

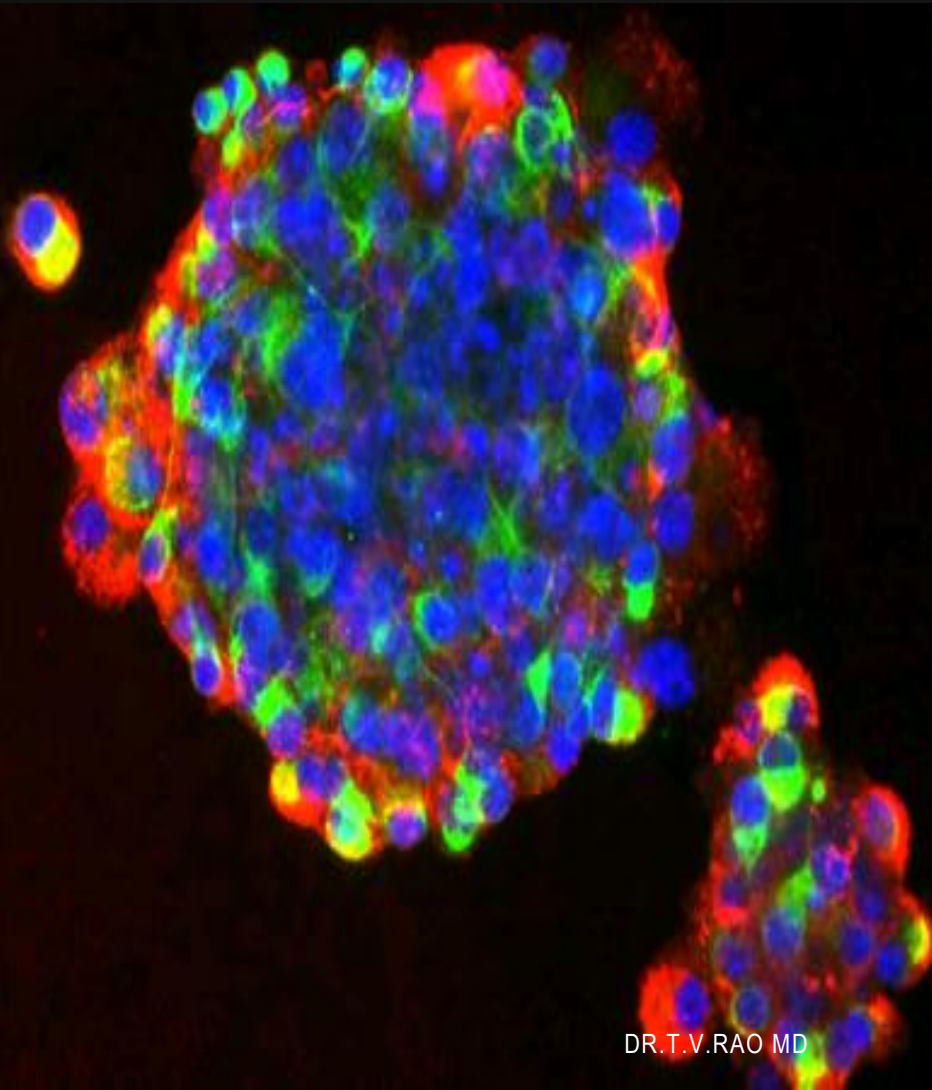
# STEM CELLS

## ADVANCES IN SCIENCE

Dr.T.V.Rao MD



# STEM CELL – DEFINITION



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

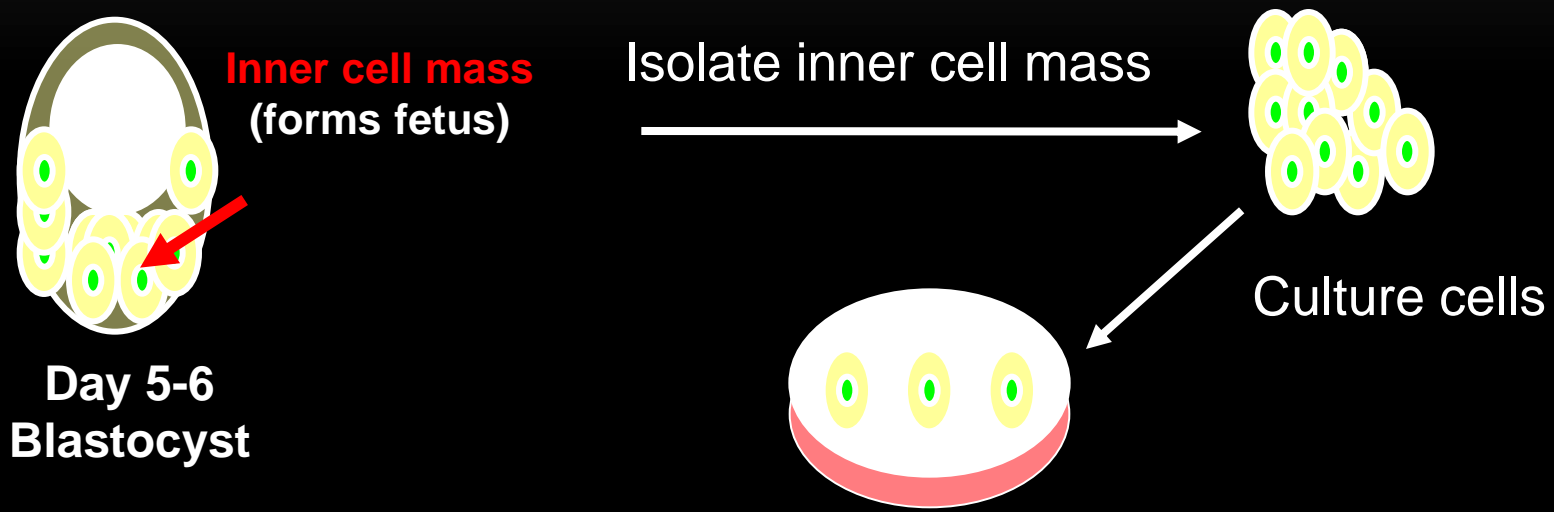
# WHAT MAKES A CELL A *STEM CELL*?

- Plasticity: A stem cell is plastic, meaning it can develop into another type of cell.
- Differentiation: The process where a stem cell specializes or develops into another type of cell.
- Self-Renewal: a stem cell can divide (renew itself) *indefinitely* (go through mitosis) and without always developing into another cell.

# STEM CELL HISTORY

- **1998 - Researchers first extract stem cells from human embryos**
- **1999 - First Successful human transplant of insulin-making cells from cadavers**
- **2001 - President Bush restricts federal funding for embryonic stem-cell research**
- **2002 - Juvenile Diabetes Research Foundation International creates \$20 million fund-raising effort to support stem-cell research**
- **2003?? - California ok stem cell research**
- **2004 - Harvard researchers grow stem cells from embryos using private funding**
- **2004 - Ballot measure for \$3 Billion bond for stem cells**

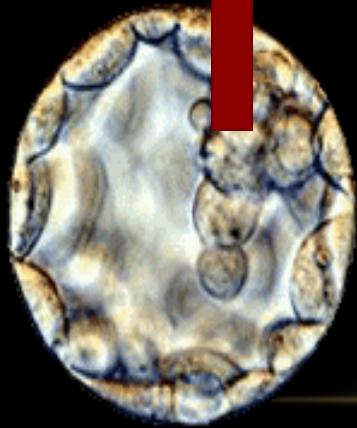
# HISTORY OF HUMAN EMBRYONIC STEM CELL RESEARCH



- In 1998, **James Thomson (University of Wisconsin-Madison)** isolated cells from the inner cell mass of the blastocyst, and developed the first human embryonic stem cell line in culture.

# HISTORY OF HUMAN EMBRYONIC STEM CELL RESEARCH

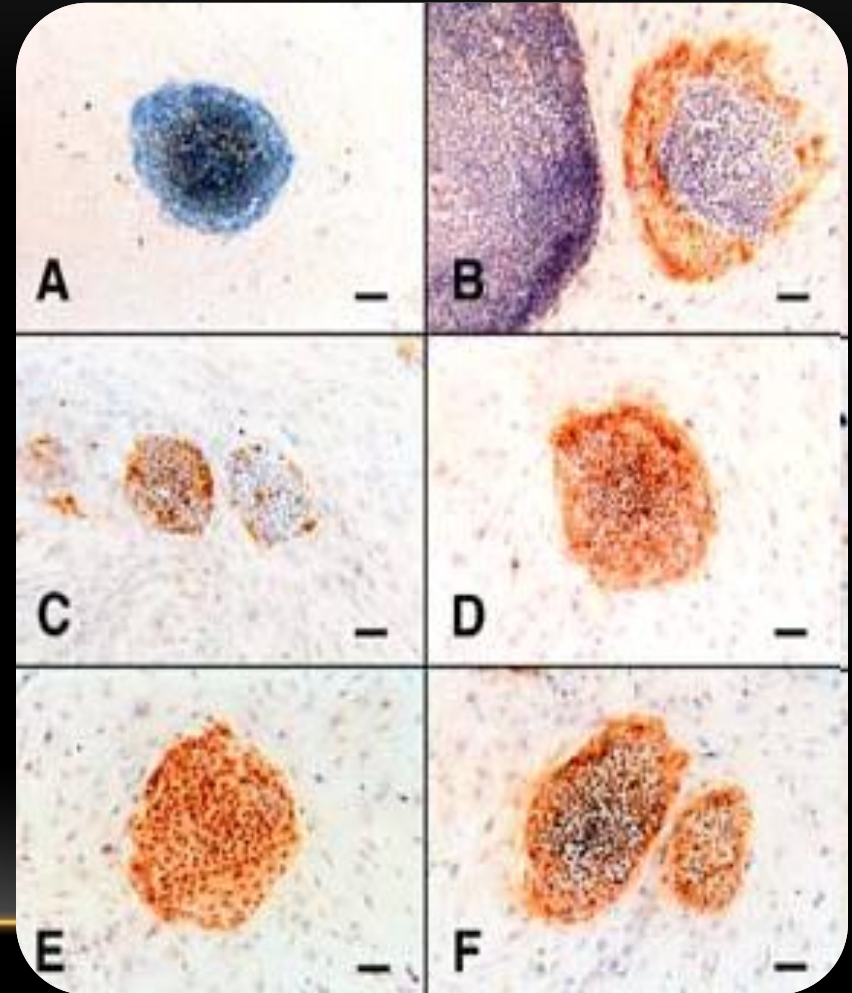
- IN 1998, JAMES THOMSON (UNIVERSITY OF WISCONSIN-MADISON) ISOLATED CELLS FROM THE INNER CELL MASS OF THE EARLY EMBRYO, AND DEVELOPED THE FIRST HUMAN EMBRYONIC STEM CELL LINES,



- **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**

# WHAT ARE STEM CELLS?

■ Stem cells are the raw material from which all of the body's mature, differentiated cells are made. Stem cells give rise to brain cells, nerve cells, heart cells, pancreatic cells, etc.



# MAJOR TYPES OF STEM CELLS

## Embryonic Stem Cells

- Totipotent : cell can develop into all cell types
- “Immortal”: can self-renew indefinitely
- Plentiful

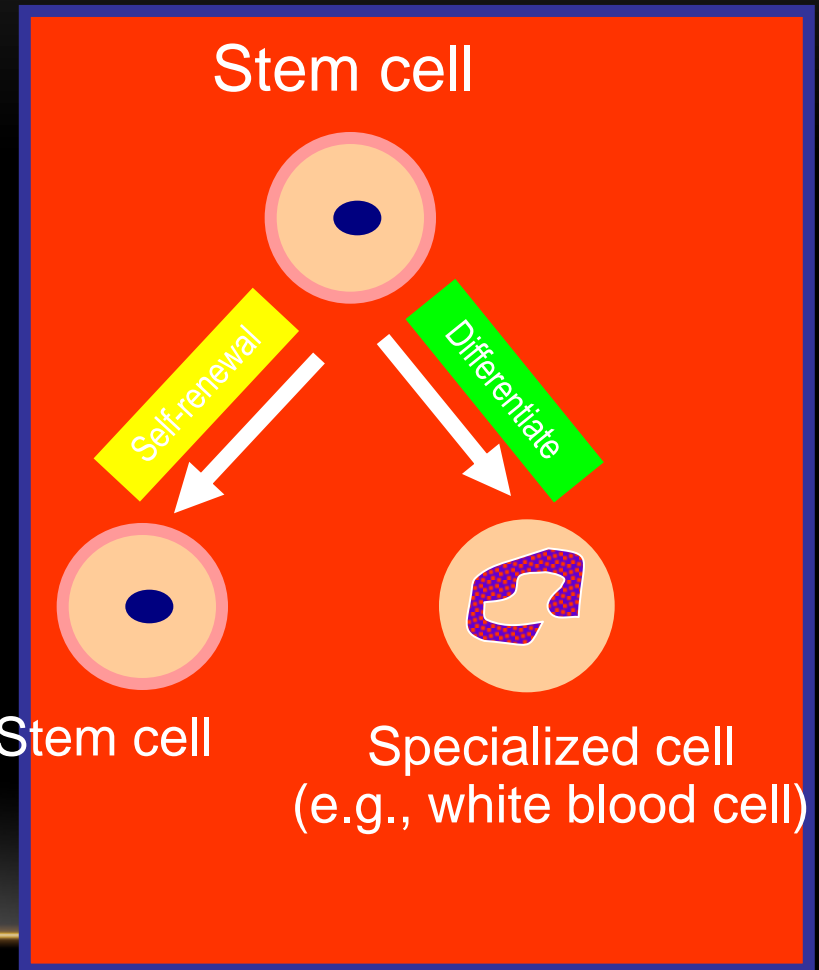
## Adult Stem Cells

- Multipotent: cell can develop into a few cell types but not all
- Located in few organs or may be unidentified
- Hard to find

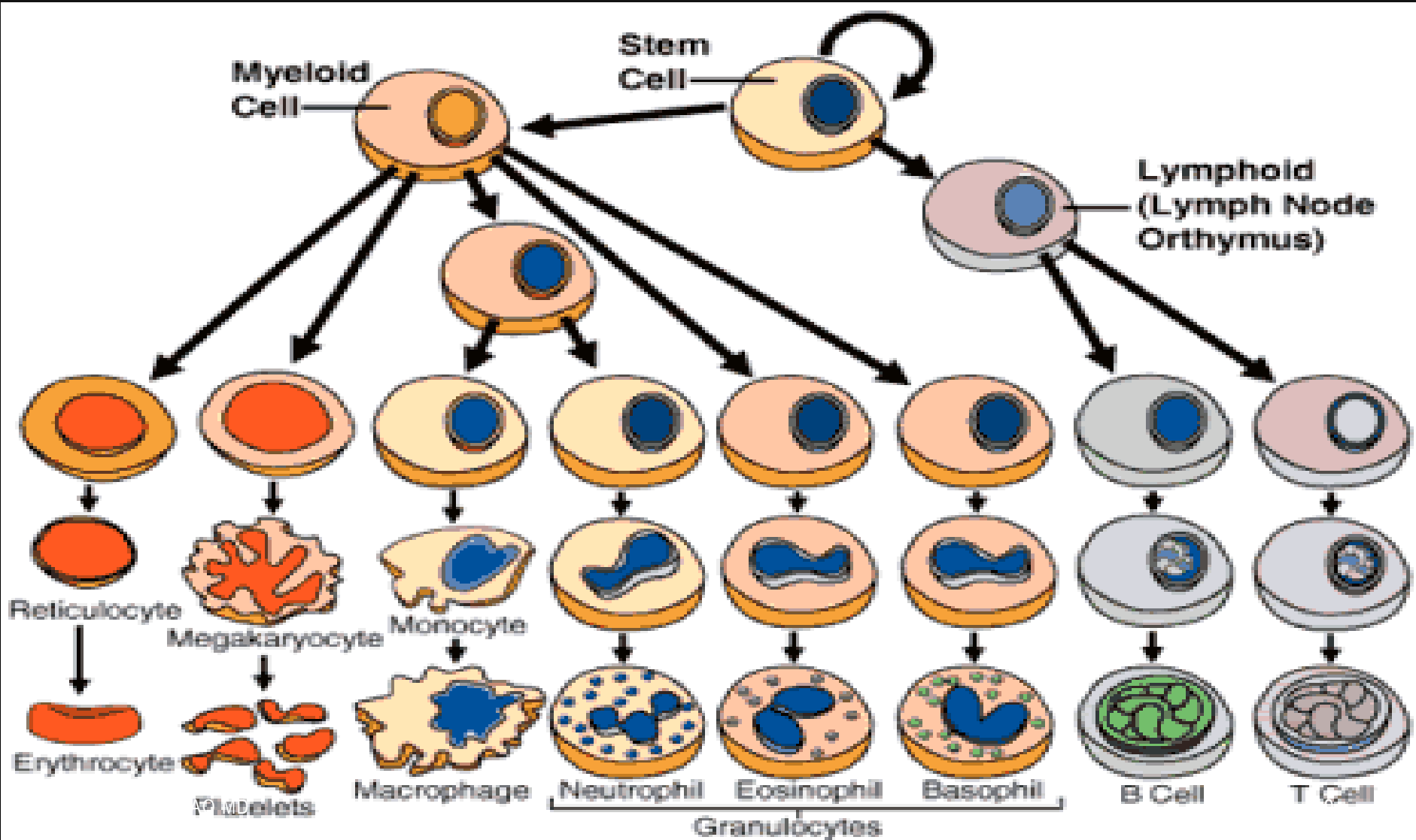


# STEM CELL – ARE DYNAMIC

- **Are undifferentiated “master” cell that do not yet have a specific function**
- **Can change to one or several different cell types (differentiate) under proper conditions**
- **Can undergo unlimited cell division, self-renewal)**



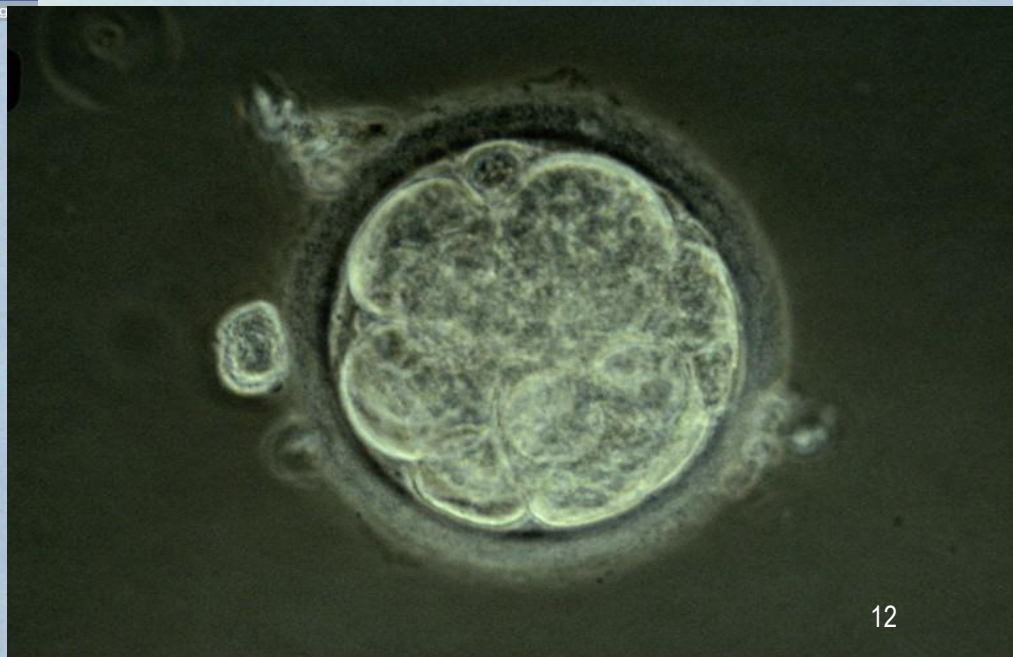
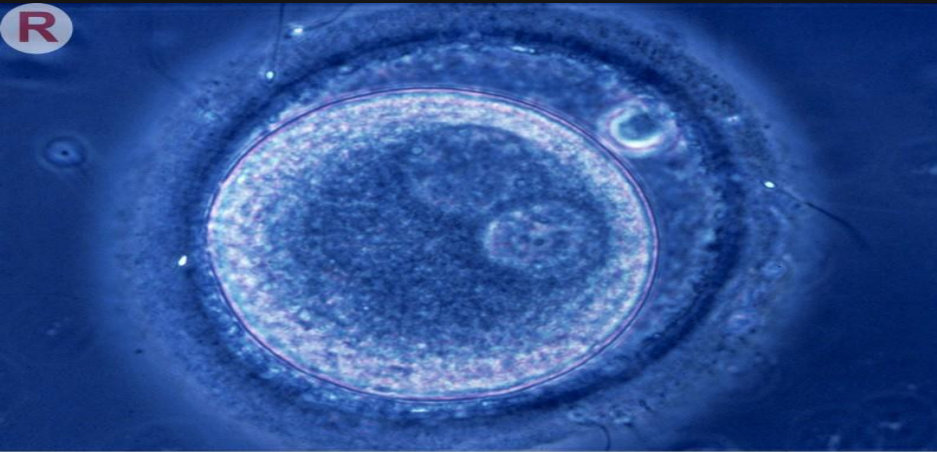
# ONE CELL - SEVERAL LINEAGES



# EMBRYOGENESIS AND DIFFERENTIATION

- Specific regions of the embryo give rise to the specific organ systems
  - **Ectoderm** generates the outer layer of the embryo and produces the surface layer (epidermis) of the skin and forms the nerves
  - **Endoderm** becomes the innermost layer of the embryo and produces the digestive tube and its associated organs (including the lungs)
  - **Mesoderm** becomes sandwiched between the ectoderm and endoderm and generates the blood, heart, kidney, gonads, bones, and connective tissues.

