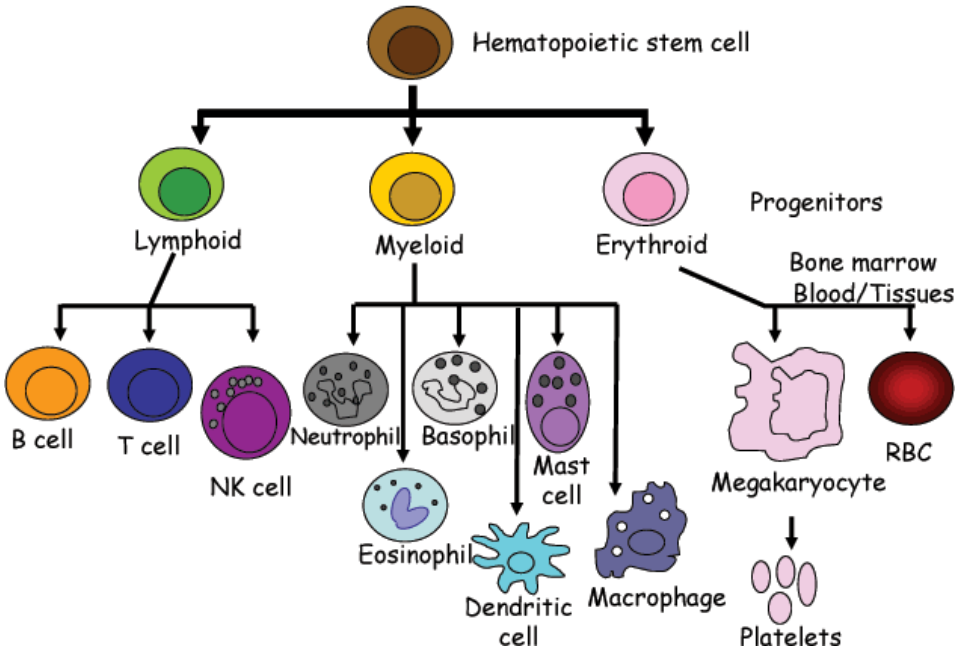
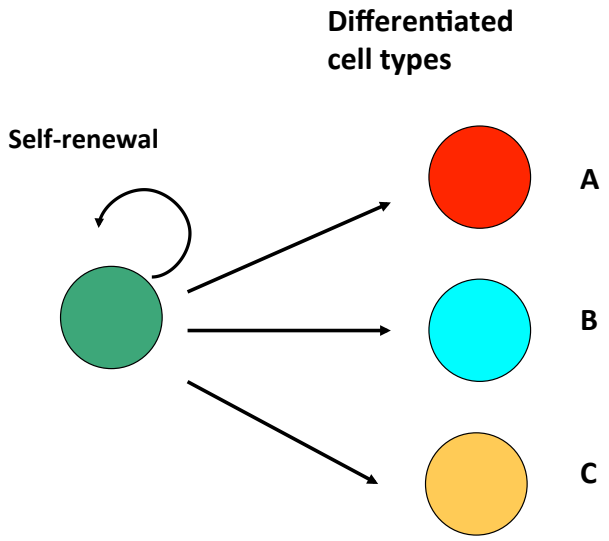
Stem Cell Biology and Ethics
HC70A Winter 2014
Dr. Pei Yun Lee

Immune cell development: Hematopoiesis



What is a Stem Cell? What are their properties?



Ability to differentiate into different cell types
Ability to self renew

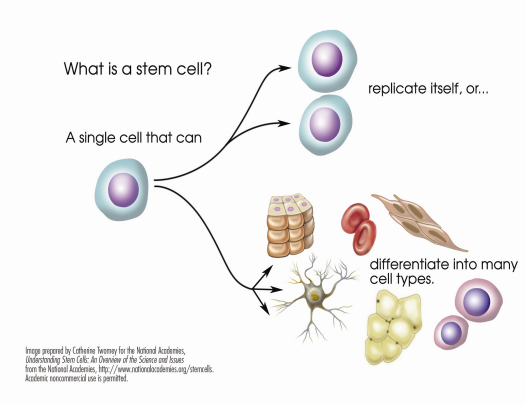
What are Stem Cells ?

- **Unique cells that can**
  1. **self-renew for the life-time of an organism**
  2. **give rise to specialized cell types (= differentiate)**

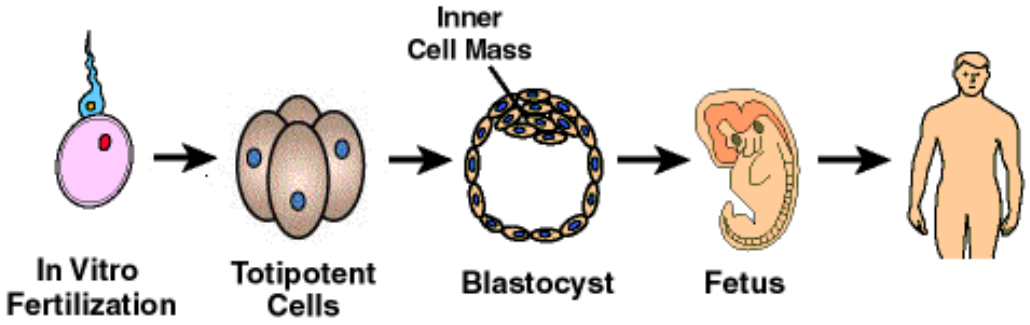
- **Self-renewal requires cell division**
  - **but** not all cell division means self-renewal!

- **Stem cell uses:**
  - **development**
  - **tissue homeostasis**
  - **tissue repair after injury**

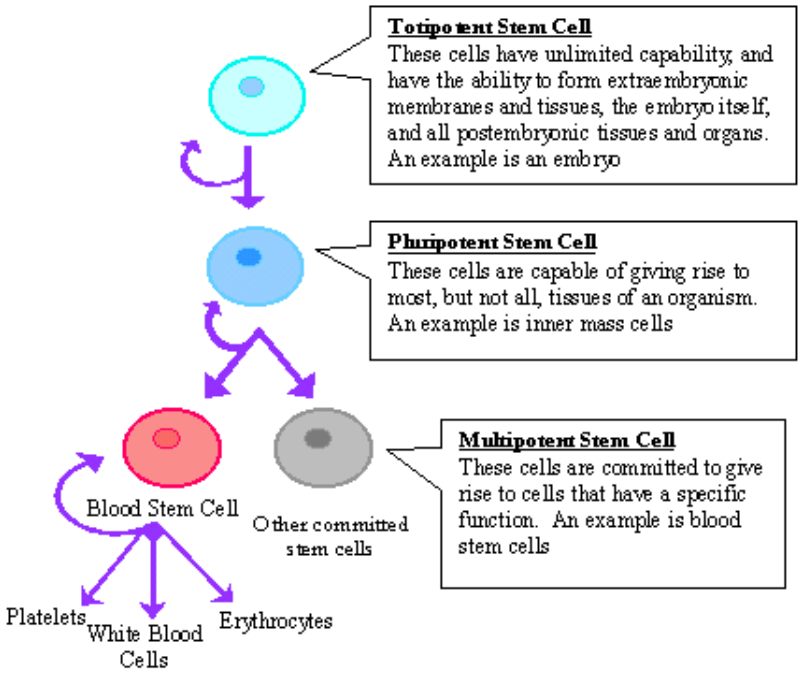
self-renew: reproduce without changing developmental potential



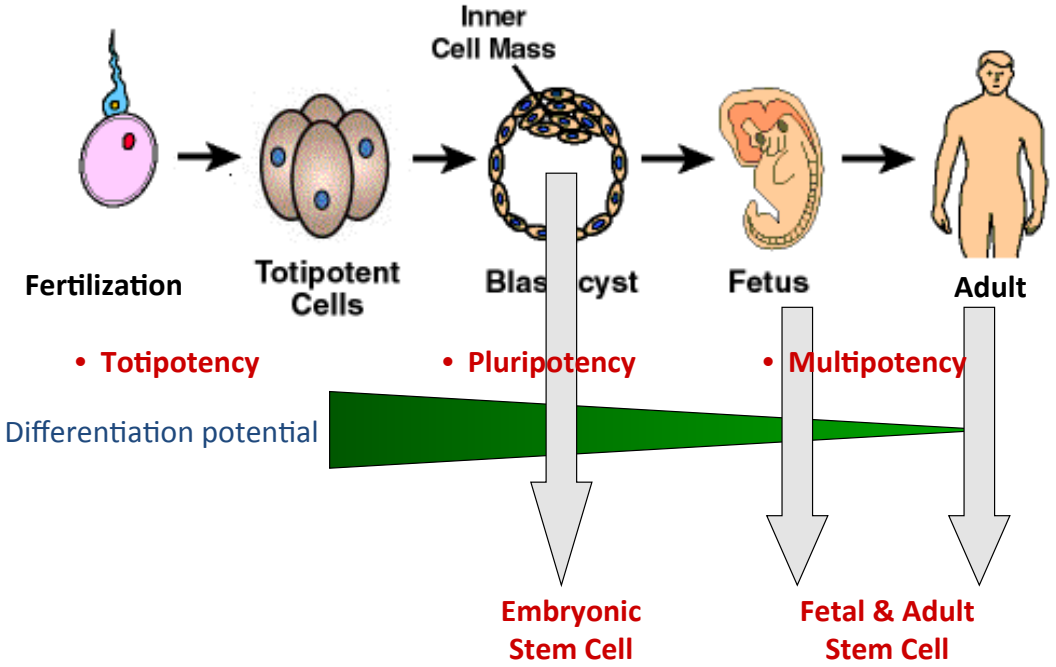
Where can stem cells be found?



