

# Genetics and Society

April 21, 2009

## Embryonic Stem Cells

# Outline

- Stem Cells
  - Multipotent vs. Pluripotent
  - Blastocysts and Chimeras
  - Embryonic Stem Cells
- Cloning
  - Somatic Cell Nuclear Transfer
  - Therapeutic vs. Reproductive cloning
- Politics of stem cells

# Stem Cells

# Stem Cells

- **Gene therapy** puts gene function in
- **RNAi** takes gene function out
- **Stem cell therapy** puts **CELL** function in.

# Questions

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What do you know about embryonic stem cells?

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What positions have you heard?

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What do you know about embryonic stem cells?

What positions have you heard?

Have you ever talked to anyone about them?

# Multipotent vs. Pluripotent

Multipotent stem cells are often referred to as **adult stem cells** (even if they come from a fetus).

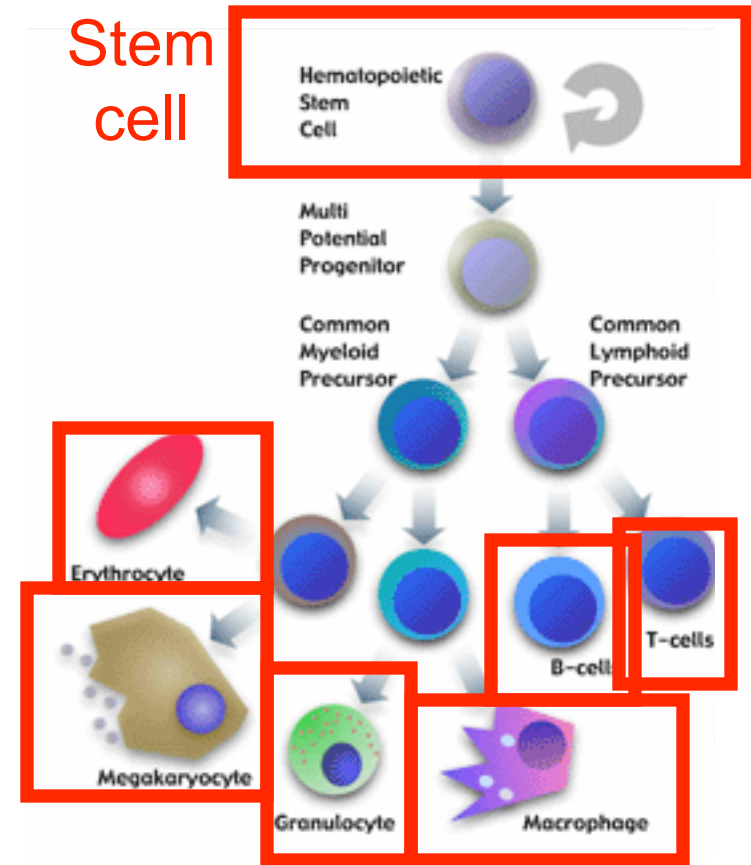
Pluripotent stem cells are often called **embryonic stem cells**.

# What is a stem cell?

**Stem cells** divide to give a **differentiated** cell and more stem cells.

Differentiated cells perform a function in the tissue but don't divide.

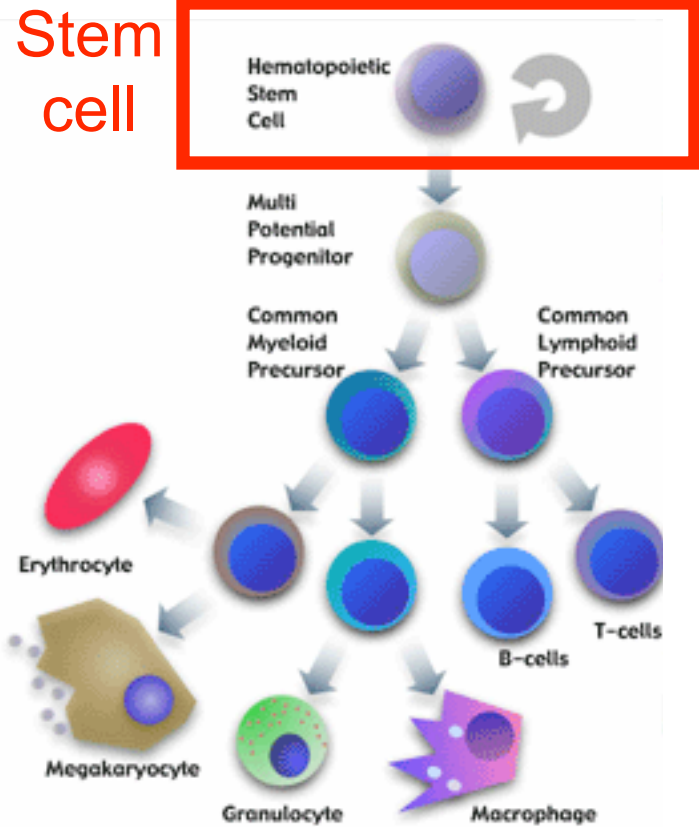
If you can affect the stem cell, you can affect all of the cells of the tissue.



**Differentiated cells**

# Multipotent stem cells

**Multipotent** stem cells are stem cells that can produce cells of multiple differentiated cell types, but all within a particular tissue, organ, or physiological system. For example, blood-forming (hematopoietic) stem cells are multipotent cells that can produce all cell types that are normal components of the blood.



# Pluripotent Stem Cells

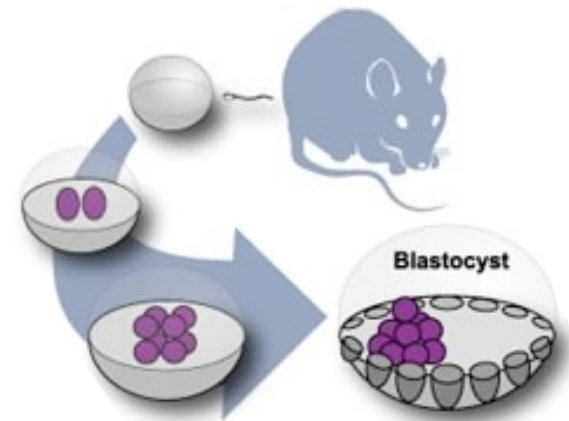
**Pluripotent** stem cells are stem cells that can become all the cell types that are found in an implanted embryo, fetus, or developed organism.

Stem  
cell



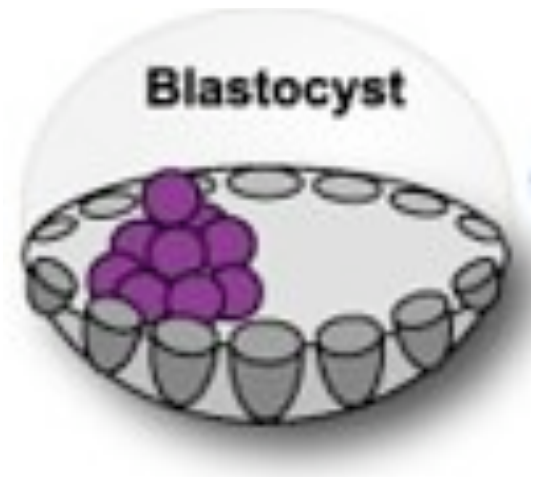
# Blastocyst

The **blastocyst** is a very early embryo consisting of approximately 150-300 cells. The blastocyst is a spherical cell mass produced by cleavage of the fertilized egg after approximately 5-7 days of cell divisions.

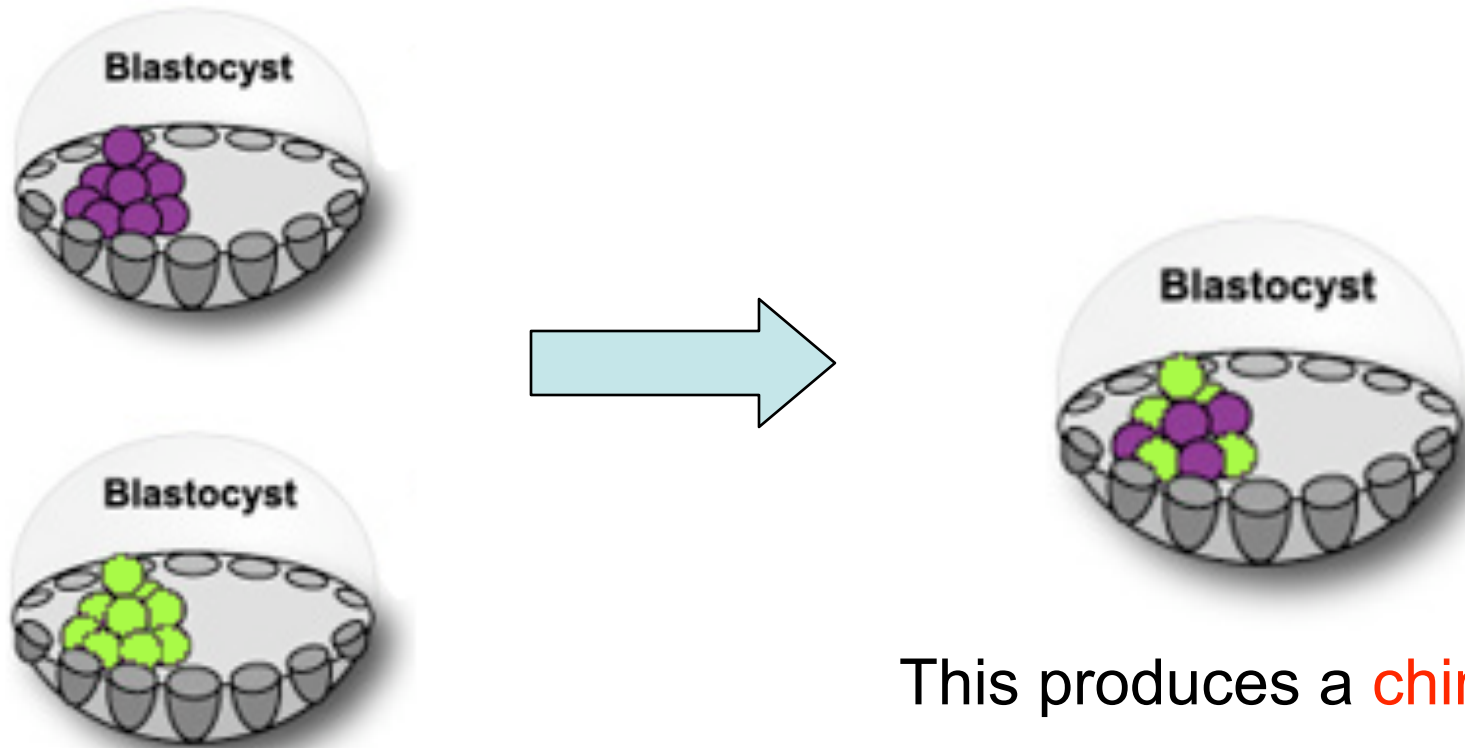


# Blastocyst

The **blastocyst** contains a microscopic cluster of cells called the inner cell mass (from which embryonic stem cells are derived) and an outer layer of cells called the trophoblast (that forms the placenta).

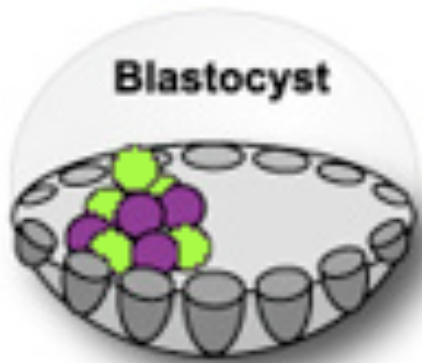


# Cells from embryos can be mixed



This produces a **chimera**

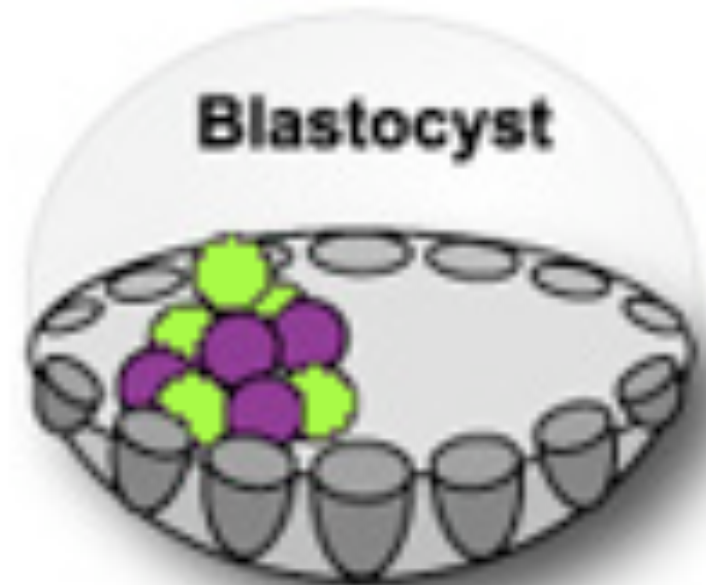
# Cells from a blastocyst can become ANY cell in the body



Chimeric mice

# Chimeras

- The DNA never mixes (they are not hybrids).
- The cells grow, divide and communicate with each other during development as one organism.



