BHARATHIDASAN UNIVERSITY

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Course Title : Stem Cell Biology & Tissue Engineering

Course Code : 18BMS48C14

Unit-III

TOPIC: Stem Cell Therapy

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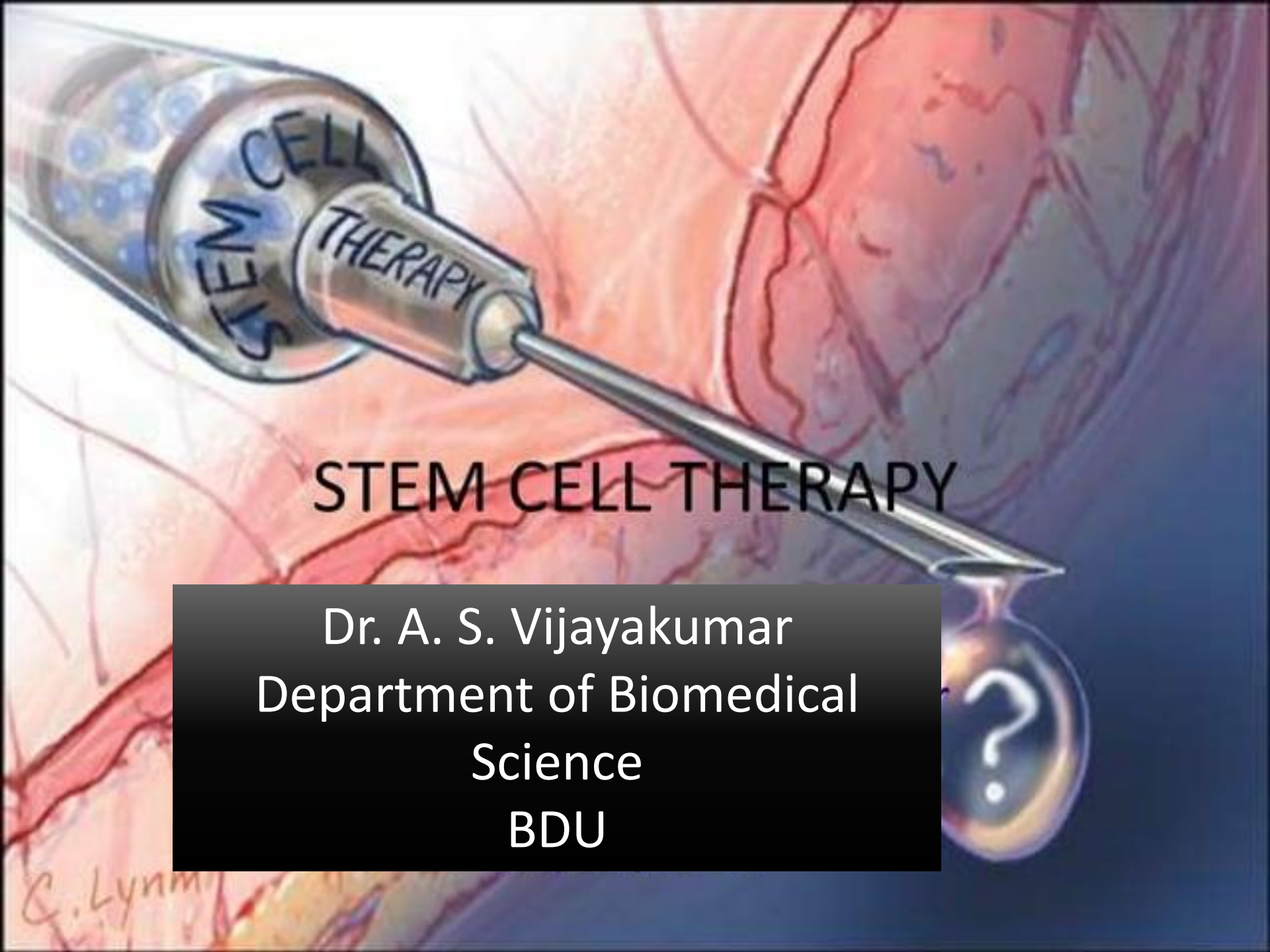

STEM CELL THERAPY

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Outline

- History of Stem cell research
- What are stem cells
- Types & sources of stem cells
- Cultivation process
- Stem cells & cloning
- Potential uses
- Stem cell therapy
- Ethical issues
- Indian status
- Conclusions

Introduction

- **Today living in the 21st century, we still do not have proper treatments for many diseases like diabetes, Parkinson's Disease, Alzheimer's Disease etc.**

- **Some light of hope for the treatment of these incurable diseases is - the Stem Cells**

Introduction

- Research on stem cells is advancing
- How an organism develops from a single cell and how healthy cells replace damaged cells in adult organisms.

- This promising area of science - investigates the possibility of cell-based therapies to treat disease, which is often referred to as regenerative or reparative medicine

History of Human Stem Cell Research

- In 1968, the first bone marrow transplant was successfully used in treatment of Severe Combined Immunodeficiency
- Since the 1970s, bone marrow transplants have been used for treatment of immunodeficiencies and leukemias

History of Human Embryonic Stem Cell Research

- In 1998, James Thomson (University of Wisconsin-Madison) isolated cells from the inner cell mass of the early embryo, and developed the first human embryonic stem cell lines.

- In 1998, John Gearhart (Johns Hopkins University) derived human embryonic germ cells from cells in fetal gonadal tissue (primordial germ cells).
- Pluripotent stem cell "lines" were developed from both sources

History of Stem Cell

- 1999 - First Successful human transplant of insulin-making cells from cadavers
- 2001 – First cloned human embryos (only to six cell stage) created by Advanced Cell Technology (USA)
- 2004 - Harvard researchers grow stem cells from embryos

History of Somatic Cell Nuclear Transfer (Cloning)

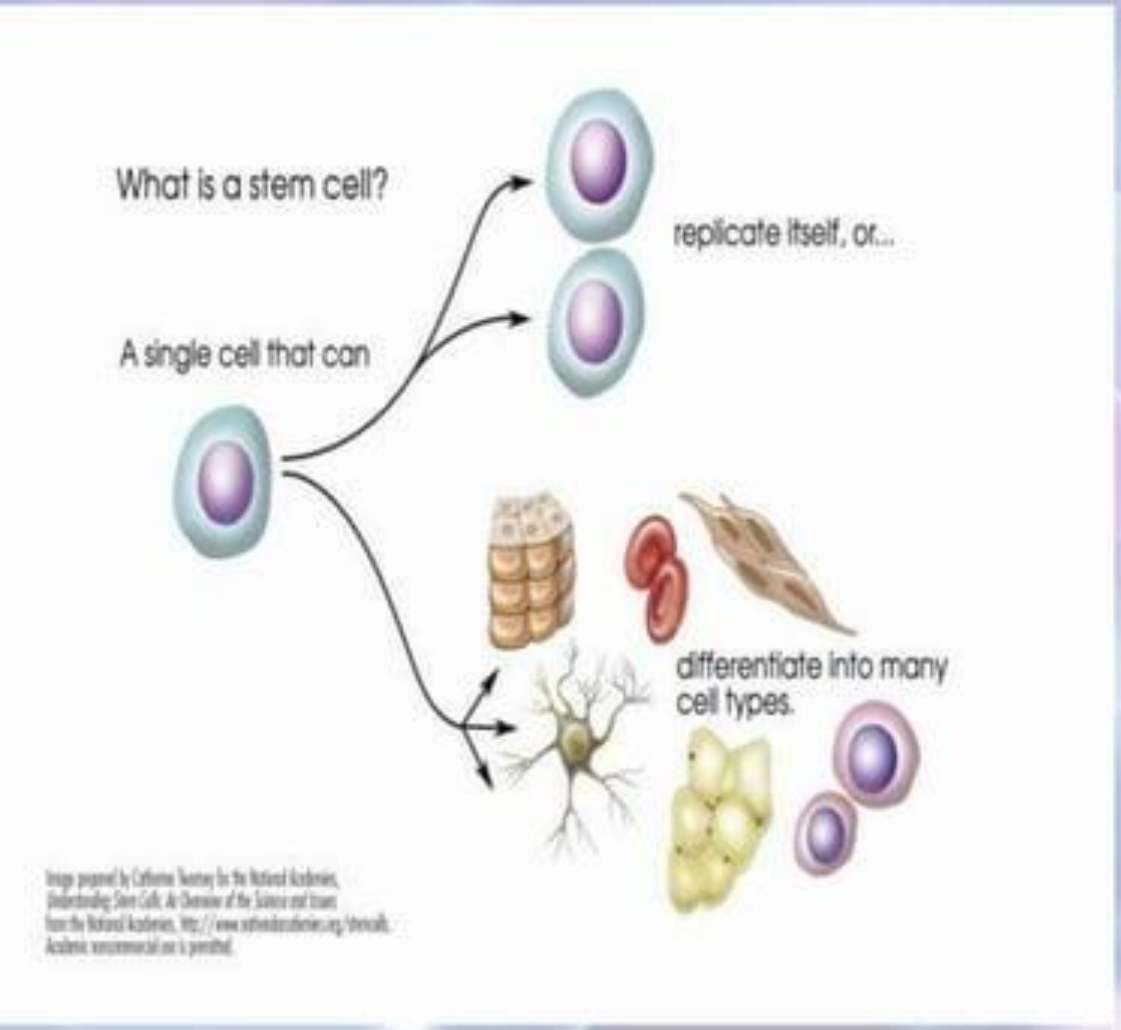
- 1952 – Briggs and King cloned tadpoles
- 1996 – The first mammal cloned from adult cells was Dolly, the sheep.