# STAGES OF DEVELOPMENT

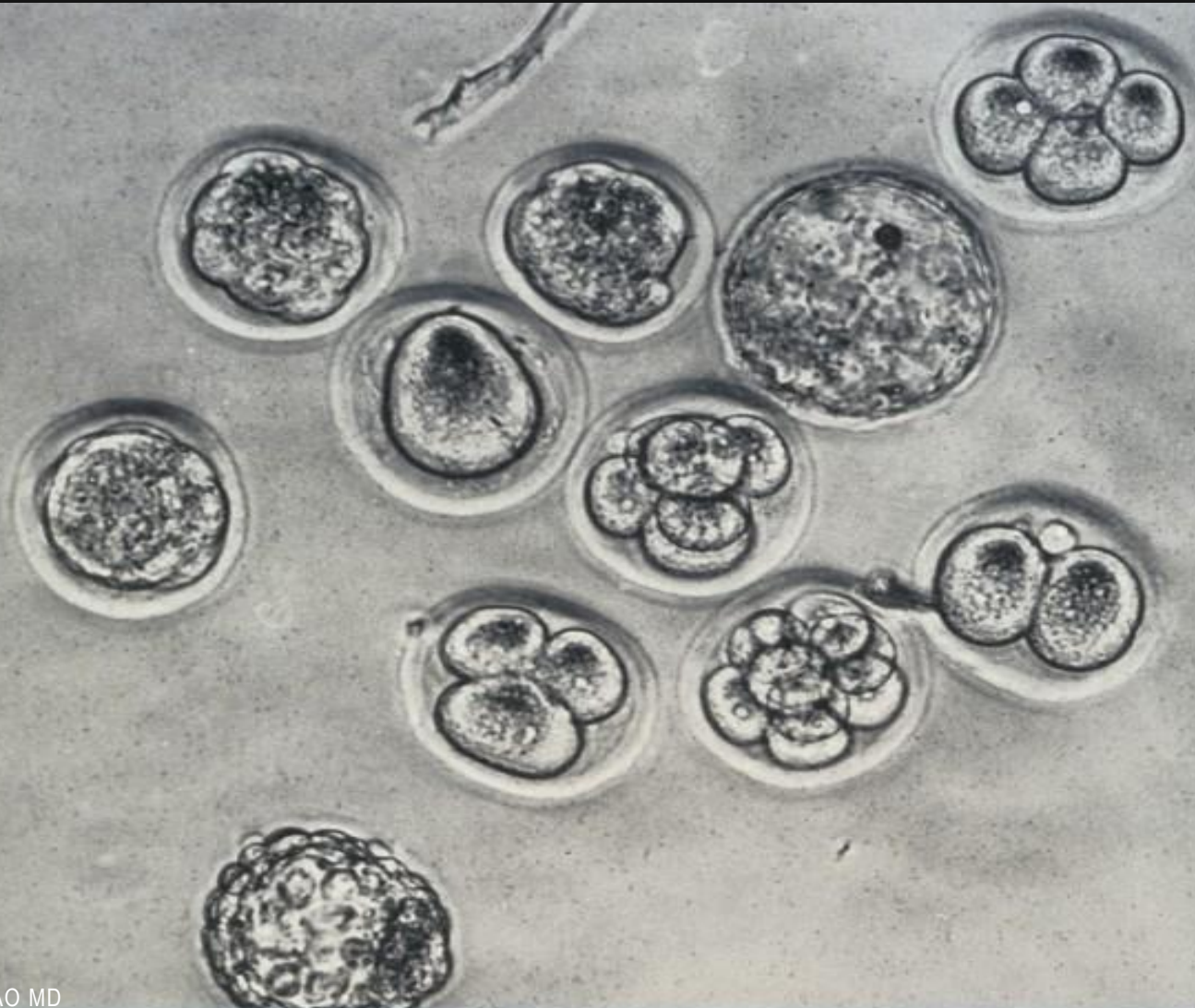


DR. T. V. RAO MD

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4-Cell Embryo

# EARLY HUMAN DEVELOPMENT



# AN OVERVIEW OF EARLY DEVELOPMENT MODELED WITH PLAY-DOUGH

Fertilized egg



Totipotent stem cells



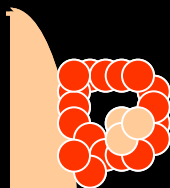
Fate Decision



Pluripotent stem cells  
(3-5 days old)

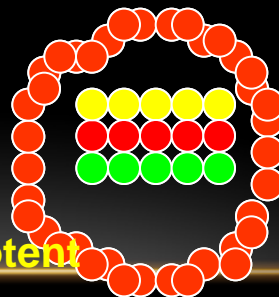


Blastocyst



Implantation

Fate Decision



Multipotent

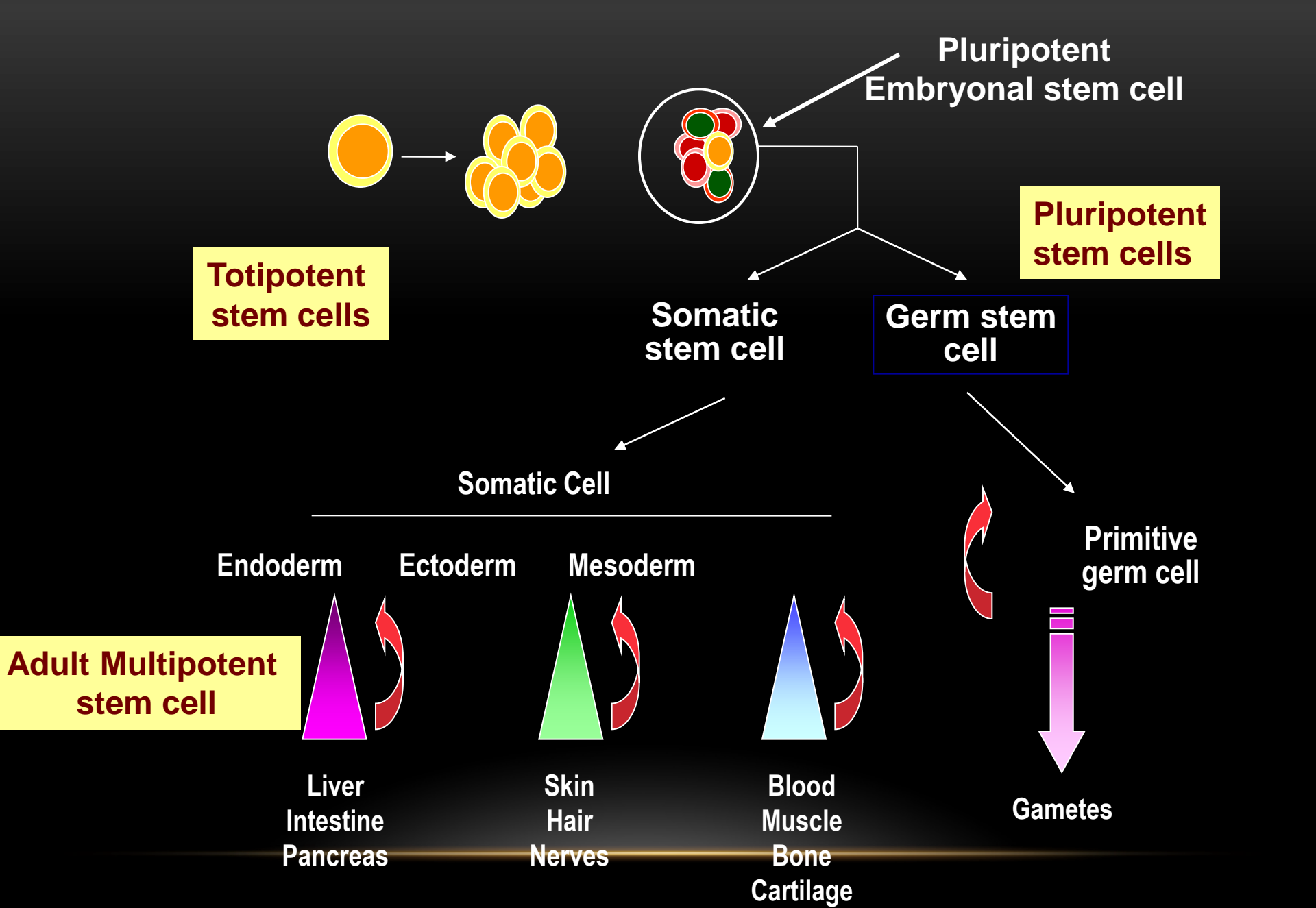
**Totipotent:** Can become any cell in body or placenta

**Pluripotent:** Can become any cell in body

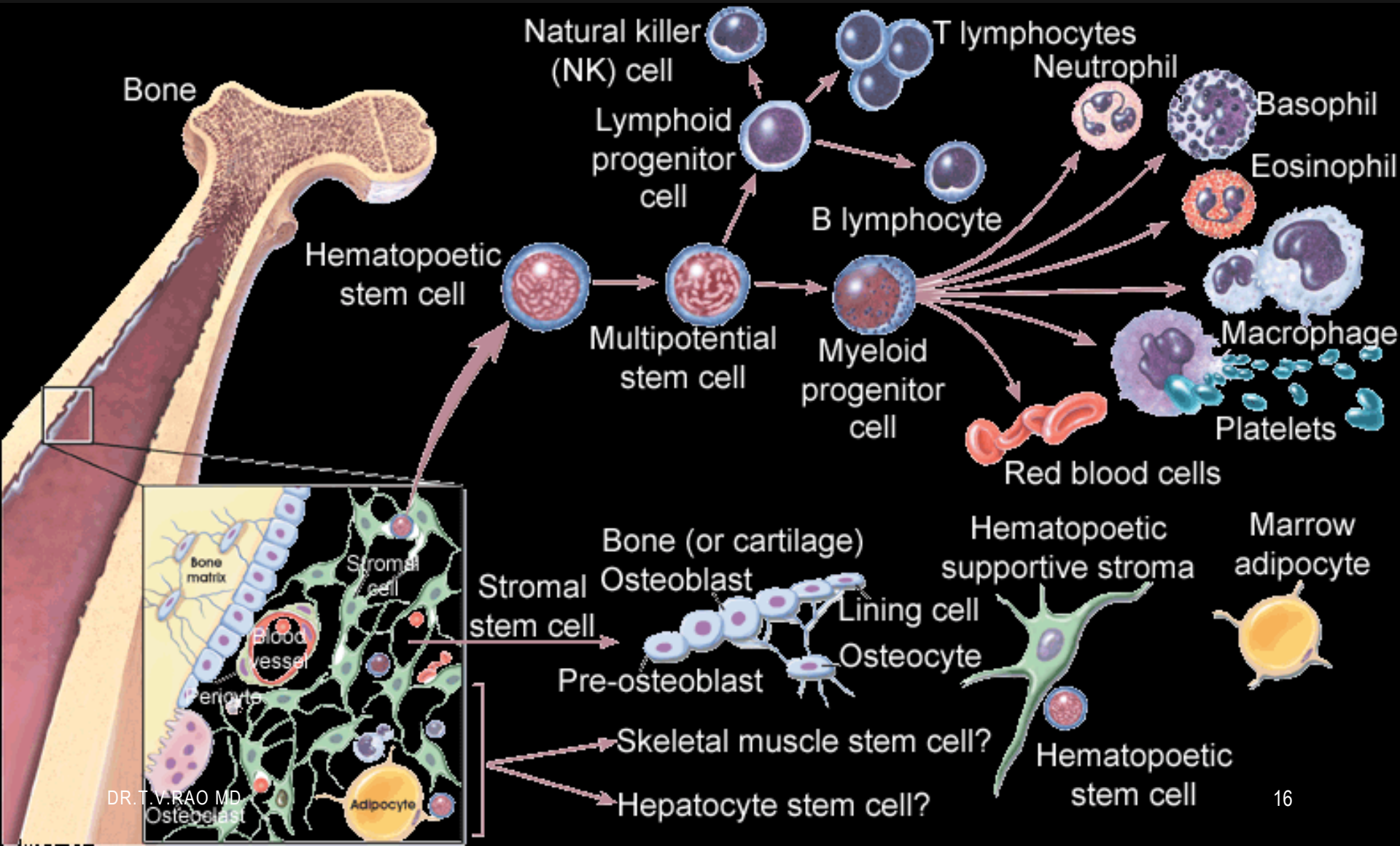
**Multipotent:** Can become any cell within a specific germ layer or cell lineage

*Embryonic stem cells come from inner cell mass of blastocyst.*

Gastrulation (day 14) leads to Primary Germ Cells  
 Endoderm (inner) → digestive tract, resp. track  
 Mesoderm (middle) → bones, blood cells, heart  
 Ectoderm (outer) → skin, CNS

