Imperial College London

BSc Immunity and Infection Module 1

Stem Cells

&

Regenerative Medicine

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Stem Cells Differentiation Laboratory
IRDB, Faculty of Medicine

Regenerative Medicine

Includes;

- Tissue engineering
- Cellular therapy
- Regeneration

EU Committee meeting Sept 2007:

Repair of functionally compromised cells, tissues or organs by biological substitutes or stimulation of endogenous processes going beyond standard therapies.

Cell Sources

- Primary Cells

- Stem Cells
  - Somatic Stem Cells
  - Embryonic Stem Cells

Sources: Primary cells

Advantage

- **Autologous**

Disadvantages

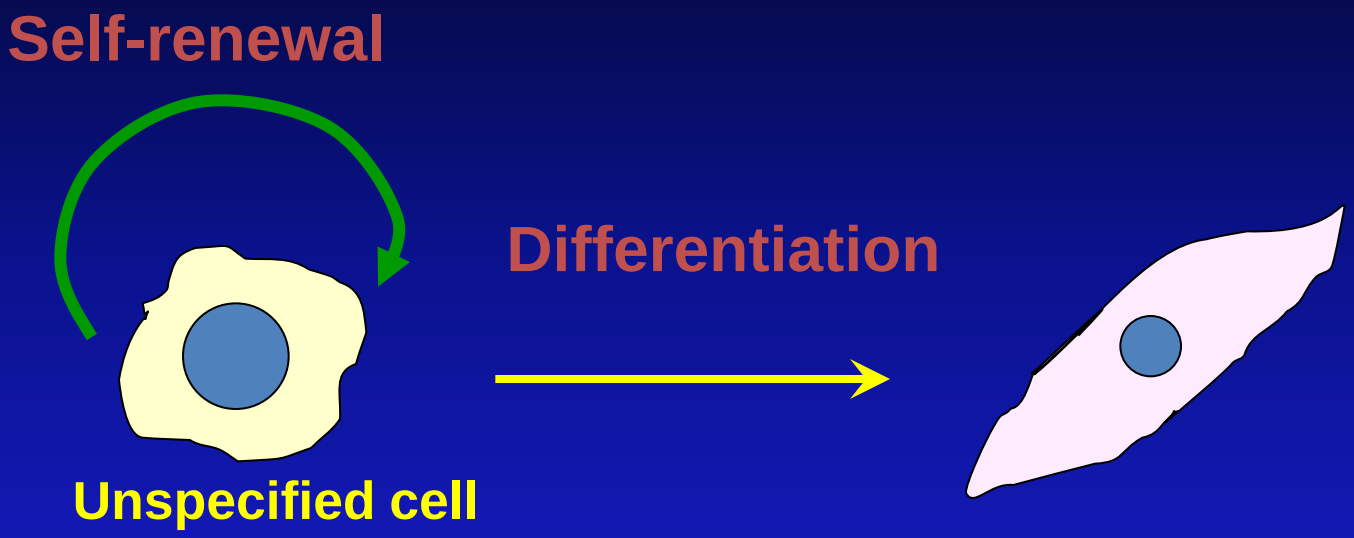
- **Limited availability**
- **Low yield**
- **Poor growth rate**

Cell Sources

- Primary Cells

- Stem Cells
  - Somatic Stem Cells
  - Embryonic Stem Cells

Stem Cells



Self-renewal: A cell divides to generate daughter cell(s) equivalent to the mother cell.

Differentiation: Give rise to specialised cell types.

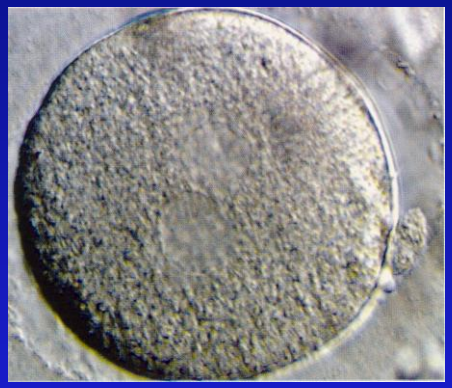
Cell Potency

The range of commitment options available to a cell.

- **Totipotent**
- **Pluripotent**
- **Multipotent**

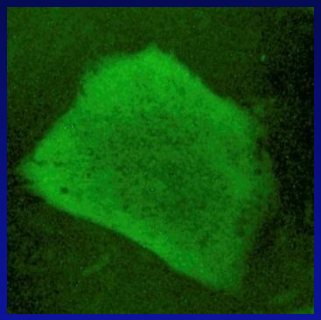
Totipotent

A totipotent cell has the capacity to form an entire organism



Pluripotent

- **Able to form all the body's cell lineages, including germ cells.**



hESC

Ectoderm

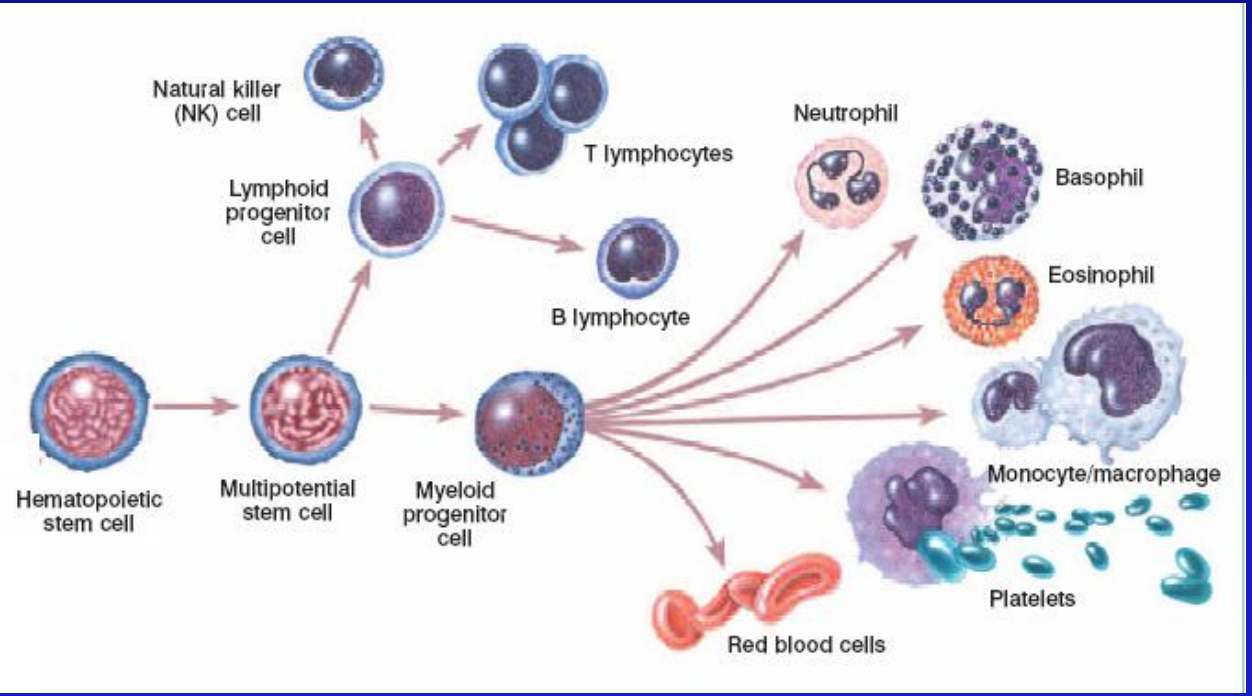
Mesoderm

Endoderm

Germ cell

Multipotent

- Can form multiple cell types that constitute an entire tissue or tissues.



