Tissue Engineering and Regenerative Medicine

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Report Documentation Page

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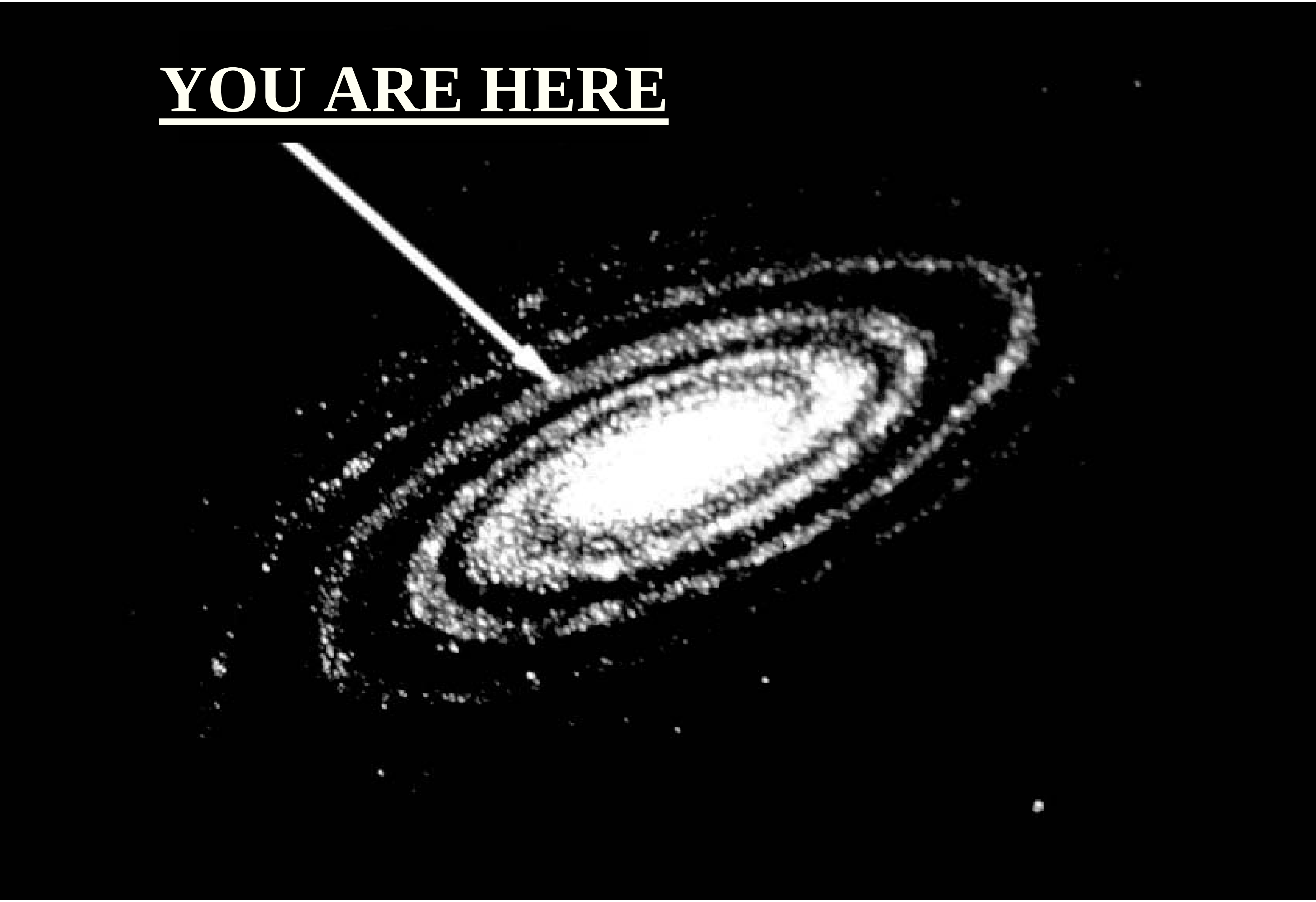

YOU ARE HERE

Combat Trauma

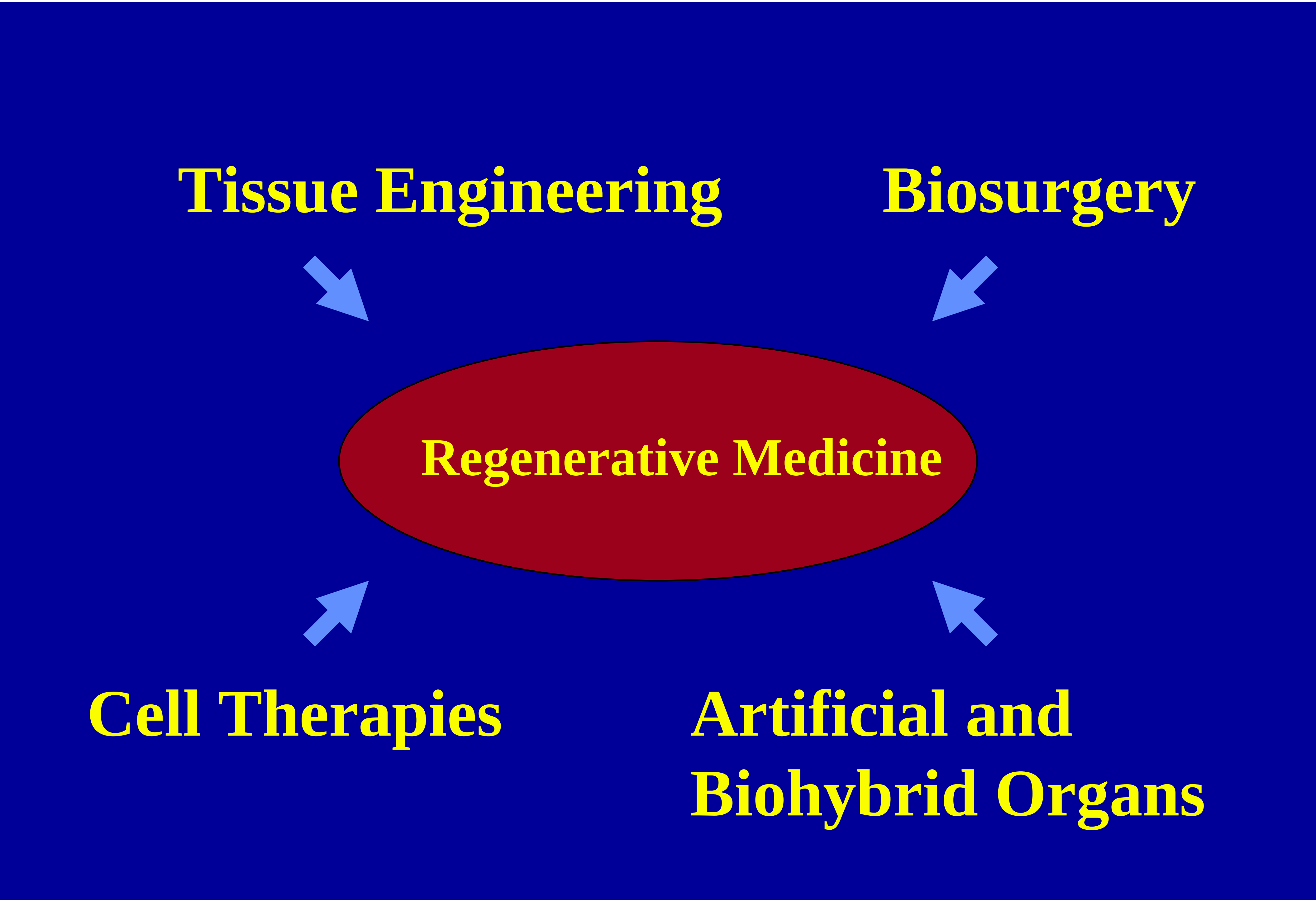
Blunt, penetrating and blast injuries may lead to soft and solid tissue and organ damage

Trauma, and its subsequent infection and inflammation all lead to tissue loss

Challenge: Replacement Tissues and Organs

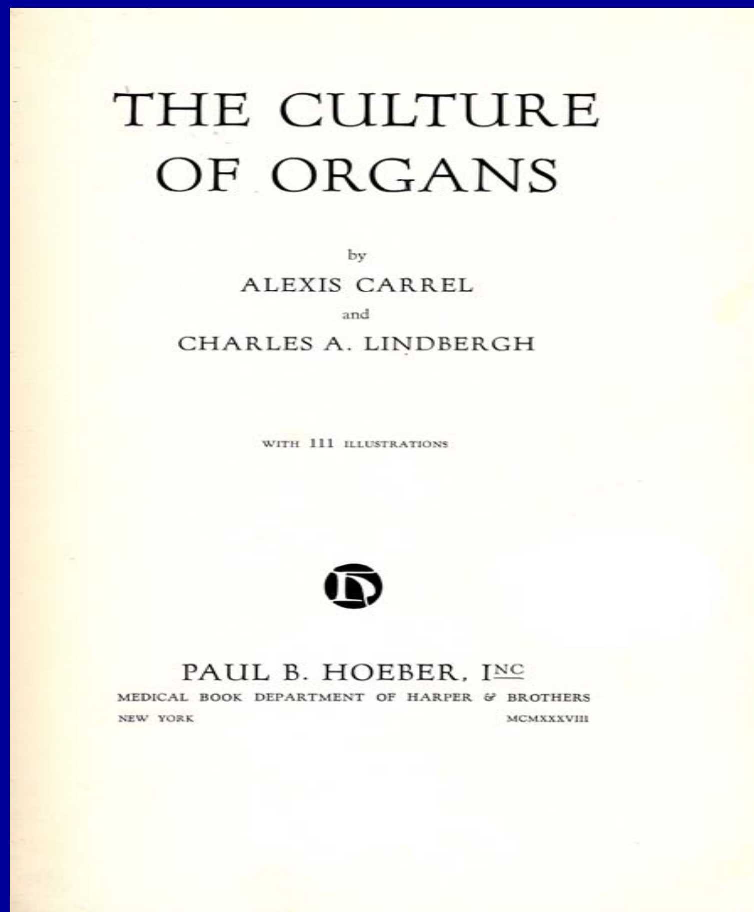
1954, First organ transplant, Boston

Today, Increasing problem: tissue and organ shortage and rejection


Tissue Engineering
Biosurgery
Regenerative Medicine
Cell Therapies
Artificial and
Biohybrid Organs

