WELCOME TO ALL

II-Msc Zoology

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DEVELOPMENTAL BIOLOGY

UNIT-III

CELLULAR DIFFERENTIATION

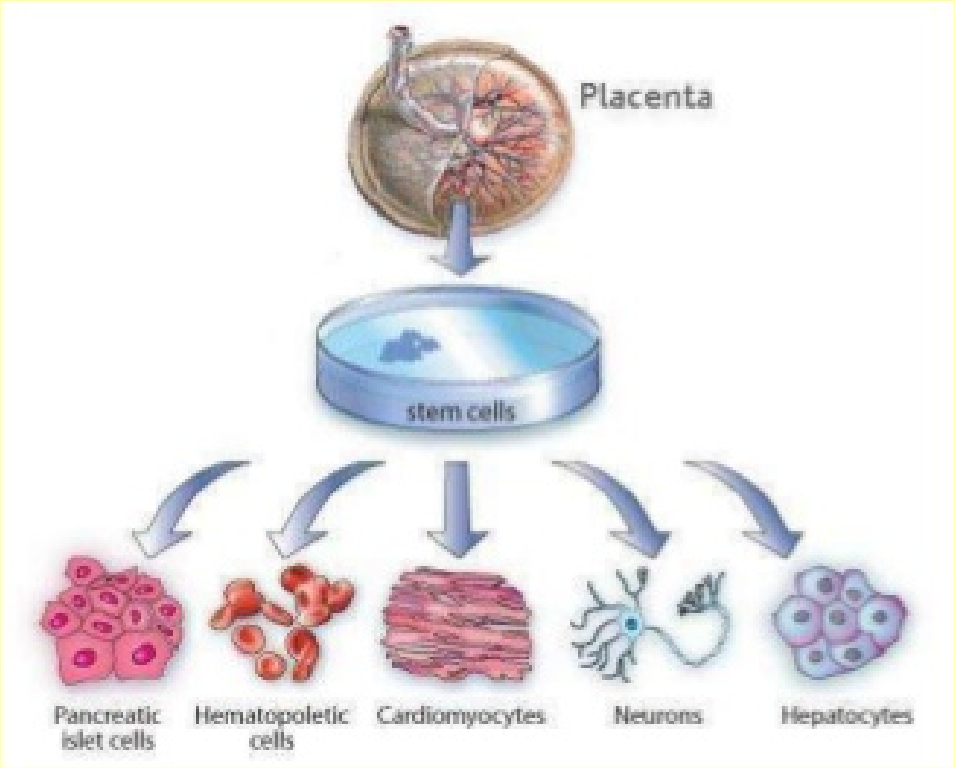
12.08.2020

Cell Differentiation

Specialized Cells

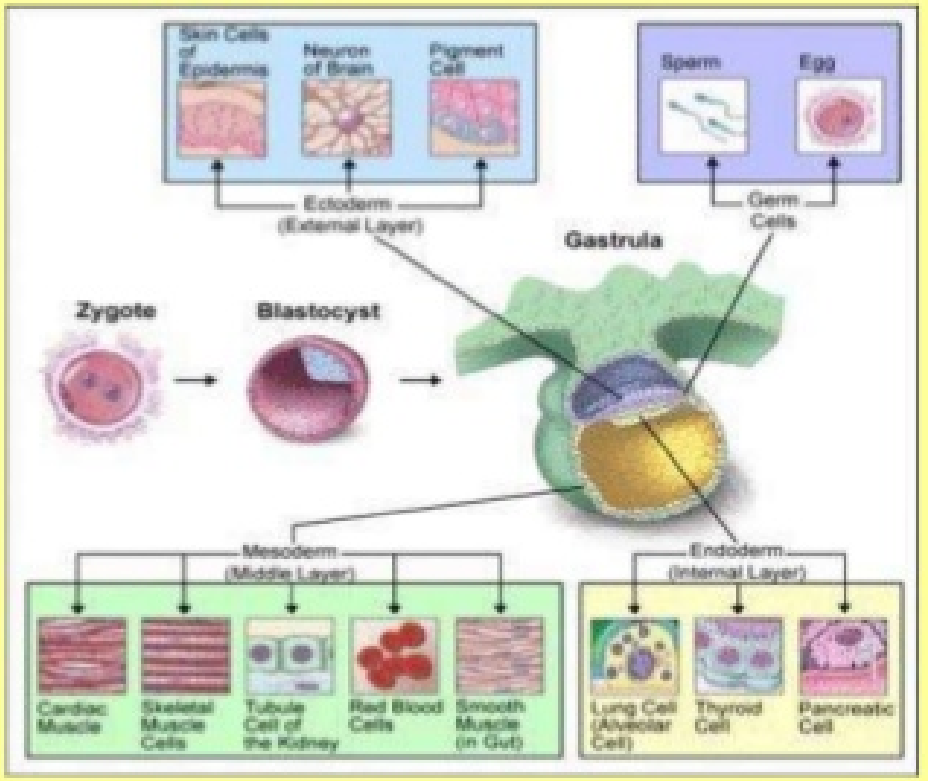
and

Stem Cells



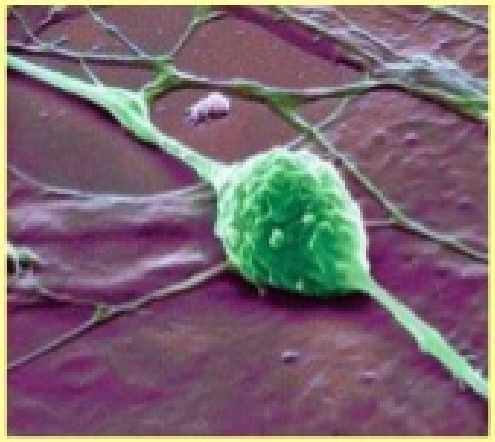
Cell Differentiation

- Multicellular organisms begin as undifferentiated masses of cells
- Variation in DNA expression and gene activity determine the differentiation of cells and ultimately their specialization
- Only specific parts of DNA are activated
- Parts activated determine the function and structure of a cell



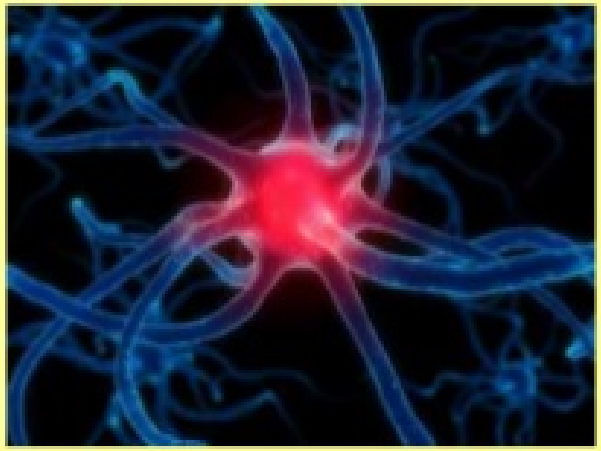
Cell Differentiation

- All cells contain the same DNA so cells initially have the potential to become any type of cell
- Cell Differentiation is irreversible
- All cells in multicellular organism have the same number of chromosomes and DNA

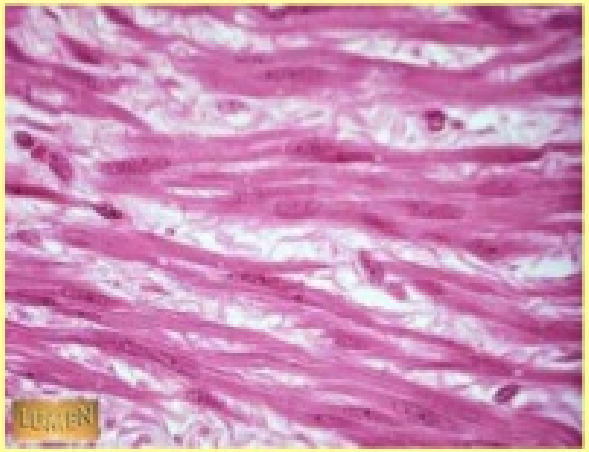


- Different parts of the genetic instructions are used in different types of cells
  - influenced by the cell's environment
- Chemical signals may be released by one cell to influence the development and activity of another cell.

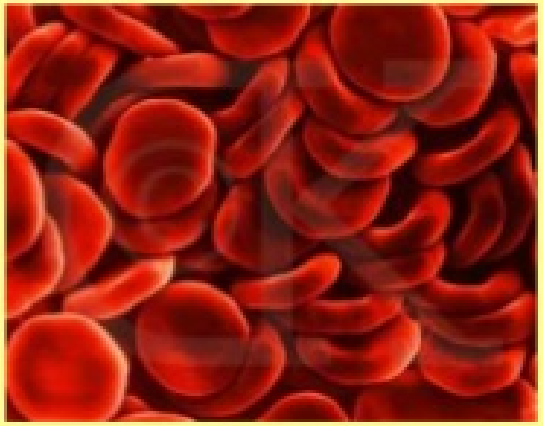
Specialized Cells



Nerve Cells communicate information either by using electric signals (within a cell) or chemical signals (between cells).

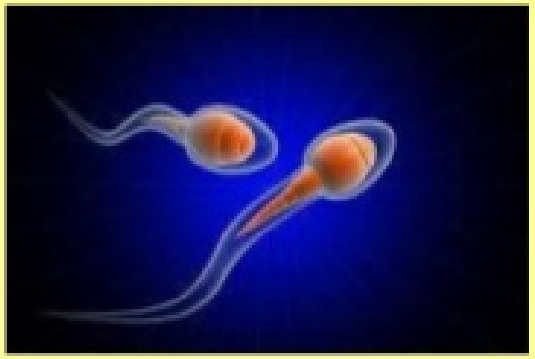


Muscle cells contain protein filaments that slide past one another, producing a contraction that changes both the length and the shape of the cell.

