The CRISPR Revolution:

How Gene Editing Technology is Accelerating Cell and Gene Therapy

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After more than two decades of successes and failures, the promise that cell and gene therapy has held for so long is finally a reality. As scientists gained, and continue to gain, a better understanding of the human genome and how to use the body's systems to fight disease, we now have therapies that have made it through clinical trials and patients whose lives have been transformed.

Today, patients with certain types of lymphoma and leukemia achieve long-lasting remission from CAR T-cell therapies such as Yescarta and Kymriah.[1] A gene therapy called Luxturna has been shown to improve vision for people with a rare degenerative eye disease called retinal dystrophy.[2] And a young woman with sickle cell anemia moves through life without pain after receiving treatment based on gene editing.

The promise of cell and gene therapy to treat the root cause of disease has led to a groundswell of innovation. Re-engineered viruses and non-viral vectors, which are used to deliver therapies, have mitigated some of the adverse reactions experienced in earlier studies. Patients receiving these therapies are experiencing greater benefit with fewer adverse reactions.[3]

A lot of this progress has been enabled by the precision genome engineering tool, CRISPR.

"Saying CRISPR has revolutionized gene therapy is not hyperbole," says Scott Burger, MD, principal for Advanced Cell and Gene Therapy, a consulting firm specializing in cell and gene therapy product development. "Most gene therapy has focused on gene replacement until recently. CRISPR allows one to potentially approach gene therapy from the standpoint of editing: correcting mutations that cause disease."

Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) gene editing promises to advance the field further, faster. Researchers have used CRISPR gene-editing technology to modify plant species, as a tool for molecular testing, and to develop models to study disease. Most recently, researchers have applied CRISPR to develop faster, more accurate COVID-19 screening methods as well as cell and gene therapies, all with exciting results.

"CRISPR is part and parcel now of pretty much every major cell therapy player out there, whether academic or industry," says Ethan Brookes, Cell and Gene Therapy Specialist for Synthego, a genome engineering company based in the San Francisco Bay Area. "It's part of the drug development process from early-stage R&D to, in many cases, all the way into the clinic."

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Scott Burger, MD
Principal for Advanced Cell and Gene Therapy

Although CRISPR presents new questions for regulatory agencies, as well as serious ethical issues related to germline modification, CRISPR gene-editing technology may solve problems that have plagued cell and gene therapy development since its inception, as well as issues that have sprouted during the recent cell and gene therapy boom.

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Ethan Brookes

Cell and Gene Therapy Specialist at Synthego

CRISPR Comes of Age

CRISPR is a family of DNA sequences and part of the bacterial immune system in nature.

The application of CRISPR as a customizable gene editing system isn't even 10 years old — Jennifer Doudna and Emmanuelle Charpentier first reported the biochemical action of the CRISPR system in 2012[4] — but it's already proven to be an efficient tool for cell and gene therapy research. Researchers are using CRISPR-Cas9 to precisely edit DNA strands with the help of programmable guide RNA and Cas9 nuclease. In medicine, this technique could enable essentially editing mutations in genes associated with cancer, auto-immune conditions, rare disease, and more.

According to The National Human Genome Research Institute, one study found CRISPR to be six times more efficient than gene-editing tools zinc finger nucleases (ZFNs) or transcription activator-like effector

nucleases (TALENs) in creating targeted mutations to the genome.[5] Large-scale genomics projects that once took several years and tens of thousands of dollars can now be completed at a fraction of time and price. Another advantage of CRISPR over ZFNs or TALENs is convenience due to its use of an easily programmable guide RNA.

Using CRISPR to Understand and Treat Diseases

In the few years since scientists first tested CRISPR therapy in a human (2016), CRISPR has been shown to have the potential to develop safer and more effective CAR T-cell therapies as well as treat sickle cell disease. It's also being explored to develop targeted therapies for liver disease, neurodegenerative diseases, Duchenne muscular dystrophy, and AIDS.

A study published in 2019 found a combination of antiviral therapy and CRISPR gene editing eliminated HIV in nine out of 23 mice that received the combination therapy.[6] If future studies confirm these results, the combination therapy could lead to a cure for the disease.

