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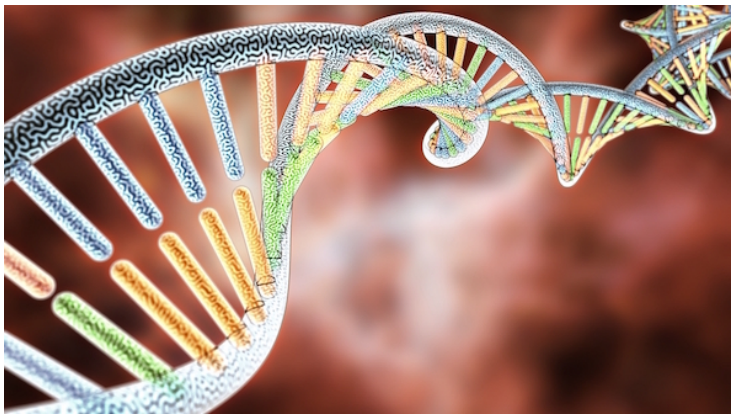
ASIA EDITION

Marvels of gene-edited meds unleashed

01 October 2021 | Analysis | By Ayesha Siddiqui

In June 2021, US-based Intellia Therapeutics announced first-ever clinical data supporting safety and efficacy of in vivo CRISPR genome editing in humans, a pivotal moment in the gene editing landscape, offering hope for genetic disorders. BioSpectrum explores the latest in the field of gene editing and what the future holds for this technology.



There are three commonly acknowledged gene editing technologies, namely, Zinc Fingers, Transcription Activator-Like Effector Nucleases (TALENs), and Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR). While all three enable gene editing, it was the advent of CRISPR in 2012 that has led to widespread use of gene editing technology within life sciences research.

Scientists Dr Jennifer Doudna (UC Berkeley, USA), Dr Emmanuelle Charpentier (Max Planck, Germany) and Dr Feng Zhang (MIT, USA) are the pioneers of CRISPR gene editing. The trio and the respective institutions backing them have founded companies to commercialise the CRISPR-Cas system. Dr Jennifer Doudna and Dr Emmanuelle Charpentier share the 2020 Nobel chemistry prize for their discovery of gene-editing technique.

Dr Doudna has founded Caribou Biosciences and Intellia Therapeutics, while CRISPR Therapeutics, ERS Genomics and Casebia Therapeutics are associated with Dr Charpentier. Editas Medicine was launched by Dr Zhang and Dr Doudna.

"Gene editing with CRISPR is a relatively simple process, allowing scientists at any level to easily apply the technology. Reagents can be obtained in days (versus several weeks for the other technologies) and generally come at a considerably lower cost. CRISPR is flexible enough to be used in any of the three main forms of gene editing - deleting, inserting, or editing DNA. A huge advantage of CRISPR is that it can be used in a 'library' format wherein thousands of gene edits can easily be made simultaneously and then the results are shifted to find specific target genes with interesting results. This has enabled scientists to begin untangling the vast collection of genomic data which has been amassed over the last 10 years, and use that information to better understand the complexities of biological processes and disease," said Eric Rhodes, CEO, ERS Genomics, Ireland.

Dublin-based ERS Genomics Limited, was formed to provide broad access to the foundational CRISPR/Cas9 intellectual property co-owned by Dr Emmanuelle Charpentier. This could be the reason CRISPR is having its moment.

In June 2021, US-based Intellia announced the first clinical data in history to demonstrate potent reduction of disease-

causing proteins with a single-dose infusion of CRISPR genome editing therapy. They were able to directly deliver lipid nanoparticles containing Cas9 mRNA and gRNA to liver cells to correct ATTR amyloidosis. This is the first case of direct gene editing in humans and appeared to be safe and very effective. These landmark data represented a momentous milestone for the patients and the biotech industry.

"Over the last years, the field has begun to transform the potential of CRISPR into medicine; however, technical challenges remain. Realising the full potential of CRISPR and the benefits of in vivo genome editing requires the ability to deliver the treatment to the right cells in the body and to the right location in the genome. Intellia is the only company that has produced clinical data indicating our ability to achieve both these criteria – a highly significant scientific and technical achievement. This is critical for establishing the broadest potential for patients across a wide range of diseases," said John Leonard, President and Chief Executive Officer, Intellia Therapeutics, USA.

Until now, scientists have used CRISPR ex vivo where editing occurs in cells outside the body and those edited cells are transferred into patients. That's why Intellia's results represent a step forward for CRISPR.

