

# Creating a Path for Gene and Cell Therapies to be Accessible to Patients

by **Helen Albert** Senior Editor

Cell and gene therapy have surprisingly long histories. Cell therapy has existed in the form of bone marrow transplant, used to treat cancers and other conditions, since the late 1950's, although it only came to prominence with the approval of the first chimeric antigen receptor (CAR) T-cell cancer therapies (Kymriah and Yescarta) in 2017.

The first gene therapy was given to a young girl with severe combined immunodeficiency in 1990. While this and other early treatments were successful, patient deaths a few years later sent the field into a tailspin. It took until 2012 for the first gene therapy—Glybera—to be approved in Europe for treatment of the rare disease reverse lipoprotein lipase deficiency (LPLD).

Driven by fast paced developments in molecular medicine and innovation in recent years, there are now 28 cell and gene therapies approved by the U.S. FDA. According to the Alliance for Regenerative Medicine, six new therapies were approved in the U.S. or Europe in 2022, with five expanding their indications or geographies. There were also over 2,000 ongoing clinical trials of new therapies taking place around the world at the end of last year.

However, many challenges still need to be overcome before gene and cell therapies can become mainstream. These include making sure healthcare providers, payers, and regulators have all the right information about these complex treatments in order to help break down barriers to patient access. Technology innovations such as allogeneic 'off the shelf' T-cell therapies can also go a long way toward getting these therapies to more people.



Rachel Salzman  
global head of corporate strategy  
Armatus Bio

## Breaking down diagnostic barriers

A key problem in the field is making sure that therapies get to patients—even after they have been approved. Glybera, also known as alipogene tiparvovec, is a cautionary tale for this issue. Despite being the first gene therapy to get approval in Europe, it was withdrawn from the market shortly afterward, and only 31 people were ever treated

with it. There were multiple reasons for its withdrawal, including high costs for manufacturers, patients, and payers; the rarity of the disease; and failure to receive approval from the U.S. Food and Drug Administration (FDA).

Rare diseases are one of the main focuses for gene therapy manufacturers around the world. Accordingly, Rachel Salzman, the global head of corporate strategy at Armatus Bio, a U.S. biotech using gene therapy and RNA silencing to target rare neuromuscular disorders, says that improving diagnosis of rare diseases will help improve access to gene therapies.

"Newborn screening is very variable in terms of the number of diseases that are screened for when a baby is born, based on



whatever state the baby was born in,” she tells *Inside Precision Medicine*. Better screening and diagnosis is needed, she says, and “then of course, the idea is to determine what’s going to be the best treatment.”

Newborn screening is increasing its reach, with diagnostic whole genome sequencing of newborns becoming more common, but if there is not already an approved therapy for a condition, it will not usually be included in standard heel prick blood testing of newborns. This can make finding patients who might benefit from gene therapies difficult.

Allyson Berent, the chief science officer at the Foundation for Angelman Syndrome Therapeutics (FAST), says, “we have



Allyson Berent  
chief science officer  
Foundation for Angelman Syndrome  
Therapeutics (FAST)

500,000 kids predicted to have Angelman syndrome in the world and we’ve identified under 10,000. To help remedy that, we’ve launched multiple newborn screening efforts, multiple diagnostic efforts for people that are under diagnosed, misdiagnosed, or not connected around the world.” There are currently no approved therapies for Angelman syndrome, a rare neurogenetic disorder, but Berent says the organiza-



Rachel Haurwitz  
co-founder, president, and CEO  
Caribou

tion is helping to advance 13 possible therapies from mouse to humans, with numerous clinical trials underway or starting in the next 18-24 months.

In the case of metachromatic leukodystrophy (MLD), an inherited rare lysosomal storage disease that is often fatal by the age of 5 years if left untreated, there is now a therapy: Libmeldy, the first hematopoietic stem cell gene therapy to be approved in Europe. But Robin Kenselaar, senior vice president and general manager, EMEA, at Orchard Therapeutics, a U.K.-based biotech that owns the drug, explains that timing is everything when it comes to its administration. “There is a window where patients can benefit from Libmeldy and if that window passes, then there is no option for these patients,” he says. Currently, many of the patients who receive a diagnosis in time to benefit do so because they have an affected sibling—but the sibling’s disease is too advanced to be treated. “Finding these patients early—I think that’s one of the key challenges to really unlock the full potential of

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gene therapy,” Kenselaar says.