Cell Sources

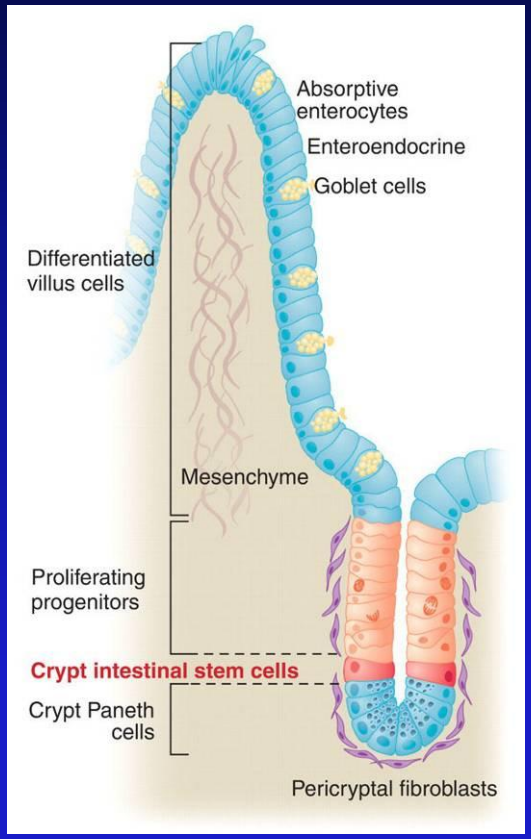
- Primary Cells

- Stem Cells
  - Somatic Stem Cells
  - Embryonic Stem Cells

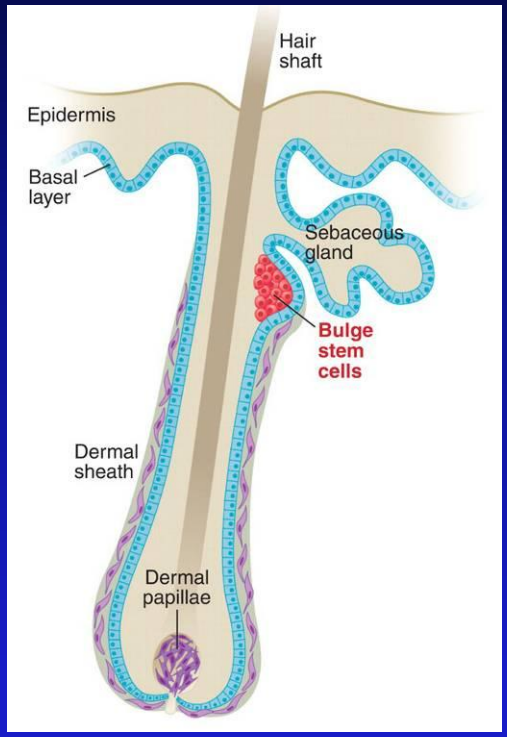
Cell Sources

- Primary Cells
- Stem Cells
  - Somatic
    - Tissue (Niche) -specific
    - Cord blood & placenta
    - Amniotic fluid
  - Embryonic

