Stem Cell Therapies: Hype and Hope

Community Medical School
December 10, 2019

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Disclosures

Research Funding

- National Institutes of Health
- Department of Defense
- Cystic Fibrosis Foundation
- United Therapeutics Inc.
- Athersys Inc.
- Medical Technology Enterprise Consortium

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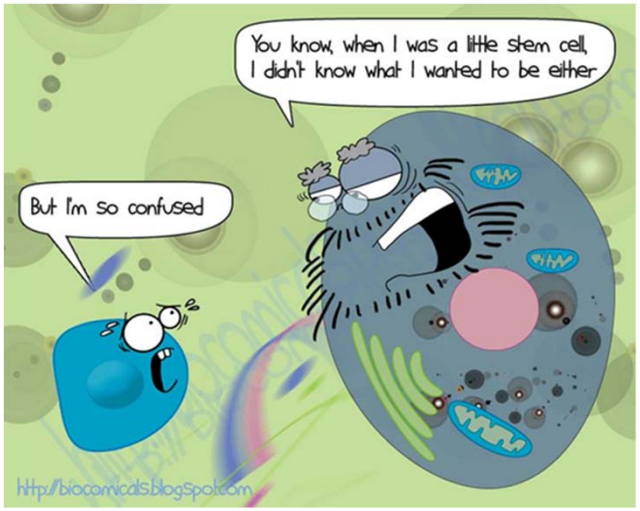
Overview

- Regenerative Medicine
- Stem Cells
  - Embryonic
  - Induced Pluripotent
  - Endogenous Progenitor
  - Hematopoietic Stem Cell (HSC)
  - Mesenchymal Stromal Cell (MSC)
- Unproven Stem Cell Therapies



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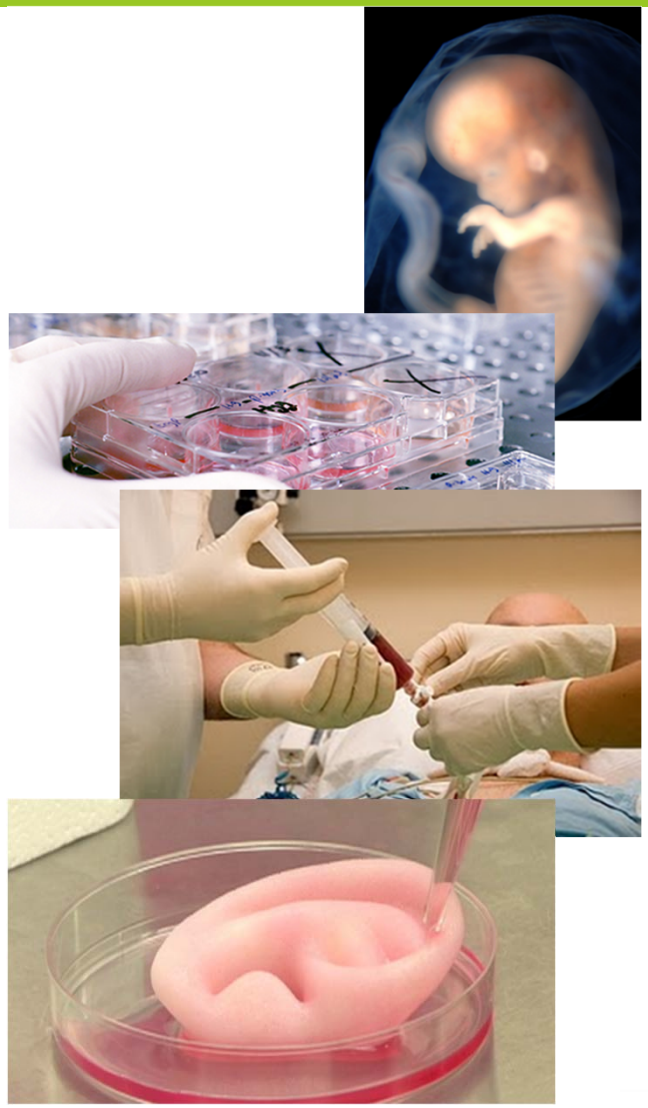
Relevance to you

- Early development and normal tissue repair
- Disease research and drug development
- Cell therapy
- Tissue engineering and regenerative medicine



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Regenerative Medicine: Bioengineering New Tissues and Organs

- Stimulating the body's own repair mechanisms to heal previously irreparable tissues or organs

Regenerative Medicine: Bioengineering New Tissues and Organs

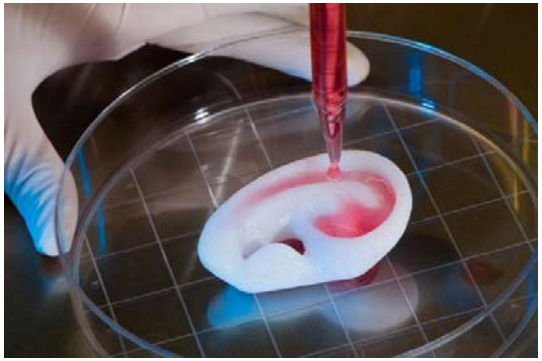
- Growing tissues and organs in the laboratory for implantation when the body cannot heal itself

Regenerative Medicine: Bioengineering New Tissues and Organs

- Growing tissues and organs in the laboratory for implantation when the body cannot heal itself

Skin, bone, cartilage

In evolution for more complex organs:
heart, lung, liver, brain

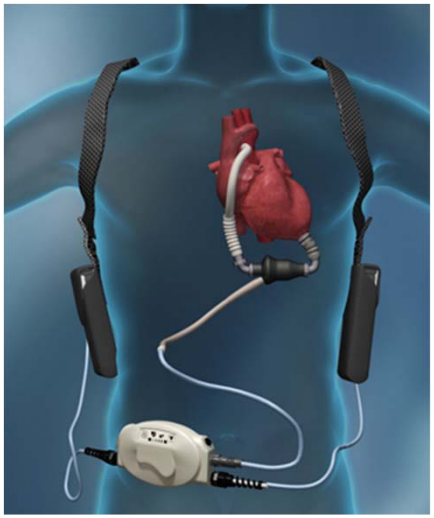


Regenerative Medicine: Bioengineering New Tissues and Organs

- Development of organ-tissue adjunct devices

  Artificial kidneys: Hemodialysis

  Left ventricular assist devices (”artificial” hearts)



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Regenerative Medicine: Bioengineering New Tissues and Organs

1st Regenerative Medicine Scientist?

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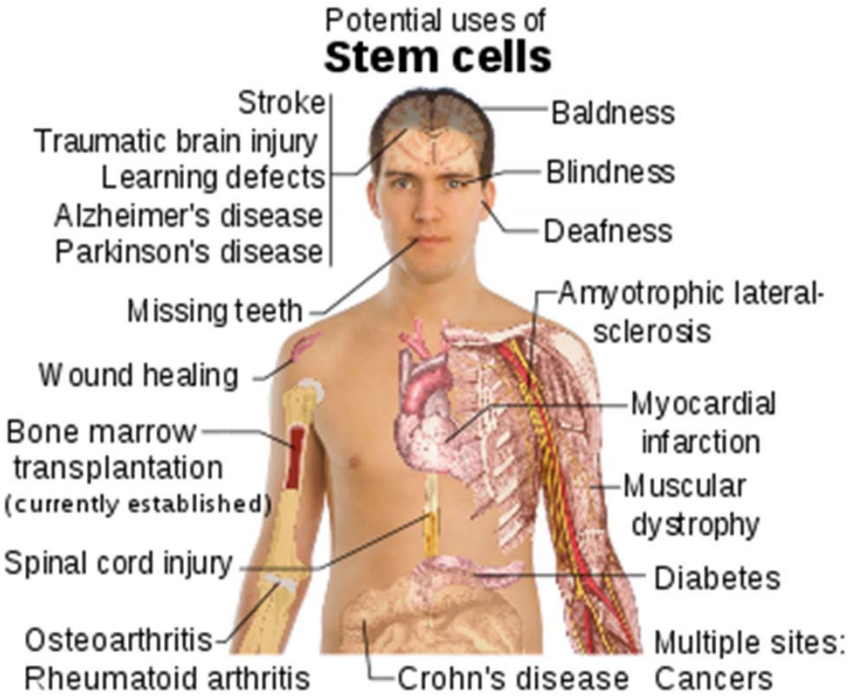
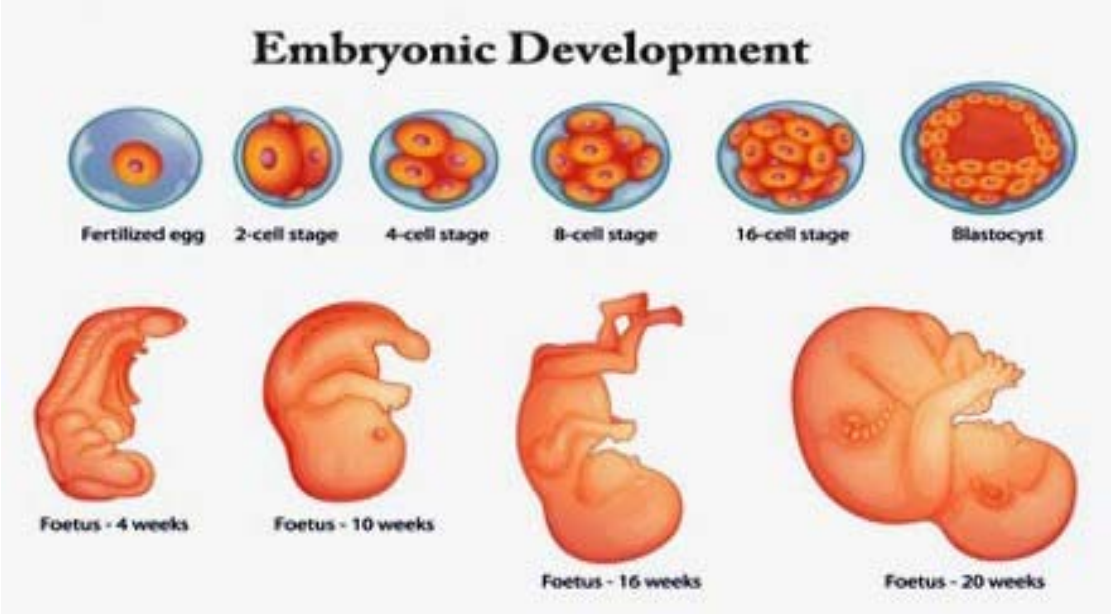
Embryonic Stem Cells



