STICKING IT

ABOVE: The hand of Sarah Nelmes, a dairymaid. Edward Jenner used the pus from her cowpox lesions to inoculate his gardener’s son against smallpox.
Smallpox was once called the scourge of mankind. The disease’s origin is unknown, but its existence can be traced to 10,000 BCE in northeastern Africa. During the 18th century, 400,000 Europeans died annually because of smallpox. In England, where a 13-year-old orphan named Edward Jenner was an apprentice to a surgeon and apothecary, the disease was also known as the “speckled monster” because of the resulting skin condition—sores filled with opaque fluid.

As an apprentice, Jenner once overheard a dairymaid say, “I shall never have smallpox for I have had cowpox. I shall never have an ugly pockmarked face.”
For centuries, it had been common knowledge that smallpox survivors became immune to the disease; and because of this, many doctors inoculated people by removing smallpox scabs or pus from an infected person, then rubbing that onto the arm of someone who was uninfected. This was called variolation. The method worked fairly well for people inoculated in this manner; only up to 2 percent died from smallpox. Yet, they were likely to pass on a severe case of the disease to someone else.

Jenner never forgot what the dairymaid had said. Years later, as a physician, he decided to research his theory that the pus in cowpox blisters protected people from smallpox.

In 1796, Jenner removed cowpox scabs from the hands of a milkmaid named Sarah Nelmes and rubbed them onto the arms of James Phipps, his gardener’s 8-year-old son. Phipps came down with a fever, but no lesions. Later, Jenner injected the boy with cowpox, but the child never developed the disease. He repeated the test, and Phipps remained in good health. Jenner successfully tested 23 other patients this way and published his findings. His results were debated in England until 1840, when the government banned variolation and provided free vaccinations using cowpox, which was deemed much safer.

To vaccinate patients, doctors scratched a person’s arm with a cowpox-covered needle; this method continued into the 20th century. Smallpox was officially declared eradicated in 1980, but some people who grew up during the first half of the 1900s may have a scar on their arm from when they were vaccinated with a needle scratch.

These scratch vaccinations were pretty effective, but far from perfect. Doctors couldn’t scratch the same way twice, which meant they couldn’t guarantee they’d deliver the same amount of vaccine each time. Vaccinations need to be reproducible. In time, intramuscular injections became popular; but Louis Falo, an MD/PhD and chair of the University of Pittsburgh’s Department of Dermatology, notes these miss the skin completely. Unlike skin, muscle does not directly elicit an immune response. So, at the cellular level, intramuscular injections are only modestly successful compared to smallpox vaccinations of the early 20th century.

Inspired by the history of scratch vaccinations, seven years ago, Falo began researching microneedle array technology, which delivers medicine through the skin.

“Microneedles, Falo says, are better than intradermal injections, which introduce a drug to the dermis (the thick layer of “living tissue” under the epidermis, the outer skin layer). Intradermal injections are hard to reproduce. Microneedles, on the other hand,
Researchers on microneedles began in the mid-1990s, when microfabrication technology facilitated their manufacture. The research was led by three isolated efforts operating in parallel at the Georgia Institute of Technology, Becton Dickinson (a medical technology company), and Alza Corporation (a pharmaceutical company).

Last year, Mark Prausnitz at Georgia Tech published the results of a phase I trial for a self-administered influenza vaccine using microneedles. Georgia Tech is also developing microneedle patches for polio, measles, and rubella vaccinations, notes Prausnitz.

There are a few different types of microneedles. For his research, Falo uses dissolvable microneedles. In this variety, a drug is mixed with the patch’s structure, and then the needles disintegrate in the skin’s aqueous environment.

Microneedles can be mass produced at a low cost, shipped in bulk, and stored at room temperature. The technology could eliminate the need for cold chain distribution, which is a series of stages of uninterrupted refrigeration, from production to storage.

The cold chain costs $13.4 billion a year globally, and vaccines sometimes expire or denature before reaching children in need, especially those in remote regions of developing countries. The World Health Organization reports that more than 50 percent of vaccines are wasted each year.

