



2021

# PLATFORMS OF HOPE

Realizing the Potential of Genetic Medicines

DECEMBER 2021



# A Letter from the CEO



As gene therapies and editing technologies rapidly advance, it is more urgent than ever to provide updates and information to the rare disease community on how these technologies can be applied across multiple diseases.

This report is the culmination of a year-long Global Genes multimedia reporting series in collaboration with the National Institutes of Health with the goal of helping the rare disease community understand emerging issues of genetic medicines, the challenges of moving these from the lab to the patient, and the issues involving equitable access to potentially curative therapies.

Through the collaboration, our partners at NIH helped to identify ideas, technologies, and advances that have broad implications for many patients and families affected by rare diseases.

While many people in the rare disease community have heard about the power of genetic medicines, this report is part of our on-going effort to help members of the community understand the challenges that remain in developing and delivering these therapies to patients who may benefit from them.

A handwritten signature in black ink, reading "D. Craig Martin".

D. Craig Martin  
CEO  
Global Genes



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## Ushering in a New Era of Genetic Medicines

**In July 2019, Victoria Gray, a 33-year-old mother of four in Forest, Mississippi, made medical history as she became the first patient to be treated with a gene editing therapy for sickle cell disease. She has been free from needing blood transfusions to treat the condition ever since.**

Though rare, sickle cell disease is the most common deadly genetic disorder. It affects more than 300,000 newborns worldwide each year. The condition hampers the ability of red blood cells to carry oxygen to the cells throughout the body. In sickle cell disease, two mutated copies of the hemoglobin gene cause the disc-like red blood cells to become misshapen and sticky. It causes chronic pain, organ failure, and early death in patients.

In the two years prior to receiving the experimental therapy, Gray suffered seven vaso-occlusive crises a year, a common complication of the condition that can send people to the emergency room as the misshapen red blood cells clump together and obstruct the flow of blood in small blood vessels and cause painful episodes.



The experimental therapy known as CTX001 that Gray received is being jointly developed by CRISPR Therapeutics and Vertex Pharmaceuticals. It is an autologous, *ex vivo* CRISPR/Cas9 gene-edited therapy. The blood forming stem cells are taken from a patient's bone marrow and gene editing is used to program the blood cells to produce high levels of fetal hemoglobin. Fetal hemoglobin is present in the womb and at birth but is turned off and adult hemoglobin becomes activated.

At the end of December 2020, researchers reported in the *New England Journal of Medicine* that all three sickle cell disease patients treated in the study were free of vaso-occlusive crises ranging at the time from three to 18 months after treatment.

### A New Era of Genetic Medicines

Sickle cell has become an area of great innovation where a number of companies are advancing toward market with gene replacement and gene editing therapies. Those advances, though, come at a time of rising consciousness about inequities in the healthcare system for a disease that is often used to exemplify the different levels of investments that have been made into research and the different ways patients are treated within the healthcare system.

It is also a noteworthy disease because while there are about 100,000 patients in the United States with the condition, a disproportionate number of whom are Black—there are an estimated 6.4 million people globally living with sickle cell disease, many of whom live in developing economies where delivering expensive and



complex therapies poses additional challenges.<sup>1</sup> Sickle disease has its greatest prevalence in Sub-Saharan Africa. It also disproportionately affects people of South and Central America, the Caribbean, Saudi Arabia, India, and Mediterranean countries.

Although emerging genetic medicines offer great promise to free people from the burden of the disease, the economics of these therapies, as they are being conceived as commercial products today, raise a range of issues about access and affordability. Even in the developed world, where the population of patients is large enough to make it a potentially lucrative pursuit and there is significant commercial interest in developing these medicines, access and affordability will likely be an issue for most patients.

## A Critical Role for the National Institutes of Health

While the \$3 billion Human Genome Project set the stage for an age of genetic medicine, innovation is happening rapidly to advance the field today within the private sector, which can move faster than government research and has been adept at tapping large pools of capital to advance technologies and potential therapies. The National Institutes of Health invests in genetic medicines through a variety of programs across its 27 institutes and does not report its investment in this area as such. As an example, though, consider the NIH's Somatic Cell Genome Editing program, one of the most significant and focused NIH efforts in this area. NIH launched the program in 2018 and committed to investing \$190 million over six years. By contrast, private investment in genetic medicines has far outstripped that funding. In 2020 alone, genetic medicines companies raised a total \$8.2 billion through public and private financings, according to Global Genes and DealForma.

Technologic innovation is moving us away from an era of big science that federal programs were well suited to address to a new era where technologies like artificial intelligence, cloud computing, and tools for genetic manipulation are accessible to the smallest companies. That raises the question as to what role the National Institutes of Health should play in this changing world and what are the foundational problems it can address to enable the broad development and availability of genetic medicines?

The answers lie in understanding the challenges of developing and delivering genetic medicines, in particular for ultra-rare genetic diseases where patient populations may be too small to entice commercial interest. Despite early successes of gene therapies that have come to market, many challenges remain. These include the ability to diagnose patients accurately and early enough in the life of a genetic disease so they can benefit from these therapies, delivery challenges of getting these therapies to cells and tissues within the body where they are needed in order to provide benefit, avoiding off-target effects, and manufacturing them in a scaled and affordable way. Addressing these challenges that can be shared and applied broadly across a range of therapies has the potential to increase the speed with which a therapy can move from conception to patient and reduce the cost of doing so with the potential of increasing the number of patients and conditions that can be treated.

"If you do not have federal funding in drug delivery, you will not have drugs that reach the clinic in new tissues, period. The private investors for the companies that are developing these drugs are not set up to perform the fundamental, high-risk, early-stage

*If that work isn't federally funded, it's just too risky for private investors to take on, and it just won't happen.*

— JAMES DAHLMAN, GEORGIA INSTITUTE OF TECHNOLOGY AND EMORY UNIVERSITY



science that's needed," said James Dahlman, associate professor in the department of biomedical engineering at the Georgia Institute of Technology and Emory University and an NIH-funded researcher who is working to develop nanoparticle vectors for genetic medicines. "As a result, that work has to be done via federal funding. If that work isn't federally funded, it's just too risky for private investors to take on and it just won't happen. And if it doesn't happen, you're going to see all these drugs that could be cures for horrible genetic diseases just not get developed."

The other extraordinary need the NIH is situated to address is one driven by the mathematics of rare



disease. With somewhere in the neighborhood of 10,000 rare diseases and only 300 or so that have approved therapies today, there is little reason to have confidence that industry will address the need felt by patients with most of these conditions. Despite the tremendous scientific strides that have been made in understanding the genetic basis of many rare diseases and how to correct them, a therapeutic gulf exists.

Though rare diseases affect an estimated 400 million people worldwide, the prevalence of the vast majority of these diseases make them unlikely pursuits for commercial drug developers for economic reasons. The investment needed in bringing a therapy to market would not likely be recouped through sales, let alone be profitable.

Consider a 2019 study in the *European Journal of Human Genetics* that analyzed the prevalence of 6,172 unique rare diseases identified in the Orphanet database and found that 149 rare diseases affect about 80 percent of all people with rare diseases. The most prevalent of these rare diseases affect between 100 to 500 people per million. The next most prevalent

small molecule drug for common ailments, such as high blood pressure or high cholesterol, won't work if the patients with rare genetic diseases hold hope for a therapy that will correct the underlying mutation driving their condition. As Chris Austin, the former director of the National Center for Advancing Translational Sciences has noted, it would take 2,000 years at the current rate of drug development to develop treatments for each known rare disease, let alone the more than 250 new ones discovered each year.

"That is unacceptable. We have to envision a future where this is radically sped up—not 2000 years, not 200 years, but 20 years." Austin said during a three-day NIH workshop in June 2021 on gene-targeted therapies. "Given the kinds of technologies that we're talking about, that is possible."<sup>3</sup>

The solution, he said, is to stop talking about these diseases as individual diseases that have nothing to do with each other. He said that's not true because they are related in some way or other. By moving from a one-disease-at-a-time approach researchers should look across these conditions for commonalities that can affect many diseases at once. The same

is true for treatment strategies. Instead of developing a treatment for one disease at a time, the NIH has embraced a platform approach to accelerate the preclinical development of gene therapies by using the same vector to carry different genetic payload to treat multiple diseases. Through programs like its Platform Vector Gene Therapy Program and its Bespoke Gene Therapy Consortium, it is seeking to develop genetic medicines for multi-

ple conditions as a way to accelerate the process of moving a gene therapy from concept to treatment of a patient.

While private industry is moving at a rapid pace to capitalize on the understandings of the genetic basis of rare disease to design genetic medicines that can translate into new therapeutic approaches, more is needed to ensure the benefits of these scientific breakthroughs can translate into treatments and cures for a global population of patients afflicted with rare diseases. Although industry can play a role in addressing some of those challenges, many of them will require investment and resources that for-profit entities will not have the need, motivation, or wherewithal to make. ■

A circular portrait of Chris Austin, a man with short brown hair, wearing a dark suit, white shirt, and a red patterned tie. He is smiling and looking towards the camera.

