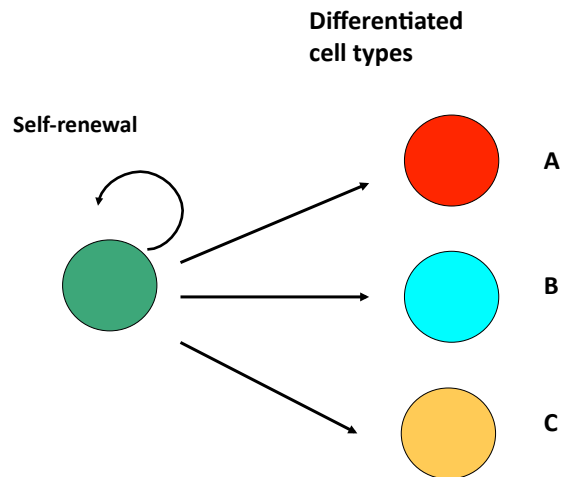




Stem Cell Biology and Ethics  
Dr. Pei Yun Lee

What is a Stem Cell? What do they do?

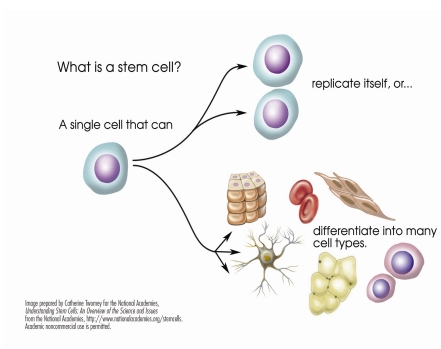


Ability to differentiate into different cell types  
Ability to self renew

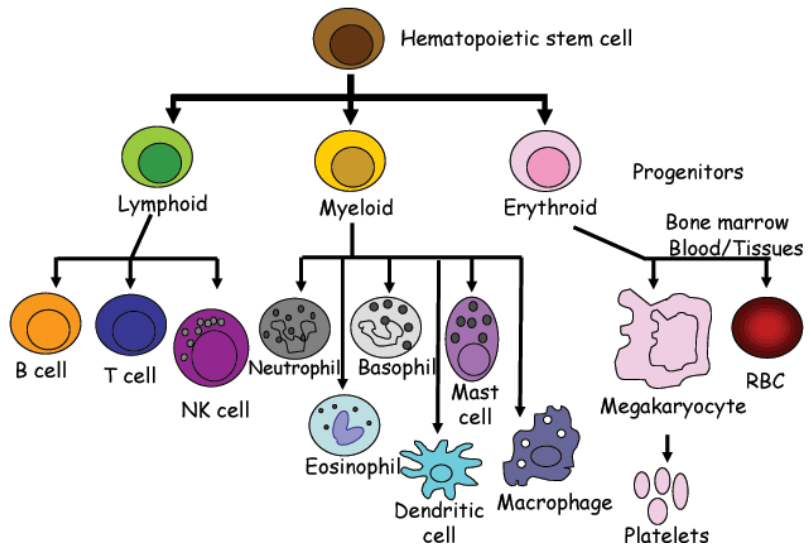
## What are Stem Cells ?

- 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

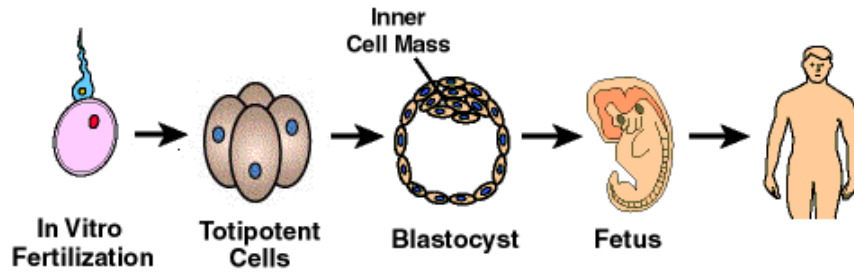
**self-renew:** reproduce without changing developmental potential



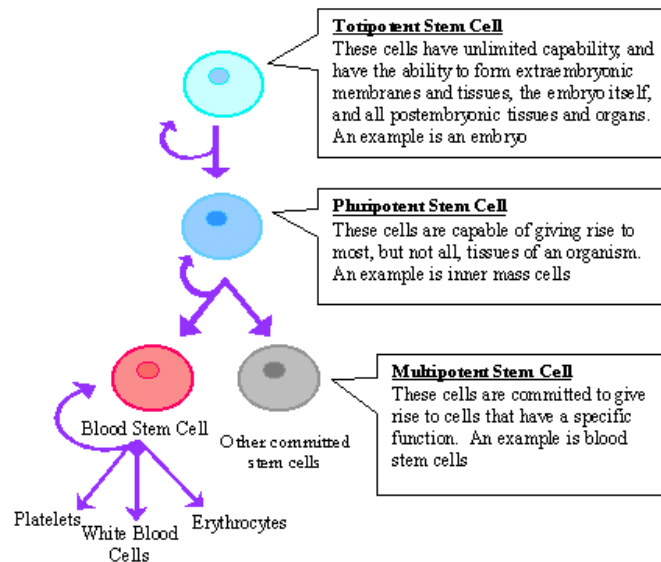
## Immune cell development: Hematopoiesis