One June afternoon, Pitt’s Geza Erdos, a PhD and assistant professor of dermatology, and Oleg Akilov, MD/PhD and director of the Cutaneous Lymphoma Program and Extracorporeal Photopheresis Unit, show off the narrow area where the microneedles are made. Akilov slides open an unassuming counter drawer. It’s full of tiny, white patches that could eliminate melanoma-plagued cells. Akilov picks up a patch with two fingers and presses it against his forearm.

“It feels like Velcro,” he says.

Joseph Lane (not his real name), who participated in the clinical trial, agrees that the patches feel like Velcro, and he insists they don’t hurt when inserted. “But you can definitely feel it being pushed in,” he says.

Lane, a lecturer at Pitt, was diagnosed with folliculotropic mycosis fungoides in 2009. With this disease, the body is the site of a traffic jam of sorts; but instead of cars, it’s T cells that get waylaid. “They get confused about where to go because of how they’re made,” Lane says. “So they go to my hair follicles.”

Lane gets cancerous lesions; they can appear wherever he has hair. He has itchy, red patches of skin on his hands, forearms, legs, and lower back. He says the disease has been manageable since he finished the microneedles trial earlier this year. “If I could freeze it like this, I would,” he says of his condition.
Akilov embraced the notion that experienced dermatologists could have powers akin to palm reading. Just by examining the skin, they could tell you the patient’s profession, diet, and how much time had been spent in the sun.

The shape permits the needles to hold multiple drugs. One therapy can be in the tip, while one or two more can be stored in the shaft. Falo and his team are experimenting with doxorubicin, a chemotherapeutic, in the tip and, in the shaft, one or two adjuvants (i.e., artificially made molecules that stimulate and improve immune response by imitating the types of danger created by bacteria or viruses). Microneedles are easily broken, and that’s the point. (Sorry about the pun.) Once they are inserted into the skin, they break off and dissolve, releasing medicine.

Holding the patch with two fingers, I accidentally snap it in half, and Akilov and Erdos laugh.

“Oh my God, now we’re going to charge you,” Akilov says.

“Two thousand bucks,” Erdos adds. Later, Falo guesses each patch costs about two cents to make.

The lab has three unofficial team members in Falo’s children: Isabella, 15, and 18-year-old twins, Dominick and Gabriel. (During their summers, between wrestling, soccer, football, and lacrosse practices, they’ve helped with microneedle development.) Akilov says other members of the team turn to Falo for fatherly counsel.

“When he gives you a piece of advice,” Akilov says, “be sure to print it and laminate it, because that is going to be your instructions for how to live for the next couple years.”

When doctors administer chemotherapies through an IV or injection, they destroy rapidly dividing cells faster than other cells. But then the toxins flow throughout the body, producing the side effects of hair loss, nausea, and fatigue.

Falo believes microneedles can deliver a lower dose of doxorubicin straight to squamous cell carcinomas, basal cell carcinomas, and cutaneous lymphomas. The drug’s high concentration to one area would cut down on, and possibly prevent, negative side effects.

“It enters cancer cells in the skin where it is delivered and essentially doesn’t go anywhere else,” Falo says. For example, Lane did not experience side effects from the microneedle therapy.

So: It’s not possible to hit every single tumor cell with doxorubicin, and even if you could, that would not be enough to stop cancer. You’ve got to exploit the immune response. That’s how Falo’s microneedles operate.

After the microneedles release doxorubicin, the dying cancer cells let loose antigens for the immune cells to pick up. The immune response should wipe out the cancer cells that the microneedles missed. There are two benefits to this. One is obvious: This kills skin cancer in the patient. In addition—similar to a vaccination—immune memory is developed. The T cells can mount a response if the disease metastasizes or if a new skin cancer forms.

“You don’t have to go through the whole process of stimulating a new immune response again,” Falo says. “The T cells are already there, waiting for [cancer] to come again.”

This element of the response is crucial, Falo explains, because researchers interested in developing cancer vaccines struggle to find common antigens. It’s not like the flu, where there’s one antigen, one protein, and everyone is immunized against that protein. Tumors have multiple antigens, and there is an individualization to them. Your squamous cell carcinoma or basal cell carcinoma might look very different from mine, antigenically speaking.

In this regard, treating skin cancer with microneedles is personalized medicine, says Falo.