In: **FACTS**, Methods and Technology at yourgenome.org

What is genome editing?

Genome editing is a way of making specific changes to the DNA of a cell or organism. An enzyme cuts the DNA at a specific sequence, and when this is repaired by the cell a change or 'edit' is made to the sequence.

What is genome editing?

- Genome editing is a technique used to precisely and efficiently modify DNA within a cell.
- It involves making cuts at specific DNA sequences with enzymes called 'engineered nucleases'.
- Genome editing can be used to add, remove, or alter DNA in the genome.
- By editing the genome the characteristics of a cell or an organism can be changed.

What is genome editing used for?

- Genome editing could be used to edit the genome of any organism.
- It is against the law to use genome editing in human embryos that will be allowed to develop beyond 14 days.
- Genome editing can be used:
  - **For research:** Genome editing can be used to change the DNA in cells or organisms to understand their biology and how they work.
  - **To treat disease:** Genome editing has been used to modify human blood cells that are then put back into the body to treat conditions including leukaemia and AIDS. It could also potentially be used to treat other infections (such as MRSA) and simple genetic conditions (such as muscular dystrophy and haemophilia).
  - **For biotechnology:** Genome editing has been used in agriculture to genetically modify crops to improve their yields and resistance to disease and drought, as well as to genetically modify cattle that don't have horns.

How does genome editing work?

- Genome editing uses a type of enzyme called an 'engineered nuclease' which cuts the genome in a specific place.
- Engineered nucleases are made up of two parts:
  - A nuclease part that cuts the DNA.
  - A DNA-targeting part that is designed to guide the nuclease to a specific sequence of DNA.
- After cutting the DNA in a specific place, the cell will naturally repair the cut.
- We can manipulate this repair process to make changes (or 'edits') to the DNA in that location in the genome.

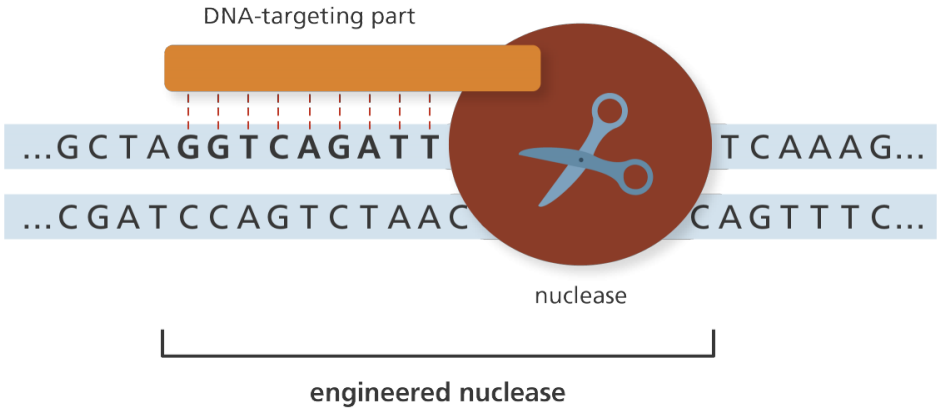

Illustration showing the basic structure and function of engineered nucleases used for genome editing. Image credit: Genome Research Limited

Types of genome editing

Small DNA changes

- A nuclease enzyme is engineered to cut at a specific location in the DNA.
- After cutting the DNA with the engineered nuclease, the cell's normal DNA repair machinery will recognise the damage and join the two cut ends of DNA back together.
- This simple repair process is not 100 per cent perfect and often a few bases are lost or added around the site of the cut when it is repaired.

- This small change (mutation) in the DNA will affect the function of that section of DNA, which may mean a gene doesn't function properly or doesn't function at all.