# Chimeras

- Cells from different species can be mixed and they will grow together into one organism.



# Chimeras

- Some humans have been found that are natural chimeras
- Some of their tissues have one genotype, the rest of their tissues have a different genotype.

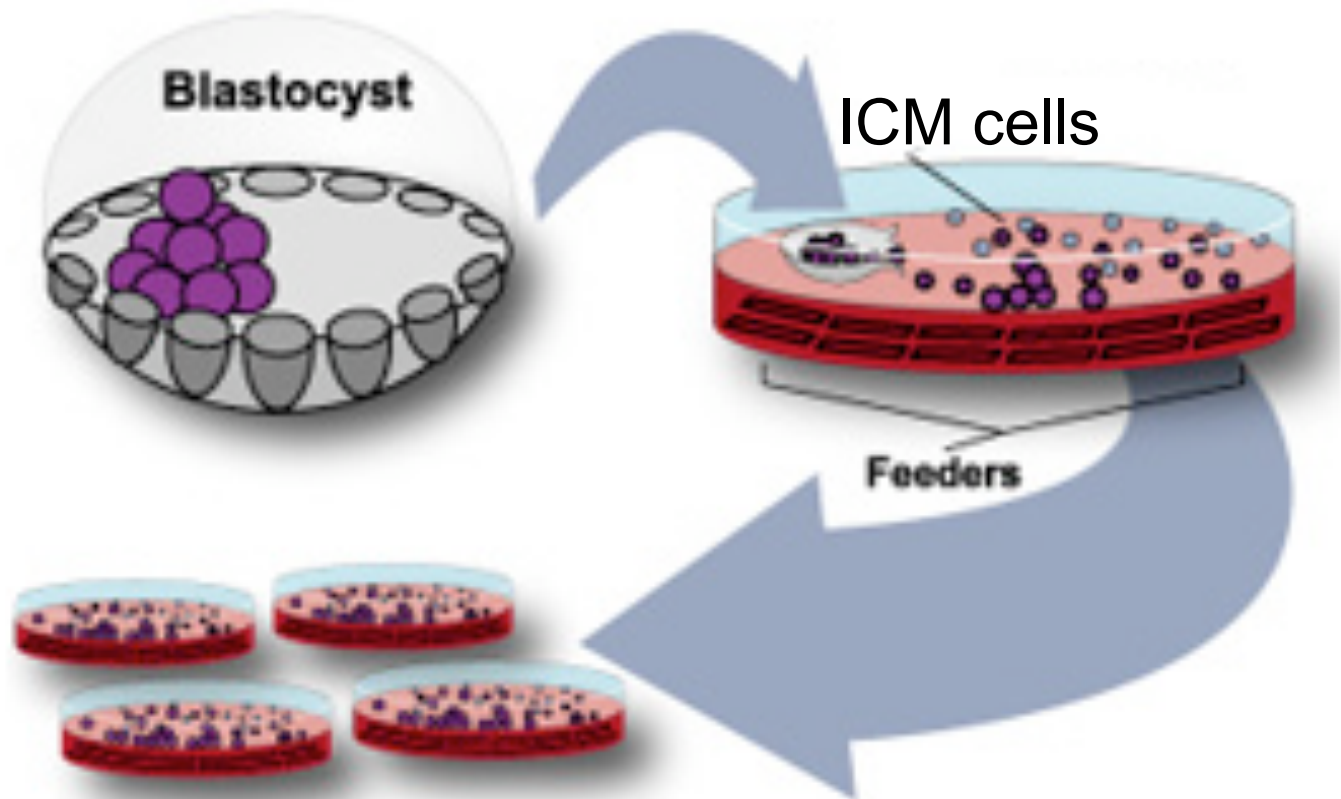
# Chimeras

- Chimeras show that early embryonic cells respond to signals in their environment to fill any role in an organism.

# Embryonic Stem Cells

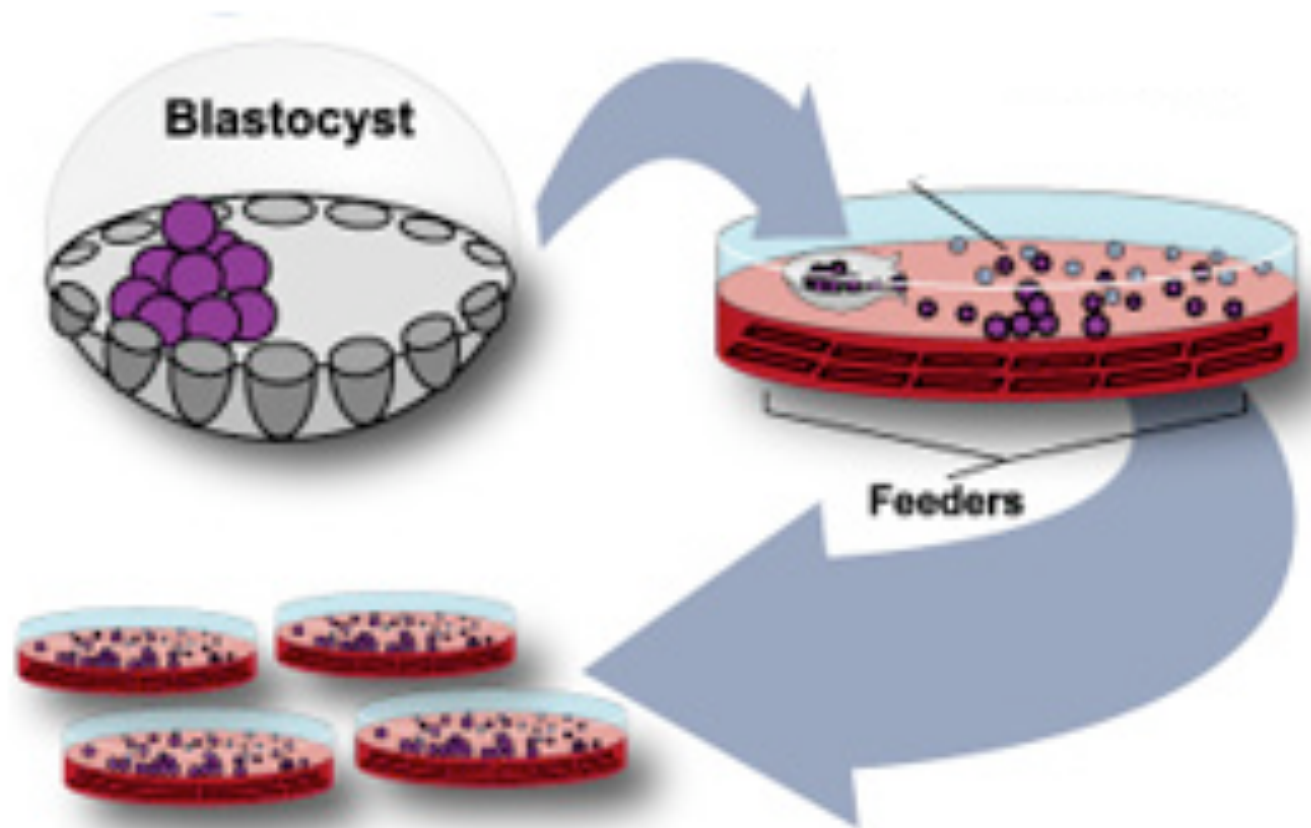
- In the same way that the ES cells can become any part in the body when mixed in an embryo, they will take the place of damaged cells when added to an adult animal.

Cells from the inner cell mass can be cultured in a dish.



Embryonic stem cells

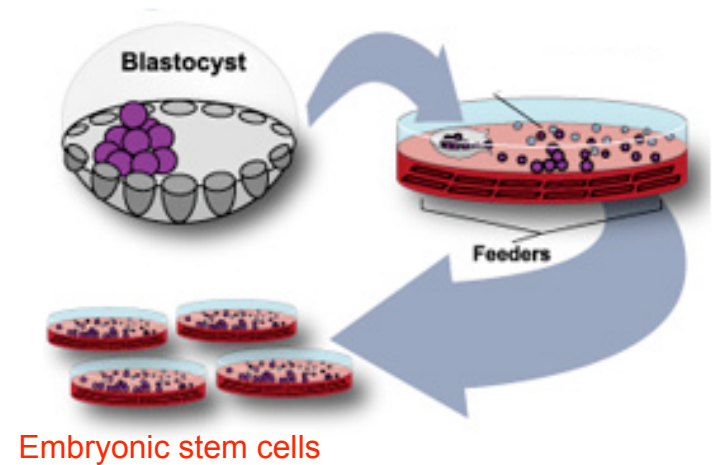
Cells from the inner cell mass can be cultured in a dish.



Embryonic stem cells

# Cells from the inner cell mass can be cultured in a dish.

By growing the ES cells in a dish huge numbers of cells can be made, so that they can be used to treat disease.



# Diseases

Stem cells can be applied to any disease where cells are dead or dying and need to be replaced:

- Parkinson's disease
- Spinal chord injury
- Diabetes
- Heart disease
- Muscular dystrophy
- Multiple sclerosis

# Some other uses of embryonic stem cells

- Understanding cancer.
- Making models for genetic diseases.
- Making models for drug testing.
- Learning to stimulate our own stem cells to treat disease.
- Learning about the process of aging.

These uses will probably happen before stem cells are widely used to treat patients

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# Cloning

# Immune response is a problem with using stem cells

The immune system will recognize any cell that is foreign.

Adult stem cells from the patient or a carefully matched relative will work.

Non-matched transplants into the brain or eye will work (the immune system can't get into the brain).

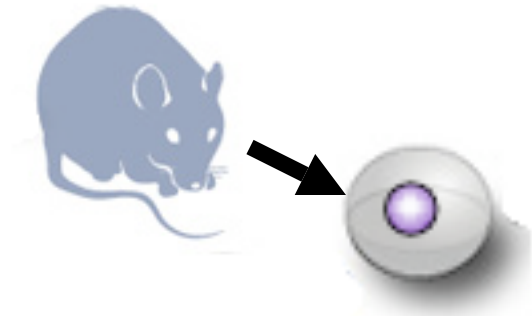
# Immune response is a problem with using stem cells

To use stem cells for other tissues, we need to make stem cells (preferably pluripotent) that are a genetic match to the patient.

# Somatic Cell Nuclear Transfer (SCNT): “cloning”

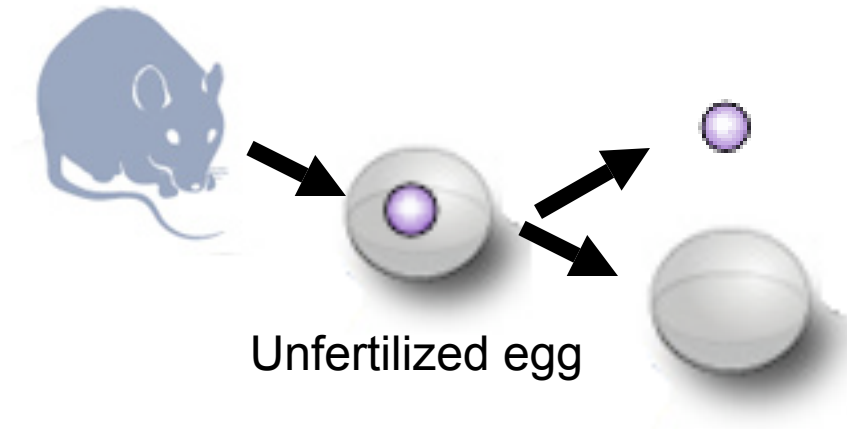


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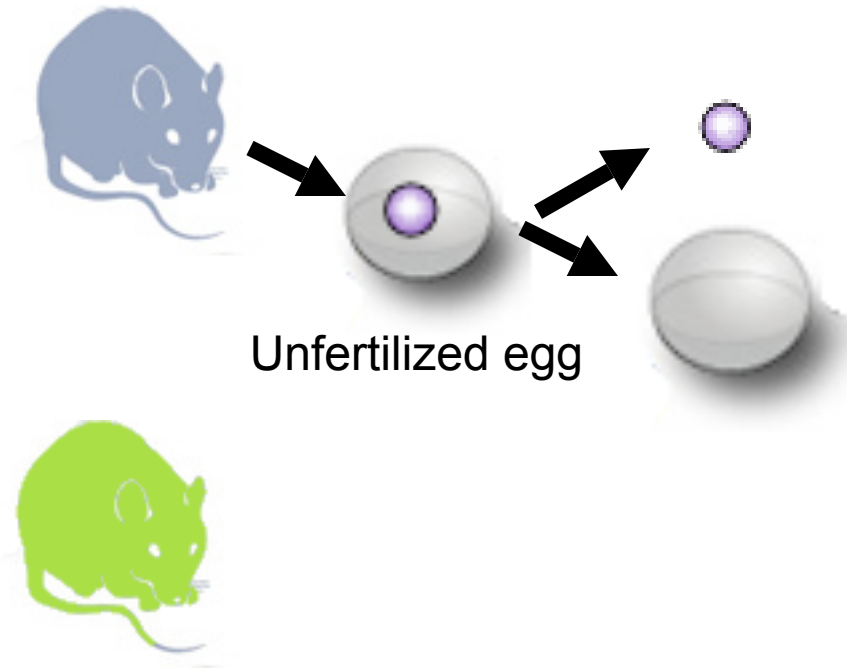