***We have to envision a future where this is radically sped up—not 2000 years, not 200 years, but 20 years.***

— CHRIS AUSTIN, FORMER DIRECTOR OF THE NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES

rare diseases—those affecting between 10 and 100 people per million include another 241 rare diseases. Together these 390 diseases affect at least 98 percent of all people with a rare condition. The remaining diseases in the database affect less than 10 people per million, but they account for about 85 percent of all rare diseases.<sup>2</sup>

Given the small number of diseases for which there is an approved therapy, and the rate at which new therapies are developed and approved, patients with most of these diseases would not benefit from the advances now within our grasp unless new approaches are pursued for the discovery, development, approval, manufacturing, and delivery of these therapies. Applying a model that may work well for a





# The Promise of Genetic Medicines

**If the molecules that make up the human body were words, proteins would be verbs. These large molecules are responsible for the action that goes on within the body.**

They are necessary for growth and development, but they also play other essential roles. Certain proteins, known as enzymes, are catalysts in biochemical processes within the body, such as metabolizing food. Another type of protein, known as antibodies, fight pathogens. Still other proteins, known as hormones, signal cells, tissues, and organs to carry out certain biological processes. Proteins may carry and store needed nutrients, provide structure, and more. When something goes wrong in a genetic disease, it involves an error in the code for making a needed protein.

Traditional approaches to medicine have targeted proteins with small molecule drugs that can bind to receptors and alter their activity. These drugs addressed symptoms of diseases but did nothing to treat their underlying causes.

As the field of biotechnology emerged, new therapeutic approaches became possible. The development of recombinant proteins enabled such things as enzyme replacement therapies for lysosomal storage disorders, a type of metabolic condition caused by the lack of a needed enzyme; factor replacement therapies for different forms of the bleeding disorder hemophilia; or monoclonal antibodies to disrupt the cascade of events that cause the body to attack itself in autoimmune conditions. While these therapies made it possible to treat conditions that otherwise went untreated, they are imperfect solutions and do nothing to correct the underlying cause of a disease.

Genes provide instructions for making proteins. When a mutation occurs to a gene, it can lead to the absence of a needed protein or create a pathogenic protein. In the genomic age when the connection between genotype and phenotype can be discerned, new ways of treating and potentially curing diseases are possible. Genetic medicines can be used to replace a faulty gene with a functional copy of one, silence the activity of a faulty gene that is causing damage, add a gene to perform a needed function, or edit a gene to correct the error in coding to restore proper function.



While these new approaches provide a biologic elegance that can move us from treating symptoms to addressing causes and potentially cure genetic diseases, the challenges of designing, manufacturing, and delivering genetic medicines are complex in practice. The analogies used to describe these new therapies, such as comparing gene editing to word processors that can edit misspellings in genetic code, provide an easy-to-grasp concept, but can be deceptive in its seeming simplicity. Carrying therapeutic genetic material into cells where it is needed without causing unwanted consequences represents a large number of challenges that still need to be tackled before the full potential of genetic medicines can be realized. ■





## New Consortium Seeks to Identify Unknown Rare, Genetic Diseases

**While advances in genetic medicines are making it possible to treat and potentially cure rare, genetic diseases, patients can't benefit from these advances if doctors are unable to diagnose their conditions.**

The National Institutes of Health in July 2021 announced plans to award nearly \$80 million to support the establishment of the Mendelian Genomics Research Consortium and the development of novel methods and approaches that help researchers identify the genetic causes of single-gene diseases.

More than 400 million people worldwide have been diagnosed with one of about 7,000 Mendelian diseases, which are disorders generally thought to be caused by mutations in a single gene. Researchers have been identifying about 250 Mendelian disease genes each year using whole-exome sequencing. This method sequences all the regions of the genome responsible for encoding proteins. However, whole-exome sequencing has not been successful in identifying the genes responsible for many Mendelian diseases, requiring new ways of approaching the problem.

The awards will be provided by the National Human Genome Research Institute, part of NIH, and are expected to support the consortium over a period of five years. Current methods can identify a mutation in only about 50 percent of people with a rare disease.

"The idea is to look for the missing causes and genome changes that lead to these rare conditions. This has a lot to do with our ability to interpret the impact of rare variation in the genome," said Deborah Nickerson,

professor of genome sciences at the University of Washington School of Medicine and a principal investigator on the new grant. "It's from rare, impactful differences in our genomes that provide insights into the parts of the genome that are important for structure and function in humans."

The Mendelian Genomics Research Consortium will develop innovative methods to increase the rate at which the genes responsible for all Mendelian diseases can be identified. It will include four clinical sites and one data coordination center. The clinical sites use new genome sequencing technologies to identify unknown Mendelian disease genes, create novel analytical approaches, and foster international data sharing that includes appropriate patient consent.

Research teams will also plan outreach and education efforts to empower the broader research community to perform more robust Mendelian gene discovery projects.

The consortium's goal is to significantly increase the number of Mendelian disorders for which the genetic cause is known.

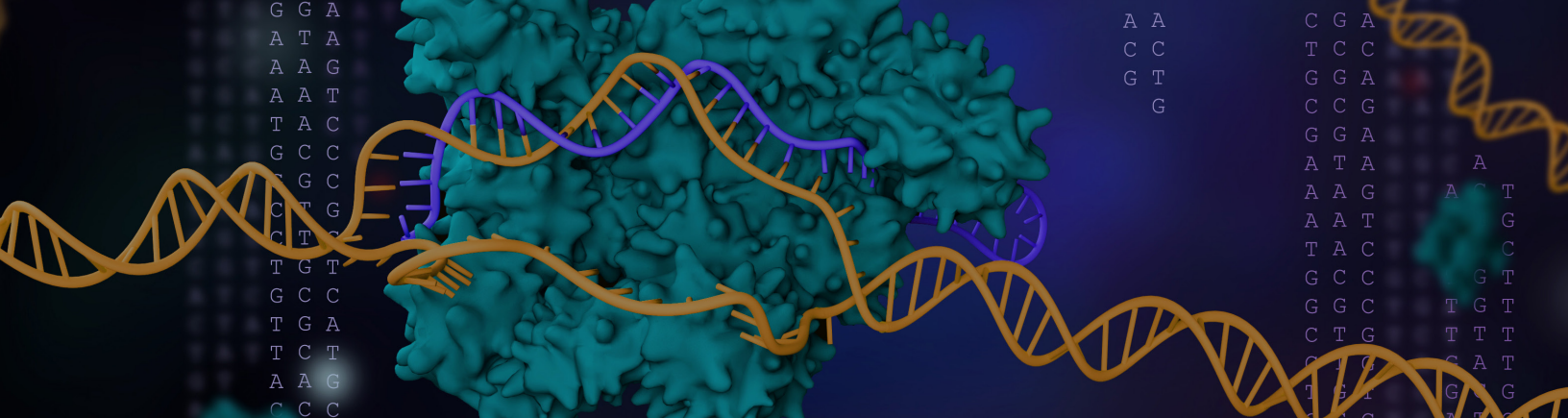
The teams will perform enhanced data sharing and collaboration, and focus on applying new technologies, genome-sequencing strategies, and analytical approaches.

"This consortium goes a significant step beyond NHGRI's already successful efforts in this area but adds a more intense focus on data sharing and enabling the broader research community to tackle challenging diseases whose genetic causes were eluding identification by researchers," said Carolyn Hutter, director of the NHGRI Division of Genome Sciences. ■



DEBORAH  
NICKERSON





## Get Me Rewrite

**It was only at the end of 2020 that the U.S. Food and Drug Administration approved Zokinvy, the first drug to treat Hutchinson-Gilford Progeria Syndrome, an ultra-rare genetic disease that causes people to age rapidly. Less than two months later, the prospect of using gene editing to correct the underlying mutation in progeria, has come to life.**

On the heels of the Zokinvy approval, researchers published a study in the journal *Nature* that suggests *in vivo* gene editing could correct the root cause of the disease. The study in mice by researchers at the Broad Institute, the National Institutes of Health, the Progeria Research Foundation, and elsewhere provides hope that a newer form of gene editing could arrest the disease.

Progeria is a fatal pediatric disease that affects about 400 children worldwide. Children with progeria die of heart disease at an average age of 14.5 years, due to premature atherosclerosis resulting in heart attacks. The recently approved therapy Zokinvy increases average lifespan by 2.5 years and improves some symptoms of progeria, but it does not address the genetic mutation that causes the disease.

The condition is caused by a point mutation—a single letter change in the LMNA gene, which encodes the lamin A protein. The result of the change is the production of an aberrant protein known as progerin. Lamin A protein is part of the structural scaffolding that holds the nucleus together. Researchers believe that progerin may make the nucleus unstable, and that cellular instability may lead to the process of premature aging in progeria.

Researchers found by using a form of gene editing known as base editing, they could reverse the mutation that causes progeria in mouse models. Researchers showed they were able to improve disease symptoms and increase lifespans.

