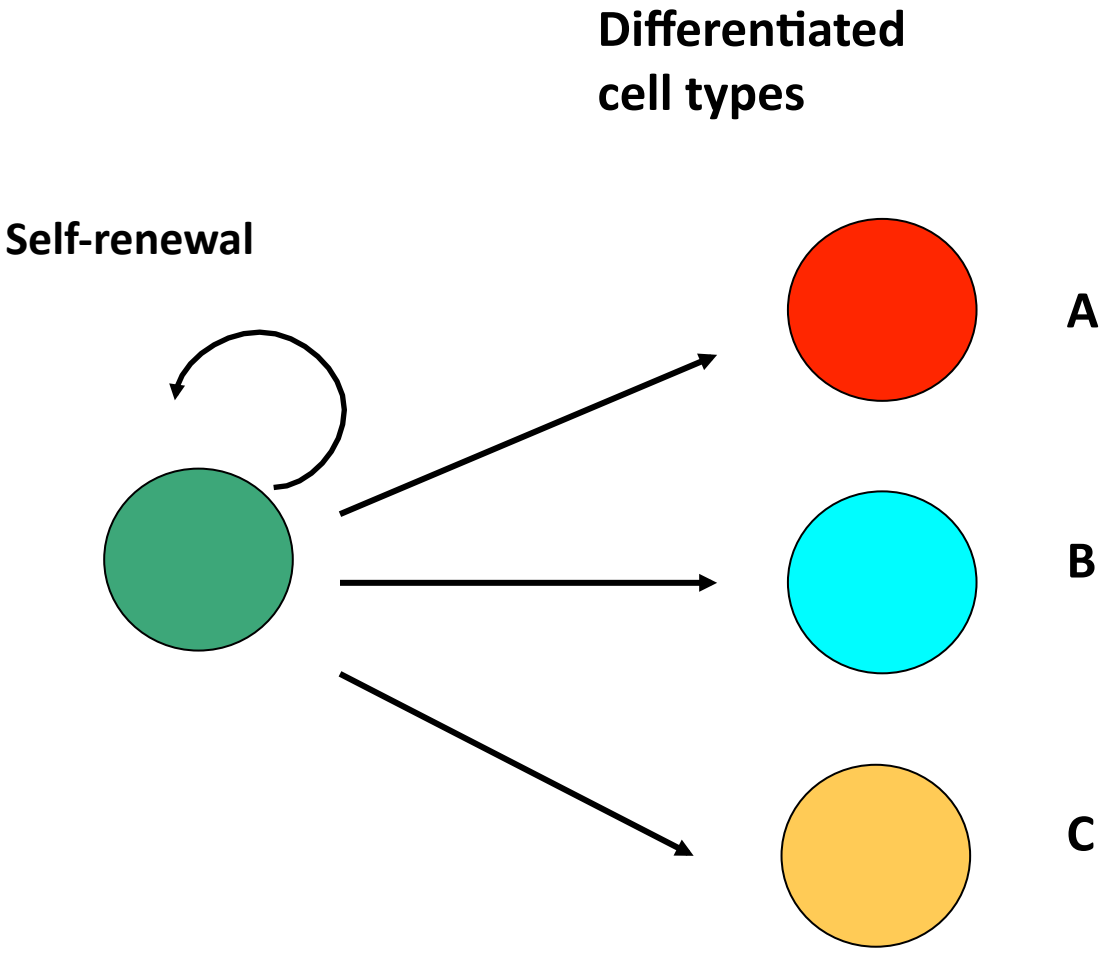
Stem Cells: Hype vs. Reality?

Dr. Pei Yun Lee

How long have doctors been using stem cells to treat disease?

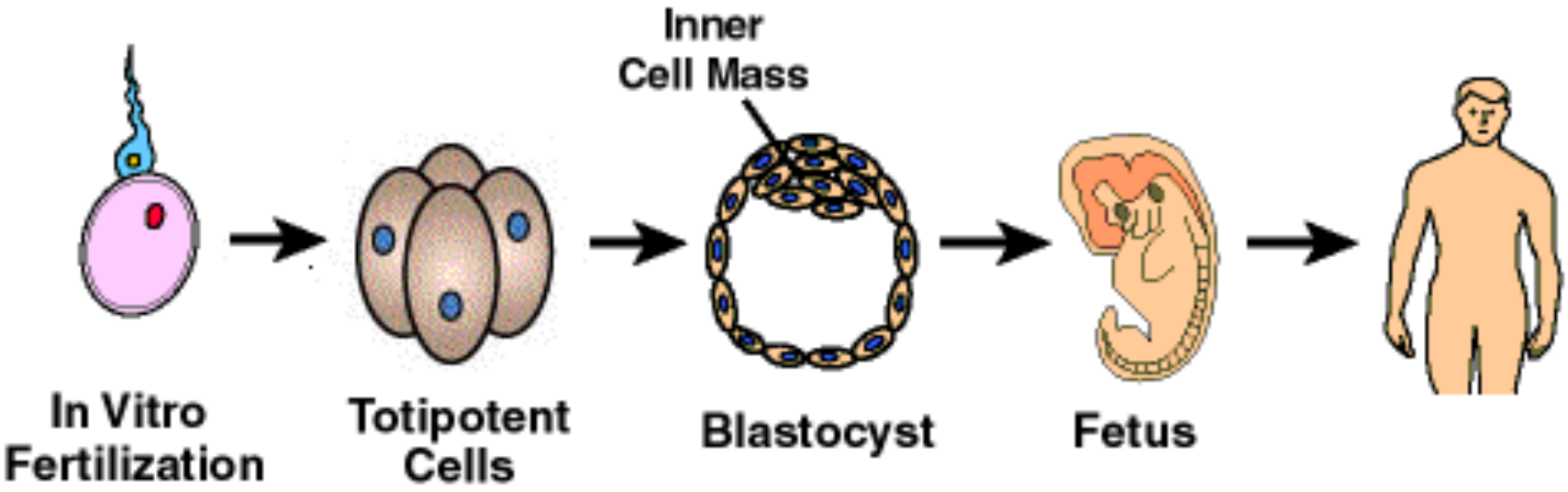
a) 5 years
b) 10 years
c) 20 years
d) 50 years
e) Still waiting for the day to come

What is a Stem Cell? What do they do?

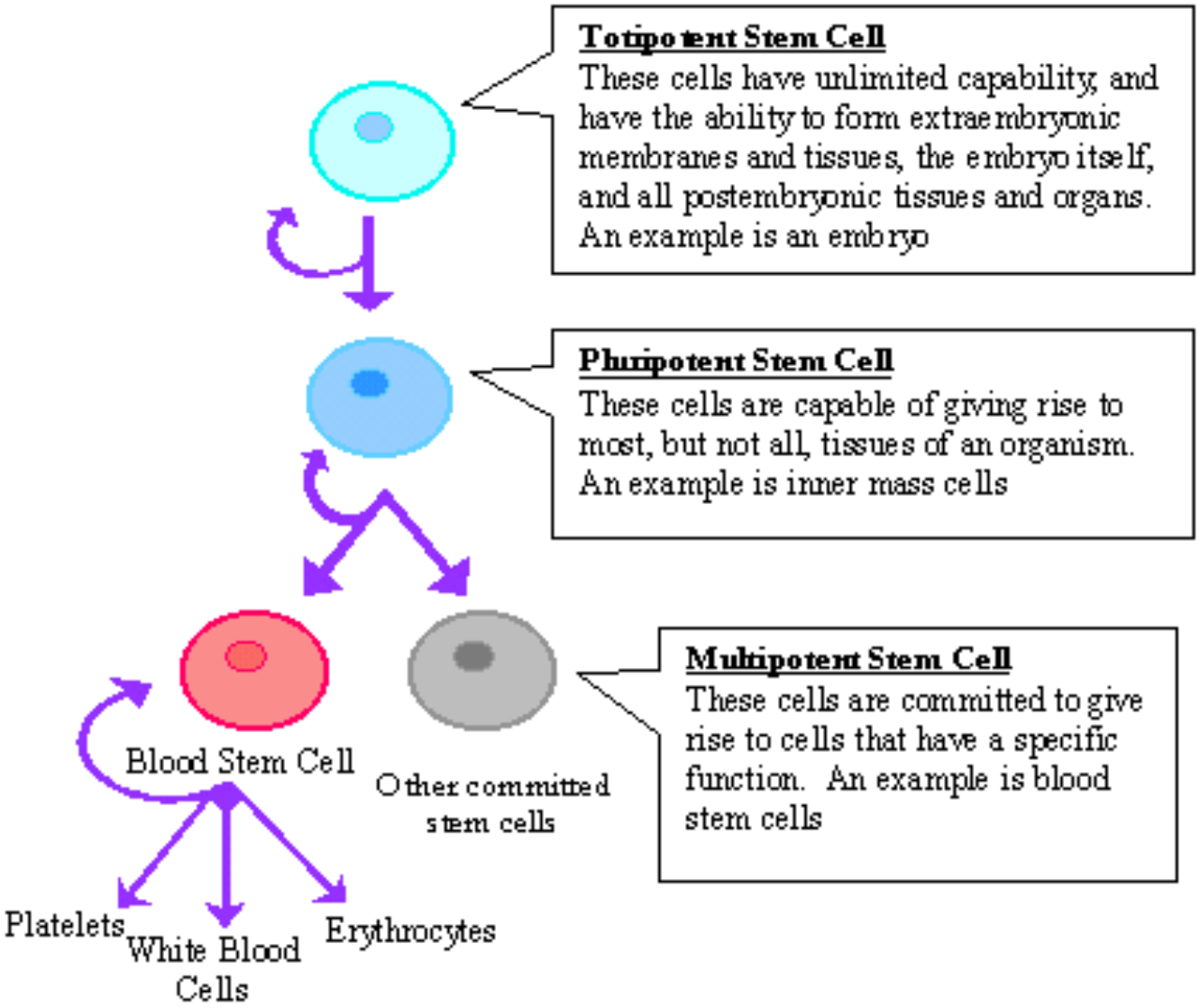


Ability to differentiate into different cell types
Ability to self renew

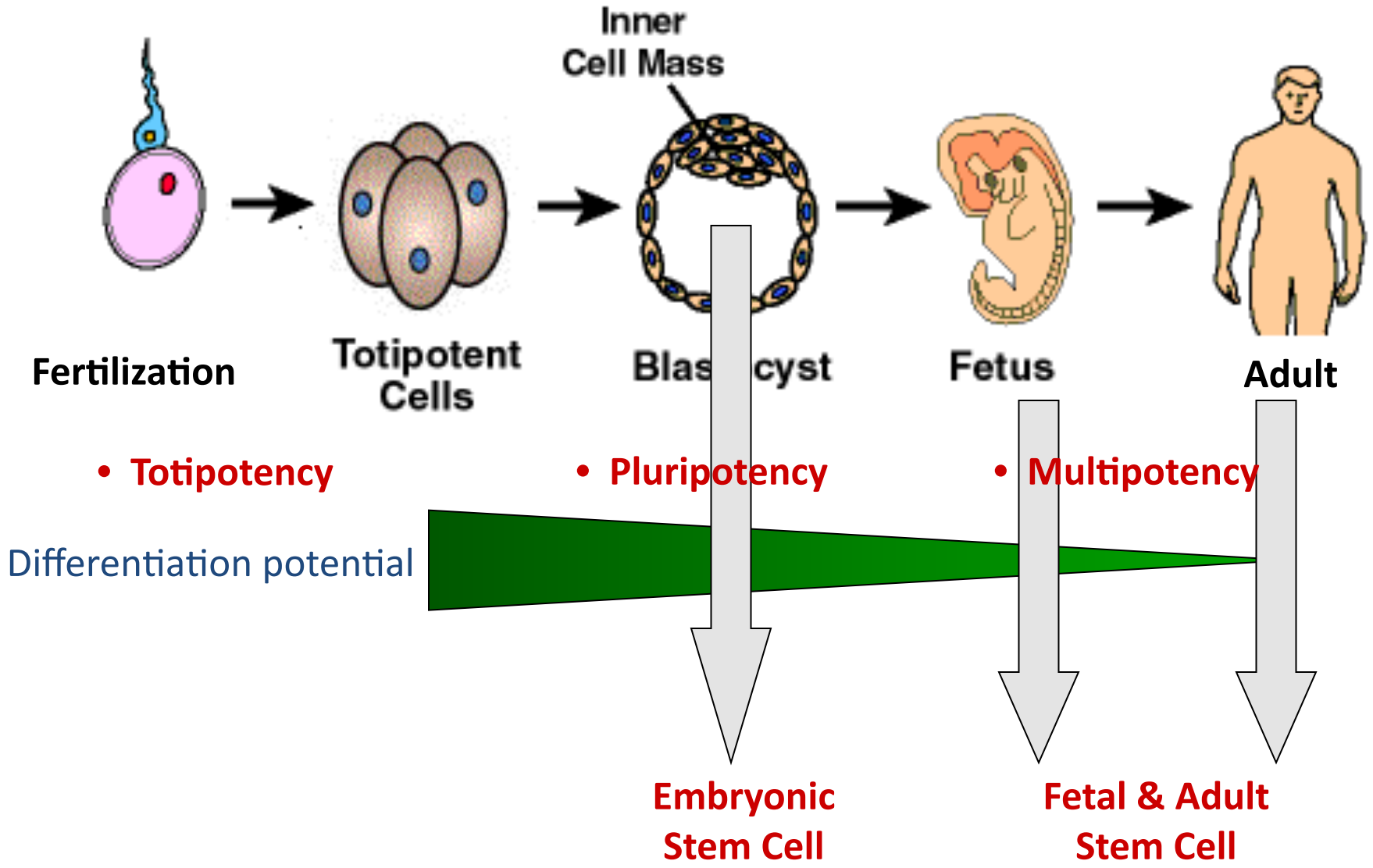
Where can stem cells be found?



Stem cells have different developmental potentials



Progressive Restriction of Differentiation Potential



How were stem cells discovered?

