

The science behind developing EB therapies

We fund medical research into the development of different types of therapies for all types of EB, therapies that work in different ways to treat the causes and/or symptoms of EB in the skin or throughout the body.

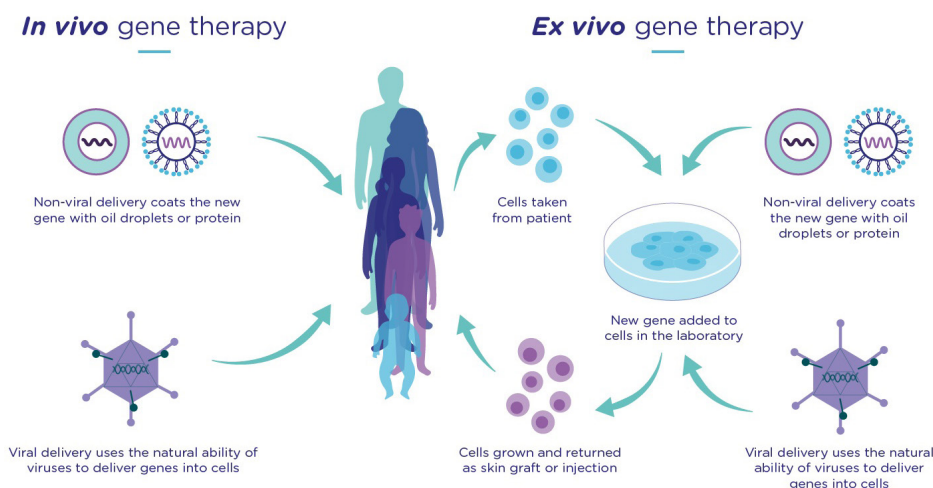
Find out more about how EB therapies work below.

EB gene therapy

Gene therapy is a way of treating a genetic condition by correcting the mistakes in a person's genes that are responsible for their symptoms. This is different to treating the individual symptoms themselves. Genes are the recipes for the proteins that our bodies are made of. They can have errors in them that prevent working proteins from being made. When a person's body can't make certain skin proteins, this causes EB symptoms that could be treated by adding a working gene back into the cells that need it. Sometimes a mistake in a genetic recipe makes a protein that isn't just broken, it actually interferes with the working proteins around it. This can cause dominant conditions where adding in a working gene may not help.

How does gene therapy work?

Gene therapy uses natural processes from viruses and bacteria to create working genes and puts them into cells where a gene is missing or broken. This can be done either by taking a sample of a person's cells into the laboratory to make the genetic corrections then returning them (this is called *ex vivo*) or by treating a person directly with an injection or gel that puts the working gene into the cells in their body that need it (this is called *in vivo*). Getting new genes into our cells can be difficult but once a new, correct gene has been put into a person's cells it can be used by the cell to begin making the protein that was missing.



Viruses are often used to put new genes into cells because this is what they naturally do. Gene therapy makes a virus harmless by removing its ability to replicate itself. It makes the virus useful by replacing the genes that it would put into our cells to make us ill with a new gene that will make us healthy. Another way of getting genes into our cells involves coating them with oil or protein. Genes on their own are easily destroyed by sunlight and naturally occurring proteins called enzymes.



This video from the American Society of Gene and Cell Therapy explains gene therapy: <https://youtu.be/Q6qk6Wh6cXU>

How does the immune system react to gene therapy?

Different viruses are used to put bigger or smaller genes (longer or shorter protein recipes) into our cells.

These viruses have been changed so they cannot make us ill, but we may already have had an illness caused by the type of virus used for the gene therapy. This means we may have an immune reaction to *in vivo* therapy using that type of virus. We may also have an immune reaction if *in vivo* gene therapy is repeated. The gene therapy won't work so well inside our bodies if our immune system destroys the gene therapy virus before it can deliver the new gene to our cells.

Sometimes our immune system reacts to the new, correct protein as if it is a germ. Researchers must check that a gene therapy does not cause an immune response.

