-blonde hair and full lips, Stockton is here regularly for what are common cosmetic treatments for much older women — injectable fillers, chemical peels, pulsed light rejuvenation. • For Stockton, these skin treatments have meant so much more. They've helped give her back her smile. • **Stockton was 15 years old** when she came out of a surgery born into a new life. No longer would she have to hide at home from germs like the common cold virus. No longer would there be panicked, middle-of-the-night emergency room trips, the constant struggle to breathe, the gasping for air. • The oxygen machines, the vasodilators, the feeding tubes, a childhood spent living in fear — all tossed. • From this day forward, Stockton could be almost like other teenagers — go out on dates, hang at the lake, go to school every day even during the germ-filled winter months. She could play soccer in PE, have a first kiss, go to prom. Breathe deeply. Belong. • The day Stockton woke up out of the anesthesia six years ago after a 13-hour surgery at the Transplant Center at Lucile Packard Children's Hospital Stanford, she breathed in oxygen with newly transplanted lungs, and breathed out sobs. Tears streamed down her face. • "At first, I thought she was in pain," says her mother, Jennifer Scott, who stood by her side. But that wasn't it. Stockton was overwhelmingly sad because she now knew her new lungs were the gift of a child. • It was Dec. 6, 2009, just before Christmas. The death of someone else's child had given her a whole new life. • Six years later, Stockton's sickly childhood has become a thing of

**BY TRACIE WHITE**

PHOTOGRAPH BY MAX AGUILERA-HELLWEG

MEDICATIONS CASSIE STOCKTON TOOK AS A TRANSPLANT RECIPIENT HAVE LEFT HER SKIN VULNERABLE TO CANCER.

the past. But as an organ transplant recipient she faces new medical challenges. A daily regimen of immunosuppressant medications — a handful every morning and night — is essential for keeping her body from rejecting her new lungs, but they caused an increased susceptibility to diabetes and a high risk of skin cancer. Now she's a diabetic whose strict, daily, self-care regimen includes insulin injections and waging war against a barrage of skin cancers.

Every four months, she and her fiancé make the four-hour drive from their home in Bakersfield, California, past the oil rigs and cattle farms to Stanford's Redwood City-based dermatology clinic for her skin cancer screening. It's been two years of treatments: freezings, laserings, a total of eight outpatient skin surgeries — the most significant resulting in the removal of the left half of her lower lip. The dermatologic surgeon removes the skin cancers, and then gets to work to repair the damage.

"It's heart-breaking to have to remove the lip of a 21-year-old woman," says Tyler Hollmig, MD, clinical assistant professor of dermatology and director of the Stanford Laser and Aesthetic Dermatology Clinic, who leads Stockton's treatment and keeps her looking like the young woman she is, restoring her skin, rebuilding her lip, making sure she keeps her smile.

Stockton doesn't complain about any of it. It's her job to take care of the lungs given to her by that child, she says. She knows she got a second chance at life.

"After the transplant I felt like I threw half of everything bad away," Stockton says. "Now I stay on a strict regimen of medications. I can't skip a day of it. The more I work out at the gym, the more it helps my lungs. I protect my skin and stay out of the sun. A lot depends on how well you take care of yourself. Finally I can breathe."

## BORN PREMATURE

Stockton's own lungs never really had a chance. Born premature, the newborn was intubated the first two weeks of life, then sent home with her mother and an oxygen tank. She remained on oxygen 24 hours a day for the first two years of her life.

Eventually, she was diagnosed with bronchopulmonary dysplasia, a chronic lung disorder more common in infants who get mechanical ventilation to treat respiratory distress syndrome.

"She was always so sick," says her mother. She and Stockton are together at the Scotts' home in Bakersfield looking at childhood snapshots scattered across the dining room table — a 1-year-old Cassie with oxygen tubes in her nose, a smiling Cassie posing at the prom in a short skirt and high heels.

"She was always short of breath and prone to lung infections," Scott says. "She would not thrive. She didn't walk until a year and a half."

To protect her baby from the lung infections that resulted in repeated emergency room visits, Scott kept her at home away from any possible germ sources, including playmates.

"She was always congested," Scott says. "She would sit in my lap and I'd pat on her chest saying, 'Come on lungs, come on lungs.' That was what she said when she first started to talk."

At the age of 2, Stockton was able to come off the oxygen machine during the day, but remained on oxygen during the night. She was still sickly, but she could do a bit more, ride her tricycle, run around. But during visits to the park, mother and daughter sat alone at a bench away from any germs and watched the other kids play.

"I remember being angry, really angry," says Scott. "I just wanted her to be able to get up and play."

At 5, Stockton got sick again, this time with the flu, and was back in the hospital, intubated once more.

'After the transplant I felt like I threw half of EVERYTHING BAD AWAY. NOW I STAY ON A STRICT REGIMEN OF MEDICATIONS. I CAN'T SKIP A DAY OF IT. THE MORE I WORK OUT AT THE GYM,THE MORE IT HELPS MY LUNGS. I PROTECT MY SKIN AND STAY OUT OF THE SUN.'

"This time Cassie's lungs were destroyed," Scott says. "Doctors told me it may be years from now, but she would need a double-lung transplant. After that there was a huge change in Cassie. She couldn't ride her tricycle anymore, she could barely breathe to walk.

"She was so skinny, so frail, even malnourished. She was always breathing so hard, burning up calories. At 6 years old, she was just 25 pounds," her mother recalls.

A physician kept Stockton, who also had a gastric reflux condition, on a feeding tube for the next two years. Eventually she got strong enough to go to a small, private kindergarten and on to first grade at a public school. By homeschooling Stockton during the germ-filled winter months, her mom was able to keep her out of the ER for the next decade. Then at 15, Stockton came down with pneumonia.

That year there were heavy wildfires surrounding Bakersfield, the smoke and smog settling thick as soup into the Central Valley's bowl-like basin. It affected a lot of people's lungs. Stockton was an eighth grader at Fruitvale Junior High.

"One day we were sitting at the table at home, eating cookies and drinking milk," Scott says. "Cassie wanted her lip pierced. I said no. She got mad and went to her room. When I peeked in, she was crying."

But it wasn't about the piercing. Stockton was having really bad chest pain. It was pneumonia. The two headed back to the ER. This time, Stockton's lungs wouldn't survive the attack.

Afraid her lungs were too weak to keep her alive, the staff at Children's Hospital in Madera inserted a catheter into the main artery of her neck and connected her to an ECMO (extracorporeal membrane oxygenation) machine. ECMO is a life-support system. Oxygen-depleted blood from the patient flows through the machine where it gets re-oxygenated and sent back to the body. Then they sent her to Stanford, well-known for its expertise in transplant medicine.

"She was in complete lung failure," her mom says.

Over the next two weeks while at Stanford, Stockton was slowly weaned off the ECMO machine until she was able to walk around her unit. She wasn't going to die, not yet at least. But she needed a lung transplant as soon as possible. Stockton, not her mother, would need to give her own approval to undergo the life-changing surgery.

"The doctors told me, 'It's not up to you,'" her mom says. "'Cassie's old enough to make that decision herself.'" When they asked Stockton, she refused.

"I was shocked," her mother says. "I guess she was just so sick, so tired of all of it."

As Stockton listens to her mom tell the story of her childhood, the tears continually start and stop. Maybe it's more for her mother than for herself, but lines of mascara stream down her cheeks. She walks off to the kitchen to compose herself, circles back into the dining room, then walks away again, the tears still flowing.

Through it all she keeps smiling.

"I was scared," Stockton says, remembering back to the transplant decision. Two weeks later, after talking to other young transplant patients at the hospital, she changed her mind. She agreed to the surgery, was put on the lung transplant waiting list, and went home — to wait.

Six months later, in December, they got the call.

"We got in the car and drove to Stanford," Scott says. "It was a 13-hour surgery that lasted all night long."

During the four-month recovery period spent living in the Ronald McDonald House at Stanford, Stockton's first order of business was studying for her online driving test. She couldn't wait to start life as a "normal" 16-year-old.

## ADOLESCENCE

Her transplant had come at a particularly tricky age, smack dab in the middle of those rebellious adolescent years. Stockton's pulmonologist knew there would be battles to come. Teenage rebellion for transplant patients isn't allowed. It's too risky.

"They have the worst outcomes, adolescents," says Carol Conrad, MD, a Stanford pediatric pulmonologist who has been Stockton's physician since she first transferred to Stanford from Madera on the ECMO machine.

"They forget things, or they think they are going to live forever. I tend to be very strict and very clear that my patients have to follow every single one of my directions because we really don't have options for treatments after transplants. Poor Cassie, she wanted to be so normal, to look like everybody else, to get up and get out of the house, to go out and date boys."

After the transplant, Stockton did turn into a full-time teenager just like she wanted. She hung out at the lake. She drank sodas. Got a tan. Dated boys. Nothing so rebellious, but she soon learned that as a post-transplant patient with diabetes, she had a new set of rules to follow. Conrad helpfully pointed these rules out.

"One time, I showed up at her office drinking a Gatorade," Stockton says, the sugar-filled drink off limits to diabetics.

"Dr. Conrad told me to 'throw that out.'"

Another time, she showed up at an appointment wearing

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# getting under their skin

**Renowned for her groundbreaking solo theater** performances about race, social justice and equality, Anna Deavere Smith sees herself as a chameleon and an interpreter. Inspired by Walt Whitman's idea "to absorb America," she began creating a series of theater pieces in the 1990s, calling it: *On the Road: A Search for the American Character*. Like a Seurat painting, *On the Road* is filled with dots, specks and colors that build a detailed scene — in Smith's work, a portrait of an America still striving to perfect itself. Whether the play's subject be cities in civil strife (*Fires in the Mirror* and *Twilight: Los Angeles*), the frailties of the health-care system (*Let Me Down Easy*) or the struggle between the press and the presidency (*House Arrest*), her cumulative work is a curated display of the nation under a magnifying glass.

In a new work in progress, she examines the school-to-prison pipeline that propels youth in underserved communities from school to incarceration and a lifelong interaction with the criminal justice system. She calls it "the moral dilemma of our time."

Widely known for her television roles in Showtime's *Nurse Jackie* and NBC's *The West Wing*, Smith has won multiple awards in the theater and distinguished honors in the arts that place her in a class virtually alone: a MacArthur Foundation Fellowship "Genius Award," the National Humanities Medal bestowed by President Obama and the Dorothy and Lillian Gish Prize. The former Stanford drama professor is now on the New York University faculty. Because this issue of *Stanford Medicine* is about skin, who better than Smith to help us look at what's under it? She spoke with the magazine's executive editor, Paul Costello.