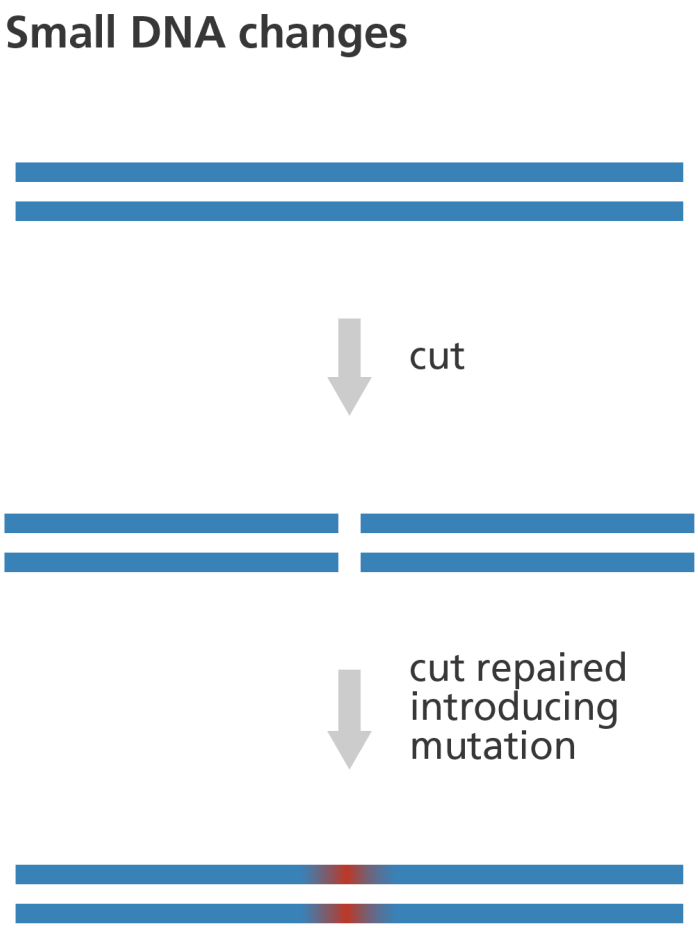

Illustration showing how genome editing can introduce a mutation into a section of DNA. Image credit: Genome Research Limited

Removal of a section of DNA

- To remove a section of DNA, nucleases are engineered that make cuts in the DNA either side of the section that we want to remove.

- After the engineered nucleases cut the DNA, the cell's normal DNA repair machinery will recognise the damage but may mistakenly join the wrong ends of DNA together, removing the DNA in between the two cuts.

