STEM CELL-BASED THERAPIES: CHALLENGES & OPPORTNITIES

Bruce Fishman, MD, MPH, FICS

Objectives

1. Learn about different types of stem cells, and their function.
2. Understand how stem cells work in the treatment of disease and injury.
3. Discover some of the current medical uses and diseases being treated with stem cells.
4. Discuss the FDA codes in regulating the approach to implantation/infusion of human cells, tissues, and cellular-based products.
5. Explore future directions in stem cell research to improve health and quality of life.

Why Discuss Stem Cells at a W/C Conference?

We are occasionally getting authorization from the carrier to treat work injured patients with Ortho-biologics including **Stem Cells** and platelet rich plasma.

Peer Review Services Division
Peer Review Report

Referral Date:	05/19/2017	**Review Type:**	Workers Comp
Claimant's Name:	[redacted]	**Group/Policy/ Claim Number:**	301666335600001
MES Case Number:	[redacted]	**Service:**	Prospective Pre-Certification
Client:	Sedgwick	**Referred By:**	[redacted]

DATA REVIEWED AND CONTACT INFORMATION:
Data reviewed consisted of the Sedgwick CMS referral form and the submitted clinical documentation.

- Sedgwick Referral Form
- Request for Authorization dated 5/12/2017
- Primary Treating Physician's Progress Report dated 5/12/2017

I called the attending provider (AP) on 5/23/17 at 1:44 PM ET. I spoke Dr. Fishman advised the claimant has limited range of motion (ROM), and tenderness. She had had extensive conservative care including physical tenderness (PT), and splinting/bracing. There have no cortisone injections because the claimant has been a diabetic since she was a child. She is insulin dependent. They are limited as to the treatment is capable of having for her condition. He was going to be faxing the MRI report as there was significant pathology.

MES called the AP on 5/23/17 at 5:00 pm EST regarding the request below. The determination was left with Carlos.

SUMMARY OF RECORDS:
On 5/12/17, the claimant presented to Dr. Bruce Fishman for follow up. The claimant completed 8 sessions of PT which seemed to be helping at least the last few sessions. She felt slightly stronger while walking. She continued to feel occasional weakness in the left ankle as well as stiffness and aching pain most over the lateral aspect of the foot. Examination of the left ankle/foot revealed dorsiflexion was 15 degrees on the right and 10 degrees on the left, plantarflexion was 90 degrees on the right and 80 degrees on the left, inversion was 30 degrees on the right and 20 degrees on the left. There was tenderness to palpation noted at the deltoid ligament anterior talofibular ligament (ATFL) and Calcaneofibular Ligament Injury (CFL) and lateral malleolus.

REVIEW QUESTION (S):
1. Is Stem Cell/Platelet Rich Plasma joint injections to left ankle/foot; medically necessary?

Stem Cell/Platelet Rich Plasma joint injections to left ankle/foot; is medically necessary.

W/C Authorization

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W/C Authorization

Bruce E. Fishman, MD
Family Urgent Care & Industrial Medical Clinic
412 West Avenue J
Suite D
Lancaster, CA 93534

Utilization Review Recommendation
Certified
Utilization Review Number: 0002-3745-7800

Notification Date: 9/26/2017

Claimant Name: Donna J Hobbs	Client: Walmart- CA UR
Claim Number: 6325692	Adjuster: Mardy Hopper
Date of Injury: 3/22/2011	
Date Request Received: 9/20/2017	UR Nurse: Elizabeth Thomas RN
Date Completed Medical Received: 9/20/2017	Decision Date: 9/26/2017

Requester: Bruce E Fishman, MD

Services Requested	Determination
Stem Cell/Platelet Rich Plasma Injection, Left Knee	Certified

Services approved from: 9/26/2017 - 11/10/2017

Diagnosis Codes/Descriptions:
S83. 282D-Oth tear of lat mensc, current injury, left knee, subs, M17. 12-Unilateral primary osteoarthritis, left knee

What is a Stem Cell?

A primal, undifferentiated cell from which a variety of other cells and tissue types can develop.

Societies Fascination with Stem Cell Treatment Continues to Permeate the Media

CNN Stem Cell Video

CNN Stem Cell Video

TIME Magazine

named fat stem cell extraction one of the 50 Best Inventions of the Year!*

As Seen in Newspapers…

Stem Cells have brought the field of regenerative medicine to the forefront

Bruce Fishman, MD, MPH, FICS

What is Regenerative Medicine?

