

2010 Military Health System Conference

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

Report Documentation Page				Form Approved OMB No. 0704-0188	
Public reporting burden for the collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to a penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number.					
1. REPORT DATE JAN 2010		2. REPORT TYPE		3. DATES COVERED 00-00-2010 to 00-00-2010	
4. TITLE AND SUBTITLE Advances in Tissue Regeneration				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S)				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Armed Forces Institute of Regenerative Medicine,US Army Medical Research and Materiel Command,504 Scott St,Fort Detrick,MD,21702-5012				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION/AVAILABILITY STATEMENT Approved for public release; distribution unlimited					
13. SUPPLEMENTARY NOTES Presented during the Military Health System Conference Held January 24 - 27, 2011 at National Harbor, MD					
14. ABSTRACT					
15. SUBJECT TERMS					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT Same as Report (SAR)	18. NUMBER OF PAGES 37	19a. NAME OF RESPONSIBLE PERSON
a. REPORT unclassified	b. ABSTRACT unclassified	c. THIS PAGE unclassified			

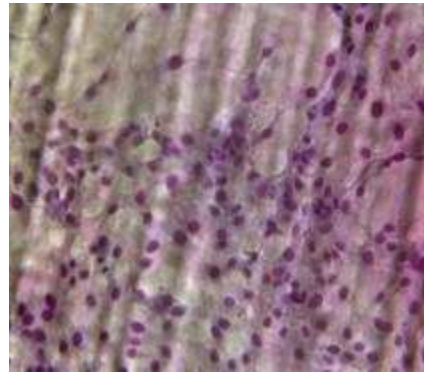
1954, First organ transplant, Boston



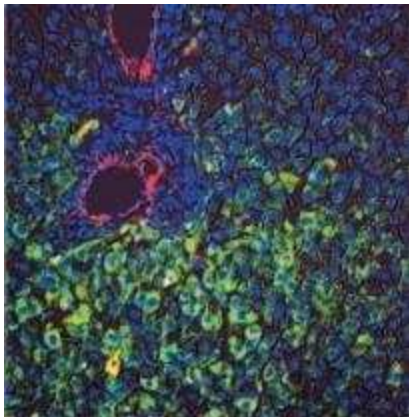
Today, Increasing problem: tissue and organ shortage and rejection



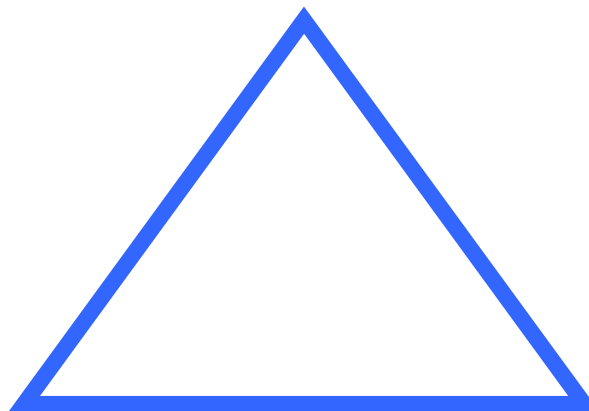
What is Regenerative Medicine?



Tissue Engineering and
Biomaterials



Cellular Therapies

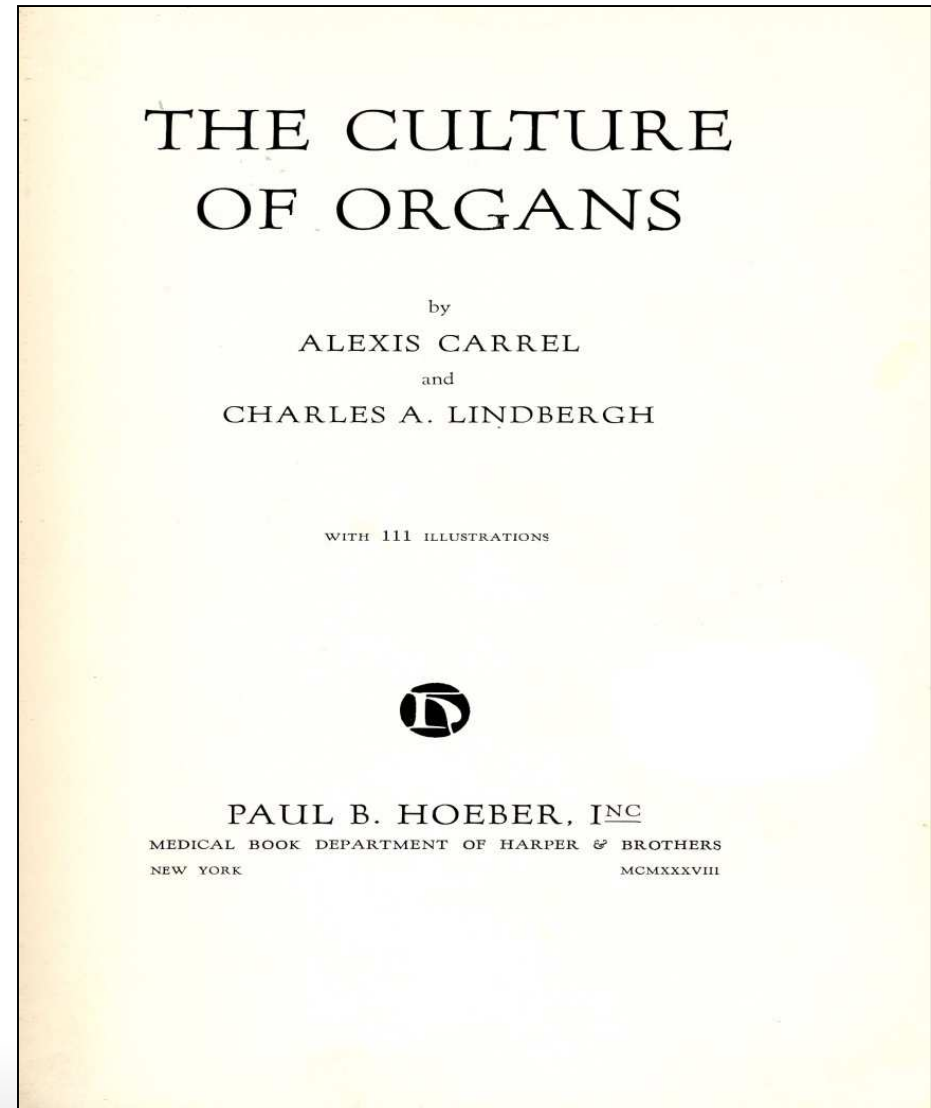


Medical Devices and Artificial
Organs

Regenerative Medicine / Tissue Engineering



- Based on the field of cell transplantation (started in 1930s)
- First clinical application: engineered skin for burn patients, 1981



Regenerative Medicine / Tissue Engineering



- 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

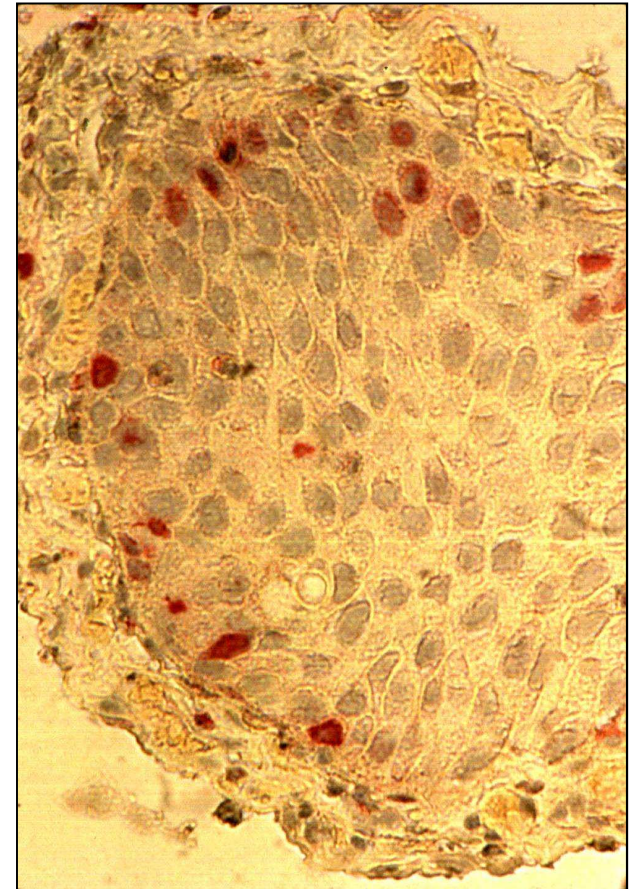


1 cm²

Day 1 (5 X 10⁴ cells)



