THE NEW ERA OF REGENERATIVE MEDICINE

Dozens of biotech companies and university labs are developing ways to replace or regenerate failed body parts. Here are a few of the projects:

**BONE**
Bone-growth factors or stem cells are inserted into a porous material cut to a specific shape, creating new jaws or limbs. A product that creates shinbones is in clinical trials.

**COMPANIES:** Creative Biomolecules, Orquest, Sulzer Orthopedics, Genetics Institute, Osiris Therapeutics, Regeneron.

**SALIVA GLANDS**
Proteins called aquaporins that allow cells to secrete water are used to recreate saliva glands damaged by disease or radiation. Glands are also being engineered to secrete healing drugs. The technique has proven successful in mice.

**COMPANIES:** None yet.

**SKIN**
Organogenesis’ Alipgraf, a human-skin equivalent, is the first engineered body part to win FDA approval, initially for leg ulcers. Other skin is in the works for foot ulcers and burns.

**COMPANIES:** Organogenesis, Advanced Tissue Sciences, Integra LifeSciences, LifeCell, Ortec International.

**URINARY TRACT**
Cartilage cells are taken from the patient, packed into a tiny matrix, and injected into the weakened ureter, where they bulk up the tissue walls to prevent urine backup and incontinence. The method is in late-phase clinical trials.

**COMPANIES:** Reprogenesis, Integra LifeSciences.

**PANCREAS**
Insulin-manufacturing cells are harvested from pigs, encapsulated in membranes, and injected into the abdomen. The method has been tested in animals and could be in human trials in two years.

**COMPANIES:** BioHybrid Technologies, Neocrin, Circe Biomedical.

**LIVER**
A spongy membrane is built up and then seeded with liver cells. Organs the size of a dime have been grown, but a full-size liver could take 10 years due to its complexity.

**COMPANIES:** Advanced Tissue Sciences, Human Organ Sciences, Organogenesis.

**HEART VALVES, ARTERIES, AND VEINS**
A 10-year initiative to build a heart has just started. Genetically engineered proteins have been successfully used to regrow blood vessels.

**COMPANIES:** Organogenesis, Advanced Tissue Sciences, Genetech, LifeCell, Reprogenesis.

**TEETH**
Enamel matrix proteins are used to fill cavities. It works in dogs; human trials are a few years away.

**COMPANIES:** Biora, Atrix Laboratories, Creative BioMolecules.

**BREAST**
In preclinical studies, several companies have been able to create a cosmetic nipple by inserting a ball of cartilage. Researchers are now trying to grow a whole cosmetic breast.

**COMPANIES:** Reprogenesis, Integra LifeSciences.

**COMMENTS**

**BLADDER**
Doctors at Children’s Hospital in Boston have grown bladders from skin cells and implanted them in sheep. They are about to try the same process on a patient.

**COMPANIES:** Reprogenesis.

**CARTILAGE**
A product is already on the market that regrows knee cartilage. A chest has been grown for a boy and a human ear on a mouse.

**COMPANIES:** Genzyme Tissue, BioMatrix, Integra LifeSciences, Advanced Tissue Sciences, Regen Biologics, Osiris Therapeutics.

**SPINAL CORD NERVES**
Scientists are in-wheeling nerve-growth factors, injecting them at the site of damage to encourage regeneration or seeding them along biodegradable filaments and implanting them. Rats have been made to walk again.

**COMPANIES:** Acorda, Regeneron, CytoTherapeutics, Gullford Pharmaceuticals.
Regenerative Medicine (RM) replaces or regenerates cells, tissue or organs to restore impaired function.

RM is a broad field that encompasses

1. Cell Therapies
2. Regenerative Compounds
3. Tissue Engineering
4. Tools & Enabling Devices
5. Aesthetic Medicine

... that have the capacity to:

1. Cure diseases;
2. Regenerate damaged tissue; and
3. Reverse degenerative changes associated with aging.
THE RM FIELD IS AT A KEY INFLECTION POINT

RM MARKET: KEY METRICS

### Rapidly Expanding Market
- $23.8B in 2015
- $67.5B in 2020
- **CAGR of 23.2%**
- 1st mover advantage

### Increased Funding in 2015:
**$10B+ (up 106% compared to 2014)**
- VC, PIPEs, IPO’s, Deals: $8B+
- Governments (NIH, CIRM, etc.): $2B+

