Stem Cell Therapies: Hype and Hope
Community Medical School
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Daniel J. Weiss MD PhD
Professor of Medicine
University of Vermont
UVM Larner College of Medicine
Vermont Lung Center

Chief Scientific Officer
International Society for Cellular Therapies

Emeritus Chairman
ATS Stem Cell Working Group
Disclosures

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• Medical Technology Enterprise Consortium
Overview

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

- Early development and normal tissue repair
- Disease research and drug development
- Cell therapy
- Tissue engineering and regenerative medicine
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)
Regenerative Medicine: Bioengineering New Tissues and Organs

1st Regenerative Medicine Scientist?
Embryonic Stem Cells

Potential uses of Stem cells

- Stroke
- Traumatic brain injury
- Learning defects
- Alzheimer's disease
- Parkinson's disease
- Missing teeth
- Wound healing
- Bone marrow transplantation (currently established)
- Spinal cord injury
- Osteoarthritis
- Rheumatoid arthritis
- Crohn's disease
- Multiple sites: Cancers
- Amyotrophic lateral-sclerosis
- Myocardial infarction
- Muscular dystrophy
- Diabetes

Theoretically Unlimited Potential
Where do we get Human Embryonic Stem Cells?

Embryonic Development

- Fertilized egg
- 2-cell stage
- 4-cell stage
- 8-cell stage
- 16-cell stage
- Blastocyst
- Foetus - 4 weeks
- Foetus - 10 weeks
- Foetus - 16 weeks
- Foetus - 20 weeks
Embryonic Stem Cells

Mouse: 1960’s

Human: 1998

Differentiate into all adult tissues
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
  • Ophthalmologic: 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”
Issues with using Induced Pluripotent Stem Cells (iPS)

• Teratomas: same as ESCs

• Epigenetic memory
  • Once a skin cell, always a skin cell
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
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
Interim Summary

- Regenerative Medicine
- Stem Cells
  - Embryonic
  - Induced Pluripotent
  - Endogenous Progenitor
  - HSC
  - MSC
- 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
History of US Drug Regulation

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

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

1962– FDCA amended to require **efficacy** testing
*(PMDA established in 2000)*
History of US Drug Regulation
FDA Pathways for New Therapies

FDA Pathways for New Therapies

**Drug Development Process**

- **Drug Discovery**: 10,000 compounds
- **Pre-Clinical**: 250 compounds
- **Clinical Trials**:
  - Phase I: 20 to 100 patients
  - Phase II: 100 to 500 patients
  - Phase III: 1,000 to 5,000 patients
- **FDA Review**: 5 compounds
- **FDA Approved Drug**: 1

*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
Medical Tourism

Travel to a country with less stringent regulations

Obtain treatment not otherwise available
Stem Cell Medical Tourism

- 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
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
Stem Cell Clinics: Target Aging Demographics

Turner and Knoepfler 2016
Businesses offering unproven stem cell interventions

- Misleading advertisement
  - Direct-to-consumer advertising
  - Patient testimonials
  - Registration to clinicaltrials.gov

- 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

- Weak or absent scientific rationale
  - Premature translation of preliminary, pre-clinical findings
  - Scientific literature appearing in websites is scant, outdated or irrelevant

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

- Tokens of scientific legitimacy
  - Accreditations
  - Ethics review (Flawed informed consent)
  - Boards and advisers
Businesses offering unproven stem cell interventions

**Misleading advertisement**
- Direct-to-consumer advertising
  - Social media
- Registration to clinicaltrials.gov
Businesses offering unproven stem cell interventions

**Misrepresentation of risks and benefits**
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Businesses offering unproven stem cell interventions

Patient targeting

• Patient seminars (essentially sales pitch)

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Not covered by insurance
Businesses offering unproven stem cell interventions

**Tokens of scientific legitimacy**
- Accreditations
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An unproven/unauthorized use of cell therapy disaster

Vision Loss after Intravitreal Injection of Autologous “Stem Cells” for AMD
Fighting Back

U.S. F.D.A. Regulatory Action on HCT/Ps: The last 10 years
Increasingly negative public perceptions of unproven “stem cell” interventions

Highly publicized cases of patients harmed by unproven cell-based interventions

Negative coverage by lay press

Los Angeles Times

The stem cell therapies offered by this La Jolla clinic aren’t FDA approved, may not work — and cost $5,000.

Tampa Bay Times

Unsatisfied former patient files class-action lawsuit against Lung Institute

The Washington Post

Miracle cures or modern quackery? Stem cell clinics multiply, with heartbreaking results for some patients.

CR Consumer Reports

The Trouble With Stem Cell Therapy

A new industry is booming. But critics worry that the treatments are ineffective and dangerous. Here’s how to protect yourself.
Fighting Back

Ken Picard
Seven Days
Kudos to Google for banning stem cell ads. Other tech companies should follow

By JEREMY SNYDER / SEPTEMBER 24, 2019

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.
Resources

• ISSCR - A patient-centered online guide: http://www.closerlookatstemcells.org/

• ISCT – A reference guide on unproven cellular therapies: http://www.celltherapysociety.org/

• Cytotheraphy, 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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