6.7 Gene therapy

Using somatic cell therapy and germline cell therapy to treat genetic disorders

Gene technologies can be used to treat some genetic disorders, and this use is called **gene therapy**. In its most basic sense, the idea is to insert fully working copies of a certain gene into a cell which only contains dysfunctional and non-working copies of a gene, so that they cell or cells may begin transcribing the proper gene, and hopefully relieve the patient of their symptoms.

Developments brought about due to the Human Genome Project also further the possibilities of gene therapies, including the potential use of **RNA interference** (RNAi) which could silence genes by binding to mRNA. At present, the only use for this is to treat *cytomegalovirus* infections in AIDS patients by blocking the replication of the **cytomegalovirus**.

Somatic cell gene therapy

As organisms grow, cells become specialised to certain functions. Within specialised cells, certain genes are switched on and others are switched off. Although the cell still contains a full genome, relatively few will be active in producing proteins: those which are switched on depend upon the nature of the cell and its function. Types of **somatic cell therapy** include gene therapy through adding and killing genes:

- gene therapy by *adding genes* (**augmentation**) – some conditions are caused by the inheritance of faulty alleles leading to the loss of a functional gene product (polypeptide), and engineering a functioning copy of the gene into the relevant specialised cells means that the polypeptide can be synthesised and the cells function normally
- gene therapy by *killing specific cells* – cancers can be treated by eliminating certain populations of cells; using genetic techniques to make cancerous cells express genes to produce proteins, such as cell surface antigens, that make the cells vulnerable to attack by the immune system could lead to targeted cancer treatments

Germline cell gene therapy

All embryos begin when a sperm cell fertilises an egg cell to form a *zygote* that undergoes mitotic division. Each cell of an early embryo is a **stem cell**. It can divide and specialise to become any cell type within the body. Each could also potentially become a new being, and so are called **germline cells** (germ cells are those that give rise to the production of *gametes*). Engineering a certain gene into the sperm, the egg, the zygote or all the cells of an early embryo, will mean that as the organism grows, every cell will contain a copy of the engineered gene. This can then function within any cell where that gene would normally be required. This is called **germline cell therapy**.

Some transgenic animals have been genetically engineered, and the functioning gene they obtain can be passed on by heredity to their offspring, which cannot happen with somatic cell therapy, which restricts the genes to **somatic cells** (body cells). A somatic cell is any cell in a multicellular organism which is not a gamete, germline cell or stem cell.

The table below outlines some of the issues concerning gene therapy.

Somatic cell gene therapy	Germline cell gene therapy
Since the functioning gene is introduced to specific target cells, techniques to get the gene to target locations must be used, or the cells must be removed, treated and replaced (*ex vivo* therapy), which is complicated	The functioning allele of the gene is introduced directly to the sperm, egg, zygote or early embryo, and so techniques of administering are more straightforward
Introduction into somatic cells is short-lived and needs to be repeated regularly, as the functioning genes are not passed on when cells divide	Introduction to germline cells means that all cells will contain a copy of the functioning gene, and there is also the possibility of passing it onto offspring
There are difficulties introducing the gene to the genome, as normally modified viruses are used, but the host becomes immune to them, and so upon second treatment the immune system rejects the therapy (in response, liposomes may be used as a vector instead, but these are not always very efficient)	Although more straightforward, most people consider it unethical to genetically modify a human embryo – it is not possible to identify whether the allele has been successfully introduced without any unintentional changes to the embryo which may prove damaging

Ethical concerns regarding engineering

Genetic manipulation has its obvious advantages, but there are many ethical weaknesses which surround it. One of the big benefits is the growing research into **xenotransplantation**, the use of engineering certain animals for organs for transplantation into humans. This area of research has increased because of the massive shortage of donor organs, for a number of reasons. It is estimated that 60% of patients on a donor organ waiting list die before surgery.

A large risk of any transplantation method is **rejection** from the host's immune system. This is why all transplant donors are checked for immuno-matches and immunosuppressants are given post-surgery, to reduce the chance of rejection. Obviously, the biggest obstacle with xenotransplantation is rejection, as other organisms are even less similar to ourselves (making human **allotransplantation** – transplants between the same species – seem more effective).

In recent years, pigs have been successfully developed which have been modified to lack an enzyme which is a key trigger for graft rejection in humans, called **α-1,3 transferase** and even more recently, modified human enzymes have been placed into these treated pig tissues and a reduction in immunological activity has been observed. It is hoped that further research and developments in this field will lead to the development of successful xenotransplantation.

There are other advantages of genetic manipulation, but equally there are the ethical drawbacks associated with them, and the table below outlines the benefits and drawbacks of engineering on various organisms:

Organism	Example of benefit	Example of drawback
Humans	Gene therapies have been developed and further research is occurring to help treat genetic disorders	Ethical objections: • effects of gene transfer are unpredictable • individuals resulting from germline therapies would have no say in whether their own genetic material should be modified • not only might germline therapies be used to eliminate disease but also breed '*designer children*' as parents become able to choose and enhance favourable characteristics
Animals	Pharmaceutical chemicals can be produced, e.g. in milk Increased milk or meat production Production of compatible organs is becoming possible for transplantation	Animal welfare issues arise due to the treatment, suffering and genetic manipulation of animals Sometimes such research may contradict strong views held by some religious groups (e.g. orthodox Jews and Muslims consider pigs unclean, and Hindus consider cows sacred)
Plants	e.g. accumulation of beta-carotene in the endosperm of rice in Golden Rice™ Developing crops which are resistant to pesticides allows the use of weedkillers and insecticides to increase yields	Genetic variation may be reduced as inserted genes can be passed to wild relatives Favourable genes might be transferred to unwanted weeds and other crops, which damages agriculture Modified plants may be toxic to other organisms or cause allergic reactions in humans
Microorganisms	Genetically modified microorganisms such as bacteria can be used to produce useful products, such as human insulin or human growth hormone	Microorganisms may escape from containment and pass on their modified genes to other, pathogenic organisms with unknown effects Techniques often involve using genetic markers of antibiotic resistance, which can be passed on, increasing widespread resistance to antibiotics among bacteria