

Somatic genome editing: promise and practicalities

November 2019

The development of genome editing tools, including the discovery and refinement of CRISPR-based techniques and associated technologies, is fuelling a new wave of advances in genetic medicine. Somatic genome editing offers enticing opportunities for treating rare genetic conditions, alongside improvements in the treatment of more common conditions such as cancer. In this policy briefing we explore the current and future uses of somatic genome editing for health.

Summary

- Unlike traditional drug therapies, genome editing makes permanent changes to the genome, treating the cause rather than the symptoms of disease, and may be curative rather than simply therapeutic
- Genome editing tools are made up of several modifiable parts, many of which can be altered independently. Alongside the circumstances in which these techniques are applied, all parts contribute to the effectiveness of the individual application
- Editing precision, tool delivery and public image remain amongst general challenges for using genome editing to treat disease
- Genome editing is not a 'cure-all' for genetic disease, but could have an important impact in several areas of unmet clinical need

Genome editing can be performed in germline cells (sperm, eggs or embryos) to induce heritable genetic changes or in somatic cells (other cells) to induce non-heritable changes. Somatic cell editing is much closer to clinical implementation, yet has received far less media attention. In this series of briefings we consider different aspects of somatic genome editing.

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Genome editing tools

Three tools commonly used for genome editing are: ZFNs, TALENs and CRISPR-Cas, all of which have been developed within the past 30 years. Each of these tools comprise a guidance system and a nuclease – a DNA cutting enzyme. The guidance system targets the nuclease to the correct part of the genome where it changes the DNA sequence by cutting it, leading to deletion or allowing new DNA to be inserted. A delivery system is also needed - usually a virus that transports the editing tool into target cells. Method of delivery, alongside other components and the context in which these techniques are applied, are highly flexible and changes can be made to each of these parts, each affecting how the editing tool performs.

How might somatic genome editing be useful for health?

Genome editing techniques make permanent changes to the genome, treating the cause rather than the symptoms of disease. In some instances this makes treatments theoretically curative by limiting or preventing damage caused by disease.

Editing takes place either within the body (*in vivo*) or outside of the body (*ex vivo*) in cells extracted from the patient or a donor. *Ex vivo* approaches are currently more common due to lower associated risks and the nature of the conditions being investigated.

Which disease areas show promise?

Currently, there are no genome editing treatments available in mainstream healthcare in the UK, but several therapies are being investigated in clinical trials internationally. The therapies under investigation are primarily for rare diseases caused by mutations in a single gene, which often lack a suitable treatment. Genome editing therapies are a more viable option in diseases where many patients share the same or similar disease-causing DNA change. This means a genome editing treatment designed for one patient may form the basis for treating others. Promising areas of research and examples of treatments in development include:

Blood disorders

Blood disorders are particularly amenable to genome editing approaches, partly because editable cells are easily extracted from blood and production of new 'fixed' cells is relatively quick once edited 'parent' cells have been returned to the body.

The first human trials are underway for therapy **CTX001**, a **CRISPR** treatment for blood disorders such as **β-thalassemia** and for **sickle cell** which are characterised by abnormally low levels of functional haemoglobin production. The patient's bone marrow cells are edited *ex vivo* to allow production of foetal haemoglobin to alleviate symptoms of the disease.

Eye disorders

The eye is a useful target organ for genetic medicines since it is relatively easy to deliver treatments e.g. injection into the retina, and has a tightly moderated immune environment which makes severe immune reaction to therapies less likely. However the non-dividing nature of these cells means only certain types of alteration are easy to make. A clinical trial is underway for an *in vivo* CRISPR-based treatment for one type of Leber congenital amaurosis, an inherited condition where the eye's photoreceptors stop working properly, leading to sight loss. This is the first *in vivo* CRISPR therapy to be tested in humans.