Stem cells have different developmental potentials

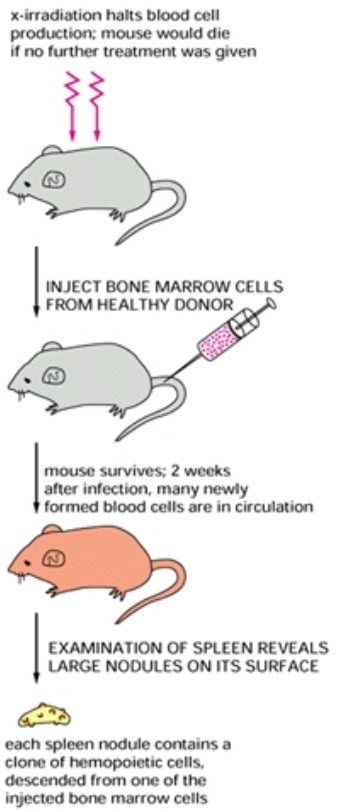


Progressive Restriction of Differentiation Potential



Alexander Maximow 1909

Unitarian theory of hematopoiesis (blood formation)
-all blood cells descended from a common precursor "stem" cell

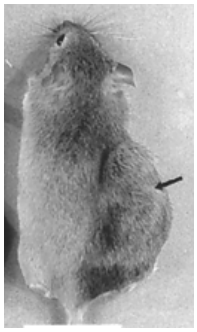


McCulloch and Till were the first to idenfity stem cells!

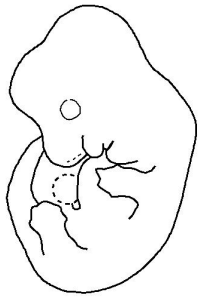
Analysis of the cells in the spleen demonstrated that the cells in each nodule were clones

Leroy Stevens

Mouse lines are inbred and therefore genetically identical!



Strain 129!

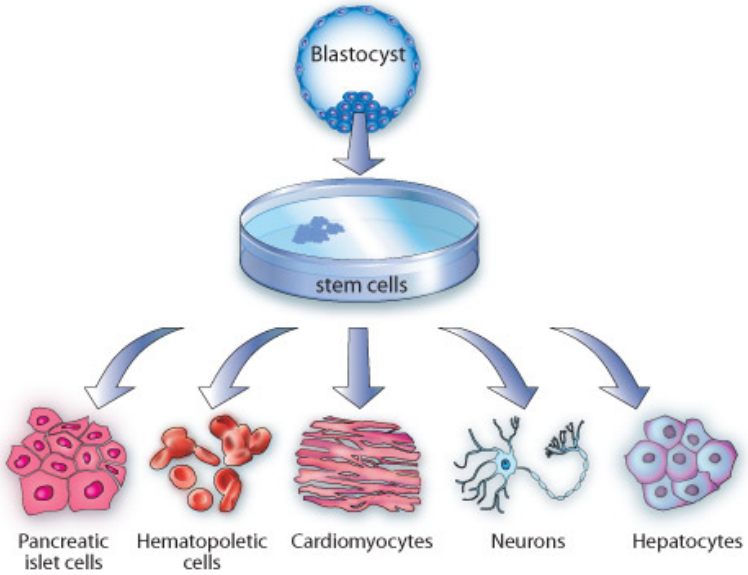


Isolate cells from mouse embryos

Transplant into adult mouse testes

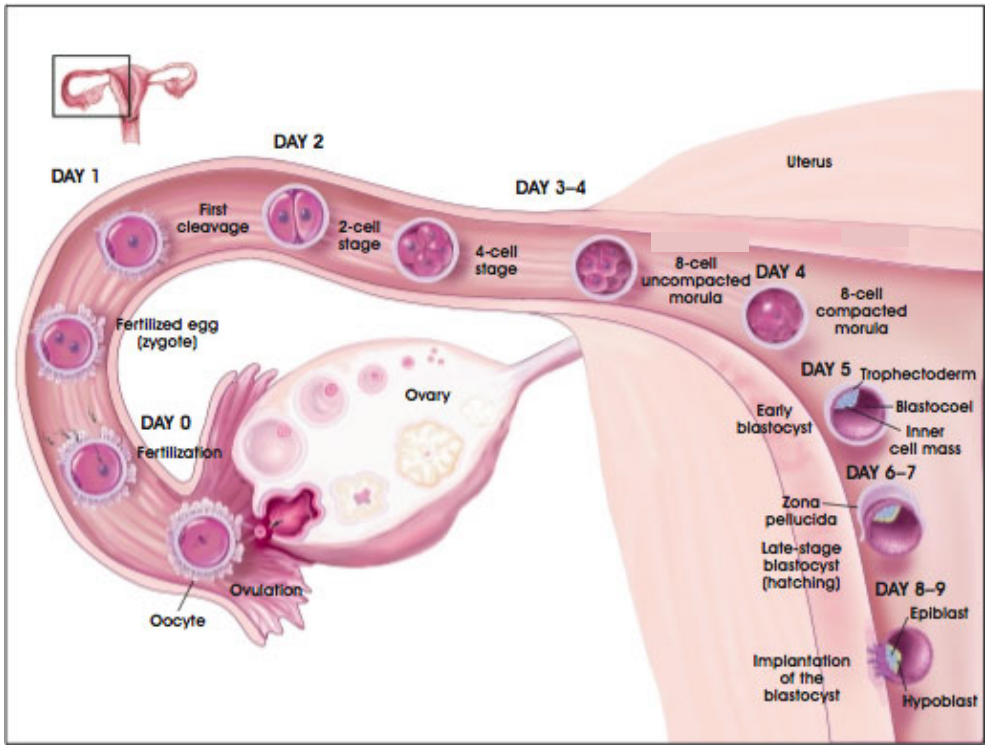
Teratomas!

Pluripotent stem cells have the potential to develop into any cell in the human body!

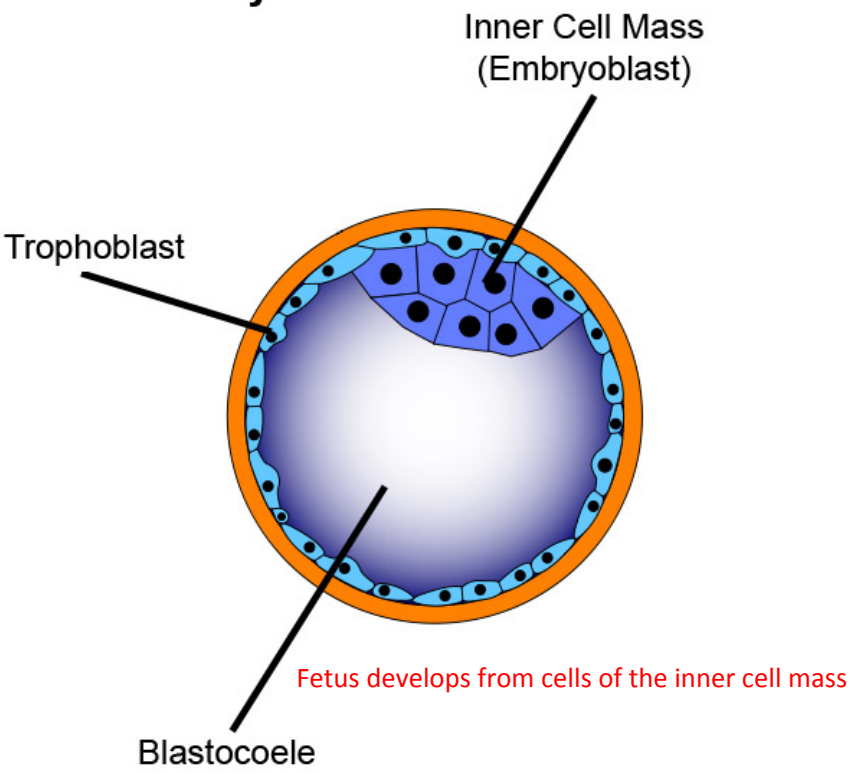


ES cells are pluripotent stem cells!

What developmental stage is a blastocyst?

