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Introuduction to Stem Cell Research

BY :

Dr. Mona Elsafadi

Introducing....stem cells!

Parkinson's disease

IVF

SCNT

Human eggs

Drug research

Cure

Grow

iPS cells

Stem cells

Research

Ethical

Pluripotent

Embryo

Leukaemia

Backlash

treatment

Cloning

Hope

Controversy

Cord blood

ART

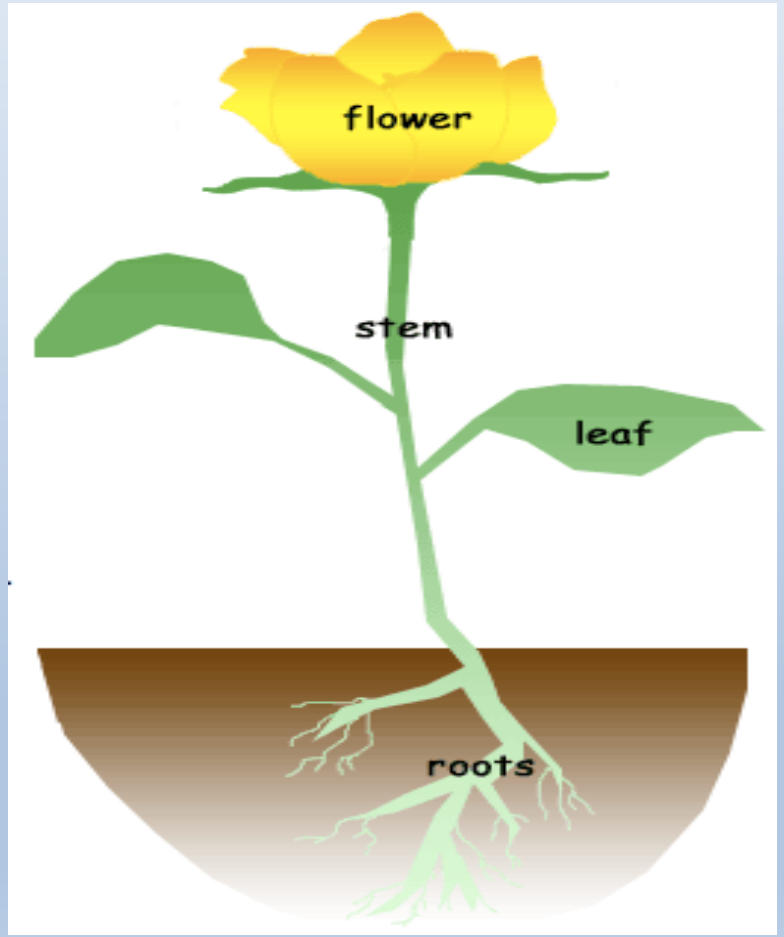
Debate

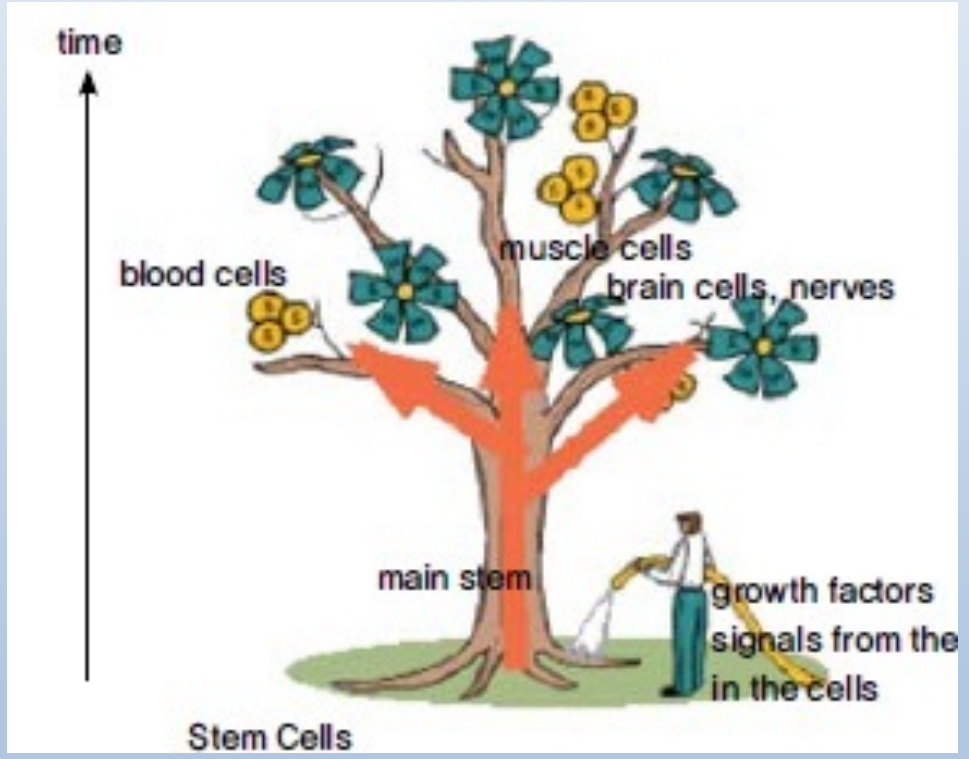
Therapy

BREAKTHROUGH!

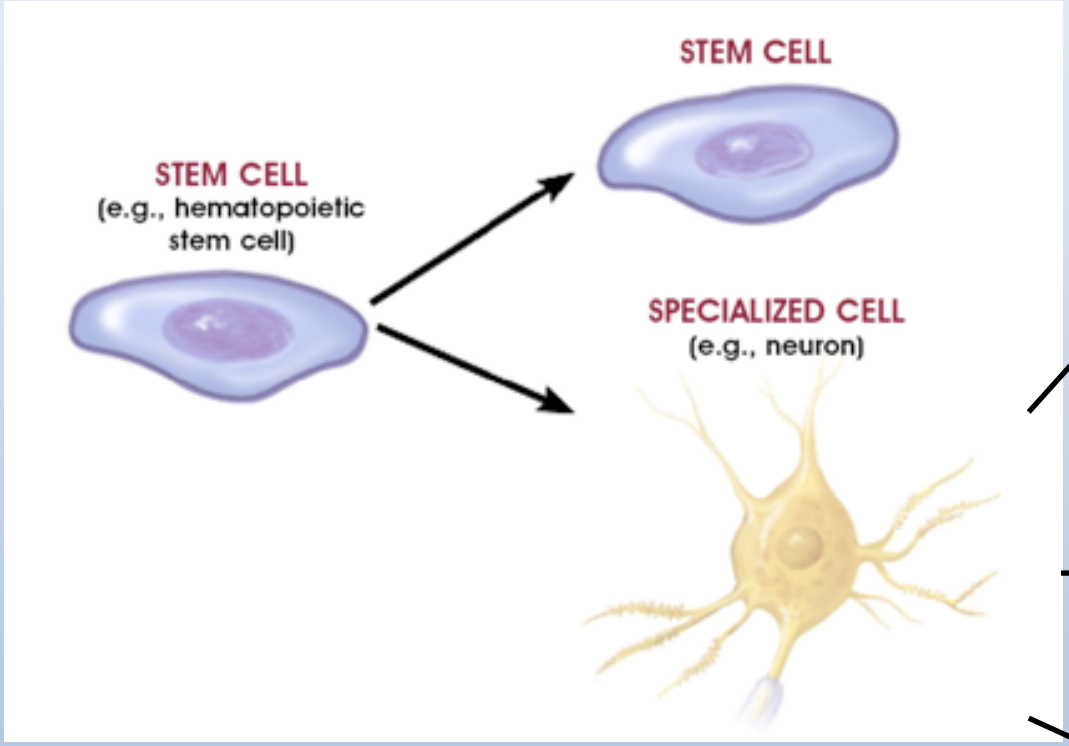

cure

Stem Cells

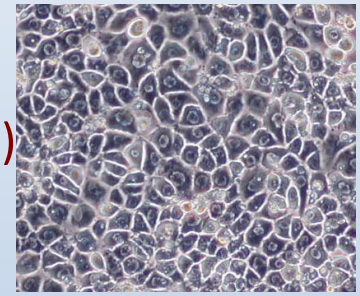

flower
stem
leaf
roots


time
blood cells
muscle cells
brain cells, nerves
main stem
growth factors
signals from the
in the cells
Stem Cells

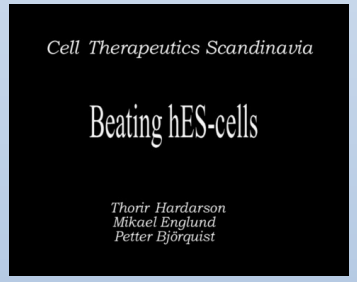
Unique Characteristics of Stem Cells



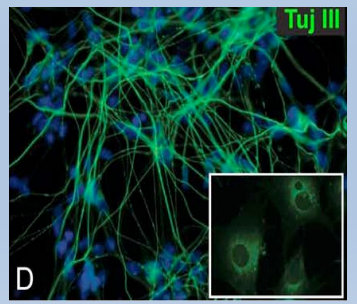
Endoderm (hepatocytes)



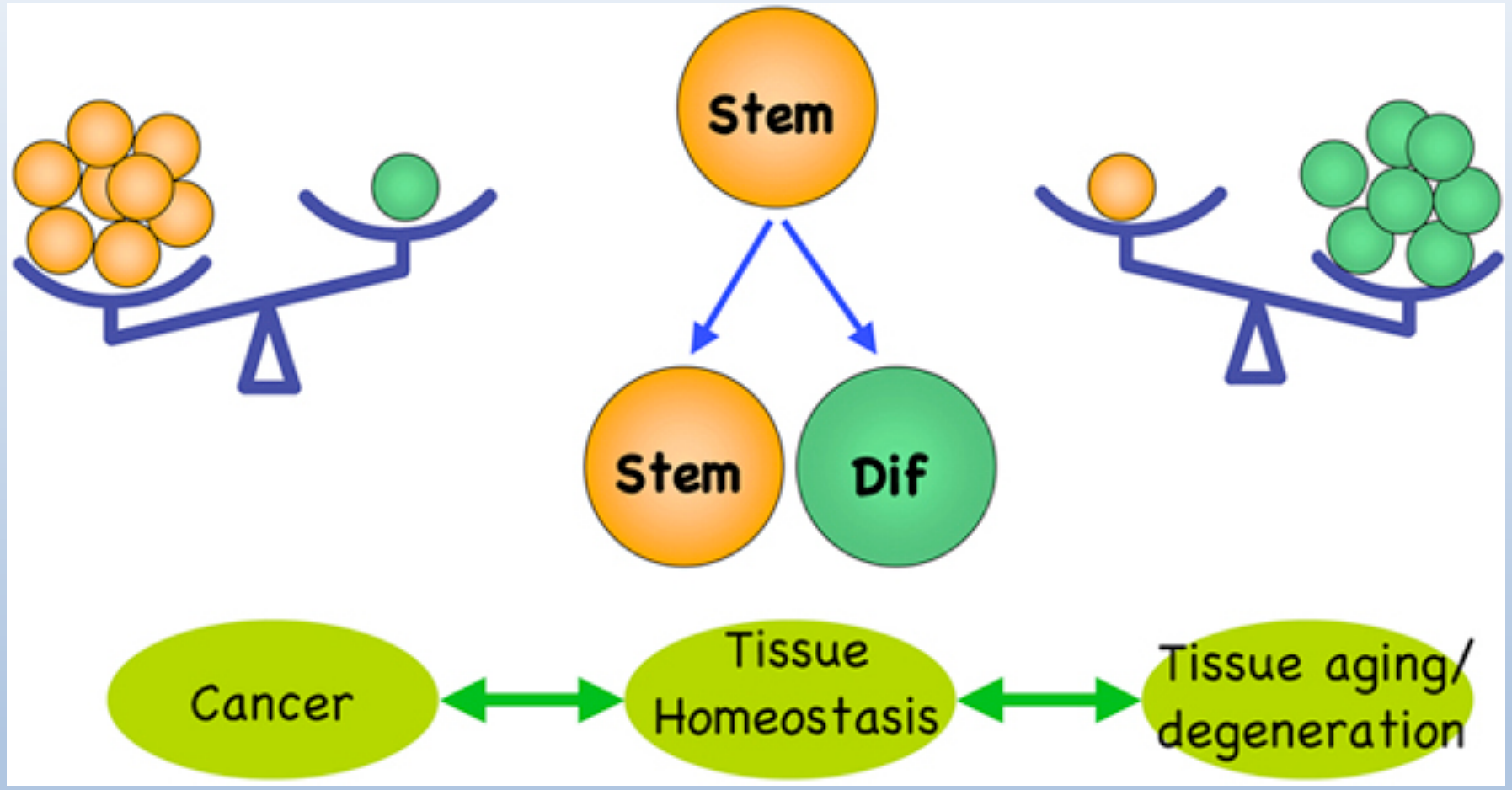
Mesoderm (cardiac myotubes)



Ectoderm (Neurons)



- Unlimited self renewal (Regeneration)
- Differentiation (eg. beating cells of the heart muscles):
  - Internal signals (specific genes)
  - External signals (GF, cytokines)

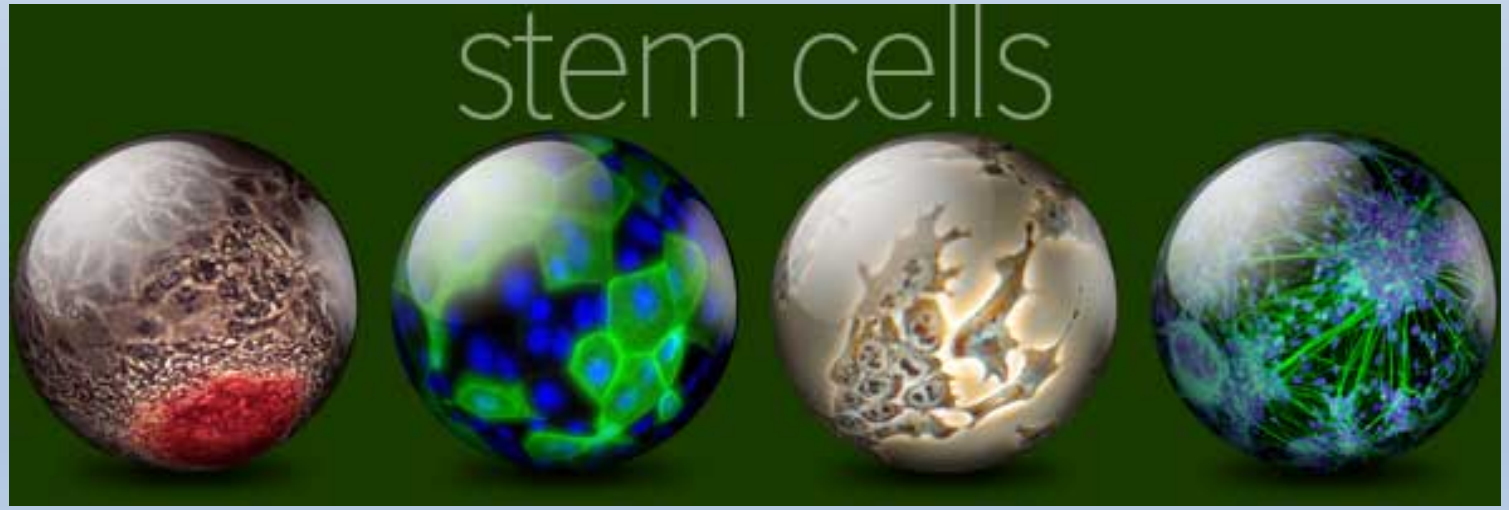

Stem
Stem
Dif
Cancer
Tissue Homeostasis
Tissue aging/ degeneration

What are Stem Cells?

