Review: Sexual Reproduction

We are born with 46 chromosomes, 23 maternal and 23 paternal

How many chromosomes does a cell have…

…after Telophase of *mitosis*?

…after Prophase I of *meiosis*?

…after Telophase II of *meiosis*?

Which part of meiosis is responsible for increasing genetic diversity in daughter cells? How does this occur?

Squarecap: YVS6XG

Review: Sexual Reproduction

How many chromosomes does a cell have…

…after Telophase of *mitosis*?

46 chromosomes, daughter cells are identical to parent cells in mitosis

…after Prophase I of *meiosis*?

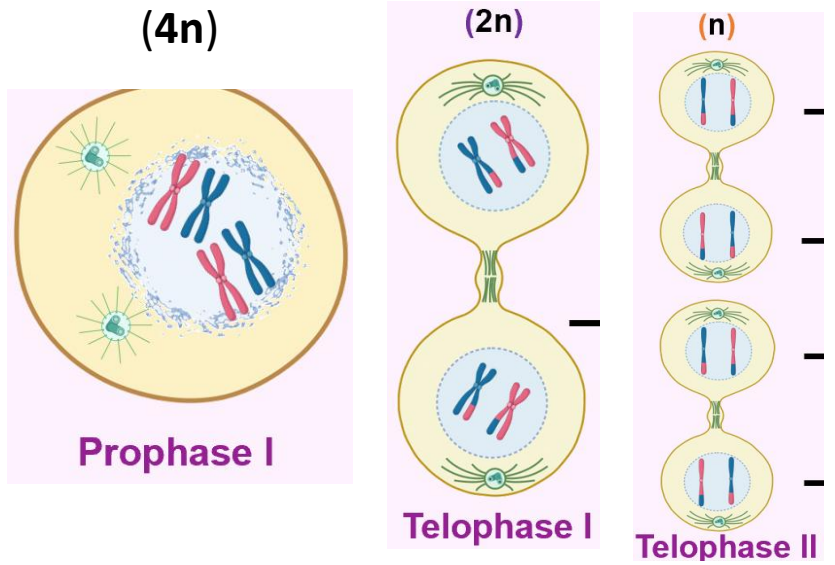
92 chromosomes (4n), as full sets of chromosomes are duplicated during S phase to ultimately produce 4 haploid (n) daughters

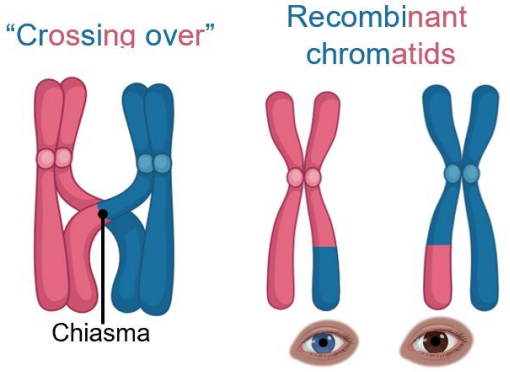
…after Telophase II of *meiosis*?

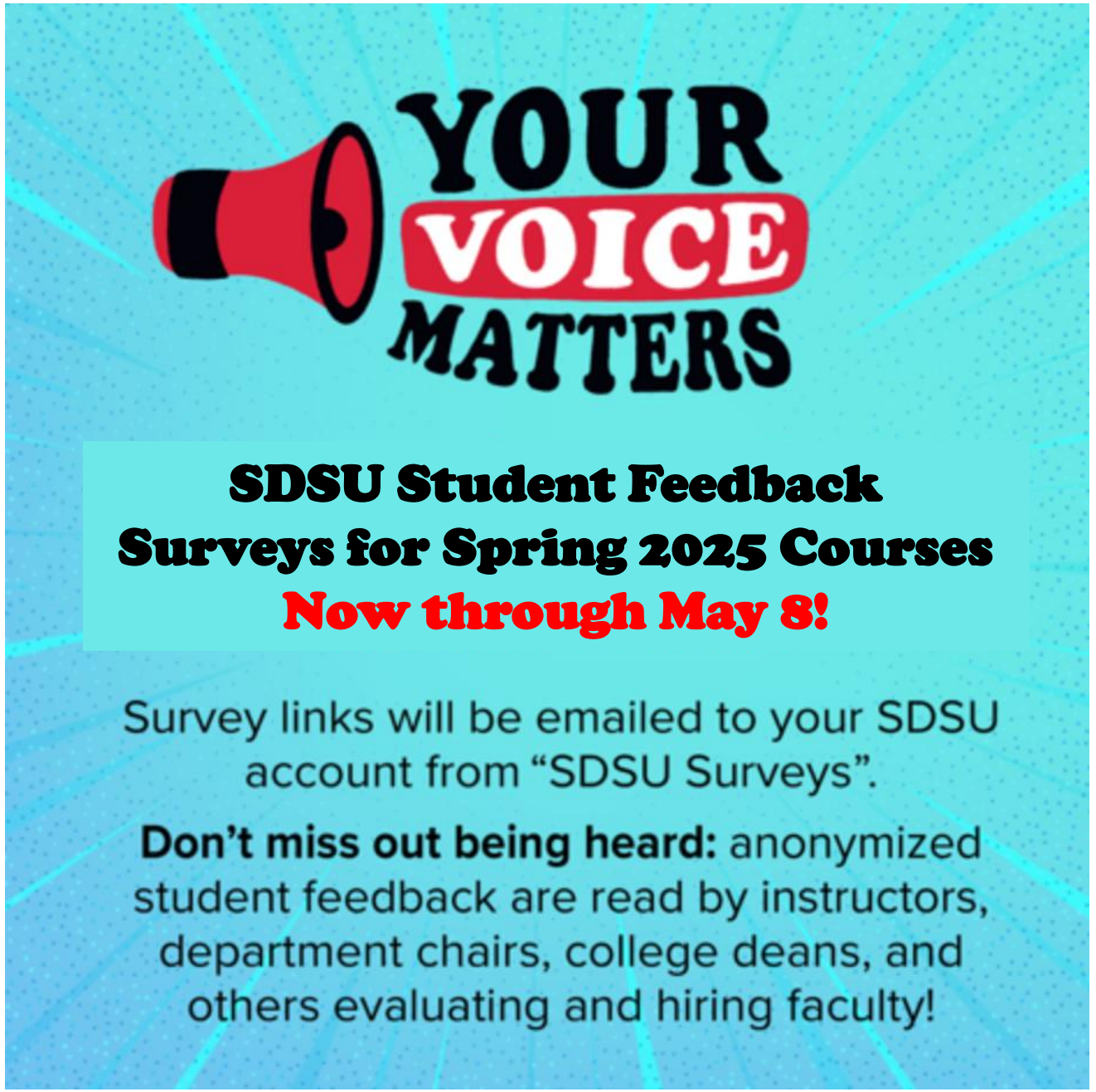
23 chromosomes, at the end of meiosis the number of chromosomes is reduced in half (2n → n)

Which part of meiosis is responsible for increasing genetic diversity in daughter cells? How does this occur?

Prophase I, crossing over between the paired homologous chromosomes occurs here to exchange sections of maternal and paternal DNA to subsequently be transmitted to offspring



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Cell Communities, Tissues and Disease

Chapter 20: Part I
BIOL 366
May 1, 2025
Matthew Ellis, PhD

Learning Objectives for Today's Lecture:

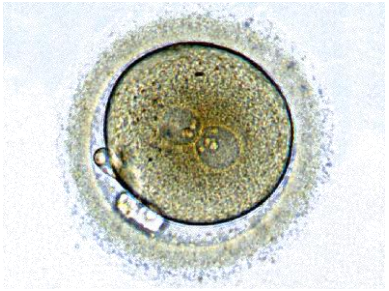
Upon completing this module, **you should be able to**:

- Understand how **stem cells** give rise to the specialized cell types of the body and how these functions relate to their **potency**
- Explain how stem cells and mutations lead to the development of **cancer**
- Define induced pluripotent stem cells (**iPSCs**) and explain how these can be used to study disease
- Follow along with a detailed example of using iPSCs and apply this knowledge to case studies

Key Terms

- **Cellular differentiation**: the process by which unspecialized cells become specialized in order to carry out distinct functions
- **Self-renewal**: ability of a cell to to continually divide/proliferate to maintain a pool of cells identical to itself
- **Cell fate decision**: the decision a cell makes to self-renew or differentiate
- **Cell lineage**: the developmental history of a differentiated cell
- **Potency**: a cell's ability to differentiate into other cell types
- **Totipotent**: stem cells with the capacity to form an entire organism, including placenta
- **Pluripotent**: stem cells that give rise to all cell types of the body (but not the placenta)
- **Multipotent**: a cell's ability to differentiate into the various cell types in a family of related cells

Human somatic cells undergo asexual reproduction via mitosis during development

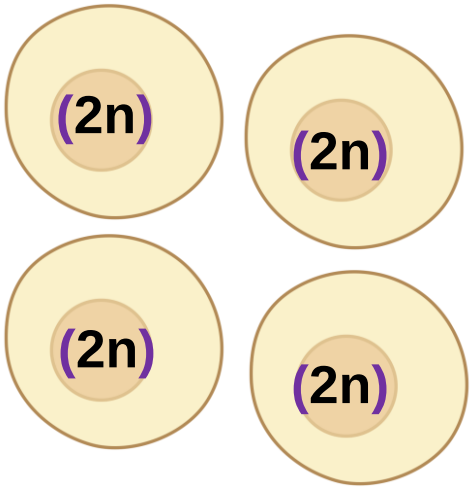


Zygote

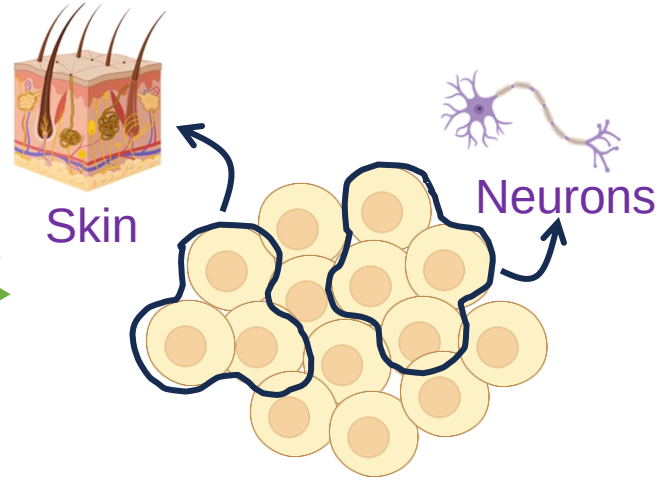
Diploid (2n)
46 chromosomes

Mitosis

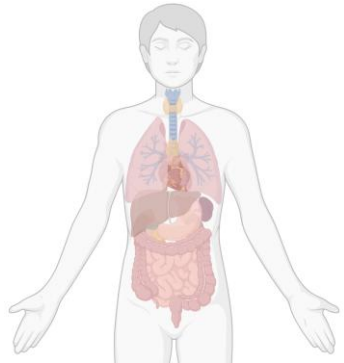
Mitosis



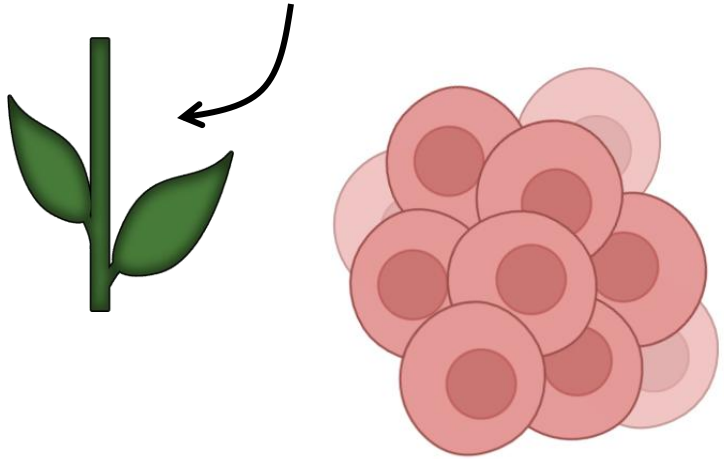
Mitosis



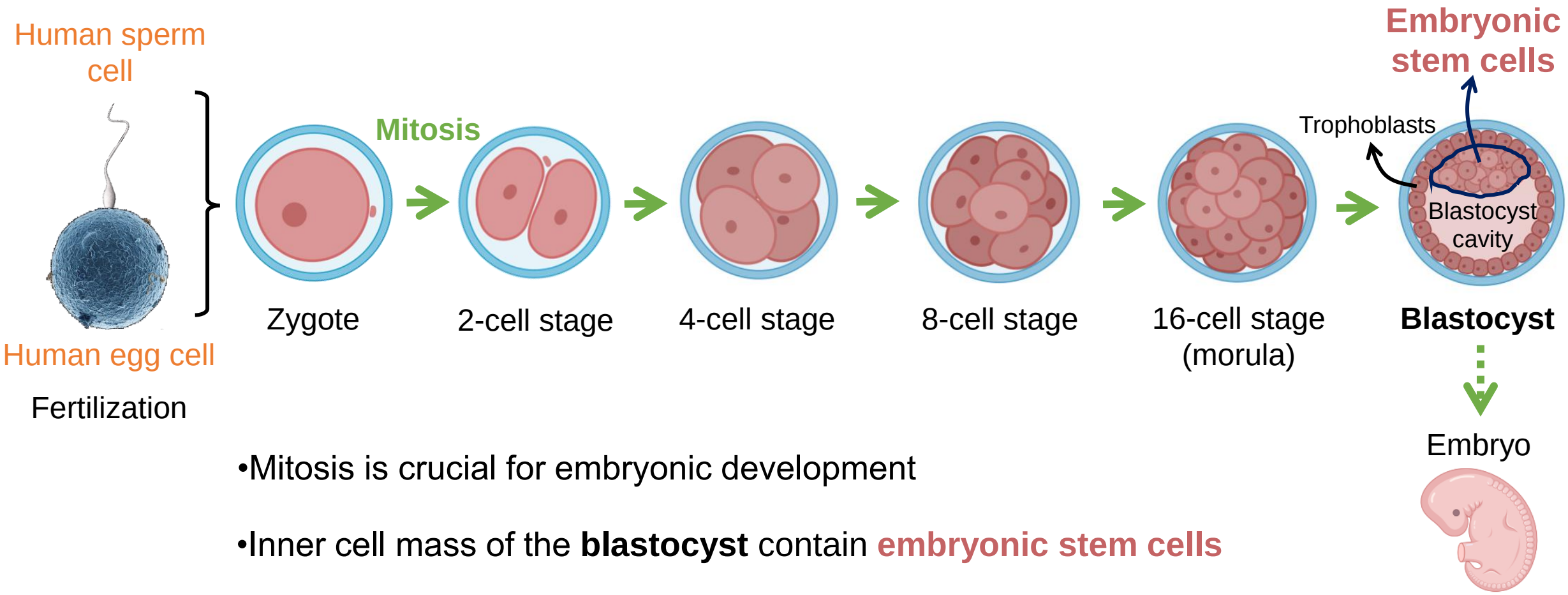
Diploid (2n) cells differentiate into specialized cell types