- 1998 – Mice cloned
- 1998 – Cows cloned
- 2000 – Pigs cloned

History of Cloning

- 2001 – Cat cloned
- 2002 – Rabbits cloned
- 2003 – Mule cloned
- 2004 – Bull cloned
- 2005 – Dog cloned

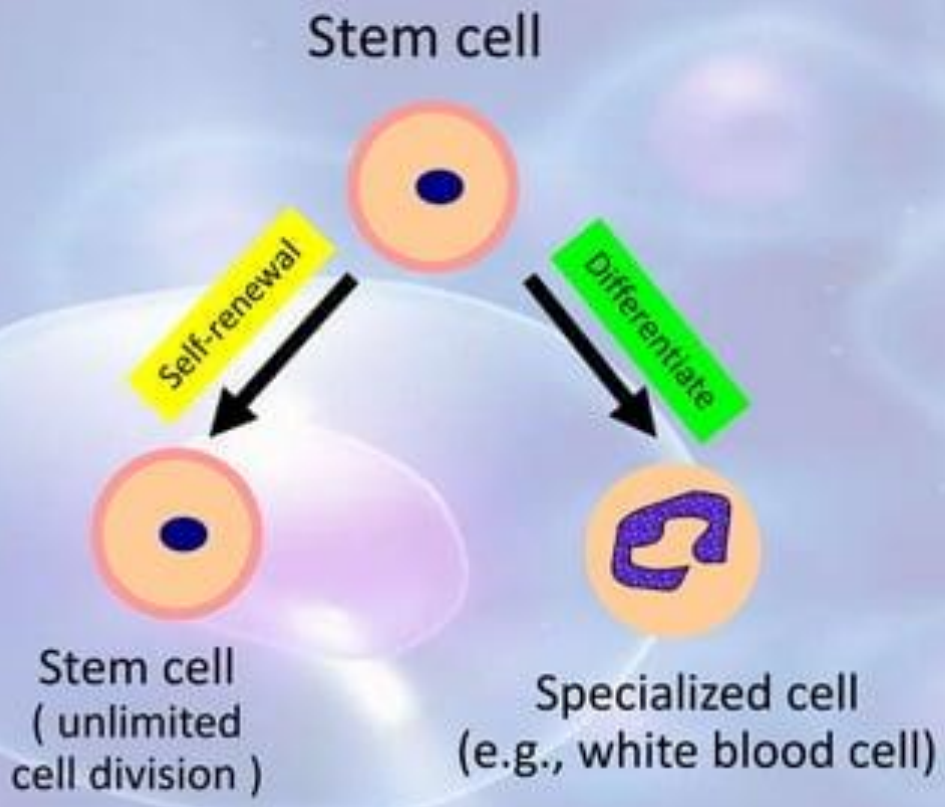
Stem Cell – Definition



- A cell that has the ability to continuously divide and differentiate (develop) into various other kind(s) of cells/tissues

Properties of Stem Cell

- All stem cells—regardless of their source have three general properties
  - They are capable of dividing and renewing themselves for long periods
  - They are unspecialized
  - They can give rise to specialized cell types


Stem cell
Self-renewal
Differentiate
Stem cell
(unlimited
cell division)
Specialized cell
(e.g., white blood cell)

Self - Renewal (Regeneration)

- Stem cells are capable of dividing & renewing themselves for long periods
  - This is unlike muscle, blood or nerve cells – which do not normally replicate themselves
  - These cells are capable of long-term self-renewal

Unspecialization

- Stem Cells are unspecialized
  - They do not have any tissue-specific structures that allow for specialized function

Specialization of Stem Cells: Differentiation

- Differentiation: unspecialized stem cells give rise to specialized (differentiated) cells in response to external and internal chemical signals
  - Internal signals: specific genes causing differential gene expression
  - External signals :
    - Chemicals secreted by other cells such as growth factors, cytokines, etc.
    - Physical contact with neighboring cells

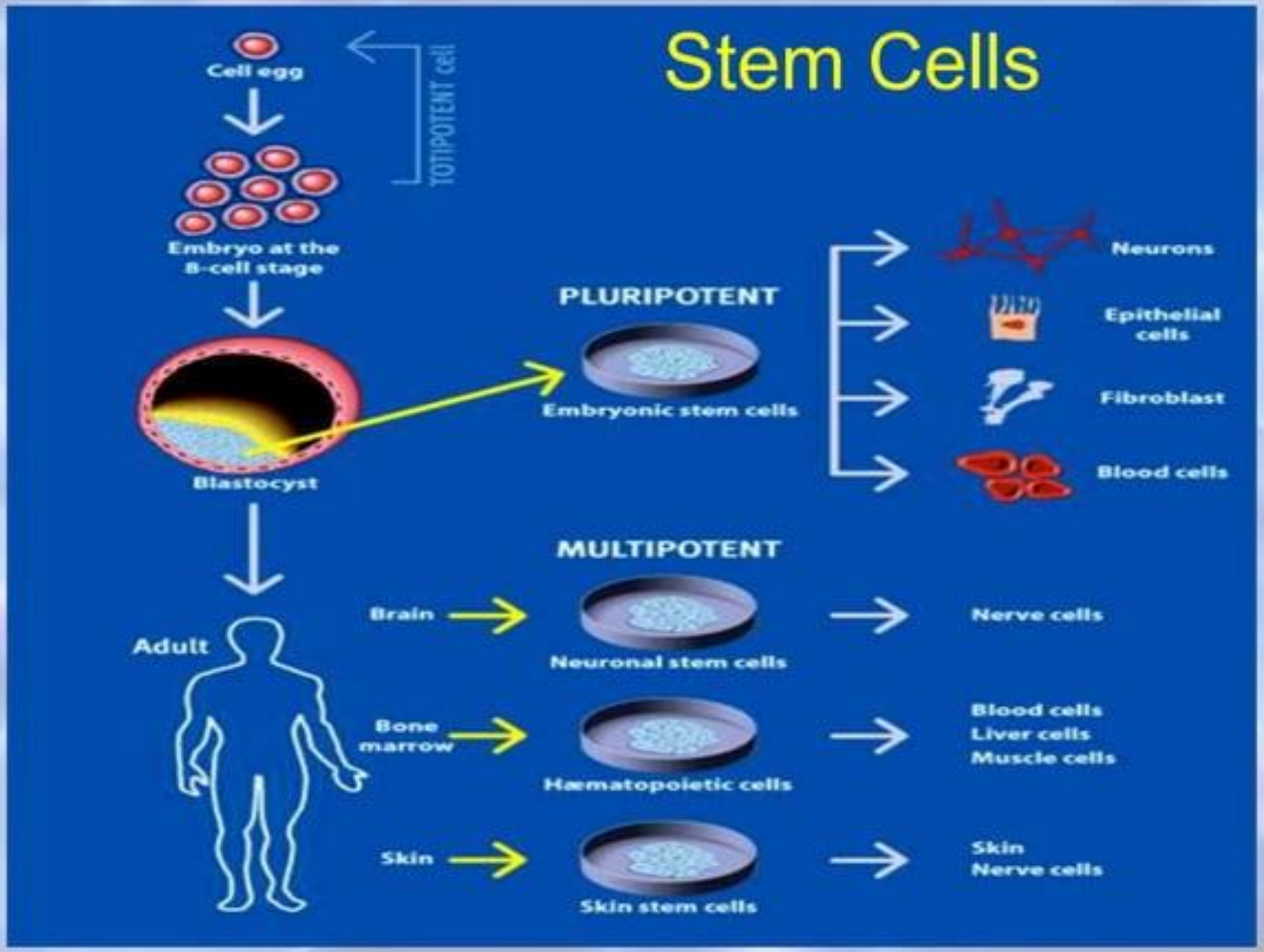
Stem cell Types

- **Totipotent**
  - **the ability to differintiate into all types;** *can form any cell of the embryo as well as the placenta*
  - **Ex:** morula

- **Pluripotent**
  - **the ability to differentiate into almost all types** *except placental tissue*
  - **Ex:** cells from inner cell mass of blastocyst

Stem cell Types

- **Multipotent**
  - can **differentiate into multiple specialized cells** of a closely related family of cells
  - **Ex:** hematopoietic stem cells
- **Oligopotent**
  - **the ability to differentiate into a few cells**
  - **Ex:** lymphoid
- **Unipotent**
  - these cells **only produce one cell type**., but have the property of self renewal which distinguishes them from the non stem cells
  - **Ex:** muscle stem cells, cardiac stem cells


Stem Cells
Cell egg
TOTIPOTENT cell
Embryo at the 8-cell stage
Blastocyst
PLURIPOTENT
Embryonic stem cells
Neurons
Epithelial cells
Fibroblast
Blood cells
MULTIPOTENT
Adult
Brain
Neuronal stem cells
Nerve cells
Bone marrow
Haematopoietic cells
Blood cells
Liver cells
Muscle cells
Skin
Skin stem cells
Skin
Nerve cells

Adult stem cells

Function

To replace physiologically lost cells

e.g. Blood (Hematopoietic stem cells).