CRISPR also shows promise in rare disease treatment in both children and adults. “This is an area where you can provide meaningful, life-changing therapeutics,” says Beckinam Nowatzke, MSc, RAC, CBA, Quality Leader for GMP and RUO sgRNA for Synthego. “Many of the powerful therapeutics developed are too toxic for children, and many cell and gene therapies are too expensive to research for small populations. “CRISPR lowers the cost of research and development. The ability to find and target the genetic sequence causing illness in an orphan population presents a huge opportunity for CRISPR.”

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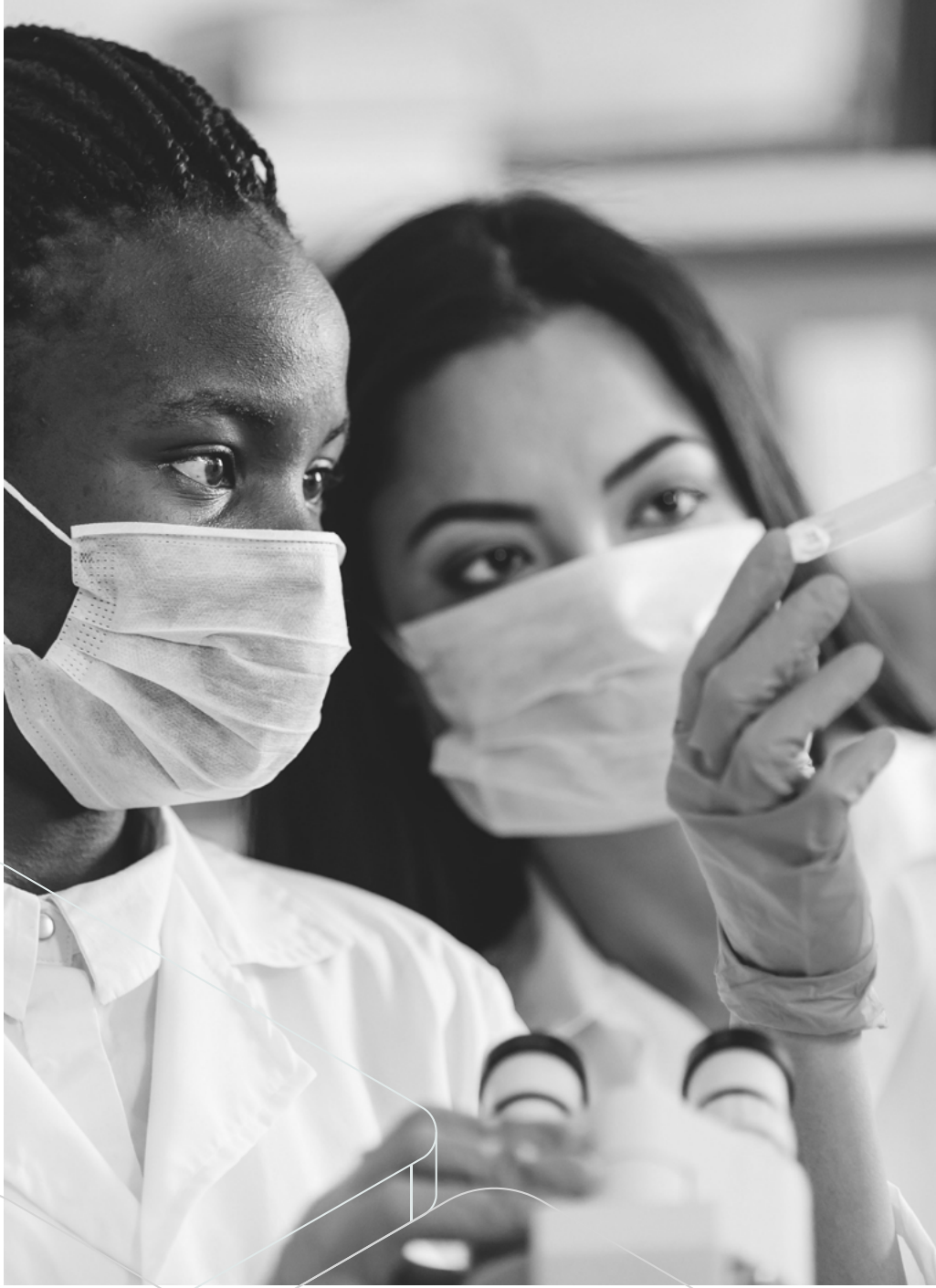
Cell and Gene Therapy: The CRISPR Solution

While cell and gene therapy hold promise because of their curative powers, the pharma/biopharma industry must address a few issues before they can reach full potential. Scalability and manufacturability top the list: Pharma and biopharma companies rely on CMO/CDMOs to develop these therapies, but few have the capabilities required for cell and gene therapy development. Regulatory support and the ever-present cost conundrum must also be addressed.



