CATHOLIC JUNIOR COLLEGE
H2 Biology JC1

CORE IDEA 1] THE CELL AND BIOMOLECULES OF LIFE

1.5 STEM CELLS

Narrative from H2 Biology 9744 Syllabus:
This concept highlights the diversity in cell type and morphology in an organism. In an organism, all cells except the gametes are genetically identical. Yet, a liver cell, a rod cell in the eye and an epithelial cell in the ileum differ significantly in terms of morphology and function due to differential gene expression. The same genome gives rise to a wide range of cells which further forms tissues, organs and systems in an organism.

The ability of stem cells to divide and their potential for self-renewal allows growth. Stem cells replace cells that die or are damaged. During embryogenesis, cell division and differentiation allow the development of an entire organism *in utero* from a single-cell zygote.

Stem cells hold great potential as medical treatments. Haematopoietic stem cells are used in blood marrow transplants in cancer treatments. Skin stem cells may be used to culture skin cells to treat patients with massive burns. Ethical debates over the use of stem cells are primarily concerned with the use of embryonic stem cells. Use of adult stem cells faces fewer of such ethical issues.

Candidates should be able to:

Subtopic	Learning Outcomes
UNIQUE FEATURES OF STEM CELLS	**1(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 which have ability to differentiate into ANY cell type to form whole organisms and so are also pluripotent and multipotent), ii. **pluripotency** (e.g. embryonic stem cells which have ability to differentiate into ALMOST any cell type to form any organ and so are not totipotent but are multipotent) and iii. **multipotency** (e.g. lymphoid and myeloid stem cells which have ability to differentiate into a LIMITED range of cell type and so are not pluripotent or totipotent)
NORMAL FUNCTIONS OF STEM CELLS	**1(u)** Explain the **normal functions** of stem cells in a living organism, including embryonic stem cells and blood stem cells (lymphoid and myeloid stem cells)
ETHICAL IMPLICATIONS OF STEM CELL APPLICATIONS	**1(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.)

CONCEPT MAP OF STEM CELLS (SC)

STEM CELLS

Characteristics :

1. **Proliferate indefinitely**
   - Divides by **mitotic** cell division
   - Telomerase is activated to prevent apoptosis.
2. **Self-renewal**
   - **One of the two** daughter cells remain in the pool of stem cells
3. **Unspecialised**
   - Cannot perform any specialised functions due to **absence of tissue-specific structures**
4. **Able to differentiate**
   - Can become other cell types **in the presence of suitable conditions or chemicals**

APPLICATIONS

Applications of stem cell :

- **Regenerative medicine** to treat Type II diabetes, Alzheimer's, Parkinson's, rheumatoid arthritis, cancer, cardiovascular disease
- **Gene therapy / gene correction** to replace faulty gene with a normal gene using retroviruses
- **Drug screening** to test new drugs on specialised cells to determine effective dosage instead of animal testing
- **Disease modelling** to make phenotypic comparisons of normal and diseased cells

ETHICAL IMPLICATIONS

Controversy in stem cell research arise from the sources SC are obtained:

- **Unwanted IVF embryos**
- **Frozen embryos**
- **Aborted foetus**
- **Stillborn**

Ethical implications:

- Destroying an embryo which is a life
- Intentional abortion to obtain stem cells
- Commercialisation of gametes, embryos

Principle of Ethics :
1. RESPECT & JUSTICE
2. INFORMED CONSENT
3. MAXIMUM BENEFITS . MINIMUM RISKS
4. NON-COMMERCIALISATION

TOTIPOTENT stem cells

- Can differentiate into **ANY** cell type to form whole organisms
- INCLUDING extra-embryonic tissues

Example:
Zygotic stem cells
(2 to 8-celled stage)

PLURIPOTENT stem cells

- Can differentiate into **ANY** cell type to form any organ
- EXCEPT extra-embryonic tissues

Example:
Embryonic stem cells

- **Inner cell mass** of blastocyst
- **Germ cells** in gonads of foetus

MULTIPOTENT stem cells

- Can differentiate into **LIMITED** range of cell types

Example:
Adult stem cell or **Somatic stem cells** (in the organs)

- **Haematopoietic stem cells** in bone marrow

induced PLURIPOTENT stem cells

Overcoming the controversy with alternative source of stem cells

Reprograming differentiated skin fibroblasts
+
4 types of **transcription factors**
↓
human induced pluripotent stem cell (iPSCs)

NO ETHICAL ISSUE
SAFE . EFFECTIVE

DEVELOPMENTAL POTENTIALS OF STEM CELLS

Types	Zygotic SC (early ESC)	Embryonic SC	Fetal SC *	(Umbilical) Cord SC	Infant / Adult SC
Source	**single-celled zygote; 2-celled to 8-celled stage** (0-1 Day; 2 to 4/5 Days)	**Inner Cell Mass of blastocyst** (5/6 Days to 6/7 Weeks)	**fetal tissues** (after 8 Weeks)	**Umbilical Cord / Cord Blood; Placental Tissue**	1. **Neural SC** 2. **Cardiac SC** 3. **Bone Marrow SC**
Developmental Potential	**Totipotent**	**Pluripotent**	**Pluripotent or Multipotent**	**Pluripotent or Multipotent**	**Multipotent**
Normal Function	able to differentiate into **All** cell types including those of extra-embryonic membranes to form the whole organism	able to differentiate to **MOST** cell types <u>except</u> those of extra-embryonic membranes	able to differentiate to **MOST** cell types or **MULTIPLE but LIMITED RANGE** of cell types	able to differentiate to **MOST** cell types or **MULTIPLE but LIMITED RANGE** of cell types	able to differentiate into **MULTIPLE but LIMITED RANGE** of cell types

*including tetracarcinorma (or germ cell tumour) that may be found in the fetus

1] UNIQUE FEATURES OF STEM CELLS

1.1 UNIQUE FEATURES OF <u>ALL</u> STEM CELLS

1. Stem Cells are able to PROLIFERATE INDEFINITELY

- Stem cells has **unlimited proliferative potential** (**divide many times** through **mitotic** cell division), unlike differentiated cells which can only divide for a set number of replicative cycles.
- **Telomerase** in stem cells is **activated**, hence their telomere do not shorten to a critical length that induce cell apoptosis.

2. Stem Cells are capable of SELF-RENEWAL

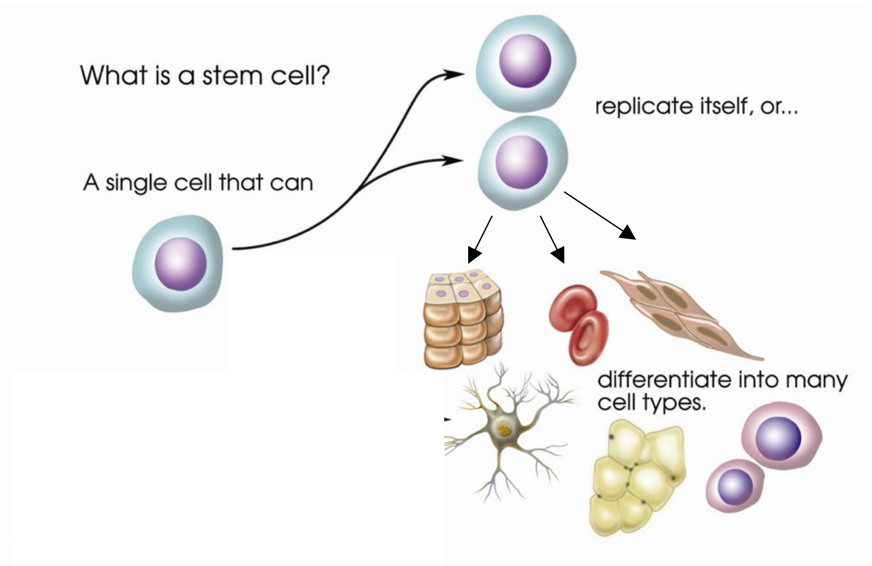
- When a **stem cell divides**, **one daughter cell remains as a stem cell** while **the other takes on a specialized function**.
- This ensures that the stem cells are always present for future cell divisions.

3. Stem Cells are UNSPECIALISED cells

- There is an **absence of tissue-specific structures,** therefore, unable to perform specialised functions.

4. Stem Cells are capable of DIFFERENTIATION / SPECIALISATION under appropriate conditions

- Stem cells respond to **intracellular** and **extracellular** signals to regulate the rate of cell division and gene expression by re-modeling of the chromosome. Cell differentiation is controlled at chromatin level.
- The **intracellular signals** are controlled by the genes, which carries coded instructions for all the structures and functions of a cell. Genes that are required for specialized functions are activated by **acetylation of histones or demethylation of DNA**.
- The **extracellular signals** are **chemicals** secreted by **other cells**, physical **contact** with neighbouring cell and **certain molecules** and **compounds surrounding a cell** in an organism.



<u>Fig. 1: Characterisitics of stem cells</u>

The developmental potential depends on the type of stem cells and the source from which the stem cells are extracted. Depending on the **degree and extent of differentiation capability**, stem cells can be described as either totipotent, pluripotent or multipotent.

1] UNIQUE FEATURES OF STEM CELLS

1.2 DEVELOPMENTAL POTENTIAL (or CELL POTENCY) OF STEM CELLS

CELL POTENCY: This describes a cell's ability to differentiate into other cell types.