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



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.**

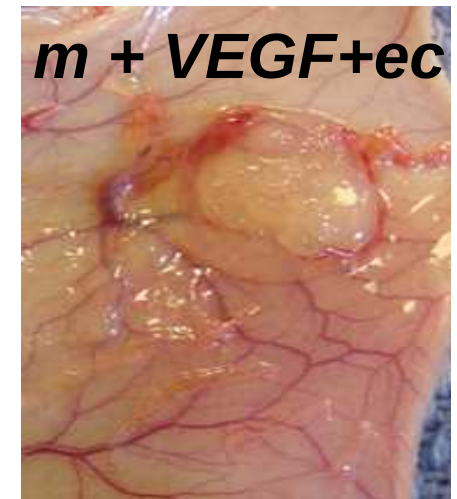
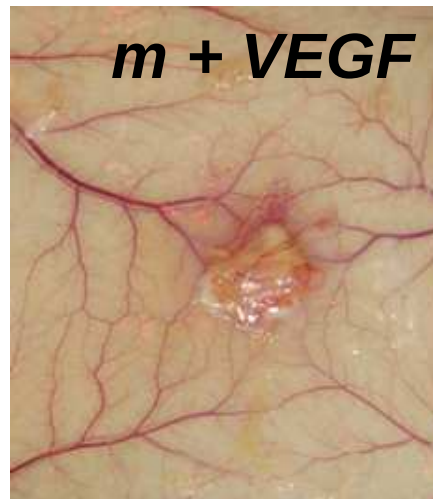
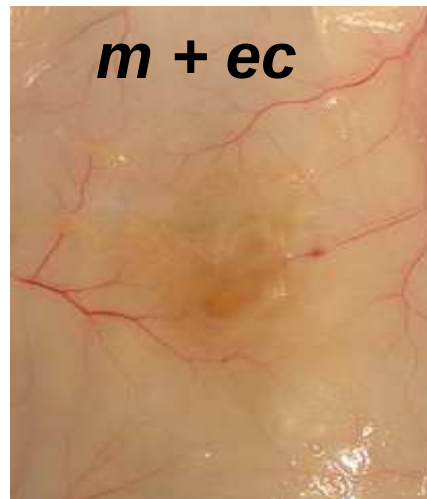


Scaffold in the shape of a human ear

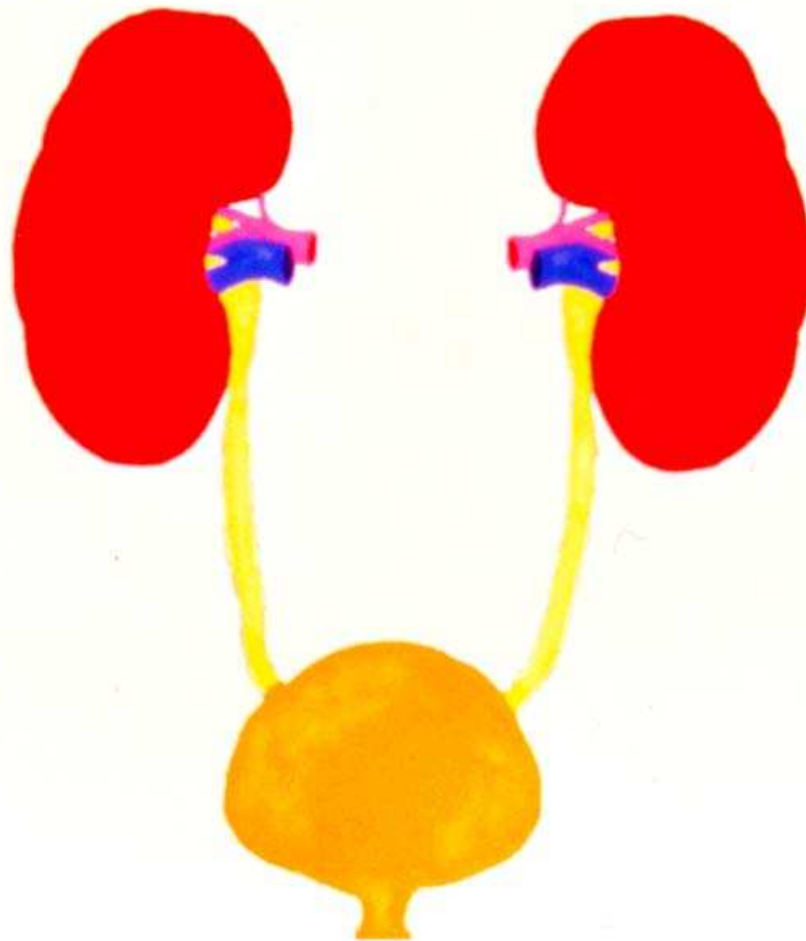
Vascularity: Problem



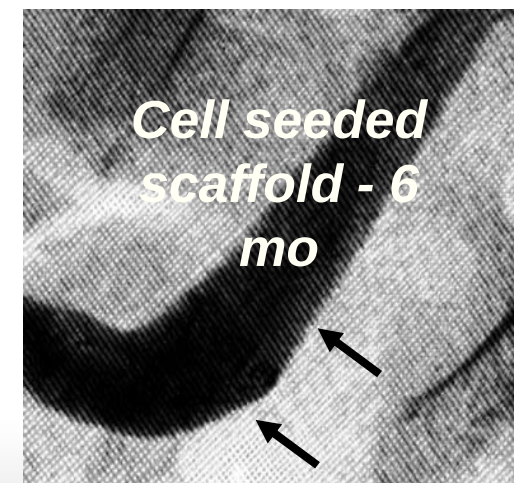
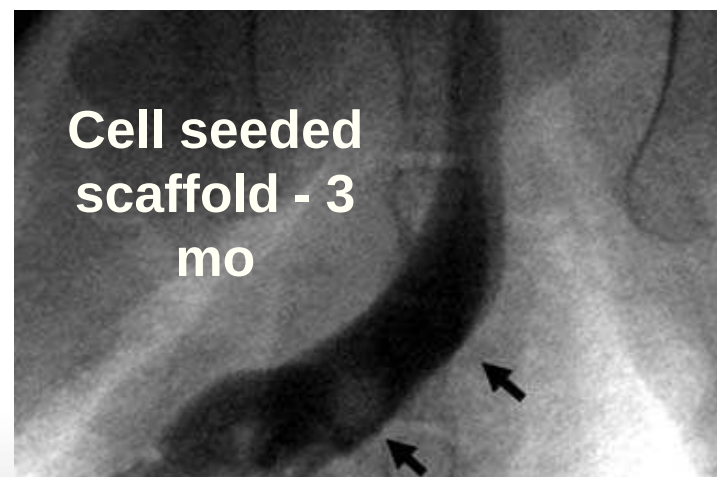
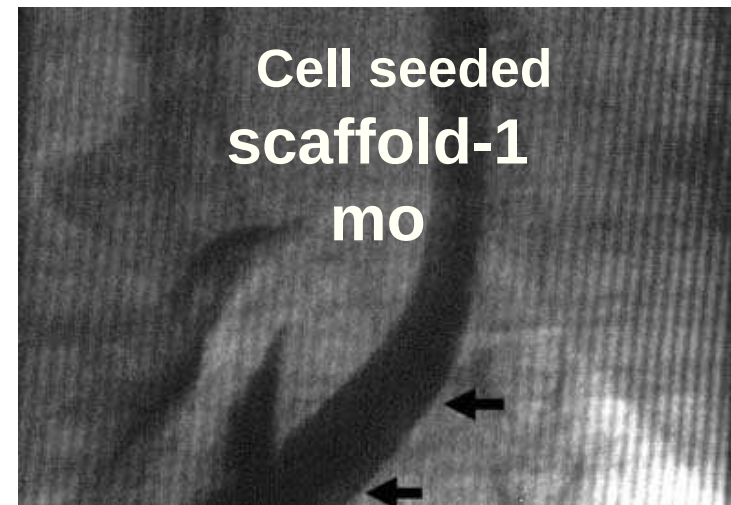
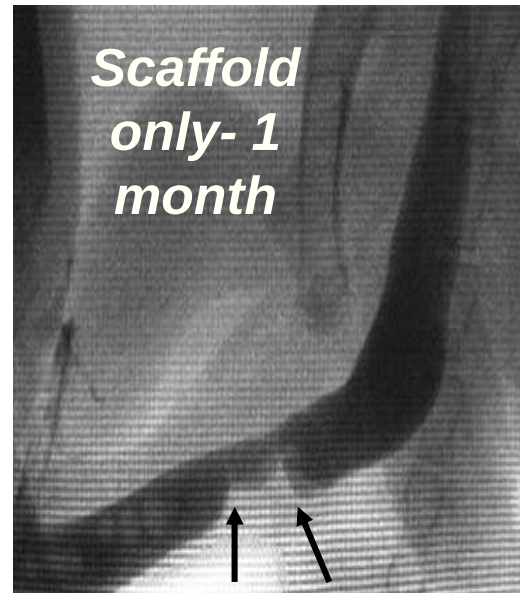
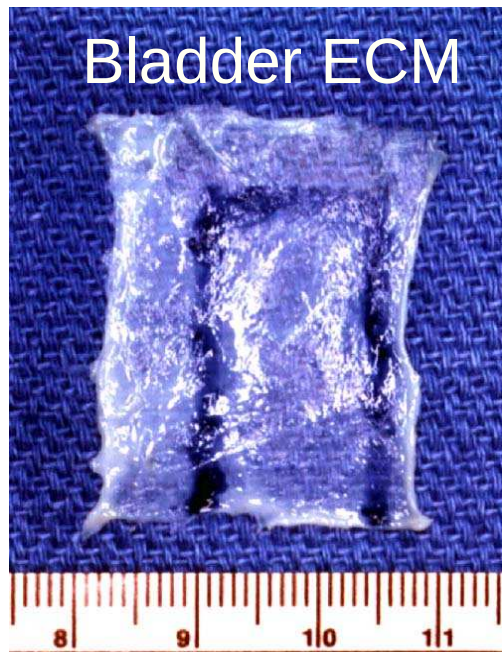
- Cells cannot be implanted in volumes greater than 3 mm³ (the size of a pencil eraser)
- Nutrition to the cells is limited (limited vascularity)