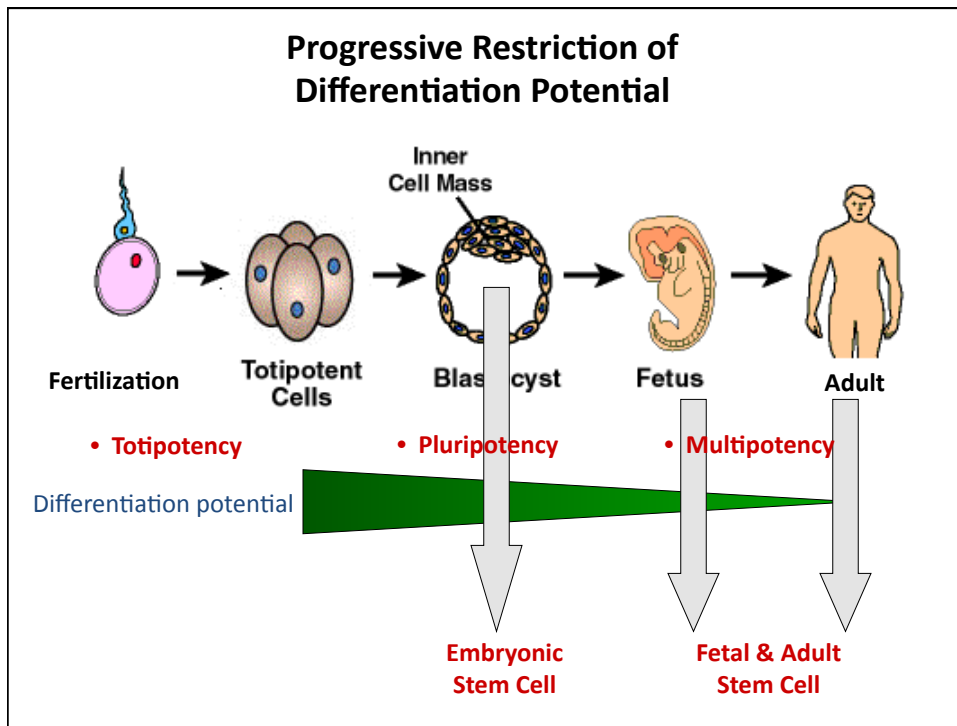


## Where can stem cells be found?



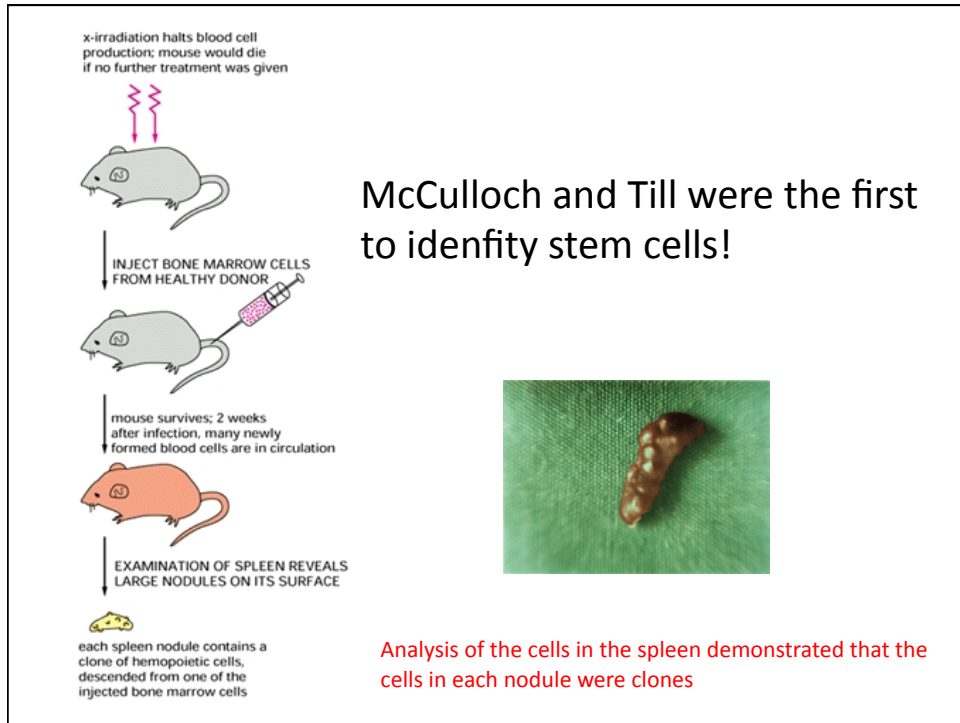
## Stem cells have different developmental potentials

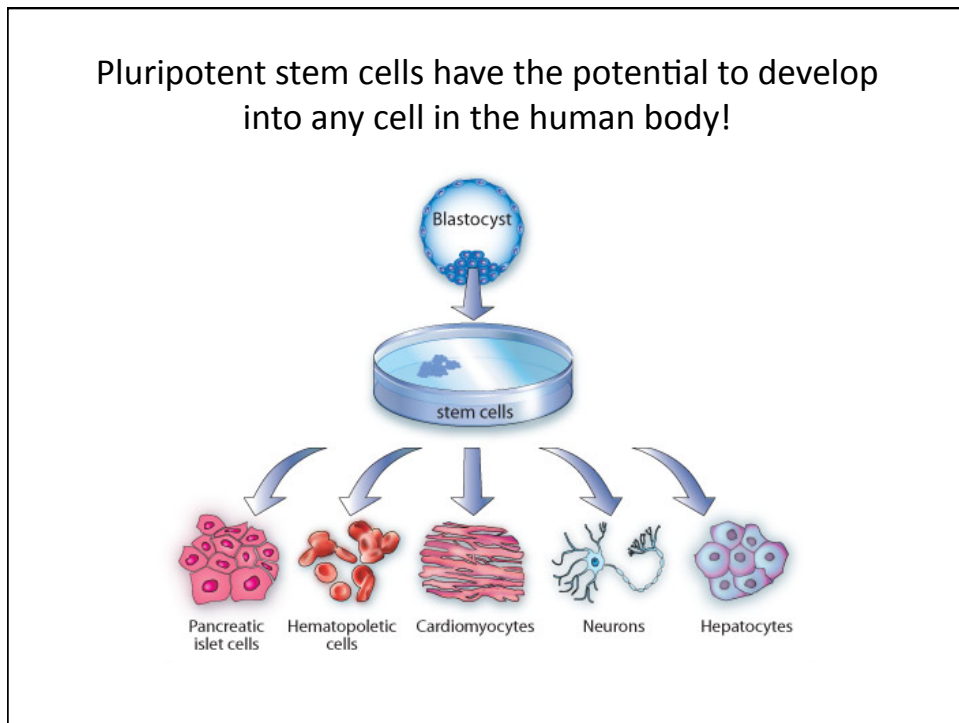
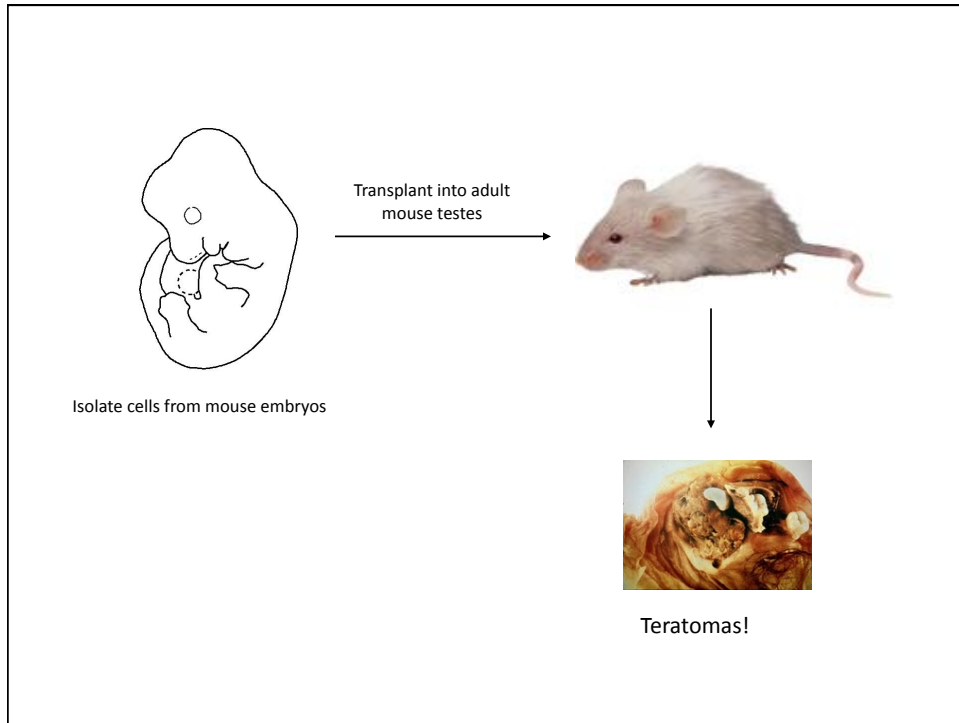