TINA BERNING

**PAUL COSTELLO:** You grew up in segregated Baltimore in the '50s and '60s. What did the word "skin" mean to you as a child and later?

**ANNA DEAVERE SMITH:** My relationship with skin color is complicated. Everyone in my family is a different color. There was this value system, where I grew up, that light skin was more privileged. I grew up with anxieties about skin color from so many points of entry. When I first got out of acting school, there was this one agent in San Francisco who we all had to talk with to try to get a job. When I met her, she said, "Well, I can't possibly send you out because you will antagonize my clients." I said, "What do you mean?" She said, "Well, you don't look like anything. Would you be black or would you be white? You don't look like anything." In the early part of my career it was a big stumbling block. There were stereotypes. As a woman, if you didn't fit into the idea of a tragic mulatto or mammy it was really hard to situate yourself. Now, it's not so for young women

because we've come to understand black people look all kinds of different ways.

**COSTELLO:** Early on in your career, you said you were really interested in talking to people who weren't like you. Essentially, you wanted to get into the skin of others. Why that need?

**SMITH:** I grew up in a segregated environment. My desire to go toward that thing that is not me has helped me feel more like I belong. It has counteracted my natural feeling of alienation, which stemmed from my youth and adolescence and even from the time I was in the conservatory. I was one of very few African Americans — maybe two at some points, three at others — at the American Conservatory Theater when I trained there. And I was never in the cool group there, which also tended to be male dominated. When I became a professional in the theater, the same was true. The theater is a very subjective community. You can't really have "affirmative action" in the arts. I am lucky that some theaters and some arts organizations have extended hospitality to me — but I had to develop the work I do outside of the theater. I only say all this in the event that some young artist happens upon this Q-and-A. They should not belabor looking for a community in which to do their work. They should create their own sense of belonging. I really love the fact that I've taught myself to find a sense of home in environments that are not my own. I claim my nomadism. The fact of my being nomadic *is* my home. My journey has been to absorb America word for word. My grandfather used to tell me, "If you say the words long enough, they become you." So I learn about America through repeating the words of others and, so far, by using the theater as a place to express that journey. It is not an obvious journey for those who watch my work, but it is implied.

I often quote a line from Mary Ellen Mark, a great photographer, who wrote in the book accompanying her "American Odyssey" exhibition that the camera gave her the necessary distance to get close to people. My work in the theater and my tool — a tape recorder — enables me to do the work, to create a distance, yet it gets me much closer to the person. My tape recorder is my microscope.

**COSTELLO:** Your newest theater work is *The Pipeline Project*. What does it focus on?

**SMITH:** It is in line with current discussions about inequality and the big gap we have in this country between those who have and those who do not. My interest in the school-to-prison pipeline begins with my interest in education. I was raised by teachers and I've taught for 40 years. The kids of *The Pipeline Project* get shoved out of school into the juvenile justice system and on from there, with a likelihood to be in correction facilities for part or much of their lives. The current tendency to immediately suspend students whose deeds might in different, more privileged environments be regarded as mischief is traced back to zero-tolerance policies that were created in the 1990s. This *is* a current moral dilemma, which is aligned with a larger moral dilemma about mass incarceration and, as I indicated a moment ago, a moral dilemma about the ways in which so many people lack opportunity to have productive lives and to be productive members of our society. The pathologies related to poverty and the ones related to severe punishment must be curtailed.

**COSTELLO:** Do you see the reform of the criminal justice system as a health issue?

**SMITH:** It's definitely a health issue. Poor people are suffering not only because of economic disparity but because of the trauma and violence with which they live. It's also a mental health issue. I was really disturbed by a recent *New York Times* article about the "disappearing black man." [Perhaps the starkest description of the situation is this: More than one out of every six black men who today should be between 25 and 54 years old have disappeared from daily life. *New York Times*, April 20, 2015.] What does that do to communities? What's the health of a community like with these staggering statistics? What does this mean in terms of the well-being of women and men who have lost their partners or the potential to have them? What does it mean in terms of the lack of fathers for boys and girls? Historically, people have tended to focus on the ramifications of the loss of fathers to young boys. It's a major loss for girls too.

**COSTELLO:** You just finished the seventh season of Showtime's *Nurse Jackie*, where you play a hospital administrator. You played a physician on the CBS drama *Presidio MD*, and you wrote and performed in a solo performance about health care and the body. Why are medical environments so interesting to you?

**SMITH:** Well, for one thing, the medical environment is about life and death. On another level, perhaps [laughing] there's something sexy about a doctor who is good at what they do because it's a form of intimacy. So ever since Ben Casey and Dr. Kildare there have been television shows about good-looking doctors. On the serious side, the fact that a stranger could be touching you in ways that only people in your family or your most intimate relationships would touch you is no small thing. I'm glad that some doctors are waking up to the fact that it's really a potential intrusion — in the same way that a disease is an intrusion. Stanford's Abraham Verghese writes and talks about the necessity of bringing touch back into medicine. A really good doctor uses their knowledge to figure out what's going wrong in your body and to find a way to make things right again. A really excellent doctor is taking care of you and providing healing on a much deeper level. Those are the ones who manage to get under our skin and root out what's wrong. **SM**

*This interview was condensed and edited by Paul Costello.*

**WEB EXTRA**
Hear the conversation at http://stan.md/1FE38HD

# the rarest of rashes

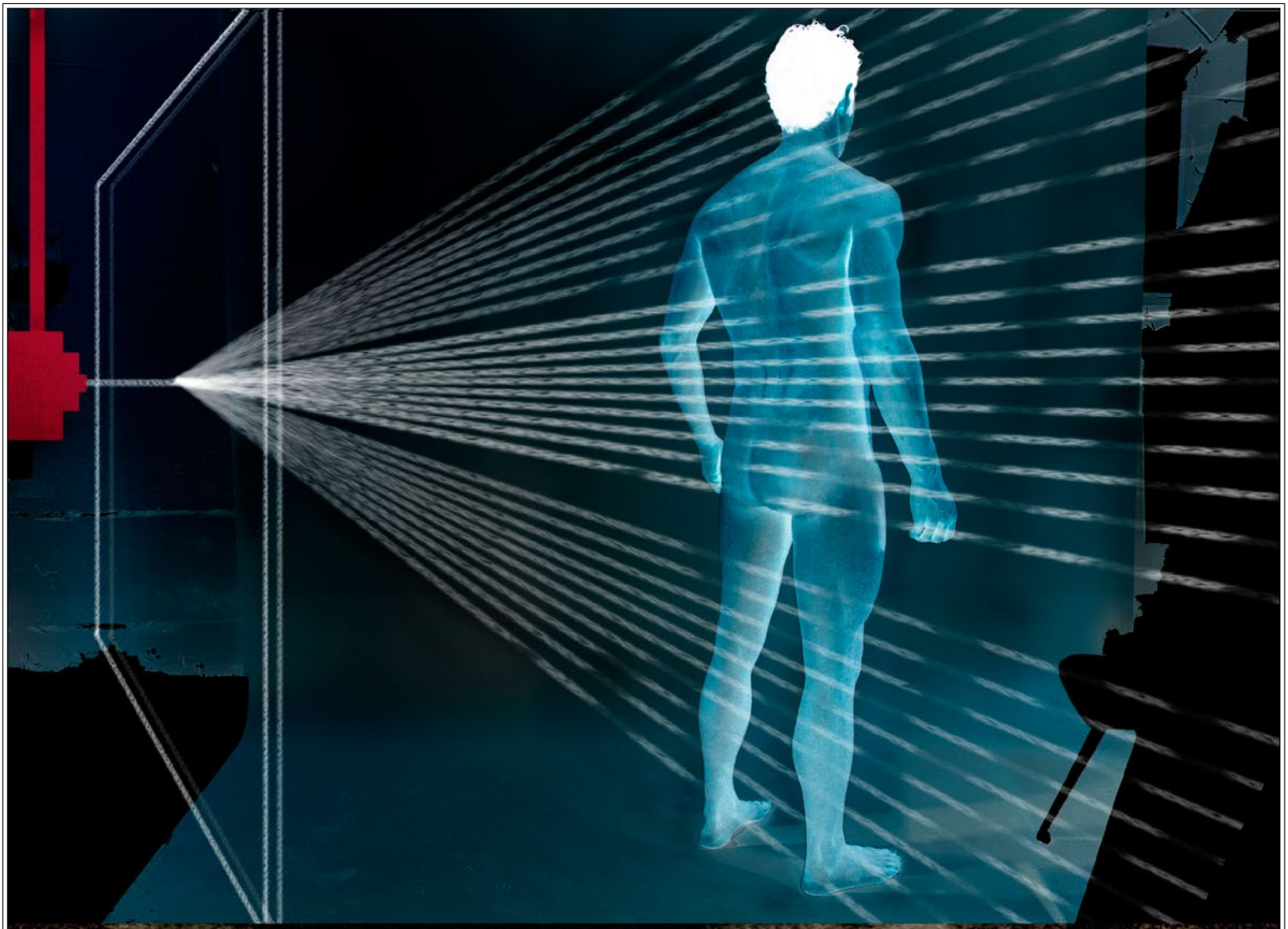
## CURING THE SKIN'S ROGUE CANCER

**By Sarah C.P. Williams**

ILLUSTRATION BY JONATHON ROSEN

By the time he came to Stanford, Joe Carey had been sick for a decade. In 1993, in his mid-40s, he'd noticed a scaly red patch of skin on one thigh. Then other, similar patches had started to appear all over his body.

His dermatologist told him to rub a mild cortisone cream on the spots, but they persisted, uncomfortably itchy eyesores that Carey was sure weren't normal. Yet tests for allergies, psoriasis and eczema came up empty handed. A full two years after he'd first noticed the patches on his skin, a doctor at the Mayo Clinic finally gave him a diagnosis: cutaneous T-cell lymphoma, a rare cancer. Over the next eight years, Carey underwent 200 sessions of UV light therapy and 36 radiation treatments, tried countless creams, and injected himself with medicine multiple times a week. But the cancer always came back. • "My symptoms were getting worse. I wasn't happy with my life and where this was going, and I felt like I needed to bring in the heavy artillery," Carey says. That's when he scheduled an appointment at Stanford, a short plane flight away from his home in Arizona. • In the United States, only about 1,500 people a year are diagnosed with cutaneous T-cell lymphoma, mostly older adults, like Carey, who's now in his late 60s. It's a cancer of T lymphocytes, immune cells that normally circulate in the bloodstream to help the body fight invading pathogens. But when a person has cutaneous T-cell lymphoma, the lymphocytes grow uncontrollably in a place they're not supposed to: inside the skin. Most cases of the condition, including Carey's, begin as mycosis fungoides — which loosely means "mushroom-like fungal disease." And although it can look like a fungus, there's no microorganism involved. The rash associated with mycosis fungoides is a mix of infiltrating cancer cells and the skin's reaction to the cancer cells.



