Esteban Abarca and I wait in a dermatology clinic in Santa Cruz, California. We’re there to donate biopsies of the skin and upper layers of flesh from our heels. Scientists will study the 3-millimeter-wide punch-outs — half the diameter of a pencil — to examine how his severely damaged nerve endings differ from my healthy ones. We both know it will hurt. But Abarca is sweating. It will hurt him more than either of us imagine.

Abarca, 32, has a short crew cut and a well-trimmed goatee. He works as a truck driver in Oakland. Nine years ago, he found out why his feet hurt so intensely. He’d thought his thick yellow calluses and scorching pain were just “bad feet.” But after visits to the right doctors and a genetic test, he heard the rare, tongue-twisting diagnosis: pachyonychia congenita (pak-ee-o-NEE-kee-a kon-GEN-i-ta), or PC.

PC is not life-threatening, but that’s little comfort for the 1,200 patients (one in 6 million people) worldwide. Caused by the smallest of DNA mutations, PC can mean shaving calluses with a razor blade and trimming fingernails with a power tool. Patients sometimes crawl rather than walk. The disease disfigures feet, hands, and nails. For now, there is no treatment.

But a decade ago, shortly before Abarca’s life-changing diagnosis, a genealogist in Salt Lake City resolved to do something for PC patients. Her activism inspired biochemists in Santa Cruz to launch a company dedicated to treating the disease. Now that company, TransDerm, prepares for clinical trials that could bring PC patients back to their feet. Their treatment silences the genetic mutation responsible for the disease. It’s injected via microneedles — thinner than a hair and short enough to barely pierce the skin. A preliminary human trial five years ago showed enough promise to merit continued funding from the National Institutes of Health (NIH).

If TransDerm succeeds, millions with other skin disorders may also benefit from their technology. But that’s a far-off dream for the small company. The ongoing pain for PC patients, in contrast, is very real. They watch the company’s progress with anxious anticipation. It’s their best hope.

Roots of the disease

German dermatologists first named PC in 1906, describing the case of “E.C.,” a 15-year-old girl with thick fingernails and toenails. “They cannot be cut with a scissors,” the dermatologists wrote. “The father has to trim them with a hammer and chisel.” The disease’s name, “pachyonychia,” is Greek for “thick nails.” Over the years, frustrated doctors tried radiation
and thyroid medications, among other treatments, with no success.

In 1994, scientists in Scotland identified a key gene responsible for the disease. PC is caused by a point mutation, a change in a fundamental unit of DNA. The mutation may occur in any of five genes encoding keratin, a protein found in hair and skin. Keratin supports cells like a wooden frame supports a house. The mutated gene overwhelms the four normal genes and turns that frame into small fragments, weakening its structure, and leaving the skin vulnerable to damage. Even a little friction inflicts a wound, leaving an exquisitely sensitive callus. (See sidebar: Profiles in Pain.)

PC affects the keratin found in nails, palms, and soles. Not all PC patients have the same mutation. One specific mutation, called K6a N171K, is shared by only 14 known patients worldwide.

In 2001 Mary Schwartz, a Salt Lake City genealogist, read in Reader's Digest about efforts to cure a rare liver disorder in a 13-year-old boy. Schwartz pondered the heroics of the researcher in the article and thought of her daughter-in-law and two grandsons, all afflicted with PC. She decided to act.

It seemed simple in her mind: Keep researchers funded until they found a cure. "It's like the cure existed, like gold, and you went out and found it," Schwartz says. "I was wrong on every point."

In 2003 Schwartz founded the non-profit PC Project. With no scientific background (her only degree, she says, is as a grandma — a "GMa"), she organized a conference the next year in Park City, Utah, and called for scientists who could offer plans for clinical treatments.

Santa Cruz biochemist Roger Kaspar attended as an invited scientist on behalf of his employer, Somagenics. A tall man with dark wavy hair and a narrow face, Kaspar had taught biochemistry at Brigham Young University before coming to California's central coast.

Kaspar first presented his company's technology, then mentioned a new and more potent approach that could halt PC at a genetic level. Intrigued, Schwartz began a detailed dialogue with him. Kaspar told Schwartz that funding a series of academic grants probably would not lead to a treatment. Researchers and students work on many different projects and constantly seek more funding, he said. Employees, though, could sustain a focused effort.

"I said, 'If you want to start a company and the goals line up with yours for the next few years then, yeah, I might be interested,'" Kaspar recalls. In 2005, with initial angel funding, TransDerm opened its doors with Kaspar as CEO.

At first, Kaspar wondered whether he was making a mistake. But he's reminded why he made the choice whenever he meets patients. "You realize these people are depending on you," he says.

Breaking into stubborn skin

Today, TransDerm has seven employees, with offices less than a mile from a monarch butterfly sanctuary overlooking Monterey Bay.

Kaspar's first challenge was to quash the mutated keratin gene. Genes build keratin by sending single strands of genetic material, called messenger RNA, to protein-building areas of the cell. TransDerm's approach, known as RNA interference (RNAi), chops the mutated-gene-RNA in half with targeted synthetic RNA. This prevents the cell from forming defective keratin. Other unmutated keratin genes are then free to build strong cell-supporting filaments.

