Stem Cells and Infectious Disease

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Bioscience in the 21st Century
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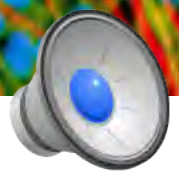


www.gothamgazette.com/.../stemcell/stem_cell.jpg

Overview

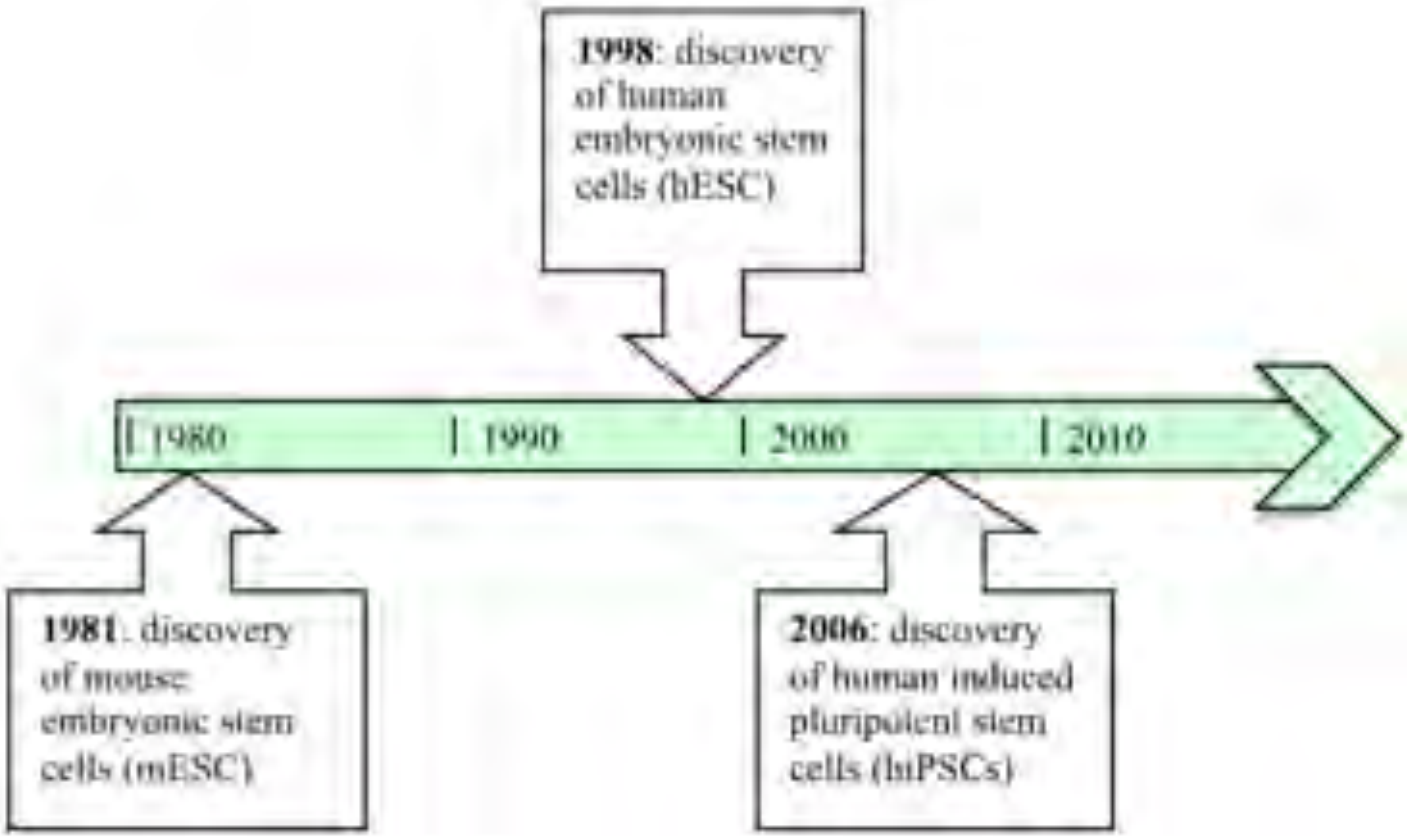
- **Setting the stage for the discussion**: historical perspective and prospects in regenerative medicine
- **Stem Cell Basics**:
  - What are stem cells?
  - Where do stem cells come from?
- **Selected Stem Cell Advances in the News**
- **HIV Infection and Prospects for Stem Cell Therapy**