Regenerative Medicine / Tissue Engineering

Based on the field of cell transplantation (started in 1930s)



THE CULTURE
OF ORGANS

by
ALEXIS CARREL
and
CHARLES A. LINDBERGH

WITH 111 ILLUSTRATIONS

PAUL B. HOEBER, INC
MEDICAL BOOK DEPARTMENT OF HARPER & BROTHERS
NEW YORK MCMXXXVIII

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

Wake Forest Institute for Regenerative Medicine

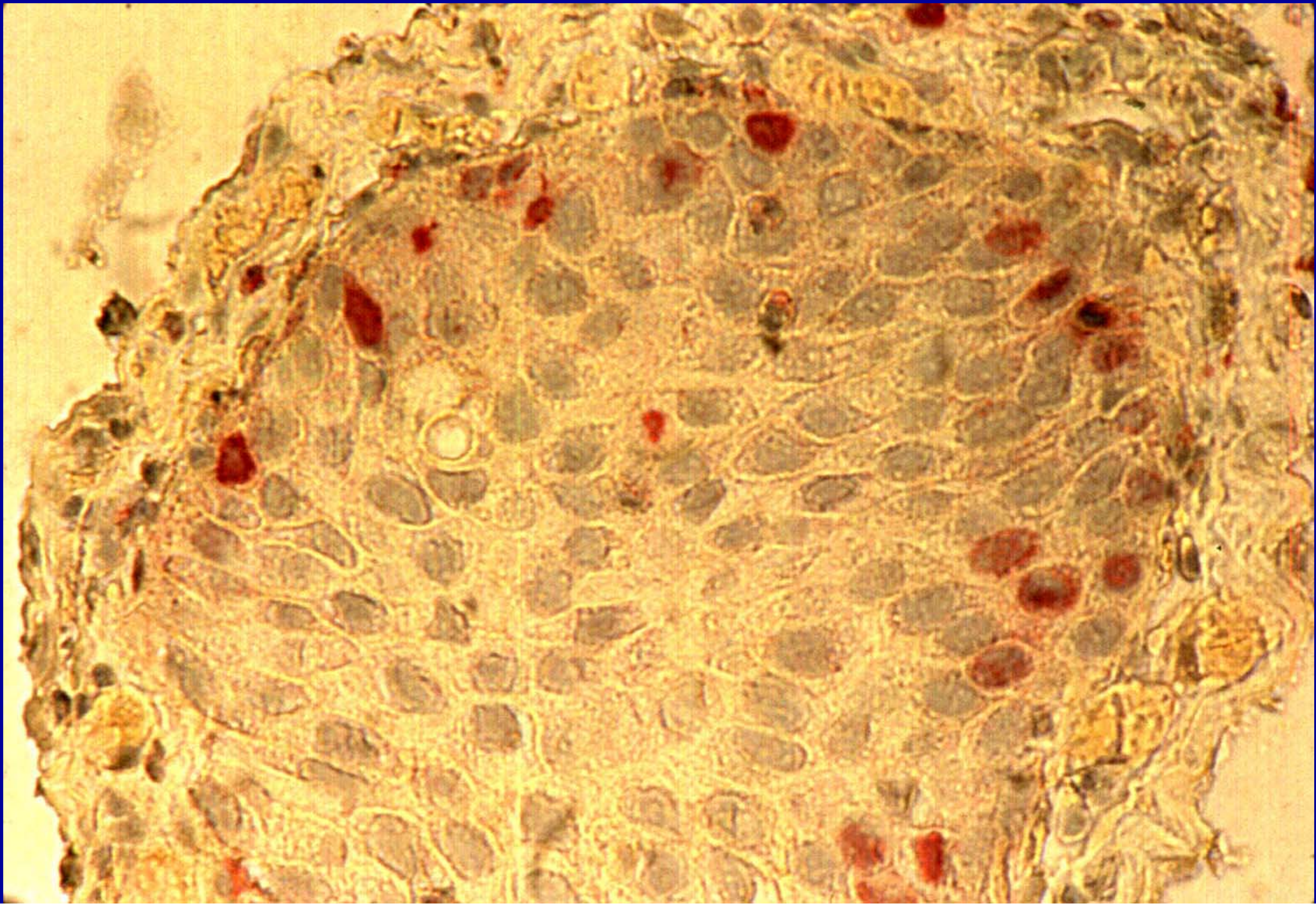
Growth factor biology

Cell Differentiation

Molecular mechanisms

Cell-matrix interactions

Targeted Committed Progenitor Cells



Progenitor Cells and Specific Growth Factors: Expansion Potential

1 cm^2

Day 1 (5×10^4 cells)

⬇

Day 60 (50×10^9 cells)

Enough cells to cover a football field

Cell Types Grown at the Wake Forest Institute for Regenerative Medicine

- Heart
- Kidney
- Esophagus
- Bladder
- Sm/Sk Muscle
- Cartilage
- Urethra
- Vessels
- Salivary glands
- Trachea
- Bone
- Breast
- Lung
- Retina
- Uterus
- Nerve
- Liver
- Pancreas

CELL DELIVERY VEHICLES

Biocompatibility
Cell attachment
Cell viability

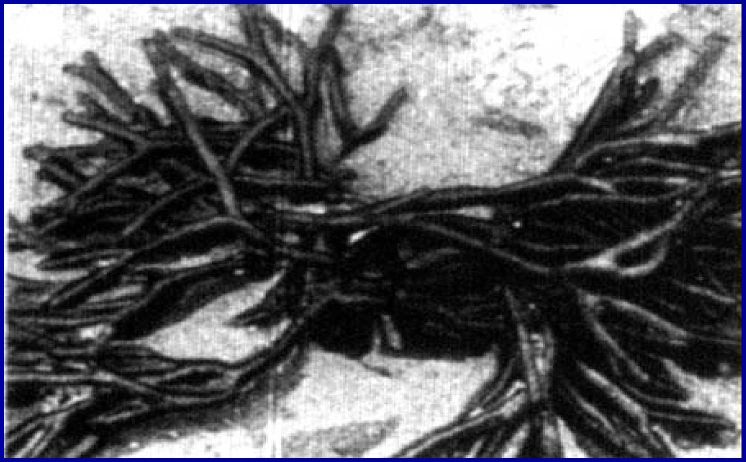
Degradation curves
Inflammatory responses
Biomechanical properties

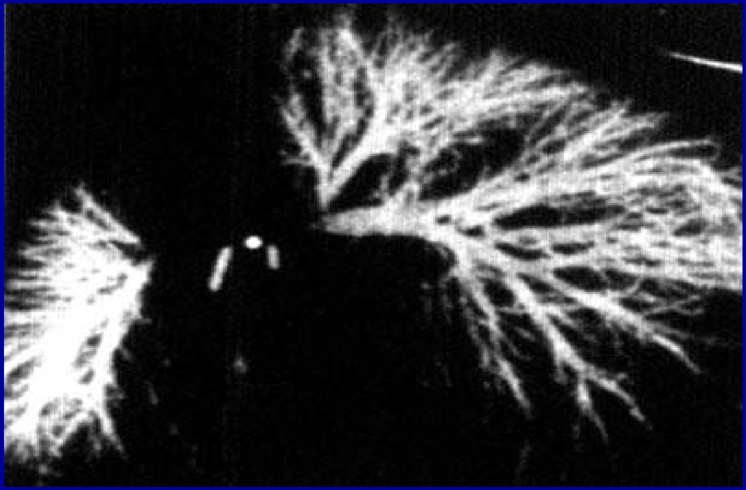
The scaffold should replicate the biomechanical and structural properties of the tissue being replaced