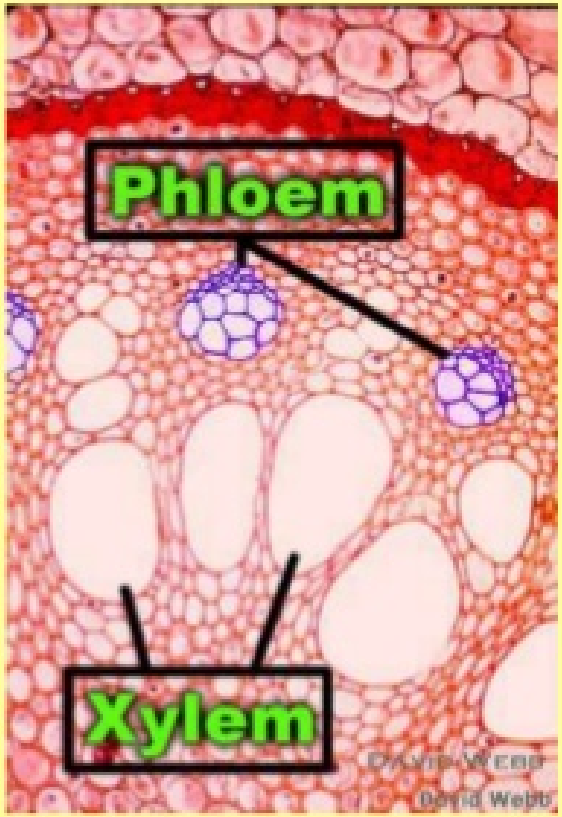


Blood cells are the most common type of blood cell and the vertebrate organism's principal means of delivering oxygen to the body tissues

Specialized Cells



Sperm cells are the male reproductive cell;
the male gamete;

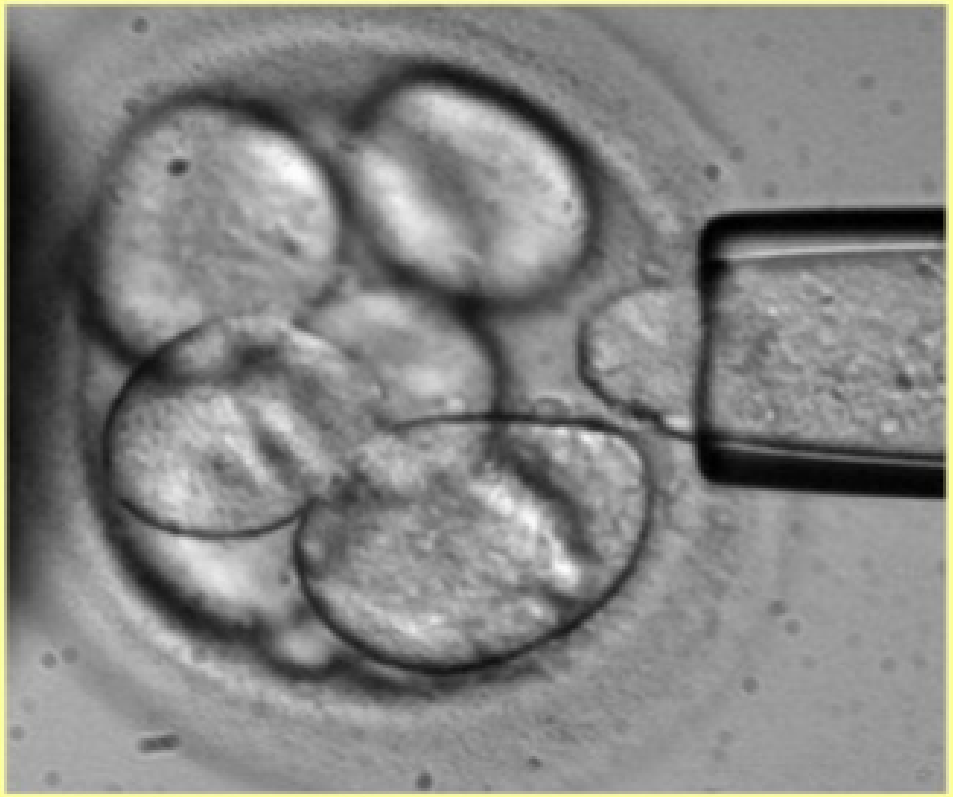


Xylem are the long trachea elements that transport water in a plant.

Phloem is part of a plant that carries food down the stem, and carries sugar, and protein to all parts of the plant that need them.

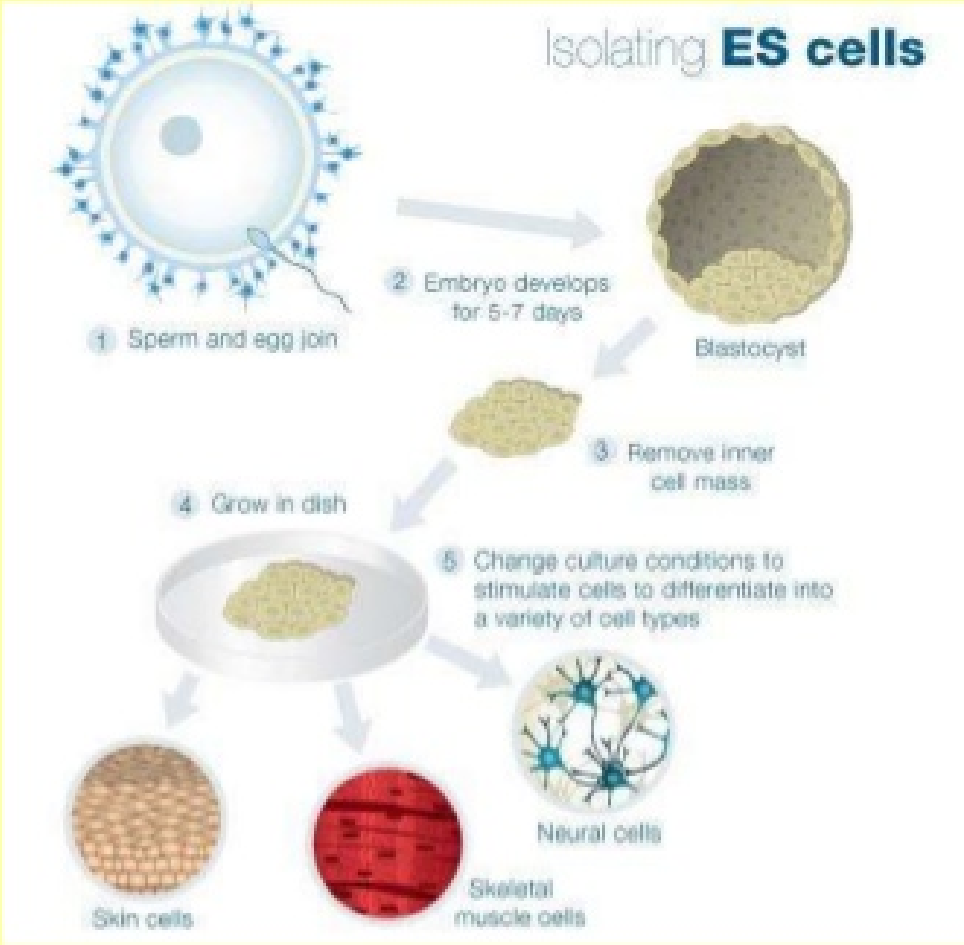
Stem Cells

- Internal repair syste
  - divide without limit, to replenish other cells as long as the organism is living.
- When a stem cell divides, each new cell has the potential either to remain a stem cell or become another type of cell with a more specialized function:
  - i.e. muscle cell, a red blood cell, or a brain cell.
- Unspecialized but can give rise to specialized cells



Types of Stem Cells

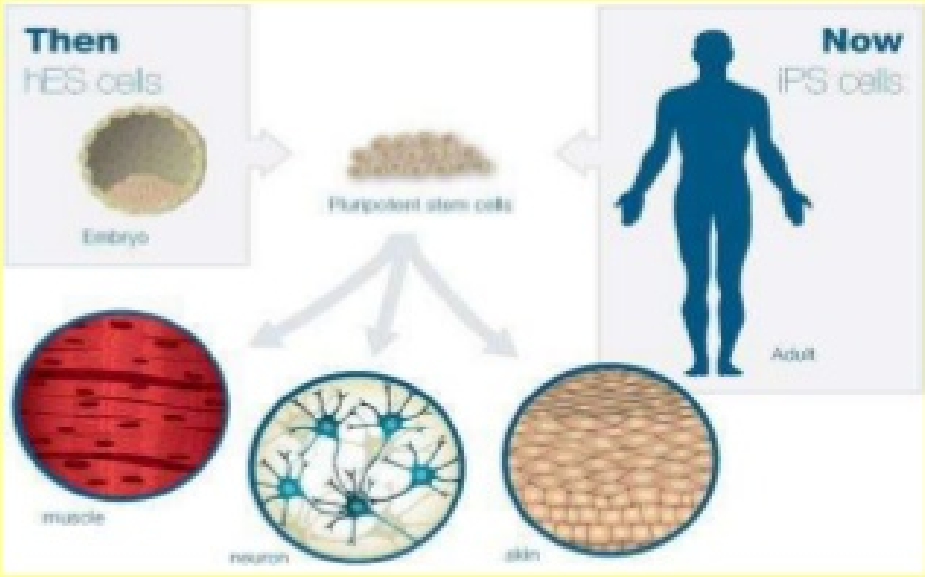
- Embryonic Stem Cells (ES cells)
  - derived from a four- or five-day-old human embryo in the blastocyst phase of development.
  - embryos are usually extras created in IVF (in vitro fertilization) clinics where several eggs are fertilized in a test tube
    - only one is implanted into a woman.



