

'Gene therapy in a box' effective, reports Nature Communications

October 20 2016

A table-top device that enables medical staff to genetically manipulate a patient's blood to deliver potential new therapies for cancer, HIV and other diseases would eliminate the need for multi-million-dollar "clean rooms," making gene therapy more possible for even the poorest of countries.

The so-called "gene therapy in a box," developed by scientists at Fred Hutchinson Cancer Research Center, delivered modified blood [stem cells](#) that were as good as—or better—than those manufactured in highly regulated clean rooms—and required less than half the staff, according to a study that will be published on Oct. 20 in *Nature Communications*. The adapted cells also successfully repopulated the blood system when tested in two different animal models, the study noted. It hasn't been tested in humans.

The portable device suggests a solution to one of the most vexing challenges of gene therapy: How to make these emerging, high-tech treatments accessible and affordable beyond a handful of specialized research centers to clinics worldwide.

"We either had to think about how to build million-dollar-infrastructure and clean-room facilities in clinics all around the world, which is not feasible, or we had to think about simplifying this process into what I originally envisioned as a black box," said Fred Hutch researcher Dr. Jennifer Adair, the study's lead author. "This was the first proof that 'gene therapy in a box' could work."

Gene therapies or cell therapies that involve genetically modified cells today are available at only a limited number of research centers that can afford the necessary technology and the highly trained staff. Adair said there are a dozen or so worldwide.

No [gene therapies](#) are approved yet for use in the United States. But thousands of patients with at least 15 or 20 inherited or infectious diseases and cancers are being treated with experimental therapies, and many are showing promise.

The semi-automated "point of care" delivery system developed by Adair's team using instrumentation available from Miltenyi Biotec reduces the space required to produce the modified cells from 500 square feet to less than 5 square feet and the staffing from five or 10 people to one or two, according to oncologist Dr. Hans-Peter Kiem, a Fred Hutch and University of Washington cell and gene therapy researcher and the paper's senior author.

"This is truly transformative," Kiem said. "It will change the way we manufacture and deliver cell and gene therapy products and will have a major impact on making stem cell gene therapy and transplantation and likely also immunotherapy available to patients with genetic diseases, HIV and cancer worldwide."

The "box" itself costs about \$150,000 to purchase—a one-time investment that would be used for thousands of patients. An individual kit specific to the disease being treated would cost about \$26,000, Adair said. Though not inexpensive, the box could drive down costs of gene therapy because it requires less infrastructure and staffing. Even putting aside the clean-room and other infrastructure costs, it could be less than what cell-based gene therapy treatment costs research institutions now—between \$38,000 and \$55,000, according to Adair.

What's more, the cost of what could be a one-time treatment compares favorably to lifetime care for many diseases. Take HIV, for example: lifetime treatment with antiretroviral drugs to suppress the virus is estimated to cost about \$600,000.

An idea takes root

The innovation can be traced to 2008, when Kiem hired Adair to run a clinical trial for a gene therapy to treat glioblastoma, the deadliest form of [brain cancer](#). The study called for extracting a patient's [blood stem cells](#) and inserting a special "resistance" gene designed in the laboratory to protect [blood cells](#) from damage by chemotherapy drugs. Infused back into the patient, the resistant cells would multiply and allow glioblastoma patients to receive higher doses of the cancer-killing chemo than they otherwise could withstand.

Stem cell-based gene therapy involves removing blood or bone marrow from patients, separating out the stem cells—which give rise to all blood and immune cells in the body—and using a deactivated virus to transfer genetic instructions for treating or preventing a disease into the cells. (Scientists also are investigating the use of targeted nucleases such as CRISPR to edit genes, but most gene therapies now being tested in humans rely on viral vectors.) After being infused back into the patient, the stem cells propagate new cells that carry the modification.

For Adair, the idea for gene therapy in a box was planted in 2009. She was on her way home in a taxi at 1 a.m. after having delivered genetically modified cells to the first patient in the newly launched brain cancer trial. Snatching only a few hours for sleep, Adair spent most of four days in a strictly regulated clean room where every bathroom break meant having to wash and suit up again in sterile clothing. The 96-hour marathon of time-sensitive, near-constant work left her physically and mentally exhausted.

"How are we ever going to be able to do this for more than one cancer patient a week?" she remembered thinking. "It just seemed harrowing."