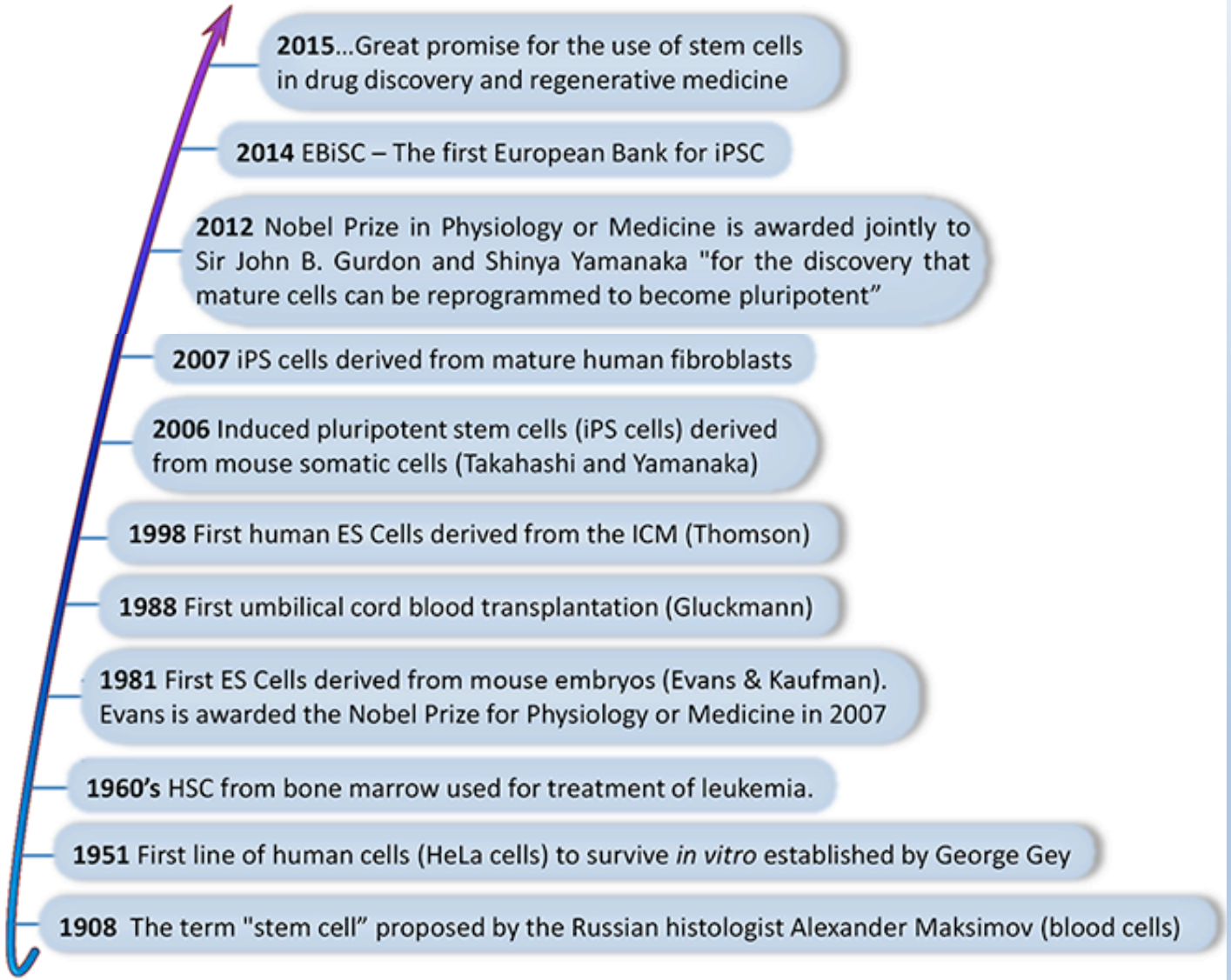
A cell that has the ability:

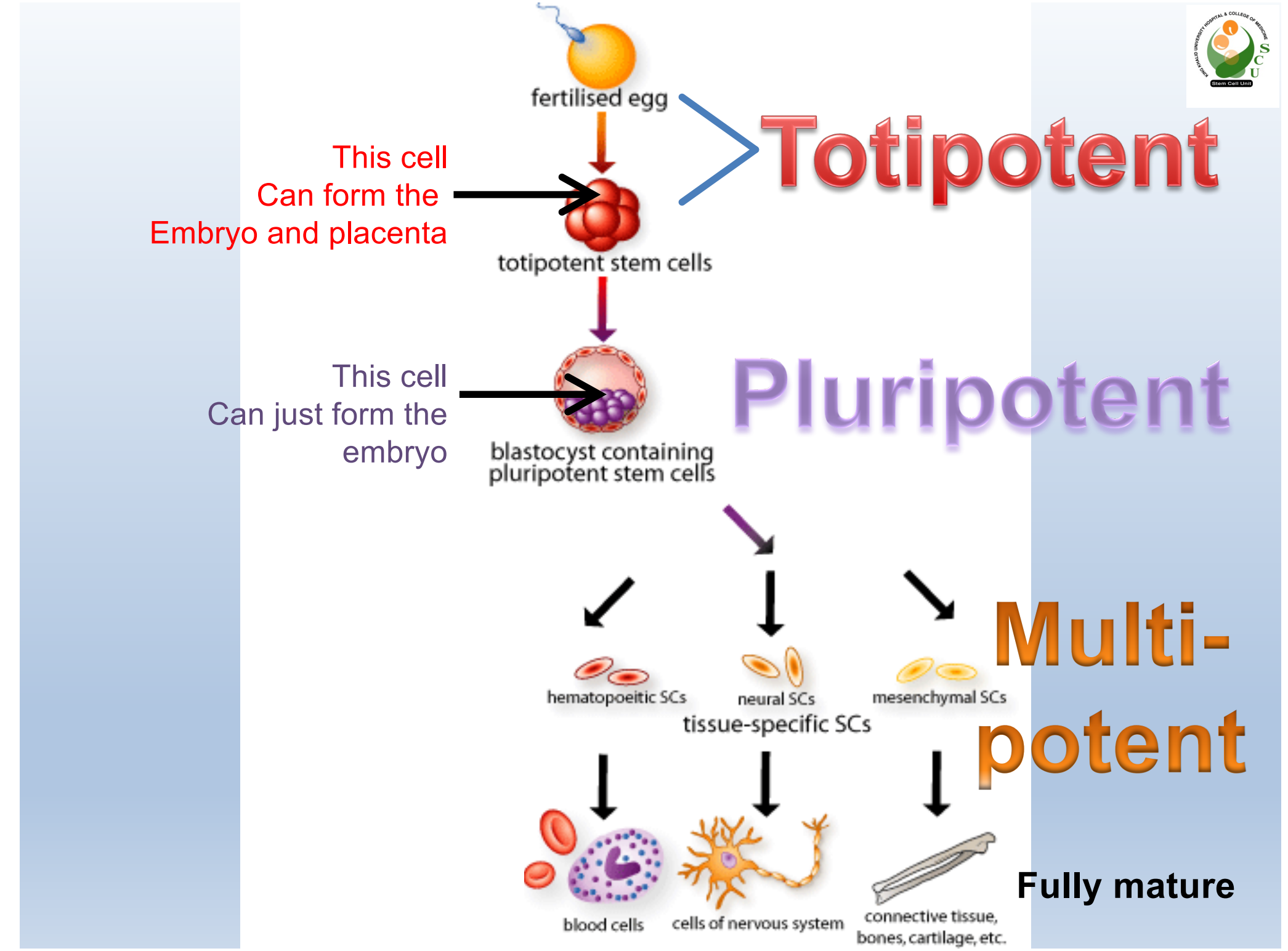
- to continuously divide and give rise to new copy of itself (self-renew)
- and other specialized (differentiated) cells/tissues.

Stem cells divide to new cell that has the potential to either remain a stem cell or become another type of cell with a more specialized function as cells of the **blood**, **heart, bones, skin, muscles, brain** etc, serving as a sort of repair system for the body.



The History of Stem Cells




fertilised egg
This cell
Can form the
Embryo and placenta
totipotent stem cells
Totipotent
This cell
Can just form the
embryo
blastocyst containing
pluripotent stem cells
Pluripotent
hematopoeitic SCs
neural SCs
mesenchymal SCs
tissue-specific SCs
Multi-
potent
blood cells
cells of nervous system
connective tissue,
bones, cartilage, etc.
Fully mature

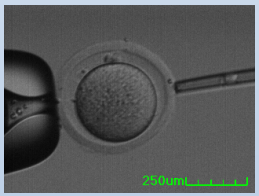
Classification of Stem Cells "1" (Potency Based)

Potency	Description
Totipotent	1-3 days, differentiate into embryonic and extraembryonic cell types
Pluripotent	Descendants of totipotent cells and differentiate into cells of 3 germ layers
Multipotent	Produce cells of a closely related of cells (e.g. hematopoietic)family stem cells
Oligopotent	Differentiate into ONLY a few cells, such as lymphoid or myeloid stem cells
Unipotent	Produce ONLY one cell type (e.g. muscle stem cells)
Nullpotent	The terminal cell

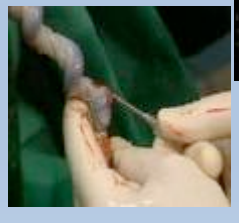
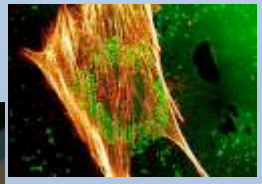
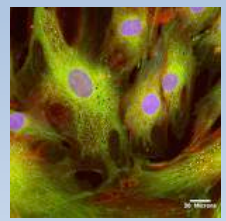
Sources of Stem Cells

- **Embryonic Stem Cells (ESC)**
  - IVF embryos
  - Aborted embryos
  - cloned embryos





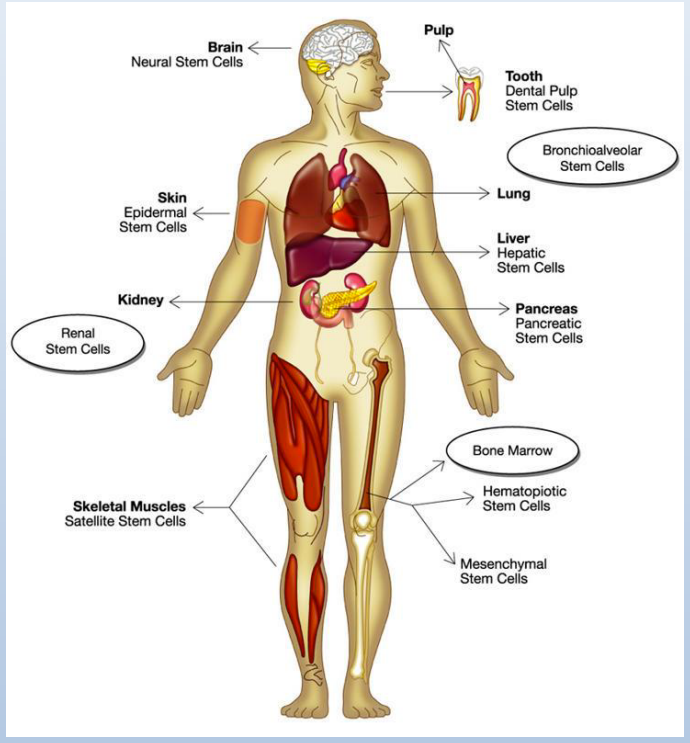
- **Adult Stem Cells (ASC):**
  - Bone Marrow
  - Placental Cord
  - Mesenchymal Stem cells

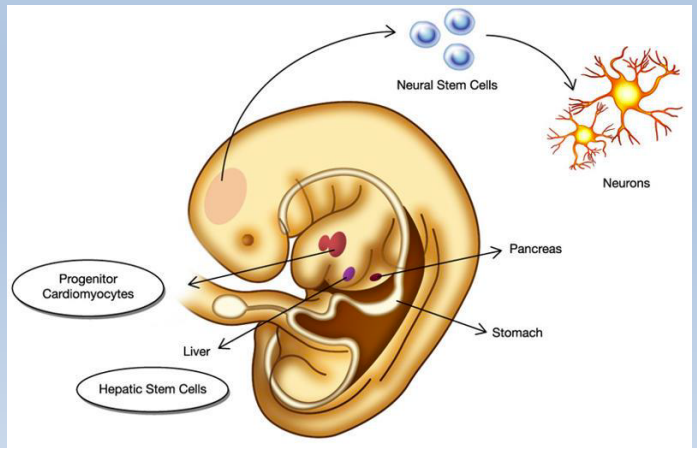




Adult stem cells (Tissue Specific Stem Cells)

- Found in specific mature body tissues as well as the **umbilical cord** and **placenta** after birth.

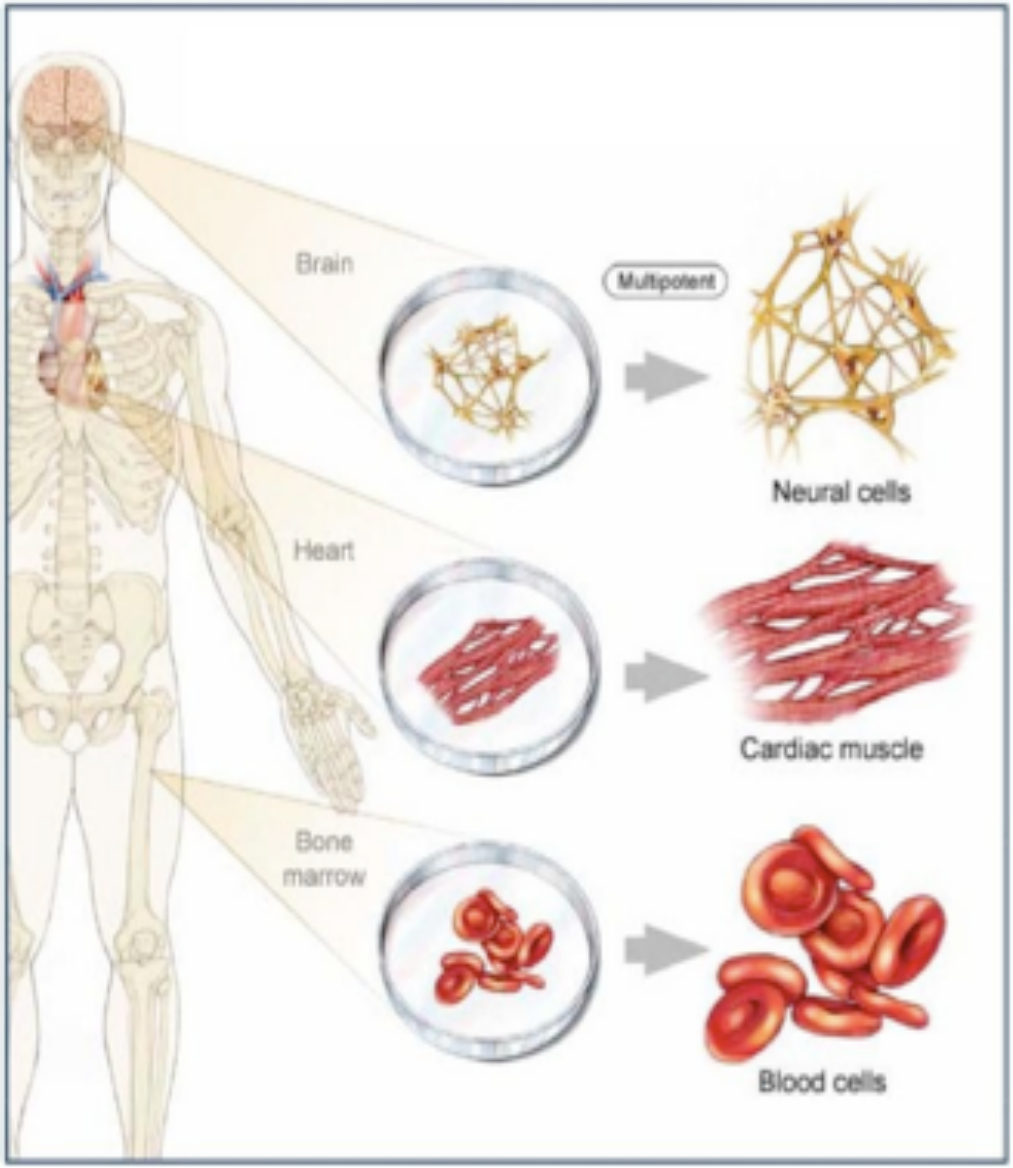
- They also can be isolated of **developing embryos' different tissues**