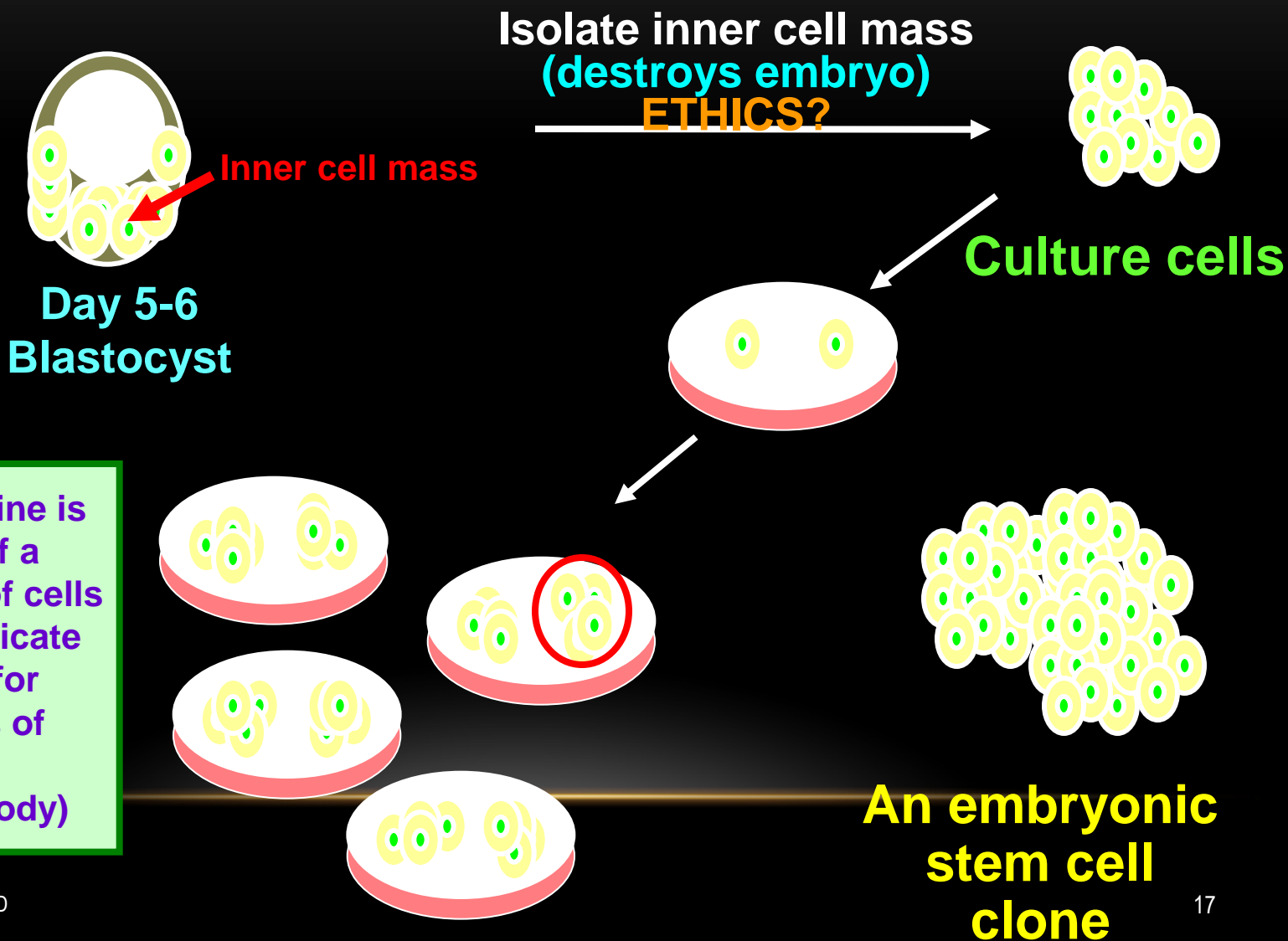


# BONE MARROW STEM CELLS





# HOW TO DERIVE AN EMBRYONIC STEM CELL LINE?

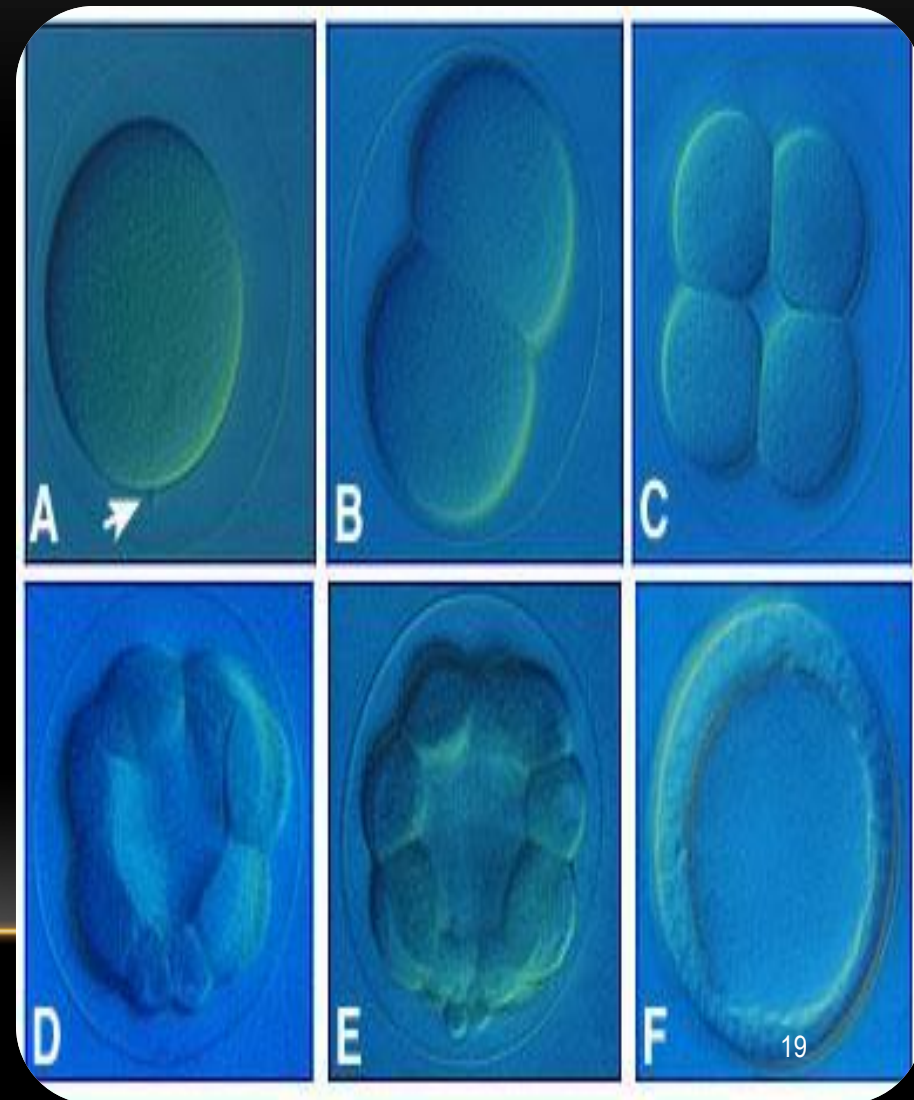


# THE SCIENCE OF STEM CELLS

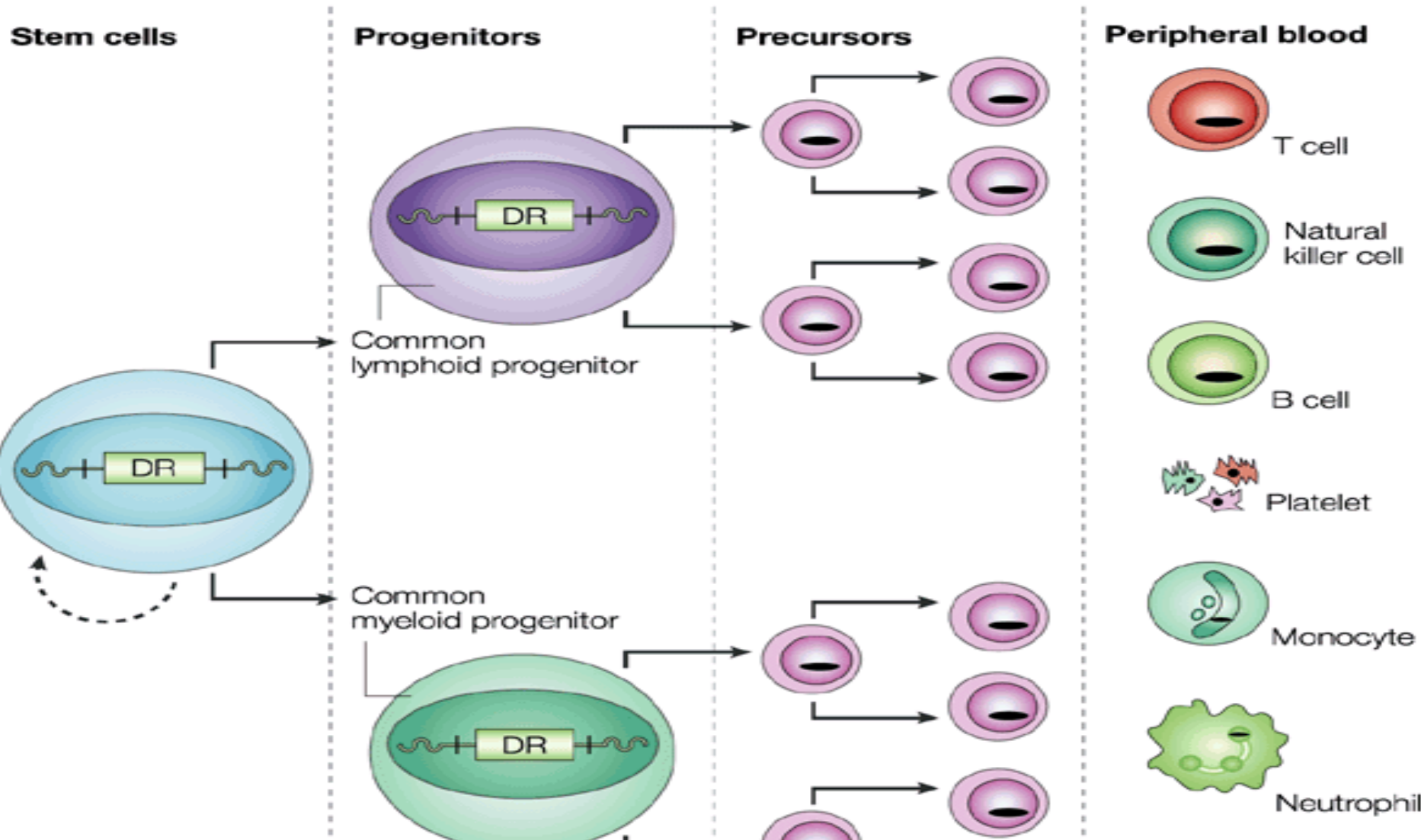
- Stem cells have the ability to continually reproduce themselves while maintaining the capacity to give rise to other more specialized cells.
- Stem cells are found at all stages of development, from embryonic stem (ES) cells that can differentiate into all specialized cells found in the human body, to adult stem cells capable of regenerating their tissue of origin.
- **Stem cells occur from the earliest stages of development and provide the starting material for every organ and tissues.**

# EMBRYONIC STEM (ES) CELLS

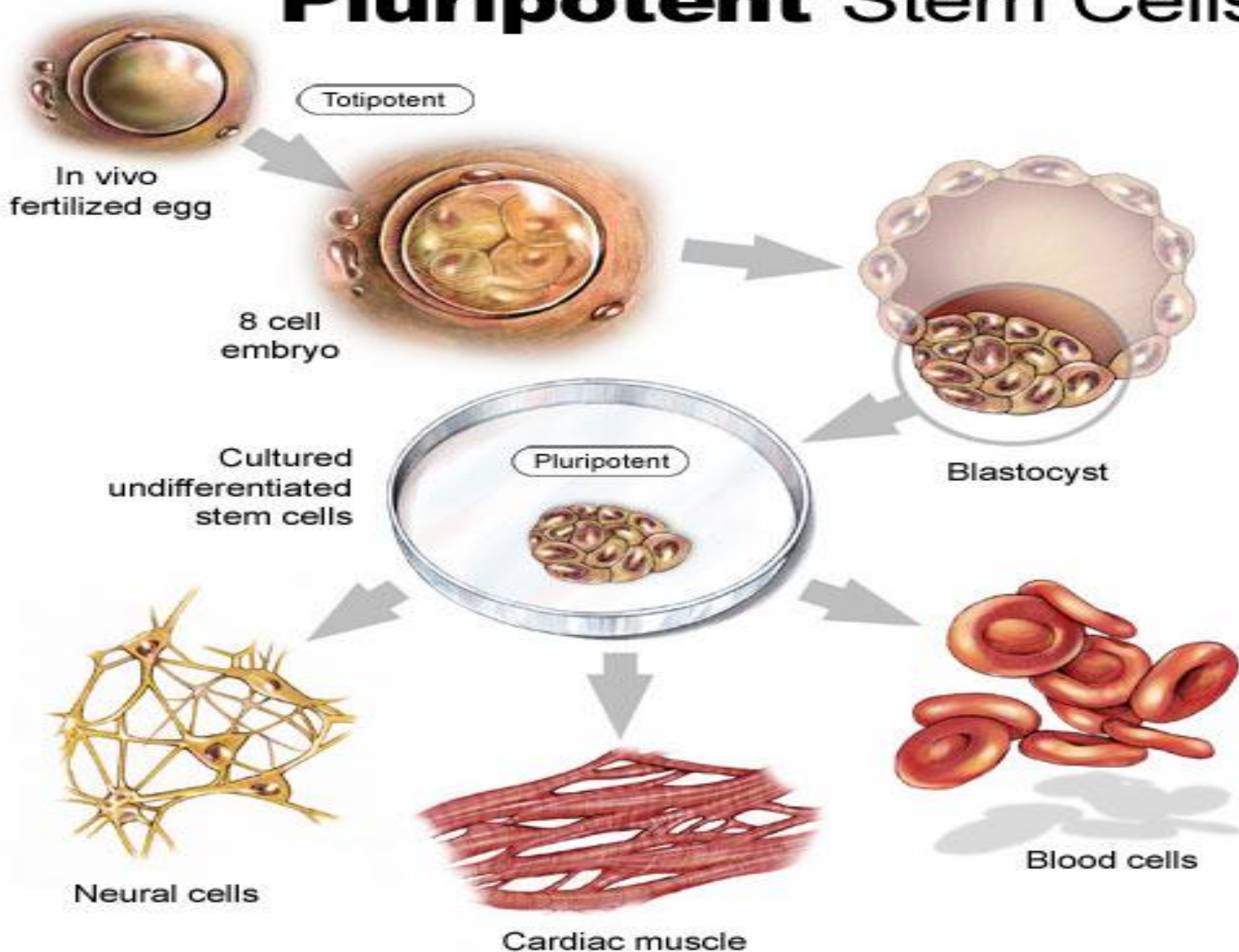
- ES cells are found at the blastocyst stage, four to five days after the union of the sperm and egg, before the embryo implants in the uterus.



# ES CELLS ARE "PLURIPOTENT" - I.E. CAPABLE OF FORMING EMBRYONIC TISSUES

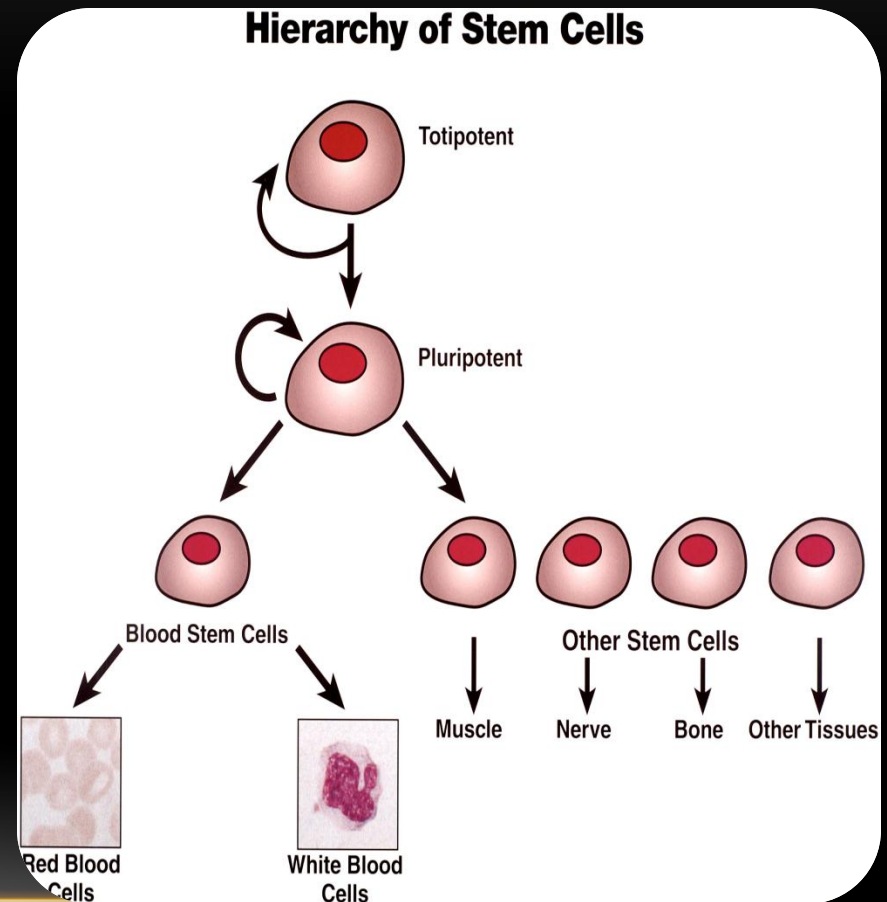


# Pluripotent Stem Cells



# SOURCE OF STEM CELLS

- Stem cells may be derived from autologous, allogeneic or xenogeneic sources. Histocompatibility is prerequisite for transplantation of allogeneic stem cells. Fetal tissue is the best current tissue source for human neural stem cells, however ethical issues are a major concern.

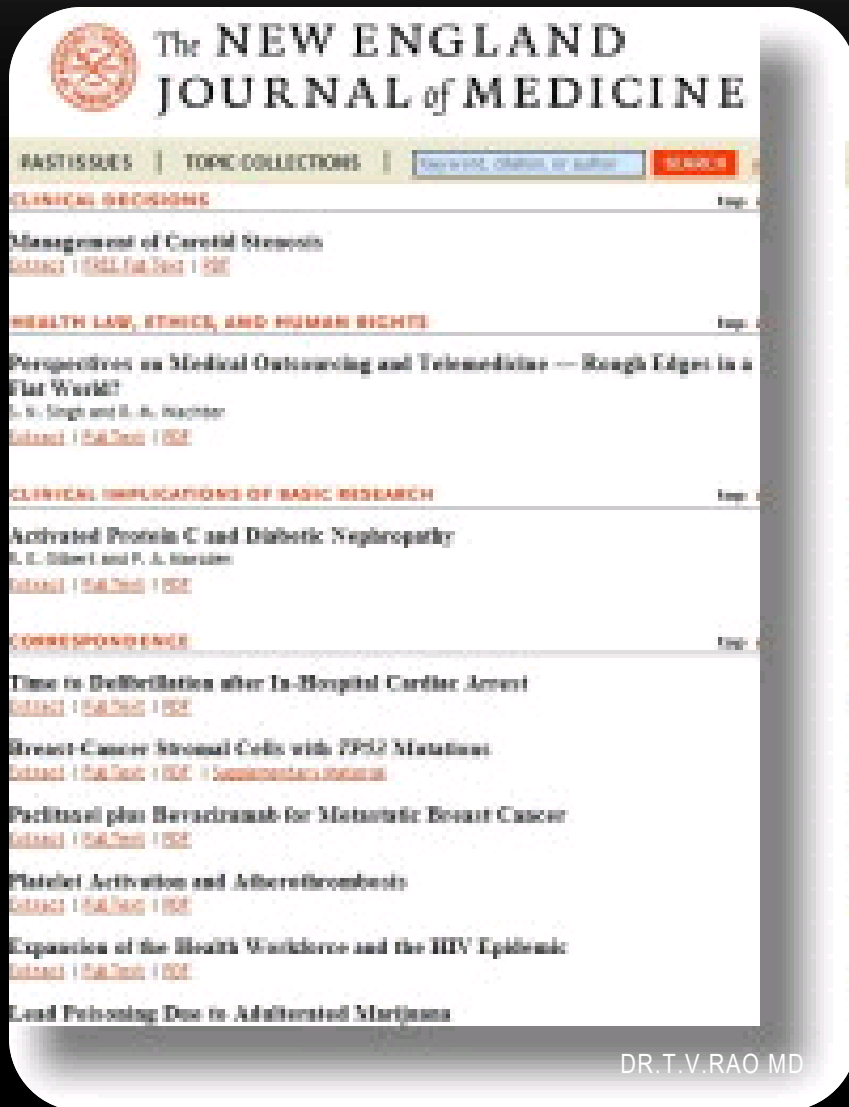


# PLACENTA A SOURCE OF STEM CELLS

- Placental stem cells, like umbilical cord blood and bone marrow stem cells, can be used to cure chronic blood-related disorders such as sickle cell disease, Thalassemia, and leukaemia.



# • Placental Blood as a Source of Hematopoietic Stem Cells for Transplantation into Unrelated Recipients



- REPORT OF PRELIMINARY RESULTS OF TRANSPLANTATION USING PARTIALLY HLA-MISMATCHED PLACENTAL BLOOD FROM UNRELATED DONORS.