Types of Stem Cells

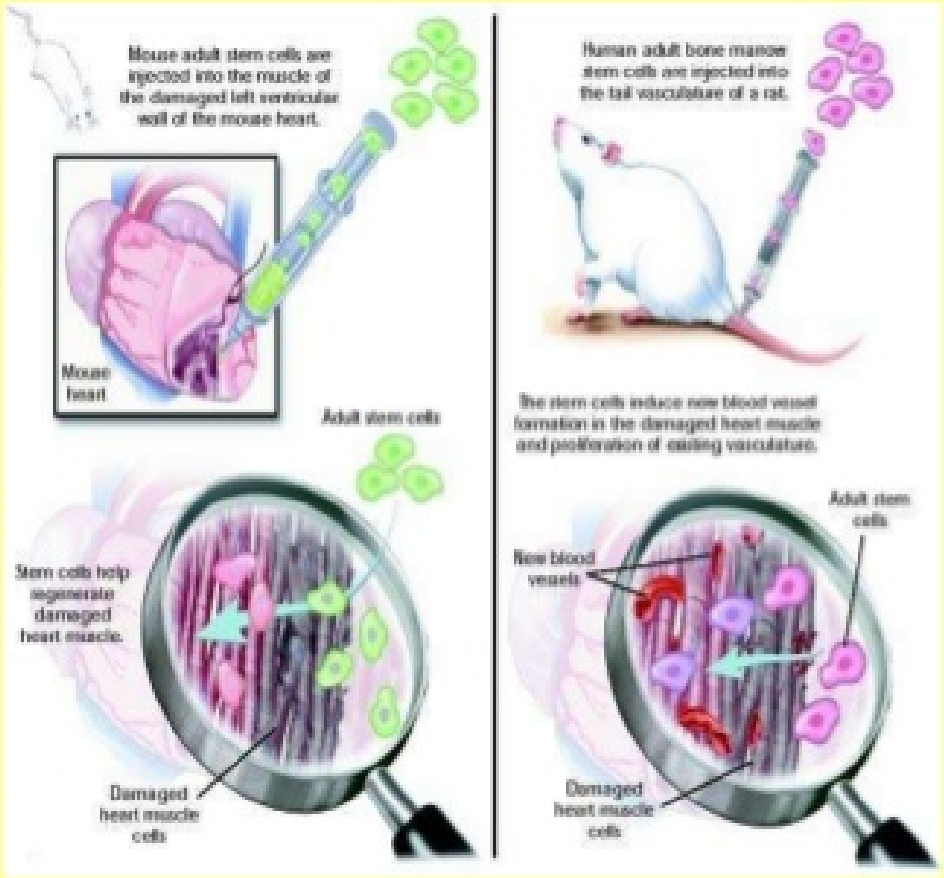
- An adult stem cell is thought to be an undifferentiated cell, found among differentiated cells in a tissue or organ that can renew itself (like bone marrow) and can differentiate to yield some or all of the major specialized cell types of the tissue or organ.

- Induced pluripotent stem cells (iPSCs) are adult cells that have been genetically reprogrammed to an embryonic stem cell–like state by being forced to express genes and factors important for maintaining the defining properties of embryonic stem cells.



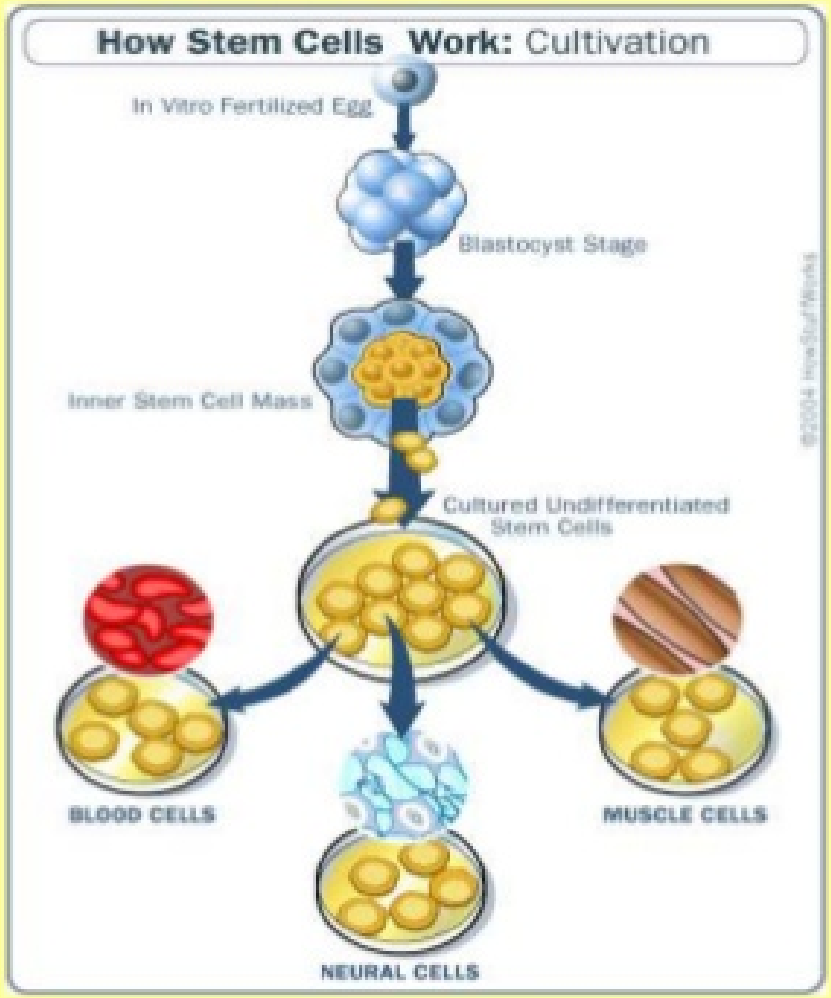
Potential Uses of Stem Cells

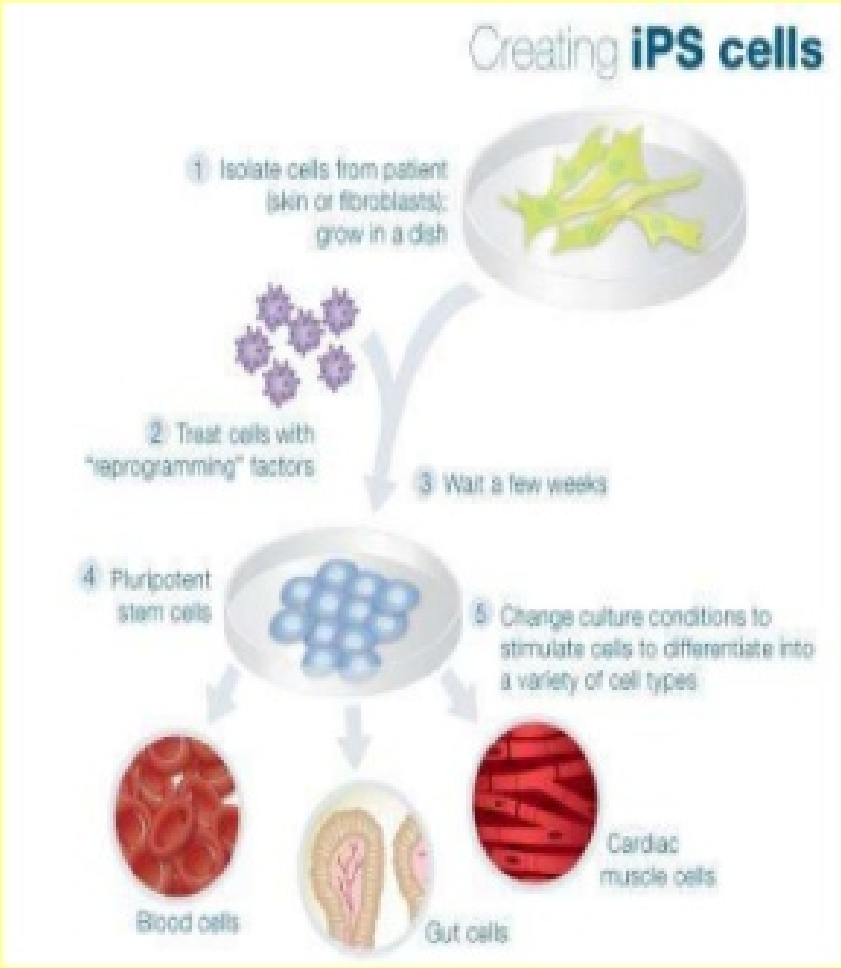
- Test new medicines
- transplantable tissues and organs
- treat diseases including Alzheimer's diseases, spinal cord injury, stroke, burns, heart disease, diabetes, osteoarthritis, rheumatoid arthritis, and cancer
- Bone marrow contains blood-forming stem cells (hematopoietic stem cells) have been used for decades to treat blood cancers and other blood disorders. Umbilical cord blood is another source of hematopoietic stem cells that is being used in treatment.
  - http://marrow.org/Physicians/When_to_Transplant/Diseases_Transplanted.aspx



