Confocal microscope image of stem cells labelled with fluorescent markers ×2250

Stem cells in research

Growing body parts in the laboratory

Lizzy Ward

The world waits for stem cell transplants to revolutionise medicine. Yet behind the scenes, they have already transformed research without leaving the laboratory. Developmental biologist Lizzy Ward explains how stem cells are used to study and heal the body

EXAM LINKS

AQA Most of a cell's DNA is not translated
OCR A The potential uses of stem cells
OCR B Stem cells
Pearson Edexcel A Stem cells
Pearson Edexcel B Stem cells
WJEC Eduqas Use of stem cells

The root of many diseases is a cell's inability to perform its normal functions. Patients are given drugs to improve their quality of life, but in many cases the problem remains. Their cells are faulty and there is no cure. For decades, doctors have been looking for more permanent ways to restore normal function in the body. The aim of regenerative medicine is to replace, or otherwise fix, faulty cells. By regenerating damaged parts of the body, people suffering from debilitating diseases can lead longer, healthier lives. Stem cells have spearheaded this mission.

From body to laboratory

Animal cells are not immortal. They continuously die throughout our lives and are replaced from pools of adult stem cells all over our bodies. Stem cells have two key properties that define them:

- They can transform into other, more specialised cell types.
- They can **self-renew** – dividing by mitosis many times to form daughter cells. Each daughter cell either remains as a stem cell or transforms into a specialised cell type.

This process of transformation is known as differentiation – the cell, quite literally, becomes different. Adult stem cells are **multipotent** – they can only differentiate into a limited number of cell types. However, it is now known that different types of adult stem cells are associated with nearly every organ of our body, each forming its own set of specialised cell types (see Figure 1). These stem cells are vital for maintaining and healing the body throughout our lives.

The ultimate stem cell is the embryonic stem cell. These cells are found in an embryo at the earliest stages of development, when it is just a tiny cluster of cells. Embryonic stem cells are **pluripotent**, meaning they have the potential to give rise to every cell type in the body, from skin to bone, head to tail and everything in between.

One major obstacle in the study of stem cells was finding ways to grow them in the laboratory while preventing them from differentiating into other cell types. In the 1980s, a method for extracting and growing mouse embryonic stem cells was devised. By 1998, this method had been adapted successfully for human cells. This laid the foundation for a new era of stem cell research.

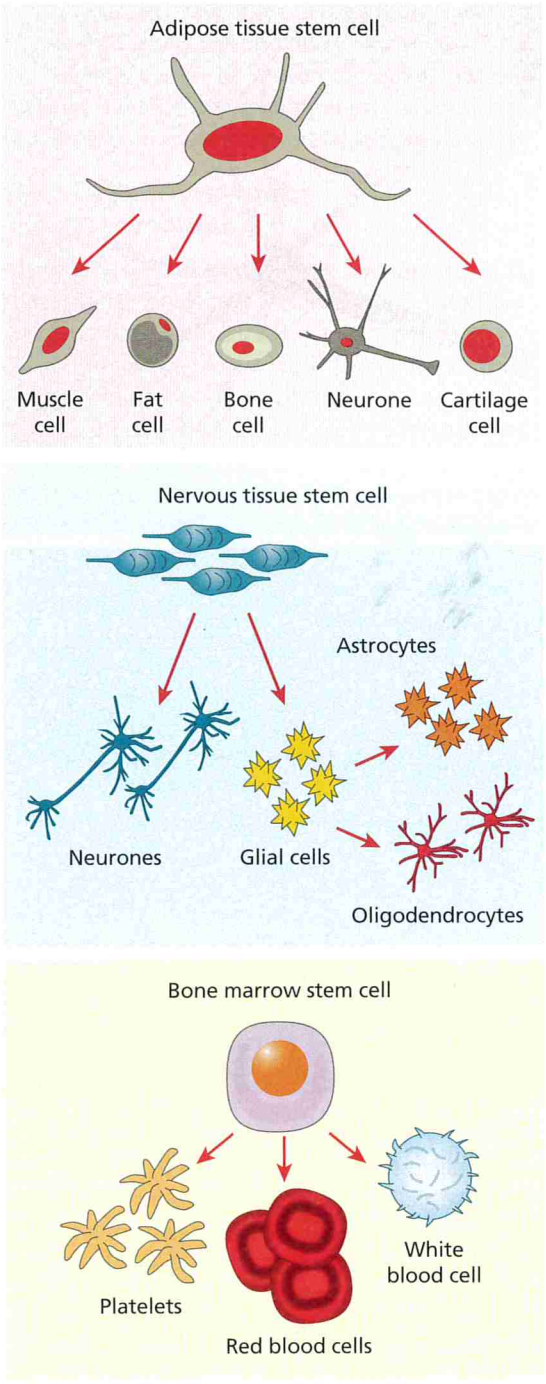
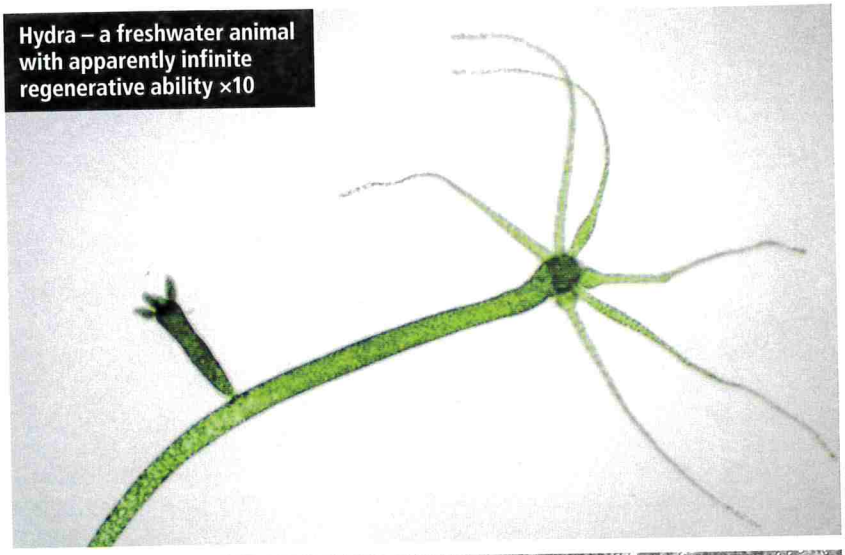


