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TEACHER'S NOTES
GENE THERAPY

OVERVIEW

Aimed at key stage 4 pupils.
This is a worksheet-based activity to help pupils find out about gene therapy – what it is, how it might work and how it might be used to treat cystic fibrosis.

LEARNING OBJECTIVES

- To understand why gene therapy is proposed as a treatment to some conditions, such as cystic fibrosis
- To understand the theory behind gene therapy and why using it is challenging

CURRICULUM LINKS

- **KS4**: The ways in which organisms function are related to the genes in their cells
- **KS4**: the use of contemporary scientific and technological developments and their benefits, drawbacks and risks
- **KS4**: to consider how and why decisions about science and technology are made, including those that raise ethical issues, and about the social, economic and environmental effects of such decisions

Activity

- Review the cause of cystic fibrosis – changes in the *CFTR* gene lead to the CFTR protein not working as it usually would
- Review that genes are instructions that help cells work and that sometimes changes in genes mean that cells no longer work in their normal way
- You could show pupils films from **www.genesareus.org** to help pupils understand more about different genetic conditions
- Introduce the idea of gene therapy – treating genetic conditions by adding a working copy of the gene into the cells that need it
- Give pupils the worksheet and give them 5 minutes to answer questions 1 and 2
- Ask pupils to move on to the next part of the worksheet and answer question 3
- Bring pupils back for a group discussion around question 4
- Ask pupils to move on to the final 'true/false' activity (question 5)

ANSWERS

1. In one minute, write down as many different types of diseases and illnesses that you can

This list is obviously not exhaustive, but answers could include: 'flu; common cold; cancer; Huntington's disease; Alzheimer's disease; Parkinson's disease; sickle cell anaemia; Down syndrome; asthma; multiple sclerosis (MS); eczema; arthritis, and so on.

2. Now write next to all of the illnesses you've listed whether they are: G, G + E or E (refer to table below)

G	***Conditions caused only by a change in one of a person's genes***
G + E	***Conditions caused by a combination of a person's genes and environmental factors***
E	***Conditions caused only by the environment***

Cancer and conditions caused by immune dysfunction (such as MS, eczema, asthma and so on) should be listed as G + E; all infectious disease should be listed as E. More able pupils might be interested to know that:

- An individual's genes can affect (a) their susceptibility to certain infectious diseases and (b) their ability to respond to and clear infectious diseases.
- The likelihood of certain cancers can be dramatically increased by changes in a single gene, to the extent that they effectively become a genetic condition.

3. Pick one genetic condition and think about how you might treat it with gene therapy:

NOTE: *You might prefer to suggest one genetic condition for the class to focus on, rather than each pupil choosing one.*

NOTE: *Chromosomal disorders* ***cannot*** *be treated by gene therapy – pupils should consider a single gene condition.*

ANSWERS continued

a) Which cells do you need to treat? (For example, every cell in the body, or just some?)

b) How would you get your vector to those cells?

c) Draw a diagram to show the path the DNA takes once the vector has reached the cells and explain the steps that are involved

d) Highlight where you think there might be problems in step 3

It's likely that pupils won't have listed that many genetic conditions in Q1/2, but if you would rather focus the class on one condition you could suggest CF or X-SCID (the latter has actually been successfully treated using gene therapy).

a) Highlight that, although every cell in the body has the changed DNA causing the condition, it is only necessary to treat those cells directly affected by the change. In the case of CF those are primarily the cells of the lung; for X-SCID it's the bone marrow.

b) The population of cells being treated affects how they are approached. For CF it makes sense to use a nebulizer to deliver the vector in an aerosol format. In X-SCID the bone marrow is removed from patients and treated with vector *ex vivo* (outside the body); those cells that were successfully treated were then selected and put back into the body. For most genetic conditions, which affect discrete tissues, it is unlikely that a vector could simply be injected into the blood.

c) Their diagram should show:
- The vector outside the cell
- The vector 'mixing' with the cell membrane and the DNA being inserted into the cell
- The DNA travelling to the nucleus
- The DNA entering the nucleus and (optionally) integrating into an existing chromosome
- The new DNA making its gene product (usually a protein)

d) There are challenges at each step of this
- The immune system could destroy the vector while it is outside the cell
- The DNA may be destroyed by the cell as it passes through the cytoplasm
- The DNA may not integrate into the chromosome and therefore be diluted by cell division (not a problem in non-dividing cells, such as neurons)
- The new protein is likely to be interpreted as 'foreign' by the immune system and cells producing it might therefore be destroyed

4. Without treatment Jesse Gelsinger would have died of his disease. Is it acceptable for terminally ill patients to be given potentially risky experimental treatments that only have a slim chance of success?

There is no right or wrong answer to this, but it might elicit some strong opinions on either side of the debate.