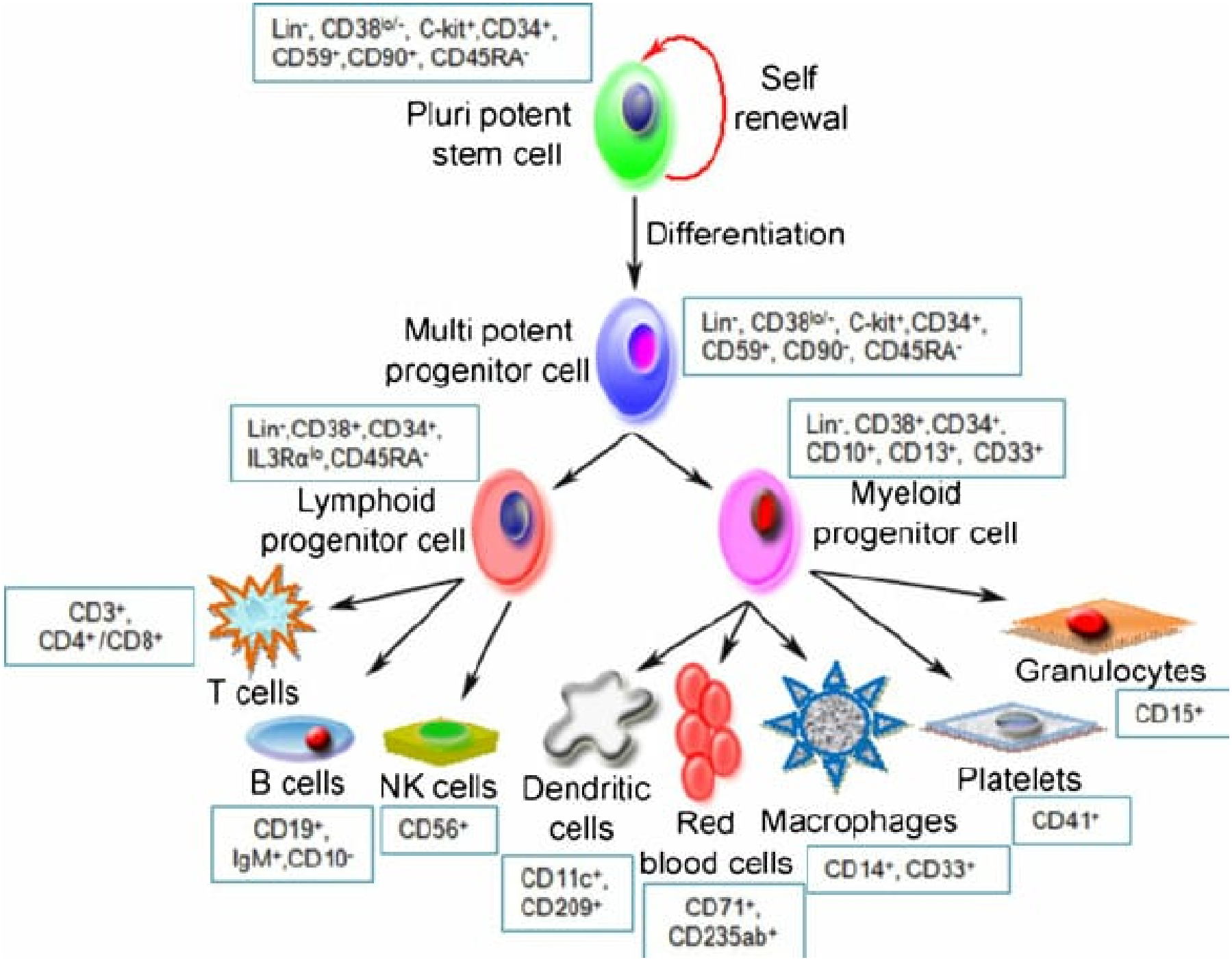
Stem Cells

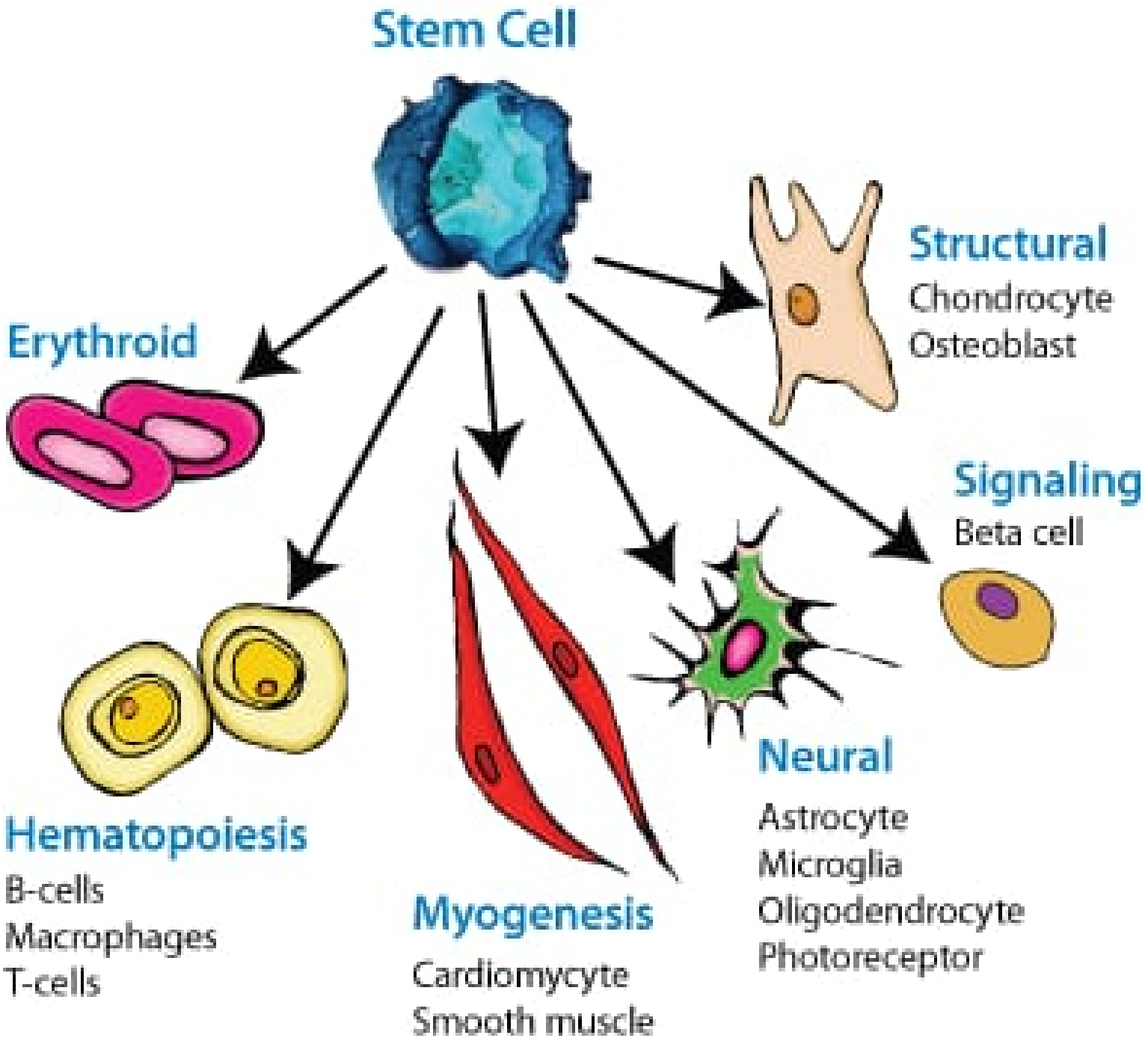
- http://learn.genetics.utah.edu/content/tech/stemcells/scintro/
- http://www.pbs.org/wgbh/nova/body/stem-cells-breakthrough.html
- http://www.youtube.com/watch?v=tJnmyBTJgkQ