Alexander Maximow 1909

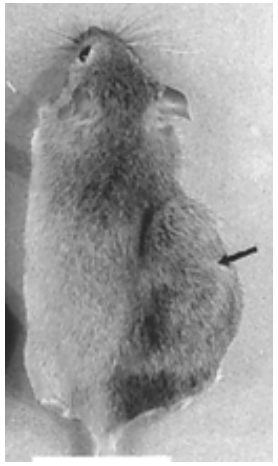
Unitarian theory of hematopoiesis (blood formation)

-all blood cells descended from a common precursor “stem” cell

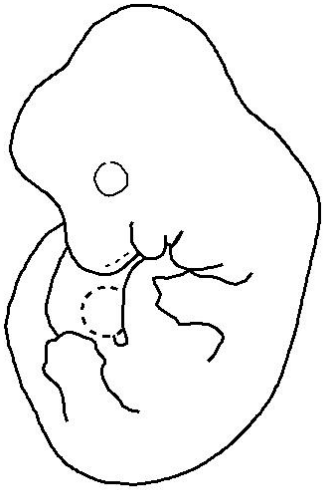
Leroy Stevens

Dissect and expose to mouse

Observe for cancer

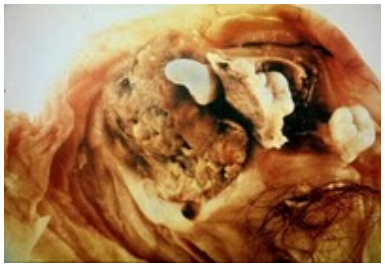


Bred mice and select for cancer



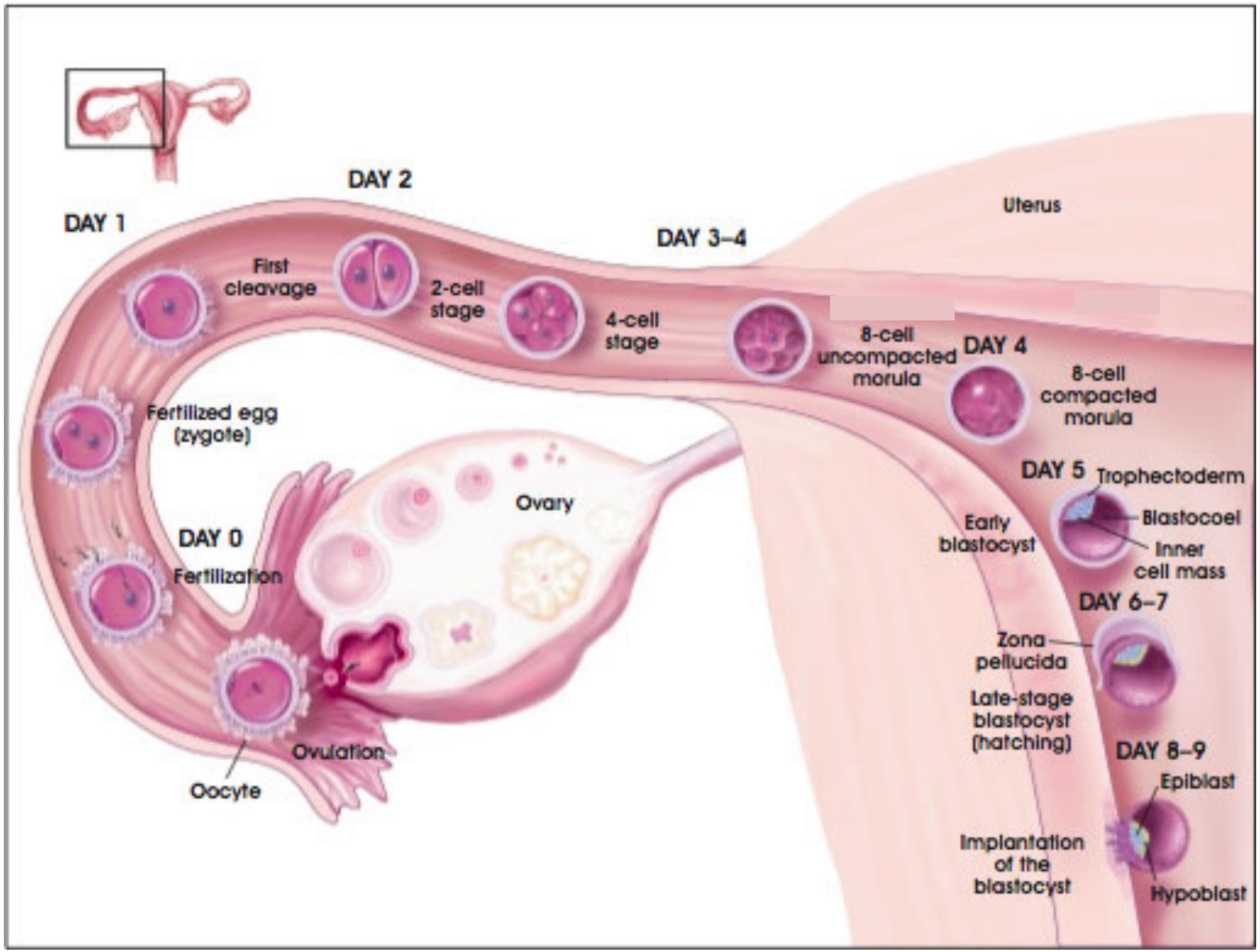
Isolate cells from mouse embryos

Transplant into adult mouse testes

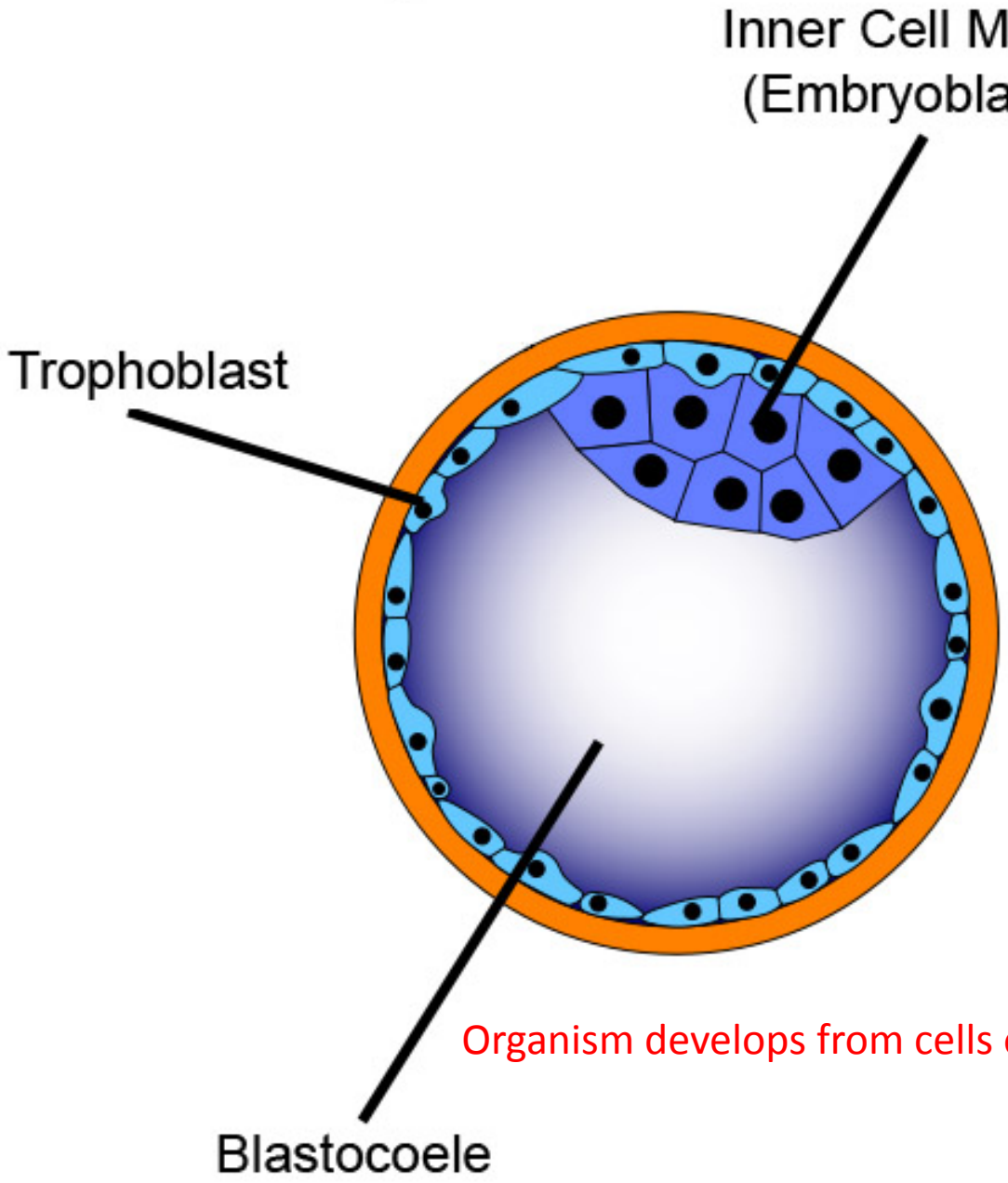


Teratomas!

What developmental stage is a blastocyst?