Theoretically Unlimited Potential

Where do we get Human Embryonic Stem Cells?

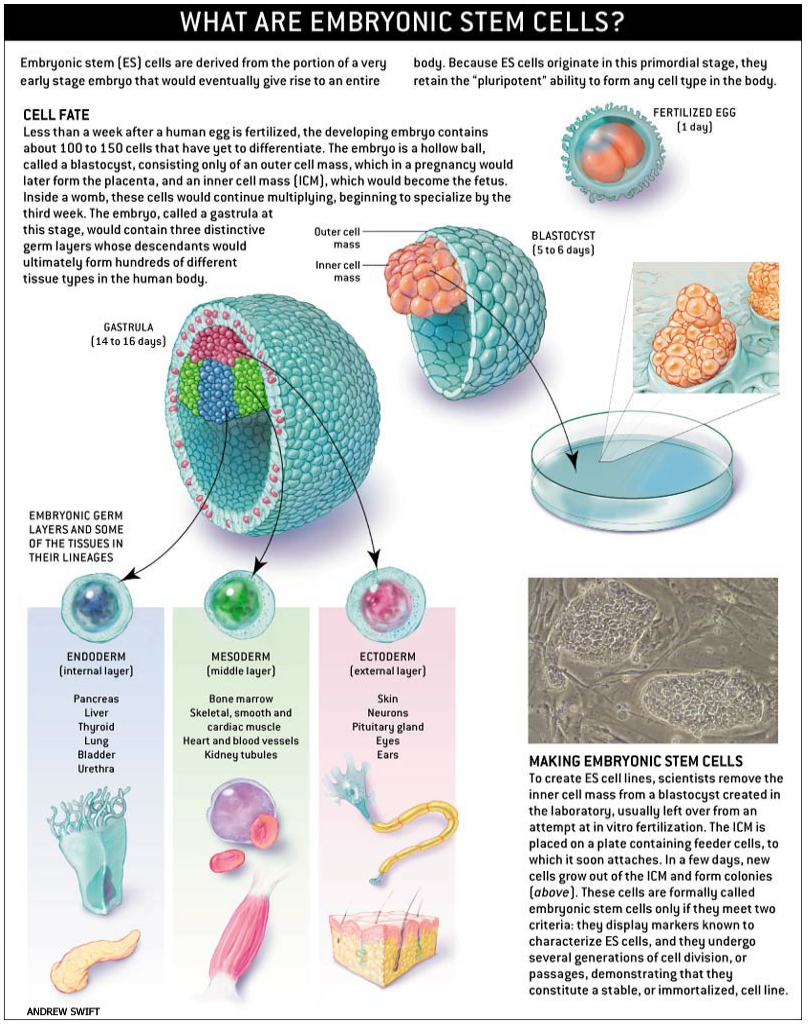


Embryonic Stem Cells

Mouse: 1960's

Human: 1998

Differentiate into all adult tissues



Lanza and Rosenthal
Scientific American 2004

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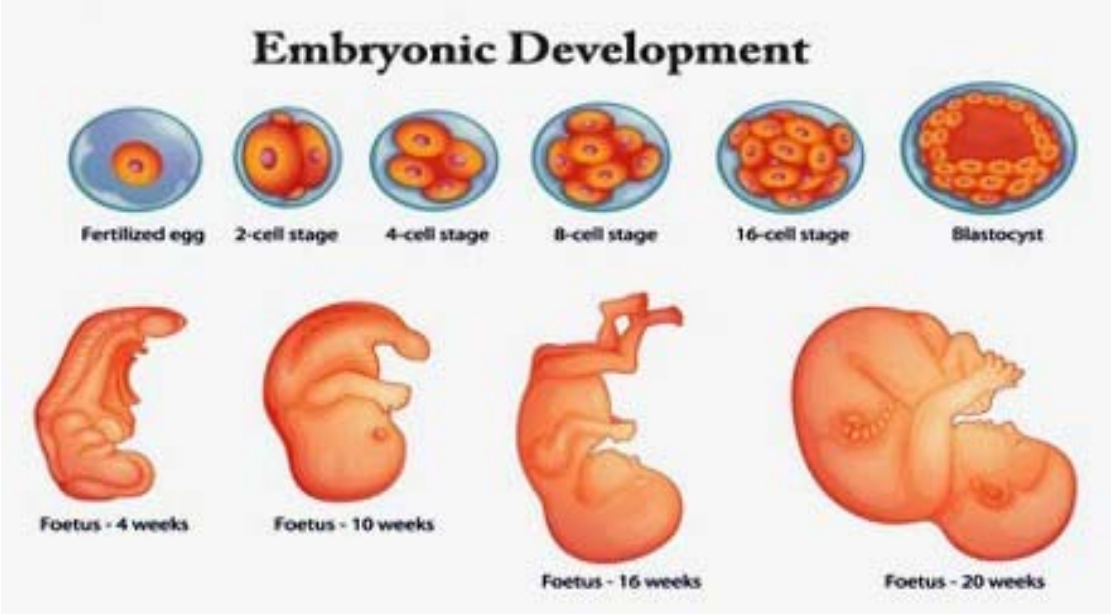
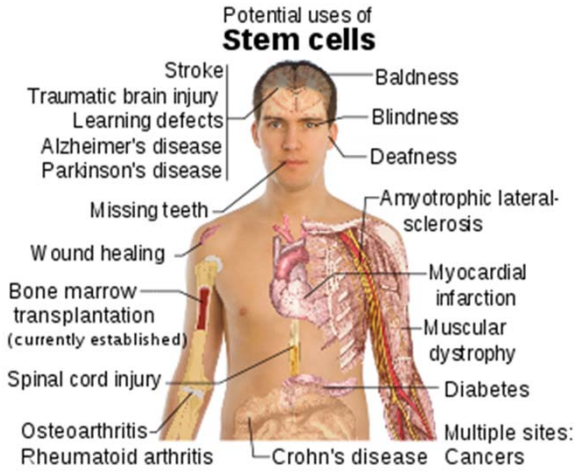
Where do we get Human Embryonic Stem Cells?



How can ESCs be potentially used?