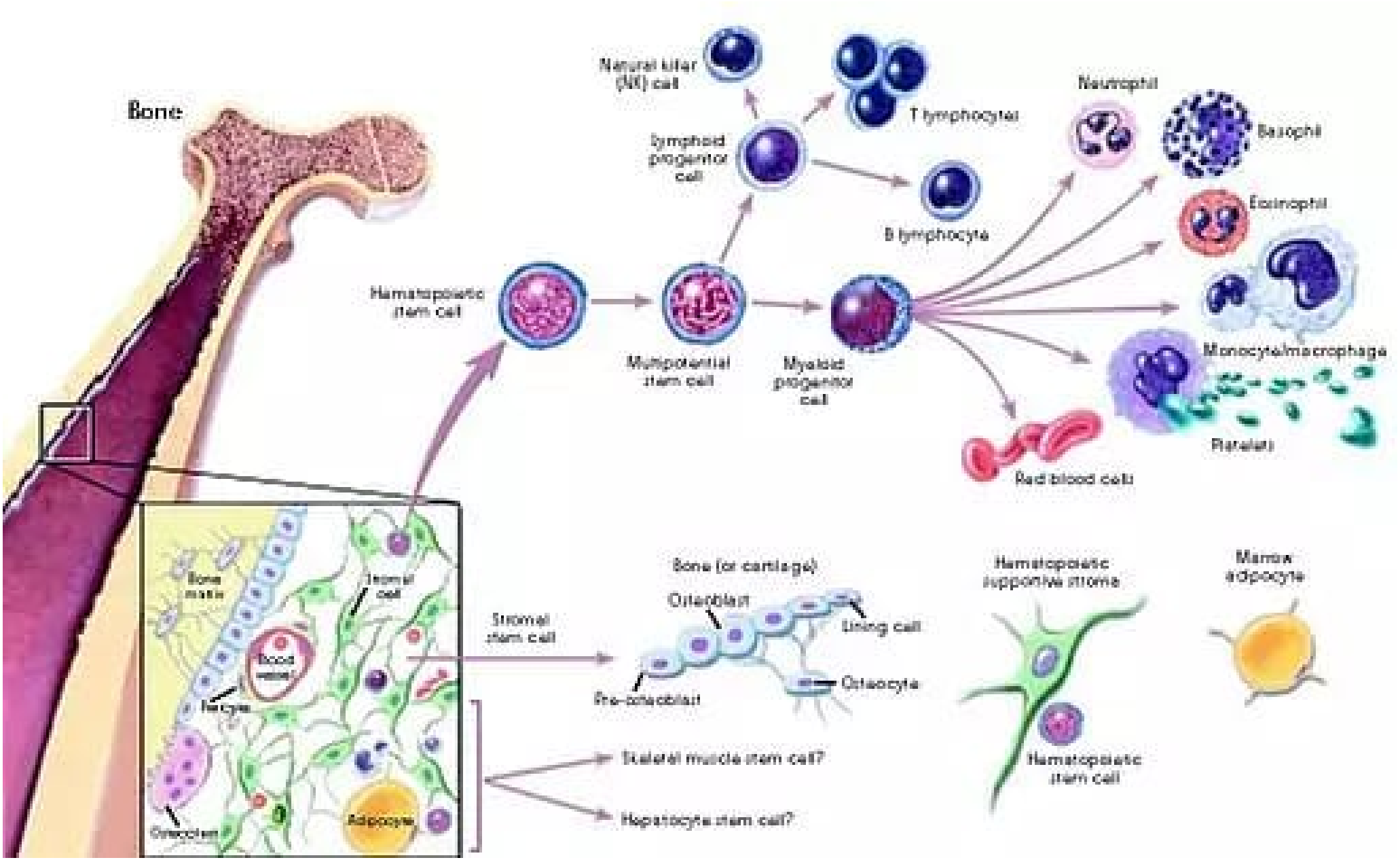




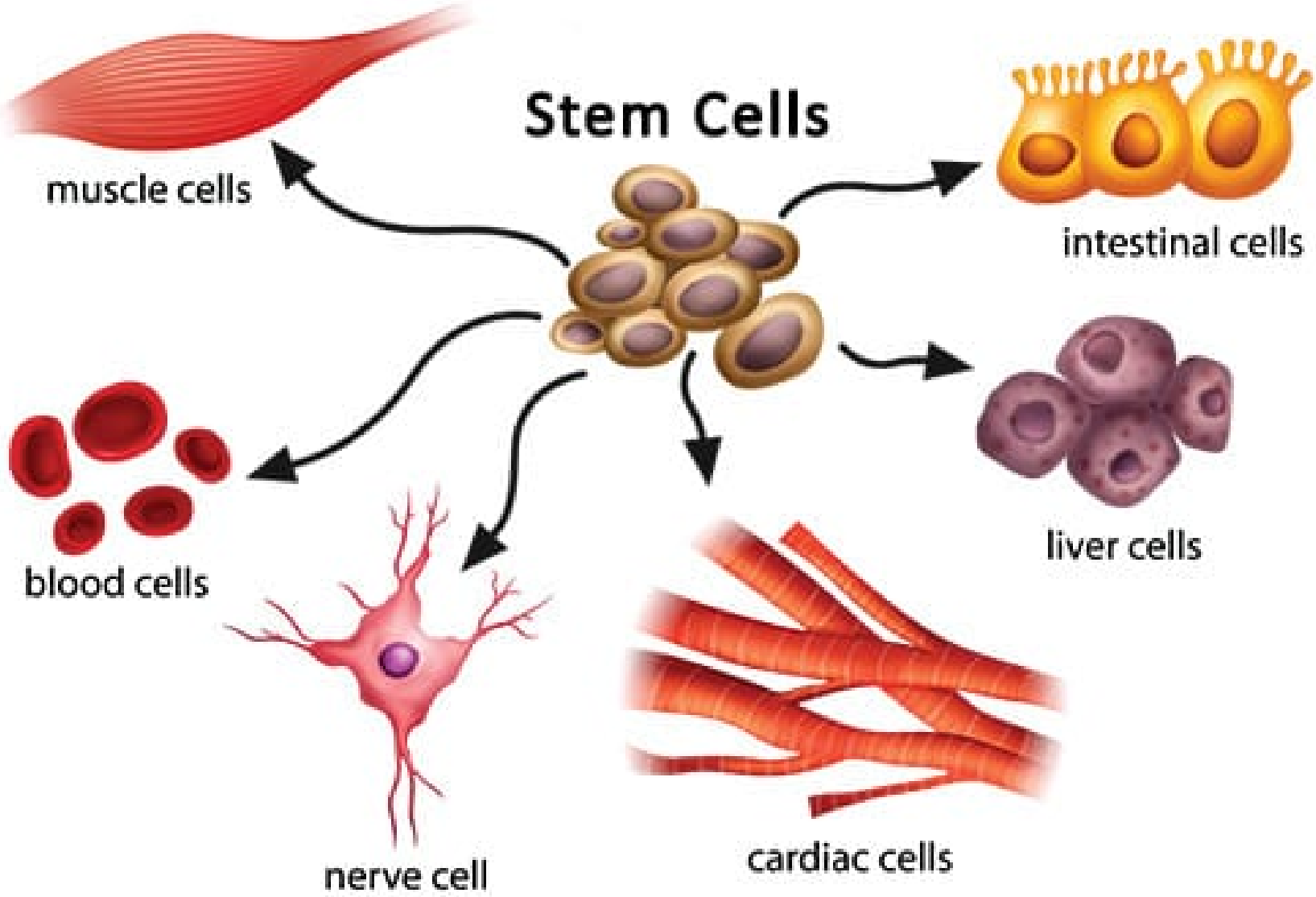
http://www.pbs.org/wgbh/nova/body/stem-cells-research.html

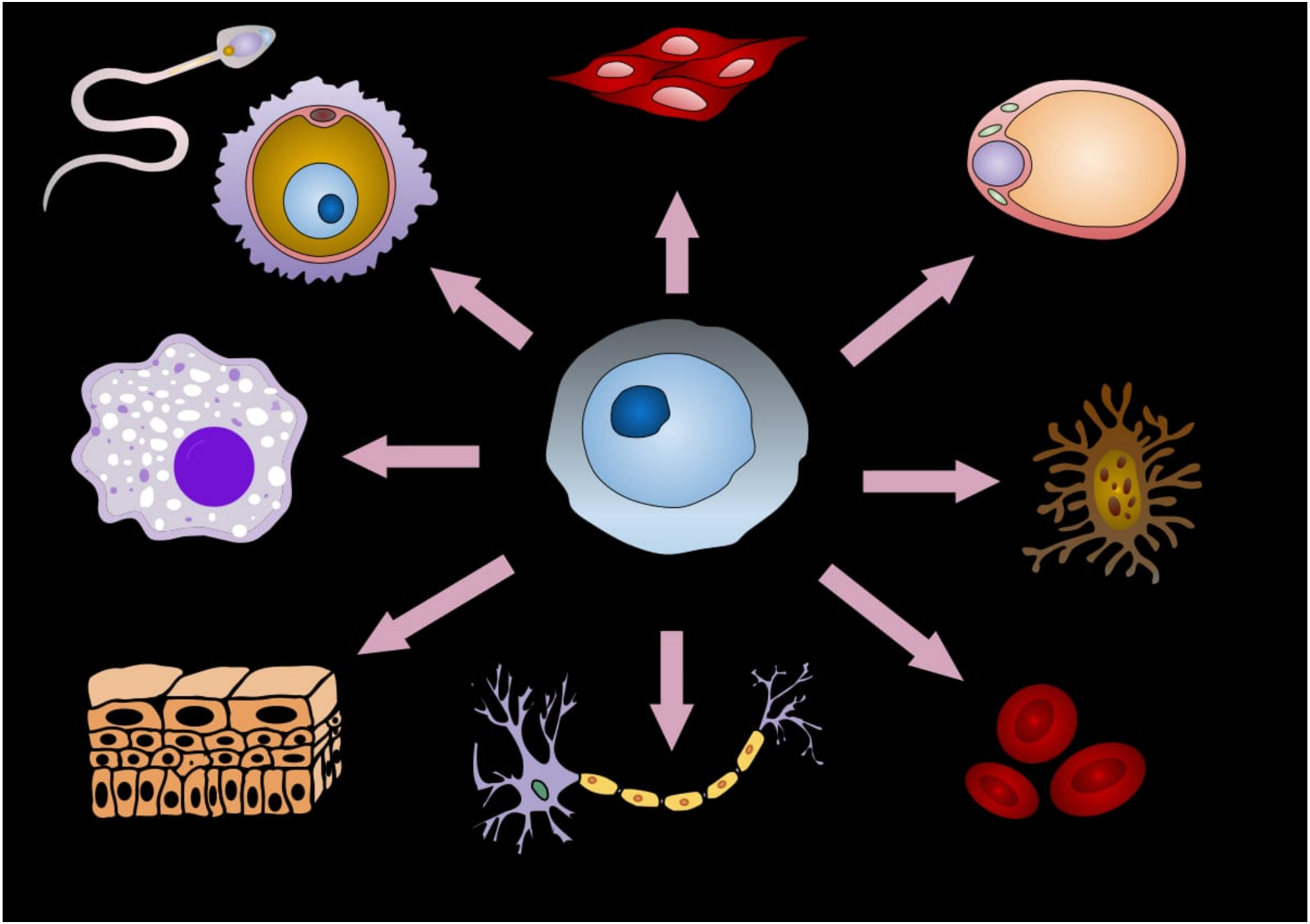

Lin-, CD38lo/-, C-kit+,CD34+, CD59+,CD90+, CD45RA-
Pluri potent stem cell
Self renewal
Differentiation
Multi potent progenitor cell
Lin-, CD38lo/-, C-kit+,CD34+, CD59+, CD90-, CD45RA-
Lin-,CD38+,CD34+, IL3Rαlo,CD45RA-
Lymphoid progenitor cell
Lin-, CD38+,CD34+, CD10+, CD13+, CD33+
Myeloid progenitor cell
CD3+, CD4+/CD8+
T cells
B cells
CD19+, IgM+,CD10-
NK cells
CD56+
Dendritic cells
CD11c+, CD209+
Red blood cells
CD71+, CD235ab+
Macrophages
CD14+, CD33+
Granulocytes
CD15+
Platelets
CD41+

