Stem Cells and Stem Cell Medical Tourism

Vermont State House
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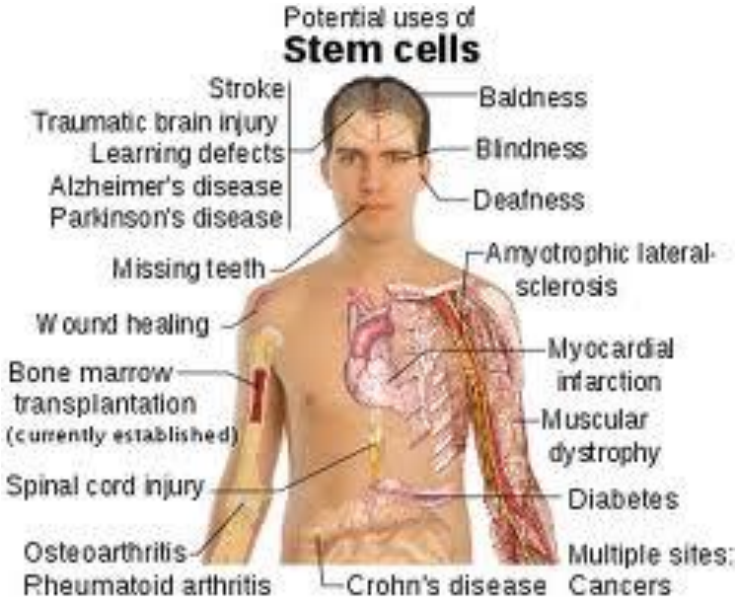
Disclosures

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

Overview

- Stem Cells
  - Embryonic and Induced Pluripotent
  - Hematopoietic (HSC)
  - Mesenchymal (MSC)
- Current FDA-approved use of stem cells
  - HSCs only: bone marrow transplantation
- Unproven, unauthorized use of stem cells
  - MSCs
  - Scope of problem
- Countering the problem

What can you do with ESCs?



<u>Goal: Repair damaged or diseased tissue</u>

A) Administer ESCs

Go to damaged organ and differentiate into organ-specific cells

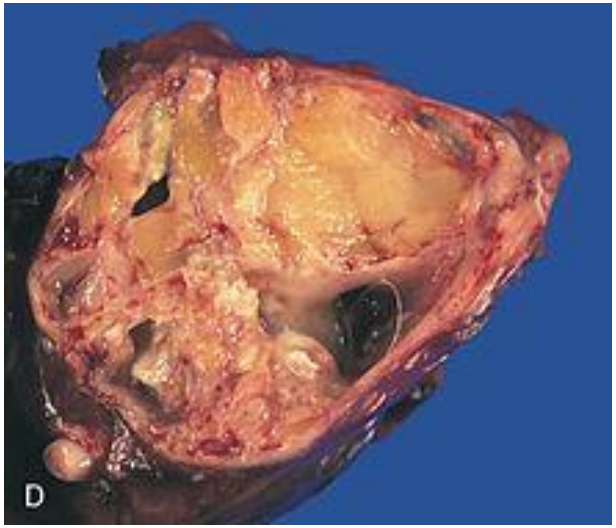
B) Differentiate the ESCs to the desired cells or tissue in culture and then administer

Theoretically unlimited potential

Problems with ESCs

- Ethical, moral, religious, political
- Source?
- Teratomas

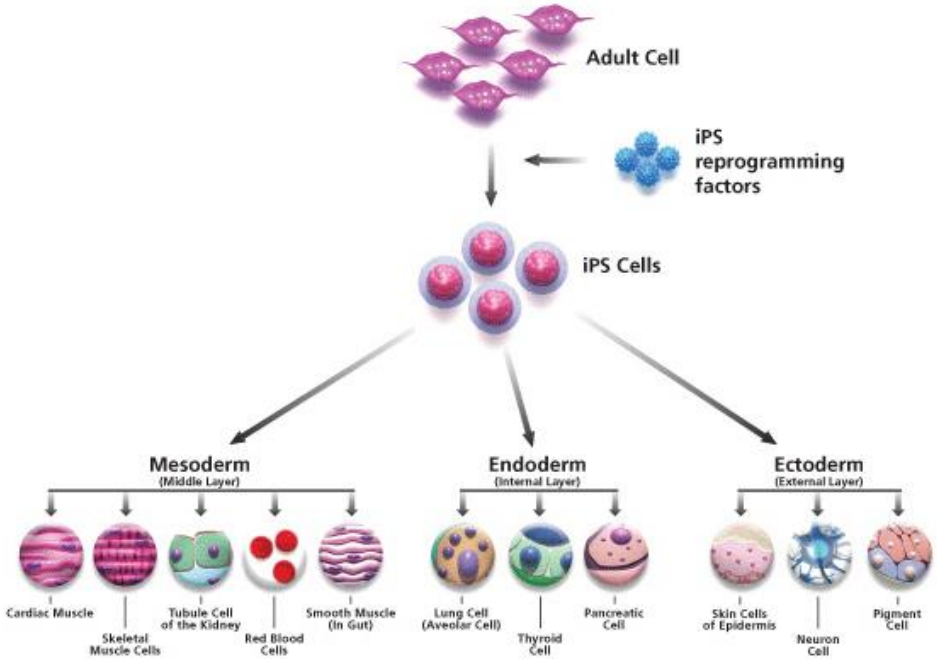
  Tumors containing multiple types of tissues
  Skin
  Muscle
  Bone
  Hair
  Teeth