### Reducing complexity and increasing treatment speed

The cell therapies that are currently available, such as autologous CAR T cell therapies for blood cancer, often take too long to get to patients, and are complex and expensive to produce. To solve these problems, many companies are currently trying to bring an allogeneic, “off-the-shelf” CAR-T cell therapy to market.

In December last year, U.S.-based Atara Biotherapeutics achieved a world first when it received EMA approval for its allogeneic T cell therapy, made with donor cells, for treatment of Epstein-Barr virus-positive post-transplant lymphoproliferative disease.

“We’re focused on allogeneic, or ‘off-the-shelf’ cell therapies for a few reasons... and I’d say the largest of those is patient access,”

Another company in this space is Caribou Biosciences, which boasts CRISPR Nobel prize winner Jennifer Doudna as a co-founder and is using CRISPR to help create allogeneic CAR-T and CAR natural killer (NK) cell therapies. “We’re focused on allogeneic, or ‘off-the-shelf’ cell therapies for a few reasons... and I’d say the largest of those is patient access,” explains Rachel Haurwitz, another co-founder and the current president and CEO of Caribou. “The autologous patient-specific therapies are an incredible proof of the power of the human immune system. But manufacturing one dose for each and every patient from their own bespoke material is not something that can scale to serve the much broader patient population that could benefit from these kinds of cellular therapies.”



Sarah Emond  
executive VP and COO  
Institute for Clinical and Economic Review

If allogeneic cell therapies become more common, they have the potential to improve access for patients in a number of ways. First, getting the therapies should become faster, as there will not be a treatment delay while the therapy is created. Second, the costs will go down. Third, the T cells used to create the therapy will not be exhausted or damaged, which is a common problem using the autologous approach.

Finally, an allogeneic approach could actually improve patient quality of life. “In the autologous setting, because it’s the patient’s own cells that are being used to manufacture the therapy, the patient has to be at the clinical site to have their blood drawn, so that’s one trip. Then they typically have to receive lymphodepletion ... and then they have to receive their therapy and be at the clinical site for some period of time afterwards. It’s ultimately several different visits,” says Haurwitz.

“The allogeneic approach starts to meaningfully take things off that list. No longer does the patient have to go for their blood



Caroline Horrow  
researcher  
Regulation, Therapeutics, and Law  
Harvard University

to be drawn. They have to show up for the lymphodepletion and then for receiving the therapy—at least, that’s our approach.”

The main issue with allogeneic cell therapies is the potential for rejection. To try to prevent this, Haurwitz says, “we’re doing what we call immune cloaking, basically trying to protect the CAR T from the patient’s immune system.”

Due to the specialized expertise and lab facilities needed to create cell and gene therapies, particu-

