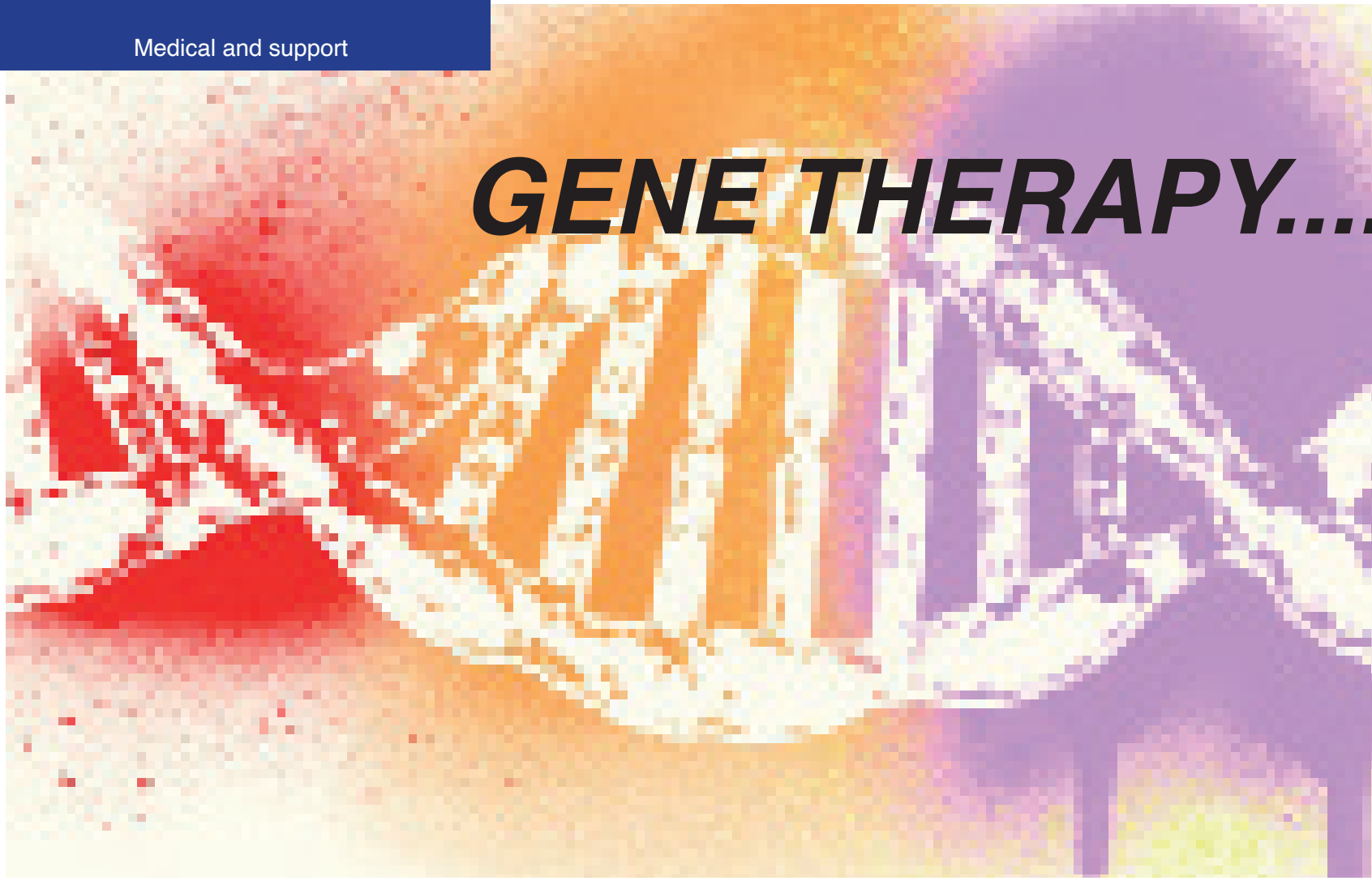


GENE THERAPY....