Urinary System



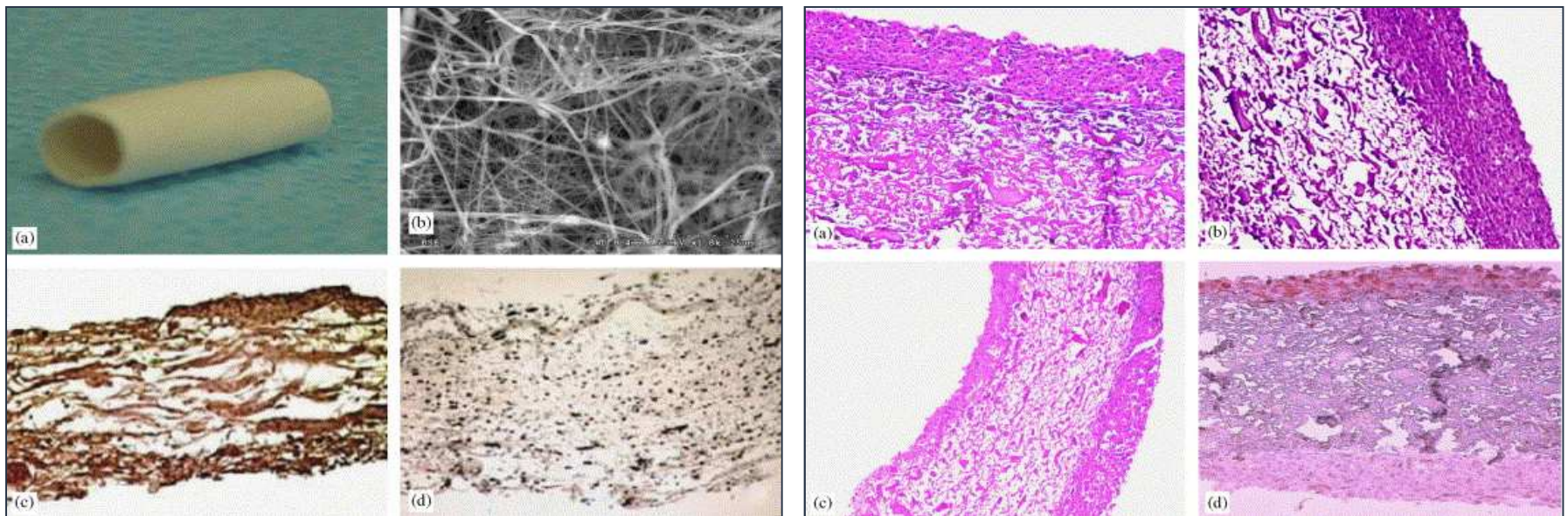
Engineered Urethras



Fabrication of a vascular substitute

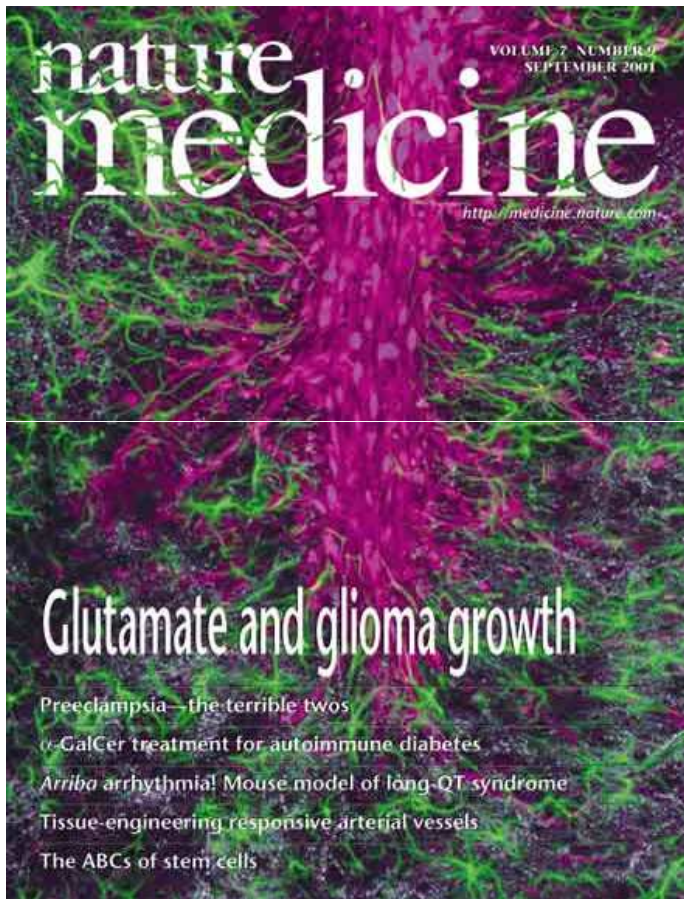


Electrospun nanofiber substrate, with endothelial and smooth muscle cells



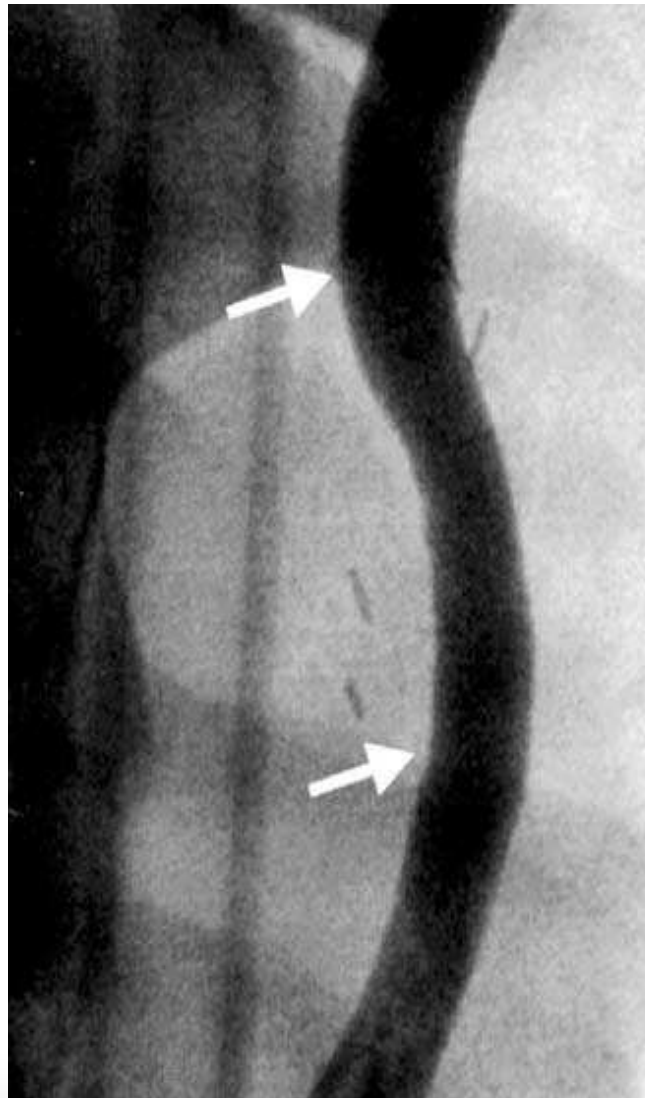
Stitzel et al., *Biomaterials*, 2005.