The effects were dramatic. With a single injection of a base editor designed to correct the disease-causing mutation, mice survived 2.5 times longer than control untreated progeria mice. That improvement gave them a lifespan that corresponded with the start of old age in healthy mice. All of the treated mice also retained healthy vascular tissue. In children with progeria, the loss of vascular integrity is a predictor of mortality.



DAVID LIU

“To our knowledge, this work resulted in the strongest rescue of the symptoms of progeria by multiple measures,” said The Broad Institute’s David Liu, who is co-lead and co-corresponding author on the *Nature* study. “Five years ago, we were still finishing the development of the very first base editor. If you had told me then that within five years, a single dose of a base editor could address progeria in an animal at the DNA, RNA, protein, vascular pathology, and lifespan levels, I would have said ‘There’s no way.’”

### Addressing Common Challenges

In 2017, the National Institutes of Health held a series of workshops focused on gene editing with stakeholders from industry and academia who identified a number of gaps, challenges, and needs.



Among the conclusions of the workshops was that new genome editors, new delivery systems to get them to the cells and tissues they needed to target, and new means of measuring their safety and efficacy were all needed to advance the field. Doing so carried the promise of addressing a wide range of diseases including the potential to cure rare genetic diseases.

impeding the development of gene editing with the hopes of accelerating the translation of these tools into therapeutics to target tissue throughout the body to address a wide range of genetic diseases. Backed with \$190 million over six years, the program involves 72 principal investigators at 38 institutions pursuing 45 projects.



***We have never had in the history of biomedicine a technology that has such a major potential to make an impact in the lives of so many people for whom currently there are not options.***

— FYODOR URNOV, UNIVERSITY OF CALIFORNIA, BERKELEY

In response to those workshops, the NIH Common Fund, which supports collaborations between multiple NIH institutes and centers, in 2018 launched the Somatic Cell Genome Editing program. The program has assembled groups of multidisciplinary teams to address critical challenges

of California, Berkeley and director of technology and translation at the Innovative Genomics Institute.

He said that despite the large investments being made in the for-profit sector, industry isn't configured to help people suffering from ultra-rare diseases.

"We have never had in the history of biomedicine a technology that has such a major potential to make an impact in the lives of so many people for whom currently there are not options," said Fyodor Urnov, a professor of molecular and cell biology at the University





“The Somatic Cell Genome Editing Consortium will really shine bright in the annals of biomedical history as an example of when the federal government stepped in at the right time in the right way,” he said. “They are saying, ‘Look, we can’t wait for the forces of the market to play themselves out and over the next ten years there will be more and more CRISPR cures, but the time has come to invest in research that makes gene editing more efficient, more versatile, safer, more able to access organs or cell types in the human. This will be one of those situations where the rising tide lifts all boats.’”

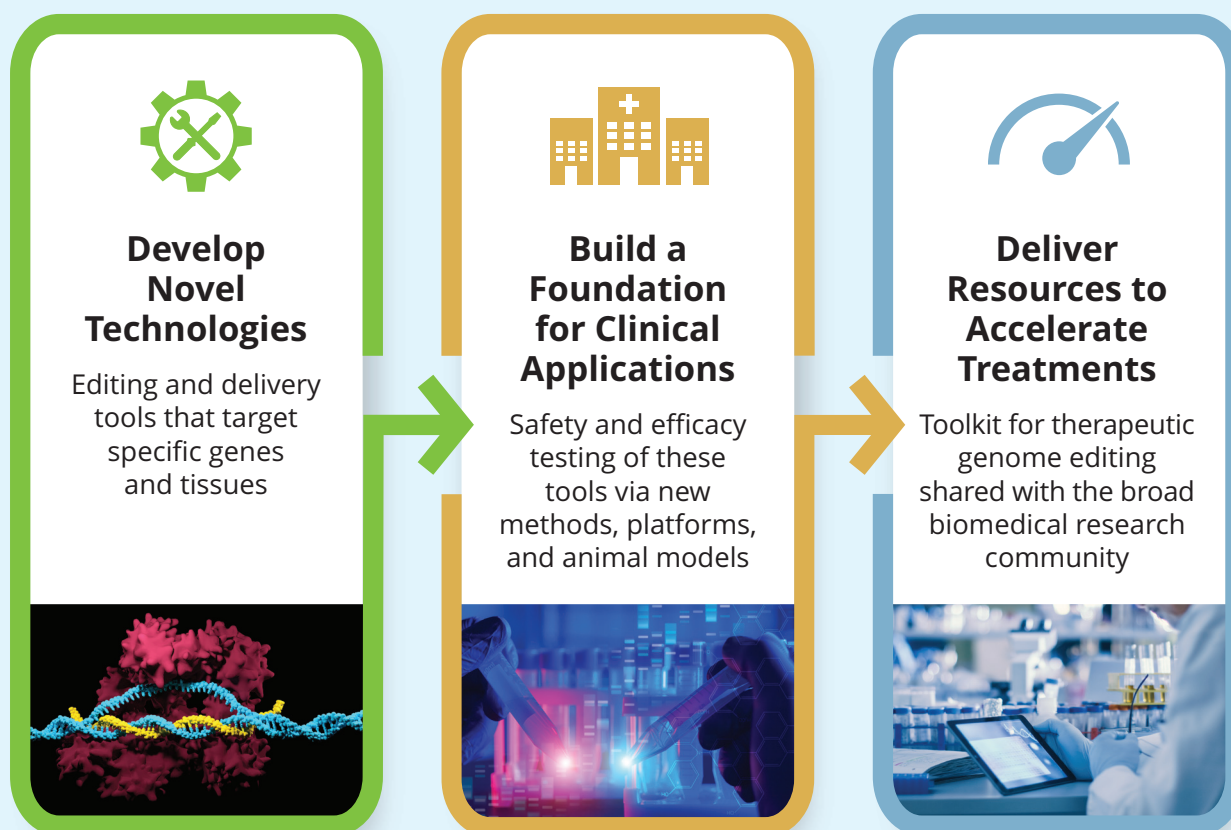
The Somatic Cell Genome Editing Program (SCGE) is working to improve gene editing to treat both rare and common diseases. The program is focused only

on somatic cell genome editing, rather than germline, so that genetic changes are not passed on to future generations. In fact, in the United States there is a moratorium on the use of genetic editing of the human germline in human embryos and the government is prohibited from supporting any such work.

The SCGE is working on such things as improving existing gene editing tools, developing targeted delivery systems, creating methods for detecting unintended effects, and discovering better animal models for testing all of this. The consortium said it will share the learnings, tools, and technology with the research community to accelerate the timeline and improve the efficiency of developing new gene editing therapies.

## Somatic Cell Genome Editing Program

**Goal:** To improve the efficacy and specificity of genome editing approaches to reduce the burden of disease

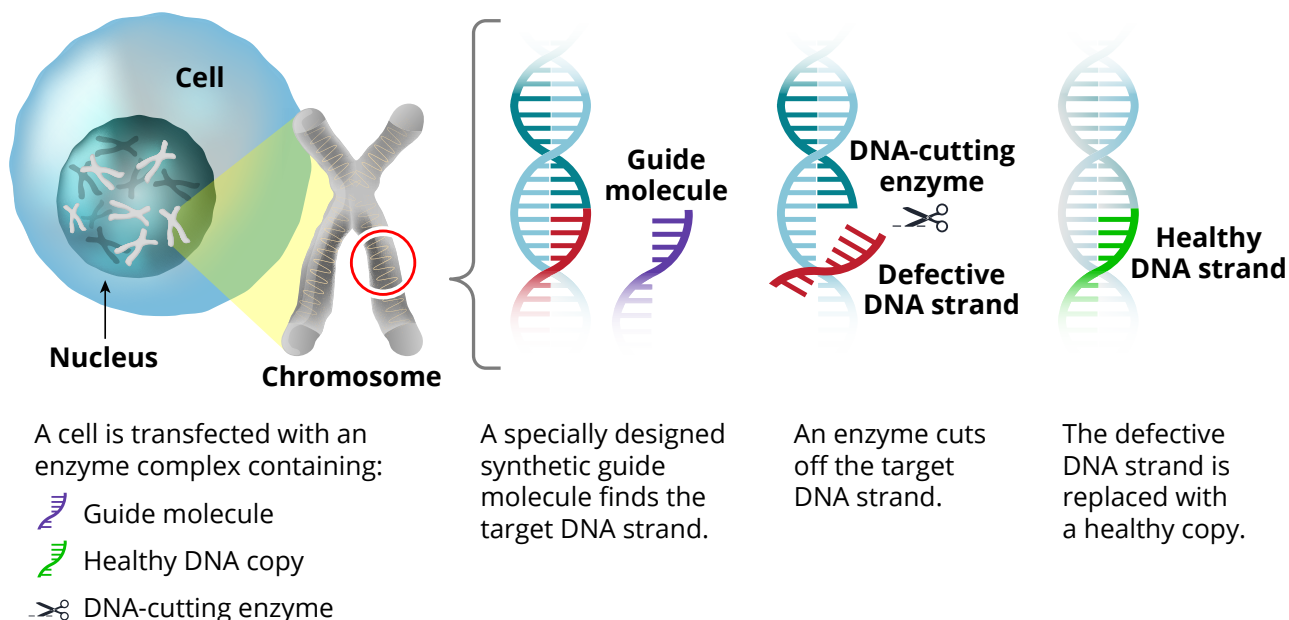


Source: National Institutes of Health



# How Gene Editing Works

A DNA editing technique, called CRISPR/Cas9, works like a biological version of a word-processing program's "find and replace" function.



