



BY JOHN TUCKER
PHOTOS BY JOHN T. CONSOLI

THE AGE OF SKIN

A UMD researcher of a rare disease that fatally ages children has discovered how an obscure blue compound could help us all look younger.

WHOEVER SAID “TIME MAY BE A GREAT HEALER, but it’s a lousy beautician” would be stunned by a skin care aisle today. Soft-cheeked girls as young as 8 flood cosmetics stores in search of anti-wrinkle products, spawning the hashtag #SephoraKids. “Skinfluencers” permeate our social media feeds with reviews of \$120 peel pads and \$325 lotions to add to our daily regimens. On TikTok, filters transform our timeworn faces into eerily realistic teenage versions.

For a generation that grew up on selfies and now lives on Zoom, the pursuit of youthful-looking skin has never felt so extreme, yet so accepted. Recent headlines include “Gen-Z Is Already Worried About Looking Old,” “I’d Rather Die Hot Than Live Ugly” and “Kim Kardashian Would ‘Eat Poop’ to Look Younger.” The global skin care industry will balloon 67% in the next eight years to nearly \$200 billion, according to some predictions.



Since Cao launched Mblue Labs, its Blueelene-labeled skin care products have rung up more than \$1 million in annual sales and earned accolades from the U.S. Chamber of Commerce.

While we can't stop aging, business opportunists are always hawking miracle bronzers, serums and toners to fend off its effects on our faces, sometimes based on dubious science. But as technology has advanced, research-backed companies have also emerged with real promises.

Mblue Labs, founded in 2018 at the University of Maryland, is touting a splash in the fountain of youth with products featuring a 150-year-old antioxidant called methylene blue that penetrates skin all the way into the cell. By extending cellular life, it appears to slow outward signs of aging.

Mblue says its customer base extends into 42 countries. Kevin Harrington of

"Shark Tank" fame endorsed its flagship face cream. In September, the U.S. Chamber of Commerce named Mblue one of America's top 100 small businesses, praising its "groundbreaking skin health technology" backed by "rigorous scientific research."

The person behind the science is Kan Cao, a professor with UMD's Department of Cell Biology and Molecular Genetics. Since first using methylene blue to turbocharge a skin cell in a petri dish, she has ascended as a national authority on skin aging.

But Cao wasn't looking for a way to help 50-year-olds look 30 when she made this discovery. She was trying to save teenagers born with a rare genetic disease from dying.

HUTCHINSON-GILFORD PROGERIA SYNDROME is better known as simply progeria—"prematurely old" in ancient Greek. After appearing typical at birth, children with the disease develop skin that becomes veiny and wrinkled like an elderly person's. Other symptoms include a beaked nose, small chin, fragile joints, hardened arteries and the loss of hair and body fat.

It's also a killer. The average kid with progeria dies at 14, typically from heart attack or stroke. Symptoms that emerge during the toddler years send mystified parents scrambling for answers until the devastating diagnosis arrives.

For 15-year-old Carlos Silva, the news came at age 3, after his hair had begun falling out and his skin appeared burned in places. "My whole life I knew, because people stare at you," he says. "My mother taught me from a young age that I was different but shouldn't feel ashamed." Still, "the hardest part is others' reactions," he acknowledges. Many people ask if he has cancer.

The disease is incredibly rare. Only about 400 cases are thought to exist worldwide, including 13 known progeria patients in the United States. Unsurprisingly, the medical community didn't prioritize it. Then in 1999, a Massachusetts physician whose son had the disease co-founded the Progeria Research Foundation to seek a cure. Among other things, the organization arranged for patients' skin cells to be donated to science. That got the attention of a physician named Francis Collins.

In the modern era of genetics, Collins is the LeBron James of his field. The longest-serving director of the National Institutes of Health, spanning three presidencies, he led the team that in 2003 mapped the human genome. By then, he'd met two progeria

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patients whose stories moved him, and he made it his mission to search for a treatment, maybe even a cure.

His lab was able to identify the genetic mutation that caused the disease, but questions remained. Among the more than 20,000 genes in the human body, a lone "typo" in one of them—switching a chemical building block of DNA that goes by the letter C to another called T—results in a toxic protein dispatched to a cell's nucleus, where it wreaks havoc.

Collins' next step was to hire a researcher to find out why progeria cells deteriorate so quickly: a young cell biologist named Kan Cao.



Cao attends a progeria conference with Sammy Basso. The oldest-known person with the disease, he died last year at 28.

