Gene therapy for blistering skin disease appears to enhance healing in Stanford clinical trial

By Krista Conger

Grafting sheets of a patient's genetically corrected skin onto open wounds caused by the blistering skin disease epidermolysis bullosa appears to be well-tolerated and improves wound healing, according to a Phase 1 clinical trial conducted by researchers at the Stanford University School of Medicine. "The results mark the first time that skin-based gene therapy has been demonstrated to be safe and effective in patients" said M. Peter Marinkovich, M.D. and Jean Y. Tang, Associate Professors of Dermatology and senior authors of the study.

The researchers will report the results of 4 adult patients with the excruciatingly painful genetic skin disease (RDEB, recessive dystrophic epidermolysis bullosa) in the Nov. 1 issue of the *Journal of the American Medical Association*. Senior scientist Zurab Siprashvili, PhD, is the lead author of the research.

"Our Phase 1 trial shows the treatment appears safe, and we were fortunate to see some good clinical outcomes," said Tang. "In some cases, wounds that had not healed for five years were successfully healed with the gene therapy. This is a huge improvement in the quality of life for these people."

People with epidermolysis bullosa lack the ability to properly produce a protein called type VII collagen that is needed to anchor the upper and lower layers of the skin together. As a result, the layers slide across one another upon the slightest friction, creating blisters and large open wounds. The most severe cases are fatal in infancy. Other patients with a version of the disorder called recessive dystrophic EB can live into their teens or early adulthood with supportive care. Often these patients die from squamous cell carcinoma that develops as a result of constant inflammation in response to ongoing wounding.

The Stanford group showed that it was possible to restore functional type VII collagen protein expression in patient skin grafts to stop blistering and allow wounds to heal. They demonstrated continued expression of the replacement protein and improved wound healing after over a year of follow up.

Looking to build upon results

The researchers seek to build upon these promising early results in a new trial that will include patients ages 13 and older.

Moving into the pediatric population may allow us to intervene before serious chronic wounds and scars appear," said Marinkovich, who directs the Stanford Blistering Disease Clinic. Repeated rounds of wounding and scarring on the fingers and palms, for example, often lead to fusion of the skin and the formation of what's known as a "mitten hand."

Siprashvili used a virus to deliver a corrected version of the type VII collagen gene into batches of each patient's skin cells that had been harvested and grown in the laboratory. He coaxed these genetically corrected cells to form six sheets of skin about the size of an iPhone 5. The sheets were then surgically grafted onto the patient's chronic or new wounds in six locations.

The researchers tracked the status of the grafts at one-, three- and six-month intervals for at least a year, checking to see if they stayed in place and caused wound closure. They also looked for any evidence of an immune reaction against the grafts, and whether the grafts continued to make the corrected type VII collagen protein.

All 24 grafts were well-tolerated, the researchers found. Furthermore, they could detect expression of the type VII collagen protein in the correct location of the skin in nine out of 10 tissue biopsies at three months. After 12 months, they were able to detect the collagen protein in five out of 12 biopsies.

Wound healing

Similar results were seen with wound healing. After three months, 21 of the 24 grafts were intact. This number dropped to 12 out of 24 after one year.

"Even a small improvement in wound healing is a huge benefit to the overall health of these patients," said Tang. "For example, it may reduce the likelihood of developing squamous cell carcinoma that often kills these patients in young adulthood." Coupling grafts with hand surgery to break up scarred, fused tissue may also help patients maintain the use of their hands, Marinkovich said.

Tang, Marinkovich and their colleagues will continue to monitor the patients in the Phase 1 trial throughout their lifetimes to assess any long-term effects of the grafts.

The completion of the Phase 1 trial and the potential to improve upon these outcomes is due to a concerted, long-term effort at Stanford to find ways to help young patients with this

devastating disease. The researchers are now starting a Phase 2 clinical trial and are looking for new patients (please contact tangy@stanford.edu, or mpm@stanford.edu)

"This trial represents the culmination of two decades of dedicated clinical and basic science research at Stanford that began with the arrival of the former dean of the School of Medicine, Eugene Bauer, who set up the multidisciplinary EB Center at Stanford" said Tang. "We have been working for a long time to get to this potential therapy into patients. We had to discover the genes and proteins involved and the responsible mutations. We then had to learn to deliver the corrected gene and grow those cells into sheets suitable for grafting."

"We could not have reached this point without the support of the EB patients and their families," said Marinkovich. Since the time of my research training in the laboratory of Robert Burgeson Ph.D., who discovered type VII collagen, I've been deeply motivated to contribute to the EB community and its very satisfying to be able to finally see this molecular therapy come to fruition".

The work is an example of Stanford Medicine's focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill. This work also benefitted greatly from the expertise of pediatric dermatologists Alfred Lane M.D., and Phuong Khuu M.D., dermatopathologist Kerri Reiger M.D., researcher Ngon Nguyen, Dermatologist investigator Paul Khavari, M.D., Ph.D., plastic surgeon Peter Lorenz M.D., and anesthesiologist Louise Furukawa M.D. The research was supported by the National Institutes of Health (grant R01 AR055914), the Epidermolysis Bullosa Medical Research Foundation and the Epidermolysis Bullosa Research Partnership.

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