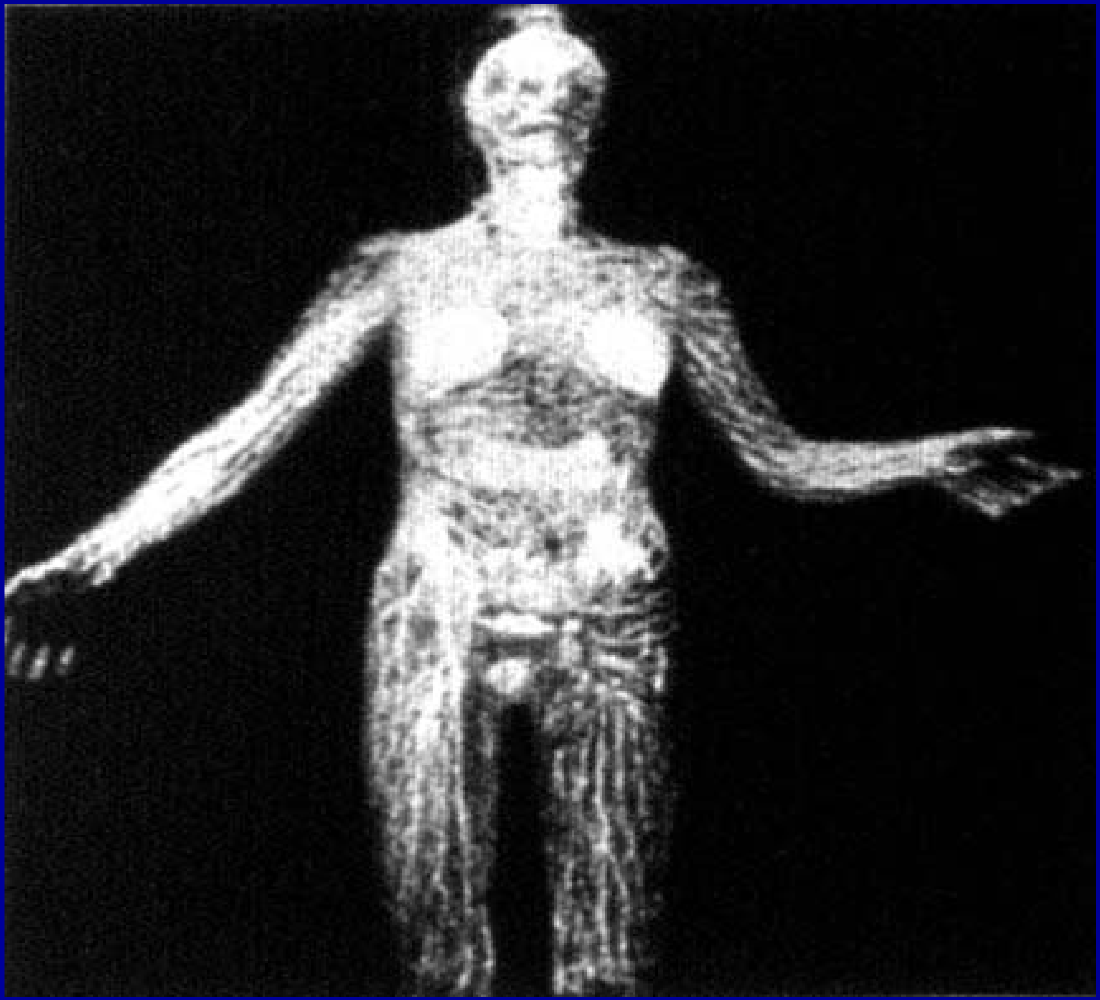
Vascularity: Problem

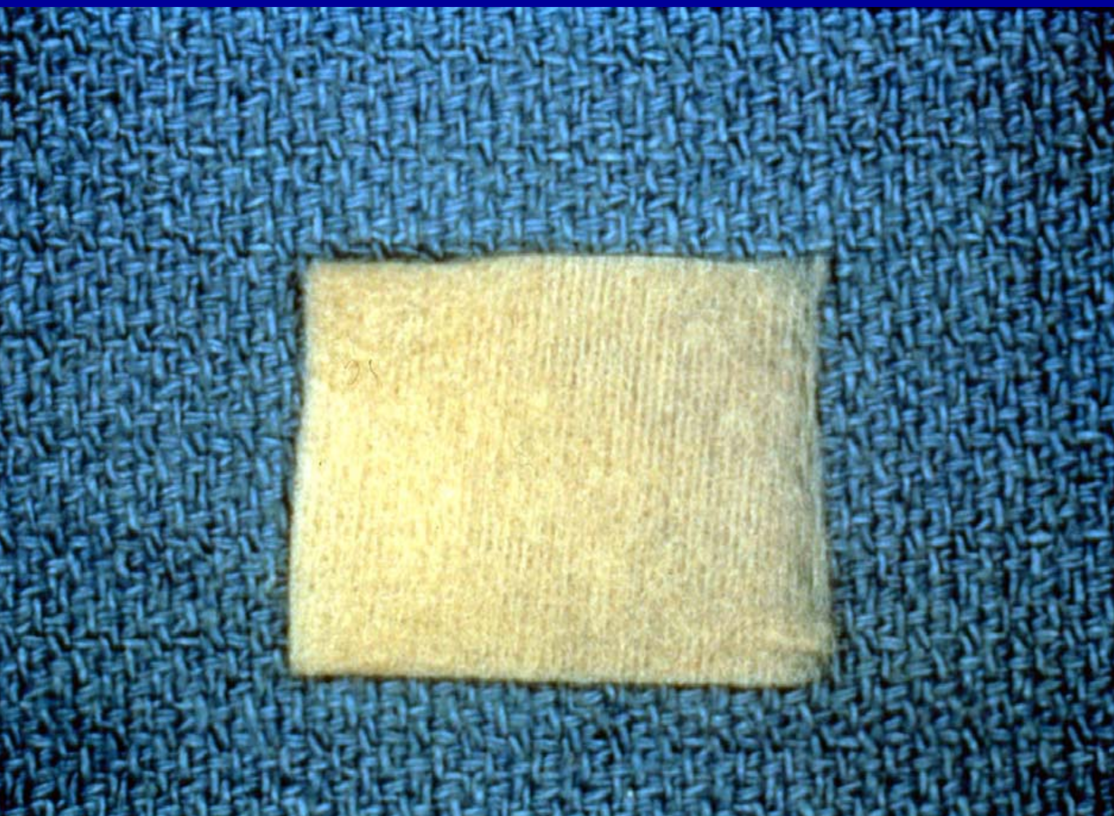
Cells cannot be implanted in volumes greater than 3 mm^3 (the size of a pencil eraser)

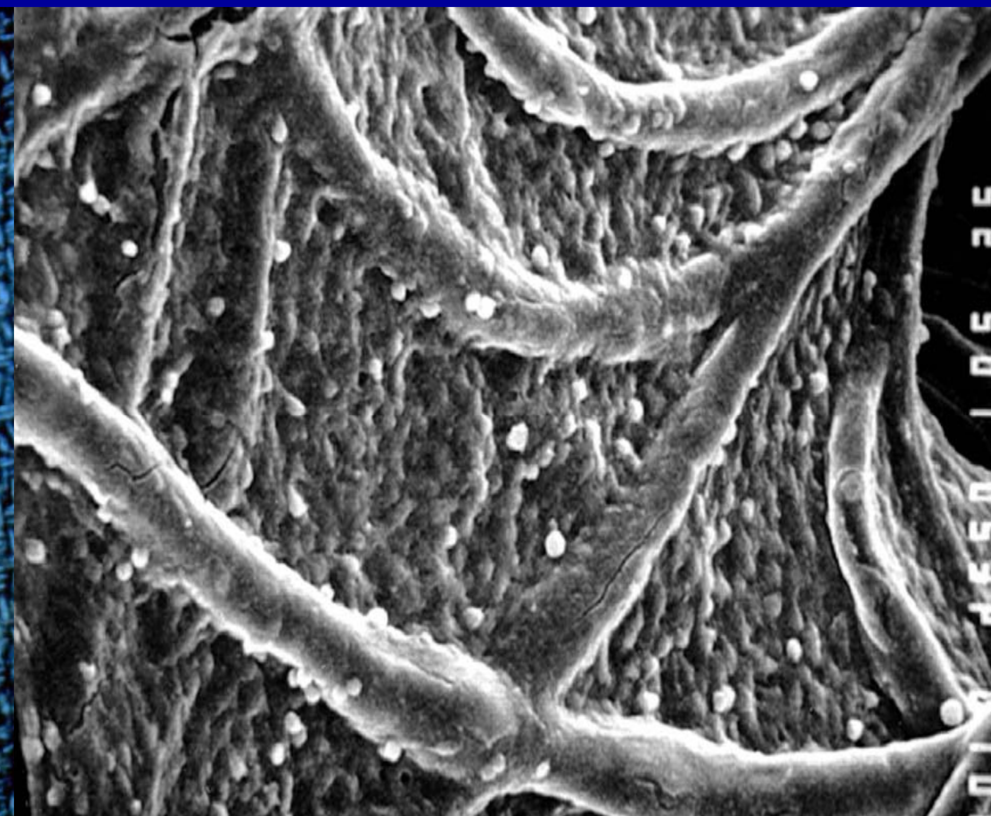
Nutrition to the cells is limited (limited vascularity)