Stem Cells

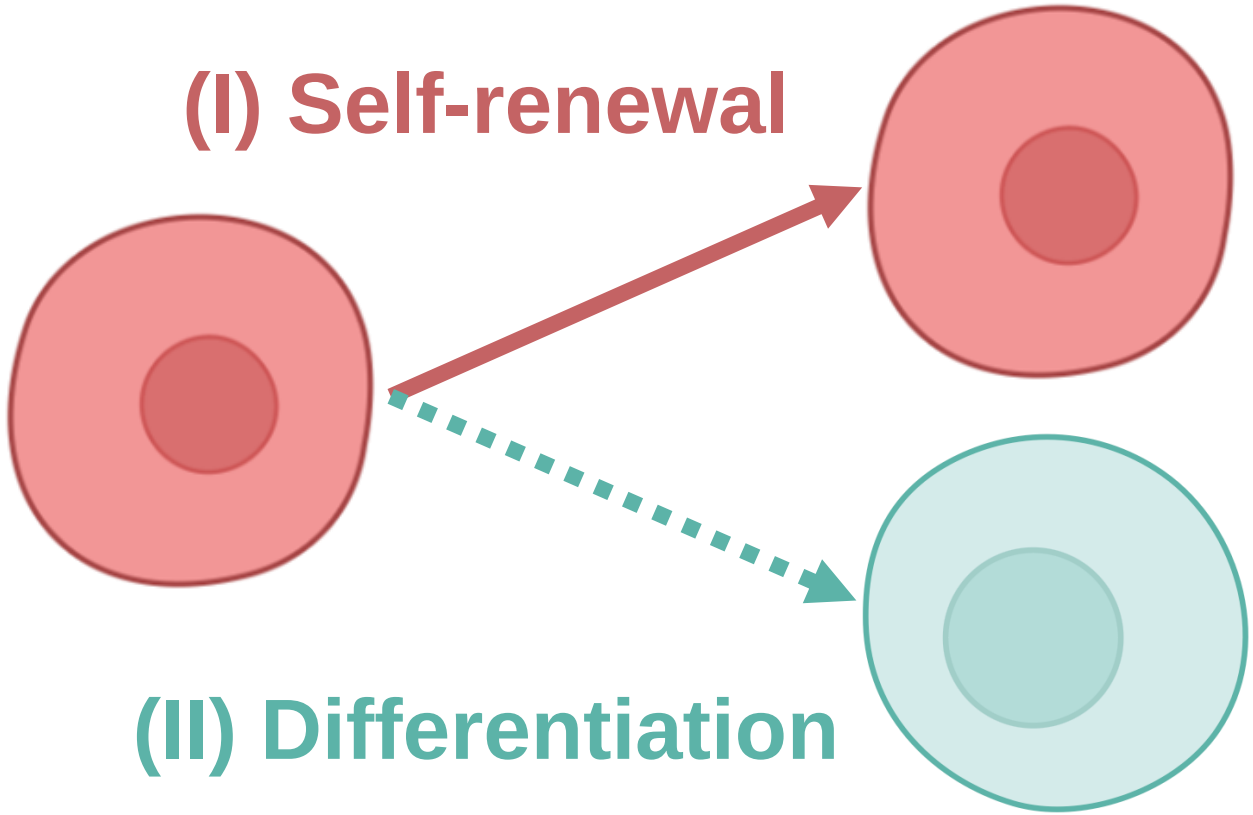


Stem cells are initially generated during embryonic development

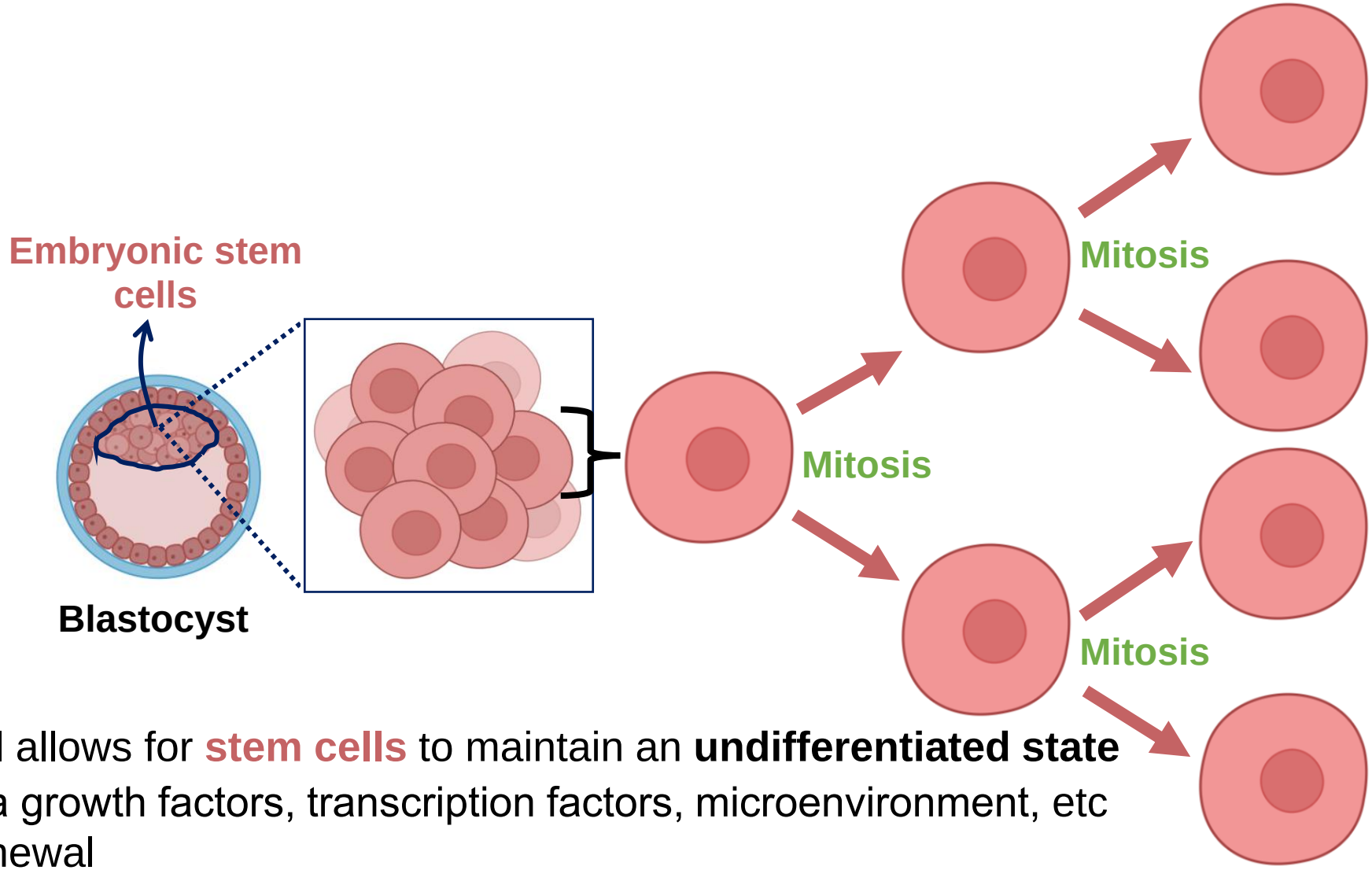


- Mitosis is crucial for embryonic development
- Inner cell mass of the **blastocyst** contain **embryonic stem cells**

Stem cells have two fundamental properties

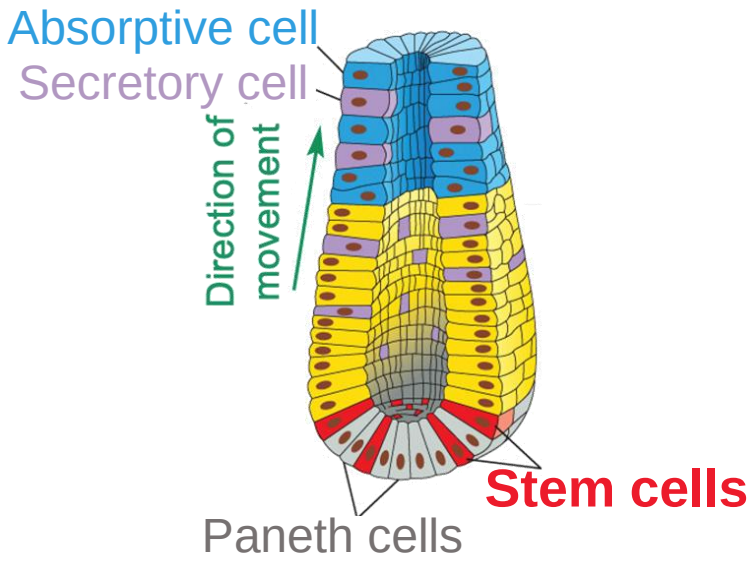


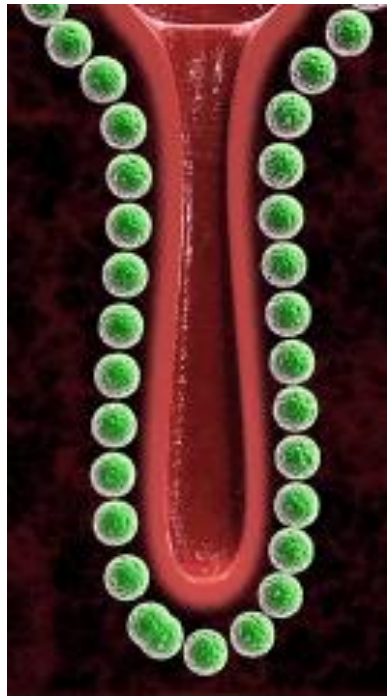
Stem cells are maintained via self-renewal



- Self-renewal allows for **stem cells** to maintain an **undifferentiated state**
- Signaling via growth factors, transcription factors, microenvironment, etc aid in self-renewal

Stem cell self-renewal is crucial for tissue repair and regeneration in adults

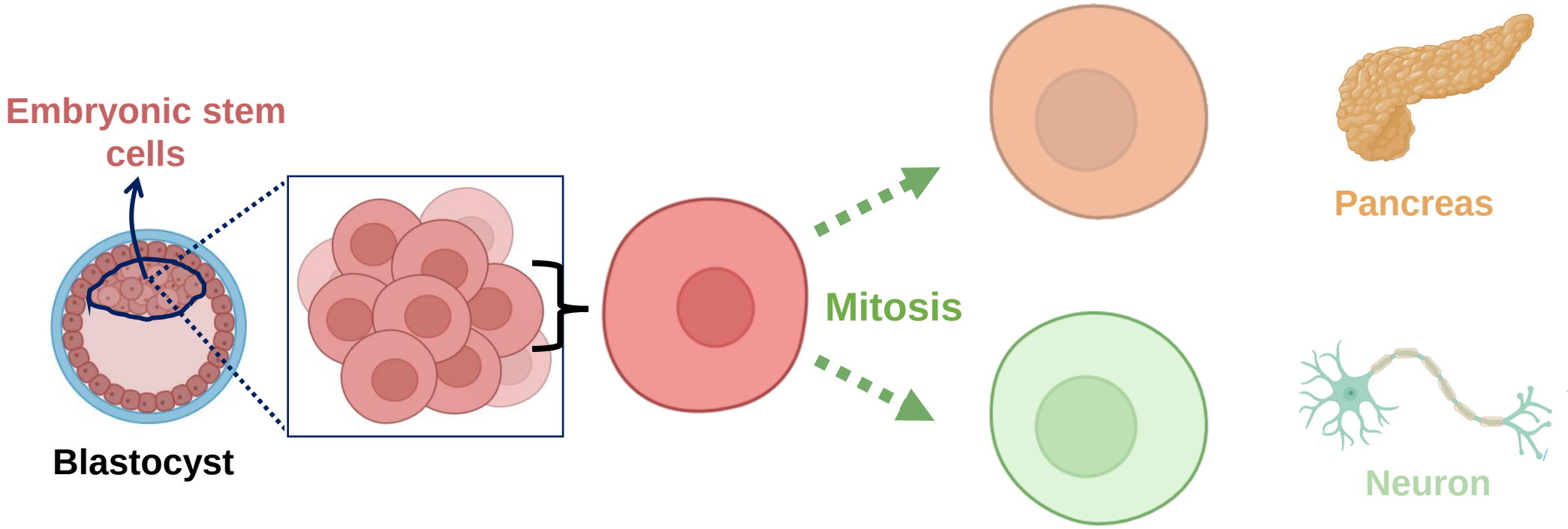




Stem cells reside in a **"niche"** where they are provided resources to remain undifferentiated but are poised to differentiate when needed

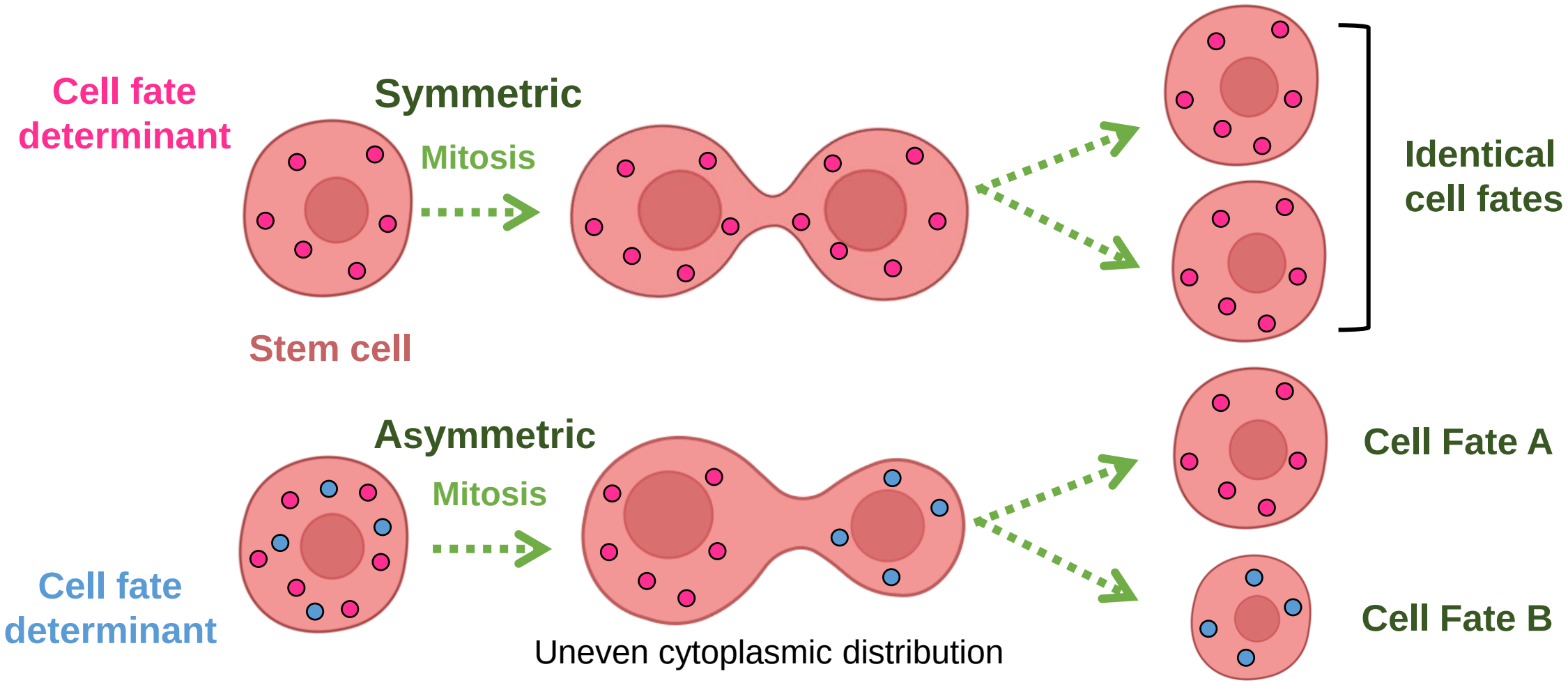
Adult (somatic) stem cells are present in specific tissues and organs for repair and regeneration (e.g., basal layer of epidermis, intestinal tract, cornea, retina, liver).