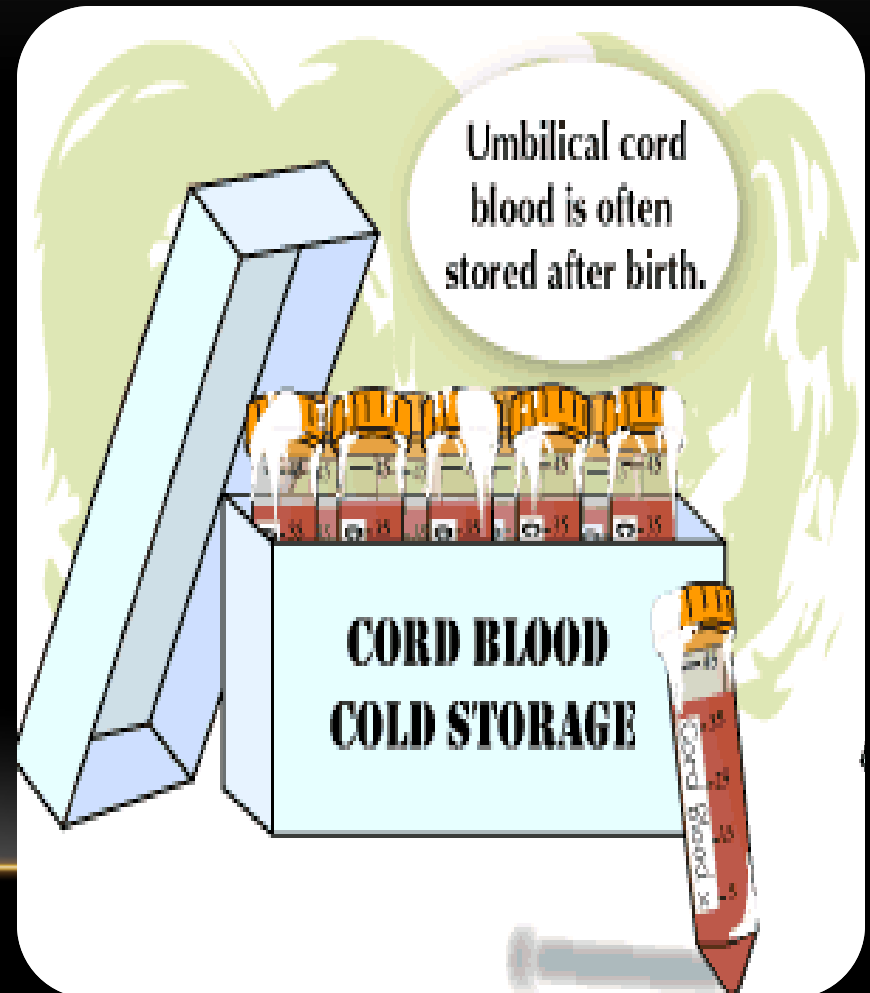
□ **JOANNE KURTZBERG, M.D. ET AL**



# UMBILICAL CORD BLOOD STEM CELL TRANSPLANT

- Umbilical cord blood stem cell transplants are less prone to rejection than either bone marrow or peripheral blood stem cells. This is probably because the cells have not yet developed the features that can be recognized and attacked by the recipient's immune system

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# KINDS OF STEM CELLS

Stem cell type	Description	Examples
Totipotent	Each cell can develop into a new individual	Cells from early (1-3 days) embryos
Pluripotent	Cells can form any (over 200) cell types	Some cells of blastocyst (5 to 14 days)
Multipotent	Cells differentiated, but can form a number of other tissues	Fetal tissue, cord blood, and adult stem cells

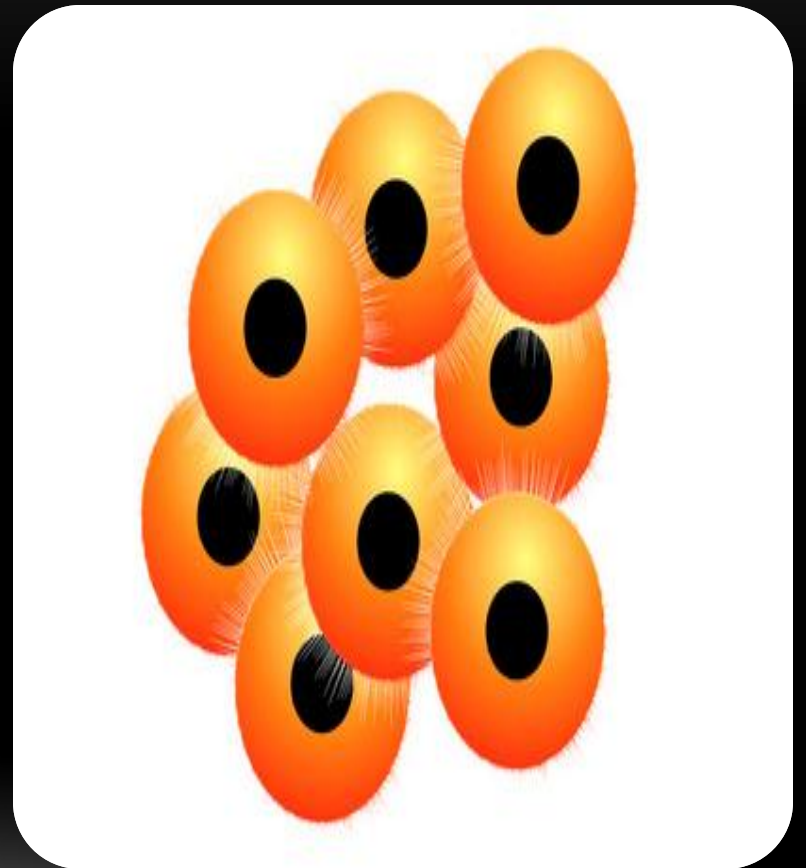
# WHAT'S SO SPECIAL ABOUT STEM CELLS?

- They have the potential to **replace cell tissue** that has been damaged or destroyed by severe illnesses.
- They can replicate themselves over and over for a very long time.
- Understanding how stem cells develop into healthy and diseased cells will assist the search for cures.



# TWO KINDS OF STEM CELLS

- Embryonic (also called “pluripotent”) stem cells are capable of developing into all the cell types of the body.
- Adult stem cells are less versatile and more difficult to identify, isolate, and purify.



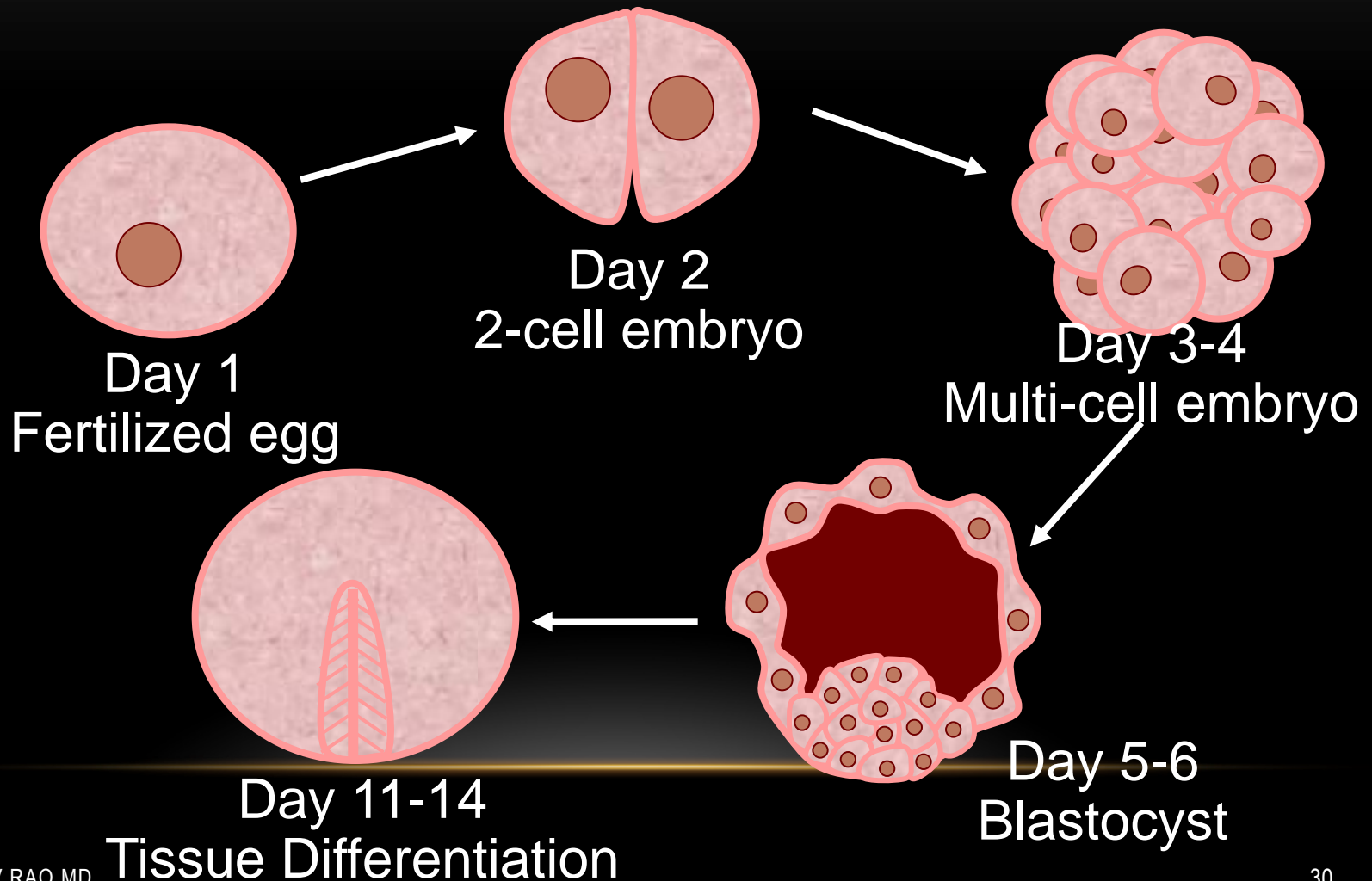
# EMBRYONIC STEM CELLS

**Embryos** are formed in labs that help couples get **pregnant**. An egg and sperm **fertilize** a **zygote** and are inserted into a woman's uterus to develop into an embryo and then **fetus**.

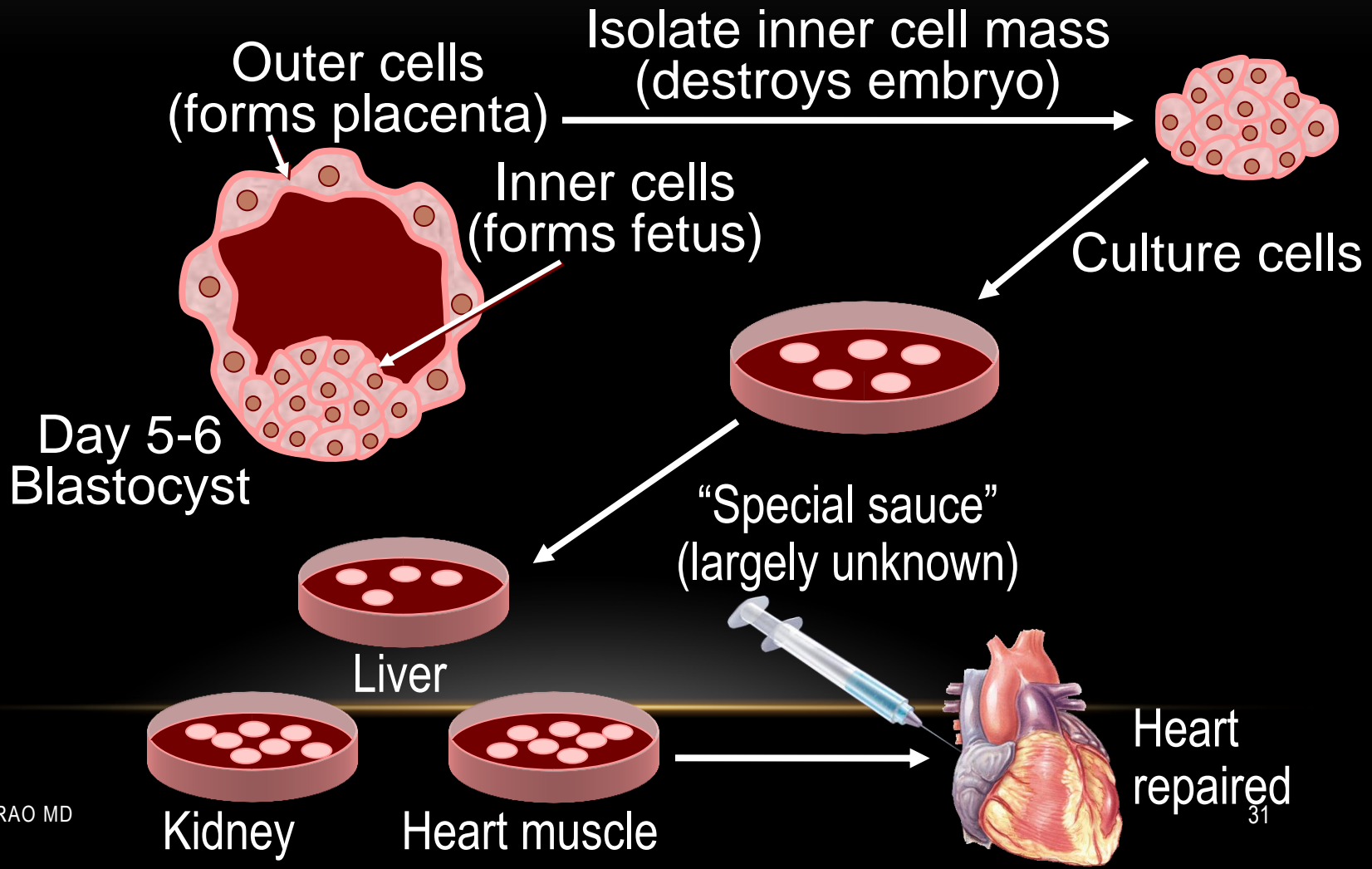


[http://biodidac.bio.uottawa.ca/thumbnails/filedet.htm?File\\_name=HUMN150B&File\\_type=GIF](http://biodidac.bio.uottawa.ca/thumbnails/filedet.htm?File_name=HUMN150B&File_type=GIF)

# STAGES OF EMBRYOGENESIS



# DERIVATION AND USE OF EMBRYONIC STEM CELL LINES

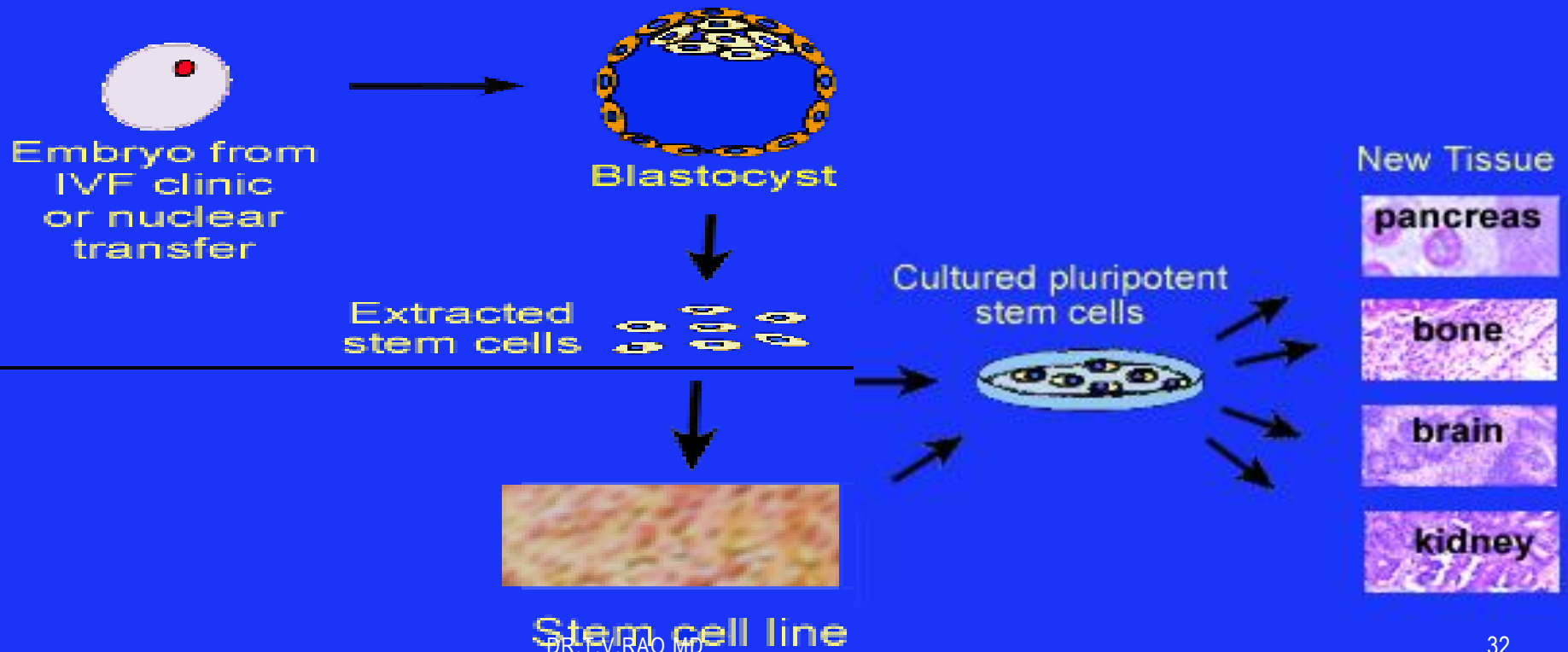


# EMBRYONIC STEM CELLS:

Researchers extract stem cells from a 5-7 days old **blastocyst**.

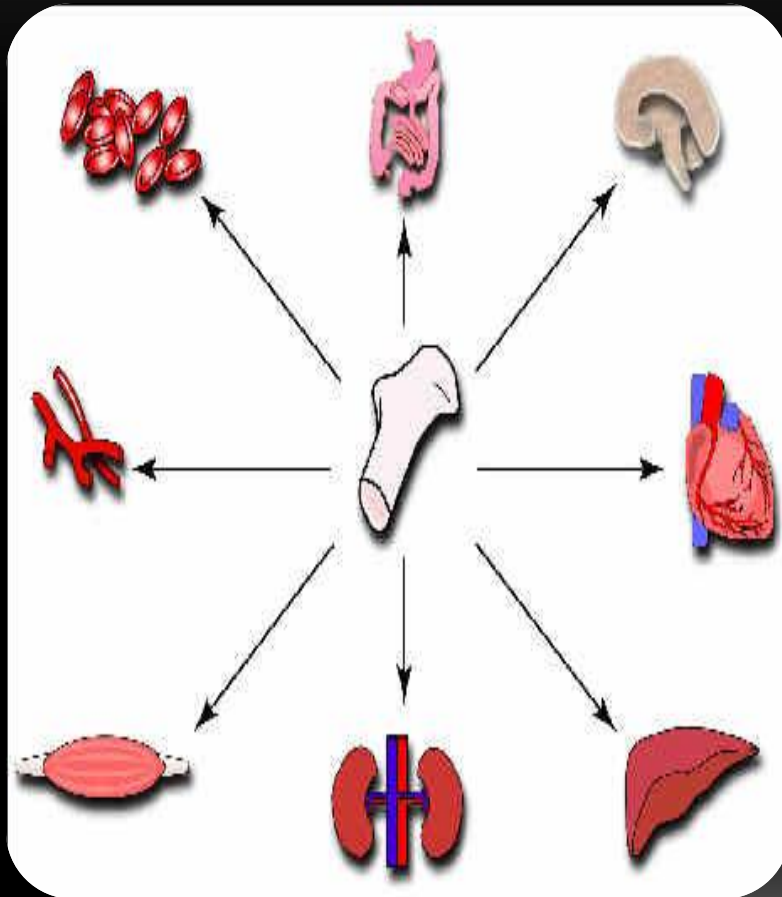
Stem cells can divide in culture to form more of their own kind, thereby creating a stem cell line.

The research aims to induce these cells to **generate healthy tissue** needed by patients.





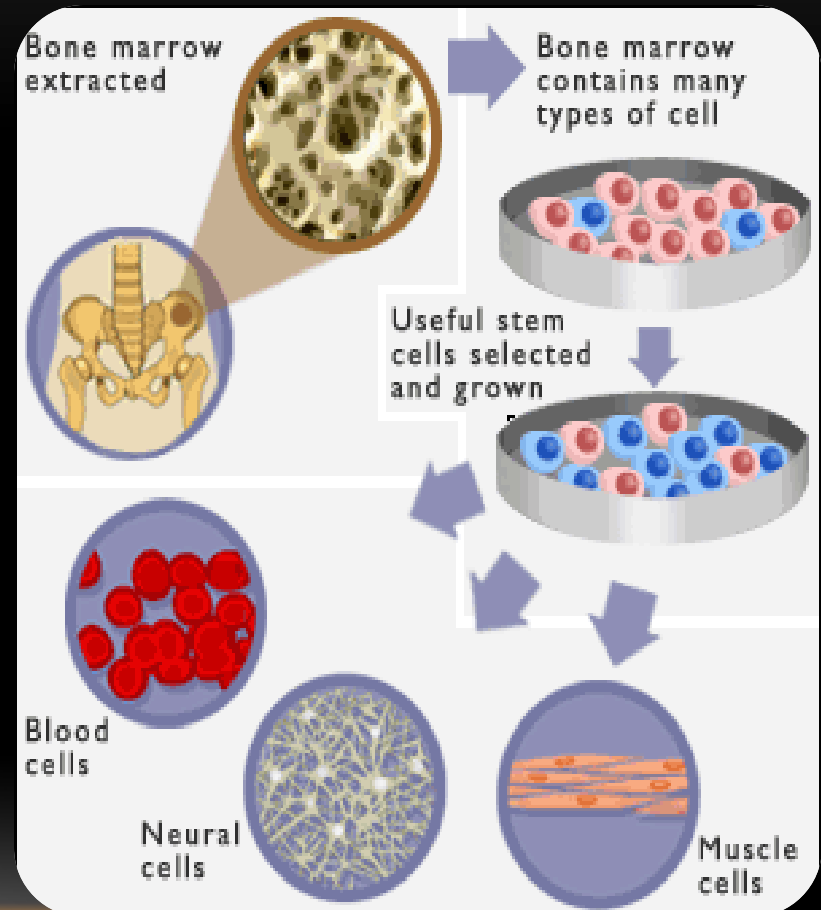
# ADULT STEM CELLS



- Adult stem cells are called **somatic** or body stem cells. Some people call these adult because they are found after an embryo develops into a fetus and are no longer an embryonic stem cell. **Not only adults have adult stem cells!** Some organs are believed to lack stem cells and these cells grow and replace dead cells with **mitosis**.

