

Cell therapy for all

“Since gene and cell therapies first started to emerge, people have believed that they will only ever be available to people in the developed world. But what if you could make them for everybody? What if it was possible to modify one cell, and make it available to put into anybody?”

Chad Cowan, Ph.D., Assistant Professor of Medicine and Harvard Medical School and Beth Israel Deaconess Medical Center. Leader of the HSCI Diabetes Program



Harvard Stem Cell Institute (HSCI)

Our mission is to discover cures for human diseases. We aim to:

- Stimulate healing in patients by harnessing the potential of stem cells
- Create targeted treatments by combining new gene- and cell-based therapies with traditional medicines
- Accelerate drug discovery by developing novel stem cell-based tools.

Our network of over 1,000 biomedical researchers, from across Harvard and its eight affiliated hospitals, is advancing stem cell biology and translational medicine in a way no other single entity can.

Chad Cowan is on a quest for the **universal donor**, which would make cell therapy available to populations – not just individuals.

- Harvard scientist Chad Cowan aims to make off-the-shelf cellular products, and democratize access to new medicines.
- His lab is working to make cellular therapies that can work for anyone, not just a single patient.
- Their ambitious goal is to modify therapeutic cells that can be transplanted into many people, without being rejected.

Ultimately, the goal of our research is to help people. For the past seven years we’ve been trying to do something that people say is impossible: making cells into pharmaceuticals.

The first wave of medicine was small molecules. The miracle of small molecules is that you can produce them cheaply, and pretty much anyone can take them. So you can take any small-molecule drug that works, manufacture it, and deploy it worldwide.

In Africa, the HIV epidemic is continuing to spread, and we’re treating

it as best we can with the antiretrovirals that were developed here in the U.S. And that's possible only because small molecules can be sent around the world.

What kind of medicine are you working on?

I've been part of a second wave of medicine, which is gene and cell therapy. Since these therapies first started to emerge, people have believed that they will only ever be available to people in the developed world. I can understand that, because there are these seemingly huge barriers to the democratization of cellular medicines.

The main barrier is the way we think of cellular medicine right now, which is like a designer dress, or tailored suit. We harvest cells from a patient, do something to those cells, and put them back in the same patient. Custom-made therapeutics like that are difficult to scale, or to make in any kind of readily accessible form.

Anything so highly customized will necessarily be inaccessible to most people.

What is a "cell therapy"?

A great example is immuno-oncology, or CAR-T therapies, which is a cellular therapy that you hear a lot about. CAR-T is where you take a patient's own immune system and unleash it on the cancer. That sounds really exciting, and it is! It's one of the first times in medicine where we're seeing recovery rates for some cancers at 90% or higher. We're taking patients who had no other hope for survival, training their T cells to attack their tumors, and giving them a cure.

That's also true for the first gene therapies, where we take cells from patients who are missing a gene, put the gene back in those cells, and put the

cells back in the patient. The best example of that is a rare immunodeficiency that was the subject of "The Boy in the Plastic Bubble" - a movie with John Travolta. These kids are born without an immune system, and as a result they die relatively young, usually from common infections.

But one clinical trial of gene therapy saved 40 of these kids. They took out their bone marrow cells, transduced them with the missing genes, and put the bone marrow cells back in. The kids are cured, for the rest of their lives, of this immune deficiency that would have killed them.

Both cases involve bespoke treatment for individuals, using their own cells as medicine. But the process by which you take them out, manipulate them, check them, and put them back in is incredibly time consuming, laborious and expensive. It costs thousands of dollars per patient.

"At the end of the day, I want to say, here are 40 kids who are alive today because of research we were a part of. That's success. That's what we're doing it for."

Is it possible to democratize access?

So we started asking: What if you could do something like that for everybody? What if it was possible to modify one cell, and make it available to put into anybody?

Everybody says it's impossible, because your whole immune system is developed to tell the difference between you and somebody else. This is why kidney transplantation is so difficult - we're always having to find 'matched' donors, because your whole body is set to reject tissue that isn't yours.

It wasn't until recently that we started to have sufficient information about the immune system to even begin to fathom how you might utilize that information, and circumvent the system to create a cell that you could potentially put into all people.

That's been the goal of our research.

Has it worked before?

The most ambitious example is HIV. It has been spread across the world, and wealthier countries have been able to contain it. But we're just treating the symptoms of the disease, not curing it. There's been a race to identify the equivalent of a vaccine like we've used for polio. But time and again, efforts to make a proper antiretroviral for this disease have failed.