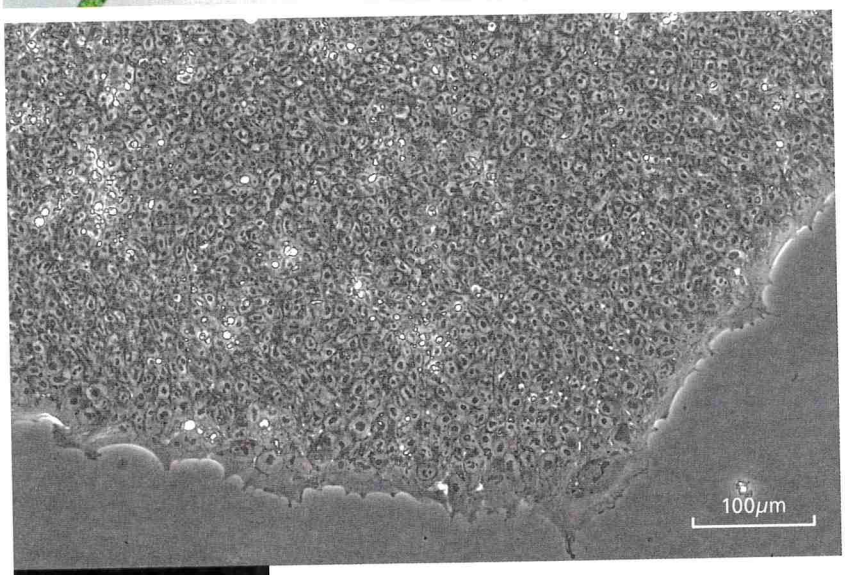
Figure 1 Differentiation capabilities of multipotent adult stem cells from different tissues

Super-humans: regenerating the body using stem cells

Some animals have remarkable powers of regeneration. The hydra, an aquatic invertebrate, can regenerate its entire body from just a small tissue fragment. Humans lack such regenerative abilities. However, since the discovery of stem cells, scientists have looked to harness their abilities to enable regeneration. If we cannot regenerate naturally, perhaps we can use stem cells to help us become a bit more 'hydra'.