Goal: Repair damaged or diseased tissue

Administer ESCs

Go to damaged organ and differentiate into organ-specific cells

Differentiate the ESCs to the desired cells or tissue and then administer

Clinical Trials of ESCs

Initial trial in spinal motor atrophy (Geron)

- Trial halted after possible allergic reactions

Currently 22 trials listed on clinicaltrials.gov

- Opththalmologic: ESC-derived retinal cells
  - Macular degeneration
- Cardiac: ESC-derived cardiac cells
  - Heart failure: 1 safety trial in France
- Neurologic
  - Parkinson's disease: ESC-derived neural cells (China)
  - ALS: ESC-derived neural cells (Israel)

Many years from clinical use

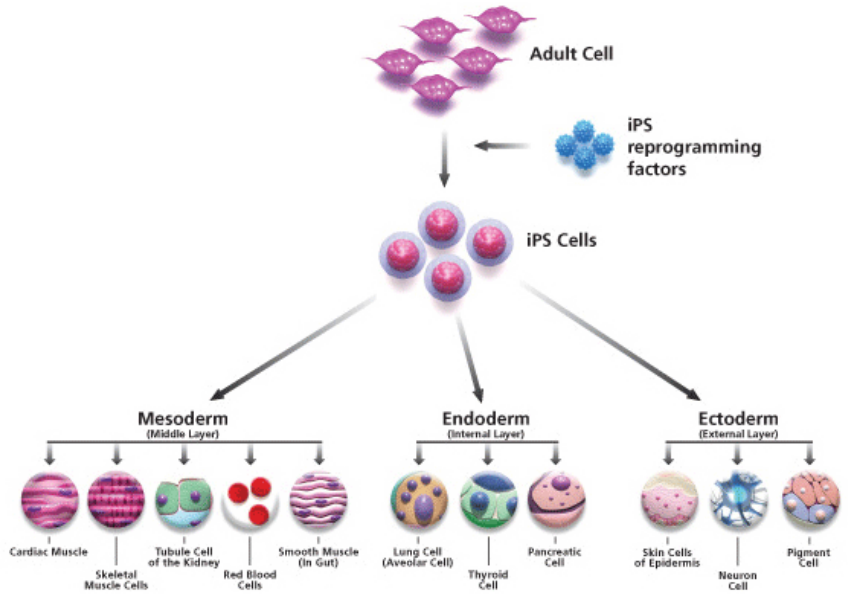
Issues with using ESCs

- Ethical, moral, religious, political
- Teratomas

Tumors containing multiple types of tissues
Skin
Muscle
Bone
Hair
Teeth

Induced Pluripotent Stem Cells (iPSC)

- Turn on genes essential for normal embryonic development that are turned off in adult cells
- De-differentiate adult cells to a functional equivalent of ESCs



2012 Nobel Prize in Medicine to Shinya Yamanaka
"Yamanaka Factors"

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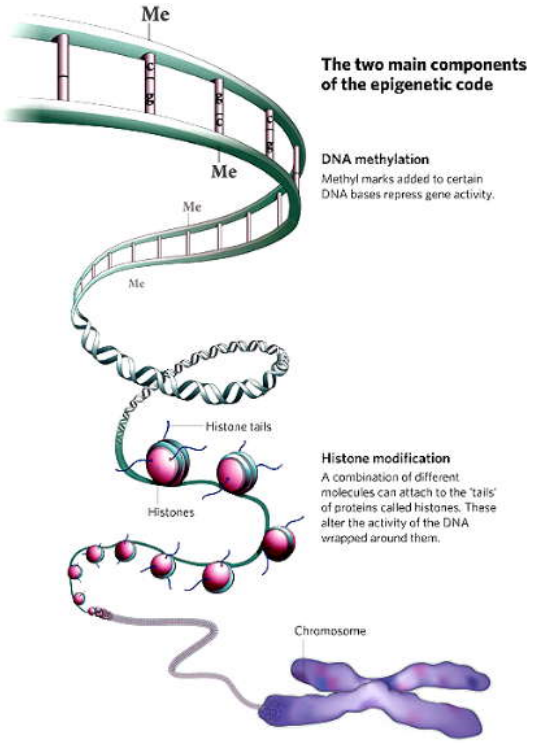
Issues with using Induced Pluripotent Stem Cells (iPS)

- Teratomas: same as ESCs
- Epigenetic memory
  - Once a skin cell, always a skin cell



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Clinical Trials of iPSCs

- Currently 37 trials listed on clinicaltrials.gov
  - All to obtain tissue: generate disease-specific iPSCs
  - No interventional trials Many years from clinical use

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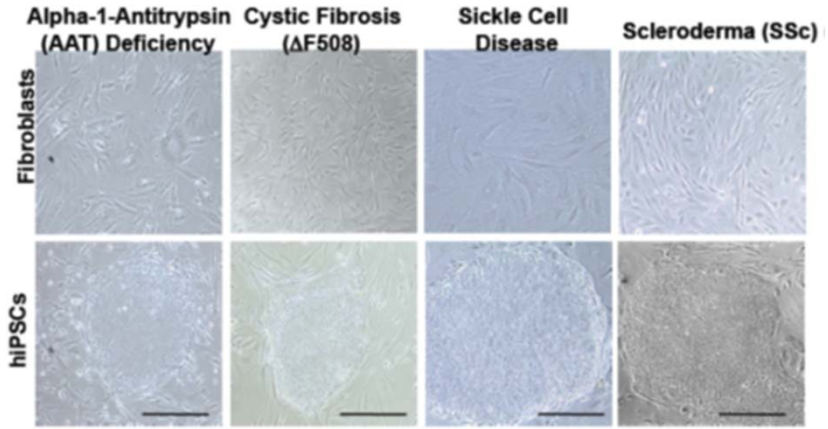
Current Uses of iPSCs

Disease-specific iPS cells
Drug testing

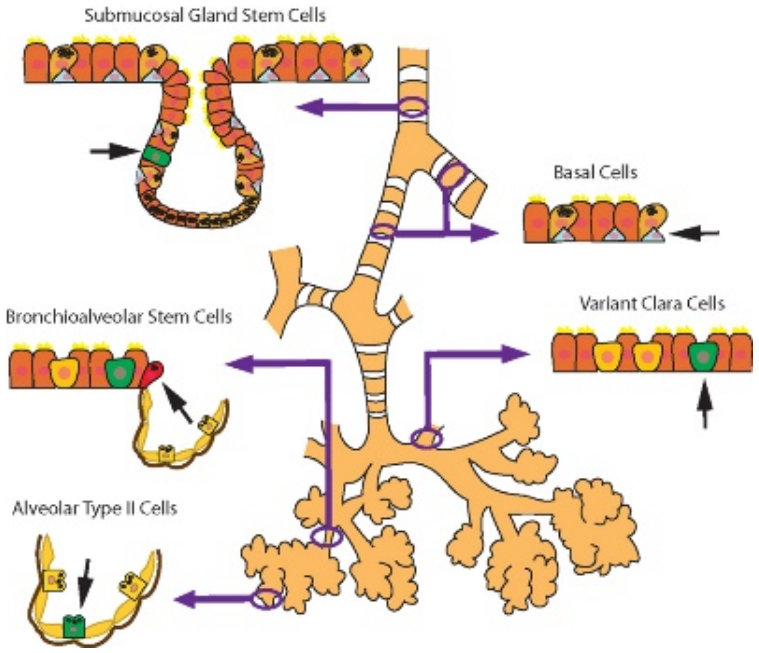


Somers et al. Stem Cells 2010

Alternatives to ESCs/iPSCs: Endogenous Progenitor Cells

- Every organ has its own stem cells
- Respond to injury/aging within the tissue

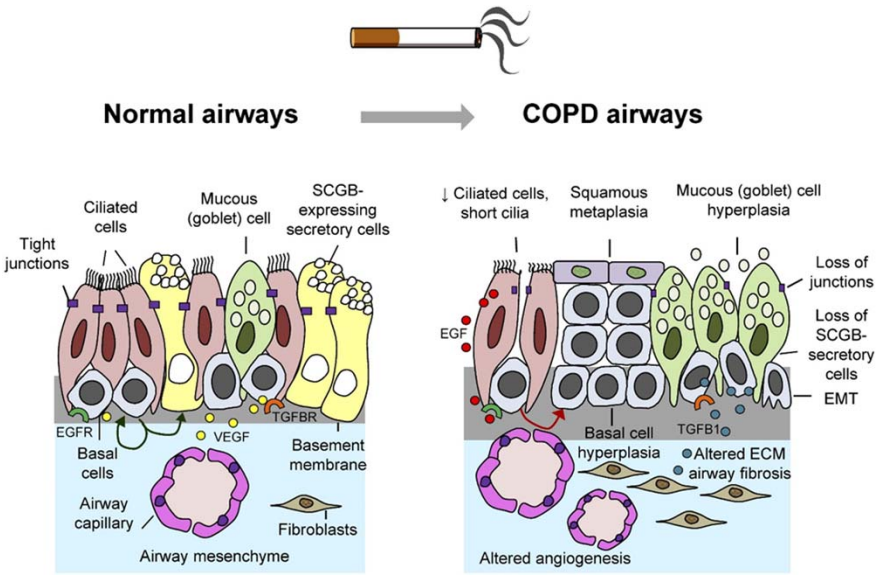
  - Found in:
    - Marrow
    - Blood vessels
    - Brain
    - Muscle
    - Skin
    - Pancreas
    - Liver
    - Lung
    - Teeth



Endogenous Progenitor Cells

- Function in development, repair, aging (?)
- Found in every organ
- Most data in mice: less information in humans
- Homeostasis not well understood
- Potential role as cancer stem cells