Circumventing the CDMO

The groundswell of cell and gene therapy development means increased demand for viral and non-viral vectors, as well as the manufacturing capability to produce those products at scale. While facilities are emerging, to date it's not enough to match the pace of innovation.

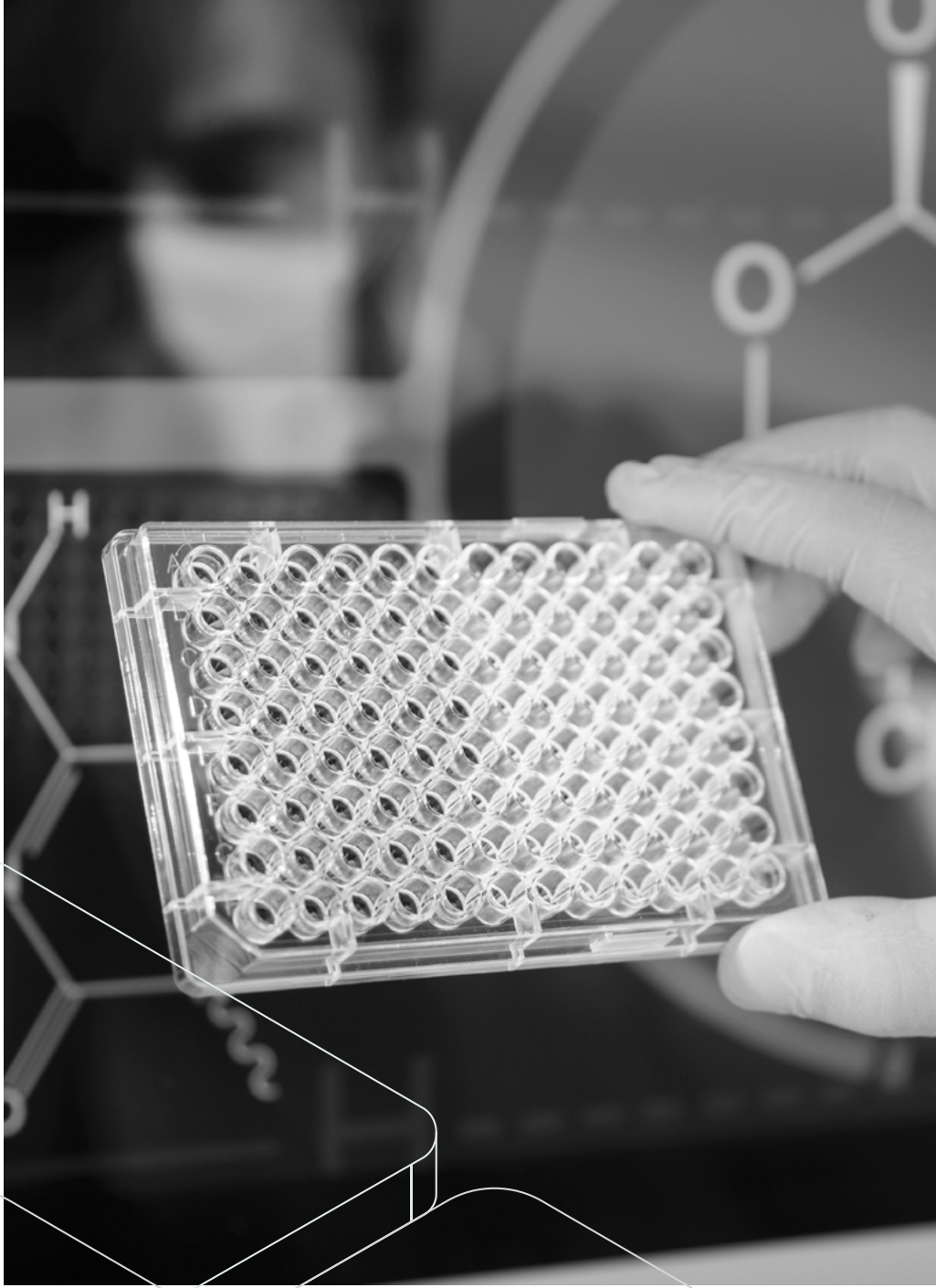
To date, the FDA has received more than 900 investigational new drug (IND) applications for cell and gene therapies. Currently, more than 3,000 therapies are in development according to ClinicalTrials.gov. Between 1997 and 2010, the FDA approved two: cell therapy Carticel (1997), and immunotherapy Provenge (2010).