Tissue Engineered Arteries



Kaushal et al

2010 MHS Conference

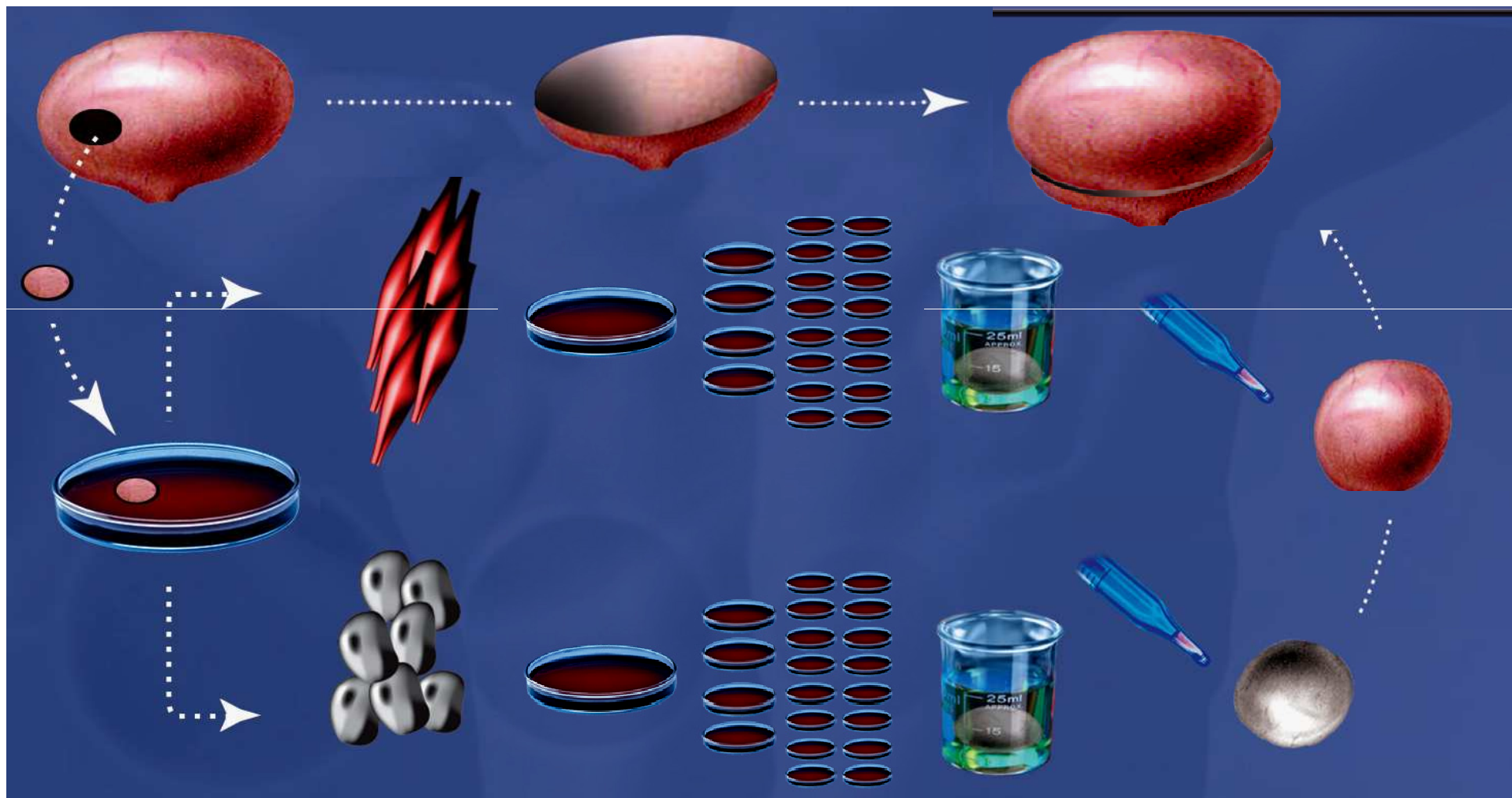


Engineered Artery



Native Artery

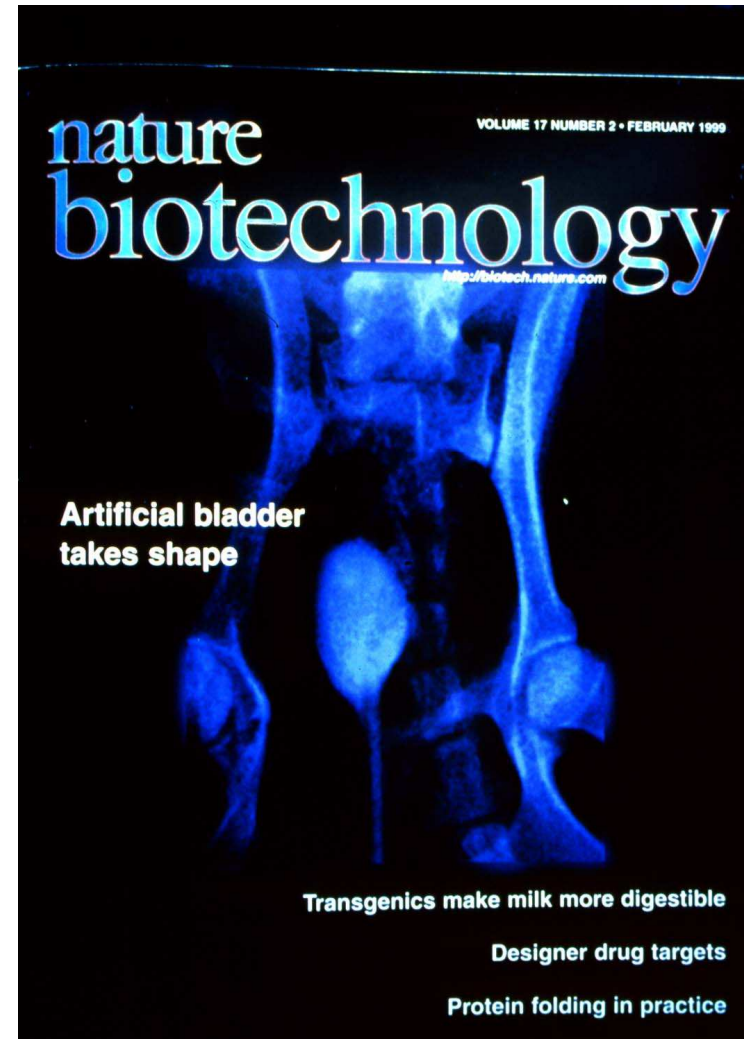
Creation of the First Engineered Organ: Bladder