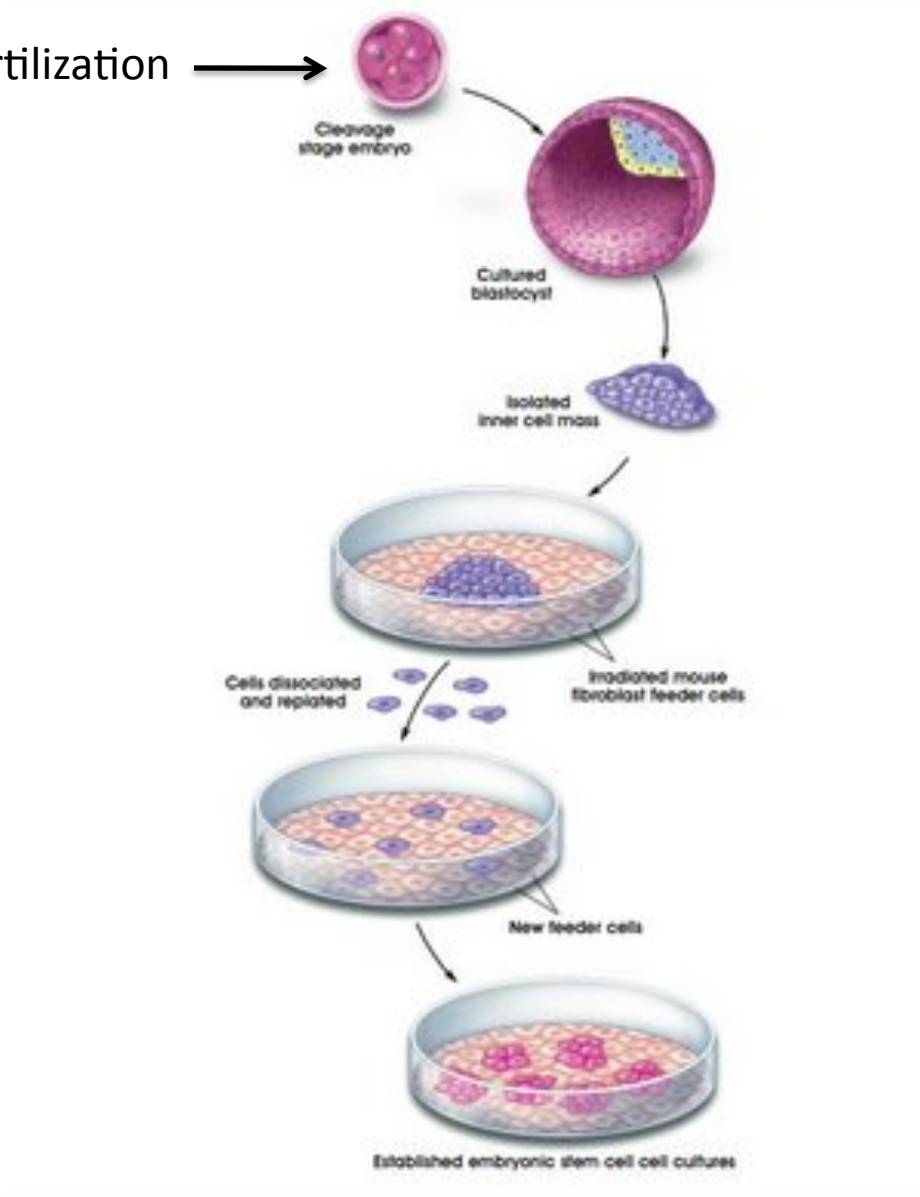
The Blastocyst

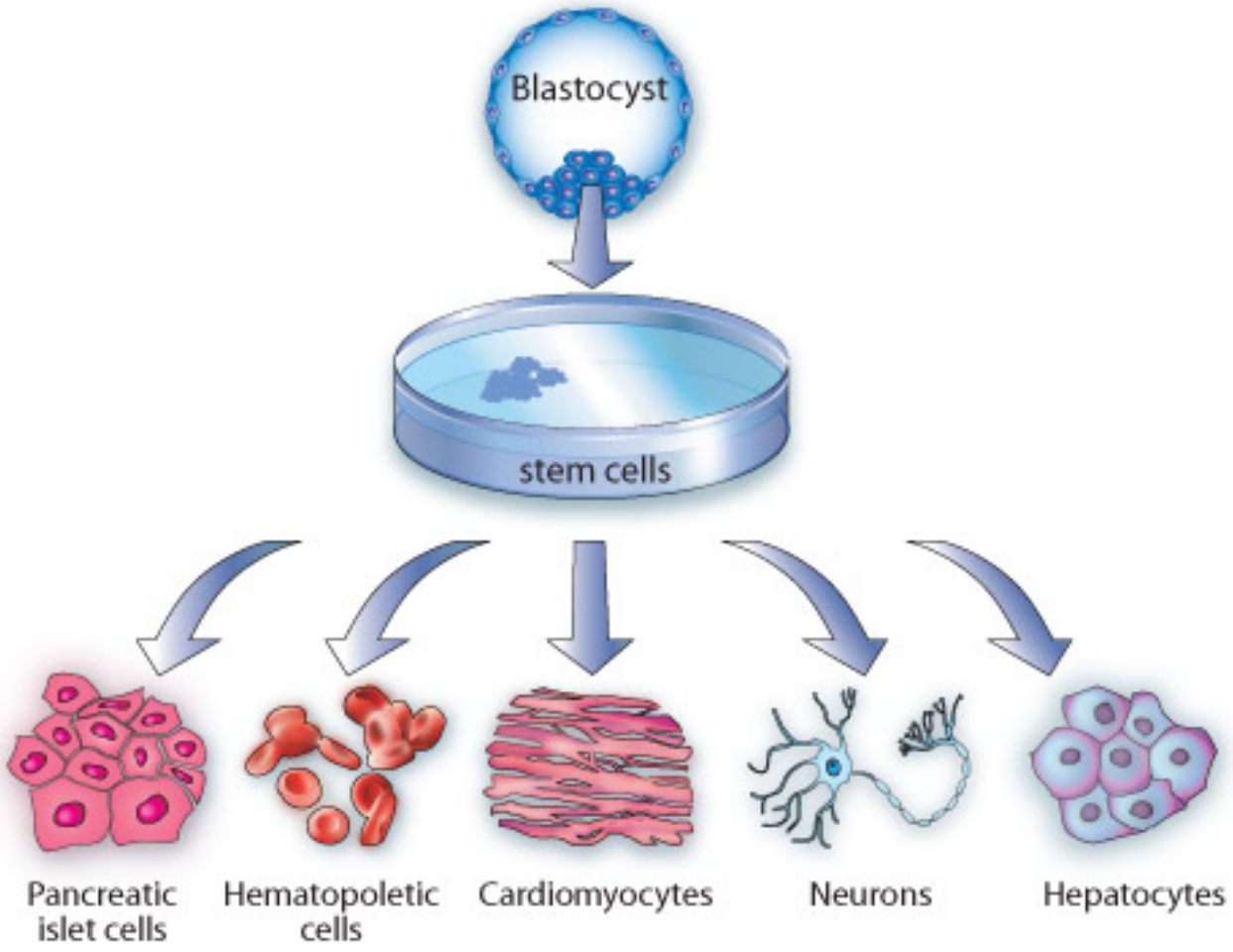


Organism develops from cells of the inner cell mass

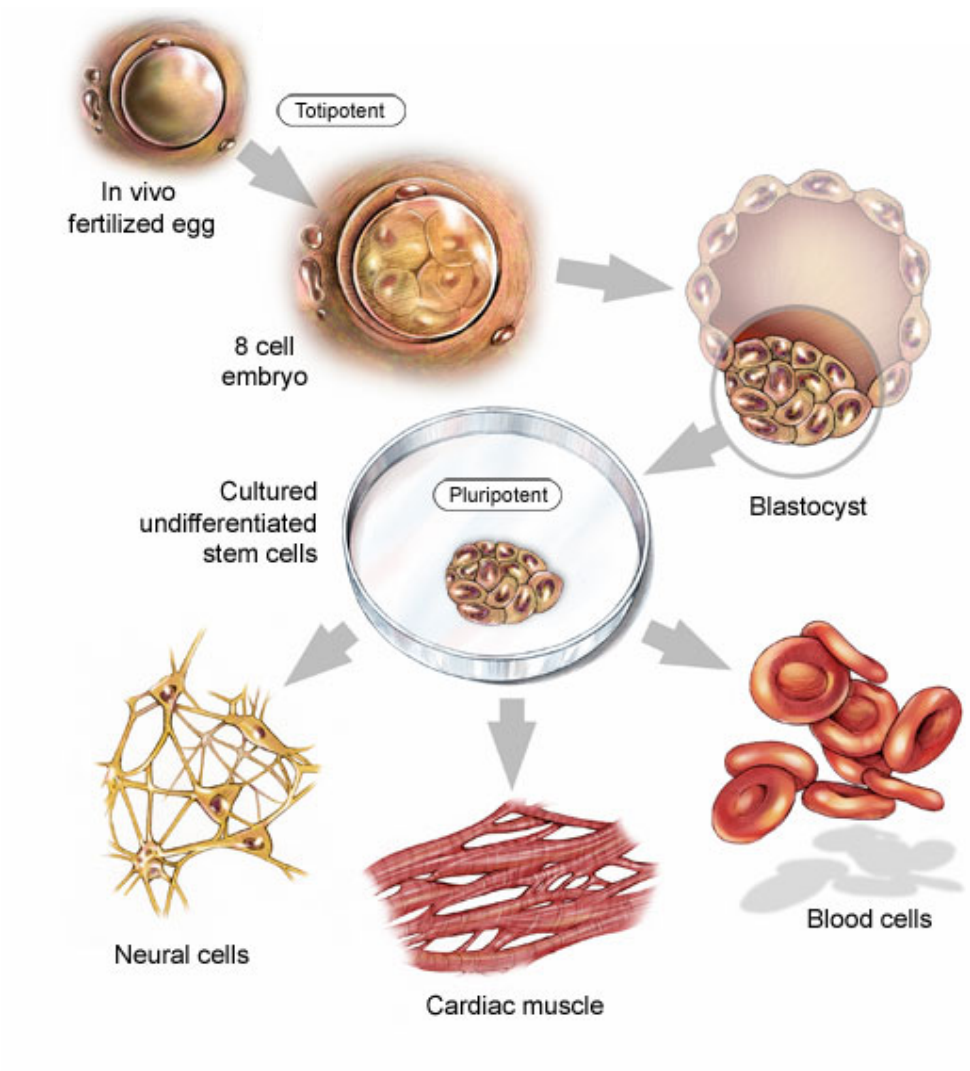
How are embryonic stem cells isolated?

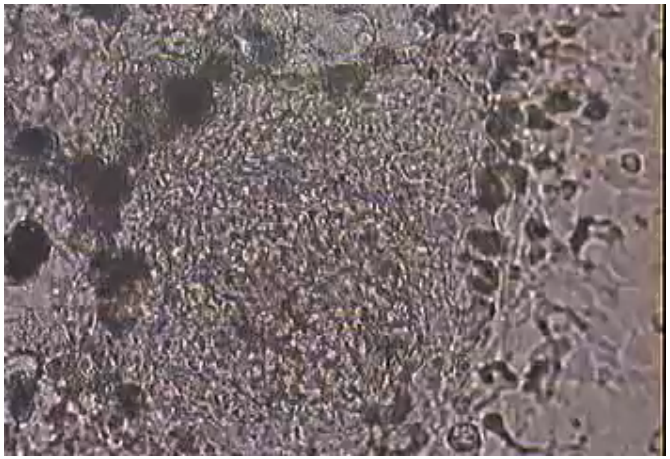
In vitro fertilization →

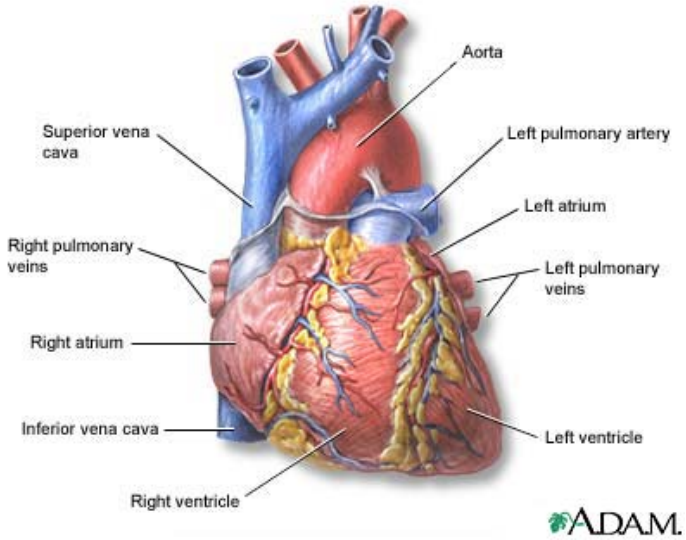



Blastocyst
stem cells
Pancreatic islet cells
Hematopoletic cells
Cardiomyocytes
Neurons
Hepatocytes

Beating heart muscle from ES cells!







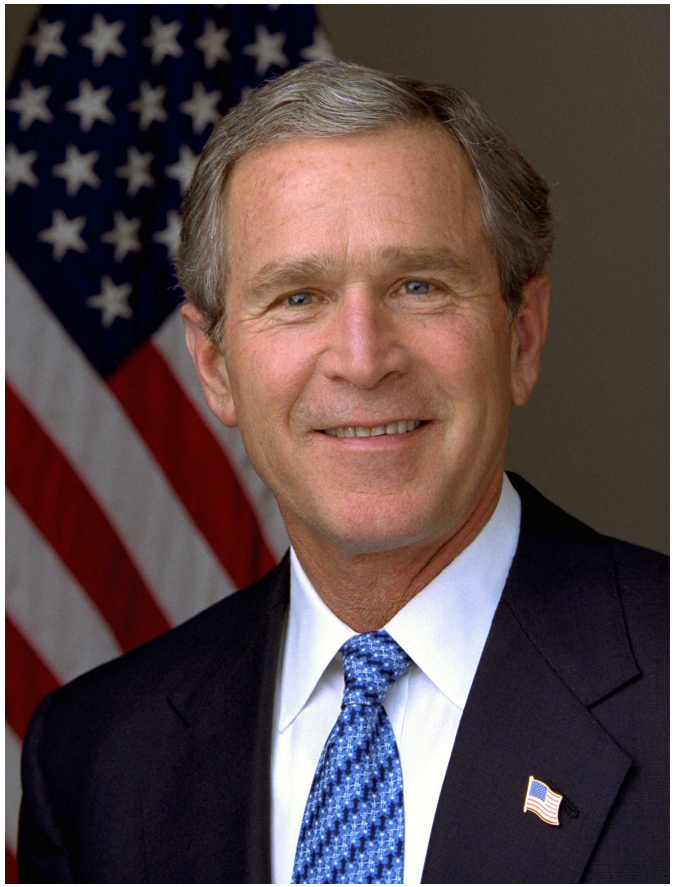
Do you think that the blastocyst embryo has the same moral status as a person, and therefore the same rights and privileges?

a) Yes
b) No
c) Not sure/don't know

When does the human entity acquire “moral status” as a person?

a) Fertilization
b) Implantation in uterus
c) Ability to survive outside uterus
d) Birth
e) Development of self awareness

Policy under George W. Bush



August 9, 2001

Federal funds may be awarded for research using human embryonic stem cells if the following criteria are met:

- The derivation process (which begins with the destruction of the embryo) was initiated prior to 9:00 P.M. EDT on August 9, 2001.
- The stem cells must have been derived from an embryo that was created for reproductive purposes and was no longer needed.
- Informed consent must have been obtained for the donation of the embryo and that donation must not have involved financial inducements.

June 22, 2007

Executive order 13435

- For purposes of this order, the term ''human embryo'' shall mean any organism, not protected as a human subject under 45 CFR 46 as of the date of this order, that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells.

Fertilization to implantation!

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

- 8/23/2010—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

Should the government restrict certain types of research?

a) Yes
b) No

Who should determine the types of research that can/ cannot be carried out?

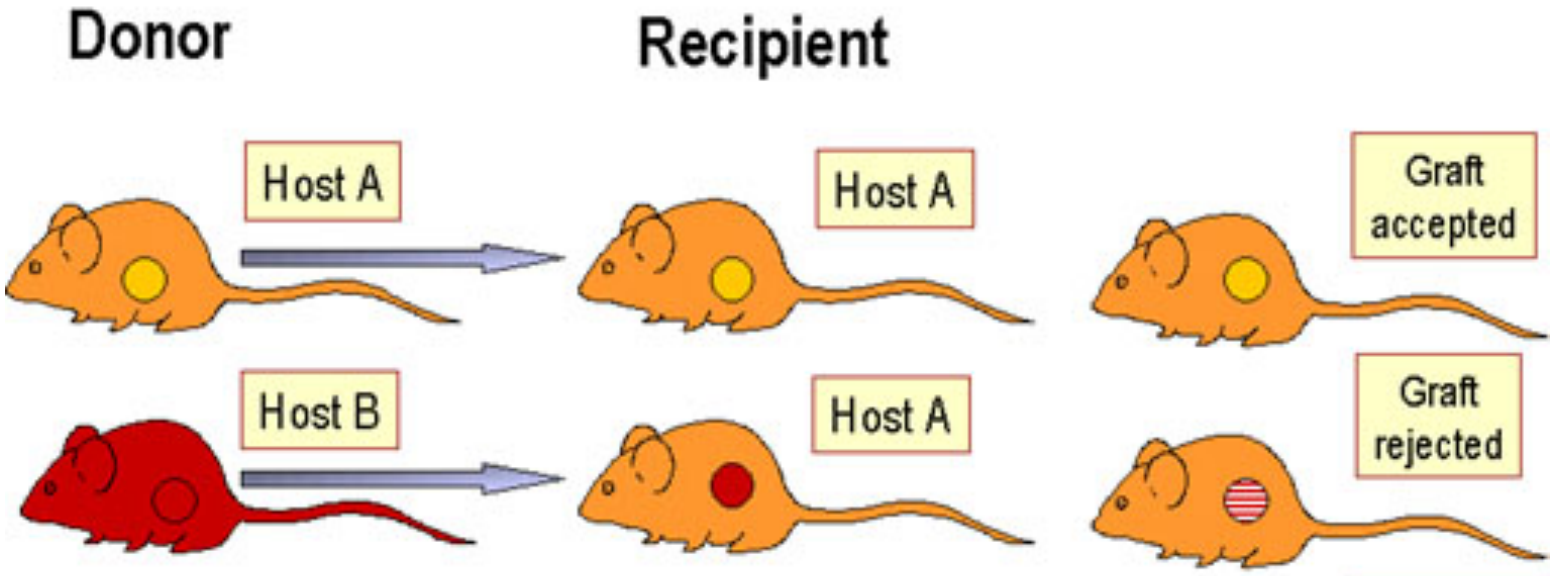
a) Scientists
b) Legislators
c) Ethicists
d) The people
e) All of the above

Should there be restrictions on stem cell research/funding for stem cell research?

a) Yes
b) No

If we already have stem cell lines, why do we need to create more ES lines or clone embryos?

Our bodies can recognize self vs non-self



Human MHC genes are highly polymorphic

Table 17.3

MHC Class II Alleles

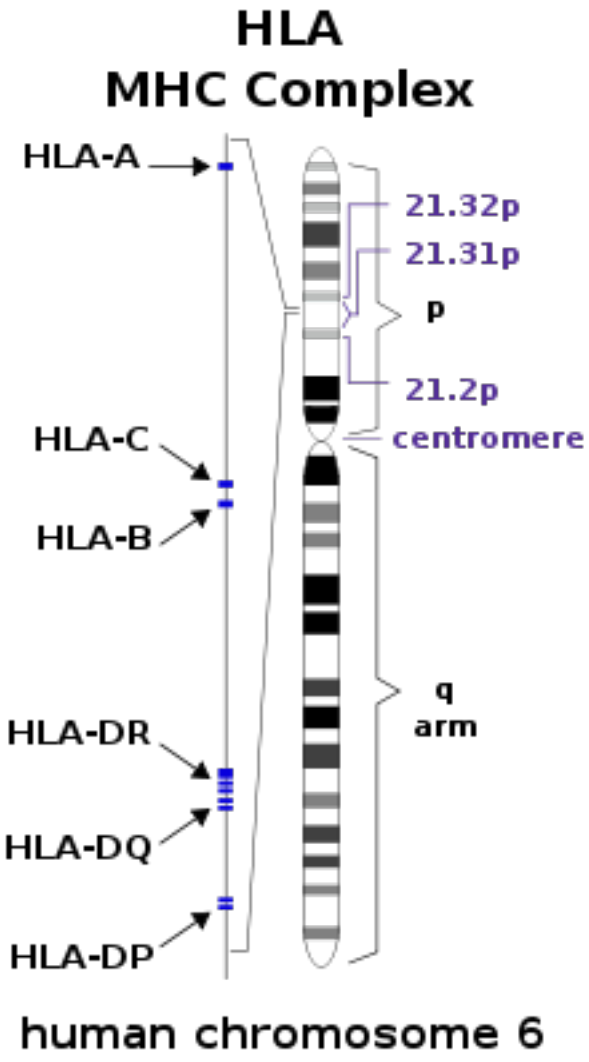
	Locus	Number of Alleles
	HLA-DRA	3
*	HLA-DRB	542
	HLA-DQA	34
	HLA-DQB	73
	HLA-DPA	23
	HLA-DPB	125
	HLA-DMA	4
	HLA-DMB	7
	HLA-DOA	12
	HLA-DOB	9

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.

