Introduction on the topic of genome editing for rare disease patients

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In early 2016, health and science news outlets were talking about research studies using mouse models and human cells in which Duchenne Muscular Dystrophy was partially treated using genome editing. This is just one example of an increasing build-up of editorials, blog posts, reviews and position statements surrounding recent scientific advances in genome editing technologies. Why so much interest and debate? How is it different to gene therapy? How does it work?

What can genome editing do?

Genome editing essentially allows DNA in a living cell to be modified in a predetermined manner. This technology has the potential to treat many genetic diseases which are caused by alterations in the genetic code (mutations). All genes are made of DNA and form the blue prints of the proteins that build the body. When a gene is mutated, part of the DNA is changed in such a way that the protein it encodes no longer functions correctly. Theoretically, genome editing technology could allow these mutations to be corrected, restoring the function of the protein, and potentially alleviating the disease.

This is an exciting prospect as currently most genetic diseases do not have a cure. If treatments are available they are usually aimed at managing the symptoms or slowing the progression of the disease. Genome editing tools allow scientists in the lab to address the cause and not just the symptoms of genetic diseases by performing a sort of genetic surgery. Technically, they are able to change genes by adding, replacing and/or removing sections of DNA, thus correcting the mutation responsible for causing the disease. The latest genome editing system is called CRISPR/Cas9, and is faster, cheaper, and more accurate than any other system. It is also technically easy to use, which means that it is accessible to a large number of scientists and laboratories. **Importantly, this technology is still being developed and it may be many years before genome editing could directly benefit rare disease patients.**

How is genome editing different to gene therapy?

Traditional methods of gene therapy generally involve adding a functional copy of a gene to a patient's cells without removing the original mutated copy. In cases where the mutated gene stops producing a protein, or the protein it produces is harmless, this added gene method works well. However, if the mutated gene

produces a harmful protein, adding a healthy copy will not treat the disease. Genome editing could be successful in these situations.

The main advantage of genome editing over gene therapy is that it aims to correct the original altered (mutated) gene rather than trying to compensate for the dysfunction induced by the mutation. Whereas gene therapy introduces a healthy gene to a random location (which in some cases could cause unwanted disturbances), genome editing targets specific sequences within the genome.

How does CRISPR/Cas9 work?

While genome editing tools have existed for a number of years, CRISPR is considered by many experts as a breakthrough in genetics. CRISPR /Cas9 is derived from bacterial enzymes and uses a guide molecule (made from RNA – a molecule similar to DNA but present in much shorter lengths in the cell) to bring the DNA-cutting Cas9 enzyme to the specific part of the DNA that contains the disease-causing mutation. Once the Cas9 enzyme cuts the DNA at that target site, the system can then replace the faulty DNA sequence with a healthy version, based on the guide molecule.

Why is there such a hype and debate around CRISPR?

There is currently a lot of interest about CRISPR because it creates a much more accessible and inexpensive way of editing genes, can be programmed to act on several locations of the genome at once, and has been shown to be highly accurate in identifying and cutting out the unwanted DNA.

Although very promising with potentially a wide range of future clinical applications, significant scientific challenges still need to be overcome before the technique can benefit patients. One of the main challenges, and why there is reason to take a cautious approach, is concern about safety. There is the possibility of “off-target” events that could occur when genome editing accidentally change a different location within the genome. Another challenge is to develop accurate and efficient methods to deliver the system to the patient’s cells. Given the unprecedented pace at which the field is developing, there is an urgent need to establish guidelines for the development of CRISPR-based pre-clinical research ahead of any potential clinical applications.

Furthermore, the big debate that currently animates the international community evolves around the potential to correct genes in human embryos – a practice that is unlawful in many countries. This could involve removing harmful gene mutations from egg or sperm (germ cells) prior to in vitro fertilisation, and thus making permanent changes to the DNA of subsequent generations. Thus genome editing has implications for national and international communities. Discussing and anticipating health, safety and ethical issues before the introduction of these techniques into the clinic, will be a priority for clinicians, scientists, ethicists, policy makers, and patient representatives.

Further information (in English only):

For more information on research studies on Duchenne Muscular Dystrophy using genome editing, see:

- Long C et al. (2016) Postnatal genome editing partially restores dystrophin expression in a mouse model of muscular dystrophy *Science* **351(6271)**:400-403
- Nelson CE et al. (2016) In vivo genome editing improves muscle function in a mouse model of Duchenne muscular dystrophy *Science* **351(6271)**:403-407
- Tabebordbar M et al. (2016) In vivo gene editing in dystrophic mouse muscle and muscle stem cells *Science* **351(6271)**:407-411

For more detailed scientific information on genome editing, see for example :

- Cox et al. (2015) Therapeutic genome editing: prospects and challenges *Nature Medicine* **21 (2)**:121-131
- Doudna JA and Gersbach CA (2015) Genome editing: the end of the beginning *Genome Biology*. **16**: 292
- Maeder M and Gersbach CA (2016) Genome-editing Technologies for Gene and Cell Therapy *Official Journal of the American Society of Gene and Cell Therapy* **24(3)**:430-446
- Kanchiswamy C et al. (2016) Fine-Tuning Next-Generation Genome editing Tools *Trends in Biotechnology* **34(7)**:562-574

For a video explaining how CRISPR/Cas9 works, see for example McGovern Institute for Brain Research at MIT : https://www.broadinstitute.org/what-broad/areas-focus/project-spotlight/crispr

For more information on gene therapy, see for example the website of European Society for Gene and Cell therapy : http://www.esgct.eu/

For examples of position statements, see:

- http://www.nationalacademies.org/gene-editing/Gene-Edit-Summit/index.htm
- http://www.hinxtongroup.org/hinxton2015_statement.pdf
- https://ec.europa.eu/research/ege/pdf/gene_editing_ege_statement.pdf

For examples of blog posts from patient organisations, see:

- http://community.parentprojectmd.org/profiles/blogs/finding-hope-in-crispr-cas9-1
- http://www.geneticalliance.org.uk/genome-editing-.htm