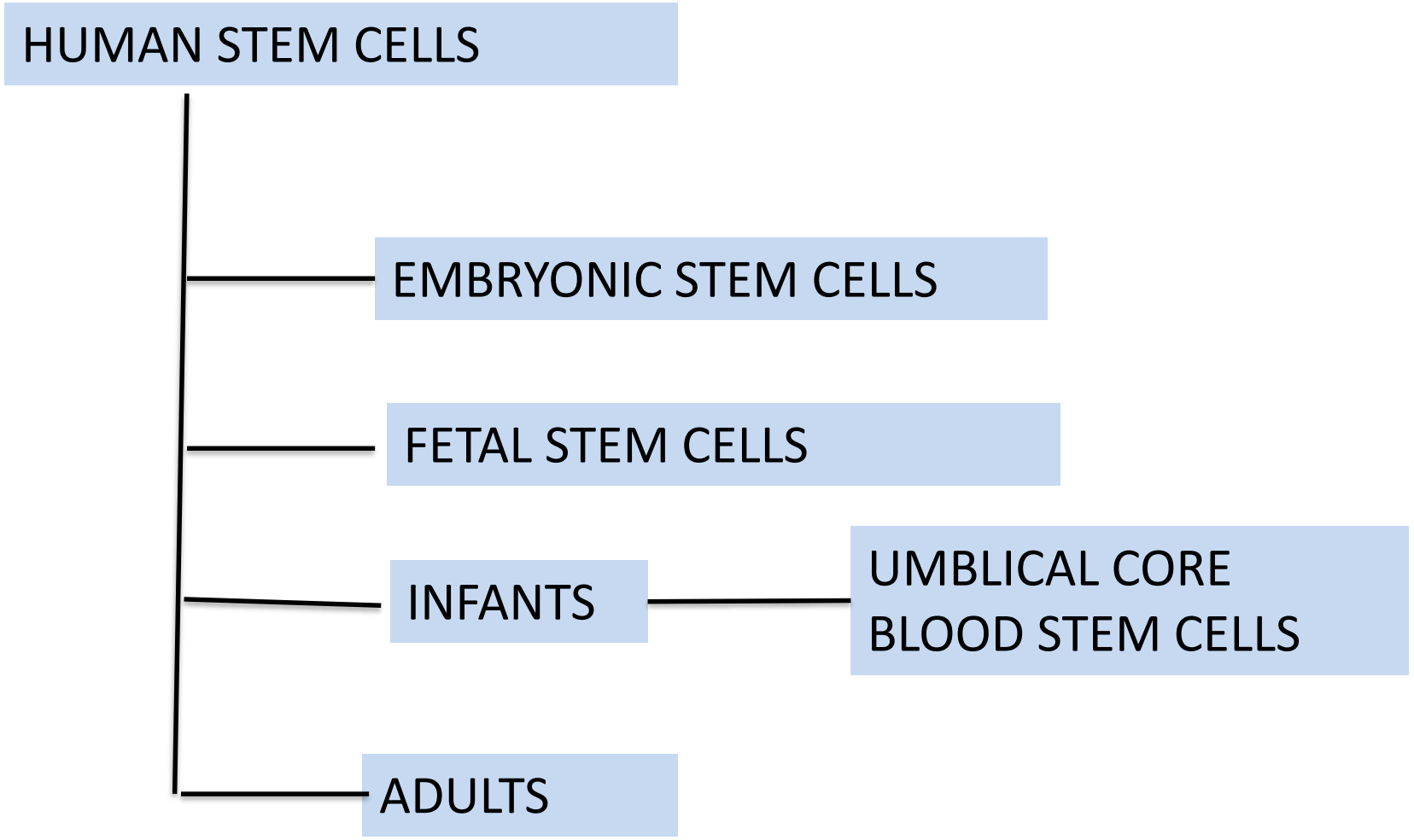
GIT epithelial cells

Skin & Hair (epidermis, hair follicles, and sebaceous glands are replaced by stem cells).

To divide in response to tissue injury or infection

e.g. Skeletal Muscle regeneration as a response to exercise or injury

CLASSIFICATION OF HUMAN STEM CELLS

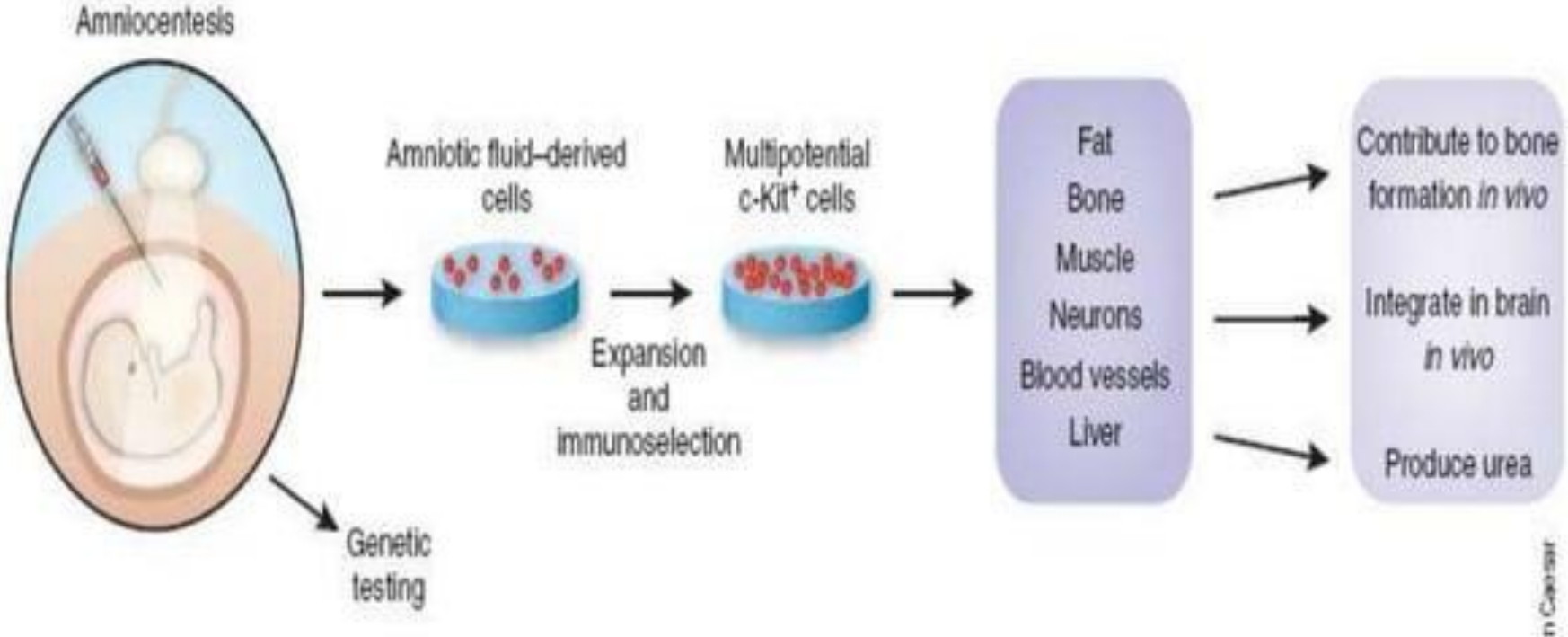


Umbilical cord Stem Cells

- At the time of delivery, cord blood is collected, stored, and frozen.
- UCB contains two classes of stem cells.
  - Haematopoietic stem cells (HSC).
  - Mesenchymal stem cells (MSC).
- Can be used to cure chronic blood-related disorders such as sickle cell disease, Thalasemia, and leukaemia.

Amniotic Stem Cells

- Multipotent stem cells are found in amniotic fluid
- Amniotic stem cells can differentiate in cells of adipogenic, osteogenic, myogenic, endothelial, hepatic and also neuronal lines.