Source: Reuters; Nature; Massachusetts Institute of Technology

## The CRISPR Revolution

While there have been a number of gene editing techniques, such as zinc finger nucleases and transcription activator-like effector nucleases, the therapeutic potential of gene editing has been limited because of delivery challenges, as well as the cost, time, and lack of efficiency of these tools. In 2012, though, the emergence of CRISPR-Cas9 opened up new possibilities for gene editing because it provides a relatively fast, easy, and affordable means to accomplish genome editing.

CRISPR has been embraced because it can be directed in a precise way to cut DNA at a desired location. It's widely used in research labs and has become not only a tool used for biomedical applications, but can be employed to alter DNA in plants, microorganisms, and animals. Perhaps its greatest promise, though, lies in using it to address genetic diseases.

Scientist discovered CRISPR (an acronym for clustered regularly interspaced short palindrome repeats) by studying the way bacteria defend

themselves against pathogens. It's that machinery that scientists have repurposed as a gene editing tool. Bacteria use CRISPR to cut the DNA of invaders, store the snippets in their own DNA, and make copies of the invaders' DNA as RNA. A bacterial enzyme known as Cas9, takes the snippets and patrols cells for matches.

"It's like a law enforcement official with a photograph of distinguishing features of somebody they're interested in apprehending," said the Innovative Genomics Institute's Urnov. "If an invader shows up and has a match to the little snippet of sequence Cas9 carries, Cas9 will cut up the nucleic acid material of the invader coming in."

The realization by Emmanuelle Charpentier of the Max Planck Unit for the Science of Pathogens and Jennifer Doudna of the University of California at Berkeley that this naturally occurring defense mechanism could be repurposed as a powerful gene editor that could be programmed to act as a pair of genetic scissors, led to the duo winning the Nobel Prize in Chemistry in 2020.



EMMANUELLE  
CHARPENTIER



JENNIFER  
DOUDNA



“There is enormous power in this genetic tool, which affects us all,” said Claes Gustafsson, chair of the Nobel Committee for Chemistry in announcing the award. “It has not only revolutionized basic science, but also resulted in innovative crops and will lead to ground-breaking new medical treatments.”<sup>4</sup>

By constructing a small piece of RNA that matches the DNA where scientists want to cut, the CRISPR-Cas9 is guided to the precise point to make the cut. If the goal is to eliminate the particular function of a gene, once the cut is made, the DNA will heal itself on its own and close with the gene eliminated. If the goal is to fix or edit a gene, or swap an alternative, scientists can construct a DNA template to insert new DNA where the cut is made.

While CRISPR Cas 9 has become synonymous with gene editing, it is only one tool in an emerging toolbox of gene editors. Researchers are working to expand the number of gene editors available in the belief that expanding the number of platforms will allow for a broader set of capabilities. As elegant as the biology sounds in concept, it can be far more challenging in practice.

CRISPR is often referred to as genetic scissors, which is an apt term because it is good at cutting. This could be particularly useful for removing a pathogenic gene and it is good for removing genetic anomalies that either give rise to pathogenic proteins or impede the production of ones that are needed.

An April 2021 perspective piece published in the journal *Nature* took a comprehensive look at the Somatic Cell Genome Editing program and the challenges it is working to address. It noted that while these editing techniques can be used to alter cells extracted from patients that can then be infused back into the body, so-called *ex vivo* applications, doing so is “logistically complex, expensive, and hard to scale” because it requires “substantial cell manufacturing infrastructure.”<sup>5</sup> However, they note that *in vivo* editing, the ability to inject a gene editing therapy into a patient and allow it to make its edits within the body, faces a number of different obstacles, which includes issues of safety, efficacy, and the ability to reach tissue beyond the liver and eye.

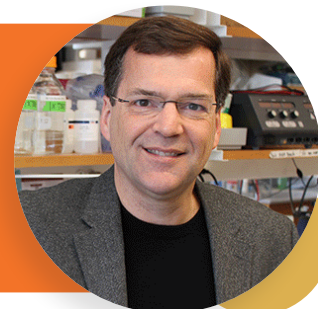
“Everybody acknowledges that there is not one particular platform and there is not one particular tool that

is going to serve every need for every type of genome edit in every potential tissue,” said Erik Sontheimer, co-chair of the Somatic Cell Genome Editing consortium steering committee and a professor in the RNA Therapeutics Institute and program for molecular medicine at the University of Massachusetts. “The more options we have, the better off we will be.”

He noted that while there are a substantial number of researchers in the consortium who are focused on CRISPR Cas9, some are working on CRISPR Cas12, which exploits a different microbial enzyme. Still other

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— ERIK SONTHEIMER, UNIVERSITY OF MASSACHUSETTS



researchers, such as Jillian Banfield and Doudna at UC Berkeley, are working to identify a range of other CRISPR variations by exploring the world of microbes.

One of the big obstacles for CRISPR, though, is its reliance on a natural process for healing the cuts made to DNA. This process is known as homologous-directed repair (HDR). The problem is that it is not an effective mechanism in differentiated cells that are no longer able to divide. These cells, known as post-mitotic cells, are vital to the function of brain, heart, and other tissue. This represents an obstacle to using CRISPR gene editing as it stands to treat a wide range of genetic diseases.

“The current inability to easily and accurately program specific sequences into the genome—given that HDR is largely ineffective in differentiated, post-mitotic cells—is a fundamental obstacle to the broad use of genome editing in the treatment of genetic disease,” wrote Saha et al. in the *Nature* piece. “Accordingly, new technologies that enable sequence-specific alternations—such as base editing and prime editing—are also part of the SCGE Consortium’s portfolio of projects.”

Indeed, the consortium is exploring a broader range of gene editing platforms. Base editing and prime editing, both developed in the lab of David Liu of the Merkin Institute for Transformative Technologies at



the Broad Institute of MIT and Harvard, are promising examples of such approaches.

“The CRISPR Cas9 form that I liken to molecular scissors can be quite useful if your goal is to disrupt a gene. And there are some diseases, including some clinical trials going on now where simply messing up a gene, simply disrupting it, can have a therapeutic benefit,” said Liu. “But for most genetic diseases and for most mutations associated with genetic disease, in order to benefit the patient, we believe that you need to fix the broken gene and turn it back into a normal gene or into something that behaves like a normal gene rather than simply messing it up further.”

That’s what Liu’s lab did working with researchers at the National Institutes of Health and the Progeria Research Foundation and elsewhere in an animal model of the ultra-rare disorder progeria, which causes premature aging.

Liu notes that the first classes of base editors his lab created used the DNA homing machinery from CRISPR to accurately target DNA without cutting as the consequence. His lab has since developed newer base editors that are being used widely now that don’t use CRISPR, but instead rely on proteins called tail repeatase to target the DNA. Among the advantages of this approach is that it allows the delivery of CRISPR-free base editors into the mitochondria, an important part of the cell that has previously been resistant to CRISPR because of the inability to get CRISPR guide RNAs—the component of CRISPR gene editors that programs their DNA specificity—into the mitochondria to edit the DNA within.

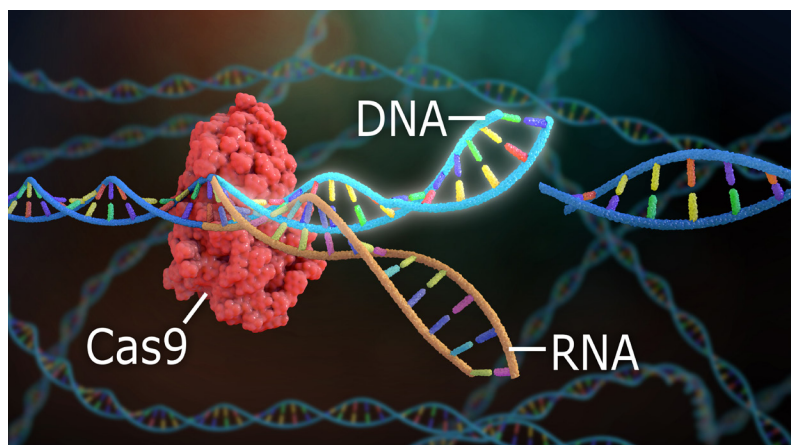
Prime editors represent a subsequent advance. While CRISPR Cas9 is commonly referred to as genetic scissors, prime editing is likened to the search and replace function of a word processor. Base editors represented an advance in gene editing in that they could be used to correct certain mutations without making a double strand break to DNA, but they are limited in the changes they can make to DNA.