Stem cells differentiate into cells with specialized functions



•Stem cell differentiation depends heavily on gene expression (transcription factors), growth factors, signaling transduction (e.g., autocrine signaling), etc.

Stem cell self-renewal vs. differentiation occurs via mitosis

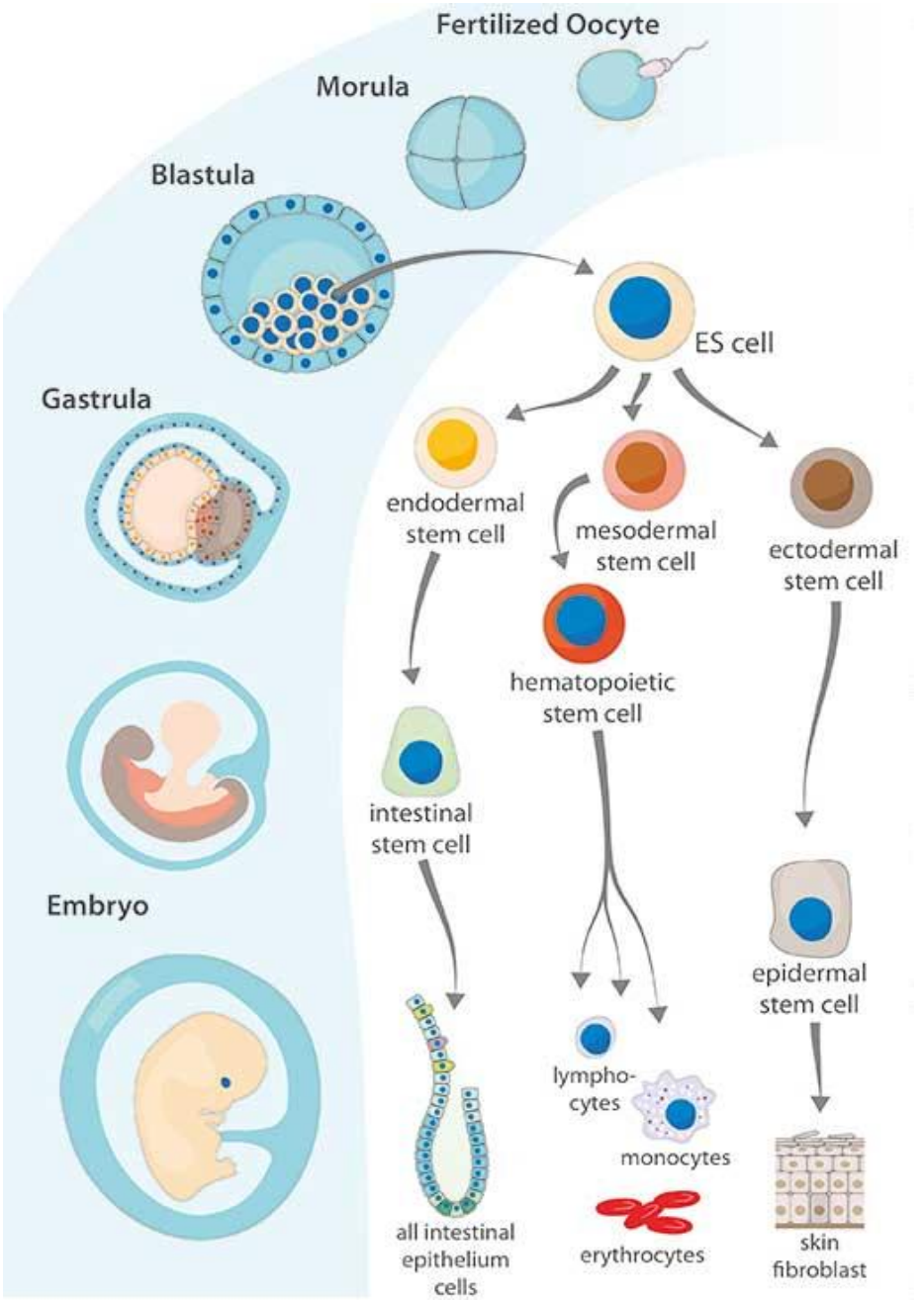


Examples of **cell fate determinants**: growth factors**,** cytoplasmic proteins**,** transcription factors, organelles, mRNA

Stem cell potency

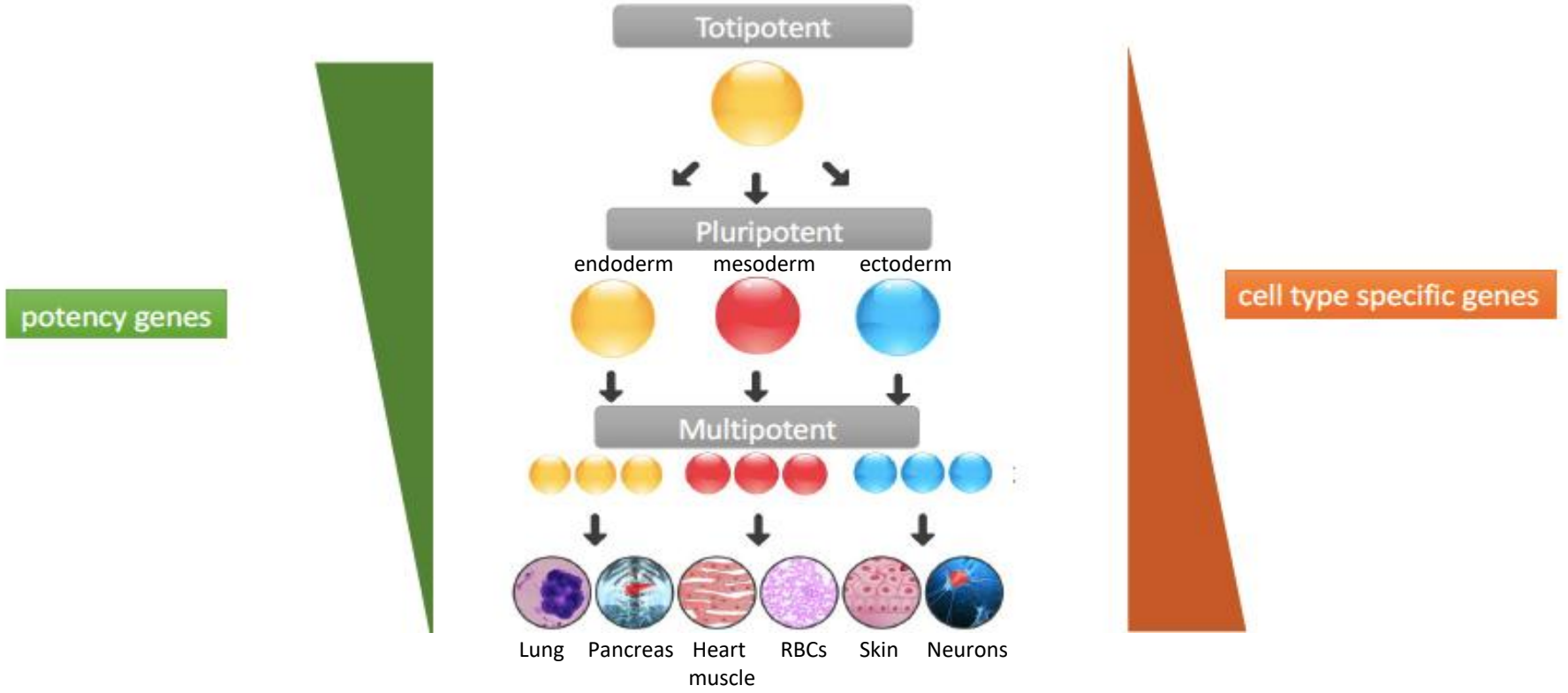
The ability for a stem cell to differentiate various tissue lineages in the body (germ cells, endoderm, mesoderm, ectoderm) depends on its *potency*

- **Totipotent** cells can become any cell type including placenta
- **Pluripotent** cells can become any embryonic cell lineages (non-placental)
- **Multipotent** cells can only differentiate into a specialized subset of cell lineages



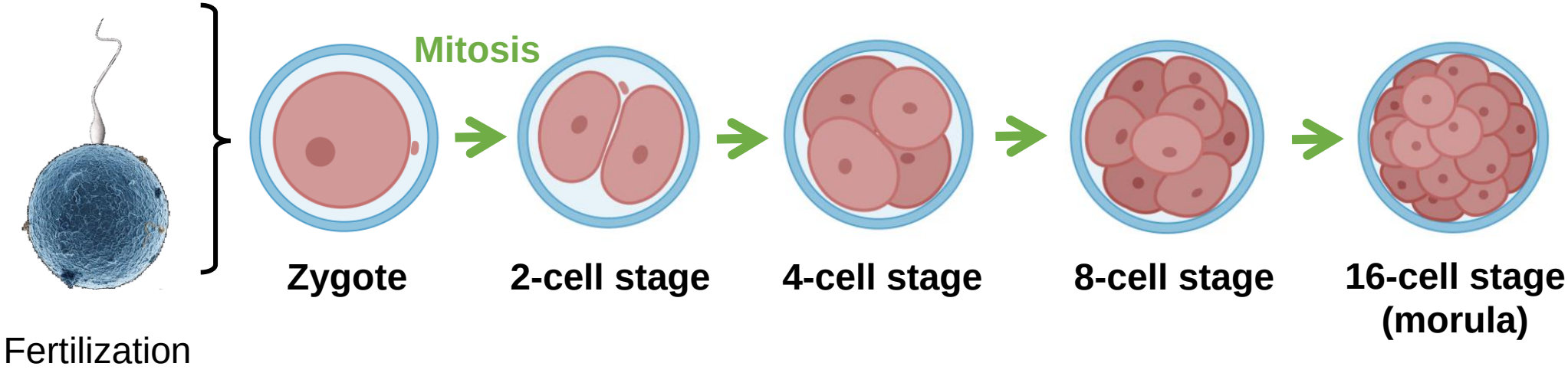
https://www.enzolifesciences.com/science-center/technotes/2019/august/stem-cells-from-embryonic-origin-to-induced-pluripotency-an-overview/

As differentiated state increases, potency decreases



Embryonic stem cells are totipotent or pluripotent, while adult stem cells are multipotent

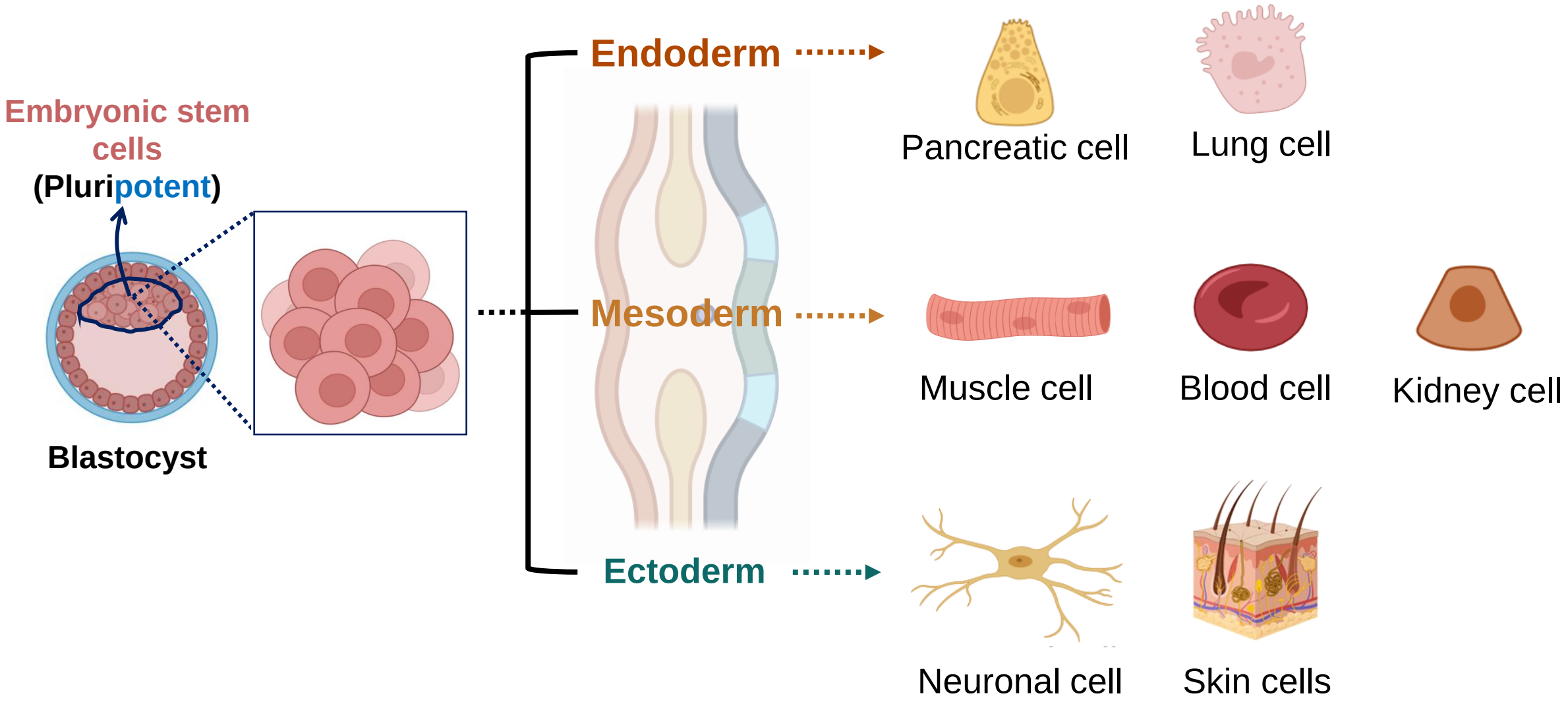
Totipotent stem cells differentiate into all cell types of an organism