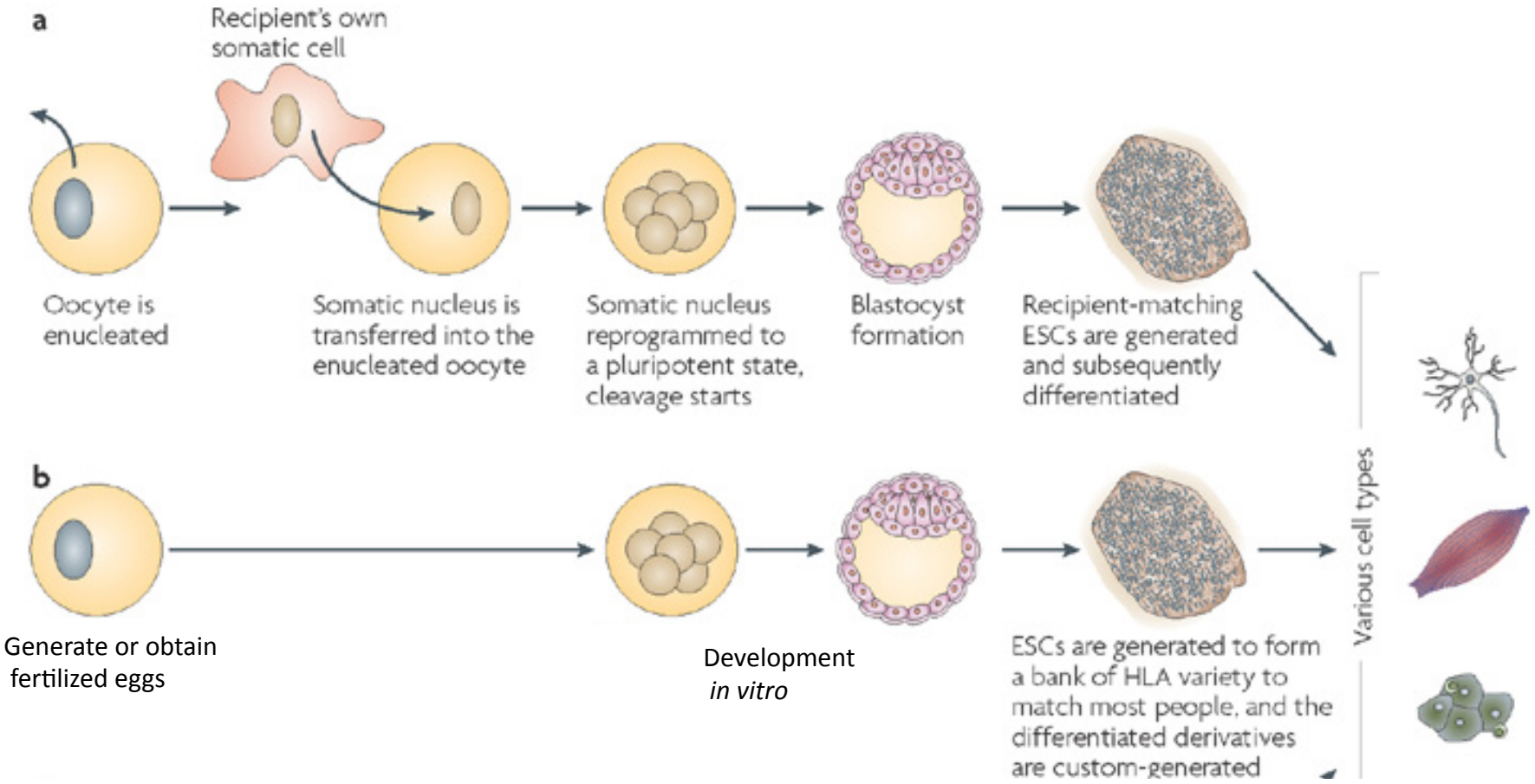
Table 17-3 Cell and Molecular Biology, 5/e (© 2008 John Wiley & Sons)

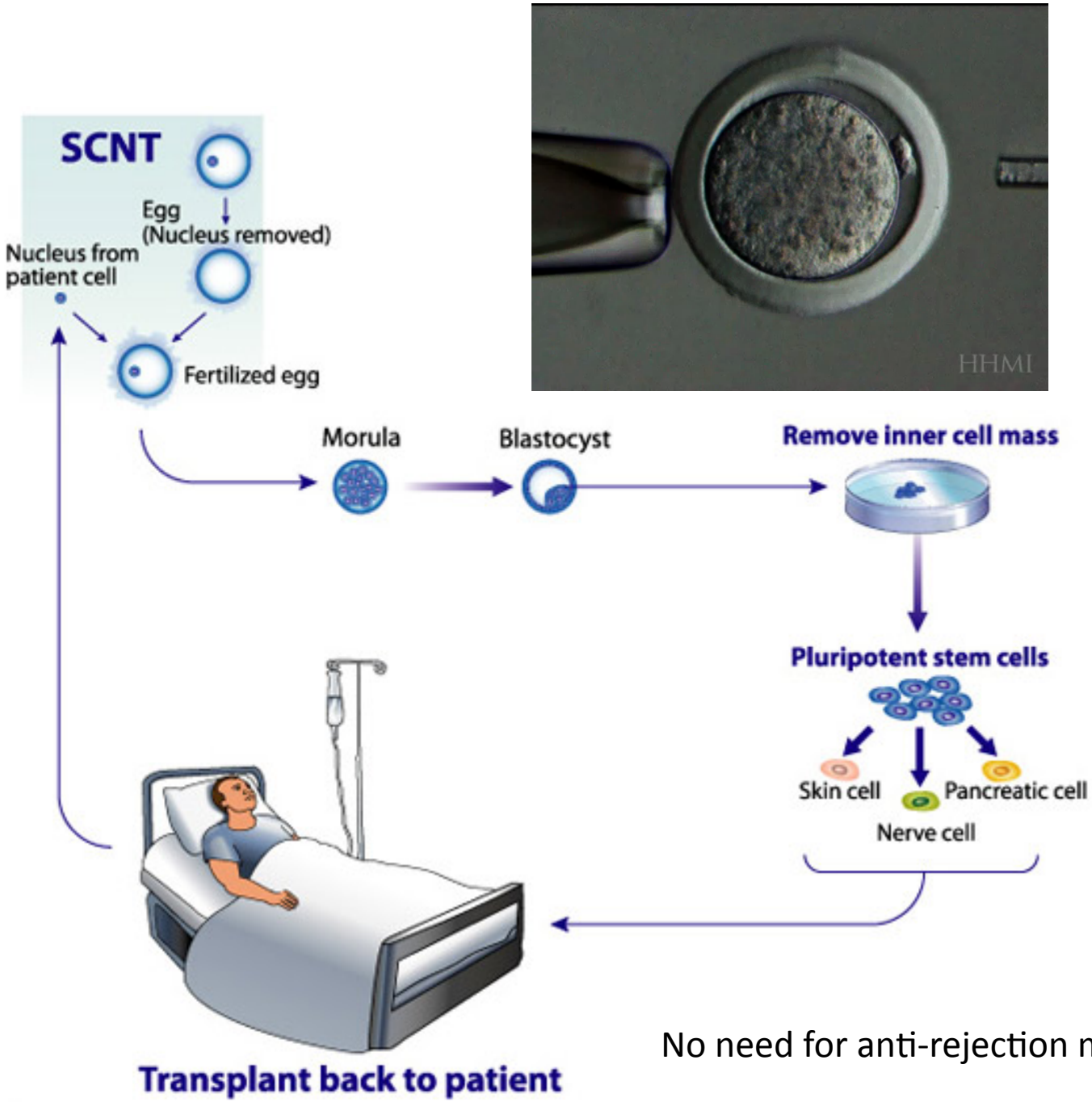


Solutions to the Tissue Rejection Problem

- 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!

Using ES cells to treat disease



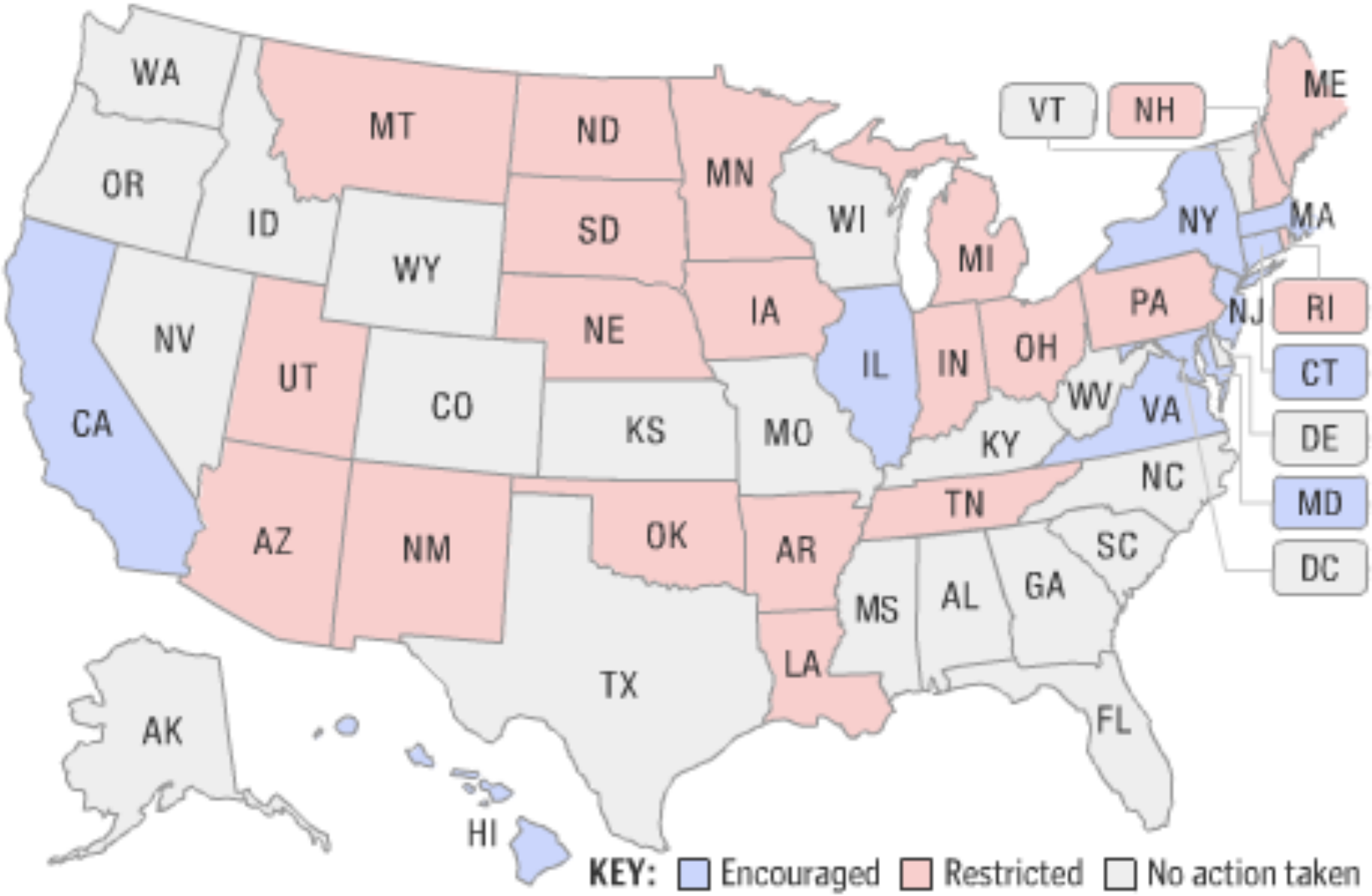


No need for anti-rejection medication!