While the mycosis fungoides form of cutaneous T-cell lymphoma can be slow-growing at first, lasting anywhere from months to years, if cancer cells escape the skin and begin flowing through the bloodstream or lymphatics, the disease becomes exponentially more serious — and harder to treat.

"Currently, we lack curative treatments," says dermatologist Youn Kim, MD, the Joanne and Peter Haas, Jr. Professor for Cutaneous Lymphoma Research, who directs the Stanford multidisciplinary cutaneous lymphoma group. "Patients with advanced disease with adverse factors have a median life expectancy of less than five years." Over the past decade, however, scientists have developed new treatments. Also, international collaborations, for the first time allowing large sample sizes of cutaneous T-cell lymphoma patients, are yielding results on how to manage the disease.

"What we have now is a larger armamentarium of new medicines which are somewhat more effective and less toxic," says Steven Horwitz, MD, an oncologist at Memorial Sloan-Kettering Cancer Center who specialized in lymphomas. But there's still work to be done. "We haven't yet turned the corner in terms of fundamentally changing our approach to the disease," Horwitz adds. "We're still mostly treating to minimize symptoms, not to cure." But researchers around the world, including Kim and her team at Stanford, and Horwitz's group at Memorial Sloan-Kettering, are working to change that.

## THE DREAM TEAM

Most lymphomas — a type of blood cancer — respond well to chemotherapy. Cocktails of drugs halt rapidly dividing cancer cells to keep the lymphoma at bay. But with cutaneous T-cell lymphoma, chemotherapy rarely works.

"We don't know why yet," says assistant professor of blood and marrow transplantation Wen-Kai Weng, MD, PhD, a Stanford oncologist and member of the cutaneous T-cell lymphoma group. "Maybe the drugs just can't reach the skin."

It's just one of the things that makes treating the lymphoma so frustrating and complicated, and one of the reasons that Stanford's group has turned to a team approach to fighting the disease. When patients with advanced cases of the condition visit Stanford for the first time, they're not evaluated by just one physician. Instead, they walk into a room that's full of representatives from diverse specialties: oncologists, pathologists, hematologists, dermatologists, radiation specialists and transplant doctors. Together, the team reviews and discusses the patient's case, considering what each might offer. It's a more focused version of the "tumor boards" that meet to discuss a broad array of cancer cases at most medical centers.

"I was very impressed with the team approach," says Carey. "It's almost a little bit intimidating because you're sitting there in a gown in an exam room and a dozen people descend on you. But it also makes you confident they're working together to do everything they can for you." Of course, different parts of the exam are performed by different, individual doctors — one at a time — and each specialist has different questions, but the idea is that the clinicians collaborate on each patient.

To combat the skin symptoms of mycosis fungoides, the team often first turns to a special form of radiation. Aiming a beam of ionizing radiation at a small site, as is typical for breast or lung cancer, usually won't work because mycosis fungoides occurs on many areas of the body at once.

In the 1950s, though, a group of Stanford doctors came up with an approach that could be used for this disease: They developed a technique to scatter electrons across a broader area. In the years since, researchers have further perfected what's known as the "Stanford technique," and today Stanford and many other institutions use total skin electron radiation.

A patient with cutaneous T-cell lymphoma being treated by the updated "Stanford technique" stands about 10 meters from a radiation source, with a large acrylic sheet in between to scatter the electrons. Then the patient carefully assumes six different positions.

"They even hold their arms in different positions so every bit of their body is hit. In the end, the entire circumference of the patient can be treated," explains professor of radiation oncology Richard Hoppe, MD, the Henry S. Kaplan-Harry Lebeson Professor in Cancer Biology and co-director of the Cutaneous Lymphoma Clinic.

Hoppe and his colleagues are still optimizing the treatment; recently, they've discovered that when it comes to radiation for this illness, less can be more.

"What we've actually done recently is reduce the standard dose, which minimizes side effects," says Hoppe. The reduced dose, they found, is just as effective at killing off cancerous T cells, but can be used more often throughout the course of a disease. And often, it's incredibly effective at treating the skin tumors associated with the disease.

"One of the most rewarding things about working with this disease is that when a treatment works it benefits the patient so immensely," Hoppe says. "They're often very symptomatic and have horrible-looking, horrible-feeling skin. The treatment benefits their quality of life immensely."

Now, Hoppe and his team are researching whether combining certain drugs with the radiation therapy might make the disease even more responsive to the therapy.

## ‘One of the most REWARDING THINGS ABOUT WORKING WITH THIS

disease is that when a treatment works it benefits the patient so immensely. They’re often very symptomatic and have horrible-looking, horrible-feeling skin.’

Of course, radiation doesn’t always work. Then it’s back to the drawing board, and back to the interdisciplinary cutaneous lymphoma group to discuss the case.

### STEM CELLS OFFER NEW HOPE

Like Carey, Paul Raffer’s disease began with a rash. A rash that covered his entire torso and arms. A rash so itchy he couldn’t sleep and his skin started flaking and peeling off from the scratching. A doctor himself — a neurologist in San Diego — Raffer was used to looking for the most common diagnosis to fit a set of symptoms. “When you hear hoofbeats, think of horses not zebras,” doctors are taught. But Raffer had a gut feeling that his rash was something serious. And indeed, after visiting multiple specialists, he was diagnosed with cutaneous T-cell lymphoma, a zebra.

When cutaneous T-cell lymphoma spreads from the skin to the blood, it gains a new moniker: Sezary syndrome. And by the time both Carey and Raffer visited Kim’s group at Stanford, their diseases had progressed to Sezary syndrome, and stage 4 of the cancer. “As a doctor, I did all the reading, and the reading was not very positive. I had an incurable disease,” says Raffer. “In my experience, stage-4 disease means the curtains are closing.”

But the team at Stanford had a new option for both of them: a blood stem cell transplant. Stem cells nestled inside a person’s bones act as constant factories of blood and immune cells, including the T cells affected by lymphoma. By taking the blood stem cells from a healthy person and giving them to a cutaneous T-cell lymphoma patient, doctors hope to take over their bloodstream with non-cancerous donor T cells.

Typically, stem cell transplants for lymphomas are tried after heavy doses of chemotherapy — with the aim to destroy a patient’s own blood cells before giving them new ones. But recently, Stanford doctors have started trying a new approach with the cutaneous disease.

“People have been doing transplants to treat lymphomas for a long time, but it’s never been successful with this particular lymphoma,” says Weng. “We’ve changed that over the last five years.”

Since chemotherapy is so rarely successful in minimizing cutaneous T-cell lymphoma’s growth, Weng decided to skip the chemotherapy that’s been considered a prerequisite to stem cell transplants. Instead, patients are prepared for the transplant with whatever combination of drugs and radiation the Stanford team deems most applicable to their disease — and that varies by person. The goal, Weng says, is to curb the spread of their disease as much as possible, and eliminate skin tumors, before sending in the new stem cells to finish the job.

For Joe Carey, it meant trying something new, after the constant itching from new tumors all over his body seemed like too much to handle. “I was at my wits’ end and things were moving in a bad direction,” says Carey. “I pleaded with Dr. Kim that I needed something to give me relief right away.” She suggested a clinical trial — for a new drug called mogamulizumab, produced by a Japanese pharmaceutical company. Within weeks of beginning the drug, Carey’s symptoms — which by then had lasted more than 15 years — began to wane. Tests showed his skin lesion clearing, lymph nodes shrinking and the number of cancerous cells in his blood dropping. In May 2011, stem cells were harvested from a donor in Europe (who had been identified as a match with Carey through an international database), flown across the Atlantic, and infused into Carey’s blood.

For Paul Raffer, preparing for his stem cell transplant took a different course. To lower the number of cancerous cells circulating through his body, Stanford doctors removed some of his blood, exposed it to ultraviolet radiation, and put it back in his body. Then, he was given a series of drugs — some of which worked, many of which didn’t — as well as Hoppe’s total skin electron beam radiation. Finally, in February 2011, Raffer received his stem cell transplant. Coincidentally, his cells also came from a European donor, who Raffer’s family has stayed in touch with to this day.

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# VACCINE HUN


ON APRIL 28, 1954, CHARLOTTE JACOBS, MD, BECAME ONE OF THE FIRST CHILDREN TO RECEIVE THE SALK VACCINE FOR POLIO. • Her hometown, Kingsport, Tennessee, was one of the sites chosen for the vaccine's trial. • "When I was a child, polio cast a shadow over every summer, as it did for others around the world," says Jacobs, the Ben and A. Jess Shenson Professor of Medicine Emerita at Stanford. Nearly a year after she received her shot, Salk's vaccine was declared a success, and the world celebrated. "Salk became the greatest hero of my generation," Jacobs says. • Decades later, as an oncologist and biographer, Jacobs set out to learn more about the man whose name became synonymous with eradicating polio. But she found no formal biography of Salk, so she decided to write one herself. This would be her second: In 2010 she published *Henry Kaplan and the Story of Hodgkin's Disease*. • In her research for the Salk book, she uncovered much she didn't know about the scientist, including his humble beginnings, a fame he resented, his work on vaccines for influenza and AIDS, and his rocky relationship with the scientific community. "It was an incredible journey trying to discover the man behind the legend," she says. • The following excerpt is from *Jonas Salk: A Life*, published by Oxford University Press this spring.

In the summer of 1916, New York's playgrounds stood empty. No children splashed in public swimming pools; none sold lemonade on the sidewalks. No cats roamed the alleys, peering into garbage cans. Troops of sanitary workers in white uniforms hosed down the city streets. Fathers hurried home from work, fear imprinted on their faces, averting their glances from the tiny wooden caskets lined up outside the tenements. Policemen patrolled the streets. New York was a city under siege.