Unfertilized egg

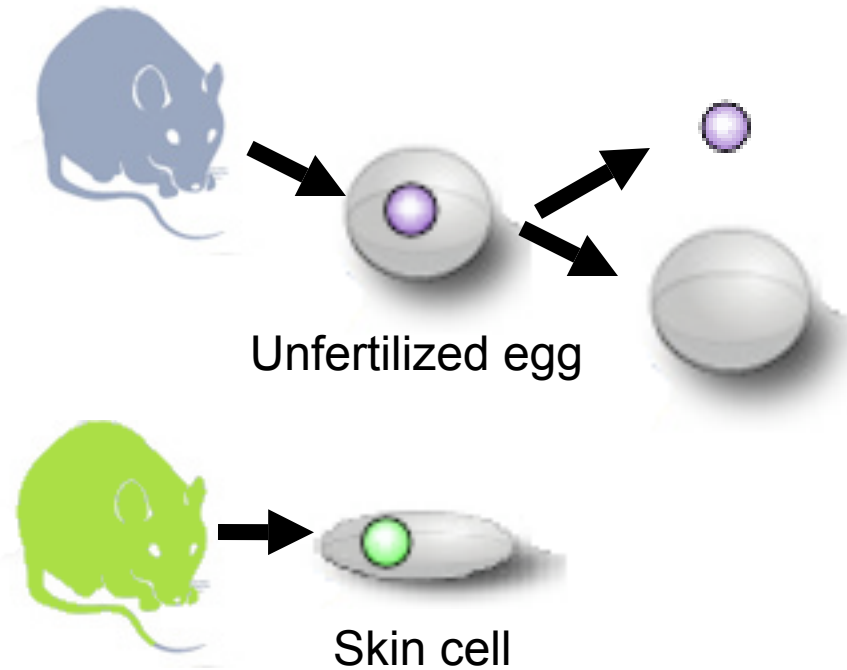
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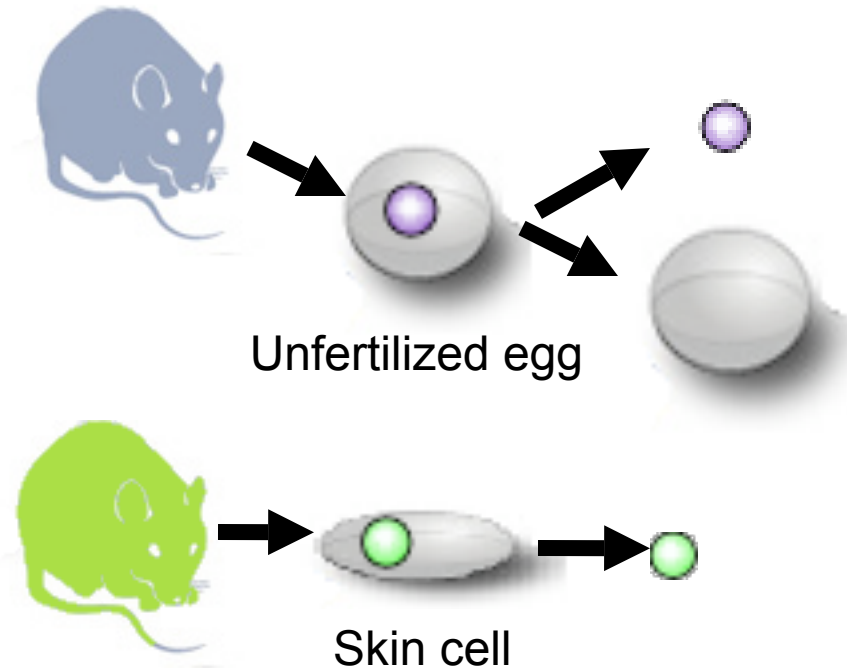
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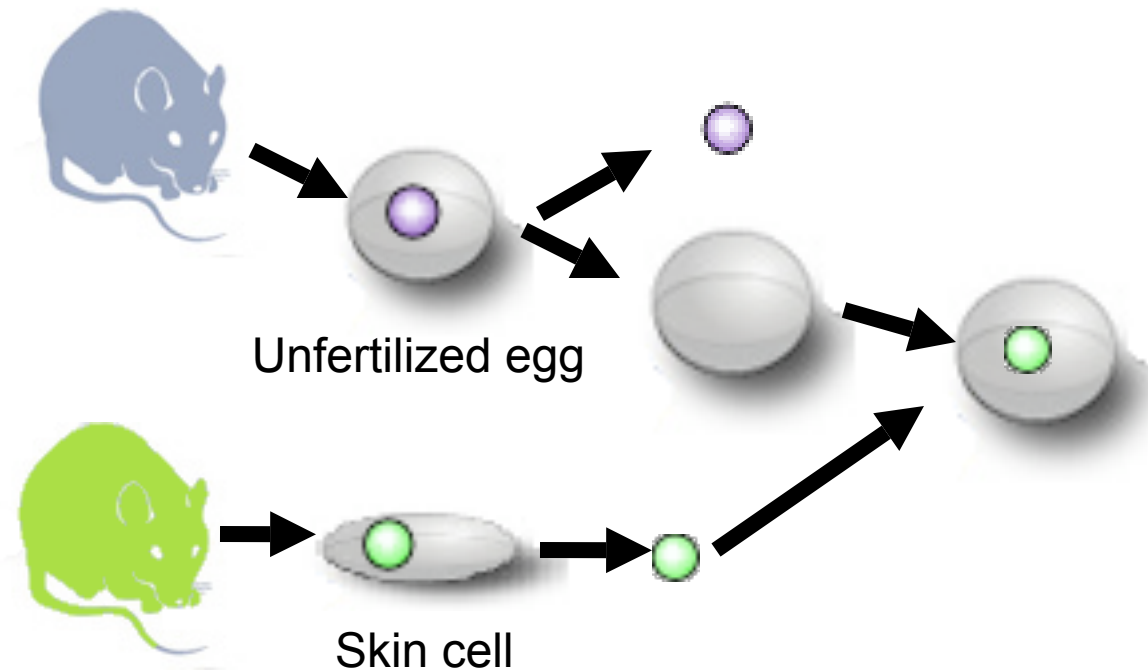
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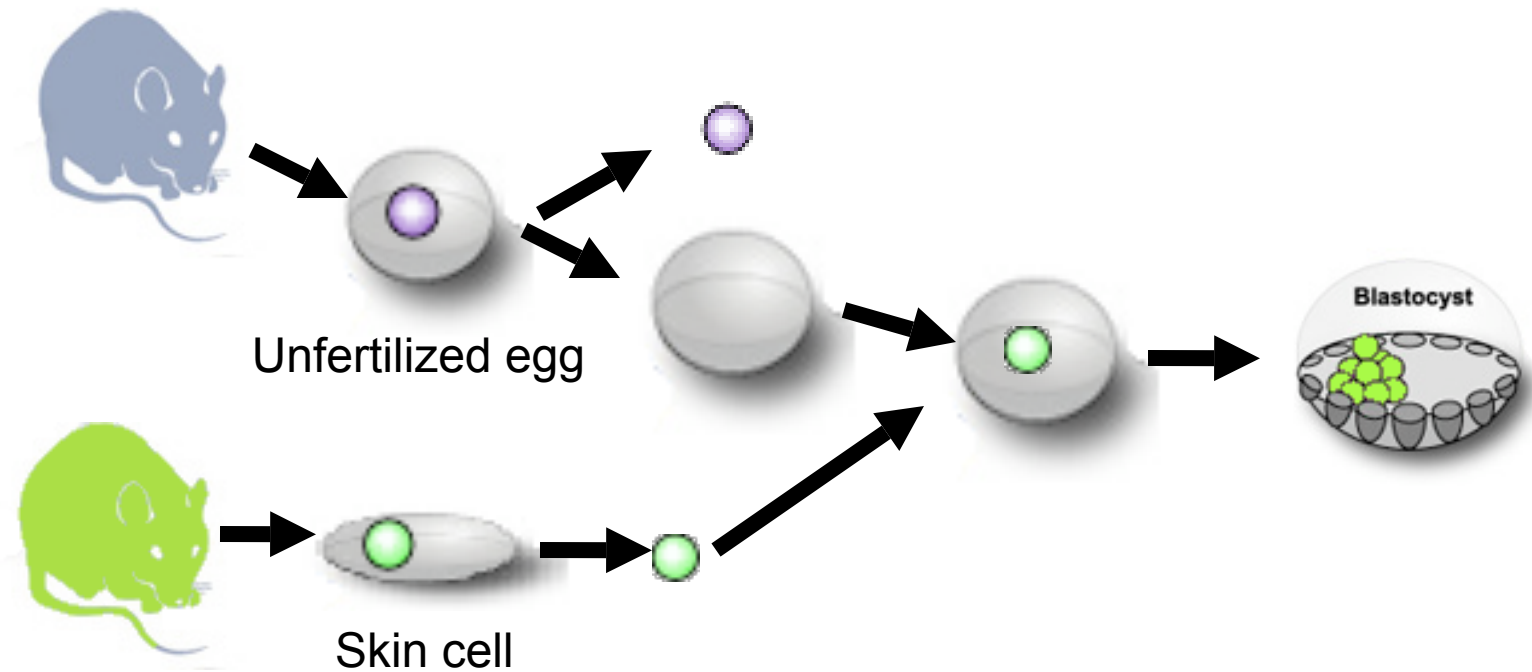
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How does SCNT work?

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Unfertilized egg



Skin cell

# How does SCNT work?



Unfertilized egg

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Skin cell

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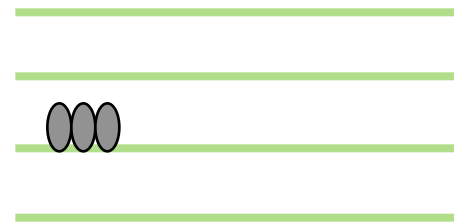
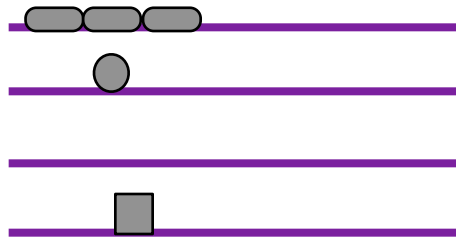
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Unfertilized egg



Skin cell



Transcription factors

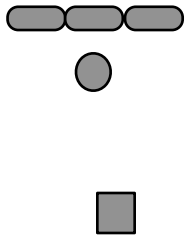
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Unfertilized egg



Skin cell

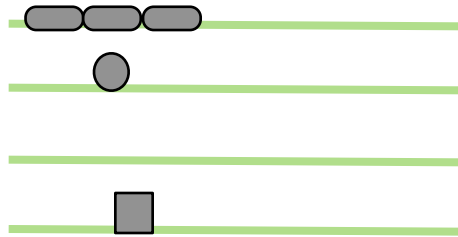


Transcription factors

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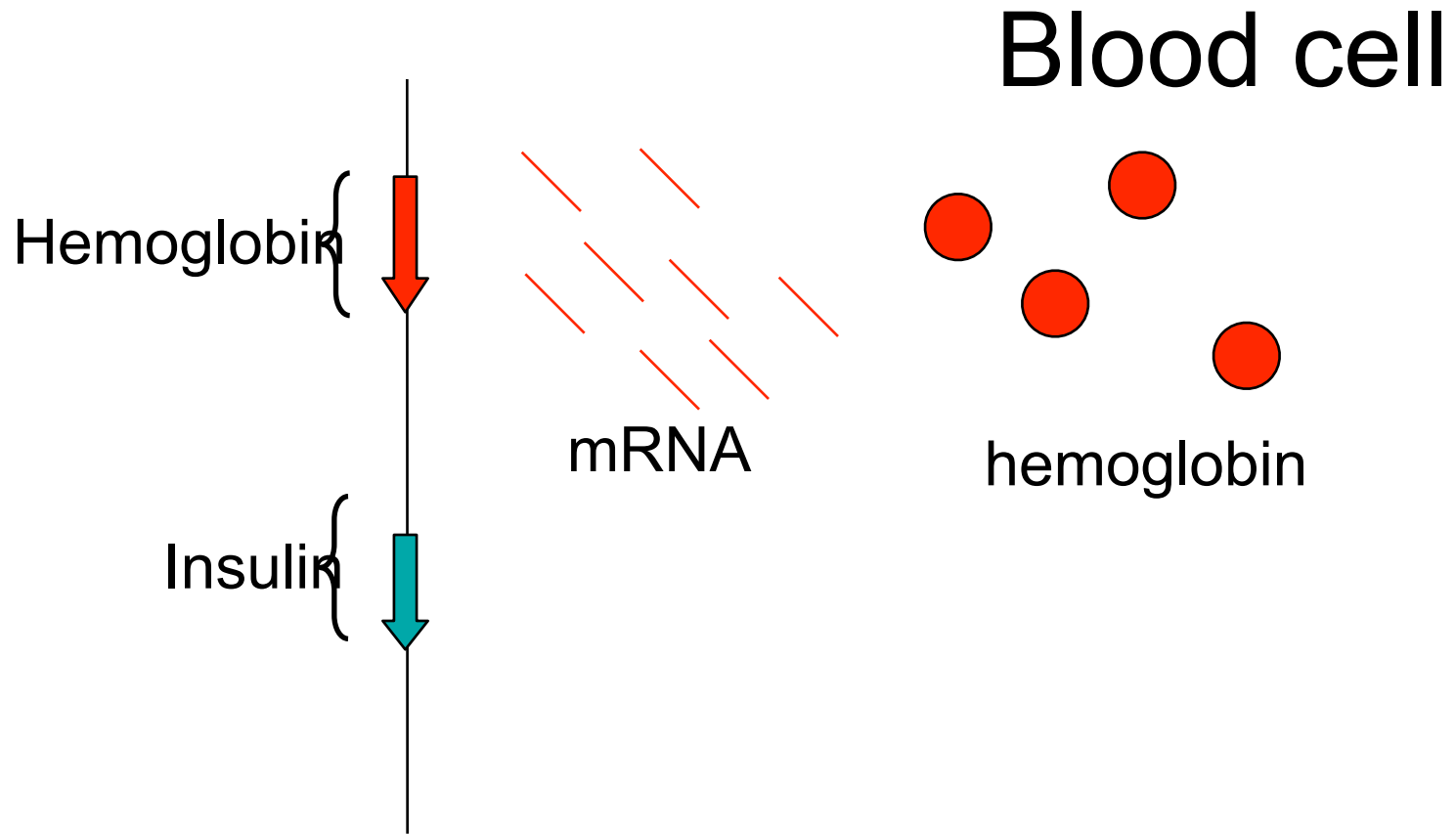