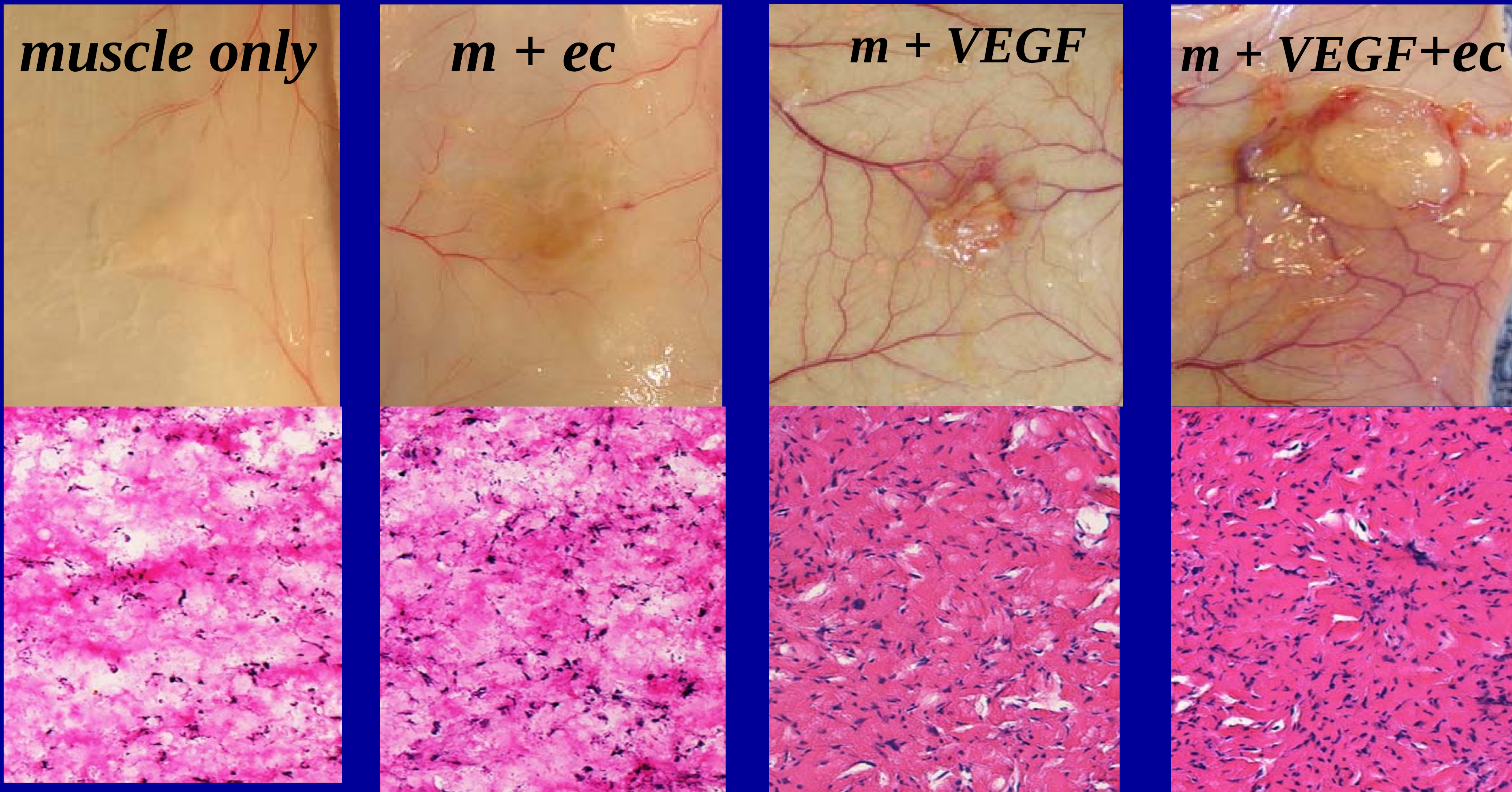




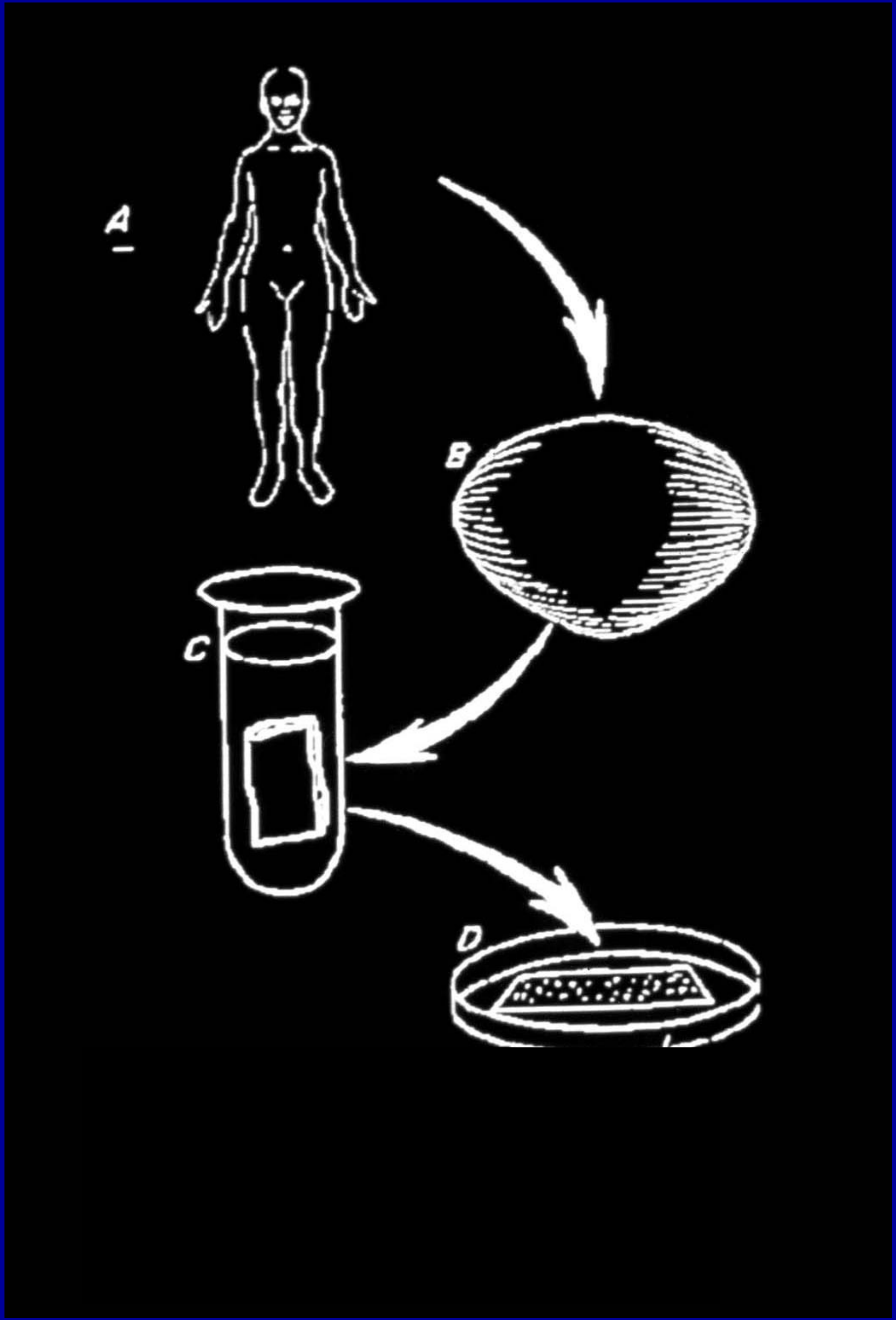




Tissue Formation in Vivo

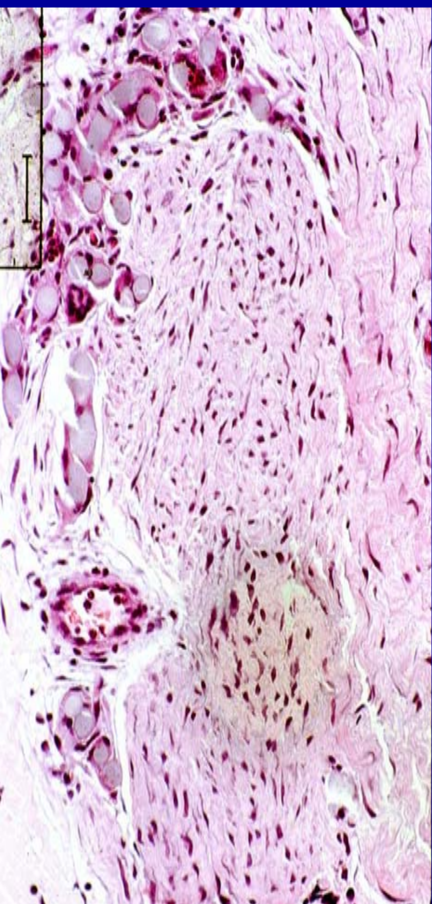


G Schuch et al, Blood 100:4622, 02.
WT Godbey et al, Gene Ther, 03.
G Schuch et al, Angiogenesis 5:181, 02.
RC Smith et al, Hum Gene Ther 13:697, 02
M Nomi et al, Mol Aspects Med 23:463, 02.