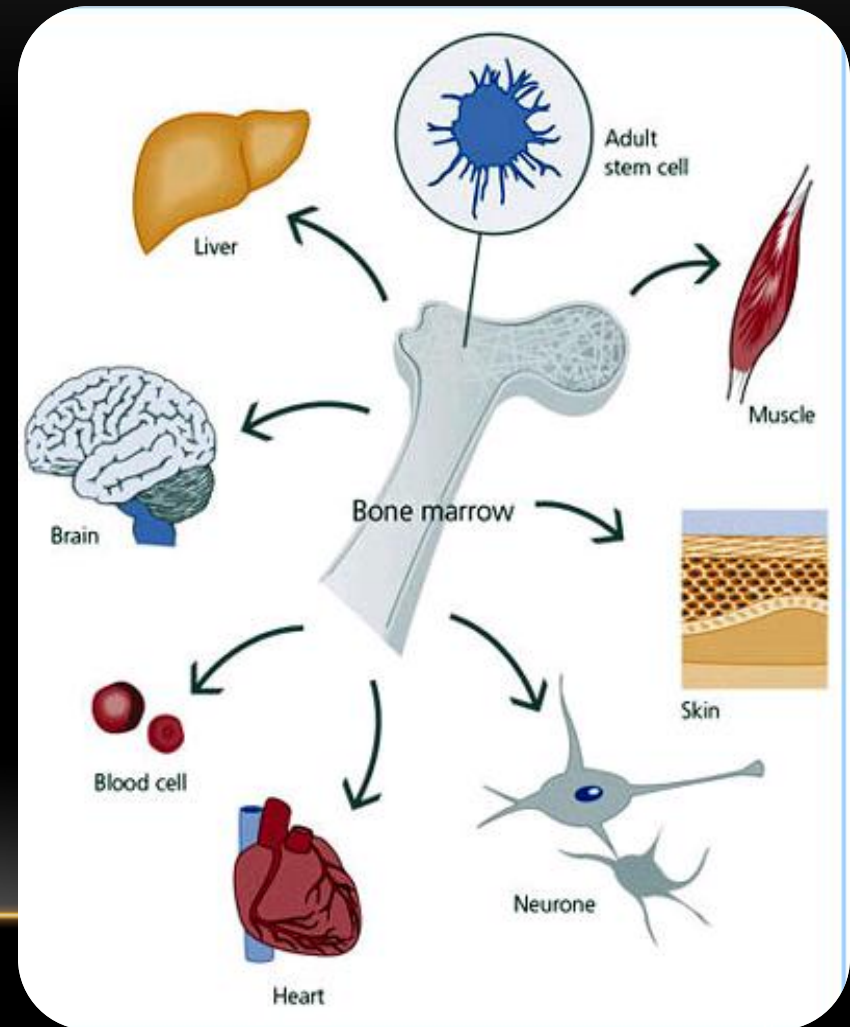
# ADULT STEM CELLS

- Adult stem cells develop into a few cell types. These **Multipotent** cells are used in bone-marrow transplants and will develop into all the blood cells. These cells are important, but some organs may not have adult stem cells and these cells can be difficult to find



# 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
- This procedure is easier, unlike a bone marrow harvest, it can take place outside of an operating room and the patient does not have to be under general anaesthesia.



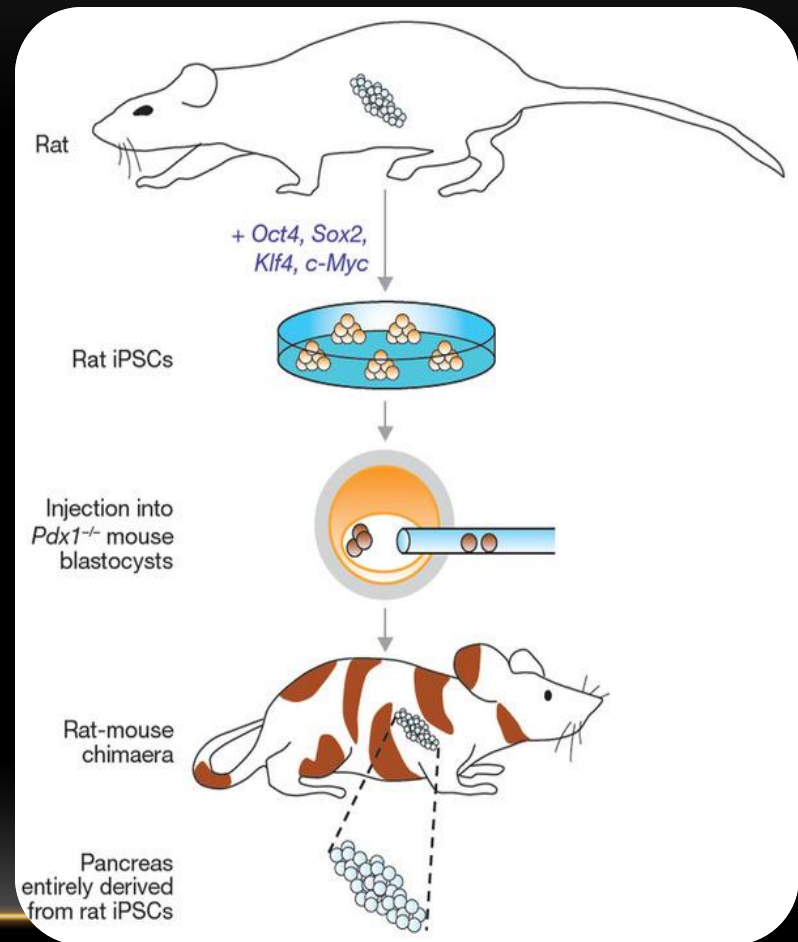
# ALLOGENEIC – STEM CELLS

- 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



# XENOGENEIC - STEM CELLS

- In this stem cells from different species are transplanted, e.g. striatal porcine fetal ventral mesencephalic (FVM) xenotransplants for Parkinson's disease. This has no major ethical concerns and a large amount of tissue is available, however life long immunosuppression and risk of rejection are the major limitations

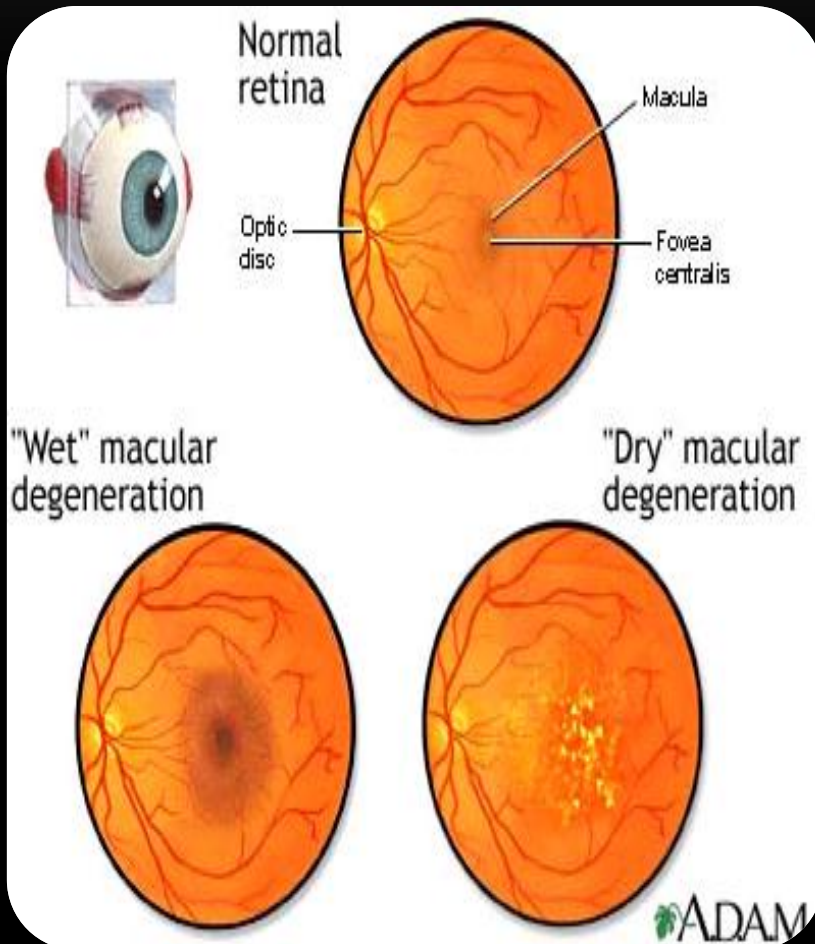


# HOW DOES CELL THERAPY WORK?

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- **Bone marrow transplants** are an example of cell therapy in which the stem cells in a donor's marrow are used to replace the blood cells of the victims of leukemia.
- Cell therapy is also being used in experiments to **graft new skin cells** to treat serious burn victims, and to **grow new corneas** for the sight-impaired.
- **In all of these uses, the goal is for the healthy cells to become integrated into the body and begin to function like the patient's own cells.**

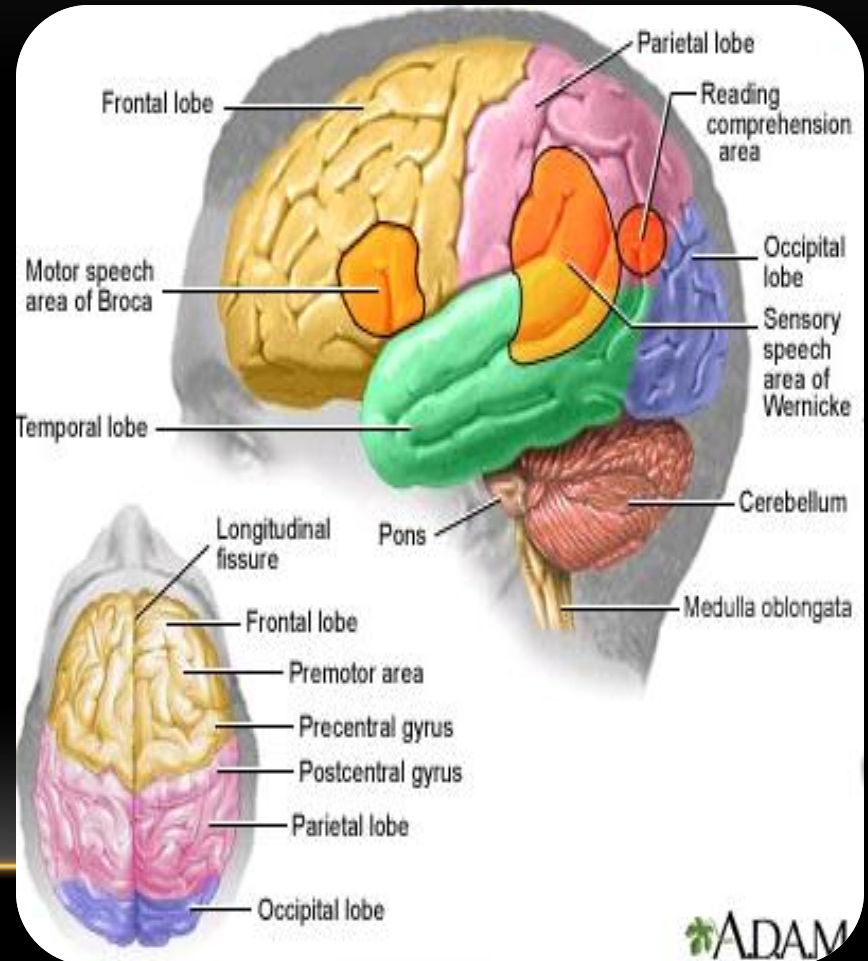
# WHAT DISEASES CAN BE CURED BY STEM CELL THERAPIES



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

# MAJOR PROGRESS IN SEVERAL IMPORTANT HEALTH PROBLEMS

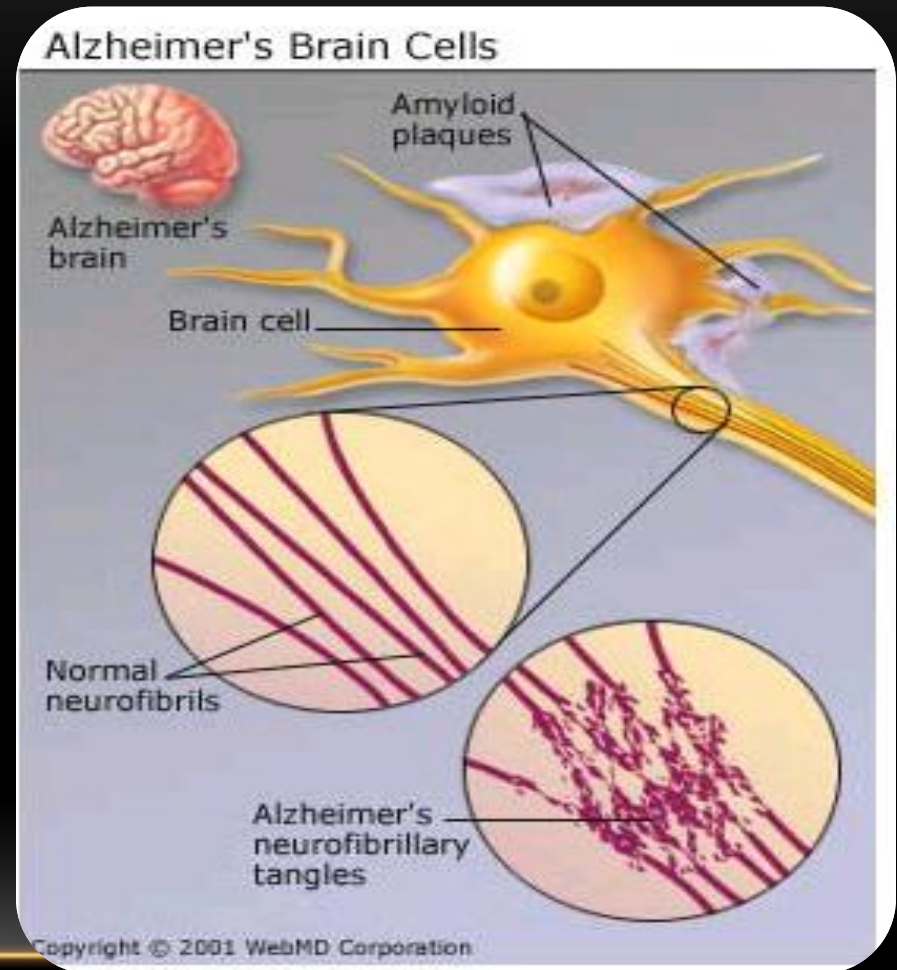
- *Alzheimer's disease*
- **Parkinson's disease**
- *Spinal cord injury*
- **Heart disease**
- *Severe burns*
- **Diabetes**





# ALZHEIMER'S DISEASE AND CAN STEM CELLS HELP?

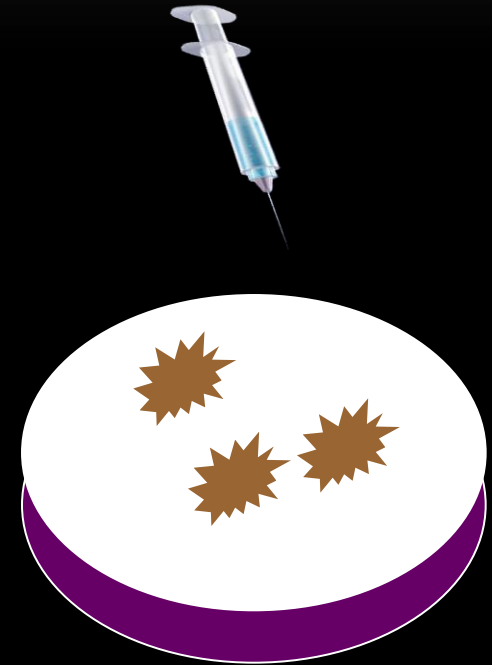
- Stem cells could, however, be genetically modified so as to deliver substances to the Alzheimer brain, to stop cells from dying and stimulate the function of existing cells. A recent clinical trial (Phase I) has shown this approach to be of some benefit to patients with Alzheimer's disease, by slowing down the progression of the disease.



# DRUG TESTING

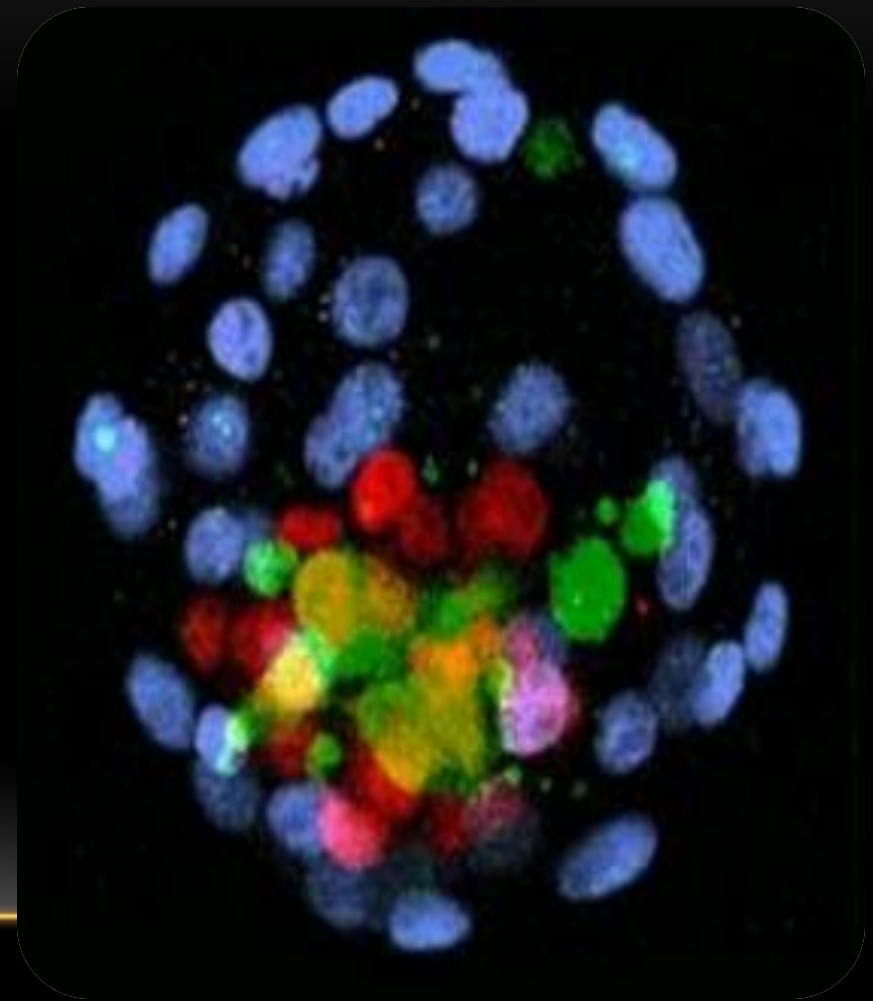
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- Stem cells could allow scientists to test new drugs using human cell line which could speed up new drug development.
- Only drugs that were safe and had beneficial effects in cell line testing would graduate to whole animal or human testing.
- It would allow quicker and safer development of new drugs.