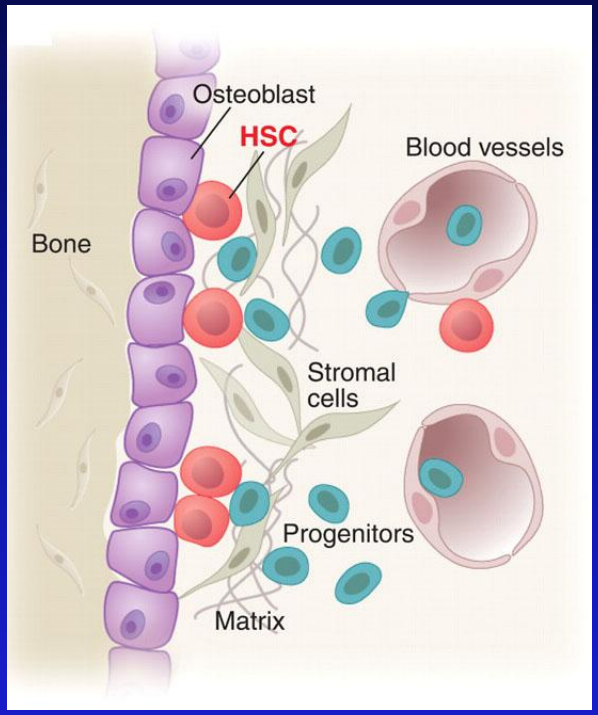
Adult (Niche-specific) Stem Cells



Intestine

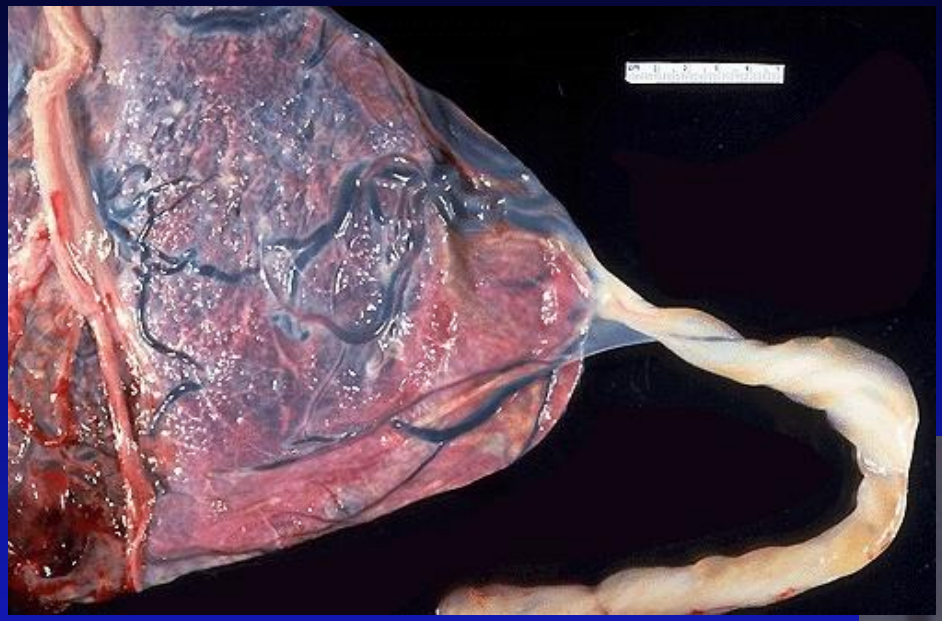


skin



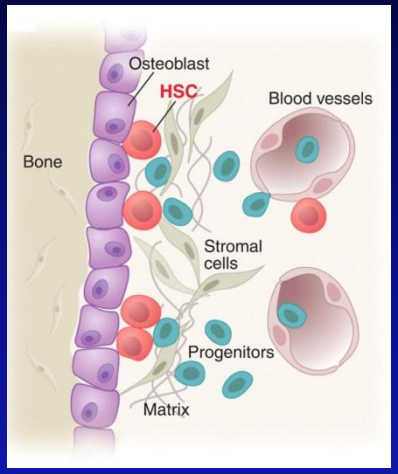
Bone marrow

Cord blood stem cells

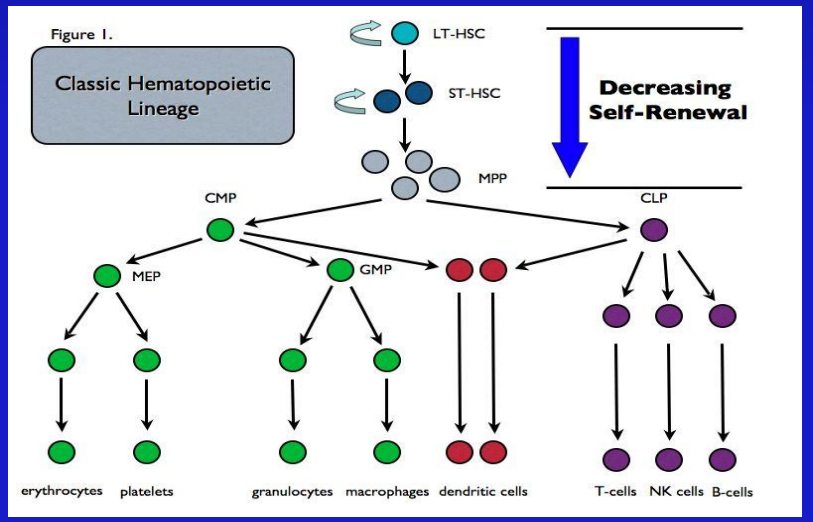


Features of Somatic Stem Cells

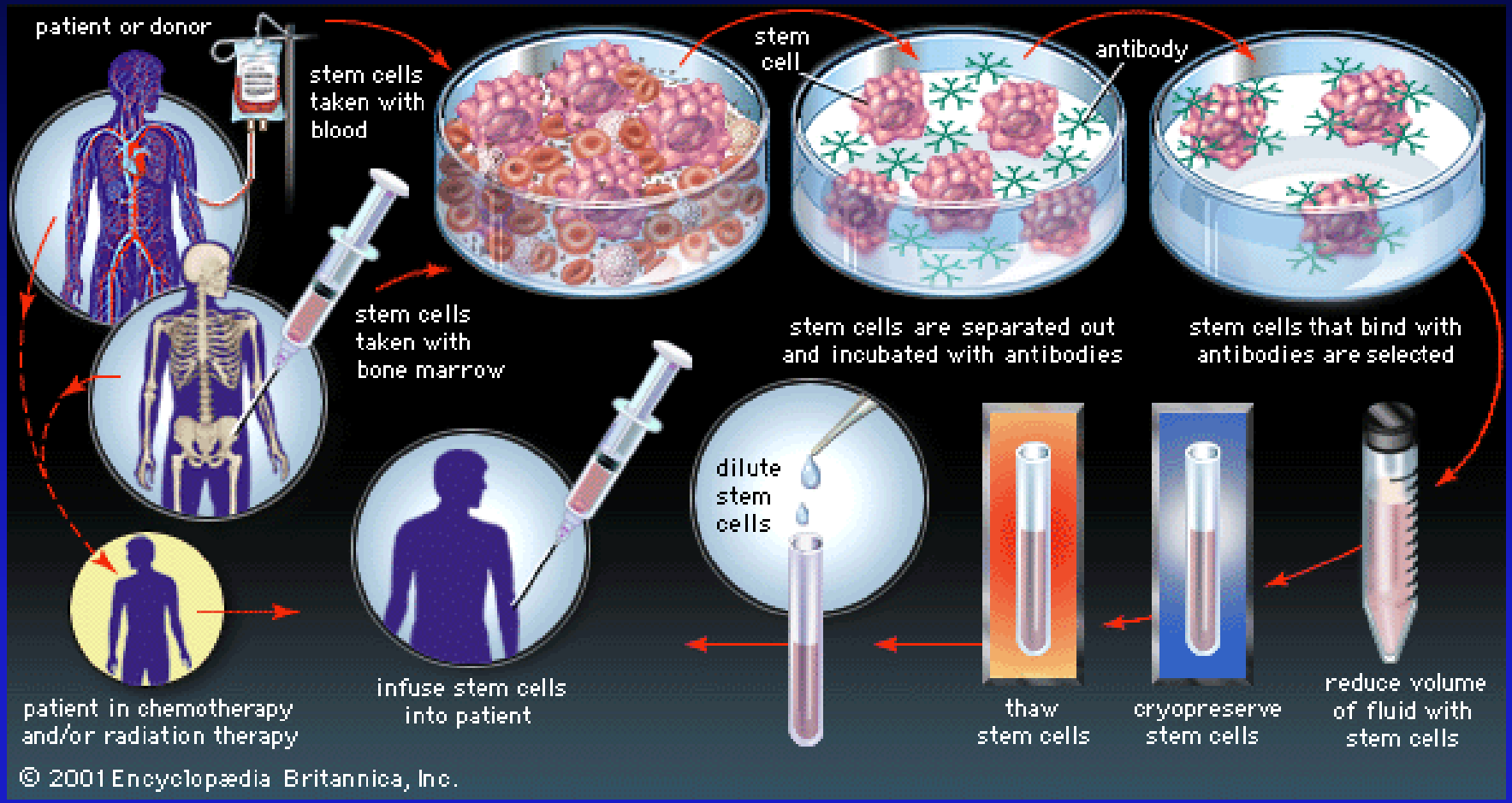
- **Limited self-renewal capacity:**
  - Niche-dependent self-renewal;
  - Capable of life-long self-renewal.



- **Multipotent lineage commitment**
  - Ready for transplantation;
  - Lower plasticity (potency);
  - No teratoma formation



Bone Marrow Transplantation



‘Mesenchymal Stem Cells’

- **BMSC (bone marrow stromal cell):**
  - A subpopulation of bone marrow cells displaying skeletal differentiation potential (bone, cartilage and fat);
  - Rapid adherence to tissue culture plastic;
  - Fibroblast-like appearance;
  - Have colony-forming unit capacity.

- **MSC:** (exist in BM, liver, adipose tissue,….)
  - A conceptual postnatal progenitor of most if not all derivatives of mesoderm.

Bianoco et al., Cell Stem Cell (2008) 2:313;

‘Mesenchymal Stem Cells’ in Transplantation

- **Treat other diseases:**
  - heart failure.

By production of cytokines and other factors

- **Enhance engraftment of other stem cells.**

English et al., Cell Stem Cell (2010) 7:431.