“Presently, there are many active clinical trials employing some level of gene editing. These include random integration using lenti-based systems and targeted editing using CRISPR and TALEN-based technologies. Most of the current work is ex vivo where cells are modified outside the body and then delivered back for therapeutic effect. We are getting very good results in disrupting a gene using CRISPR or TALENS where more than 90 per cent editing is becoming common”, said Jason Potter, Director of Genome Editing, Thermo Fisher Scientific, USA.

Though CRISPR is the toast of the town at the moment, there’s scope for other gene editing technologies too. US’ Sangamo’s Therapeutics is using its proprietary Zinc Finger (ZF) platform to develop therapies for a wide variety of diseases.

French firm Cellectis uses TALEN to develop therapies for cancer as does Bluebird bio of the USA.

Ethical concerns

In 2018, when Chinese scientist Dr He Jiankui, announced that he had created the world’s first gene-edited babies using CRISPR, it sparked a controversy and raised ethical concerns about the use of such technologies.

Since then, the World Health Organisation (WHO) has banned the germline cell editing and in June 2021 issued new recommendations on human genome editing for the advancement of public health.

The reports deliver recommendations on the governance and oversight of human genome editing in nine discrete areas, including human genome editing registries; international research and medical travel; illegal, unregistered, unethical or unsafe research; intellectual property; and education, engagement and empowerment. The recommendations focus on systems-level improvements needed to build capacity in all countries to ensure that human genome editing is used safely, effectively, and ethically.

A CRISPR Future

By virtue of its ease of use and low cost, CRISPR has already opened up the use of genome editing to disciplines that had previously not even considered it as a possibility.

"It is likely to become a major player in the treatment of genetic diseases. Perhaps much in the same way that software has evolved to manipulate computer and robotic hardware, so too will gene editing serve as a 'coding tool' for exploring and exploiting the biological hardware of living systems. The ethics surrounding gene editing are also becoming an important topic as the technology evolves and applications expand", said Dr Rhodes.

The biggest barrier to overcome in gene editing is to demonstrate its effectiveness and safety. Current trials reveal that the process can be safe and long lasting. However, most applications are still focused on untreatable orphan diseases and very sick people so the affected populations are small.

"As gene editing is proven safe and as we better understand how to deliver it for best effect, it will be applied to more common diseases, like some forms of diabetes, where there are currently established therapies. A lifetime of being on a drug could be replaced by a single gene editing treatment to cure the disease. Debilitating childhood diseases could be cured

early, allowing for a more normal development", added Potter.

Ryan Donnelly, Senior Product Manager, Gene Editing Reagents, Horizon Discovery, UK, outlines how gene editing will evolve in the future. From research to therapy, Horizon Discovery drives the application of gene editing and gene modulation. “The scale and number of experiments and/or edits made will rapidly increase. Instead of interrogating a single gene, experiments could be set up to investigate an entire network of pathways, or to engineer cell models capable of mimicking polygenic diseases with multiple causative mutations”, said Donnelly.

“The type of cells being manipulated will continue to expand. While immortalised cell lines are relatively easy to edit and therefore great for proof-of-principle work, they are limited in how similar they are to non-cancerous cells found in vivo. As such, groups will look to work with cell types that more accurately represent cells found in vivo e.g., differentiated induced Pluripotent Stem Cells (iPSCs), primary cells, 3D cell models and organoids, as to have stronger confidence in results. It will continue to evolve beyond gene editing. 'CRISPR without the cut' systems use deactivated or 'dead' Cas9 (dCas9) which utilises guide RNAs to target the CRISPR-dCas9 complex to a specific DNA region but instead of cutting the DNA, the dCas9 is linked to additional protein(s) e.g., activators, inhibitors, epigenetic modifiers, affinity tags, or fluorophores, the options are endless”, added Donnelly.

Therapies using CRISPR will revolutionise medicine. Early success stories on the use of CRISPR to correct disease causing mutations in humans show that CRISPR-based therapies are a reality. However, targeting these therapies to difficult-to-access organs such as the brain may continue to pose issues.

Gene editing is advancing so rapidly that next-generation technologies are already on the heels of CRISPR-Cas9. One such example is base editing. US’ Beam Therapeutics is pioneering the use of proprietary base-editing technology to develop powerful, uniquely precise genetic machines that rewrite genetic code.

Another American firm Editas Medicines recently released data on a new gene editing technology termed SLEEK (SeLection by Essential-gene Exon Knock-in). SLEEK enables high efficiency, multi-transgene knock-in of iPSCs, T cells, and Natural Killer (NK) cells.

Although still in the research and development phase, gene-edited medicines will inevitably transform the lives of millions of patients and transform the industry when they are launched in the market.

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