1.2.1 TOTIPOTENCY

- **Totipotent Stem Cells** have the **ability to differentiate into ANY or ALL cell types, including cells of the extra-embryonic membranes, to form whole organisms.**

- Example: **ZYGOTIC stem cells**

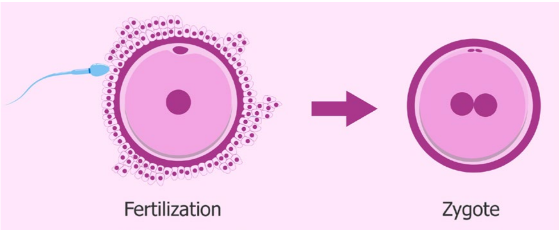
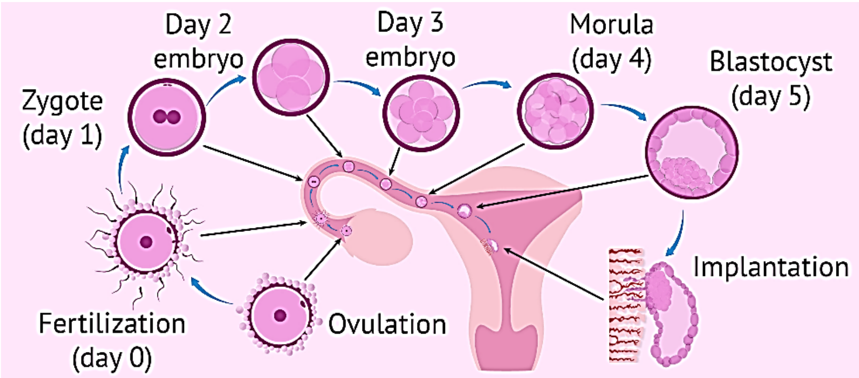


Fig. 2: The first diploid cell after fertilisation of the egg cell by sperm nucleus is the **zygote.**



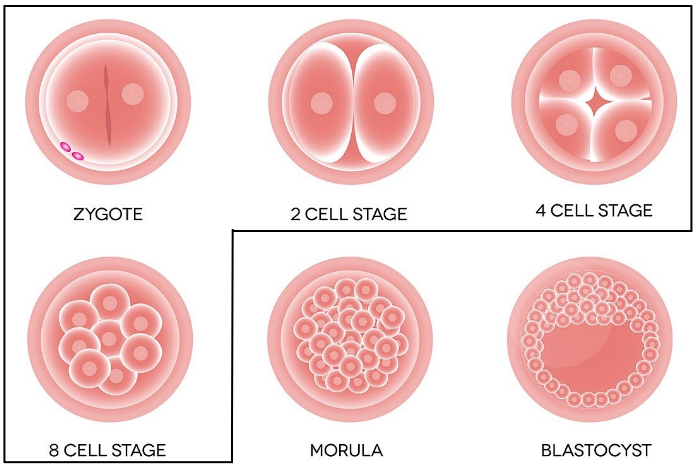


Fig. 3: Zygotic stem cells are derived from the **first 4 or 8 cells** produced by the cleavage / cell division of the zygote.

Fig. 4: A blastocyst

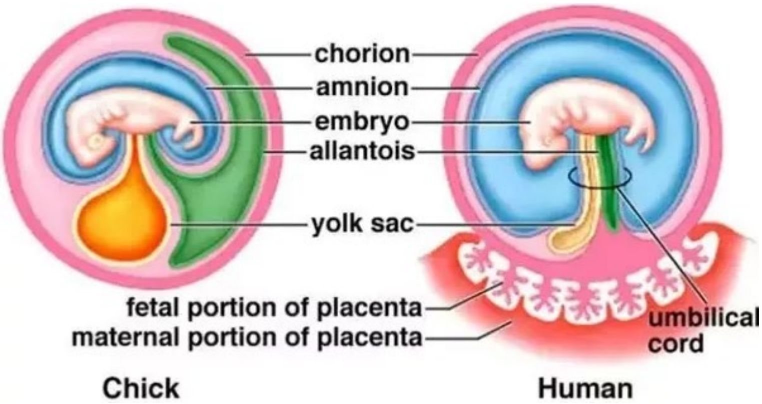


Fig. 5: Zygotic stem cells are able to differentiate into any cell type of the extra-embryonic membranes comprising **chorion, amnion, allantois, yolk sac, placenta**

1] UNIQUE FEATURES OF STEM CELLS

1.2 DEVELOPMENTAL POTENTIAL (or CELL POTENCY) OF STEM CELLS

1.2.2 PLURIPOTENCY

- **Pluripotent Stem Cells** have the **ability to differentiate into any cell type, tissues or organs** EXCEPT cells of the extra-embryonic membranes
- Example: **EMBRYONIC stem cells**

Embryonic stem cells are derived from the **inner cell mass of the blastocyst**.

The blastocyst is a ball of cells about 5 days after fertilization, which gives rise to the embryo and ultimately the foetus.

The blastocyst comprises :

- INNER CELL MASS, which is the source of embryonic stem cells
- Blastocoel, which is a hollow cavity
- Trophoblast, which is the layer of cells that surround the blastocyst

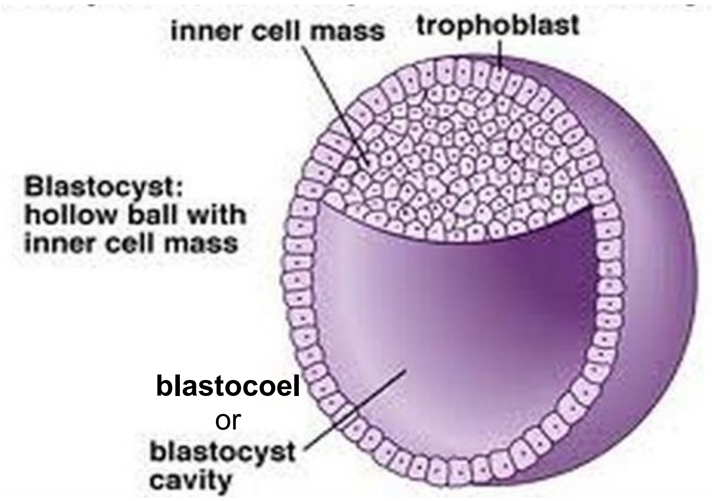


Fig. 6: A blastocyst: Embryonic stem cells derived from the inner cell mass of the blastocyst.

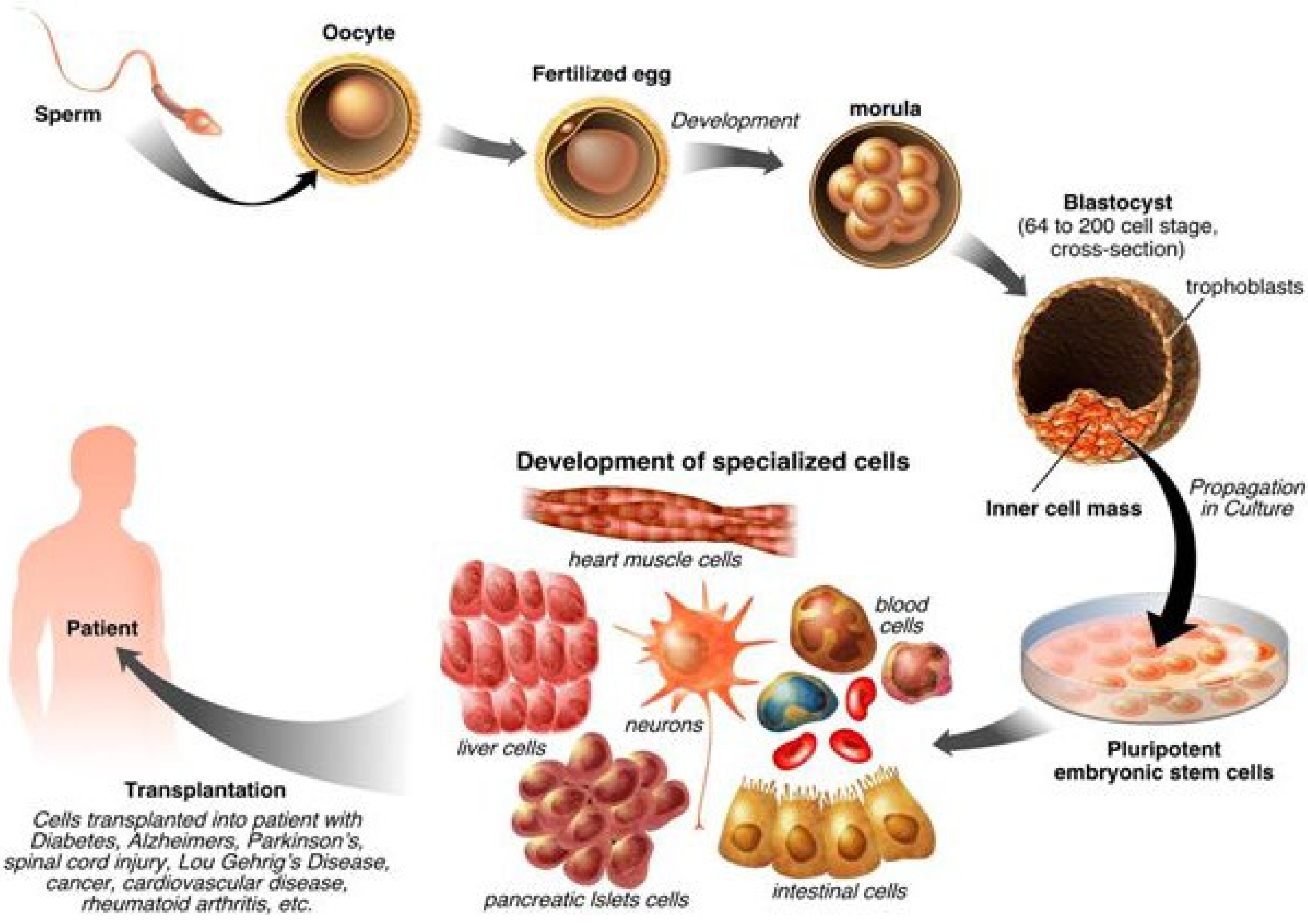


Fig. 7: Embryonic stem cells can differentiate into any cell types to form tissues and organs.