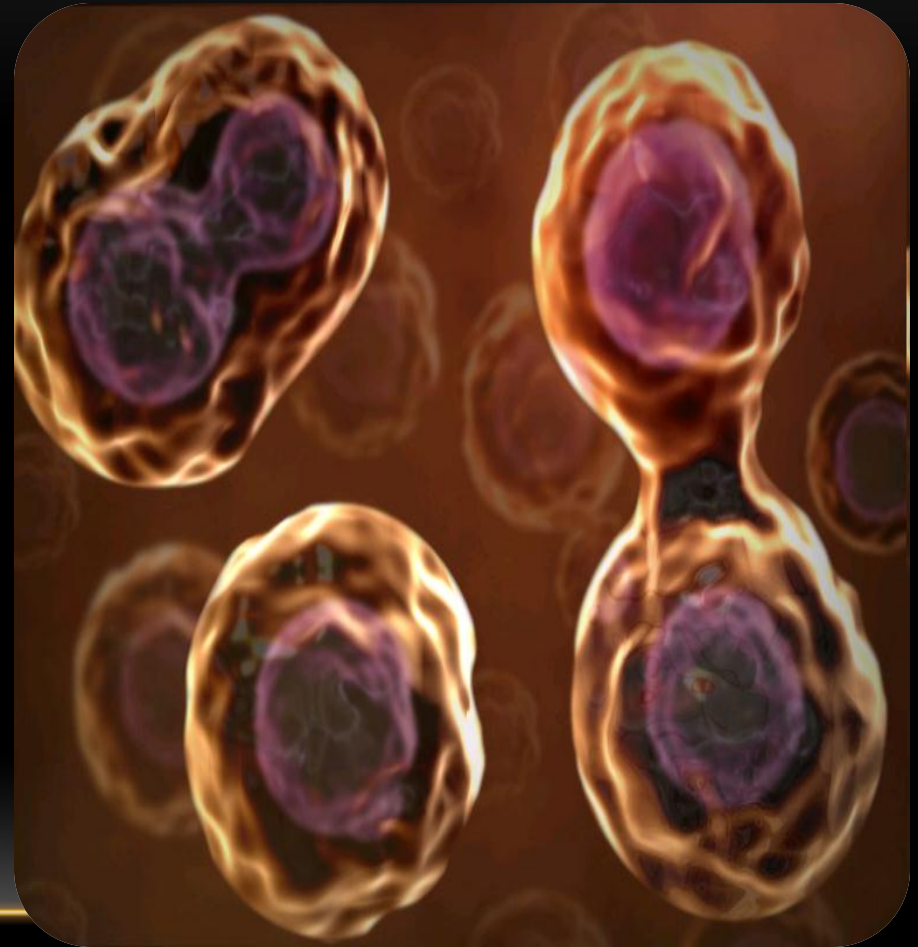
# MAJOR TYPES OF STEM CELLS

- The two broad types of mammalian stem cells are: **embryonic stem cells** that are isolated from the inner cell mass of blastocysts, and **adult stem cells** that are found in adult tissues. In a developing embryo, stem cells can differentiate into all of the specialized embryonic tissues. |



# STEM CELLS ACT AS PROGENITOR CELLS

- In adult organisms, stem cells and **progenitor cells** act as a repair system for the body, replenishing specialized cells, but also maintain the normal turnover of regenerative organs, such as blood, skin or intestinal tissues.



# HISTORY OF ANIMAL CLONING

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- Since, then, animals including mice (1998), cows (1998), pigs (2000), cats (2001), and rabbits (2002) were successfully cloned.

MOUSE

Cattle

PIG

CAT

RABBIT

# HOW SUCCESSFUL WAS ANIMAL CLONING? VERY LOW (~1-3%)

Dolly ( <b>sheep</b> )	1 live birth out of 29 cloned embryos	3%
Cloned <b>mice</b>	31 live births out of 2468 cloned embryos	1%
Cloned <b>pigs</b>	5 live births out of 335 cloned embryos	1%
Cloned <b>goats</b>	3 live births out of 85 cloned embryos	3%
Cloned <b>cattle</b>	30 live births out of 496 cloned embryos	6%
Cloned <b>cat</b>	1 live birth out of 87 cloned embryos	1%
Cloned <b>rabbits</b>	6 live births out of 371 of cloned embryos	1%

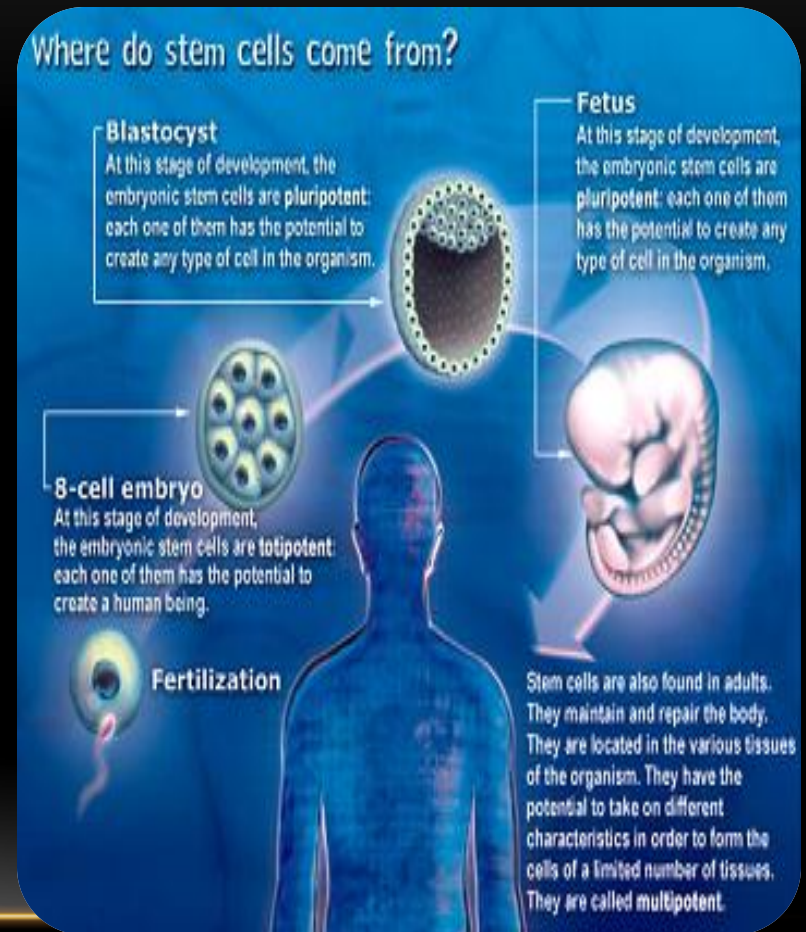
# FIRST SUCCESS OF HUMAN EMBRYO CLONING

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- **On February 12, 2004, South Korean scientists, Dr. Woo Suk Hwang and Dr. Shin Young Moon of Seoul National University, reported the successful creation of 30 cloned human embryos developed to the blastocyst stage and then destroyed by stem cell extraction, yielding one embryonic stem cell line.**

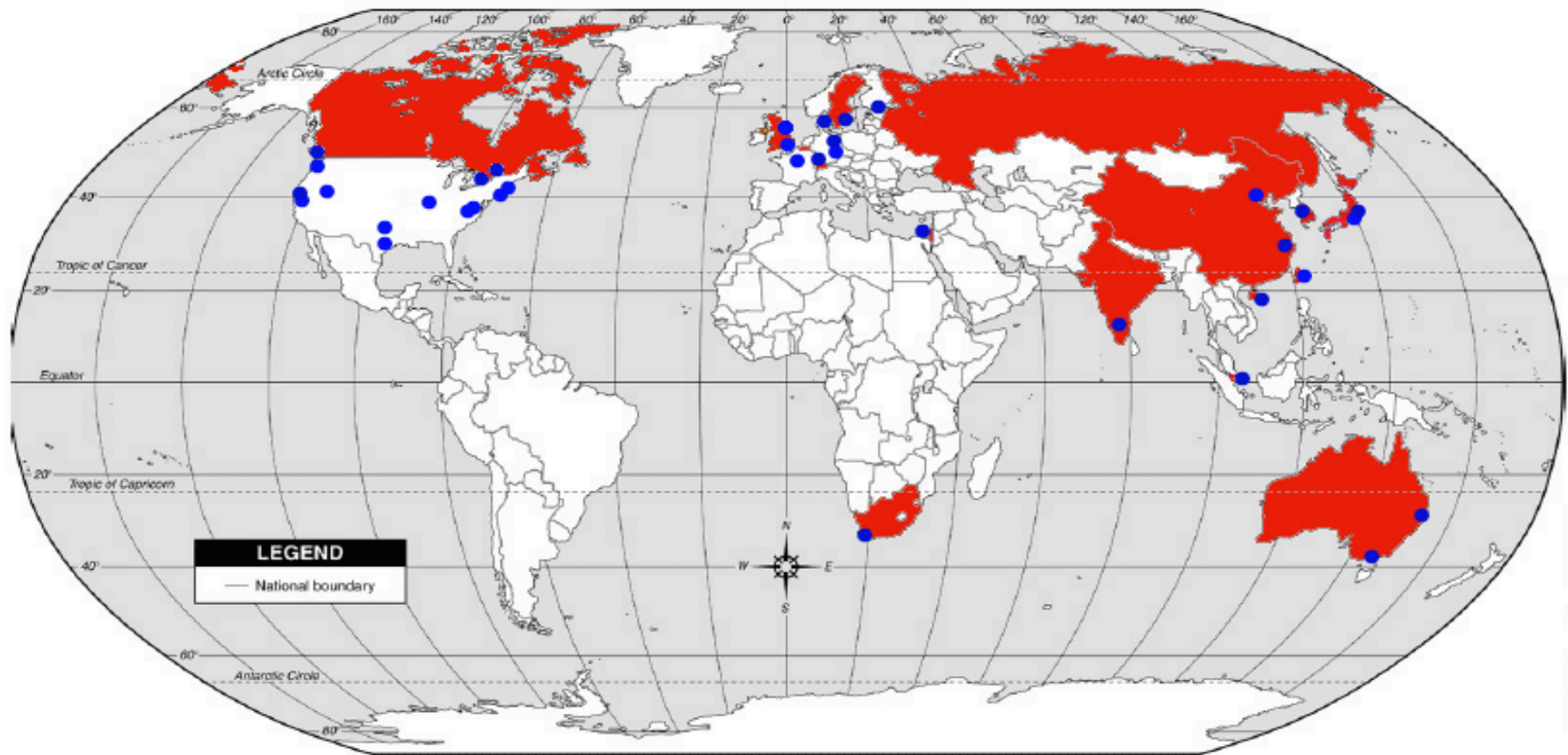
# SOURCE OF STEM CELLS FOR MEDICAL THERAPIES

- Tens of thousands of frozen embryos are routinely destroyed when couples finish their treatment.
- These surplus embryos can be used to produce stem cells.
- Regenerative medical research aims to develop these cells into new, healthy tissue to heal severe illnesses.





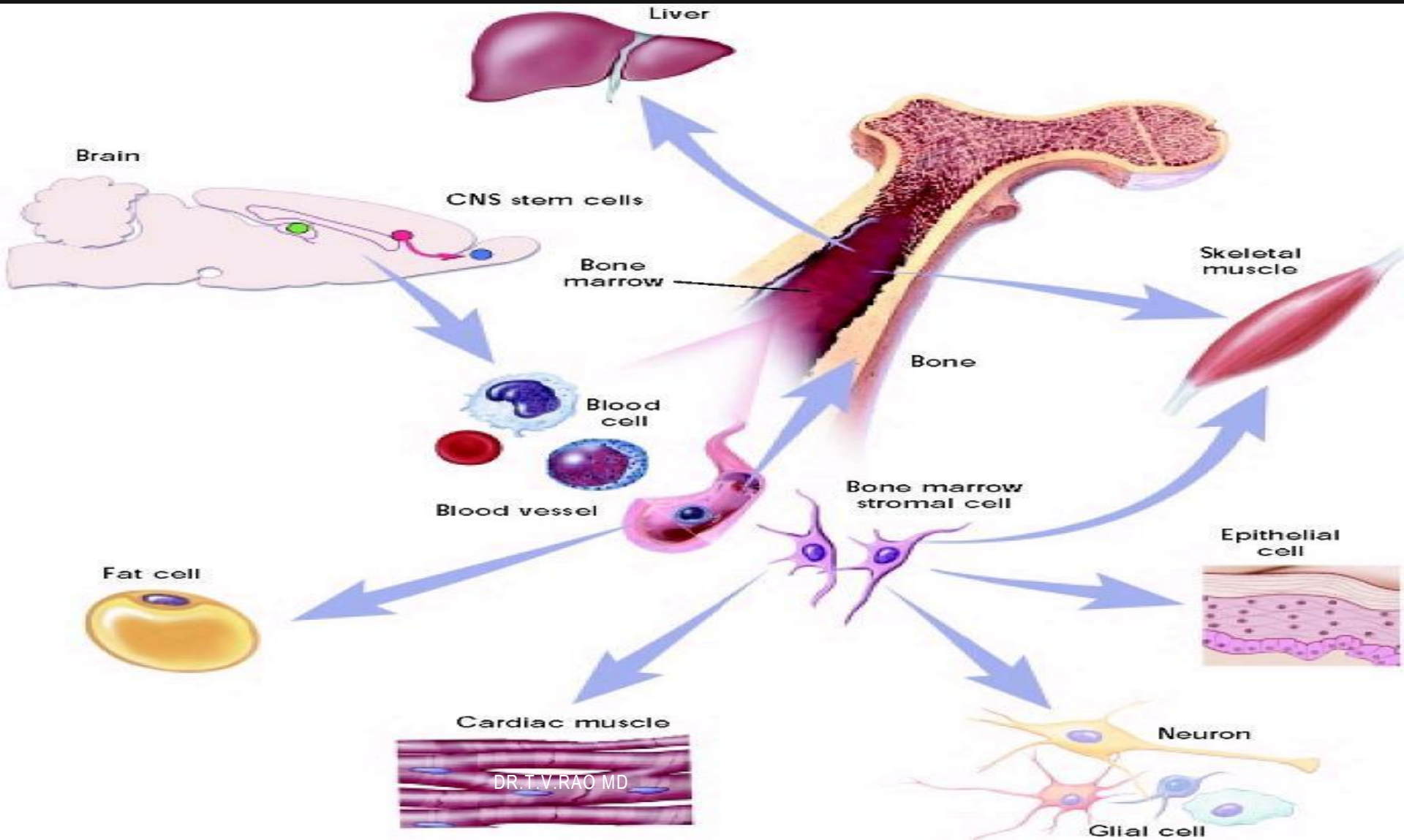
# STEM CELL RESEARCH WORLDWIDE



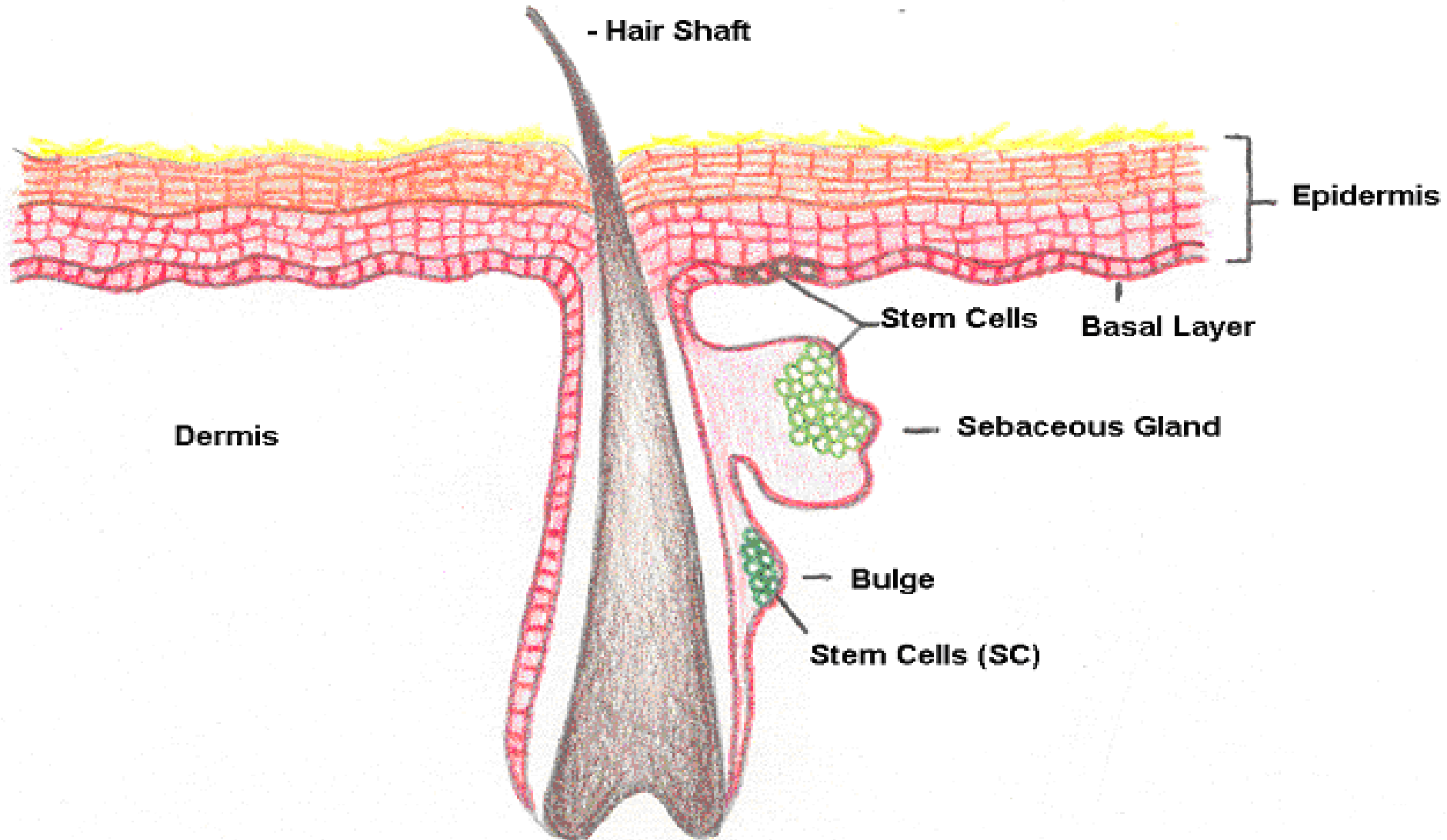
Countries with a permissive or flexible policy on embryonic stem cell research (in red)

