VICTORIA JUNIOR COLLEGE
BIOLOGY DEPARTMENT
YEAR ONE LECTURE 2024 (H2 9744 & H1 8876)

CORE IDEA 1: THE CELL AND BIOMOLECULES OF LIFE
Stem Cells

Learning Outcomes:

Candidates should be able to:

(t) describe the unique features of stem cells, including zygotic stem cells, embryonic stem cells and blood stem cells (lymphoid and myeloid), correctly using the terms:
- i. totipotency (e.g. zygotic stem cells)
- ii. pluripotency (e.g. embryonic stem cells)
- iii. multipotency (e.g. lymphoid and myeloid stem cells)

(u) explain the normal functions of stem cells in a living organism, including embryonic stem cells and blood stem cells (lymphoid and myeloid)

(v) discuss the ethical implications of the application of stem cells in research and medical applications and how human induced pluripotent stem cells (iPSCs) overcome some of these issues (procedural details of how iPSCs are formed are not required).

Note: LO **(p) – (r)** in H1 syllabus

Contents:

1. FEATURES AND POTENCY OF STEM CELLS

LO: Describe the unique features of stem cells, including zygotic stem cells, embryonic stem cells and blood stem cells (lymphoid and myeloid), correctly using the terms: i. totipotency (e.g. zygotic stem cells) ii. pluripotency (e.g. embryonic stem cells) iii. multipotency (e.g. lymphoid and myeloid stem cells)

(a) Introduction to stem cells

- A stem cell is a cell from an embryo, foetus or adult that is **unspecialised**, and has the ability to divide for long periods (**self-renewal**) or, in the case of adult stem cells, throughout the life of the organism.

- It can, under certain conditions, **differentiate** to give rise to the tissues and organs of the body.

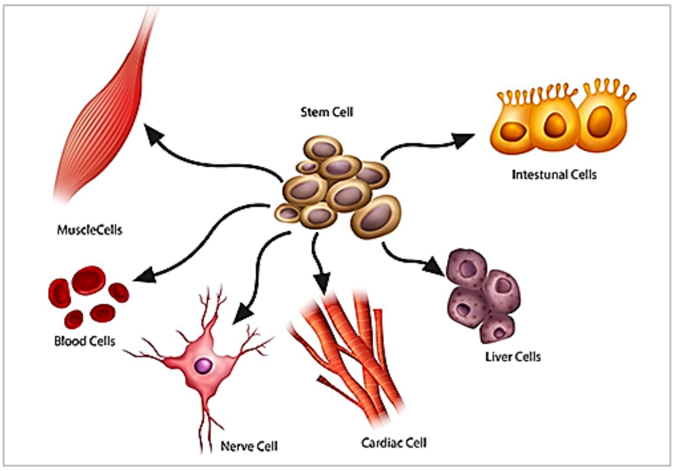


Fig. 1. Differentiation of stem cell

(b) Features of Stem Cells

- Stem cells differ from other kinds of cells in the body. All stem cells, regardless of their source, have the following features:
  - (i) They are **capable of dividing** (mitotic cell division) and renewing themselves for long periods (**long term self-renewal**).
  - (ii) They are **unspecialised** and are able to give rise to specialised cell types under appropriate conditions (**differentiation**).

(i) Long term self-renewal

- Stem cells are capable of making **identical copies** of themselves via **mitotic cell divisions** for the lifetime of the organism. This characteristic is referred to as **self-renewal**.
  - Stem cells may replicate many times. When cells replicate themselves many times over, it is called **proliferation**.
  - A population of stem cells that proliferates for many months in the laboratory can yield millions of cells. If the resulting cells continue to be unspecialised, like the parent stem cells, the cells are said to be capable of **long-term self-renewal**.

- Stem cells can either undergo **symmetric** division to give rise to 2 identical daughter cells, or they can undergo **asymmetric** division to form 2 different daughter cells, in which 1 remain as a stem cell and the other differentiates into a specialised cell.

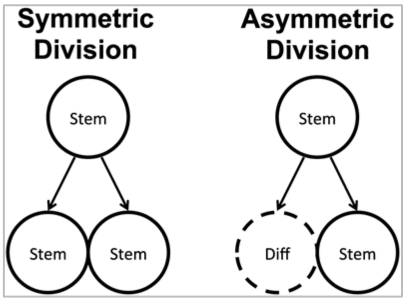


Fig. 2 Symmetric and asymmetric divisions.