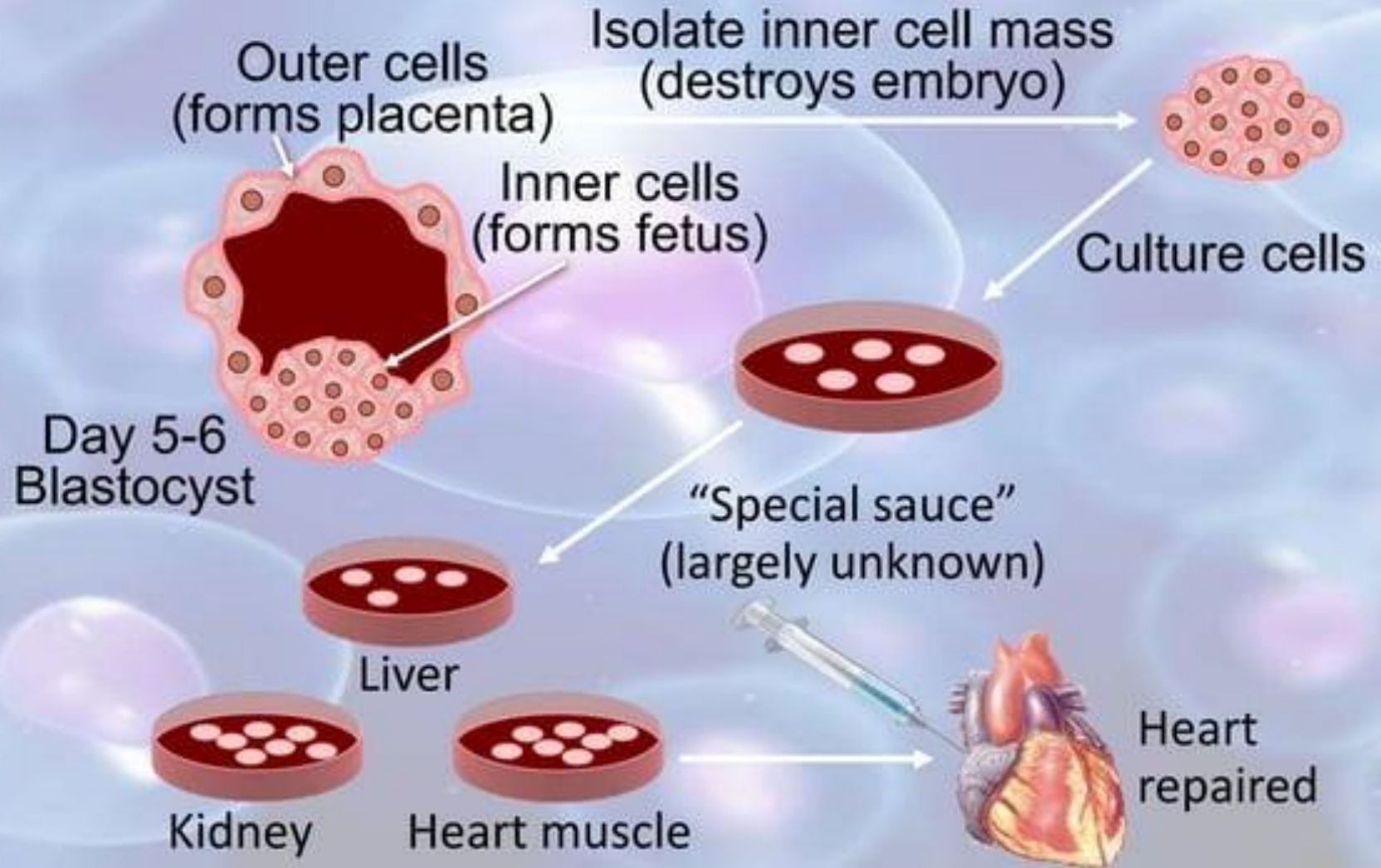
Fetal Stem cells

- derived from aborted fetal tissue
- Their ability to renew themselves is limited
- it is more difficult to produce normal tissues from these cells.

Embryonic Stem Cells

- Embryonic stem cells (ES cells) are derived from the cells in the inner cell mass of the developing blastocyst
- Human ES cells are derived from embryos that developed from unused eggs that were fertilized in vitro in an in vitro fertilization clinic
- They have been donated for research with informed consent of the donors.
- Human ES cells are not derived from eggs fertilized in a woman's body.

Derivation and Use of Embryonic Stem Cell Lines



Adult Stem cells

- Bone Marrow Stem Cells
- Peripheral Blood Stem Cells
- Neuronal Stem Cells (from olfactory bulb, spinal cord)
- Muscle Stem Cells
- Liver Stem Cells
- Pancreatic Stem Cells
- Renal stem cells
- Corneal Limbal Stem Cells
- Dental pulp

Embryonic vs Adult Stem Cells

- Totipotent
  - Differentiation into ANY cell type
- Large numbers can be harvested from embryos
- May cause immune rejection
- Potential for undesired tumor formation (teratoma)
- High ethical controversy & uncertain legal status

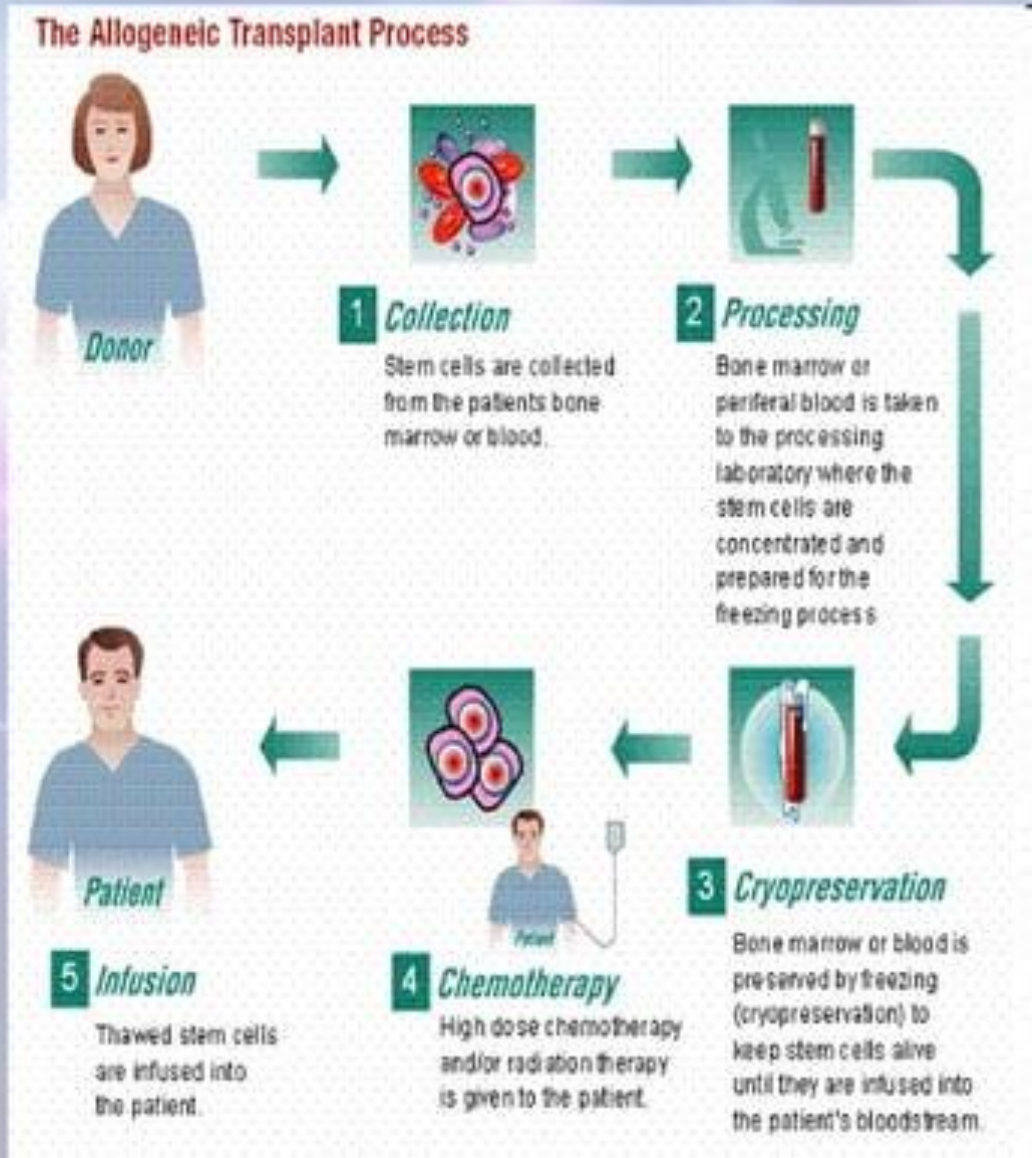
- Multi or pluripotent
  - Differentiation into some cell types, limited outcomes
- Limited numbers, more difficult to isolate
- Less likely to cause immune rejection, since the patient's own cells can be used
- Less likely to form tumors
- Less moral & legal contoversy

Autologous Stem Cells

- Sources of the patient's own stem cells (autologous) are either the cells from patient's own body or his or her cord blood.
- For autologous transplants physicians now usually collect stem cells from the peripheral blood rather than the marrow

