# Scientists See Foam as Starting Point of a Path to Bedside Gene Therapy

Bioengineer Matthias Stephan developed a quick-foaming solution that he hopes could correct genetic defects—such as sickle cell disease—in bone marrow stem cells.

November 28, 2025 By Sabrina Richards and Fred Hutch News Service

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The special properties of methylcellulose foam could make it a vehicle for bedside genetic engineering, according to a proof-of-principle study from bioengineers at Fred Hutch Cancer Center.

In the paper, recently published in Molecular Therapy Methods & Clinical Development, the team used a preclinical bone marrow model to show that the foam, combined with an already-approved method to extract and concentrate bone marrow stem cells, can efficiently deliver targeted gene therapy vectors prior to reinjection of the cells into the bone marrow.

“We show that we can use our foam to genetically modify bone marrow stem cells at a very high efficiency,” said Fred Hutch bioengineer and senior author Matthias Stephan, PhD.

In his study, the foam delivered higher amounts of the gene therapy vector than either a viral or lipid nanoparticle delivery system. Stephan envisions that combining this efficiency with a bedside method of concentrating bone marrow stem cells would enable development of outpatient gene therapies aimed at correcting genetic defects in bone marrow stem cells.

## Removing hurdles between gene therapy and patients

Stephan works to make therapeutic genetic engineering more accessible to patients, by streamlining the process and bringing down costs. He has developed strategies to engineer cancer-fighting immune cells within the body or deliver them in more effective, concentrated and smaller doses. His mRNA and nanoparticle-based platform for reprogramming immune cells was exclusively licensed to Tidal Therapeutics, Inc., which was purchased by Sanofi in 2021.

Stephan’s latest strategy focuses on improving therapies designed to correct genetic defects in bone marrow stem cells.

Our bone marrow incubates the stem cells that give rise to our oxygen-carrying red blood cells,

our infection-fighting immune cells and our clot-forming platelets. A wide range of diseases can arise from genetic defects in the precursors to any of these cells.

These diseases include thalassemias (blood disorders that cause reduced hemoglobin), sickle cell disease (blood disorders in which abnormal hemoglobin warps the shape of red blood cells), hemophilia (which causes impaired clotting) and Wiskott-Aldrich syndrome, which causes immunodeficiency and low platelets.

“In theory, if you could genetically modify stem cells, you could treat all these diseases, because the stem cell differentiates into all these cell types,” Stephan said.

In 2023, the U.S. Food and Drug Administration approved the first two gene therapies that could cure sickle cell disease by fixing the underlying mutations. These therapies could cure patients of sickle cell disease, which causes attacks of debilitating pain, anemia and strokes.

But the procedures cost upwards of $2.2 million, takes about a year of one’s life to undergo, and can only be given at authorized centers, of which there are fewer than 50 worldwide. The preconditioning regimen to wipe out the defective bone marrow stem cells, ensuing immunosuppression and recovery are also very physically taxing.

“There is a critical need for having more simplified, accessible and affordable gene therapy options for patients with genetic diseases like sickle cell disease or thalassemia which affect millions of patients,” said Fred Hutch gene therapy expert Hans-Peter Kiem, MD, PhD. Kiem, who holds the Stephanus Family Endowed Chair for Cell and Gene Therapy is collaborating with Stephan to move the foam toward the clinic. “Anything we learn from these studies for sickle cell disease will also benefit millions of patients with other genetic diseases affecting bone cells.”

These hurdles are too high for most patients to clear, Stephan said.

“There’s no option for a patient to really quickly access this in a minimally life-disruptive way, like a colonoscopy: go in and go out,” Stephan said.

That’s his dream: gene therapy as an outpatient procedure that takes an afternoon and is cheap enough for anyone to get.

His other projects also focused on innovative ways to deliver the technologies that can rewrite certain cells’ DNA to improve health. Last year, Stephan had a new brainwave: foam. He and his team developed a methylcellulose-based foam that could be mixed with a gene therapy vector.