- When a stem cell divides by mitosis, one of two possible outcomes occur:
  - By **symmetric division**, both daughter cells retain the property of self-renewal to ensure that a pool of **stem cells is constantly replenished** in the adult organ.
  - By **asymmetric division**, one daughter cell remains a stem cell capable of self-renewal while the other daughter cell undergoes differentiation to become a specialized cell (such as a muscle cell, a red blood cell, or a brain cell).

(ii) Differentiation

- One of the fundamental properties of a stem cell is that it does not have any **tissue-specific structures** that allow it to perform specialised functions.
  - Tissue-specific structures refer to **specific proteins** found in certain types of cells that give them their **specific functions**.

- Without tissue-specific structures, a stem cell cannot perform specialised functions such as to pump blood through the body (like a heart muscle cell), carry oxygen through the bloodstream (like a red blood cell), or relay electrochemical signals (like a nerve cell).

- However, unspecialised stem cells can give rise to specialised cells, including heart muscle cells, blood cells, or nerve cells.

- When unspecialised stem cells give rise to specialised cells, the process is called **differentiation**.

- Once a cell becomes specialised, it has a very limited capacity to produce new cells.

- These new cells and tissues are used to **repair or replace damaged or diseased cells** in the body.

- Scientists are just beginning to understand the cell signalling that trigger stem cell differentiation.
  - The signals for differentiation include chemicals secreted by other cells, physical contact with neighbouring cells, and certain molecules in the environment.

  - These signals may lead to expression of specific genes to form tissue specific structures on the specialized cells.

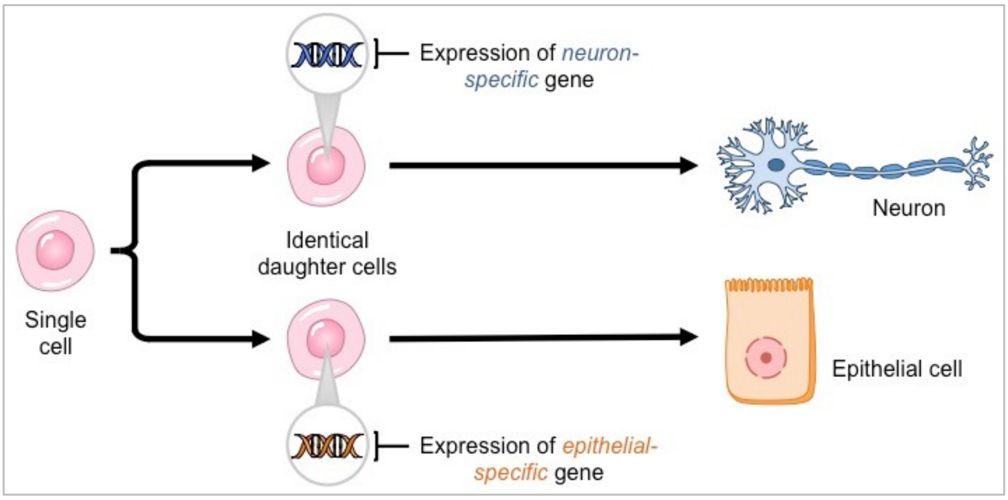


Fig. 3. Expression of different types of genes lead to differentiation of stem cell

(iii) Potency of Stem cells

- Potency specifies the differentiation potential (the potential to differentiate into different cell types) of the stem cell. Stem cells can be classified under different levels of potency:

Totipotency	ability of the cell to differentiate into **any cell type** to **form the whole organism**.
Pluripotency	ability of the cell to differentiate into **almost any cell type** to form any organ or type of cell (except the placenta or other extra-embryonic membranes)
Multipotency	ability of the cell to give rise to a **limited** range of cells and tissues appropriate to their location.
Unipotency	ability of the cell to give rise to only one type of cells

2. TYPES OF STEM CELLS AND THEIR NORMAL FUNCTIONS

LO: Explain the normal functions of stem cells in a living organism, including embryonic stem cells and blood stem cells (lymphoid and myeloid)

(a) Zygotic stem cells

- These are **totipotent** stem cells derived from the **morula** during the zygotic stage of development. They are also pluripotent and multipotent.

- **Totipotency** refers to the ability of a cell to differentiate into any cell type to form a whole organism.

