



Pachyonychia Congenita Project

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We hope that making available the relevant information on Pachyonychia Congenita will be a means of furthering research to find effective therapies and a cure for PC.

By Aaron Rowe

Shoestring gene therapy



An RNA synthesizer Courtesy of Alnylam, photography by J. Earle

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On a frigid weekend in the winter of 2004, a **medical charity** held a meeting at the Yarrow Hotel in Park City, Utah, to discuss a problem. It had been nearly ten years since geneticists Irwin McLean and Frances Smith had discovered the genetic underpinnings of pachyonychia congenita, a rare and extremely painful skin disorder. But a cure was nowhere in sight.

Between runs down nearby ski slopes, several scientists threw out ideas for treating the disease. And one of them stuck. “We had decided that probably the most promising approach was gonna be siRNA-based technology,” says Sancy Leachman, a dermatologist from the University of Utah who helped organize the meeting.

Since pachyonychia congenita is an autosomal-dominant condition caused by the production of misshapen keratin 6a molecules, it seemed reasonable that knocking down the mutant gene could remedy the disorder. The disease affects approximately 5,000 people worldwide, and causes massive calluses on their hands and feet. Those lesions are so painful that they literally bring some patients to their knees, forcing them to crawl around their homes instead of walking.

Months after the Park City meeting, biochemists Roger Kaspar and Robyn Hickerson started a small biotech firm, TransDerm, and decided to design and test siRNA sequences that could halt the production of bungled keratin 6a molecules without affecting the wild-type protein. Working with Dharmacon, a biotech that specializes in RNA interference, they found a sequence that worked in human embryonic kidney cells.

With a drug candidate in hand, the team looked into running a clinical trial. But they found the process was so daunting and convoluted that it seemed almost impossible for a **grassroots organization** to handle. Someone needs to write a “Clinical Trials for Dummies” book, Kaspar says.

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While attending the 2006 Obstacles to Translation conference in San Francisco, Kaspar had a lucky break—lunch with an FDA employee. The regulator walked him through the intricacies of earning orphan drug status for the experimental treatment.

With guidance from the orphan drug office, the path forward started to make sense, but writing an investigational new drug application proved difficult. It takes an expert to fill out each section, and it became clear that the researchers would need more help. So **they** hired a gaggle of consultants, who wrote the clinical, manufacturing, and toxicity sections of the application.

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With those experts in their corner, the team flew to Washington for a meeting with the FDA, and explained their situation. They didn't have the resources to do a lot of animal safety studies (they weren't even done with their rabbit safety studies at the time of the meeting), but their plans did not seem particularly risky. They intended to inject unmodified siRNA directly into lesions on their patients' skin. siRNA molecules have an extremely short half-life, so they could not make it very far if any of it did enter patients' circulation. They got the green light.

Although the consultants had offered to do much of their work pro bono, the budget for the human trial project was skyrocketing. It became clear that the experiment would require RNA made up to the standards of good manufacturing practices. And that would cost nearly \$800,000. Then, once the drug was made, it had to go through an expensive finishing process that entailed shipping the siRNA to a lab at the University of Iowa, where it was mixed with saline and packed into vials.

Once the investigational drug was ready in 2008, a woman with pachyonychia congenita agreed to participate in the trial. She endured dozens of siRNA injections, shot directly into the massive calluses on one of her feet, and also suffered through control doses in the other foot. The shots were so painful that she needed to pop painkillers and get a nerve block before each treatment.

For months, it seemed like nothing was happening; then, after half a year of the painful injections, one of the lesions nearly disappeared. It was the first time that the patient had ever seen one of her calluses vanish. "This had never happened before to this patient at any time in the past," says Leachman.

The experimental treatment was a success—at least as a proof of concept—but it was completely unsuitable for routine use.

So now, Kaspar along with Christopher Contag of Stanford University and Leonard Milstone of Yale are trying to find a better way to deliver siRNA topically. They are testing everything from creams to microneedles. If they find a technology that works, it could mean relief from countless skin disorders, from warts to melanoma to pachyonychia.