A branch of medicine and research involving tissue engineering and molecular biology to regenerate human cells, tissues, or organs to restore normal functions.

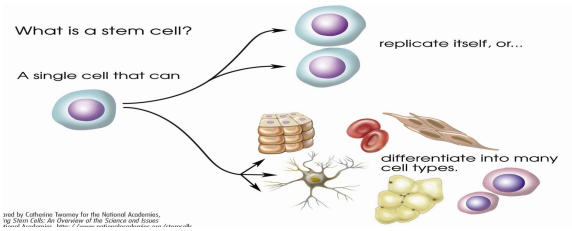
This is a game changing area of medicine, utilizing biologics and offering solutions and hope for people who have conditions that today are beyond repair

Bruce Fishman, MD, MPH, FICS

Biologics in Regenerative Medicine Include:

- Stem cells
- Platelet rich plasma (PRP)
- Growth factors
- Cytokines (inflammatory modulators)

Stem Cell Capabilities

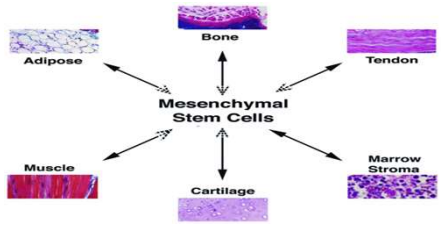


Specialized kind of cell with unique capacity to continually renew itself, give rise to other specific cells or tissues, and control inflammation.

How do Stem Cells Repair Injured/Damaged Tissue?

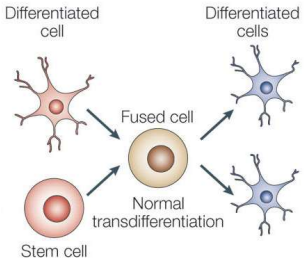
- Direct methods
- Indirect methods

Direct Repair Methods



Stem cells directly differentiate into the damaged cell types.

Direct Repair Methods

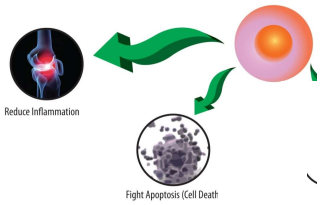


Cell fusion

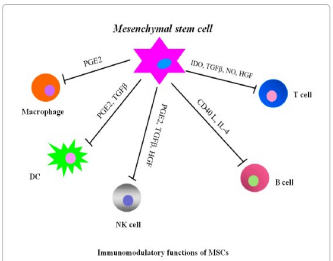
- Stem cells fuse with normal or injured cells and help regenerate damaged tissue

Indirect Repair Methods

- Secrete growth factors and limit inflammation
- Inhibit programmed cell death (apoptosis)

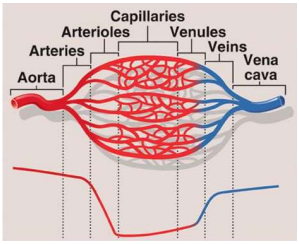


Indirect Repair Methods



Immuno-modulation affects T lymphocytes, macrophages, and other cells in or immune surveillance system.

Indirect Repair Methods



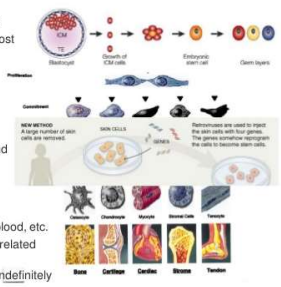
Stimulates re-establishment of blood supply, which is fundamental for recovery of damaged tissue .

Different Types of Stem Cells

Embryonic Stem Cells (ESCs)
- Derived from the blastocyst of a 5 day-old embryo
- Are pluripotent, i.e., they can differentiate into almost any cell type in the body (primary-like cells)
- Can renew themselves indefinitely

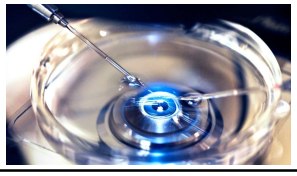
Induced Pluripotent Stem Cells (iPSCs)
- Generated from reprogrammed somatic cells
- Similar or equivalent to ESCs, i.e., pluripotent and the ability to renew themselves indefinitely

Adult Stem Cells (e.g. MSCs, NSCs, ADSCs)
- Isolated from adult tissues, organs or blood, cord blood, etc.
- Are multipotent – i.e., can give rise to a number of related cell types
- Can renew themselves a number of times but not indefinitely

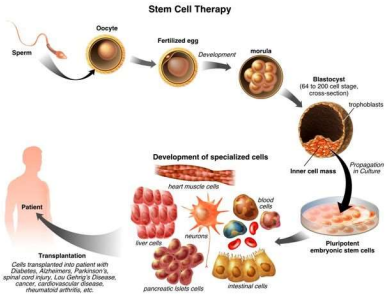


Embryonic Stem Cells (ESC)

Human embryonic stem cells are created from embryos generated by in-vitro fertilizations, a process where eggs are mixed with male sperm in a petri dish and eggs are fertilized.