Allogenic Stem Cells

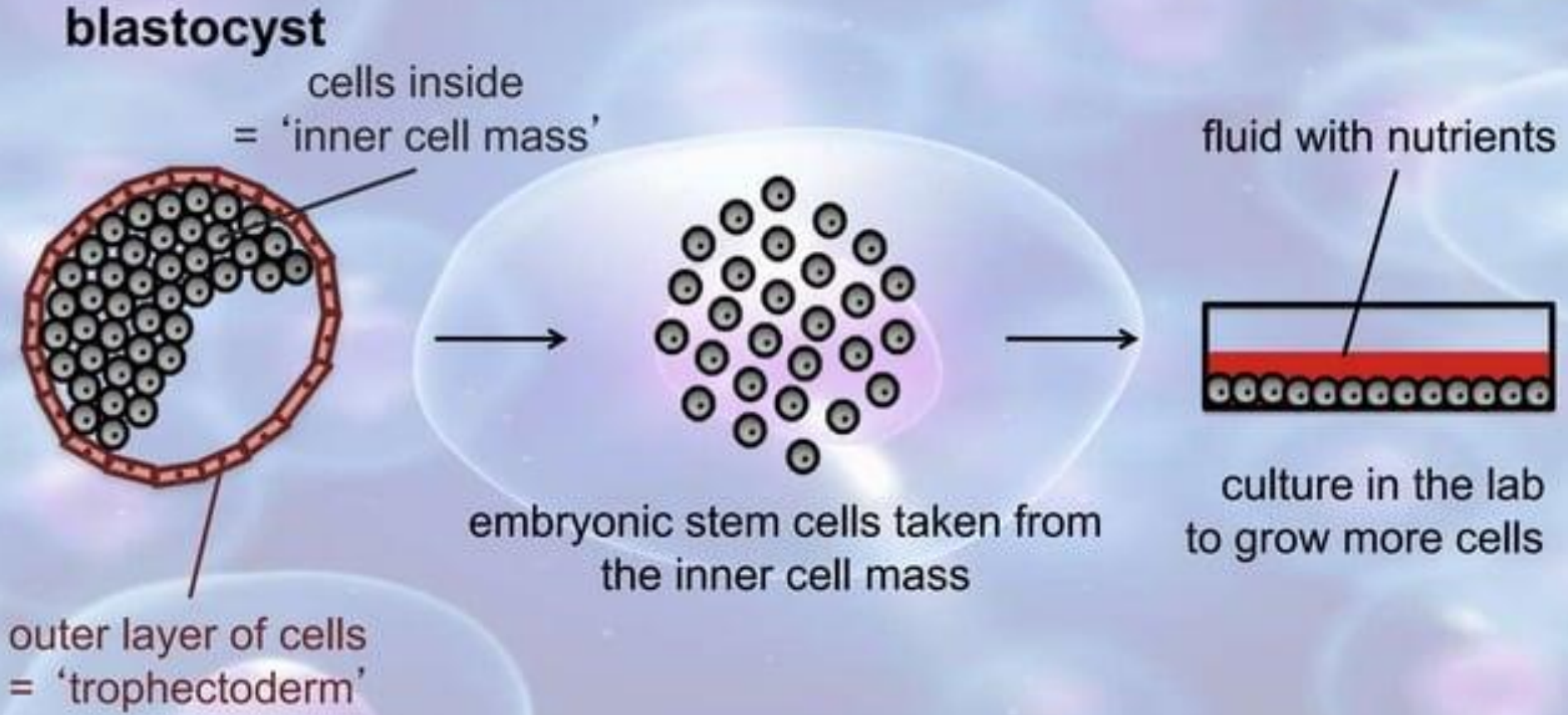
- Sources of stem cells from another donor (allogeneic)
- are primarily relatives (familial-allogeneic) or completely unrelated donors (unrelated-allogeneic)
- The stem cells in this situation are extracted from either the donor's body or cord blood



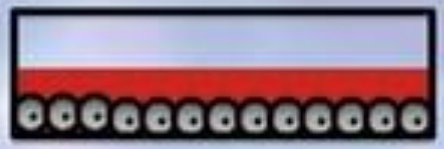
Cultivation of Stem Cell

- Embryonic stem (ES) cells
- Tissue (Adult) stem cells
- Induced pluripotent stem cells (iPS cells)
- Somatic cell nuclear transfer (therapeutic cloning)

Embryonic stem (ES) cells:

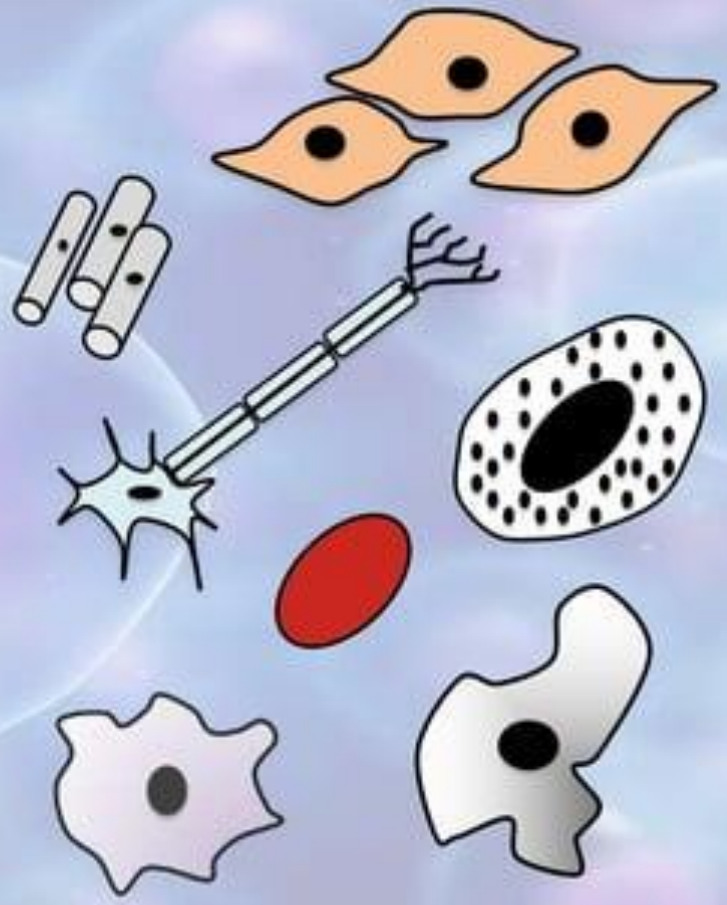


Embryonic stem (ES) cells:



embryonic stem cells

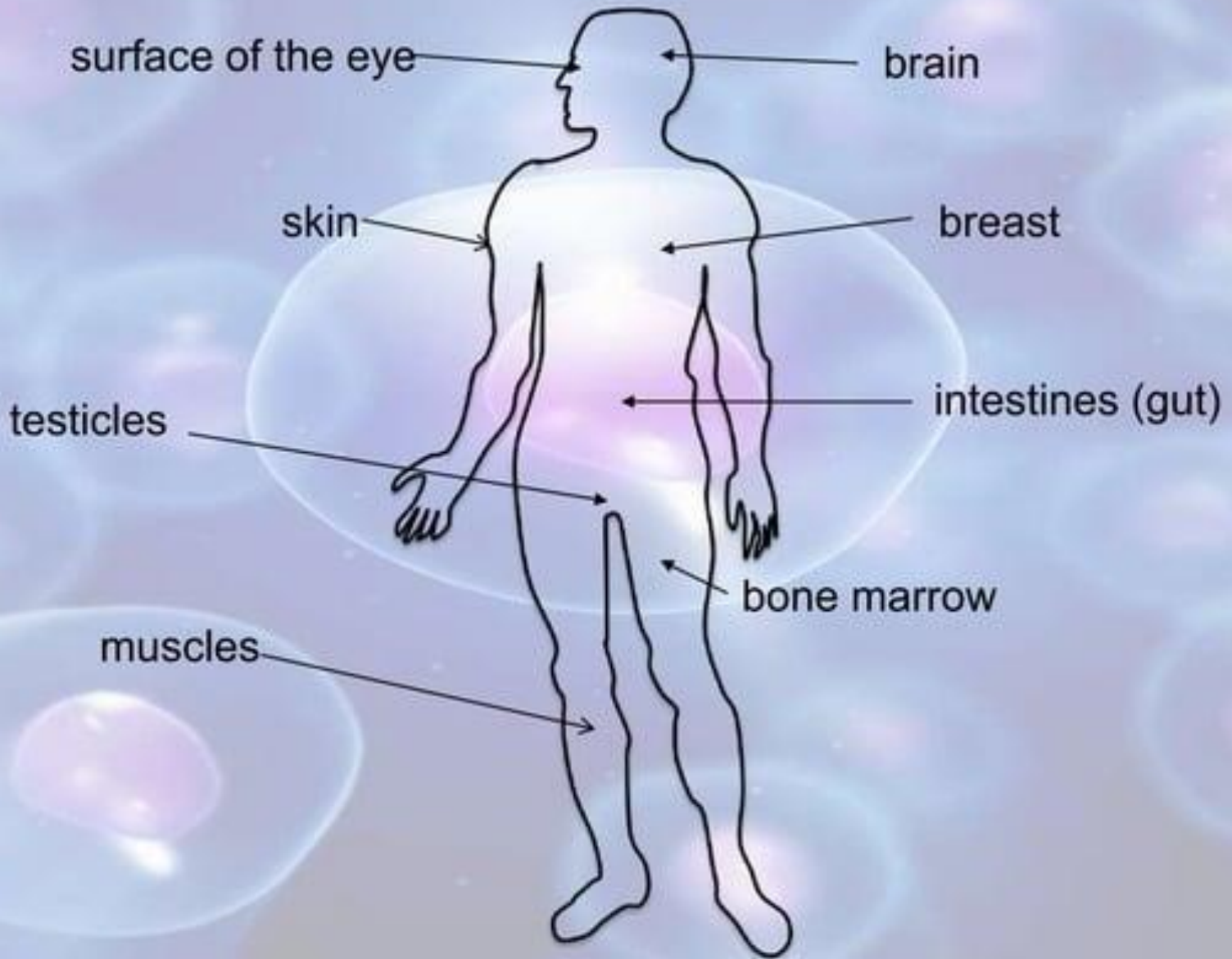
differentiation



all possible types of specialized cells

PLURIPOTENT

Tissue stem cells:

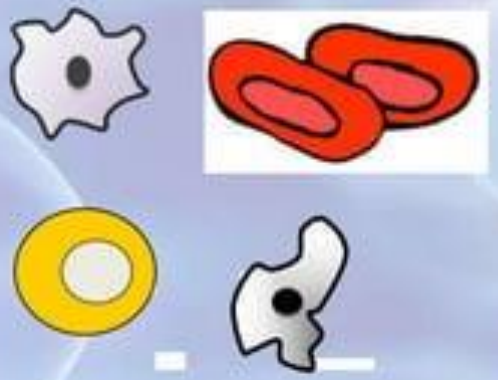


Tissue stem cells:

blood stem cell

found in
bone marrow

differentiation



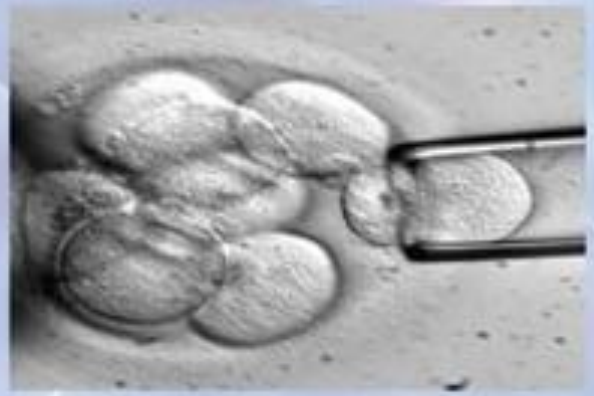
only specialized types of blood cell:
red blood cells, white blood cells,
platelets

MULTIPOTENT

Novel methods

- Extraction of single blastomere without damaging embryo and developed into independent hESC lines

Chung et al ,Nature 2006; 439:216-19



- Altered Nuclear Technique (ANT) genetically modifying the somatic nucleus so that induced pluripotent stem cells are produced

Meissener & Jaenisch Nature 2006;439:212-15

- Somatic Cell Nuclear Transfer / Therapeutic cloning

Induced pluripotent stem cells

Starting cells from donor tissue

Induced change in gene expression

pluripotent stem cells

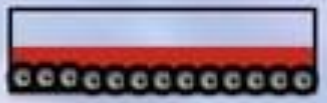
- derived from adult cells in 2007
- can be grown indefinitely in culture in an undifferentiated state
- similar properties to embryonic stem cells as can differentiate into many different tissue types – **pluripotent**
- can create stem cells directly from a patient for research
- **Advantage: no need for embryos!**

Induced pluripotent stem cell

'genetic reprogramming'
= add certain genes to the cell

cell from the body

induced pluripotent stem (iPS) cell
behaves like an embryonic stem cell



culture iPS cells in the lab

differentiation

all possible types of specialized cells

Somatic cell nuclear transfer

- A nucleus from an adult donor cell is inserted into a recipient egg cell from which the nucleus has been removed
- The resulting cell is then stimulated to divide as a zygote later forming embryo genetically identical to the adult donor cell

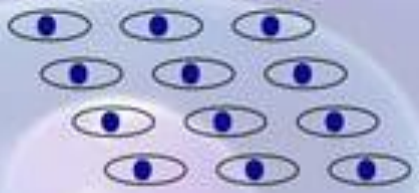
- **May be ethically acceptable as embryos by conventional methods are not used**

Somatic cell nuclear transfer is an alternate source of embryonic stem cells

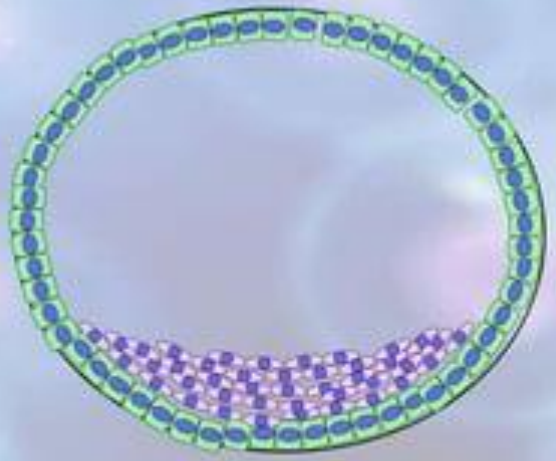
Unfertilized egg

Fusion with patient's cell

Fertilized egg "equivalent"



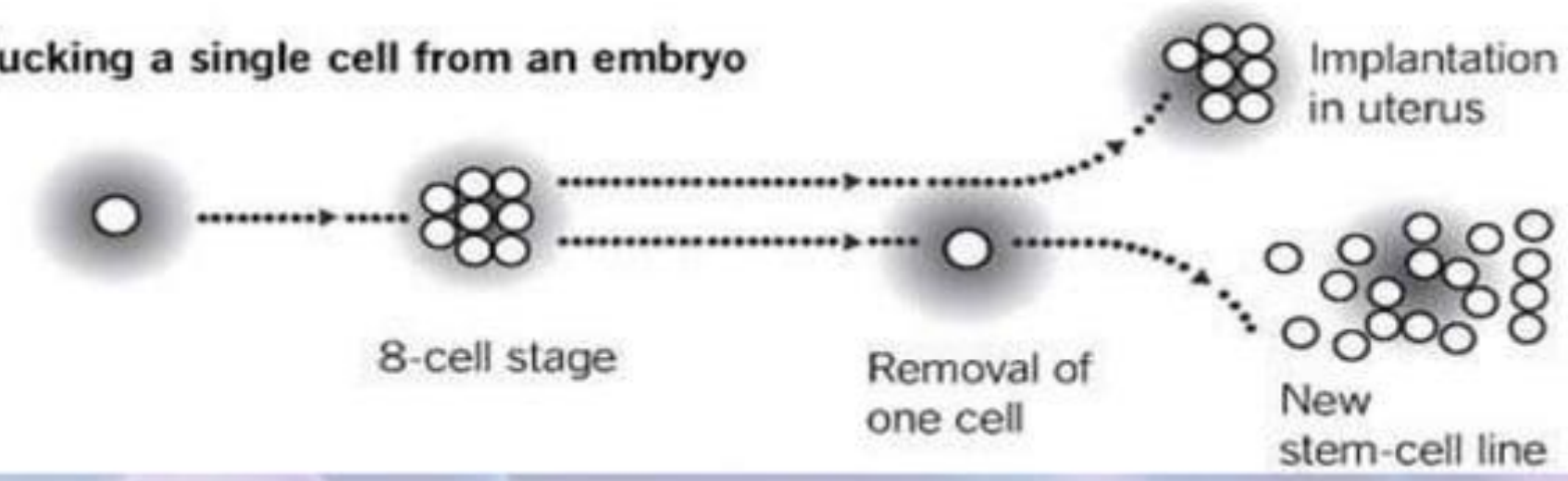
Patient-Specific Stem Cells



Blastocyst

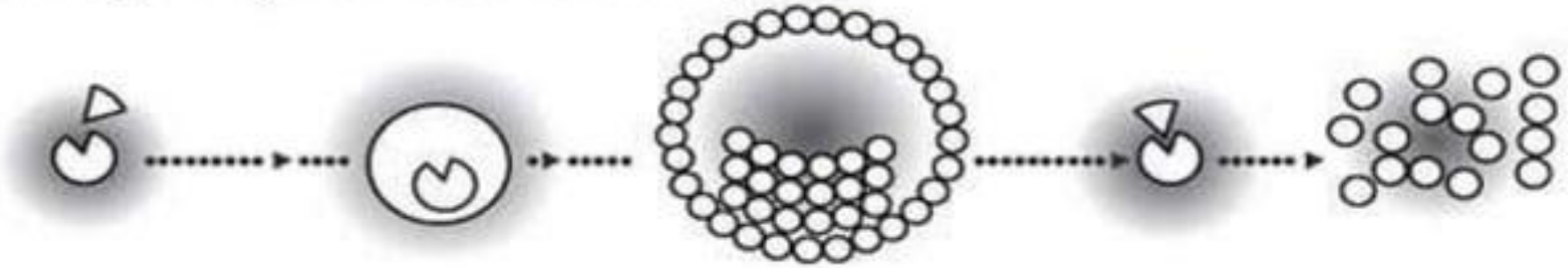
Stem cell work may bypass objections / Ethical Issues

Studies show the possibility of collecting stem cells without destroying viable human embryos.



Stem-cell work may bypass objections / Ethical Issues

Creating embryos that cannot develop



Genes are modified to prevent normal growth

Nucleus with modified genes inserted into cells

Cell multiplies into blastocyst that yields stem cells

Genetic modification removed

New stem-cell line

Novel Methods

- Many questions remain to be explored before these novel methods can be used in the clinic:
  - are they really equivalent to human embryonic stem cells?
  - are they stable over a long time?
  - will they be safe and effective for treatment?

Development in Stem Cell Research

The patient's lower limbs were paralyzed after an accident in 1985; damaged her lower back and hips. Afterward she spent her life in bed or in a wheelchair

The stem cell transplantation (adult stem cells from umbilical cord blood)was performed on Oct. 12, 2004 and in just three weeks she started to walk with the help of a walker.

Regenerative Medicine

For the first time researchers reconstitute a complete organ. New bladders were made by growing bladder cells from the patients on a biodegradable scaffolding.

- Reported in the *Lancet* (April, 2006)

World's first transplant of a whole organ grown in lab

- November 2008
- Claudia Castillo
- damaged windpipe
- lower chance of rejection

Potential Uses of Stem Cells

- Basic research – clarification of complex events that occur during human development & understanding molecular basis of cancer
  - Molecular mechanisms for gene control
  - Role of signals in gene expression & differentiation of the stem cell
  - Stem cell theory of cancer

Potential uses cont.