How long does gene therapy last?

Some types of gene therapy aim to be single treatments while others will require repeated applications.

Skin is renewed continuously; old skin cells die and flake off and new cells replace them. The new cells come from deeper in the skin where cells grow, make a new copy of all their genes then divide into two repeatedly to continuously create new, replacement skin cells.

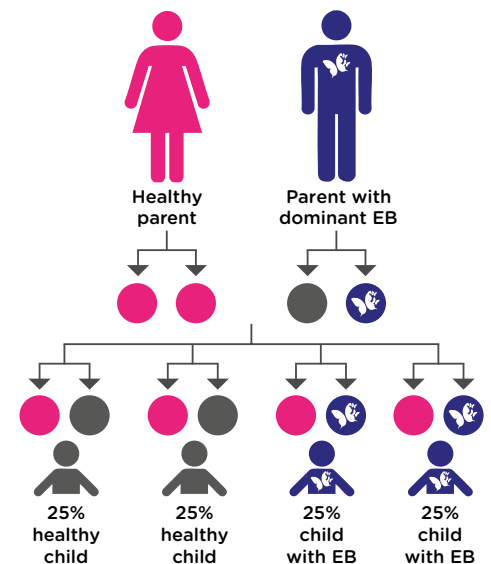
Cells that have had new genes put into them by gene therapy will naturally die and be replaced by newer cells so the gene therapy may need to be repeated. The new gene will only be copied into new cells if it has become a part of one of our chromosomes. This is called integration.

Chromosomes are long pieces of DNA buried deep inside our cells and each of our genes is a part of one of these chromosomes. If we think of each gene as the 'recipe' for making one of the proteins that our bodies are built out of, each chromosome is like a recipe book. Pasting the new recipe into one of the recipe books means it will be copied.

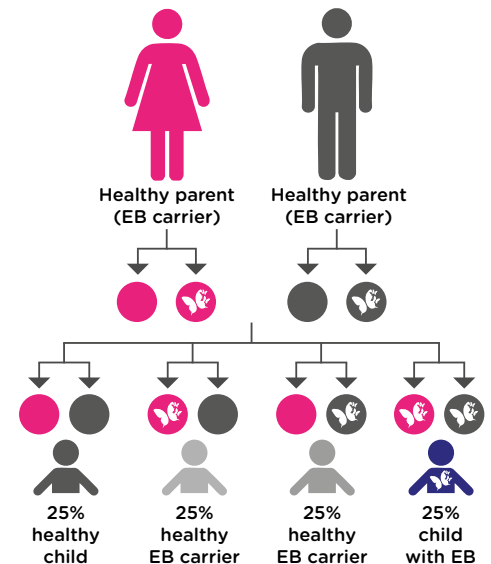
Some gene therapies will integrate the new gene into a chromosome, and some will not. This can change how long the treatment works to control symptoms.

If a new gene is integrated, it is important that it doesn't interrupt any of the other genes and stop them from working. Imagine accidentally pasting the new recipe over part of another recipe. Researchers must make sure that gene therapy will not cause mistakes in any other existing genes.