- **Few clinical trials**
- **Many years from clinical use**
- **No approved therapies**

Induced Pluripotent Stem Cells (iPS)

- Functional adult ESC equivalent
- No ethical, religious, moral, political concerns
- Same problems: teratomas



- **Few clinical trials**
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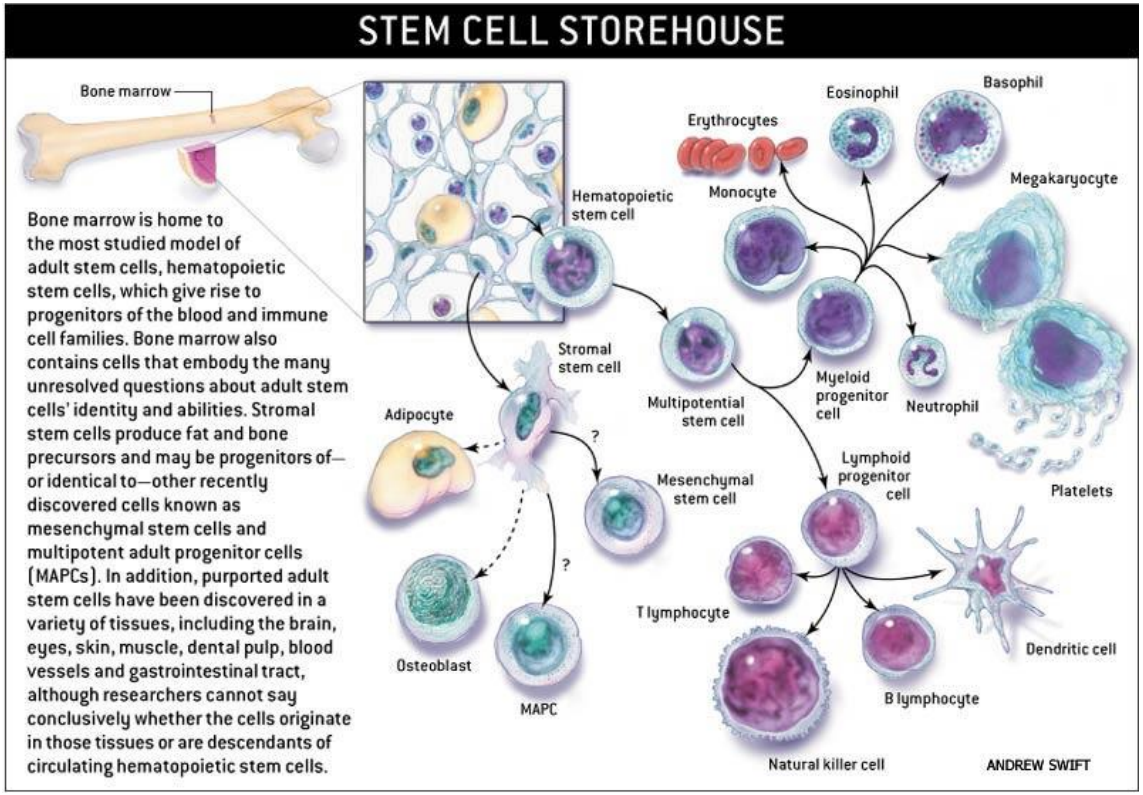
Adult Stem Cells

Bone marrow, adipose, cord blood, placenta, etc.

Bone marrow produces several different types of stem cells

Hematopoietic stem cell (HSC)

Mesenchymal derived stromal cells (MSC)



Lanza and Rosenthal Scientific American June 2004

Hematopoietic Stem Cells

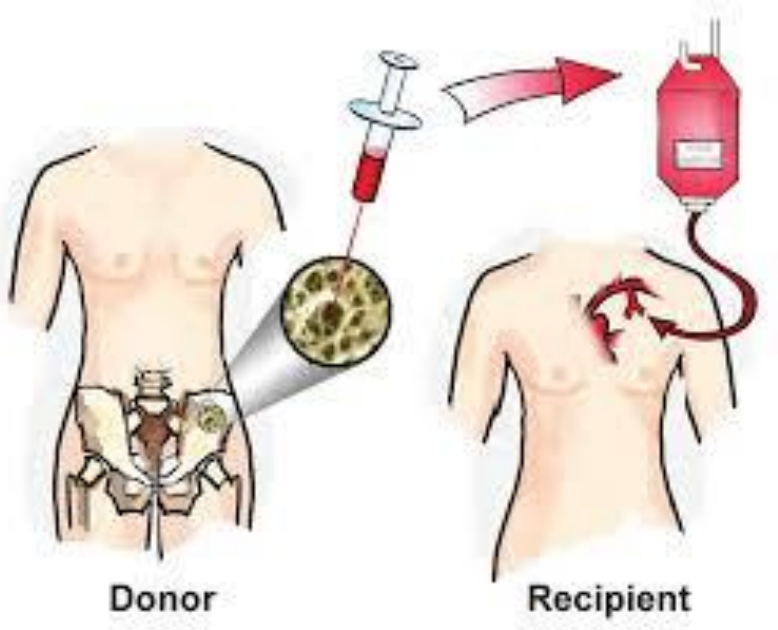
Bone marrow, circulating adult blood, umbilical cord blood