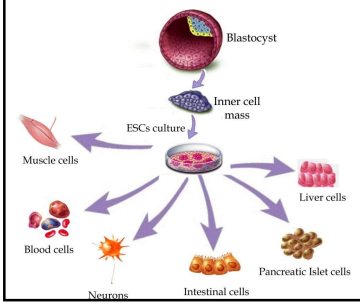


Embryonic Stem Cells (ESC)



The fertilized egg is allowed to divide for about five days to form a hollow ball or blastocyst .

Advantages of Embryonic Stem Cells



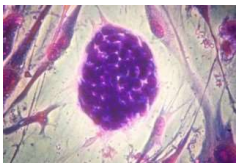
They are "pluripotent". That Means that they can form any type of cell in the entire body.

Disadvantages of Embryonic Stem Cells

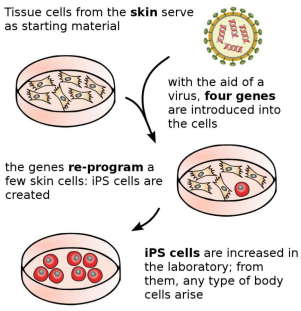
The political, religious, and moral controversy surrounding unborn embryo use in medicine.

Disadvantages of Embryonic Stem Cells

Reports from the medical literature indicate rare tumor formation using embryonic stem cells.



Induced Pluripotent Stem Cells (iPSC)



* Induced pluripotent stem cells are created by taking a normal adult cell (usually skin) and genetically modifying it

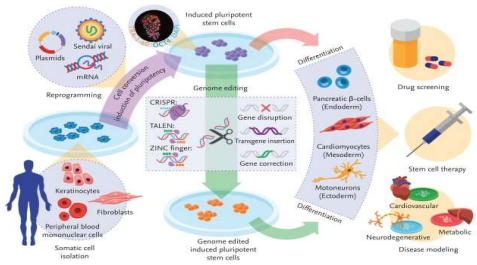
Advantages of iPSC

- iPSC are genetically identical to the donor's own cells, reducing the risk of immune rejection
- Eliminates the need for immunosuppressive medications
- Eliminates the political, moral and ethical problems of working with unborn embryos

Disadvantages of iPSC

Integration of the gene segments in to the cell DNA with a viral vector could possibly cause hazardous mutations.

iPSC Research



Extensive research is currently taking place throughout the world on inducible pluripotent stem cells.

Adult Stem Cells

Potential of Adult Stem Cells

Adult stem cells are multi-potent, not pluripotent. They can become many different cell types, but not all cell types.

Adult Stem Cells

Adult stem cells are the type currently being utilized today at most clinics for the treatment of injury and disease.

Regulations

In 1997, the FDA set forth in title 21, CFR part 1271 regulations indicating its approach to regulating the use of human cells, tissues and tissue-based products (HCT/Ps) intended for implantation, transplantation, infusion, or transfer into a human recipient.

Regulations

This regulation was enacted in order to "prevent the transmission of communicable diseases."
(21 CFR part 1271)

Regulations

Low risk HCT/Ps are regulated by section 361 of the Public Health Service Act which requires only that products be manufactured under good tissue practices to prevent the introduction, transmission, or spread of communicable diseases.

These "361 products" do not require pre-market clinical studies or approval before marketing.

Regulations

Higher risk products are regulated under section 351 of the Public Health Service Act, whereby they also must be manufactured according to good tissue practices as well as additional manufacturing specifications determined on a case-by-case bases by the FDA during a preclinical developmental process.