Cell Sources

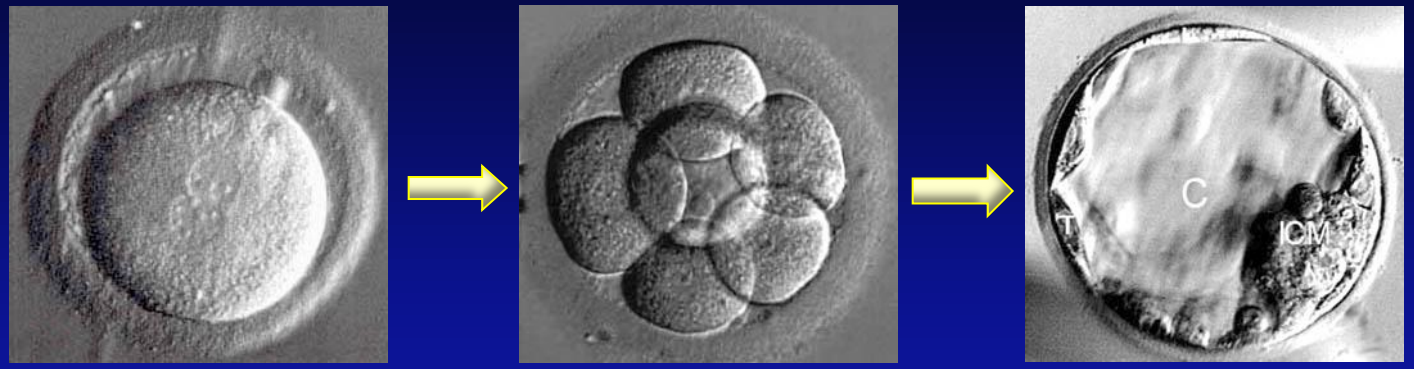
- Primary

- Stem

  - **Somatic**
    - Niche-specific
    - Cord blood & placenta
    - Amnionic fluid

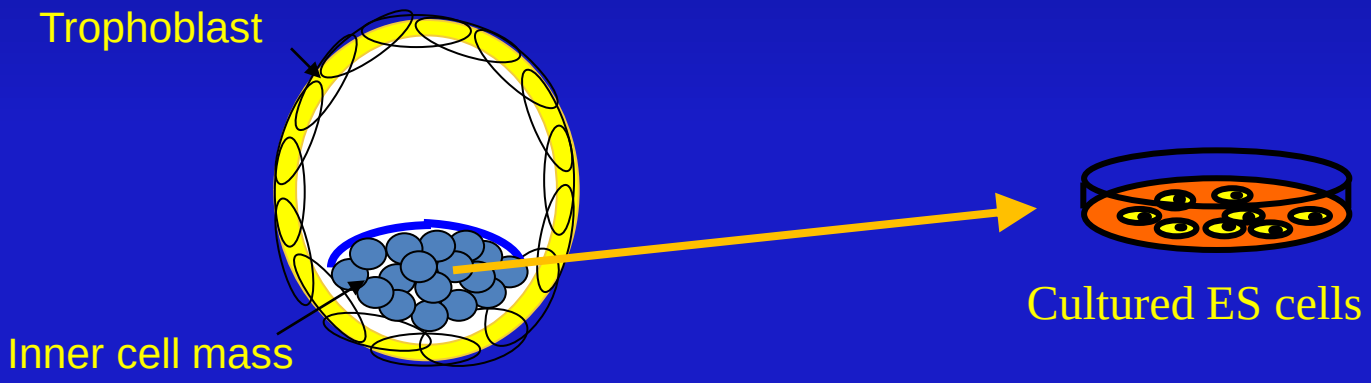
  - **Embryonic Stem Cells**

Embryonic Stem Cells (source)



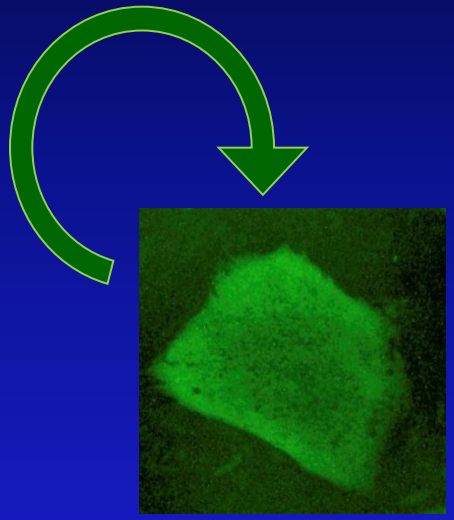
Zygote 6-8 Cells Blastcyst

http://www.advancedfertility.com/embryos.htm



Features of Embryonic Stem Cells

Unlimited Self-renewal



hESC

Pluripotent

Blood cells

Neural cells

Cardiac cells

Myoblasts

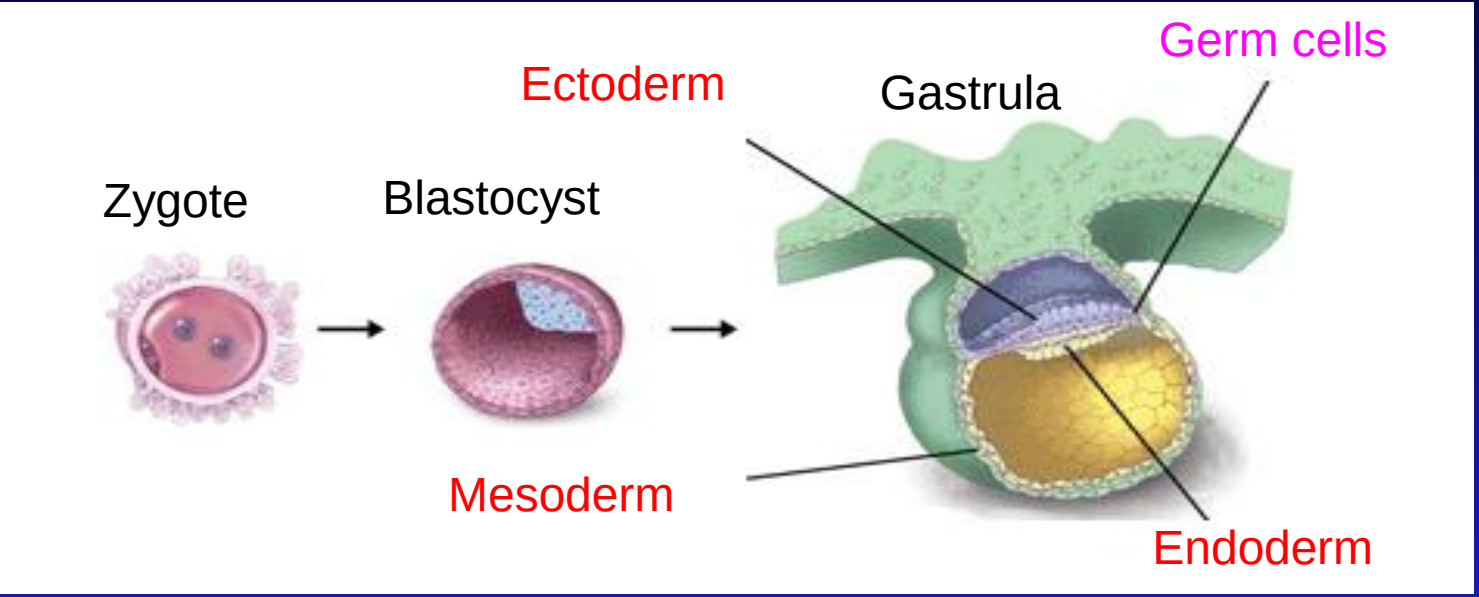
hepatocyte

Pancreas

Osteoblasts

Germ cells
etc

Embryonic Germ layers



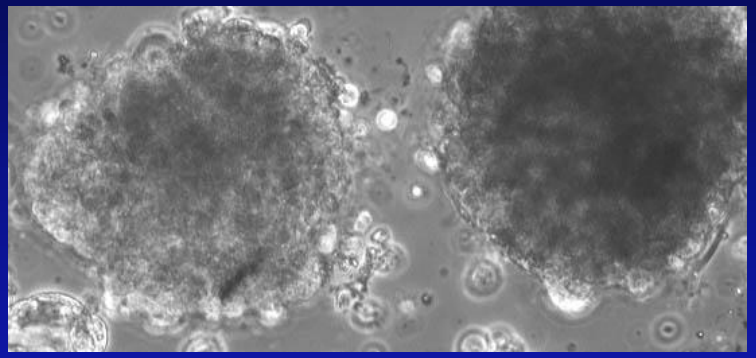
Ectoderm: Neural lineages, skin cells, etc;

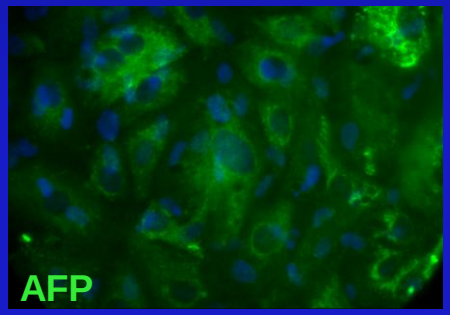
Mesoderm: Bone, muscle, blood cells, etc;

Endoderm: Liver, pancrease, lung, etc.