Poliomyelitis had crept into Brooklyn while the public was busy watching the war unfold in Europe. It smoldered for a while between Henry Street and Seventh Avenue. Health officials barely paid attention, assuming it would soon die out. But it didn't. When the press began to attach names and faces to the disease, the community became alarmed. Helen Downing, paralyzed just before graduation from Public School No. 134, received her diploma in bed. After 5-year-old Frederick Chaplin made his kindergarten's honor roll, his brother took him to Coney Island. Five days later, he was dead.

Before long, the names and faces gave way to numbers,



PHOTOS AT LEFT AND RIGHT, COURTESY OF THE MARCH OF DIMES FOUNDATION; PHOTO AT CENTER, COURTESY OF UNIVERSITY ARCHIVES, IOWA STATE UNIVERSITY LIBRARY

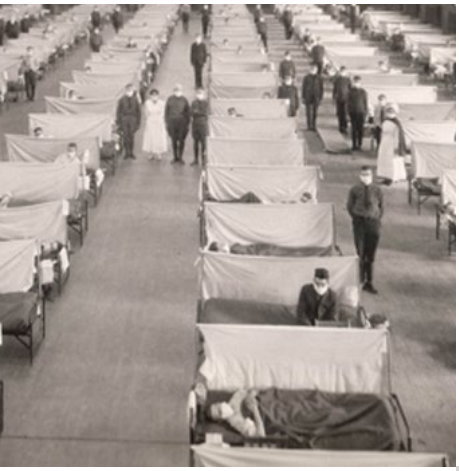
# TTER

## THE LIFE AND TIMES OF JONAS SALK

**An excerpt from *Jonas Salk: A Life* by Charlotte Jacobs**

PORTRAIT BY MAX AGUILERA-HELLWEG

and they kept escalating. On June 28, Health Commissioner Haven Emerson announced that Brooklyn might be experiencing an epidemic. Although a scientist had identified the poliovirus eight years earlier, no one knew how it spread. Assuming it behaved like other contagious diseases, the commissioner ordered every family bearing a case quarantined. A placard was placed in the window; bed linens and clothing were disinfected; windows were screened to prevent flies from disseminating the disease. Street cleaners worked overtime to collect garbage and cleanse tenement halls and stairwells. Stray cats, suspected of harboring the virus, were rounded up and exterminated — 72,000 by summer's end. The commissioner closed playgrounds and banned children from theaters. He instructed parents to keep food covered and to wash their youngsters' noses and throats with saltwater daily. But filth and flies and cats had nothing to do with the spread of poliomyelitis, and even with these precautions, more children contracted the disease.



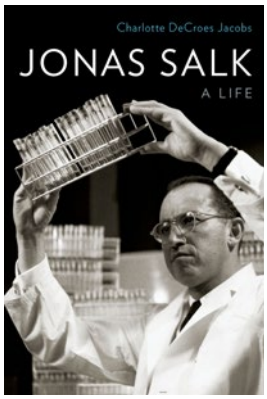

**RAVAGED BY EPIDEMICS**
FROM LEFT: ISOLATED CHILD IN THE 1916 POLIO EPIDEMIC, INFLUENZA WARD IN IOWA IN 1918, A SIGN OF THE TIMES DURING THE 1916 POLIO EPIDEMIC.

The illness started innocently enough — a sore throat, a runny nose. At the end of the day, the child spiked a fever, became restless. Then the pains began — electric shocks that darted through the back, legs, neck and shoulders. Muscles twitched, and spasms twisted him into a peculiar posture, the shoulders pulled forward, hips rotated, toes pointing downward. All night, the child thrashed about in his bed, drenched in sweat; his face became pallid. When the fever broke, he appeared to be recovering — a deceitful interlude as poliovirus left the bloodstream and invaded the nervous system.

Within a day or two, paralysis struck as abruptly as the fever had, and no one could predict the nature of its onslaught — a weak leg which improved in a few days or an arm dangling useless forever. Poliomyelitis impaired motor control of either one muscle or a group of muscles, yet it left sensation intact. The puzzled child could feel his feet but not move them. Three-quarters of those afflicted survived, many condemned to life in a wheelchair, on crutches or in bed. They joined a generation of cripples.

If the poliovirus attacked the nervous system higher up, in the base of the brain, death soon followed. Paralyzed throat muscles impeded swallowing. A sip of water streamed out the youngster's nose or drained into his windpipe, causing him to sputter and cough. Unable to swallow saliva, he foamed at the mouth. Breathing gave way to gurgling. As his mother wiped the blood-tinged froth from his lips, he gasped for air, drowning in his own secretions. The struggle over, his eyes rolled back, followed by a few muscle jerks, and the mother held her lifeless child.

**Poliomyelitis seemed** to have a predilection for striking infants and toddlers. During the second week of July, 412 new cases were reported in New York; the next week, 712. Terrorized parents watched the figures more closely than the stock market. The disease erupted in Staten Island, Manhattan, the Bronx; it didn't distinguish between immigrants and the upper class. Those who could fled. Mothers swarmed into Grand Central Station and the ferry docks, dragging their children into the crowds they should have avoided. The exodus of almost 1,200 children a day halted when towns began to bar them. In Hoboken, New Jersey, guards patrolled city entrances. Policemen blocked 150 families trying to enter Hastings-on-Hudson. Distraught, they returned to New York, where the death toll continued to rise.




FAMED FOR HIS POLIO VACCINE, JONAS SALK ALSO WORKED TO ERADICATE INFLUENZA AND AIDS.

Families unable to afford medical assistance at home were ordered to deliver their infected children to Brooklyn's Kingston Avenue Hospital for Contagious Diseases, where they were held in isolation for eight weeks. Prohibited from visiting, parents heard stories of hallways lined with metal cribs, children crying out in pain or pleading for water with no one to hold them. A knock at the door and a telegram notified parents to come retrieve their child's body. When parents looked up at the dark, looming fortress of Kingston Avenue Hospital, many turned away, hiding their youngsters at home. But once a public health nurse discovered a poliomyelitis case in a neighborhood, the Sanitary Squad conducted a house-to-house search for others. Watching a policeman snatch a child from her mother's arms reminded some of the pogroms that they had fled.

By August, every isolation bed in New York was occupied; many held three children. A baby died approximately every two and a half hours. Fear, bordering on hysteria, permeated the city. Then, when the weather turned cool, poliomyelitis disappeared just as unexpectedly as it had come. In America's first major poliomyelitis epidemic, the poliovirus had infected approximately 8,900 in New York, leaving 2,400 dead and many of the remainder paralyzed. Nationwide it had afflicted 27,000, mostly children under 5 years of age. For the next 40 years, the carefree spirit of summertime was marred by the specter of this disease, now known simply as polio. Two years later, another disease ravaged New York — influenza.

In 1917, with the country preparing to join the war in Europe, reports of a few cases sounded no alarm. Outbreaks occurred every winter. Characterized by fever, muscle aches and intense exhaustion, the disease usually ebbed in a week, posing a threat mainly to the elderly and infirm. But in the fall of 1918, influenza metamorphosed into a vicious monster. With no warning, a previously healthy person complained of an excruciating headache, like a demon pounding his temples with a hammer, stabbing his eyes. A temperature spike up to 105 degrees ushered in agonizing muscle pains, profuse sweating and shaking chills. When the fever broke and relief seemed at hand, the coughing began. Mild at first, the cough deepened; the sputum turned bloody. A viscous fluid filled the lungs, and the patient gasped for breath, suffocating. No longer did it prey on the elderly; they

CONTINUES ON PAGE 52

BY AUGUST, EVERY ISOLATION BED IN NEW YORK was occupied; many held three children. A baby died approximately every two and a half hours. Fear, bordering on hysteria, permeated the city. Then, when the weather turned cool, poliomyelitis disappeared just as unexpectedly as it had come.

CHARLOTTE JACOBS IS AN ONCOLOGIST AND AN AUTHOR. HER NEW BIOGRAPHY IS OF ONE OF HER HEROES: POLIO VANQUISHER JONAS SALK.

# HEART

## CHOICES

### SHOULD MORE HIGH-RISK ORGANS BE USED FOR TRANSPLANTS?

At first, when Linda qualified for the heart transplant waiting list, she never wandered far from a phone, expecting a call any day telling her to get to the hospital quick.

The 52-year-old chemical engineer, who lives in Oakland, California, was told that the typical waiting time was six to 24 months, and not to travel farther than four hours' driving distance from the Stanford Hospital operating room — the clock starts ticking as soon as a donor heart is found. • Then she waited. And waited. • That was over a year and a half ago, just after her cardiologist had diagnosed right-side heart failure. He had pointed out on her echocardiogram how the blood streamed straight through the right side of the heart without the valve even pumping, "just like it was an open pipe." Diagnosed almost 20 years ago with right ventricular dysplasia, a rare genetic disease that causes dangerous heart rhythm abnormalities, she has been living with a surgically implanted device that jolts her heart back into a normal beat — on occasion knocking her to the ground to keep her alive. Finally at 50, her cardiologist said the disorder had greatly enlarged her heart, and she was running out of time. • "He told me this is just going to get worse so I went through a battery of tests to be qualified for the heart transplant list," says Linda, who has asked to use her first name only. "I told a few friends and my family, prepared for surgery, and then nothing happened." • Despite advancements in medications and mechanical assist devices, heart transplant remains the best treatment for heart disease at its most severe. It's a successful procedure that

**BY TRACIE WHITE**

ILLUSTRATION BY PAUL BLOW

adds years to the lives of deathly ill patients. The problem is that an estimated 20,000 people across the nation, including Linda, could benefit from receiving a new heart, with only a few thousand receiving transplants on average per year.

Many wait for years. Many die waiting.

The general assumption is that there simply are not enough donor hearts available to meet a growing demand. But new research is questioning that assumption. Some researchers and surgeons claim that thousands of donor hearts that could be used are turned away each year. The hearts are considered marginal because they come from older, sicker or riskier donors, but many argue they are safe for transplant, and could be saving lives.


"As patients wait longer, they often get sicker, and we often lose patients," says Stanford cardiologist Kiran Khush, MD, whose research reports that 65 percent of available heart donations are discarded because of stringent acceptance criteria. Yet the criteria have not been critically evaluated, she says. "Increasing the supply of donor hearts is, of course, a great concern of mine."

Linda says she doesn't understand all the criteria for choosing or rejecting a donor heart, but she does know she wants to get a new heart as soon as possible. She's open to considering a "high-risk" heart, but like most people, isn't sure what that means. The definition seems to vary depending on whom you ask. As a patient, it's doubtful she'll play much, if any, role in choosing her own donor heart anyway.