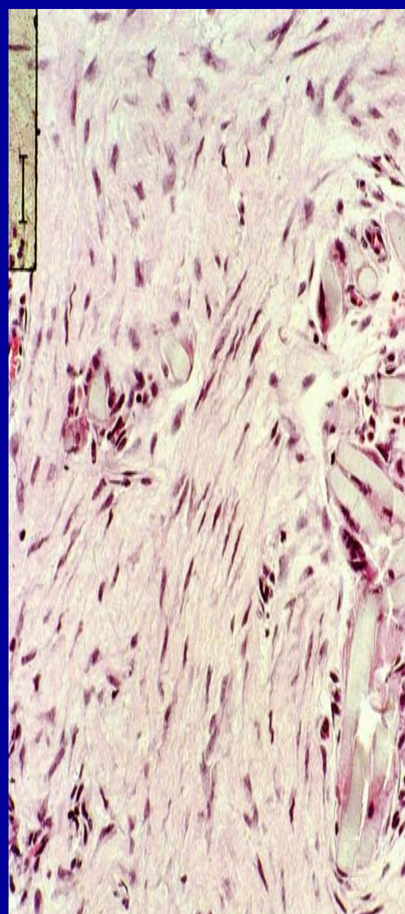

A
B
C
D

Building Blocks for the Engineering of Tissues and organs

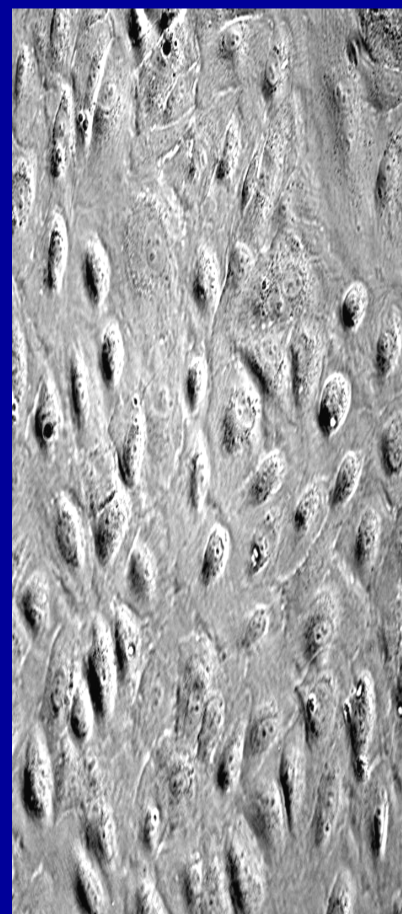
Muscle



Heart mm

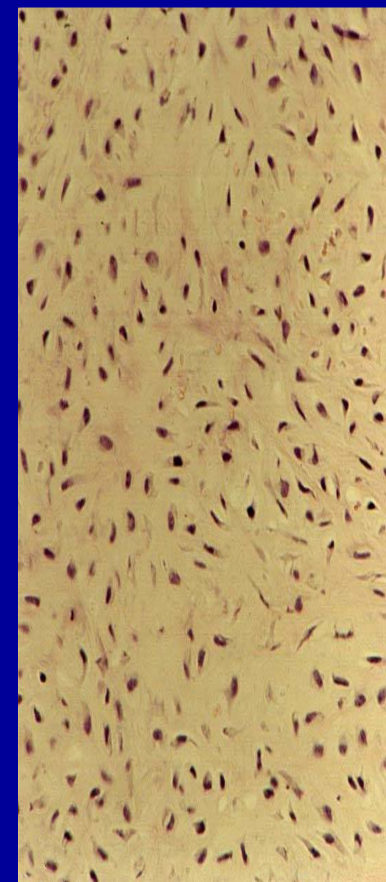


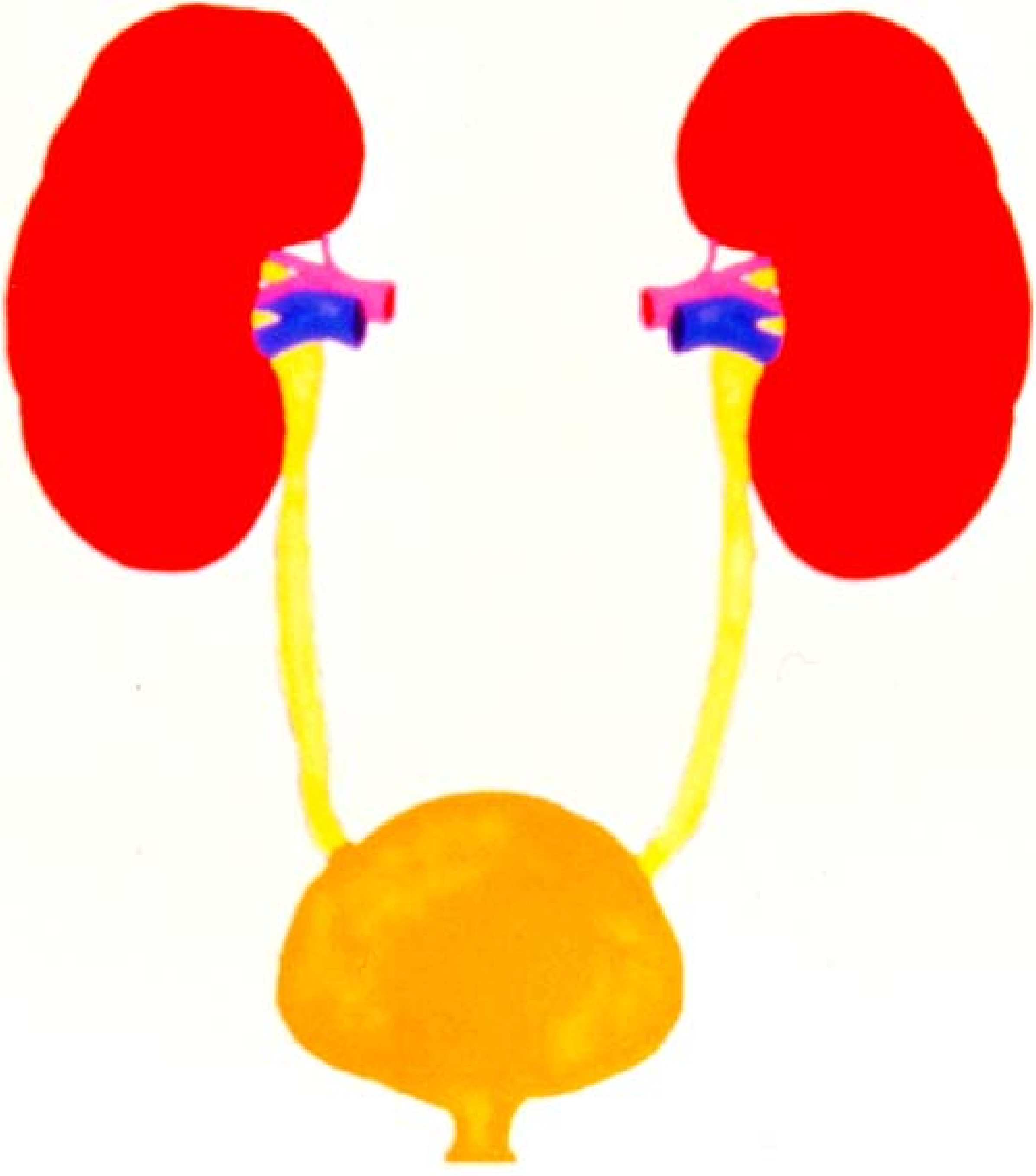
Endothelium

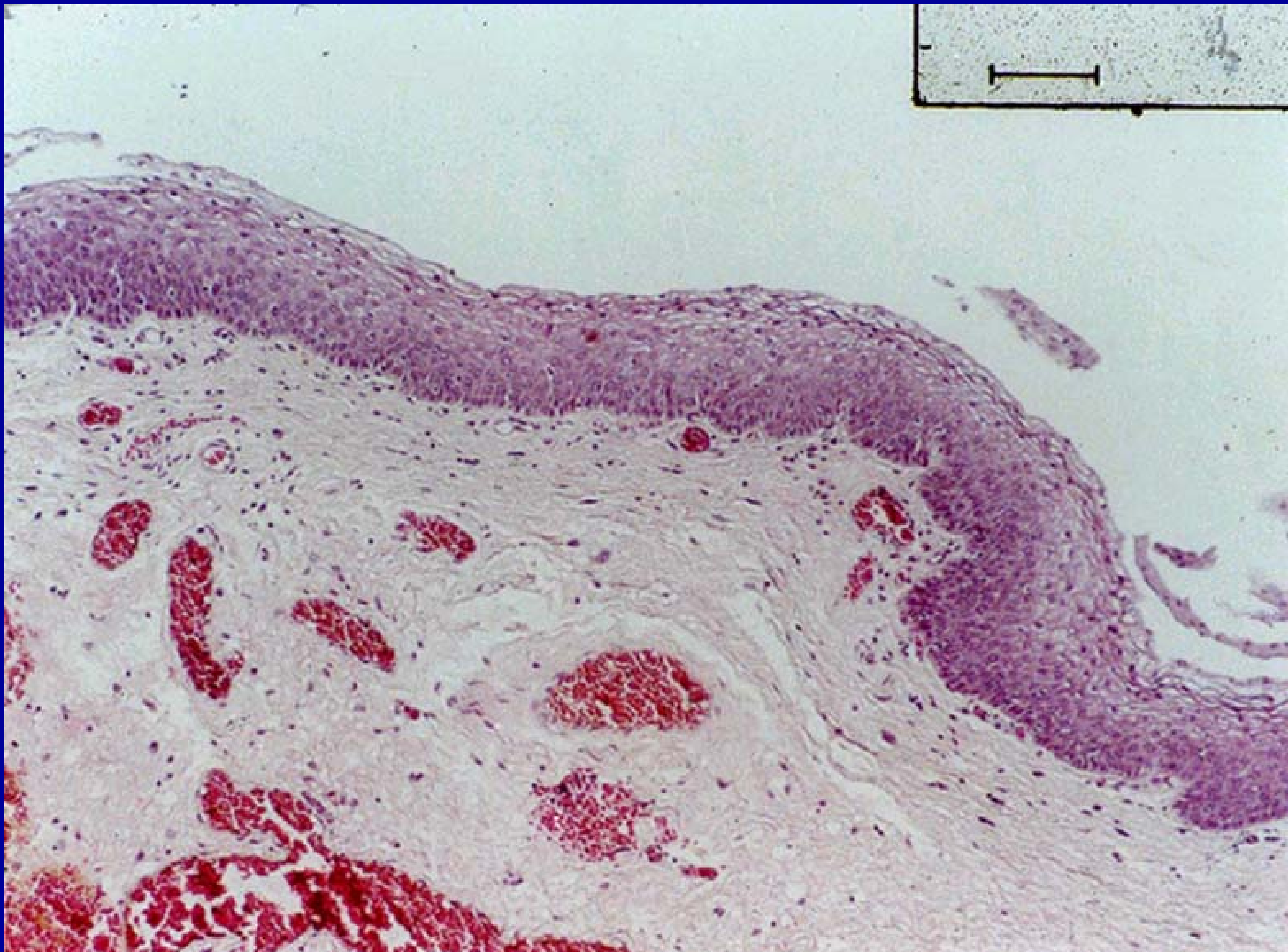


Bone

Cartilage







J Urol 162:1148, 99.

F Chen et al, Urology 54:1, 99.

RE DeFilippo et al, J Urol 168:1789, 02.

AW El-Kassaby et al, J Urol 169:170, 03.