- Biotechnology(drug discovery & development) – stem cells can provide specific cell types to test new drugs
  - Safety testing of new drugs on differentiated cell lines
  - Screening of potential drugs
    - Cancer cell lines are already being used to screen potential anti-tumor drugs
    - Availability of pluripotent stem cells would allow drug testing in a wider range of cell types & to reduce animal testing

Potential uses cont.

- Cell based therapies:
  - Regenerative therapy to treat Parkinson's, Alzheimer's, spinal cord injury, stroke, severe burns, heart disease, diabetes, osteoarthritis, and rheumatoid arthritis
  - Stem cells in gene therapy
    - Stem cells as vehicles after they have been genetically manipulated
  - Stem cells in therapeutic cloning
  - Stem cells in cancer

STEM CELL THERAPY

- **Stem cell therapy** is introduction of new adult stem cells into damaged tissue in order to treat disease or injury.
- The ability of stem cells to self-renew and give rise to different cells, that can potentially replace diseased and damaged areas in the body, with minimal risk of rejection and side effects.

- A number of stem cell therapies exist, but most are at experimental stages, costly or controversial.

What Diseases Can be Cured by Stem Cell Therapies?

- Any disease in which there is tissue degeneration can be a potential candidate for stem cell therapies

Alzheimer's disease
Parkinson's disease
Spinal cord injury
Heart disease
Severe burns
Diabetes

Tissue Repair

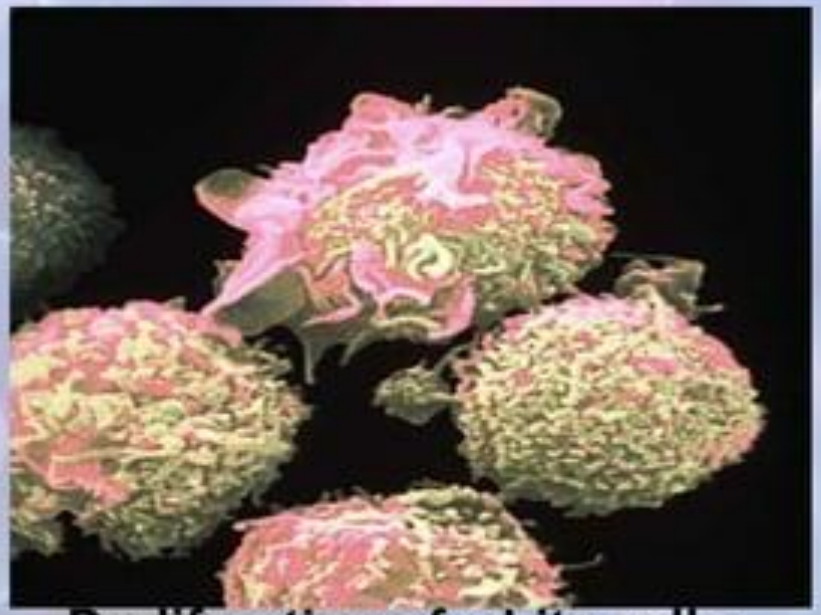
- Regenerate spinal cord, heart tissue or any other major tissue in the body.

Heart Disease

- Adult bone marrow stem cells injected into the hearts are believed to improve cardiac function in victims of heart failure or heart attack

Leukemia and Cancer

- Leukemia patients treated with stem cells emerge free of disease.
- Stem cells have also reduces pancreatic cancers in some patients.



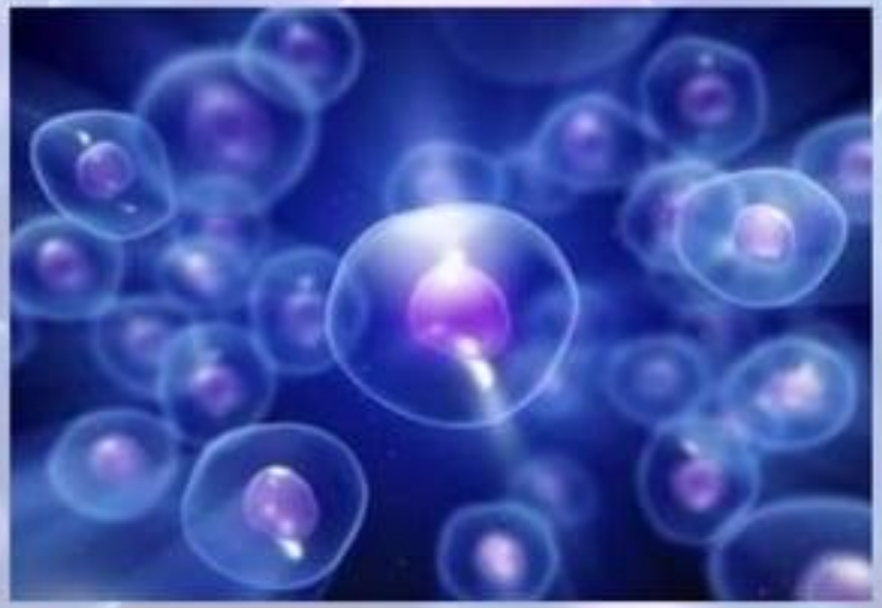
Proliferation of white cells

Rheumatoid Arthritis

- Adult Stem Cells may be helpful in starting repair of eroded cartilage.

Type I Diabetes

- Embryonic Stems Cells might be trained to become pancreatic islets cells needed to secrete insulin.



Challenges to Stem Cell Research

- Source - Cell lines may have mutations
- Delivery to target areas
- Prevention of rejection
- Suppressing tumors
- Stem Cell regenerated tissue viability
- Political and religious obstructions
- *Inability to obtain source material due to ethical concerns*

EMBRYONIC STEM CELL CONTROVERSY

- There is wide-spread controversy over the use of human embryonic stem cells. This controversy primarily targets the techniques used to derive new embryonic stem cell lines, which often requires the destruction of the blastocyst.

- At present, there are alternative sources for stem cells which have achieved considerable success when used as medical therapies. These alternatives do not require the destruction of an embryo, such as the use of umbilical cord blood, milky teeth stem cells, bone marrow stem cells or using induced pluripotent stem cells.

- However, non-embryonic stem cells may have limitations.

The Ethical Debate

In favor of ESCR:

- Embryonic stem cell research (ESCR) fulfills the ethical obligation to alleviate human suffering.
- Since excess IVF embryos will be discarded anyway, isn't it better that they be used in valuable research?
- SCNT (Therapeutic Cloning) produces cells in a petri dish, not a pregnancy.

Against ESCR:

- In ESCR, stem cells are taken from a human blastocyst, which is then destroyed. This amounts to "murder."
- There is a risk of commercial exploitation of the human participants in ESCR.
- ESCR will lead to reproductive cloning.

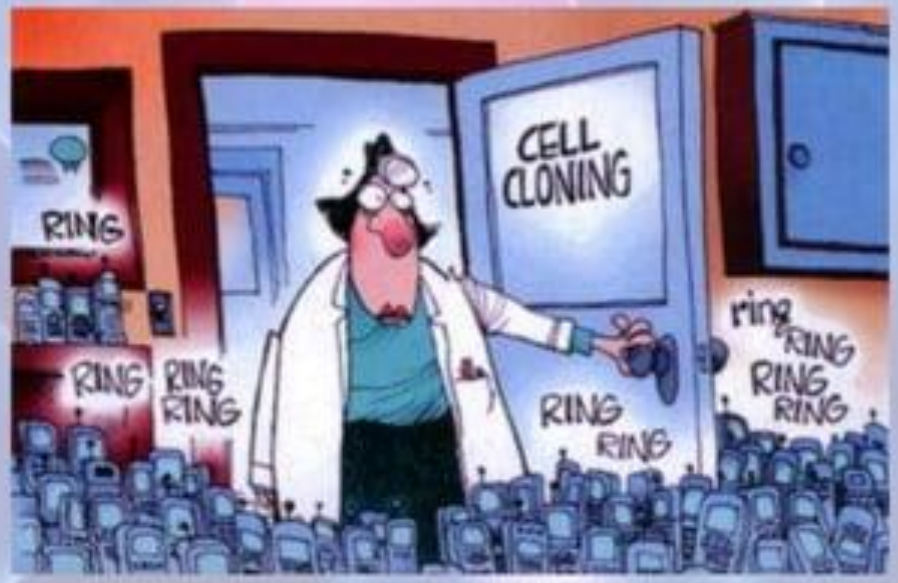
Day 5-6
Blastocyst

Stem Cell Ethics

- This *is* an ethical issue.
- Science is designed to tell us what is possible – what we can do.
- Science is not designed to tell us what is right – what we should do.
- To evaluate this technology one must employ *some* ethical system that comes from outside of science.

Stem Cell Ethics

- "Can we" vs. "Should we"
  - Dramatic advances of modern molecular genetics
  - Should we ask the morality questions before attempting the "can we" questions?