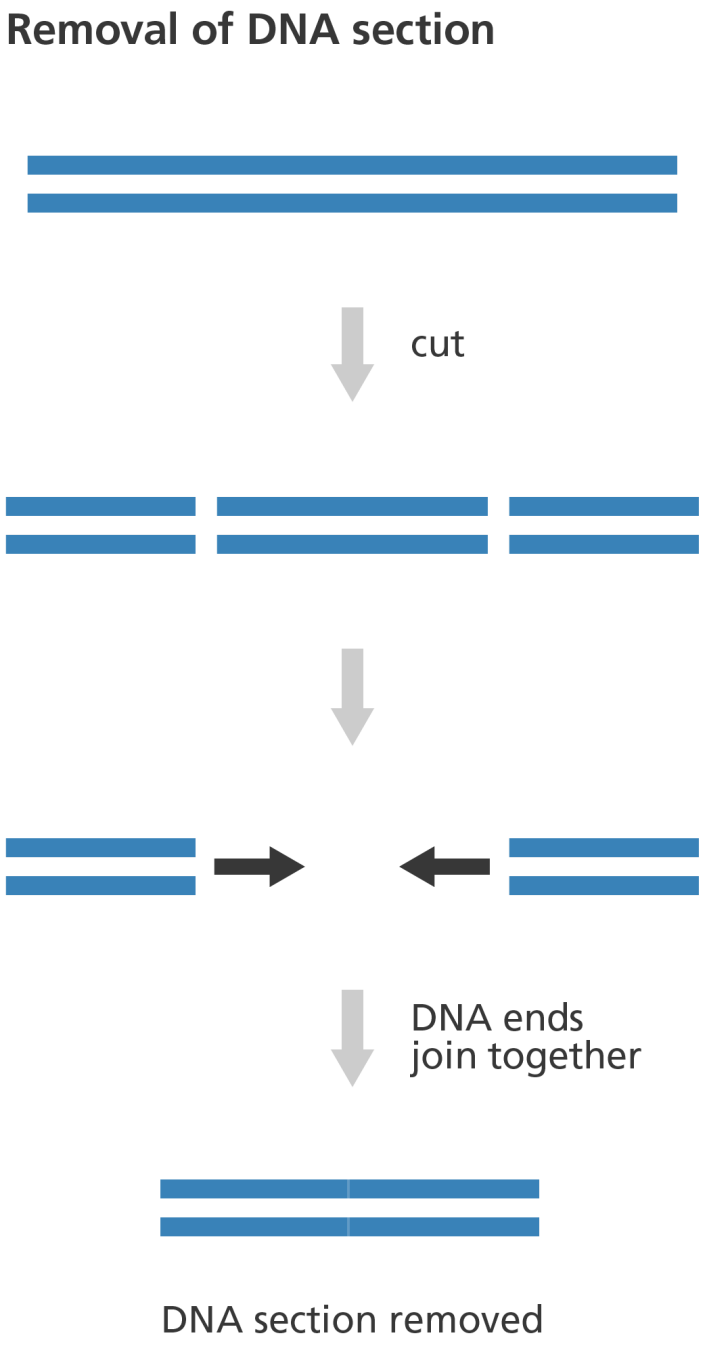

Illustration showing how genome editing can remove a section of DNA in a genome.
Image credit: Genome Research Limited

Insertion of section of DNA

- A natural DNA repair system can be hijacked to insert a section of DNA into a genome by genome editing.
  - Normally before a cell divides , all of its DNA is copied so that the two resulting daughter cells can receive a complete copy of the genome.

    - If there is a break in one copy of the DNA, the cell repairs the break by using the other copy as a template. This process ensures that both copies of the DNA match again and is called 'homology-directed repair'.

- It's possible with genome editing to take advantage of this DNA repair system to 'trick' the cell into inserting a section of DNA.
    - A nuclease enzyme is engineered to cut at a specific location in the DNA.
    - After the DNA has been cut, a modified piece of DNA similar in sequence to the site of the cut is introduced.
    - The cell uses the modified piece of DNA as the template to repair the break, filling the break with a copy of the new DNA.

- This approach can be used to insert a new section of DNA, or to replace an existing section of DNA with an altered version, for example, to correct a point mutation within a gene.