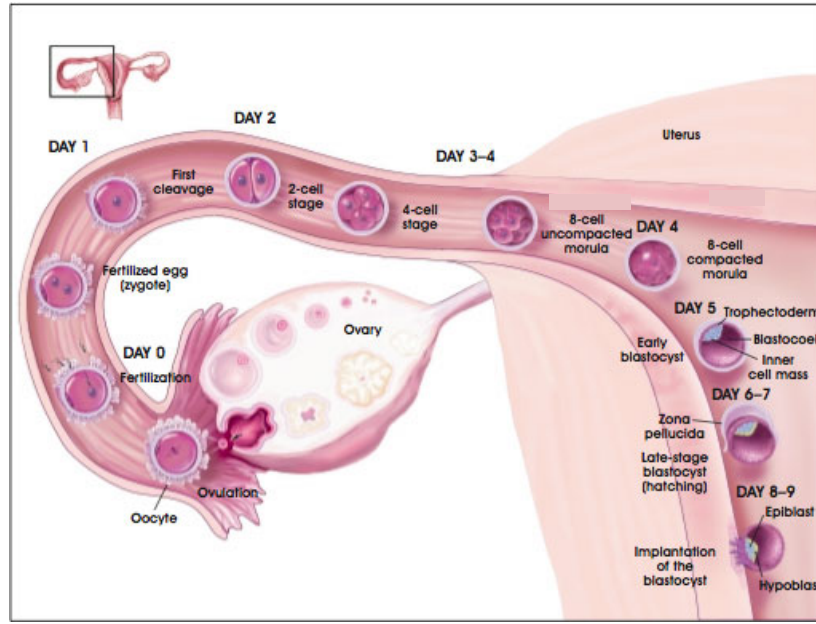
Alexander Maximow 1909

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

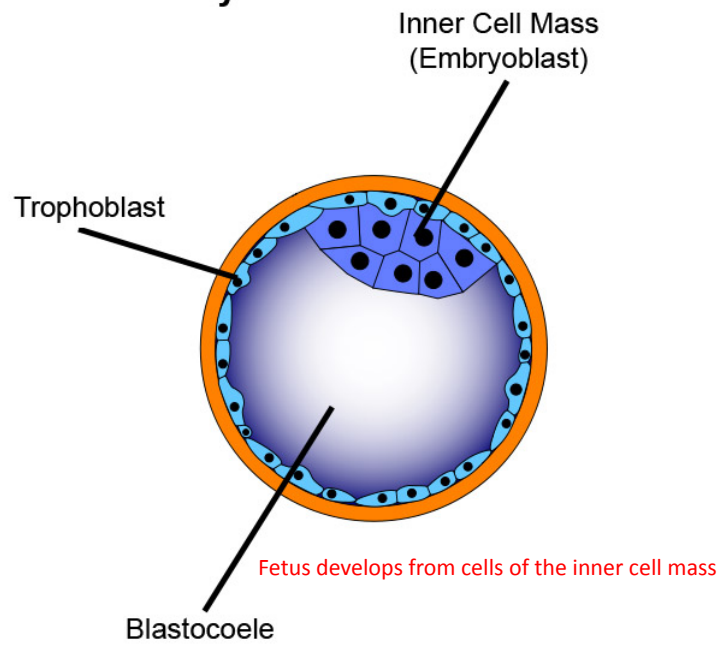




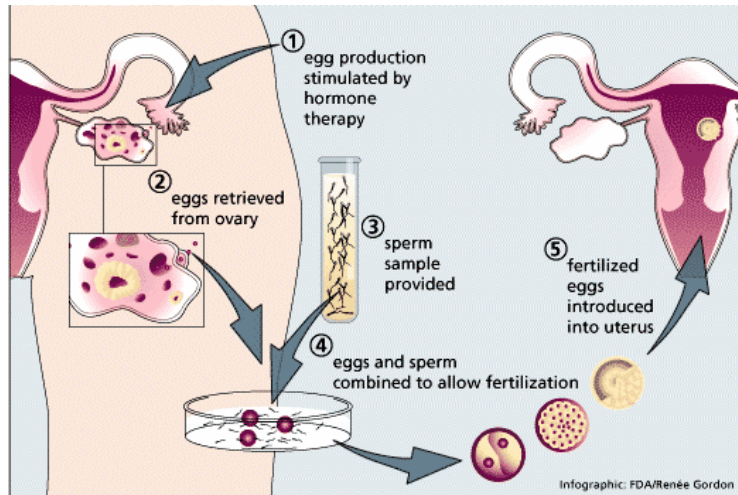
What developmental stage is a blastocyst?



### The Blastocyst

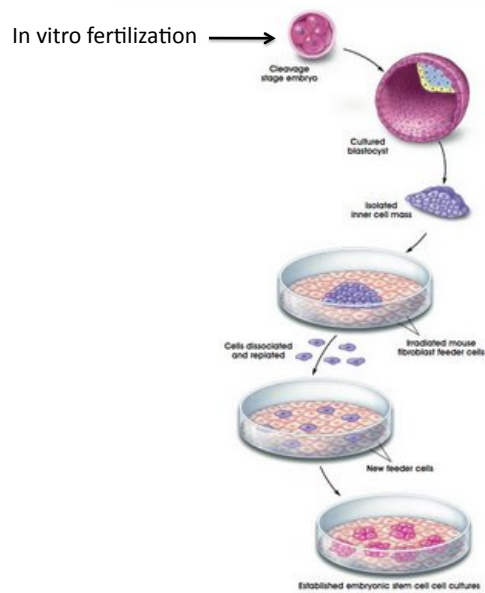


### Embryos for ES cell research are obtained through *in vitro* fertilization



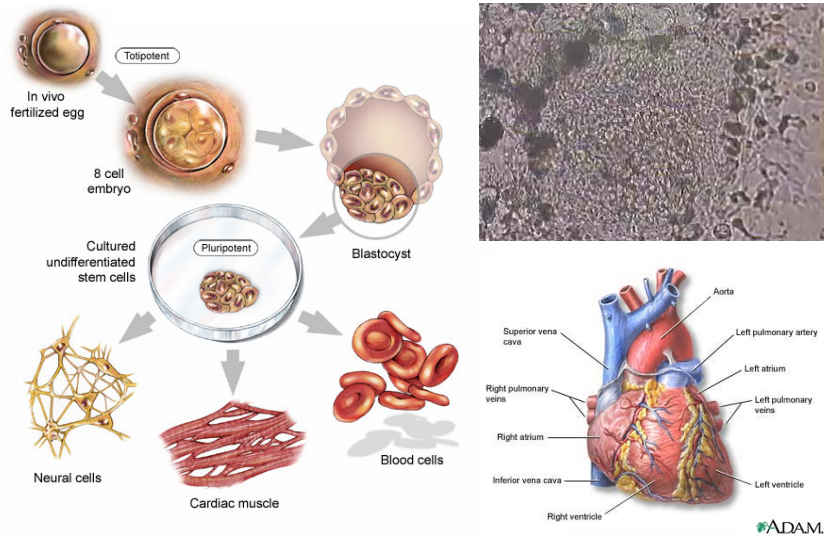
Accounts for 99% of ART procedures  
 Estimated 3 million worldwide (1% of all US births)