Hydra – a freshwater animal with apparently infinite regenerative ability ×10



Light micrograph of a two-dimensional colony of induced pluripotent stem cells growing in culture

The biggest advance in stem cell medicine has been the development of treatments for blood disorders such as acute myeloid leukaemia (AML). Red blood cells, platelets and white blood cells are derived from haematopoietic stem cells in the bone marrow (see Figure 1). In patients with AML, the formation of some types of white blood cell is disrupted, resulting in the build-up of immature, non-functional white blood cells. After killing these faulty cells with chemotherapy, AML patients can be treated with a stem cell or bone marrow transplant from a donor. This treatment is not without risks. The donor must have the same tissue type as the patient to reduce the risk of the transplant being rejected. However, if successful, healthy stem cells replace the faulty stem cell pool of the patient and form normal, disease-fighting white blood cells.

The challenges of embryonic stem cells

Some tissues cannot be repaired using adult stem cells, which only have multipotent capability. Because of this, scientists looked to pluripotent embryonic stem cells. However, a number of obstacles stand in the way of embryonic stem cell therapy.

There is a risk that transplanted donor embryonic stem cells are rejected by the body's immune system, in the same way that a donor organ would be. Additionally, cell division is a key property of stem cells, but also one of the hallmarks of cancer. Unless controlled, it is possible that stem cell transplants could develop into malignant tumours. Research into how a patient's own body might affect cell division in the transplant, as well as thorough clinical trials and detailed monitoring of transplant patients, can overcome these obstacles.

More difficult to overcome are ethical dilemmas surrounding embryonic stem cells, which are collected from surplus embryos discarded after fertility treatment. Many people believe that the destruction of embryos in this way is wrong. Several countries have banned the extraction of embryonic stem cells for research. In 2006, a new discovery promised to solve this problem forever.

Induced pluripotent stem cells: the holy grail of regenerative medicine?

The process by which a stem cell turns into a specialised cell is specific to each cell type. But one thing is consistent to all – transformation is a one-way street. Once an animal cell begins its journey through differentiation, it cannot turn back. Or so it was thought.

In 2006, a research group in Japan defied common understanding by reversing differentiation. Culturing mouse skin cells in a dish, the researchers introduced four 'reprogramming factors' to switch on genes that are known to be important in embryonic stem cells. After a few weeks, they observed a gradual loss of skin cell characteristics. The emerging cells formed clusters and could self-renew many times, just like embryonic stem cells. Furthermore, these reprogrammed skin cells had the potential to differentiate into any other type of cell in the body (see Figure 2). What the scientists had created was a cell that looked and behaved exactly like an embryonic stem cell, but without the need to destroy embryos. They named these cells induced pluripotent stem cells, or iPSCs. In 2012, the leader of the research team, Professor Shinya Yamanaka, shared the Nobel Prize in Physiology or Medicine.

iPSCs, like embryonic stem cells, offer hope for patients in which adult stem cell therapies are impossible or unsuccessful. But they have another major advantage over embryonic stem cells. They make it possible for a transplant to be created from a patient's own cells, reducing the risk of rejection. For people suffering from inherited diseases such as **thalassemia**, caused by DNA mutations passed down through families, this offers a new ray of hope. Scientists are working to create iPSC

TERMS EXPLAINED

Multipotent Stem cells that can give rise to a limited number of different cell types.

Pluripotent Stem cells that can give rise to every type of cell in the body.

Self-renewal Division by mitosis to make more, identical cells.

Thalassemia An inherited blood disorder, characterised by production of abnormal haemoglobin.

transplants made from the patient's own cells in which the disease-causing mutation is 'fixed'. This is made possible by gene editing technologies, such as CRISPR-Cas9 (see Biological Sciences Review, Vol. 29, No. 4, pp. 10–13), which allow researchers to target and alter specific DNA sequences in the genome with pinpoint accuracy.

In Japan and the USA, clinical trials are underway to treat Parkinson's disease with transplants of neurones generated from both donor- and patient-derived iPSCs. A similar approach has been used to treat patients suffering from age-related macular degeneration – a disease that causes sight loss. Early results suggest these transplants are safe, but only time will tell whether patients experience a life-changing reversal of their disease.

It has been nearly 15 years since iPSCs were first created. For many experts, the long wait for clinical trials is disappointing. But we must be realistic. All new treatments take time. Developing a reliable and reproducible method must come first. Then the treatment must be proved to be both safe and effective. Despite this, leading stem cell researchers believe iPSC transplants have enormous potential.