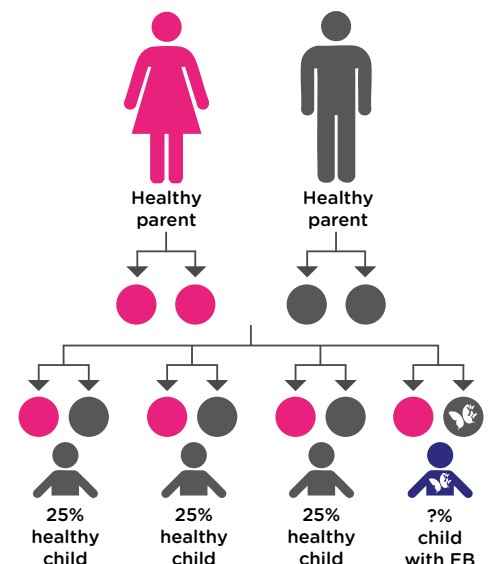
Autosomal Dominant Inheritance



Autosomal Recessive Inheritance



De Novo Inheritance



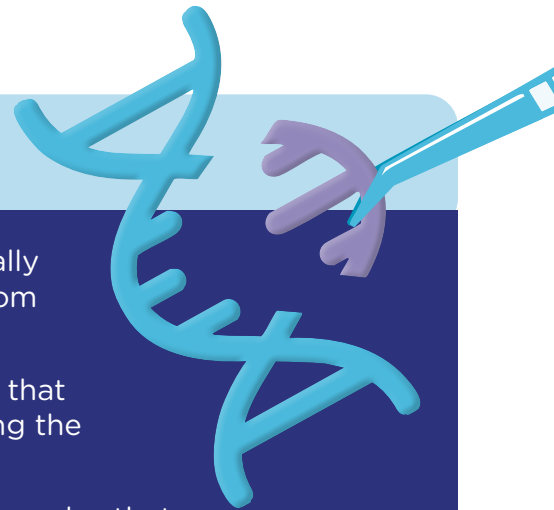
EB gene editing

Gene editing is a type of gene therapy that is based on naturally occurring methods used by bacteria to protect themselves from viruses.

Instead of delivering a new, working genetic recipe to cells so that they can make a missing protein, gene editing is a way of fixing the existing, broken gene to correct a person's own recipe.

It is important that the process doesn't make changes anywhere else that could introduce new mistakes into other genes. It is also important that no changes are made to egg or sperm cells that could mean a child is born with genetic changes they have not consented to.

Gene editing is carried out as an *ex vivo* gene therapy rather than an *in vivo* treatment. A person's own stem cells could be collected, have genetic mistakes corrected, and be returned to them.



This video explains a type of gene editing using the CRISPR/Cas9 system: <https://youtu.be/UKbrwPL3wXE>

EB cell therapy

Some potential EB treatments are based on stem cells, a specific type of cell often taken from bone marrow but can come from other parts of a donor's body too, that can transform themselves into other types of cell. Cell therapy treatments can put stem cells from somebody who doesn't have EB into the blood stream of somebody with EB. These cells can travel to the skin and other parts of the body affected by EB and become cells that are able to make the missing protein that causes EB symptoms. This could be a way of treating EB symptoms all around the body.

Mesenchymal stromal cells (MSCs) are a type of cell with similar properties to stem cells that are being trialled in EB.



Find out more about stem cells in this video: <https://youtu.be/jF2iXpoG5j8>

EB drug therapy

Drug therapy is when symptoms are treated with substances that actively affect how our bodies work. They could be in a pill we swallow, an injection into the skin or muscle, a transfusion through a needle into the blood stream or a cream, spray, gel or eye drop.

EB is an inflammatory disease, and doctors have a good understanding of how inflammation happens in our bodies. This means they can choose drugs that reduce inflammation in other conditions to repurpose for EB.

The pain of EB wounds can be treated with pain relieving drugs or sedatives.



This video explains how medicines can work inside our bodies: <https://youtu.be/uOcpsXMJcJk>

EB protein therapy

Protein therapy involves replacing the protein that is missing in people with EB because of a genetic change in the recipe encoding it.

Instead of changing the genetic recipe for a skin protein (gene therapy), protein therapy tries to add the missing protein 'ingredient' back to skin that isn't working properly. It is a bit like trying to add the filling into your pie after it has come out of the oven rather than changing the broken pie recipe. Researchers must understand how to get the protein to where it needs to be. This could be with an injection, through blood which would carry it around the body or directly to eyes or wounds where the skin doesn't act as a barrier.

The protein needed for protein therapy can be manufactured in laboratory-type facilities where bacteria or yeast cells containing the correct genetic recipe are grown and used as little protein factories. This technology can efficiently create large amounts of a human protein. For example, human insulin is produced this way to routinely treat people with diabetes.