### Derivation of an ES cell line

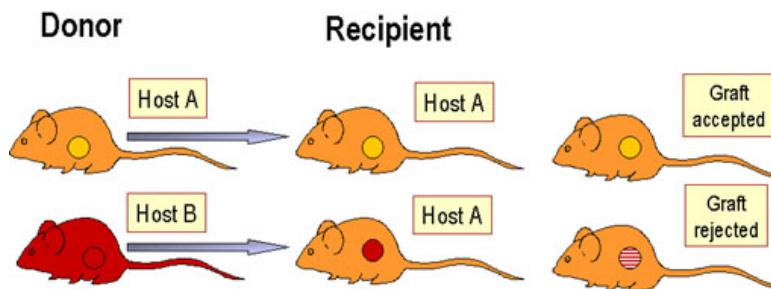




# Beating heart muscle from ES cells!



# Our bodies can recognize self vs non-self



## Human MHC genes are highly polymorphic

**Table 17.3**

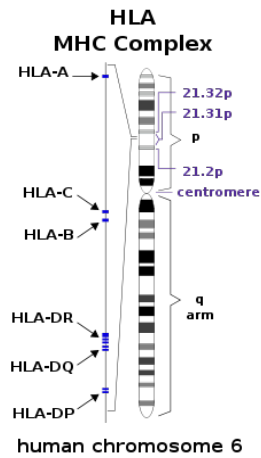
MHC Class II Alleles	
Locus	Number of Alleles
HLA-DRA	3
* HLA-DRB	542
HLA-DQA	34
HLA-DQB	73
HLA-DPA	23
HLA-DPB	125
HLA-DMA	4
HLA-DMB	7
HLA-DOA	12
HLA-DOB	9

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)



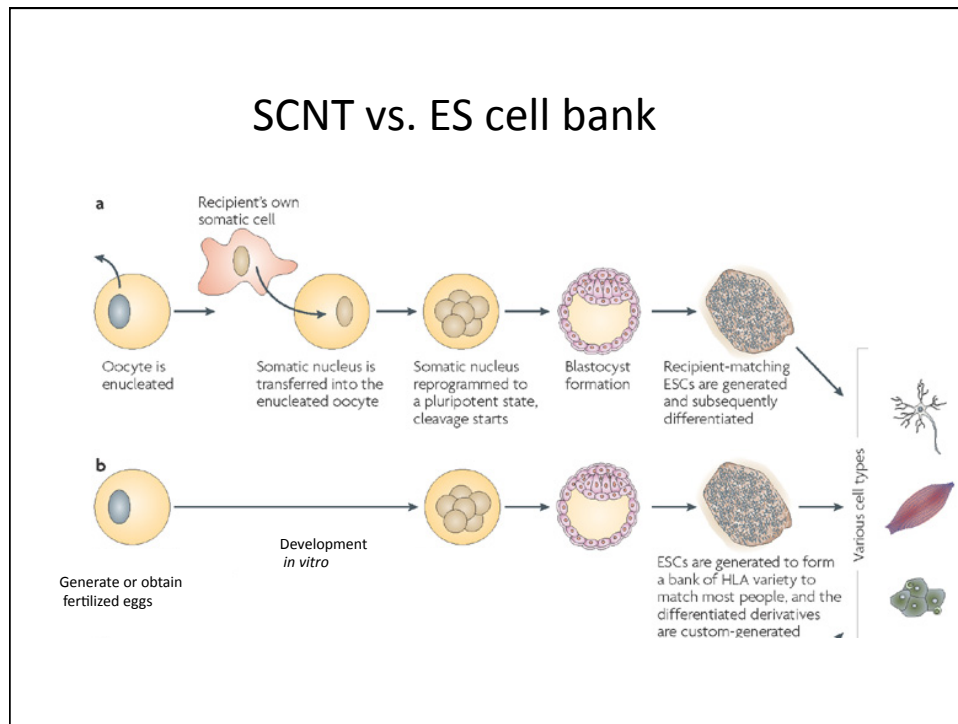
What is the probability that a full sibling will be a genetic match?

## 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

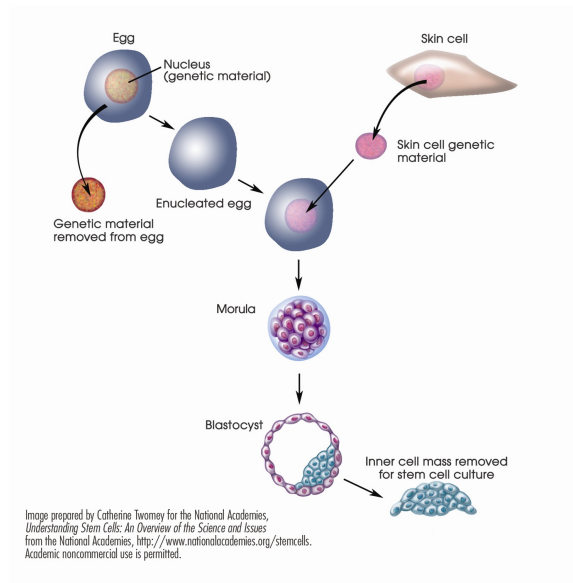
Mixed-race individuals face greater challenges



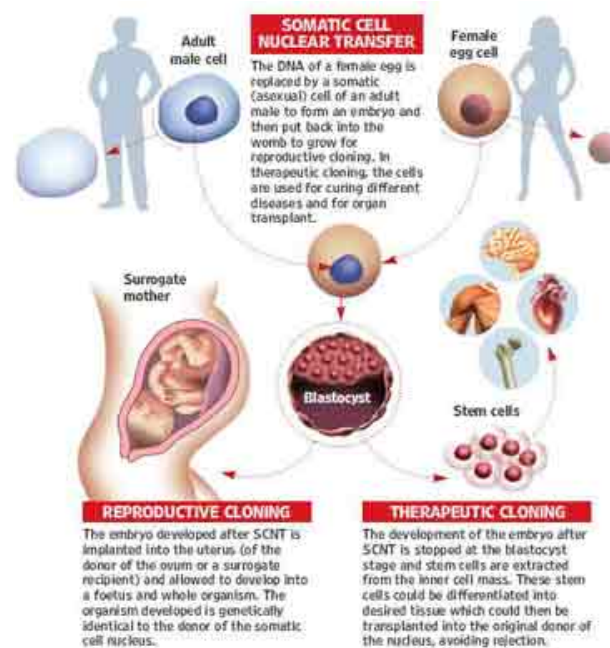
## Solutions to the Tissue Rejection Problem