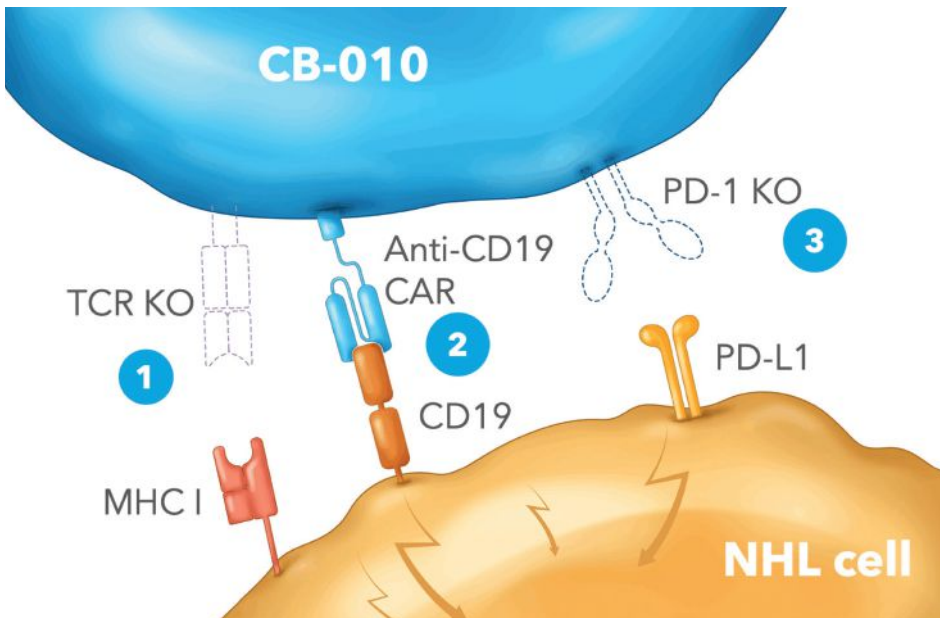
larly autologous treatments, they are often created at specialist companies or academic centers of excellence. This can make access difficult for patients living in smaller cities or remote regions. Centralization of manufacturing and development of advanced therapeutics can also impact rare disease treatments. “We don’t have qualified treatment centers in all countries in Europe... We work with centers that have capabilities on the transplant side, so they need to be accredited for stem cell transplants and have the facilities to handle cryopreserved cells. The centers also need to have expertise in neurometabolic diseases, so that this is a very select group,” notes Kenselaar.

However, some moves are being made to make cell and gene therapy access more decentralized. For example, a company called Orgenesis in the U.S. is trying to make it easier for cell and gene therapies to be prepared on site. They can install mobile labs as bus-like units to produce autologous cell and gene therapies at non-specialist hospital centers when needed.

### Navigating pricing and payment

Gene and cell therapies are not cheap to produce and have commensurately high price tags. Although these therapies have attracted a lot of negative press around pricing—for example, Glybera was dubbed the ‘million-dollar drug’ by media outlets—assuming they have long-lasting or curative effects, these therapies can reduce healthcare costs in the long run.

“It’s difficult to get over the initial price hurdle—our list price in Europe has been announced at €2.875M—so if you just look at that in the context of one year’s healthcare budget, that’s really difficult,” concedes Kenselaar.



CB-010 is an allogeneic anti-CD19 CAR-T cell therapy engineered using Caribou Biosciences Cas9 CRISPR hybrid RNA-DNA (chrDNA) technology. CB-010 is the first allogeneic chimeric antigen receptor (CAR)-T cell therapy in the clinic with a PD-1 knockout (KO), a genome-editing strategy designed to improve antitumor activity by limiting premature CAR-T cell exhaustion. CB-010 is being evaluated the ANTLER trial in patients with relapsed or refractory B cell non-Hodgkin lymphoma (r/r B-NHL).

“For a lot of small payers, paying for even one patient in their covered population could have a really big impact on their budget, especially when a lot of them are constricted to annual budgets,” says Horrow.

“The other big challenge they face is the clinical uncertainty of cell and gene therapies, that [the therapies’ developers are] promising this long-term durable effect, but there’s limited evidence for that at the time that these therapies are approved.”

Some possible options for health insurance companies to cover cell and gene therapies include paying in installments rather than all at once; paying for performance, meaning that money is returned if the therapy doesn’t work; re-insurance, where a payer itself is insured against having to pay out for a cell or gene therapy; and a risk-pooling model where payers join together to spread the risk.

“If, however, you consider the benefit that this drug can bring over time for patients, then it becomes digestible.”

Sarah Emond, executive VP and COO at the Institute for Clinical and Economic Review, which has assessed the cost effectiveness of many cell and gene therapies, notes that “we have a healthcare system that reacts strongly to high prices, without thinking about value.”



Carlo Russo, MD  
CMO, Genenta Science

She thinks that re-assessing overall healthcare costs to better consider value can help integrate these kinds of therapies into healthcare systems. “If we are going to pay fairly for a gene therapy, and we’re going to say that the price is fair at \$2 million, because of all of the benefits it brings to patients, then that means we need to stop overpaying for things that are bringing less benefit to patients.”