### Clinical Programs
- **5600+ Clinical Trials**
- **1800+ “New RM” Technologies**
- **200+ In Late Stage (PIII/PIV)**

### Commercial Products
- **40+ Cell Therapies/TE Products on Market**
- **1st Approved Gene Therapy (2014)**

### 1.4M+ Patients Treated with RM Products
- **60K+ Stem Cell Transplants/Year**

### RM Companies
- **700+ Co’s involved in RM**
- "Pure" RM Co’s
  - **300+ Private Co’s**
  - **100+ Public Co’s with $40B+ Total Market Cap**
- **Gene & Immunotherapy Co’s** Leading

**Source:** Proteus Investor Forum Workshop: “Horizon Scoping: Why Invest In Stem Cells And Regenerative Medicine” – May 2015
RM BUSINESS MODEL: AUTOLOGOUS V. ALLOGENEIC

**Autologous Model**
- **Patients Own Cells/Tissue**
  - Personalized Medicine
- **Advantages:**
  - Easier Regulatory Path (GTP)
  - No Immune Response
- **Challenges:**
  - Difficult to Scale
  - High COGS

**Allogeneic Model**
- **Universal Cells in a Bottle**
  - Big Pharma “Drug Model”
- **Advantages:**
  - Scalable
  - Low COGS
- **Challenges:**
  - More Difficult Regulatory Path
  - Immune Response

**Service vs. Product**

THE RM MARKET IS GROWING RAPIDLY: **23.2% GAGR**

Source: Allied Market Research; Regenerative Medicine Market 2013-2020, June 2014.
GLOBAL RM LEADING COMMERCIAL CELL THERAPY PRODUCTS

<table>
<thead>
<tr>
<th>Sampling of Marketed Cell Therapies by Jurisdiction</th>
<th>Sampling of Leading Commercial Cell Therapy Products</th>
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</thead>
<tbody>
<tr>
<td><strong>United States</strong></td>
<td><strong>Company</strong></td>
</tr>
<tr>
<td>Dermagraft</td>
<td>Advanced Biohealing, a Shire company</td>
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<tr>
<td>Osteocel</td>
<td>Allosource distributed by NuVasive</td>
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<tr>
<td>PureGen</td>
<td>Alphatec Spine</td>
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<td>BionDfacor</td>
<td>Anterogen</td>
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<tr>
<td>BioDefence</td>
<td>Avita Medical</td>
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<tr>
<td>IaViv</td>
<td>BioDlologics (distributed by Amedica)</td>
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<tr>
<td>Provenge</td>
<td>BioDefence</td>
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<tr>
<td>Carticel</td>
<td>Dengreon</td>
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<tr>
<td>Epicel</td>
<td>Fibrocell</td>
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<tr>
<td>AmnioGraft</td>
<td>Genzyme, a Sanofi company</td>
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<td>Organogenesis</td>
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<td>OsirisTherapeutics</td>
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<td>TiGenix</td>
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<td>Zimmer and ISTOTechnologies</td>
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<td><strong>Europe</strong></td>
<td><strong>Product</strong></td>
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<tr>
<td>MySkin</td>
<td>Dermagraft</td>
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<td>CryoCell</td>
<td>AlloStem</td>
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<td>ReCell</td>
<td>BioSeed-C</td>
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<td>Carticel</td>
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<td>MACI</td>
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<td>ChondroCelect</td>
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<tr>
<td><strong>Other Regulated Jurisdictions</strong></td>
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<tr>
<td>Cupistem (S. Korea)</td>
<td>J-TEC Cartilage (Japan)</td>
</tr>
<tr>
<td>Heartcellgram (S. Korea)</td>
<td>J-TEC Corneal Epithelium (Japan)</td>
</tr>
<tr>
<td>Cartiistem (S. Korea)</td>
<td>CuroXcell (Israel)</td>
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<tr>
<td>J-TEC Epidermis (Japan)</td>
<td>Prochymal (Canada &amp; NZ)</td>
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**Over 40 Cell Therapy Products Commercially Available**

- Non-healing wounds: 35%
- Musculoskeletal: 35%
- Skin: 11%
- Cancer: 10%
- Ocular: 7%
- Cardiovascular: 2%

OVER 5600 CLINICAL TRIALS WORLDWIDE INVOLVING STEM CELLS

Source: ClinicalTrials.gov
RM CLINICAL TRIALS BY PHASE AND BY THERAPEUTIC CATEGORY