Replenish bone marrow damaged by cancer treatments

Not directly treating cancers

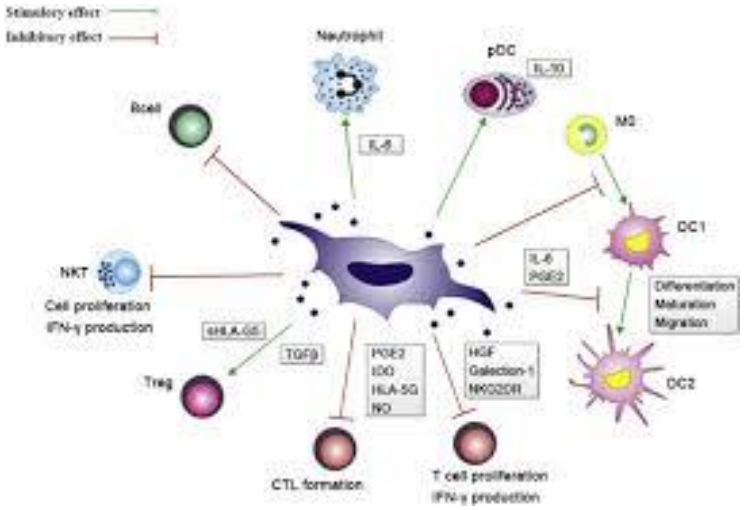
FDA approved for leukemias and lymphomas
- Autologous
- Allogeneic

Widely and successfully utilized



Immunomodulation: Mesenchymal Stem (Stromal) Cells

- Initially isolated from bone marrow: fat, placenta, cord blood
  - Do not circulate in adult blood
- Differentiation ability: bone, fat, cartilage
- Immunomodulatory role
  - Sample and react to inflammatory environments
- Immunoprivilege
- Many clinical trials
- Approved for limited indications in Canada and New Zealand



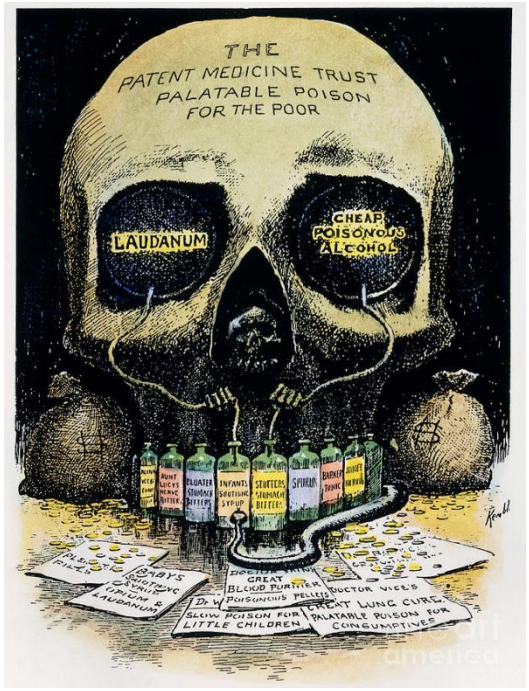
No FDA-approved use in US

Nothing on-label: no justifiable “off-label” uses

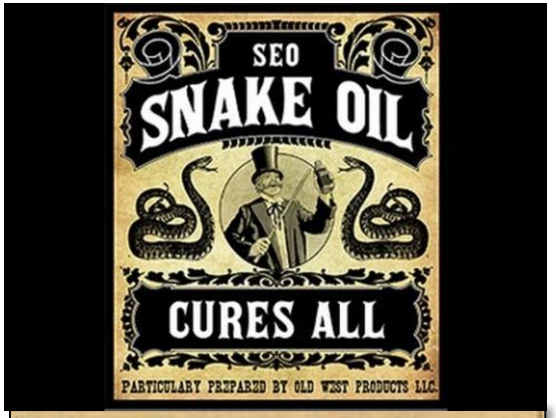
Unproven Stem Cell Therapies

- 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

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, to effect 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.

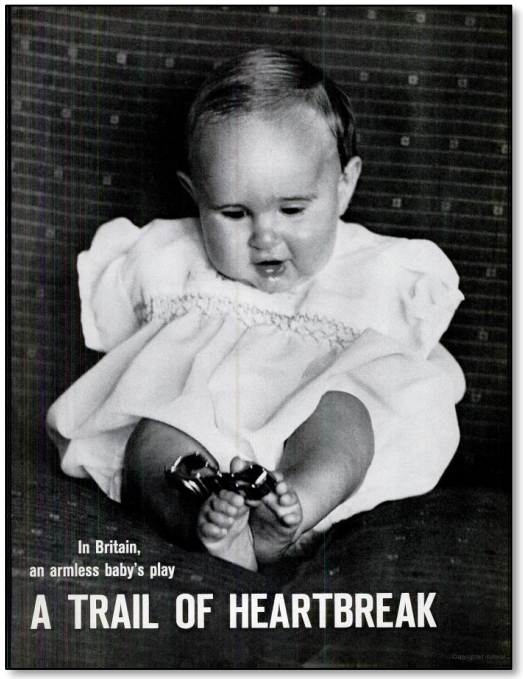
Every agent of the United States Food and Drug Association, said Dr. Morris Fishbein, spokesman of the Medical Association, is scouring the country to recover the bottles. By some time on Monday, said J. G. Clarke of the Food and Drug Administration, it is hoped that all of the "outstanding" shipments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

[illegible] in the fact that large dosages are customary with sulfanilamide preparations.