While manufacturing at scale remains an issue once therapies move into late-phase studies, CRISPR allows cell and gene therapy developers to go farther on their own before they require a CMO or CDMO partner. Companies such as Synthego have expanded from a supplier to more full-service partners, collaborating with companies that want to use their guide RNAs for both nonclinical and clinical research.

CRISPR's efficiency also allows researchers to accomplish more on their own. Where ZFN and TALEN gene editing took months or years to make one edit, CRISPR does the job in weeks or days. "You can get the reagents you need quickly and you can pivot on a dime," says Brookes. "All you have to do is change a small sequence of RNA, and now you're editing a different locus. CRISPR has democratized gene editing."

Regulatory Hurdles

The FDA supports cell and gene therapy innovation and continues to issue guidance documents around research and design. Yet, the field is so new, the agency's existing framework doesn't fit the pace and scope of innovation.



"You can't plug and play the framework of small molecule drug development to cell and gene therapy," says Nowatzke. "When discussing CRISPR, there are so many new questions: How do we confirm our sequence? What type of sequence testing do we do before we release a sequence? If you administer a cell or gene therapy, and it provides relief, how durable is that relief? And using a CRISPR-edited guide RNA, there are always questions around what happens if there's a mistake."

Regulatory guidance will continue to evolve. Staying abreast of any changes, as well as shoring up practices — using GMP-grade materials, developing a thorough risk management plan, adequate validation — will go a long way toward a smoother regulatory process.

Inconsistency: What Could Go Wrong?

During preclinical development, researchers have leeway to experiment. When a therapy enters clinical trials, standardization is critical to ensure safety, efficacy, and regulatory approval.

“When you change vendors of a critical raw material between research and clinical stages, or during clinical development, you run the risk of unintended changes in your process because the reagents may not be equivalent,” says Dr. Burger. “You may end up with results that are not comparable. That can have disastrous consequences.”

Repeating preclinical research due to a discrepancy in materials would lead to months to years and millions of dollars lost. “Six months can mean the difference between getting the IP and becoming first to market or just being an also-ran and your therapy doesn’t get prescribed or used,” says Brookes.

Sticking with the same vendor from bench to clinic brings repeatable, reliable results, provided they have the quality materials. Look for a vendor that provides GMP-grade sgRNA and other materials. “This is a major risk reduction in your process development,” says Dr. Burger.

A New Vision for CRISPR–based Cell and Gene Therapies

The evolution of CRISPR-Cas over the past five to seven years parallels other life sciences advances. Researchers have sequenced the entire human genome. The cost of sequencing has dropped 100,000-fold. Artificial intelligence allows scientists to analyze large data sets in a way that wasn't possible before. Combined, these developments create a perfect storm for cell and gene therapy breakthroughs.

We're seeing them already. For example, the first patient to receive CRISPR-based therapy for sickle cell disease, Victoria Gray, is doing well one year and counting after treatment. Her treatment doesn't just ease the pain she used to feel, she no longer needs blood transfusions..

This type of result is what genetics researchers have hoped for from the beginning. And as more therapies reach the end of the development pipeline and receive regulatory approval, we may have many more Victoria Gray-like stories to tell.

"The field is just beginning to mature," says Dr. Burger. "What distinguishes more recent approvals from those that have gone before is their large therapeutic effect. We see that with CAR T-cell products. They deliver major therapeutic effects to people with devastating cancers. We're only at the beginning of having approved treatments that can reach large numbers of patients."