Unfertilized egg

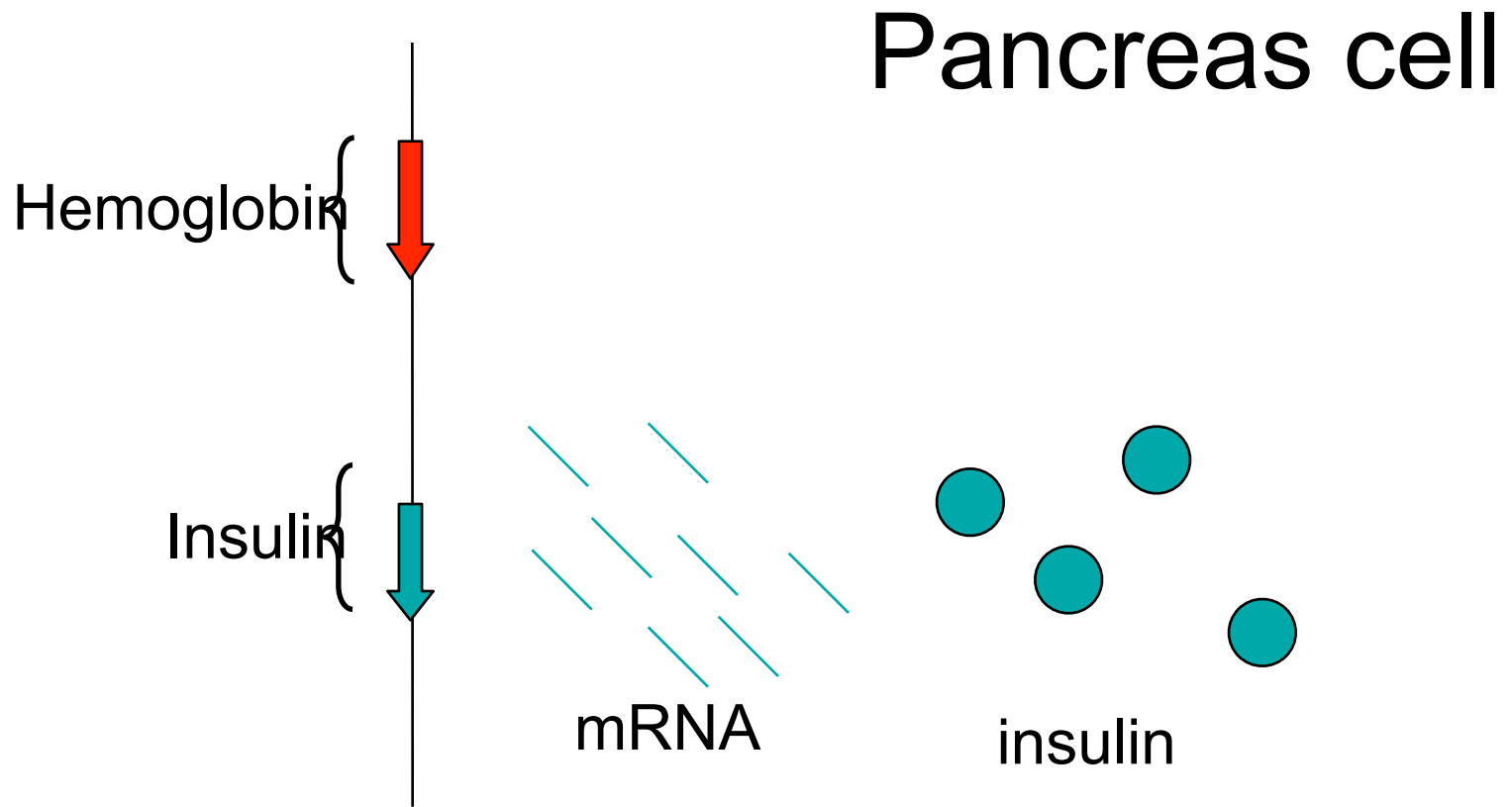


Transcription factors

# Different cells copy different parts of the DNA into RNA

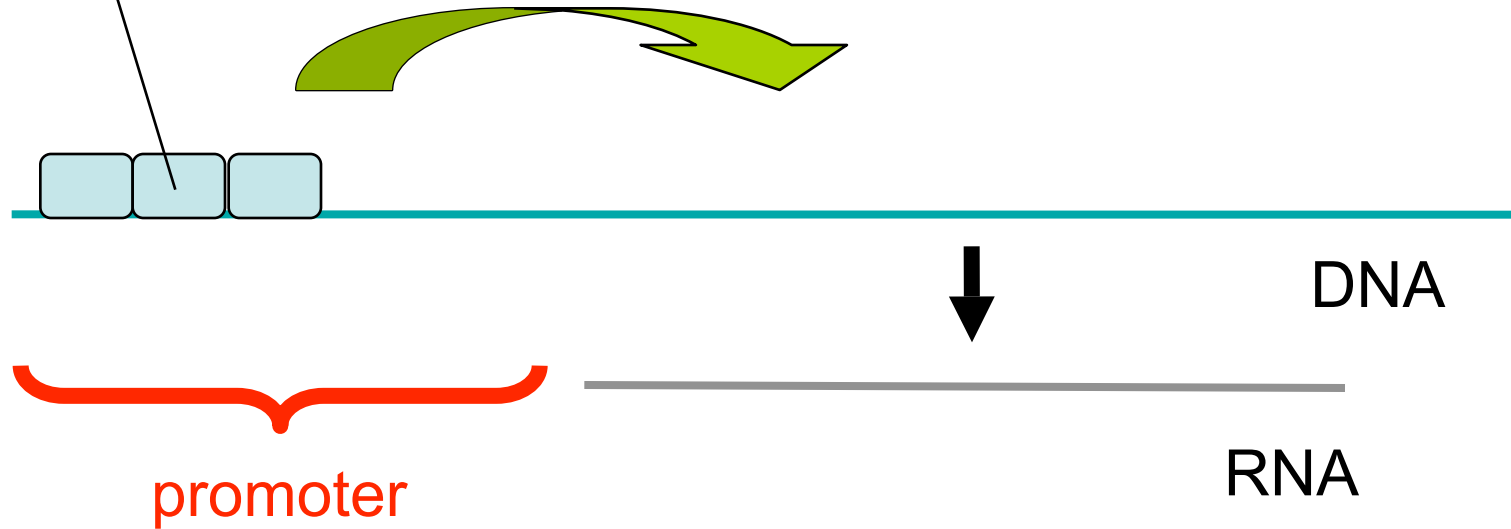


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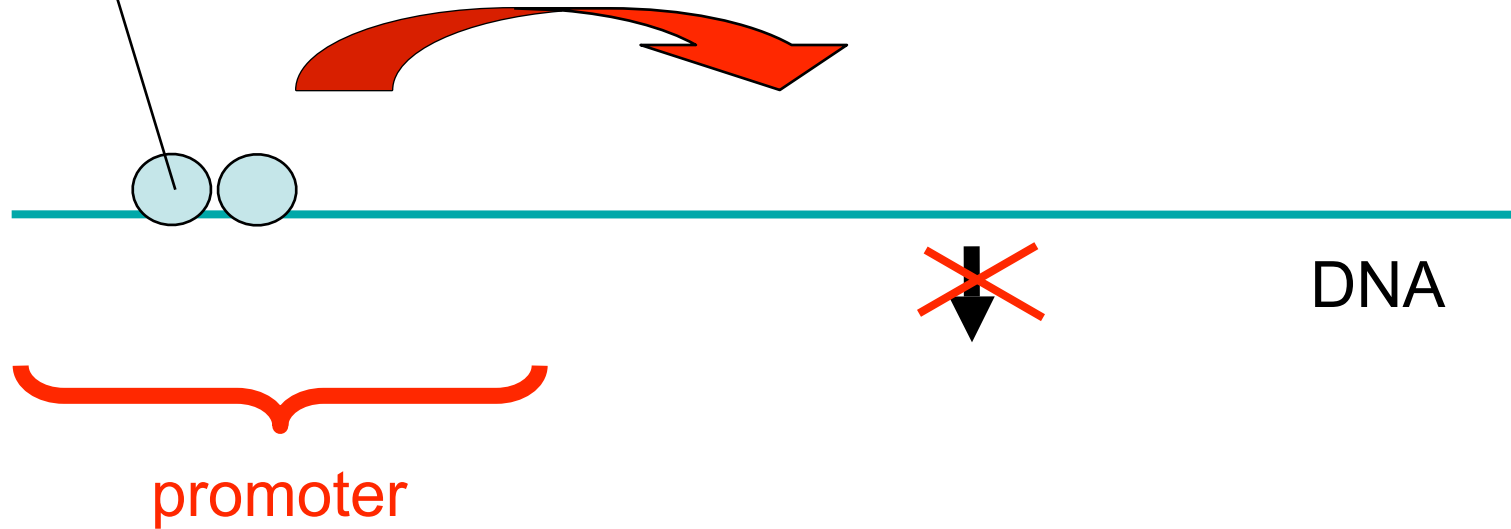
# Transcription factors control gene expression

Transcription factor



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# Why does SCNT work?



Unfertilized egg



Skin cell

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Unfertilized egg

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Skin cell

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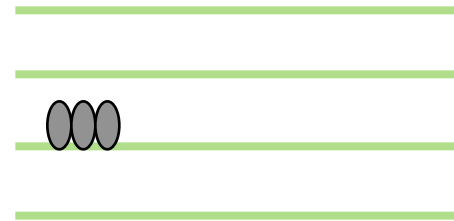
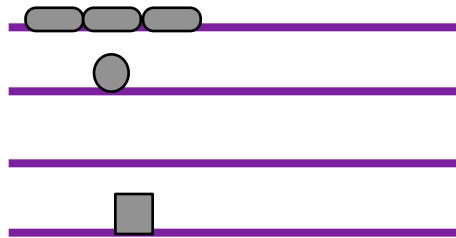
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Transcription factors

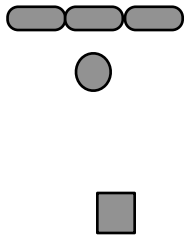
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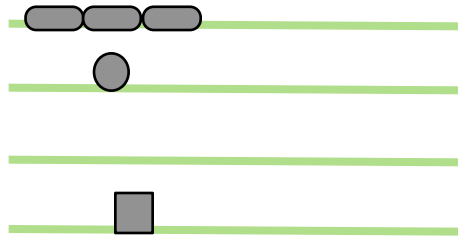


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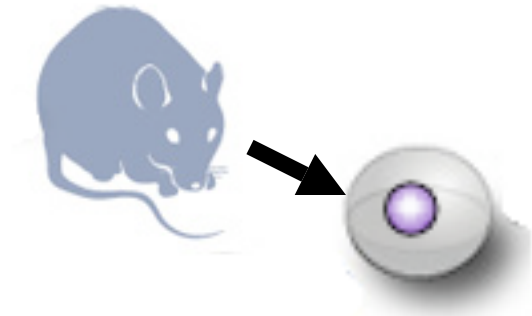