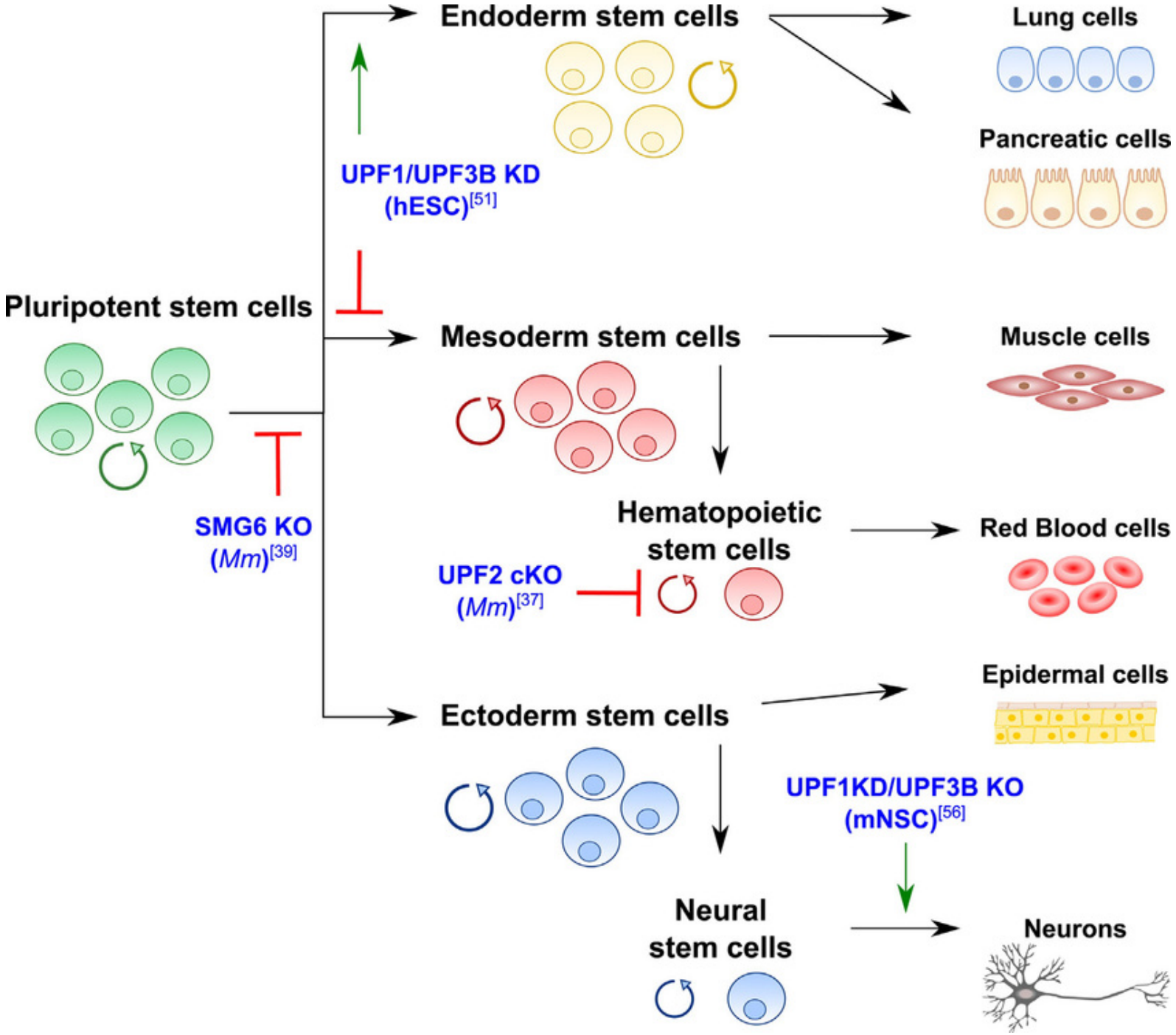

Stem Cell
Erythroid
Structural
Chondrocyte
Osteoblast
Signaling
Beta cell
Neural
Astrocyte
Microglia
Oligodendrocyte
Photoreceptor
Hematopoiesis
B-cells
Macrophages
T-cells
Myogenesis
Cardiomycyte
Smooth muscle

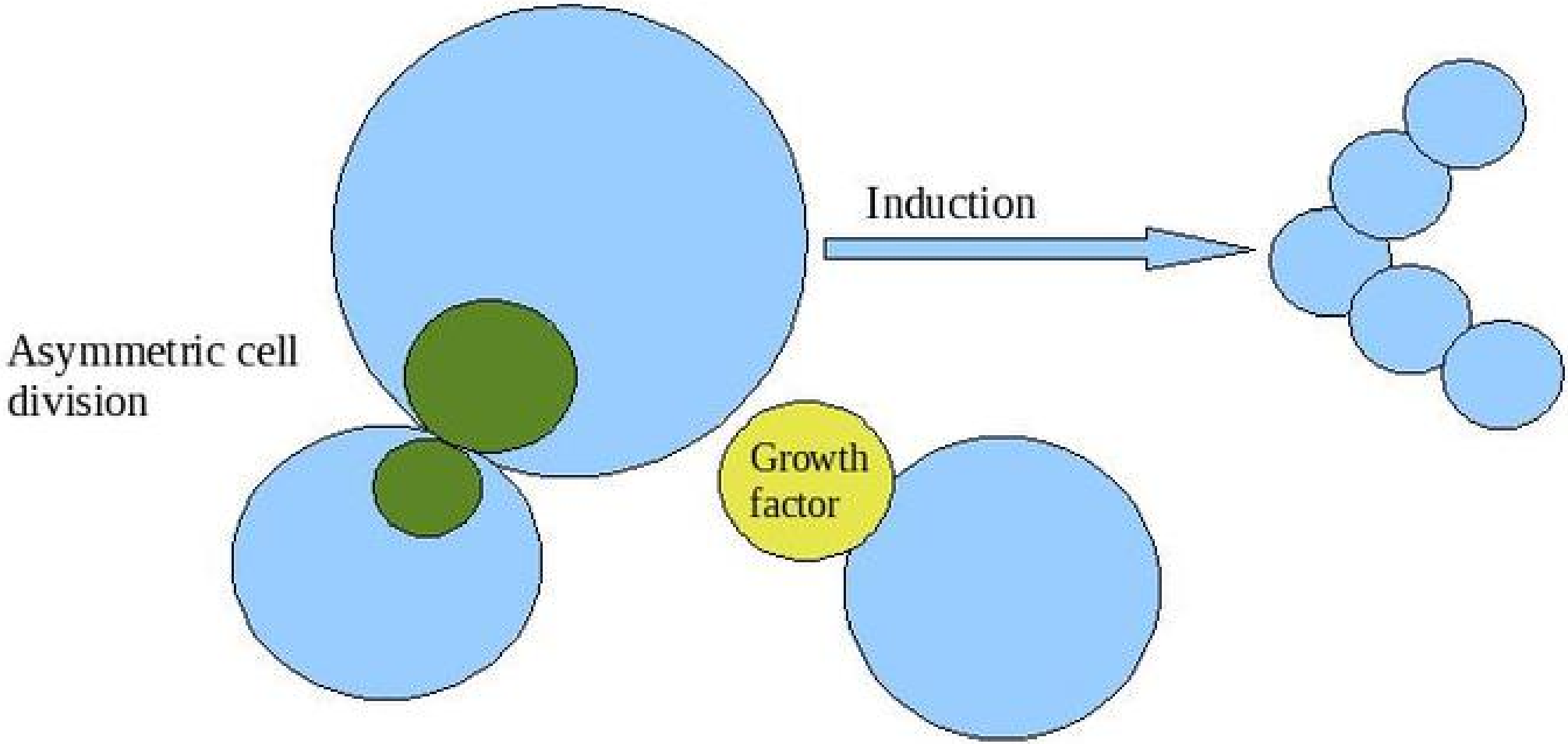

Bone
Natural killer (NK) cell
T lymphocytes
Neutrophil
Basophil
lymphoid progenitor cell
B lymphocyte
Eosinophil
Hematopoietic stem cell
Multipotential stem cell
Myeloid progenitor cell
Monocyte/macrophage
Platelet
Red blood cells
Bone marrow
Stromal cell
Blood vessel
Fat cell
Osteoclast
Adipocyte
Stromal stem cell
Bone (or cartilage)
Osteoblast
Lining cell
Osteocyte
Pre-osteoblast
Skeletal muscle stem cell?
Hepatocyte stem cell?
Hematopoietic supportive stroma
Hematopoietic stem cell
Marrow adipocyte