State restrictions to research on embryos

- AR, IN, LA, MI, and ND have banned research on cloned embryos
- MO, MN, OH and PA have laws against research on embryos
- AZ and NE prohibits use of public monies for reproductive cloning

Stem cell research policy by state:

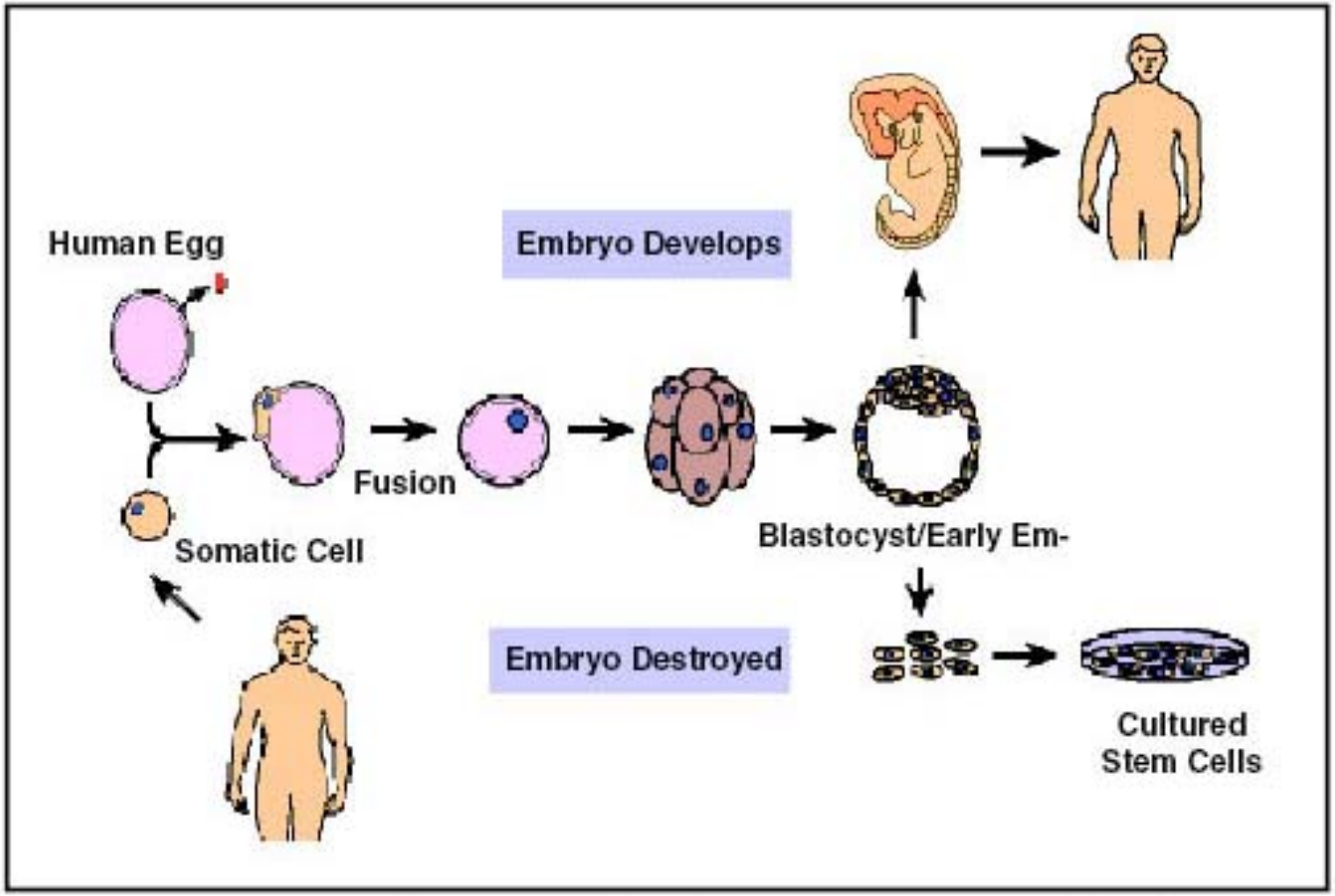


Reproductive vs. Therapeutic Cloning

Reproductive cloning: to generate an animal that has the same nuclear DNA as another currently or previously existing animal.

Therapeutic cloning: also called "embryo cloning," is the production of human embryos for use in research. The goal of this process is not to create cloned human beings, but rather to harvest stem cells that can be used to study human development and to treat disease.

SCNT CLONING OPTIONS



Graphic courtesy National Institue of Health, US Department of Health and Human Services (adapted).

If you have the means to do so, will you clone a pet or a person?

a) Yes, a pet
b) Yes, a person
c) Yes, anything goes!
d) No way!

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

Should reproductive cloning be illegal?

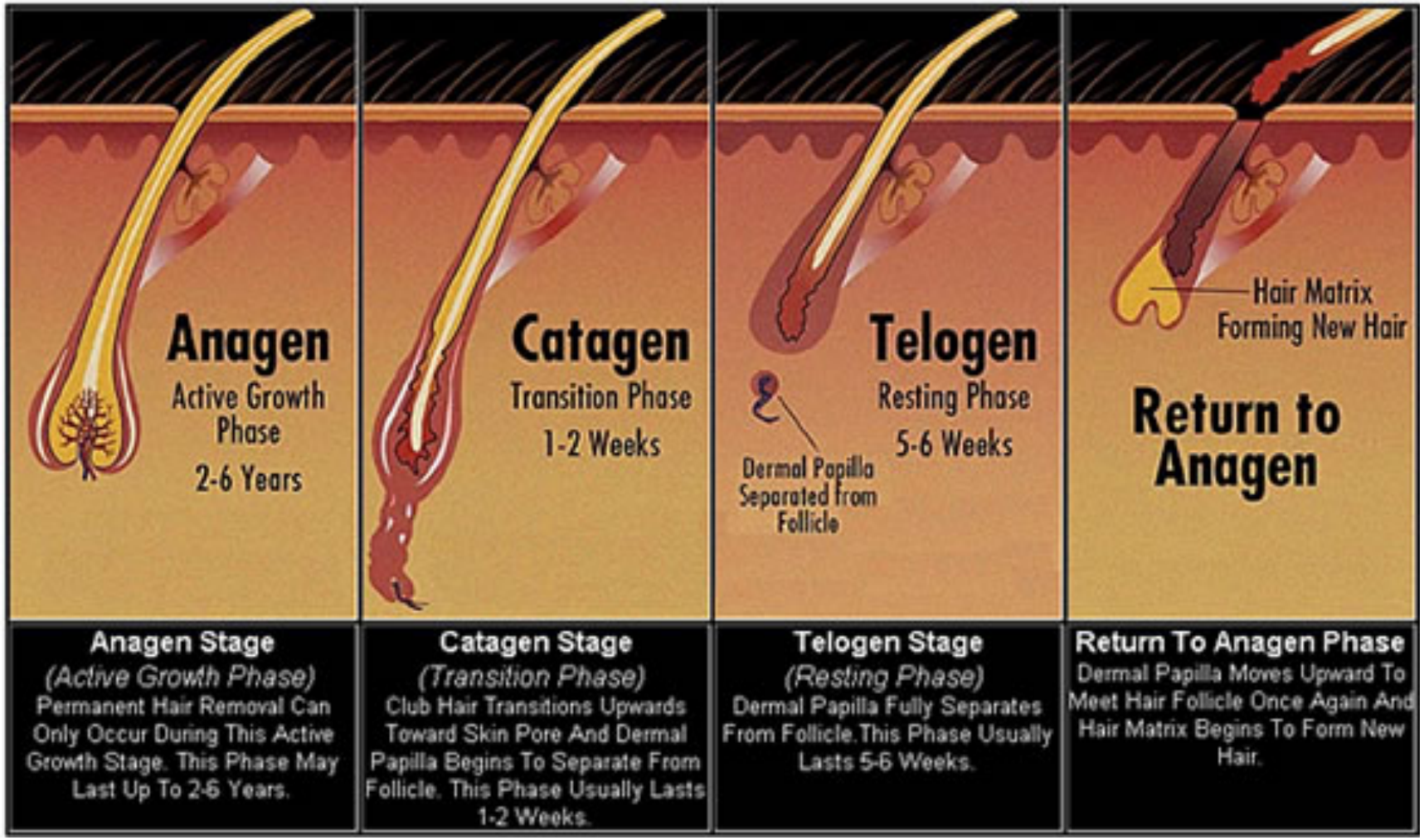
a) Yes
b) No
c) Don’t know/not sure

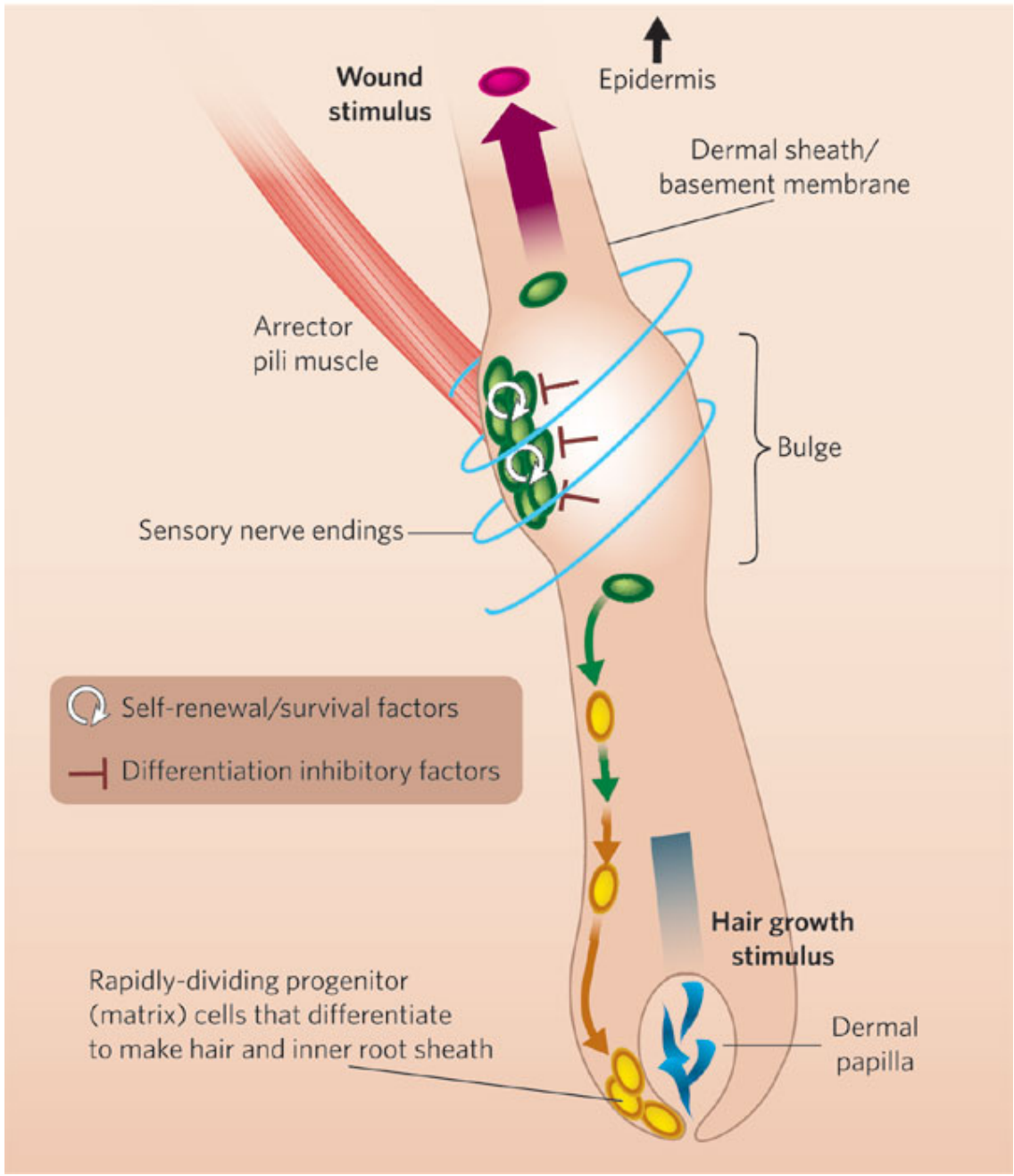
How about “adult” stem cells?

Adult stem cells are…

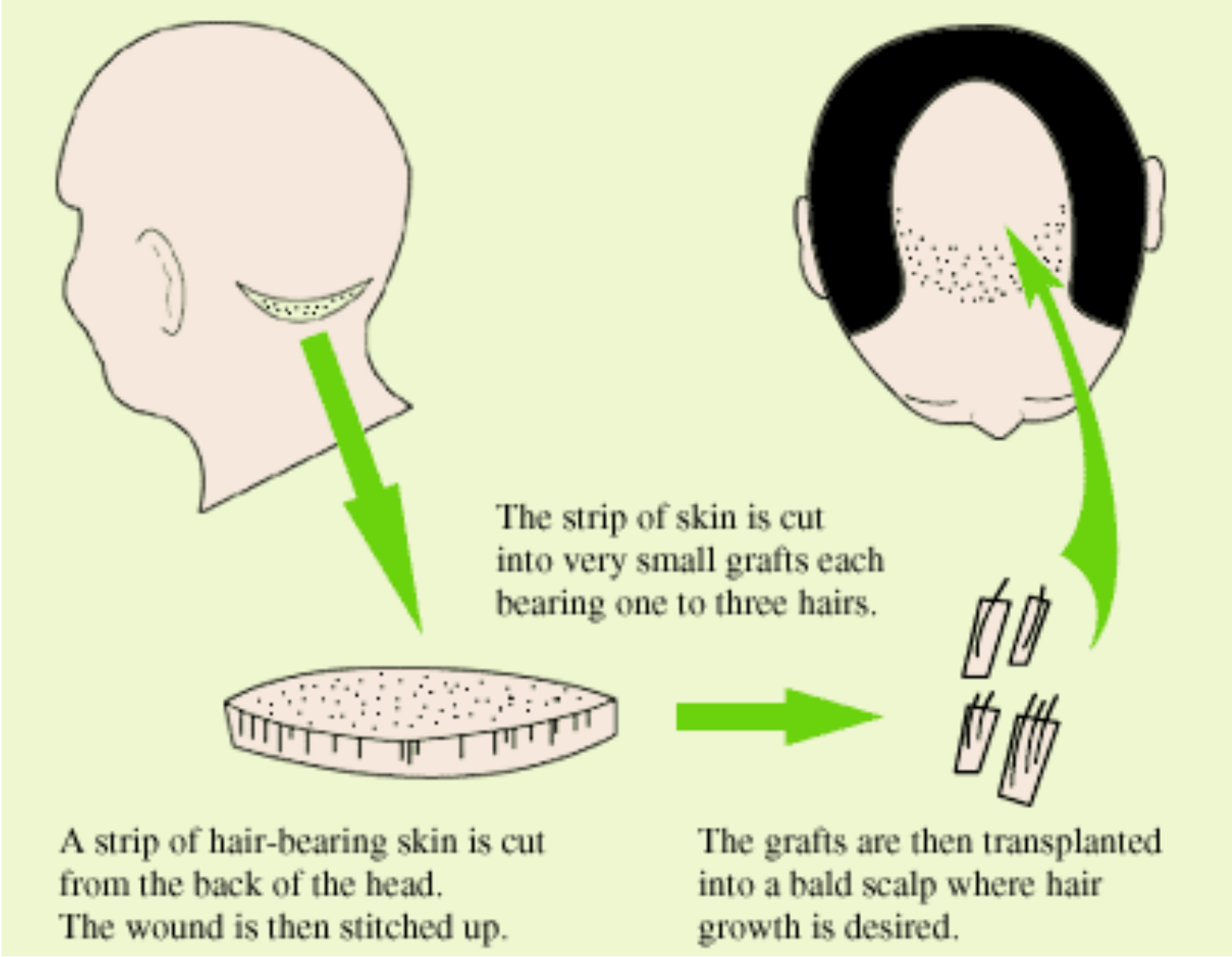
- Also present in children
- Have limited differentiation potential, usually restricted to a few cell types

Stem Cells in the Hair Follicle




Wound stimulus
Epidermis
Dermal sheath/ basement membrane
Arrector pili muscle
Bulge
Sensory nerve endings
Self-renewal/survival factors
Differentiation inhibitory factors
Hair growth stimulus
Rapidly-dividing progenitor (matrix) cells that differentiate to make hair and inner root sheath
Dermal papilla

Hair Transplantation is Stem Cell Therapy!



