Gene Editing Breakthroughs: A New Hope for Patients

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Gene Editing Breakthroughs: A New Hope for Patients

This article was originally published on ***This Month in Transformative Medicine*** *on May 24, 2023.*

Anshul Mangal *President of Project Farma and Precision ADVANCE and* ***Cynthia Pussinen****, Advisor & Executive Consulting Partner share how the latest breakthroughs in gene editing technology have the potential to dramatically improve outcomes for patients.*

Gene editing technology has rapidly evolved over the past decade. From the initial breakthrough of sequencing the first human genome, to researchers today having the ability to create genetically modified mice in as little as four weeks. CRISPR Cas-based gene editing, which acts as a pair of genomic scissors, is at the core of these innovations. The revolutionary technology has enabled rapid genome sequencing and editing to spur advancements in disease research and treatment. The Cas9 or Cas12 enzyme is leveraged to make cuts in the DNA allowing for new genes or segments to be inserted or replaced, giving rise to infinite applications for treating genetic diseases. The technology has forever changed the way we can research and treat genetic diseases with the power to rapidly screen genes for clinically actionable data and information within the span of a few days.

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Today CRISPR continues to evolve and is now capable of altering multiple DNA sequences or base pairs at once in a technique called multiplex base editing. Researchers not only have the ability to cut and insert genes but can now permanently change a single base pair without breaking DNA via the precise method of base editing. This technology has broad implications for genetic diseases caused by a single point mutation. Base editing is advantageous compared to other historical methods of editing, due to its ability to be precise and specific while leaving the DNA intact, thereby eliminating the need for complex repair mechanisms. The ability to alter a single base pair also provides an opportunity to solve for genetic diseases without targeting a genetic mutation sequence and can address the core problem or protein. This technique is a critical advancement as patients suffering with the same disease may have different underlying mutations that cause it. If a gene editing treatment was developed to treat only one type of mutation, it would leave the other subset of the patient population unserved.

This time last year a 13-year-old girl became the first ever patient to receive base edited cells to treat her seemingly incurable T-cell acute lymphoblastic leukemia. After all traditional methods of treatment failed the patient and her family, she was enrolled in a study where she received base-edited donor T-cells that were genetically modified to hunt and destroy the cancer cells. Within 28 days she was in remission, remarkable results for the patient and her family. In this case, base edited cells offered a more desirable option in treating T Cell lymphoma compared to traditional CAR-T therapy, as CAR-T manufactured cells destroy both the cancer cells and each other prior to administering them to the patient.

The Gene Editing Pipeline

Several companies in the gene editing space have seen exciting developments in their efforts to harness the power of CRISPR technologies to improve the lives of patients.

Within the next year Vertex and CRISPR therapeutics are expected to receive a decision from the FDA for their CRISPR-based ex vivo cell therapy exagamglogene autotemcel (exa-cel) sickle cell and beta-thalassemia treatment. The companies are seeking approval for the first-in-modality genome-editor in the US, EU, and UK for the treatment of two haemoglobinopathies. Clinical trials showed promising results for a potentially curative treatment for patients suffering with sickle cell. In a race to save lives, the companies have requested a priority review with the FDA and based on the positive clinical data the agency has allowed Vertex and CRISPR to begin a rolling approval application. If approved the therapy would be the first CRISPR technology to market.

Last month, the FDA cleared the first study of CRISPR gene editing in human patients. Intellia Therapeutics got the green light to begin clinical trials for CRISPR gene editing in vivo. The product aims to treat patients with hereditary angioedema, a rare and serious genetic condition that causes swelling in the face and airways. To date, CRISPR has been utilized to edit cells and tissues outside of the body which are then reintroduced to the patient.
This landmark decision from the FDA means that Intellia can now introduce CRISPR directly into the patient. From there, the company's proprietary non-viral platform deploys lipid nanoparticles to bring the liver a two-part genome editing system, guiding RNA specific to the disease-causing gene, and messenger RNA that encodes the Cas9 enzyme, which together carry out the precision editing. The benefit of this application could reduce costs for patients and open up a new host of potential for in vivo gene editing. In vivo treatments are currently approved in other countries including the UK.

> With continued innovation, the possibility of **gene editing applications are endless**.

Patients suffering with HIV/AIDS may have a new hope for a cure. For years researchers have been improving the standard of care for patients living with AIDS, and with these advancements many patients are living longer and healthier lives than ever before. However, the virus still takes a serious toll on those afflicted. A recent study used dual CRISPR technology in combination with the current standard of care to successfully eliminate HIV virus in mice. The results were promising with researchers demonstrating the ability to eliminate the virus in ~60% of the models, up from 29% in 2019. The study shows the exciting possibilities and potential of gene editing for diseases that have long been without cures, but also highlights the need for better therapeutic delivery options. With continued innovation and solutions for drug delivery the possibilities of gene editing applications are endless.

Barriers to Overcome

The application of gene editing technologies has the potential to help many patients currently living with hereditary conditions and those who face limited treatment options. Researchers are working aggressively to identify roadblocks and find solutions in therapeutic development, delivery, and accessibility to ensure that this life saving technology can reach patients and provide the best possible outcomes. Viral vectors have been the most common choice of therapeutic delivery methods, but can come with issues in safety, efficacy, and challenges in manufacturing scalability. To overcome these issues scientists are exploring alternative delivery methods like extracellular vesicles and virus-like particles that can offer the same benefits as viral vectors' delivery function, while improving safety for the patient. As companies march their gene editing products to the finish line, the question of pricing for these novel therapies is once again front and center. If the industry wants to see meaningful advances in CRISPR based treatments, developers must work to find ways to reduce cost for the patients and ensure accessibility.

Gene editing technology has seen rapid and incredible innovation in the past decade. With researchers continuing their diligent work to find solutions for delivery and accessibility roadblocks, the sector is poised to create meaningful change for patients living with genetic diseases.

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About the Authors

Anshul Mangal
Anshul Mangal is President of Project FARMA & Precision ADVANCE. Anshul founded and grew PF into a leading global biologics and advanced therapy engineering consulting firm. Under Anshul's leadership, PF pioneered the industrialization of advanced therapies including two notable, commercially approved cell and gene therapies. PF was acquired by Precision Medicine Group in 2020 to be the cornerstone of Precision ADVANCE. ADVANCE is a collection of Precision's services uniquely focused on the complexities of research and clinical development, regulatory, manufacturing, and commercial needs to successfully bring an advanced therapy to market.

Cynthia Pussinen
Cynthia Pussinen has more than 25 years' experience leading global organizations and high performing teams in the life sciences industry. Her expertise spans the drug development continuum from research through commercialization. She has led the development, licensure, commercialization and subsequent delivery to patients, of more than fifteen new medical therapies for patients globally, including Obizur® (Antihemophilic Factor (Recombinant), Porcine Sequence), Eraxis® (anidulafungin), ZMAX® (azithromycin) and of LUXTURNA® (voretigene neparvovec-rzyl), the first gene therapy approved in both the United States and the European Union. Cynthia has served on the Drexel University Solutions Advisory Board, and as a Board Director for Spark Therapeutics UK Ltd. and Spark Therapeutics Ireland Ltd. She is currently a Board Advisor for an enterprise software and solutions focused company valued at more than $1.5B.

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