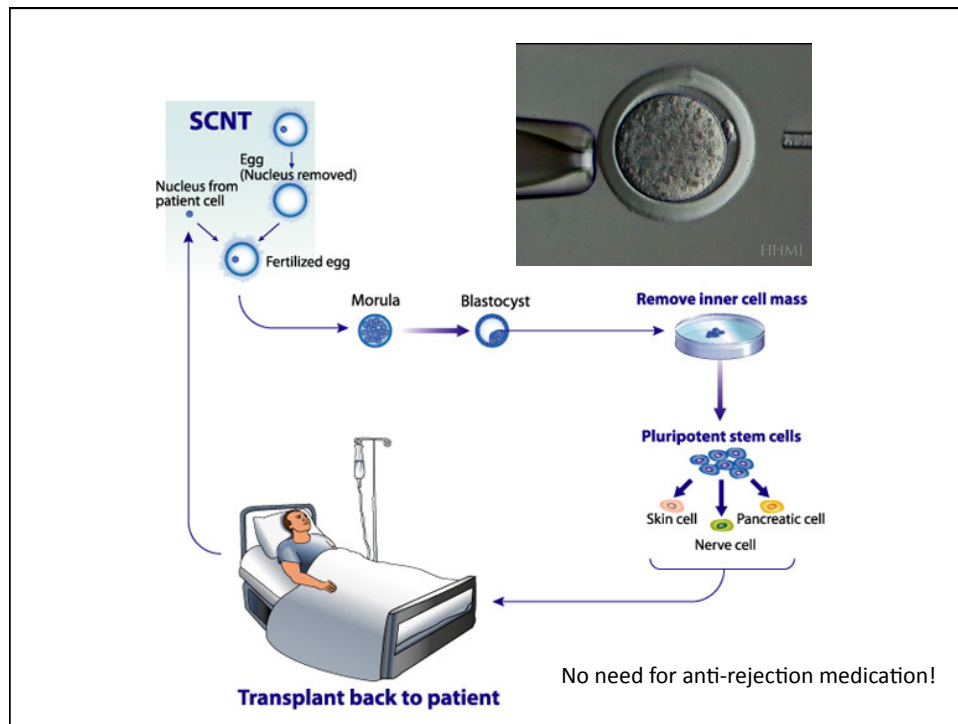
- Have a bank of ES cells of different HLA haplotypes representative of different populations
  - similar to bone marrow registry where chances of a match is related to what is available in the bank
- Obtain ES cell lines for each individual through somatic cell nuclear transfer (SCNT) or cloning
  -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

## How do you "clone" a human embryo?



## Reproductive vs. Therapeutic Cloning



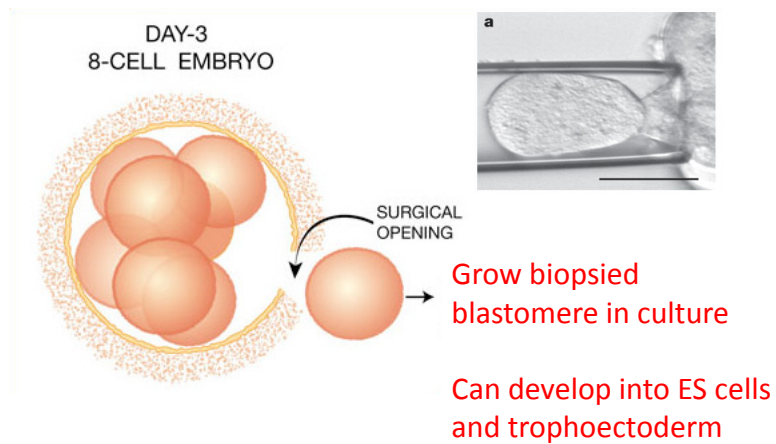


## Human Reproductive Cloning Laws

- 15 states have laws relating to reproductive cloning
- They are:
- 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

Can we generate pluripotent stem cells without destroying an embryo?

ES cells can be derived from a single blastomere



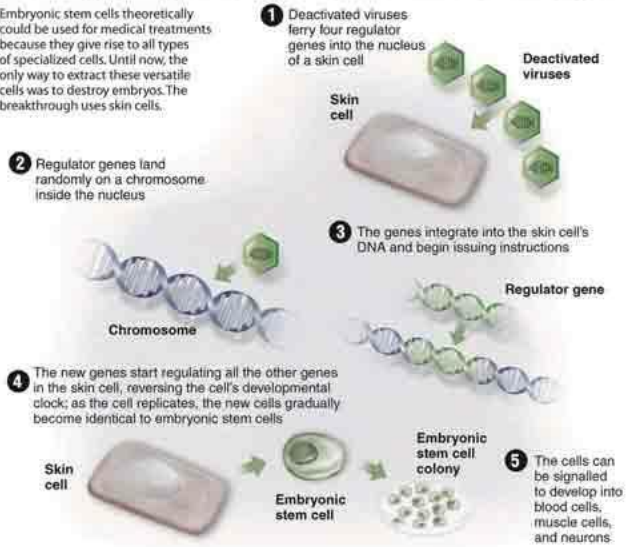
Uses same technique as that for PGD  
No babies have been born from biopsied embryos

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

### Making embryonic stem cells without embryos

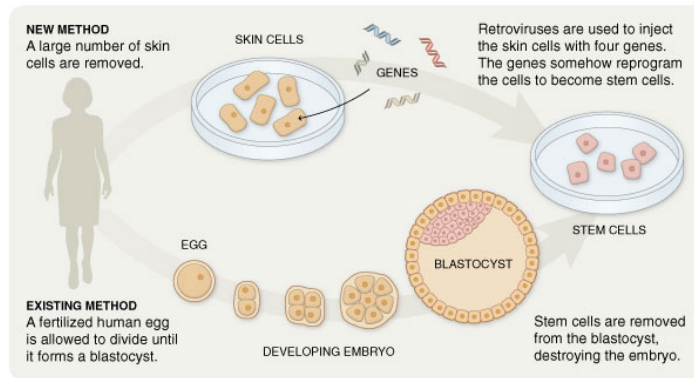
Embryonic stem cells theoretically could be used for medical treatments because they give rise to all types of specialized cells. Until now, the only way to extract these versatile cells was to destroy embryos. The breakthrough uses skin cells.



© 2007 MCT  
Source: Whitehead Institute for Biomedical Research  
Graphic: Robert West, Philadelphia Inquirer