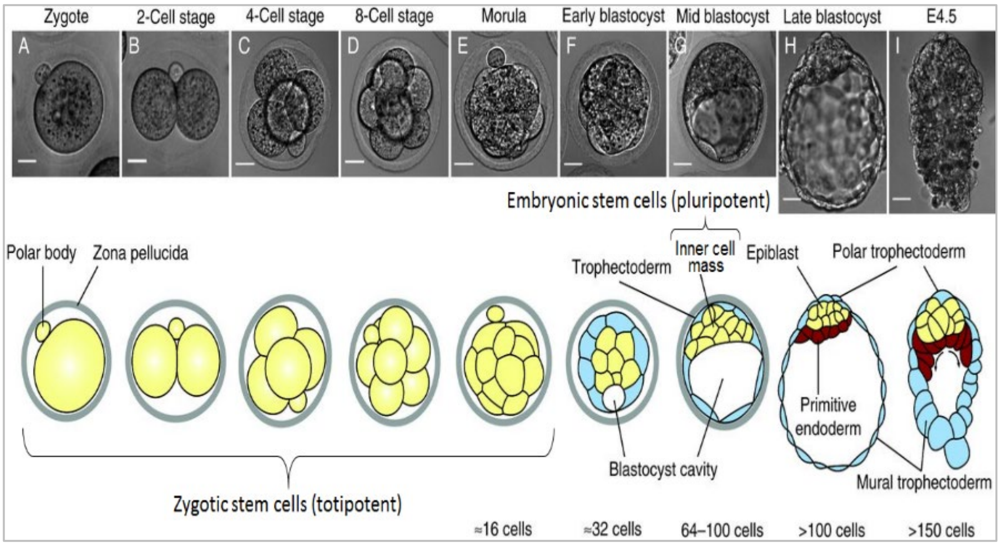


Fig. 4. Development of the human embryo - Embryogenesis

(b) Embryonic stem cells (Pluripotent stem cells)

- **Embryonic stem cells** are **pluripotent** stem cells derived the **inner cell mass**, which is part of the early (5 – 6 day) embryo called the **blastocyst**. They are also multipotent, but not totipotent.

- **Pluripotency** refers to the ability of a cell to differentiate into almost any cell type to form any organ or type of cell.

- Under normal conditions in the uterus, these cells would go on to form the entire foetus. The embryonic stem cells are unable to form the placenta or other extra-embryonic membranes (e.g. chorion). Thus, they cannot be used to form a whole organism.

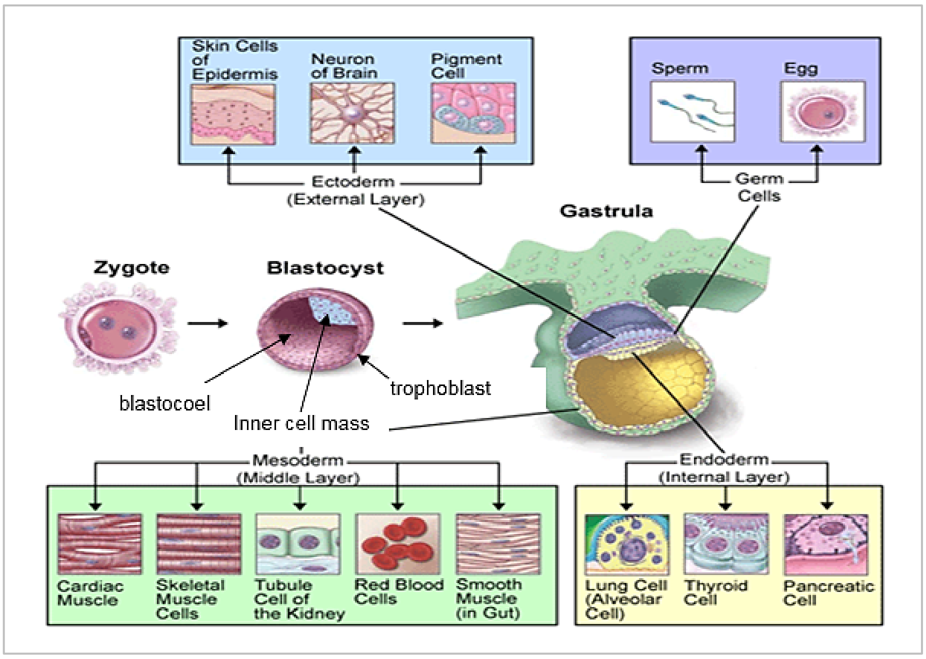
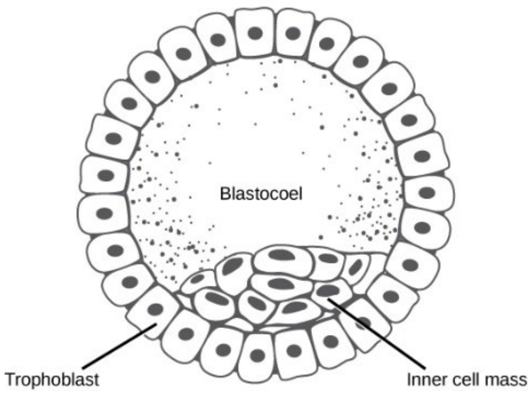


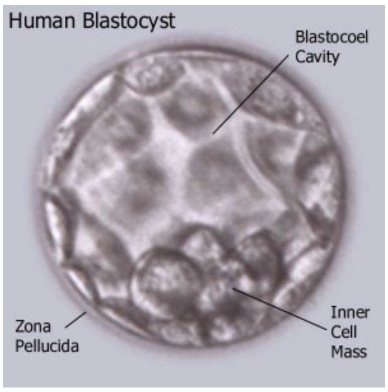
Fig. 5. Development of embryonic stem cells.