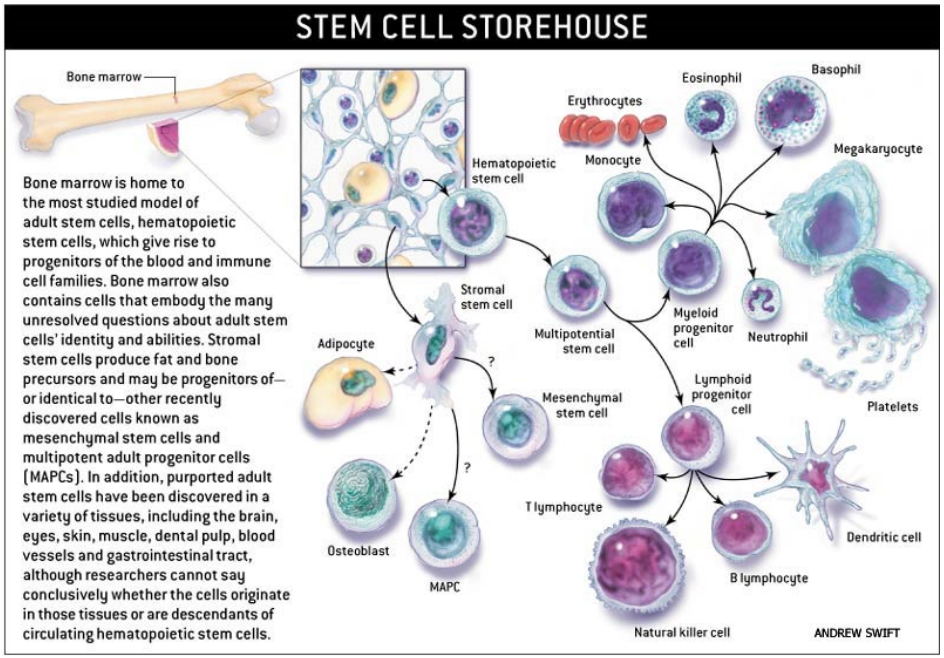
- Many years from clinical application



Adult Stem Cells

Bone marrow contains several different types of stem cells

- Hematopoietic stem cell (HSC)
- Mesenchymal stromal cell (MSC)



Lanza and Rosenthal Scientific American June 2004

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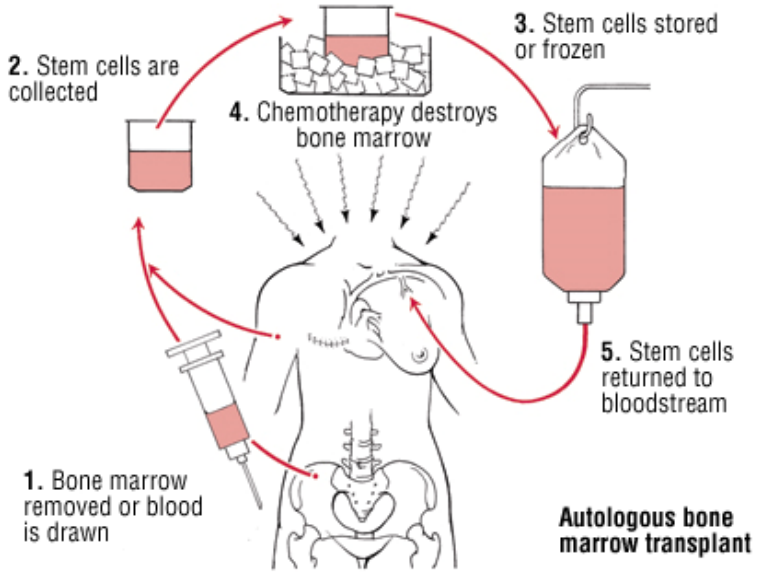
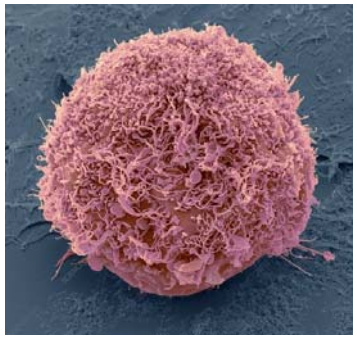
HSCs and Bone Marrow Transplantation

- HSCs are obtained from bone marrow or blood
  - Autologous
  - Allogeneic
- Administered after chemo or radiation therapy to restore bone marrow
- FDA-approved uses
  - Leukemias
  - Lymphomas
  - Other hematologic diseases



MSCs

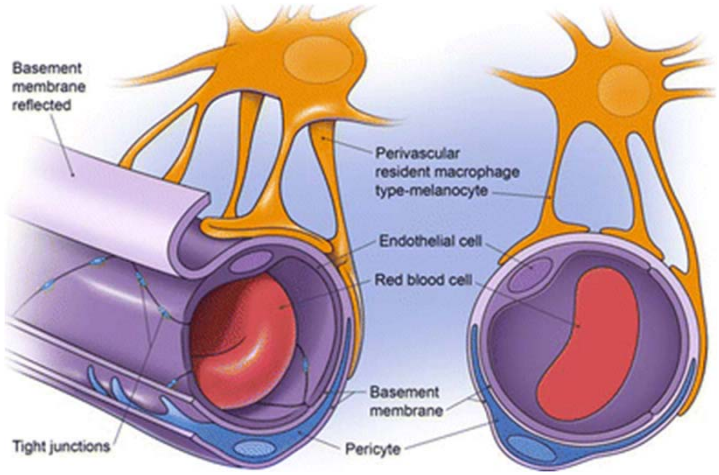
- Initially isolated from bone marrow
- Adipose, placenta, cord blood, other tissues
- Differentiation ability: “stem cell” role
  - Bone, fat, cartilage



- Immune regulation

  Live along blood vessels

  Sample and react to inflammatory environments



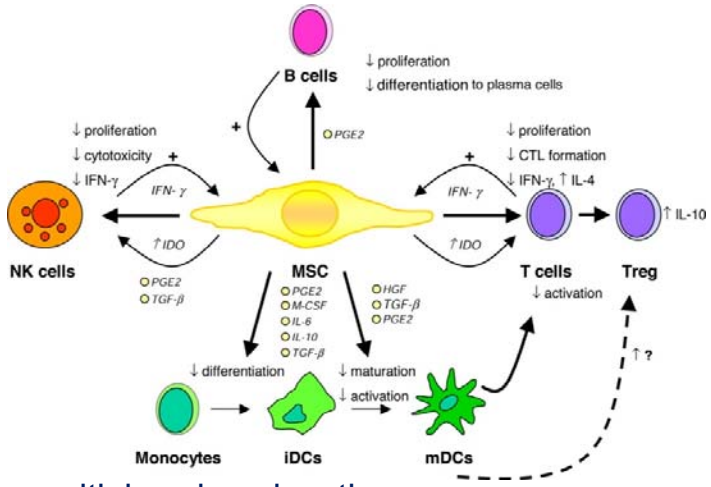
MSC Immunomodulation

Immune Regulation

-Inhibit immune cells

Don't provoke immune response

- Don't express immune markers
- Allogeneic use



Clinical Application

Clinical trials: graft vs host disease (GVHD), Crohn's, multiple sclerosis, others

Approved/Marketing Authorization

Refractory graft vs host disease:	Canada, Japan, New Zealand
Perianal fistulas in Crohn's disease:	European Union
Critical Limb ischemia (Buerger's disease):	India

No MSC-based cell therapy is approved in the US

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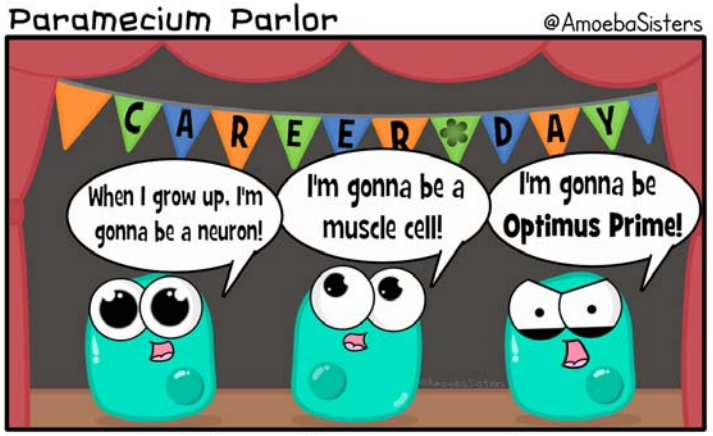
Interim Summary

- Regenerative Medicine
- Stem Cells
  - Embryonic
  - Induced Pluripotent
  - Endogenous Progenitor
  - HSC
  - MSC



Stem cells on career day

- Approved/proven uses of HSCs
- Promising research for others
  - No approved therapies in US

Unproven Stem Cell Therapies

- Research and Clinical realities:
  - Few cell-based therapies are standard-of-care or approved by regulatory agencies
- Patient expectations:
  - Patients with chronic or end-stage diseases will seek unproven (stem) cell treatments motivated by therapeutic hope
  - High global demand for (stem) cell-based therapies
- The (problematic) answer:
  - Worldwide proliferation of “stem cell” clinics
  - Unproven, untested and potentially dangerous (stem) cell treatments
  - Different regulatory frameworks exacerbate the problem

Unproven Stem Cell Therapies

Right Need

Wrong Answer

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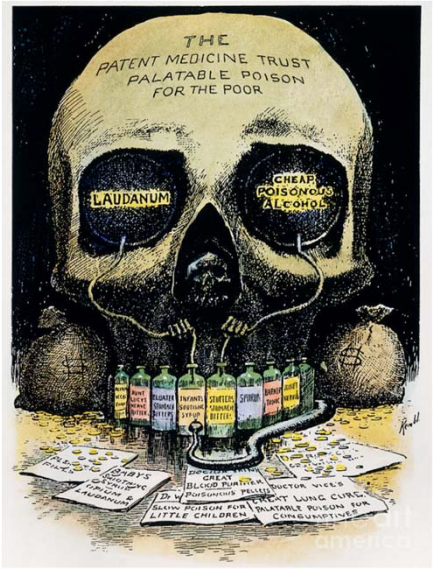
History of US Drug Regulation



1906 – US FDA established; accurate **labeling**

U. S. Races Death to Save 700 From Elixir

Recovery of Pint Bottles Sold to Patients Goal as Deaths From Poison Reach 36

By Associated Press.