Historical Perspective and Prospects for Regenerative Medicine

Historical Perspectives

- Major changes in regenerative medicine (replacement of damaged or diseased cells and tissues with new cells and tissues) due to advances in stem cell technologies
- Some stem cell therapies in existence for over 50 years. First successful bone marrow transplant done in 1956 on leukemia patient. Bone marrow contains **adult-derived** hematopoietic stem cells (able to regenerate tissues similar to the specialized tissues in which they are found.
- **Embryonic stem cells** believed to have greater potential. This line of stem cell research has been the most controversial.

KEY STEM CELL DEVELOPMENTS



modified from www.intechopen.com

IMPACT :

- Understanding birth defects

- Possibility of generating patient-specific stem cell lines to study the mechanism of different diseases in the laboratory

- Creation of models for drug discovery and testing the toxic effects of drugs

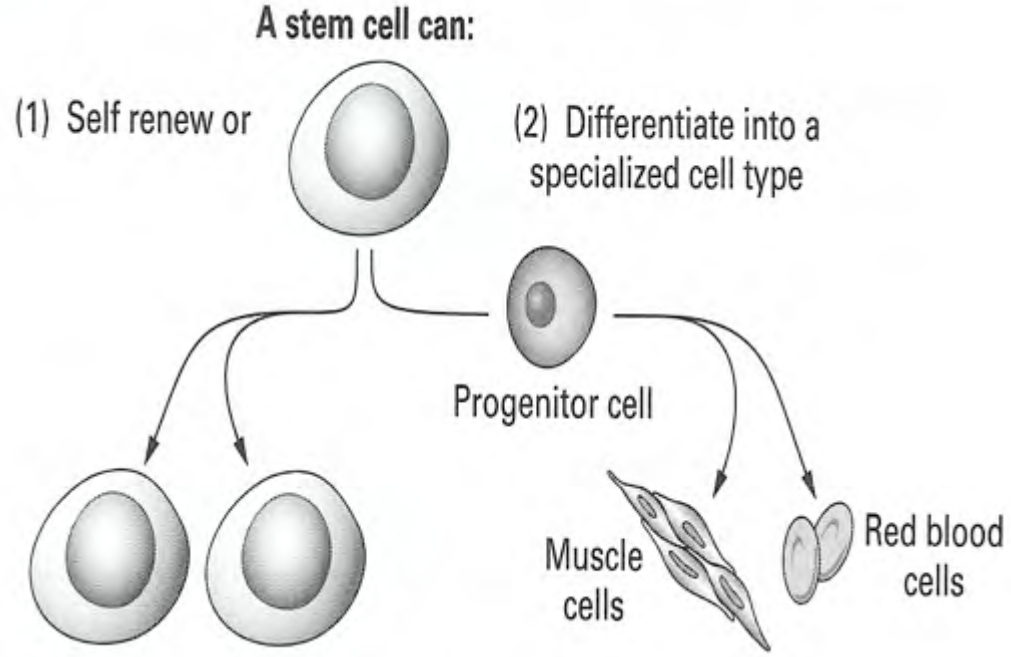
- Tissue engineering (e.g., use of progenitor cells to make organoids)

- Prospects for treating individuals with chronic infections and autoimmune diseases (e.g., HIV infection, rheumatoid arthritis, lupus)

STEM CELL BASICS

I. What are stem cells?

Basic Characteristics of Stem Cells



Stem cells properties:

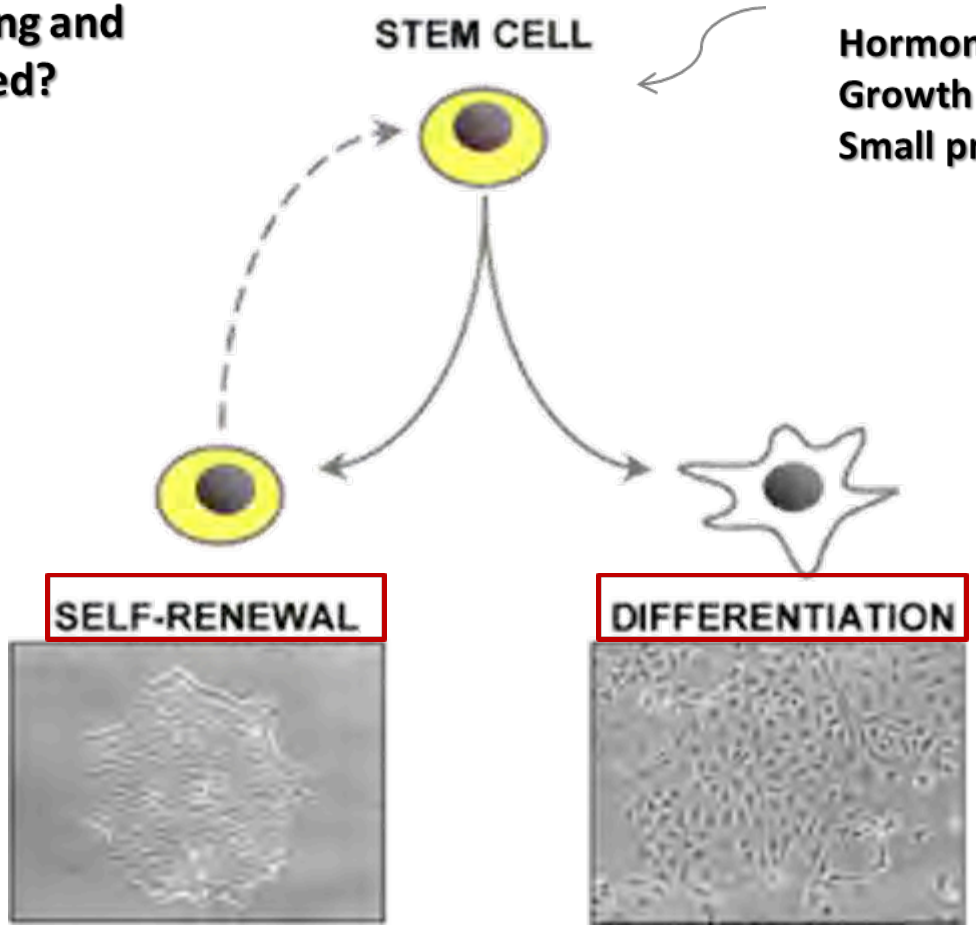
1. Capable of dividing and renewing for long periods
2. They are unspecialized.
3. They give rise to specialized cells.

Adapted from *Stem Cells and Cloning* by Kelly A. Hogan;
http://stemcells.nih.gov/info/basics/basics2.asp

How do cells remain self-renewing and unspecialized?

What are the SIGNALS ???

Hormones
Growth factors
Small proteins



All stem cells are not alike!