(FYI) During a developmental process known as gastrulation, the inner cell mass can differentiate into three primary layers: ectoderm, endoderm, and mesoderm. Cells in each the three germ layers can eventually differentiate to form specialized cell types that make up the various organs or tissues of the foetus.

- In the laboratory, cells from the inner cell mass can be removed from the blastocyst and cultured into embryonic stem cells for research and medical purposes.

- Such embryonic stem cell cultures are “immortal”, i.e. these cells can **reproduce indefinitely** and divide for long periods in an **undifferentiated state**.





(c) Adult Stem Cell

- An adult stem cell is an **undifferentiated** cell that occurs in a **differentiated** tissue.

- It is **multipotent** and is capable of renewing itself and producing all the specialised cell types of the tissue from which it originated.

- Adult stem cells are capable of making identical copies of themselves for the lifetime of the organism. Their main function is to divide to **replenish dying cells and regenerate damaged tissues.**

- Sources of adult stem cells include bone marrow, cornea and retina, brain, skeletal muscle, dental pulp, liver, skin, lining of the gastrointestinal tract and pancreas.

- Examples include: bone marrow stromal (mesenchymal) cells for bone / cartilage / connective tissue; neural stem cells for different types of neurons; epithelial stems cells for different types of specialised cells in small intestine; skin stem cells for repair and replacement of the skin; etc.

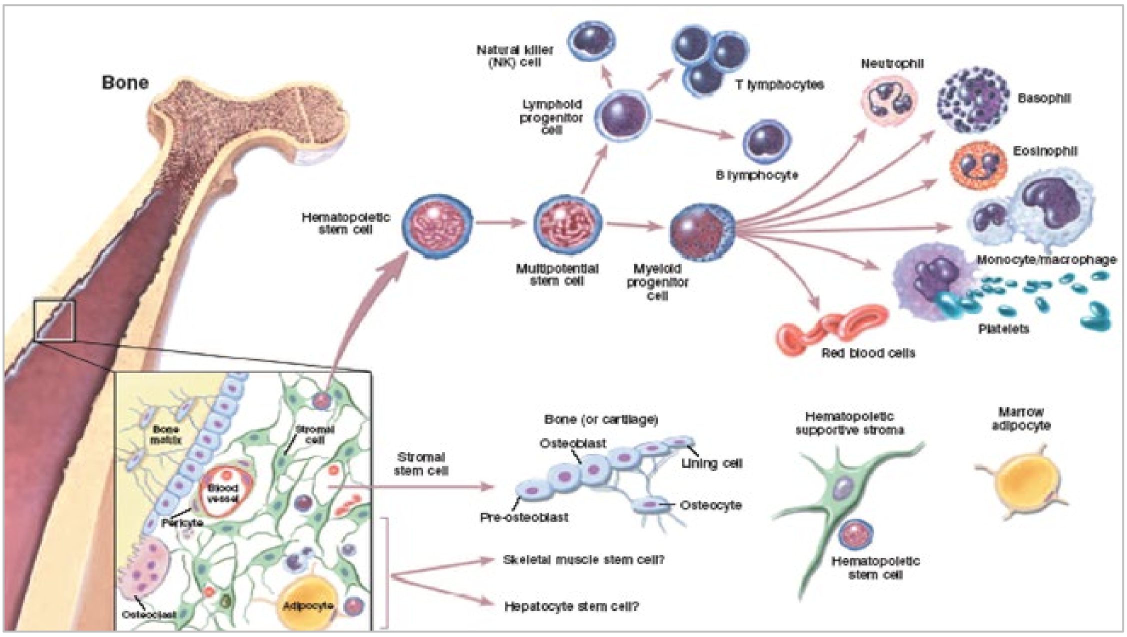


Fig. 6. Differentiation of adult stem cells found in the bone marrow

Named example: **Blood (hematopoietic) stem cell**

- Blood stem cell, also known as hematopoietic stem cell, is an example of "adult" **multipotent stem cell**.