Urethra: Clinical Experience

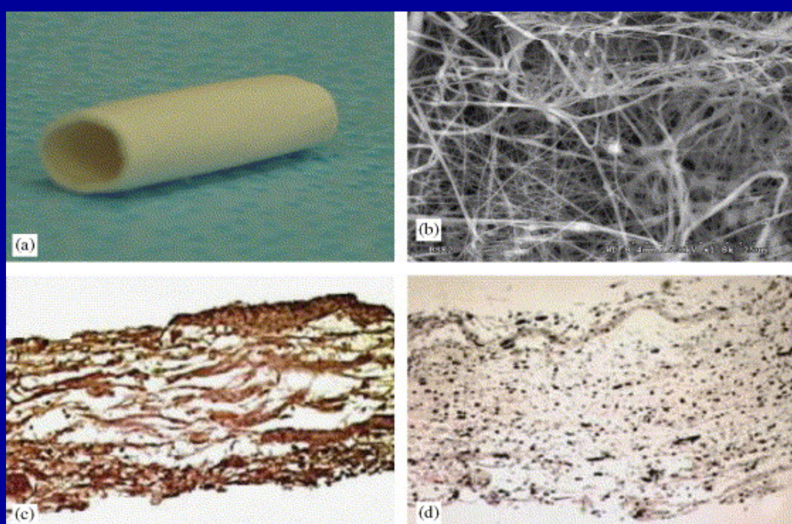
Over 100 patients treated to date

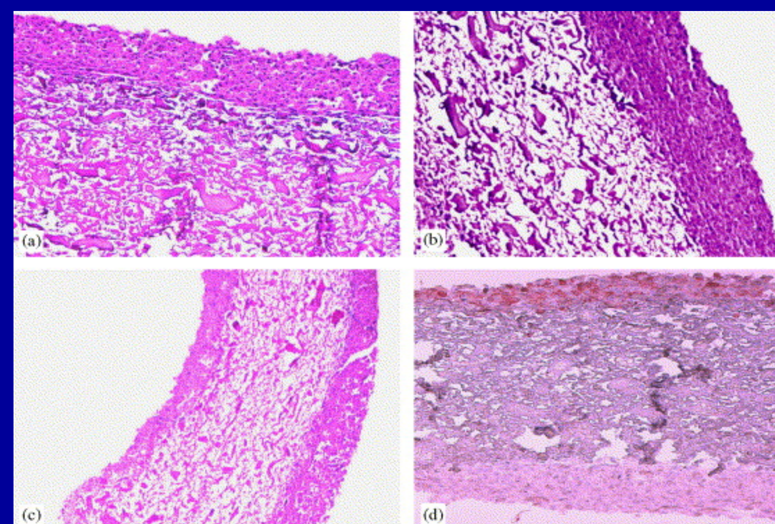
Over a 5 year follow-up

80% Success rate

Fabrication of a vascular substitute

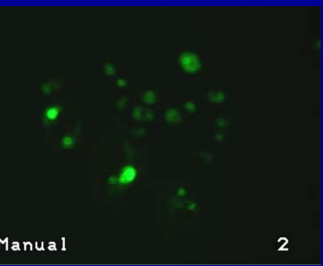
Electrospun nanofiber substrate, with endothelial and smooth muscle cells





Stitzel et al., *Biomaterials*, 2005.

Peripheral Blood-derived Endothelial Cells for the Creation of Tissue Engineered Blood Vessels



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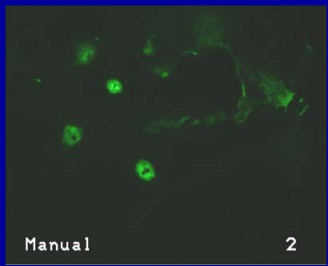
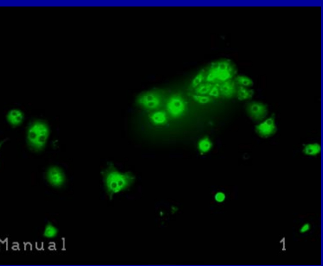
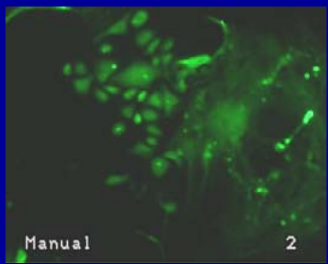