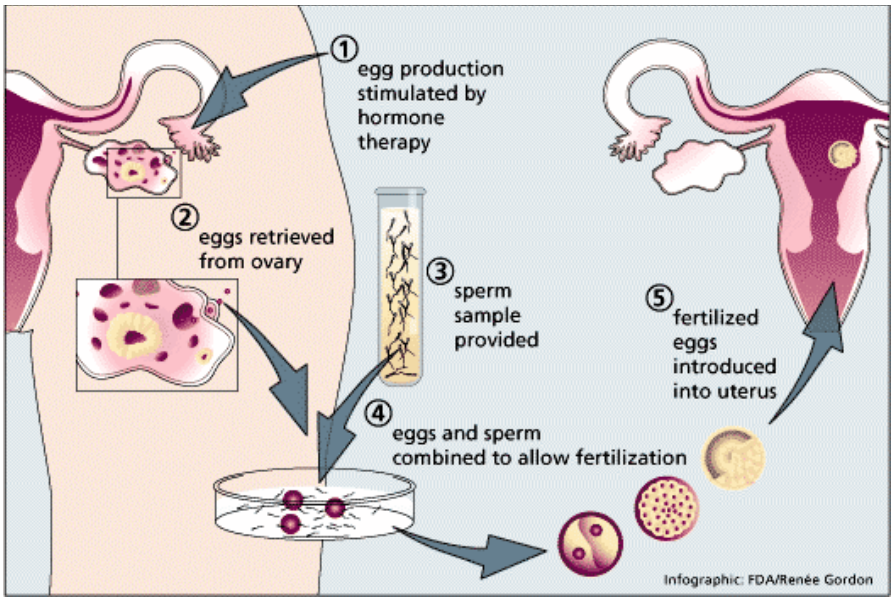


The Blastocyst



Fetus develops from cells of the inner cell mass

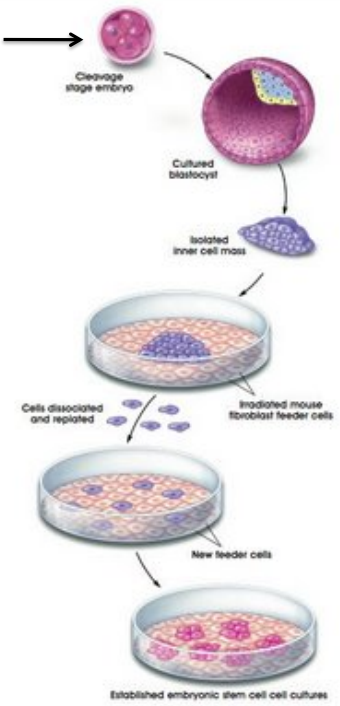
Embryos for ES cell research are obtained through *in vitro* fertilization



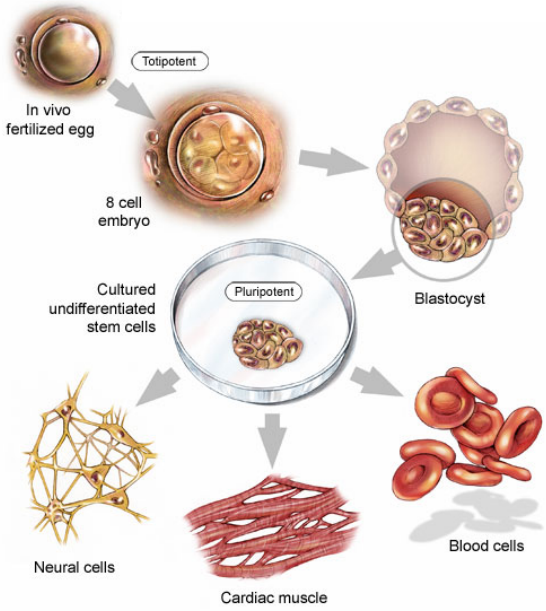
Accounts for 99% of ART procedures
Estimated 3 million worldwide (1% of all US births)

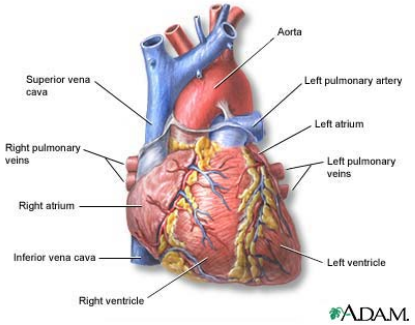
Derivation of an ES cell line

In vitro fertilization →

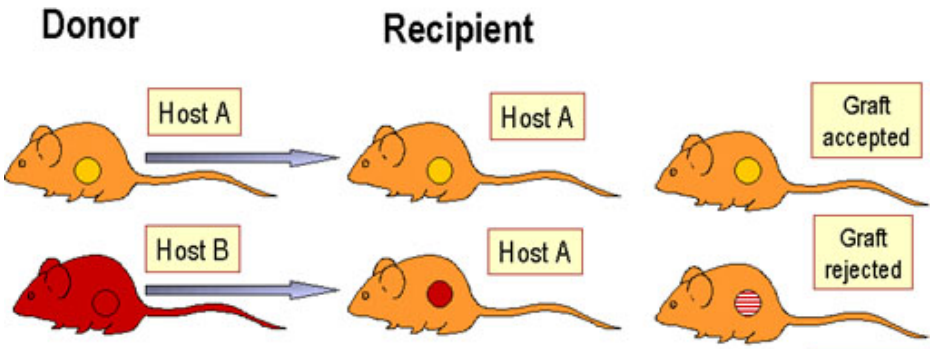


Beating heart muscle from ES cells!





Our bodies can recognize self vs non-self



Human MHC genes are highly polymorphic

Table 17.3

MHC Class II Alleles

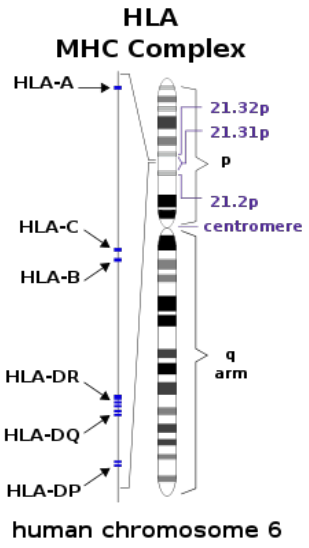
	Locus	Number of Alleles
	HLA-DRA	3
*	HLA-DRB	542
	HLA-DQA	34
	HLA-DQB	73
	HLA-DPA	23
	HLA-DPB	125
	HLA-DMA	4
	HLA-DMB	7
	HLA-DOA	12
	HLA-DOB	9

MHC Class I Alleles

	Locus	Number of Alleles
*	HLA-A	479
*	HLA-B	805
	HLA-C	257
	HLA-E	9
	HLA-F	20
	HLA-G	7

Note: Several other class I alleles are not listed.

Table 17-3 Cell and Molecular Biology, 5/e (© 2008 John Wiley & Sons)



What is the probability that a full sibling will be a genetic match?

Probability of finding bone marrow match in the general population

	Caucasian	African-American	Asian	Hispanic
Caucasian	1/8,000			
African-American	1/133,000	1/127,000		
Asian	1/270,000	1/2,000,000	1/37,000	
Hispanic	1/45,000	1/370,000	1/370,000	1/39,000

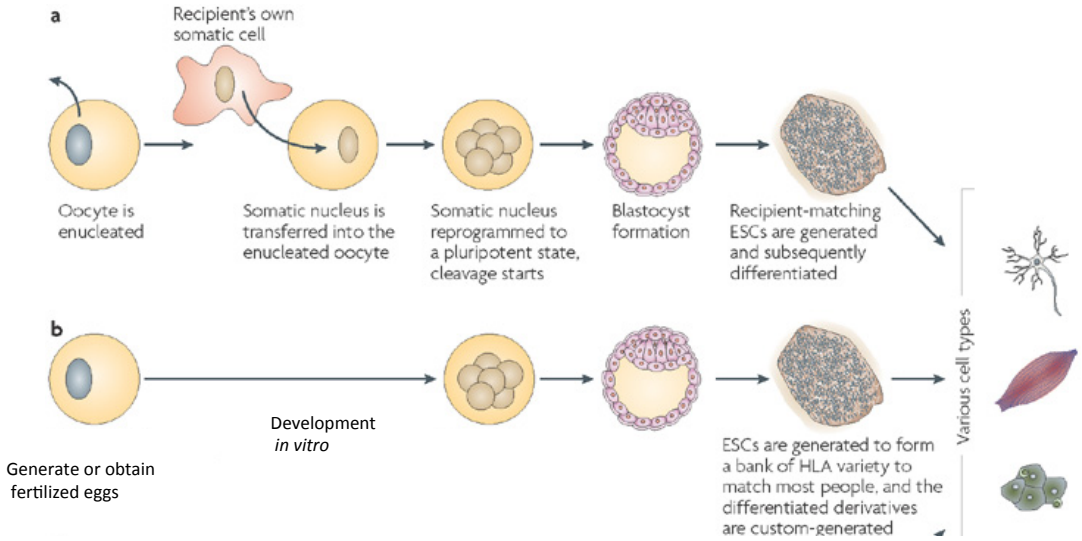
Probability of finding a match is greatest within own ethnic group