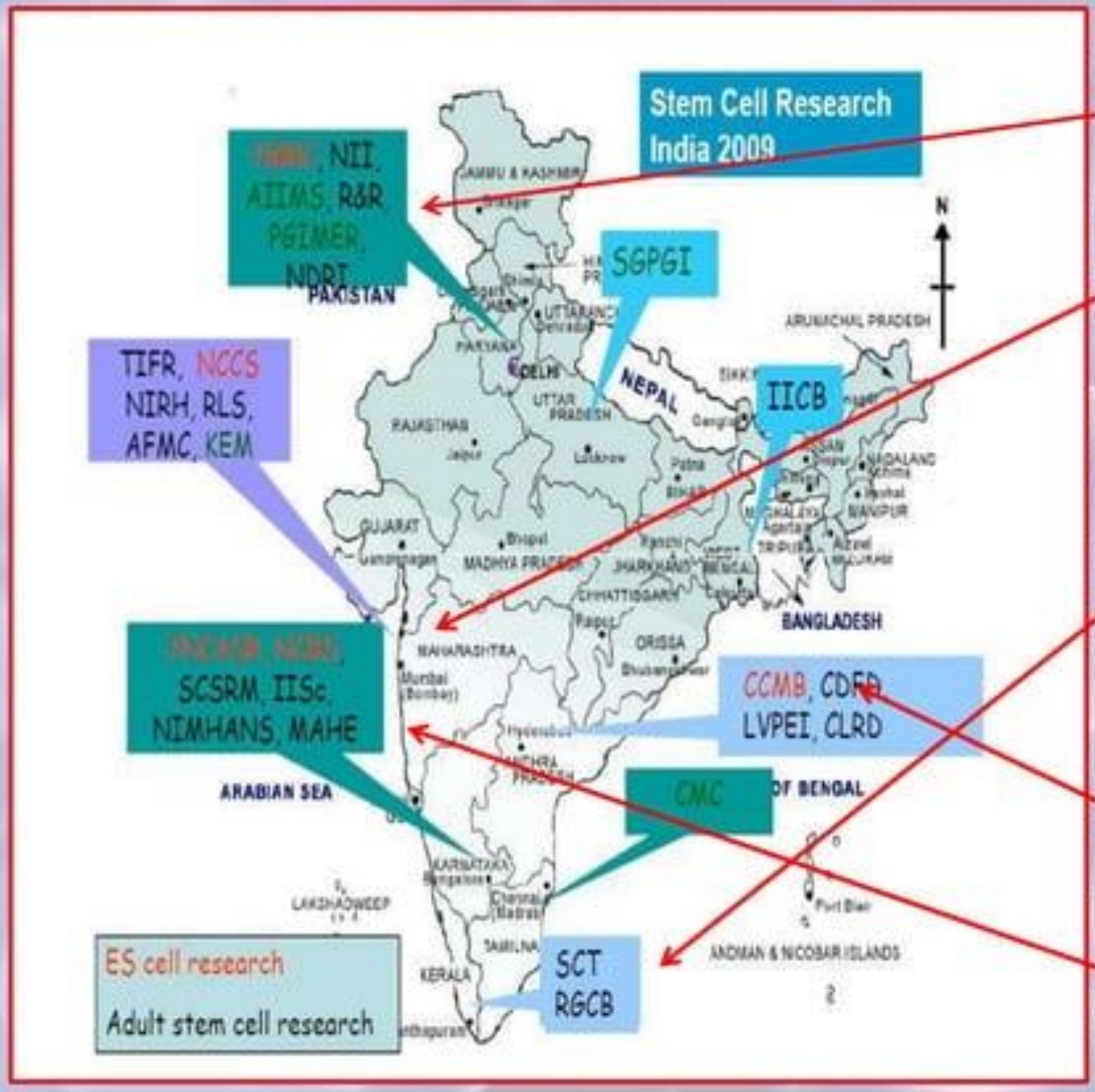


Stem Cell Ethics

- Encourage development of sound research and therapy.
- Prevent any misuse of human embryos and fetuses.
- Protect patients from fraudulent treatments in the name of stem cell research

Current status in India

- Keeping in view of its potential therapeutic applications, both basic and translational research are being promoted in various institutions, hospitals and the industry.
- Till date, more than 55 programmes have been identified and supported on various aspects of stem cell research.



ALL INDIA INSTITUTE OF MEDICAL SCIENCES NEW DELHI

National Institute for Research in Reproductive Health (ICMR) Mumbai

National Center for Cell Science, Pune

Rajiv Gandhi Center for Biotechnology
Trivandrum , Kerala, India

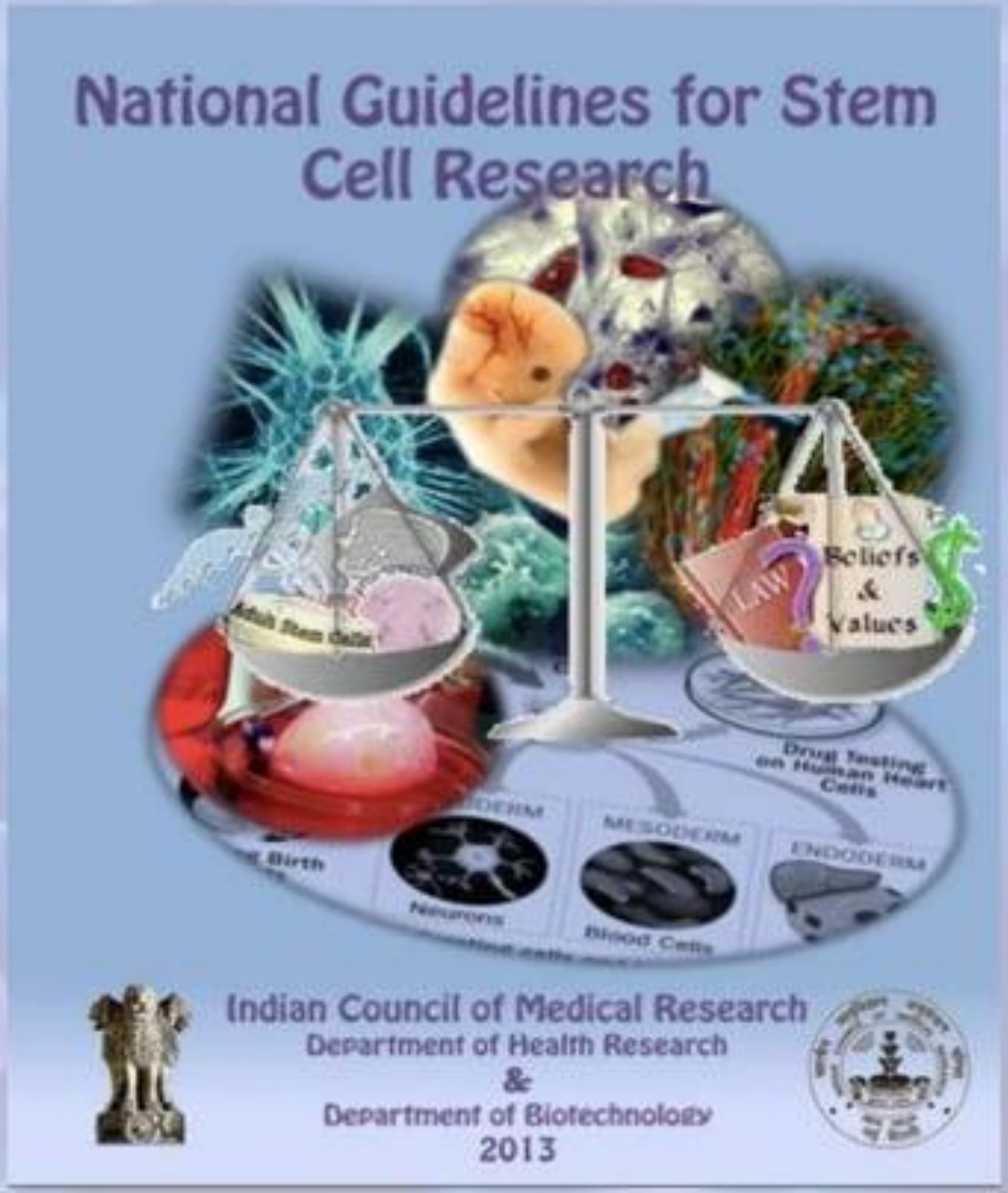
Center for Cellular and Molecular Biology, Hyderabad

The Stem Cell Institute (SCSRM)
Center for Cellular and Molecular Platforms
Karnataka

Stem Cell research: Indian Guidelines

- Due to ethical and religious concerns related to research with human embryos, the Indian Government has decided to come clear on the scope and purview of stem cell research in the country.
- National Guidelines for Stem Cell Research was published by ICMR in 2013.

Stem Cell research: Indian Guidelines



Conclusions

- Stem cells show great promise for regenerative medicine
- There is enormous potential in human stem cell research

  Both adult and embryonic stem cells should be studied
- Much research needed before therapies are realized
- Ethical concerns need to be taken into account
- Proper guidelines are needed to ensure appropriate conduct of the research

REFERENCE:

- Stem cells : Scientific facts and fiction,Christine L. Mummery, Anja Van de Stolpe,Bernard Roelen, Hans Clevers, (2021) 3rd Edition, Elsevier

- Stem Cells in Regenerative Medicine, Science, Regulation and Business Strategies, Alain A. Vertes, Arnold I. Caplan, Lee E. Babiss, Nasib Qureshi, 2015. Wiley.


THANK YOU!