"At first I would think, well no, of course I wouldn't accept a high-risk heart. You are taking a higher risk than if you wait. But the trade-off is, if you wait, it may be too late."

## HOW YOU GET A DONOR HEART

The process that matches recipients with donor hearts is complex and somewhat astounding. Many factors figure into the national system that matches kidney, liver, lung, pancreas, and small bowel donations with recipients, but heart transplants are particularly fraught because of the short shelf life of a donor heart. Ideally, a heart should be transplanted within two to four hours of its removal.

The process begins with a phone call.

On a recent Wednesday, John Nguyen — a nurse who leads a team that coordinates organ donations for the Oakland-based Donor Network West — receives two such phone calls. One is from a hospital in nearby Walnut Creek, the other from a hospital in Modesto, about 80 miles east. The first call is to report that a 40-something woman had suffered a large, hemorrhagic stroke. The second, to tell him about a young man who has shot himself in the head. Both are approved as potential heart donors.

Donor Network West is one of 58 federally designated organ procurement organizations set up across the country as the first gatekeepers for donor organs. They are the middlemen who connect donations with transplant centers. Nguyen and his team provide care and procurement of organ donations in Northern California and Nevada. Once potential organ donors have been declared brain dead — as was the case of the patients in Walnut Creek and Modesto — Nguyen sends his team members into the hospital's intensive care unit to facilitate care of the donor. Over the next 36-72 hours, they will evaluate the organs, provide medical care for the donor to keep the organs functioning well, and give support to grieving family members often still at the bedside.

"Technically the patient is dead because their brain has complete and irreversible loss of function — but the heart is still beating," Nguyen says. "But they are still in the ICU and still on a ventilator to maintain organ function. From a distance, they look like any other ICU patient."

This is the first point in the screening process for organ donations. In the case of most organs, including hearts, if they are too sick or damaged, too infected or old, they'll get rejected here. To determine whether a heart is donation-worthy, the team orders blood tests to check for infectious diseases. Electrolyte replacement helps optimize organ function, antibiotics ward off any potential infections and medi-

cations maintain blood pressure. An EKG and echocardiogram test the functioning of the heart.

Ultimately, the goal of the organ procurement organizations is to approve and offer as many hearts as possible to patients on the waiting lists. The hearts that get rejected by these middlemen, in this case the team led by Nguyen, tend to be from donors over 65, and those with advanced coronary artery disease or other serious heart diseases — any hearts from donors over 45 get tested for these. Cancer is another variable that will get a heart rejected. Or HIV infection or hepatitis C.

After reviewing the two potential California donors' medical history records and the results of their tests, Nguyen's team clears them both for transplant.

The hearts can now be offered to transplant centers. Nguyen enters basic information into a federal electronic database — age, height, weight, blood type of the donor — and gets back the name of the sickest patient on the waiting list in his area that matches. He then calls the patient's transplant center. A representative at the center collects any pertinent information, including the results of the heart tests, and then calls the patient's surgeon immediately, no matter the time, day or night.

Now the future of the heart is in the surgeon's hands. Rarely do patients themselves have a say in whether the heart is accepted or rejected at this point. Most often, it's the surgeon, or the surgeon and the patient's cardiologist who decide.

Transplant surgeons say no to donor hearts for many reasons: In addition to the factors that Nguyen's team has already screened for, others include small size, advanced age and illnesses such as hypertension and diabetes.

"Beyond that, there are a lot of criteria that vary from surgeon to surgeon and center to center," Khush says. "With factors like mild thickening of the heart muscle, as can be seen in donors with high blood pressure, or drug abuse, it is really up to the transplant center or the surgeon."

In this case, Nguyen is able to successfully match both hearts. The heart from the young suicide victim gets accepted on the first offer to nearby Stanford Hospital. For the heart from the 40-something stroke victim, he had to return to the waiting list five times before it was finally accepted outside the region at Loma Linda University Medical Center in Southern California.

"It was an older donor and was a little complicated because of the small size. Size matching can be complicated. No one locally was able to use the heart."

Nguyen says he has recently seen a disturbing uptick in the number of hearts he offers for transplant that get rejected.

"We work up these hearts because we feel they have potential for transplant," he says. "Then we see differences in acceptance practices from area to area. Sometimes we offer a heart throughout the whole nation and it's not accepted. Some hearts get wasted."

## NEW RESEARCH

Nguyen has joined the growing number of medical professionals concerned that potential organ donations are going to waste. He co-authored a study with Stanford's Khush that found a majority of donor hearts do, in fact, get rejected. And that number has been increasing.

The study, published in February in the *American Journal of Transplantation*, also found that the rejection of "marginal" donor hearts — those with undesirable qualities, such as being small or coming from an older donor — varied significantly across geographical regions. In other words, some hearts rejected in one region of the country are accepted in another.

"We've become more conservative over the past 15-20 years in terms of acceptance, which is particularly troubling because of the national shortage of donor hearts and the growing number of critically ill patients awaiting heart transplantation," says Khush, who has begun a new study to provide some of the missing, scientifically based criteria for choosing or rejecting a donor heart by collecting data from 5,000 donors over a period of five years.

To look at national trends in donor-heart use for transplant, the recent study examined data from the federal government's Organ Procurement and Transplantation Network on all potential adult cardiac donors from 1995-2010.

Of 82,053 potential donor hearts, 34 percent were accepted and 48 percent were declined. (Eighteen percent were used for other purposes, such as research.)

"Only one in three available donor hearts is currently accepted for transplantation, which greatly limits heart transplant rates nationwide," the study says.

Other studies have shown similar concerns about other organs for donation. A recent analysis of organ sharing data by surgeons at the University of California found that 84 percent of patients who died waiting for a liver had received at least one organ offer and an average of six offers. Most were declined by the surgeons due to donor age or quality of the organ. The author cited stigma associated with "non-ideal" livers as the reason for rejection, not lack of available donations.

Heart surgeons themselves admit it can be a difficult decision for them to make.

"There are multiple variables to consider and donor suitability may vary by region," says heart surgeon Joseph Woo,

MD, professor and chair of cardiothoracic surgery at Stanford. "In Europe, surgeons are much more proactive in using older hearts. Europeans would say we are giving up on too many hearts. One of our counterarguments would be we have very good outcomes. However, I do think we could expand our donor criteria and utilize more hearts."

Jon Kobashigawa, MD, director of the largest heart transplant center in the nation, at Cedars-Sinai Medical Center in Los Angeles, points out that because of improvements in helmet and speeding laws over the past two decades, younger donors are becoming much less prevalent. Statistics show that the average donor heart is much sicker and older today than 20 years ago. If heart transplant lists are going to get shortened, surgeons have to be more open to using more of the older, higher risk hearts.

"It's really a complex issue," he says. "I still question myself. I know hearts are not being used that could be used. Everyone wants a 20-year-old donor. But if you are a 58-year-old heart failure patient on the waiting list and you won't take anything but a 20-year-old heart, you're not going to make it."

The competing variables that come into play in order to choose a heart also make it easier for outside influences to hold sway. Increased scrutiny by regulatory agencies of the 140 or so transplant centers across the country may also have had the unintended consequence of making transplant surgeons more risk averse, Khush says. As a result, the decision of whether to accept a heart is not based solely on scientific criteria.

"Creating a more systematic way of evaluating these hearts based on scientific evidence could increase the number of heart transplants," Nguyen says.

> 'In Europe, surgeons ARE MUCH MORE PROACTIVE IN USING OLDER HEARTS. EUROPEANS WOULD SAY WE ARE GIVING UP ON TOO MANY HEARTS. ONE OF OUR COUNTERARGUMENTS WOULD BE WE HAVE VERY GOOD OUTCOMES. HOWEVER, I DO THINK WE COULD EXPAND OUR DONOR CRITERIA AND UTILIZE MORE HEARTS.'

## THE SURGEON'S DECISION

When Texas-based heart surgeon Gonzalo Gonzalez-Strawinski gets a call from an organ procurement organization offering a donor heart, it's usually the middle of the night, say around 3 a.m.

"When I get the call, I ask right then for the story," says Gonzalez-Strawinski, chief of heart transplantation at Baylor University Medical Center in Dallas. "At 3 in the morning you want to hear about it and get it done. They might say it's a 26-year-old female who died of a gunshot wound to the head, who is currently in Nashville, Tennessee. The echo shows an ejection fraction of 55 percent and there are no IV drips delivering medication to help the heart contract."

Most often Gonzalez-Strawinski says yes to the heart. He's earned a reputation as an aggressive surgeon who will accept high-risk hearts at an institution with the second-highest volume of heart transplants in the country, averaging about 100 a year. He says that by making small changes in the donor acceptance criteria, his transplant team has been able to greatly increase the center's volume, while maintaining low mortality rates.

"My next question is: Who does it come up for? Who do we match for?" After reviewing the history of the patient on the waiting list matched with the heart being offered, he next wants to know the size of the donor heart and its blood type. Then he starts to search for red flags. He asks about the donor's medical history, smoking, diabetes, obesity, all indicators that the heart needs to be screened for coronary artery disease. "If there's jail time or drug use, you think of viruses."

It's the variability in selection criteria from surgeon to surgeon and region to region that concerns researchers like Khush. She wants more broadly defined acceptance criteria based on scientific research available to all players involved in screening donor hearts. This would entail a more clear definition of what "high risk" actually means, and when, or if, those hearts can be used for transplant.

"High-risk" hearts as defined by the Centers for Disease Control are those that come from donors who were IV drug users, hemophiliacs or prostitutes, or anyone with high-risk sexual activity, exposure to HIV or time spent in jail. If a surgeon accepts any of those hearts for transplant, this is the one time he or she is required to get patient approval before transplantation.

"Twenty percent of our donors are 'high-risk,' according

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**FEATURE**

## The butterfly effect

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In May, the team presented preliminary evidence at the annual conference of the Society for Investigative Dermatology that, for the first three patients, the grafted skin expressed type-7 collagen at the basement membrane junction and appeared to have a normal number of anchoring fibrils across the dermis and epidermis.

"Even though my grafts are only the size of a playing card, the results have been life-changing," says Martinez. "If you can minimize skin breakage, you minimize pain in that area, you minimize the chance of skin cancer in that area. It may not seem like a big deal, but this has really improved my quality of life."