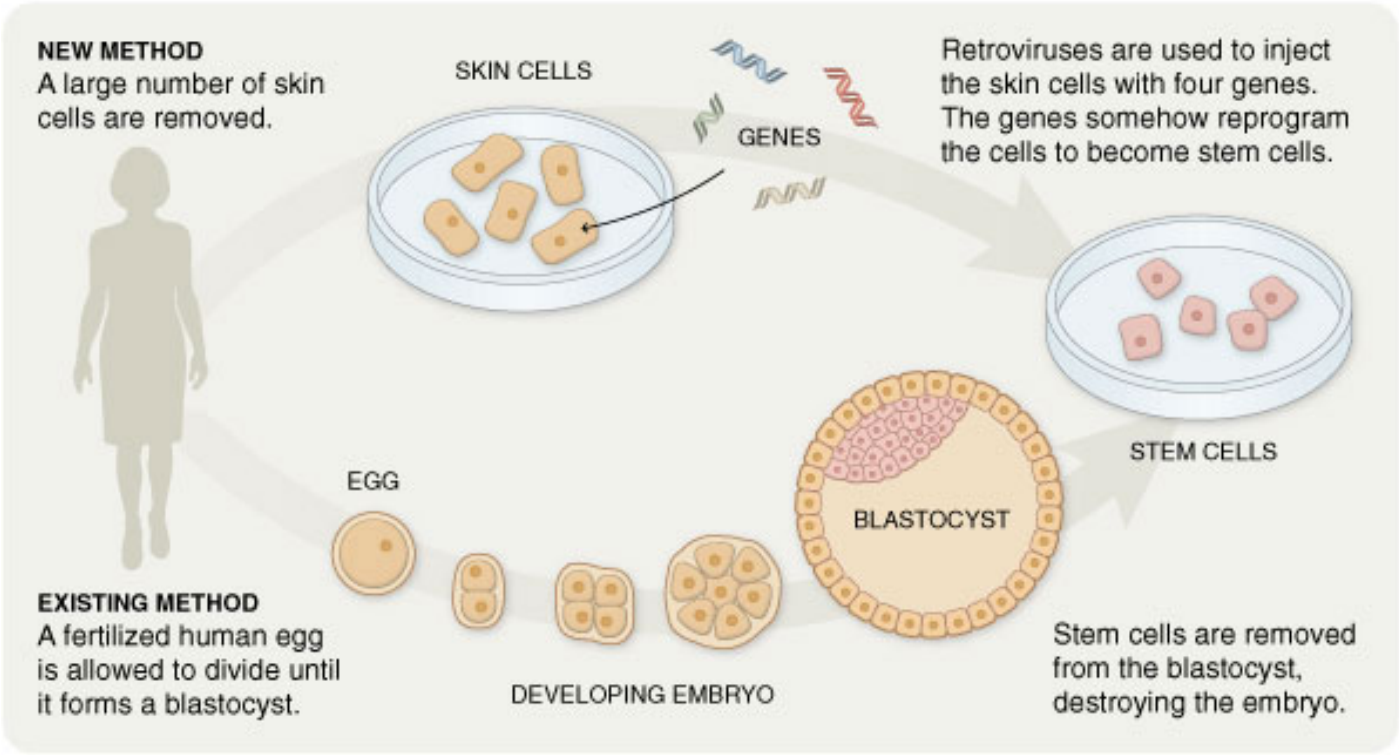
If we have adult stem cells, why do we need ES cells?

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

Since the nucleus contains all the genetic information to create a new organism, can we get a fully differentiated cell to become pluripotent?

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

July 1995
Congress bans federal financing of research on human embryos.

July 1996
Dolly is born. The lamb is the first clone of an adult mammal.

Nov. 1998
First isolation and cultivation of embryonic stem cells. The cells are derived from fertilized human eggs.

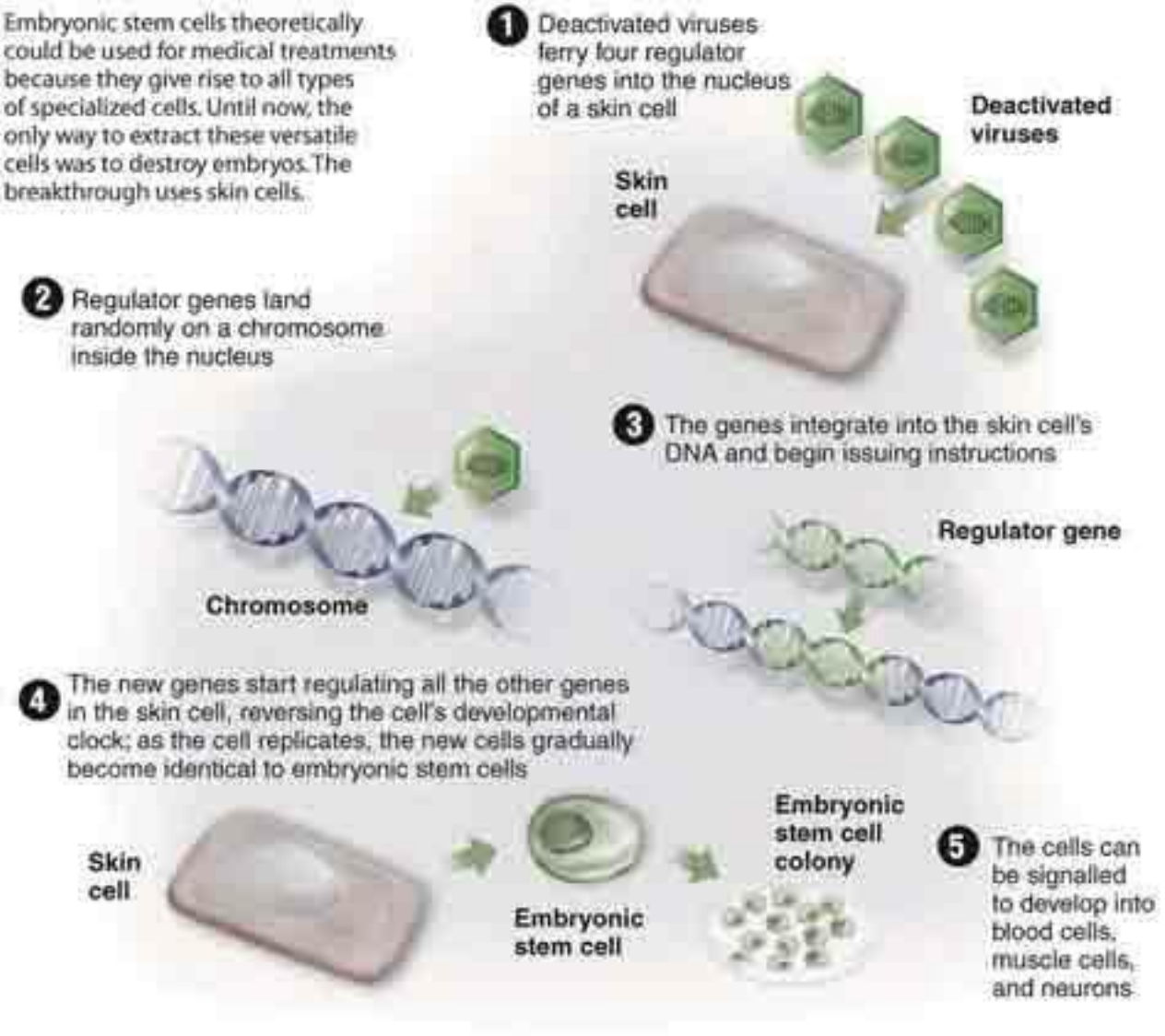
Aug. 2001
President Bush announces that federal money will pay for research on existing stem cell lines, but not new lines.

Nov. 2004
California voters approve a measure to spend $3 billion over 10 years on embryonic stem cell research.

Nov. 2007
New Jersey voters reject a measure to borrow $450 million for stem cell research.

Making embryonic stem cells without embryos

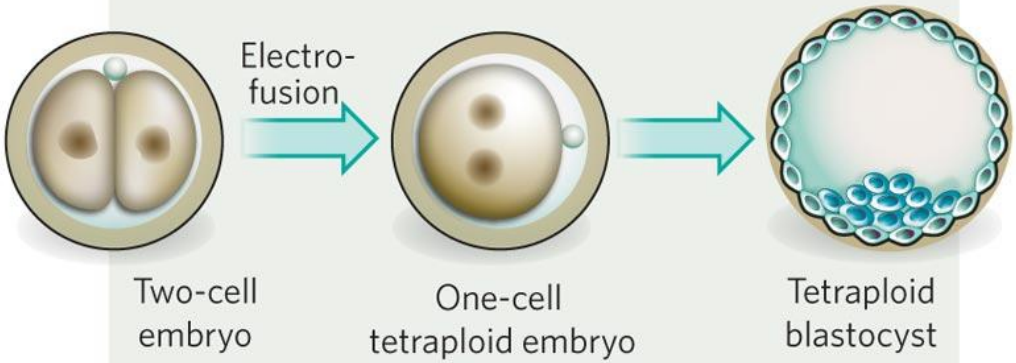
Embryonic stem cells theoretically could be used for medical treatments because they give rise to all types of specialized cells. Until now, the only way to extract these versatile cells was to destroy embryos. The breakthrough uses skin cells.



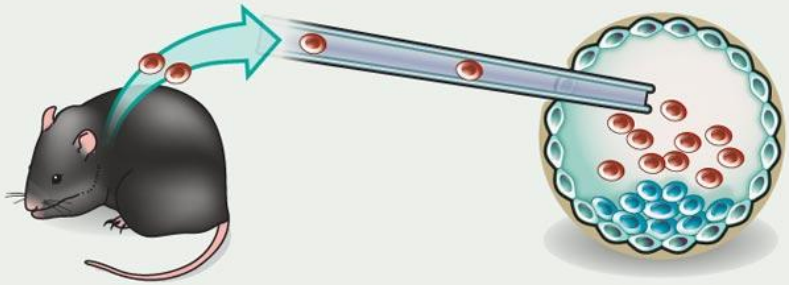
Source: Whitehead Institute for Biomedical Research
Graphic: Robert West, Philadelphia Inquirer

MAKING AN iPS-CELL MOUSE

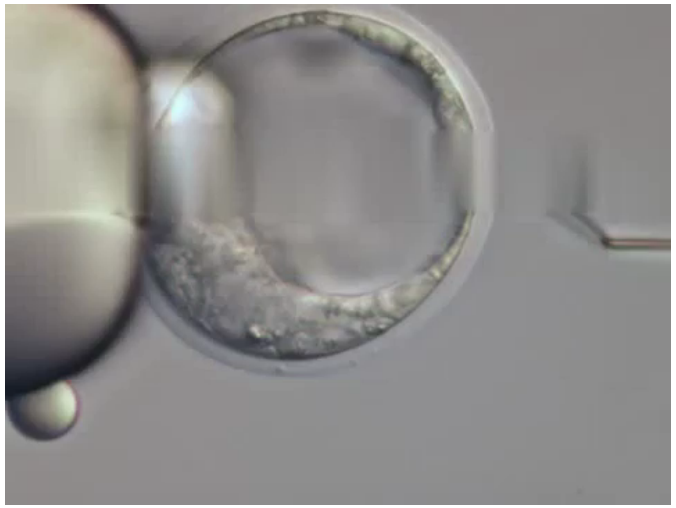
Two-cell embryo is fused to generate a tetraploid blastocyst



iPS cells are injected into the tetraploid blastocyst, which then steer development



Developing embryo is implanted in surrogate mother



Are iPS cells the “magic bullet”?

Use iPS cells to study diseases!