Mixed-race individuals face greater challenges

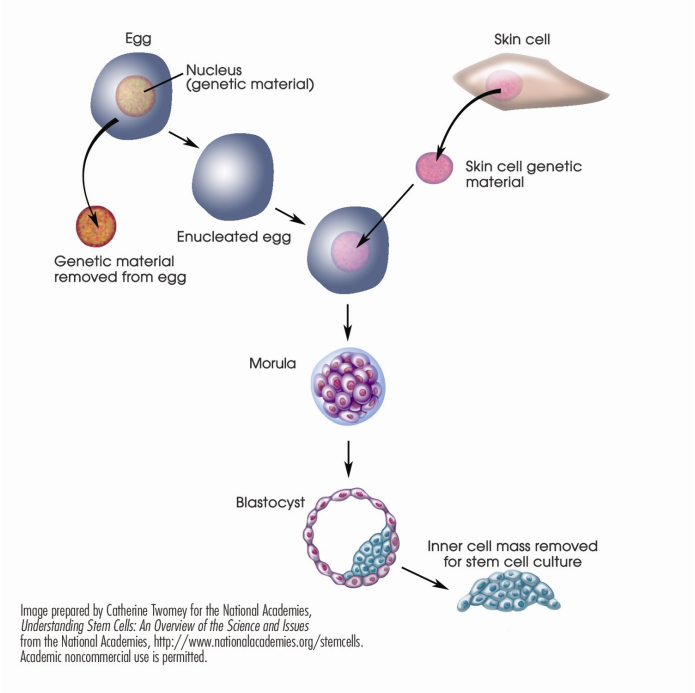
Solutions to the Tissue Rejection Problem

- Have a bank of ES cells of different HLA haplotypes representative of different populations
  - similar to bone marrow registry where chances of a match is related to what is available in the bank
- Obtain ES cell lines for each individual through somatic cell nuclear transfer (SCNT) or cloning
  - Personalized medicine!

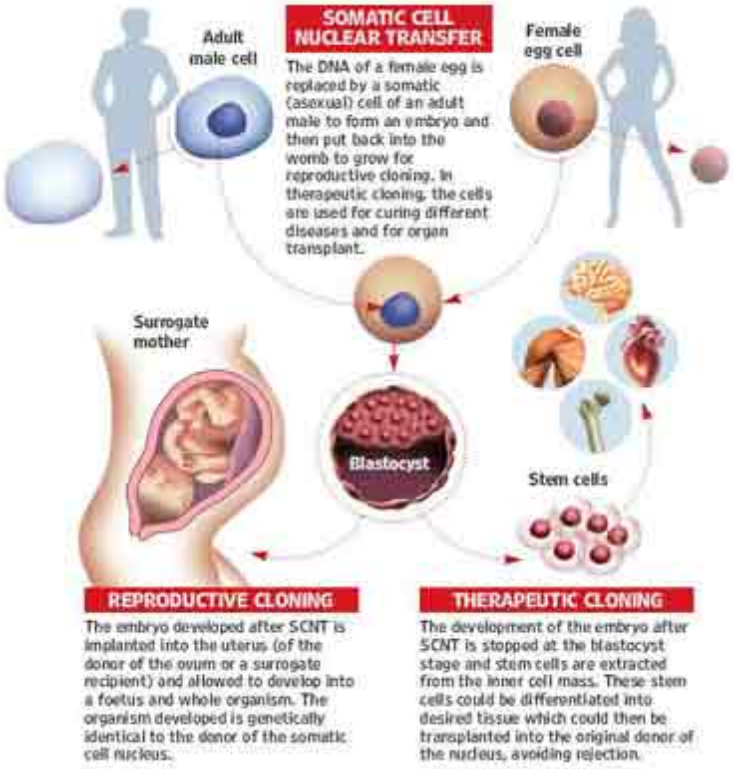
SCNT vs. ES cell bank

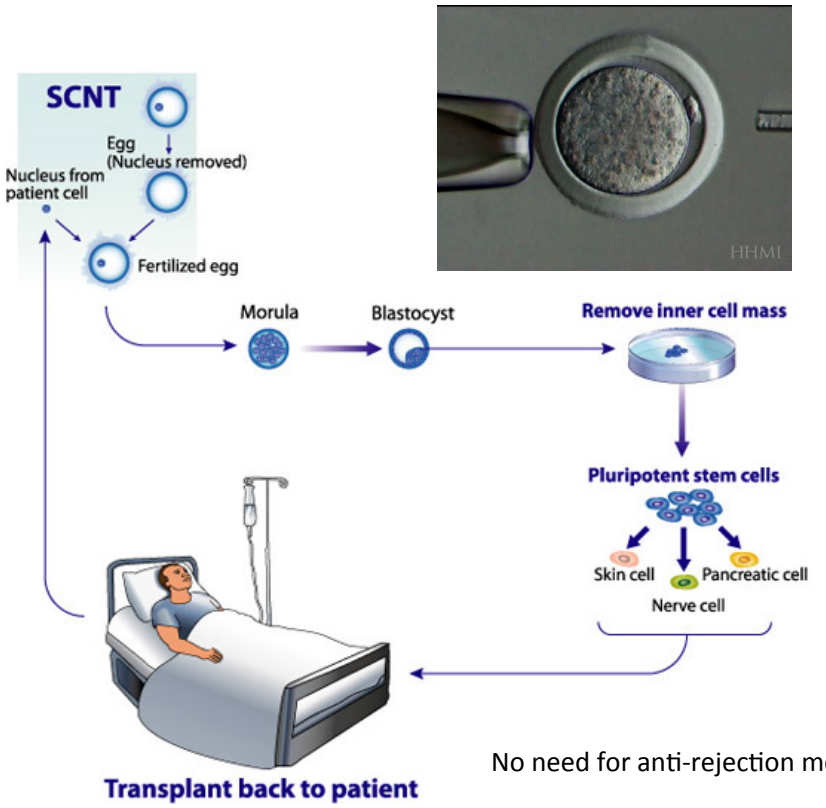


How do you "clone" a human embryo?



Reproductive vs. Therapeutic Cloning





No need for anti-rejection medication!

Human Reproductive Cloning Laws

- 17 states have laws relating to reproductive cloning
- AR, CA, CT, IN, IA, MD, MA, MI, NJ, ND, RI, SD, VA have banned reproductive cloning
- AZ and MO prohibits use of public monies for reproductive cloning
- There is currently no Federal ban

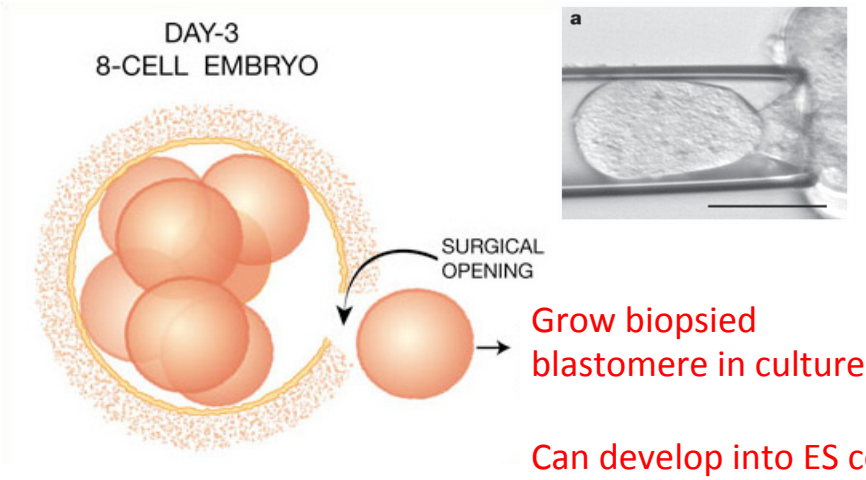
Why is there controversy surrounding human ES cell research?

Moral Status

- Have protection afforded by moral norms
  - Owe obligation to such individuals

- Who should have moral status?
- What criteria should be used to determine whether a person (or animal) has moral status?