With this new tool, scientists can find and replace genetic code without making a cut to the DNA that can cause unwanted changes. These approaches are believed to have the potential to address more than 89 percent of known disease-causing mutations,

according to a 2019 article in the journal *Nature* by Andrew Anzalone et al.<sup>6</sup> Anzalone, a post doc in Liu’s lab, conceived of the approach.

Base editing can be used to correct what are known as transition mutations—changing a C to T, a G to an A, an A to a G, and a T to a C—without requiring a double stranded break to DNA. There are, however, eight other possible transversion mutations that may need correcting in genetic diseases. Prime editing provides a single tool that can correct all of 12 possible base-to-base conversions and combinations in human cells without requiring double strand breaks to DNA.

“Prime editing offers much lower off-target activity than Cas9 at known Cas9 off target loci, far fewer by-products and higher or similar efficiency compared to Cas9-initiated HDR, and complementary strengths and weaknesses compared to base editors,” the



researchers wrote. “By enabling precise targeted insertions, deletions, and all 12 possible classes of point mutations without requiring [double-stranded] breaks or donor DNA templates, prime editing has the potential to advance the study and correction of the vast majority of pathogenic alleles.”

As an indication of how rapidly the technology is advancing, Prime Medicine, a company of which Liu and Anzalone are scientific co-founders, unveiled itself in July 2021 with \$315 million in funding. The funding included a \$115 series A round completed nine months earlier and a subsequent \$200 million series B round. Anzalone serves as the head of prime editing platform for the company. Delivery, though, continues to represent a challenge and the larger payload of prime editors adds another nuance to the problems that need to be overcome. ■





# A Platform Approach to Developing Gene Therapies

**The advancement of gene therapies offers the promise of delivering life-changing benefits and potential cures to patients with rare diseases caused by a mutation to a single gene, but working through the process of developing these treatments one at a time has proven too slow and costly to deliver therapies to address the thousands of monogenic conditions known to exist today, not only because of the volume of diseases, but also because most affect populations too small to attract commercial interest to pursue them.**

With that in mind, the National Institute of Health's National Center for Advancing Translational Sciences in collaboration with the National Institute of Neurological Disorders and Stroke, the National Human Genome Research Institute, and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development launched Platform Vector Gene Therapy (PaVe-GT), a pilot program intended to accelerate the development of gene therapies for rare diseases and make them more accessible to patients.

Doing all of the preclinical work necessary to advance an experimental gene therapy to a clinical trial for a single disease can be costly and take many years. Even though many rare diseases affect too small a number of people to make gene therapies commercially viable for drug companies to pursue, it doesn't change the fact that delivering a functional copy of a gene to the right cells in patients could address many of these conditions.

PaVe-GT is testing whether the use of the same gene therapy vector and manufacturing process could be applied to multiple rare diseases in gene therapy clinical trials. By using a common platform for multiple diseases, the belief is that the time and cost of advancing a therapy to a clinical trial could be dramatically reduced.

## Developing Multiple Therapies at Once

Under the pilot program, PaVe-GT researchers are using the same AAV vector to treat four different rare genetic diseases. The genetic payload will be unique to the particular condition they are treating. The four diseases being targeted in the pilot program are Dok7 deficiency, Collagen Q deficiency, propionic acidemia, and isolated methylmalonic acidemia.

The program will work to improve the efficiency of the vector, and, to the extent possible, conduct a single set of preclinical studies that can be used to address the scientific and regulatory requirements across the conditions to advance them to clinical studies.

The decision to focus on an AAV vector reflects the fact that their ability to target a large variety of cells makes them disease-agnostic. Their applicability for a given disease will depend on such things as the route of administration, dose, and genetic mechanisms that need to be addressed, rather than by the specifics of the disease itself.



The program focuses on the use of a modified adeno-associated virus (AAV) vector that could be used as a delivery vehicle for multiple gene therapies. The program calls the AAV vector a “programmable multi-purpose vehicle that can be used to deliver a variety of different therapeutic payloads to disease-relevant cells.” The belief is that the more similar a group of diseases are with regards to the genetic mechanism of the disease and the cells that must be targeted to treat it with a gene therapy, the more streamlined an approach can be developed.<sup>7</sup>



***This one-disease-at-a-time approach results in duplication of effort, as well as suboptimal use of time, funding, animals, and other scarce resources.***

— P.J. BROOKS, NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES

“This one-disease-at-a time approach to clinical development does not fully leverage the platform capacity of AAV vectors, capitalize on any commonalities in preclinical development, or promote sharing of knowledge across individual therapeutic programs,” wrote NCATS’ P.J. Brooks, deputy director of the Office of Rare Diseases Research in the National Center for Advancing Translational Sciences with his colleagues in the journal *Human Gene Therapy* in a special report discussing the PaVe-GT program. “This results in duplication of effort, as well as suboptimal use of time, funding, animals, and other scarce resources.”<sup>8</sup>

With a working vector, and the preclinical studies and documentation to support its advancement to clinical studies, the hope is that a researcher could essentially treat different diseases that would require targeting the same cells by swapping out the genetic payload and doing minimal preclinical work prior to dosing a patient.

## Sharing Needed Data

As part of the plan, PaVe-GT says scientists will share their data publicly. It is also working with the U.S. Food and Drug Administration to discuss the progress of preclinical toxicology, distribution, safety, and other studies, as well as manufacturing and clinical trial design. While these discussions and the FDA

feedback is generally kept secret by trials sponsors for competitive reasons, PaVe-GT will make them available to the public to support future efforts to advance to clinical studies new gene therapies using the same vector. The hope is that this will allow small companies, academic researchers, and rare disease patient organizations to avoid most of the time and expense of preclinical gene therapy development and essentially use a template to advance an experimental gene therapy with the proven vector to a clinical study.

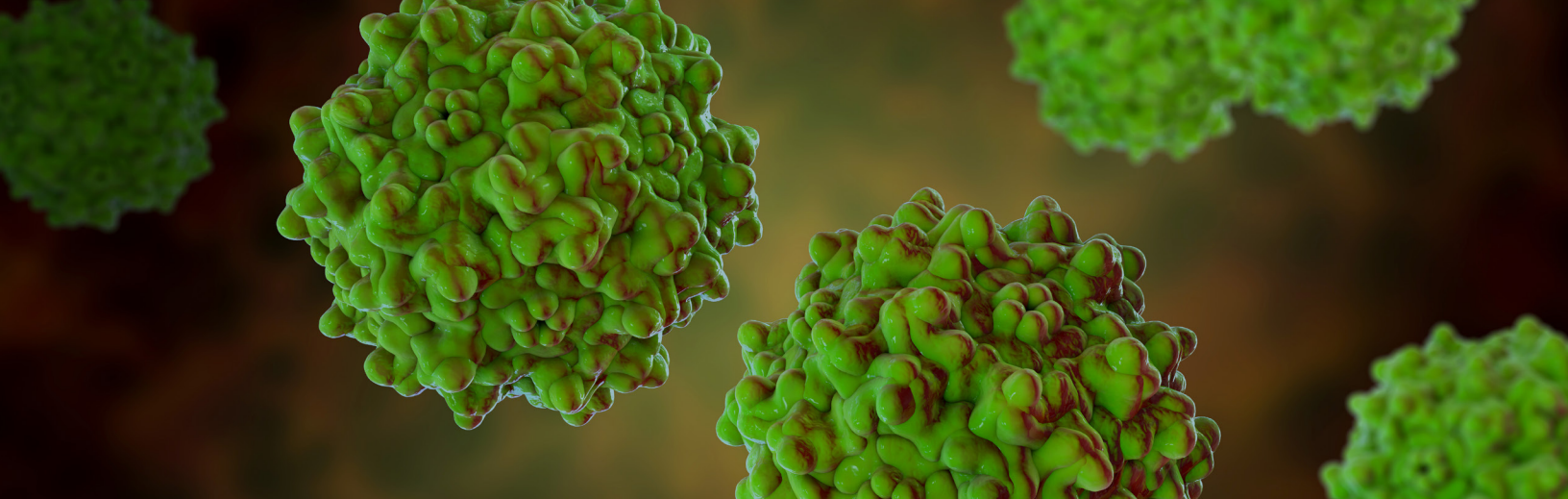
“Some companies are already using similar approaches to study groups of diseases, but certainly not in such a systematic and transparent way,” said Carsten Bönnemann, pediatric neurologist and neurogeneticist with the National Institute of Neurological Disorders and Stroke, who leads two of the PaVe-

GT studies. “Our goal is to show the feasibility of and the potential roadblocks—as well as opportunities—in an approach to treating more than one disorder at a time. People can track the entire gene therapy development process, from the preclinical studies in the lab to a clinical trial.”<sup>9</sup>

Regulators appear to be aligned with the approach. Peter Marks, director of the FDA’s Center for Biologics Evaluation and Research, which is responsible for overseeing gene therapies, noted common vector backbones are often used for gene therapies and that by leveraging information about the vector it could be possible to speed the development process safely and efficiently by allowing a genetic payload for one disease to be swapped with a genetic payload for another.