- Haematopoietic stem cells are **multipotent cells** with the ability to differentiate into the different **blood cells** and **immune cells**. They can be used to treat a range of blood disorders and immune system conditions such as **leukaemia** and **sickle cell anaemia**.

- Major sources of haematopoietic stem cells include adult **bone marrow** and **umbilical cord blood**.

- A multipotent hematopoietic stem cell can differentiate into two types of multipotent stem cells: **myeloid stem cell** and **lymphoid stem cell**. Myeloid and lymphoid stem cells are able to give rise to different types of blood cells.

- **Myeloid stem cell** may differentiate to give rise to cells such as monocytes, macrophages, neutrophils, basophils, eosinophils, erythrocytes (red blood cells) and platelets, while **lymphoid stem cell** may differentiate to give rise to cells such as T cells, B cells and natural killer cells. (Details and functions of the various types of blood cells will be covered in Immunology extension topic.)

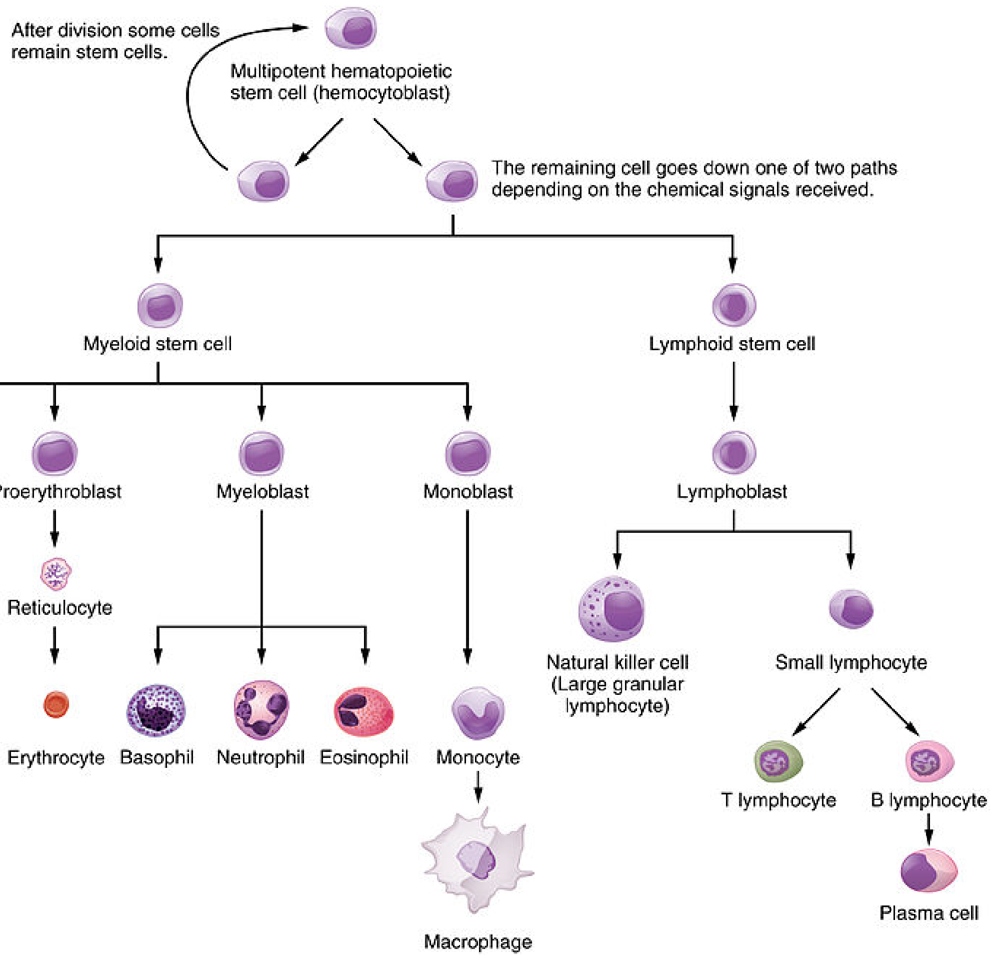


Fig. 7. Blood cell development.

Bone marrow

- All the various types of blood cells are produced in the **bone marrow,** particularly in the ribs, vertebrae, breastbone and pelvis. These cells arise from a single type of cells called a **hematopoietic stem cell** (an adult multipotent stem cell).