1] UNIQUE FEATURES OF STEM CELLS

1.2 DEVELOPMENTAL POTENTIAL (or CELL POTENCY) OF STEM CELLS

1.2.3 MULTIPOTENCY

- **Multipotent Stem Cells** have the **ability to differentiate into several or limited cell types**
- can be found in most organs of the body and usually replace dead or damaged cells
- Example: **BLOOD stem cells** (**HAEMATOPOIETIC stem cells)**

  They found in the **bone marrow**, particularly the ribs, vertebrae, sternum, and pelvis.

  They form two cell lineages that gives rise to **all types of blood cells**.

  The **lymphoid stem cell lineage** differentiates into immune cells, **B- and T-lymphocytes**.

  The **myeloid stem cell lineage** differentiates into **all other blood cells** (red blood cells, macrophage, eosinophil, basophil and neutrophil) **and platelets**.

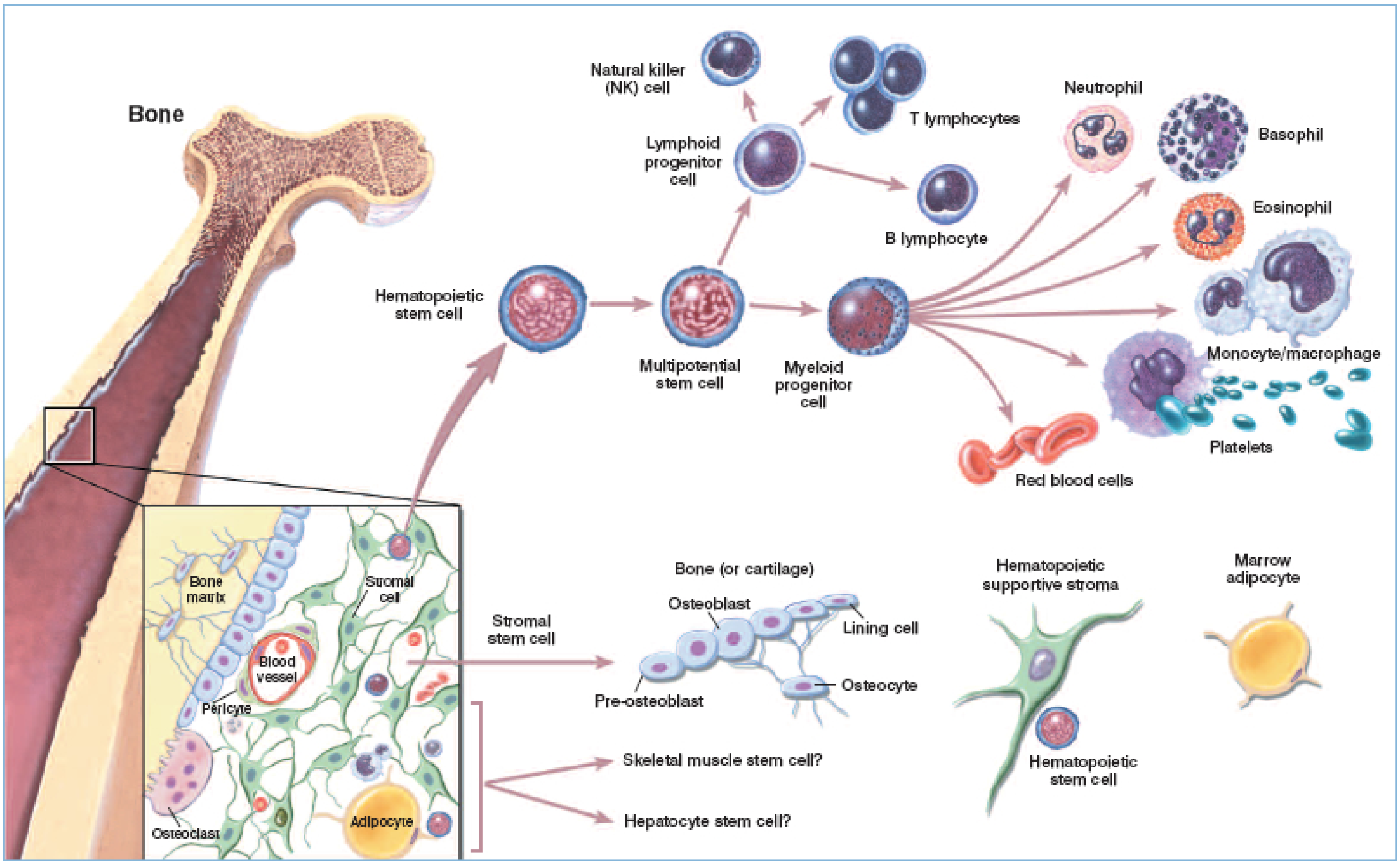


Fig. 8: Differentiation of blood stem cells

2] NORMAL FUNCTIONS OF STEM CELLS

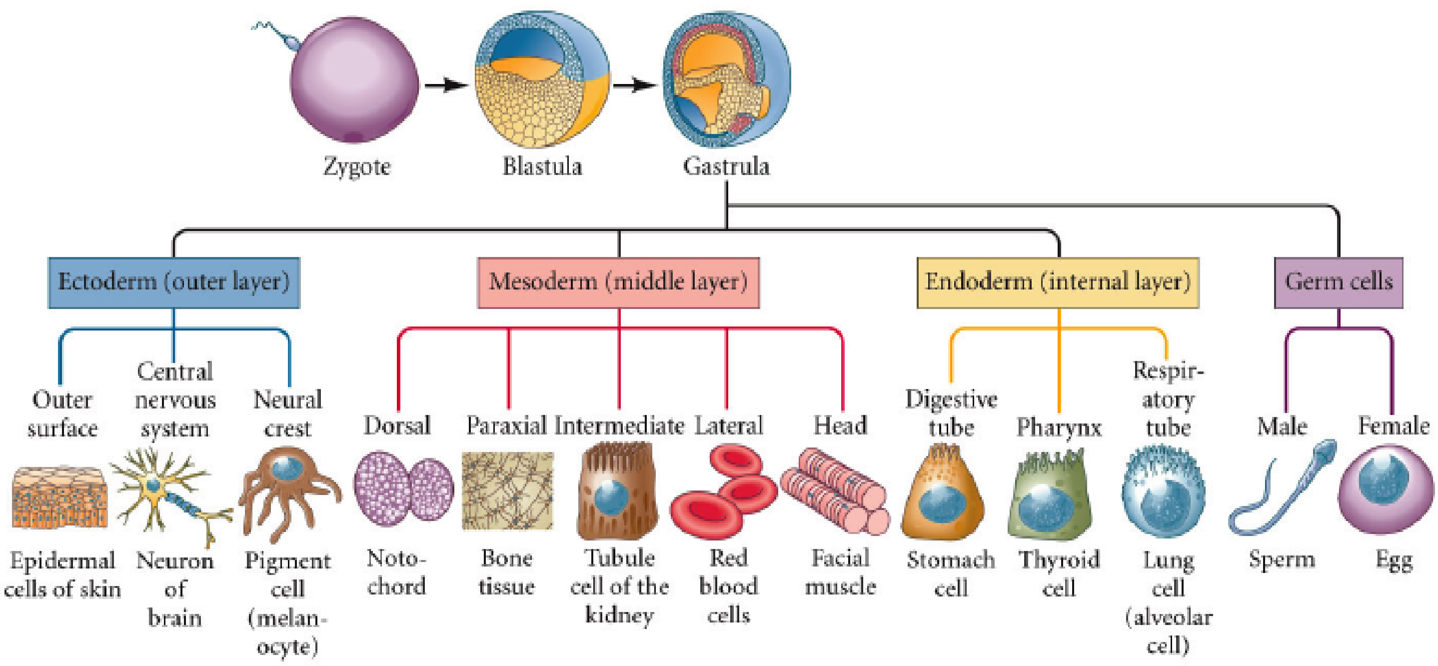
2.1 EMBRYONIC STEM CELLS

1. The embryonic stem cells first differentiate into the **3 primary germ layers**:
    a. ***Ecto*derm**
    b. ***Meso*derm**
    c. ***Endo*derm**

2. Together, the **differentiation of the 3 primary germ layers give rise to entire fetus / whole organism**.

ECTODERM	MESODERM	ENDODERM
• Epidermis of skin and its derivatives (including sweat glands, hair follicles) • Epithelial lining of mouth and anus • Cornea and lens of eye • Nervous system • Sensory receptors in epidermis • Adrenal medulla • Tooth enamel • Epithelium of pineal and pituitary glands	• Notochord • Skeletal system • Muscular system • Muscular layer of stomach and intestine • Excretory system • Circulatory and lymphatic systems • Reproductive system (except germ cells) • Dermis of skin • Lining of body cavity • Adrenal cortex	• Epithelial lining of digestive tract • Epithelial lining of respiratory system • Lining of urethra, urinary bladder, and reproductive system • Liver • Pancreas • Thymus • Thyroid and parathyroid glands

<u>Fig. 9: Differentiation of embryonic germ layers into cells, tissues and organs in the whole organism</u>



<u>Fig. 10: Differentiation of embryonic stem cells into all cell types in the whole organism</u>

2] NORMAL FUNCTIONS OF STEM CELLS

2.2 ADULT STEM CELLS: BLOOD STEM CELLS (HAEMATOPOIETIC STEM CELLS)

1. Cells in the tissue may be lost because of **diseases**, **tissue injury** or **normal wear and tear**.
   - Adult stem cells act a reservoir of cells to **maintain** and **repair** the **TISSUES in which they are found.**
   - Adult stem cells **regenerate of new functioning cells to REPLACE worn-out or damaged cells.** *[Common misconception : Adult stem cells 'repair cells'.]*