The reason for this is scientifically interesting, and difficult. You would have thought that if it's a virus people were able to overcome naturally, we would have found people who were resistant to the virus already. In fact, we weren't able to find those people until around 15 years after the initial discovery of HIV.

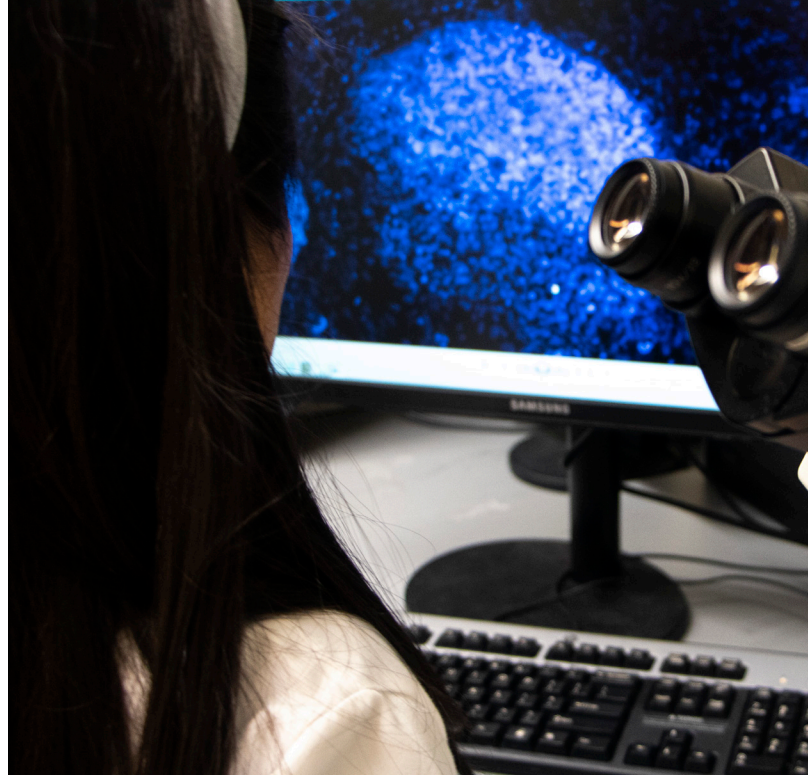
Actually, when we first realized what the virus looked like, we decided as scientists that it was going to be impossible. Its structure was so complex that we thought no antibodies could ever be made that would stick to it and neutralize it.

It turns out we were wrong. Of course Mother Nature found a way. It's just incredibly rare - one person out of many millions can make antibodies to HIV that are broadly neutralizing. Their immune systems work on overdrive to create a huge array of antibodies until they make one that's the right shape. It neutralizes the virus, and they become immune to HIV.

When you or I produce antibodies to target viruses, our antibody-producing cells go through this rapid shape-shifting process called hypermutation. They make mutations in the genes that produce antibodies, so they keep making different shapes until one locks on to the infecting virus and stops it. A person who can make antibodies against HIV? That person's antibody-producing cells are shape-shifting over 10 times more than anyone else's.

How can we imitate that?

It's going to be hard to make a vaccine for everyone that would activate this kind of hypermutation rate. But, well, why couldn't we do that? What's the cell involved here?



Say I got the polio vaccine as a kid, so I'll never get polio the rest of my life. That's because my immune system produces an antibody that neutralizes the polio virus, which is much less tricky to do than HIV. The cells that produce the antibody will stay in my bone marrow and keep secreting an antibody - so when I'm 80, you'll see I'm still making anti-polio virus antibodies.

So what if we could make an antibody-producing cell that makes anti-HIV antibodies from a cell we could transplant into anyone? If we could do that, we could protect the world from HIV. That's a bold idea, that we could use a cellular therapy to combat diseases that affect millions of people.

That's our goal: making off-the-shelf cellular products so that you could democratize access to medicines.

What do you hope to achieve?

At first, I wanted to make a difference in human health - make a person suffering from a disease, better. But why not cure a person entirely? Why not eliminate a disease?

I would be truly satisfied if I could take any disease, even one that only 50 people have, and find a cure. At the end of the day, I want to say, here are 40 kids who are alive today because of research we were a part of. That's success. That's what we're doing it for.