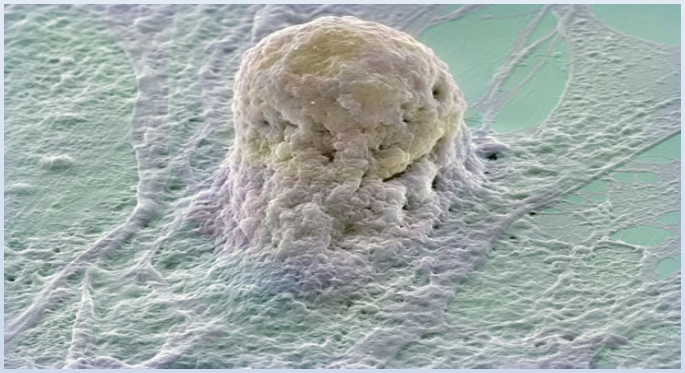


Embryonic Stem Cells

Adult Stem Cells

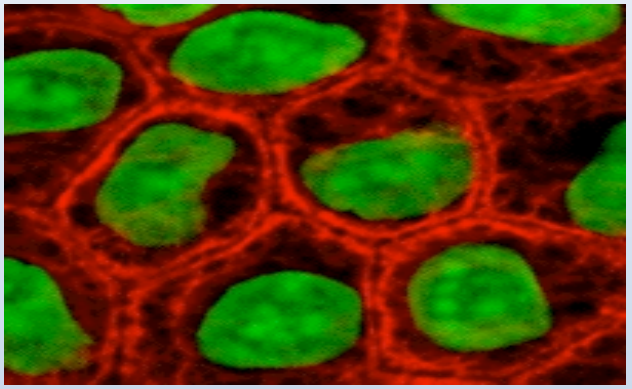


ESC



- Pluripotent
- large number can be harvested
- May cause immune rejection
- Ethical concerns

ASC

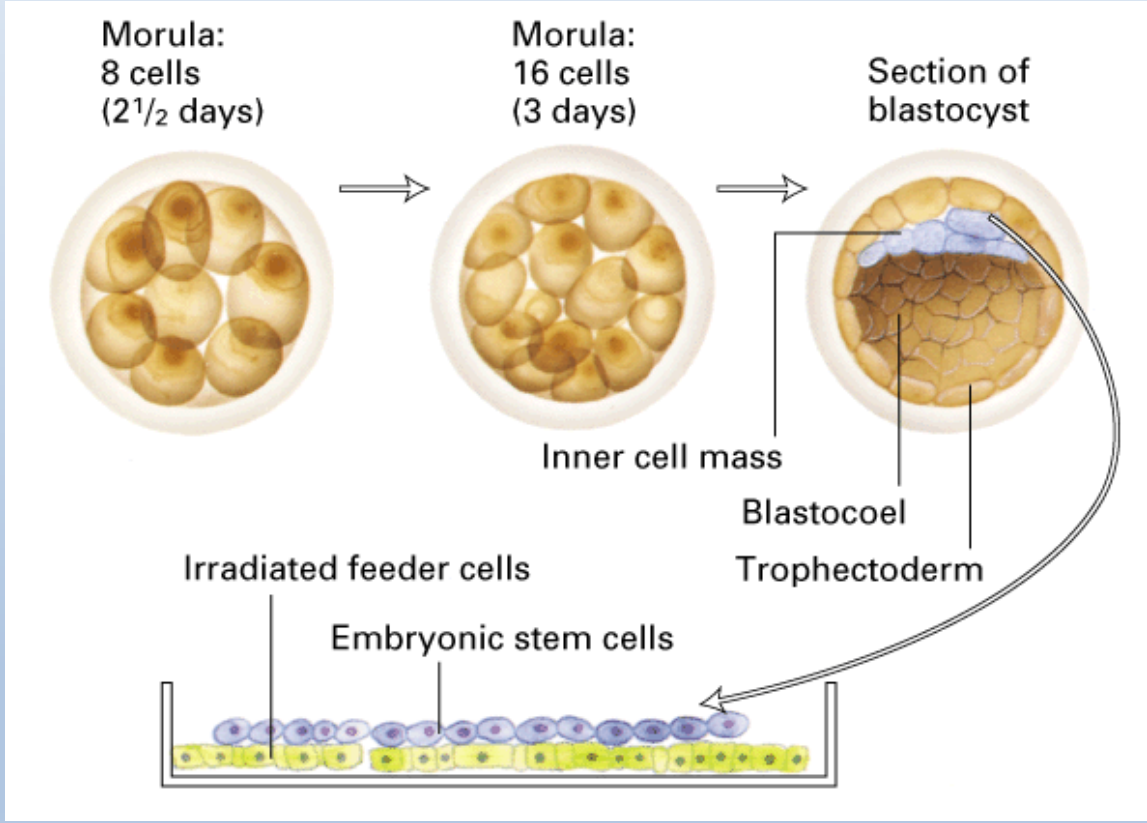


- Multipotent
- Limited numbers and more difficult to isolate
- No immune rejection
- No Ethical concerns

Generation of embryonic stem cells

- Embryonic human stem cells were first isolated in 1995 by Dr. James Thomson.

- derived from 4-5 day old embryo (Blastocyst):
  - Trophoblast
  - Blastocoel
  - Inner Cell Mass (ICS)

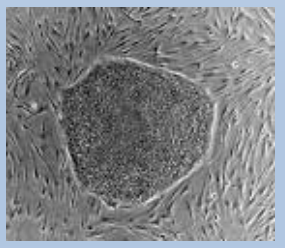


Generation of embryonic stem cells

- Isolate and transfer of ICS into culture dish in culture media

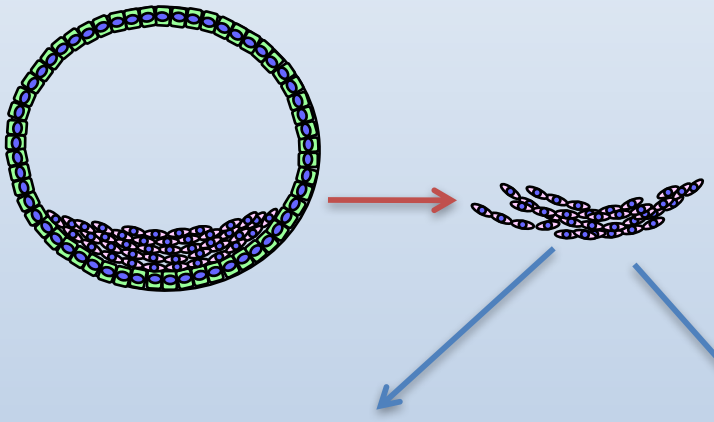
- Culture at 37c and 5% CO_2

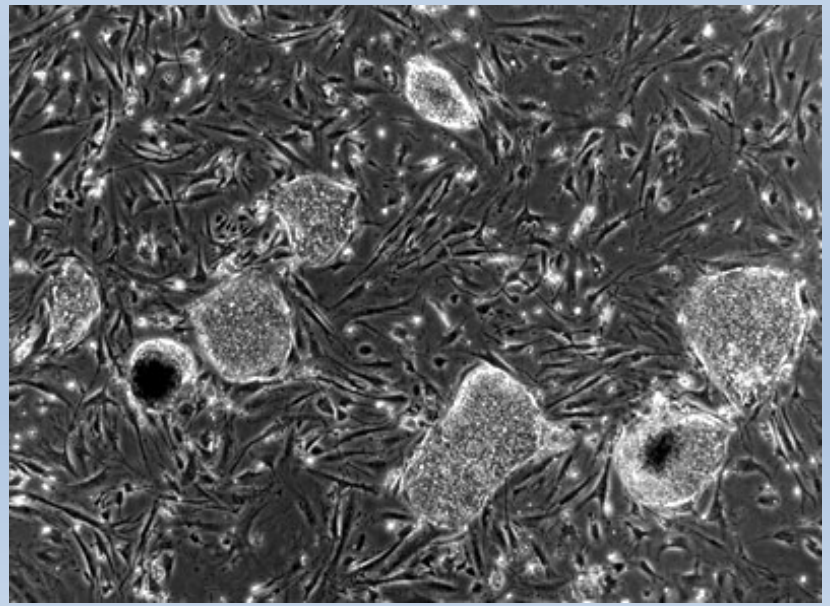
- Inner surface of culture dish is coated with inactivated MEFs as a feeder layer:
  - provides sticky surface for attachment
  - release nutrients

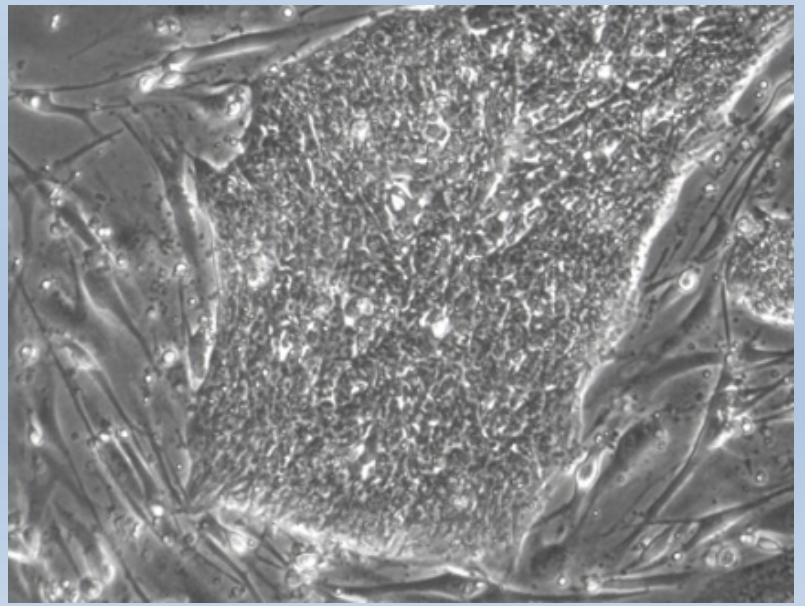


- Cells divide and spread over the dish
- ESCs are removed gently and plated into several different culture plates.