**SPAULDING WAS NOT A PARTICIPANT** in the phase-1 trial. For one thing, he wasn't yet an adult when the trial was launched. For another, he may not have the "right" mutation in his type-7 collagen gene.

Researchers have found dozens of mutations that can lead to EB. To enter the trial, patients had to have a particular type of mutation near the beginning of the gene. These patients would make just a small portion of the type-7 collagen protein. Exposure to this bit of the protein may reduce the chance that the patient's immune system will react to, and try to destroy, the full-length protein made by the corrected gene.

"Garrett's biopsy was inconclusive," says Montello. "It's possible that he may have an extra mutation that may preclude him from the trial. But we're going to check again."

Meanwhile, life goes on.

"I've been working with these patients since the early '90s," says Marinkovich. "Yet, I'm still affected every time I see these patients and their families. I could in no way do what they do. They overcome so much just by getting up in the morning. The types of obstacles I face in my life and my research seem minimal in comparison."

Pain management is always a challenge, of course, with patients attempting to balance the need for comfort with the side effects of medications.

"I have a very high tolerance, and don't take any pain medication," says Martinez. "I cherish my mind a lot. Rather than feel like a zombie, I prefer to feel the pain and feel alive."

Stanford's EB team hopes to publish preliminary results of the phase-1 clinical trial this summer, but they'll continue to monitor the impact on the participants for the rest of their lives. Like their patients and their patients' parents, they are elated that the research has finally progressed this far.

"In the seven years since Jackson was born, we've seen tremendous progress," says Jamie Silver, of the fundraising and advocacy organization, EB Research Partnership, whose son has EB. "This idea of gene therapy for EB wasn't a reality at the time. It was in the lab, but it wasn't anywhere near a human. Now, at Stanford, it is in clinical trials. We are seeing tangible progress. That gives us as parents and us as an organization the drive to keep going."

Spaulding is now a studious young man with a shy, sweet smile and a passion for Apple products. Confined now to a wheelchair, he looks much younger than his 18 years. He struggles with kidney problems and last year he had all his teeth removed because of ongoing dental issues. He's recently assumed the CEO position in a newly formed family business selling artisan olive oil and vinegars — a position he juggles along with his Advanced Placement classes as a junior at Orestimba High School, in Newman, California. His family started the business when Spaulding expressed a desire to make an impact with his life, however short it may be.

Not surprisingly, some of his doctors were also his first customers.

"They are some of my best friends," says Spaulding, who has, of course, known many of them all his life. "Dr. Lane talks with me on the phone, and they are always keeping me up-to-date on the latest advances. Their research has already definitely helped me. Some of the new bandaging and skin care techniques have really made a huge difference." Aggressive bandaging has kept his fingers separated and maintained his hand function — the better to use the new iPad he received from the Make-A-Wish Foundation to do homework and run his business, Montello Fine Foods.

When asked about the ongoing clinical trial, Spaulding is noncommittal, expressing a concern that participation in a future phase could interfere with his school work. But, with his trademark forward-thinking attitude, what he really wants to talk about is olive oil, balsamic vinegar and recipes.

"When he had his teeth removed, I was worried about him," says Montello. "Here we were starting a business based entirely on food, and he can't eat. About two weeks after the surgery, I asked him, 'How are you doing, Garrett? How are you really doing? Are you still the happy little camper I remember, or is this getting to be too much?' And he looked at me, and smiled that smile, and said, 'You know, Mom, as long as things don't get any worse, I wouldn't mind living to be 100.'" **SM**

*— Contact Krista Conger at kristac@stanford.edu*

**FEATURE**

## Wither youth

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BBL improved not only the visible appearance of the older women's skin — less fine wrinkling and discoloration, and an overall healthier look to the professional eye — but also restored the activity levels of about 1,300 of the 2,300 age- and damage-altered genes of the older women's skin to a semblance of their "youthful" counterparts' profile.

"We could detect those changes a full six weeks later," Anne Chang says. "These treatments, rather than just making the surface of the skin look better, may actually have anti-aging effects." She says she'd like to study

these patients at six months or one year after treatment to find out how long the effect lasts.

One could speculate that it might not be such a bad idea to slather on a ton of sunblock and then soak up lots of sun every day. Although that could well turn out to be correct, Chang isn't suggesting it. Just which wavelengths of light are exerting exactly which effect on which biochemical pathways remains to be nailed down. For her part, Chang is digging deeper into the question of precisely what molecular mechanisms are driving the seemingly inexorable aging of skin and how it might be prevented, slowed, stopped or turned around.

Interestingly, a healthy number of genes whose activity levels are altered by aging and, in reverse, by BBL are known to be under the influence of NF-kappa-B, suggesting that BBL might indeed be having at least some of its restorative effect by messing with that key pro-inflammatory transcription factor.

Howard Chang is well-known in scientific circles for pioneering the exploration of so-called long noncoding RNAs, or lncRNAs (pronounced "link" RNAs), which instead of coding for proteins, as do most other lengthy RNA molecules, act directly on the genome. He's shown that lncRNAs play a key role in determining which genes in a cell will be active or remain dormant. A recent study led by Anne Chang analyzed skin samples from 120 women of northern European descent who live in the San Francisco Bay Area and range in age from 18 to 93. In this study Chang and her colleagues (including Howard Chang) isolated a new variety of lncRNA that is most scarce in individuals with younger-appearing skin. The discovery potentially unlocks the door to a totally new way of controlling skin aging: manipulating levels of this lncRNA molecule in skin through drugs or other approaches.

Looking ahead, Chang hopes to explore the degree to which the genes she has associated with aging skin may also be associated with aging in any of the body's internal organs. She's also started compiling her own registry of Ashkenazi Jews located in the San Francisco Bay Area.

This skin-aging business is a lot more than skin deep to Chang. "Nearly 74,000 new melanoma cases are expected this year," she says. "The rate of melanoma among American men in their 80s is double that of men in their 60s. Melanoma is a disease of aging and, more than that, a disease of aging skin. There may be ways to prevent or reverse that process. Youthful skin is more than a cosmetic convenience." Millions of aging baby boomers, gazing into the bathroom mirror, nod their heads in wistful agreement. **SM**

*— Contact Bruce Goldman at goldmanb@stanford.edu*

**FEATURE**

Surviving melanoma

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argued in a 2014 commentary in *Nature*, should be implemented more widely by primary care providers in the United States, following appropriate training to enhance skin cancer detection and triage. (Well under a quarter of U.S. adults receive a skin exam in any given year, she says.)

If people are going to tan, though, another project that Swetter's involved in could help ward off cancer. Jean Tang, MD, PhD, an associate professor of dermatology, is heading up the research, which searches for compounds that decrease melanoma risk. One promising candidate so far: vitamin D supplements.

"When you add vitamin D to melanoma cells growing in the lab, it reduces their growth," Tang explains. "And when you give vitamin D to mice with melanoma, it also shrinks their tumors." In 2011, Tang published a study in the *Journal of Clinical Oncology* that retrospectively compared vitamin D intake among the population of women enrolled in the Women's Health Initiative. Indeed, those with a history of skin cancer who had received the vitamin were less likely to develop melanoma. Now, she's just completed a trial in which women were randomly selected to either receive 4,000 IU of vitamin D a day (a much higher dose than most multivitamins contain) or none of the vitamin. The results are still being analyzed.

With Swetter, she's also studied the protective effects of aspirin and other pain relievers — some studies have found that a daily aspirin for five years lowers a person's risk of melanoma — but more work is needed before recommendations are made to routinely take either vitamin D or aspirin.

For now, she echoes Swetter's advice that protecting one's skin from the dangers of the sun, learning the clinical warning signs for melanoma and other skin cancer, and regular skin exams, are the best medicine to prevent melanoma. But she knows not everyone hears her.

"It's frustrating," Tang says. "I think sometimes it's like fighting obesity. I can tell you what's good for you, but people are looking for the magic pill." And for now, at least, there's no magic pill — just a pile of evidence against tanning, and drugs to treat melanoma that are getting better every year.

Trista McNeill, the patient who is being helped by the new melanoma drugs, is hesitant to say she's cured, but she knows from her regular checkups that her body has few signs left of her cancer. "In many ways, I can't believe that I have cancer, and coming to grips with the fact that life will never really be the same is a tough pill to swallow," says McNeill. "But I'm hardly ever overwhelmed because I have such a strong support team. I feel pretty lucky." **SM**

*—Contact Sarah C.P. Williams at medmag@stanford.edu*

**FEATURE**

New lungs, new life

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a tank top and a tan. The no-tan rule took a little longer to sink in.

"She told me to, 'Please throw the tank top away,'" Stockton says, laughing. "It took me a while to get used to Dr. Conrad. It was

like having a second mom. We have hot, humid weather in the summers in Bakersfield, and it's torturous. Everybody likes to go to the lake. My friend has a boat."

"She would come very, very red to clinic," Conrad says. "She would say she was out at the beach. I kept on telling her, 'You can't do that.'"

About two years post-transplant, Stockton began to understand why.

## SKIN CANCER

One of the drugs that Stockton was prescribed after her transplant put her at a high risk of skin cancers. (It was voriconazol, an antifungal to protect against fungal diseases such as Valley Fever, which is common in Bakersfield.)

No signs of skin cancer appeared until Stockton turned 17. She went to Pismo Beach with her family one weekend, and thought it was strange that her hands got burned even though it was a chilly, windy day. Then over a short period of time, dark spots began to appear on her hands, on her lower lip, on her chest, even on her scalp.

"I got a little concerned," she says. Conrad sent her to the dermatology clinic. And thus began another merry-go-round of doctor visits, this time to battle an onslaught of basal and squamous cell skin cancers.

Since 2012, Stockton has undergone a wide assortment of dermatological treatments at Stanford including liquid nitrogen to freeze off precancerous growths and eight rounds of a procedure known as Mohs surgery to remove deeper, more serious cancerous growths: several on her chest, scalp and, the most severe, on her lower lip.

"At 21 years old, Cassie has significant sun damage to her skin," says Hollmig, who was the surgeon for the Mohs procedure that resulted in the removal of the left half of her lower lip. "She had two recurrent, high-risk squamous cell cancers invading the visible portion of the lower lip. We were forced to excise almost half the lip to clear the tumors." Stockton's lip cancer could have metastasized and traveled to her lymph cells, a deadly risk. She had the procedure done in one day at the end of September.