1. Animal studies
2. Human clinical studies to prove safety and efficacy
3. Must pass a premarket approval process involving clinical studies with an active investigational new drug (IND) application in place
4. Obtain and approved Biologics license

Regulations

Differentiation of low risk 361 products from high risk 351 products is based on four criteria:

1. Minimal manipulation
2. Homologous use (products must carry out the same biologic function as it normally would)
3. Non-combination with other products
4. Lack of systemic effects

Regulations

Certain tissues have been excluded from regulation for the HCT/Ps classification including:

1. Minimally manipulated bone marrow
2. Xenograft
3. Blood products
4. Secreted or extracted products

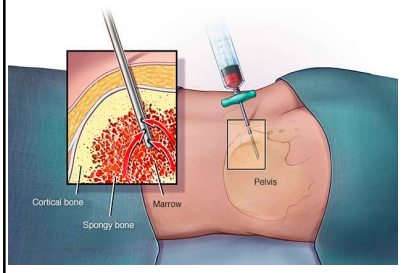
Sources of Adult Stem Cells

- Stem cells harvested from one's own body (autologous stem cell)
- Stem cell harvested from other sources such as placenta, umbilical cord, blood, amniotic fluid (allogenic stem cells)

Adult Stem Cells Harvested from One's Own Body

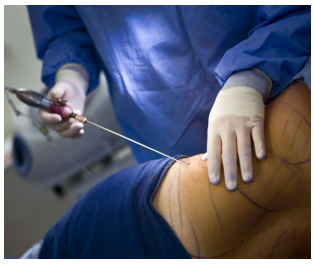
- Most Common sites for harvest:
  - Bone marrow
  - Adipose tissue (fat)
  - Blood

Bone Marrow Harvest



Adult bone marrow stem cells are harvested from the iliac crest of the pelvis.

Adipose Tissue Harvest



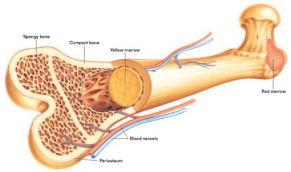
Adult adipose tissue (fat) derived stem cells are harvested utilizing a liposuction technique to obtain stromal vascular fraction.

Laboratory Separation of Stem Cells

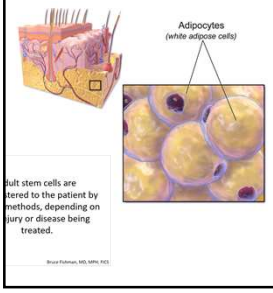
Adult bone marrow and adipose-derived stem cells are put through a laboratory process to separate and concentrate the stem cells.

Adipose Tissue vs Bone Marrow

- Bone marrow extraction yields approximately 5,000-60,000 cells
- These can be cultured over several days into a few million cells prior to deployment



Adipose Tissue vs Bone Marrow



- Adipose tissue has the ability to provide a larger number of stem cells, yielding as many as 10-40 million
- These stem cells are extracted from the stromal vascular fraction (SVF) portion of the adipose tissue from a single procedure

Adult stem cells are administered to the patient by several methods, depending on the injury or disease being treated.

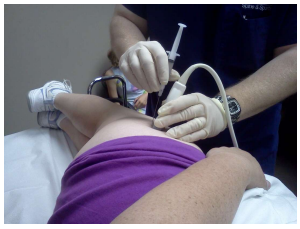
Bruce Fishman, MD, MPH, FICS

Deployment Methods

Direct injection into the injured/diseased areas.

Injections

Knee injection

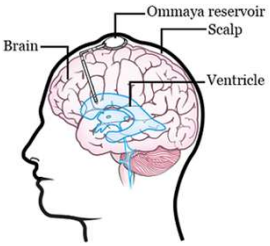


Hip injection

Injections

Spine injection

Injections



Direct injection into the brain

Injections

Intra-abdominal injection

Nebulizer

Breathing in aerosolized stem cells

IV Infusion of Stem Cells

IV infusion augments direct injections for more diffuse/systemic disease injuries and processes.

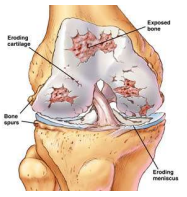
Stem Cell Treatment

Stem cell treatment is being utilized by multiple medical specialties under approved institutional review board protocols.

Orthopedics

Orthopedics

Stem cell treatment of degenerative joint arthritis.



Arthritic Knee

Arthritic Hip

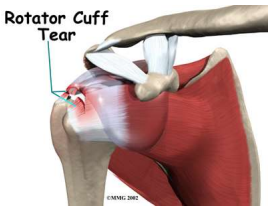
Arthritic Shoulder

Orthopedics

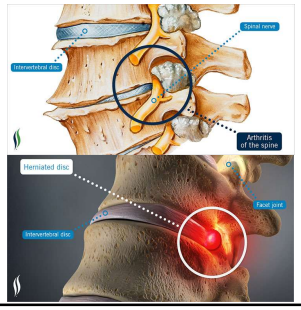
Stem cell treatment of ligament injuries.