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Diseases with unmet clinical need

Genome editing research is beginning to show progress in rare diseases that have proven to be challenging to treat using other methods:

- **Duchenne muscular dystrophy (DMD):** In DMD, faults in the dystrophin-producing gene result in a degenerative and life-limiting muscle disorder primarily affecting boys. Although the cause has been known for decades, the large number of associated symptoms and the huge size of the gene have hampered the development of effective treatments. Last year, researchers used CRISPR-based genome editing to successfully restore dystrophin production in a small, short-term trial using dogs with the disease¹. Canine DMD closely mirrors both the genetic and symptomatic features of human DMD and, unlike other therapies (in which there has been some success in DMD mice), genome editing has the potential to produce permanent effects. Trials investigating longevity of effects and confirming safety will be required before potential treatments are progressed to human trials.
- **Hunter syndrome:** in 2017, testing began of the first *in vivo* genome editing therapy, specifically for Hunter and Hurler syndrome. Patients with these metabolic diseases lack an important enzyme, resulting in the accumulation of damaging compounds in the body, advancing tissue damage and a shortened lifespan. The prospective therapy uses ZFNs to edit cells of the liver, where many metabolic enzymes are found. Initial trial results suggest the therapy is safe in the few patients that have been treated, though its effectiveness has not been established²

New cancer treatments

Cancer immunotherapies such as **CAR-Ts** involve the *ex vivo* editing of immune cells from a patient to target blood cancers. Genome editing is being used to make cell modification more precise, avoiding damage to healthy genes. It can also make the use of donor cells possible by additionally altering immune genes which could otherwise lead to treatment rejection, making therapies suitable for a larger number of patients. The first application of CRISPR-edited cells to fight cancer in humans occurred in China in 2016.

Beyond therapy

Genome editing is helping researchers to more quickly identify the most viable biological targets for drugs and other treatments through quick and efficient disabling of genes in cell lines, alongside aiding research into disease mechanisms. Techniques that use CRISPR as a tool to aid disease diagnosis are also being explored.

Current obstacles to therapeutic genome editing

While genome editing approaches could provide important treatment advantages, there are technical hurdles to be overcome before these techniques can be applied more routinely and provide real patient benefit. Amongst others, two technical concerns are:

- **Editing tool delivery:** editing tools need access to the genome, which is held in the nucleus of the cell and is especially difficult for large molecules to access. Components of genome editing tools are usually packaged inside viruses for delivery, some of which carry their own safety considerations such as potential damage to healthy genes. Many of the safer delivery mechanisms have a limited carrying capacity - the smaller the tool, the broader the range of possible delivery mechanisms. Research into the development of smaller editing tools and improvement of delivery methods continues
- **How edited DNA is repaired:** in cells, the breaks in DNA caused by genome editing tools are automatically repaired by one of two major cell mechanisms. The mechanism most commonly employed by human cells is also the less accurate, increasing the likelihood of repair errors. This could have unintended negative consequences, such as causing unwanted changes in a gene

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The future of genome editing for health

While genome editing is not a 'cure-all' for genetic disease - indeed in many cases other therapies will be more appropriate and effective - there have been important advances, and we are likely to see further improvements in therapy development as research and clinical trials continue. Considerable efforts are also being made to increase the efficiency and safety of editing tools for clinical applications and research.

Looking ahead, there is potential for genome editing therapies to treat diseases where other approaches have not been successful, but long-term data on efficacy is needed. There are also ethical and regulatory challenges to be considered to support future use of this technology, which we outline in a third policy briefing.

References

1. Amoasii L. *et al.* Gene editing restores dystrophin expression in a canine model of Duchenne muscular dystrophy. *Science*. 2018. 362(6410), 86–91. doi:10.1126/science.aau1549
2. Sangamo Therapeutics. Sangamo Announces Interim Results Of Phase 1/2 CHAMPIONS Study Showing Preliminary Evidence Of In Vivo Genome Editing In Patients With MPS II Treated With SB-913. <https://investor.sangamo.com/news-releases/news-release-details/sangamo-announces-interim-results-phase-12-champions-study>. 2019

Authors: Emma Johnson and Laura Blackburn

Contact: intelligence@phgfoundation.org

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