Mohs surgery, developed in 1938 by Wisconsin surgeon Frederic Mohs, MD, is a type of microscope-controlled surgery used to treat common types of skin cancer. It involves slicing off thin layers of the cancerous tissue, then studying the slice under the microscope as soon as a slide of the tissue is prepared. If the surgeon sees any cancer cells left along the borders of the excised tissue, the patient gets called back in from the waiting room for another tissue excision. This process continues until the surgeon is certain the last bit of tissue removed is completely free of cancer cells at all its borders. Studies show it's by far the most effective and efficient way of eliminating dangerous skin cancers and those arising in important anatomic regions such as the eyelids, nose and lips since it removes the entire skin cancer while sparing the maximum amount of normal skin cells, Hollmig says.

"It takes about 15-20 minutes to remove each layer," Hollmig says. "Patients have to plan to be there all day. To identify every cancer cell we want our slides to be perfect. It takes 45 minutes to over an hour to make these high-quality slides of the removed tissue so that we can see every cell at the edge of the skin cancer.

"Cassie's largest skin cancer was removed with three layers of Mohs surgery. We got all the cancer out but it had extended to invade the muscle of the lower lip so a substantial portion of muscle, in addition to skin, had to be removed. As such, rebuilding her lip required a relatively large reconstructive procedure."

That procedure was an hour-long "advancement flap" surgery. The idea was to use skin from a nearby area on her body to fill in the U-shaped gash where the left half of Stockton's lower lip used to be.

"The best way to do that was to borrow some 'extra' skin from the right side of the remainder of the lower lip area," Hollmig explains. He cut further down into the U-shaped wound left behind by the Mohs surgery to loosen up the muscle of the entire lower lip area. This created an even deeper V-shaped opening, but it also made it possible to stretch the entire right side of the lower lip across to fill the opening in.

Hollmig then sutured the two sides of the lip area together, reconnecting the inner lining of the mouth, the muscle and skin.

"Now her lip functions fine. She can talk. She can whistle." Still, there was an unavoidable side effect from the surgery that had Hollmig worried. Stockton's normally plump, full, lower lip was left thin and scarred on the left side. She was only 21, and recently engaged to be married. He wanted to help get back her rounded lips for future wedding photos.

"I didn't have much of a lip left. It was very, very thin. I hated it," Stockton says. "I've always had puffy lips and that's what I'm used to. It was hard having half of a full lip."

## SCARS

To further battle the skin cancer, Hollmig worked with Conrad in pulmonology to change Stockton's antifungal medication, helping find alternatives that can help prevent fungal diseases like Valley Fever but without the skin cancer side effects.

"Working with Dr. Hollmig has been incredibly useful," Conrad says. "He came up with alternatives that I was completely clueless about." Now they are together working to make the same medication changes for other transplant patients.

The new medications along with Stockton's own efforts to protect her skin from the sun — using spray tans and sun block, tinting her car windows and visiting the lake less often — have slowed the spread of the skin damage and skin cancers. Things are getting better. Stockton returns regularly to the dermatology clinics for skin checks and restorative skin procedures.

Since the September surgery, her full lips have been restored through injections with a protein filler. Laser treatments have helped

soften the scar. It's still there, a faded line dissecting her lower lip, but she can deal with that. She's got "puffy lips" back. And she's accepted her scars, in fact, pointing them out with something akin to pride.

"This one is from the ECMO machine," she says, indicating the scar on her neck from her bout with pneumonia, deftly hidden under makeup.

"I always check my scalp now," she says, running her hands through her hair to find the first of the Mohs scars, a slight dent in her scalp.

Then she discreetly lifts her shirt to show the scar from the feeding tube in her abdomen. And next to it the long transplant scar that dissects her chest.

"It's crazy to think I've had all these procedures," she says.

Her health is now better than expected. The average life of transplanted lungs is about five to six years, but with good self-care, Stockton has stretched hers to a life expectancy of about 10-15 years, says Conrad.

"She's an excellent patient," Conrad says. "She takes care of herself very well. She's beat the statistics."

Now, Stockton's looking ahead to the future. Marriage, children, a normal life. She and her doctor are afraid pregnancy would be too dangerous for her, so she's considering surrogacy. She'll make it all work out somehow."It's been quite a journey," she says. **SM**

*— Contact Tracie White at traciew@stanford.edu*

**FEATURE**

The rarest of rashes

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For both patients, preparing for the stem cell transplants presented a whole new host of challenges, including temporarily moving to Palo Alto for the course of the treatment. "I got really anxious that something would go wrong with the donor," Carey adds. "If they got into a car accident or got sick, I wouldn't be able to get the transplant." But the cells destined for both Carey and Raffer made it across the Atlantic, and in 2011 they became two of the first handful of cutaneous T-cell lymphoma patients to receive a stem cell transplant using the new, non-chemotherapy regimen that Weng developed. Today, 32 patients have undergone the procedure at Stanford.

## AN INTERNATIONAL COMMUNITY

Despite its reputation as a hot spot for cutaneous T-cell lymphoma research and treatment, Stanford still sees a relatively small number of patients with the cancer — less than a hundred new cases per year. After all, only 1,500 people a year are diagnosed with the disease in the United States, and there are only about 16,000 patients total in the country. With those kinds of numbers, it can be hard to conduct research.

"When people publish single-center data, it can be interesting anecdotally," Kim says. "But a small sample size doesn't give you interpretable results." To prove that a new radiation approach, drug or stem cell therapy is working, researchers need large numbers of patients to undergo the treatment. Not only does that let them have the statistical power to show whether it's effective, Kim says, but it gives them the ability to find trends — to see which subgroups of patients it does or doesn't work for.

That idea of statistical power is why Kim and the rest of the group at Stanford are leading the launch of an international consortium for cutaneous T-cell lymphoma research. In December 2014, representatives from 51 clinical research centers around the world convened at Stanford to discuss the disease and team up.

"Collaborations like this are absolutely essential for an orphan disease like cutaneous lymphoma, and Youn Kim has really been a leader at organizing this," says Horwitz, who's on the consortium's board of directors. "In this field, more than any other I've worked in, people are much less competitive and more collaborative. We have to pull together to make things better."

One of the first projects that Kim is spearheading through the consortium is the search for biomarkers — tests that can clump patients into groups predicting who will respond best to which treatment. By combining all their data sets, members of the consortium hope they can find genes, blood tests or immunological markers that can tell them whether, for instance, someone is likely to have a worse case of the disease and should be funneled toward a transplant earlier than other patients.

For cutaneous T-cell lymphoma, this kind of research is especially important, Kim says. "We don't have any home-run mutations that explain a high number of cases like many other cancers do. There's no mutation that's present in 40 or 50 percent of our patients. This is an example of personalized medicine where in each person we have a different, relevant finding." Rather than taking the trial-and-error approach largely used now to find the right treatment for each patient, Kim hopes the consortium can make it a more rational process.

The international group is also sharing approaches that have already worked for them. At a meeting in Paris, Weng presented his non-chemotherapy transplant approach and the detailed data he's kept on just how well it's worked for his patients.

"Already a large group in the U.K. has switched from using heavy doses of chemotherapy to adopting our protocol," Weng says. In addition, a doctor at the University of Iowa just completed the first cutaneous T-cell lymphoma stem cell transplant there using the Stanford approach, and a large health-care system in Italy is considering making the switch.

Weng admits, though, that the approach might not work for every patient. That's part of why he wants more centers to start trying it out.

"Transplant has a certain art to it. Why one thing works and not another is not always explained by science," he says. "We

want other people to generate more experience with our approach, so that if they have different results we can figure out why."

It's that kind of collaboration that's moving the field forward, says Horwitz. "Five years ago, it was hard to see how we would ever be doing fundamentally better with this disease," he says. "Now, we can at least see how we might get there."

As for Raffer and Carey, both are still disease-free. Within a few months after each received his fresh donor stem cells, tests revealed that the donor cells had taken over the blood and eliminated the cancer. Four years later, they're both pushing the limits on what can be expected after a cutaneous T-cell lymphoma diagnosis.

"We just saw Paul [Raffer] back in our clinic yesterday," Kim said in late February. "He's now four years out and still has no evidence of cancer cells. He would not be alive today if he didn't go through the transplant. His life expectancy was less than a year. Paul is living evidence that finally we can cure this cancer. We are making transformative advances that give hope for our patients, their families and the physicians." Today, Raffer is once again a practicing neurologist, has written a novel based loosely on his experiences with lymphoma, and enjoys spending time with his grandchildren. Carey, too, is enjoying his new lease on life, and credits his wife and a positive attitude for getting him through the ordeal. "I have no symptoms and I feel great," he says. "I started this process when I was diagnosed at 45 years old and finally at 63 I got my life back." **SM**

*— Contact Sarah C.P. Williams at medmag@stanford.edu*

**FEATURE**

## Vaccine hunter

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seemed to be immune. Instead, this virulent form of influenza picked young, healthy adults as its victims.

No one was prepared for its fury. Initially the military was the hardest hit as overcrowded camps and close quarters aboard ships favored its rapid transmission. In September, more than 12,000 soldiers at Camp Devens, outside Boston, contracted influenza. Before long, it spread to civilian populations. As the point of embarkation for troops, New York felt the brunt of the disease early on. The city came to a standstill as taxi drivers, telephone operators and teachers lay ill. Garbage went uncollected, mail undelivered. When news got out that Franklin D. Roosevelt lay near death, it became clear that this disease ignored socioeconomic boundaries. Trying to allay the growing panic, the New York health commissioner, Royal Copeland, issued positive reports — "no reason for alarm" and "disease on wane." Newspapers reported otherwise: 50,000 flu masks dispensed by the Red Cross, an acute nursing shortage, mansions converted into temporary hospitals.

Although the responsible microbe had not been identified, the New York City Health Department designed a control plan based on its experience with tuberculosis. This plan staggered business hours to diminish crowding on subways and elevated trains, suspended book circulation in public libraries and encouraged theaters to sell only half their tickets, leaving a seat empty between patrons. An amendment to the Sanitary Code directed people to cover their mouths when coughing and noses when sneezing; spitting became a misdemeanor. Despite these measures, death notices filled the newspapers. Pictures of stalwart-looking young men in uniform and glowing young brides in wedding gowns added poignancy to the printed words. On Oct. 12, in a defiant demonstration of patriotism, President Wilson and a crowd of 25,000 paraded down New York's "Avenue of the Allies." The next week, 2,100 New Yorkers succumbed to influenza.