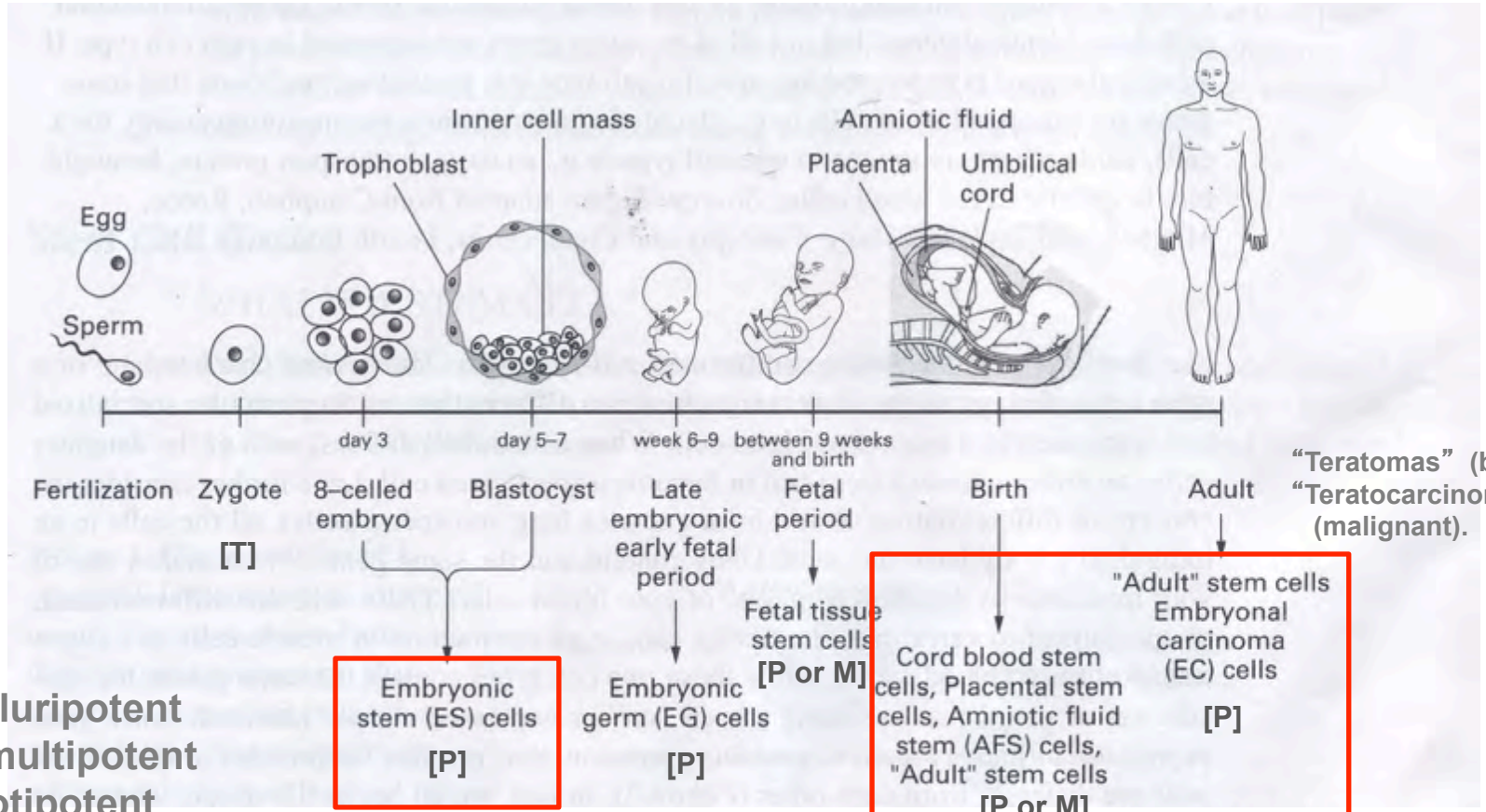
- Some stem cells have more potential than others. **POTENCY** describes the cell's ability to differentiate into other cell types.
- **Unipotent** stem cells form only one type of specialized cell type.
- **Multipotent** stem cells can form multiple types of cells and tissue types.
- **Pluripotent** stem cells can form most or all cell types in the adult.
- **Totipotent** stem cells can form all adult cell types as well as the specialized tissues to support development of the embryo (e.g., the placenta)

STEM CELL BASICS

II. Where do stem cells come from?

Different sources of stem cells during development

Adapted from *Stem Cells and Cloning* by K.A. Hogan



"Teratomas" (benign);
"Teratocarcinomas" (malignant).

[P] = pluripotent
[M] = multipotent
[T] = totipotent

Isolation of Human Embryonic Stem Cells

First done by Dr. James Thompson and colleagues at the University of Wisconsin (1998).