ES cells can be derived from a single blastomere



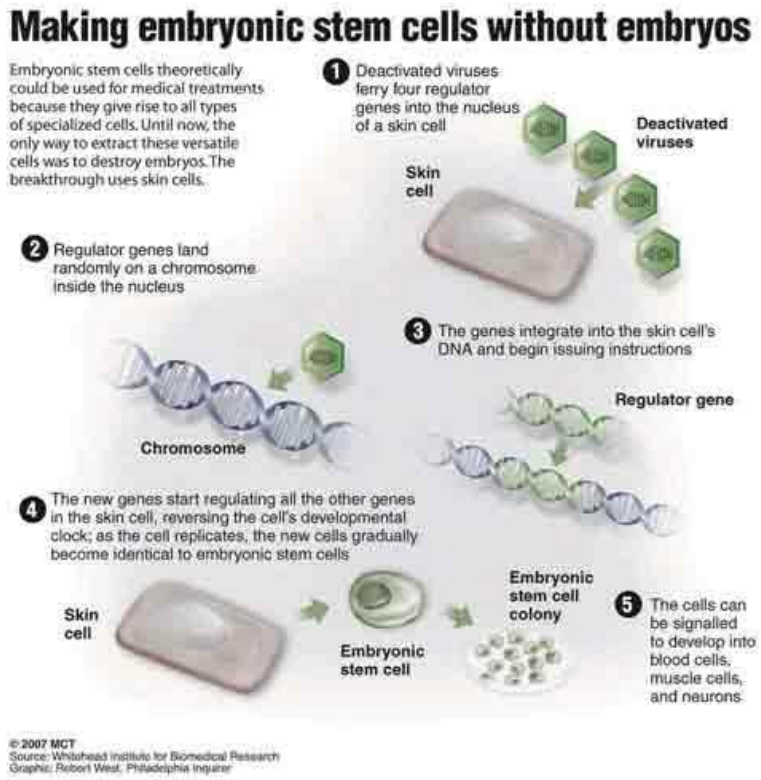
Grow biopsied blastomere in culture

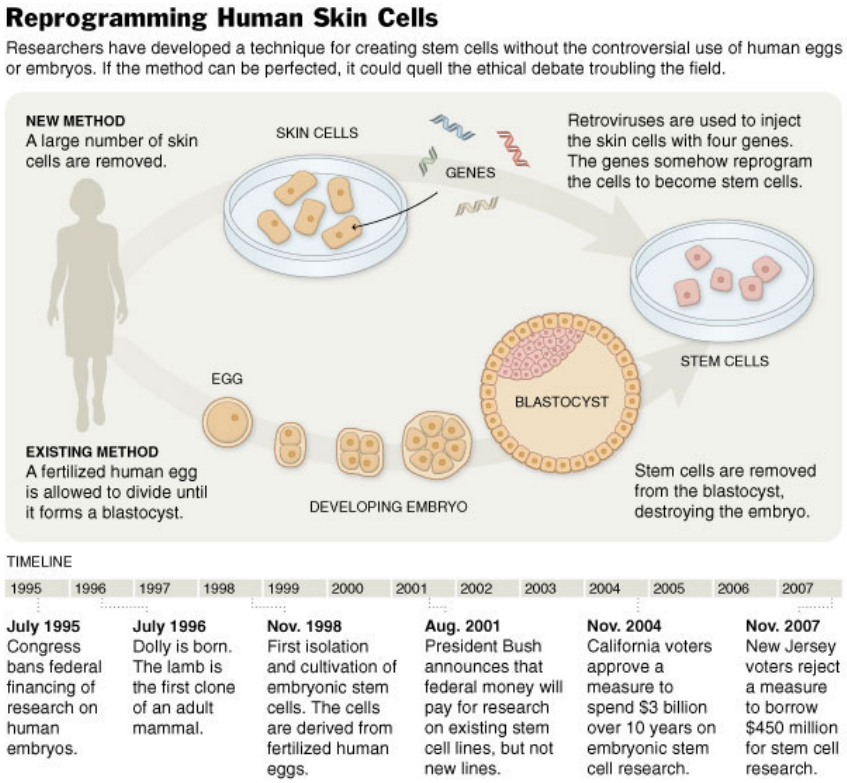
Can develop into ES cells and trophoectoderm

Uses same technique as that for PGD
No babies have been born from biopsied embryos

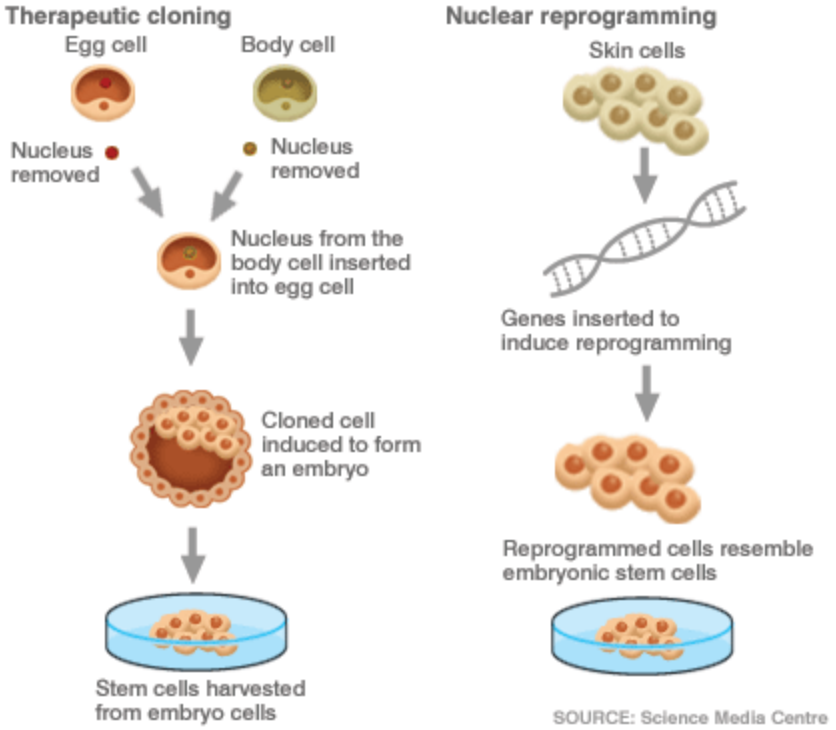
Deactivated viruses have viral genes replaced with targeted human gene

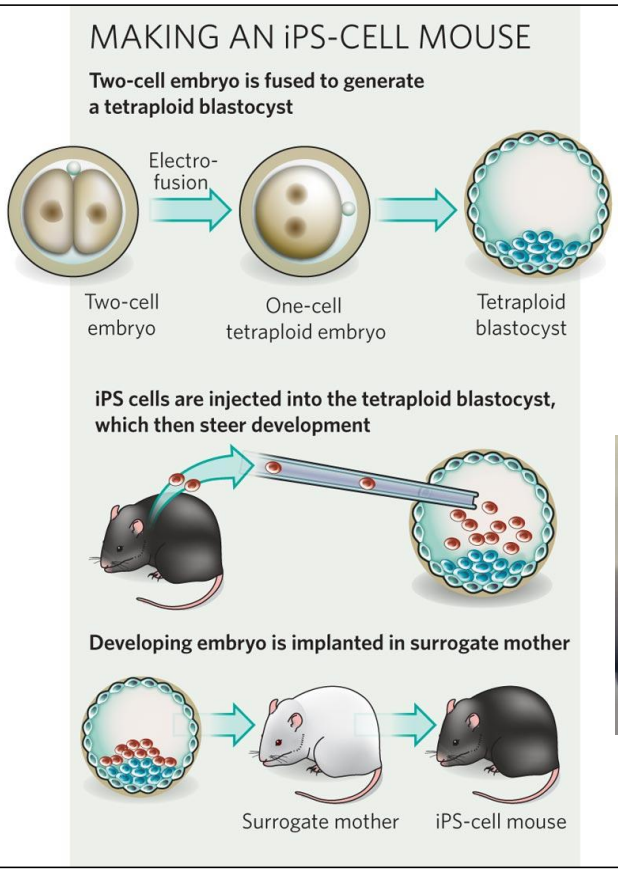
Human gene(s) are inserted into the chromosome of the infected cell and directs the expression of the inserted gene

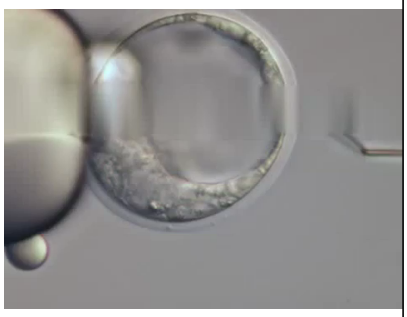




SCNT vs. IPS cells







Use iPS cells to study diseases!