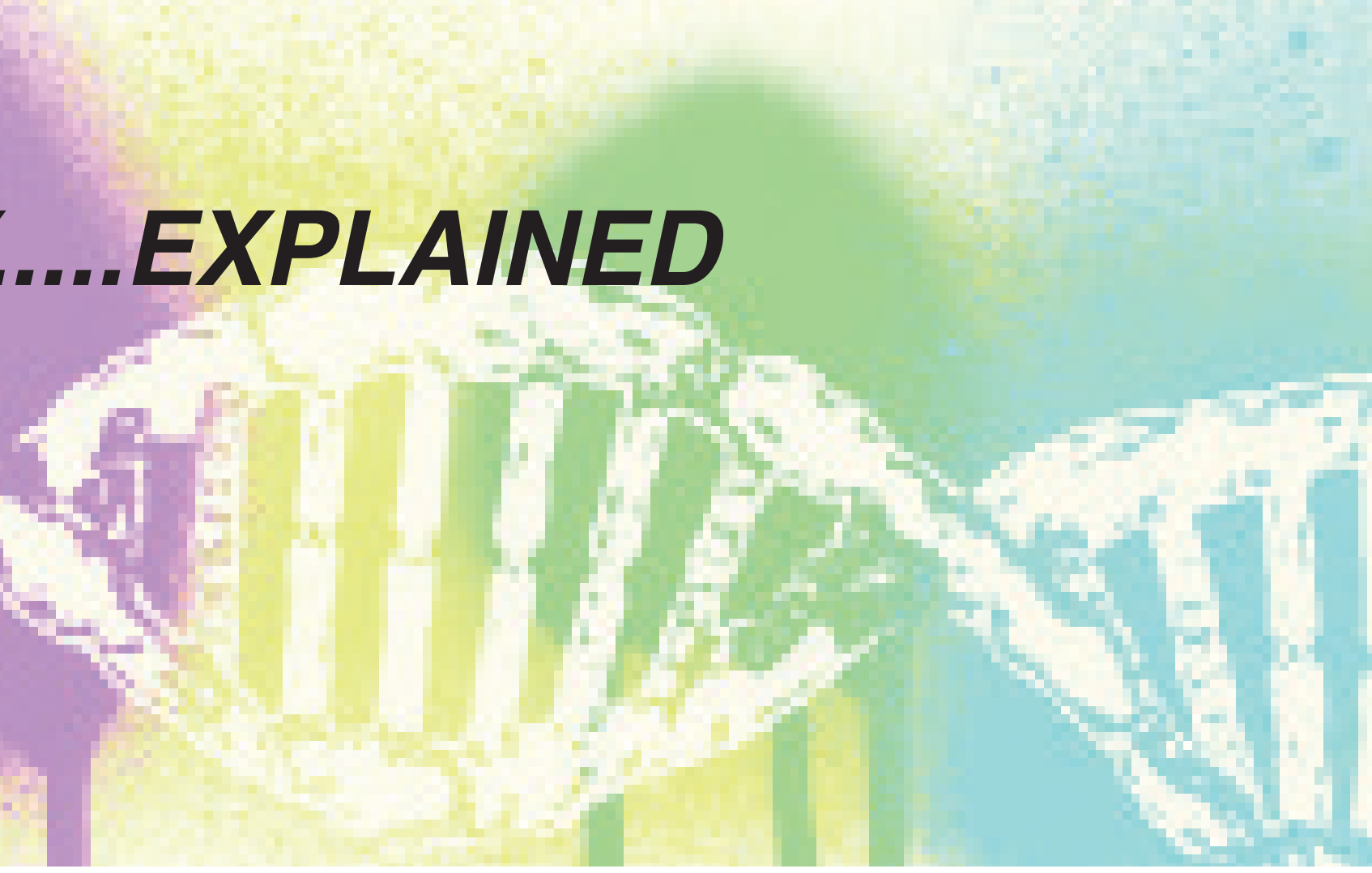
These are exciting times in the world of thalassaemia research and development, with the recent European conditional approval for gene therapy potentially opening up new avenues of treatment. We are all eagerly waiting to see what changes these may bring, but with so many medical buzzwords flying around, it can get confusing! That's why we thought it would be a good time to look at the science behind gene therapy and explain the concepts in basic terms, so we can all understand what it means. We will start off by looking at what a gene actually is and then describe the process of gene therapy. This is a very simple overview and if you want to find out more, you can speak to your haematologist and get more information.

Please note that we are certainly not advocating the use of gene therapy; that is for you to decide (if you are eligible), under the guidance of your medical and nursing team. As with any new treatment, there are risks, challenges and unknowns but that discussion is not the purpose of this article here.

What is a gene?

Let's go back to the very basics and start by describing some biological concepts. Each of your cells has a nucleus that contain chromosomes. Chromosomes carry the genes that contain the instructions for making new cells in all the tissues and organs in your body, and then directing them to do their work.

A gene is a small packet of information that controls a characteristic in your body, by making very specialised protein molecules. It is a section of DNA, the unique molecule that makes up your chromosomes. Genes make us who we are; they determine our characteristics, for example, the colour of our hair, our height and so on.