Apprehension and grief pervaded the city. No one knew who harbored the influenza germ or who might fall ill; but everyone knew someone who had died. And there was no place to hide. Even if one had the means, leaving New York proved futile, since influenza was engulfing the country, terrorizing even the smallest towns. With no effective treatment, physicians felt helpless. This contagion was overwhelming the nursing force; many of the young and healthiest had already perished. If a visiting nurse was spotted on a street, a crowd surrounded her, begging for help. Desperate to ward off the illness, people wore camphor balls; others had their teeth extracted, believing they harbored the germs that caused influenza. Home remedies proliferated: red peppers, strychnine, whiskey, chloroform — all to no avail.

By the first week of November 1918, the death toll in New York reached 12,357. The deluge of patients swamped the wards and hallways of every hospital. Covered in white except for their eyes and hands, nurses resembled angels, or ghosts, moving through a sea of the ill — groaning, writhing, struggling to breathe. Photographs from the time reveal makeshift infirmaries set up in armories, gymnasiums and dance halls, with hundreds of cots lined up, each occupied by a body — some alive, some still. Obituaries listed entire families dead. The air reeked of decaying flesh as days passed before a death cart collected the deceased. Undertakers ran out of coffins; packed morgues closed their doors. Two thousand corpses lay unburied in Queens until sanitary workers came to assist the gravediggers. In desperation, some families buried their own. In a matter of months, an estimated 21,000 New York children became orphans.

Influenza traveled around the world with ferocity. Daily, the number of dead from the contagion almost equaled the tally of war casualties. The Nov. 11, 1918, celebration over Germany's surrender was tempered by the scourge, which continued to stalk young adults worldwide. By the spring of 1919, the disease had run its course, killing more than 33,000 in New York, 850,000 in the United States, 20 million worldwide. And still no one knew what microbe had massacred a generation or how to prevent its horrifying return.

**BORN ON OCT. 28, 1914**, in East Harlem, Jonas Salk was just a child when these two plagues preyed upon New York. Spared, he would one day play a major role in the prevention of both. Salk's work on the influenza vaccine would go largely unrecognized. His polio vaccine, however, would catapult him into a world of celebrity from which he could never extricate himself. When a waiting world learned on April 12, 1955, that his vaccine could prevent poliomyelitis, Salk, just 40 years old, became a hero overnight. Born in a New York tenement and humble in manner, he had all the makings of a 20th-century icon — a knight in a white coat. He had not anticipated the backlash from the scientific community, the one group whose adulation he craved. With the public awaiting his next medical triumph and his laurels tarnished by a cadre of academic naysayers, Jonas Salk had half a lifetime to prove himself. **SM**



**FEATURE**

## Heart choices

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to the CDC definition," says Gonzalez-Strawinski. With high-risk factors such as prostitution, drug use or prison time, the fear is transmission of viral diseases. But, according to Gonzalez-Strawinski, "everybody screens for those, and if the screening tests are negative, there is zero chance of infection." Others aren't so certain, so the issue often comes under debate.

For hearts from donors with a history of any of these high-risk factors, he always talks to the patient about the risks, and explains that he would never offer any heart to a patient that he wouldn't accept himself.

As Gonzalez-Strawinski considers the many variables involved with matching a heart with a patient, location comes into play. One of the benefits of being centrally located in Texas is that the surgical fellow with an ice cooler who flies out to surgically remove and bring back the donor heart can be most anywhere in the continental United States within three hours. This further broadens the number of donor hearts available to him, Gonzalez-Strawinski says.

"I can push transport time out to six hours with a young heart," he says. "That's where the secret of donor matching comes into play."

A heart shouldn't immediately be rejected because it's too old, too far away or comes from a patient with a history of infectious disease, he says. "If the heart comes from a 61-year-old retired physician-triathlete who had fallen from the back of his truck and cracked his head, and your selection criteria uses 60 as a cutoff age, you've lost a good heart." If your only option is a donor heart infected with hepatitis C, perhaps you still transplant it, but then treat its new owner with hepatitis C medications.

"For some people it is black and white," he says. "What I believe is that if you understand your risk factors, you can use them to your advantage to avoid having a problem."

What it comes down to is this, he says: "The guy who is donating the heart is definitely not on a heart transplant waiting list, so what's the problem?"

FOR LINDA, THE CHEMICAL ENGINEER who has been on the waiting list for more than a year and half, no one has yet called offering her a "high-risk" heart. She's still waiting for any call at all. For now, she focuses on limiting her activities, taking a multitude of medications, reserving her energy, carefully monitoring her diet — a Chinese-food meal, notorious for high sodium content, could put her in the ER — and doing her best to be grateful she is alive. Unfortunately, she's learned that there is almost zero chance of her getting a call as long as she's able to live outside of the hospital. There will always be a heart-failure patient who is sicker than she is higher on the waiting list.

"The thing my cardiologist is most worried about is that I'll go into this rapid degradation and be hospitalized but not get a heart in time. Even though I seem OK, I struggle to do a lot of things. And I hide it. I'm kind of faking my way through life right now.

"I would get a transplant today if I could," she says. **SM**

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# TAKE COVER

## YOU'RE NEVER TOO YOUNG TO START PROTECTING YOUR SKIN

Mornings can be hectic for Kristin Nord as she helps her three young children get ready for the day. But despite the scramble to make sure their faces are washed and teeth are brushed, she always makes time for one more step: applying sunscreen. • Nord, MD, a clinical associate professor of dermatology at Stanford, knows that limiting exposure to the sun's ultraviolet radiation will decrease her children's chances of developing skin cancer and other skin disorders later in life. • "My hope is that the habits they develop in childhood, just like brushing their teeth twice a day, will naturally stay a part of their daily routine throughout life," she says. • Developing those skin-care habits is important because one in five Americans will develop skin cancer in their lifetime, Nord points out. Even people with darker skin can get skin cancer. And we now live in a time when we have many options for protecting our skin. • For instance, consumers can find a variety of lightweight, nongreasy lotions designed specifically for the face and neck. "Your sunscreen should be considered your facial lotion," says dermatology professor Susan Swetter, MD. "It works to moisturize the skin as well as to prevent photoaging and skin cancer."

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And in recent years, companies have begun offering stylish sun-protective clothing and hats. The fabrics block more of the harmful rays than typical summer wear, and hats often have longer backs that cover more of the neck. In fact, Nord says the colorful hat worn by one of her daughters has prompted classmates to ask their parents for "a hat like Kendall's."

The dermatologists say they cover up before spending more than a few minutes outdoors. Sunscreen, hats, visors and sunglasses are a given, but Nord takes some additional measures. For swimming she uses rash guards — shirts popular among surfers to prevent abrasions from their boards. And if her arms are exposed while driving, she wears cool, pull-on sleeves (available at some sporting goods stores and elsewhere) and lightweight gloves to protect her hands.

Serving as skin-care role models is crucial to Swetter and Nord, as parents and as dermatologists. Teenagers — who tend to shun protective measures — are a particular challenge, says Swetter. Yet skipping those precautions could have dire consequences, particularly for athletes who spend hundreds of hours practicing and competing outdoors every year.

"It's difficult to get young athletes to take sun-protective measures, mainly because young people aren't thinking about the harm that current sun exposure will cause 20 or 30 years down the road," says Justin Gordon, MD, a clinical assistant professor of dermatology who helped found the Stanford University Network for Sun Protection Outreach, Research and Teamwork, launched in 2012.

SUNSPORT, as it's known, seeks to educate Stanford athletes, coaches, fans and community groups about ways of limiting the sun's harmful effects. For example, the program encourages athletes to avoid sun exposure between 10 a.m. and 4 p.m., when the radiation is most potent; check their skin each month; and see a doctor if a spot grows, bleeds or changes in appearance.

Gordon came up with the phrase "stretch and slather" to remind athletes to apply sunscreen while they're warming up. A runner who also plays golf and tennis, Gordon says he religiously adheres to the "slather" part of the slogan.

"But I'm not the best about stretching," he adds. "I guess that's because I'm a dermatologist." — SUSAN IPAKTCHIAN

**WEB EXTRA**

More details on skin protection at http://stan.md/1KyUryi

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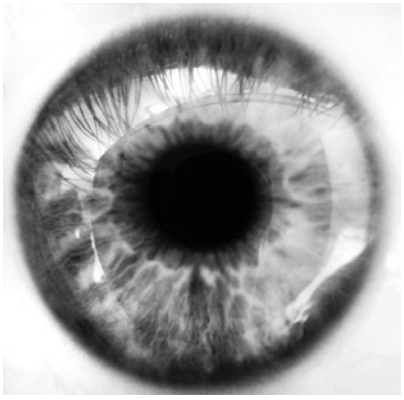
# Sharp sight

## AN IMPLANT DESIGNED TO BOOST VISION WHEN RETINAS FAIL

**A tiny chip — implanted in the eye — could improve sight** for patients suffering from disorders striking the retina, such as macular degeneration. These diseases, which include genetic conditions as well as impairments related to age, affect millions of people. If findings in animal studies are borne out in humans, the new device would offer a big improvement over existing implants — which require a major surgery, use wires and boost vision to only about 20/1,200, says Daniel Palanker, PhD, professor of ophthalmology, whose team developed the system.



He anticipates the implant could eventually restore vision to 20/120. "Based on our current results, we hope that human recipients of this implant will be able to recognize objects and move about," says Georges Goetz, a graduate student in electrical engineering in Palanker's lab. The device will enter clinical trials in France next year through a company called Pixium Vision. The first participants will be patients who have retinitis pigmentosa, which leaves them nearly blind.

Device users wear special glasses, which send wireless, light-based signals to an implanted photovoltaic chip made of silicon. Implanting the chip requires only a minimally invasive surgery. The chip electrically triggers healthy cells within the retina, which usually remain functional even if photoreceptors — cells known as rods and cones — are disabled by disease. By using these healthy cells, the implant takes advantage of natural vision-processing networks, leading to a more precise image.

Like natural vision, these chips acclimatize to a static image and can track moving images. The devices are also thought to be durable. In tests with rats, the implants have lasted for a year or more. "The performance we're observing at the moment is very encouraging," Goetz says.

Palanker's team is refining the device by making the hexagonal chips smaller and adding a prong to each chip that will protrude into the cell layers, ensuring the signals reach the healthy cells and travel on to the brain.

The implant is one of his most sophisticated creations, says Palanker, who has a history of developing ophthalmologic technology — including a laser widely used to repair cataracts. — BECKY BACH



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