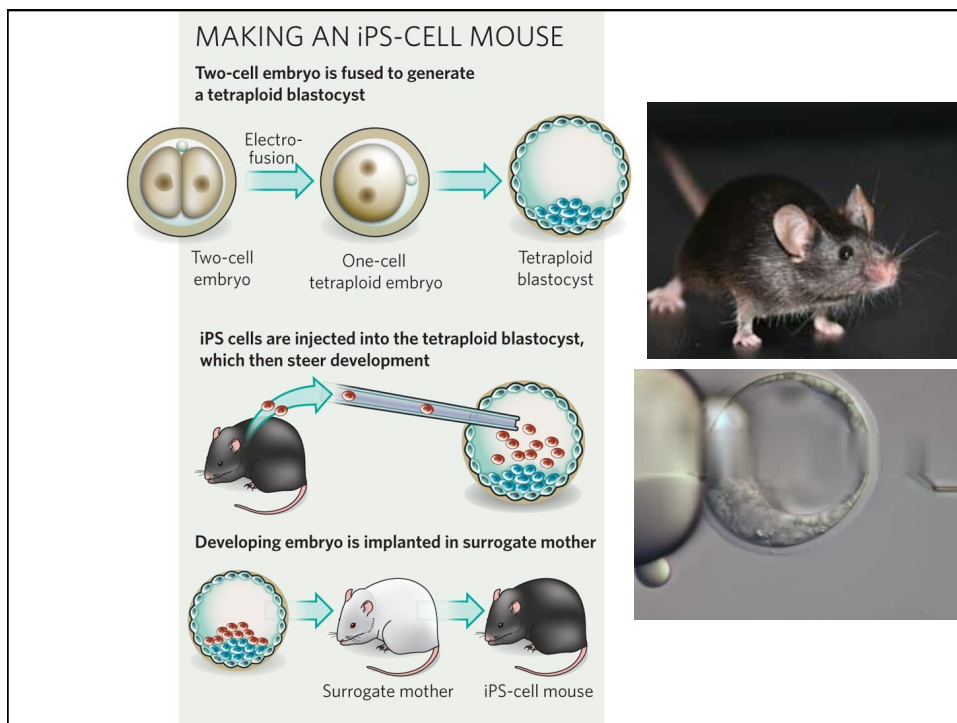
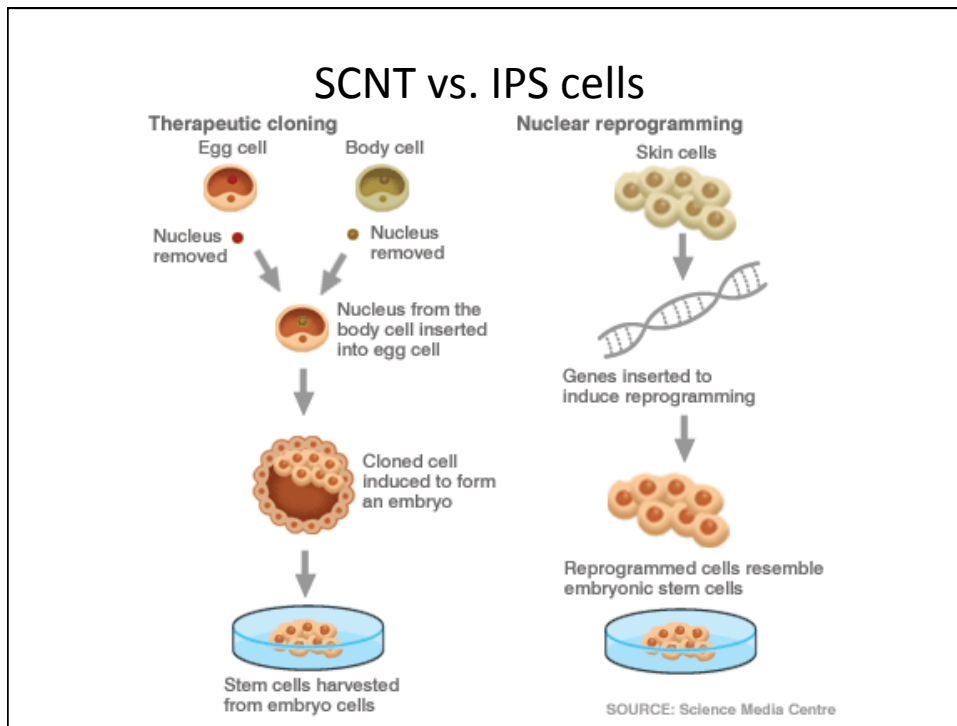
### Reprogramming Human Skin Cells

Researchers have developed a technique for creating stem cells without the controversial use of human eggs or embryos. If the method can be perfected, it could quell the ethical debate troubling the field.



TIMELINE

1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
<b>July 1995</b> Congress bans federal financing of research on human embryos.	<b>July 1996</b> Dolly is born. The lamb is the first clone of an adult mammal.		<b>Nov. 1998</b> First isolation and cultivation of embryonic stem cells. The cells are derived from fertilized human eggs.			<b>Aug. 2001</b> President Bush announces that federal money will pay for research on existing stem cell lines, but not new lines.			<b>Nov. 2004</b> California voters approve a measure to spend \$3 billion over 10 years on embryonic stem cell research.			<b>Nov. 2007</b> New Jersey voters reject a measure to borrow \$450 million for stem cell research.





Use iPS cells to study diseases!

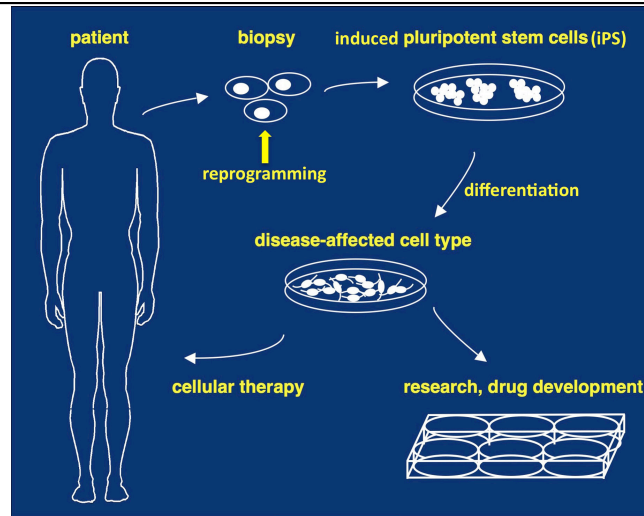


Table 1. iPS Cells Derived from Somatic Cells of Patients with Genetic Disease

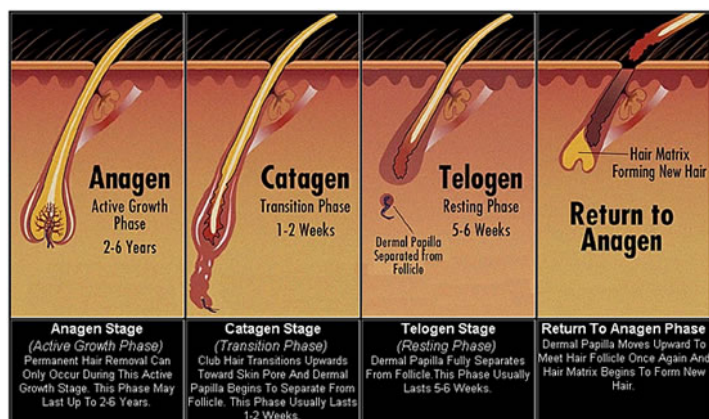
Name	Disease	Molecular Defect	Donor Cell	Age	Sex
ADA	ADA-SCID	GGG > AGG, exon 7 and Del(GAAGA) exon 10, ADA gene	Fibroblast	3 M	Male
GD	Gaucher disease type III	AAC > AGC, exon 9, G-insertion, nucleotide 84 of cDNA, GBA gene	Fibroblast	20 Y	Male
DMD	Duchenne muscular dystrophy	Deletion of exon 45-52, dystrophin gene	Fibroblast	8 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

What about “adult” stem cells?