- *FYI: These stem cells are very rare (only about one in 10,000 bone marrow cells). They are attached to osteoblasts (cells that lay down new bones) lining the inner surface of bone cavities.*

- These stem cells will divide mitotically to give rise to 2 kinds of cells – one that will remain as a **hematopoietic stem cell**, the other will differentiate into a **myeloid stem cell** and a **lymphoid stem cell** which may differentiate into **various kinds of blood cells** such as red blood cells and white blood cells (e.g. lymphoctyes, monocytes, neutrophils, basophils, eosinophils and macrophages) and megakaryocytes.

- Which differentiation path the cell takes is regulated by cytokines and / or hormones. (Note: Cytokine is a protein secreted by a cell that signals to other cells.)

Umbilical cord blood

- Umbilical cord blood is **blood from the placenta and umbilical cord** that is rich in hematopoietic stem cells.

- Umbilical cord blood is collected after the umbilical cord has been detached from the newborn, and utilised as a source of stem cells for transplantation.

- The advantage is that umbilical cord blood stem cell transplants are less prone to rejection than bone marrow.
  - This is because the cells in the umbilical cord blood have not yet developed features that can be recognised and attacked by the recipient's immune system.

  - Umbilical cord blood also lacks well-developed immune cells, so there is less chance that the transplanted cells will attack the recipient's body.

3. ETHICAL IMPLICATIONS OF STEM CELLS IN RESEARCH AND MEDICAL APPLICATIONS

LO: Discuss the ethical implications of the application of stem cells in research and medical applications and how human induced pluripotent stem cells (iPSCs) overcome some of these issues

(a) Potential Uses of Stem Cells

Harvesting of embryonic stem cells (FYI)

- Traditionally, embryonic stem cells were harvested by destroying the human embryo in a process called somatic cell nuclear transfer (SCNT).

- A somatic cell is simply a body cell that is neither an egg nor a sperm cell. In this procedure, the nucleus is removed from a somatic cell, and it is then implanted into a donor egg that first had its nucleus removed.

- The egg cell is essentially fooled into thinking it has been fertilised. It has its own DNA and after stimulation, it divides just as a normally fertilized egg would, before forming an embryo.

- Cells from the inner cell mass are extracted and cultured to provide embryonic stem cells but the technique destroys the embryo.

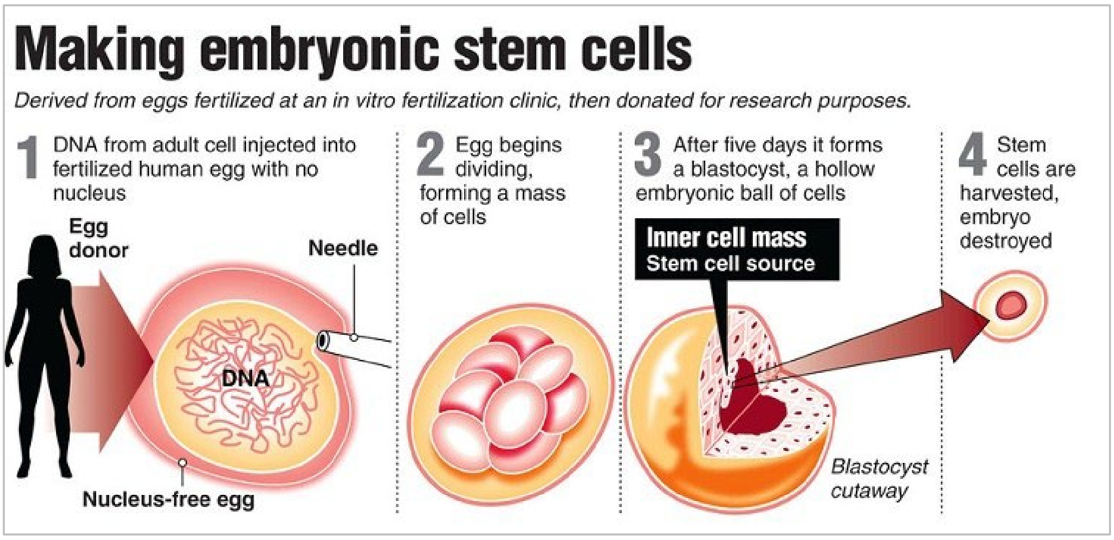


Fig. 8. How ES cells can be made from donated eggs

- Stem cells can have potential uses in many different areas of research and medicine:

(i) Replace damaged tissue

- Human stem cells could be used in cell-based therapies, in which specialised cells or tissues grown from stem cells in the laboratory are transplanted into patient.

- Due to their ability to replace damaged cells in the body, stem cells could be used to treat a range of conditions including heart failure, spinal injuries, diabetes and Parkinson disease. It is hoped that transplantation and growth of appropriate stem cells in damaged tissue will regenerate the various cell types of that tissue.
  - For example, haematopoietic stem cells could be transplanted into leukaemia patients to generate new blood cells, or neural stem cells may be able to regenerate nerve tissue damaged by spinal injury.