With CRISPR's ability to perform highly precise gene editing, the possibilities are endless. "We're getting to an age of truly curative medicine," says Brookes. "CRISPR is going to allow us to take control of our biology at a fundamental level to effect change."

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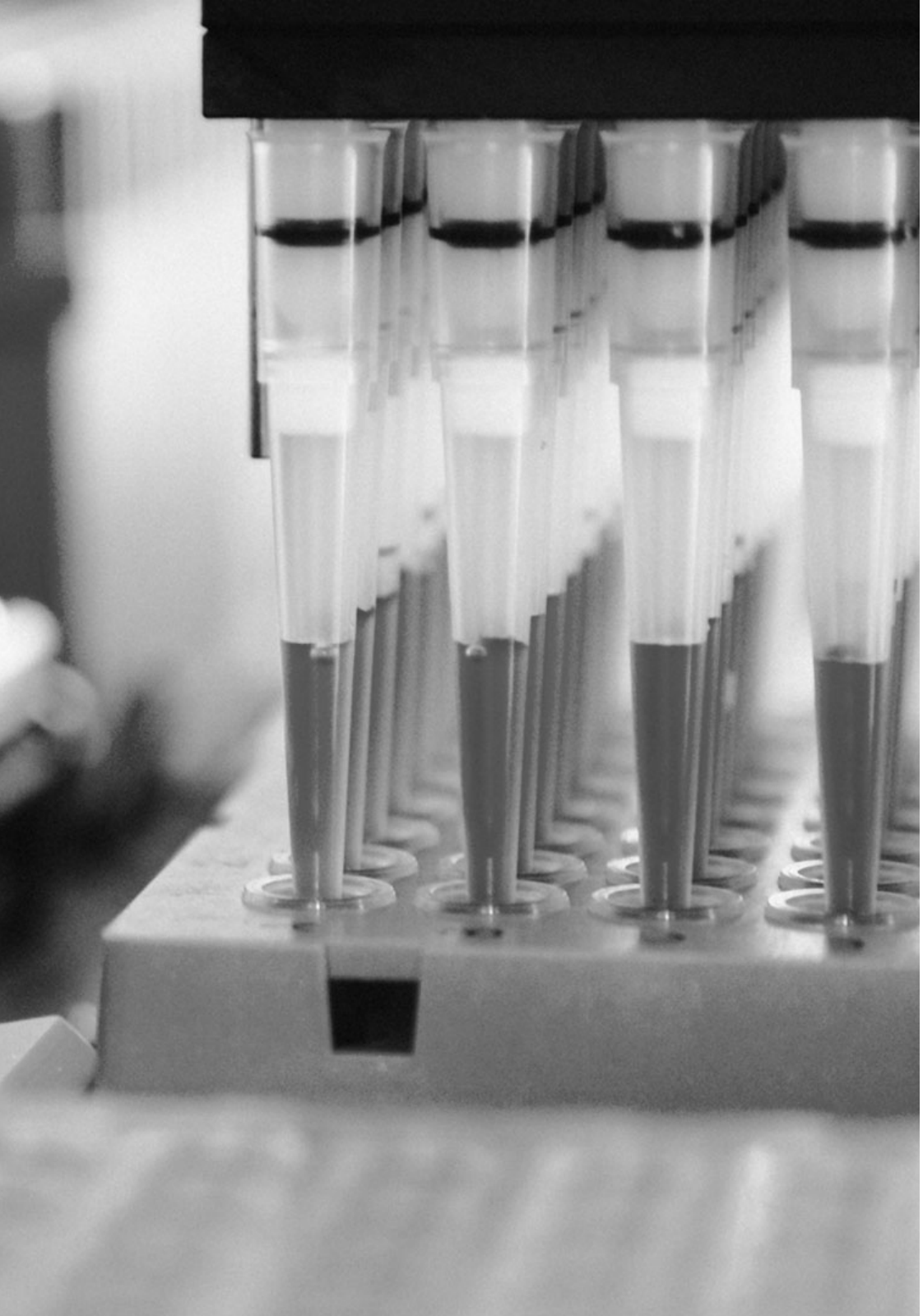

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About

Synthego is a genome engineering company that enables the acceleration of life science research and development in the pursuit of improved human health. With its engineering foundations, the company leverages machine learning, automation, and gene editing to build platforms to advance both basic research and therapeutic development programs.

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