- Denotes Genome Sequencing Center

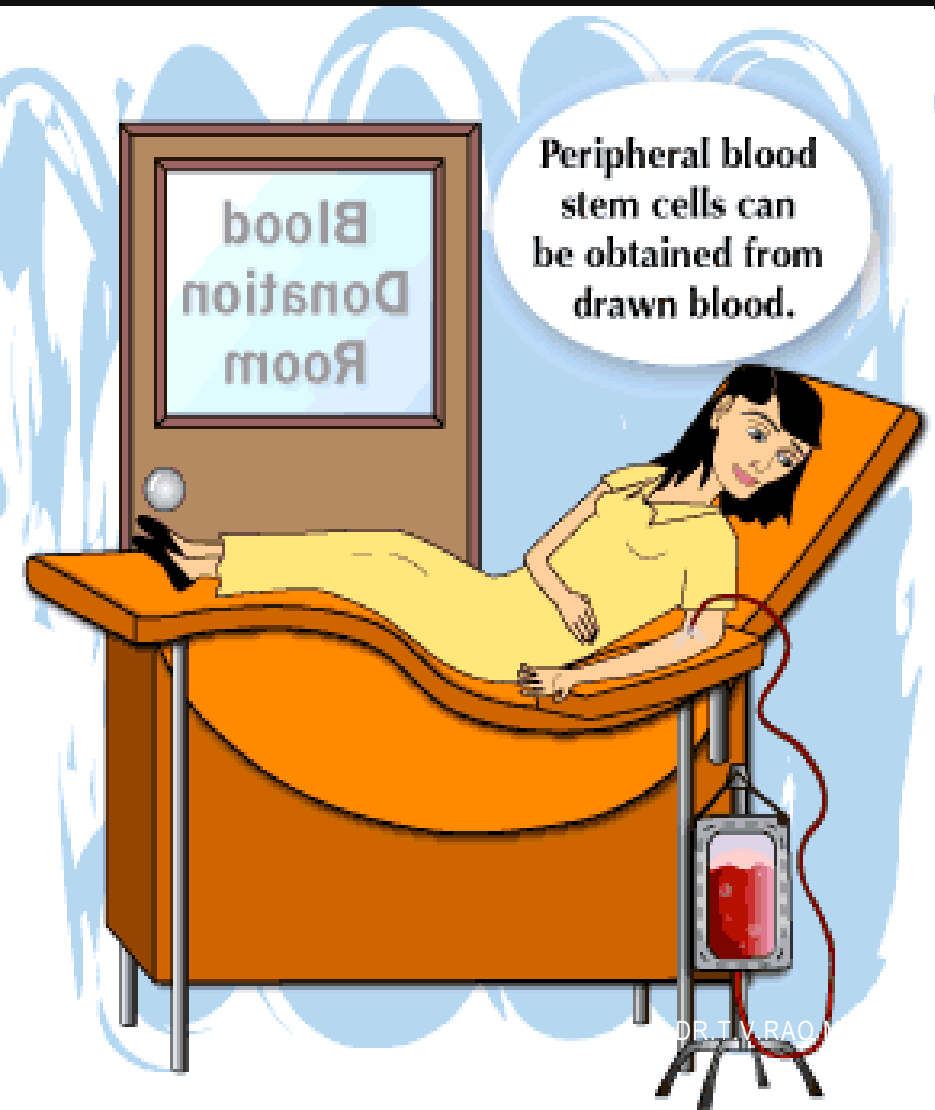
# ADULT MULTIPOTENT STEM CELLS



# Adult Stem Cells



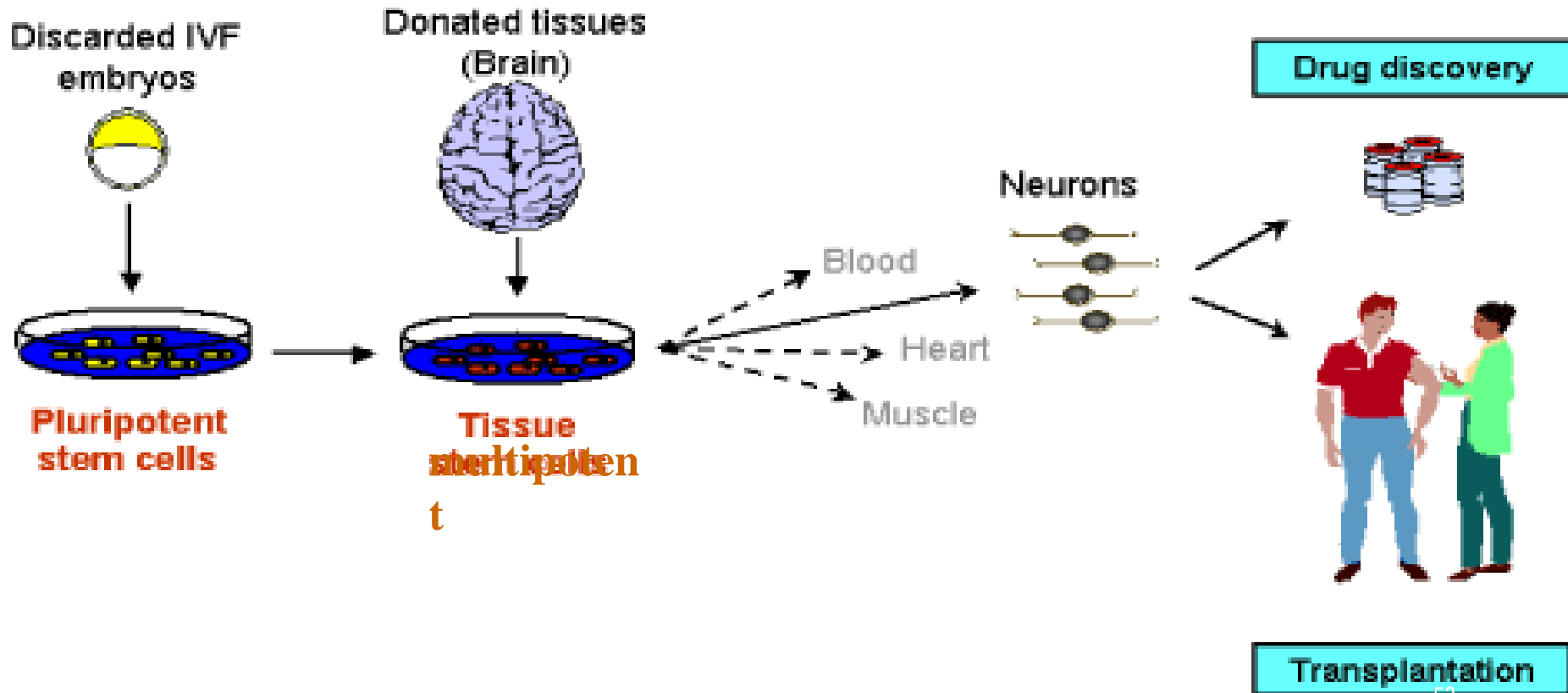
# AUTOLOGOUS – STEM CELLS



- While most blood stem cells reside in the bone marrow, a small number are present in the bloodstream. These Multipotent peripheral blood stem cells, or PBSCs, can be used just like bone marrow stem cells to treat leukaemia, other cancers and various blood disorders

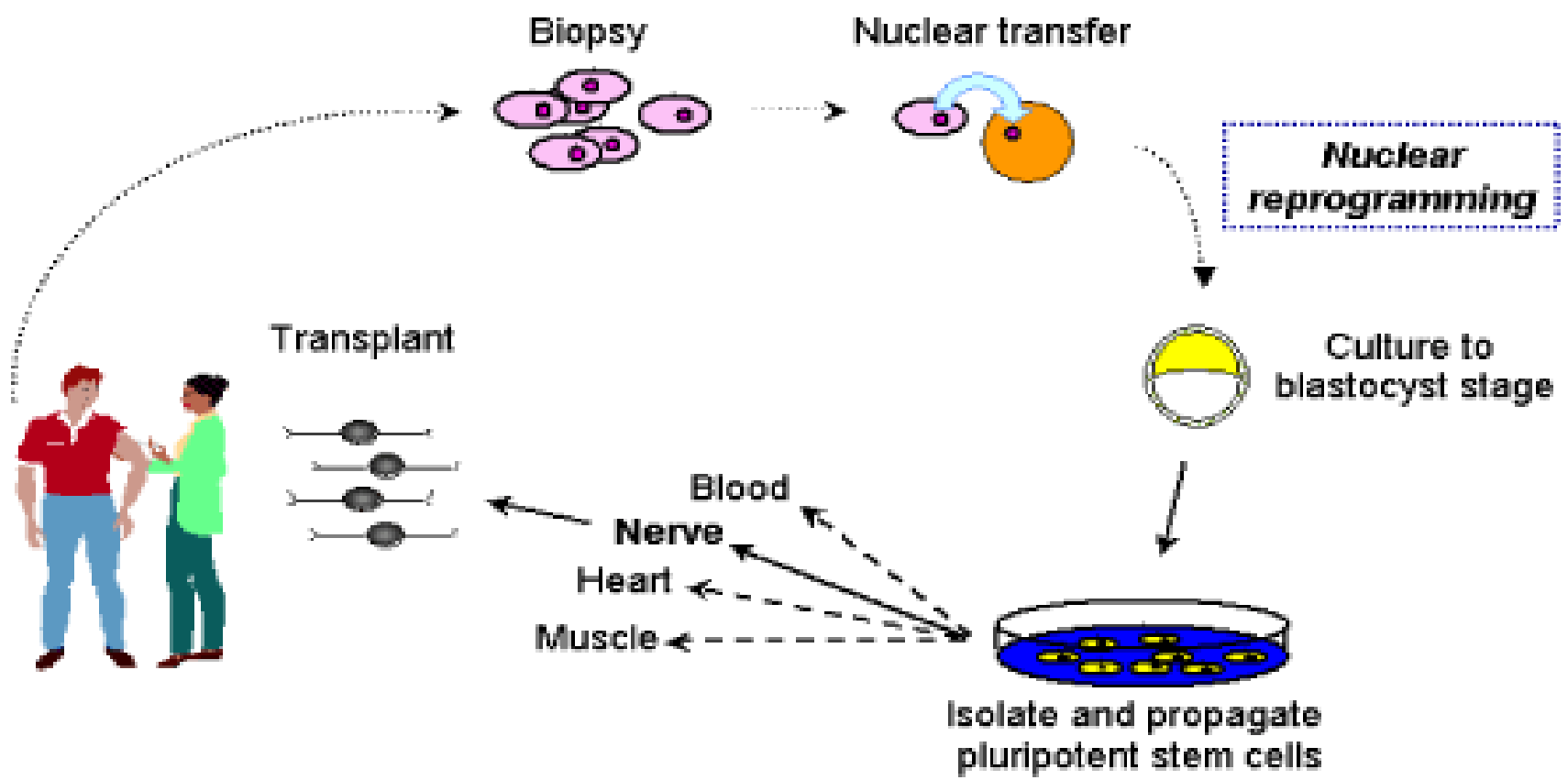
# Speculation

## Stem Cell Medicine



# TREATMENTS BECOMES SPECIFIC

## Patient-Specific Stem Cell Therapy



# APPLICATIONS OF STEM CELLS

- **Cell Replacement Therapies**
  - Cells could be stimulated to develop into specialized cells that represent renewable sources of cells and tissue for transplantation.
  - Cell replacement therapy could treat injuries and various genetic and degenerative conditions including muscular dystrophies, retinal degeneration, Alzheimer disease, Parkinson's disease, arthritis, diabetes, spinal cord injuries, and blood disorders such as hemophilia.

# UNDERSTANDING CELL SPECIALIZATION

- Studying human pluripotent stem cells can lead to the identification of factors responsible for differentiation of stem cells into specialized cell types.
  - these factors may ultimately be used to drive tissue regeneration and repair if administered therapeutically.
- This work will provide basic knowledge on cell determination and differentiation, human development, genomic imprinting and somatic cell aging.



# DEVELOPMENT AND TESTING OF DRUGS

- Researchers could study the beneficial and toxic effects of new medications on human pluripotent stem cells that have been developed to mimic the disease processes.



# CAN SEX MAKE DIFFERENCE IN STEM CELL THERAPY ?

- Are there sex-specific differences in the biology of stem cells? (short-long term)
- • How do sex-specific differences play out in terms of self-renewal and differentiation? (mid-long term)
- Is there existing evidence that the sex of stem cells affects success of the transplant?

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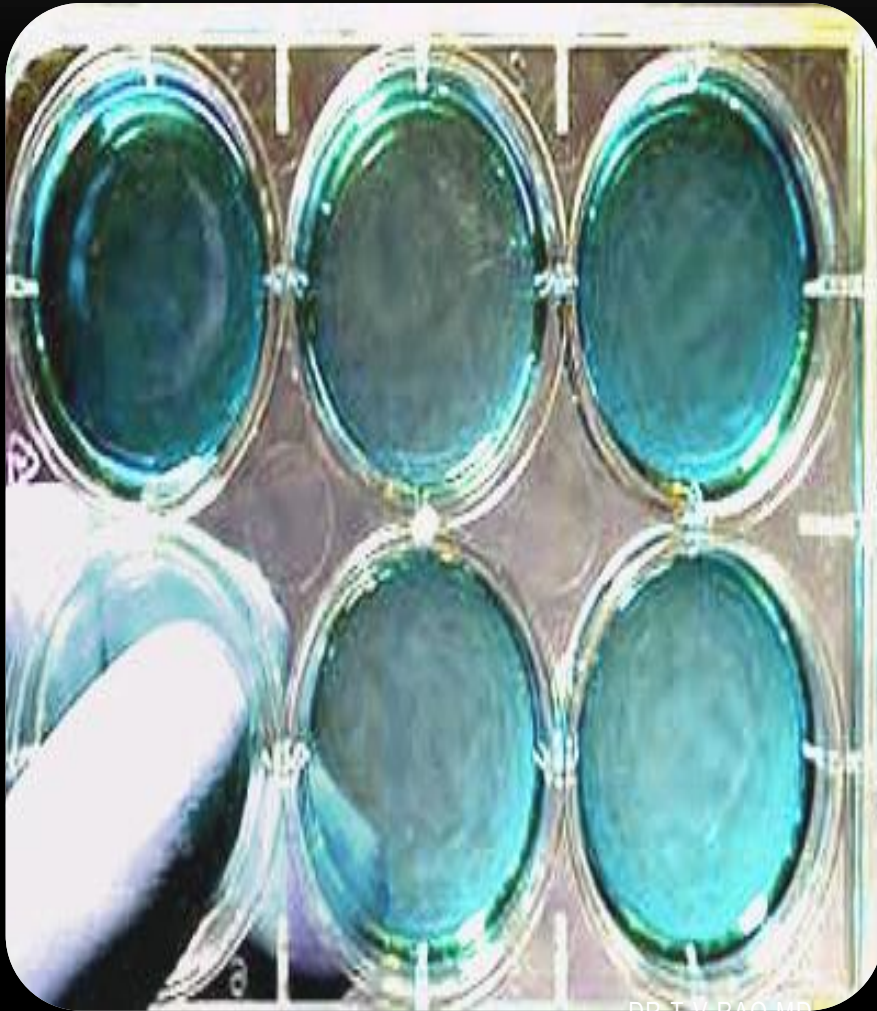
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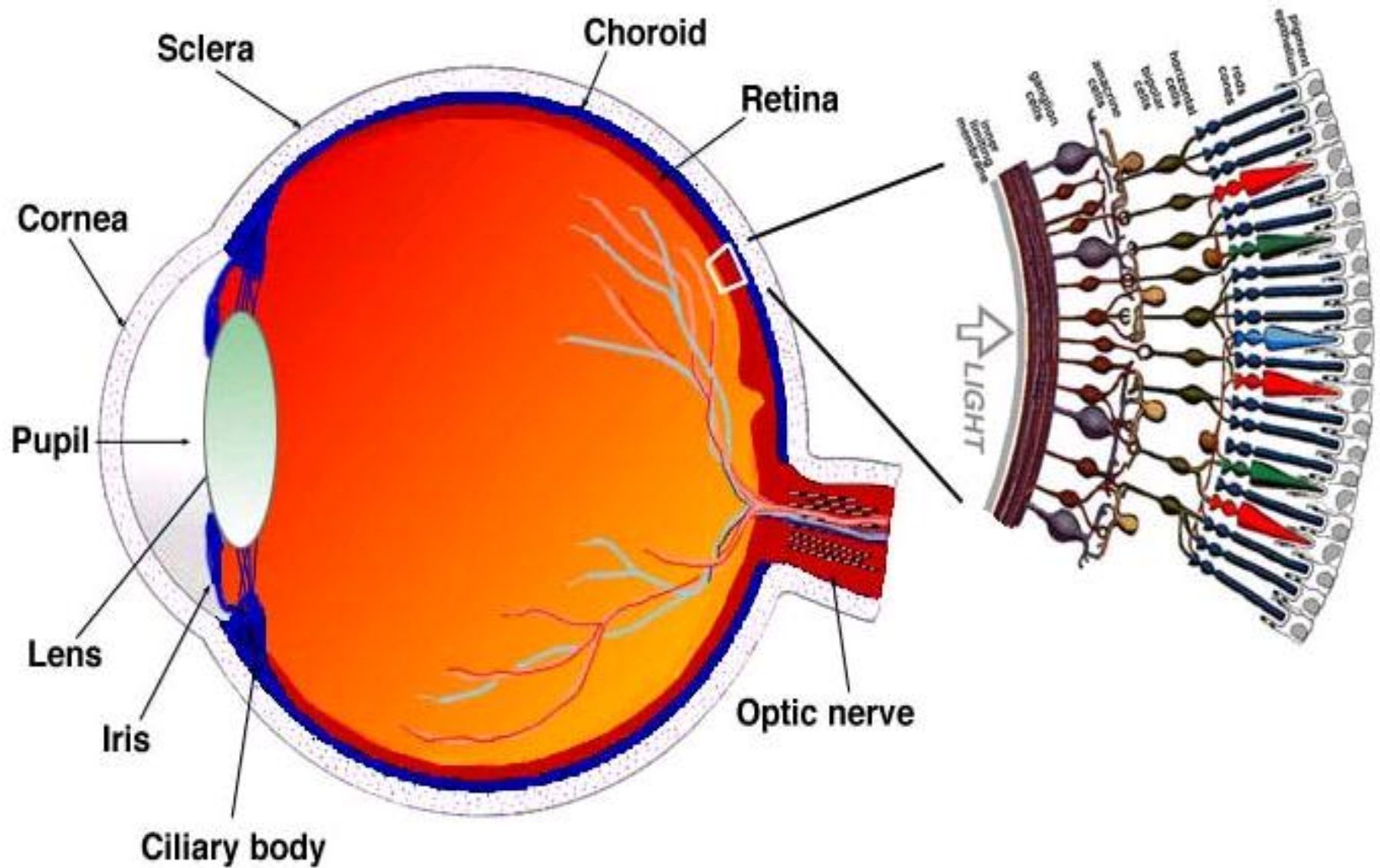


# STEM CELLS – BLINDNESS



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- In clinical trials at Moorfields Eye Hospital in London, surgeons restored eye sight for six patients who lost their sight after chemical accidents and genetic diseases. The patients went under successful stem-cell transplant.