Transcription factors

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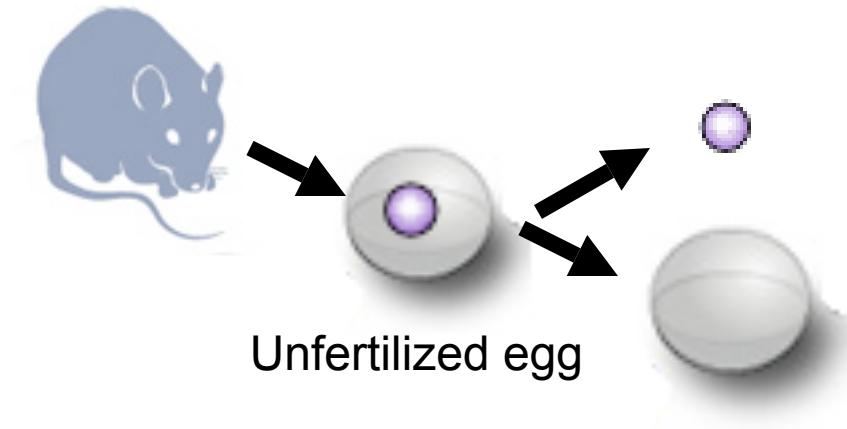


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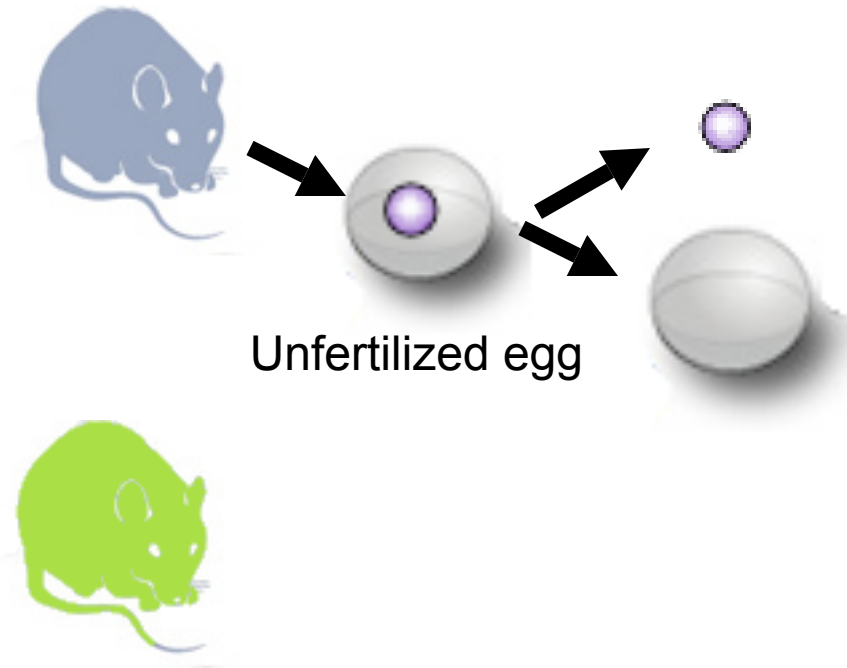


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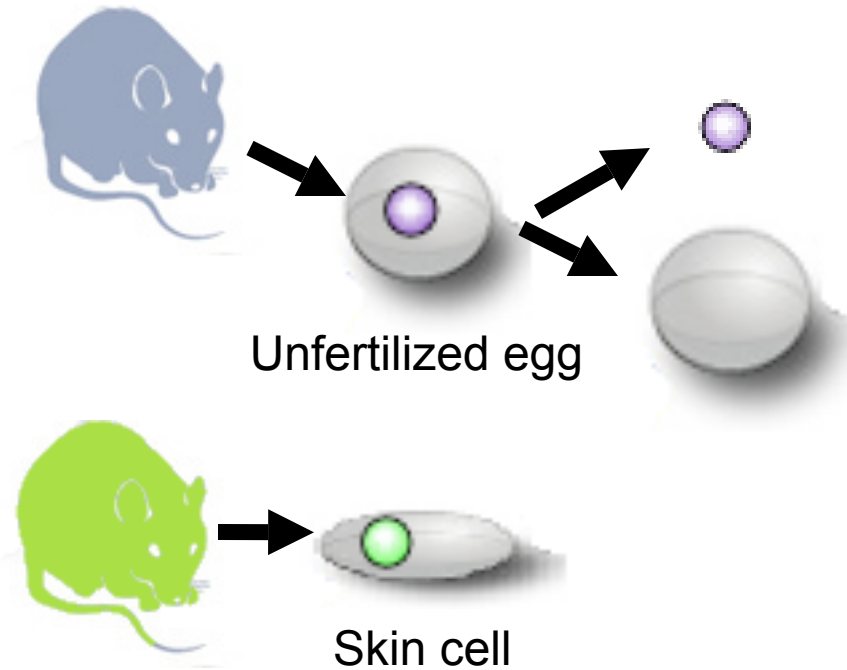
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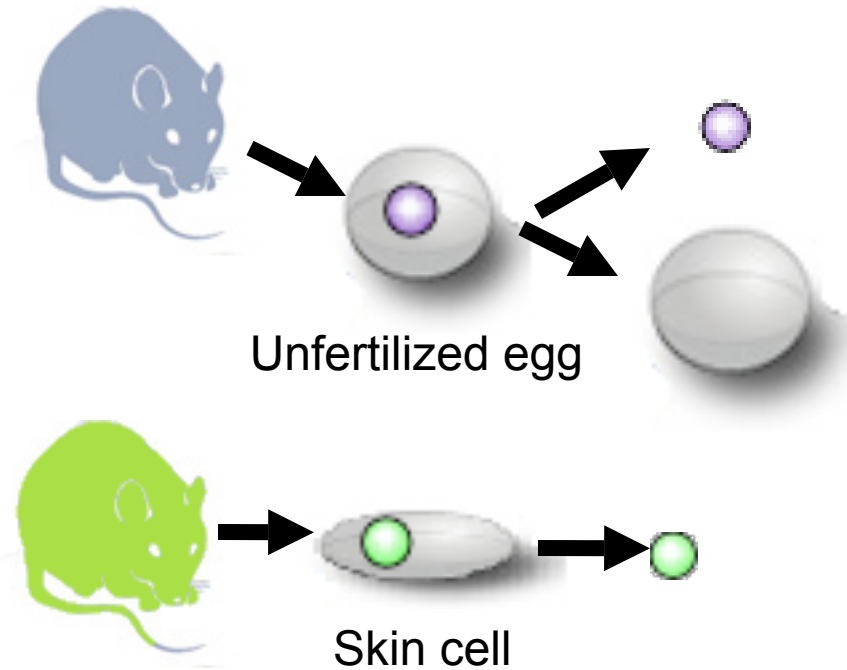
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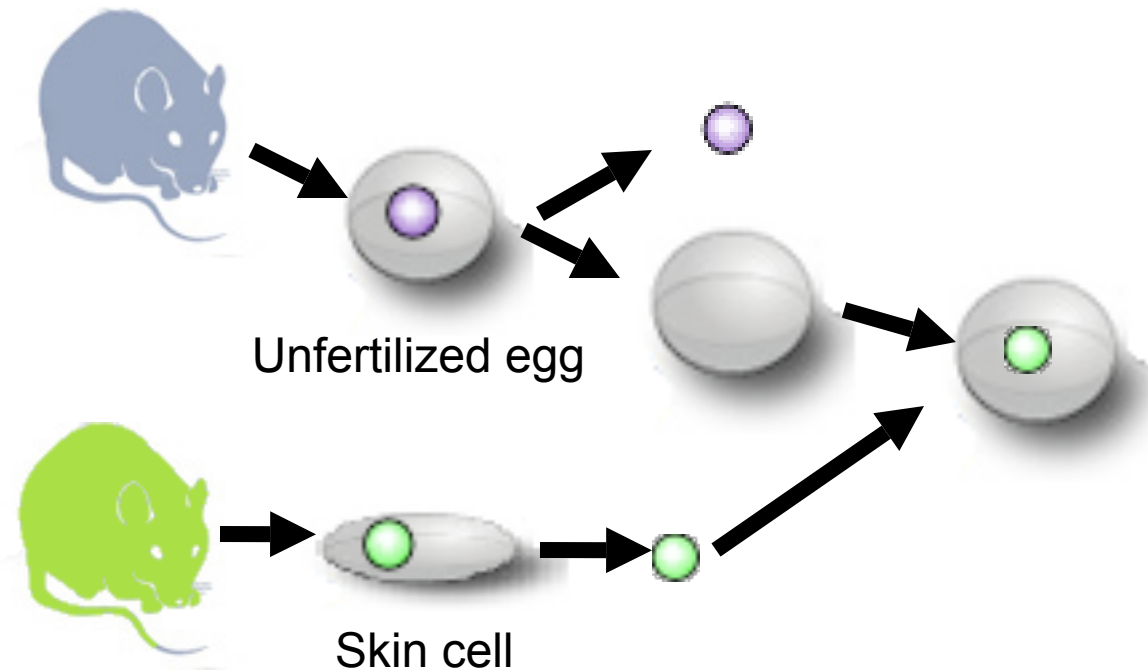
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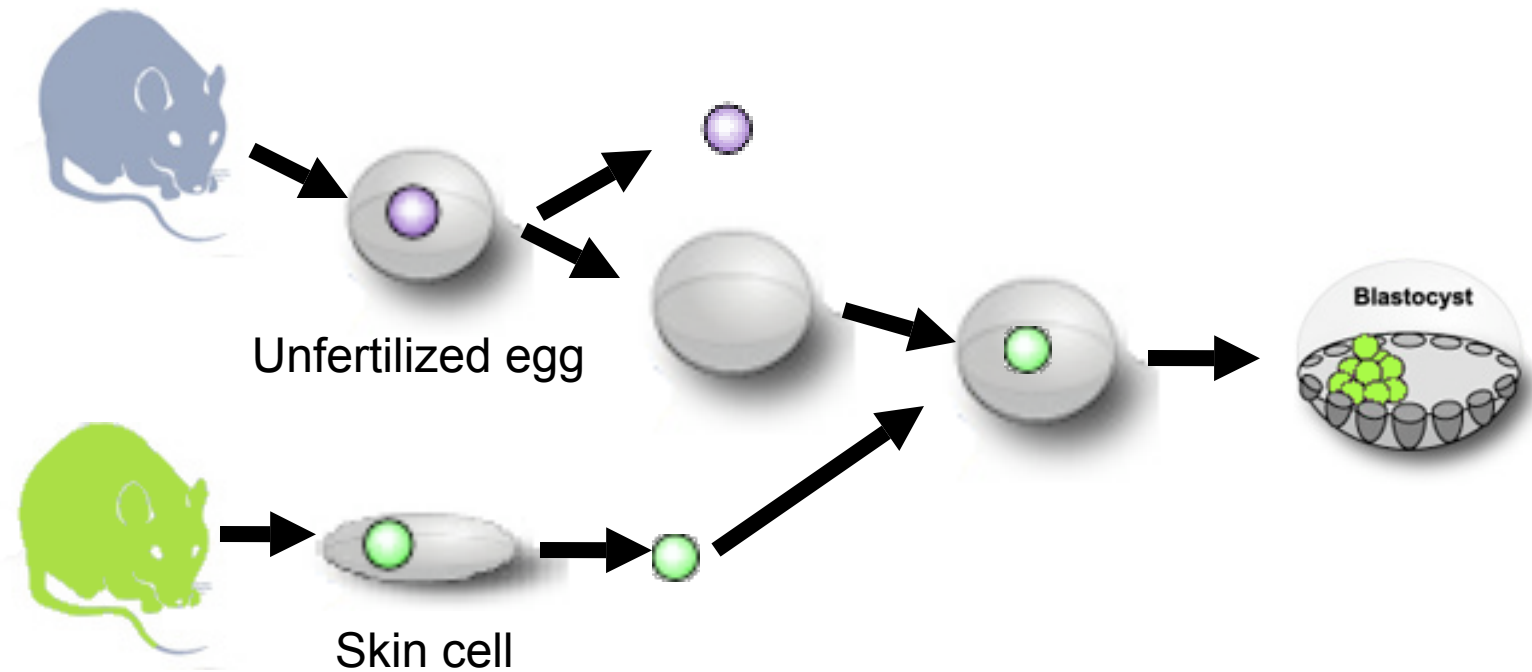
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# Human SCNT requires eggs

Egg donation, for in vitro fertilization and for SCNT experiments is a risky and uncomfortable procedure.

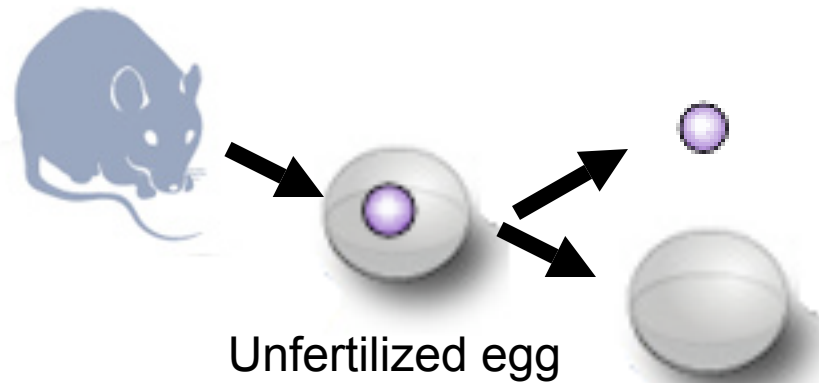
Egg donors for SCNT experiments are not paid.