The foam is a special mixture of bubbles surrounded by thin, continuous layers of liquid called lamellae. The bubbles’ structure allows a small volume of liquid to spread over larger space and keeps it from seeping away and the thin liquid layers concentrate the vector. Together, these characteristics maximize contact between the vectors and target cells, improving the efficacy while reducing the dose.

## Bedside gene therapy?

Currently, a patient receiving gene therapy to correct sickle cell disease can expect to devote about a year to their treatment. After their bone marrow stem cells are harvested, the process during which they are cultured and genetically engineered takes about six months.

From the blood stem cell's perspective, it's an inefficient process, Stephan said.

"Most of [the stem cells] don't make it. … By the time you culture them [for months], they lose their homing property and they also lose their 'stemness,'" he said.

This means that few cells remain that can give rise to all three types of blood cells — if they make it back to the bone marrow at all.

Stephan hopes to use his foam to skip these steps and maximize the number of healthy, genetically modified stem cells that can seed new blood cells.

Like several of Stephan's other strategies, his bedside gene therapy approach mixes already-available ingredients and techniques in an innovative way. The new approach capitalizes on an easy-to-perform method to extract, concentrate and reinject bone marrow stem cells (called bone marrow aspirate concentrate, or BMAC) that's already widely used in sports medicine.

Patients undergo temporary sedation while their stem cells are harvested and concentrated before being reinjected with BMAC to help regenerate damaged tissue and joints. It only takes a few hours.

Stephan and his team showed they could add one quick step to this process, mixing the BMAC with his gene therapy-infused foam. It takes less than a minute to hand-froth the foam in sterile syringes that can then be connected to a sterile, fully enclosed BMAC system. The concentrated bone marrow stem cells can then be mixed with the foam before being reinjected.

His team mimicked stem cell reinjection using a lab-based model of bone marrow to show that BMACs exposed to the foam mixture take up gene therapy vectors (either mRNA-based nanoparticles or a virus-based vector) more efficiently than BMAC that encounter the vector in a standard liquid format. Concentrating the key gene therapy targets — the bone marrow stem cells — prior to mixing with the foam also limits exposure of non-stem cells to the foam.

"The first novelty of the paper is that it's an outpatient procedure: There's no preconditioning, no apheresis," Stephan said. "The idea is to inject genetically modified stem cells back into the bone marrow, so there's no infusion."

And unlike the standard genetic engineering approach, which requires stem cells to be cultured over weeks or months, this strategy would keep manipulation of the stem cells to a minimum, Stephan said.

“The process would be minutes and the stem cells don’t need any special cytokines to keep them alive, because they never leave their physiological environment,” he said.

To boot, the strategy would steeply reduce the amount of gene therapy vector needed to engineer a therapeutically relevant number of stem cells. It’s a matter of double concentration: the BMAC procedure highly concentrates the stem cells, making it easier for the foam-concentrated vector to reach them.

“So the advantage is really that you don’t need as much gene transfer vector. And you don’t systematically expose the patient to the vector, to potential off-target editing,” Stephan said.

If successful, the strategy wouldn’t need expensive equipment, time or hospital real estate like the clean rooms in which cells currently undergo genetic engineering. This would make it easy to adopt in any community hospital, Stephan said.

## Next steps

Stephan is working to bring his approach closer to the clinic by testing in more-relevant animal models and by using vectors that can target specific cell types.

“Specificity is always important to minimize any off-target effects, and the ability to incorporate more specific targeting of the relevant cells populations with Matthias’s foam-based therapy will be an important next step,” Kiem said.

Stephan cautioned that even if successful, the approach would not be appropriate for every genetic engineering application. In this case, altering the DNA of the stem cells means that all their progeny will have the same DNA alterations, so the risk and benefit must be worth it, he said.

Applications in which cells only temporarily produce a protein or where there’s no need to alter the DNA of a whole cell lineage, such as with certain cancer cellular immunotherapies, should not get this treatment.

“This would be a situation where you’re aiming for a cure,” Stephan said.

The work was supported by the National Institute of Diabetes and Digestive and Kidney Diseases, the Fred Hutch Immunotherapy Initiative and the Bezos Family.

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