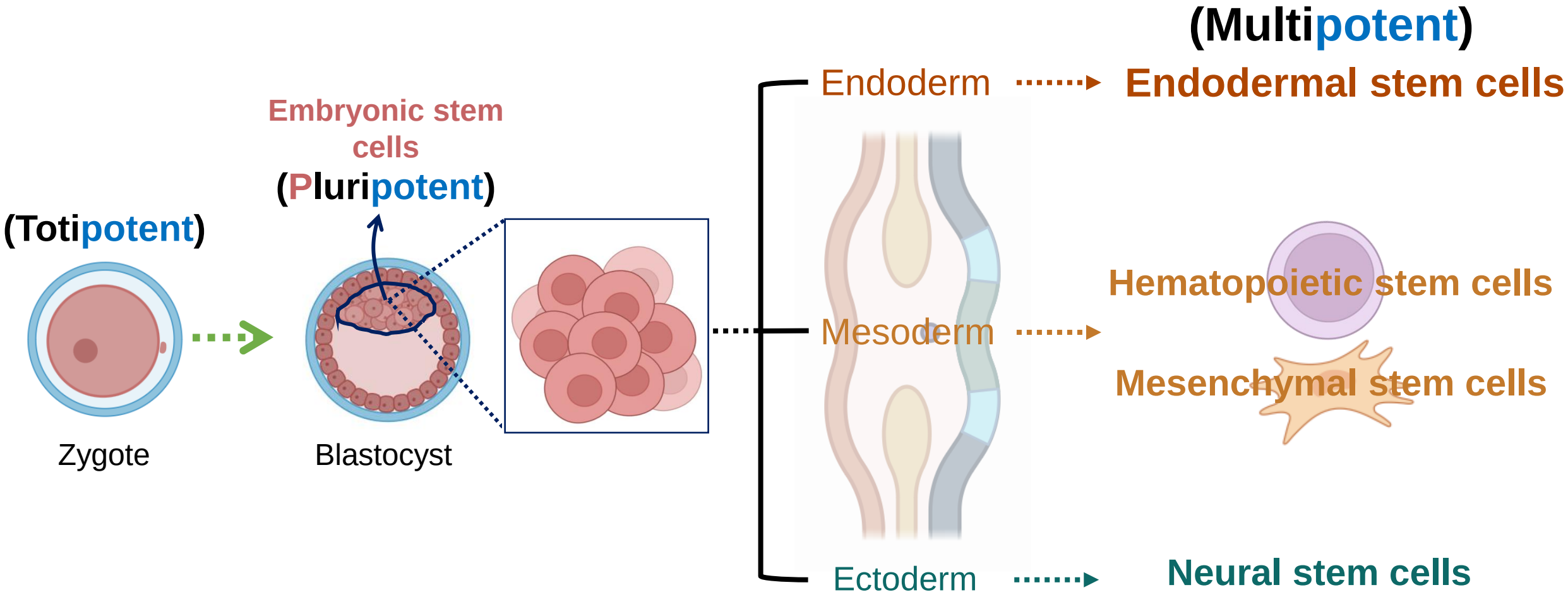
- **Totipotent stem cells** are only present in the **zygote and 2-16 cell stages** of development

- **Totipotent stem cells** differentiate into extraembryonic tissues (e.g., placenta) in addition to the entire organism

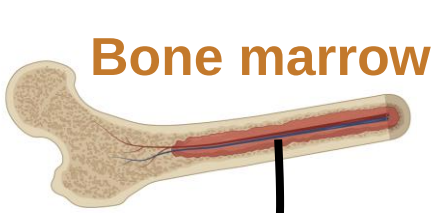
Pluripotent stem cells differentiate into the germ layers of the body



Multipotent stems cells are derived from the germ layers



Hematopoietic stem cells undergo lineage commitment



Bone marrow

Hematopoietic stem cell

e.g., IL-7

Common myeloid **precursor**

e.g., IL-3

Megakaryocyte-erythroid **precursor (MEP)**

e.g., IL-3

Megakaryocyte

Erythrocytes

e.g., IL-11

Platelets

Granulocyte-macrophage **precursor (GMP)**

Monocyte

Macrophage

Dendritic cell

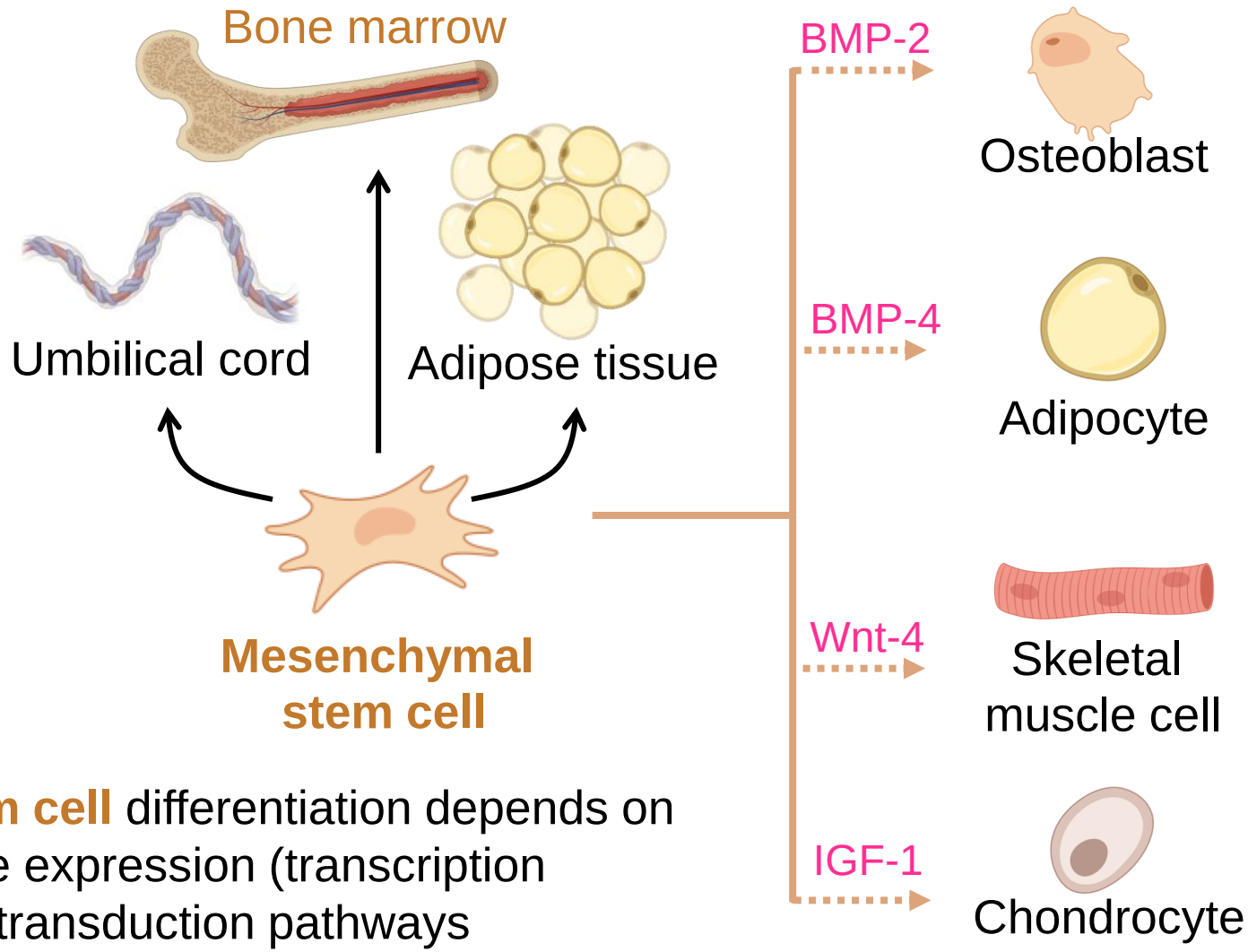
Basophil

Neutrophil

Eosinophil

- **Hematopoietic stem cell** differentiation depends on growth factors, gene expression (transcription factors), and and signal transduction pathways

Mesenchymal stem cells give rise to non-hematopoietic cells



- **Mesenchyma stem cell** differentiation depends on growth factors, gene expression (transcription factors), and signal transduction pathways

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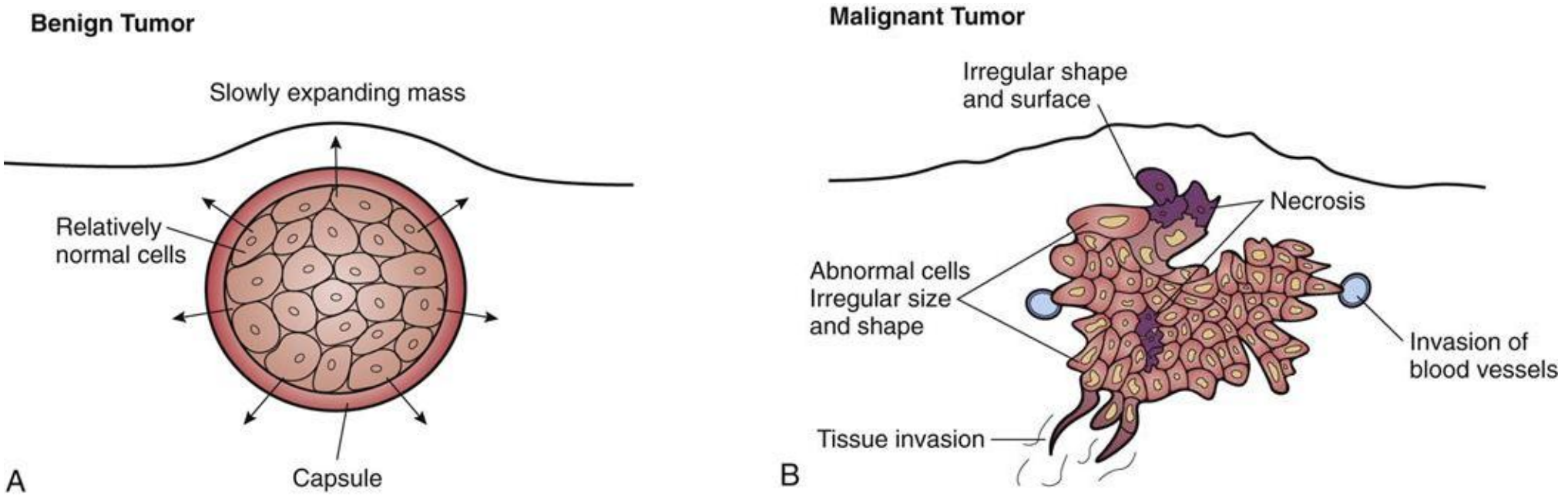
- Follow along with a detailed example of using iPSCs and apply this knowledge to case studies

Tumors consist of abnormally growing cells

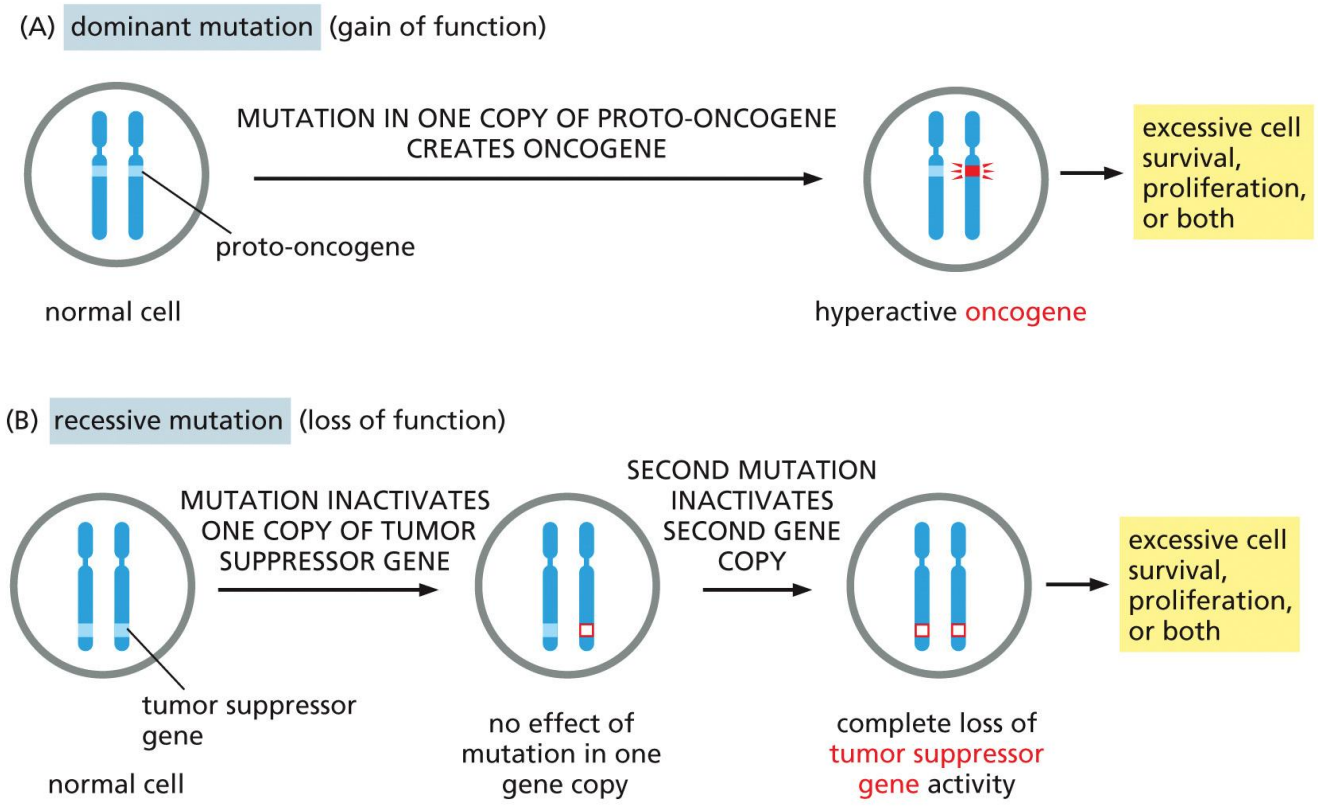
- **Benign** tumors are NOT cancer– The abnormal cells in benign tumors do not spread to other parts of the body. They can be removed, and pose little to no risk of reappearing (i.e. no recurrence)