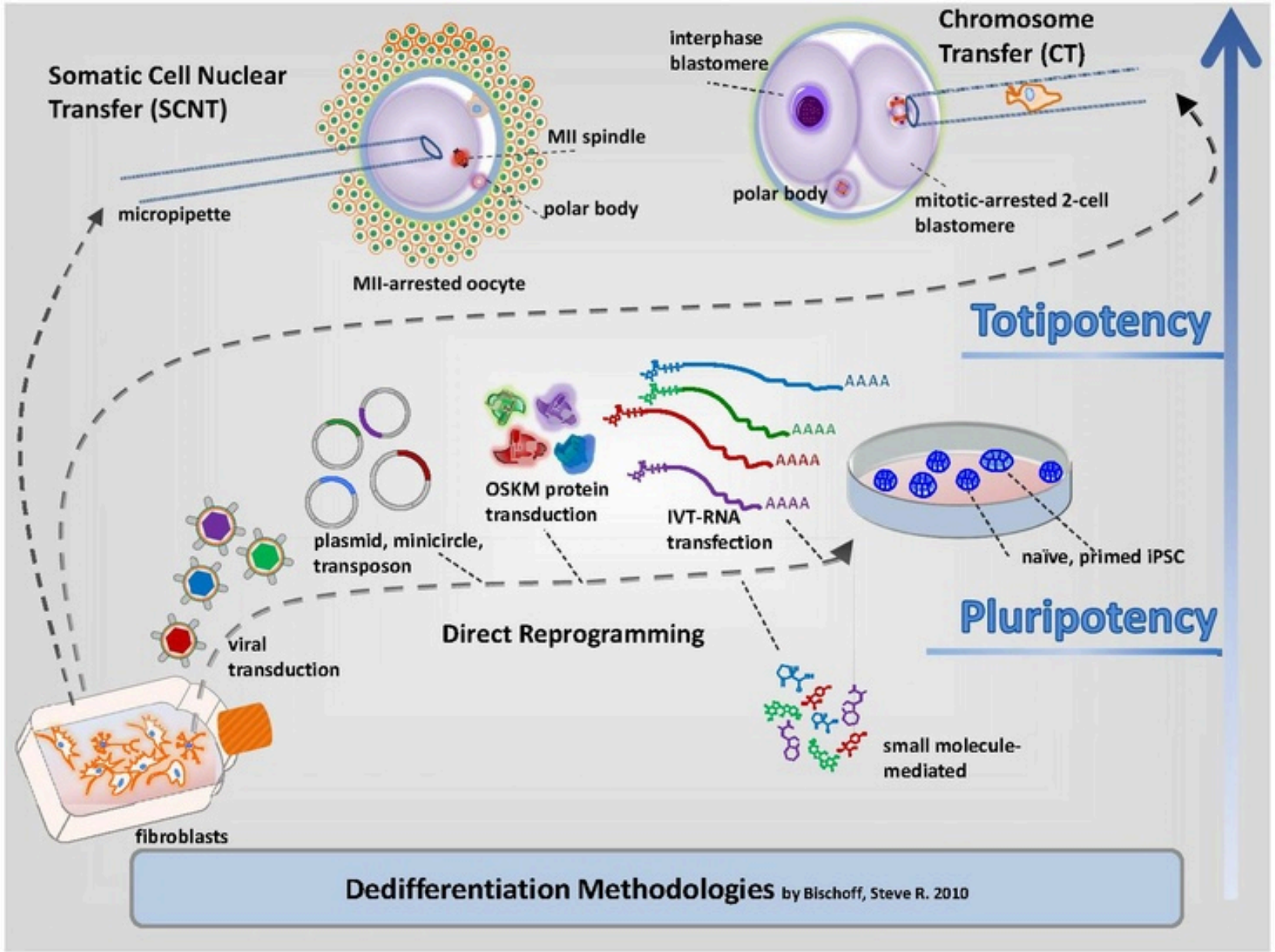
Cell Differentiation






Endoderm stem cells
Lung cells
Pancreatic cells
UPF1/UPF3B KD
(hESC)[51]
Pluripotent stem cells
Mesoderm stem cells
Muscle cells
SMG6 KO
(Mm)[39]
Hematopoietic
stem cells
Red Blood cells
UPF2 cKO
(Mm)[37]
Epidermal cells
Ectoderm stem cells
UPF1KD/UPF3B KO
(mNSC)[56]
Neural
stem cells
Neurons


Induction
Asymmetric cell division
Growth factor


Somatic Cell Nuclear Transfer (SCNT)
MII spindle
polar body
micropipette
MII-arrested oocyte
interphase blastomere
Chromosome Transfer (CT)
polar body
mitotic-arrested 2-cell blastomere
Totipotency
AAAA
AAAA
AAAA
AAAA
OSKM protein transduction
IVT-RNA transfection
plasmid, minicircle, transposon
naïve, primed iPSC
Pluripotency
Direct Reprogramming
viral transduction
small molecule-mediated
fibroblasts
Dedifferentiation Methodologies by Bischoff, Steve R. 2010

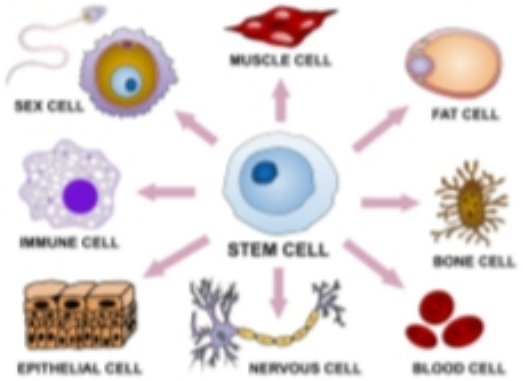
Cellular Differentiation

- Every nucleus of every cell has the same set of genes. A heart cell nucleus contains skin cell genes, as well as the genes that instruct stomach cells how to absorb nutrients.
- Therefore, for cells to differentiate, certain genes must somehow be activated, while others remain inactive.
- Genes instruct each cell how and when to build the proteins that allow it to create the structures, and ultimately perform the functions, specific to its type of cell.

Cellular Differentiation

- Each of us originated as a single, simple-looking cell -- a fertilized egg, or zygote -- so tiny that it can barely be seen without a microscope. (*A human egg cell is about 1/100th of a centimetre in diameter, or a bit smaller than the width of a human hair.*)
- Shortly after fertilization, the zygote begins dividing, replicating itself again and again. Before long, a growing mass, or blastula, of dozens, then hundreds, then thousands of cells called stem cells forms; each stem cell is only one-fourth to one-tenth the diameter of the original zygote, but otherwise nearly identical to it

Cellular differentiation



Stem cell differentiation into various tissue types.

Differentiation continues in adulthood as adult stem cells divide and create fully differentiated daughter cells during tissue repair and during normal cell turnover. Some differentiation occurs in response to antigen exposure. Differentiation dramatically changes a cell's size, shape, membrane potential, metabolic activity, and responsiveness to signals. These changes are largely due to highly controlled modifications in gene expression and are the study of epigenetics. With a few exceptions, cellular differentiation almost never involves a change in the DNA sequence itself. Thus, different cells can

have very different physical characteristics despite having the same genome.

A specialized type of differentiation, known as 'terminal differentiation', is of importance in some tissues, for example vertebrate nervous system, striated muscle, epidermis and gut. During terminal differentiation, a precursor cell formerly capable of cell division, permanently leaves the cell cycle, dismantles the cell cycle machinery and often expresses a range of genes characteristic of the cell's final function (e.g. myosin and actin for a muscle cell). Differentiation may continue to occur after terminal differentiation if the

capacity and functions of the cell undergo further changes.

Among dividing cells, there are multiple levels of cell potency, the cell's ability to differentiate into other cell types. A greater potency indicates a larger number of cell types that can be derived. A cell that can differentiate into all cell types, including the placental tissue, is known as ***totipotent***. In mammals, only the zygote and subsequent blastomeres are totipotent, while in plants, many differentiated cells can become totipotent with simple laboratory techniques. A cell that can differentiate into all cell types of the adult organism is

known as ***pluripotent***. Such cells are called meristematic cells in higher plants and embryonic stem cells in animals, though some groups report the presence of adult pluripotent cells. Virally induced expression of four transcription factors Oct4, Sox2, c-Myc, and Klf4 (Yamanaka factors) is sufficient to create pluripotent (iPS) cells from adult fibroblasts.[4] A multipotent cell is one that can differentiate into multiple different, but closely related cell types.[5] Oligopotent cells are more restricted than multipotent, but can still differentiate into a few closely related cell types.[5] Finally, unipotent cells can differentiate into only one cell type, but are capable of self-

Mammalian cell types

Three basic categories of cells make up the mammalian body: germ cells, somatic cells, and stem cells. Each of the approximately 37.2 trillion (3.72×10^{13}) cells in an adult human has its own copy or copies of the genome except certain cell types, such as red blood cells, that lack nuclei in their fully differentiated state. Most cells are diploid; they have two copies of each chromosome. Such cells, called somatic cells, make up most of the human body, such as skin and muscle cells. Cells differentiate to specialize for different functions.[Z]

Development begins when a sperm fertilizes an egg and creates a single cell that has the potential to form an entire organism. In the first hours after fertilization, this cell divides into identical cells. In humans, approximately four days after fertilization and after several cycles of cell division, these cells begin to specialize, forming a hollow sphere of cells, called a blastocyst.[8] The blastocyst has an outer layer of cells, and inside this hollow sphere, there is a cluster of cells called the inner cell mass. The cells of the inner cell mass go on to form virtually all of the tissues of the human body. Although the cells of the inner cell mass can form virtually every

type of cell found in the human body, they cannot form an organism. These cells are referred to as pluripotent.[9]

Pluripotent stem cells undergo further specialization into multipotent progenitor cells that then give rise to functional cells. Examples of stem and progenitor cells include:

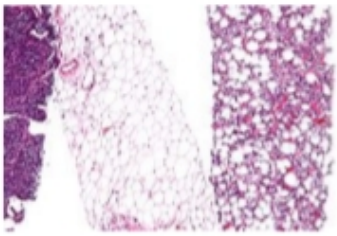
- *Radial glial cells* (embryonic neural stem cells) that give rise to excitatory neurons in the fetal brain through the process of neurogenesis.[10][11][12]
- *Hematopoietic stem cells* (adult stem cells) from the bone marrow that give

rise to red blood cells, white blood cells, and platelets

- *Mesenchymal stem cells* (adult stem cells) from the bone marrow that give rise to stromal cells, fat cells, and types of bone cells
- *Epithelial stem cells* (progenitor cells) that give rise to the various types of skin cells
- *Muscle satellite cells* (progenitor cells) that contribute to differentiated muscle tissue.

A pathway that is guided by the cell adhesion molecules consisting of four amino acids, arginine, glycine, asparagine,

Dedifferentiation



Micrograph of a liposarcoma with some dedifferentiation, that is not identifiable as a liposarcoma, (left edge of image) and a differentiated component (with lipoblasts and increased vascularity (right of image)). Fully differentiated (morphologically benign) adipose tissue (center of the image) has few blood vessels. H&E stain.

Dedifferentiation, or integration is a cellular process often seen in more basal life forms such as worms and amphibians in which a partially or terminally differentiated cell reverts to an earlier developmental stage, usually as part of a regenerative

process.[13][14] Dedifferentiation also [illegible] in plants.[15] Cells in cell culture can l[illegible] properties they originally had, such as protein expression, or change shape. This process is also termed dedifferentiation.[16]

Some believe dedifferentiation is an aberration of the normal development cycle that results in cancer,[17] whereas others believe it to be a natural part of the immune response lost by humans at some point as a result of evolution.

