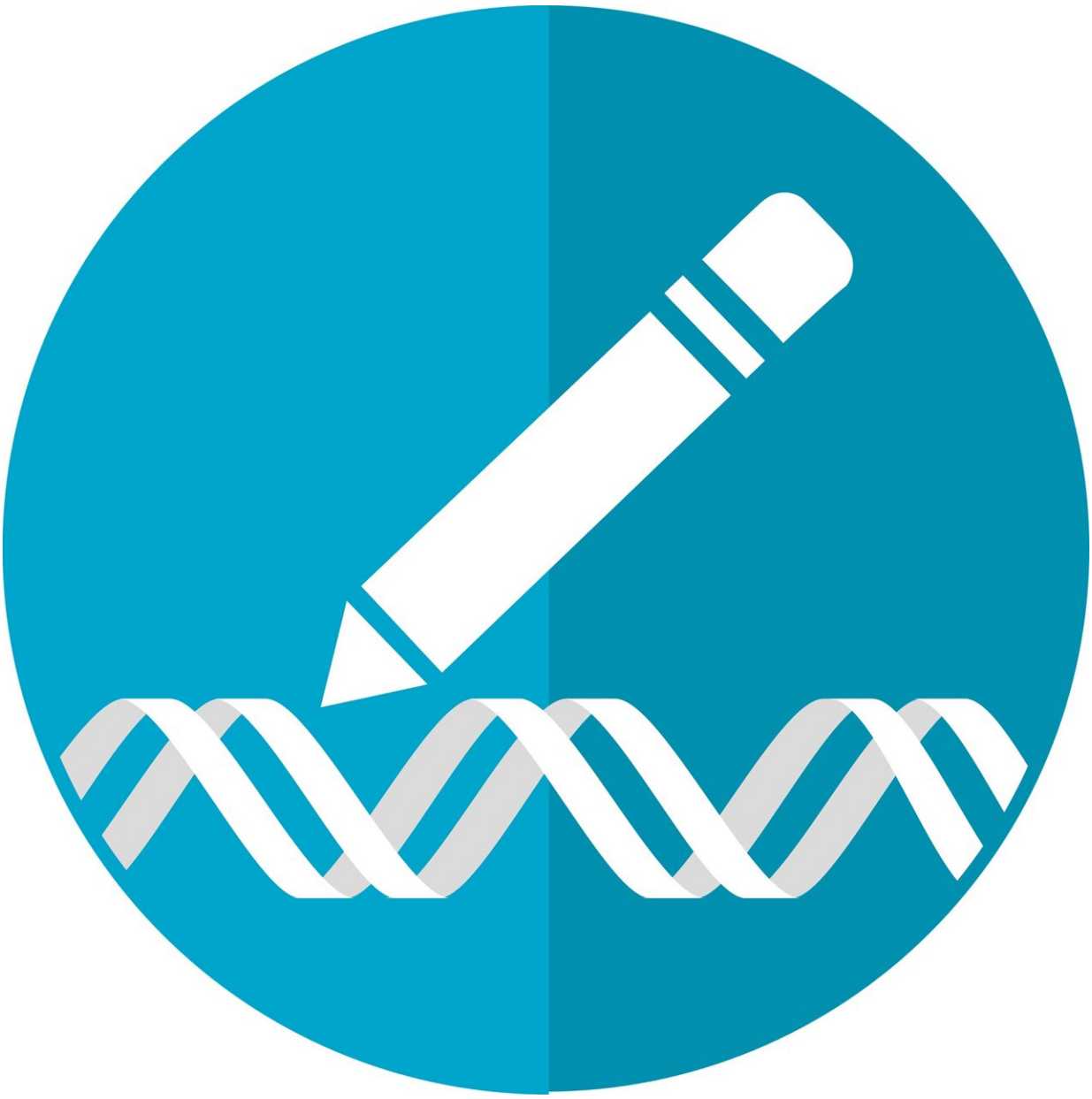
After a decade, CRISPR gene editing is a 'revolution in progress.' What does the future hold?

January 31 2023, by Karen Weintraub



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Medical innovations typically take 17 years from the time a lightbulb goes off in a scientist's head until the first person benefits.

But every once in a while, an idea is so powerful and so profound its effects are felt much faster.

That's been the case with CRISPR gene editing, which celebrates a 10th anniversary this month. It has already had a substantial impact on laboratory science, improving precision and speeding research, and it has led to clinical trials for a handful of rare diseases and cancers.

Over the next decade, scientists predict, CRISPR will yield multiple approved medical treatments and be used to modify crops, making them more productive and resistant to disease and climate change.

"It's a revolution in progress," said Dr. Eric Topol, a cardiologist who founded the Scripps Research Translational Institute, where he serves as director.