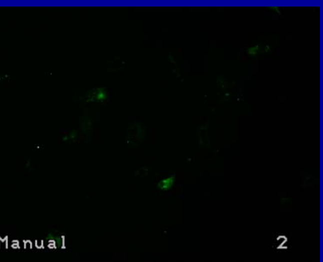
CD31



BS1

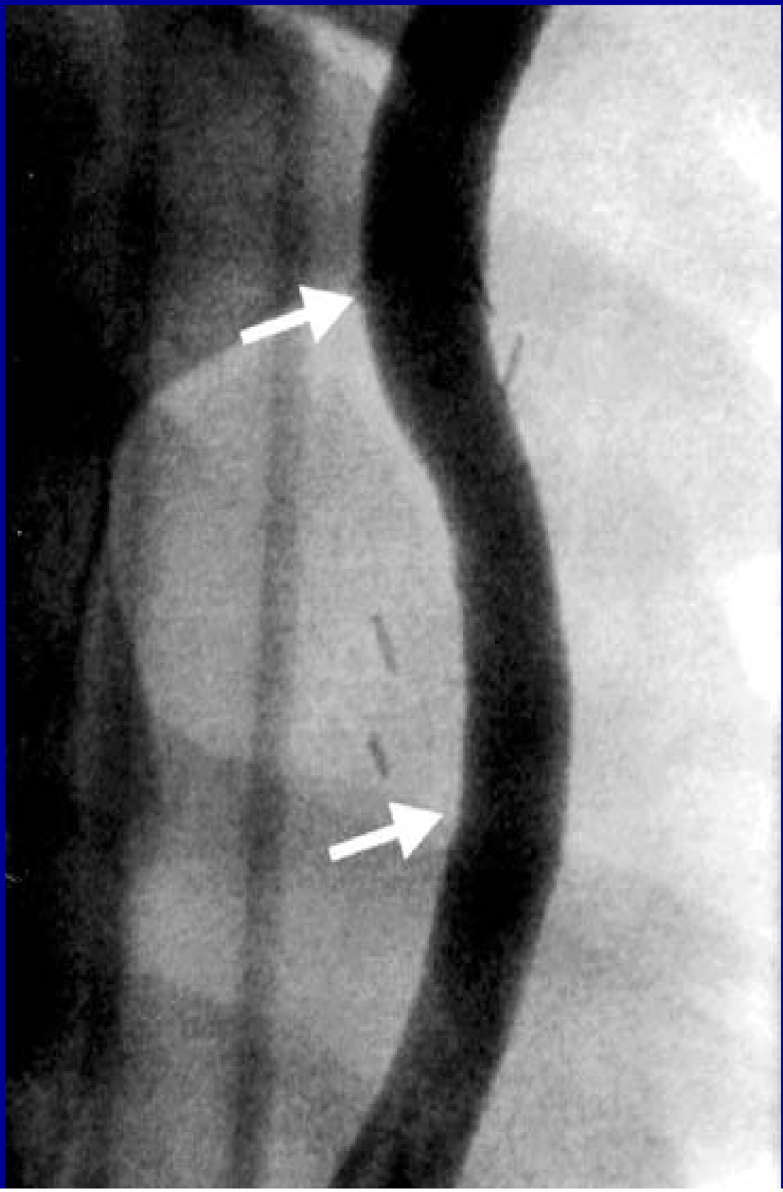


F VIII



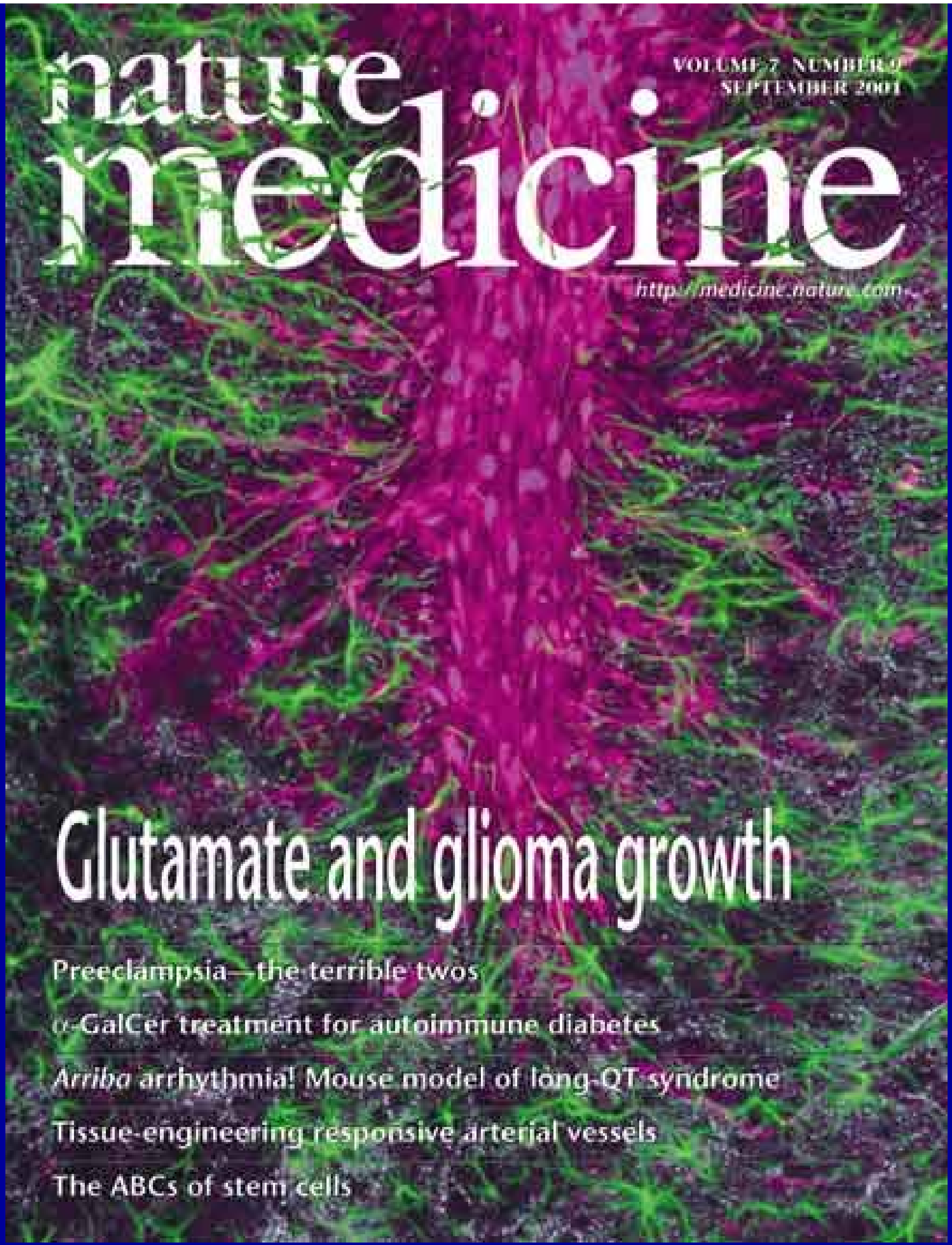
CD14

Control



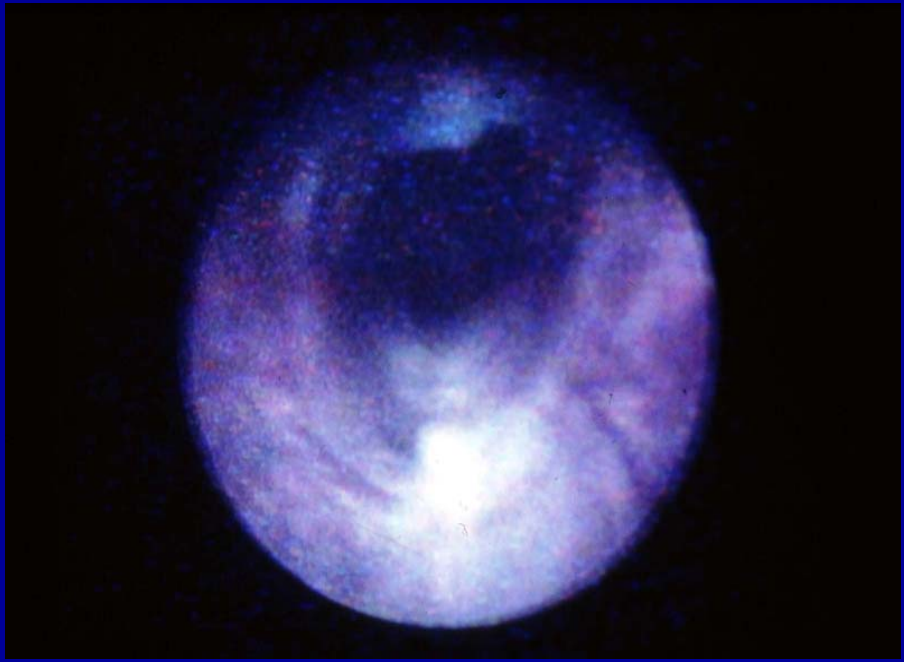
Engineered Artery

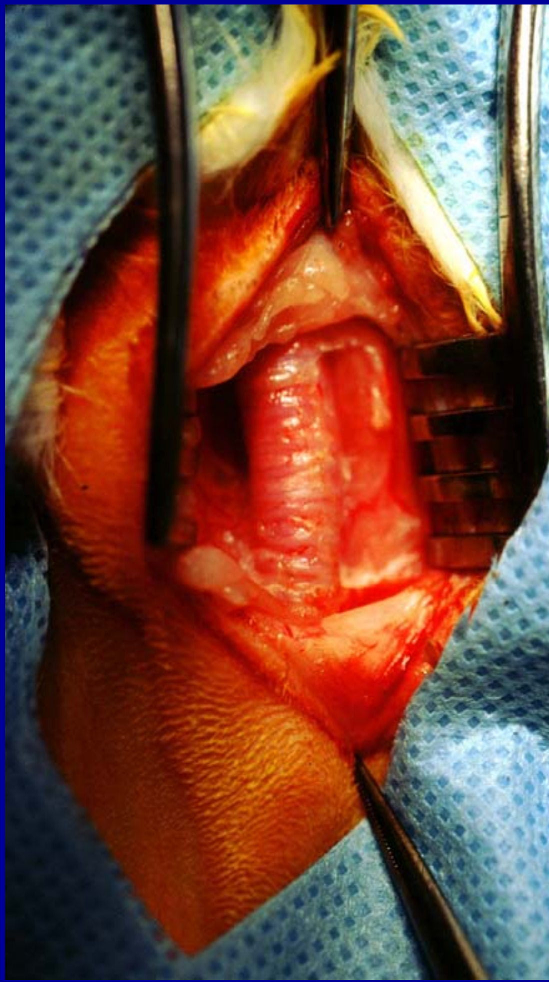
Native Artery



S. Kaushal et al

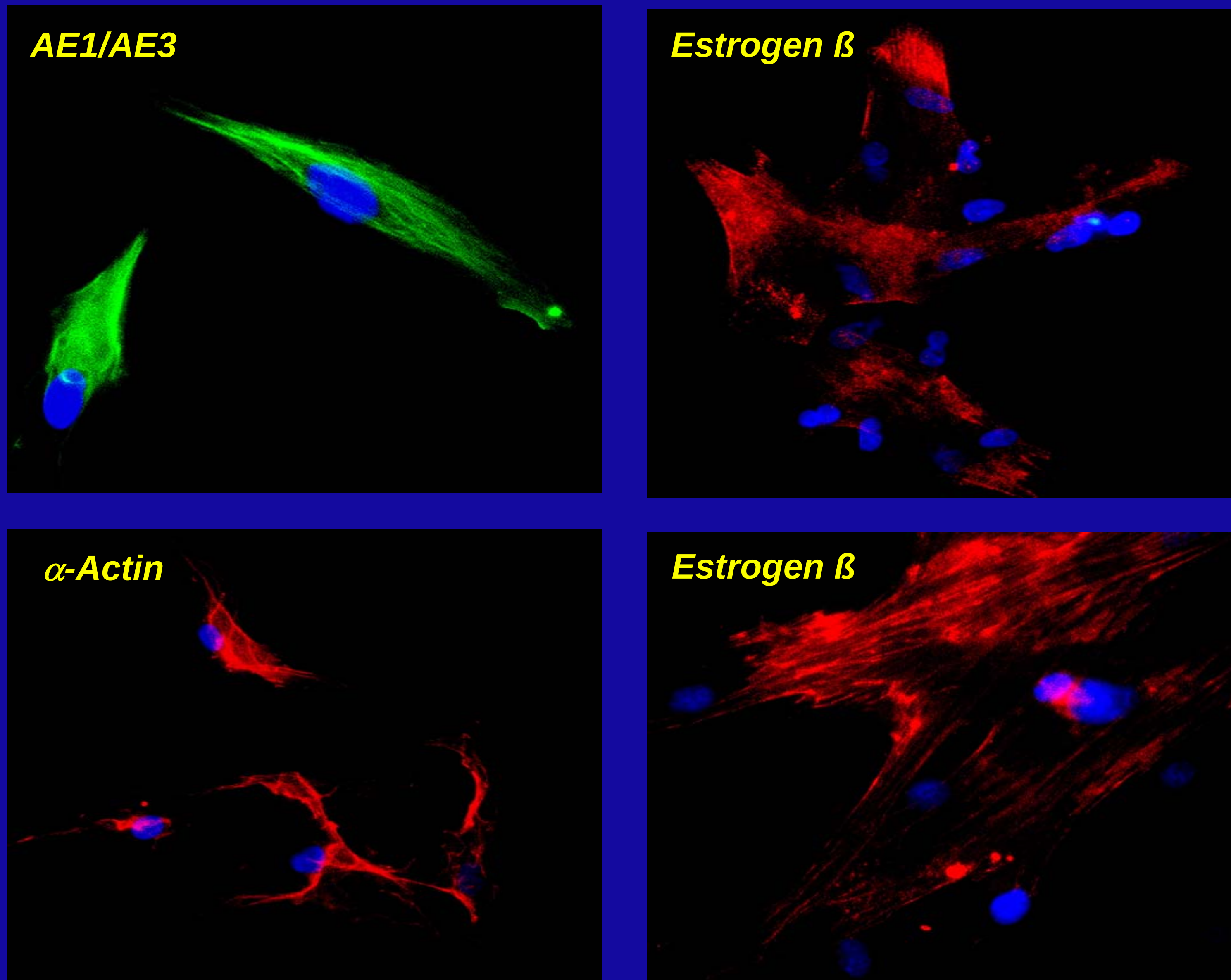
Engineered Trachea





Vaginal Epithelial Cells