Stem cells in research: a quiet revolution

Although iPSCs are not yet the magic bullet that many predicted for disease, they have revolutionised medical research. Historically, much of our knowledge of how the body works, and what happens when it goes wrong, has relied on studying animal models such as rats and mice. But none of them is a perfect replica of the human body. There are many examples of drugs showing great promise in animal trials, only to fail in humans. iPSCs provide a way of studying our own, unique biology using human cells, including testing the effectiveness of potential drugs.

iPSCs enable researchers to create cell types that carry a disease-causing genetic mutation, simply by taking skin or blood cells from an affected patient. These cells are then studied in the laboratory and compared with healthy cells, helping our understanding of a disease or for testing new drugs. Using iPSC models to test drugs and treatments ensures that only drugs with a high success rate in human cells make it through to clinical trials. This means less animal testing, fewer failed clinical trials, and an increased chance of finding new treatments.

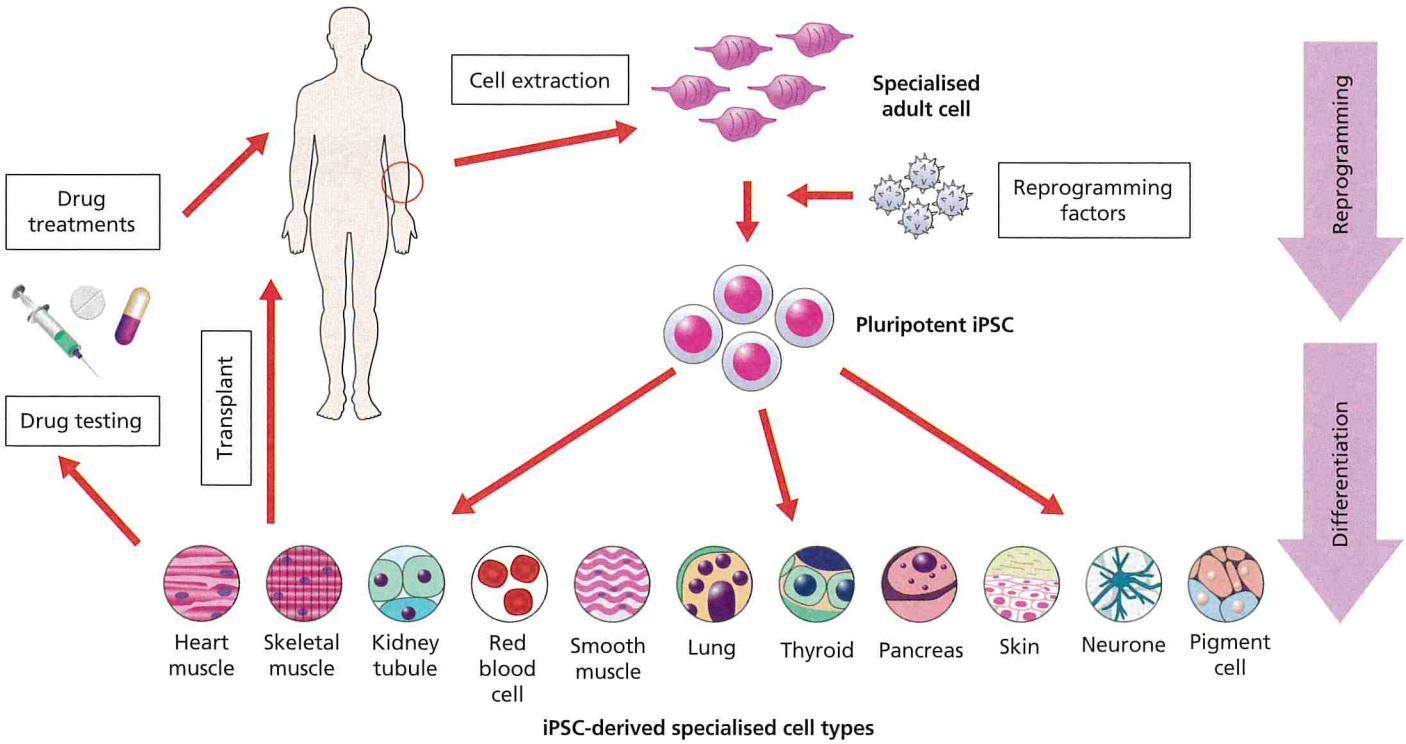


Figure 2 Making and using induced pluripotent stem cells (iPSCs). Adult cells – usually from blood or skin – are reprogrammed into iPSCs. These pluripotent stem cells can be induced to differentiate into any cell type in the body. These cells can then be used as a transplant or to test new treatments

Exam-style questions

Use information from this article and your own knowledge to answer the following questions.