Fast-forward five years, and blood stem cell-based gene therapy, though still experimental, was exploding. Patients in that early-phase brain cancer trial were living months or even years longer than most people with glioblastoma survive. Adair was running additional clinical trials, including one for a rare blood disorder called Fanconi anemia, and Kiem got a grant to investigate cell and gene therapy for curing HIV, the virus that causes AIDS—once considered unimaginable.

It was at a 2014 conference on that HIV cure research that Adair had her second epiphany, this time about costs.

More than 25 million of the estimated 36.7 million people worldwide living with HIV are in sub-Saharan Africa, according to the World Health Organization. No country there could support multi-million-dollar clean rooms or afford the sky-high costs of whatever therapies might come out of them.

Adair remembers sitting at the conference and thinking, "If we cure HIV in a patient in the U.S., how are we ever going to get this to the countries that need it?"

'Why not now?'

Adair had heard other gene therapy researchers dismissing questions about accessibility by saying, "First we have to show gene therapy works, and then we'll worry about that."

She wasn't buying it.

"Why not now?" she remembered thinking. "Is there a way we could do this, in a simplified fashion?"

With Kiem's encouragement, when Adair became head of her own lab in 2014, she used her Fred Hutch start-up funding to work on finding a way to make these still experimental therapies available and affordable wherever they are needed.

In the brain cancer clinical trial, Adair used a first-generation device made by Miltenyi Biotec to separate the stem cells from other blood cells. It involved adding specialized metal beads to bone marrow removed from patients, then used a magnet to pull out the stem cells.

But when she started working on a clinical trial for Fanconi anemia, a rare genetic disorder that leads to bone marrow failure, she needed something faster. Such patients have a tiny number of stem cells to begin with, and those are very susceptible to damage from exposure to ambient oxygen. To limit their exposure time, Adair had to find a way to speed up the process of separating and modifying the cells.

Serendipitously, Miltenyi had just sent over a demonstration model of a second-generation machine that automated and sped up the bead and magnet process and also happened to be capable of processing the exact volumes of bone marrow Adair needed for the trial. Working with Miltenyi's Tim Waters, Adair directed reprogramming of the device to see if it could meet her timetable. When initial tests worked, the Hutch bought the new machine and got federal approval to use it in the Fanconi anemia trial, treating the first patient in 2014.

The whole time she was thinking, "I want to make this device do everything."

The Miltenyi machine, called the CliniMACS Prodigy™, was small

enough. It was a closed system, meaning no exposure to ambient air. It could be automated. Its interface was similar to an apheresis machine, another clinical device that separates blood into its components and which hospital staffs in many developing countries already are trained to use.

Adair shared her grand vision with Waters, who is a co-author on the Nature Communications paper. It called for reconfiguring and reprogramming the device to do all of the steps, including the clean-room jobs of adding the viral vector and removing residual reagents, then developing components specific to each disease that would be available in "kits" and kept in pharmacy freezers. Included in each kit would be disposable tubing to carry the patient's blood cells from a sterile bag into the machine. A nurse would attach the bag to the machine, add chemical reagents from the kit to pull out the stem cells, nutrients to support the growth of those cells and the viral vector engineered to do the gene transfer for that disease. Additional disposable tubing would carry the modified cells to a second sterile bag that would go right into the patient's IV.

Reconfiguring the device meant tedious calculations, mechanical tests and relearning physics principles she'd forgotten from college—things she hadn't imagined ever doing, said Adair.

Adair and her team, which includes other Fred Hutch researchers and scientists at Washington State University, spent the last 18 months developing the device, comparing the products produced to those manufactured in clean rooms and testing the modified cells in animal models, key prerequisites to obtaining U.S. Food and Drug Administration consent to test the products in humans. She is hoping to send a box to a clinic that is not in a high-tech research center to test its ease of use.

"There are probably 1,000 modifications that could improve how efficient it is," she said. "But by making a platform that doesn't require you to be at one of the expert academic institutions for gene therapy, we're facilitating more people being able to explore these processes and potentially incorporate their own changes."

More information: Jennifer E. Adair et al. Semi-automated closed system manufacturing of lentivirus gene-modified haematopoietic stem cells for gene therapy, *Nature Communications* (2016). [DOI: 10.1038/ncomms13173](https://doi.org/10.1038/ncomms13173)

Provided by Fred Hutchinson Cancer Research Center

Citation: 'Gene therapy in a box' effective, reports *Nature Communications* (2016, October 20) retrieved 2 May 2024 from <https://medicalxpress.com/news/2016-10-gene-therapy-effective-nature.html>

<p>This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.</p>
--