Human Embryonic Stem Cell Colony

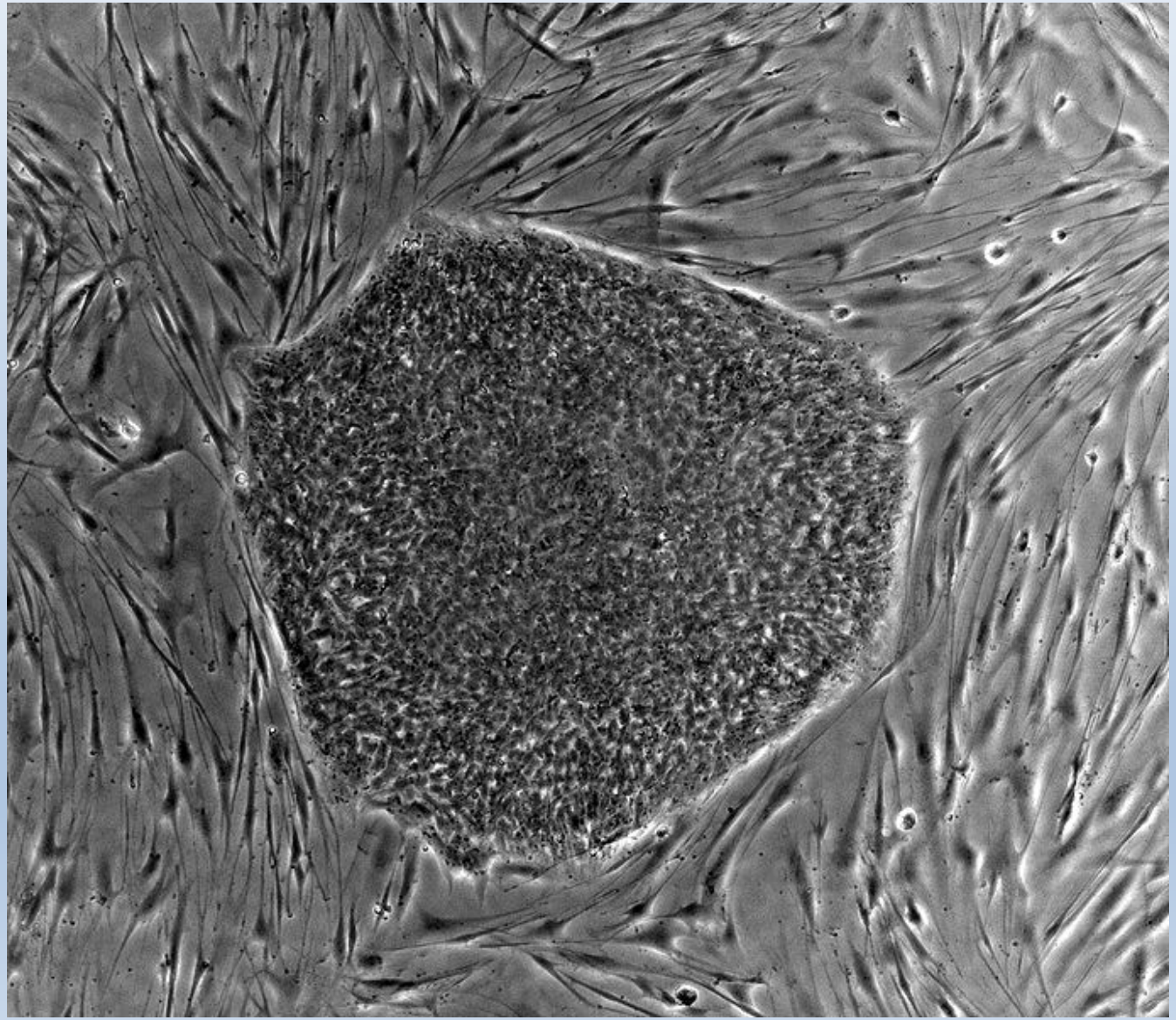




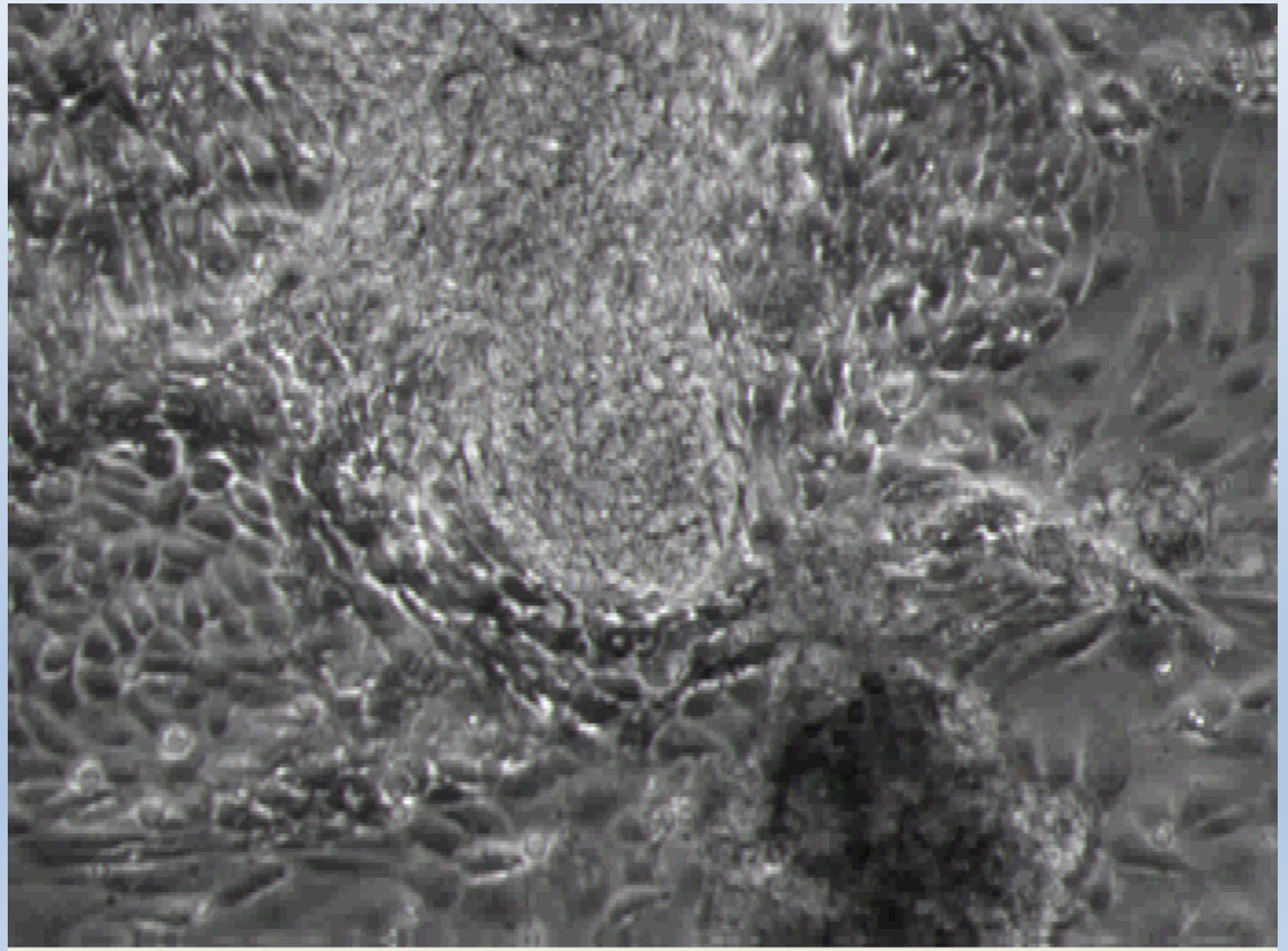


Embryonic stem cells in the dish

What do cultured ES cells look like?



Beating cardiomyocytes derived from hESCs



Challenges with Embryonic Stem Cells

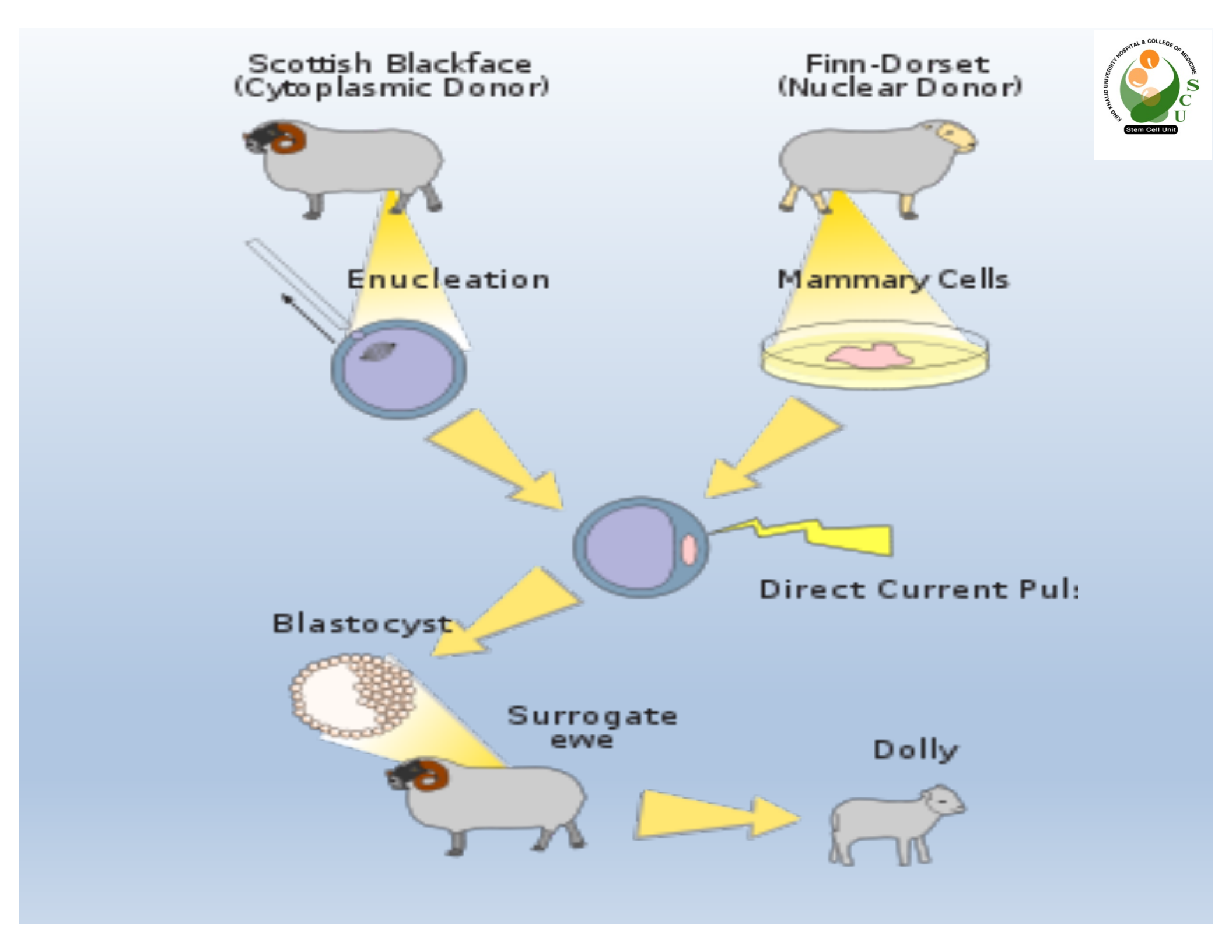
- Abnormalities in chromosome number and structure were found in some human ESC lines.
- Stem cells need to be differentiated to the appropriate cell types *before* they can be used clinically.
- Stem cell development or proliferation must be controlled once placed into patients.
- The use of mouse “feeder” cells to grow ESC could result in problems due to xenotransplantation.
- Possibility of rejection of stem cell transplants as foreign tissues is very high.

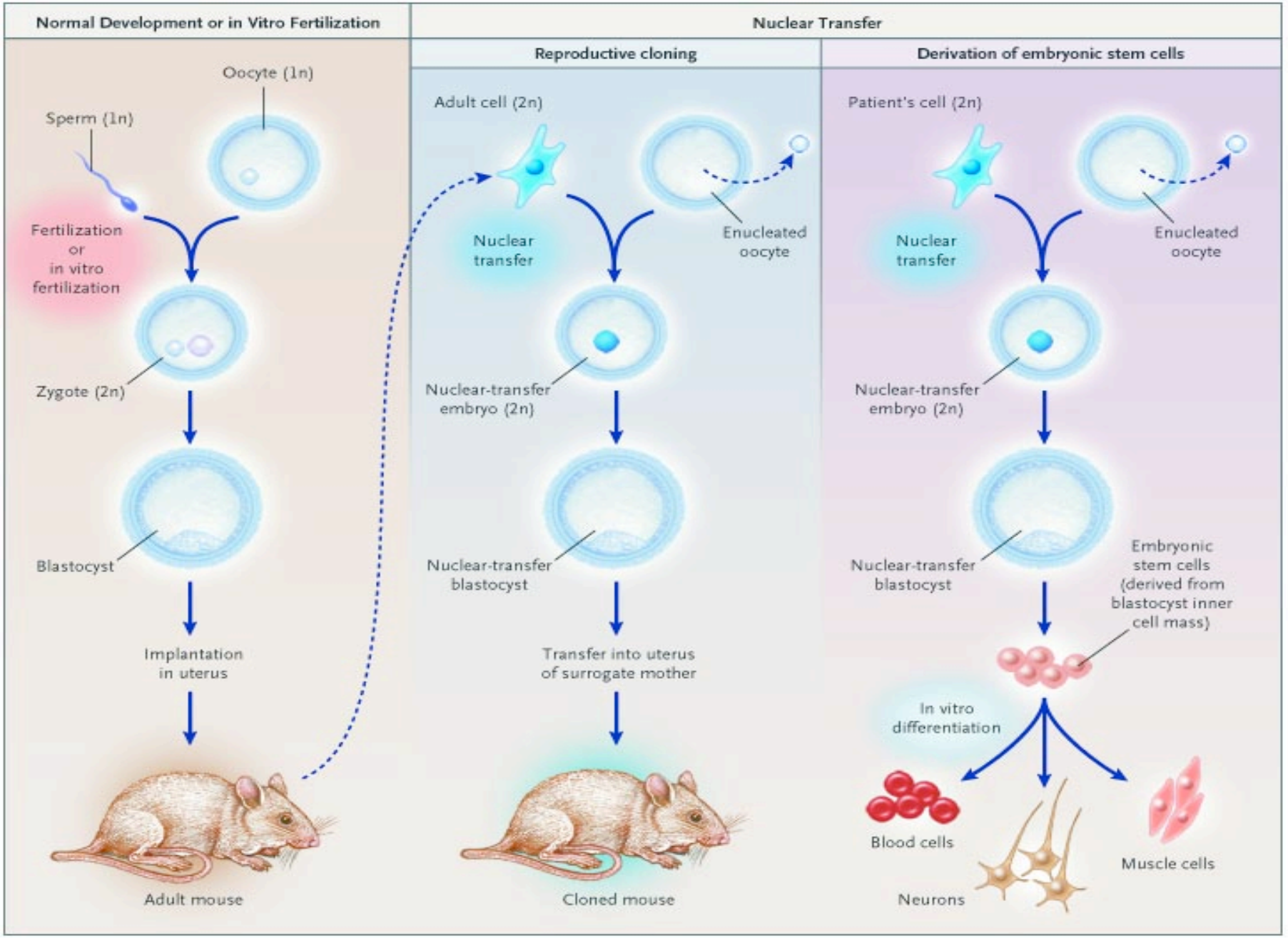
Somatic Cell Nuclear Transfer
SCNT

CLONING

REPRODUCTIVE CLONING

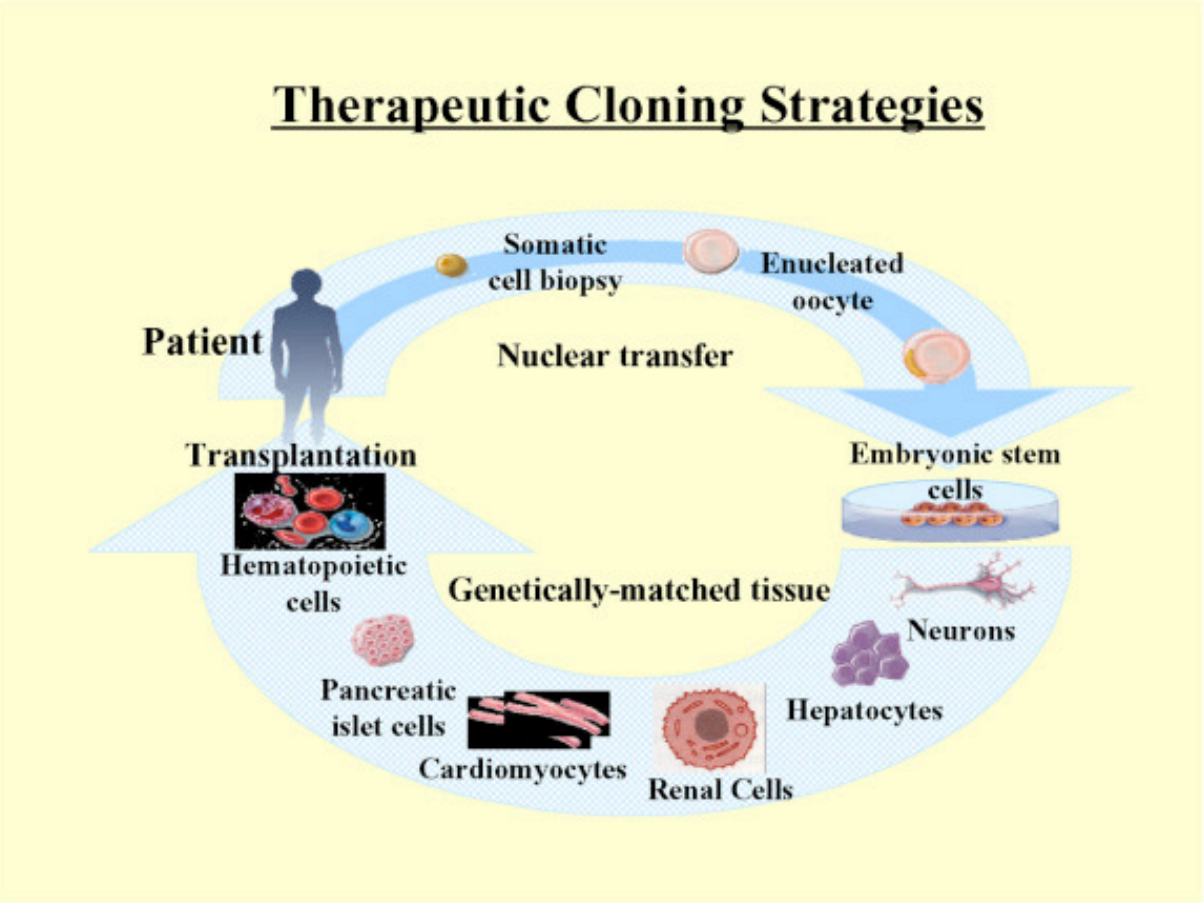
(July 1996 – February 2003)


Scottish Blackface
(Cytoplasmic Donor)
Finn-Dorset
(Nuclear Donor)
Enucleation
Mammary Cells
Direct Current Pul
Blastocyst
Surrogate
ewe
Dolly

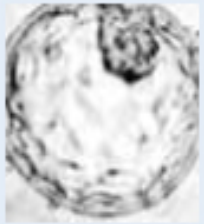
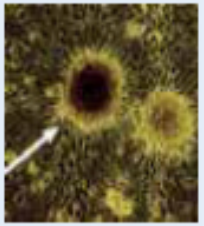

Normal Development or in Vitro Fertilization
Nuclear Transfer
Reproductive cloning
Derivation of embryonic stem cells
Oocyte (1n)
Sperm (1n)
Fertilization or in vitro fertilization
Zygote (2n)
Blastocyst
Implantation in uterus
Adult mouse
Adult cell (2n)
Nuclear transfer
Enucleated oocyte
Nuclear-transfer embryo (2n)
Nuclear-transfer blastocyst
Transfer into uterus of surrogate mother
Cloned mouse
Patient's cell (2n)
Nuclear transfer
Enucleated oocyte
Nuclear-transfer embryo (2n)
Nuclear-transfer blastocyst
Embryonic stem cells (derived from blastocyst inner cell mass)
In vitro differentiation
Blood cells
Neurons
Muscle cells

