What's new in clinical CRISPR?

In the past year, there has been more CRISPR news than the awarding of the Nobel Prize in Chemistry to Jennifer Doudna and Emmanuelle Charpentier. Gene editing has continued its forward momentum in major ways, and scientists are beginning to see results.

Carrie Arnold

2020 was marked by a win for CRISPR-Cas9 sciences, when Jennifer Doudna and Emmanuelle Charpentier received the Nobel Prize in Chemistry for their work.

Although the Swedish accolades may have once again catapulted CRISPR into the headlines, clinical advances in genome editing have also made great strides in the past year. From the development of more-effective editing tools to progress in trials for cancer and Mendelian blood disorders, CRISPR has finally begun to cross the finish line into actual clinical use.

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Clinical trials

Biopharmaceutical startups such as CRISPR Therapeutics and Beam Therapeutics (both based in Cambridge, Massachusetts) have turned their attention to hemoglobinopathies such as β-thalassemia and sickle-cell disease. Both diseases result from single-base mutations in genes encoding hemoglobin proteins and can cause life-threatening illness.

Instead of using CRISPR to replace the mutated gene with a healthy copy, biopharmaceutical startups have used genome editing to alter the gene-regulation machinery that normally switches off another hemoglobin-encoding gene early in fetal development. This fix provides enough healthy, alternative hemoglobin to compensate for the mutation. In November 2020, CRISPR Therapeutics announced early success from their CTX001 therapy, which delivers CRISPR-Cas9 to hematopoietic stem cells via electroporation. After a patient's own hematopoietic stem cells are chemically eliminated with busulfan, the CRISPR-edited stem cells are infused back into the patient. Four patients treated with CTX001 no longer depended on transfusions for the treatment of their β-thalassemia or sickle-cell disease.

"This is a huge win," says Ross Wilson, a molecular biologist at the Innovative Genomics Institute at the University of California, Berkeley. The idea that scientists could go from figuring out the biochemistry of Cas9 in 2012 to curing someone in 2020 is "astounding," he concluded. "This isn't a theoretical cure, this is pretty much a known cure."

Another CRISPR clinical trial by Editas Medicine, in which the gene-editing machinery is delivered directly to the eye to delete the mutation that causes a form of inherited blindness called 'Leber's congenital amaurosis 10', has also recently gotten underway.

Multiplex base editors

Harvard University chemist David Liu and then-postdoctoral fellows Nicole Gaudelli and Alexis Komor developed a variant of CRISPR called 'base editing'. In 2016, Komor and Liu fused a CRISPR-Cas9 complex to a cytidine deaminase, which allowed them to directly change cytidine to uridine. The next year, Gaudelli and Liu published the development of another base editor that would deaminate adenine into inosine, which polymerases treat as guanine. Gaudelli and Komor founded Beam Therapeutics to bring their discovery to the clinic.

In July 2020, a collaboration between Liu and Doudna revealed the 3.2-angstrom-resolution structure of the first base editor in a paper in *Science*, which Liu says will provide insights into the development of other base editors. In a discovery published in *Nature*, Liu showed that fusing the cytidine deaminase to a bacterial toxin could enable CRISPR-free base editing in the mitochondria.

"Mitochondria have remained one of the few corners of biology untouched by precision genome editing," Liu says. "You can now use this to introduce, for the first time, purposeful changes in the sequence of mitochondrial DNA in a living cell."

In 2020, a preclinical test of a base editor directly injected into the inner ear of a mouse model of genetic deafness partially restored hearing in the animals, according to a June *Science Translational Medicine* paper. That same month, three papers published simultaneously in *Nature Biotechnology* showed that base editors could be multiplexed and could make multiple edits at the same time.

"And if you have really high efficiency, then you're killing four birds with one stone," Gaudelli says — and this is a strategy that she believes will be especially useful in engineering T cells for cancer therapies.

Cancer immunotherapy

In February 2020, University of Pennsylvania cancer biologist Carl June published, in *Science*, the first report of patients with cancer (here, myeloma or drug-resistant metastatic sarcoma) treated with CRISPR-edited T cells. Two months later, a team of Hong Kong scientists showed that a similar approach could be used to treat patients with refractory non–small-cell lung cancer.

At the University of Minnesota, cancer researcher Branden Moriarity is using CRISPR to target the previously drug-refractory protein CISH, an intracellular immune-checkpoint protein. His team is also working to engineer natural killer cells through the use of CRISPR to create an equivalent to CAR T cell therapy that selectively eradicates cancer cells.

"In a number of patients, the tumors don't just stop," Moriarity says. "Natural killer cells are kind of like a backup plan to kill the cancer."

Delivery

Beam Therapeutics' Gaudelli says her company has begun to investigate the use of cationic lipid–based nanoparticles to deliver their proprietary genetic editing therapeutics for various hereditary liver diseases. In November, Intellia Therapeutics (co-founded by Doudna) delivered CRISPR-Cas9 encased in a lipid nanoparticle to people with hereditary transthyretin amyloidosis, a systemic disease that creates clumps of amyloid protein in organs.

At Harvard Medical School, virologist Luk Vandenberghe has begun building better viral vectors for CRISPR delivery. Adeno-associated viruses (AAVs) are small and therefore can package only a small amount of DNA—a major barrier, given the large size of most Cas nucleases. While some scientists are searching for smaller Cas proteins, Vandenberghe is working to alter the AAV to enable it to carry a larger DNA payload and to target specific cell types. Work with a synthetic AAV vector that targets the inner ear showed success in June when it was tested in mice.

COVID-19

The COVID-19 pandemic may have altered global events, but it also gave CRISPR a chance to shine. Two biotech diagnostic companies, Mammoth Biosciences, located in San Francisco, California, and Sherlock Biosciences, in Cambridge, Massachusetts, each quickly developed a CRISPR-based diagnostic test for SARS-CoV-2. Although Sherlock's test received Emergency Use Authorization by the US Food and Drug Administration in May 2020, Mammoth's test is still gearing up for such approval. Although these tests have yet to be widely used, their strong performance against a backdrop of testing problems makes their future use even more promising, Wilson says.

And if CRISPR can be used to detect viruses, scientists are also turning to gene editing to fight them. In February 2020, just as the world was beginning to wake up to the threat posed by the novel coronavirus, a team of virologists from Temple University tested a CRISPR gene-editing technology developed by Excision BioTherapeutics that cured a subset of humanized mice of infection with human immunodeficiency virus (HIV). Although antiretroviral medications can reduce HIV levels to near zero, the virus can survive by inserting its genome into host DNA. After treating the mice with high-dose antiretroviral agents, Excision programmed CRISPR-Cas9 to target HIV genetic sequences in host cells and chop up the sequence, which eradicated viral reservoirs and cured the mice of HIV infection.

"We really are excited that we've demonstrated this in an animal model for the first time," says Daniel Dornbusch, CEO of Excision. ❐

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