Clinical Trials by Therapeutic Category

- Oncology: 258 trials
- Cardiovascular: 78 trials
- Infectious diseases: 43 trials
- Central nervous system: 41 trials
- Musculoskeletal: 38 trials
- Dermatology: 35 trials
- Ophthalmology: 34 trials
- Immunology & Inflammation: 27 trials
- Hematology: 14 trials
- Surgery: 9 trials
- Respiratory: 5 trials
- Genitourinary disorders: 5 trials
- Ear diseases: 2 trials
- Lymphatic diseases: 1 trial
- Radiation injury: 1 trial
- Dental: 1 trial

Clinical trials underway by year-end 2015:
- Ph. I: 192 trials
- Ph. II: 376 trials
- Ph. III: 63 trials

RM REGULATORY ENVIRONMENT: MULTIPLE AGENCIES

GAME CHANGER: JAPAN’S “DISRUPTIVE” REGULATORY CONDITIONAL PATHWAY FOR CELL THERAPIES
WHY THE HEALTHCARE SECTOR IS GOING TO REMAIN HOT

Half of all lifetime care expenditure occurs at 65 years of age upwards!

CAPITAL IS FLOWING INTO THE FIELD

Source: Alliance for Regenerative Medicine (ARM) – 2015 Annual Data Report on Gene and Cellular Therapies and the Regenerative Medicine Sector
FACTORS DRIVING INVESTMENT IN BIOTECHNOLOGY

• Aging population
• Rise of chronic disease
• Pharma is cutting back on R&D
• Pharma’s patent cliff problem has not been solved
• Better clinical trial design improving chances of success
• Improved regulatory environment

REGENERATIVE MEDICINE STAKEHOLDERS

Source: http://alliancerm.org/page/promise-and-potential
GLOBAL COMPANY DISTRIBUTION

672+
Regenerative Medicine Companies Worldwide,
Including Gene and Cell Therapies

349
North America

185
Europe & Israel

112
Asia

10
South America

1 Africa

15
Australia & New Zealand

Revolution: Stem cells & Cell Therapy

The promise

DEFINITITIVE TREATMENT FOR INCURABLE AND CHRONIC DISEASES
Our multidisciplinary management Team
Our MAIN therapeutic focus

Acute and chronic musculoskeletal diseases

- Joint Injuries
- Discal Hernias
- Osteoarthritis
- Tendinopathies
- Fibromyalgia
- Muscle Tears
- Low Back Pain
Solution: Our Product

Cell collection (Adipose tissue)

Cell processing GMP Lab (Isolation, engineering, expansion, characterization)

Stromal Vascular Fraction Ad-MSCs + Other cells

Washing solution

Collagen + Adipocytes

Oil

Re-injection

Formulation

Quality Control

Our Product
Media impact of Muse-AT discovery

**The Economist**

**Babbage**

**Science and technology**

Stem-cell research

**Much to muse about**

Jun 8th 2013 | 17:17 BY C.H. | NEW YORK

LIPOSUCTION has long epitomised unbridled vanity. Now those who undergo the procedure can claim to be serving the public good. According to a paper published in the Public Library of Science by Gregorio Chazenzakt, of the University of California, Los Angeles, and his colleagues, fatty tissue extracted during liposuction may prove instrumental in a sort of stem-cell therapy.

Until now the most exciting advances in regenerative medicine have centred on two types of stem cell. James Thomson became the first scientist to isolate stem cells from human embryos 15 years ago. Embryonic stem cells promise to repair tissue damaged by disease or injury because they are able to become any sort of cell in the body, or pluripotent in the argot. But because extracting them involves destroying the embryos, their use has been controversial. Then, in 2007, Dr Thomson and Shinya Yamanaka, in separate projects, showed how to use genes to reprogram adult human cells back to a pluripotent state. (Dr Yamanaka won the Nobel prize for his work last year.) Although IPS cells avoid the ethical quagmire of embryonic stem cells, they can sometimes cause cancer.

...to renew themselves, but cannot become any cell.

**Forbes**

**Pharma & Healthcare**

**Have Scientists Finally Found Truly Pluripotent Adult Stem Cells?**

Jun 8, 2013 @ 11:06 AM | 5,505 VIEWS

**John Farrell, CONTRIBUTOR**

I cover science and technology. FULL BIO

Opinions expressed by Forbes Contributors are their own.

A new research paper in PLOSOne this past week claims to have found a fatty tissue source of pluripotent adult stem cells.

The team of scientists, led by Gregorio Chazenzakt, an associate researcher with UCLA Obstetrics and Gynecology, have dubbed these cells, MUSE-AT (multilineage-differentiating stress-enduring cells, derived from adipose tissue) because their claimed pluripotent status seems to have been activated by the extreme conditions to which they were subjected.

