Advances in Tissue Regeneration

Sharing Knowledge: Achieving Breakthrough Performance
COL Bob Vandre, DDS, MS
26 & 27 JAN 2010

Armed Forces Institute of Regenerative Medicine

The views expressed in this presentation are those of the author and may not necessarily represent the views of the U.S. Army
Advances in Tissue Regeneration

Presented during the Military Health System Conference Held January 24 - 27, 2011 at National Harbor, MD
1954, First organ transplant, Boston

Today, Increasing problem: tissue and organ shortage and rejection
What is Regenerative Medicine?

Tissue Engineering and Biomaterials

Cellular Therapies

Medical Devices and Artificial Organs
Based on the field of cell transplantation (started in 1930s)
First clinical application: engineered skin for burn patients, 1981
A field of research for over 60 years. Why so few clinical advances?

- Inability to expand cells in vitro
- Inadequate biomaterials
- Inadequate vascularity
Progenitor Cells

1 cm²
Day 1 (5 X 10⁴ cells)

Day 60 (50 X 10⁹ cells)
Enough cells to cover a football field

2010 MHS Conference
CELL DELIVERY VEHICLES

- Biocompatibility
  - Cell attachment
  - Cell viability
- Degradation curves
  - Inflammatory responses
  - Biomechanical properties
- The scaffold should replicate the biomechanical and structural properties of the tissue being replaced.

Scaffold in the shape of a human ear
Vascularity: Problem

- Cells cannot be implanted in volumes greater than 3 mm³ (the size of a pencil eraser)
- Nutrition to the cells is limited (limited vascularity)

* muscle only  m + ec  m + VEGF  m + VEGF+ec
Urinary System
Engineered Urethras

Bladder ECM

Scaffold only- 1 month

Cell seeded scaffold-1 mo

Cell seeded scaffold - 3 mo

Cell seeded scaffold - 6 mo

2010 MHS Conference
Fabrication of a vascular substitute

Electrospun nanofiber substrate, with endothelial and smooth muscle cells

Creation of the First Engineered Organ: Bladder
Clinical Studies

- Patients with high pressure /low capacity bladders
- All failed medical therapy and were considered candidates for bladder reconstruction

Oberpenning et al, 1999
Bioengineered Bladder
Bioengineered Bladder

Pre-Op

Post-Op
Bioengineered Bladder

“Tissue-engineered autologous bladders for patients needing cystoplasty”

Clinical Experience
Phase 1, 2 trials completed
Over 10 year follow-up
Work still in progress

April 2006
Anatomy & Function of the Phallus

- Complex organ composed of skin, muscle, nerves, and blood vessels (arteries and veins)

Corpus cavernosum

Corpus spongiosum
Penile Replacement: Study Overview

Autologous cavernosal cell harvest

Cells are grown and expanded

Cells are seeded on decellularized penile corpora matrices

Analyses

Retrieval of engineered corporal tissue

Corporal tissue penile replacement
Engineered Phallus
Total Corpora Replacement, Cavernosography

Native corpora

Matrix with cells

Matrix without cells

Excision only
Cavernosometry

Pressure (CmH2O)

- Normal
- Unseeded
- 1 Mo
- 3 Mo
- 6 Mo

2010 MHS Conference
Engineered phalanges are functional

Vaginal swab (+) / Pregnancy rate

<table>
<thead>
<tr>
<th>Group</th>
<th>Rate</th>
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<tbody>
<tr>
<td>Experimental (with Cells)</td>
<td>33%</td>
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<tr>
<td>Control (Without Cells)</td>
<td>0%</td>
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</table>

PNAS, Chen et al, 2009
Human Embryonic Stem Cells

- Pro: very high replicative potential
- Con: tumor potential, issues with rejection

J. Thomson, 1998
Amniotic fluid and placental derived stem cells

- Pro: very high replicative potential, low tumor potential
- Con: issues with rejection

AFS cells
## Stem Cell Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Embryonic</th>
<th>IPS</th>
<th>Amniotic/Placenta</th>
<th>Marrow/Fat</th>
<th>Tissue Specific</th>
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<tbody>
<tr>
<td><strong>Growth Potential</strong></td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
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<td>++</td>
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<tr>
<td><strong>Tumor Free</strong></td>
<td></td>
<td></td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
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<tr>
<td><strong>Rejection Free</strong></td>
<td></td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+++</td>
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<tr>
<td><strong>Lineage Potential</strong></td>
<td>+++</td>
<td>+++</td>
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What is the Armed Forces Institute of Regenerative Medicine?

- Two consortia working together with the US Army Institute of Surgical Research (230 scientists)
  - 27 Universities
  - 114 investigators – 30% of which are clinicians
  - 46 graduate students
  - 70 post-docs

- Total 5 yr funding of >$250M
  - $100M US Government funding from:
    - Army, Navy, Air force, VA, and NIH
  - $68M Matching funds from:
    - State governments, and participating universities
  - $109M in pre-existing research projects directly related to the deliverables of the AFIRM
    - From NIH, DARPA, Congressional plus-ups, NSF, philanthropy

www.afirm.mil

2010 MHS Conference
Goal: To Heal our Wounded Warriors
Five Areas of Emphasis:

- Healing Without Scarring
- Cranio-Facial Reconstruction
- Compartment Syndrome
- Limb and Digit Salvage and Reconstruction
- Burn Repair

www.afirm.mil
### Wake Forest – Pittsburgh
- The Wake Forest Institute for Regenerative Medicine (NC)
- The McGowan Institute for Regenerative medicine (Univ. of Pittsburgh)
- Allegheny Singer Research Institute
- Carnegie Mellon University
- Georgia Tech Univ
- Institute for Collaborative Biotechnology (ICB) that includes UC Santa Barbara, MIT and Caltech
- Oregon Medical Laser Center
- Stanford University
- Rice University
- Tufts University
- University of Texas Health Sciences Center-Houston
- Vanderbilt University

### Rutgers – Cleveland Clinic
- Rutgers /New Jersey Center for Biomaterials
- Cleveland Clinic Foundation
- Carnegie Mellon University
- Case Western Reserve University
- Dartmouth Hitchcock Medical Center
- Massachusetts General Hospital / Harvard Medical School
- Massachusetts Institute of Technology
- Mayo Clinic College of Medicine
- Northwestern University
- State University of New York at Stony Brook
- University of Cincinnati
- University of Medicine and Dentistry of New Jersey
- University of Pennsylvania
- University of Utah
- University of Virginia
- Vanderbilt University

Stem Cells for Regenerative Medicine and Tissue Engineering

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<th>US Rank</th>
<th>University</th>
<th>In AFIRM</th>
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### Top Publishing US Scientists (2001-2007)

**Stem Cells for Regenerative Medicine and Tissue Engineering**

<table>
<thead>
<tr>
<th>US Rank</th>
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<td>Anthony Atala</td>
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<td>Antonios Mikos</td>
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[www.afirm.mil](http://www.afirm.mil)
AFIRM: clinical trials scheduled for FY 10

Hand Transplants

Face transplants

Skin Graft Stretching

www.afirm.mil
Cell spraying in place of skin grafting for burn patients (ReCell)

Autologous engineered skin grafts

Using Extracellular matrix to regrow lost muscle tissue.

Not shown: Fat injections to reduce burn scars and increase mobility.

www.afirm.mil
Cultured Epithelial Autograft (ReCell)

www.afirm.mil
ReCell: Scar Revision

www.afirm.mil