The rise of CRISPR is "unmatched and unparalleled" in science, added Brad Ringeisen, the executive director of the Innovative Genomics Institute at the University of California, Berkeley. "It's changed the way we do biology."

What is CRISPR?

In nature, bacteria use CRISPR systems to identify and disable the genes

of attacking viruses.

The scientific insight was that this bacterial immune system, an acronym for "clustered regularly interspaced short palindromic repeats," could be repurposed to edit cells of plants, animals and people.

CRISPR has the ability to find a specific spot in a strand of DNA and make a cut, add or swap a genetic "letter" or even a word.

"It's truly wondrous," said Fyodor Urnov, a gene editor at the University of California Berkeley's Innovative Genomics Institute. "It has worked in every biological setting that it has been placed into. Imagine somebody who can be a stellar performer in a heavy metal band and a symphony orchestra."

In late June 2012, biochemists Jennifer Doudna and Emmanuelle Charpentier published a paper describing how CRISPR works to edit genes. (The pair earned a Nobel Prize in chemistry in 2020 for their finding.) In January 2013, two other groups of researchers from Harvard and MIT showed they could use CRISPR to edit the cells of mammals.

Earlier this month, Doudna, a professor at the University of California, Berkeley, published a paper in the journal *Science*, noting the progress CRISPR has brought so far and its continued promise.

"CRISPR has come a long way in just 10 years, farther than I could have imagined when our paper was first published," she said in a follow-up email. "Each year we're seeing more clinical trials for CRISPR therapies, and new applications."

Gene editing existed before CRISPR, but it wasn't as efficient. CRISPR is easy to use, fast and allows much more precision in the edits than earlier technologies, several experts said.

"There are many instances that without CRISPR, our life as scientists would be much more difficult," said Beverly Davidson, a neuroscientist at The Children's Hospital of Philadelphia.

CRISPR is adaptable and precise, making many lab activities simpler, she said. Even undergraduates in her lab can be readily trained to get CRISPR to work.

CRISPR can still have off-target effects—hitting genes that weren't intended—but the risk is much smaller than with other editing tools.

That also explains why the field of gene editing is moving slowly and deliberately, said Dr. John Leonard, president and CEO of Intellia Therapeutics, which is developing CRISPR-based treatments for rare diseases and cancer. Sloppy work could lead to cancers or other problems.

"Nobody wants to make a mistake that hurts the potential, because the potential is so extraordinary," Leonard said.

Using CRISPR to treat cancer

CRISPR has the potential to improve cancer treatment by ramping up the immune system.

Since 2016, it's been used in trials of patients with blood cancer, editing their own immune cells outside the body to launch an immune attack on the cancer.

This approach, called CAR-T, has been shown effective against several types of blood cancer.

Until now, CAR-Ts has to be made for each individual patient, costing

money and time the person may not have.

Caribou Biosciences is working on an "off-the-shelf" version of the treatment that will be sitting in a freezer for the next patient who needs it, said Rachel Haurwitz, company CEO, president and co-founder with Doudna. This would cut weeks of preparation time and potentially cost.

In its first clinical trial, six patients with non-Hodgkins lymphoma had no detectable cancer after a single dose of the therapy, Haurwitz said.

How CRISPR works against rare diseases

More than 6,000 rare inherited diseases are caused by a single genetic "misspelling." For these, CRISPR offers the possibility of snipping the defective gene, ramping up a different one, or subbing out genetic "letters" that are causing problems.

The first gene therapy for sickle cell disease, based on a CRISPR snip, is expected to be approved later this year.

With other diseases, "it's harder to develop a single scissors to treat all of those mutations," said said Dr. Tippi MacKenzie, a pediatric and fetal surgeon at the University of California San Francisco.

Pompe disease, for instance, which weakens heart and skeletal muscles and can be fatal, has 100 different variations, each of which would need a different gene edit to correct, said MacKenzie, who also directs The Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research at UCSF.

Researchers must either find a gene edit they can make that will correct many variants, or figure out a way to rapidly develop an edit specific to each person with the disease.

In her own work, MacKenzie is developing gene-editing approaches that can be used on a late-second or third trimester fetus, addressing diseases that are easier to treat in utero and would cause harm if the child is allowed to develop further.

Editing a fetus would correct a disease, but would not be passed on to any children that child would go on to have.

"There are multiple advantages to treating diseases before birth," MacKenzie said.

Potential for gene-editing crops

The potential for using CRISPR to improve crops is "remarkable," said Ringeisen, and could help secure food for billions of people, even as climate change threatens more floods, droughts and diseases.

Gene edited crops are still mostly theoretical, but a few have recently hit the market.