Therapeutic Cloning

- Therapeutic cloning uses stem cells to correct diseases and other health problems that someone may encounter.
- Therapeutic cloning does not cloned to make full humans but rather is used for the stem cells of embryo



COMPARISON OF THE DIFFERENT SOURCES OF STEM CELLS

	Embryonic Stem Cells		Adult Stem Cells
			
	In Vitro Fertilization	**Nuclear Transfer**	**Adult Tissues**
Attributes	• can produce all cell types • relatively easy to identify, isolate, maintain, and grow in the laboratory • large source of "excess" blastocysts from IVF clinics	• can produce all cell types • relatively easy to identify, isolate, maintain, and grow in the laboratory • stem cells may be genetically matched to patient	• demonstrated success in some treatments • stem cells may be genetically matched to patient
Limitations	• limited number of cell lines available for federally funded research • risk of creating teratomas (tumors) from implanting undifferentiated stem cells	• not yet achieved with human cells • risk of creating teratomas (tumors) from implanting undifferentiated stem cells	• produce limited number of cell types • not found in all tissues • difficult to identify, isolate, maintain, and grow in the laboratory
Ethical Concerns	• destruction of human blastocysts • donation of blastocysts requires informed consent	• destruction of human blastocysts • donation of eggs requires informed consent • concern about misapplication for reproductive cloning	• no major ethical concerns have been raised

KING KHALID UNIVERSITY HOSPITAL & COLLEGE OF MEDICINE
SCU
Stem Cell Unit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WITH STEM CELLS WE CAN GROW JUST ABOUT ANYTHING...
ETHICAL DILEMMA


LET'S PRAY FOR THE SINNERS WHO ENGAGE IN THE DEVIL'S WORK OF STEM-CELL RESEARCH!
RELIGIOUS RIGHT
LORD, HELP THEM FIND A CURE FOR DAD'S ALZHEIMER'S...
A CURE FOR MOM'S PARKINSON'S...
A CURE FOR MY CANCER...
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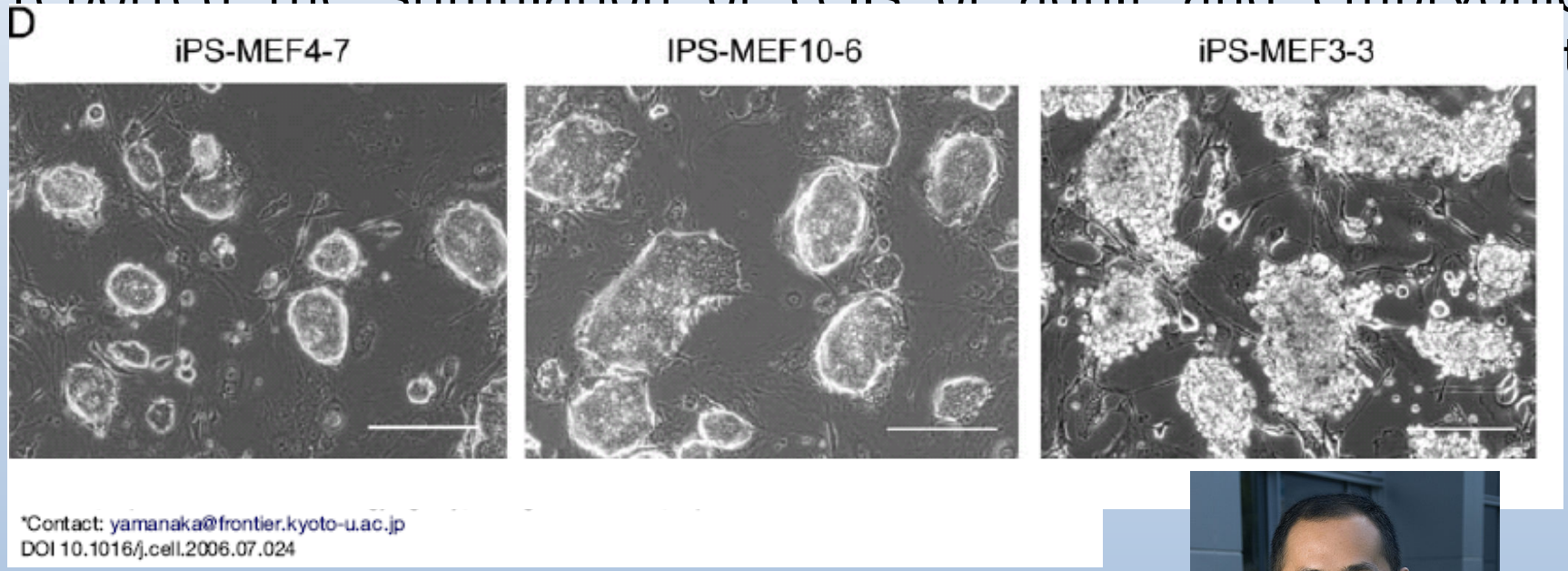
The first iPSCs

- In late 2006 the group of Takahashi and Yamanaka reported the stimulation of cells of adult and embryonic



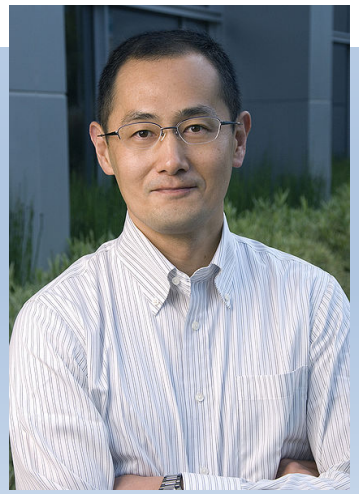


Photo: U. Montan

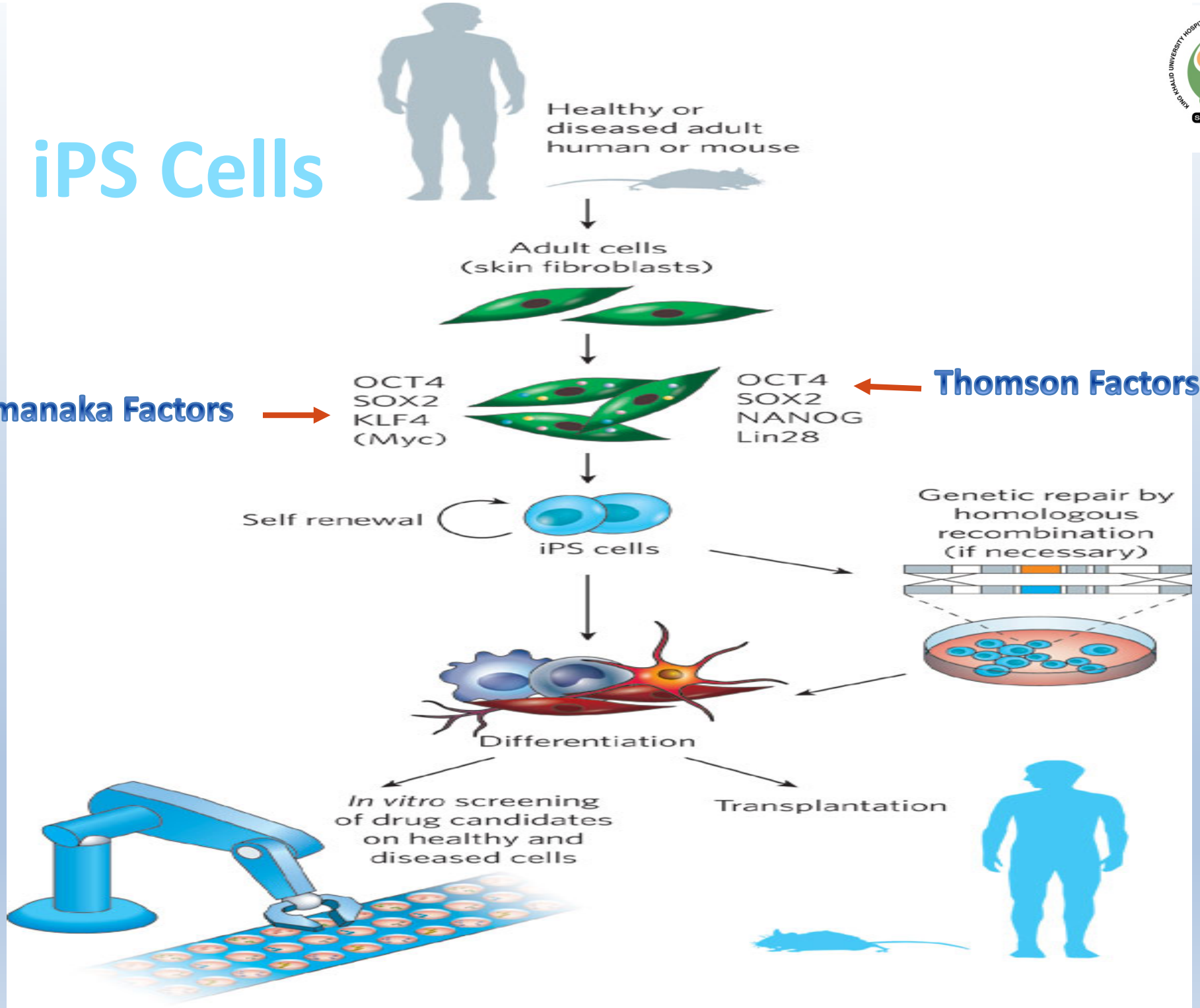
Sir John B. Gurdon

Photo: U. Montan

Shinya Yamanaka

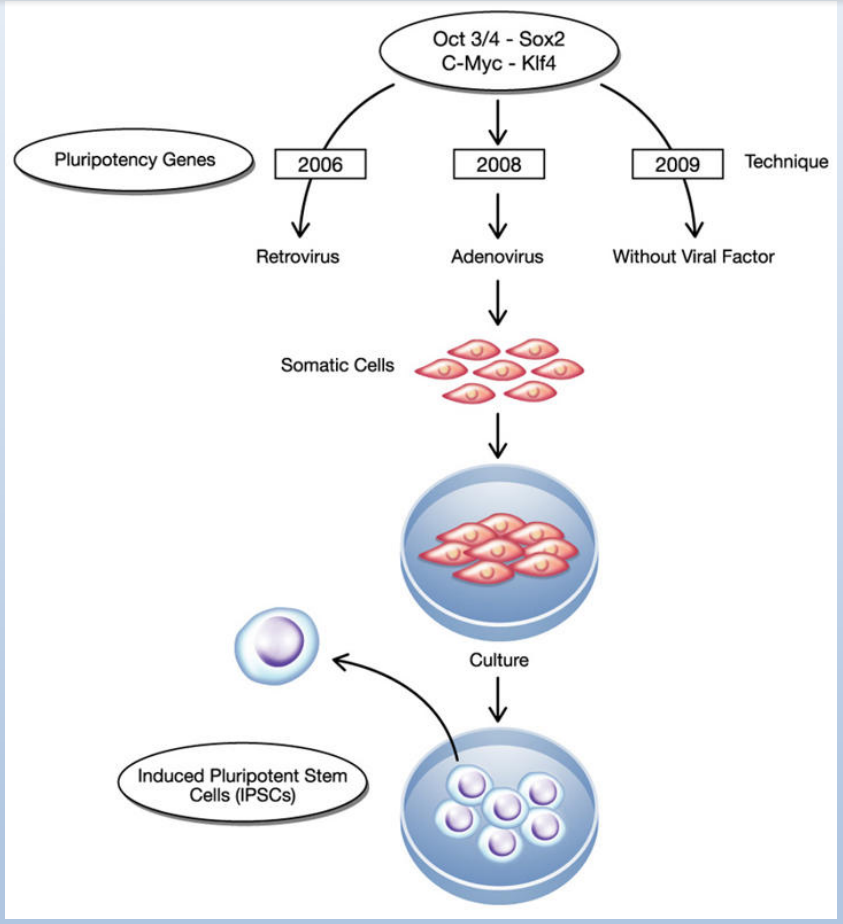
The Nobel Prize in Physiology or Medicine 2012

iPS Cells


Healthy or diseased adult human or mouse
Adult cells (skin fibroblasts)
Yamanaka Factors
OCT4
SOX2
KLF4
(Myc)
OCT4
SOX2
NANOG
Lin28
Thomson Factors
Self renewal
iPS cells
Genetic repair by homologous recombination (if necessary)
Differentiation
In vitro screening of drug candidates on healthy and diseased cells
Transplantation

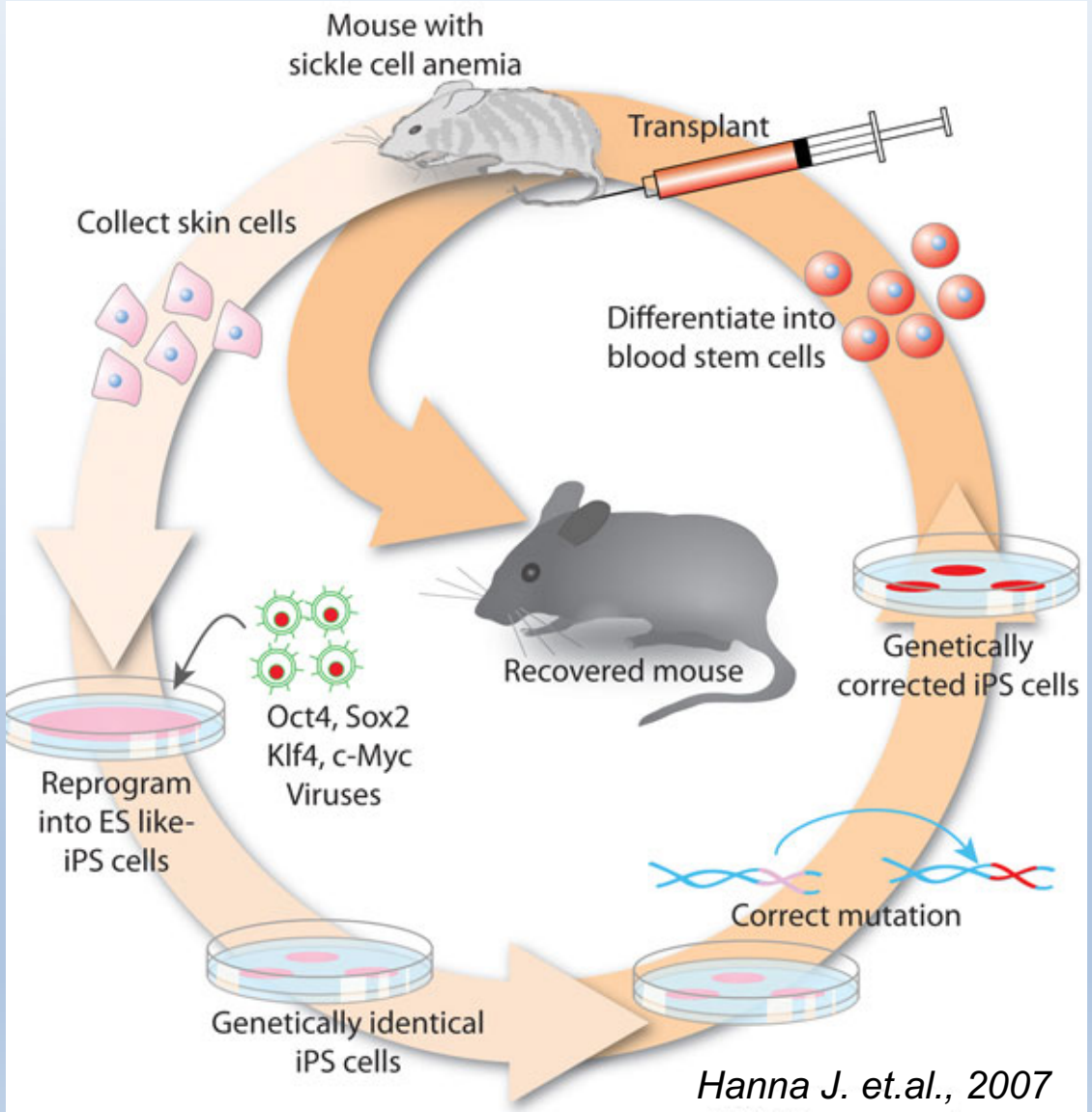
Induced Pluripotent Stem Cell (iPS) cells

- The method was described by Yamanaka in which the skin cells of laboratory mice were genetically manipulated and returned back to their embryonic state.
- iPS are somatic cells that have been reprogrammed to a pluripotent state (embryonic stem cell like state).
- Several difficulties are to be overcome before iPS cells can be considered as a potential patient-specific cell therapy.
- It will be crucial to characterize the development potential of human iPS cell line in the future.