“You can imagine you can essentially plug-and-play like this, to the extent we show this is possible, this may be a way of leveraging information from one product to another, which could be a way of enhancing access by reducing cost,” Marks said during a panel in a three-session workshop held by the National Institutes of Health in June on Gene-Targeted Therapies: Early Diagnosis and Equitable Delivery. “The current financial situation in gene therapies makes it cost prohibitive to deploy as widely as it could be to the benefit of people.”<sup>10</sup> ■





# Creating a Playbook for Bespoke Gene Therapies

**While there is a steady stream of new gene therapies expected to be approved in the next decade, there are hundreds of diseases that could benefit from gene therapies but are not pursued by drug developers because they affect too small a population to be considered commercially viable.**

In an effort to change the economics of gene therapy for ultra-rare diseases, the Foundation for the National Institutes of Health is establishing the Bespoke Gene Therapy Consortium under its Accelerating Medicines Partnership program. The proposed five-year, \$76 million program involves the National Institutes of Health's National Center for Advancing Translational Sciences, the U.S. Food and Drug Administration's Center for Biologics Evaluation and Research, and a group of commercial gene therapy developers and nonprofit organizations.

"I don't think we could have done this without the FDA's participation, because I'm not sure that industry would have the same interests as they do with FDA's active participation. That's hugely important," said P.J. Brooks, deputy director of the National Center for Advancing Translational Sciences at NIH and one of the authors of the proposal that created the Bespoke Gene Therapy Consortium. "Having the participation of some of these companies that make AAV vectors and their willingness to participate is really going to greatly increase the impact of the whole effort."

The consortium, a public-private partnership, seeks to create a playbook for developing custom gene thera-

pies for rare genetic diseases. By running pilot projects using vectors previously used in approved INDs in diseases with different prevalence, dose requirements, and routes of administration, it expects to create an understanding of the constraints on production of bespoke gene therapies. The hope is to develop what the creators of the consortium describe as a playbook, a simple manual for making this gene therapy to treat people with a variety of genetic diseases.

As part of the effort, the consortium plans to study adeno-associated virus biology to make the technology more accessible to a broader range of diseases, streamline the preclinical and product testing process, and accelerate the pace of bringing new gene therapies to patients. While the goal is focused on bespoke therapies for rare diseases, the work is expected to benefit the entire gene therapy field.

Under the program, which is expected to establish pilots for three to six test cases, the consortium will develop streamlined templates, master regulatory files, and uniform production processes to create a pathway toward the commercial viability and sustainability of gene therapies for ultra-rare diseases.

"What we've really come to be interested in at FDA are these gene therapies that could potentially be transformative for a group of patients who currently have either no, or very few, alternatives, and that is these gene therapies that are individualized or bespoke gene therapies for one or a few people," said Peter Marks, director of the FDA's Center for Biologics



Evaluation and Research and one of the architects of the consortium, during an August 2021 webinar about the program.<sup>11</sup> “The problem is not that we can’t make them, but it’s just that we can’t make them efficiently enough so that they can be commercially viable. We need to find a way forward so that we can see patients who are potentially treatable with something and can get those therapies. That’s the issue that we’re trying to get at the heart of.”

adverse events. Today, each manufacturer analyzes their own products through their own methods.

Finally, the consortium offers an opportunity to address regulatory challenges of bespoke gene therapies by developing standards for regulators to use for the analysis of a new vector. Having an agreed upon set of standardized analytics would provide a predictable and reliable means of determining whether a particular vector is safe enough to be administered to humans.

The FDA’s Marks likened vectors to the handle of a razor and genetic payloads to the razor blades that can be inserted into them. He argued that if you were reusing the same vector over and over and just changing out the genetic payload, you

would not need to recheck the razor handle each time. Rather, you would only need to understand the razor blade being used.

“One of the things we have to gain here is by using a standardized process and putting a lot of things through it, we are going to start to improve in a way that we simply don’t right now. Because when you do things as onesies and twosies, you never continuously improve as you go along,” said Marks. “And I think if we put multiple things through the same process, we’ll understand not just how to improve the manufacturing. We’ll also understand how to improve the throughput through the system and how we actually do some of the regulatory things along with this. We can hone that and make that more streamlined, ultimately, allowing things to get to people more quickly.” ■

*We need to find a way forward so that we can see patients who are potentially treatable with something and can get those therapies.*

— PETER MARKS, DIRECTOR, FDA CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

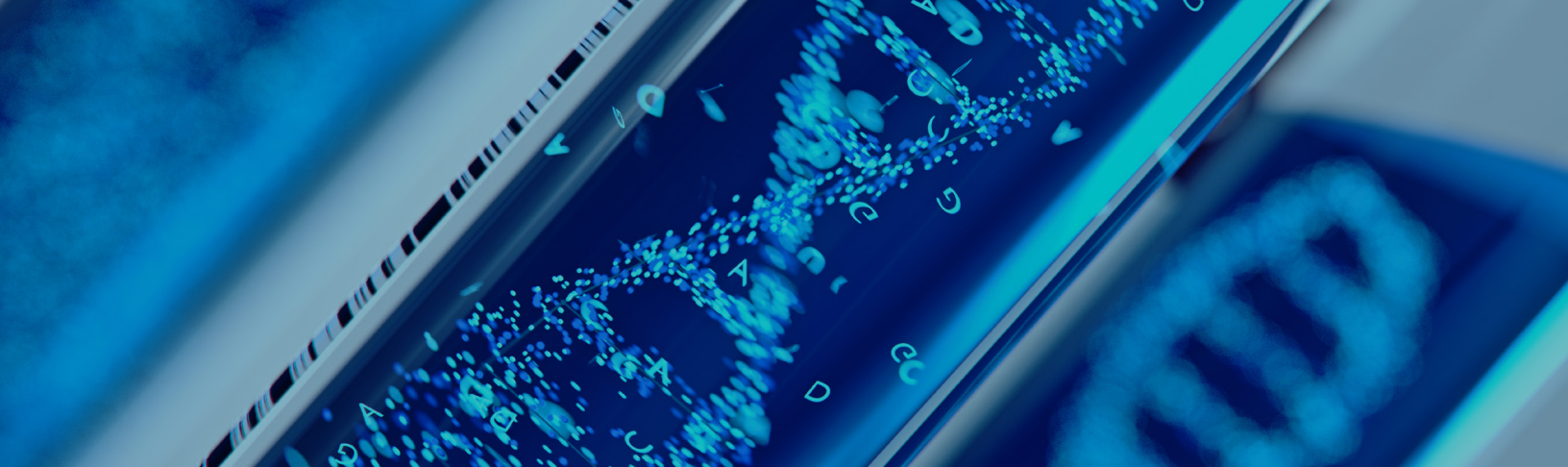
The consortium, launched in October 2021, will take a multipronged effort that extends beyond translational science challenges to include the manufacturing and regulatory issues faced in enabling bespoke gene therapies. Scientists will work to get a better understanding of the basic biology of adeno-associated viruses in order to improve the efficiency with which they are manufactured. The consortium will also explore if there are ways to improve the delivery of these therapies and their activity once a payload is released into a cell.

“What’s particularly exciting is the idea that we can screen already approved drugs to see if they might impact some of these mechanistic steps with the idea being that you could give a drug—a pill—to a patient at the same time, or just before they get the gene therapy, and the gene therapy becomes more efficient,” said NCATS’ Brooks. “Those are some of the things we’re trying to get at with the basic biology component of the BGTC.”

Understanding the basic biology of these vectors could help increase their efficiency and also help with another challenge the consortium seeks to address, which is to improve the efficiency of manufacturing these vectors. Brooks said developing a common set of analytics for all the vectors made through the consortium could help, particular when it comes to understanding







## Delivering the Goods

**To deliver a gene therapy, gene editor, or other genetic medicine into a patient, simply injecting a piece of naked genetic code into someone won't work. Instead, the instructions needed to replace, remove, repair, or disable a faulty gene must make their way into the nucleus of a cell where the DNA resides.**

In fact, delivering these medicines to the cells they need to reach to be effective remains one of the overriding challenges to realizing the full potential of gene therapy. Genetic medicines not only must be delivered to the right cells in the body, but also done in a way so that they do not cause unwanted changes to the genome or cause harm in other ways.

"You can make a compelling argument that this is the most important problem that needs to be solved," said James Dahlman, associate professor in the department of biomedical engineering at The Georgia Institute of Technology and Emory University. "If you can deliver into the tissue, you can make a huge difference in the lives of many patients. If you can't deliver into the tissue, you cannot meet your clinical endpoint and you will not get an FDA approved drug."

### Evolved for the Job

As it turns out, nature has pointed a way toward addressing the problem of gene delivery. Viruses have evolved to be adept at hijacking the machinery of the cell to replicate themselves. This ability to work their

way into the nucleus and release genetic material that integrates with the host genome and reproduce themselves makes them well suited for delivering genetic medicines.

By capitalizing on the natural ability of viruses, they can be harnessed as vectors—delivery mechanisms that carry genetic medicines where they need to go. To be effective, they need to be able to carry their genetic payloads and reliably target the right cells.