2. Blood stem cells exist in a **very small number** in **the bone marrow** and **remain non-dividing** for many years until they are **activated by disease or tissue injury**.
3. Cellular elements of the blood are **constantly replaced by blood stem cells** throughout an individual's life.
4. Blood stem cells first differentiate into **myeloid progenitor cells and lymphoid progenitor cells** which further differentiates into all **types of blood cells under appropriate conditions**.
   - **Myeloid progenitor cells are able to differentiate into neutrophils, basophils, eosinophils, monocyte/macrophages, platelets and red blood cells.**
   - **Lymphoid progenitor cells are able to differentiate into natural killer cells, T lymphocytes and B lymphocytes.**

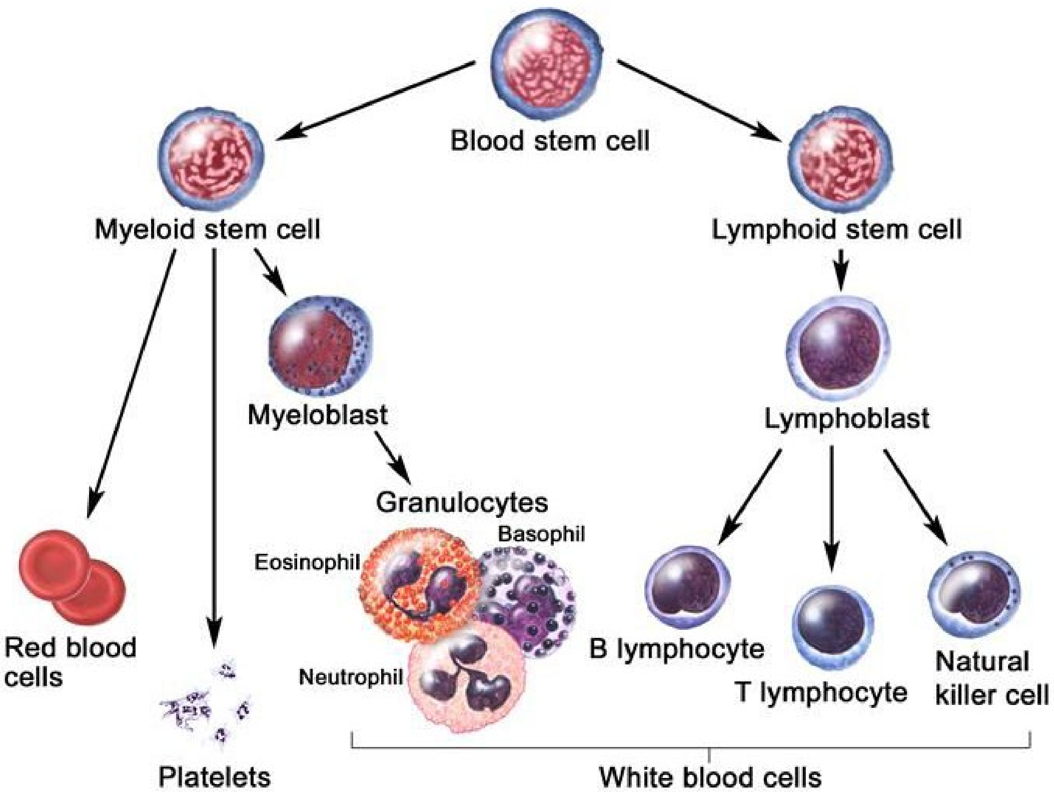


Fig. 11: Differentiation of blood stem cells into all types of blood cells

2] NORMAL FUNCTIONS OF STEM CELLS

2.2 ADULT STEM CELLS: BLOOD STEM CELLS (HAEMATOPOIETIC STEM CELLS)

The detailed roles and functions of the specific white blood cells will be covered under immunology.

Type of cell			Main Function	Typical Conc. in human blood (cells/liter) *
Erythrocytes			Transport O_2 and CO_2	5×10^{12}
Leucocytes	Granulocytes	Neutrophils	Phagocytose & destroy invading bacteria	5×10^{9}
		Eosinophils	Destroy larger parasites & modulate allergic inflammatory responses	2×10^{8}
		Basophils	Release histamine in certain immune reactions	4×10^{7}
	Lymphocytes	B cells	Make antibodies	2×10^{9}
		T cells	Kill virus-infected cells & regulate activities of other leucocytes	1×10^{9}
	Monocytes		Become tissue macrophages which phagocytose & digest invading microorganisms & foreign bodies as well as damaged senescent cells	4×10^{8}
	Natural killer (NK) cells		Kill virus-infected cells and some tumor cells	1×10^{8}
Platelets (cell fragments arising from megakaryocytes in bone marrow)			Initiate blood clotting	3×10^{11}

*For Reference only: relative abundance of each type of blood cells.

3] ETHICAL IMPLICATIONS OF STEM CELL APPLICATIONS

3.1 APPLICATIONS OF STEM CELLS

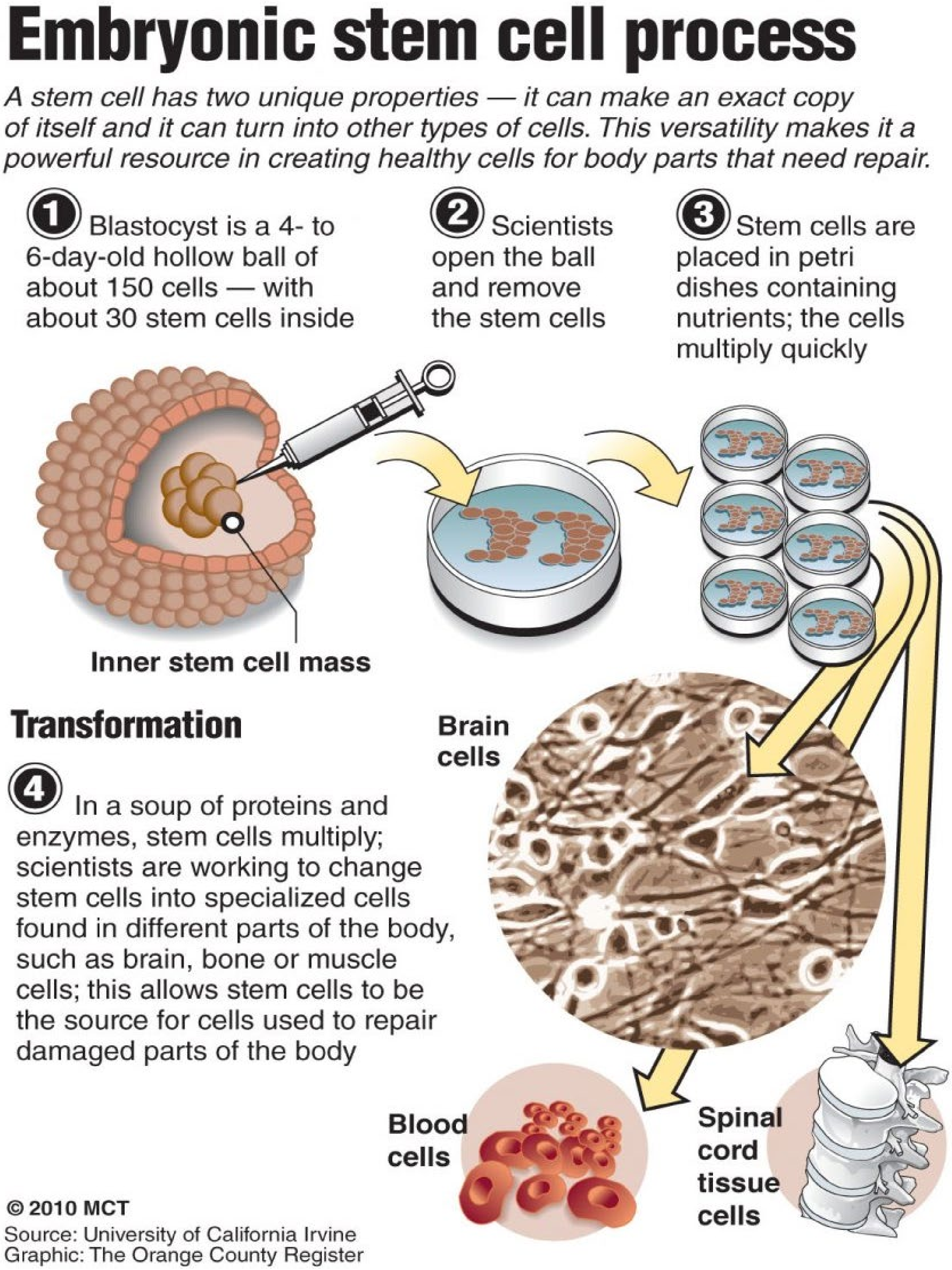
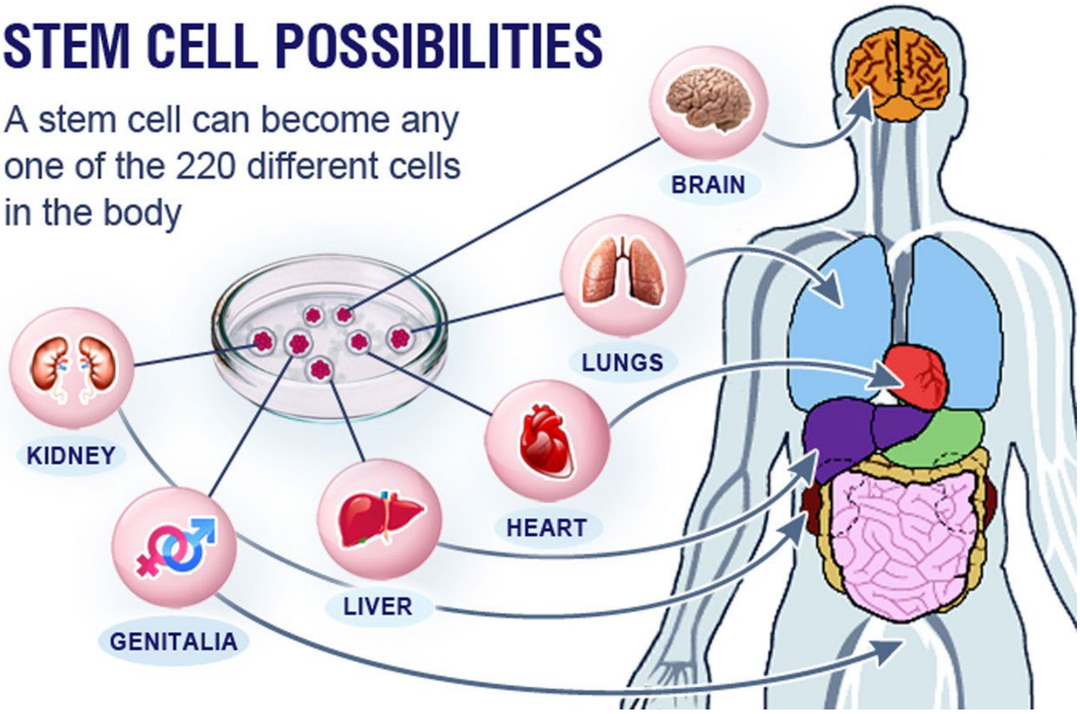