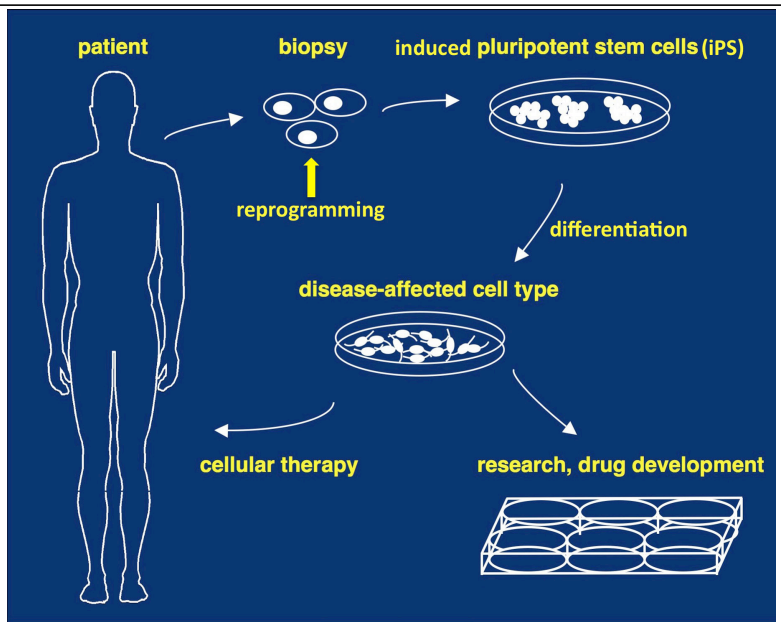


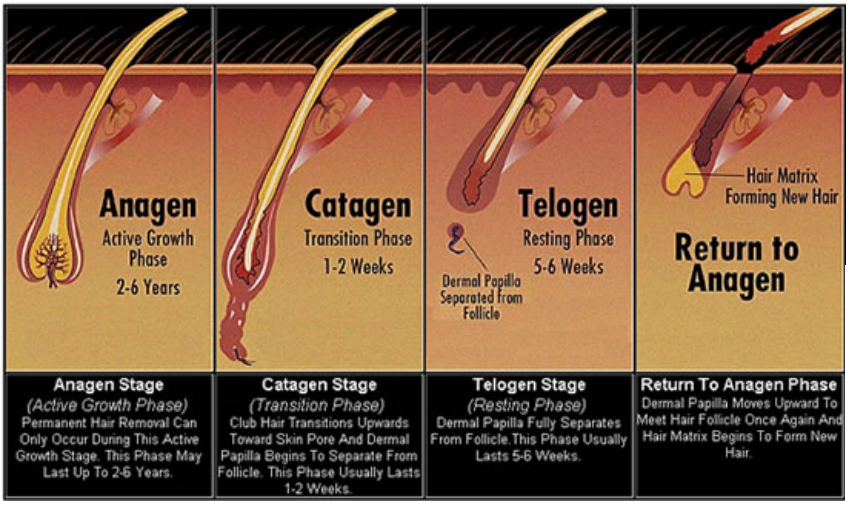
Table 1. iPS Cells Derived from Somatic Cells of Patients with Genetic Disease

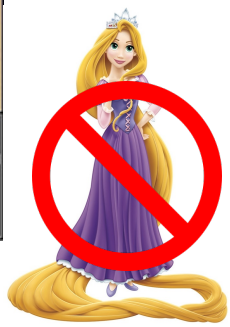
Name	Disease	Molecular Defect	Donor Cell	Age	Sex
ADA	ADA-SCID	GGG >AGG, exon 7 and Del(GAAGA) exon 10, *ADA* gene	Fibroblast	3 M	Male
GD	Gaucher disease type III	AAC > AGC, exon 9, G-insertion, nucleotide 84 of cDNA, *GBA* gene	Fibroblast	20 Y	Male
DMD	Duchenne muscular dystrophy	Deletion of exon 45–52, *dystrophin* gene	Fibroblast	6 Y	Male
BMD	Becker muscular dystrophy	Unidentified mutation in *dystrophin*	Fibroblast	38 Y	Male
DS1, DS2	Down syndrome	Trisomy 21	Fibroblast	1 Y, 1 M	Male
PD	Parkinson disease	Multifactorial	Fibroblast	57 Y	Male
JDM	Juvenile diabetes mellitus	Multifactorial	Fibroblast	42 Y	Female
SBDS	Swachman-Bodian-Diamond syndrome	IV2 + 2T > C and IV3 − 1G > A, *SBDS* gene	Bone marrow mesenchymal cells	4 M	Male
HD	Huntington disease	72 CAG repeats, *huntingtin* gene	Fibroblast	20 Y	Female
LNSc	Lesch-Nyhan syndrome (carrier)	Heterozygosity of *HPRT1*	Fibroblast	34 Y	Female

Adult stem cells are…

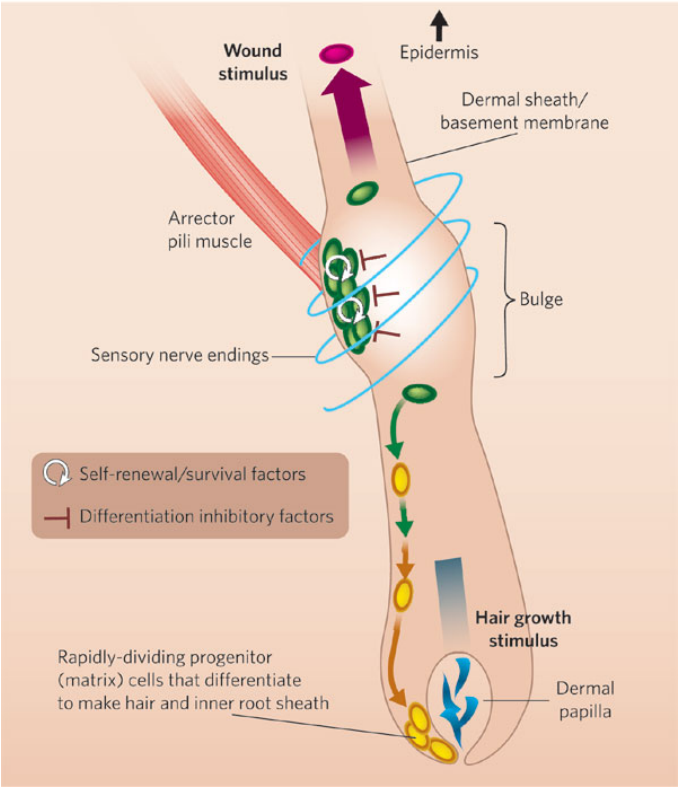
- Also present in children
- Have limited differentiation potential, usually restricted to a few cell types

Stem Cells in the Hair Follicle

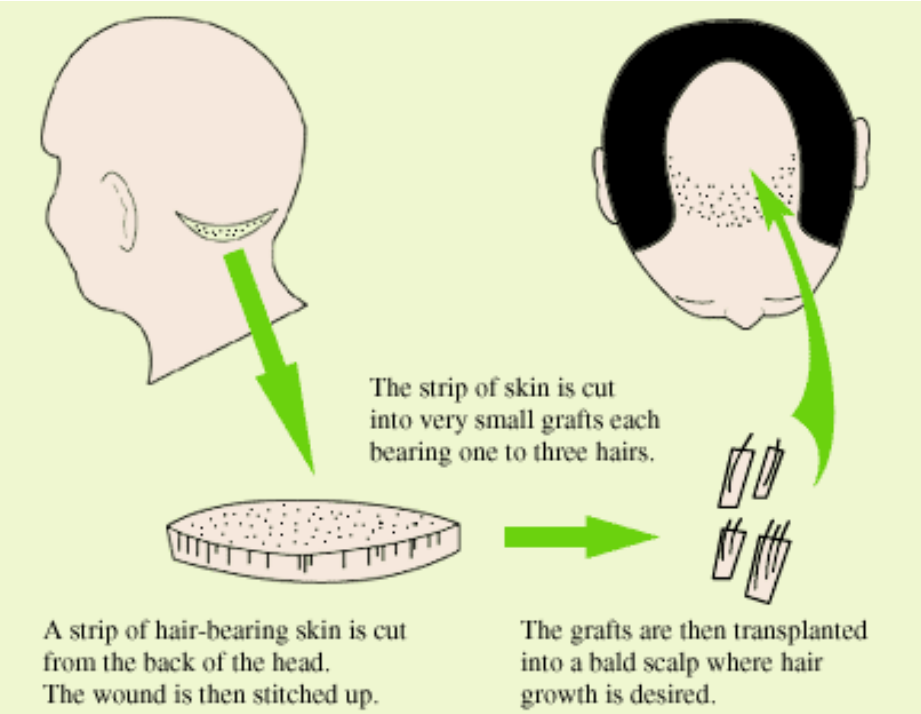




Sorry Rapunzel!



Hair Transplantation is Stem Cell Therapy!



Limitations of multipotent stem cells

- Limited developmental potential
- Difficult to find and isolate
- Difficult to grow in culture

Policy under Barack Obama

March 9, 2009
Executive order 13505

- The Secretary of Health and Human Services (Secretary), through the Director of NIH, may support and conduct responsible, scientifically worthy human stem cell research, including human embryonic stem cell research, to the extent permitted by law.
- The Presidential statement of August 9, 2001, limiting Federal funding for research involving human embryonic stem cells, shall have no further effect as a statement of governmental policy.
- Executive Order 13435 of June 20, 2007, which supplements the August 9, 2001, statement on human embryonic stem cell research, is revoked.

NIH Guidelines (July 2009)

ES cell research eligible for NIH funding if:

1. that were created using in vitro fertilization for reproductive purposes and were no longer needed for this purpose
2. that were donated by individuals who sought reproductive treatment (hereafter referred to as "donor(s)") and who gave voluntary written consent for the human embryos to be used for research purposes
3. No payments, cash or in kind, were offered for the donated embryos.
4. Decisions related to the creation of human embryos for reproductive purposes should have been made free from the influence of researchers proposing to derive or utilize hESCs in research.

Research NOT eligible for NIH funding:

1. NIH funding of the derivation of stem cells from human embryos is prohibited by the annual appropriations ban on funding of human embryo research (Section 509, Omnibus Appropriations Act, 2009, Pub. L. 111-8, 3/11/09), otherwise known as the Dickey Amendment.
2. Research using hESCs derived from other sources, including somatic cell nuclear transfer, parthenogenesis, and/or IVF embryos created for research purposes, is not eligible for NIH funding.