The medicine stops the kidneys. As 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 latest effect, although not itself classed as a poison.

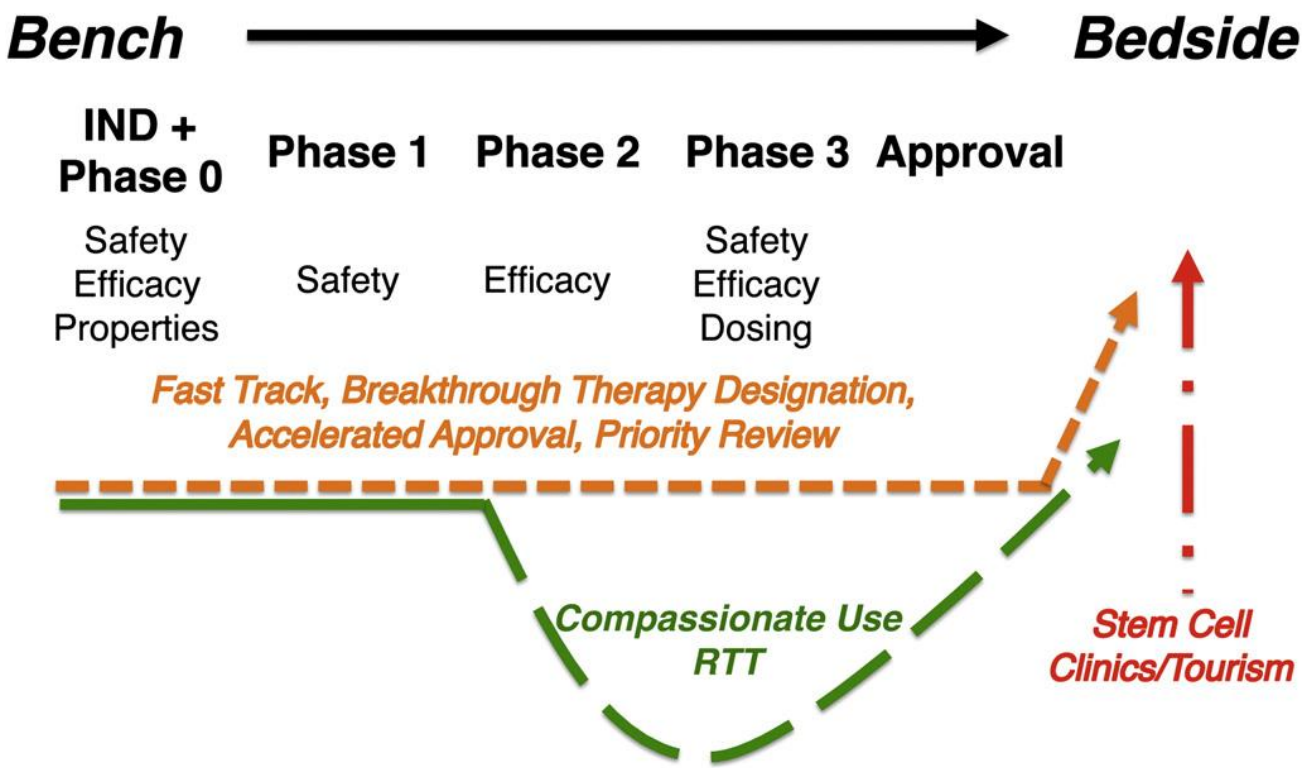
The principal shipments, said Mr. Clarke, went to the South and Midwest. But in addition consignments have been traced to the Northern Peninsula of Michigan, to a distributing house in New York City and to another in San Francisco. An