Fig. 12: Embryonic stem cell process

3] ETHICAL IMPLICATIONS OF STEM CELL APPLICATIONS

3.1 APPLICATIONS OF STEM CELLS



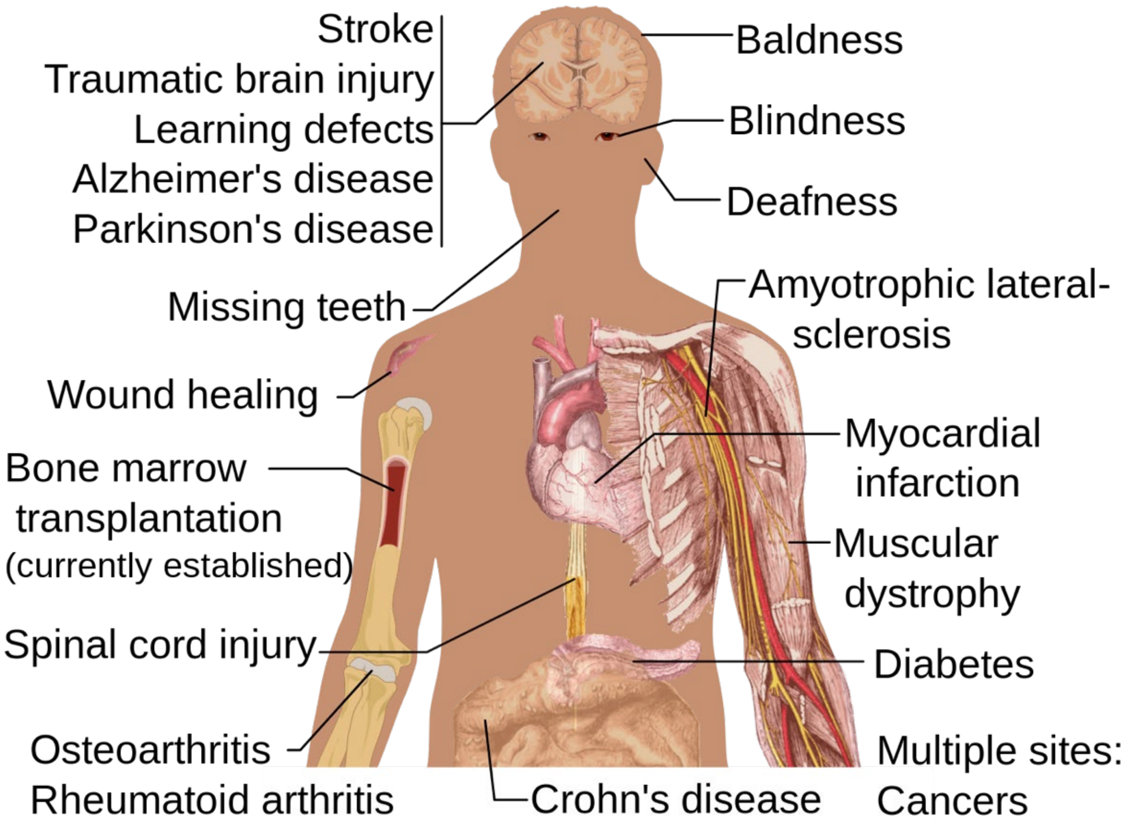


Fig. 13: Stem cells in medical research and applications

3] ETHICAL IMPLICATIONS OF STEM CELL APPLICATIONS

3.2 ETHICAL IMPLICATIONS

1. By comparison, it would be difficult, based on our modern knowledge, to treat these diseases with **adult stem cells** because of the **difficulty to locate and isolate** most types of adult stem cells **within the body** and **successfully grow them in the laboratory**.

   - Even **haematopoietic stem cells** are **elusive**. In the bone marrow, about 1 cell in 10,000 is a stem cell, yet that is enough to populate all of the blood and lymphoid cells of the body.

   - The **stem cells of most other adult tissues** are equally or more **difficult to locate**.

   - In addition, with the exception of stem cells in the blood, other types of stem cells in the adult body are **difficult to remove in sufficient numbers** for **transplantation**.

2. Contrarily, **embryonic stem cells** and **embryonic germ cells** are **easy to identify** and have the great advantage of **rapid growth** in the laboratory. For these reasons, **embryonic stem cells** and **embryonic germ cells** offer **a greater potential for transplantation**, based on our current knowledge of stem cell biology.

3. The blastocysts used in stem cell research is microscopically small and has no nervous system. Does it count as a "person" who has a right to life?

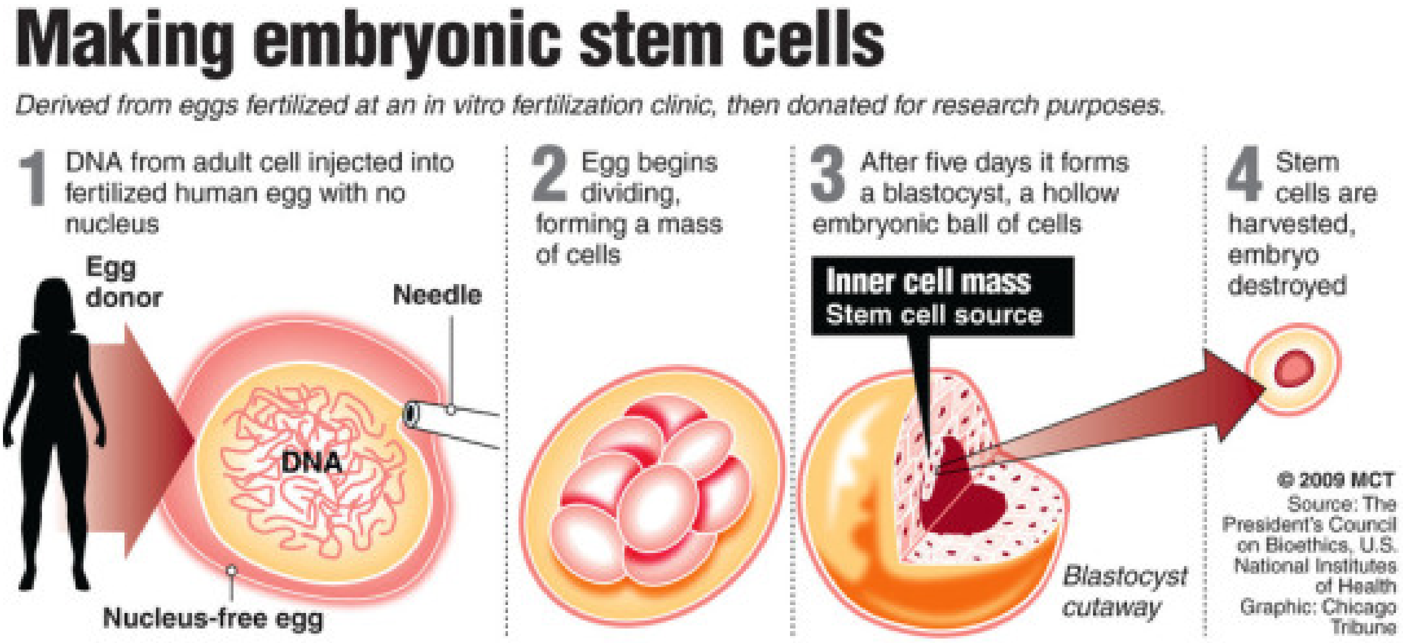


Fig. 14: Aspiration of Embryonic Stem Cells

3] ETHICAL IMPLICATIONS OF STEM CELL APPLICATIONS

3.2 ETHICAL IMPLICATIONS

The **primary issue** that raises debate is the **source of the stem cells** for research and potential treatments.

- Most **embryonic stem cells** have been derived from **human embryos** that were produced from ***in vitro* fertilisation** and were subsequently not used.

- Most **embryonic germ cells** are obtained from **aborted fetuses**.