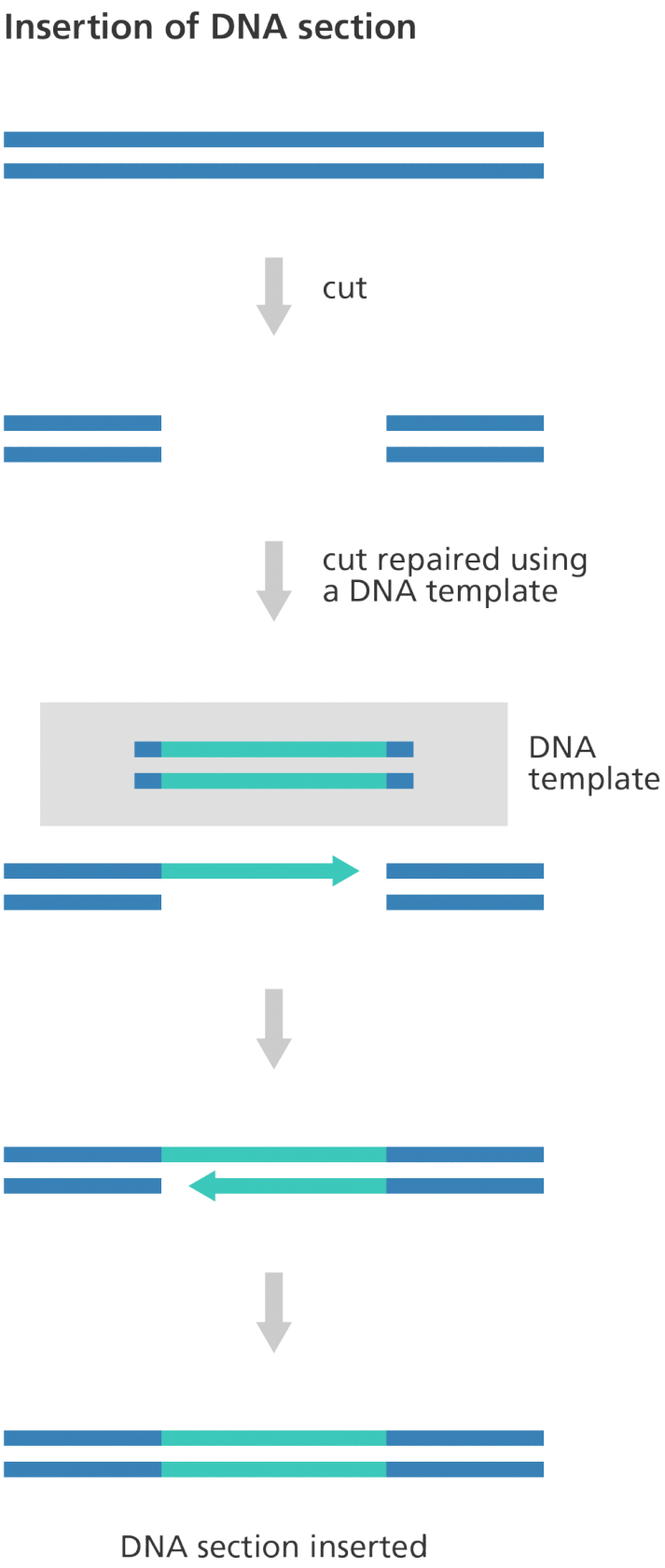

Illustration showing how genome editing can insert DNA into a genome.
Image credit: Genome Research Limited

Genome editing systems

- There are several different types of engineered nuclease used in genome editing.
- They all contain a nuclease part to cut the DNA and a DNA-targeting part to recognise the DNA sequence they cut.
- They mainly differ in how they recognise the DNA to cut:
  - RNA -based: contain a short sequence of RNA that binds to the target DNA to be cut.
  - Protein -based: contain a protein that recognises and binds to the target DNA to be cut.

CRISPR-Cas9

- CRISPR-Cas9 is the most common, cheap and efficient system used for genome editing.
- CRISPR stands for 'clustered regularly interspaced short palindromic repeats'.
- CRISPR is the DNA-targeting part of the system which consists of an RNA molecule, or 'guide', designed to bind to specific DNA bases through complementary base-pairing .
- Cas9 stands for CRISPR-associated protein 9, and is the nuclease part that cuts the DNA.
- The CRISPR-Cas9 system was originally discovered in bacteria that use this system to destroy invading viruses .

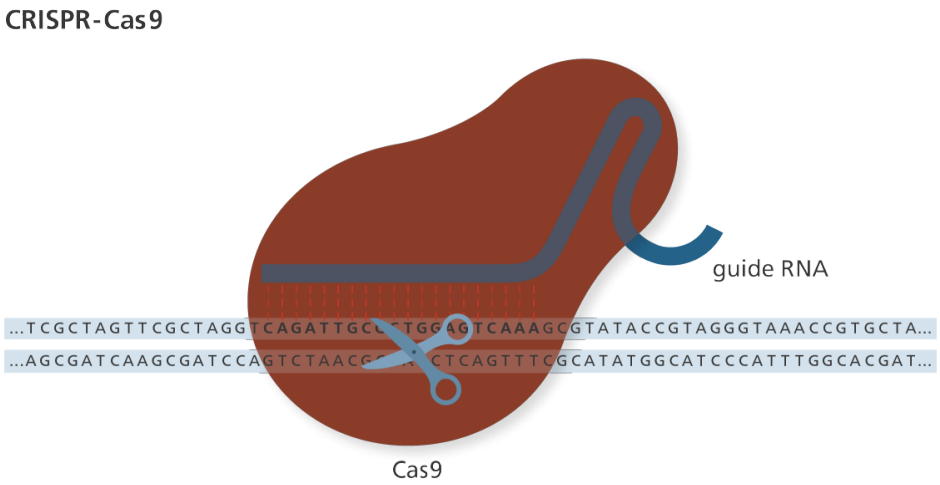

Illustration showing the components of CRISPR-Cas9. Image credit: Genome Research Limited