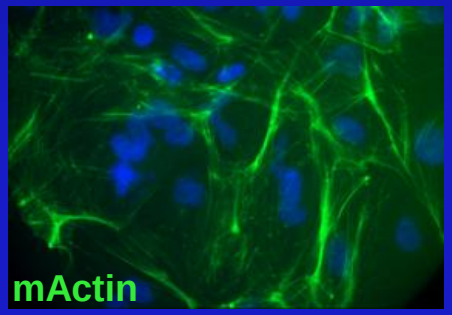
Differentiation of ESC *in vitro*

- **Embryoid body:**

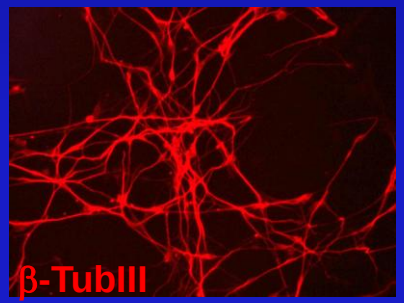




Endoderm



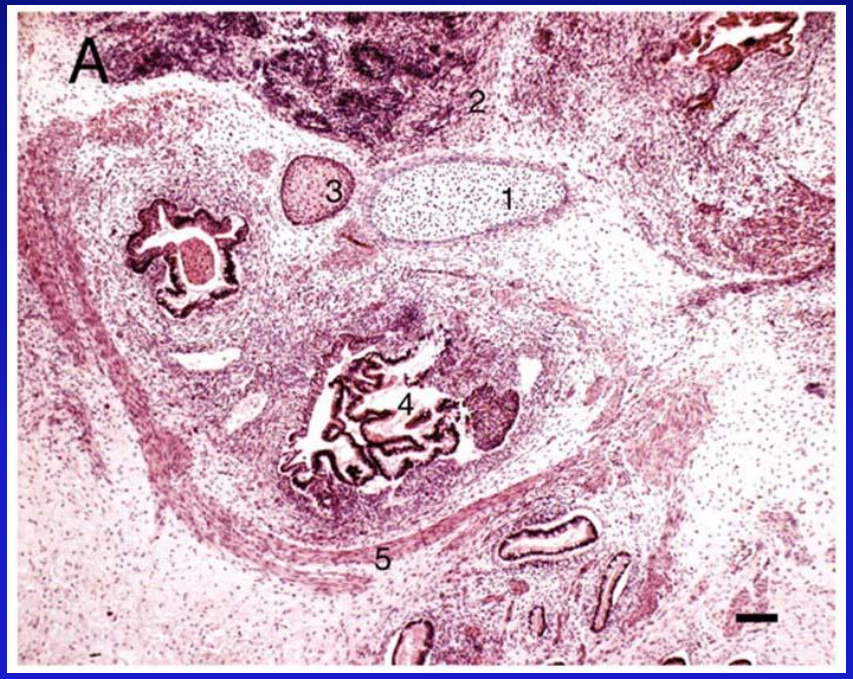
Mesoderm



Ectoderm

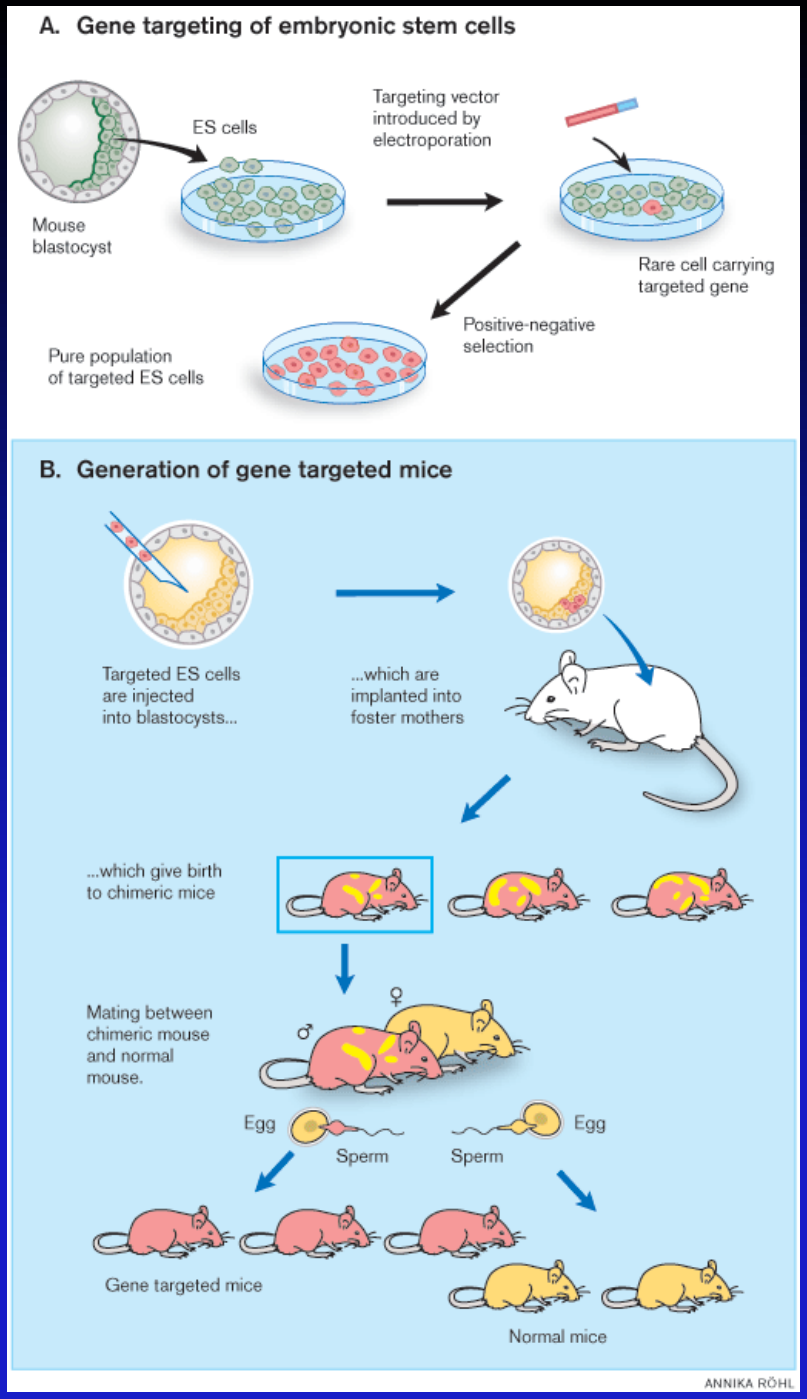
Differentiation of ESC *in vivo*

Teratomas



Chimera

Gene Targeting in Mice

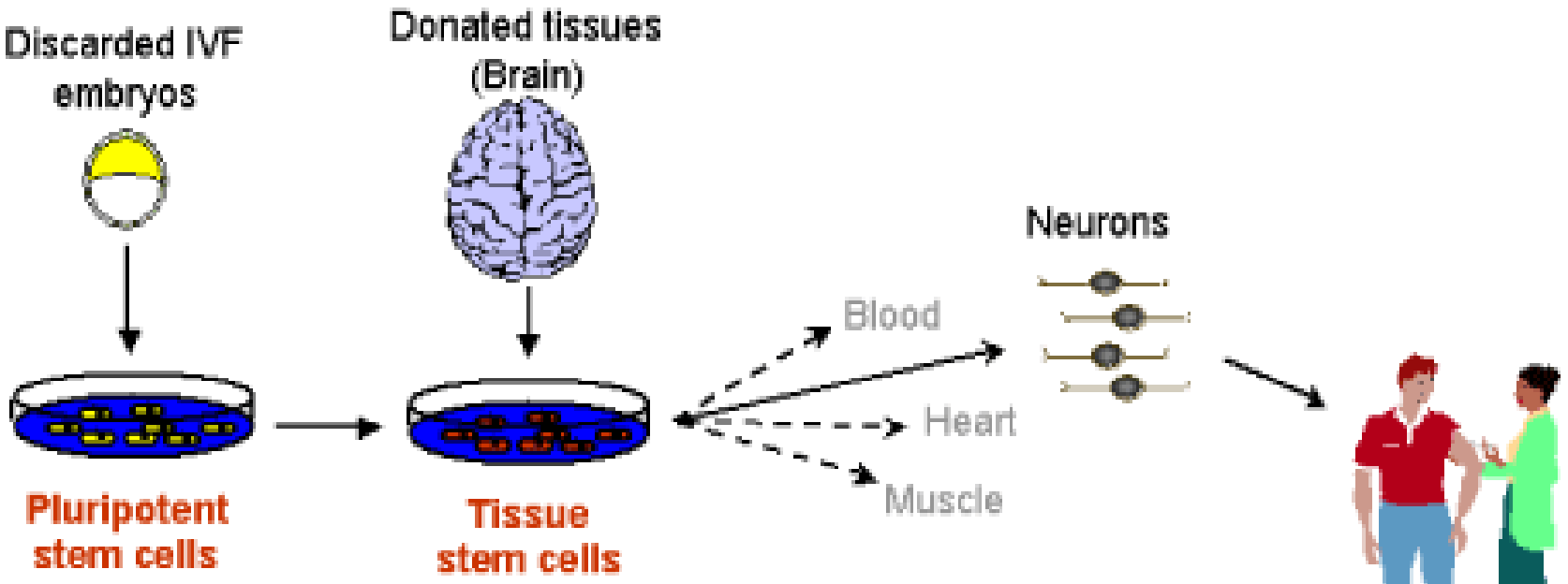


The Nobel Prize in Physiology or Medicine (2007)

Martin J. Evans
Mario R. Capecchi
Oliver Smithies

Evans & Kaufman. Nature292;154-6:1981

Regenerative Medicine



Parkinson's disease; Diabetes;

http://www.eurostemcell.org/Outreach/outreach_about_stem_cells.htm

Ethics

In vitro fertilization

Family completed

Frozen embryos

Destruction

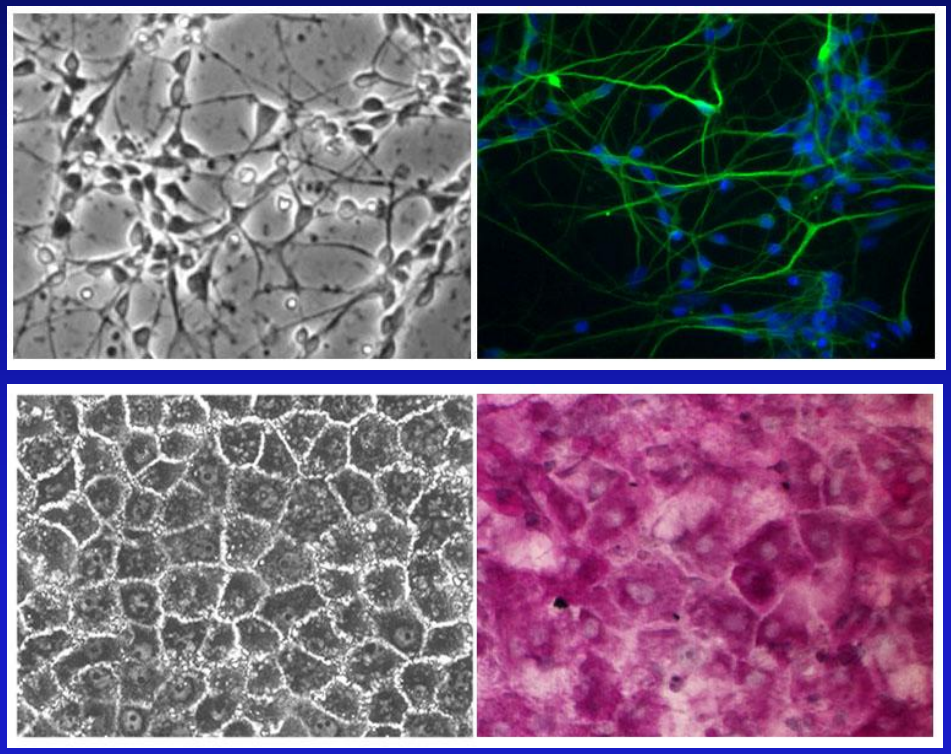
Research

Challenges & Hurdles

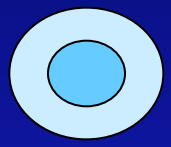
- **Challenges:**
  - Differentiation of specific cell types;
  - Integration and Survival.

‘Directed’ differentiation of stem cells

- Medium supplementation
- Co-culture
-
- Gene transduction



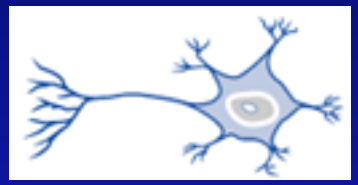
Dopaminergic Neuron Differentiation



ES Cell

Neural progenitor

DA Neuron precursor



DA Neurons

For transplantation

Challenges & Hurdles

- **Challenges:**
  - Differentiation of specific cell types;
  - Integration and Survival.
- **Hurdles:**
  - Immune rejection;
  - Tumorigenesis.

Tumorigenesis

- **Optimal culture conditions.**
  - Maintain genome stability.
- **Eliminating undifferentiated hESC before transplantation.**
  - Removing undifferentiated hESC by FACS sorting, etc.
- **Genetic modification of cells to eliminate tumour cells.**
  - Toxic ablation of tumour cells.

Reduce Immune Rejection

- Stem Cell Bank.
- Immune suppression.
- Immune tolerance.
- Reprogramming.