By 2006 Kaspar's team had a precise RNAi inhibitor, designated TD101. Two years later, the team began a clinical trial approved by the U.S. Food and Drug Administration. A single patient (out of six known at the time with TD101's target mutation) received an injection into each foot twice a week for 17 weeks. The right foot got the drug, while the left got a placebo. Neither the patient nor the physician knew until later which foot received which injection. As the trial progressed, the right foot's calluses visibly shrank. On day 98, a dime-sized piece of the treated callus fell off at the injection site. Healthy skin grew underneath.

"We have every reason to believe, but cannot prove, that the mechanism of the clinical effect was through RNA interference," the team wrote. Proof would have required a biopsy of the injection site, compromising the rest of the study.

TransDerm scientists supported their conclusion, both before and after the study, with lab experiments using cultured human cells engineered to produce either a red or green fluorescent protein. An RNAi inhibitor knocked out only the red genes. The RNAi approach appeared to be working.
But the injections of TD101 caused incredible pain in the patient’s sensitive feet. I witnessed this hypersensitivity during my foot biopsy with Esteban Abarca. He and I sat in adjacent exam rooms. My anesthesia injection hurt: a long, deep pinprick followed by burning lidocaine. As Kaspar teased me about the pain, we heard a sudden shout from the other room. “I can’t do it,” Abarca gasped. “I can’t go through with it.” For him the injection felt like a fiery, piercing stab, more intense than anyone had anticipated.

In 2009, Kaspar and his team began searching for a more “patient-friendly” way to deliver their drug to diseased cells. RNAi delivery is the technology’s stiffest challenge, says molecular biologist Steven Dowdy of the University of California, San Diego. Large RNA molecules don’t enter cells easily, he says. “Here’s this gift that can target every single gene in the body,” Dowdy says, “and the joke is that you can’t deliver it inside a cell.”

Kaspar is on “the right track,” Dowdy believes, by using inhibitors designed to overcome some of the cell’s barriers. Still, RNAi is inefficient, he says, and must be delivered precisely and frequently.

After exploring myriad delivery options, Kaspar’s team turned to an elegant concept: microneedles.

Inspired by thistles

Microneedles puncture only the top layer of skin, producing little pain. They’re not new, Kaspar says. The first microneedle-delivered flu vaccines arrived in pharmacies two years ago. But TransDerm’s manufacturing method is unique.

The man who makes the needles, Tycho Speaker, is a chemist and a tinkerer. His office is littered with tools, soldering equipment, and curled tubes of polymer gel. His expressive hands and eyebrows help him tell his story.

Speaker was working in his yard one day when he ran into a thistle. “I looked down and thought, ‘Those are microneedles,’” he says. He and his daughter plucked a few thistles, then pressed the tiny spines into clay to make a mold. But Speaker found that pouring a thick polymer into a narrow mold was tricky. “It got really burdensome, really quickly,” he says. Sticky stringers of goo kept pulling off his polymer-covered fingers. Speaker was frustrated, until he looked at the tapered stringers closely. “I put a hair dryer to it, cut it off, and poked myself. That was the first microneedle.”

Today, Speaker makes grids of microneedles (which TransDerm calls protrusion arrays) by spreading a polymer on a flat microscope slide. He puts a block of pins onto the slide and slowly draws the block away while blowing hot air over the rapidly drying needles. A finished array, with 25 needles per square centimeter, feels “like a cat’s tongue,” Speaker says.

He goes to a microscope and focuses on the Lincoln Memorial on the back of a penny. Abraham Lincoln, he says, is about a millimeter tall. He replaces the penny with a protrusion array loaded with fluorescent dyes. The polymer cones glisten, filled with alternating greens and blues, and fade into the out-of-focus distance. Each needle is between 400 and 600 microns long — half as tall as President Lincoln.

Speaker then sticks the array into his hand between his thumb and forefinger. “When they poke you in the skin, they don’t go that deep,” he says. “The skin deforms so much that they only poke you in the 150-200 micron range. Pain...
Illustration: Christina DiPaci
Filled with medicine, microneedles pierce the skin’s outermost layer, the stratum corneum (left), and penetrate to the stratum spinosum. The needle tips dissolve (center), releasing a drug that diffuses into skin cells. Healthy genes then produce the skin’s proteins properly (right).

Caring for orphans

Even though microneedles may hold promise for PC patients, NIH small business grant committees — which largely fund the company — want to see broader impacts.

Kaspar’s first application stated that TransDerm’s goal was to make RNA therapeutics for pachyonychia congenita. “The gist of the critiques was, ‘We don’t believe any self-respecting company would do this because there aren’t enough people in the world to justify that,’” Kaspar says. “We didn’t get funded.”

So, he resubmitted the application with new wording. The company hopes to treat genetic-based skin disorders, he wrote, and the lessons learned from this disease could apply to a wide range of disorders. “That grant got high scores and was funded,” Kaspar says.