ZFNs

- ZFNs stands for 'zinc-finger nucleases'.
- The DNA-binding part of ZFNs is made of zinc-finger proteins, which each bind to about three DNA bases. Different combinations of zinc-finger proteins bind to different sequences of DNA, although this is hard to predict without testing them first.
- The nuclease part of ZFNs is normally a *Fok*I nuclease, which cuts the DNA.
- Two *Fok*I molecules come together to make a cut in the DNA, so a pair of ZFNs are made, one binding to each strand.

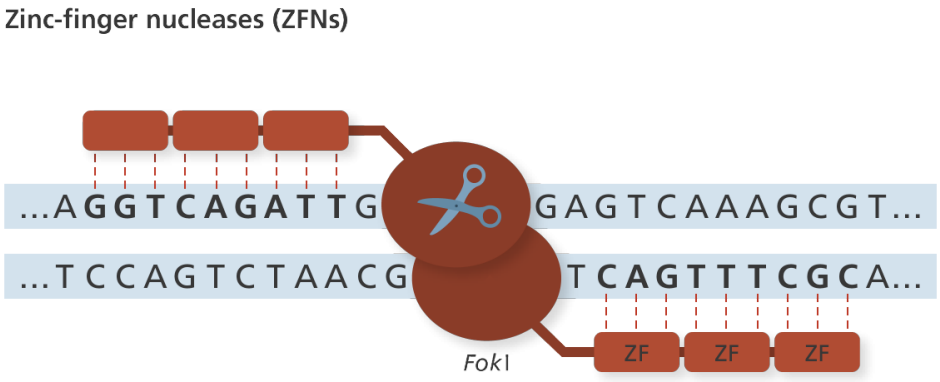

Illustration showing the components of zinc-finger nucleases (ZFNs).
Image credit: Genome Research Limited

TALENs

- TALENs stands for 'Transcription activator-like effector nucleases'.
- The DNA-binding domain of TALENs is made of transcription activator-like effector (TALE) domains.
- There are four different TALE domains, one for each DNA base, so they can be engineered to bind to specific DNA sequences much more easily than ZFNs.
- Like ZFNs, the nuclease part of TALENs is normally a *Fok*I nuclease.
- Two *Fok*I molecules must come together to make a cut in the DNA, so two TALENs are made, one for each strand.

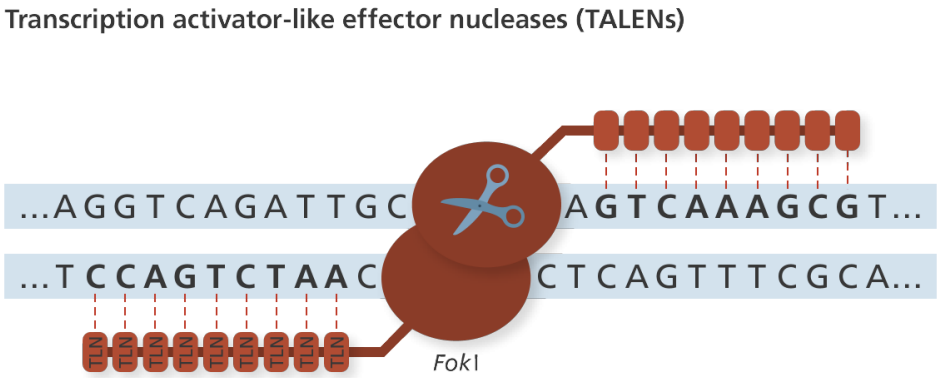

Illustration showing the components of Transcription activator-like effector nucleases (TALENs). Image credit: Genome Research Limited

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