Reduce Immune Rejection

- Stem Cell Bank:
  - ABO-antigen, HLA matching

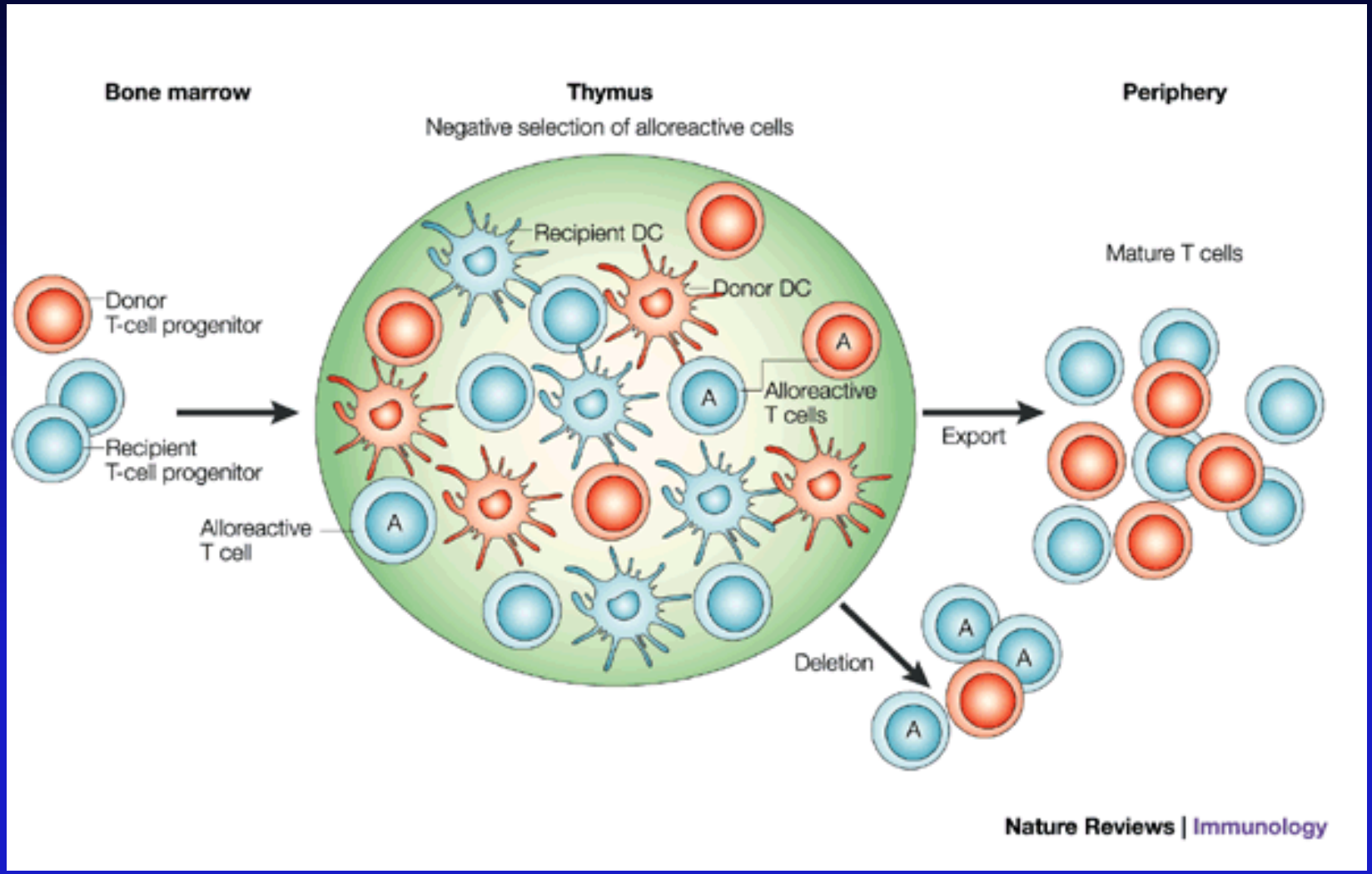
Reduce Immune Rejection

- Stem Cell Bank.
- Immune suppression:
  - Application of Immune suppression drug.

Reduce Immune Rejection

- Stem Cell Bank.
- Immune suppression.
- Immune tolerance:
  - Haematopoietic chimerism

Immune tolerance: -Haematopoietic chimerism

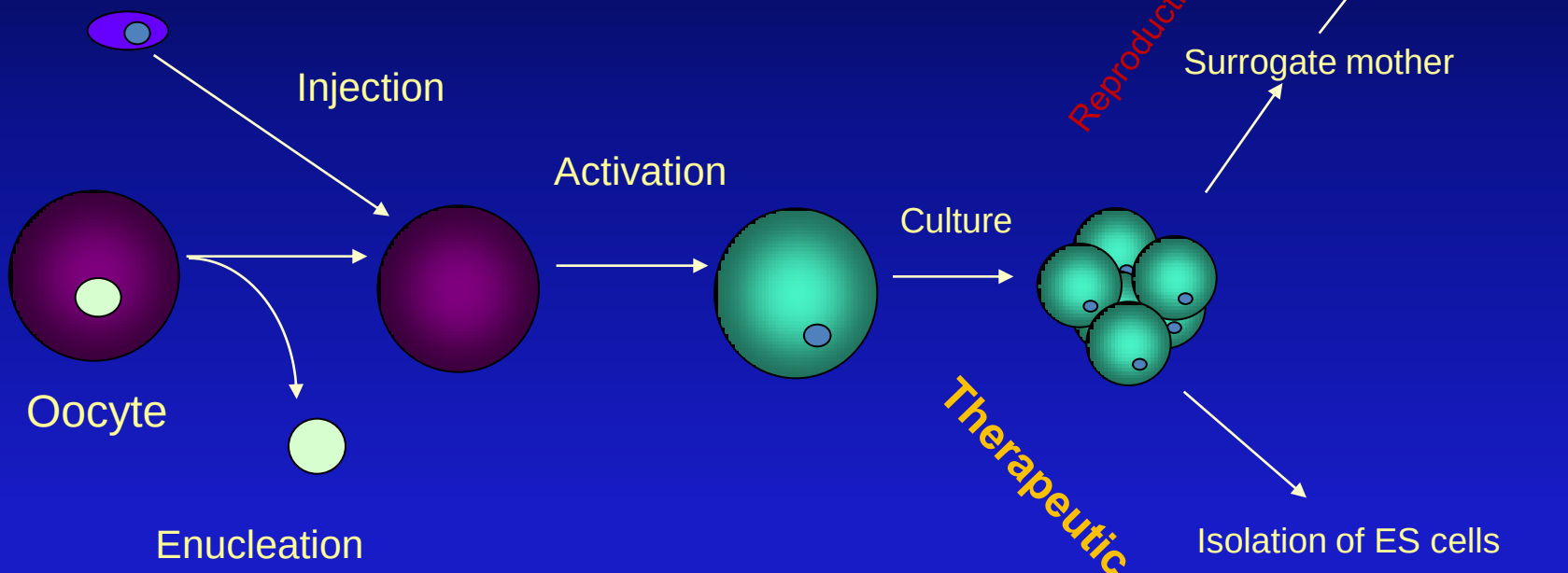


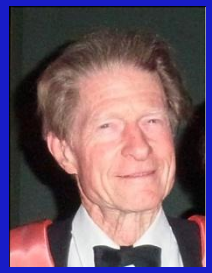
Nature Reviews Immunology (2002) **2**, 859-871

Reduce Immune Rejection

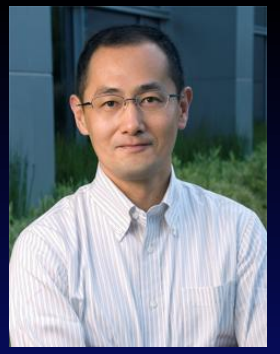
- Stem Cell Bank
- Immune suppression
- Immune tolerance
- Reprogramming:
  - Therapeutic cloning;
  - Reprogramming by other factors.