***If you can deliver into the tissue, you can make a huge difference in the lives of many patients.***

— JAMES DAHLMAN, GEORGIA INSTITUTE OF TECHNOLOGY AND EMORY UNIVERSITY



Viruses are simple structures. They consist of a viral genome that is encased in a capsid, a protein shell that scientists are able to pack with genetic materials. To prevent the viruses from causing disease, they are modified to strip out certain aspects. The therapeutic genetic code these medicines carry are also packaged with promoters and enhancers—additional genetic material—used to increase the specificity of the tissue a therapy targets and improve its performance.

And not all viruses are created equal. They vary widely in the tissue that they target, the size of the payloads they can carry, and other aspects. As such,



one of the challenges for gene therapy developers is to find the right vector for a given task.

Viruses are not the only vectors for carrying genetic medicines. Scientists are also engineering nanoparticles as alternatives to viral vectors. Though each approach has its advantages and disadvantages, the hope is that by engineering nanoparticles as vectors, it will be possible to target tissue that viral vectors have not been successful at targeting and address some of the other limitations they have.

While genetic medicines using both viral vectors and nanoparticles have been successful at winning U.S. Food and Drug Administration approval, early successes have focused on targeting the liver or eye because they are the easiest tissues to access. Experts in the de-

velopment of vectors say there is no universal solution for the delivery challenge. Instead, they argue that the vector has to be tailored to the disease being treated.

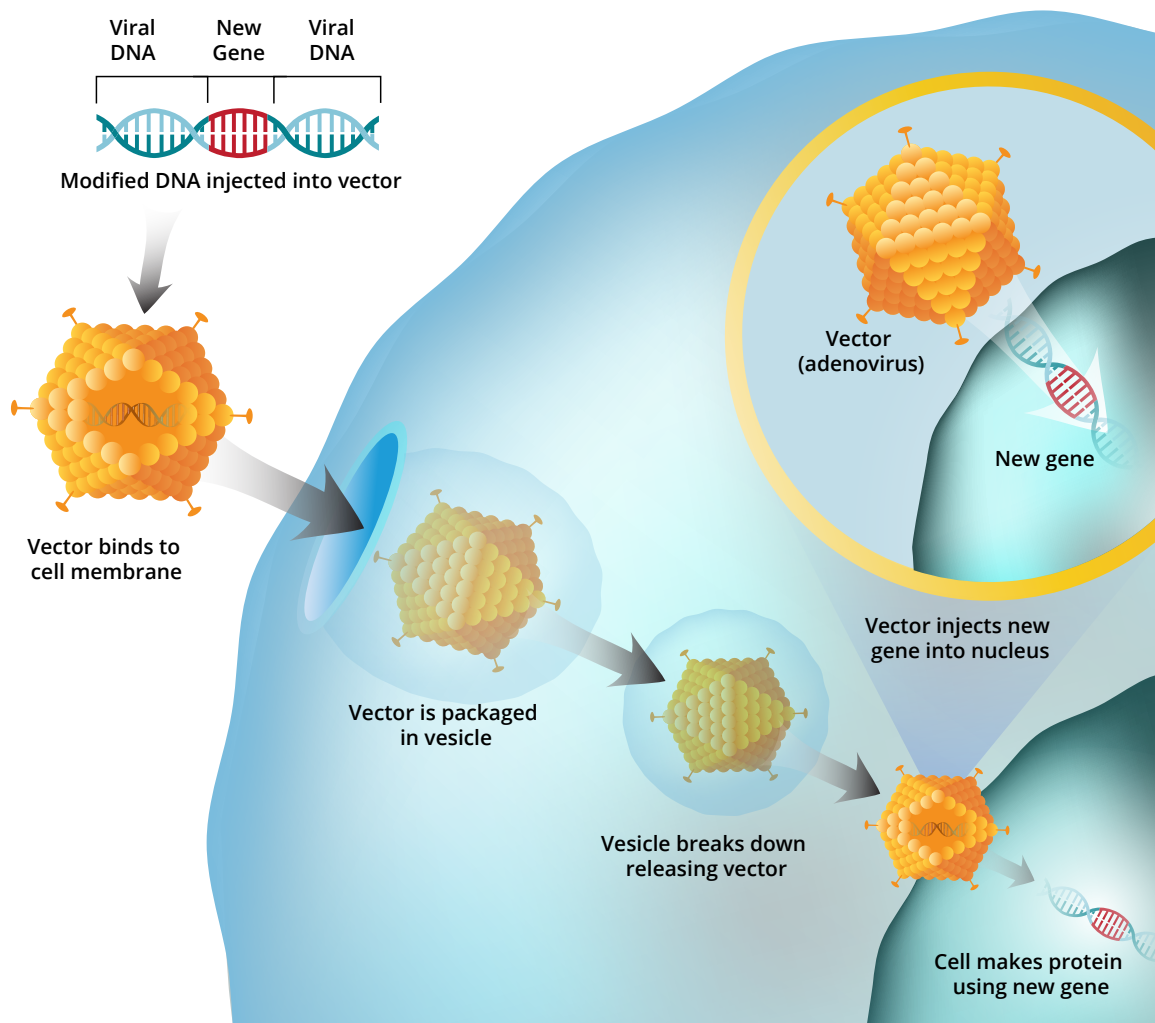
## Going Viral

Guangping Gao, co-director of the Li WeiBo Institute for Rare Diseases Research and director of the Horae Gene Therapy Center and Viral Vector Core at the University of Massachusetts Medical School, said there are certain qualities that make a good vector for gene therapies. These include the ability to efficiently deliver genes into the human body to different cells; the ability to ensure that once delivery is made, the gene remains with a single dose; the ability to



GUANGPING  
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## Gene Therapy Using an Adenovirus Vector



Source: National Institutes of Health



deliver the payload without causing new mutations to occur, and doing this without provoking an immune response.

Among the most fundamental limits of any vector is its size. Though viruses come in many different shapes and sizes, they are small and typically run between 50 to 300 nanometers.<sup>12</sup> A nanometer is one billionth of a meter. By comparison, a typical piece of paper is 100,000 nanometers thick.

For the purpose of developing a gene therapy, what is of interest is the payload capacity of a viral vector. For instance, adeno-associated viruses (AAVs) are the most popular vector being used today, but their capacity is limited. These are attractive vectors because they are efficient and can transfer genetic material into virtually any type of cell, and don't cause an immune response. They also have a low incidence of causing damage to DNA. The problem is that they can only hold a 4.5 kilobase transgene cassette, which is too small for some indications. That's about half the capacity of lentivirus vectors or adenovirus vectors, two other popular viral vectors used to carry genetic medicines.

In addition to the vector needing to be large enough to accommodate the genetic payload, there also has to be room for additional material, like enhancers or promoters. In some cases, gene therapy developers have sought to alter the payload as a way around the size limitations of vectors. For instance, consider the rare progressive muscle disease Duchenne muscular dystrophy, which is caused by a mutation in the dystrophin gene, the largest known gene. The gene codes for the protein dystrophin, which is critical for muscle health. The dystrophin gene, though, is too large to fit in an AAV capsid. One strategy that is being pursued by different companies including Sarepta Therapeutics and Solid Biosciences is to develop a gene therapy for the condition using a smaller version of the dystrophin gene, dubbed microdystrophin, which is still able to produce functional dystrophin protein.

One other limitation of viral vectors is that once a patient is dosed, they will develop neutralizing antibodies that will prevent redosing a gene therapy that uses the same viral vector. The consequence of

that is if a gene therapy's benefits fade over time, a patient will not be able to get another dose to boost its effects because the patient's immune system will be trained to attack the vector.

## Building a Better Vehicle

To address some of the limitations of viral vectors, researchers are finding ways to construct man-made nanoparticles to serve as vectors. These non-viral vectors have the advantage of allowing for redosing because unlike the viral vectors, the immune system doesn't view them as pathogens and learn to target them. They can also be constructed to overcome some of the capacity constraints of viral vectors.

## Much Work Ahead

Already nanoparticles have proved useful for delivering certain RNA therapies to targets such as the liver, but researchers are working to figure out how to design them so that they can reach other desired cells and tissue. But, experts say while they have certain advantages over viral vectors and much potential, they are currently not as adept as viral vectors at entering cells.

*The reason why viruses are very good is because they've evolved for millions of years alongside humans that make them very efficient at transducing or infecting cells.*

— PHILLIP TAI, UNIVERSITY OF MASSACHUSETTS MEDICAL SCHOOL



"One drawback of these lipid nanoparticles, or non-viral vector platforms, is that they don't have all the advantages viruses have," said Phillip Tai, assistant professor at the University of Massachusetts Medical School and a researcher with the Horae Gene Therapy Center who works on AAV vectors. "The reason why viruses are very good is because they've evolved for millions of years alongside humans that make them very efficient at transducing or infecting cells. There's still a lot to be developed in terms of non-viral vector platforms."