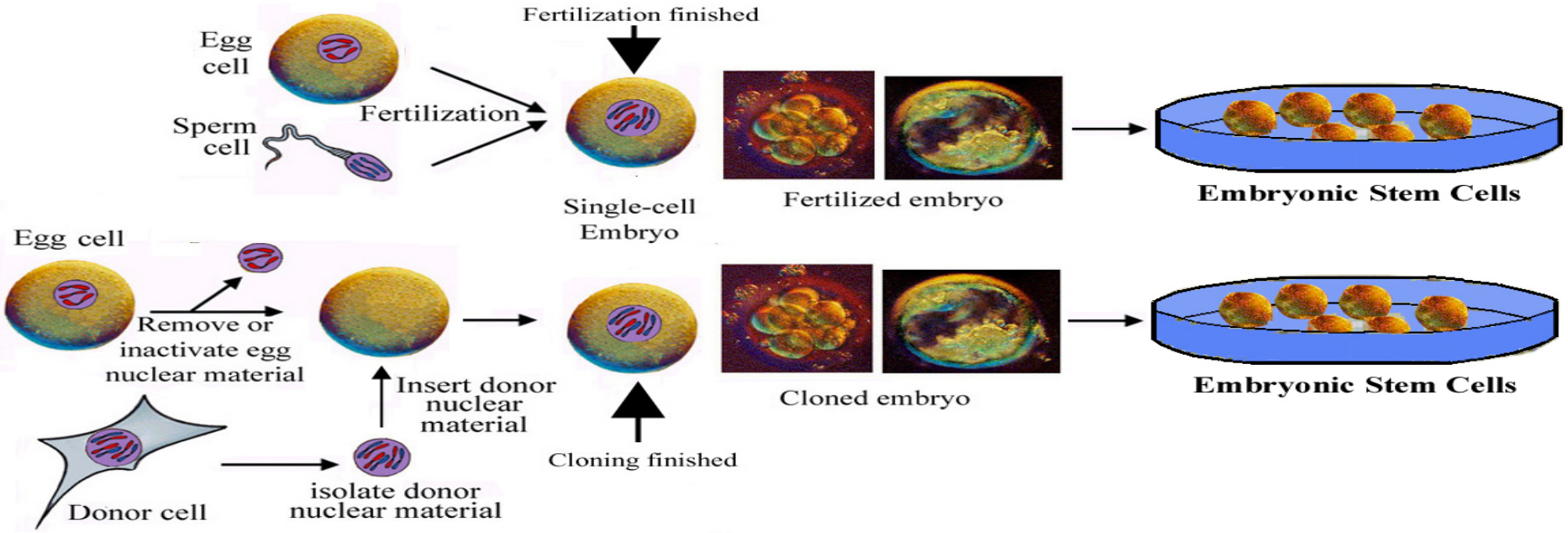
Induced Pluripotent Stem Cell (iPS) cells

- Skin cells were taken from the tail tip of a sickle-cell model mouse.
- The cells were differentiated into hematopoietic cells.
- The produced cells were transfused back into the sick mouse



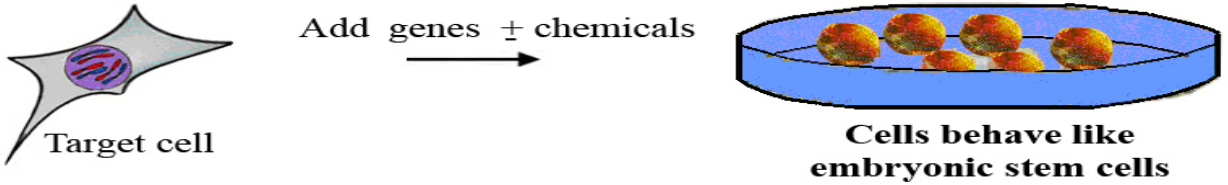
Embryonic Stem Cells

from Embryos created by Fertilization or by Cloning (Somatic Cell Nuclear Transfer)



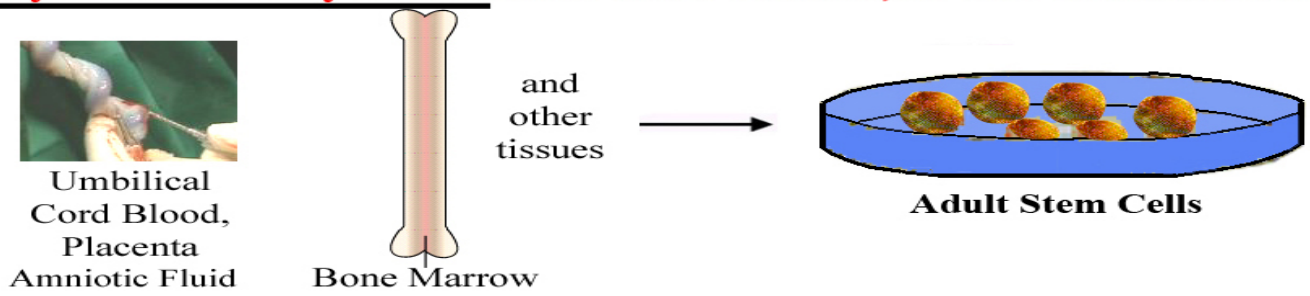
Induced Pluripotent Stem Cells (iPS cells)

from Normal Cells that are Reprogrammed to behave like Embryonic Stem Cells



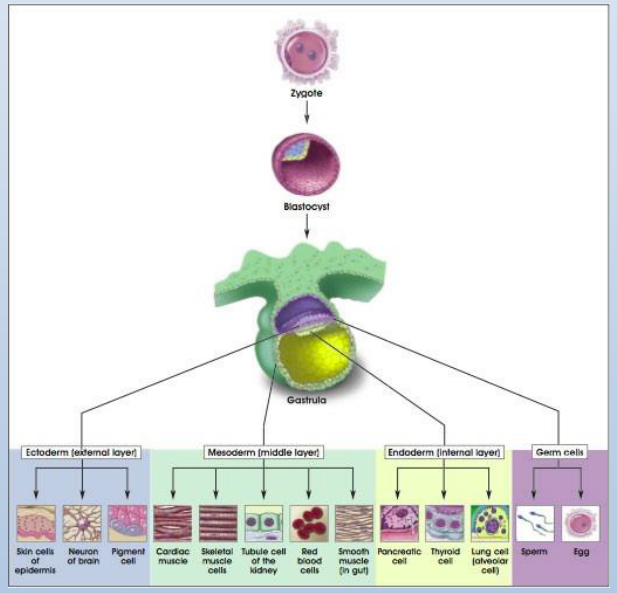
Adult Stem Cells

Stem Cells normally found in body tissues from birth onward, as well as umbilical cord, etc.

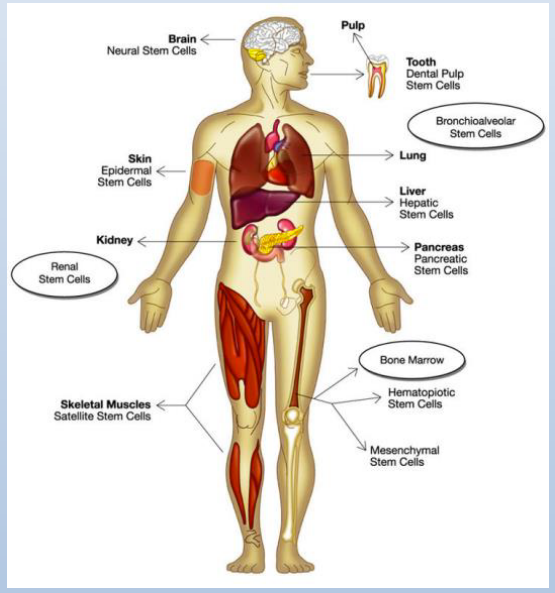


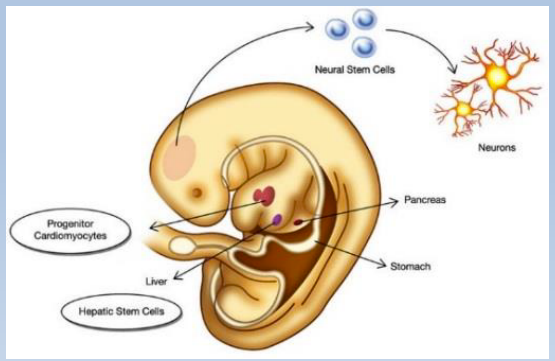
Classification of Stem Cells "2" (Source- Based)

Embryonic

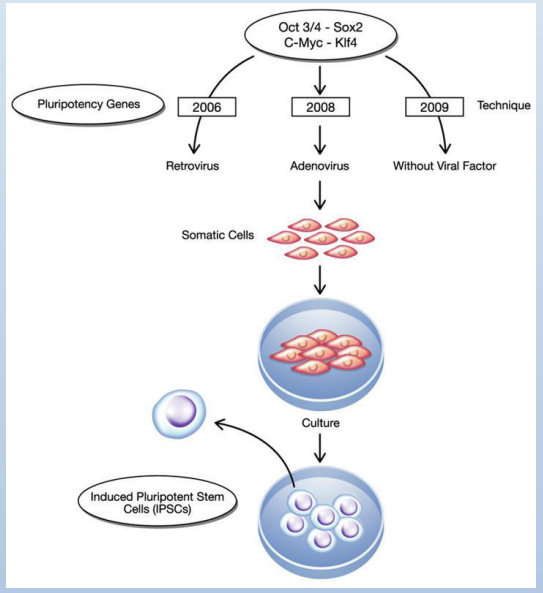


Adult (Tissue Specific)