Views SUPPORTING stem cell research

1. Although embryos deserve respect, they are not morally equivalent to human beings yet.
2. The frozen or IVF derived embryos and aborted fetuses that provide the embryonic stem cells and embryonic germ cells are **NOT going to become living individuals**, and therefore, it is **beneficial** to **study these cells** and **use them in a positive way to treat human diseases and injury**.
3. Great potential in finding cures for diseases e.g. cancer, diabetes, sickle cell anemia

As a compromise, some governments have enacted laws that limit or prohibit the use of embryos or foetuses to obtain stem cells, yet permit the use of stem cell lines that are already available in research laboratories provided there is adherence to strict guidelines on research ethics.

Ethical Principles for Embryonic Stem Cell Research

1. Principle of RESPECT and JUSTICE

- [AGAINST] Harvesting human embryonic stem cells destroys a 4-7 day old embryo (blastocyst) that has the potential to become a human baby if implanted into a uterus.
- As soon as an egg is fertilised, the resulting embryo deserves full respect that is accorded to a child or adult. An embryo is a human life which should not be damaged without justified reason(s).
- Research is allowed and supported only if the potential benefits in treating human diseases is extensive.

2. Principle of INFORMED CONSENT

- [AGAINST] Embryos are destroyed in the process of harvesting stem cells.
- Donors of embryo must grant permission in full knowledge of the possible consequences to the embryo.

3. Principle of MAXIMUM BENEFITS, MINIMUM RISK

- [AGAINST] Experiments do not guarantee any benefits to human life.
- Safety procedures are assured for those donating embryonic stem cells and manipulation of optimised conditions are needed for storage and to enhance viability of stem cells during experimentation.

4. Principle of NON-COMMERCIALISATION

- [AGAINST] Commercialisation of gametes, embryos and fetal tissues for profit.
- [AGAINST] **Fear** that this technology could lead to **intentional abortions** for the sole purpose of obtaining fetal tissues for transplantation.
- Tissues and cells should only be donated. Commercialisation of gametes, embryos and fetal tissues should be prohibited by law to prevent anyone from profiting from tissue donations.

3] ETHICAL IMPLICATIONS OF STEM CELL APPLICATIONS

3.2 ETHICAL IMPLICATIONS

To overcome the bioethical controversy, scientist have since explored other sources of stem cells including blood from umbilical cord and methods to induce differentiated cells to reverse its programing to become somatic stem cells.

	EMBRYONIC stem cells	**CORD BLOOD stem cells**	**ADULT stem cells or SOMATIC stem cells**
Availability	Easy to isolate large numbers from IVF embryos or aborted foetuses	Easily obtained but limited quantities of stem cells from one baby's cord Commercial collection and storage services already available	Difficult to obtain as there are very few of them and they are buried deep in tissues
Development potential	Can differentiate into any cell type in the body	Limited capacility to differentiate into different cell types – only naturally develop into blood cells but research may lead to production of other types	Limited capacity to differentiate into different cell types
Compatibility between donor and recipient	Likely to be genetically different from an adult patient receiving the tissue. Tissue rejection can occur without immunosuppression.	Fully compatible with the tissues of the adult that grows from the baby, so rejection do not occur.	Fully compatible with the adult tissues, so rejection do not occur.
Ethical implications	High ethical controversy and uncertain legal status. Removal of cells from the embryo kills it, unless only one or two cells are taken.	The umbilical cord is discarded whether or not stem cells are taken from it	Less moral and legal controversy. Removal of stem cells does not kill the adult from which the cells are taken
Risks	More risk of becoming tumour cells than with adult stem cells including teratomas that contain different tissue types		Less chance of malignant tumour developing than from embryonic stem cells

3] ETHICAL IMPLICATIONS OF STEM CELL APPLICATIONS

3.3 HUMAN INDUCED PLURIPOTENT STEM CELLS (hiPSCs)

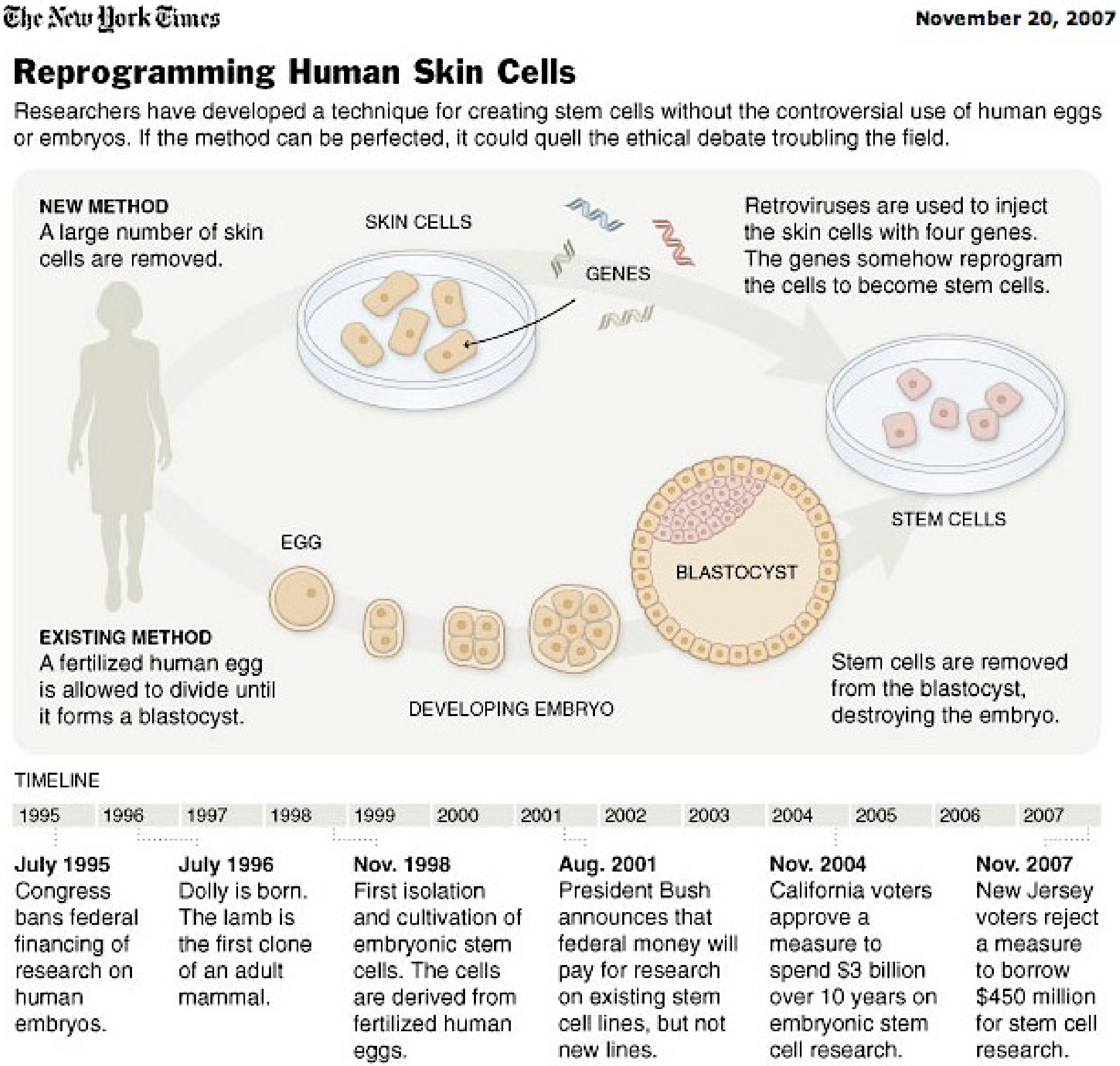


Fig. 15: Comparison of **iPSC** and **ESC methods** for obtaining stem cells

3] ETHICAL IMPLICATIONS OF STEM CELL APPLICATIONS

3.3 HUMAN INDUCED PLURIPOTENT STEM CELLS (hiPSCs)

1. If **stem cells** could be **obtained** from **adult cells** and propagated in the laboratory, an **ethical dilemma** may be **avoided** because most people do not have serious moral objections to current procedures such as bone marrow transplantation.

2. In 2006, work by Shinya Yamanaka and colleagues showed that **mouse fibroblasts** (a type of connective tissue cell) could become **pluripotent** (from a differentiated state) via the **introduction of four different genes** (into the mouse fibroblasts) that encode **transcription factors**.

3. In 2007, Yamanaka's laboratory and two other research groups showed that such **induced pluripotent stem cells** (iPSCs) can **differentiate** into **all cell types** when injected into mouse blastocysts and grown into adult mice. Though further research is still needed, these recent results indicate that **differentiated cells** can be **reprogrammed** to become **pluripotent stem cells** (not to be termed embryonic stem cells).

4. Induced pluripotent stem cells (iPSCs) **resemble** embryonic stem cells in their **capacity to differentiate into all cell types**.