Orthopedics

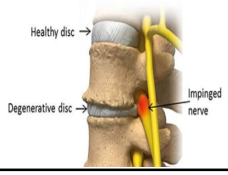
Stem cell treatment of tendon injuries.



Orthopedics



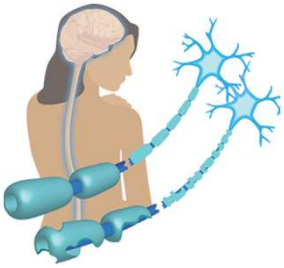
Stem cell treatment of disc injury, disc disease and degenerate arthritis of the spine.



Neurology

Neurology

Stem cell treatment for multiple sclerosis.



Neurology

Stem cell treatment for dementia.

Neurology

Stem cell treatment for Parkinson's disease.

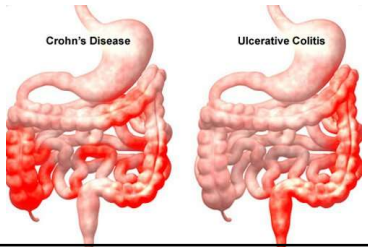
Internal Medicine

Internal Medicine

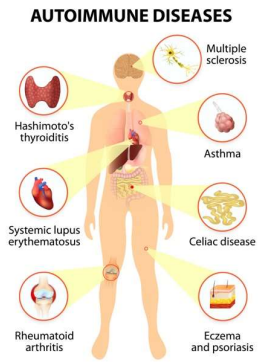
Stem cell treatment for chronic obstructive pulmonary disease (COPD).

Internal Medicine

Stem cell treatment for inflammatory bowel disease (ulcerative colitis & Crohn's disease).



Internal Medicine



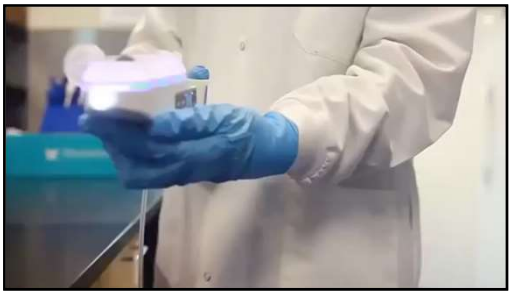
Stem cell treatment for autoimmune/connective tissue diseases.

Plastic/Reconstructive Surgery

Plastic & Reconstructive Surgery

Stem cell treatment for burn injuries.

Plastic & Reconstructive Surgery



Plastic & Reconstructive Surgery

Facial fat grafting with stem cells.

Before After

Plastic & Reconstructive Surgery

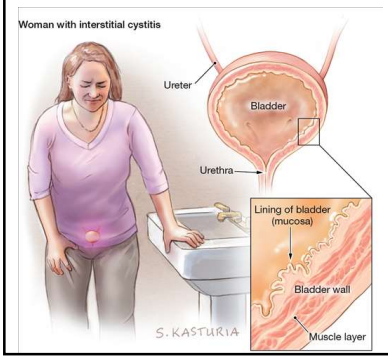
Fat grafting and stem cells for buttock augmentation.

Plastic & Reconstructive Surgery

Breast augmentation with fat grafting and stem cells.

Urology

Urology



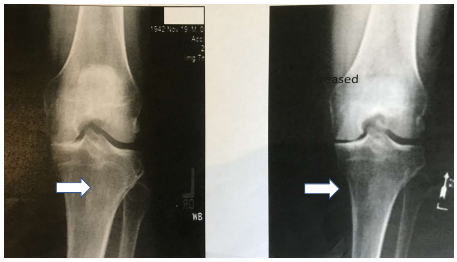
Stem cell treatment for interstitial cystitis.

Treatment with Adult Stem Cells

Bruce Fishman, MD, MPH, FICS

Knee Osteoarthritis

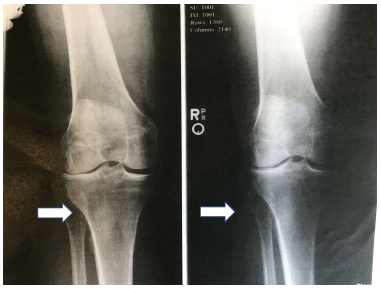
Stem cell injection medial compartment OA.