AS A GIRL GROWING UP IN ZHENJIANG, 150 miles northwest of Shanghai, Cao often sat with her grandfather, a traditional Chinese medicine doctor, as he mixed home-made recipes that would stop his patients' bleeding and lower their blood pressure. During her first year of university nearby, she blissfully observed the changing of autumn leaves and growth of green grass. She decided to study the mechanisms of life.

In 2005, after receiving her doctorate from Johns Hopkins University, Cao submitted her resume for a postdoctoral job studying diabetes in Collins' lab, but he instead outlined a position researching a disease Cao knew little about. Progeria seemed likely to satisfy her interest in cellular changes, however, and teaming up with Collins made accepting the job easy.

Cao dived into the analysis of progeria skin cells, making quick findings through experiments that were "exquisitely designed and beautifully conducted," Collins says now. She was the first to discover that progeria cells don't divide cleanly, creating conjoined daughter cells with dysfunctional nuclei. She also arrived at the curious finding that average people can develop trace amounts of the progeria protein, begging questions that would resurface later in her career about whether it contributed to normal aging.

She also made time for conferences where she met children with progeria. "It felt like a big extended family," she recalls, motivating her to work harder. Still, she avoided attachment, reminding herself that her role required distance. She also sought to ward off guilt. After all, the advances she was slowly making weren't ripe enough to prolong lives of preteens who were already afflicted. "They're all angels," she says. "I didn't want to feel solely responsible."

By the time Cao arrived at UMD in 2010, she'd become a global leader in progeria research, but she was hearing from critics who questioned her devotion to such a tiny population. Securing grant funding was challenging. Still, she says, "I had no doubts about my career choices. Never."

At the time, most progeria research focused on the cell's nucleus, where the poisonous protein existed along with most genetic material. One day, Cao decided to explore the mitochondria, which power our bodies' cells. Inside her lab she squinted through her microscope and saw something peculiar.

A healthy mitochondrion resembles a long worm with numerous folds, providing surface area for chemical reactions. But under her scope, the progeria-warped mitochondria was short and swollen, without folds. If Cao could find a drug to help it, perhaps that could trigger a more profound improvement for patients. She experimented with a few chemicals with no luck. Eventually, she reached for methylene blue, a known mitochondrial catalyzer that can recapture stray electrons.

Two weeks later, a student called her over to the petri dish. "This is so crazy," he said. "The cells look so much better."

Cao looked for herself and noticed that the nucleus, typically deformed in progeria cells to look like a popcorn kernel, resembled a healthy sphere.

But a bigger surprise was on the shelf just above, in the control group of normal skin cells infused with methylene blue.

IT'S A BEAUTIFUL COMPOUND, ITS cerulean hue resembling Capri's sea grotto or a winter twilight. Methylene blue was developed in Germany as a malaria drug in the 19th century. Later, fashion designers found they could use it as a fabric dye. These days you can order it on Amazon as a fish tank antibacterial.

Cao never expected the impact it could have on a healthy skin cell. After its application in her lab, energy production soared. Cells that typically died after three months suddenly lived four. After her discovery, Cao’s research ran on two tracks: methylene blue’s effect on progeria cells and on normal skin cells. While the former ended as new research elsewhere pointed to a cure for the disease, the latter took off. Cao used a 3D bioprinter to create a multilayer skin specimen with everything from carotenoids to connective tissue, then applied the catalyzer. The results were intriguing. Methylene blue stimulated skin proliferation, expanded thickness and healed wounds faster. It jump-started production of collagen and elastin, the hydration fibers that keep skin plump and shiny.

Cao quickly hammered out a journal article, “Anti-Aging Potentials of Methylene Blue for Human Skin Longevity.” She published it in *Scientific Reports* in 2017, intending to get back to her progeria focus.

Instead, calls came pouring in. Journalists asked for comment, including a reporter from *Allure*. Women reached out directly. “Are you guys going to make a cream?” one asked. “Hurry up, I’m in my seventies!”

The idea of creating cosmetics seemed to conflict with her principles. *I’m a researcher and professor!* she thought. *I’m doing my science!* Her colleagues meanwhile were commercializing cancer drugs, not face creams. With two kids in middle school, she also worried about the financial risks of investment.

Her research team, however, nudged her to reconsider, and Cao mulled the idea. After a dozen years committed to a small handful of sufferers, perhaps this was her chance to help more people. What’s more, she recalls thinking, “It can maybe help us understand the general process of human aging.”

She took an online course on skin care formulation, then ordered foundational emulsifiers and mixed them at home with

methylene blue. She applied the concoction to her face and liked the results. One day she arrived at her lab and doled out jars reading “MAGIC CREAM, Cao Lab.” Weeks later, students were asking for more.