- **Malignant** tumors are cancer – The abnormal cells in these tumors can invade (i.e. metastasize) nearby tissues and spread to other parts of the body

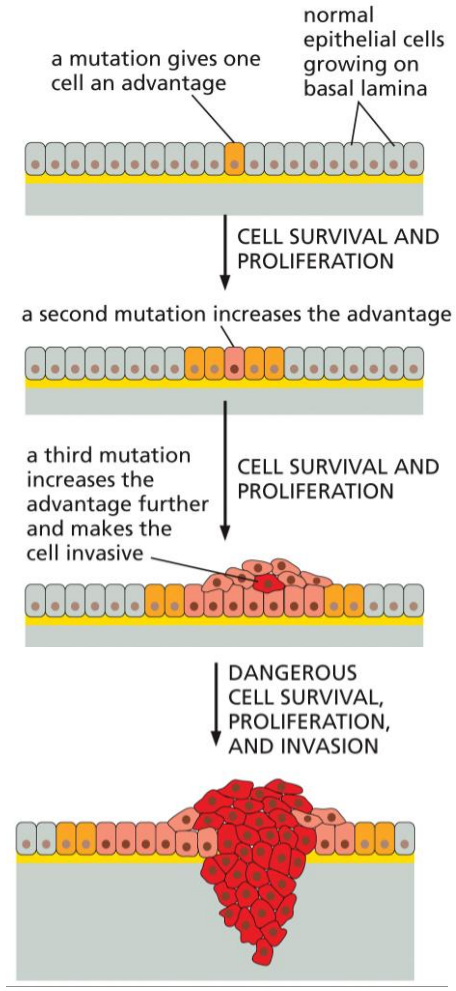


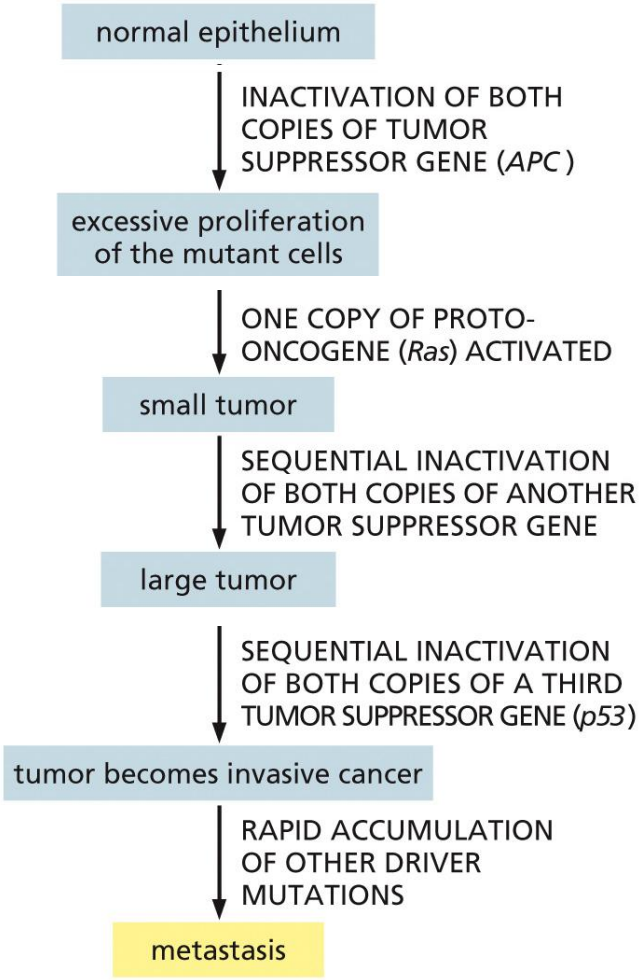
Oncogenes and tumor suppressor genes are critical for cancer

- Proto-oncogenes are genes that are normally required for cell survival or proliferation (e.g., Ras activation)
- Tumor suppressor genes are normally required for inhibiting survival or growth (e.g., p53 activation)

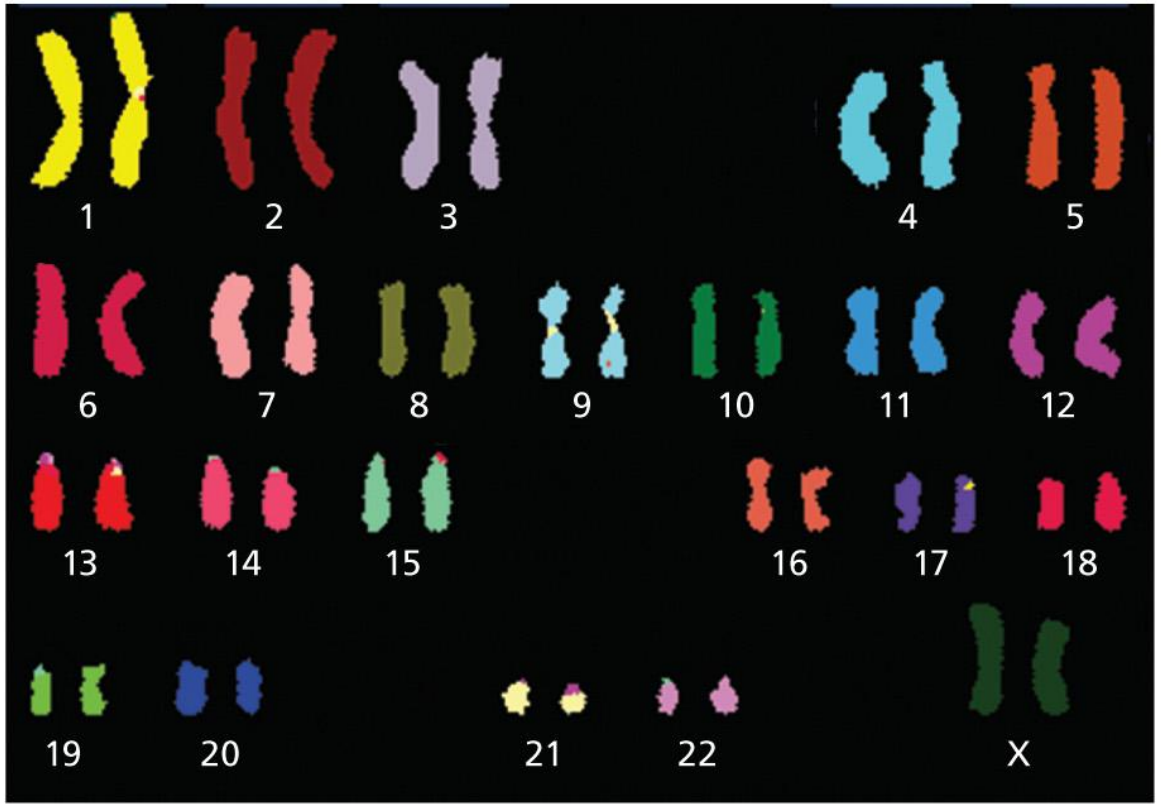


An accumulation of ~4-6 driver mutations allows cancer cells to have uncontrolled growth, invade surrounding tissues, and metastasize to distant sites

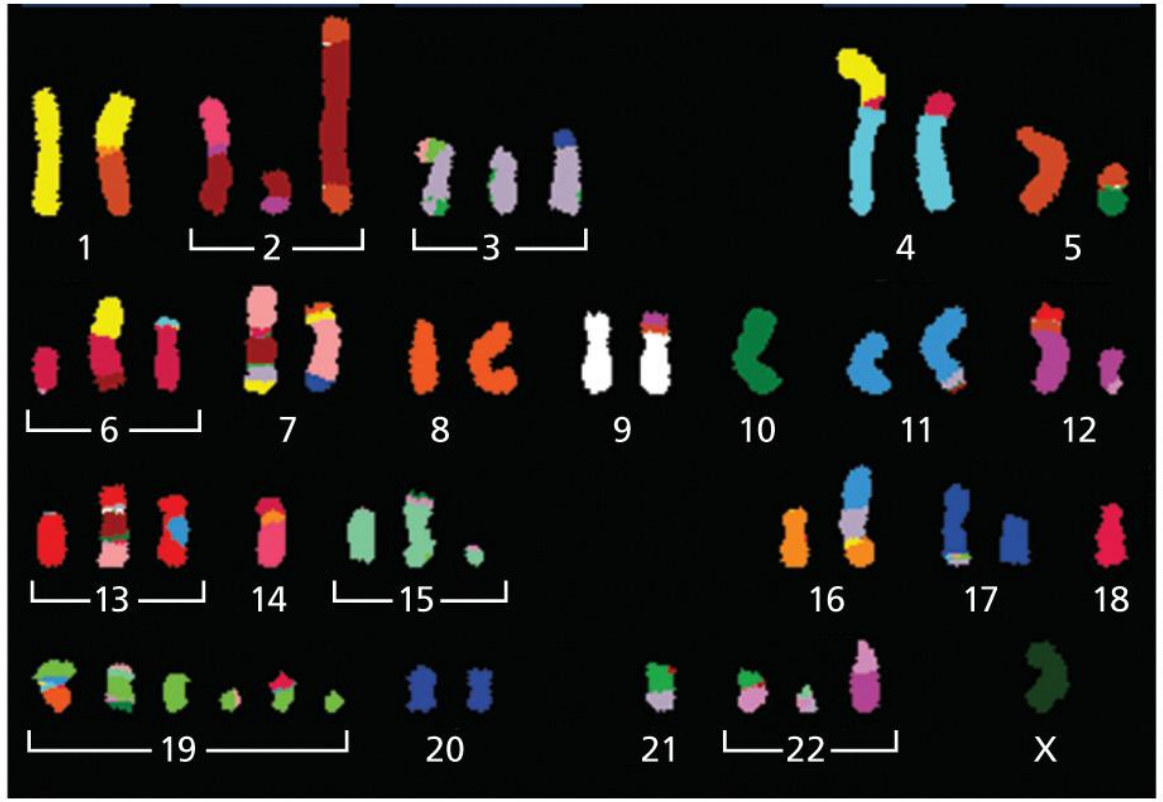




Cancer cells have highly abnormal karyotypes



(A)



(B)

Courtesy of Mira Grigorova and Paul Edwards

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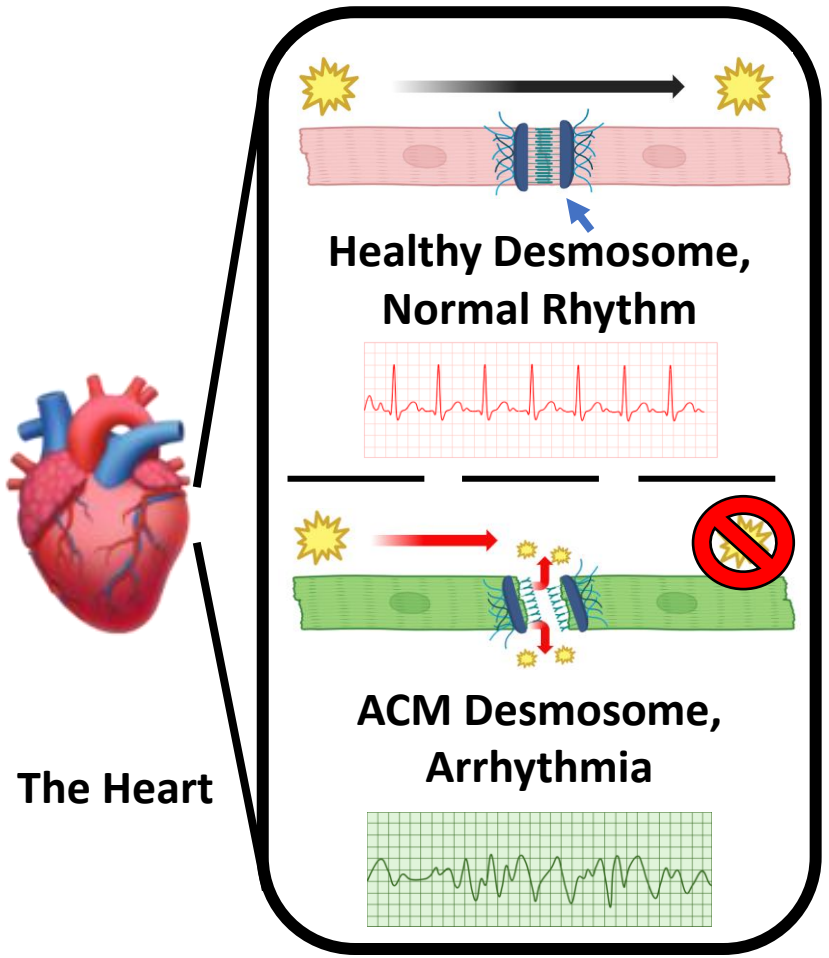
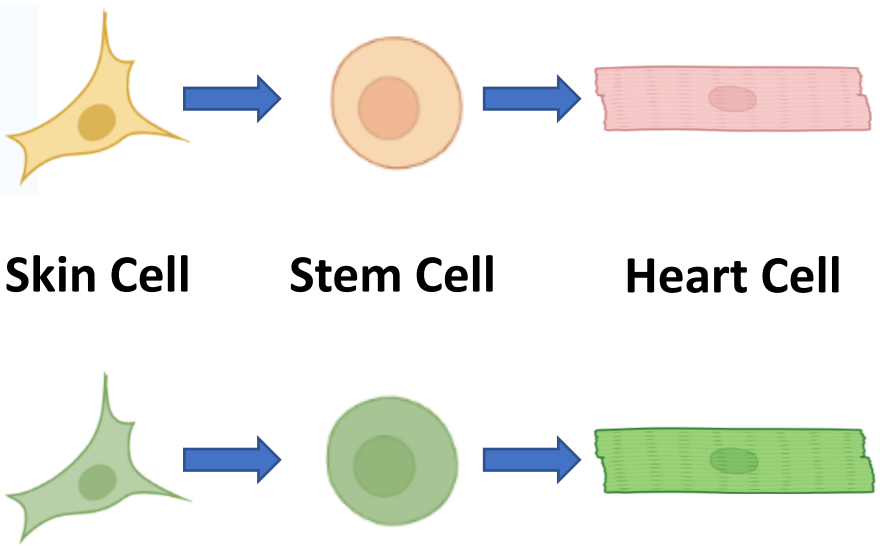
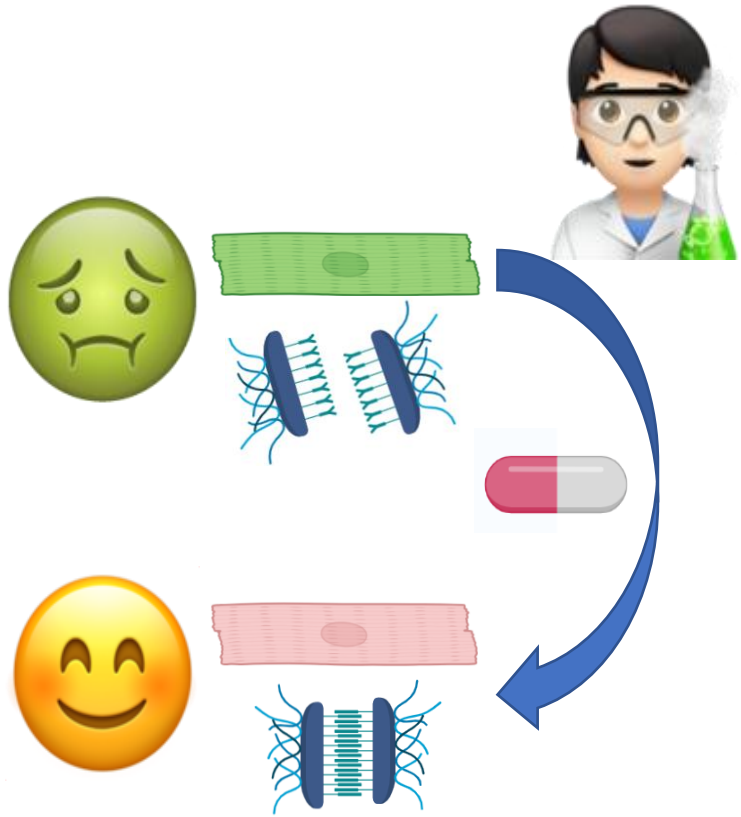