Before After

Knee Osteoarthritis

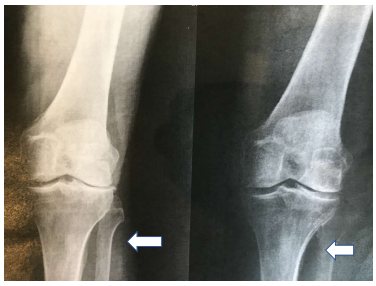
Stem cell injection lateral compartment OA.



Before After

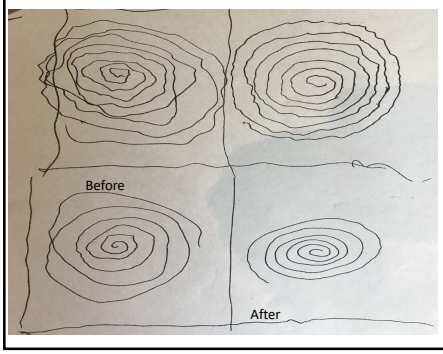
Knee Osteoarthritis

Stem cell injection lateral compartment OA.



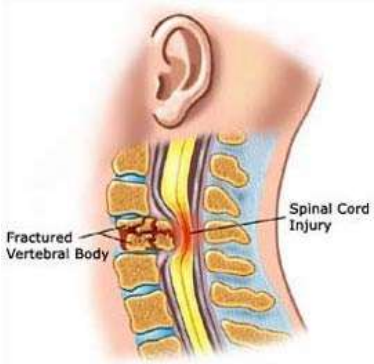
Before After

Stem Cell Treatment for Parkinson's Disease

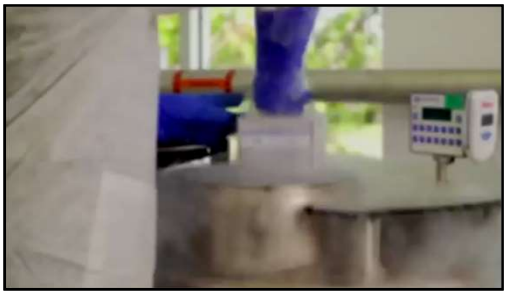


Ommaya Reservoir inserted in brain.

Stem Cell Treatment for Spinal Cord Injury



Stem Cell Treatment for Spinal Cord Injury



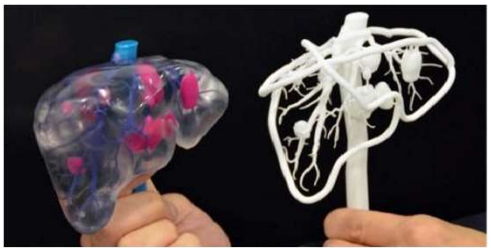
Future Directions in Stem Cell Treatments

- Replacement of injured or deformed body parts
- Construction of organs

Replacement of Injured, Deformed, or Missing Body Parts

Replacement of Injured, Deformed, or Missing Body Parts

Construction of Organs for Transplantation



Future Directions in Stem Cell Treatments

The future of stem cell treatment will require joint efforts in the fields of molecular genetics and bioengineering.

Molecular Genetics

The field of molecular genetics will determine the precise timing and specific genetic tissue signaling of growth factors to direct stem cells into the desired type of tissue or organ.

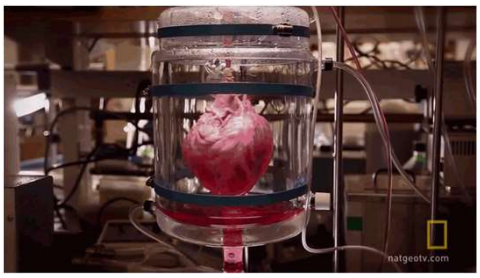
Bioengineering

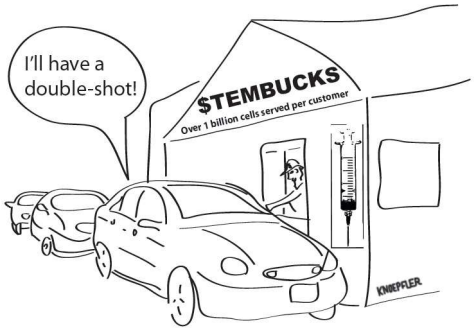
The field of bioengineering will develop sophisticated and third-generation 3D printers to construct scaffolding to be utilized for organ shape and function on which stem cells will be directed to grow and differentiate.

Future Directions in Stem Cell Treatments

- Scientists working together have developed a single chamber heart which actively functions to pump fluids
- Future more sophisticated organ function may be developed for use in transplantation medicine with each persons own genetic make-up

Beating Heart Constructed Using Stem Cells & 3D Printing





Thank You!

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