A small molecule dubbed reversine, a purine analog, has been discovered that has proven to induce dedifferentiation in

myotubes. These dedifferentiated cells could then redifferentiate into osteo[illegible] and adipocytes.[18]

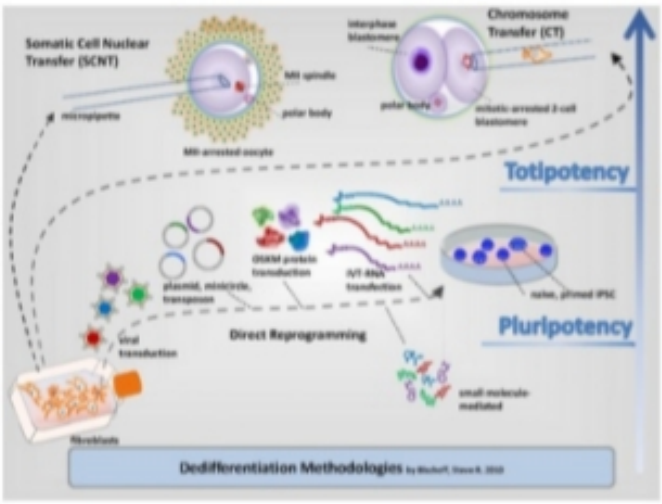
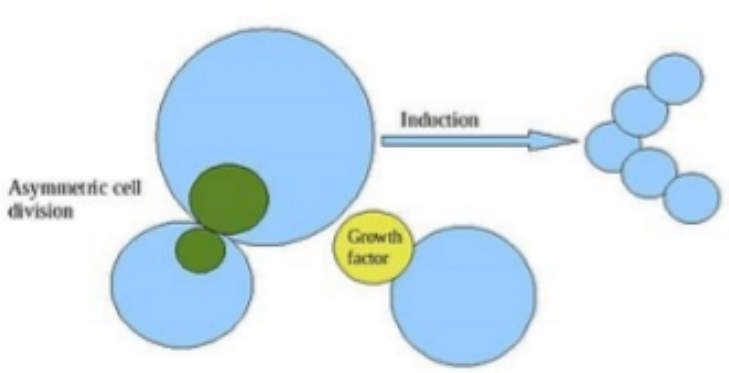


Diagram exposing several methods used to revert adult somatic cells to totipotency or pluripotency.

Mechanisms

Mechanisms



Mechanisms of cellular differentiation.

Each specialized cell type in an organism expresses a subset of all the genes that constitute the genome of that species. Each cell type is defined by its particular pattern of regulated gene expression. Cell differentiation is thus a transition of a cell from one cell type to another and it involves

differentiation during development can be understood as the result of a gene regulatory network. A regulatory gene and its cis-regulatory modules are nodes in a gene regulatory network; they receive input and create output elsewhere in the network.[19] The systems biology approach to developmental biology emphasizes the importance of investigating how developmental mechanisms interact to produce predictable patterns (morphogenesis). However, an alternative view has been proposed recently. Based on stochastic gene expression, cellular differentiation is the result of a Darwinian selective process occurring among cells. In

this frame, protein and gene networks are the result of cellular processes and not their cause.

An overview of major signal transduction pathways.

While evolutionarily conserved molecular processes are involved in the cellular mechanisms underlying these switches, in animal species these are very different from the well-characterized gene regulatory mechanisms of bacteria, and even from

those of the animals' closest unicellular relatives.[20] Specifically, cell differentiation in animals is highly dependent on biomolecular condensates of regulatory proteins and enhancer DNA sequences.

Cellular differentiation is often controlled by cell signaling. Many of the signal molecules that convey information from cell to cell during the control of cellular differentiation are called growth factors. Although the details of specific signal transduction pathways vary, these pathways often share the following general steps. A ligand produced by one cell binds to a receptor in the extracellular region of another cell,

inducing a conformational change in the receptor. The shape of the cytoplasmic domain of the receptor changes, and the receptor acquires enzymatic activity. The receptor then catalyzes reactions that phosphorylate other proteins, activating them. A cascade of phosphorylation reactions eventually activates a dormant transcription factor or cytoskeletal protein, thus contributing to the differentiation process in the target cell.[21] Cells and tissues can vary in competence, their ability to respond to external signals.[22]

Signal induction refers to cascades of signaling events, during which a cell or

tissue signals to another cell or tissue to influence its developmental fate.[22] Yamamoto and Jeffery[23] investigated the role of the lens in eye formation in c and surface-dwelling fish, a striking example of induction.[22] Through reciprocal transplants, Yamamoto and Jeffery[23] found that the lens vesicle of surface fish can induce other parts of the eye to develop in cave- and surface-dwelling fish, while the lens vesicle of the cave-dwelling fish cannot.[22]

Other important mechanisms fall under the category of asymmetric cell divisions, divisions that give rise to daughter cells

with distinct developmental fates. Asymmetric cell divisions can occur because of asymmetrically expres 22/75 maternal **cytoplasmic determinants** or because of signaling.[22] In the former mechanism, distinct daughter cells are created during cytokinesis because of an uneven distribution of regulatory molecules in the parent cell; the distinct cytoplasm that each daughter cell inherits results in a distinct pattern of differentiation for each daughter cell. A well-studied example of pattern formation by asymmetric divisions is body axis patterning in Drosophila. RNA molecules are an important type of intracellular differentiation control signal.

The molecular and genetic basis of asymmetric cell divisions has also been studied in green algae of the genus *Volvox*, a model system for studying how unicellular organisms can evolve into multicellular organisms.[22] In *Volvox carteri*, the 16 cells in the anterior hemisphere of a 32-cell embryo divide asymmetrically, each producing one large and one small daughter cell. The size of the cell at the end of all cell divisions determines whether it becomes a specialized germ or somatic cell.[22][24]

Epigenetic control

Since each cell, regardless of cell type, possesses the same genome, determination of cell type must occur at the level of gene expression. While the regulation of gene expression can occur through cis- and trans-regulatory elements including a gene's promoter and enhancers, the problem arises as to how this expression pattern is maintained over numerous generations of cell division. As it turns out, epigenetic processes play a crucial role in regulating the decision to adopt a stem, progenitor, or mature cell fate. This section will focus primarily on mammalian stem cells.

Importance of epigenetic control

The first question that can be asked is the extent and complexity of the role of epigenetic processes in the determination of cell fate. A clear answer to this question can be seen in the 2011 paper by Lister R, *et al.* [26] on aberrant epigenomic

programming in human induced pluripotent stem cells. As induced pluripotent stem cells (iPSCs) are thought to mimic embryonic stem cells in their pluripotent properties, few epigenetic differences should exist between them. To test this prediction, the authors conducted whole-genome profiling of DNA methylation patterns in several human embryonic stem cell (ESC), iPSC, and progenitor cell lines.

Female adipose cells, lung fibroblasts, and foreskin fibroblasts were reprogrammed into induced pluripotent state with the

iPSCs, somatic cells were compared. Lister R, ***et al.*** observed significant resemblance in methylation levels between embryonic and induced pluripotent cells. Around 80% of CG dinucleotides in ESCs and iPSCs were methylated, the same was true of only 60% of CG dinucleotides in somatic cells. In addition, somatic cells possessed minimal levels of cytosine methylation in non-CG dinucleotides, while induced pluripotent cells possessed similar levels of methylation as embryonic stem cells, between 0.5 and 1.5%. Thus, consistent with their respective transcriptional activities,[26] DNA methylation patterns, at

selection.[28] Increased levels of Oct4 and decreased levels of Sox2 promote a mesendodermal fate, with Oct4 actively suppressing genes associated with a neural ectodermal fate. Similarly, Increased levels of Sox2 and decreased levels of Oct4 promote differentiation towards a neural ectodermal fate, with Sox2 inhibiting differentiation towards a mesendo fate. Regardless of the lineage cells differentiate down, suppression of NANOG has been identified as a necessary prerequisite for differentiation.[28]

Role of signaling in epigenetic control

A final question to ask concerns the role of cell signaling in influencing the epigenetic processes governing differentiation. Such a

role should exist, as it would be reasonable to think that extrinsic signaling can lead to epigenetic remodeling, just as it can lead to changes in gene expression through the activation or repression of different transcription factors. Little direct dat

available concerning the specific signals that influence the epigenome, and the majority of current knowledge about the subject consists of speculations on plausible candidate regulators of epigenetic remodeling.[38] We will first discuss several major candidates thought to be involved in the induction and maintenance of both embryonic stem cells and their differentiated progeny, and then turn to one

Growth factors comprise the second major set of candidates of epigenetic regulators of cellular differentiation. These morphogens are crucial for development, and include bone morphogenetic proteins, transforming growth factors (TGFs), and fibroblast growth factors (FGFs). TGFs and FGFs have been shown to sustain expression of OCT4, SOX2, and NANOG by downstream signaling to Smad proteins.[38] Depletion of growth factors promotes the differentiation of ESCs, while genes bivalent chromatin can become either more restrictive or permissive in their transcription.[38]

Several other signaling pathways are also considered to be primary candidates. Cytokine leukemia inhibitory factors are associated with the maintenance of mouse ESCs in an undifferentiated state. This is achieved through its activation of the Jak-STAT3 pathway, which has been shown to be necessary and sufficient towards maintaining mouse ESC pluripotency.[39] Retinoic acid can induce differentia 45/75 human and mouse ESCs,[38] and Notch signaling is involved in the proliferation and self-renewal of stem cells. Finally, Sonic hedgehog, in addition to its role as a morphogen, promotes embryonic stem cell

example of specific signaling pathways in which more direct evidence exists for its role in epigenetic change.

The first major candidate is Wnt signaling pathway. The Wnt pathway is involved in all stages of differentiation, and the ligand Wnt3a can substitute for the overexpression of c-Myc in the generation of induced pluripotent stem cells.[38] On the other hand, disruption of ß-catenin, a component of the Wnt signaling pathway, leads to decreased proliferation of progenitors.

THANK YOU ALL