CHICAGO, ILL., October 24.—A nation-wide race with death, its object recovery of more than 700 bottles, mostly pints, of a new liquid medicine, named Elixir of Sulfanilamide, which has already caused 36 verified deaths, was described today at the headquarters here of the American Medical Association.

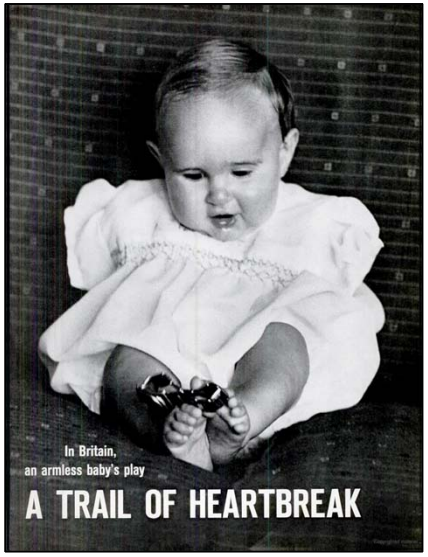
Every agent of the United States Food and Drug Association, said Dr. Morris Fishbein, spokesman of the Medical Association, is scouring the country to recover the bottles. By some time on Monday said J. G. Clarke of the Food and Drug Administration, it is hoped that all of the "outstanding" shipments will be recovered.

lies in the fact that large dosages are customary with sulfanilamide preparations.

The medicine stops the kidneys. At Medical Association headquarters its effects were said to be like those of bichloride of mercury. No antidote is known yet. The "Elixir" is made of sulfanilamide and diethylene glycol, a near relative of auto antifreeze fluid. The diethylene glycol is blamed for the lethal effect, although not itself classed as a poison.

The principal shipments, said Mr. Clarke, went to the South and Midwest. But in addition consignments have been traced to the Northern Peninsula of Michigan, to a distributing house in New York City and

1938– Passage of Food, Drug, and Cosmetic Act (FDCA); **safety** testing



1962– FDCA amended to require **efficacy** testing
*(PMDA established in 2000)

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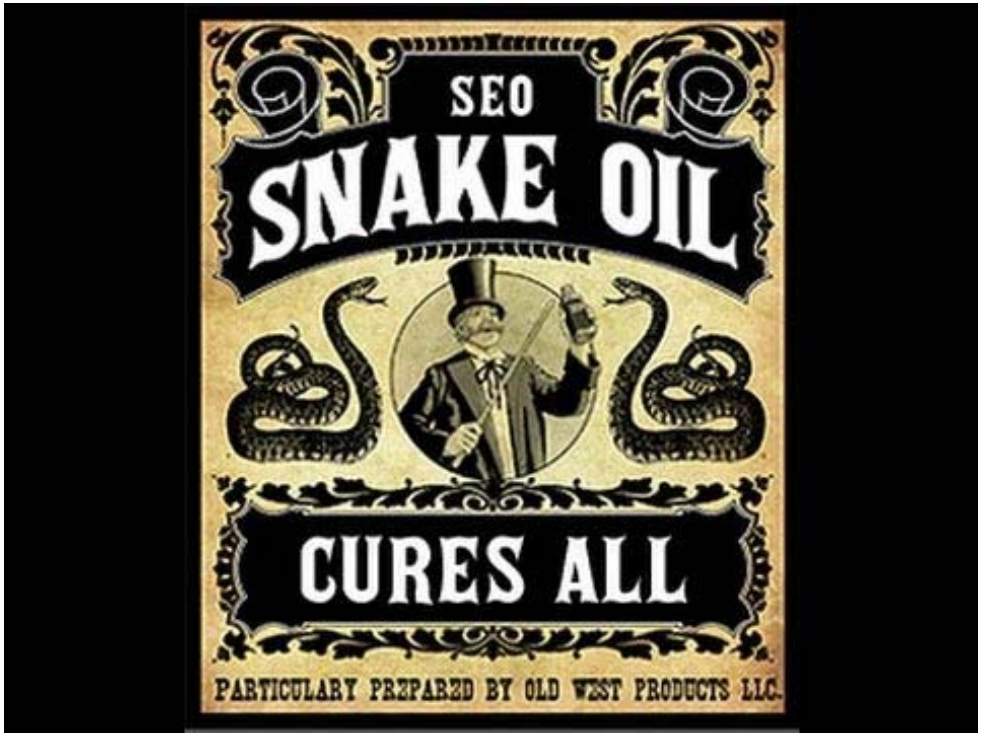
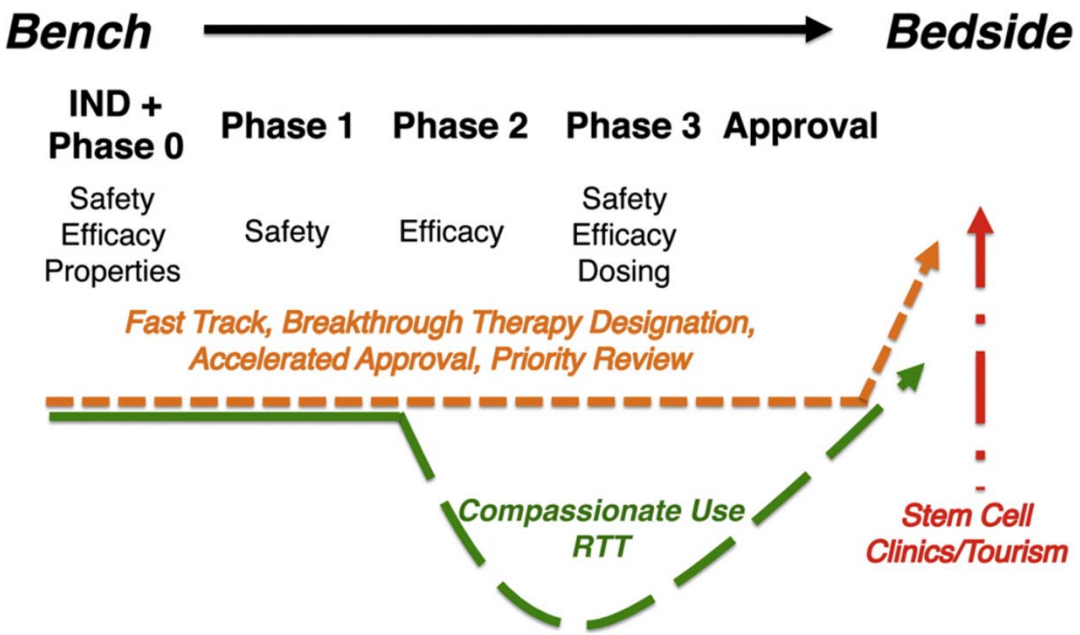
History of US Drug Regulation