Induced Pluripotency



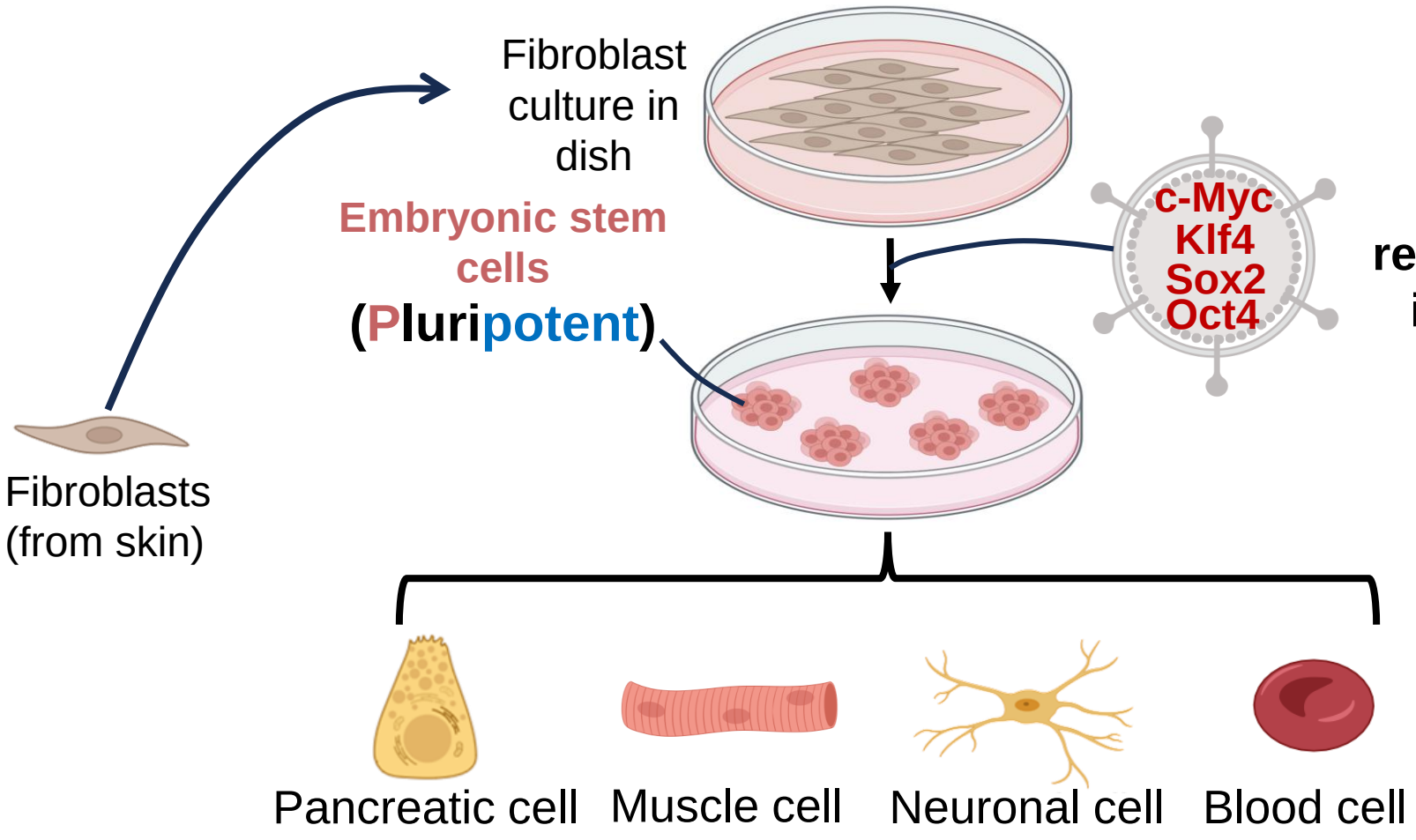


Where I study

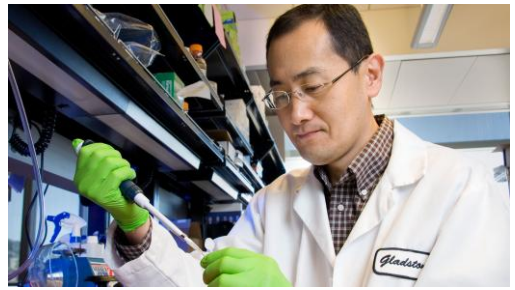
How I study it

What I do

Induced Pluripotent Stem Cells (iPSCs) reprogram somatic cells to become embryonic stem cells

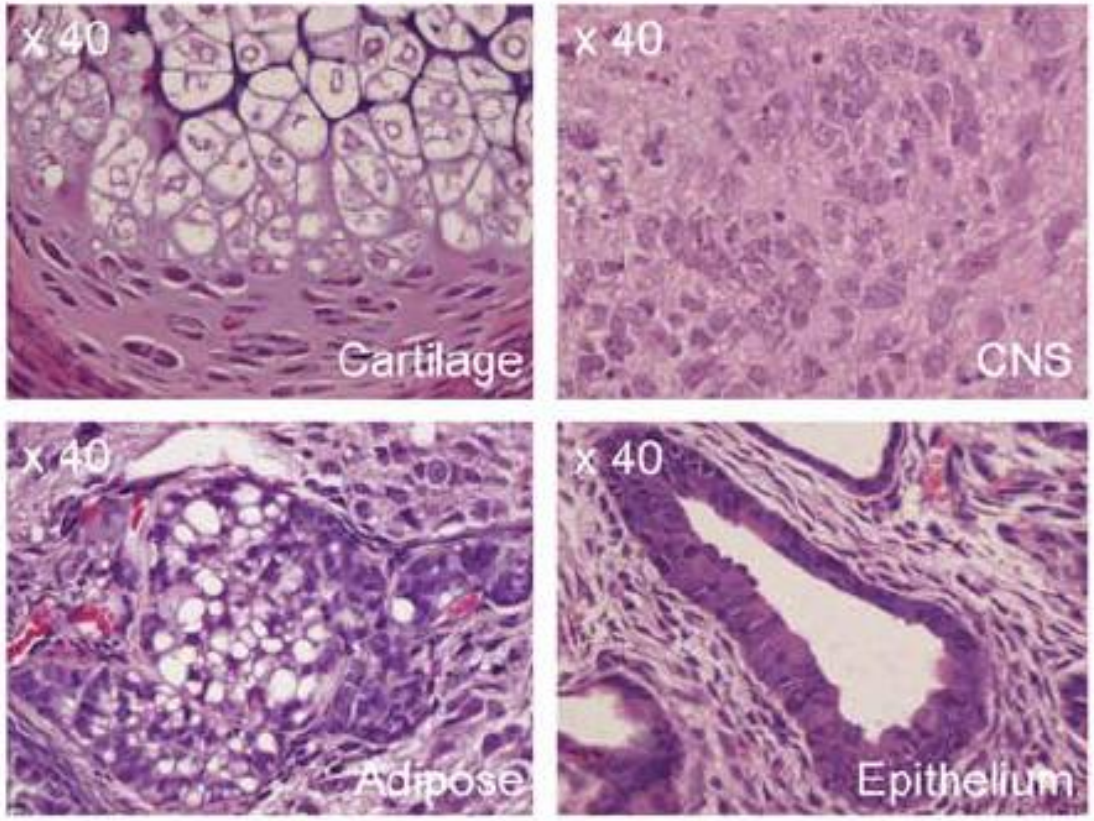


•**Yamanaka factors reprogram somatic cells into pluripotent stem cells**



Shinya **Yamanaka**;
Awarded Nobel prize in 2012

iPSCs Injected Under the Skin of Immune-Deficient Mice Spontaneously Differentiate into Germ Layers

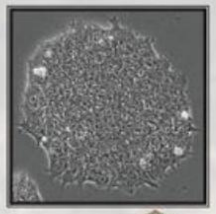


Pioneering discoveries in stem cell research

1963
Blood stem cells: Till and McCulloch

1995
Rhesus embryonic stem cells: Thomson

1998
Human embryonic stem cells: Thomson



2007
Human induced pluripotent stem cells: Thomson, Yamanaka

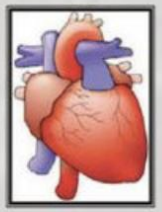
2014
Clinical trial for macular degeneration with retinal cells grown from human induced pluripotent stem cells

1981
Mouse embryonic stem cells: Martin, Evans and Kaufman

1997
Dolly the sheep by nuclear transfer: Wilmut

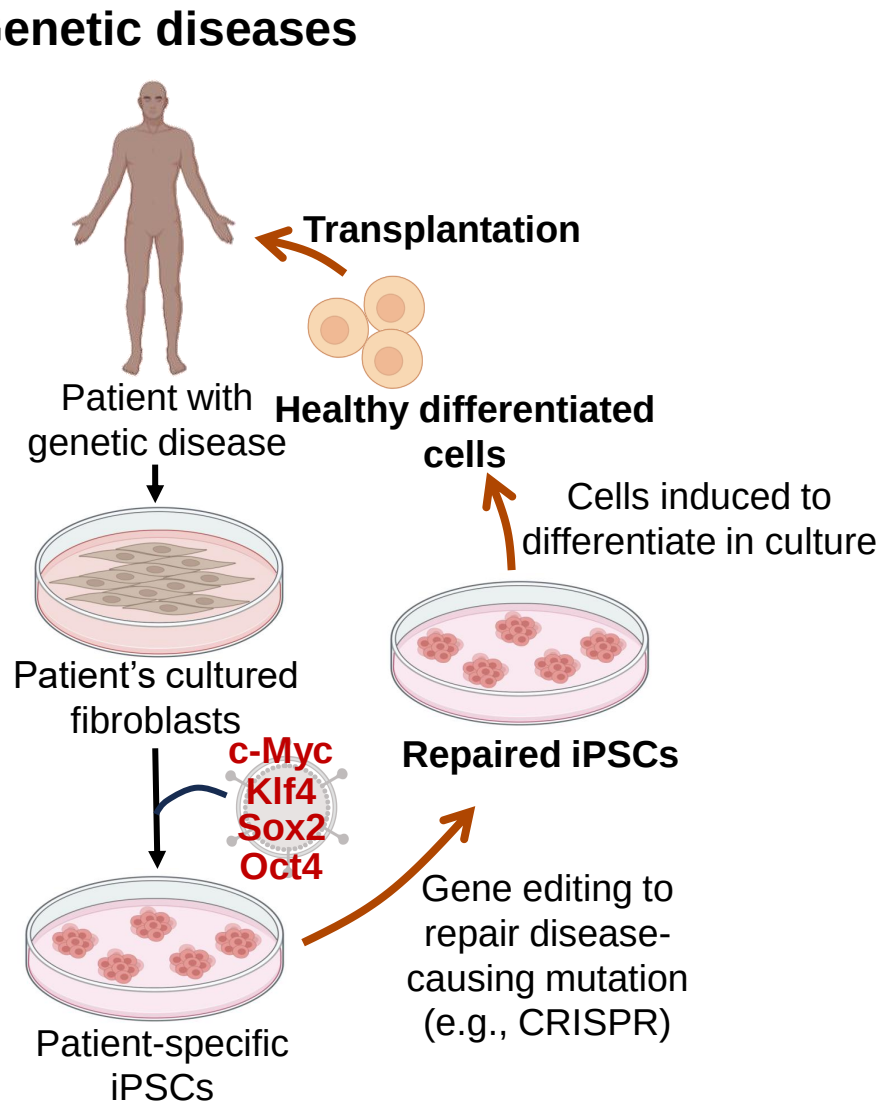
2006
Mouse embryonic stem cells: Yamanaka