Dickey-Wicker Amendment (1995)

Prohibits Dept HHS appropriations for:

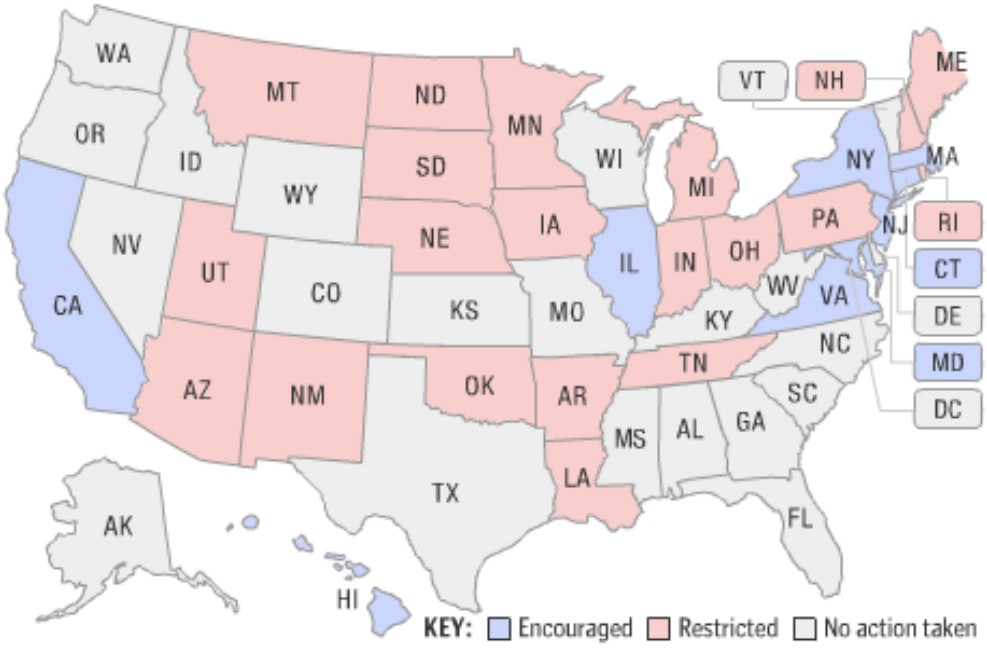
(1) the creation of a human embryo or embryos for research purposes; or

(2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero

Sherley v. Sebelius

- 8/19/2009—complaint filed challenging the legality of NIH guidelines
- 8/23/2010—preliminary injunction from DC District court blocking implementation of NIH's 2009 guidelines, saying that it violates the Dickey-Wicker amendment
- 9/9/2010—preliminary injunction lifted pending decision from US court of appeals
- 4/29/2011—injunction vacated by US court of appeals. Using the Chevron doctrine, the court concluded that the Dickey-Wicker amendment is ambiguous and that NIH has acted reasonably in concluding that public funds could be used for human embryonic stem cell research. Also, the panel that the government would be harmed by the injunction more than the plaintiffs by not having one.
- 1/7/13—US Supreme court refuses to hear appeal

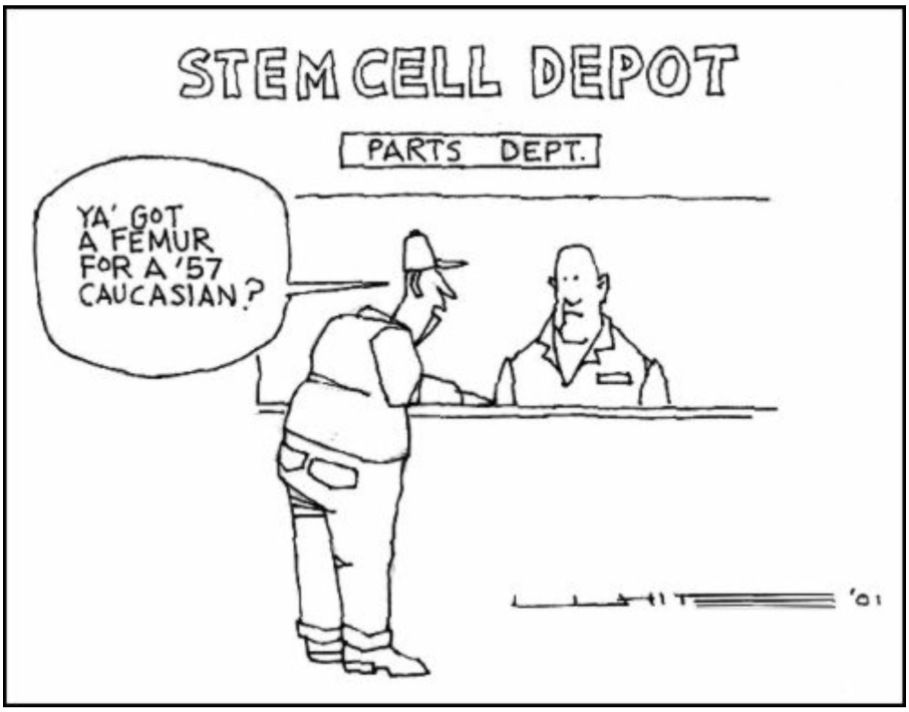
Stem cell research policy by state:

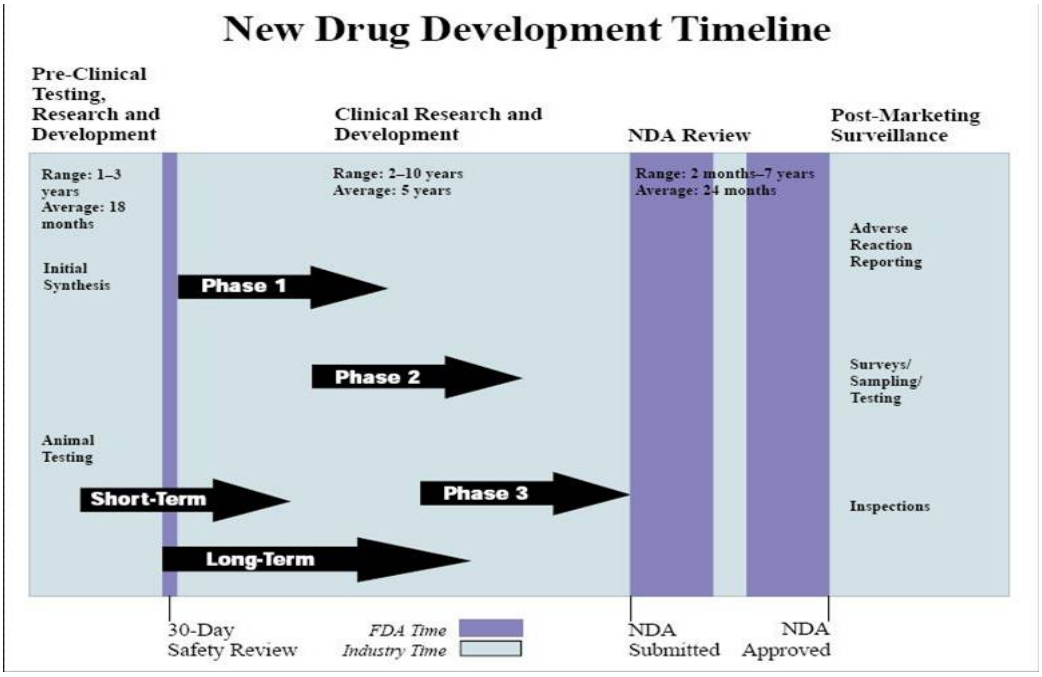


California Institute for Regenerative Medicine (CIRM)

- Created in 2004 through the passage of prop 71 (59% of vote)
  - Allocates grant money for research purposes
  - Sets appropriate regulatory standards
- Prop 71:
  - Makes conducting stem cell research a constitutional right
  - Uses general obligation bonds to fund scientific research (normally for brick and mortar projects)
  - Takes on typical federal government role of funding scientific research
  - Represents a unique example where the public decided to fund scientific research
- Issues 3 billion in grants funded by bonds over 10 years
  - Money can be used for all stem cell research, with priority for human embryonic stem cell research
- First research grants were awarded in 2007

The Promise of Regenerative Medicine





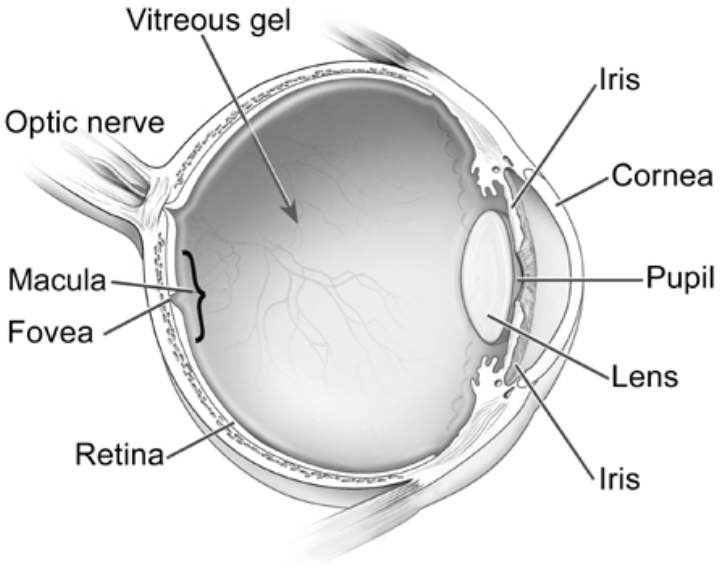
Clinical Trials

- Phase I: Safety
  - Usually includes healthy (paid) volunteers
- Phase II: Efficacy
  - Patients are involved
  - Usually where drug fails
- Phase III---Randomized controlled trial
  - Involves larger numbers of patients
  - Compares efficacy of drug against current "gold standard" treatment
  - Expensive