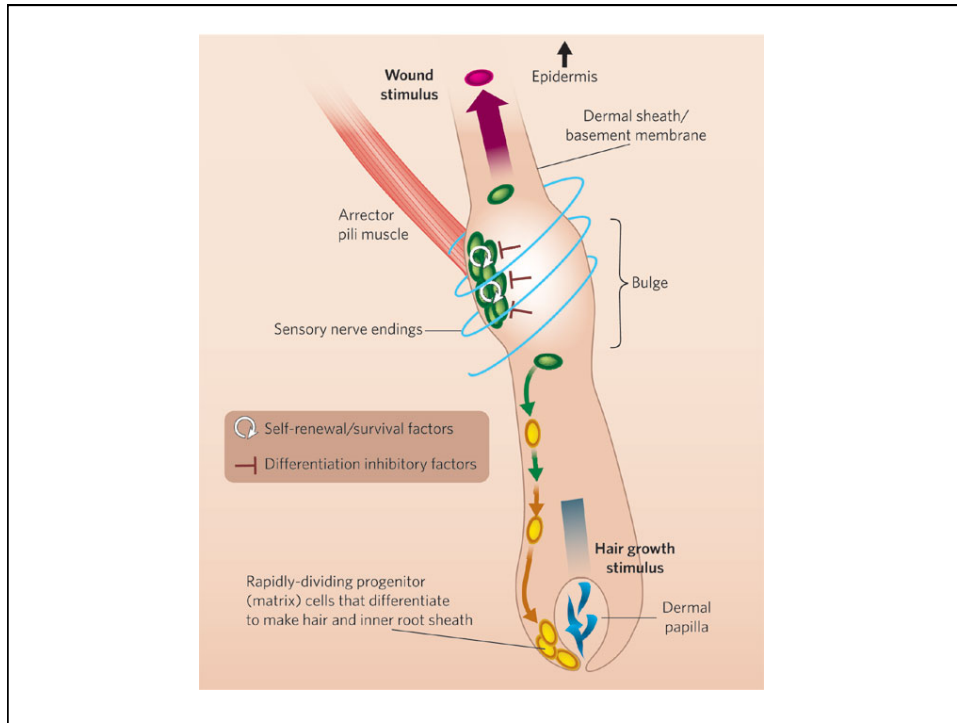
## Adult stem cells are...

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

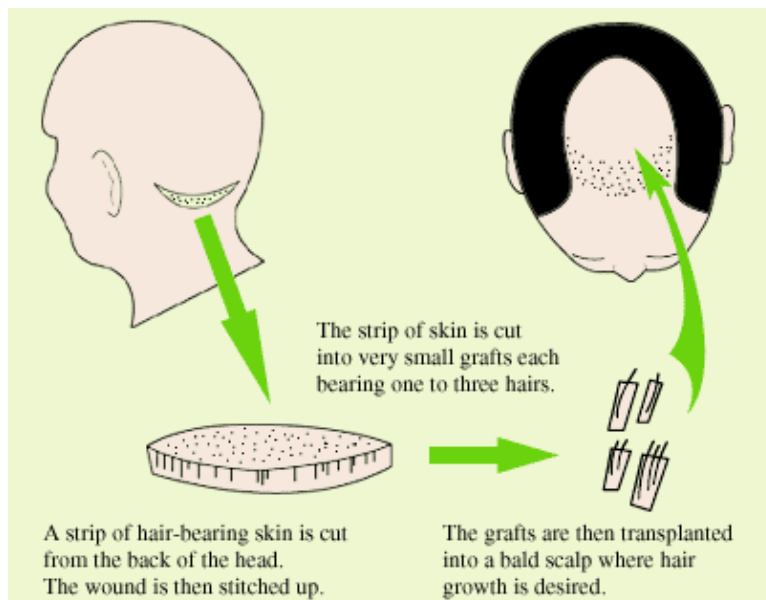
## Stem Cells in the Hair Follicle



Sorry Rapunzel!



## Hair Transplantation is Stem Cell Therapy!



## If we have adult stem cells, why do we need ES cells?

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

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?

What criteria should we use to define personhood?

## 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)

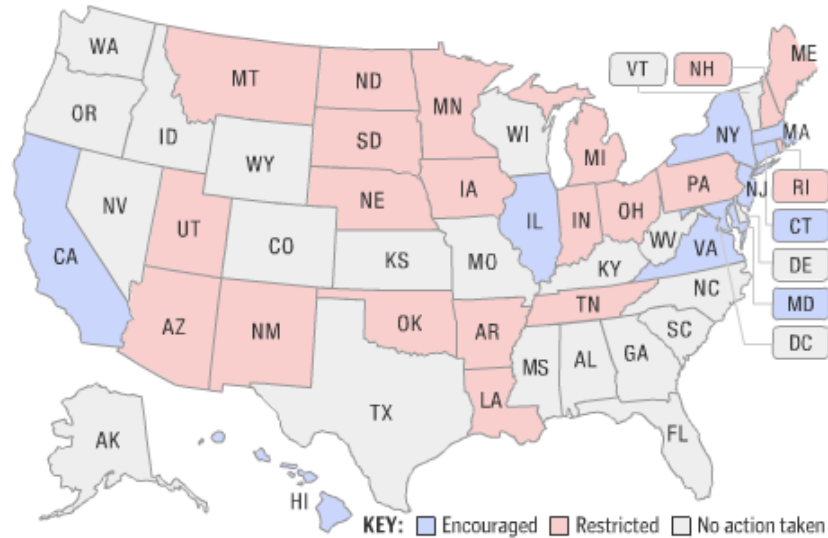
Prohibits Dept HHS appropriations for:

- (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

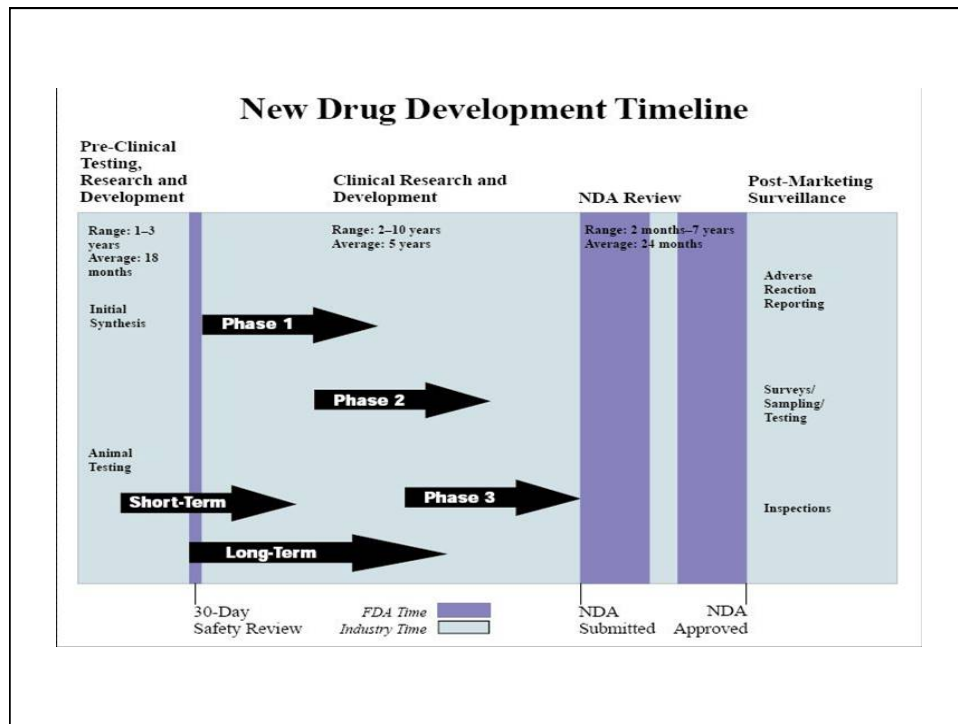
## Stem cell research policy by state:



## 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





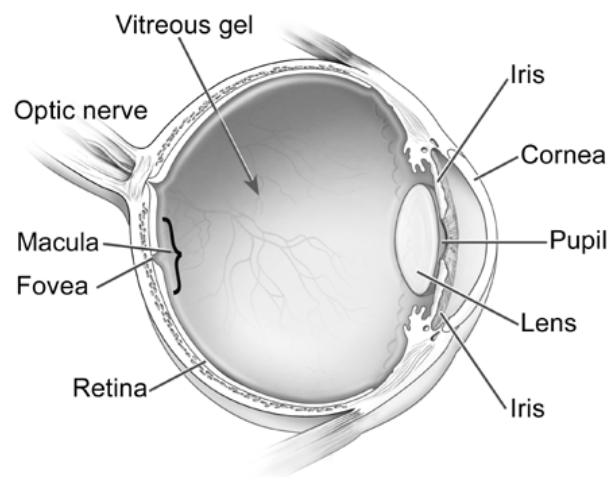
## Clinical Trials

- 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

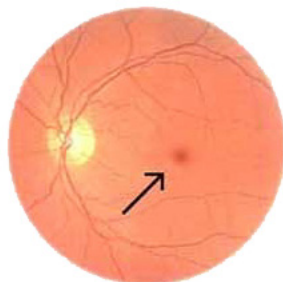


**Normal Vision**



**Macular Degeneration**

## Macular Degeneration

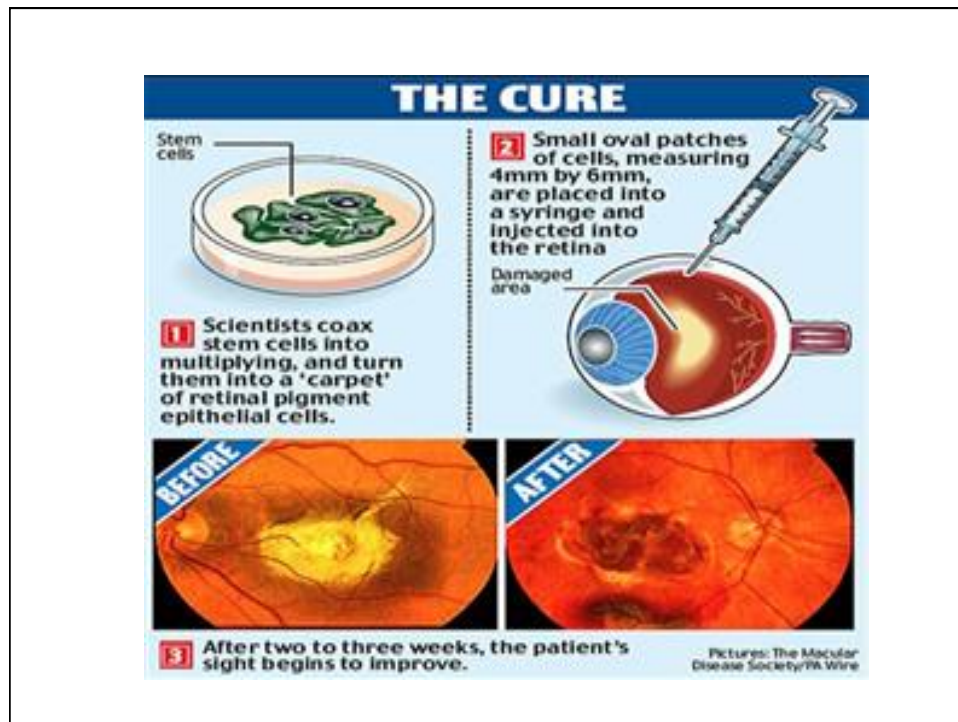


**Normal Macula**



**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

**ReLuma Stem Cell Skin Illuminating Anti-Aging Serum (1.1oz)**



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**The future of skin care...Today!**



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★★★★☆ 2 Reviews

**Price: \$245.00**

**FREE SHIPPING**

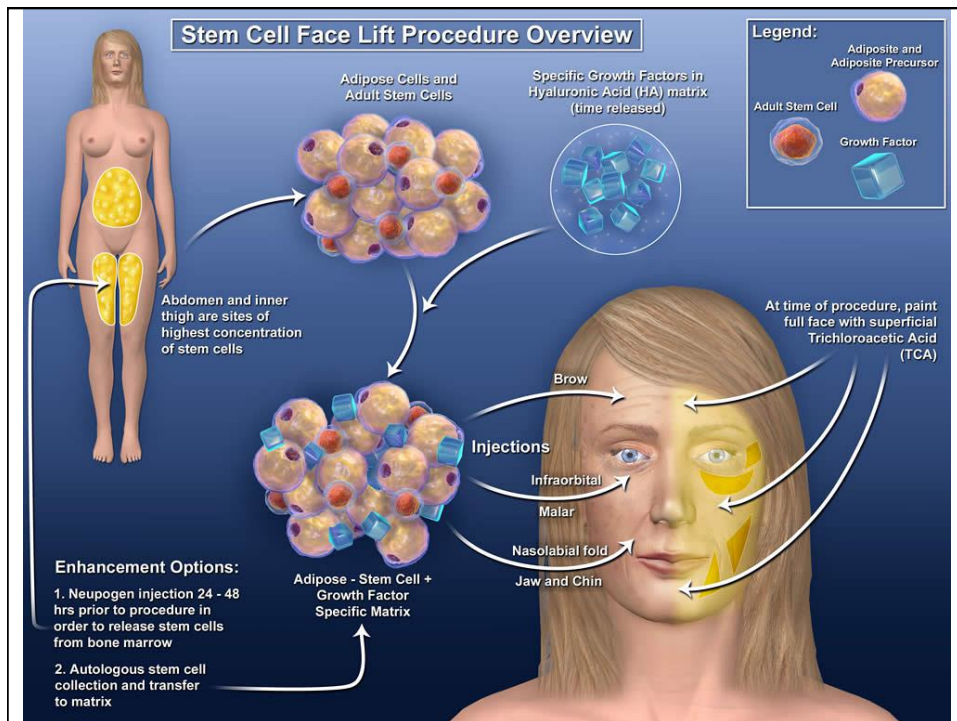
Quantity:

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**What it is:**  
A skin correcting, anti-aging cream for the face and throat.

**What it's used for:**  
DermaQuest Stem Cell 3D Complex is a revolutionary product that completely restores skin's youth, diminishes wrinkles and reverses skin damage. Biotech marine and botanical stem cell technology, powerful peptides, lighteners and antioxidants make this powerhouse product an aging skin's best friend.

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Video thumbnails with play buttons and a list of conditions: Multiple Sclerosis, Spinal Cord Injury, Rheumatoid Arthritis, Heart Failure, Chronic Fatigue

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