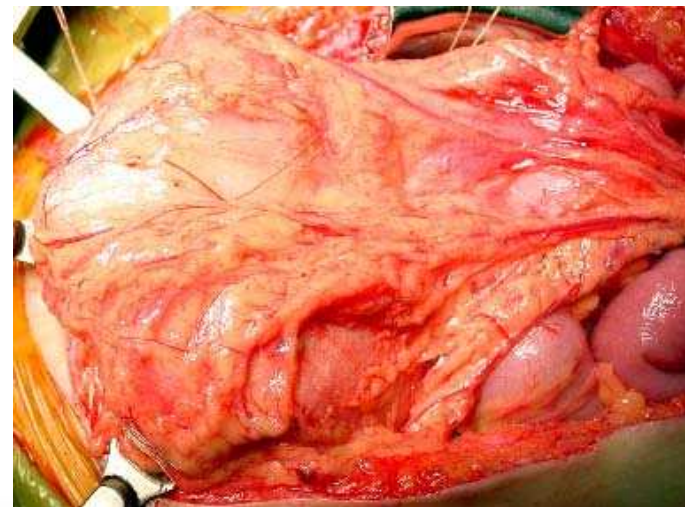
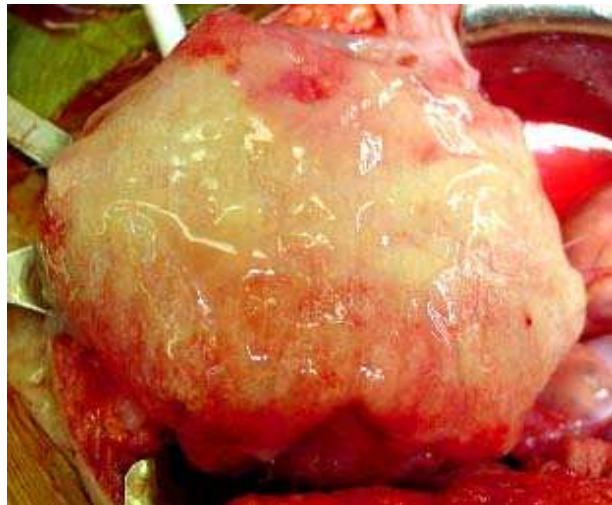
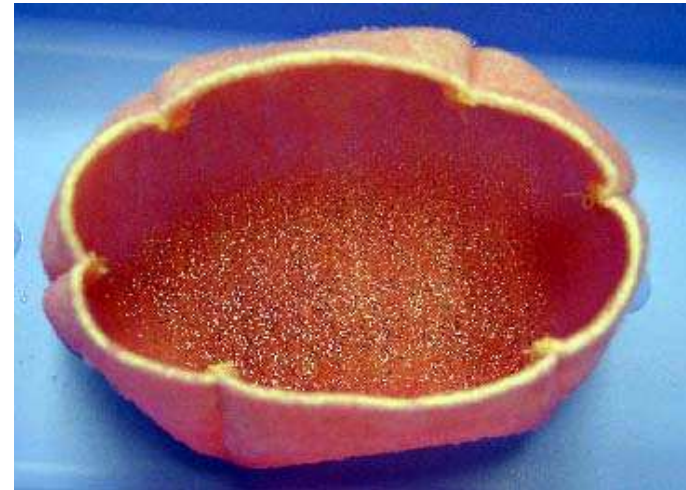
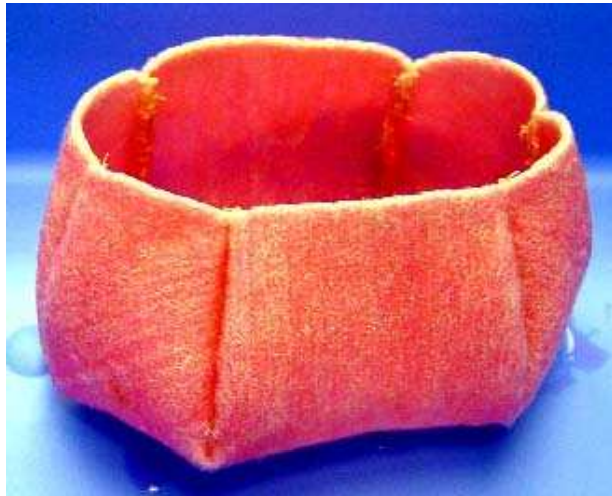
Clinical Studies



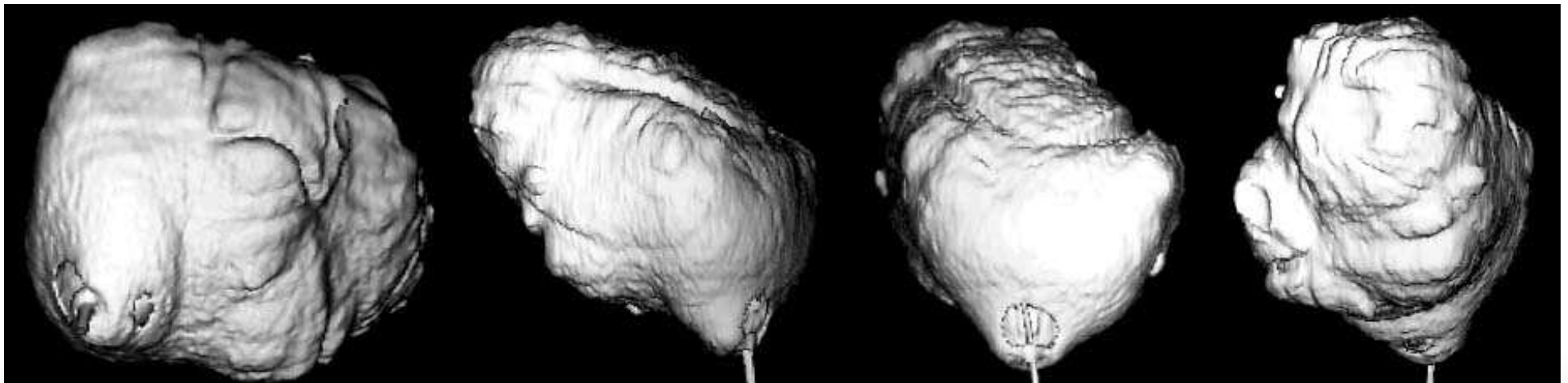
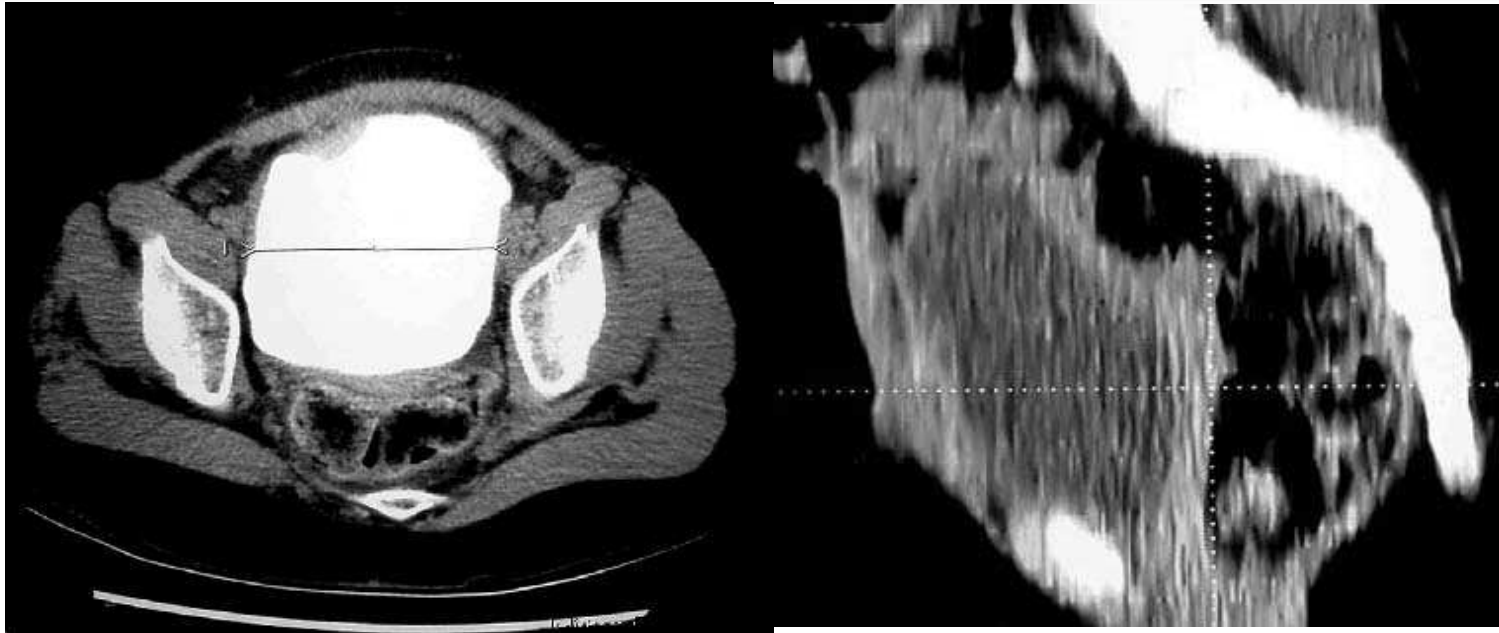
- Patients with high pressure /low capacity bladders
- All failed medical therapy and were considered candidates for bladder reconstruction