According to the UCLA Health release, the cells, were discovered by accident “when a piece of equipment failed in the laboratory, killing all the stem cells in an experiment except the Muse-AT cells.”

The abstract from the paper further notes:
Muse-AT Cells

MUltilineage differentiating Stress-Enduring Stem Cells

- Pluripotent cells (Differentiate to any cell type)
- Highly resistant to cellular stress
- Effective homing properties (Go to injury)
- No ethical concerns (Obtained from adult tissues)
- Nonteratogenics (No tumors)
- High regeneration potential:
  - Trophic effect (Growth factors production)
  - Immunomodulatory effect
  - Direct effect: Local differentiation

UCLA Patent WO 2014190150 A1
(USA, Europe, Japan & Chile)
Business model

Joint Venture
(IP Pooling)

CLUSTER BIOETHERAPEUTICS LLC

Dr Chazenbalk
UCLA Patent License
WO 2014190150 A1

Exclusive Patent Licensing
LATAM
Chile, Brazil, Colombia, Uruguay, Ecuador

Exclusive representative
(IP Pooling)

Los Angeles CA, ProChile Office, 2016
Business model

- Regenerative Medicine
  - Patients (Traumatology and Orthopedics)
  - Cashflow $
  - Data

- MSC spheroids
- Muse-AT Cell Bank
- 3D printing

- Technology & Innovation

- Research & Development
  - Clinical trials
  - Pre-Clinical trials
  - Partnering
Pipeline & Strategic partners

- **Muse-AT application**
  - **Prototype Research**
  - **Preclinical Development**
  - **Clinical trial phase I-II**
  - **Clinical trial phase II-III**
  - **Commercial LATAM**

  **Osteoarthritis**
  - Chile - Brazil

  **Acute muscle injury**
  - Chile

  **Parkinson’s disease**
  - Chile

  **Diabetic foot**
  - Ecuador

**Partner**
- Jaimovich Lab
- Hetz Lab
**Business model**

Selection of Key Novel Disruptive Technologies

“Crème de la Crème”

**LATAM**

**Regenerative Medicine**

**Technology & Innovation**

**Research & Development**

**CLUSTER BIOThERAPEUTICS LLC**
Market behavior projection

Why?

Non-invasive injectable therapy
Advantages: Integrated Cell Therapy Center

Surgery room ISO CLASS 7

Cell processing clean room ISO CLASS 6

PHARMA PASS-THROUGH
Proprietary clinical evidence (DATA)

Diagnosis:
- Severe partial rupture of Achilles tendon
- Partial intrasubstance tear
- Fibrillar soleus rupture

Allopathic treatment: Surgery (120 days recovery)

Alternative: Cell therapy treatment

60 days after cell treatment

50% less recovery TIME
Our Vision

A world in which transformative cell-based therapeutics are accessible to all.
Obrigado!

hugo.cabrera@cellus.cl

www.cellus.cl
BACK-UP SLIDES
Stem cells offer hope for diseases such as schizophrenia, Alzheimer’s disease, Parkinson’s disease, spinal cord injury, muscular dystrophy, heart disease, immune deficiencies, kidney disease, anemias, diabetes, bone marrow disorders, and leukemia, lymphoma.
What is a stem cell?

A single cell that can

Replicate itself

Differentiate into many cell types
A stem cell is either . . .

**Embryonic** (makes all tissues)

**Adult** (makes specific tissues)

- Blood
- White cells
- Red cells
- Platelets
- Bone
- Muscle
- Fat

**Induced pluripotent**
(makes all tissues)
Selling Stem Cells in the USA: Assessing the Direct-to-Consumer Industry

Figure 1. Map of Locations of Included Businesses
We conducted data collection on the cities and states of stem cell businesses including multiple locations for individual businesses. “Hotspot” cities are indicated with blue stars. See Supplemental Information for additional details concerning the production of the map.

Source: Turner and Knoepfler, Selling Stem Cells in the USA: Assessing the Direct-to-Consumer Industry, Cell Stem Cell (2016), http://dx.doi.org/10.1016/j.stem.2016.06.007
Selling Stem Cells in the USA: Assessing the Direct-to-Consumer Industry
Regenexx stem cell procedures have been studied extensively for more than a decade;

In 2016, Regenexx published the world’s largest (2,372 patients) stem cell safety paper in any medical indication (not just orthopedics).

There was no clinical evidence to suggest that treatment with MSCs of any type in this study increased the risk of neoplasm (abnormal growth of tissue).
This 2.5 day course focuses on the critical issues associated with conceptualizing, developing, and building a company in the field of regenerative medicine.