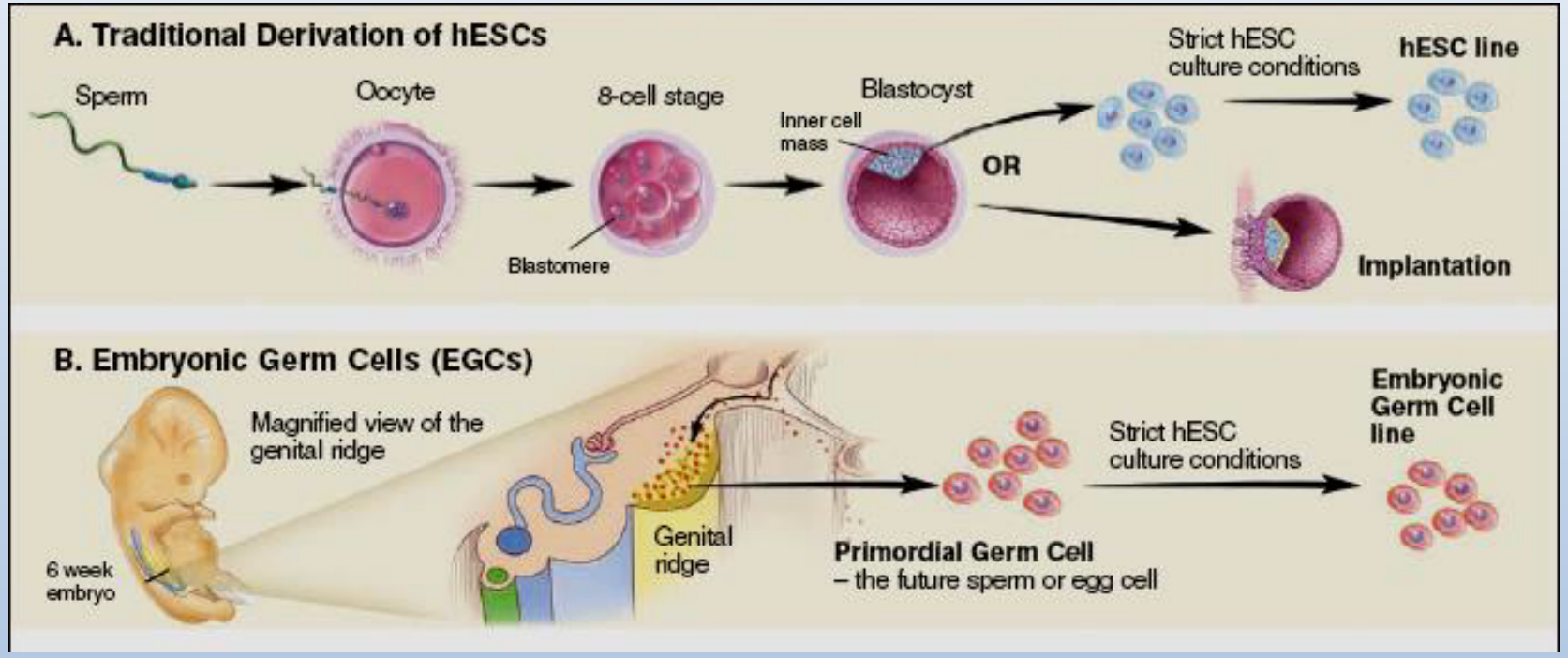


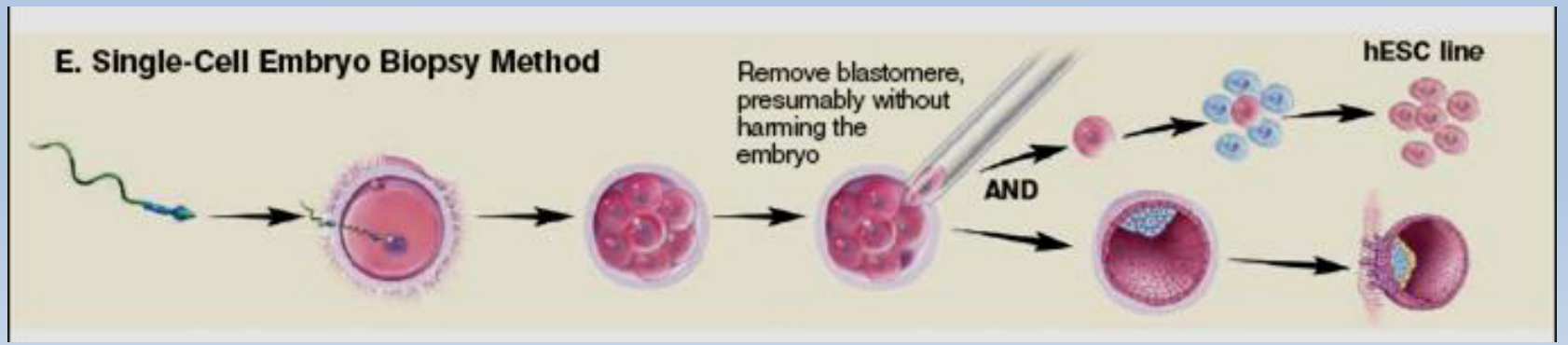


Induced

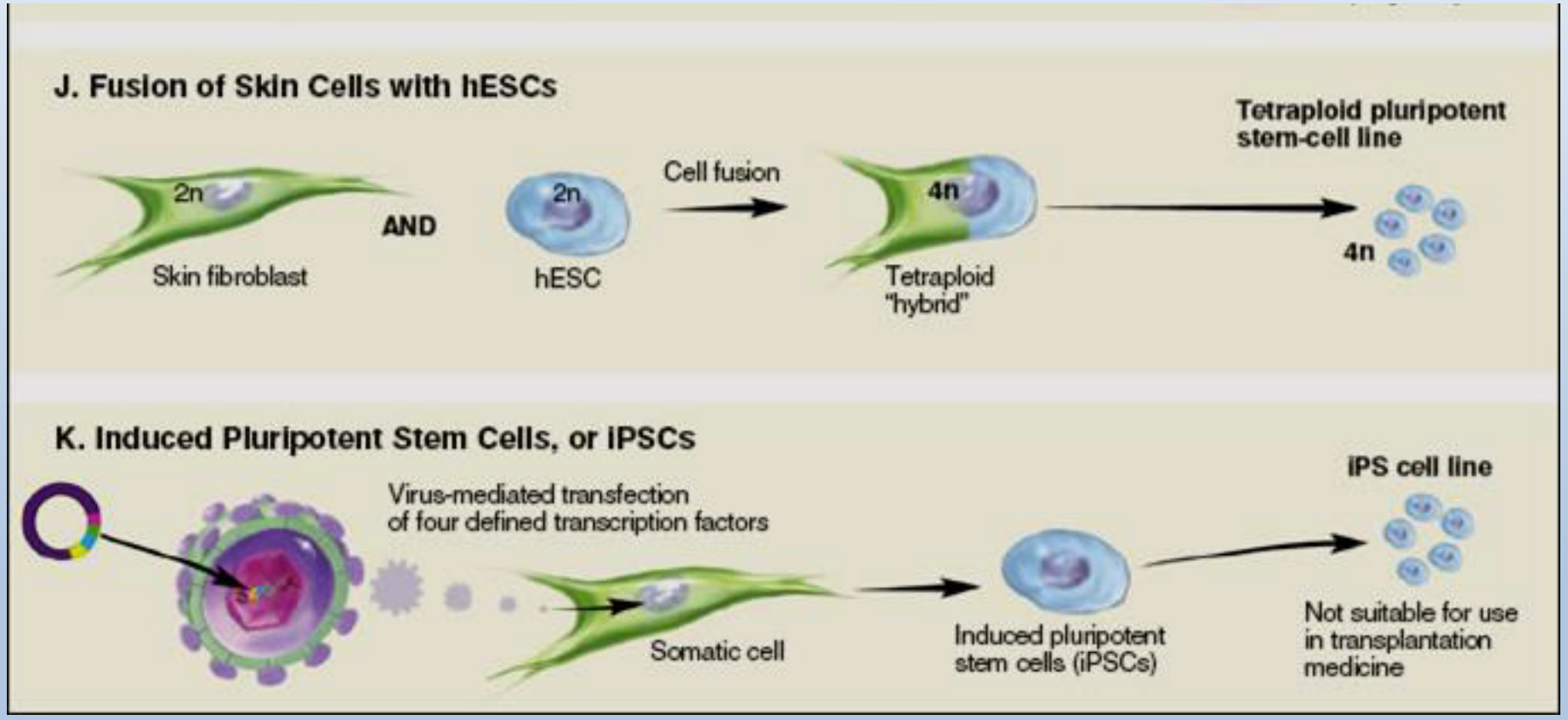


Different Approaches for Isolation of Pluripotent Stem Cells

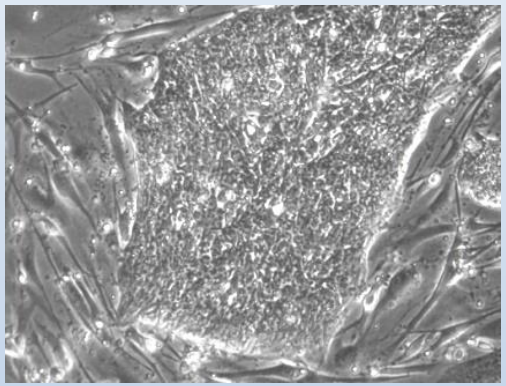


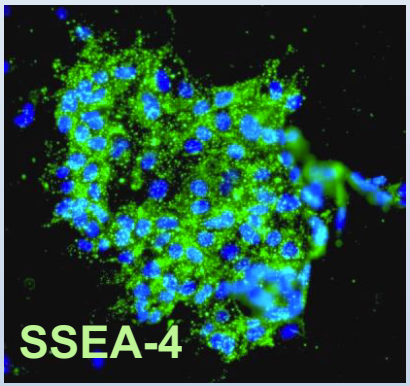


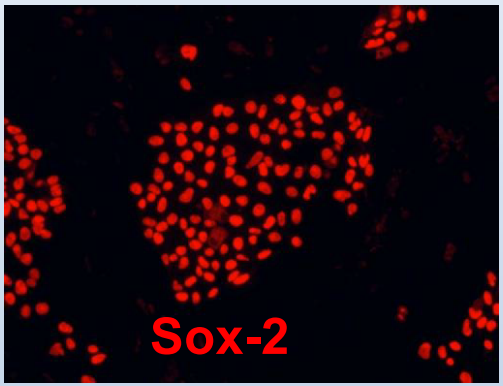
Different Approaches for Isolation of Pluripotent Stem Cells

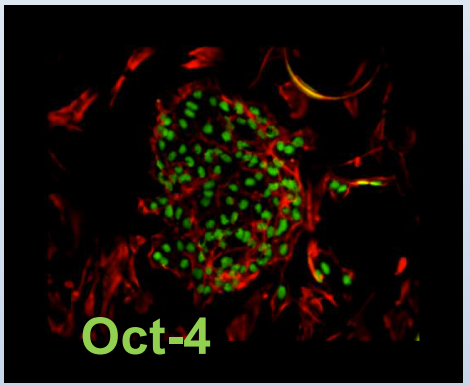


Characterization of Human Pluripotent Stem cells (ESCs)