SCNT experiments have a hard time finding donors.

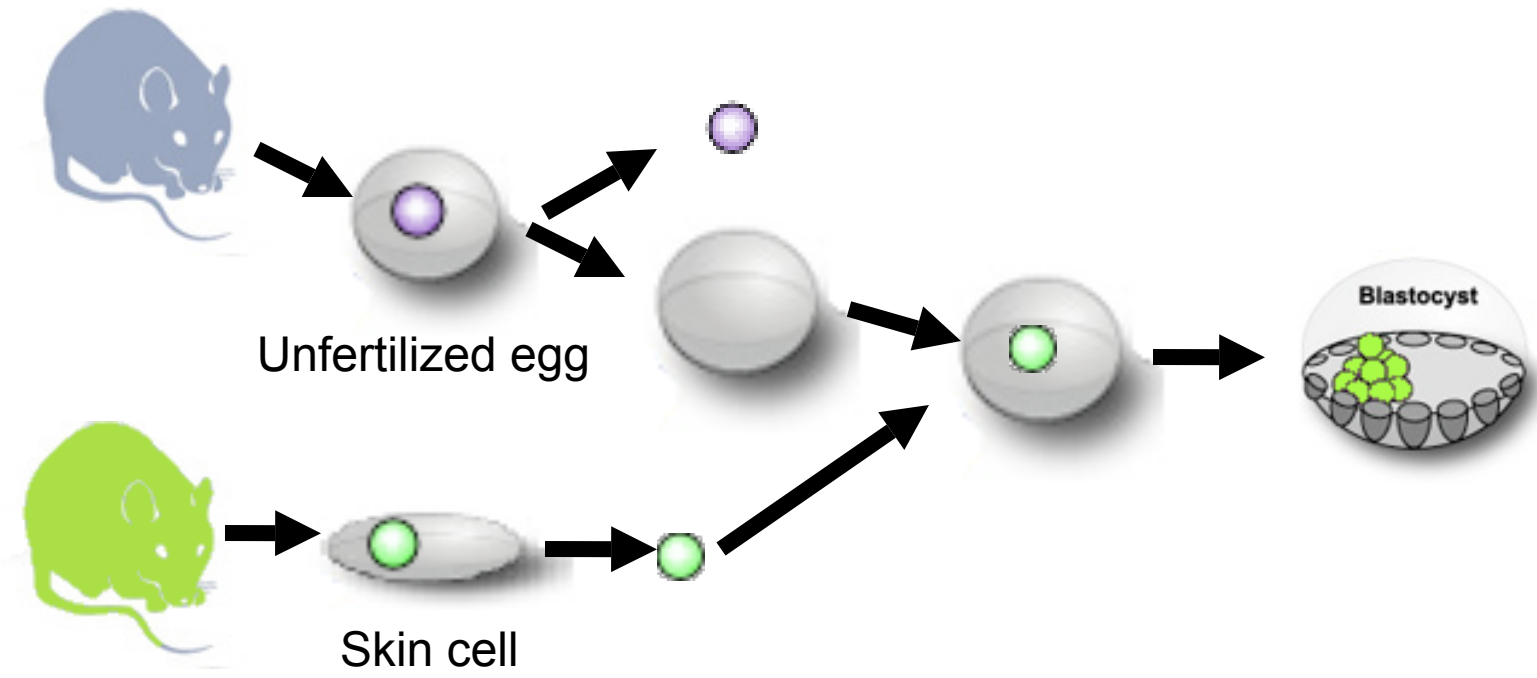
# Non-human egg donation

A separate but problematic issue with SCNT is the need for many eggs.

Rabbit eggs can theoretically be used with human nuclei to make human ES cells.

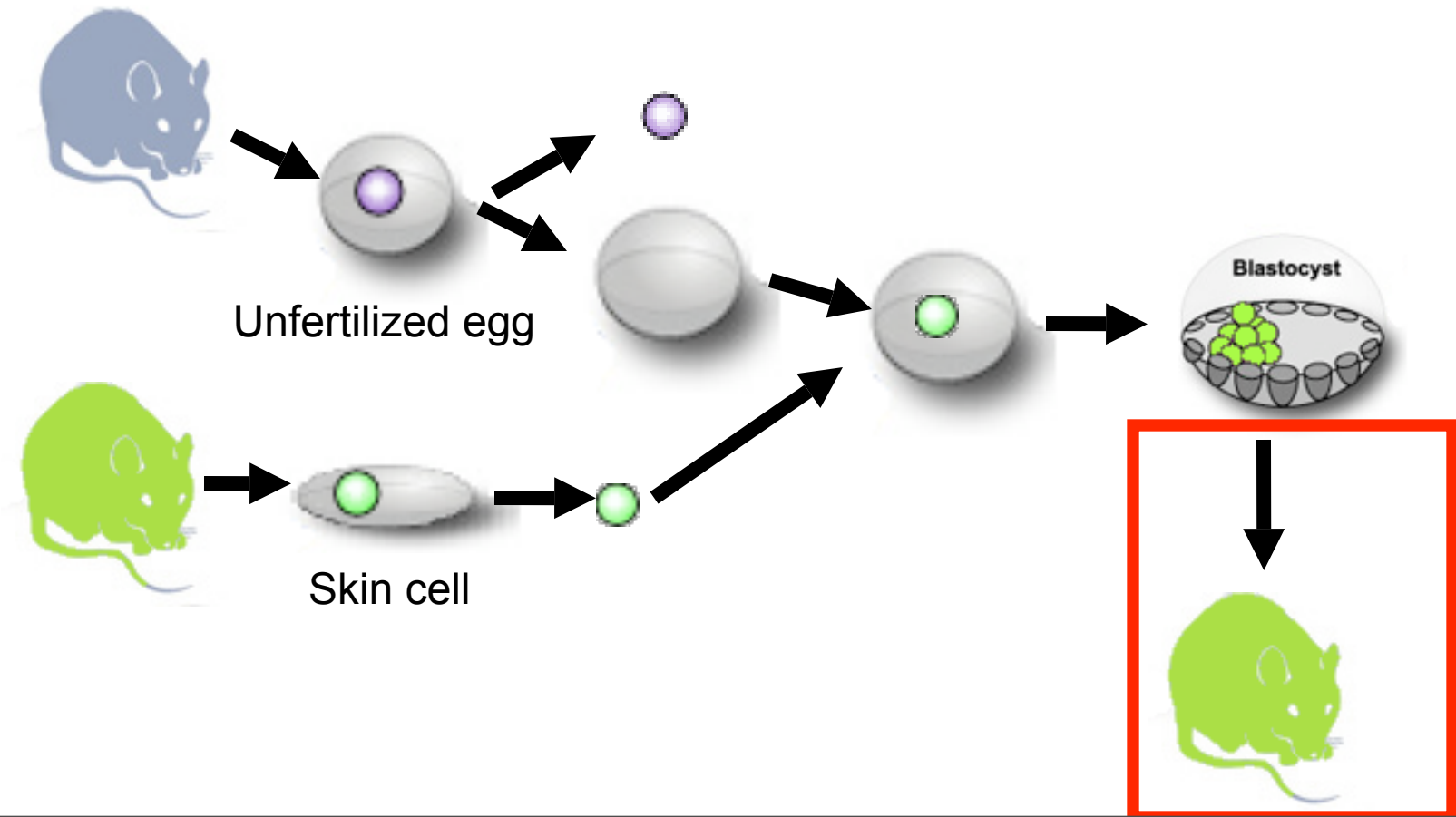


# Therapeutic vs. Reproductive



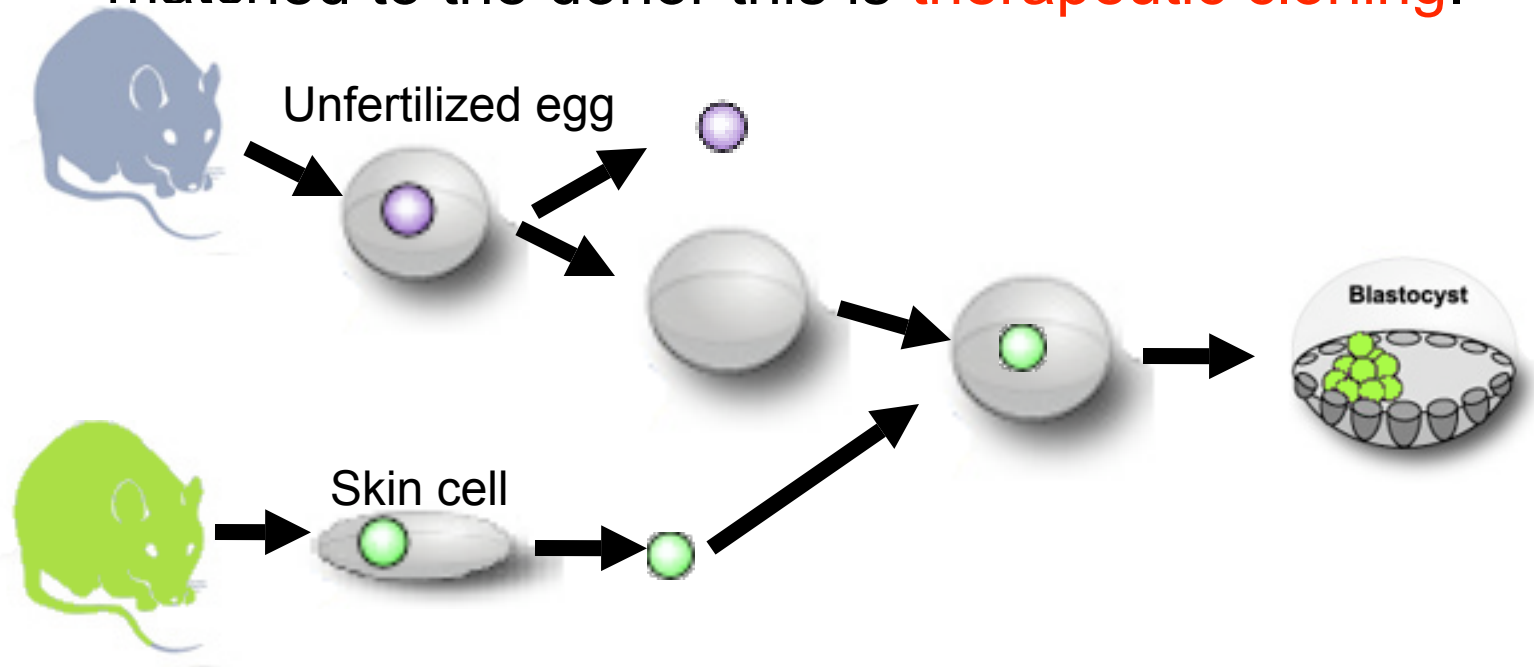
# Therapeutic vs. Reproductive

If the embryo is reimplanted to make a new organism, this is **reproductive cloning**.