Hurdles to using stem cells for disease treatment

- Reproducibly proliferate and generate sufficient tissue
- Reproducibly differentiate into the desired cell type
- Delivery to desired organ
- Survive in the recipient after transplant
- Integrate into the surrounding tissue
- Function properly
- No harm (esp. ESC)

The Eye



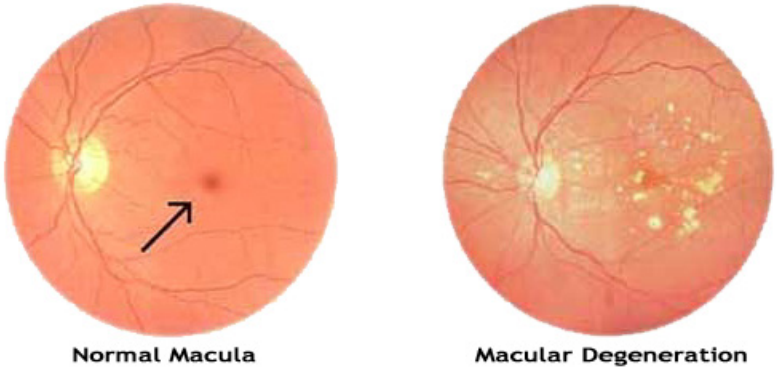
- Macular is central portion of the retina
- Important for seeing fine detail
- Photoreceptors perceive light—rods and cones
- Immune privileged

Macular Degeneration affects central vision

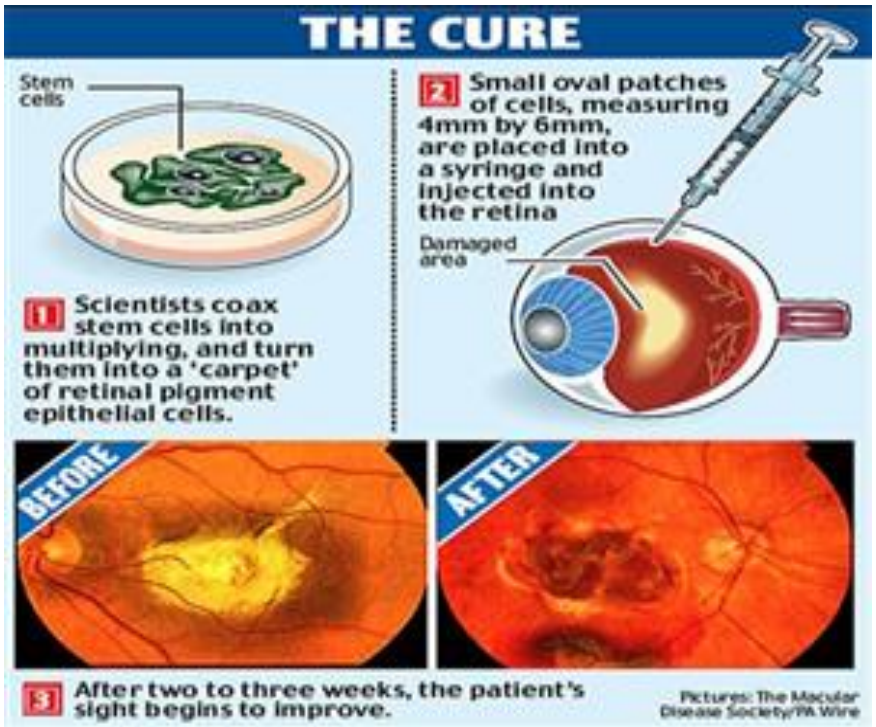
Normal Vision

Macular Degeneration

Macular Degeneration

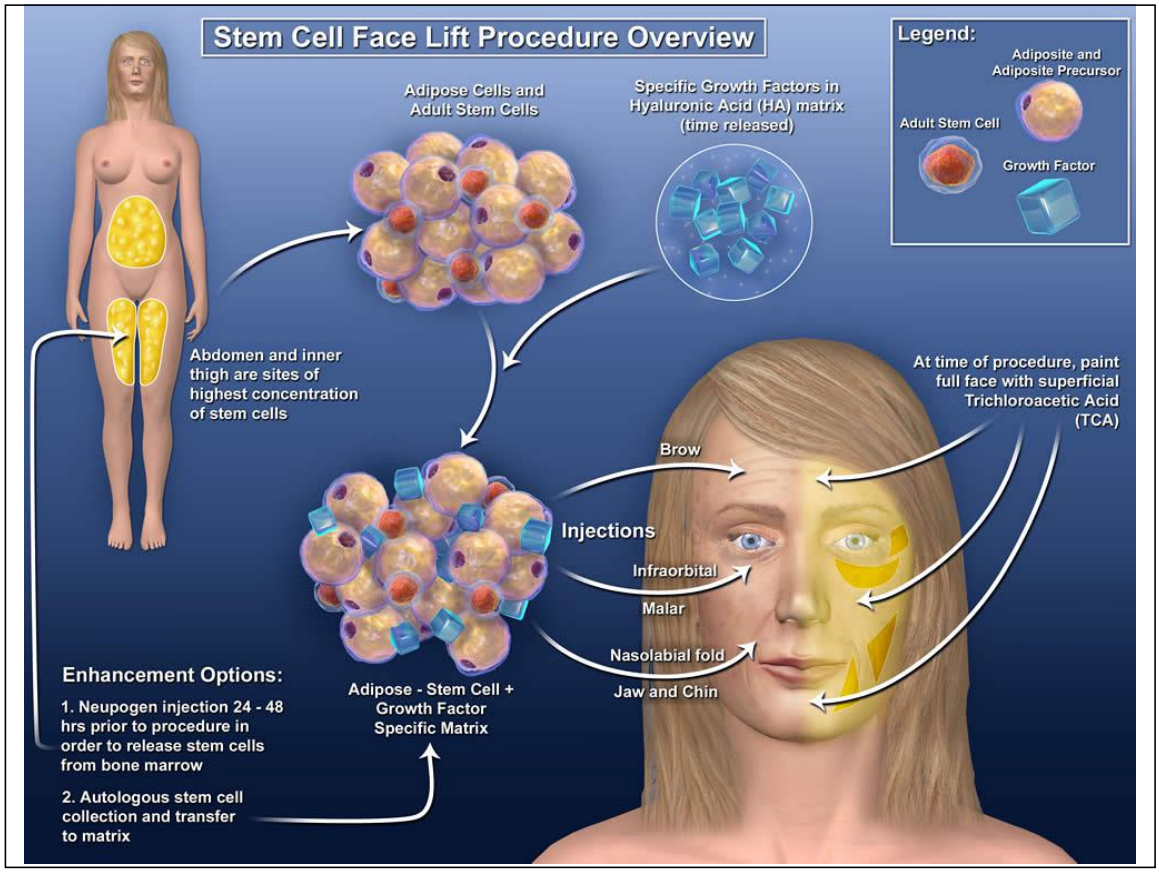


- Major cause of blindness affecting adults
- Affect 10% of adults 66 to 74 have macular degeneration; incidence rises to 30% from 75-85
- Buildup of drusen (cell debris), which affect vision. Eventually leads to death of light perception cells
- Vision loss is permanent
- Stargardts—inherited juvenile form of macular degeneration, usual onset between 6-12



Macular degeneration ES cell trial

- 2 patients—one with AMD and one with Stargardts
- ES cells induced to become RPE (retinal pigment epithelium)
- Injected cells to region of macula not completely destroyed by disease
- Lose dose immunosuppression
- No signs of animal pathogen or teratoma formation


Stem Cell Face Lift Procedure Overview
Legend:
Adiposite and Adiposite Precursor
Adult Stem Cell
Growth Factor
Adipose Cells and Adult Stem Cells
Specific Growth Factors in Hyaluronic Acid (HA) matrix (time released)
Abdomen and inner thigh are sites of highest concentration of stem cells
At time of procedure, paint full face with superficial Trichloroacetic Acid (TCA)
Brow
Injections
Infraorbital
Malar
Nasolabial fold
Jaw and Chin
Adipose - Stem Cell + Growth Factor Specific Matrix
Enhancement Options:
1. Neupogen injection 24 - 48 hrs prior to procedure in order to release stem cells from bone marrow
2. Autologous stem cell collection and transfer to matrix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