(ii) Testing of new drugs

- Stem cells can be used for drug tests before human clinical trial. The stem cells can be directed to differentiate into the particular cell types the drug works on. These cells may be more likely to mimic responses of human tissue to the drug tested, compared to the animal models currently being used. This may make drug testing safer, cheaper and more ethically acceptable to those who oppose animals testing.

- Stem cells may be useful for the screening potential toxins in substances such as pesticides before they are used in the environment.

(iii) Testing gene therapy methods

- Stem cells may prove useful during the development of new methods for gene therapy that may help people suffering from genetic illnesses.

(iv) Study human development

- Stem cells could be used to study early events in human development and how cells differentiate and function. This may help researchers find answers as to why some cells become cancerous and how some genetic diseases develop, which may lead to clues as to how they may be prevented.

(v) Toxicity testing

- Toxicity testing is conducted to determine the degree to which a substance can damage a living or non-living organisms.

- Due to the pluripotency of stem cells, it paves the way for an unlimited supply of primary human cells, such as neurons and cardiomyocytes, which are difficult to obtain in traditional ways for toxicity testing.

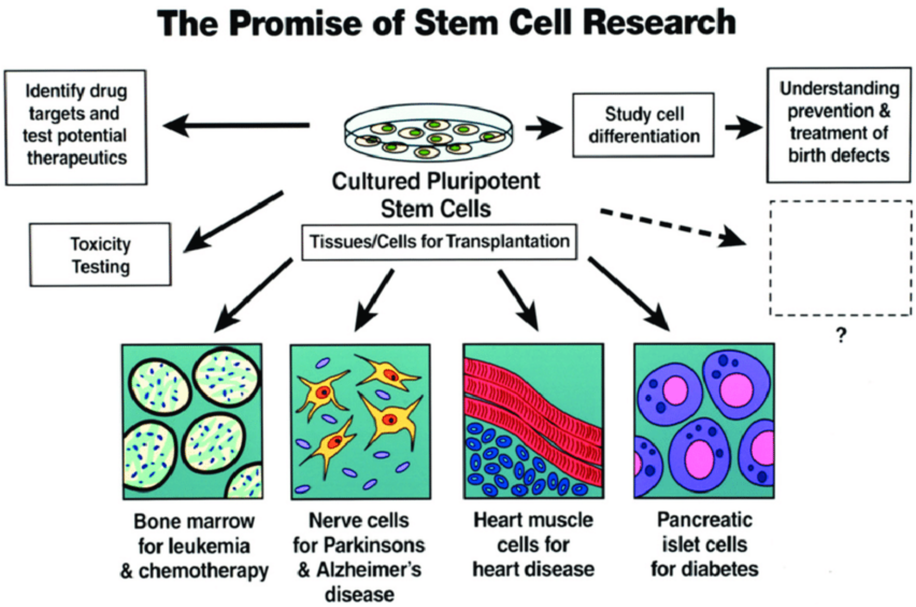


Fig. 9. Diagram depicting the expected clinical applications of some stem cell research (https://www.researchgate.net/figure/Diagram-depicting-the-expected-clinical-applications-of-some-stem-cell-research-Source_fig1_51177805)

(b) What are ethical Implications?

- When evaluating ethical considerations, students need to evaluate alternative actions as 'right' (for the greater good) and 'wrong' (more harm than good).

Some general principles to consider:

- **Universal rights** – life, liberty, personal security
- **"Do no harm"** – maybe better to do nothing than risk doing more harm than good
- **Precautionary principle** – how to cope with potential risks due to incomplete scientific understanding
- **Distributive justice** - how resources are distributed in society
- **Intergenerational justice** – fairness to other generations;
- Students should ignore discussion of religious views / offending certain communities

(c) Ethical implications in stem cell research

- Stem cell research offers great promise for understanding the basic mechanisms of human development and differentiation, as well as the hope for new treatments for diseases such as diabetes, spinal cord injury, Parkinson's disease, and myocardial infarction.

- However, human stem cell research may give rise to several ethical implications:

1. Most predominant methods used to derive human embryonic stem cells require the destruction of the embryo. The question of when a human life begins has been highly controversial and closely linked to debates over abortion.
   - Some believe that human life begins at conception and an embryo has the same moral status as an adult or a live-born child, with interests and rights that must be respected. Taking a blastocyst and removing the inner cell mass to derive an embryonic stem cell line is tantamount to murder.
   - Others hold a different view of the moral status of the embryo, that the embryo is regarded as a person only at a later stage of development. They hold the middle ground that the embryo deserves respect as a potential human being but it is acceptable to use it for research if there is good scientific justification, careful oversight, and informed consent for donating the embryo for research.