Bioengineered Bladder



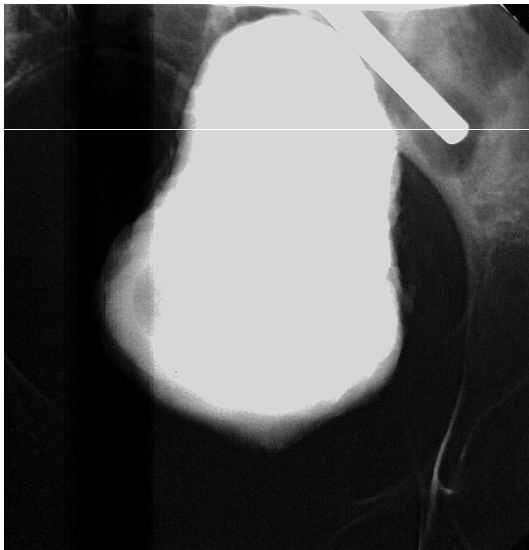
Bioengineered Bladder



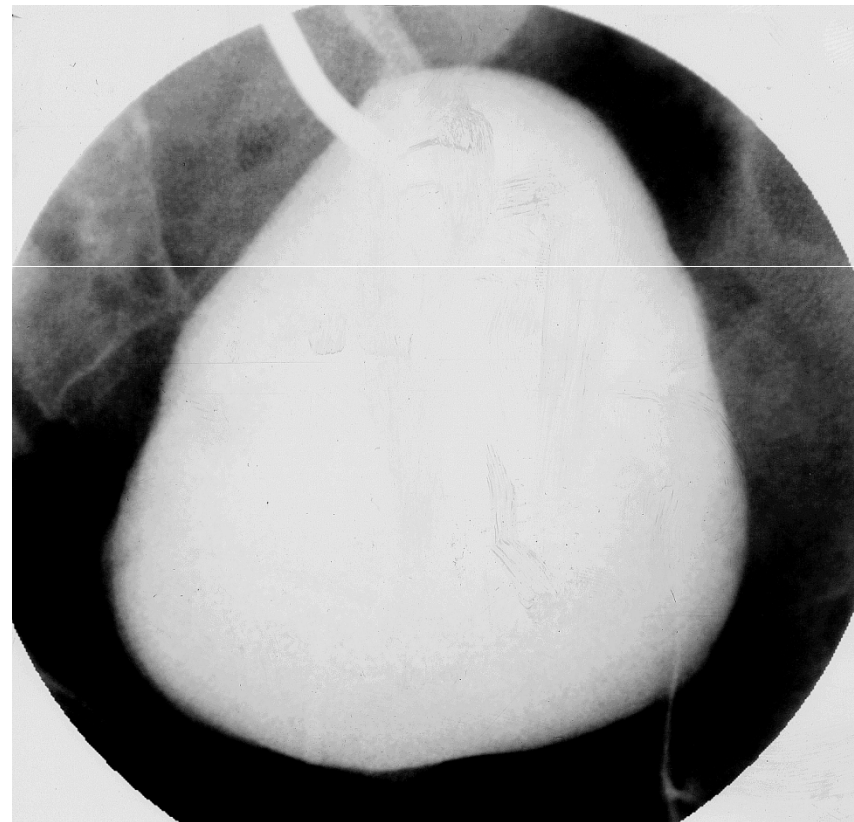
Bioengineered Bladder



Pre-Op



Post-Op



Bioengineered Bladder



THE LANCET

**"Tissue-engineered
autologous
bladders for
patients needing
cystoplasty"**

April 2006



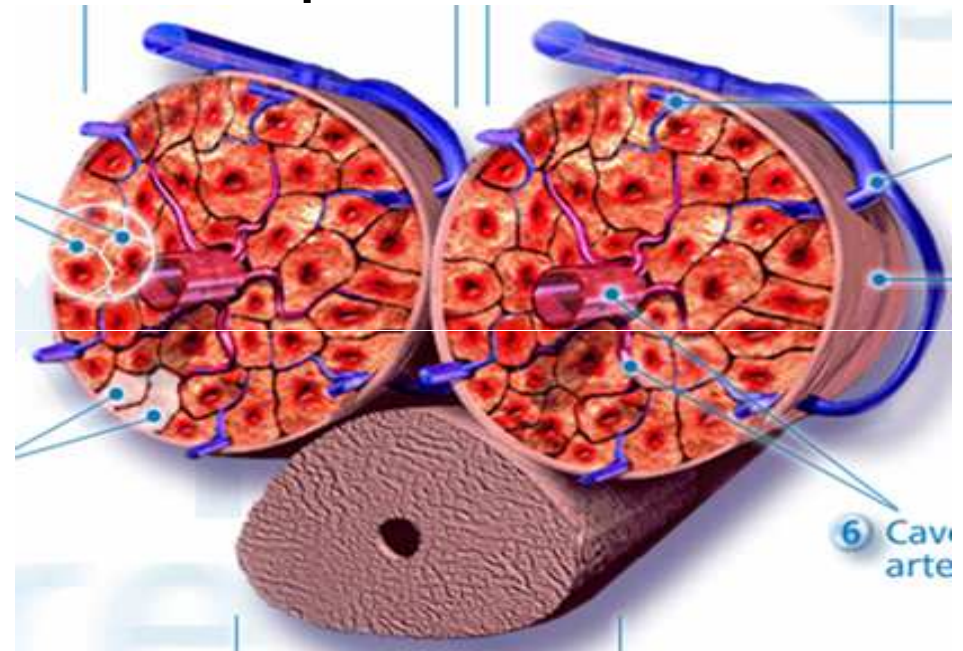
Clinical Experience
Phase 1, 2 trials completed
Over 10 year follow-up
Work still in progress

Anatomy & Function of the Phallus



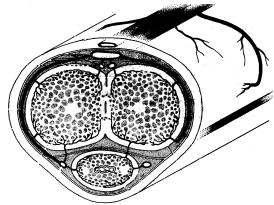
- Complex organ composed of skin, muscle, nerves, and blood vessels (arteries and veins)

Corpus cavernosum

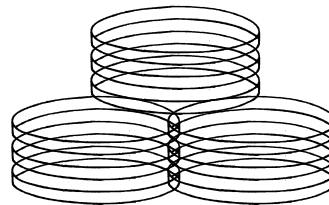
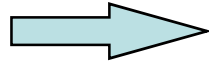


Corpus spongiosum

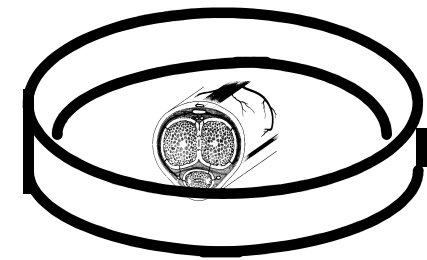
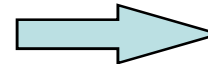
Penile Replacement: Study Overview



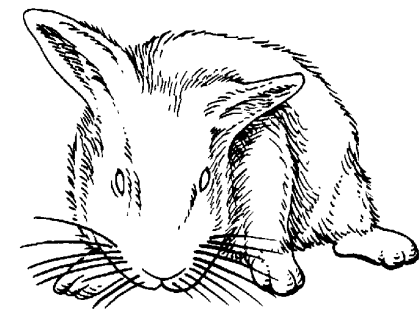
**Autologous cavernosal
cell harvest**



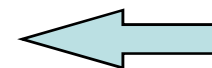
**Cells are grown
and expanded**



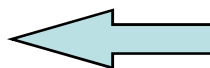
**Cells are seeded on
decellularized penile
corpora matrices**



**Corporal tissue
penile replacement**



**Retrieval of
engineered
corporal tissue**



Analyses

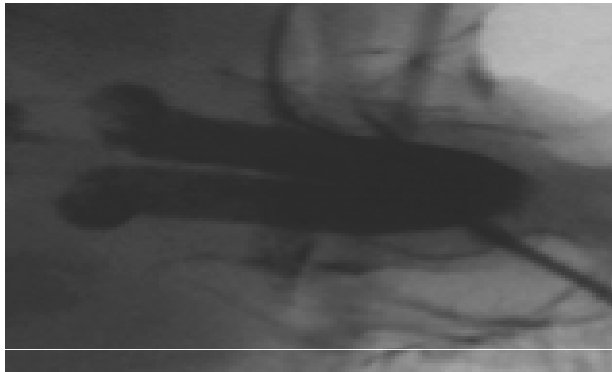
Engineered Phallus



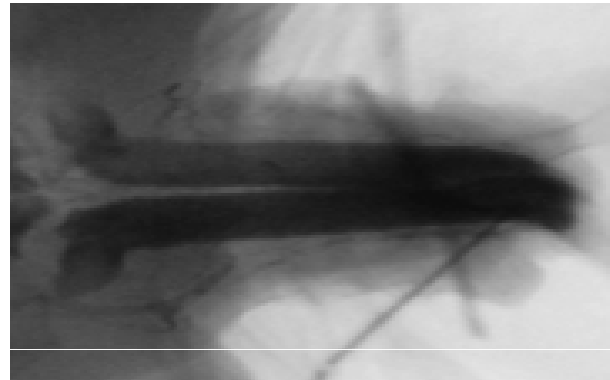
Total Corpora Replacement, Cavernosography