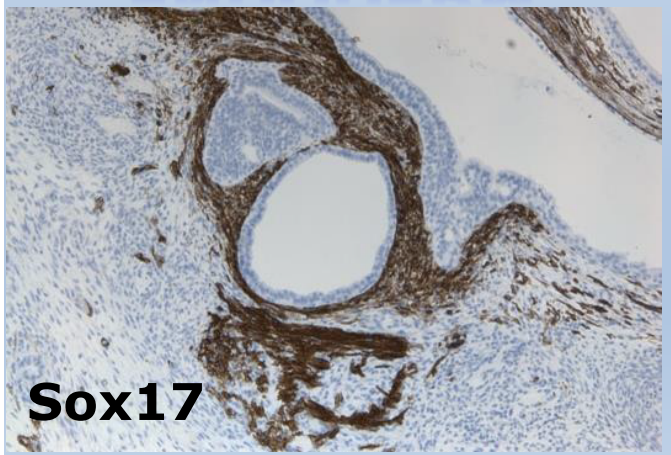




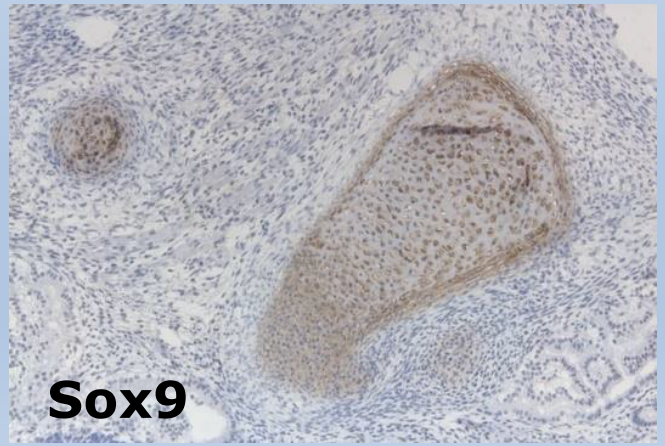




ENDODERM

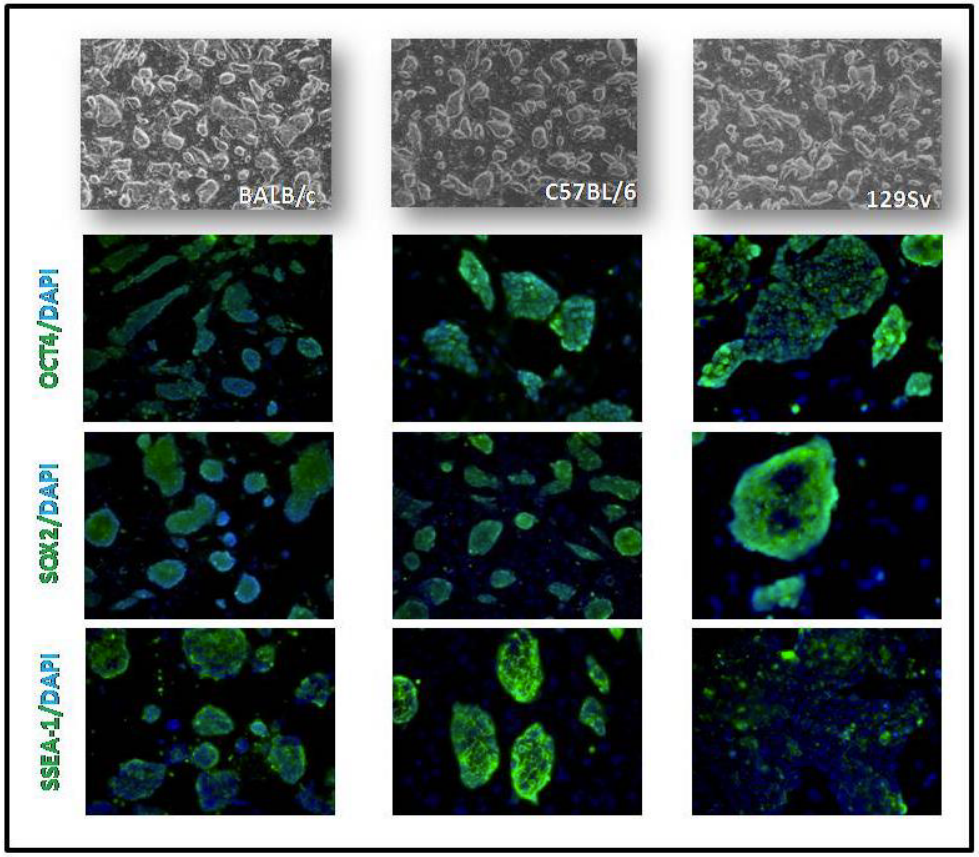


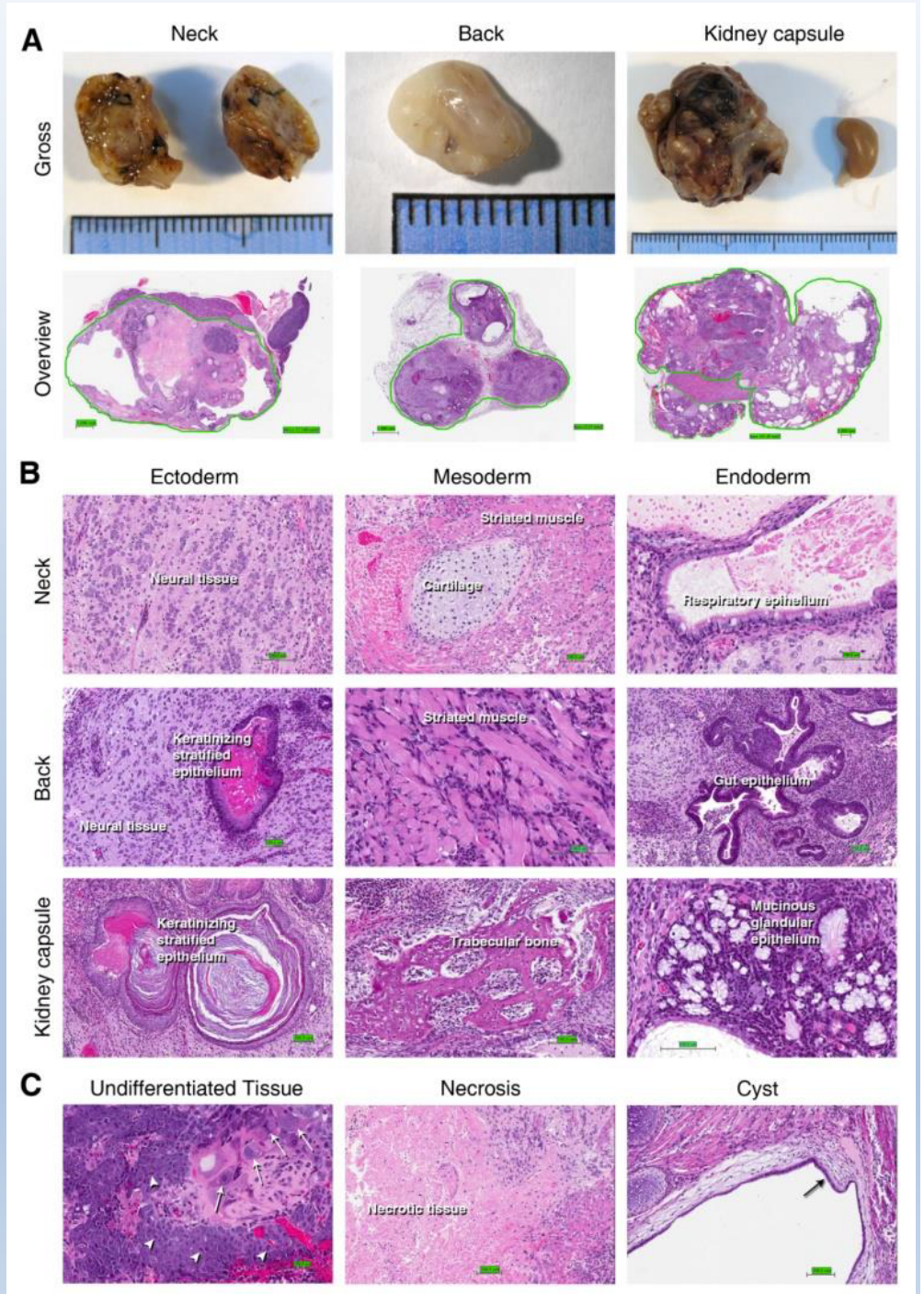
MESODERM



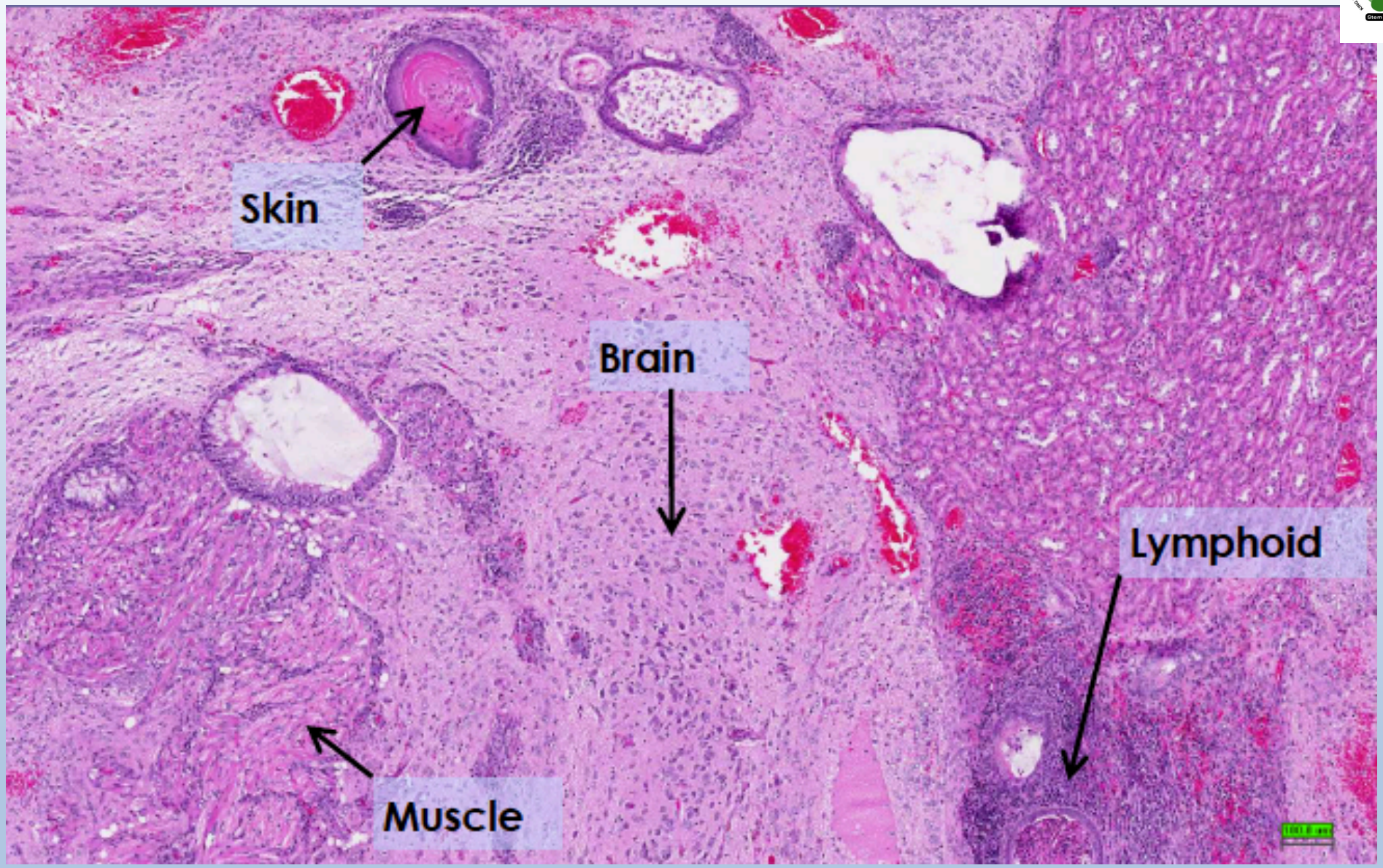
ECTODERM

Figure 1





Teratoma Formation in Immunocompetent Mice After Syngeneic and Allogeneic Implantation of Germline Capable Mouse Embryonic Stem Cells, 2013

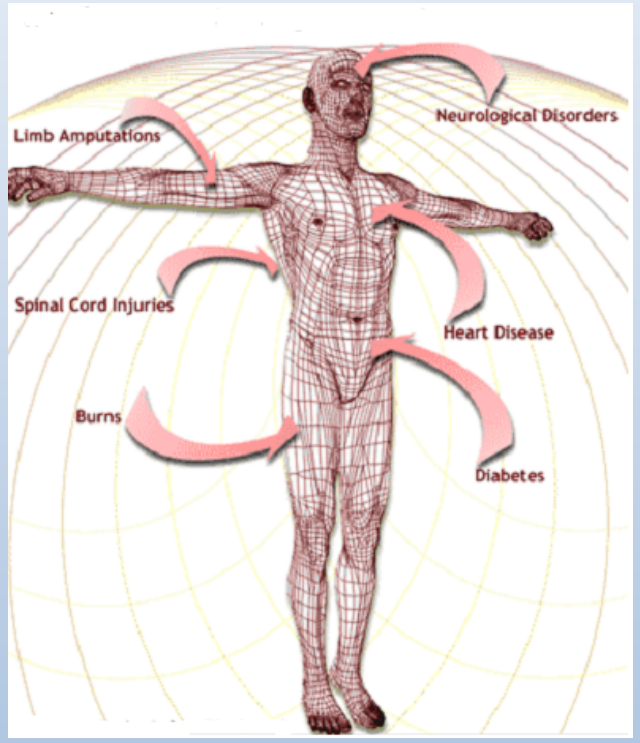


The teratoma was composed of mixed tissue patterns: skin with keratin, brain tissue, striated and smooth muscle, lymphoid tissue,….

Goal of Stem Cell Therapies

The goal of stem cell therapies is to promote cell replacement in organs that are damaged and do not have the ability for self repair

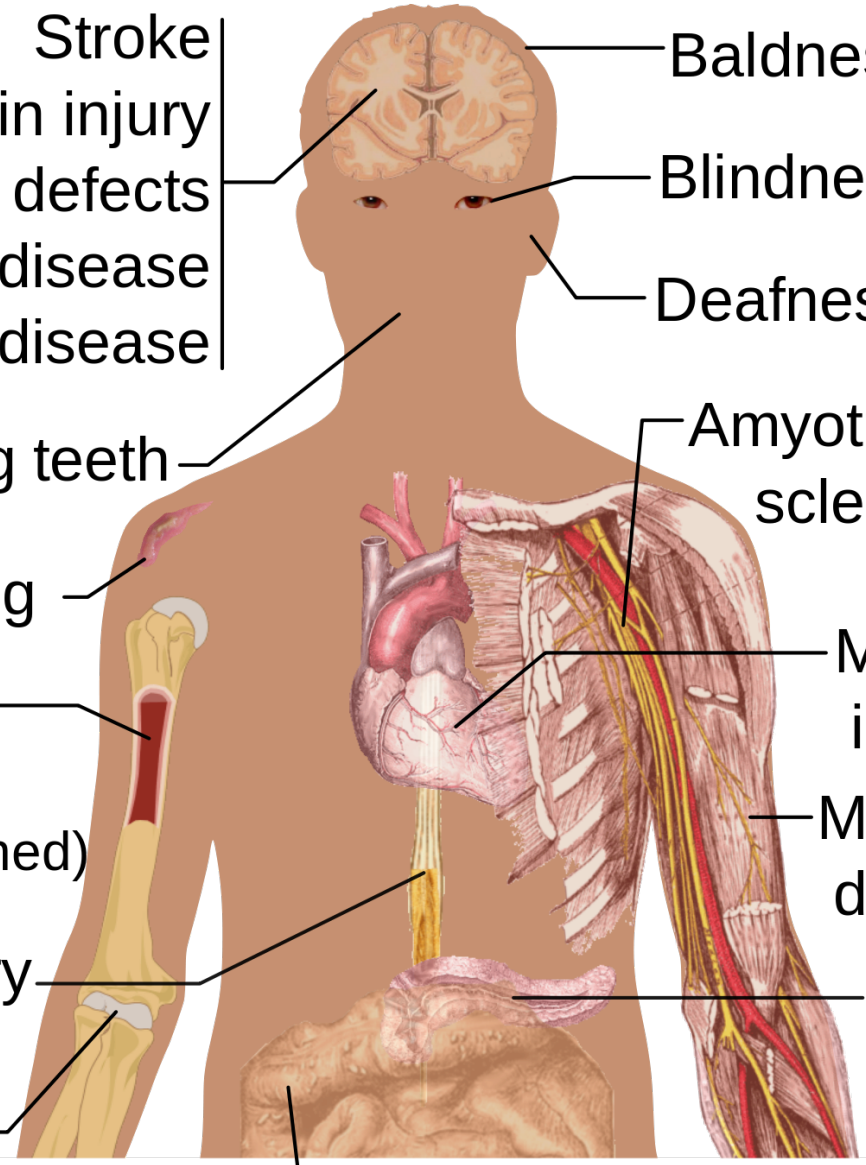
The Promise of Stem Cell Technology



- Replacement of tissues/organs
- Repair of defective cell types
- Study cell differentiation
- Toxicity testing.
- Understanding prevention and treatment of birth defects.
- Study of development and gene control.
- Study of drugs therapeutic potential.

Potential uses of

Stem cells



Stroke
Traumatic brain injury
Learning defects
Alzheimer's disease
Parkinson's disease

Baldness

Blindness

Deafness

Missing teeth

Amyotrophic lateral-sclerosis

Wound healing

Myocardial infarction

Bone marrow transplantation (currently established)

Muscular dystrophy

Spinal cord injury

Diabetes

Osteoarthritis
Rheumatoid arthritis

Crohn's disease

Multiple sites:
Cancers

People in the US affected by diseases that may be helped by stem cell research

Condition	Number of Persons Affected
Cardiovascular diseases	58 Million
Autoimmune diseases	30 Million
Diabetes	16 Million
Osteoporosis	10 Million
Cancer	8.2 Million
Alzheimer's disease	4 Million
Parkinson's disease	1.5 Million
Burns (severe)	0.3 Million
Spinal cord injuries	0.25 Million
Birth defects	150,000 (per year)
Total	**128.4 Million**

Data from the Patients' Coalition for Urgent Research, Washington, DC (according to Perry, Ref. 267).

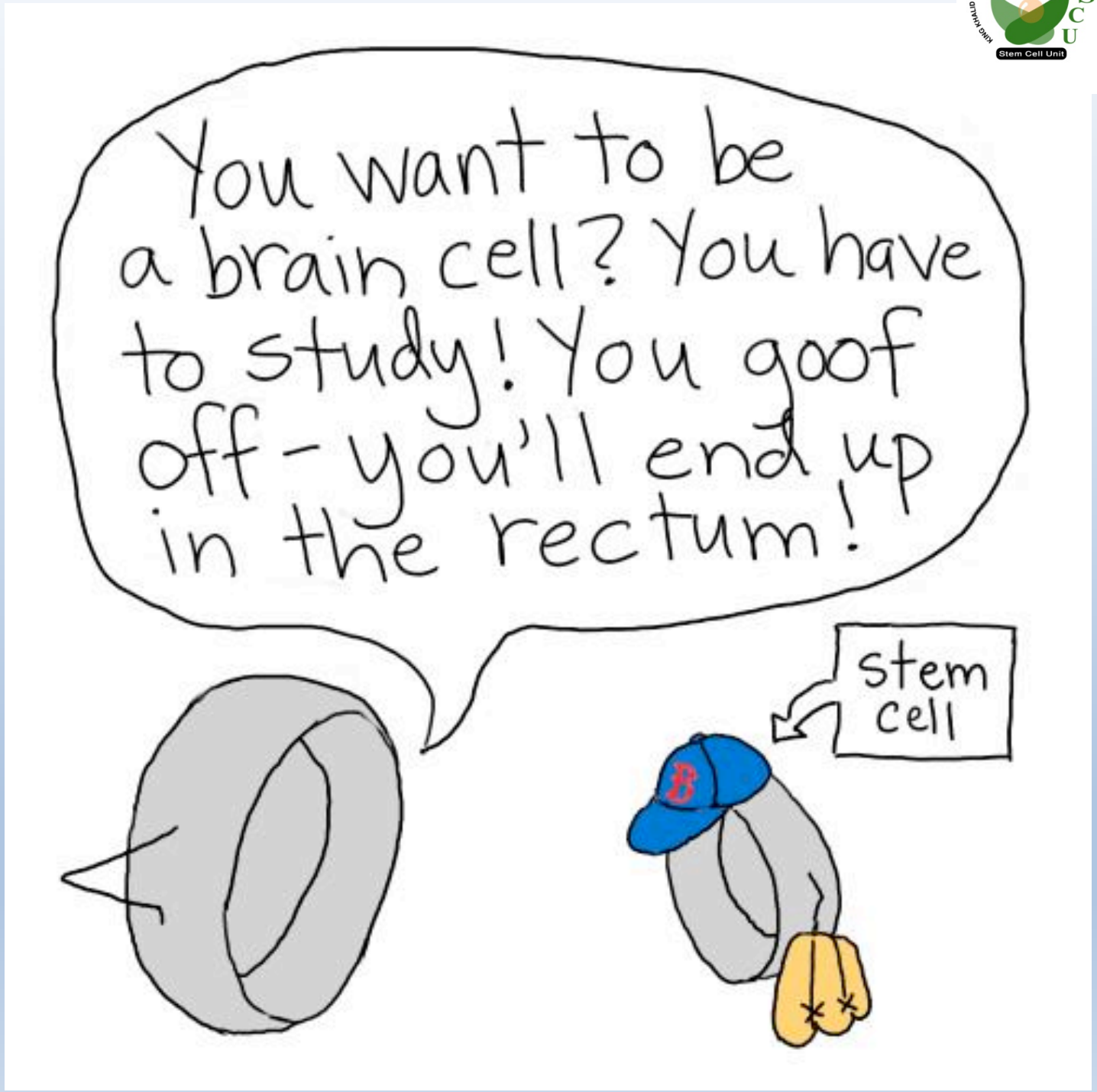
Obstacles of Stem Cell Research

- How to find the right type of stem cells?
- How to completely differentiate Stem Cells to desired cell type?
- 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.

Stem Cells Treatments - Success Rate

Disease	Number of patients	Treatment Results Degrees of Improvement			Duration of Observation
		Significant (cure)	Partial	None	
Osteoarthritis	350	90%	10%	-	1-6 yrs
Spinal Cord Injury	16	-	88%	12%	1-5 yrs
Parkinson's Disease	19	68%	32%	-	3 yrs
Alzheimer Disease	19	-	84%	16%	3 yrs
Multiple-Sclerosis	23	70%	22%	8%	3 yrs
Anti-Aging	139	86%	14%	-	5 yrs
Aesthetic Application	140	100%	-	-	5 yrs
Balding (male)	1000s	-	85%	15%	5 yrs
Erectile Dysfunction	88	60%	25%	15%	8 yrs
Diabetes Type-2	222	50%	43%	7%	8 yrs
Diabetic Foot Ulcers	1000s	90%	10%	-	8 yrs
Diabetic Retinopathy	230	84%	16%	-	5 yrs
Macular Degeneration	86	86%	12%	2%	7 yrs
Cerebral Palsy	13	-	100%	-	4 yrs
Autism (age 2 – 20 yrs)	100s	90%	10%	-	4 yrs
Buerger's Disease	23	90%	10%	-	5 yrs
End-Stage Heart Disease	250	80%	10%	10%	6 yrs
Vitiligo	10	70% Body, Head, Neck			1 yr
		10% - 40% fingers, foot, distal areas			
Liver Cirrhosis (non-Hepatitis Virus B & C)	41	-	88%	12%	3 yrs
Chronic Renal Failure (pre-dialysis only)	39	79%	21%	-	3 yrs

GIRL RECEIVES ENGINEERED TRACHEA TREATED WITH HER OWN STEM CELLS


You want to be a brain cell? You have to study! You goof off - you'll end up in the rectum!
stem cell

Question 1

- **Which of the following are pluripotent stem cells?**

a. Cells has the potential to differentiate into any adult cell type forming an entire organism

b. Cells that has limited potential to form only multiple adult cell types

c. Cells that don't have the ability for self renewal

d. Cells has the Potential to form all differentiated cell types except placenta

Question 2

- **Important limitation of using cloned ESCs (SCNT-ESCs) clinically:**
  a. Immune rejection
  b. Produce limited number of cell types
  c. Destruction of human embryos
  d. Difficult to grow and culture in the laboratory

Question 3

- **What are Yamanaka factors?**

  a. OCT3/4, SOX2, KLF4, c-Myc

  b. Growth factors

  c. Cytokines

  d. OCT3/4, SOX2, Nanog

Question 4

- **Mesenchymal stem cells are examples of:**

  a. Pluripotent stem cells

  b. Multipotent stem cells

  c. Totipotent stem cells

  d. Induced pluripotent stem cells (iPS cells)

Dr Abdullah Al Dahmash
Founder and Chairman of Stem Cell Unit

Thank You

KING KHALID UNIVERSITY HOSPITAL & COLLEGE OF MEDICINE
SCU
Stem Cell Unit