.....EXPLAINED

What does gene therapy aim to do?

In some cases a gene can be missing, defective or altered from the usual form. This can cause disease. In the case of a person with transfusion-dependent thalassaemia, they have inherited two altered ß-globin genes from their parents (one from the mother and one from the father). As a result of the altered – sometimes termed 'mutated' genes, the person cannot produce enough ß-globin, which forms part of haemoglobin. This is the substance in the red blood cell that carries oxygen.

How does gene therapy work?

There are three main approaches to gene therapy that are currently being studied:

- 'Switching off' the genes that are causing the problems.
- Removing the faulty genes and replacing them with functional ones.
- Adding functional genes to work correctly, alongside the faulty genes.

In the case of thalassaemia, it is the last method of gene addition that is currently being explored. The aim is to add copies of a functional gene so that haemoglobin production occurs effectively and the red blood cells are able to functional normally. A functional gene can be added inside (in vivo) or outside (ex vivo) the body. A patient can have an allogenic bone marrow transplant (BMT), where cells from another person, a donor, are used. Or the patient can have an autologous transplantation where their own cells are collected,treated and then returned to them. No donor is required.

Here we look at autologous transplantation BMT using the ex vivo scenario of gene therapy (the process is described on the next page).

Gene therapy: the process

Stage 1: Stem cell collection

The first stage of the gene therapy process is the collection of **stem cells**. What exactly are stem cells? Stem cells are blood cells at the earliest stage of development. All of our blood cells develop from stem cells in the bone marrow. Bone marrow is found inside our bones, mainly in the hip bone, spine, ribs and breast bone. Stem cells stay inside the bone marrow, mature and multiply and, when they are fully developed, they go into the bloodstream. Blood cells have a short life cycle. Every day the bone marrow normally makes millions of new blood cells to replace blood cells as they are needed. Stem cells are used because they have the ability to form many other types of cells in the body. You can think of them a bit like a blank canvas.

The first part in the process of collecting stem cells is to make them move from the bone marrow into the blood. This is called mobilisation (of the stem cells). Daily injections of a drug called a growth factor, stimulate the bone marrow and increase the number of stem cells it makes and help release them into the blood.

Apheresis is the name of the process to collect the stem cells. To do the actual physical collection of the stem cells, a cannula (thin tube) is inserted into a vein in each arm. Each cannula is connected by tubing to a machine called a cell separator. The blood travels through this sophisticated piece of machinery and is spun as it moves along. As it spins, the stem cells are separated out and collected in a bag. The rest of the blood and blood cells are returned to the patient through the cannula in the other arm.

Stage 2: Functional gene addition

This part of the process happens in a specialised laboratory. Functional copies of a healthy ß-globin gene is transferred into the harvested stem cells using a **vector** (which is effectively a vehicle). Often a virus is used as a vector but it has been genetically modified so that it does not cause infection. The 'corrected stem cells' or 'gene-modified cells' are then ready for infusion (insertion) into the patient.

Stage 3: Preparation treatment

The patient is prepared to receive the corrected stem cells through a process called **myeloablation** or myeloablative conditioning. This process uses high dose **chemotherapy** to wipe out the remaining bone marrow cells, to make way for those treated with the gene therapy.

Stage 4: Infusion and engraftment

Once the patient is ready after chemotherapy, the corrected stem cells are delivered by intravenous (IV, into the vein) infusion. After the gene therapy has been infused, the treated stem cells will need time to multiply. This process is called **engraftment**. In order for the production of high levels of haemoglobin, in other words, for the gene therapy to be successful, a significant number of genetically corrected stem cells need to be engrafted. Until they do settle in and multiply, the person's blood counts are very low and they are at risk of infection and may need antibiotics and/or blood transfusions, until recovery.

Stage 5: Recovery

The patient will remain in hospital until they have a sufficient number of new cells, their vital immune cells have returned to safe levels and their medical team deems it is time for them to be discharged. After the patient has recovered and is back home, they will continue to receive follow-up monitoring.

After the whole process is complete and if the gene therapy has worked successfully, the patient will be able to produce sufficient levels of haemoglobin. The process of gene therapy only needs to be administered once and if successful, this would mean that the patient no longer needs blood transfusions or chelation treatment.

It is important to note that some patients will experience a transfusion reduction, based on current data across all gene therapy programmes, so may benefit but not to the extent that they achieve freedom from transfusions.

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Clearly, the outlook is promising and ongoing studies continue to identify the safest and best regimen for gene therapy treatment of thalassaemias. Watch this space!