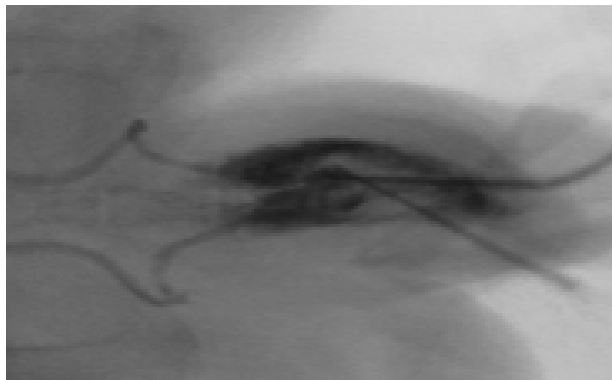
Native corpora



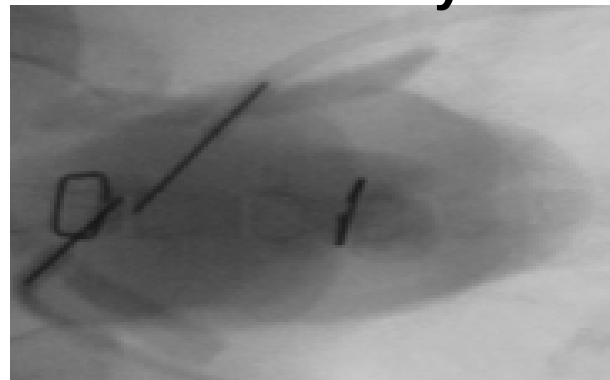
Matrix with cells



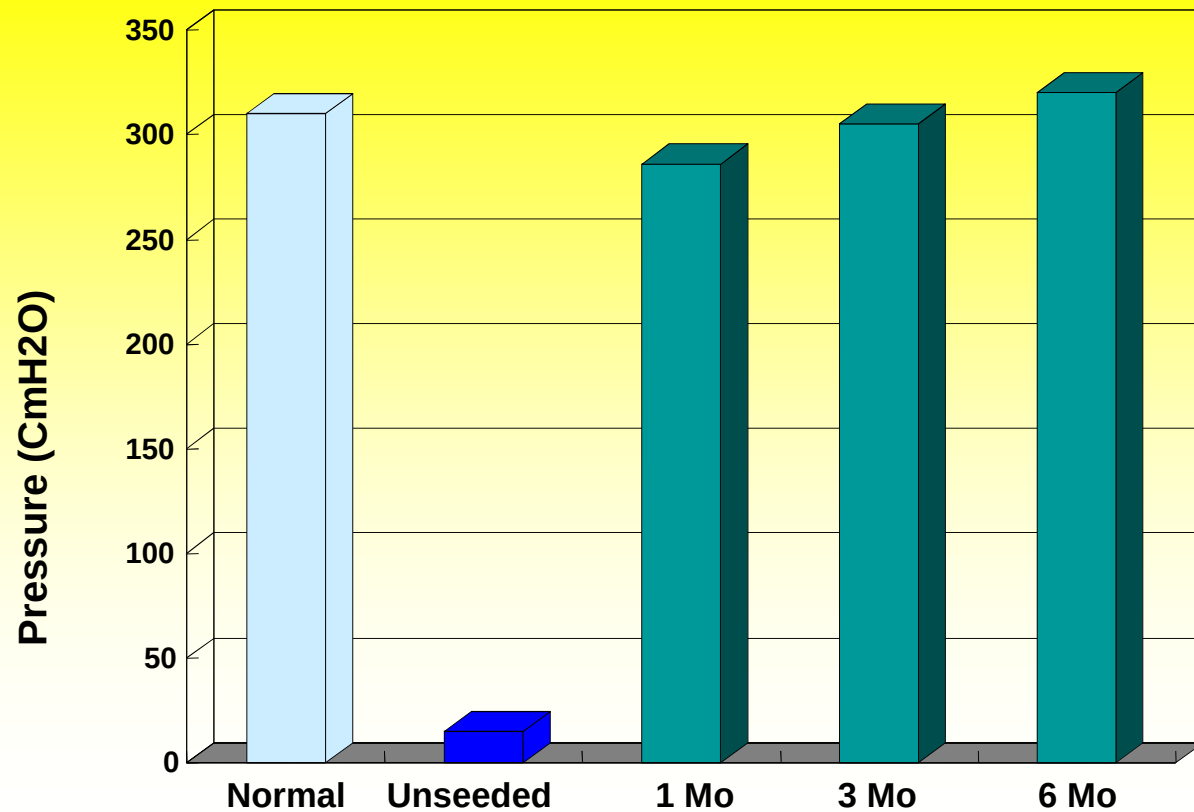
Matrix without cells



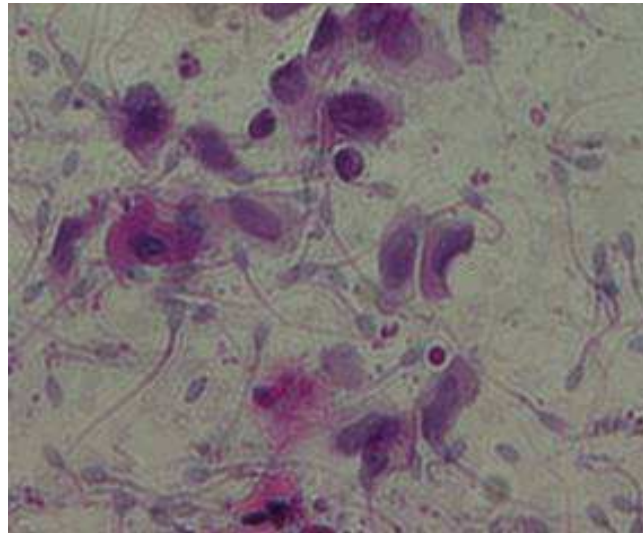
Excision only



Cavernosometry



Engineered phalluses are functional



Sperm in Vaginal swab



Bunnies

Vaginal swab (+) / Pregnancy rate

Experimental (with Cells)

33%

Control (Without Cells)

0%

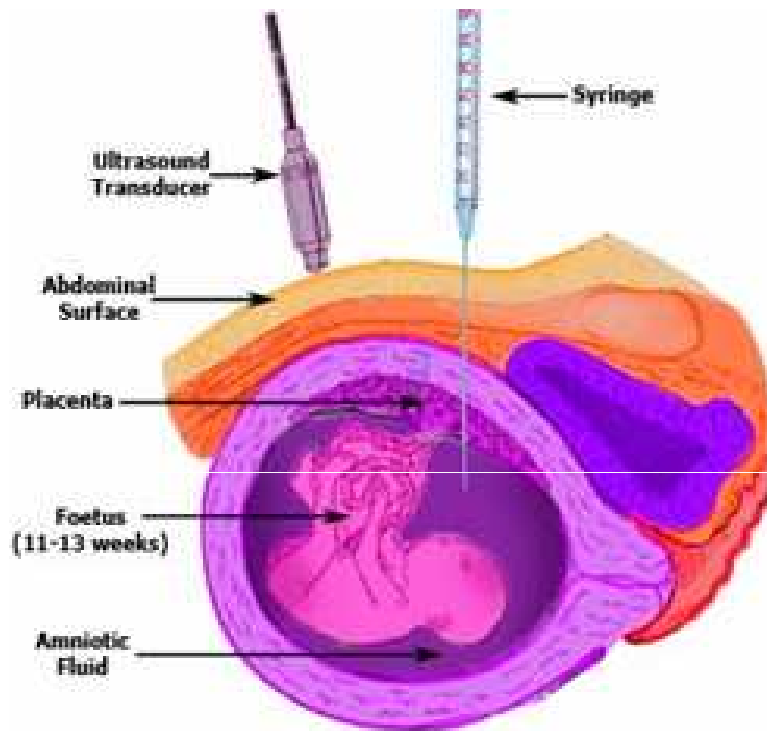
Human Embryonic Stem Cells



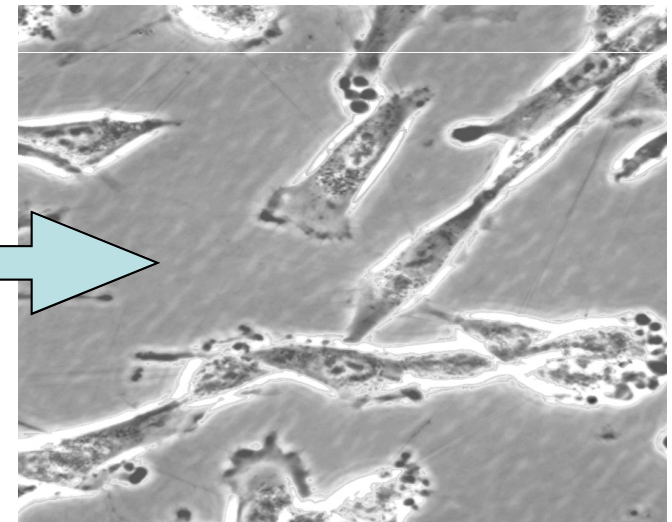
- Pro: very high replicative potential
- Con: tumor potential, issues with rejection