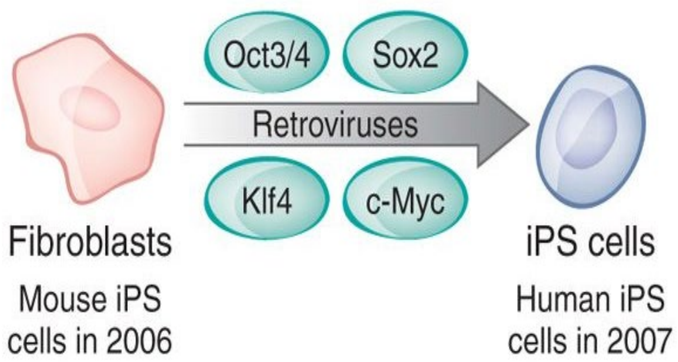


Fig. 16: Yamanaka's reprogramming factors to make induced pluripotent stem cells
(involving introduction of 4 different genes that encode these 4 transcription factors)

3] ETHICAL IMPLICATIONS OF STEM CELL APPLICATIONS

3.3 HUMAN INDUCED PLURIPOTENT STEM CELLS (hiPSCs)

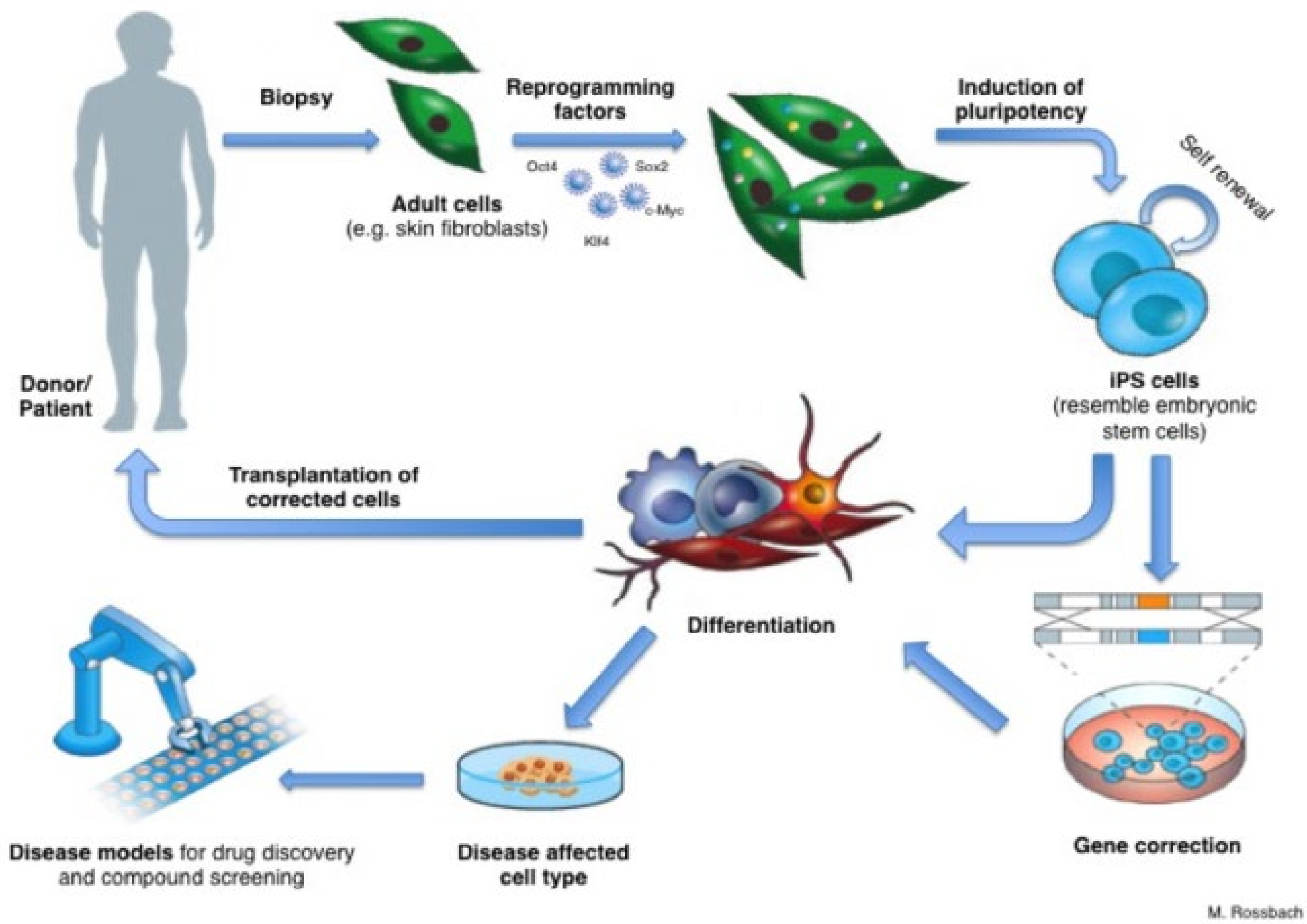


Fig. 17: New method to overcome the controversy of embryonic stem cell with human induced pluripotent stem cell application

5. In the field of **regenerative medicine**, a **patient's own cells** could be **reprogrammed** into iPSCs and then used to **replace non-functional tissues**. Developing techniques that direct iPSCs to become specific cell types for this purpose is an area of intense research, one that has already seen some success.

6. The utilisation of induced pluripotent stem cells would be **patient-specific** and hence the issue of **tissue rejection** can also be **circumvented** by the usage of iPSCs for treatment.

7. In conclusion, while **embryonic stem cells** can generate **every cell in an organism**, the **use of human embryos as their source** is **controversial**. With the intense research on **iPSCs**, these cells could eventually provide **patient-specific replacement of cells** for diseased individuals **without using any human eggs or embryos,** thus **circumventing most ethical objections**.