2010
Clinical trial for spinal cord injury with motor neurons grown from human embryonic stem cells: Geron



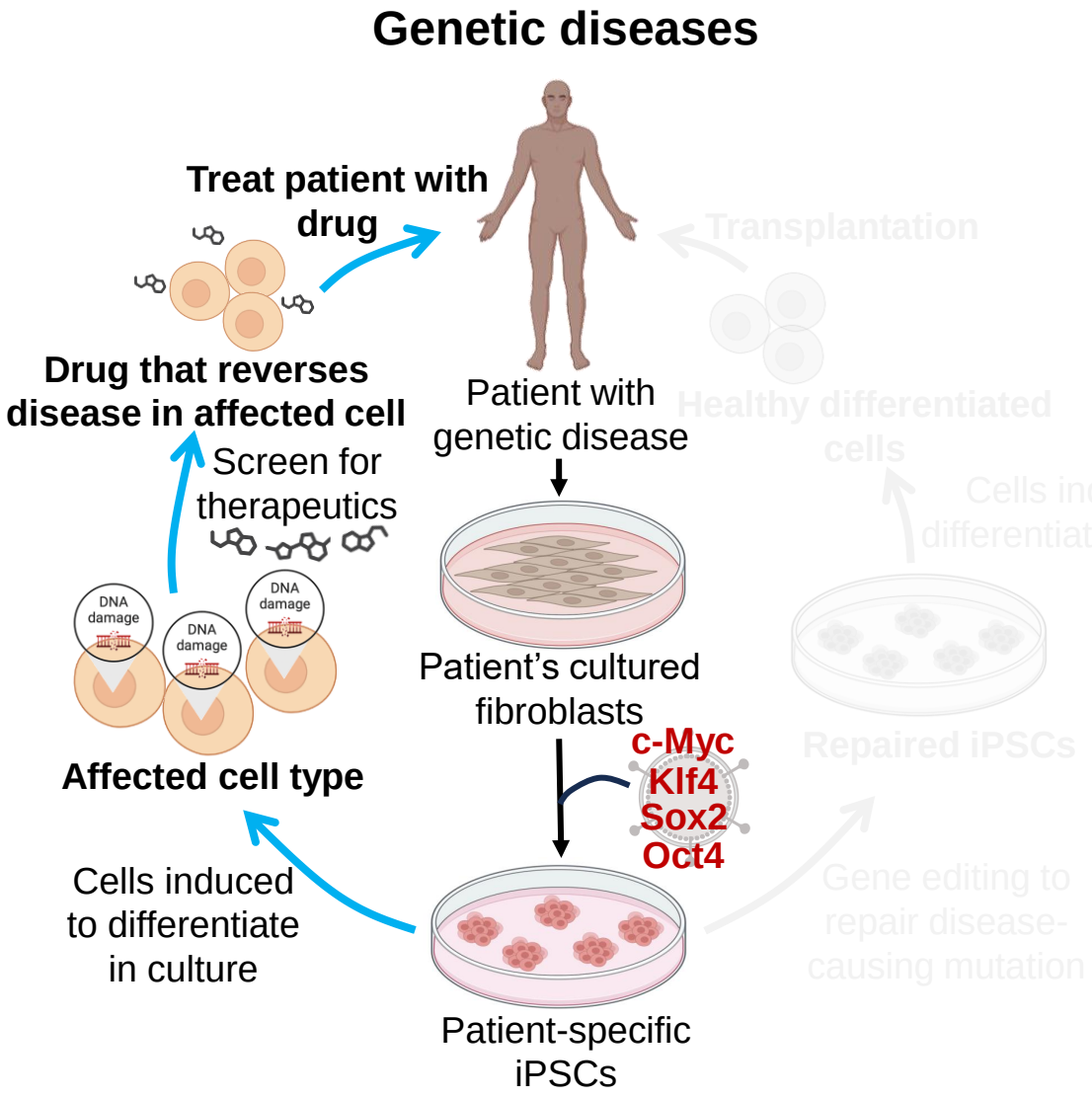
2015
Clinical trial for heart failure with human embryonic stem cell-derived cardiac progenitors: Menasché

iPSC strategies for treatment of diseases



The goal is to generate patient-specific stem cells for treatment (personalized medicine)

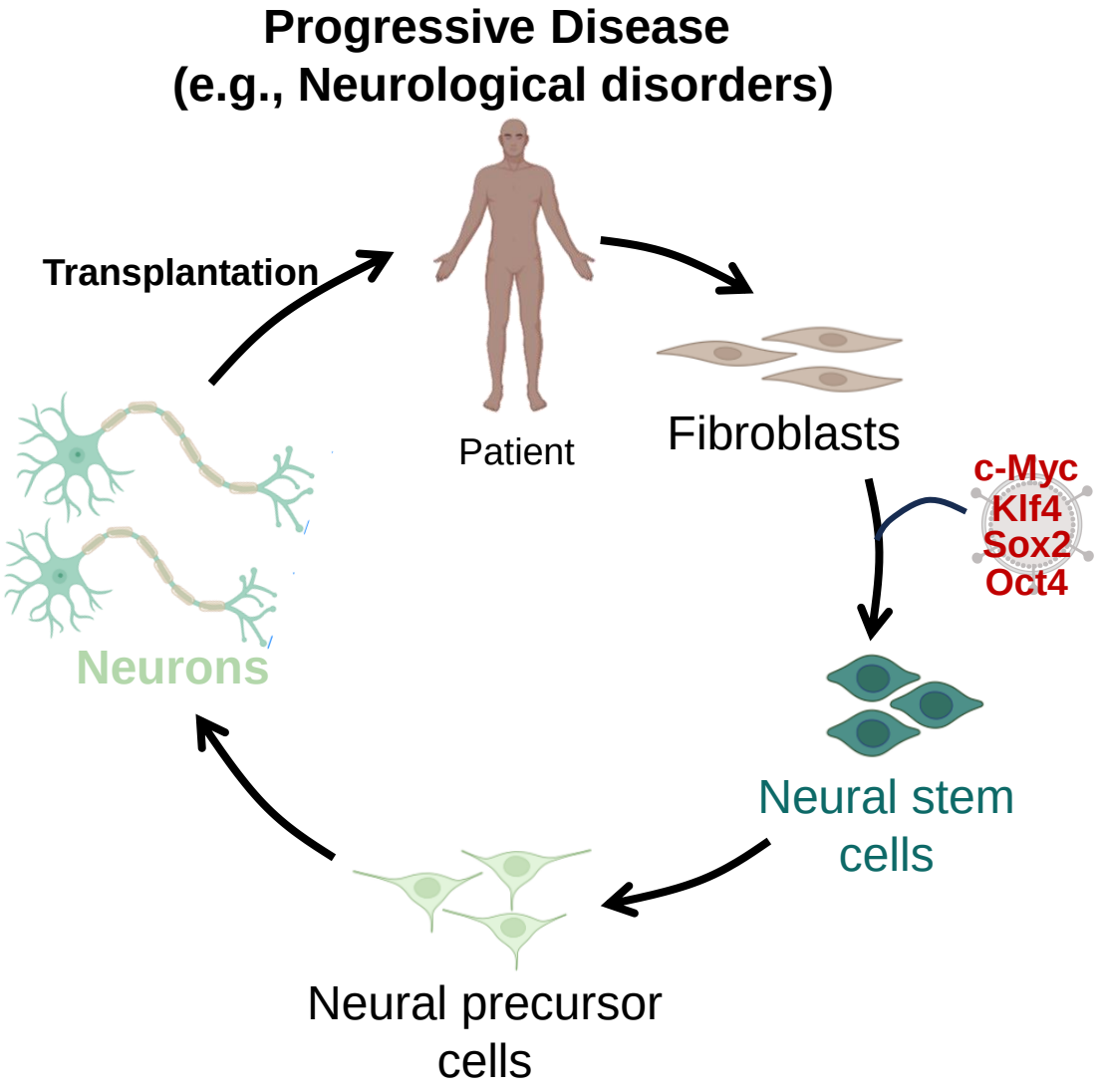
iPSC strategies for treatment of diseases



The goal is to generate patient-specific stem cells for treatment (personalized medicine)

iPSC strategies for treatment of diseases

Christopher Reeve
(1952-2004)



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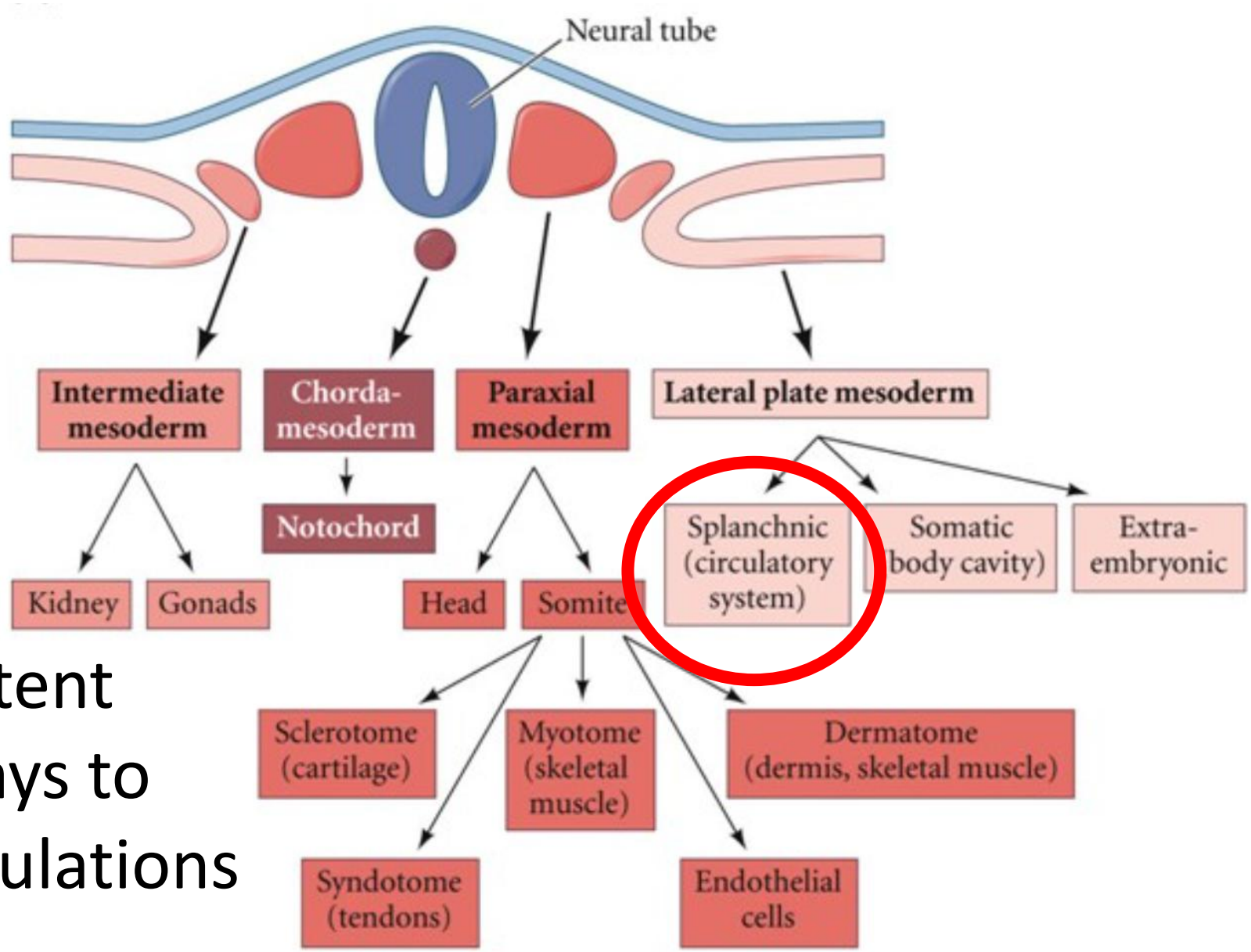
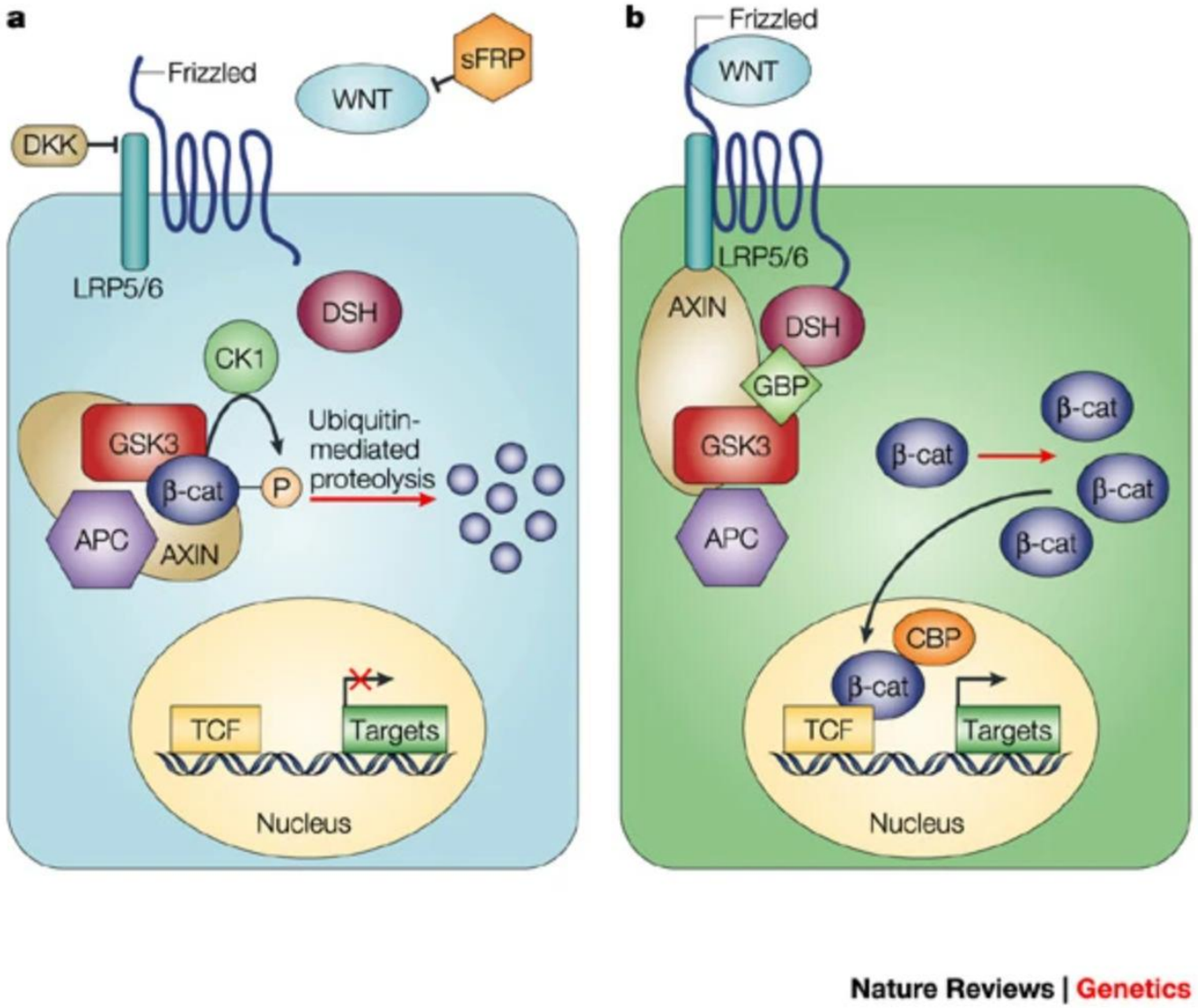
- Understand how **stem cells** give rise to the specialized cell types of the body and how these functions relate to their **potency**
- Explain how stem cells and mutations lead to the development of **cancer**
- Define induced pluripotent stem cells (**iPSCs**) and explain how these can be used to study disease
- Follow along with a detailed example of using iPSCs and apply this knowledge to case studies

