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Study finds novel gene correction model for epidermolysis bullosa

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A research team led by pediatric blood and marrow transplantation experts Mark Osborn, Ph.D. and Jakub Tolar, M.D., Ph.D. from the Masonic Cancer Center, University of Minnesota, have discovered a remarkable new way to repair genetic defects in the skin cells of patients with the skin disease epidermolysis bullosa.

The findings, published today in the journal *Molecular Therapy* and highlighted in the most recent issue of *Nature*, represent the first time researchers been able to correct a disease-causing gene in its natural location in the human genome using engineered transcription activator-like effector nucleases.

Epidermolysis bullosa (EB) is a skin disease caused by genetic mutations . Patients suffering from EB – primarily children - lack the proteins that hold the epidermis and dermis together, which leads to painful blistering and sores. The condition is often deadly. The University of Minnesota is an international leader in the treatment of EB and the research that has led to new treatment approaches.

In their latest work, Osborn and Tolar's team collaborated with genomic engineer Daniel Voytas, Ph.D., of the University of Minnesota's College of Biological Sciences, to engineer transcription activator-like effector nucleases (TALENs) that target the mutation and correct the error in the skin cells of patients with the disease. Researchers then reprogrammed these cells to make pluripotent stem cells that can create many different kinds of tissues. These amended cells were then able to produce the

missing protein when placed in living skin models.

"These results provide proof of principle for TALEN-based precision gene correction, and it could open the door for more individualized therapeutics," said Osborn, an assistant professor in the University of Minnesota Medical School's Department of Pediatrics Division of Blood and Marrow Transplantation.

By using an unbiased screening method, researchers were able to take a comprehensive approach to TALEN-mapping. This strategy helped identify three other possible locations for future research and potential therapies.

"This is the first time we've been able to seamlessly correct a disease-causing gene in its natural location in the human genome using the TALEN-based approach. This opened up options we did not have before when considering future therapies," said Tolar, director of the University's Stem Cell Institute and an associate professor in the Department of Pediatrics Division of Blood and Marrow Transplantation.

The University of Minnesota Pediatric Blood and Marrow Transplant team, led by John Wagner, M.D. and Bruce Blazar, M.D., has pioneered bone marrow transplantation as the standard of care for severe EB. Tolar and Osborn hope that the individualized "genome editing" of patient cells will provide the next generation of therapies for EB and other genetic diseases.

Provided by University of Minnesota