Georgia Tech and Emory University's Dahlman considers the delivery of genetic medicines an engineering problem. He has an interdisciplinary team



that includes medicinal chemists, RNA virologists, structural RNA scientists, chemical engineers, and mechanical engineers working to develop nanoparticles as alternatives to viruses to deliver genetic medicines. While he believes there will always be a place for viral vectors, he said because they have advantages and disadvantages, it will be a matter of application that determines what the best vector is for any given application.

“There’s always going to be a disease that makes sense to treat with a viral vector and makes no sense at all to treat with a nanoparticle, just like there are going to be other diseases where it makes no sense at all to treat with a virus, but it does make sense to treat with the nanoparticle,” he said.

Dahlman and his team construct large volumes of nanoparticle vectors. They may differ in properties such as size, shape, electrical charge, and other ways. Those physical characteristics can make one nanoparticle adept at delivering its payload to one type of tissue rather than another. To figure out whether a particle can target specific tissue, Dahlman developed a means to barcode the particles with DNA to trace their activity. The DNA barcoding serves as a molecular tag that can be used to test thousands of lipid nanoparticles simultaneously.

Because of the commercial promise of the technology, Dahlman spun out the technology from Georgia Tech in 2018 to create Guide Therapeutics, which was working to use the technology to develop lipid nanoparticle vectors for genetic medicines. In 2021, gene editing therapeutics developer Beam Therapeutics acquired Guide Therapeutics for \$120 million in Beam common stock upfront and up to an additional \$320 million in technology and product success-based milestone payments. Beam expects to use the technology to target new tissues and diseases with its genetic medicines.

Gene editing is one area where nanoparticles have a key advantage over viral vectors. That’s because viral vectors, when used in CRISPR-mediated genome editing, can provide a more extended expression in targeted cells creating a greater opportunity for off-target effects. Non-viral vectors will gradually degrade, and the gene editing process ends there.



The limitations of the different vectors often define the disease for which they will be used. Dahlman points to hemophilia as an example of a disease where you need a single protein produced for a very long time at fairly constant levels. That makes an AAV a better choice than a lipid nanoparticle. In other cases, where you’re expressing a Cas9 nuclease, it would be ideal to have it cut the genome and then go away.

“You don’t want something cutting the genome and then floating around and cutting more genome for many years,” he said. “In that case, you want a non-viral system.”

For now, lipid nanoparticles are effective at targeting the liver. For instance, the drug company Alnylam is using this as a vector for its Onpattro, an RNA interference therapy used to disrupt the production of a pathogenic form of the protein TTR that is produced in the liver to treat the progressive, rare, genetic disease hereditary transthyretin-mediated amyloidosis in adults. Dahlman said today lipid nanoparticles can effectively deliver RNA drugs to the liver, but non-viral vectors that can deliver genetic materials to other tissues still must be developed.

“The way I think about it is for every tissue we solve delivery to, you’re looking at a dozen diseases that could be cured within that tissue,” he said. “It’s really important to work on non-liver delivery because the potential impact on patients is drastic. It’s night and day. The potential is so high if we could just get something outside the liver, it could really save a lot of lives.” ■





## Making Genetic Medicines Accessible

**Fyodor Urnov notes that with a CRISPR therapy today, it is possible to correct the rare blood disorder sickle cell disease, a condition that afflicts 100,000 people in the United States.**

But the urgency of the unmet medical need extends well beyond that. In Nigeria alone, he notes, there are as many 100,000 children born with sickle cell disease each year and their life expectancy is just 5 years.

"I'm a scientist, a molecular biologist, I'm not a health-care economist. I think the first thing we have to think about is, when we solve all the technical challenges, which we will, what will it take for the world to be the kind of decent place where we deliver these life-saving cures to those most in need?" said Urnov, professor of molecular and cell biology at the University of California, Berkeley and director of technology and translation at the Innovative Genomics Institute. "Yes, we've eradicated polio, we've eradicated smallpox, but have we had a good track record of delivering life-saving cures against disease, when those cures exist, to the part of the world where there is a burning need? Honestly, I don't think we have a stellar track record."

Urnov points to Sub Saharan Africa and Southeast Asia as areas where there is severe genetic disease and great need. He notes already there are companies, such as Intellia Therapeutics and Editas, which are developing *in vivo* CRISPR therapies that are injected directly into a patient.

"The proof of concept of CRISPR in a syringe is there. Now what needs to happen, and this is a major area of focus of the Innovative Genomics Institute and the Somatic Cell Genome Editing consortium, is making

CRISPR sufficiently versatile and safe," he said. "Then we can seriously talk about putting it in a syringe and going to South Africa, Thailand, or Nigeria and looking parents in the eye and giving informed consent to parents and saying, we are here with a syringe with CRISPR, and it is safe as best as we can tell."

### Changing the Economics of Genetic Medicines

The high cost of genetic medicines is raising questions about whether only the wealthiest individuals will be able to benefit from these scientific advances and what can be done to ensure equitable access. While questions of access may be the domain of bioethicists, health economists, and policymakers, the reality is that scientists have a significant role to play in making the technical advances necessary to translate genetic medicines into a form that can be cost-effectively delivered to patients.

In October 2019, the National Institutes of Health announced a collaboration with the Bill & Melinda Gates Foundation where each committed to invest \$100 million to develop gene-based cures for sickle cell disease and HIV. The goal of the collaboration is to advance safe, effective, and durable gene-based cures to clinical trials in the United States and relevant countries in sub-Saharan Africa within the next seven to 10 years. The ultimate goal is to scale and implement these treatments globally in areas hardest hit by these diseases, particularly in low-resource areas. From the start, the effort focuses on access, scalability, and affordability of advanced gene-based strategies for these conditions.



"In recent years, gene-based treatments have been groundbreaking for rare genetic disorders and infectious diseases," said Trevor Mundel, president of the Global Health Program at the Bill & Melinda Gates Foundation. "While these treatments are exciting, people in low- and middle-income countries do not have access to these breakthroughs."<sup>13</sup>



TREVOR  
MUNDELL

Within the area of sickle cell disease, the collaboration seeks to develop an easy-to-administer, gene-based intervention to either correct the underlying gene mutations or promote fetal hemoglobin gene expression to achieve normal hemoglobin function. Part of the challenge will be to develop gene-based delivery systems capable of selectively targeting hematopoietic stem cells to promote sufficient levels of normal hemoglobin expression and function.

The issue, of course, isn't limited to emerging economies. In the United States, there are economic inequities and healthcare disparities that create obstacles to access for high-priced gene therapies. While overcoming scientific hurdles will play a critical role in making genetic medicines affordable and accessible to all, R. Alto Charo, a professor of law and bioethics at the University of Wisconsin, Madison, points to the need to address other aspects of translating a discovery into an approved medical therapy.

"It's really important to look for ways to reducing the economic and technical obstacles to making these more available to each other," said Charo, who spoke during an NIH virtual conference in June about Gene-Targeted Therapies: Early Diagnosis and Equitable Delivery. "We have to look both at how we fund research and development and how we regulate the products that emerge."<sup>14</sup>

Charo argued that existing economic incentives provided to therapeutic developers are designed to give them extended exclusive markets to allow them an opportunity to recoup their investment in developing a therapy and to incentivize them to take that risk. The consequence, though, is it keeps prices high by forestalling competition.

The question, she said, is how do you increase incentives without extending exclusivity? Her solution is to

devise a new system of incentives that focus on R&D milestone payments or rewards for solving technical challenges rather than extending exclusivity as a way to mitigate the need for high profits.

Even at high prices these therapies may be cost-effective over the life of a patient, which may be enough in a single payer system where the government is the sole insurer. In the United States, though, insurers must provide a high upfront payment and may not have a patient who receives such a therapy in their system long enough to benefit from the cost savings. To address that, another solution, Charo argues, may lie in pooling these patients across insurers to spread the upfront costs and long-term savings.

## The Medium is the Message

Peter Marks, director of the U.S. Food and Drug Administration's Center for Biologics Evaluation and Research, said one thing his agency is working to do is to harmonize regulations to remove hurdles for drug developers to make their therapies available in low- and middle-income countries. The agency is working with the World Health Organization and counterparts in other countries on this and he said he hopes to see some progress within two years, particularly in the area of rare diseases.

To make an impact on a condition like sickle cell disease, Marks said it will not be enough to just treat a small group of patients with a cell-based approach or through a stem cell transplant. Instead, he said it will require developing a way to directly deliver a gene therapy by a vector that is reasonably safe, doesn't require ancillary medication, and can be delivered by a provider who may not be an expert in gene therapy. While he said that will be a tall order, it is not out of the realm of what should ultimately be possible.

"That's the type of thing we have to aim for here, ultimately, if we want to essentially democratize gene therapy," said Marks, during the NIH virtual conference in June about Gene-Targeted Therapies. "I think it's actually a worthwhile cause to look for because ultimately, if we can do it right in the rare space, we'll be able to do it in the larger spaces and make a difference there. We have to look towards this. I don't have a perfect answer, but trying to bring down costs, trying to be able to deliver things directly, that has to be the direction to get to equitable use."<sup>15</sup> ■



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