**Fig. 1.1.** A drawing of a section through the human eye with a schematic enlargement of the retina.

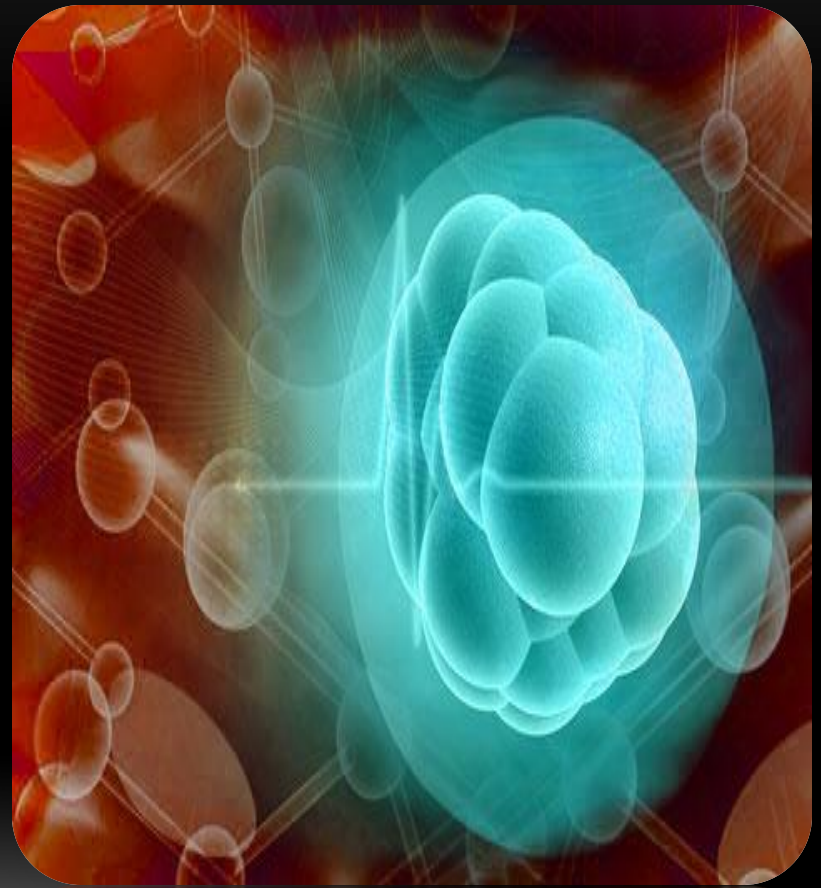
# LIMBAL STEM CELL THERAPY

- The treatment is known as limbal stem cell therapy, and the patients who received the treatment suffered from chemical burn or genetic disease know as aniridia
  - By replacing the limbal stem cells, the cornea begins to clear up as the cells are replaced with the healthy transparent layer again.



# CURRENT POSSIBLE USES

- Research in stem cells has opened up new horizons in the area of treatment of disorders such as stroke, epilepsy, neurodegeneration and trauma. Current research is aimed at finding the appropriate source of stem cells for a given indication, ways of expanding and perpetuating these cells in culture, best route of administration of these cells and methods to overcome rejection



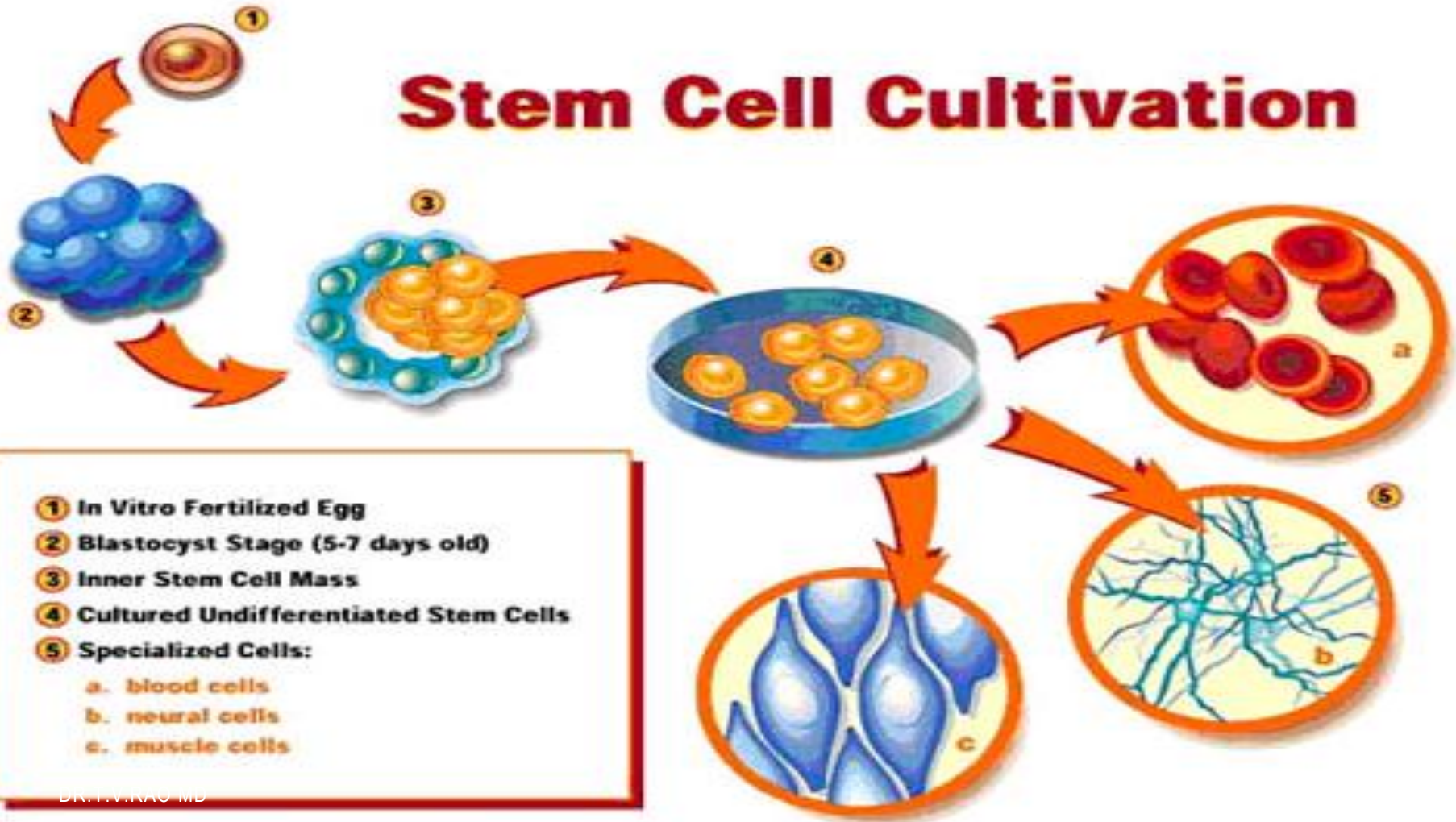
# POSSIBLE USES OF STEM CELL TECHNOLOGY

- Replaceable tissues/organs
- Repair of defective cell types
- Delivery of genetic therapies
- Delivery of chemotherapeutic agents



# FUTURE –MAKING CELLS AND REPLACING THE DISEASED CELLS ?

## Stem Cell Cultivation





# STEM CELL DEBATE

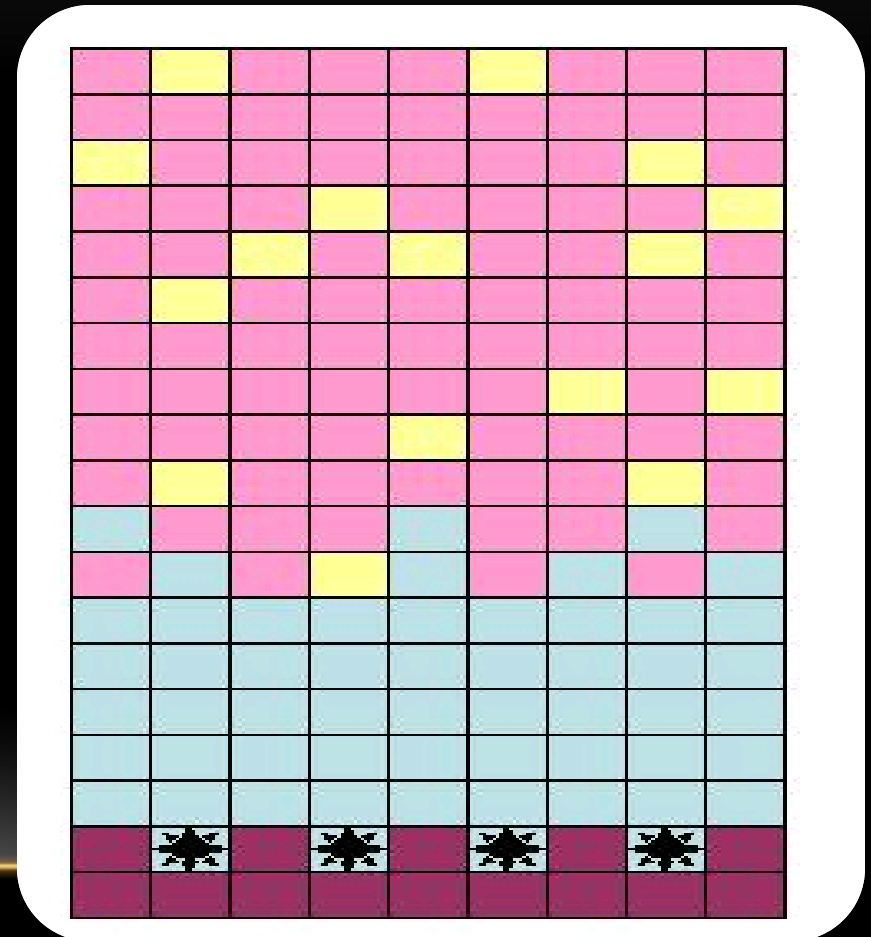
Some people **oppose** stem cell research because they believe that the 4-5 day old ball of cells is a **living human being**. What some do not understand is that **unused embryos** are trashed regardless. Many people, religious and non-religious, believe it is better to use these embryos for research on how to cure human diseases rather than to just trash them without **purpose**. The underlying issue is **the personal belief when life actually begins**.

# OBSTACLES OF STEM CELL RESEARCH

- How to find the right type of stem cells?
- How to put the stem cells into the right place?
- Will the stem cells perform the desired function in the body?
- Differentiation protocols for many cell types have not been developed.

# EMBRYONIC STEM CELLS ARE UNSTABLE AND MUTATE IN CULTURE

- Like ordinary cells, stem cells accumulate significant numbers of **mutations** over time, including several that could cause them to become tumors



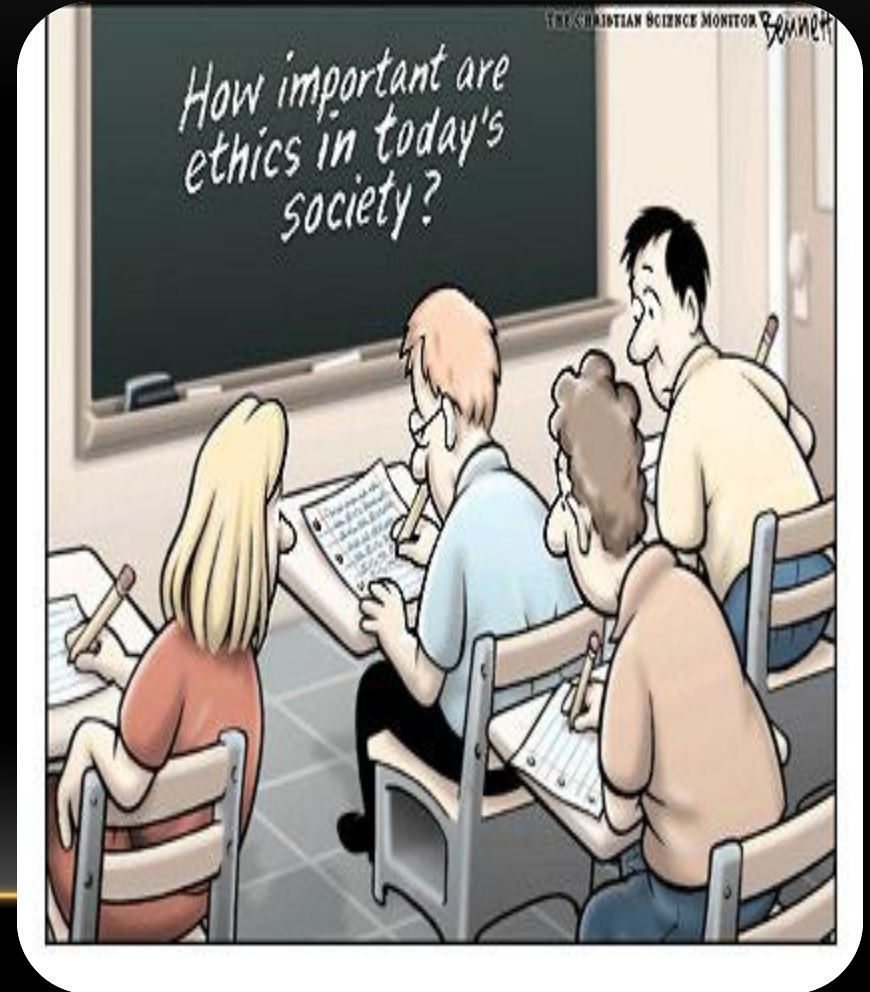
# ETHICAL DEBATE

- Harvesting ES cells destroys the blast cyst
- “This is murder”
- ES cell research requires human cells
- Could create a commercial market for human cells
- “This devalues life”



# DESTROYING LIFE TO CURE SOME ONE – ETHICAL ?

- If stem cells have such potential to relieve suffering, why are so many people so upset about their use? The reason is that the most powerful type of stem cell ❖ embryonic stem (ES) cells ❖ can only be obtained from human embryos. Many people think that it's wrong to create and destroy human embryos to treat disease



# RELIGIOUS DEBATE OVER HARVESTING EMBRYONIC STEM CELLS

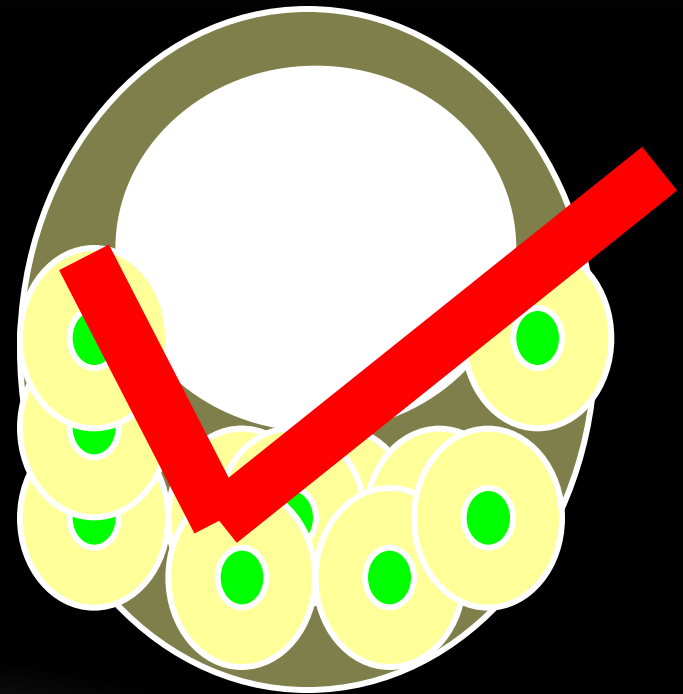
- The pro-life group generally believes that:
  - Personhood happens at, or shortly after, conception.
  - Thus, they consider the removal of stem cells from an embryo -- a procedure which kills the stem cells - - to be a form of murder of a human being.
  - They argue that no potential health benefits to even hundreds of millions of people can justify the murder of other humans.



**Day 5-6  
Blastocyst**

# RELIGIOUS DEBATE OVER HARVESTING EMBRYONIC STEM CELLS

- **The pro-choice group generally believes that:**
  - Personhood is attained much later in pregnancy, perhaps when the fetal brain develops consciousness during the third trimester.
  - Thus, extracting stem cells from an five or ten-day old pre-embryo is not murder.
  - Killing a pre-embryo, which is only a potential human being, is justified if it has the potential to cure diseases and extend the lives of people.



**Day 5-6  
Blastocyst**

# WHY WE SHOULD SUPPORT *CAN HELP SEVERAL DISABLED*

- Human embryonic stem cell (HESC) research offers great promise of cures for otherwise incurable conditions: spinal cord injuries, ALS, Alzheimer's, Parkinson's, etc.





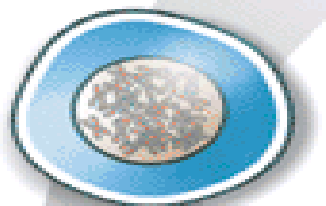
# How therapeutic cloning could work

Cloning human tissue has never been done, but one way it might be performed:

**1** Skin cell is taken from patient's body. Its nucleus contains the patient's genetic code.



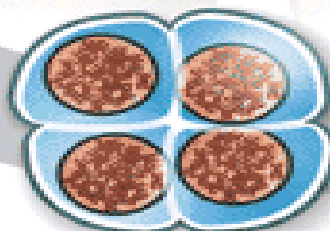
**2** Unfertilized human egg cell's nucleus is removed.



**3** Skin cell DNA inserted into enucleated egg.

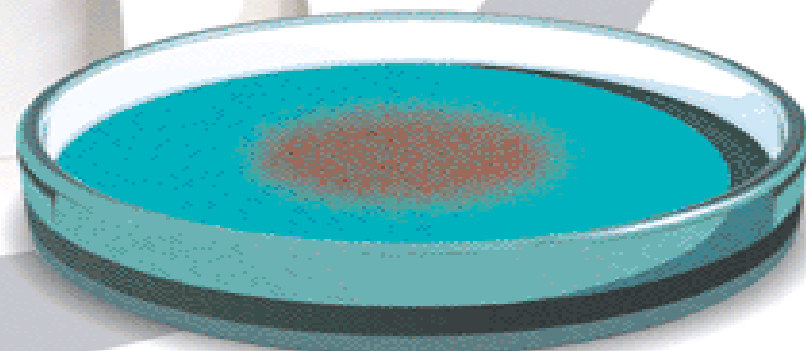


**4** Egg divides, creating stem cells.



**6** Cultured tissue cells could then be injected into patient. New, healthy cells would replace diseased or damaged body tissue, healing the patient. Patient's body wouldn't reject the cells because they would contain the patient's DNA.

**5** Stem cells would be grown in a culture dish, where they could be turned into specific tissue types such as heart or nerve cells.



# SHALL BE CLONE HUMANS ?

- Arguments for and against human cloning research. Should we ban human cloning? Why investors are moving away from human cloning and why human cloning now looks a last-century way to fight disease. Why some people want to clone themselves or even to clone the dead.



# FUTURE APPLICATIONS

Stem Cells may one day help scientists to regenerate cells lost in diseases like:

- Repair heart muscle after a heart attack
- Pancreas cells lost in diabetes
- Neurons lost in Alzheimer's
- Retinal cells causing blindness
- Understand the cell growths of cancers
- Help organ transplantation

# RESEARCH ON STEM CELLS IS PROGRESSING IN SPITE OF SEVERAL RESTRICTIONS



# ARE WE CROSSING OUR LIMITS IN SCIENCE ???



- Programme created by Dr.T.V.Rao MD from several web based and documented information for Medical and Paramedical Professionals in the Developing World

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