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



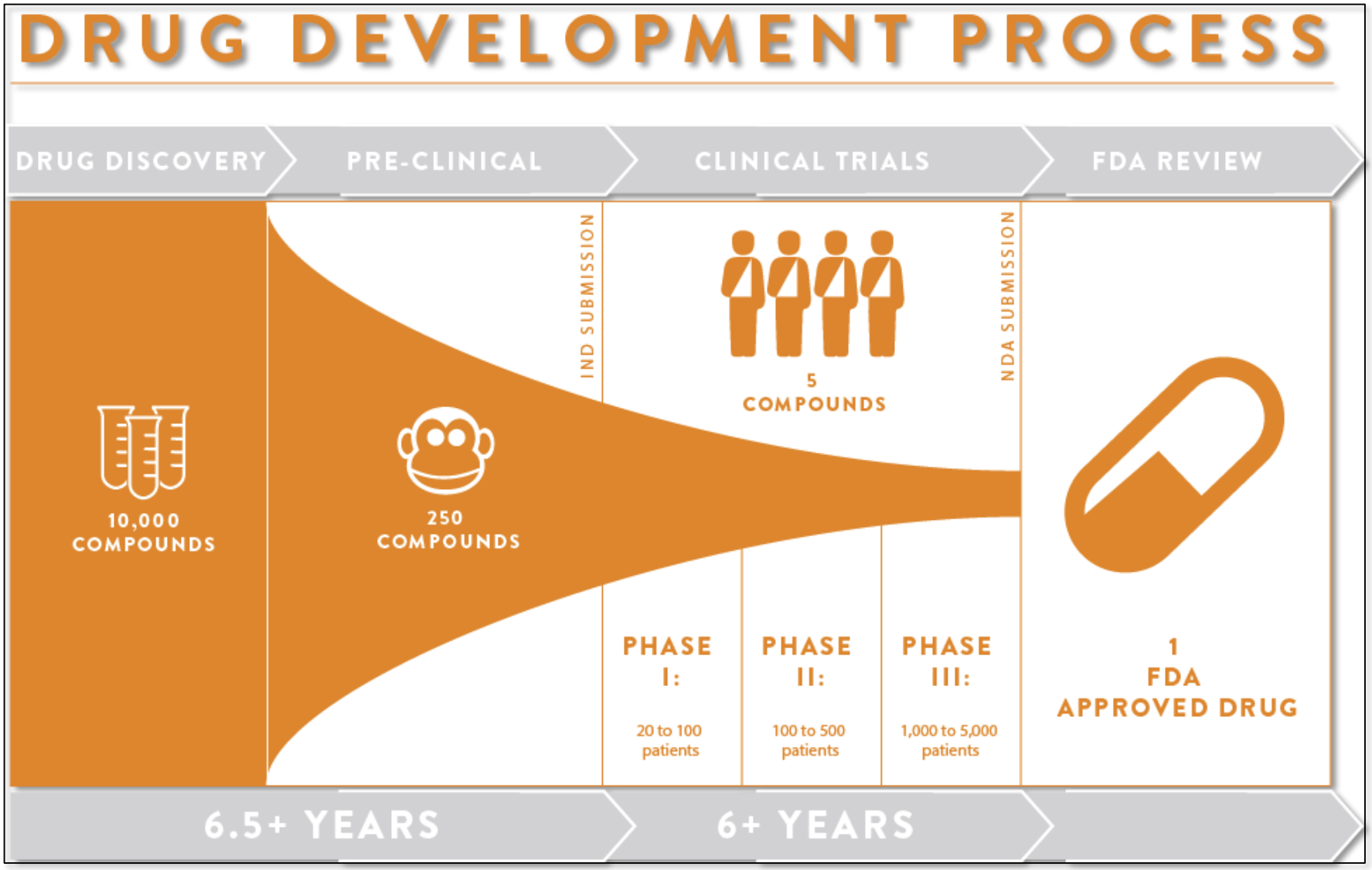
1962 – FDCA amended to require **efficacy** testing
*(PMDA established in 2000)

FDA Pathways for New Therapies



Knoepfler, Adv Drug Deliv Rev, 2015

FDA Pathways for New Therapies

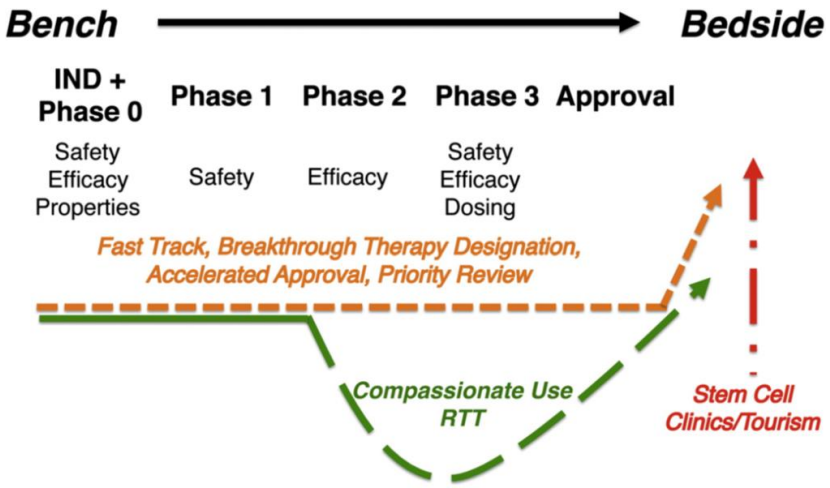


Source: www.givetocure.org

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

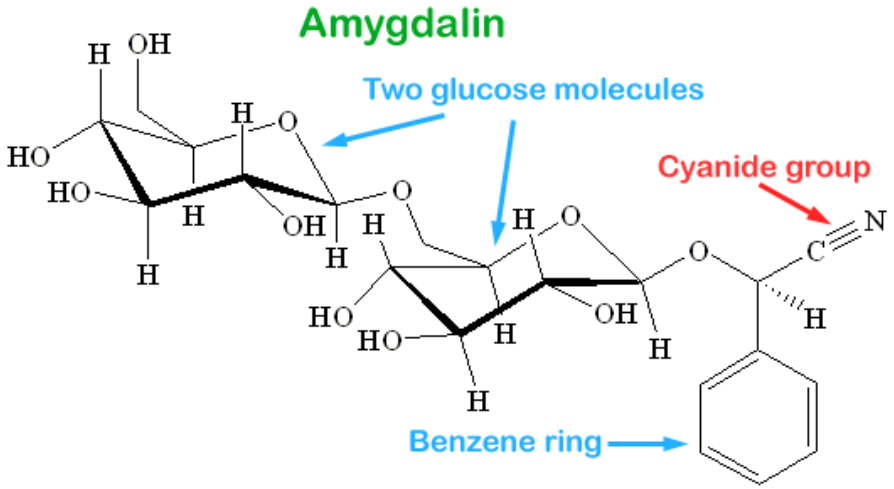
As of September 2019:

- 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

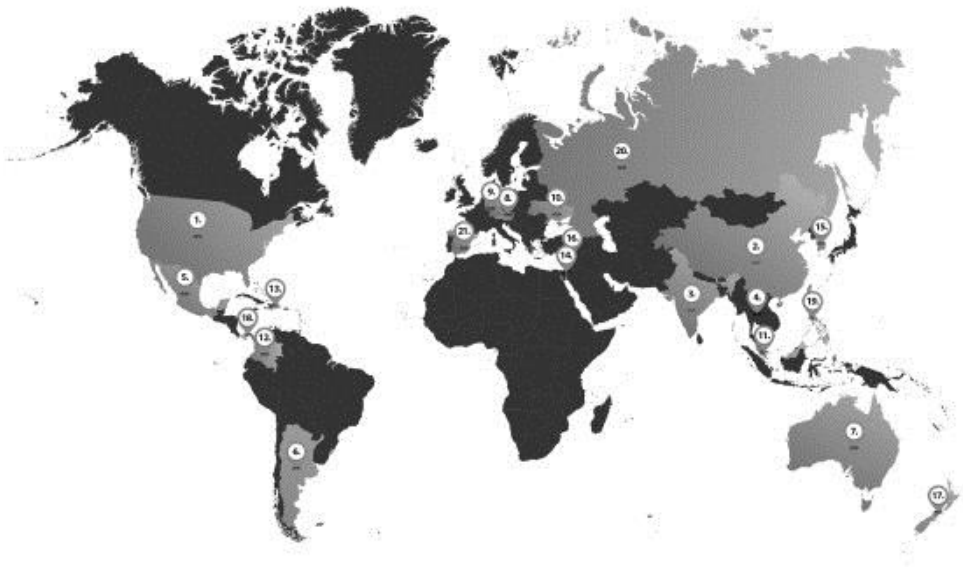
Medical Tourism

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

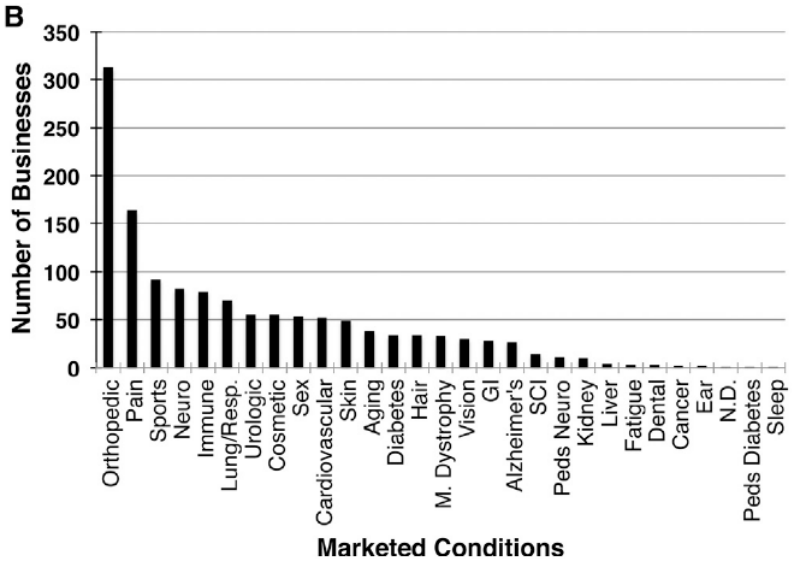
Connolly et al., Travel Med. Infect. Dis., 2014