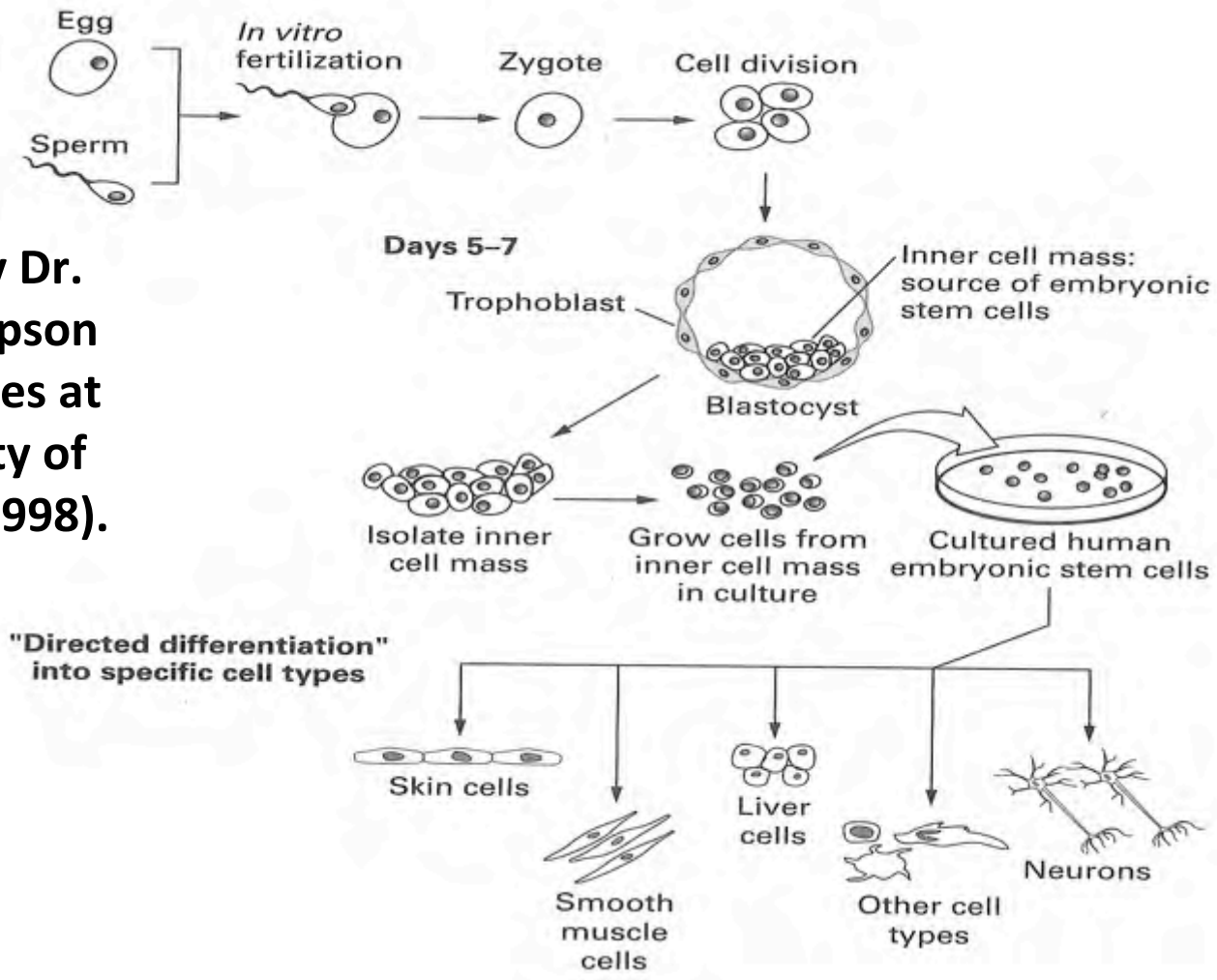
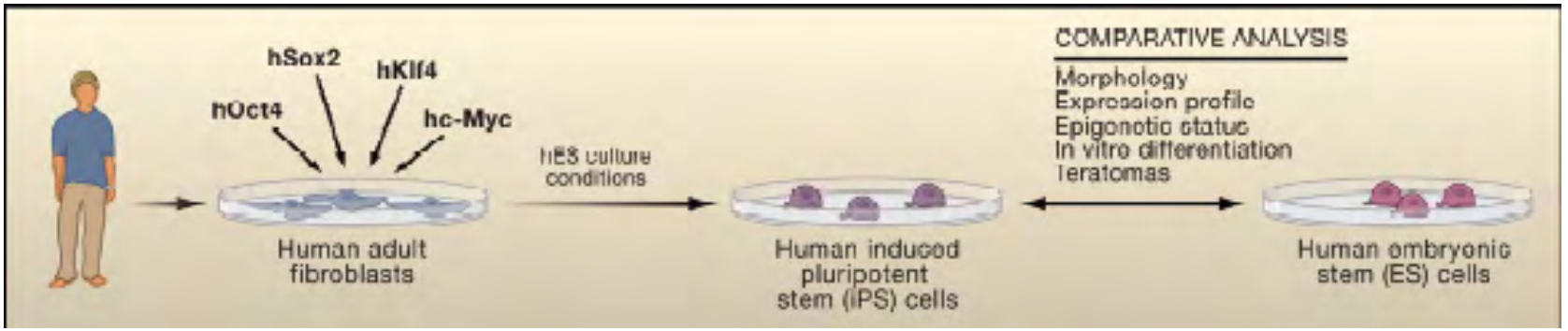