2. Another ethical controversy is whether the donor of the oocytes or embryos have informed consent regarding the use for research.
   - In *in-vitro* fertilisation procedures, oocytes that fail to fertilise or embryos that fail to develop sufficiently to be implanted are normally discarded. These could then be used for research, without the consent of the couple.
   - Also, if infertility patients have frozen embryos remaining after their treatment has been completed, they can decide to discard them, which could then be used for research instead.
   - Such frozen embryos may be created with sperm or oocytes from donors. Some argue that consent from gamete donors is not required for embryonic research because they have ceded their right to the use of their gametes.

3. Concerns about appropriate usage of oocyte donated specifically for research, as highlighted by the Hwang scandal in South Korea (https://www.nature.com/articles/439122a). In addition to scientific fraud, the scandal involved inappropriate payments to oocyte donors, undue influence on staff and junior scientists to serve as donors.

4. Potential of medical complications or health risks to donors from oocyte donation. Underlying concerns exist regarding whether donors are fully informed or aware of the health risks involved with oocyte donation.

5. At present, stem cell technologies are time-consuming and very expensive. The high costs of stem cell therapy make it available only to the rich and powerful. This may in turn widen social divisions and enhance discrimination between different classes of people in the society.

(d) Induced Pluripotent Stem Cells (iPSCs)

- One of the hurdles for the use of adult stem cells for transplants is their limited ability to generate different cell types. Recent experiments, however, showed that certain adult stem cells may be able to generate cell types of a completely different tissue in the right conditions.
    - This is called **plasticity** or **trans-differentiation**. Some researchers believe that adult stem cells may have the ability to form specialised cell types of other tissues (similar to embryonic stem cells). Research into the factors and conditions that control their differentiation is proceeding.

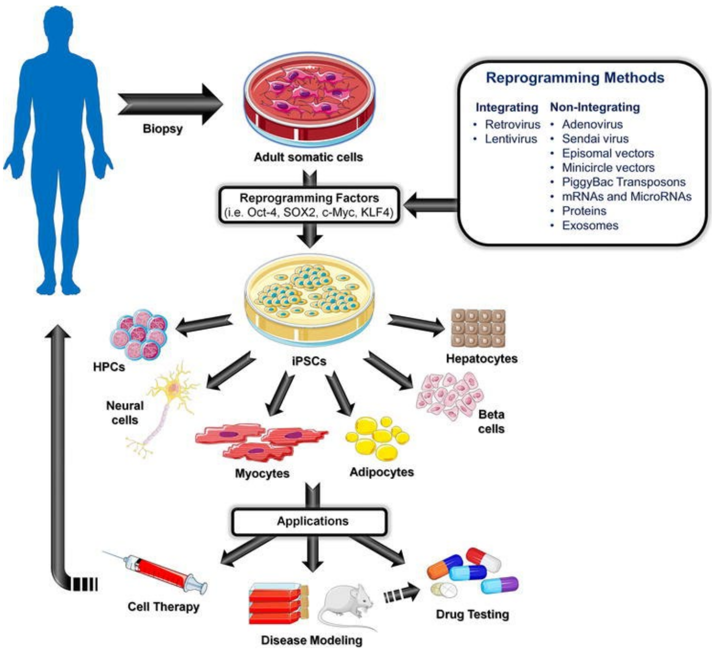


Fig. 10. Reprogramming of adult stem cells (https://www.intechopen.com/chapters/74358)

- Induced pluripotent stem cells are a type of pluripotent stem cell that can be **generated directly from adult cells**.

- Specialized adult cells can be genetically 'reprogrammed' in the laboratories to assume an embryonic stem cell-like state

- The method involves taking mature somatic cells from an adult and introducing genes that regulate function of other genes important for early steps in embryonic development.

- Use of iPSC can overcome some ethical concerns arising from the use of embryonic stem cells:
    - Since iPSCs can be derived directly from adult tissues, they **bypass the need to destroy embryos** for the extraction of stem cells.
    - As a skin biopsy to obtain somatic cells are less invasive, there are fewer risks involved for the donors compared to oocyte donation.
    - iPSCs can be made in a **patient-matched** manner, which means that each individual could have their own pluripotent stem cell line. Thus these cells can be used to generate transplants **without the risk of immune rejection**. iPSCs can also be used in the development of personalised drug and understanding the patient-specific basis of diseases.