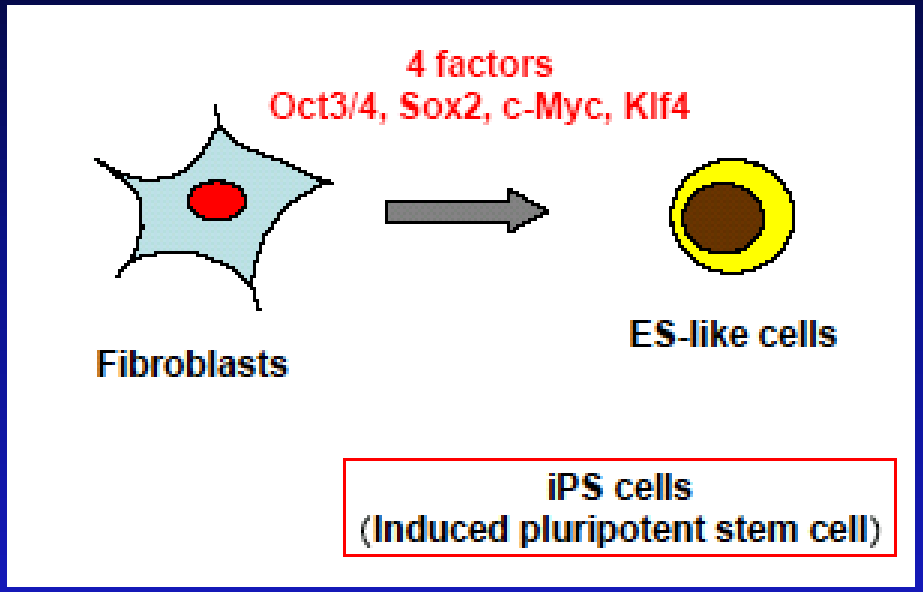
Somatic Cell Nuclear Transfer
(Cloning)

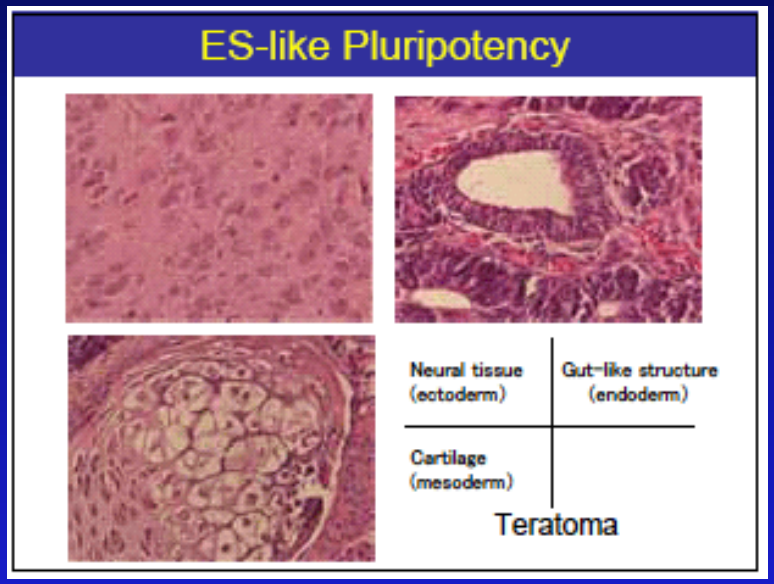


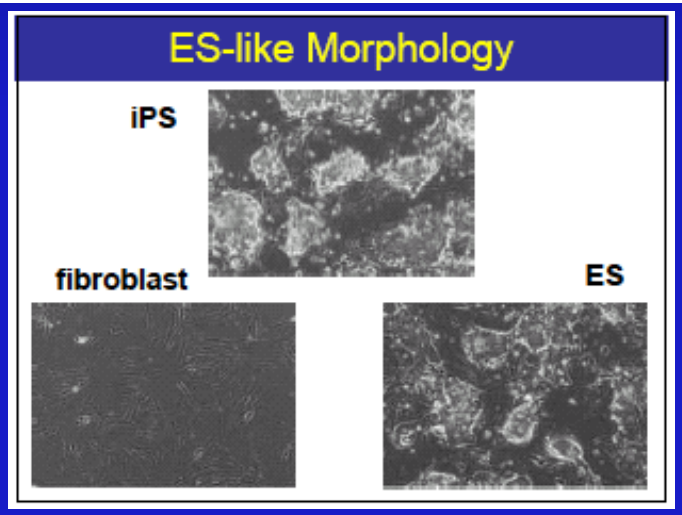


Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors

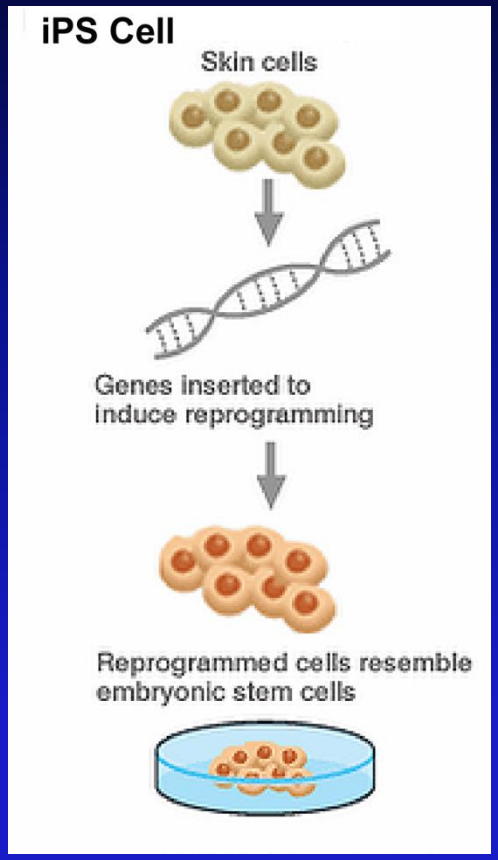








Takahashi & Yamanaka Cell 126;663:2006



- Not the same as ESCs.
- Viral delivery & transgene integration.
- May be selection of undifferentiated cells.
- Higher rates of malignancy than ESCs
- Inefficient – 1 in 5000 transfected cells

Bone marrow

vs

Embryonic

Pros:
- BM Tx is routine
- Can be autologous
- No teratomas
- Clinical trails

Cons:
- Low numbers
- Reduce with age
- Slow growth
- Limited plasticity
- Source/promotion of Ca

Pros:
- Pluripotency
- Availability
- Rapid growth

Cons:
- Safety
- Teratomas
- Immunotolerance
- *Ethics*

References

- Daley & Scadden (2008) Prospect for stem cell-based therapy. *Cell* 132:544.

- Bradley et al (2002) Stem cell medicine encounters the immune system. *Nature Review Immunology* 2: 859-871.