Cao contacted UM Ventures, which helps researchers launch products based on lab discoveries. The skin care market was saturated, Cao was warned, but her molecular formula was unique. After securing a patent to use methylene blue as an anti-aging skin cream, she got busy, filling orders, packaging creams and making post office runs. “She doesn’t have the diva complex,” says Alla McCoy MBA ’13, director of venture development for UM Ventures.

Cao needed a CEO, and UM Ventures paired her with Jasmin El Kordi ’83, an executive with a health and beauty background. “This was something brand new,” El Kordi recalls, comparing the product to the glut of exotic-sounding skin care creations that ultimately fail. “They have ingredients like algae, oil of orchids or compounds harvested from trees in Brazil, but they’re not easily patentable. There’s no deep science that focuses on the actual skin cell.”

By mid-2018, Cao’s business was official. She called it Mblue Labs, short for Magic Blue. Its initial cream was a hit on Amazon, selling nearly 1,000 units in three months. Since then, the company has rolled out nine more products under its “Bluelene” label for women and men of all ages, with 20% sold in brick-and-mortar stores like Macy’s, contributing to more than \$1 million in annual sales.

SOMETIMES CARLOS SILVA LOOKS AT his bony fingers and is reminded that he’s different from other boys. He recently dropped out of high school because he could no longer bear the bullying. He’s now homeschooled.

Yet in other ways, he’s a typical teenager. He cheers for the Red Sox and builds a mean Lego train. He envisions a career in science

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—LESLIE GORDON,
CO-FOUNDER AND MEDICAL DIRECTOR OF THE
PROGERIA RESEARCH FOUNDATION

or law. He calls his life “amazing.”

He’s also undaunted by the average lifespan of progeria patients, which he’s already eclipsed at 15. “Everyone is a different being,” he says. “Progeria shouldn’t tell you when your life should end.”

Carlos has reason to continue beating the odds. The hunt for a cure has taken a hopeful turn, through gene editing technology developed by David Liu, a Harvard University professor and the director of the Merkin Institute for Transformative Technologies in Healthcare in Cambridge, Mass. Liu’s method knocks out individual “letters” of a gene and replaces them with others, mimicking a word processor’s “find and replace” function throughout the body.

After Liu erased the mutant T associated with the disease, correcting it to a C in his lab, Cao helped validate his findings in progeria cells. In 2021, their wider research team tested the approach in genetically engineered mice with progeria. After several weeks, the mice were not just alive, but healthy, with DNA fixes across many organs. Cao co-authored the breakthrough study, published in *Nature*. Cao’s mentor, Collins, played a lead role. With human trials perhaps two years away, Collins, 74, now believes a cure in his lifetime is possible.

Until that happens, though, the pernicious protein will continue to kill, and Cao has sought quicker ways to help. Considering that

patients die of heart attack and stroke, she’s focused on the cardiovascular system.

Recently, she’s relied on a Nobel Prize-winning discovery to reprogram mature cells from progeria patients into artificial stem cells, then convert them into vascular cells, establishing “a playground for us to understand what’s inside the heart of a progeria patient,” she says.

This led to a major new finding published in October in *Aging Cell*. After manipulating a progeria stem cell into endothelial cells—which line the blood vessels and send messages to smooth muscle cells—she noticed an out-of-whack signal system that essentially instructed muscle cells to die. The cause, Cao showed, was a missing signaling

protein. When it was added back, the system normalized, restoring damaged blood vessels in mice to health. It’s a “stunning” discovery, says Collins, “that could prevent or ameliorate the vascular problems that lead to strokes and heart attacks.”

Cao hopes the breakthrough could offer temporary treatment until gene editing becomes a more permanent fix.

Cao’s decades-long research into progeria and methylene blue takes two opposing concepts—aging sped up; aging slowed down—and intertwines them like a double-helix DNA strand. “She sees a vision of how aging can inform progeria, and how progeria can inform aging, and that’s what we strive for,” explains Leslie Gordon,

co-founder and medical director of the Progeria Research Foundation, who now calls Cao a friend.

These days, Cao is returning to questions that vexed her earlier in her career. How do trace progeria proteins find their way into normal people? And are they responsible for premature wrinkles here and there? In this Era of Peak Skin Care, those questions suddenly feel more important.

In the future, Cao thinks science will find more ways to prevent skin aging, sating our desire for a fountain of youth. We are, after all, just a product of our cells, through breakdown and restoration. If the lives of our cells can be prolonged through innovation, then maybe our physical lives can be, too. **TERP**