Many of these genetic skin disorders are rare. Epidermolysis bullosa, which causes skin to blister at the slightest friction, affects one in 100,000 people. Other disorders are more common. Keratosis pilaris affects nearly half of all adults, forming red bumps on the upper arms.

The FDA designates treatments for rare diseases as “orphan drugs.” Incentives, such as FDA fee waivers and seven years of competition-free marketing, encourage pharmaceutical companies to invest in diseases with fewer than 200,000 patients. These large companies, Kaspar says, jump into markets where no current drug exists. Their investment sometimes pays off. The second-most profitable drug, Rituxan, was developed for rare cancers, but then found widespread use as a treatment for rheumatoid arthritis. Others aren’t so lucky. Even when companies successfully develop a drug, many small firms fold due to lack of funding, Kaspar says, leaving their patients without a treatment yet again.

“We don’t ever expect to make money off of drugs for PC,” he says, noting that TD101’s potential patient pool is tiny. “We’re more interested in helping people.”

This summer, ten years after the first Park City conference organized by Mary Schwartz, TransDerm will file an Investigational New Drug application with the FDA. If it’s approved, further clinical trials of a next-generation TD101 could begin this year. Eventually, TransDerm and its partners plan to develop additional RNAi inhibitors, one for each PC-affected gene. This summer’s application is the first step on a long road.

During my biopsy, I felt nothing when the doctor plunged the punch into my left heel twice. He plopped the samples into vials of yellow fixative, and reminded me that the anesthesia would soon wear off.

The next day, I hopped on one foot for 300 yards to my office. With each day I hopped less. After three weeks, I’d fully healed. But I’ll remember the twinges that caused me to question every step, and Abarca’s acute anguish. I’m walking again, but his pain doesn’t ebb or ease. At least not yet.

Sidebar: Profiles in Pain

Roseann McGrath lives near Philadelphia. She was diagnosed with pachyonychia congenita at age 4. The pain, she says, is constant. Wearing socks, or getting her feet wet, is unbearable. “When you walk on top of it, you get these blowtorch burning sensations,” she says.

Most patients use over-the-counter pain medications and stay off their feet as much as possible. But McGrath, now 46, uses a cane or wheelchair only at home, never at work. “This is a part of our lives we usually try to hide,” she says.
As a teenager McGrath heard that half of the children born to PC parents inherit the disease. She chose to never have kids of her own. "Living with something so painful and so excruciating, I felt it would have been selfish to pass it along to someone else," she says.

Eight years ago, she met another PC patient for the first time at a support meeting organized by the PC Project. It was exhilarating, she says, and almost overpowering. "This feeling of being so alone and feeling like such a freak, that nobody really understands what this is and who we are, is now negated.”

New patients continue to enter the PC “family.” One of the newest, a three-year-old in Wisconsin named Allison, is just starting to develop calluses. She doesn’t have much pain yet, so her parents encourage her to be active while she can.

Shortly after Allison’s diagnosis, her family contacted the PC Project, which helped them connect with doctors and fellow patients. Allison hasn’t even started kindergarten, but she already has met other people like her. She, and the patients to come, will never have to know the same isolation McGrath felt.

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Biographies

Paul Gabrielsen
B.S. (geology) Brigham Young University
M.S. (hydrology) New Mexico Tech
Internship: NASA Goddard Space Flight Center (Greenbelt, MD)

I grew up among the stunning red canyons and mountains of Utah. My Boy Scout adventures led to a college major in geology. Through new eyes, those same canyons and mountains from childhood hikes became colliding continents and incredible ancient landscapes. Later, studying hydrology, I learned to see humble streams as delicate, nuanced systems that affect every corner of this planet.

The fun of science is discovering something that changes how you see a river, a mountain, even a grain of sand. I have a curious daughter, and her questions about how the world works are teaching me that discovery isn’t just for a five-year-old. It’s also for her daddy, who is learning that at its essence, science is simple and clear and accessible.

Now I can share that fun through every word I write.

Paul Gabrielsen web site

Alex Babakitis
B.F.A (illustration) California College of the Arts
Internship: Isabella Kirkland, Tiffany Bozic

Alex Babakitis is a versatile illustrator with an interest in wildlife illustration, fantasy illustration, graphic novel illustration, game design, and animation. Having spent his childhood amongst the redwoods north of the Golden Gate, he finds constant inspiration in the tremendous diversity of life on planet Earth. Alex looks to continue following his
passions as a wildlife illustrator and as a student of the natural world.

Alex Babakitis web site

Christina DiPaci
B.F.A. (illustration and communication design) Parsons School of Design
Internships: Kew Gardens (London), National Herbarium of South Africa

For most of my life, I have been training and developing my skills as an artist. Fascinated by the natural world, I constantly sought out inspiration from nature. I had not considered the field of scientific illustration until an artist residency brought me to a biological research station in Peru and I began focusing on work that connected science and art. After earning my B.F.A., I immersed myself in the world of botany, gardening in the day and illustrating at night. I am eager to employ my skills in my internships and new career.

Christina DiPaci web site