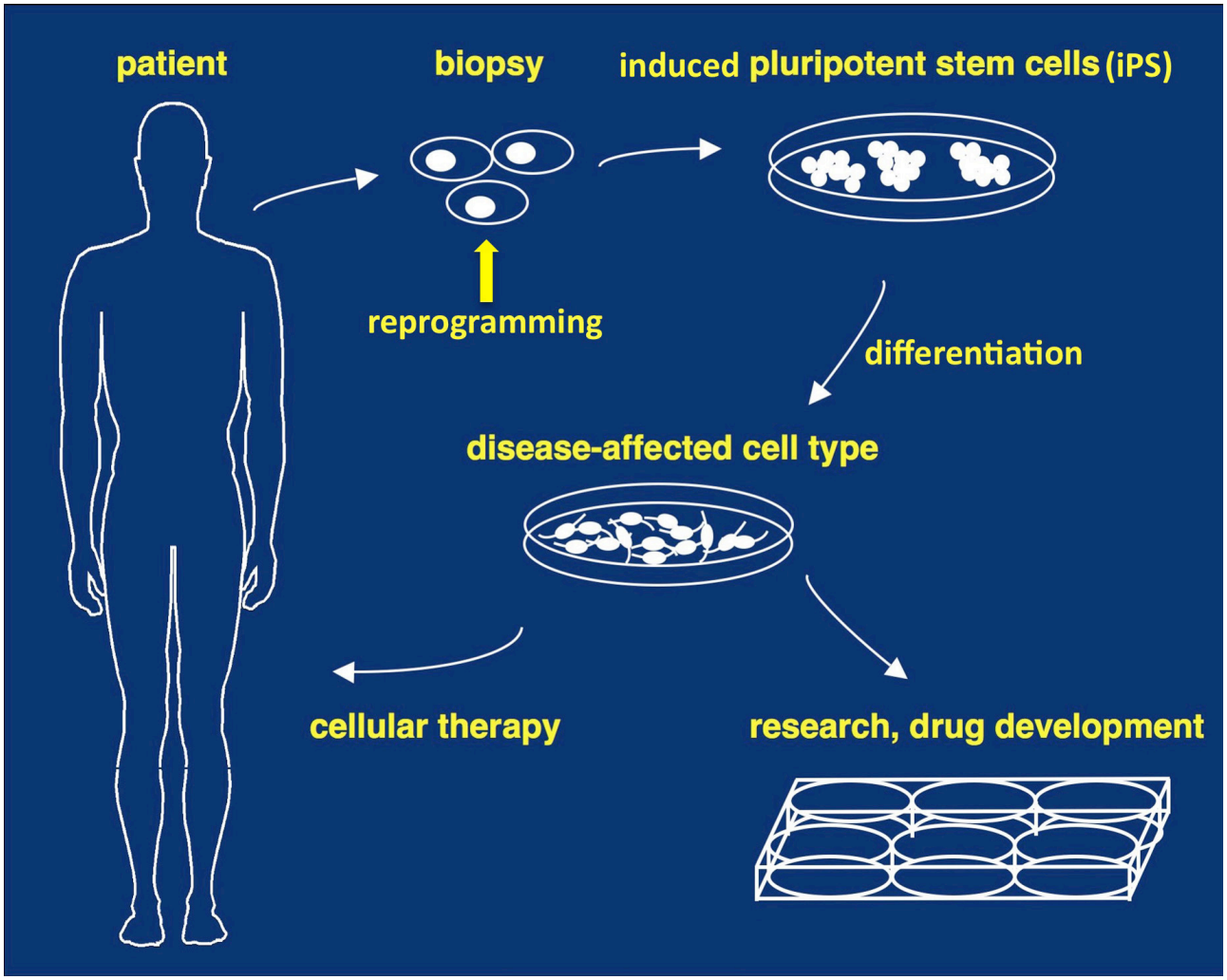


Table 1. iPS Cells Derived from Somatic Cells of Patients with Genetic Disease

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

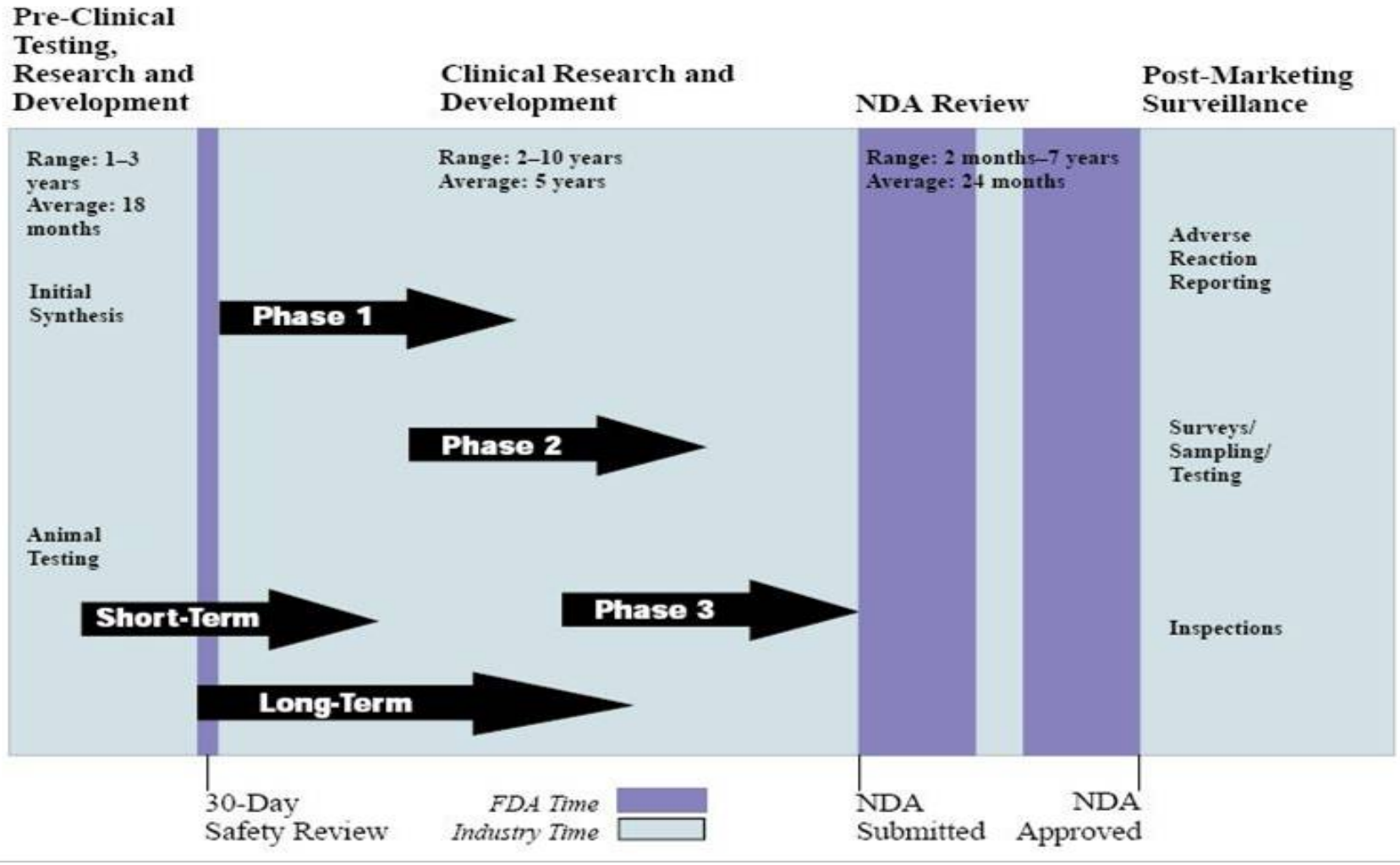
How long does it take to develop a new drug and bring it to market?

a) 1-2 years
b) 3-5 years
c) 6-9 years
d) 10-12 years
e) 12-15 years

How much does it cost to develop a new drug?

a) 50 million dollars
b) 100 million dollars
c) 500 million dollars
d) 1-2 billion dollars
e) 5-7 billion dollars