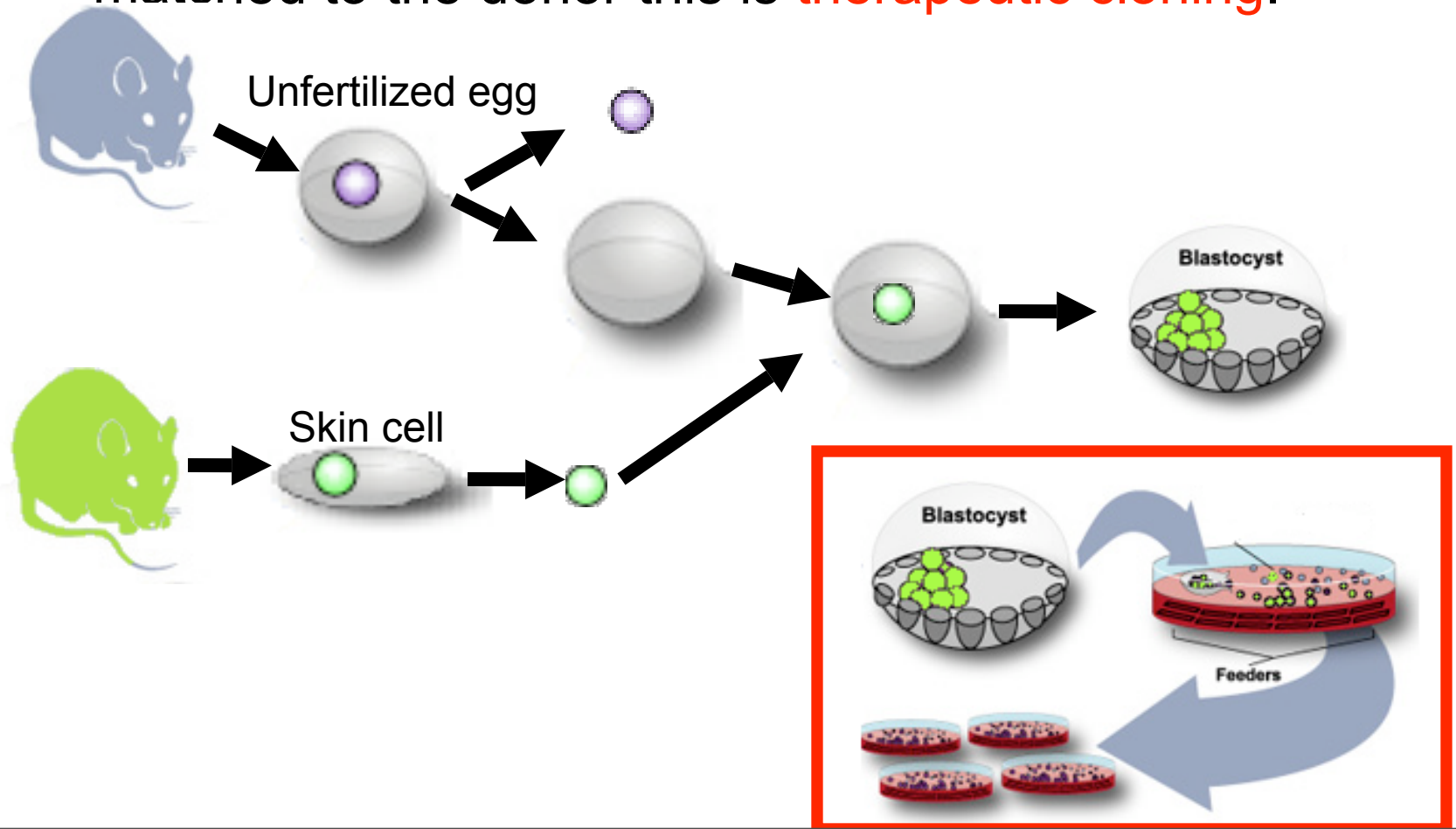
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If the embryo is used only to generate stem cells matched to the donor this is **therapeutic cloning**.



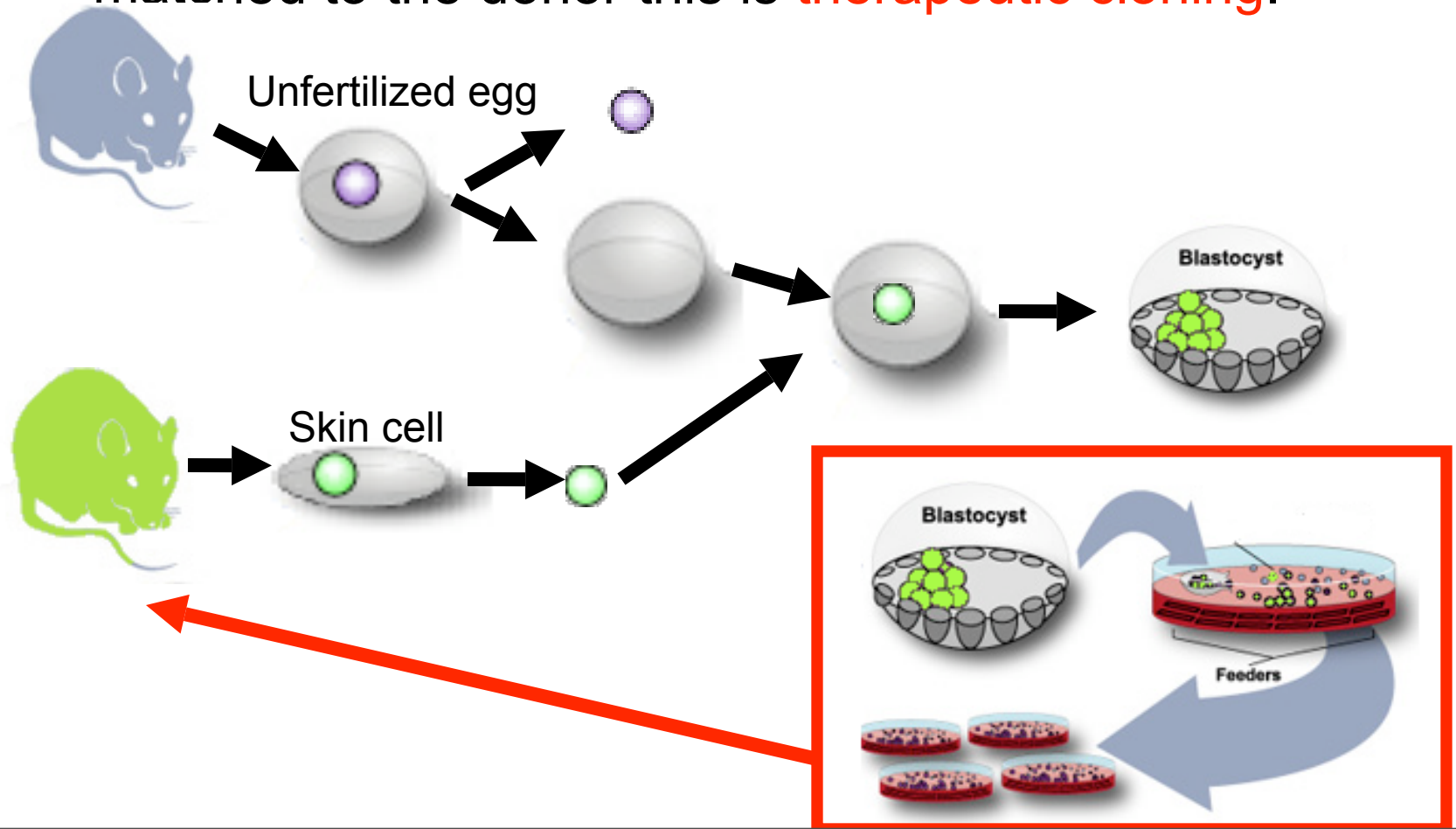
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# Reproductive cloning



<http://news.bbc.co.uk/1/hi/sci/tech/1424267.stm>

Dolly  
Rosalind 1996



<http://news.bbc.co.uk/2/hi/asia-pacific/2153490.stm>

Millie, Christa, Alexis, Carrel and Dotcom  
PPL Therapeutics 2000



<http://cats.about.com/od/advocacy/a/clonedcat.htm>

CC  
Texas A&M 2001



(FROM ACT)

<http://www.cnn.com/2001/TECH/science/11/25/cloning.act/>

George and Charlie  
Adv. Cell Tech 1999



[http://www.bbc.co.uk/czech/scitech/story/2005/08/050804\\_korea\\_cloning\\_0600.shtml](http://www.bbc.co.uk/czech/scitech/story/2005/08/050804_korea_cloning_0600.shtml)

Snuppy  
S. Korea 2005

# Clones have problems

Even though the DNA in every cell is the same, there are proteins and chemical tags on the DNA that have to be “reset” to the state of a fertilized egg for the DNA to produce an animal.

# Market for Clones

Genetic Savings and Clone, founded 2000

Produced 5 cloned cats, sold 2

Original fee: \$50,000, later reduced fee to \$32,000

Closed Oct, 2006, no market for cloned cats.

# Companies doing cloning research

- Advanced Cell Technologies (Worcester, MA)
- Genzyme Transgenics (Framingham, MA)
- Infigen (De Forest, WI)
- Pharming (The Netherlands and Rockville, MD)
- PPL Therapeutics (Scotland and Blacksburg, VA)

# Making a bank of universal donor ES cells

Immune rejection is the reason you have to do SCNT to get matched ES cells.

If you carefully select the genotypes of the embryos that you use, you only need a few dozen cell lines to be compatible with almost everyone.

You only need a few dozen embryos to get all the cells anyone will ever need.

# Reversing somatic cells to ES cells (iPS cells)

- By adding several activated genes to a somatic cell, the cells can be converted back into an embryonic cell fate.

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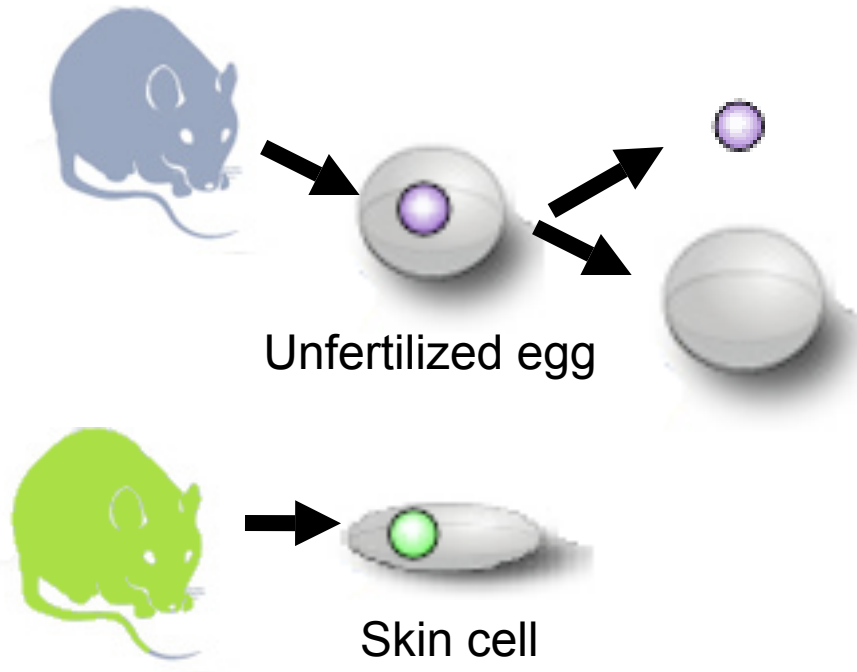
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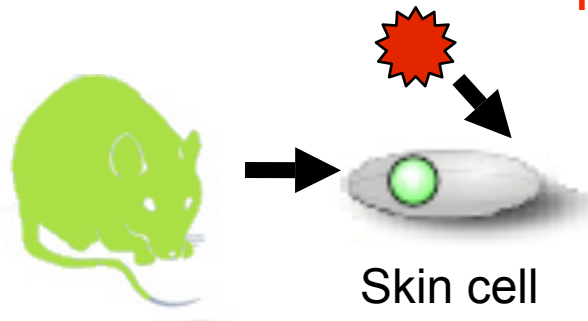
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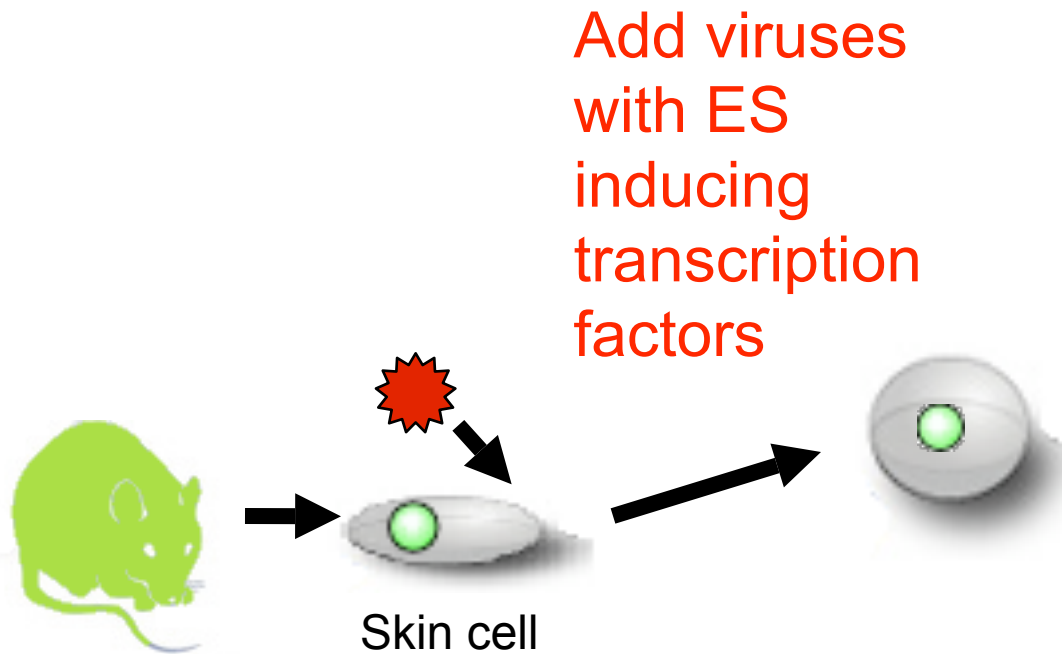
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Add viruses  
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inducing  
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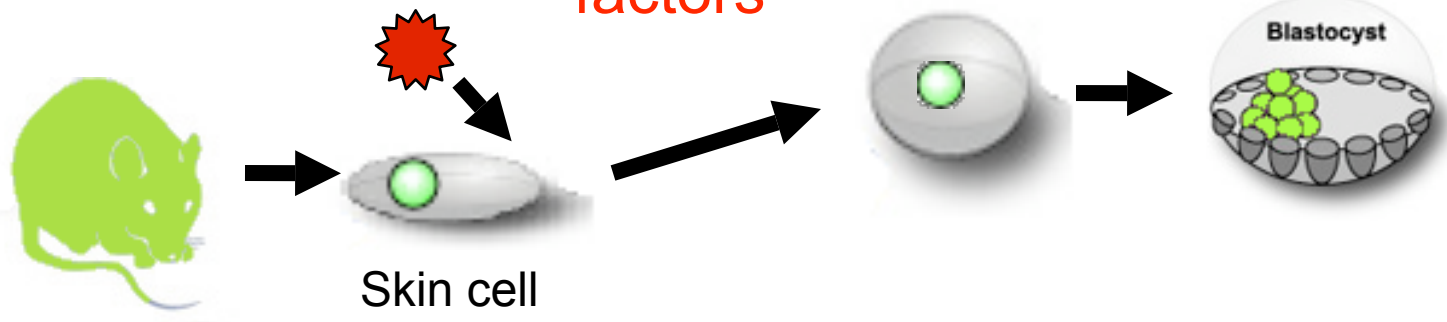
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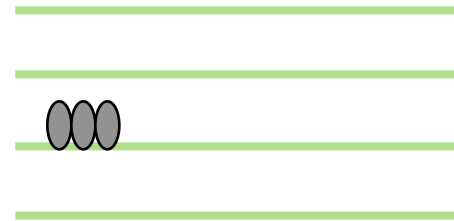
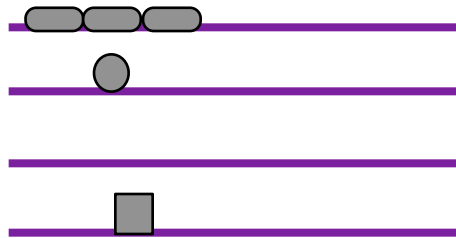
# How does SCNT work?