1 Give **two** ways in which the properties of pluripotent stem cells and multipotent stem cells are similar and **one** way in which they differ. [3 marks]

2 Outline **four** advantages of using induced pluripotent stem cells (iPSCs) rather than embryonic stem cells or adult stem cells in clinical work. [4 marks]

BiologicalSciencesReview*Extras*

Go online for the answers at
www.hoddereducation.co.uk/bioreviewextras

RESOURCES

2012 Nobel Prize in Physiology or Medicine press release: **https://tinyurl.com/y2zse4mw**

Organoids in COVID-19 research: **https://tinyurl.com/y6r8gknx**

Tiny beating human heart made from scratch, *New Scientist*: **https://tinyurl.com/plrdas5**

Lab-grown 'minibrains' differ from the real thing in cell subtypes, gene expression, *Science*: **https://tinyurl.com/rbsxzh9**

Genome editing – CRISPR-Cas9 explained: **www.youtube.com/watch?v=TdBAHexVYzc**

3D stem cells

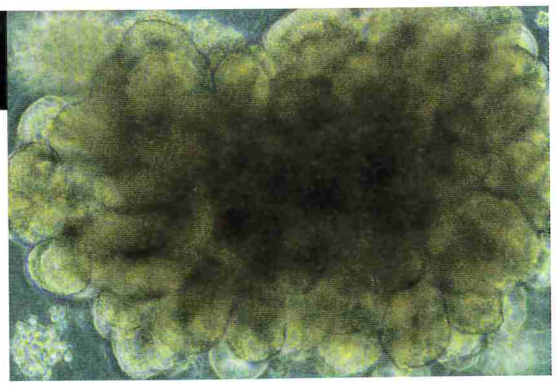
The ability to make every cell type in the laboratory is a major step for biological research. However, in the body, cells live in three-dimensional tissues. Removing a cell from its environment in the body and placing it in a dish does alter its biology. There is only so much that can be learnt from a layer of cells in a dish. So researchers have turned their attention to growing stem cells in three-dimensional culture systems. This has led to the development of 'organoids' – mini models of human organs grown from stem cells.

So far, many different organoids have been developed, from adult and from pluripotent stem cells. Heart organoids, complete with a beating ventricle, are used to study heart disease and to test drugs to treat heart attacks. Kidney organoids have been created to study renal failure. Organoids are being used in the fight against COVID-19, with tiny replicas of human alveoli being used to study SARS-CoV-2 infection in the lungs.

Perhaps most astounding are so-called cerebral organoids. Formed from stem cells, they model the neurone and blood vessel organisation of specific brain regions, including connections made between cells in three-dimensions. These 'mini-brains' allow biologists to study human brain development and what happens when this goes wrong. Cerebral organoids made from the iPSCs of patients with neurological disorders can allow us to study diseases such as schizophrenia in more detail than ever before.

However, it is important to remember that brain organoids are not exact replicas of the human brain. A recent study has shown that, although recreating many aspects of the brain, cerebral organoids do not form every neurone sub-type. Additionally, cerebral organoids are pushing iPSCs to an ethical limit. With the development of living brain tissue, philosophical questions emerge: are these organoids conscious, and how long until it is possible to create an entire 'humanoid'?

Science fiction aside, it is hoped that the development of human stem cell models such as organoids will herald a new era of 'personalised medicine'. Drugs could be trialled on tissues made from a patient's own cells to find the most effective drug for their treatment. Stem cells have the potential to revolutionise medicine. Much work lies ahead if this is to become a reality.



Light micrograph of developing 3D brain organoid ×25

KEY POINTS

- Stem cells give rise to other, specialised cell types.
- Adult cells can be reprogrammed into induced pluripotent stem cells, which can give rise to any cell type in the body.
- Scientists are developing new treatments for diseases such as acute myeloid leukaemia and Parkinson's using stem cell transplants.
- Stem cells are used in the laboratory to study disease and develop new treatments.
- 3D 'organoids', grown from stem cells in the laboratory, aim to mimic organs such as the human heart and brain.

Dr Lizzy Ward is a developmental biologist at The University of Manchester. Her research, funded by the charity *Versus Arthritis*, uses induced pluripotent stem cells to form intervertebral disc cells for studying and treating intervertebral disc degeneration, a disease that leads to severe back pain.