Figure from *Stem Cells and Cloning* by K.A. Hogan

"Scientists Turn Human Skin Cells into Stem Cells"



Induction of Pluripotency: From Mouse to Human

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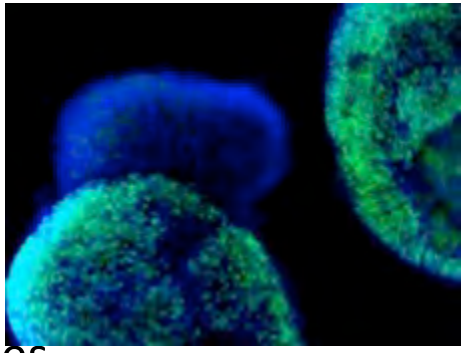
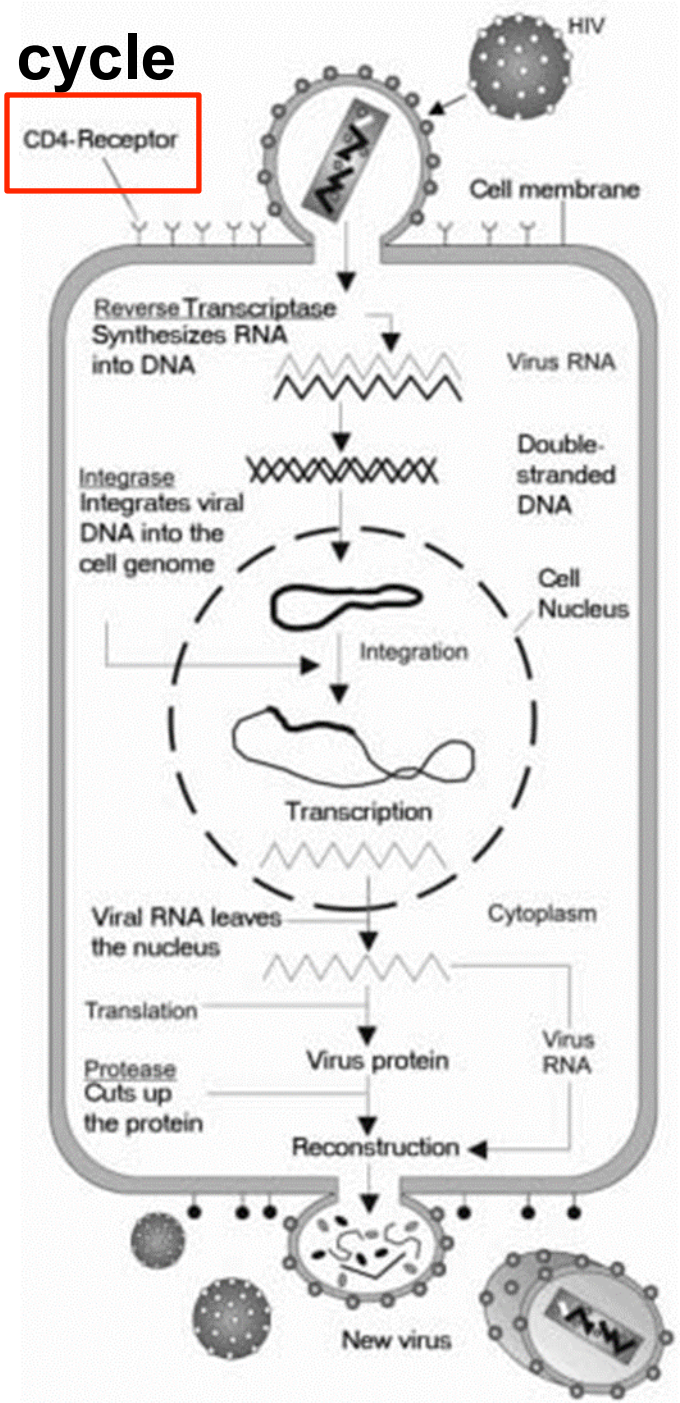
Stem Cell Research in the News!