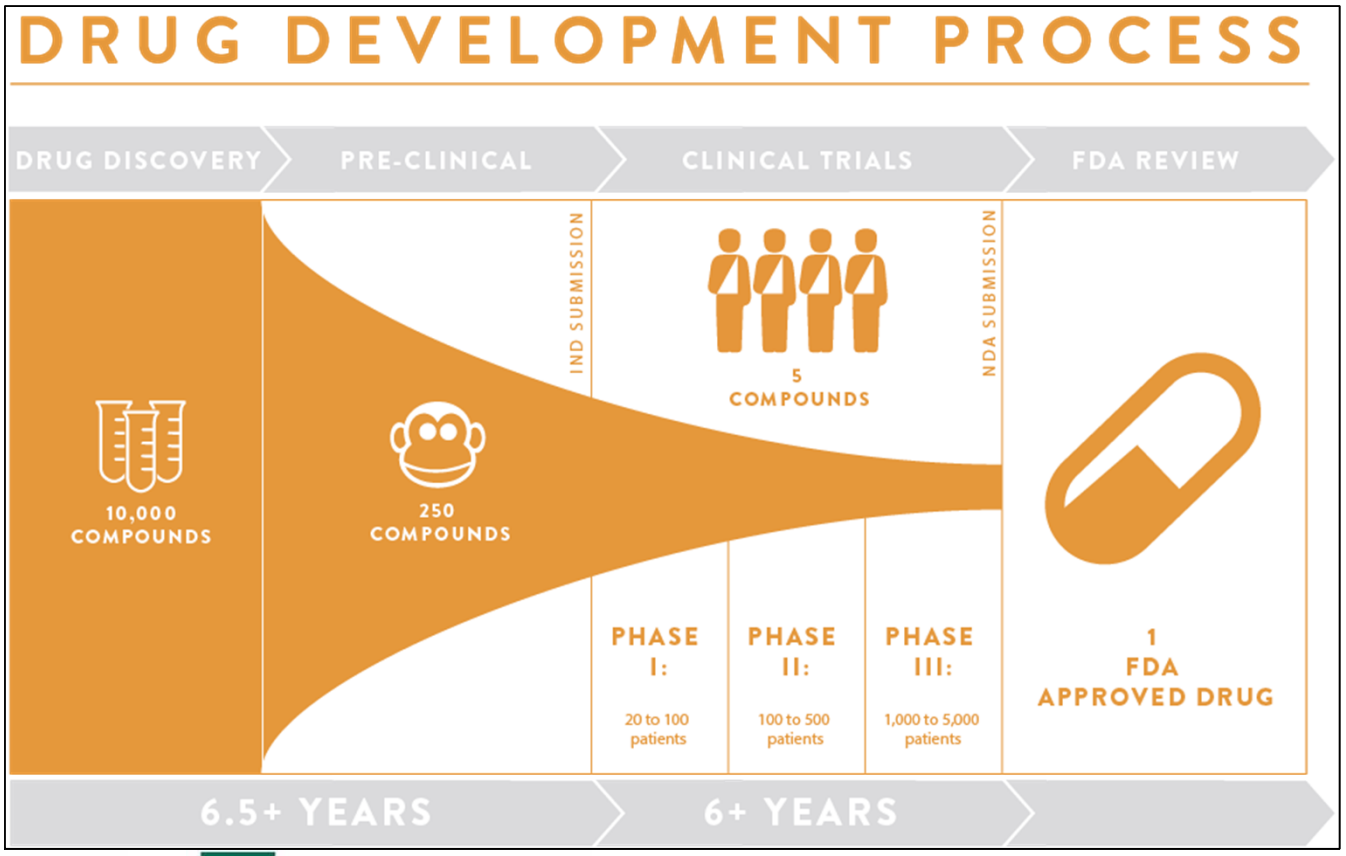


FDA Pathways for New Therapies



Knoepfler, Adv Drug Deliv Rev, 2015

FDA Pathways for New Therapies



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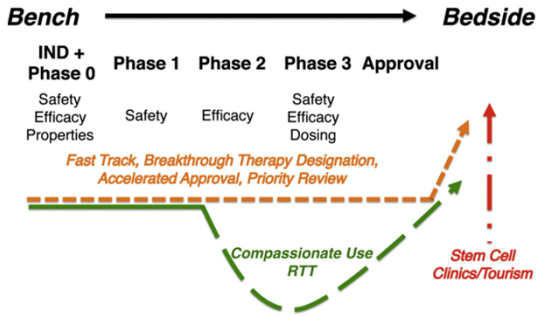
Source: www.givetocure.org

Speeding the Process: January 2019 FDA Statement

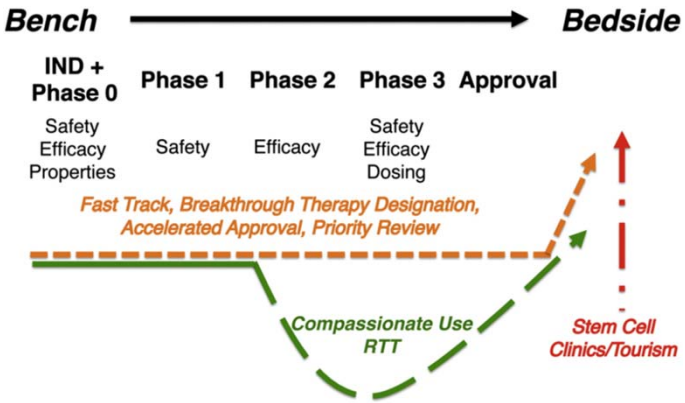


- >800 active INDs for cell or gene therapy products
- FDA's projections for cell and gene therapy products
  - By 2020, >200 INDs/year
  - By 2025, 10-20 ***approvals***/year
  - Planned to hire 50 additional clinical reviewers in 2019 to keep pace
- Guidance documents for specific diseases, cell-based regenerative medicine products
- Accelerated approval pathways
  - Regenerative Medicine Advanced Therapy (RMAT)

Speeding the Process

Regenerative Medicine Advanced Therapy (RMAT)

- Cell therapy intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition and has the potential to address unmet medical needs for such disease/condition
- Preliminary clinical evidence
- Use of real word evidence (e.g. observational data)



Speeding the Process

As of September 2019

- 108 Regenerative Medicine Advanced Therapy (RMAT) designation requests received overall
- 40 RMAT requests granted overall
- Indications vary widely – stroke, spinal cord injury, sickle cell disease, muscular dystrophy, others
- Major benefit: accelerate regulatory approval process

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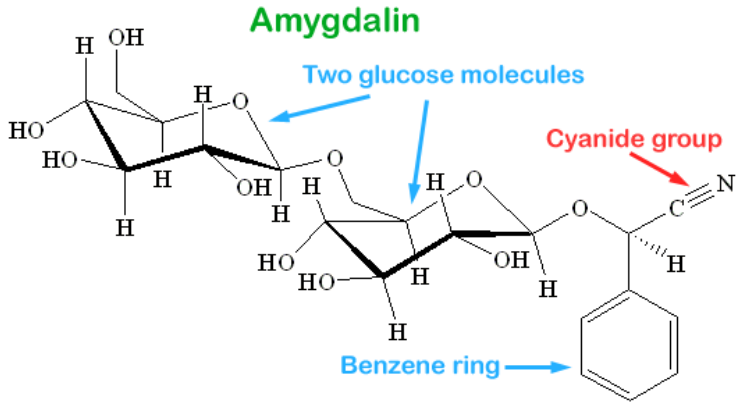
Medical Tourism

Travel to a country with less stringent regulations

Obtain treatment not otherwise available



Stem Cell Medical Tourism

COUNTRY	% OF CLINICS
1. USA	27
2. China	12
3. India	12
4. Thailand	11
5. Mexico	9
6. Argentina	3
7. Australia	3
8. Austria	3
9. Germany	3
10. Ukraine	3
11. Malaysia	3
12. Colombia	1
13. Dominican Republic	1
14. Israel	1
15. Korea	1
16. Lebanon	1
17. New Zealand	1
18. Panama	1
19. Phillipines	1
20. Russia	1
21. Spain	1

- An estimated 60,000 patients treated every year with unproven stem cell therapies
- Between $300 million and $2.4 billion spent every year on such treatments

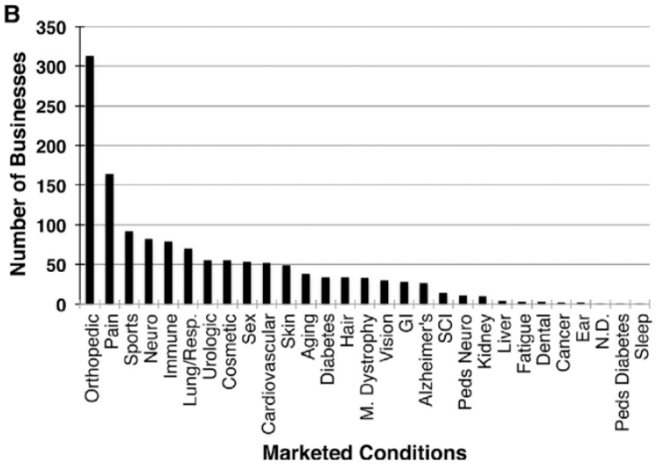
Connolly et al., Travel Med. Infect. Dis., 2014