New Drug Development Timeline

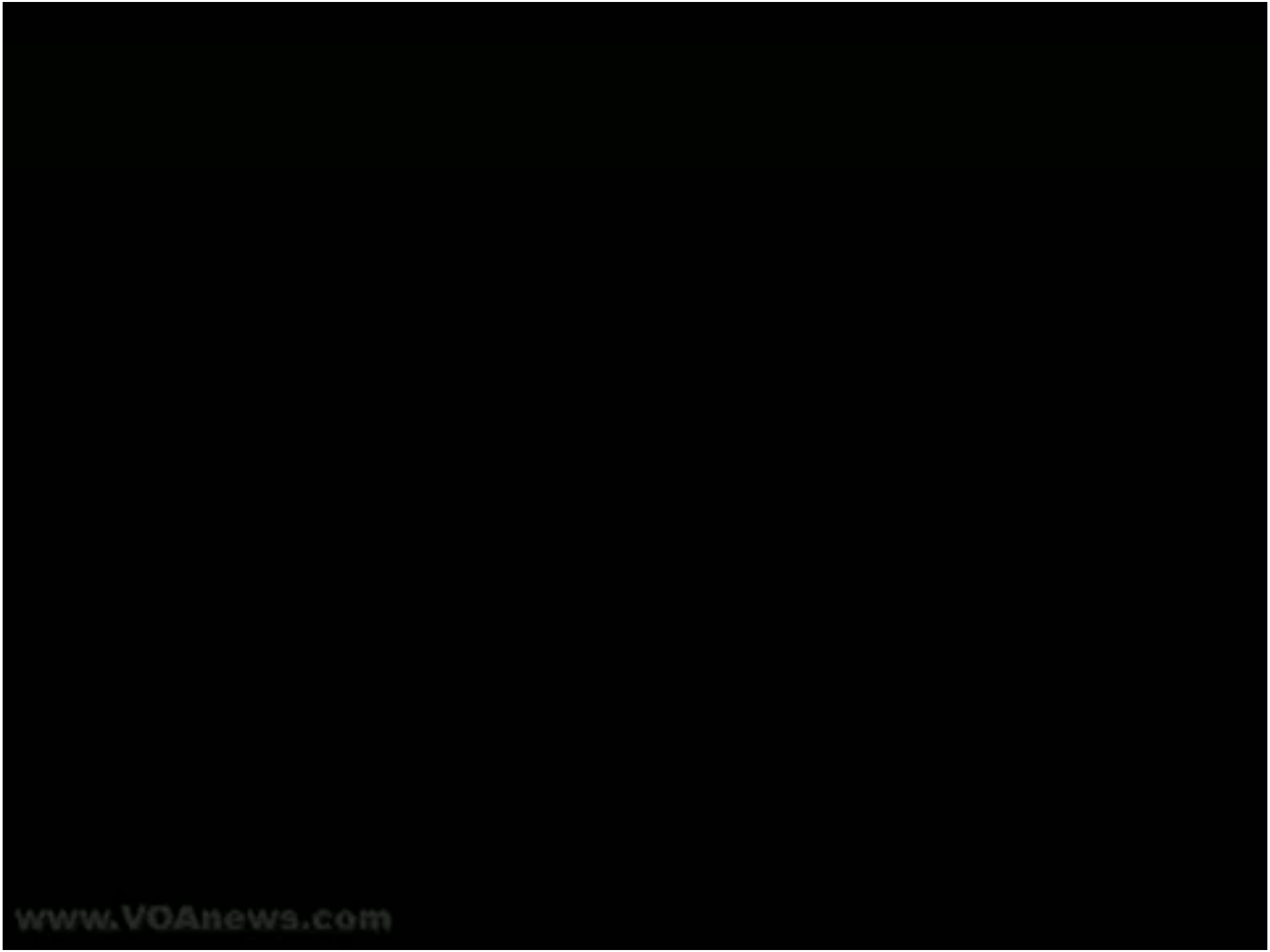


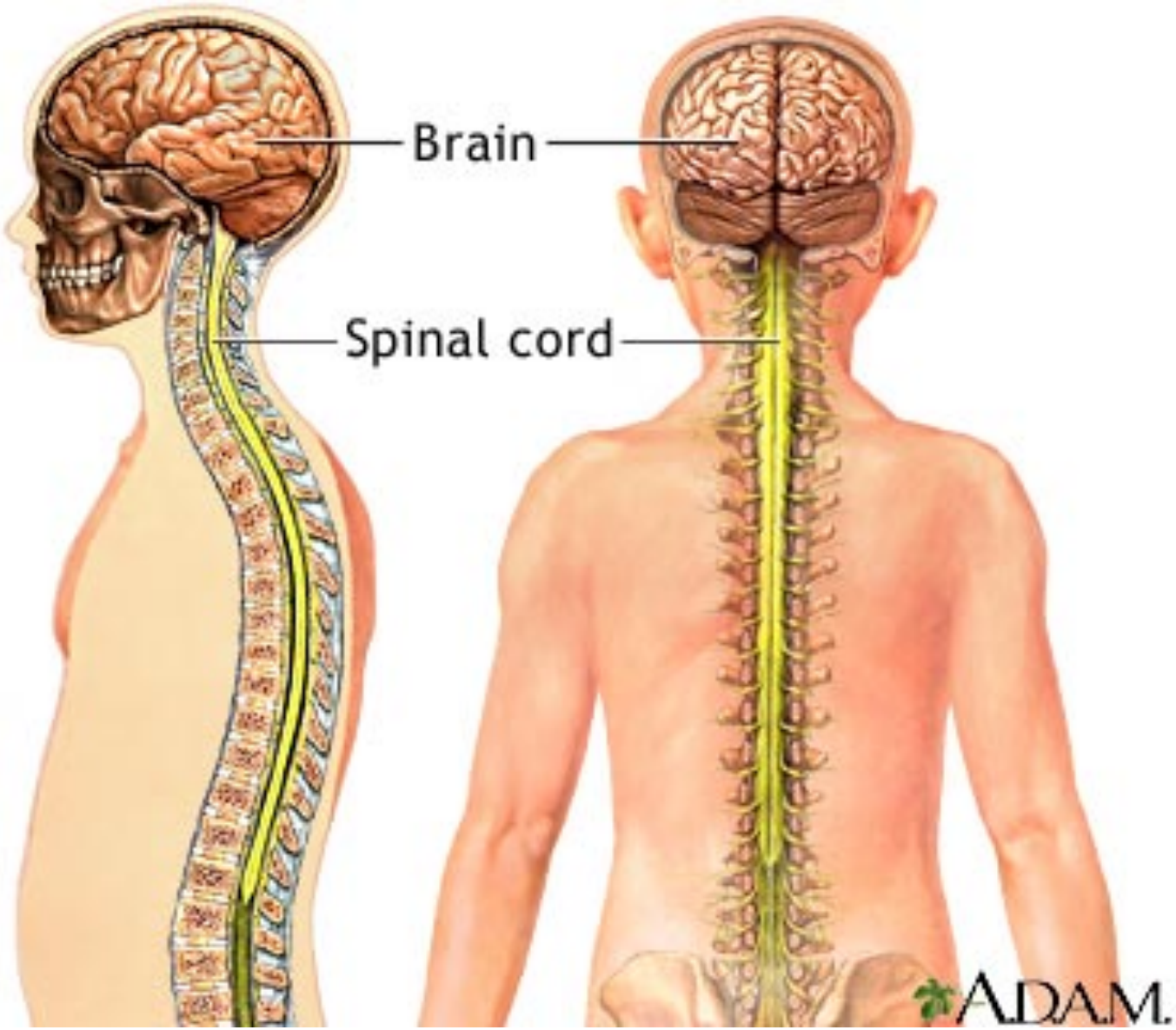
Clinical Trials

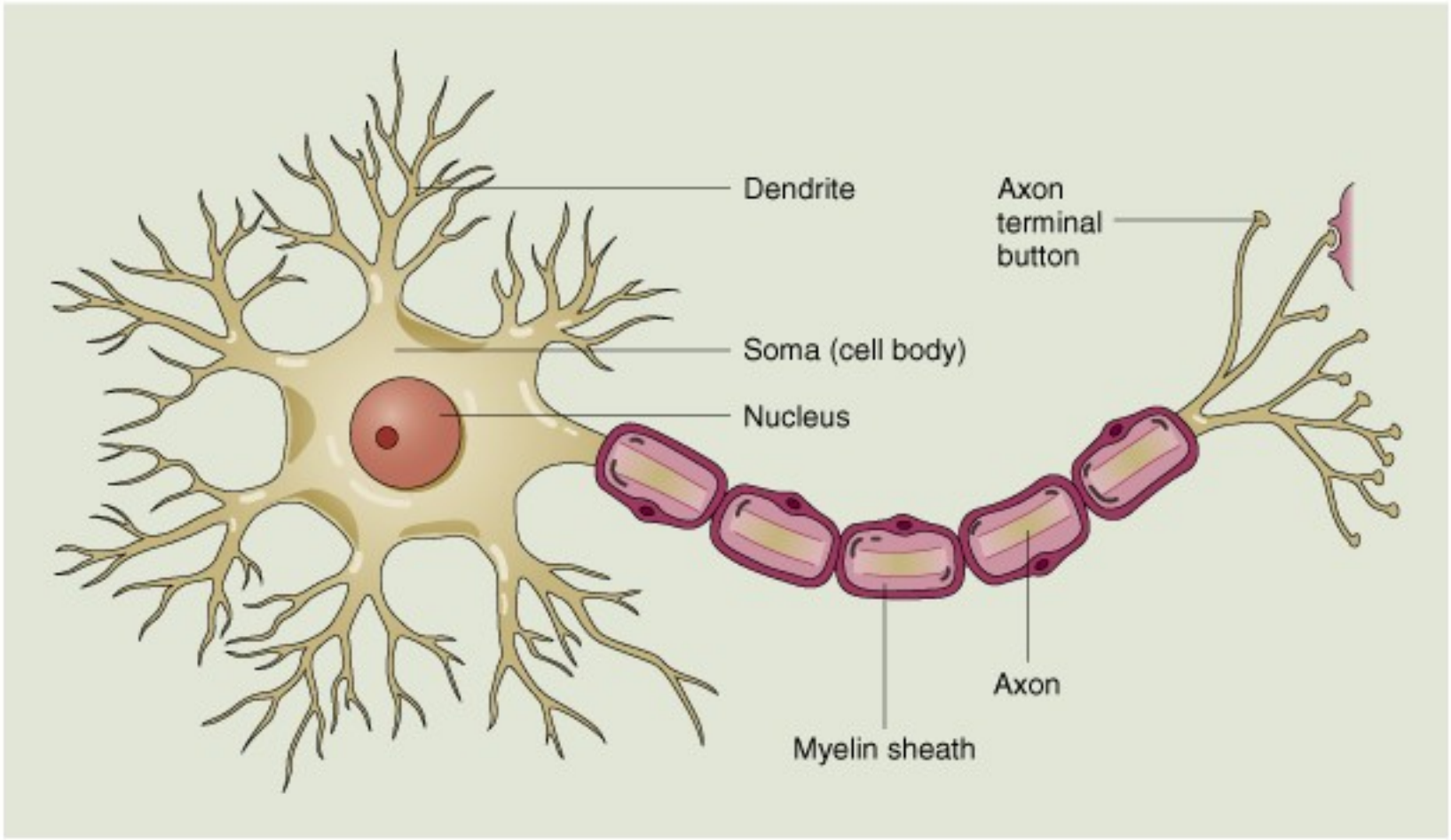
- Phase I: Safety
  - Usually includes healthy (paid) volunteers
- Phase II: Efficacy
  - Patients are involved
  - Usually where drug fails
- Phase III---Randomized controlled trial
  - Involves larger numbers of patients
  - Compares efficacy of drug against current “gold standard” treatment
  - Expensive

Clinical Trials Involving Stem Cells

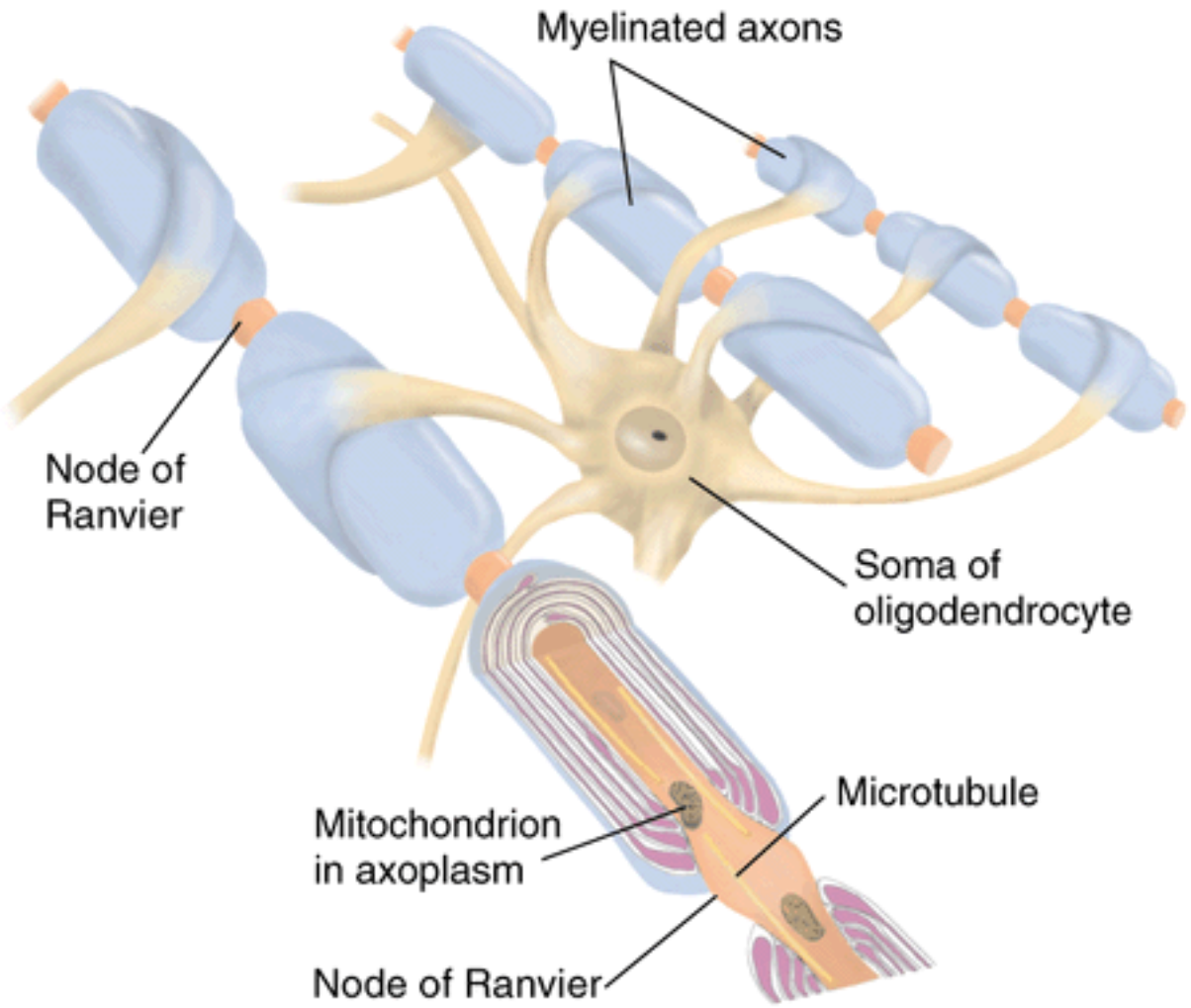
- 3260 clinical trials worldwide
- 1519 trials recruiting participants
  - 896 in US, 788 are interventional studies
    - 297 in Phase I
    - 427 in Phase II
    - 75 in Phase III
    - 636 for cancer
    - 22 for heart disease, 0 for diabetes, 0 for Parkinson's, 0 for Alzheimer's, 1 for ALS, ~20 for sickle cell disease and thalassemia
    - **Only 1 uses ES cells to treat spinal cord injury**

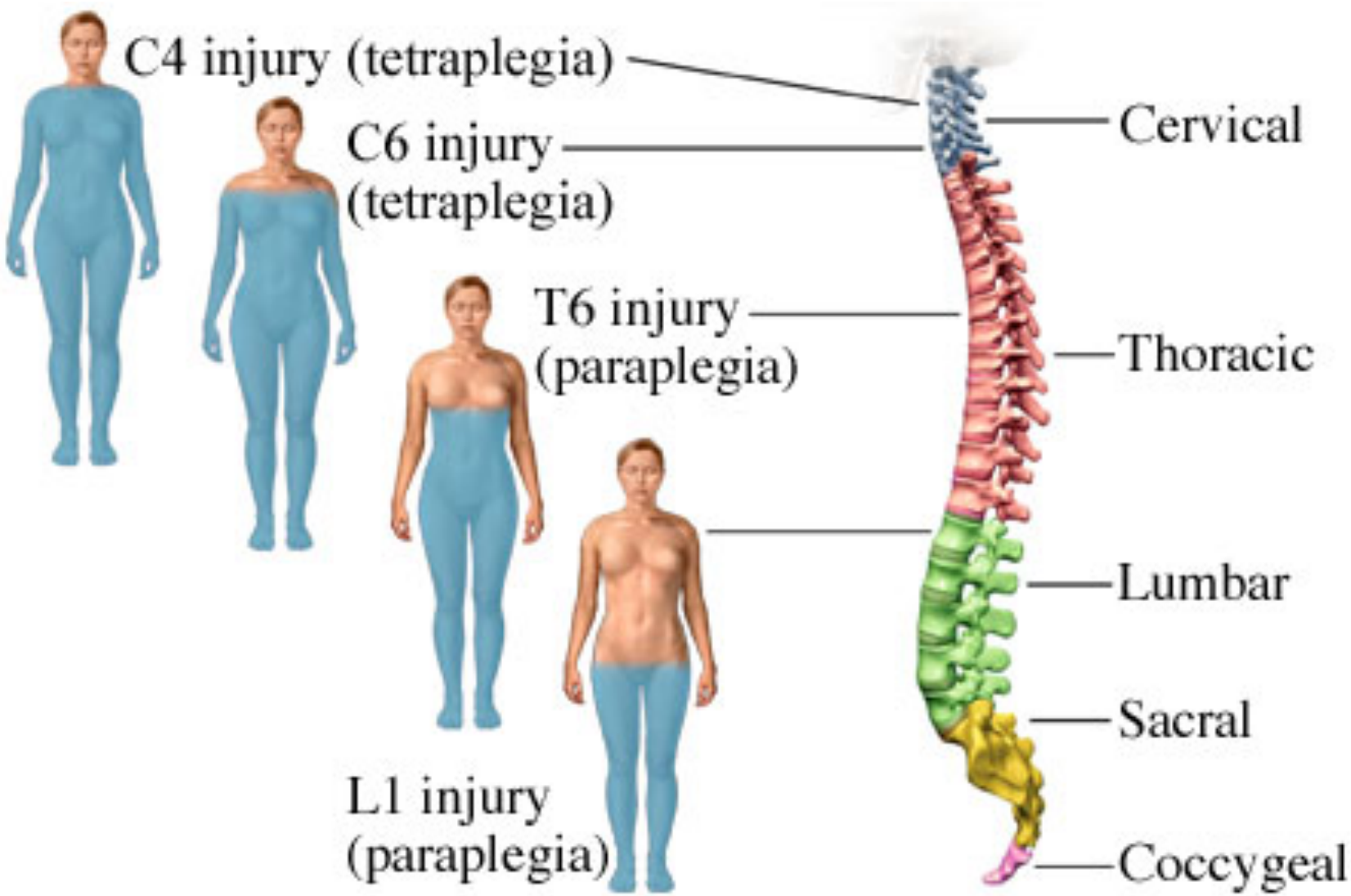

www.VOAnews.com


Brain
Spinal cord
A.D.A.M.



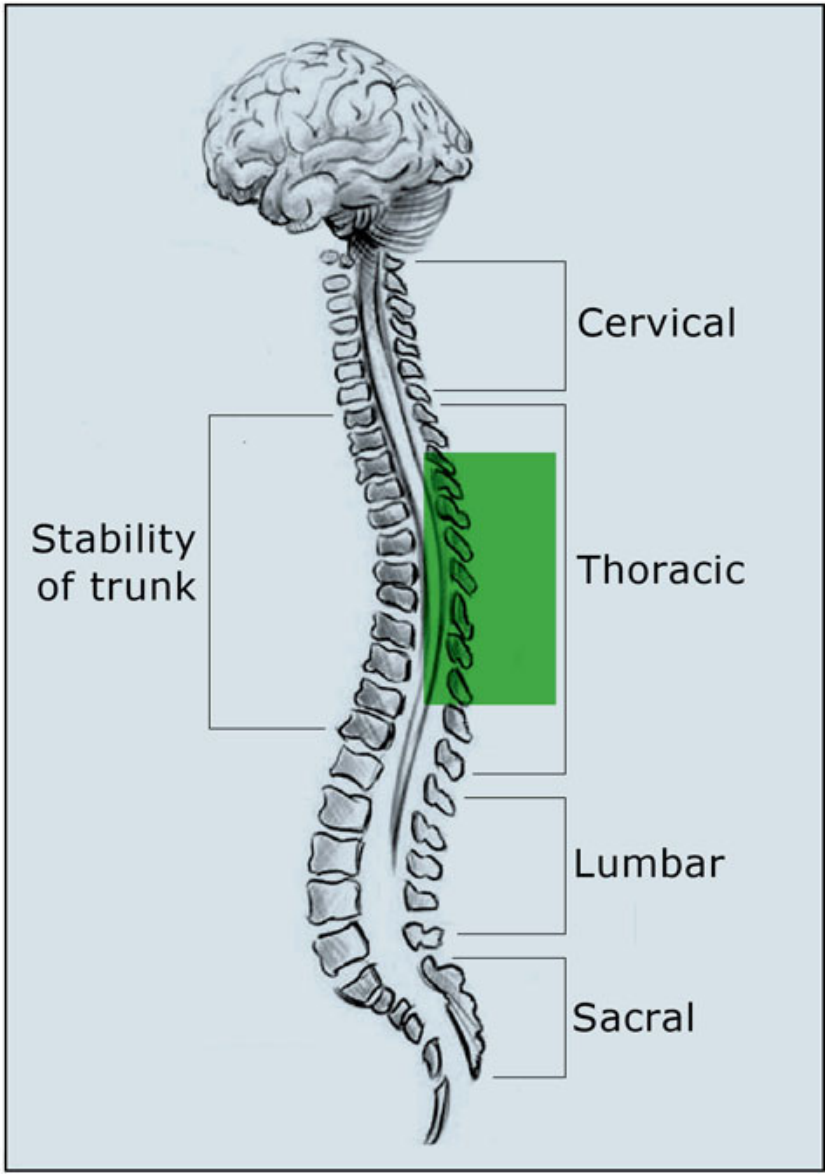
► **An Oligodendrocyte**




C4 injury (tetraplegia)
C6 injury (tetraplegia)
T6 injury (paraplegia)
L1 injury (paraplegia)
Cervical
Thoracic
Lumbar
Sacral
Coccygeal

GRNOPC1 Phase 1 Multi-Center Spinal Cord Injury Trial

- **Open Label Trial**
- **Subacute, Functionally Complete Spinal Cord Injury with a Neurological Level of T3 to T10**
- **$2x10^6$ Cells**
- **Transplant 7-14 Days Post Injury**
- **Temporary Immunosuppression with Low Dose Tacrolimus**
- **Primary Endpoint: Safety**
  - *Neurological*
  - *Overall*
- **Secondary Endpoint: Efficacy**
  - *ASIA Sensory Score*
  - *Lower Extremity Motor Score*



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)