Selected News about Stem Cells



- "Scientists Find Way to Track Stem Cells in Brain"
  (*Science,* November 2007)
- "Stem Cells Restore Memory in Mice"
  (*Journal of Neuroscience,* October 2007)
- "Stem Cells From Testes Produce Wide Range of Tissue Types
  (*Nature,* September 2007)
- "Scientists Turn Human Skin Cells into Stem Cells"
  (*Science*; *Cell,* November 2007)
- "First Neurons Created from ALS Patient's Skin Cells"
  (*Science*, July 2008 [online])
- "Identification of small molecules for human hepatocyte expansion and iPS differentiation"
  (*Nature Chemical Biology*, June 2013)
- "Photoreceptor precursors derived from three-dimensional embryonic stem cell cultures integrate and mature within adult degenerate retina"
  (*Nature Biotechnology*, July 2013)
- "Generation of functional human pancreatic beta cells in vitro"
  (*Cell*, October 2014)
- "HIV-specific Immunity Derived From Chimeric Antigen Receptor-engineered Stem Cells" (*Molecular Therapy*, June 2015)

HIV life cycle



- CXCR4 (expressed on surface of *many* cells) and **CCR5** (expressed on surface of *few* cell types) are also receptors.
- Efficient HIV infection requires one of these in addition to CD4.
- Note that individuals that are genetically lacking the CCR5 protein receptor are normal and remarkably resistant to HIV infection

http://www.bedfordresearch.org/curing-hiv-disease-with-stem-cell-therapy/

How can stem cells provide therapy for HIV disease?

Problems to overcome for therapy to be effective:

1. Must destroy all CD4+ T cells before bone marrow transplant

2. Transplanted bone marrow must be a perfect match

Proof of concept:

- Bone marrow transplant effective in treating HIV disease in patient with HIV and lymphoma (2009).
- Patient treated with bone marrow from individual who was naturally resistant to HIV infection (lacked the CCR5 receptor).
- New bone marrow cells did not become infected with HIV.

A general strategy for stem cell therapy to treat HIV disease

1. Use patient-derived stem cells from HIV-infected individual

2. Develop bone marrow stem cells from patient derived stem cells

3. Silence CCR5 gene within bone marrow stem cells to render them resistant to HIV infection

4. Transplant genetically modified bone marrow stem cells into HIV-infected patient who may be able to avoid radiation or drug-treatment to remove all HIV-infected cells.

5. Over time new cells may eventually replace the HIV-infected cells

Summary:

- **Stem cell therapies offer regenerative prospects for numerous human diseases and infections**

- **Stem cells are capable of renewal and differentiation.**

- **Stem cells are derived from numerous sources and have different potency capacities.**

- **Adult stem cells (ASCs) have been detected in numerous tissues.**

- **Induced pluripotent stem (iPS) cells offer great potential.**

- **Considerable debate surrounds the use of embryonic stem cells. Adult stem cells may offer similar prospects for therapy as do as ESCs, yet a complete understanding of stem cell applications will require a basic understanding of differentiation and renewal mechanisms in ASCs and ESCs as well.**

Additional resources: http://stemcells.nih.gov/info/basics/

Ode to a Stem Cell, Part II
by VCW

There once was stem cell stuck in the 'hood'
Dividing endlessly, but only wishing he could
Become something else, a skin cell, a hair cell, or some other type
But for weeks he sulked and uttered this gripe
"Why am I not needed?" to his friends he would say
Isn't there a call for a specialist somewhere today?
Well, if you really want to leave to get a new start,
You must change your tune, for surely there is an art
To consider what signals you hear and choices you make.
Divide once more for the special journey you take.
Dare to be different, as you differentiate!