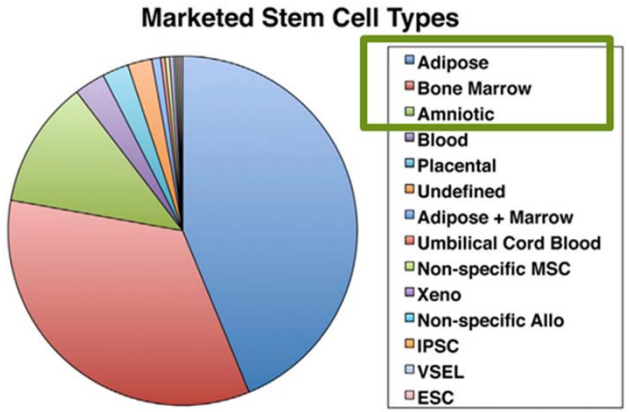
Deans et al., Cytotherapy, 2016

Defining Unproven Cell-Based Therapies

- Unclear scientific rationale to suggest efficacy
- Lack of understanding of scientific mechanism and/or biologic function to support clinical use
- Insufficient data from laboratory studies, animal models, or clinical studies to support use in patients
- Lack of a standardized approach to confirm product quality or manufacturing consistency
- Inadequate information disclosed to patients in order to obtain proper informed consent
- Use of non-standardized or non-validated methods of administration
- Uncontrolled experimental procedures in humans

Unproven Stem Cell Interventions

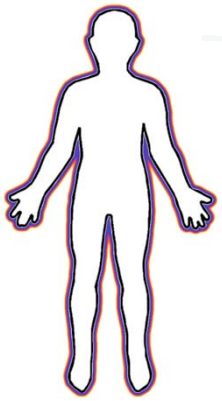




- Mode of administration:
  - Intravenous
  - Intrathecal
  - Intramuscular
  - Nebulized

Turner and Knoepfler
Cell Stem Cell 2016

Unproven Stem Cell Interventions



Fat
Blood
Bone Marrow

SVF
MSCs

Same day collection, isolation and re-administration

Turner and Knoepfler,
Cell Stem Cell, 2016

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Stem Cell Clinics and FDA Regulations

- Human cells and tissue-based products (HCT/Ps) are considered drugs (section 351 of the PHS Act): need demonstration of safety and efficacy (e.g. through clinical trials)

- Exceptions to this rule:
  - Cell products that are minimally manipulated, intended for homologous use and not combined with other articles (section 361 of the PHS Act)
  - Destined for use in the same individual within the same surgical procedure (surgical exemption)

- Most stem cell businesses in the U.S. claim these two exemptions to avoid having their products/interventions considered as drugs

Lysaght and Campbell, Cell Stem Cell, 2011
Turner, Trends Mol Med, 2015

Stem Cell Clinics: Target Aging Demographics

Turner and Knoepfler 2016

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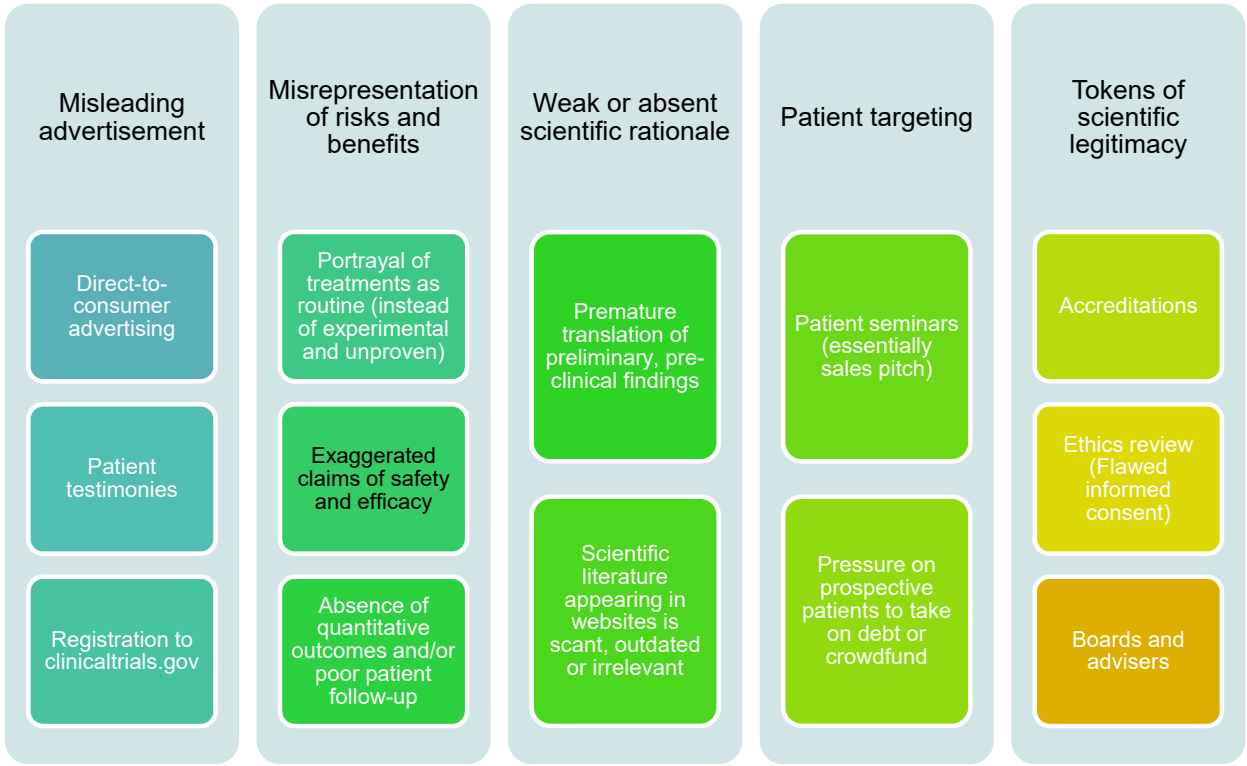
Businesses offering unproven stem cell interventions



Businesses offering unproven stem cell interventions

Misleading advertisement

- Direct-to-consumer advertising
  - Social media
- Registration to clinicaltrials.gov

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Businesses offering unproven stem cell interventions

Misrepresentation of risks and benefits

- Portrayal of treatments as routine (instead of experimental and unproven)
- Exaggerated claims of safety and efficacy
- Absence of quantitative outcomes and/or poor patient follow-up

Businesses offering unproven stem cell interventions

Patient targeting

- Patient seminars (essentially sales pitch)
- Pressure on prospective patients to take on debt or crowdfund

The Washington Post

Democracy Dies in Darkness

MONDAY, DECEMBER 2, 2019

Clinic makes its pitch: Beg, borrow and heal

Lung Health Institute offers unproven treatments to desperate patients — and even coaches them on raising the cash

BY WILLIAM WAN AND LAURIE MCGINLEY

Tammy Rivero and 34 others are seeking class-action status in a lawsuit accusing the Lung Health Institute of deceptive marketing.

Ukraine leader in risky position

CORRUPTION FIGHT MAY ANGER TRUMP

Giuliani contact is ousted in review of prosecutors

BY MICHAEL BIRNBAUM AND DAVID L. STERN

KYIV, UKRAINE — By the end of

Not covered by insurance

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Businesses offering unproven stem cell interventions

Tokens of scientific legitimacy

- Accreditations
- Ethics review (Flawed informed consent)
- Boards and advisers

An unproven/unauthorized use of cell therapy disaster

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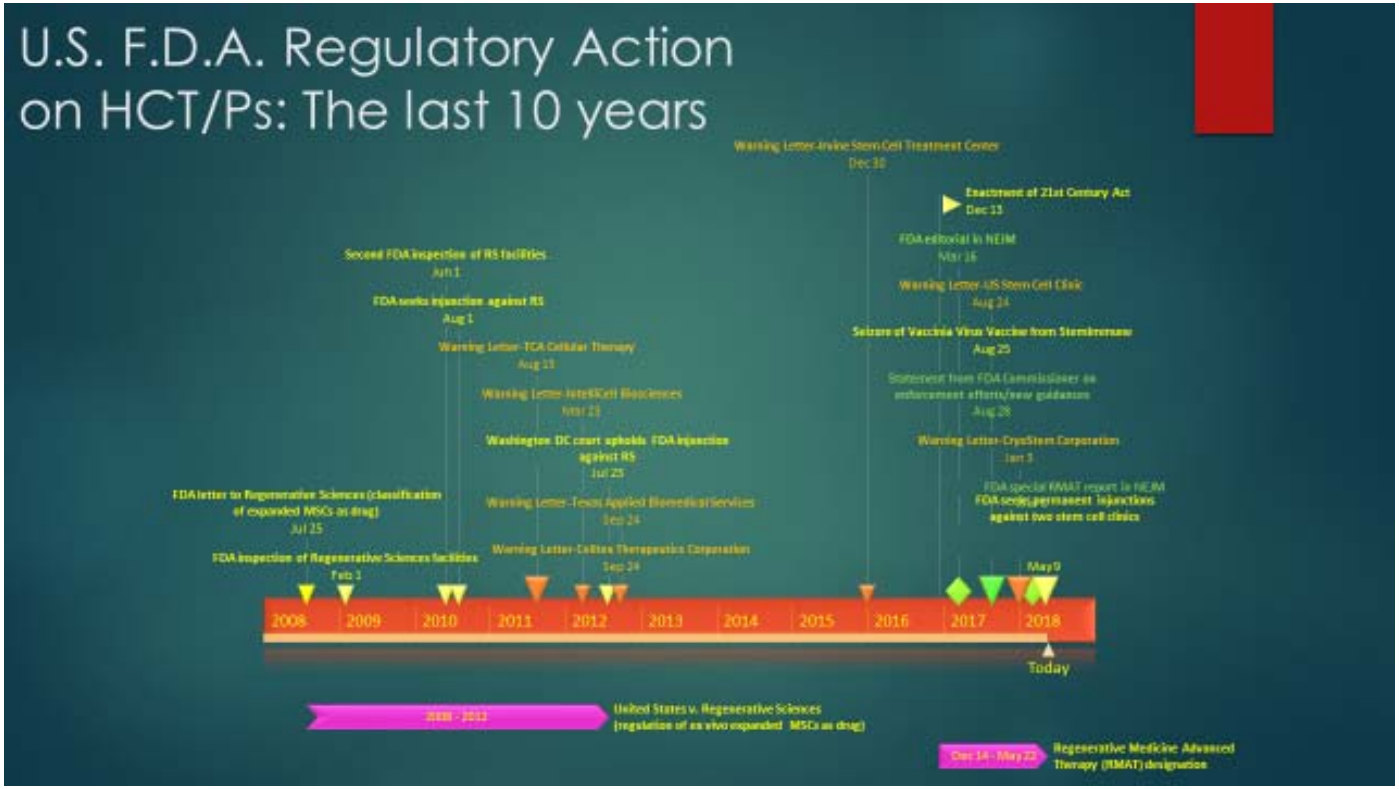
Fighting Back