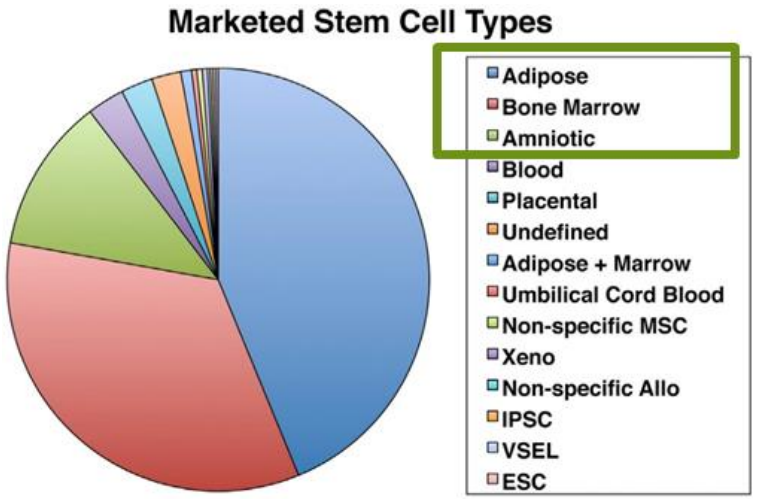
Deans et al., Cytotherapy, 2016

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

Stem Cell Clinics and FDA Regulations

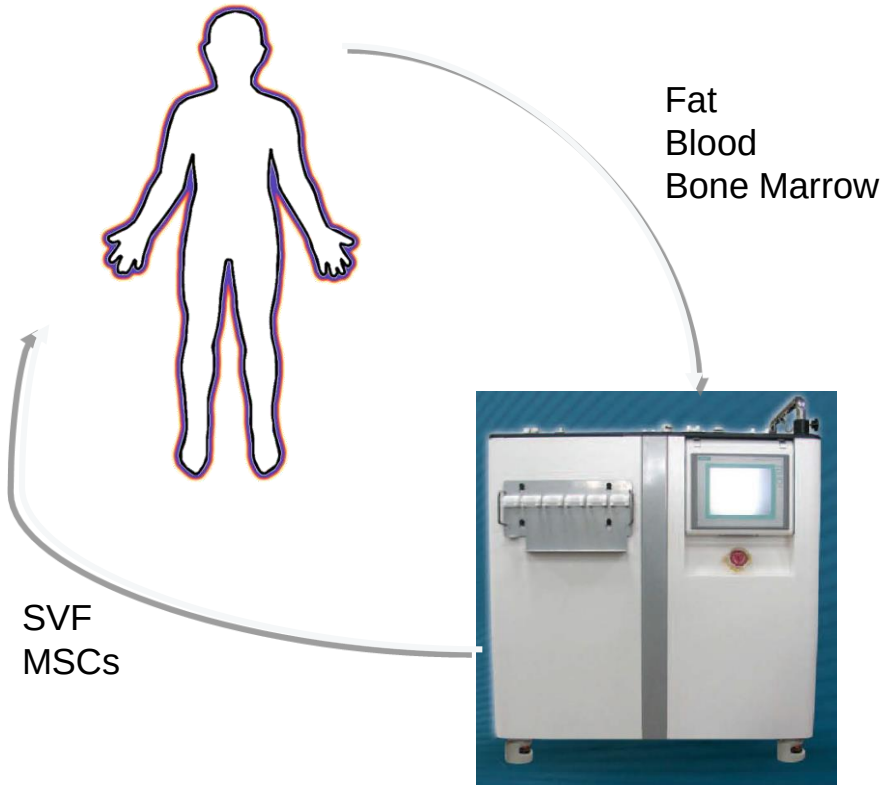
- Human cells and tissue-based products (HCT/Ps) are considered drugs (section 351 of the PHS Act): need demonstration of safety and efficacy (e.g. through clinical trials)

- 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 US 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