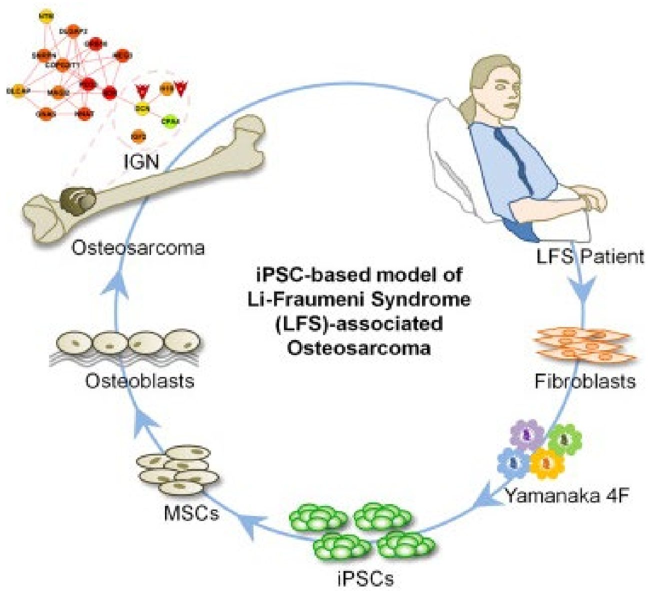


Fig. 18: Application of stem cell therapy in osteosarcoma patient

4] APPENDIX

4.1 METHODS OF MAKING iPSCs

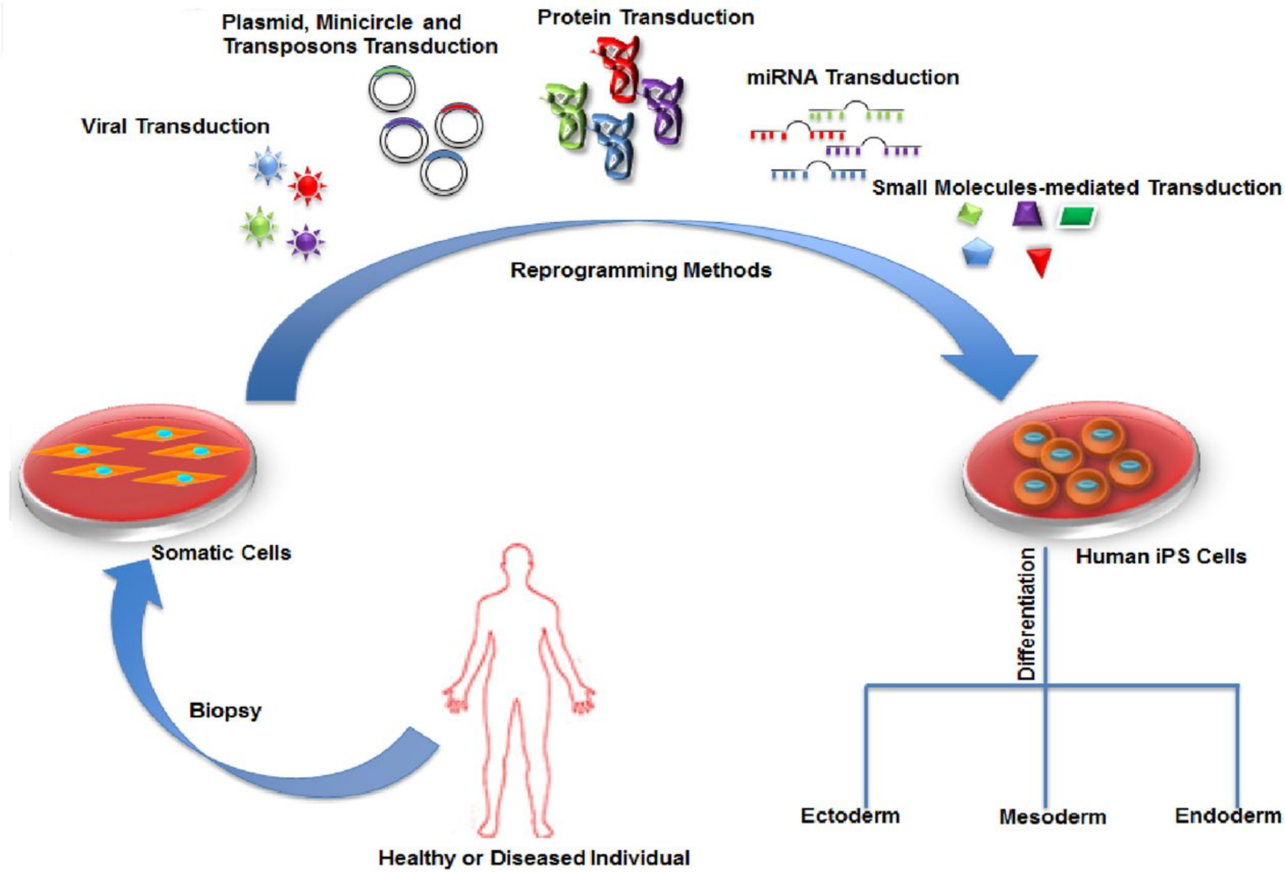


Fig. 19: Methods of making human induced pluripotent stem cells

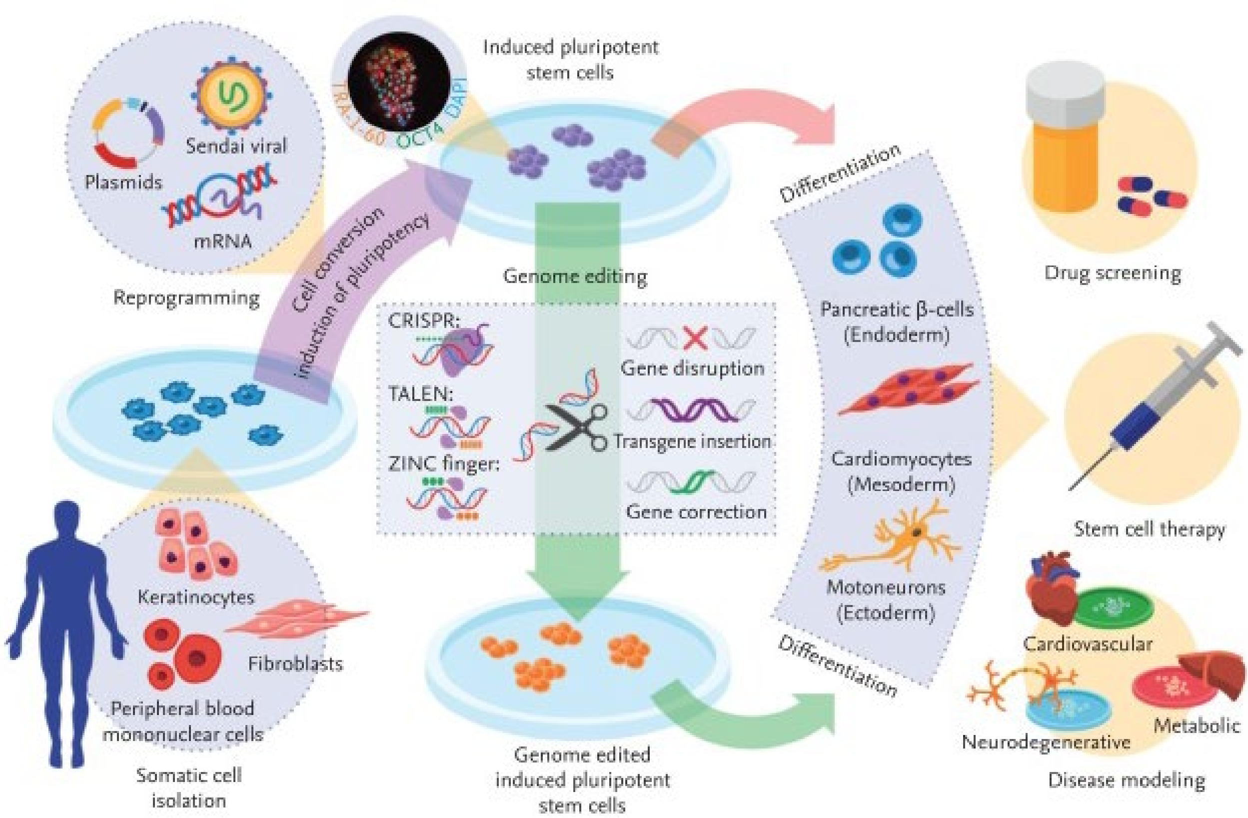


Fig. 20: Methods of making human induced pluripotent stem cells

4] APPENDIX

4.1 SIGNALS FOR DIFFERENTIATION

IN BLOOD STEM CELLS

The increased **production of each type of blood cell from multipotent haematopoietic stem cells** in the **bone marrow** is **individually controlled**:

(a) **Erythrocyte** production

- If **tissues do not receive enough oxygen** (acclimatization to living at high altitude where oxygen is scarce), it will stimulate the kidney to convert a plasma protein to a hormone called **erythropoietin**.
- Erythropoietin in turn **stimulates** the **production of erythrocytes** from a single population of **multipotent haematopoietic stem cells in the red marrow of bones** particularly the ribs, vertebrae, breastbone and pelvis
- If blood is delivering more oxygen than the tissue can use, the level of erythropoietin is reduced and erythrocyte production slows down.

(b) **Leucocyte** production

- When there is a **local infection** or **injury**, an **inflammatory response** rapidly attracts leucocytes into the affected region to fight the infection or heal the wound.
- This inflammatory response is mediated by a variety of **signal molecules** produced by **mast cells**, **nerve endings**, **platelets**, **leucocytes** and the **activation** of **complement system** (20 interacting soluble proteins made mainly by the liver that 'complement' the action of antibodies).
- Some of these signal molecules act on nearby capillaries, causing the **endothelial cells** to adhere less tightly to one another but making their **surfaces adhesive** to passing **leucocytes**.
- These leucocytes are caught by the endothelial cells with the help of receptors called **selectins**.
- The leucocytes can then crawl out of the vessel, mediated by **integrins** by squeezing between the **capillary endothelial cells** and the **basement membrane** with the aid of **digestive enzymes**.
- **Chemokines** which are secreted by damaged or inflamed tissue and local endothelial cells attract these leucocytes into the affected region.
- Other **signal molecules produced in the course of an inflammatory response** escape into the blood and **stimulate** the **bone marrow to produce cell-type specific leucocytes** from **multipotent haematopoietic stem cells** and release them into the bloodstream.

4] APPENDIX

4.1 APPENDIX: TRANSDIFFERENTIATION

IN BLOOD STEM CELLS

Blood stem cells are also capable of **transdifferentiation**, the ability to form specialized **cell types of other tissues.** For example, they may differentiate into: 3 major types of **brain cells** (neurons, oligodendrocytes, and astrocytes); **skeletal muscle cells**; **cardiac muscle cells**; and **liver cells**.

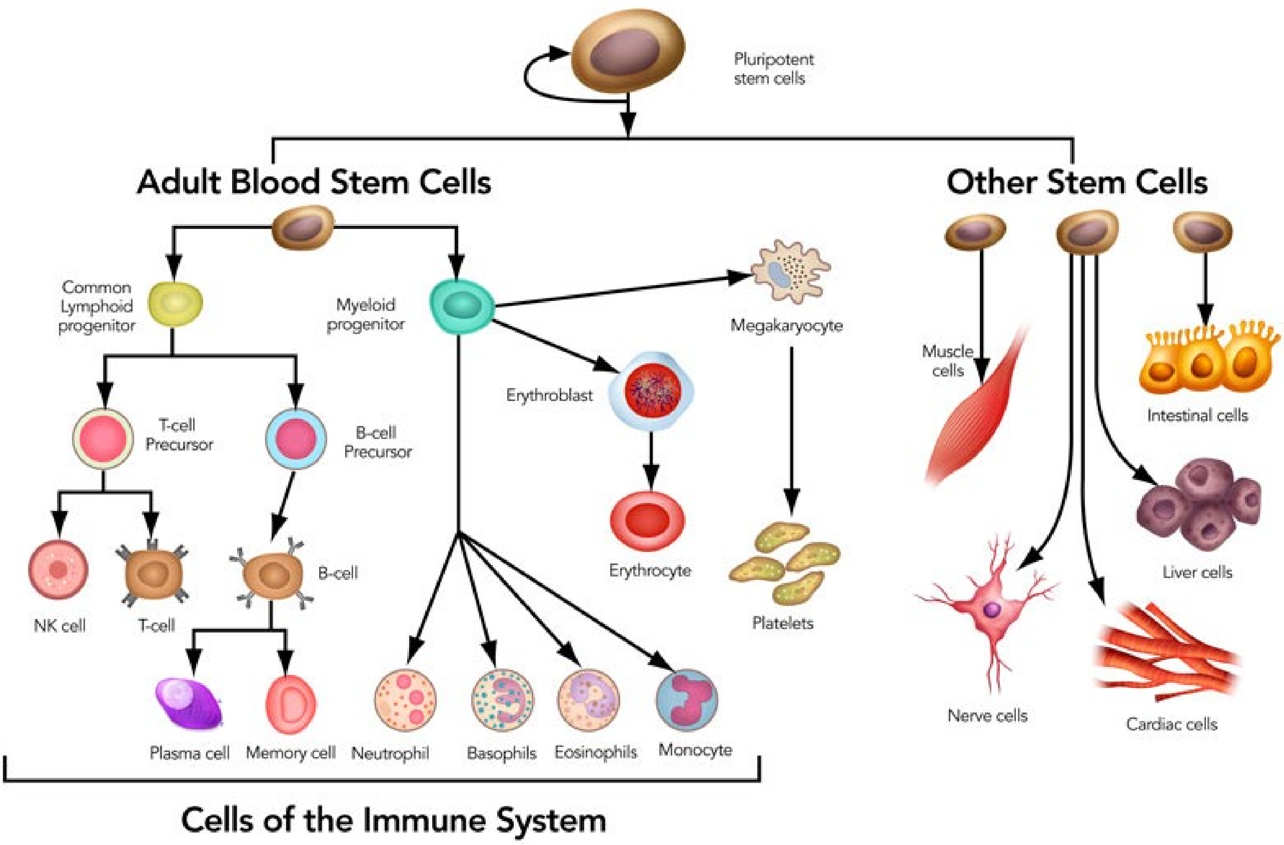


Fig. : Transdifferentiation of blood stem cells