What is a Stem Cell?

A single cell that can replicate itself, or...

differentiate into many cell types.

What is a Stem Cell?

**Self-Renewal**
- Proliferate indefinitely by mitosis
  - Proliferate means to grow and divide
- Creates population of identical cells.

**Differentiation**
- Under key signals, stem cells can specialize into specific cell types.
Stem Cell Differentiation

• Differentiation is **COMPLEX**
  - Involves turning on (**ACTIVATING**) and turning off (**SILENCING**) many genes in a coordinated pattern of expression
  - Relies on growth factors, hormones, and chemical signals from **OTHER CELLS** to help them differentiate.
    - Chemical “peer pressure”

• Some stem cells possess a greater ability to differentiate than others = **POTENCY**
  - Totipotent - zygote
  - Pluripotent - embryo
  - Multipotent - cord blood and adult cells
## Stem Cells Fall Into 3 Categories

<table>
<thead>
<tr>
<th>Totipotent</th>
<th>Pluripotent</th>
<th>Multipotent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Can become ANY adult body cell type and specialized tissue needed for development (placenta)</td>
<td>Can become one of the 220 different cells in the human body</td>
<td>Can become a limited # of different cells in the body.</td>
</tr>
<tr>
<td>Found early (first 4 days) after fertilization of an egg by sperm = ZYGOTE</td>
<td>Found later in EMBRYONIC development</td>
<td>Found in cord blood and in your body now</td>
</tr>
<tr>
<td>Significant clinical value</td>
<td>Can be cultured for a variety of different therapeutic uses.</td>
<td>Can be used for skin, blood, bone, and cells needed for growth/repair.</td>
</tr>
<tr>
<td>Biggest ethical concern</td>
<td>If implanted, embryo will continue to develop</td>
<td>Limited controversy</td>
</tr>
</tbody>
</table>

- Pluripotent cells can become any of the 220 different cells in the human body.
- Totipotent cells can become any adult body cell type and specialized tissue needed for development (placenta).
- Multipotent cells can become a limited number of different cells in the body.
Multipotent Examples

- Hematopoietic Stem Cell (Multipotent)
  - Differentiates to form:
    - Red blood cells (Unipotent)
    - White blood cells (Unipotent)
    - Platelets (Unipotent)

- Mesenchymal Stem Cell
  - Differentiates to form:
    - Osteoblasts
    - Adipocytes
    - Chondrocytes
Single Cell Embryo

- Totipotent

5-7 Day Embryo

- Embryonic Stem (ES) Cells
  - Pluripotent

- "Adult" Stem Cells
  - Multipotent

Infant

- Cord Blood Stem Cells
- Placental Stem Cells
  - Multipotent

Adult
History of Stem Cell Science

1980’s: Pioneering work in the isolation of stem cells in mice, pigs, cows, rabbits, and sheep

1998: First successful Human Embryonic Stem Cell (hESC) isolation and culturing from human blastocyst
Initial main source of hESCs - leftover embryos from IVF (in vitro fertilization)

Typically fertilize 18-22 viable eggs/IVF cycle
Usually have 16+ remaining after attempts at implantation

Couples then choose
1. Store forever
2. Donate to other couples
3. Destroy
4. Donate to scientific research

Why are ESCs important? They avoid senescence due to high levels of telomerase
Stimulating ESCs to Differentiate

- Directed Differentiation - *in vitro* coaxing of undifferentiated hESCs
  - Key to create tissues for tissue regeneration
- Focus of research was to determine exactly what signals were needed to stimulate stem cells to become discrete cell types
- Signaling substances include:
  - Growth factors
  - Hormones
  - Small peptides from neighboring cells
- How do we gauge success?
The Controversy

TOTIPOTENT

- Harvesting stem cells from the zygote results in destruction/loss of zygote
  - When does life begin? At conception? When the fetus can survive on own? At 40 weeks?

PLURIPOTENT

- Source of the cells? Possible loss of the embryo?

MULTIPOTENT

- Currently, having a baby to harvest cord blood to save another child’s life.