Q5. For each of the statements below, answer whether they are true or false:

Statement	True / False
Gene therapy is an approved treatment and is routinely used to cure genetic conditions, including cystic fibrosis	**False** – GT has only ever been used as an experimental treatment, albeit with some success
Genetically engineered viruses are one of the most promising tools to use in gene therapy	**True** – viral vectors are very good at getting genetic information into cells
Overcoming the immune system can be a major problem for gene therapy	**True** – the immune system actively tries to destroy viruses and cells infected by them
It is easy to target specific cells and introduce new DNA into them as part of gene therapy treatment	**False** – targeting a discrete population of cells is not trivial

ANSWERS continued

Statement continued...	True / False continued...
Scientists are able to control the new DNA (turn it on or off) once it is inside the body	**False** – at present, when new therapeutic genes are put into a cell they are just 'on'
Once DNA has got past the cell's outer membrane it is stable and will be used by the cell	**False** – 'foreign' DNA is likely to be targeted by the cell for degradation
The new DNA should remain active in the target cells for the lifetime of the cells	**True** – the DNA needs to remain active for a long time or the therapy will stop being curative
For the new DNA to be used by a cell it must reach the nucleus	**True** – DNA can only be transcribed (and therefore used) within the nucleus
Liposomes are made of carbohydrates (sugars)	**False** – liposomes are fatty, but they may have a chemically modified surface
To be effective, gene therapy must treat every cell containing the changed gene responsible for causing a genetic condition	**False** – it is only necessary to successfully treat a 'sufficient number' of cells; exactly what percentage needs to be effectively treated for the treatment to be curative will vary for each condition

FURTHER information

- Gene therapy is introduced in films on the 'Changing Futures' website **www.changing-futures.co.uk**
- Further details about the clinical trial for cystic fibrosis available on the CF Trust's website **www.cftrust.org**
- The Genetic Science Learning Center in Utah have produced some good teaching resources on gene therapy **http://learn.genetics.utah.edu/content/tech/genetherapy**
- Recent successes with gene therapy were reported on the BBC news, so you can search archives for reports on haemophilia and inherited blindness.

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STUDENT WORKSHEET

GENE THERAPY

Scientists think that 'gene therapy' might be a way of treating currently incurable genetic conditions such as cystic fibrosis, sickle cell anaemia, Huntington's disease and so on.

Essentially, the idea behind gene therapy is to change the genetic information inside a cell. This new genetic information would then be used by the cell and change how it works.

Gene therapy can, potentially, be used to cure or treat a large number of genetic conditions. Also, many types of cancer might be able to be cured by a gene therapy, but these treatments are still in development.

1. ***In one minute, write down as many diseases and illnesses that you can***

2. ***Now write next to all of the illnesses you've listed whether they are: G, G + E or E (refer to table below)***

G	***Conditions caused only by a change in one of a person's genes***
G + E	***Conditions caused by a combination of a person's genes and environmental factors***
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In a condition like cystic fibrosis, gene therapy is an attractive idea because a change in one gene causes the condition. So, by putting a working version of the *CFTR* gene into the cells of the lungs, those cells should be able to work normally.

To get the new DNA into the cells scientists use something called a 'vector', which is just a fancy word for a delivery vehicle. The two most common vectors are viruses and liposomes. Viruses have evolved over billions of years to insert their DNA into cells, so they're very good at it. When scientists use viruses for gene therapy, they modify them to make the viruses safe – they are not able to cause disease.

Liposomes are tiny, tiny bubbles of fat that can be used to surround a molecule of DNA. Because they are fatty, like the membrane of cells, liposomes can mix with a cell's membrane and get DNA inside a cell. Liposomes are the main vectors that have been used to try and treat cystic fibrosis.

3. ***Pick one genetic condition and think about how you might treat it with gene therapy***

a) Which cells do you need to treat? (For example, every cell in the body, or just some?)

b) How would you get your vector to those cells?

c) Draw a diagram to show the path the DNA takes once the vector has reached the cells and explain the steps that are involved

d) Highlight where you think there might be problems in step 3

Although gene therapy sounds quite an easy idea, it has proven to be really hard for scientists to crack!

Research into gene therapy has been going on for decades, but it has only ever been used experimentally. Gene therapy is currently not a standard cure for any condition. There have been lots of advances, but there have also been many challenges to overcome. Tragically, one person died as a direct result of experimental gene therapy: Jesse Gelsinger was 18 when he died in 1999 after he was given an experimental therapeutic virus; he was suffering from a genetic liver disease.

Soon after the death of Jesse, in 2002 some French boys suffering from X-linked severe combined immunodeficiency syndrome (X-SCID) were successfully treated using therapeutic retroviruses. Boys with X-SCID do not have an effective immune system so they are likely to be very ill and die due to infection when they are very young. Despite the successful treatment, some of the boys went on to develop leukaemia as a result of the treatment. Fortunately, their leukaemia was subsequently cured and their immune systems continued to work effectively.

GENE THERAPY

More recent gene therapy successes have included treatment for hereditary blindness and also a particular form of the blood clotting illness, haemophilia. A large clinical trial for gene therapy was launched in 2012 for cystic fibrosis patients. There are high hopes that this trial will generate evidence showing that using gene therapy once a month will significantly improve the health of people with cystic fibrosis.

4 ***Without treatment Jesse Gelsinger would have died of his disease. Is it acceptable for terminally ill patients to be given potentially risky experimental treatments that only have a slim chance of success?***

5 ***For each of the statements below, answer whether they are true or false***

Statement	True / False
Gene therapy is an approved treatment and is routinely used to cure genetic conditions, including cystic fibrosis	
Genetically engineered viruses are one of the most promising tools to use in gene therapy	
Overcoming the immune system can be a major problem for gene therapy	
It is easy to target specific cells and introduce new DNA into them as part of gene therapy treatment	
Scientists are able to control the new DNA (turn it on or off) once it is inside the body	
Once DNA has got past the cell's outer membrane it is stable and will be used by the cell	
The new DNA should remain active in the target cells for the lifetime of the cells	
For the new DNA to be used by a cell it must reach the nucleus	
Liposomes are made of carbohydrates (sugars)	
To be effective, gene therapy must treat every cell containing the changed gene responsible for causing a genetic condition	