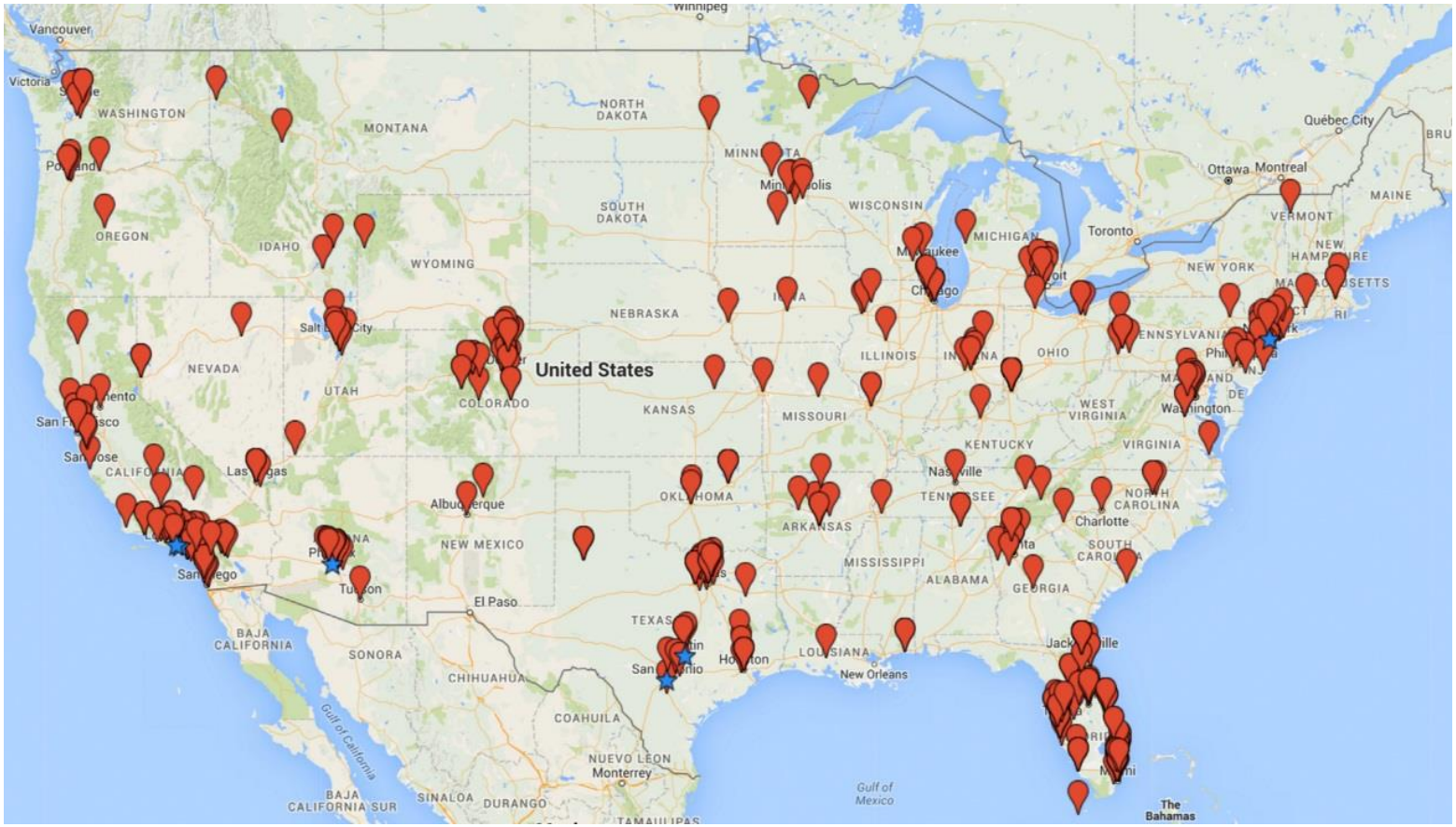
Unproven Stem Cell Interventions



Same day collection, isolation and re-administration

Turner and Knoepfler,
Cell Stem Cell, 2016

Stem Cell Clinics: Target Aging Demographics



Turner and Knoepfler 2016

Businesses offering unproven stem cell interventions

<u>Misleading advertisement</u>

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

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 Rivera 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

An unproven/unauthorized use of cell therapy disaster

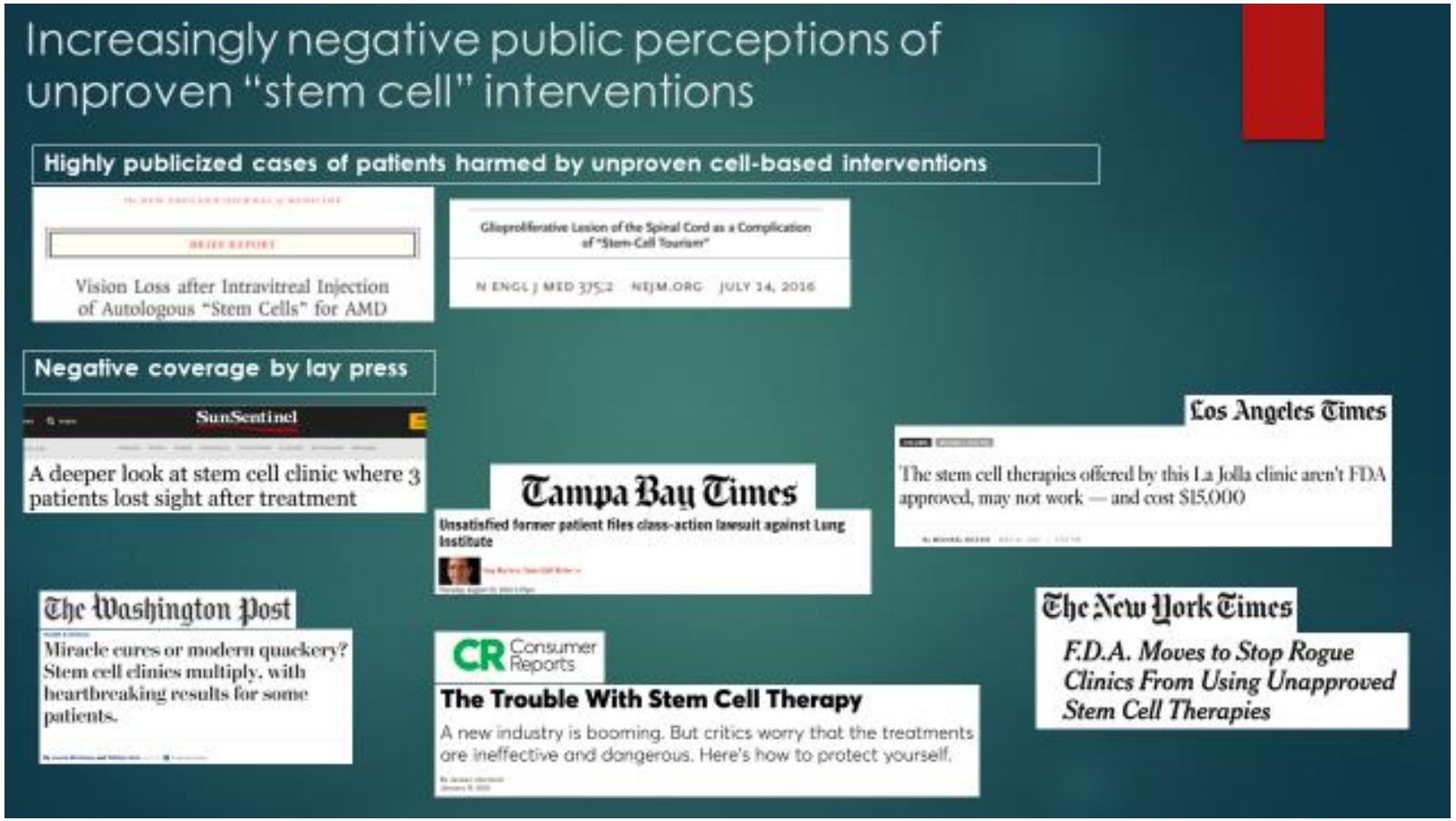
The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Vision Loss after Intravitreal Injection of Autologous "Stem Cells" for AMD

Fighting Back

Fighting Back



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

Fighting Back

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.**