Paying millions of dollars for one therapy is daunting for payers and has caused a lot of discussion in the sector about how best to address the issue. Caroline Horrow, a researcher based at Harvard University in the Program on Regulation, Therapeutics and Law, has studied different payer strategies that can be used to help get therapies to patients while at the same time keeping insurance companies working smoothly.



Robin Kenselaar  
senior vice president and general manager  
EMEA, Orchard Therapeutics

“The one I’m watching is a program of aggregating all of the cell and gene therapy spend into one entity,” says Emond. “Express Scripts and Cigna are trying this with a product they call Embarc. The idea there is a purchaser, so an employer or a health plan, pays a standard per-member, per-month fee. Then if any of my employees or members get eligible for any of the gene or cell therapies that are included in the Embarc program, I don’t get

charged anything else, they just get treated.”

Salzman supports providing education for payers on new cell and gene therapies and encourages early conversations with companies and researchers that are developing them to avoid problems later on. She has been helping to run a workshop to help support this aim at the American Society of Gene & Cell Therapy annual conference for several years.

“Payers want to understand more about the data and more about the value that the data bring,” she explains. “The good payers have said, ‘come to us early and often, maybe even when you’re designing those pivotal studies.’”

Berent advocated to also figure out ways to reduce costs in the

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earlier stages of drug development because developing these drugs can be prohibitively expensive for these rare diseases. “A lot of people said, ‘it’s a recipe book, you must do rodent, you must do monkey, you must do this, you must do that.’ I’d like to push back and say, ‘why? What information are you gaining?’ ... Really pushing back on what it should cost to develop a drug.” Another question she asks is why the virus vectors used to deliver many gene therapies are so expensive: “What can we do as a society to change that?”

### Future directions

The cell and gene therapy field continues to grow, with around 10 regulatory decisions expected this year in the U.S. alone. For example, two gene therapies for sickle cell disease are awaiting approval decisions, as well as the first gene therapy for Duchenne muscular dystrophy, and it seems likely that the first-ever CRISPR gene editing therapy will be approved.

“We are in a much better space today in the manufacturing sense than 10 years ago,” says Russo. “The science is moving really, really fast, and I see manufacturing improvement in terms of the quality of the product, the speed, and so on.”

But the high cost of these therapies and ensuring access to them may make wealth-related disparities in access to healthcare even wider than they are already. For example, the genetic testing used to diagnose a child can cost parents \$1,000, notes Salzman. “A lot of people can’t do that. Why should the people who have \$1,000 get to diagnose their child, and the people who don’t have \$1,000 don’t? That’s just completely unacceptable.”

Then there’s the problem of making the treatments palatable to payers. “If we don’t figure out how to implement these reimbursement schemes to make it feasible for payers to cover cell and gene therapies, they’re just going to find other ways to get around it to make it more affordable, either by not covering them altogether, or by trying to restrict access as much as possible,” says Horrow.



Dr. Berent’s daughters from Left to Right (Kai age 10, Quincy age 8 and Piper age 6). Quincy lives with Angelman syndrome and resides in New York City.

Things are improving, but there are still challenges that need to be overcome to reach more patients. This will become ever more important as larger patient populations—for example, those with sickle cell disease—become eligible for treatment. ■

**Helen Albert** is senior editor at *Inside Precision Medicine* and a freelance science journalist. Prior to going freelance, she was editor-in-chief at *Labiotech*, an English-language, digital publication based in Berlin focusing on the European biotech industry. Before moving to Germany, she worked at a range of different science and health-focused publications in London. She was editor of *The Biochemist* magazine and blog, but also worked as a senior reporter at Springer Nature’s *medwireNews* for a number of years, as well as freelancing for various international publications. She has written for *New Scientist*, *Chemistry World*, *Biodesigned*, *The BMJ*, *Forbes*, *Science Business*, *Cosmos* magazine, and *GEN*. Helen has academic degrees in genetics and anthropology, and also spent some time early in her career working at the Sanger Institute in Cambridge before deciding to move into journalism.



Dr. Berent and Quincy, her daughter who lives with Angelman syndrome, frolicking in the ocean waters, an activity that brings tremendous joy to Quincy and her family.