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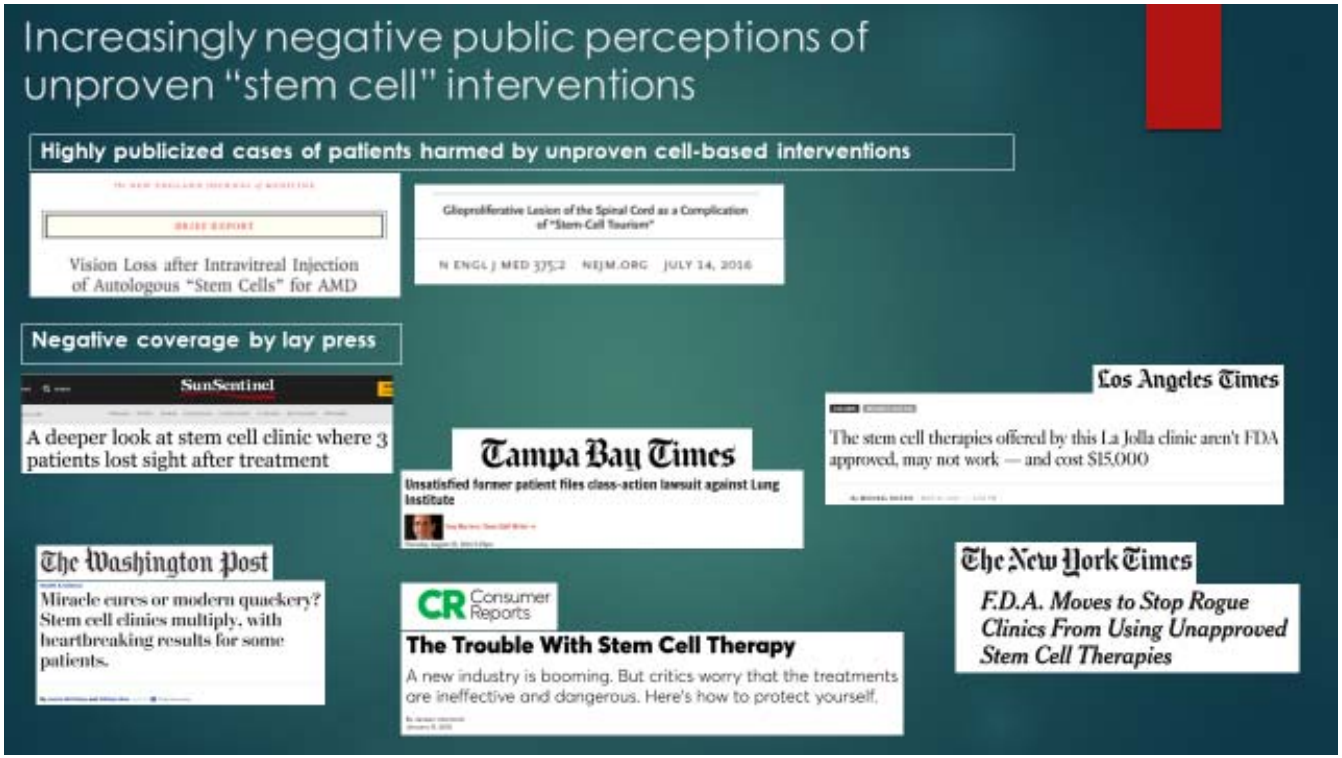
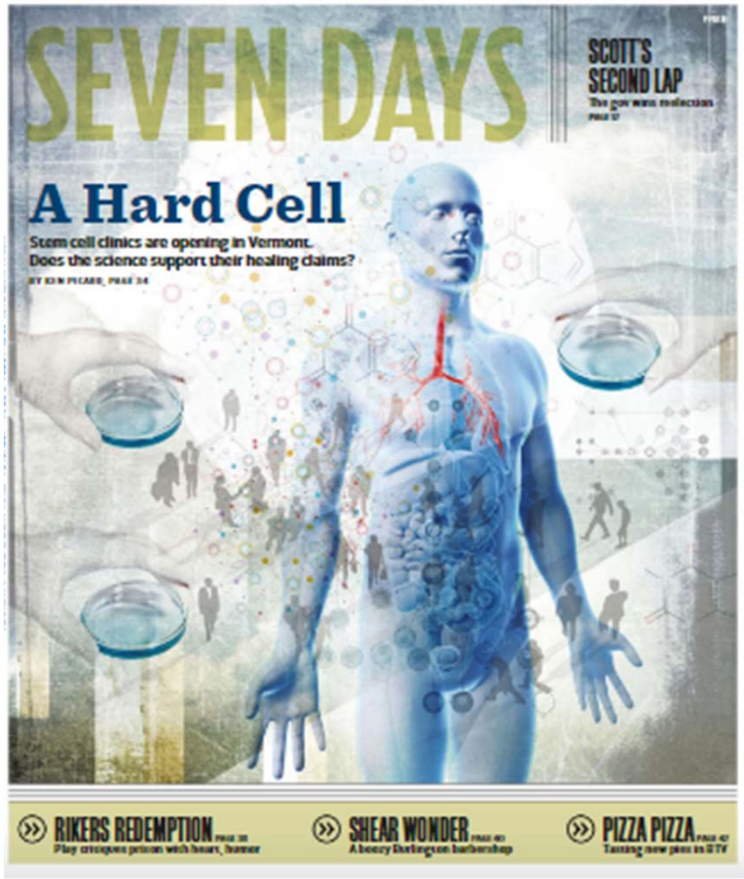
Fighting Back



Fighting Back



Ken Picard
Seven Days

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FIRST OPINION

Kudos to Google for banning stem cell ads. Other tech companies should follow

By JEREMY SNYDER / SEPTEMBER 24, 2019

DENIS CHARLET/AFP/GETTY IMAGES

Google took an important step this month toward restricting the reach of one breed of 21st-century snake oil purveyor: those selling stem cell treatments. Others need to follow its lead.

More than 600 clinics in the U.S. and many more around the world have co-opted the *potential* of using stem cell treatments to cure a range of medical conditions and now sell these treatments

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Resources

- ISSCR - A patient-centered online guide: http://www.closerlookatstemcells.org/
- ISCT – A reference guide on unproven cellular therapies: http://www.celltherapysociety.org/
- Cytotherapy, 18(1), January 2016 – A special section on Unproven Cell Therapies: http://www.celltherapyjournal.org/issue/S1465-3249%2815%29X0003-X
- Canadian Stem Cell Foundation – Short educational videos on stem cells: http://stemcellfoundation.ca/en/about-stem-cells/what-is-a-stem-cell/
- Patient information sheet: https://jamanetwork.com/journals/jama/fullarticle/2598269

VERMONT MEDICAL SOCIETY RESOLUTION

Stem Cell Clinics

- **RESOLVED, that the Vermont Medical Society disseminate evidence-based information to its members regarding stem cell clinics and therapies and encourage members to have evidence based discussions with their patients when they inquire about such services; and be it further**

- **RESOLVED, that VMS coordinate with appropriate professional licensing boards, the Attorney General's Office and other regulatory bodies to ensure that patients seeking stem cell therapies are provided safe and evidence-based information and services.**

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Summary

- Regenerative Medicine
- Stem Cells
  - Embryonic
  - Induced Pluripotent
  - Endogenous Progenitor
  - Hematopoietic Stem Cell (HSC)
  - Mesenchymal Stromal Cell (MSC)
- Unproven Stem Cell Therapies