Unfertilized egg

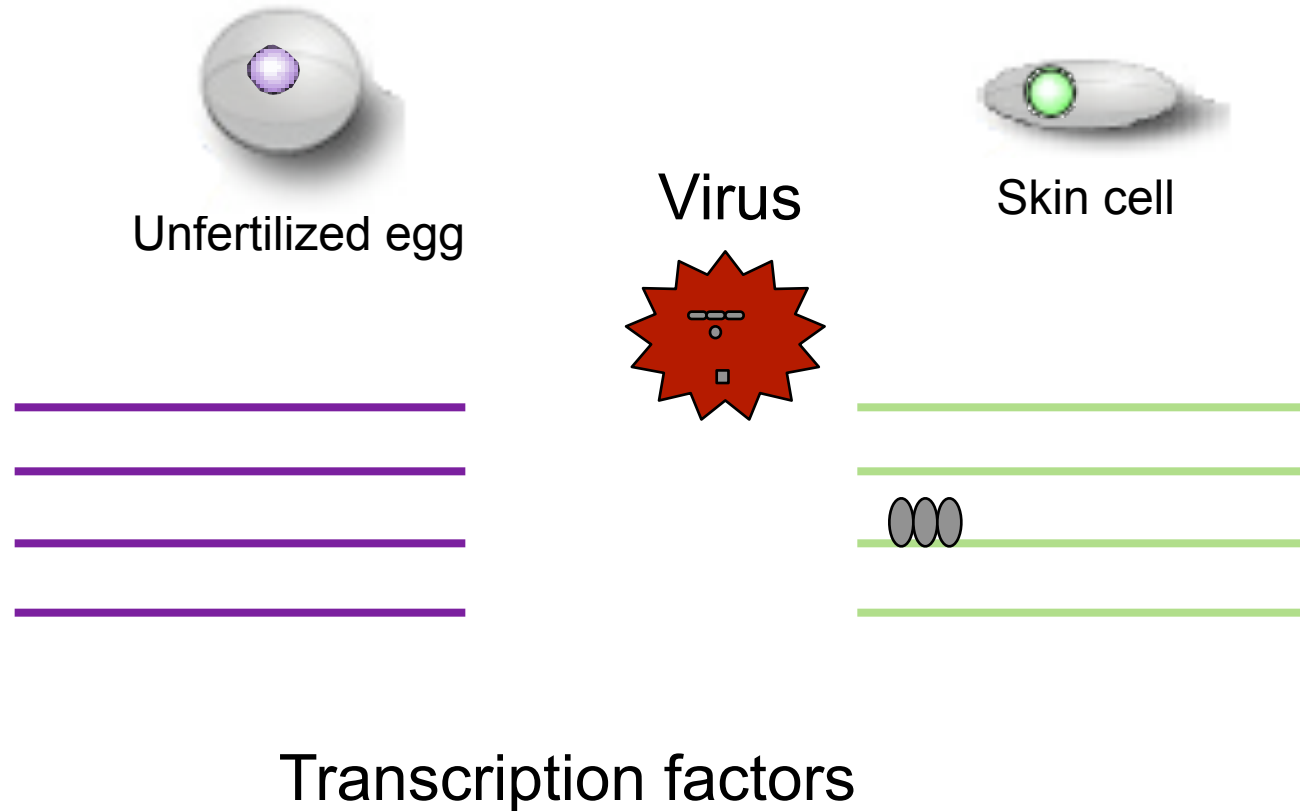


Skin cell



Transcription factors

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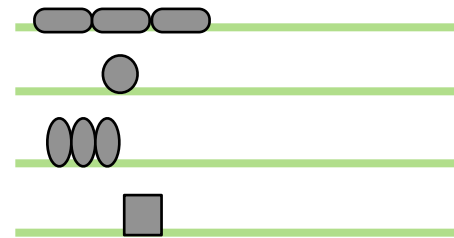
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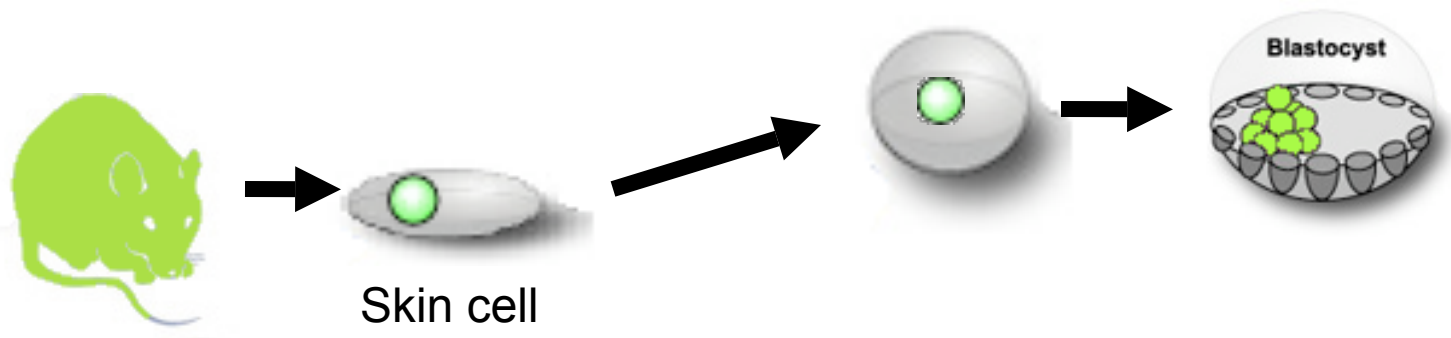
Skin cell



Transcription factors

# Reversing somatic cells to ES cells (iPS cells)

- By adding several activated genes to a somatic cell, the cells can be converted back into an embryonic cell fate.
- No SCNT and no egg is needed to make this “clone”.
- Makes tissue matched induced pluripotent stem (iPS) cells.



# Problems with iPS cells

- Viral vectors are used to introduce the new transcription factors (the virus or the new transcription factors can cause cancer)
- Expensive and time-consuming
  - iPS cell banks might help
- Reproductive cloning becomes more accessible (no need for large numbers of eggs).
- Male-derived eggs are now possible

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# Politics of Embryonic Stem Cells

# US Policy

In 2001, Bush announced that federal funds would be available only for research on approved human embryonic stem cell lines already in existence.

No new lines would be funded.

Only existing lines derived from excess embryos from in vitro reproduction could be used.

NIH currently lists 21 lines that meet these criteria.

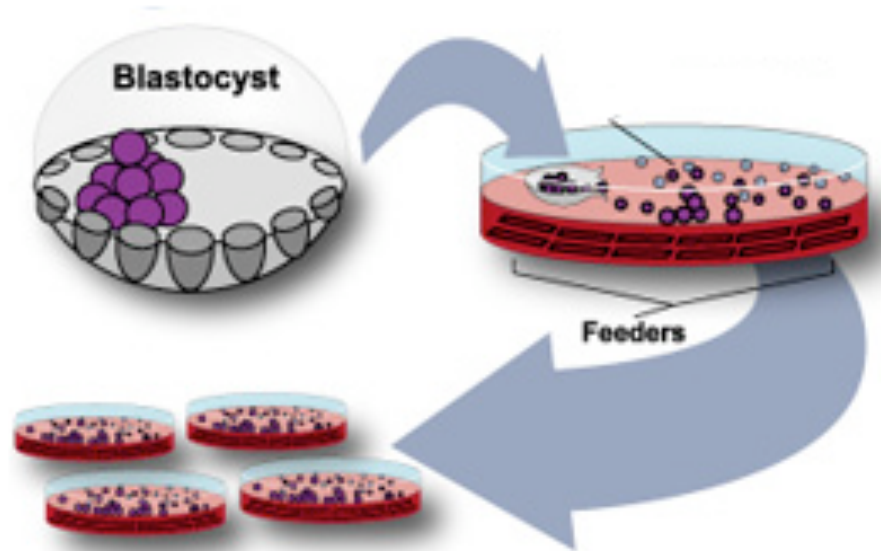
"It's not possible for me to see how we can continue the momentum of science in stem-cell research with the cell lines that we have currently at NIH that can be funded. It is clear today that American science would be better served, the nation would be better served, if we let our scientists have access to more cell lines."

Dr. Elias A. Zerhouni,  
director of the National Institutes of Health  
Statement to U.S. Congress  
March 19, 2007

# Problems with most ES cell lines

In order to stay pluripotent, ES cells have to be grown together with a “feeder layer” of other cells that signal them to stay undifferentiated.

All of the available U.S. lines were grown with feeder cells from mouse origin. Laboratories in Singapore, Israel, Sweden, and Finland have isolated lines of stem cells that don't use mouse feeder cells.<sup>1</sup>



# Viruses

- Early polio vaccine was made from virus made using cultured monkey kidney cells.
- The monkey cells were infected with monkey viruses. It was thought that no infected cells were used to make vaccine.
- SV40 (simian virus 40) was discovered in 1960, and it was found to be contaminating the polio vaccines given between 1955 and 1963 (98 million Americans potentially exposed, 10-30 million probably exposed).
- **Non-human feeder cells are a potential source of viruses**

# Research in the US is done without federal support

Universities are setting up stem cell research facilities funded from outside donors.

Companies are doing stem cell research.

In 2004, California passed a state initiative to fund stem cell research (\$3 billion)

In 2005 New Jersey gave \$5 million in stem cell grants

# Arguments for current stem cells

Many embryos are left over from fertility treatment and will ultimately be discarded. These can be used for stem cells or thrown away.

Many fertilization events fail to become fetuses in the normal case; do we have a greater duty in the lab?

“Life doesn’t begin in a petri dish”

# Orrin Hatch



"Now, the last time we introduced this bill, there was interest in the fact that I, as a strongly pro-life senator, would be the lead sponsor. I think we have put that issue behind us, as more pro-life lawmakers have expressed their support for this research. The fact is, I have never believed that life begins in a Petri dish."

[http://hatch.senate.gov/index.cfm?FuseAction=PressReleases.Detail&PressRelease\\_id=1329&Month=4&Year=2005](http://hatch.senate.gov/index.cfm?FuseAction=PressReleases.Detail&PressRelease_id=1329&Month=4&Year=2005)

Media Credit: Jeff Paulsen

<http://www.dailyutahchronicle.com/news/2002/11/12/News/Orrin.Hatch.Talks.About.Iraq.Guns.Napster-321085.shtml>

# Stem Cell Research Enhancement Act of 2005

Would have allowed funding for more human ES cell lines

Passed House by 238 to 194, Senate by 63 to 37.

First veto by president Bush.

Override failed

# Stem Cell Research Enhancement Act of 2007

Would have allowed funding for more human ES cell lines

Passed House by 247 to 176, Senate by 63 to 34.

Also vetoed by president Bush

# Obama Policy Changes

- Research can be done on any cell line derived from an excess fertility clinic embryo.
- Donors must sign written consent and can not be paid for the embryos.
- Embryos created solely for research are still prohibited (NO SCNT).
- Reaffirmed ban on reproductive cloning.

# Summary

**Embryonic stem cells** are derived from **blastocysts**. They can be grown indefinitely in a dish, and then can be turned into any cell in the body.

Making ES cells matched to a patient requires **therapeutic cloning**.

**Reproductive cloning** produces a genetic copy of an individual.

**iPS cells** might provide the advantages of cloned ES cells without cloning or producing embryos. Still in early development.