J. Thomson, 1998

Amniotic fluid and placental derived stem cells



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



AFS cells



Stem Cell Characteristics



	Embryonic	IPS	Amniotic/ Placenta	Marrow/ Fat	Tissue Specific
Growth Potential	+++	+++	+++	+	++
Tumor Free			+++	+++	+++
Rejection Free		+++		+++	+++
Lineage Potential	+++	+++	++	+	+



What is the Armed Forces Institute of Regenerative Medicine?



www.afirm.mil

- 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



Goal: *To Heal our Wounded Warriors*

Five Areas of Emphasis:



Cranio-Facial
Reconstruction



Healing Without Scarring



Limb and Digit Salvage and
Reconstruction



Compartment Syndrome



Burn Repair

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Our Partnership

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• US Army Institute of Surgical Research

▪ 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



Top Publishing US Universities (2001-2007) Stem Cells for Regenerative Medicine and Tissue Engineering



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US Rank	University	In AFIRM
1	Harvard	Y
2	MIT	Y
3	Univ. Pittsburgh	Y
4	Columbia Univ.	
5	Tufts	Y
6	Georgia Tech	Y
7	Rice	Y
8	Stanford	Y
9	Case Western	Y
10	Johns Hopkins	

From: World Technology Evaluation Center Report: International Assessment of Research and Development in Stem Cells for Regenerative Medicine and Tissue Engineering, MAR 2008



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Top Publishing US Scientists (2001-2007) Stem Cells for Regenerative Medicine and Tissue Engineering



US Rank	Researcher	In AFIRM
1	David Kaplan	Y
2	Rocky Tuan	
3	Robert Langer	Y
4	Gordana Vunjak-Novakovic	
5	Johnny Huard	Y
6	Michael Longaker	Y
7	Jeffrey Gimble	
8	Joseph Vacanti	Y
9	Anthony Atala	Y
10	Antonios Mikos	Y

From: World Technology Evaluation Center Report: International Assessment of Research and Development in Stem Cells for Regenerative Medicine and Tissue Engineering, MAR 2008



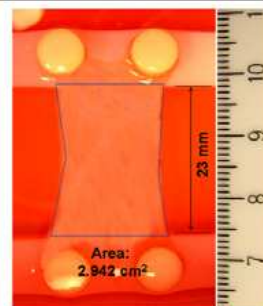
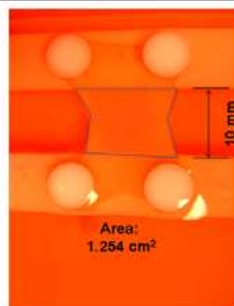
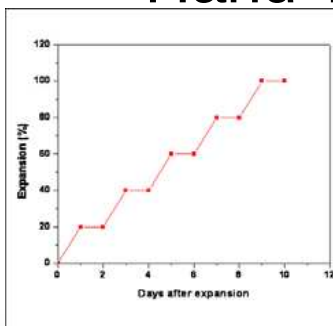
AFIRM: clinical trials scheduled for FY 10



Hand Transplants



Face transplants



www.afirm.mil



Josh Maloney

1st AFIRM Hand Transplant





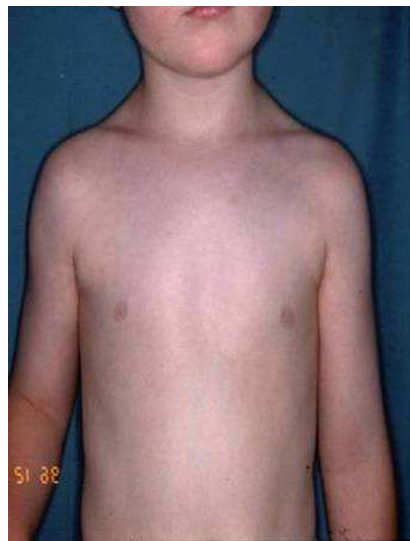
AFIRM: clinical trials scheduled for FY 10



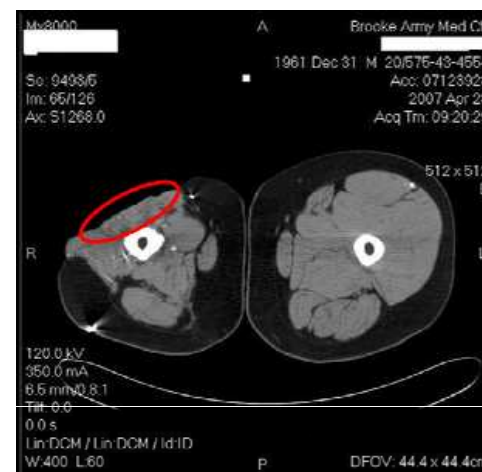
Cell spraying in place of skin grafting for burn patients (ReCell)



Before

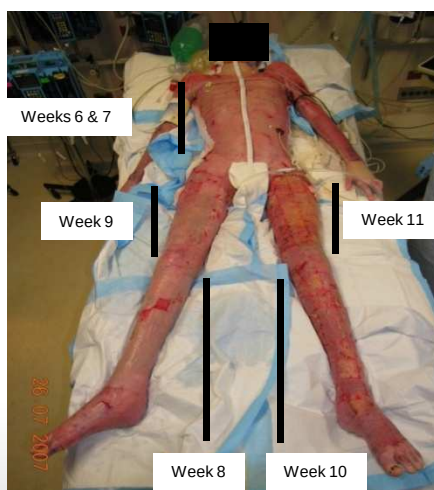


After



Using Extracellular matrix to regrow lost muscle tissue.

Autologous engineered skin grafts



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

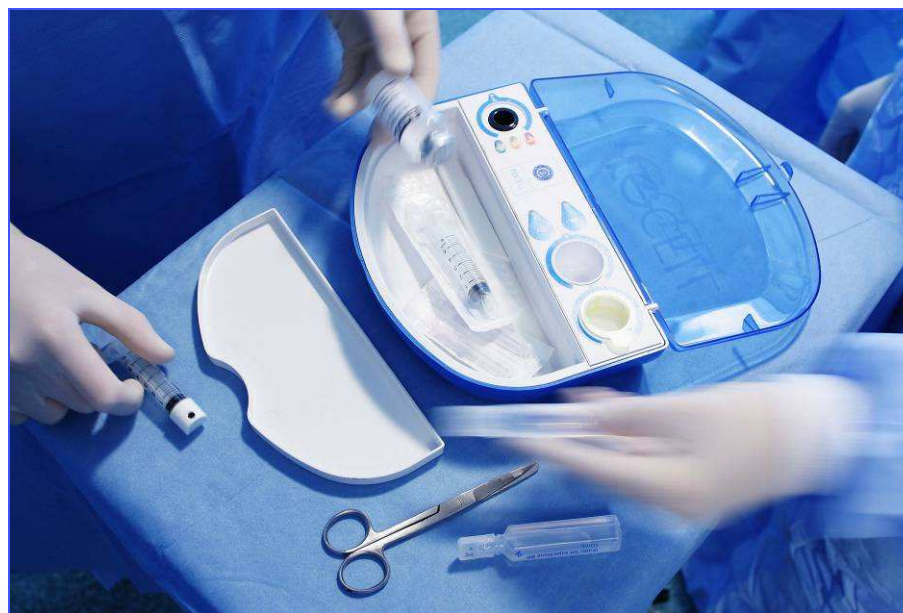


ReCell Kit



Cultured Epithelial Autograft (ReCell)

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ReCell: Scar Revision



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