Part of that is technological and part is consumer acceptance, said Zachary Lippman, a plant biologist and geneticist at Cold Spring Harbor Laboratory on Long Island, New York.

Plants that are gene edited may not technically be "genetically modified organisms" in the classical sense. GMO was defined to refer to transferring genes from one species to another, like a fish giving a plant a new ability.

Gene editing, by contrast, amplifies an ability that was already present in DNA and genes of a plant or a related species, making it more heat- or disease-resistant, faster growing or able to be planted more densely, for instance, Lippman said. These are changes that domestication of wild

plants or breeding has already achieved, he said, though it's too early to know if the public will accept them.

Lippman's own work focuses on tomatoes. He recently gene edited 10 varieties of tall-growing cherry and grape tomato plants to create dwarf versions that didn't require staking. It took him 18 months to make the three needed edits.

Whether companies will invest the time and effort in that kind of work for other crops remains to be seen, Lippman said. A company that makes a drought-tolerant soybean might be able to mark up their prices by 20% but that new soybean still has to compete with a soybean grown without CRISPR. Plus, crops that work well in one environment will likely need different edits to work in another.

"A the end of the day, this is not a panacea" that will transform crop production or enable humanity to survive climate change, Lippman said. "This becomes yet another tool in the toolkit of what conventional and modern breeding is already using."

Challenges for the next decade

The biggest controversy involving CRISPR took place in November 2018, when Chinese scientist He Jiankui was first reported to have used the gene editing tool to edit human embryos.

Most scientists and medical ethicists support the idea of using gene editing to improve the life of someone with a terrible disease. But they recoil in horror at the concept of editing the genome of a human embryo, making a change that will be passed down through the generations.

"We do not know enough about human biology to make genetic

engineering changes on behalf of the unborn," said Leonard of Intellia Therapeutics. Virtually all conditions that could benefit from such editing can be treated or prevented another way. "Nor can the unborn agree to have these procedures done to them."

Rogue actors might still be working in this area, trying to make "designer babies," but mainstream science and business are focused on solving pressing medical and social problems, he and others said.

Two other major challenges face CRISPR before it can gain widespread acceptance as a medical therapy: reducing its astronomical cost and figuring out how to deliver gene edits to more organs and cells.

Delivery "is the bottleneck that if we can break open, we'll be able to realize a much broader potential of gene editing," said Feng Zhang, who helped show CRISPR's usefulness in the cells of mammals.

So far, most of CRISPR edits have been in blood, which can be edited outside of the body; in the eye, which is relatively easy to target; or in the liver, where many cells end up as they are cleansed from the body.

The fact that even these areas can be reached is testament to other scientific advances and a deeper understanding of the biology of diseases over the last decade, said Zhang of the Broad Institute of Harvard and MIT, a biomedical research center. CRISPR is now delivered to the body inside harmless viruses or tiny balls of fat—two methods that have improved over the last decade.

It still remains challenging to deliver large molecules inside such tiny packages. This makes it particularly difficult to treat neurological disorders such as Huntington's Disease, Davidson said.

"It's an issue of delivering all of the machinery to the right cells at the

right time for the appropriate duration," she said.

Cost remains a hurdle for CRISPR and other gene editing approaches.

One therapy for adults with hemophilia, approved by the FDA late last year, costs about $3.5 million for a one-time treatment.

Three hundred million people across the globe suffer from diseases driven by a single gene, Urnov said, and the vast majority don't live in countries with well-developed healthcare systems. "Do we want a future where each of these treatments is $3 million and then we can immediately calculate where it can be available and for whom?"

Leonard said that a one-time treatment leading to a cure "can be incredibly economically efficient."

But costs are a secondary concern at the moment, expected to go down as manufacturing and other processes improve and demand increases. "First we've got to start with the innovation and then solve for the access," he said.

What else is on the horizon?

Researchers hope to one day be able to reliably edit multiple genes at once, enabling CRISPR to tackle more common, complex diseases.

George Church, who co-authored one of those papers a decade ago, said he has already managed to make up to 24,000 edits in a single cell and is working up to making 1 million.

Church, a Harvard Medical School geneticist who always pushes the edge of what's possible, hopes to restore the woolly mammoth with such multiplex gene editing, as well as help people become resistant to

dangerous viruses.

Ringeisen would like to be able to turn up or down genes that regulate inflammation, potentially treating diseases like Parkinson's or Alzheimer's. In agriculture, he envisions gene-editing plants and microbes to capture carbon and reduce global warming.

Zhang said he would like to use gene editing to restore cells to a more youthful and healthier state. The goal, he said, would not be to help people live forever, but to improve their health while they are alive.

And Urnov envisions a day when even complex diseases like heart disease can be avoided with gene editing.

"I would love a future where we would use CRISPR to prevent disease before it starts," he said.