- No controversy; We can now reprogram Multipotent stem cells into Pluripotent stem cells through chemistry.
- These are called \textit{iPS = Induced Pluripotent Stem Cells.}
Adult-Derived Stem Cells (ADCs)

- Appear in small numbers
- Can be isolated from the brain, intestine, hair, skin, pancreas, bone marrow, fat, mammary glands, teeth, muscle, and blood
- Can be removed from:
  - Living tissue through fine needle aspiration biopsy
  - Harvested from cadavers
  - Liposuction since found in adipose tissue – 500,000 liters disposed of each year
- Can be coaxed to become a different type of cell in right environment
Other Types of Stem Cells

Amniotic Fluid-Derived Stem Cells
- Found in protective fluid that surrounds a developing fetus
- Unsure if hESCs or ASCs
- Can be coaxed into limited various cells types

Cancer Stem Cells
- CSCs, AKA tumor-initiating cells
- Implicated in:
  - Cancer development
  - Tumor progression
  - Metastasis
  - Recurrence
- Can self-renew and differentiate
- Unsure of source
- Potential therapy for cancers
Tests for Pluripotency

Important to determine whether the cells are able to form other cell types. 

**In vitro**
- Demonstration of Germ Layers
  - Ectoderm, mesoderm, endoderm
- Aggregation into clusters
- DNA methylation found only in stem cells, not other cell types

**In vivo**
- Injection of ESCs into immunodeficient mice
  - Production of teratoma
  - Formation of differentiated tissues into lab mice
- Injection of ESCs into blastocyst-stage embryo
  - Resulting fetus will demonstrate chimera of combined traits

*In vivo ESCs are pluripotent for a short time; in vitro ESCs can be maintained indefinitely.*
Nuclear Reprogramming to Produce PSCs

- PSCs – Pluripotent Stem Cells
- Scientists have been working on reprogramming cell fates for 50+ years
- Effort to eliminate controversy of stem cell science due to embryonic use
- Basic idea is to alter adult cell patterns of gene expression to reprogram to an earlier stage of differentiation
  - Modification of epigenetic influence and histone changes
- Somatic cell nuclear transfer
  - Transplanting somatic cell nucleus into enucleated egg cell
  - Cell signals of egg will alter genome expression of somatic cell, forcing it to behave as an embryo
Somatic Cell Nuclear Transfer

Tissue cell donor

Cells from animal to be cloned are maintained in the lab so they do not grow or divide

Nucleus is removed

The reconstructed embryo grows for 7 days

Nucleus fuses with empty egg after electric current applied

Embryo's implanted into surrogate mother

Cloned animal is born with exact DNA as the tissue cell donor

Donor supplies unfertilised eggs

Egg cell

Nucleus is removed

Nucleus fuses with empty egg after electric current applied
Induced Pluripotent Stem Cells - iPSCs

- Form of nuclear reprogramming
- Revolution in stem cell biology
- First success was in Japan
  - Converted mouse fibroblasts to an earlier stage of development
  - Used a retrovirus to deliver 4 transgenes
  - Final cells were indistinguishable from hESCs
- Since the Japan study, success in other animal cells including human, rat, and monkey
The Limitations of iPSCs

- iPSCs alleviate some of the stem cell controversy of ESCs
- iPSCs also present a number of challenges
  - Inefficient – works only 1 in 1000 attempts
  - Requires constant attention to maintain cell lines
  - Reduced viability once frozen
  - Prone to tumor formation
  - Can spontaneously differentiate into mature cell type
  - Difficult to direct differentiation
- Research is progressing at rapid pace to better understand capabilities
Chapter Wrap Up – Application and Ethics

- Select a MAIN TOPIC that interests you
  - Potential Applications
  - Challenges and Regulations
  - Ethical Issues

- Read that section in the textbook
  - Online test ONLY
  - Pages 537 - 544

- Write an essay about ONE of the issues that falls into the category you selected to learn more about
  - SOLID essay
  - Research-based with references (MLA format, no in-text citations required)
  - DUE TUESDAY 4/18/2017
Potential Applications of Stem Cells

• Stroke
• Heart attack
• Parkinson’s disease
• Alzheimer’s disease
• ALS
• Spinal cord injuries
• Diabetes
• Autoimmune disorders
• Osteoporosis
• Severe burns
• Cancers
• Blindness
• Regenerative medicine for transplant
• Brain injury
• Sickle cell disease
• Therapeutic cloning
## Challenges and Regulations

### Challenges
- Hype
- *In vitro* success vs *in vivo* success
- Tumor formation
- Unanswered questions
  - Genetics of self-renewal?
  - Factors that trigger division?
  - Best cells to use?
  - Safety?

### Regulations
- International guidelines
- National guidelines
  - NIH funding
- FDA approval
- Funding through private foundations
- Medical tourism for use
- Who decides?
Ethical Issues Involving Stem Cells

- Source of stem cells?
- Wide range of ethical questions to consider
- Faith/Religious considerations
- Tax-funding of research and public opinion