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Exploring the Role of mRNA in CRISPR-Cas Gene Editing

Announcer:
Welcome to *Innovations in Medicine,* sponsored by Moderna. This is a non-certified educational series produced and controlled by ReachMD and is intended for healthcare professionals only. On this program, we'll hear from Dr. Piotr Kowalski, an HRB funded Emerging Investigator for Health and a Senior Lecturer in Advanced Therapies at the School of Pharmacy at University College Cork in Ireland. Let's hear form Dr. Kowalski now.

Dr. Kowalski:
Gene editing tools really enable the replacement or alteration of gene expression by introducing site-specific modification into genome of themselves, and two ways we can do it is either to use in ex vivo gene editing, which is performed outside of patient's body on his own cells, or in vivo, which is usually performed directly in the patient tissue. So mRNA technology is actually applicable to both types of gene editing, and it's really had a transformative role in enabling to utilize nonviral approaches for delivery of gene editing tools. So for example, in contrast to plasma DNA, which is often delivered using viral vector, the mRNA-based delivery would carry no risk associated with the integration of the nuclease into the host genome.

Currently, older generation of gene editing tools, such as protein-guided nucleases including, for example, zinc finger nucleases or TALENs, or transcription activator-like effector nucleases, are being phased out by RNA-guided nucleases, such as CRISPR-Cas which are simpler to design and use therapeutically. So the breakthrough of potential of this CRISPR technology has actually been recognized with a Nobel Prize in 2020 in the Nobel Prize in Chemistry.

So safety and efficacy of delivery of this CRISPR-Cas complement to the target cells is really the major the major barrier, and especially if we think about applications of these therapies to different diseases that affect organs outside of the liver. This is another big challenge in the field. So currently we're able to deliver CRISPR tools to liver potentially lungs and muscle cells, so anything else outside of these tissues would be still very challenging to treat. Other aspects of utilizing CRISPR tools for therapy would include actually or would be more associated with how the CRISPR system works. So for example, potential for imperfect DNA targeting specificity leading to off target off target effects, so Cas9 nucleases can sometimes make mistakes, and cut outside of the desired region in the genome.

So this is one challenge to increase the specificity and limit those type of target effect. With these tools, another important aspect would be low efficacy of genome editing for gene replacement or gene correction strategies, which often require an additional delivery of DNA template together with a CRISPR-Cas component. So right now, there's a lot of efforts in the field to also develop a new types of gene editing tools, called Prime or Grant editing tools, which obscure the need for the use of these DNA templates and making the delivery a little bit easier, and the reliance on, for example, cell division in order to introduce changes in the genetic information.

So, I think that the take-home message would be that the application of mRNA technology has been really transformative for therapeutic applications of gene editing tools in vivo, really paving the way for nonviral genome editing therapies. So, initial clinical data looks also very encouraging in terms of safety and as well, the efficacy which really is reassuring and holds the promise for gene editing through drugs making their way into the market in the near future.

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