Overview of Mammalian Mesoderm Development



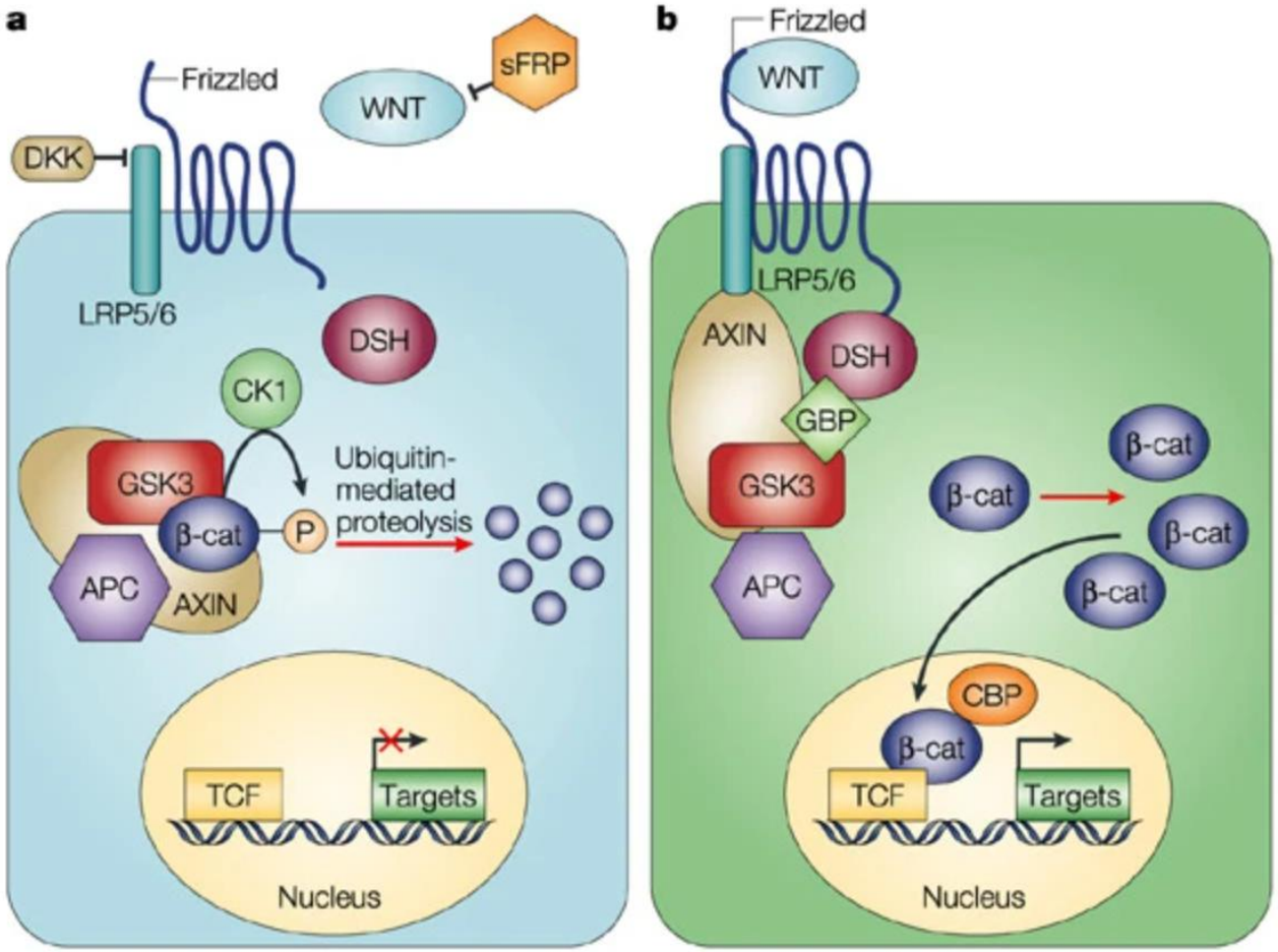
Goal: To direct pluripotent developmental pathways to obtain highly pure populations of a desired cell type

Wnt Signaling in Cardiovascular Development



- Wnt binding to the receptor leads to β-catenin dependent transcriptional activation
  - Essential in early mesodermal lineage specification
- However, there is a biphasic role of Wnt/β-catenin singling during embryonic cardiogenesis driven by a *negative feedback* loop
  - Wnt activates DKK1, inhibiting further Wnt signaling, leading to β-catenin degradation via GSK3 phosphorylation
  - DKK1 inhibition drives cardiac lineage specification towards splanchnic mesoderm which produces heart cells

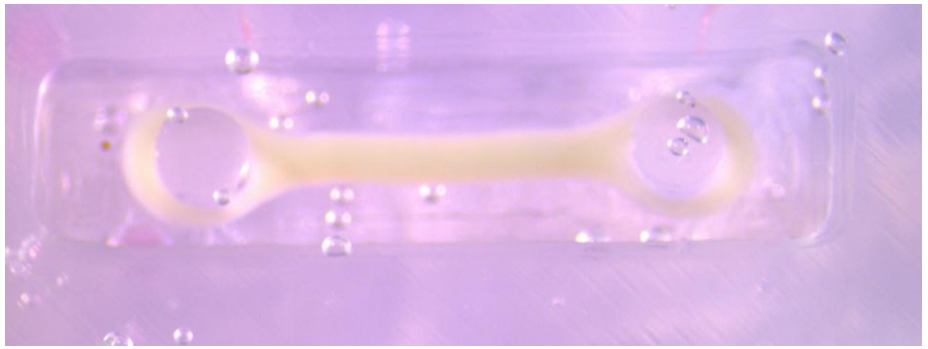
In vitro Approach for iPSC-Cardiomyocyte Differentiation



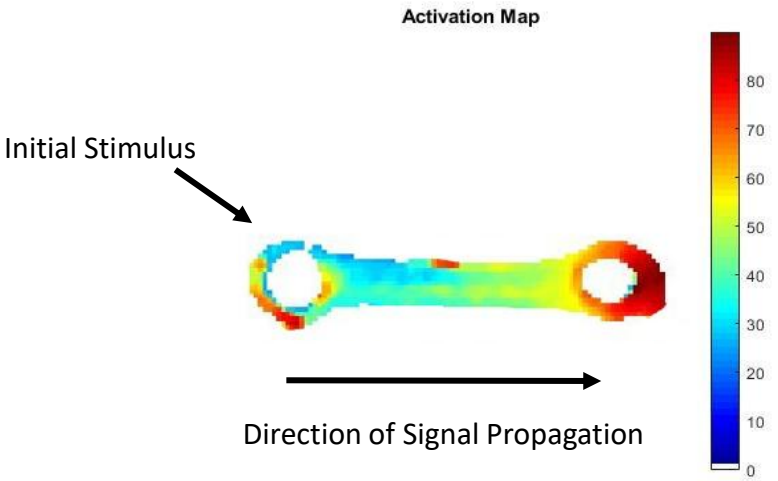
Nature Reviews | Genetics

- Wnt *activation achieved indirectly* through inhibition of glycogen synthase kinase 3 (GSK3) for 24-48 hours
  - No β-catenin phosphorylation, no degradation
- Wnt *inhibition is achieved directly* through the use of small molecule inhibitor (e.g., IWP4)

I generate cardiomyocytes (heart cells) from iPSCs

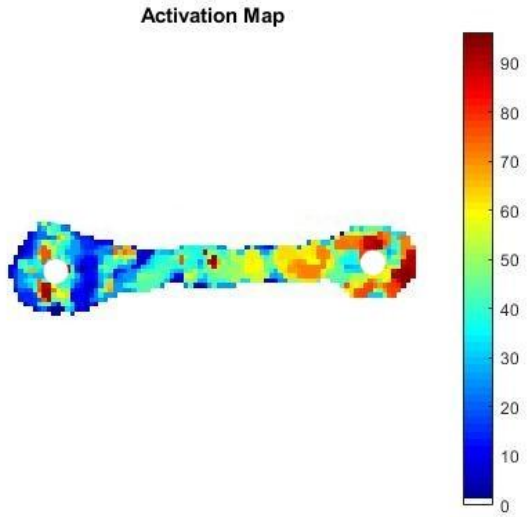


I use iPSCs to study cardiac rhythm disorders



Engineered Heart Tissue made from **Healthy** iPSC-derived cardiomyocytes

Demonstrates smooth conduction of voltage → **no arrhythmia**

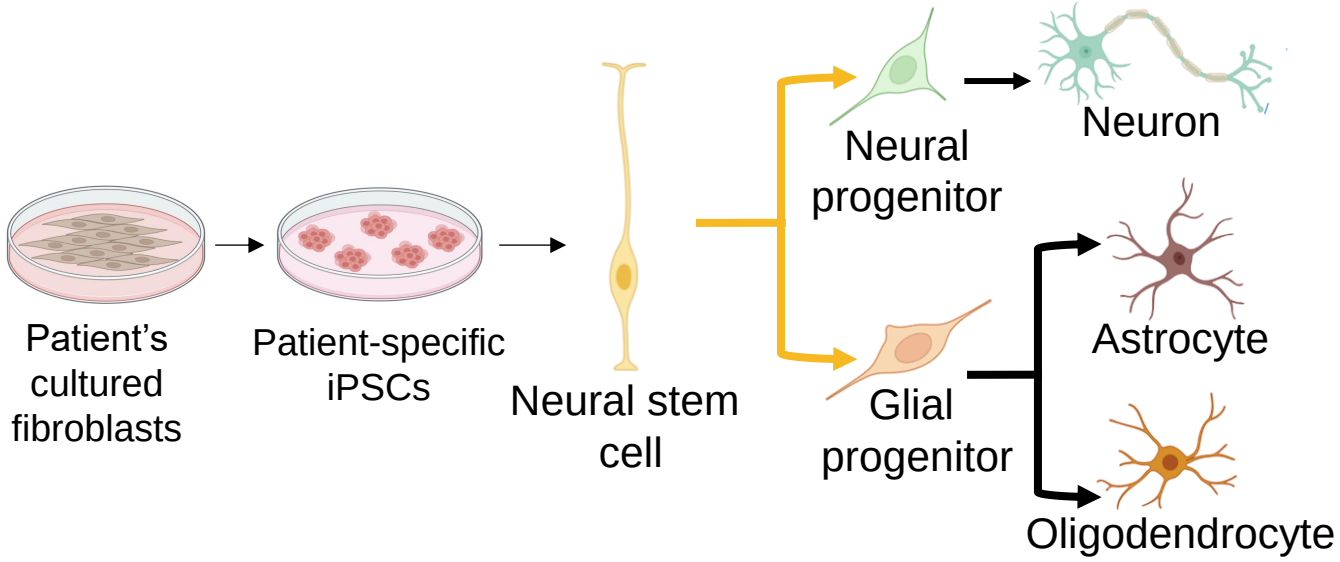


Engineered Heart Tissue made from iPSC-derived cardiomyocytes with a **desmosomal genetic defect**

Demonstrates impaired conduction of voltage → **arrhythmia**

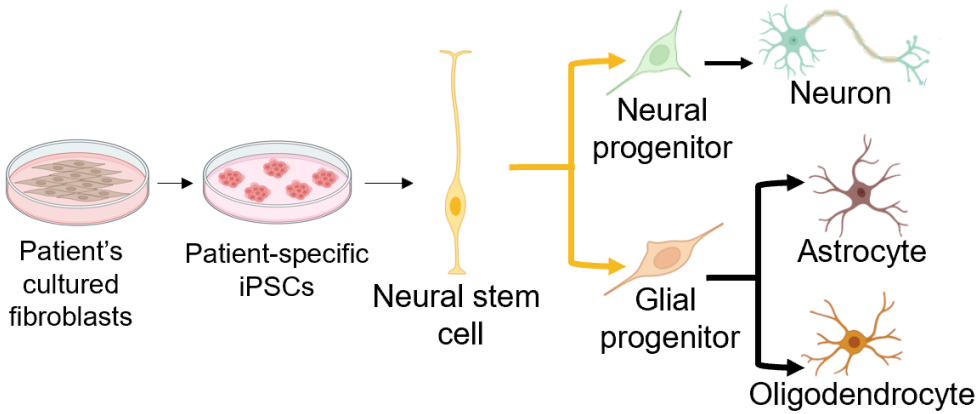
Case Study

You are a medical doctor who recently admitted a patient with a spinal cord injury. To develop a personalized treatment strategy for the patient, you collect the patient's fibroblasts and culture them into iPSCs to differentiate into neuronal cells. During and after successful differentiation, you record the following results from your culture:



1. Are the neural stem cells totipotent, pluripotent, or multipotent?
2. Why do glial progenitor cells not differentiate into neurons?
3. In general, can neural stem cells self-renew when differentiation does not occur? If so, how is this possible? If not, why not?
4. How did you differentiate these iPSCs to produce the specialized cell types?

Case Study



1. Are the neural stem cells totipotent, pluripotent, or multipotent?
   - Multipotent, as they can give rise to multiple different neuronal lineages, but only neuronal lineages
2. Why do glial progenitor cells not differentiate into neurons?
   - Glial progenitors have already surpassed the fate decision that would allow them to produce neurons, they are less potent than neural stem cells and once sufficiently down a developmental path it cannot be reversed
3. In general, can neural stem cells self-renew when differentiation does not occur? If so, how is this possible? If not, why not?
   - Yes, this is a hallmark of stem cells. It is made possible by the stem cell niche that allows self-renewable to remain favorable
4. How did you differentiate these iPSCs to produce the specialized cell types?
   - With the addition of appropriate growth factors at the appropriate time to mimic the natural developmental process

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Metacognitive Reflection Form