Vaginal Smooth Muscle Cells

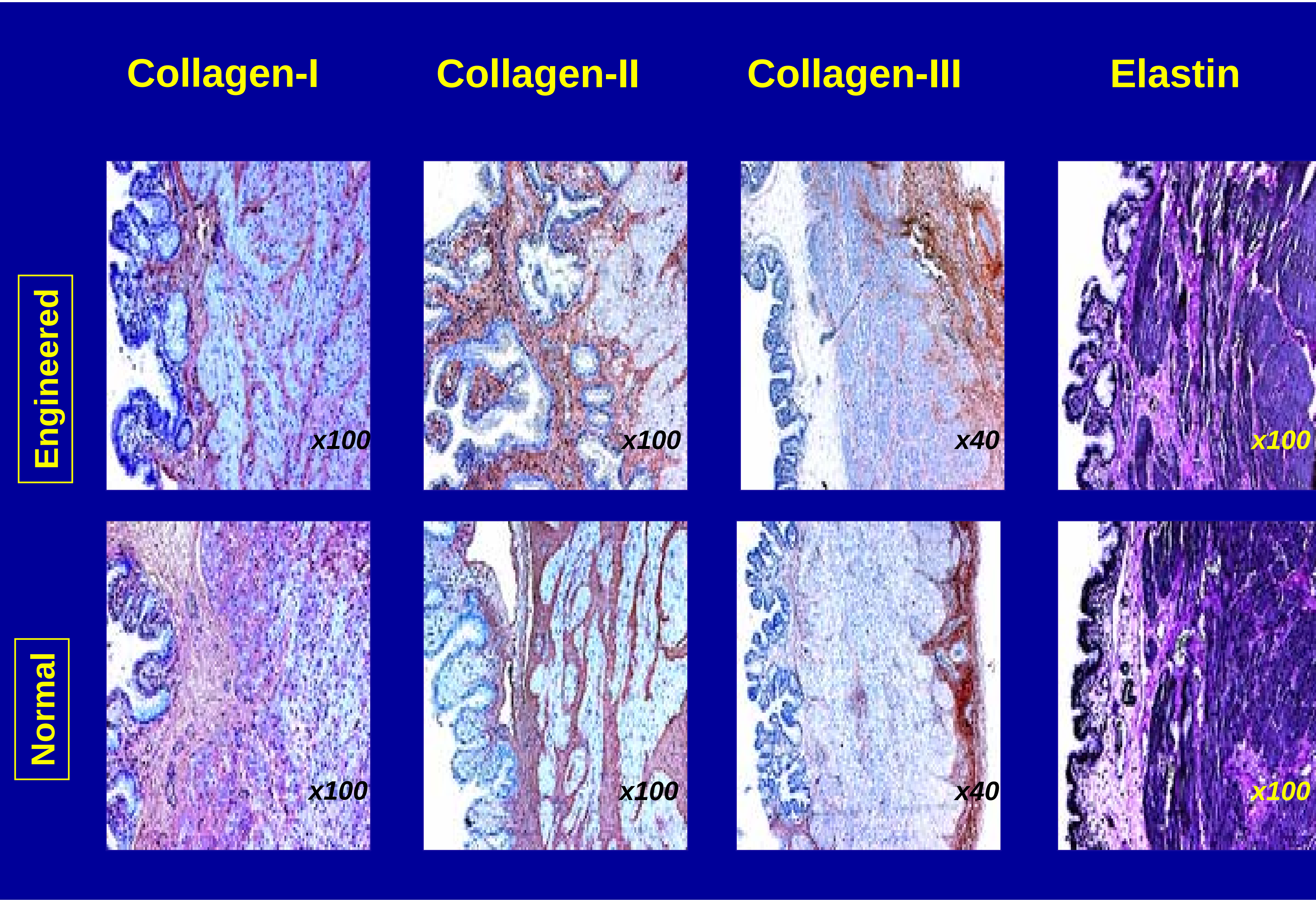


Gross Examination

1 Mo

3 Mo

6 Mo


Collagen-I
Collagen-II
Collagen-III
Elastin
Engineered
Normal
x100
x100
x40
x100
x100
x100
x40
x100

Organ Bath Studies

EFS | AR Stimulation

30 Hz | 60 Hz | Phenylephrine

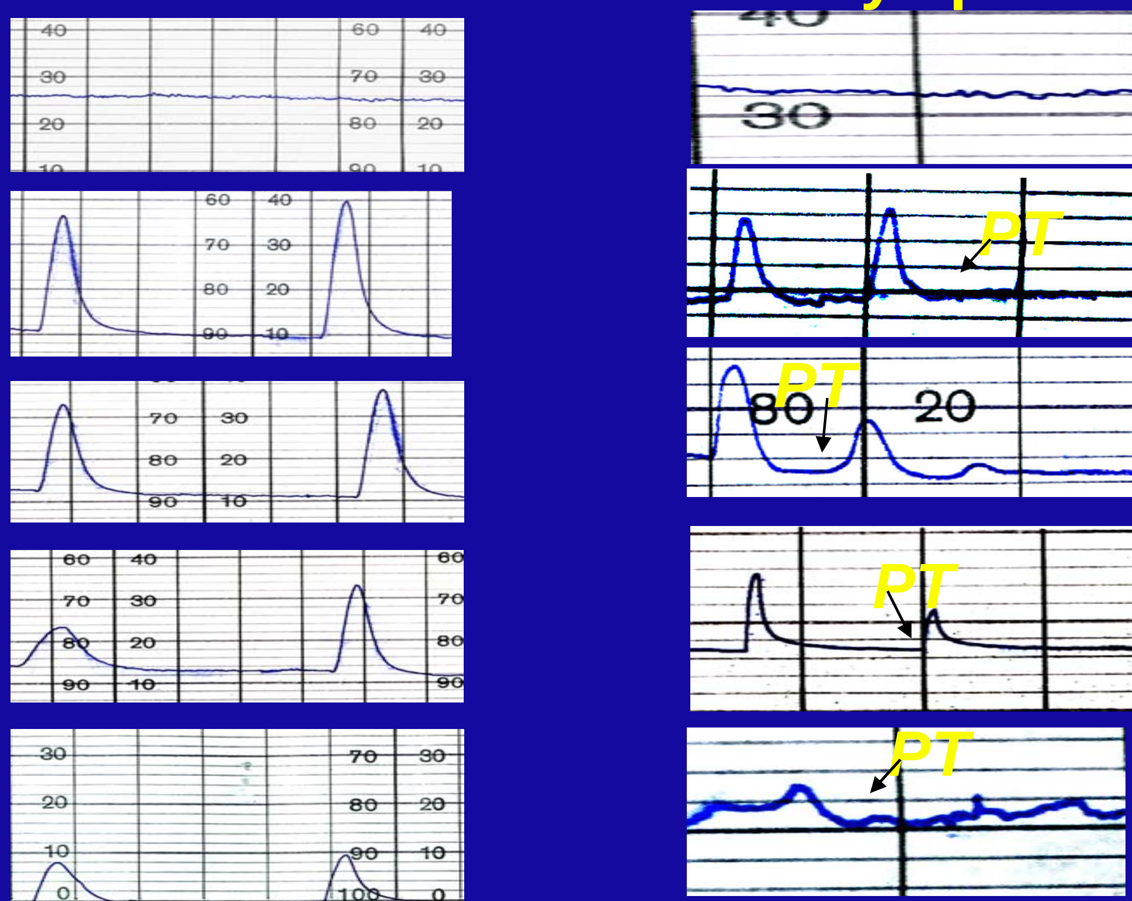
Unseeded

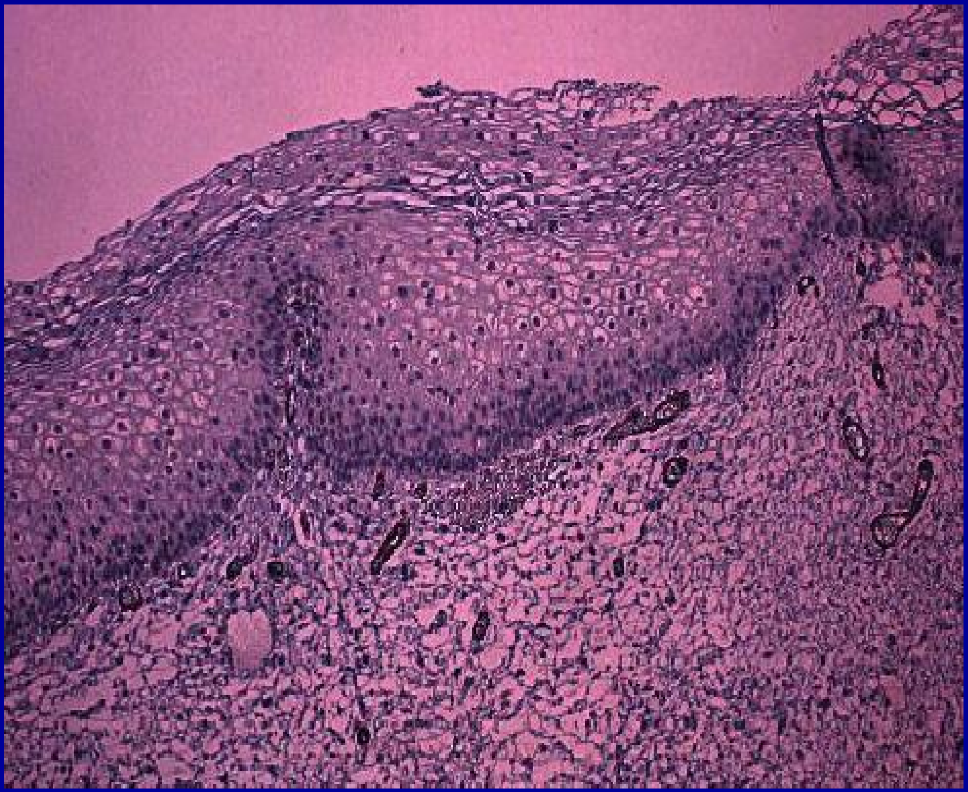
NL Vagina

6 Months

3 Months

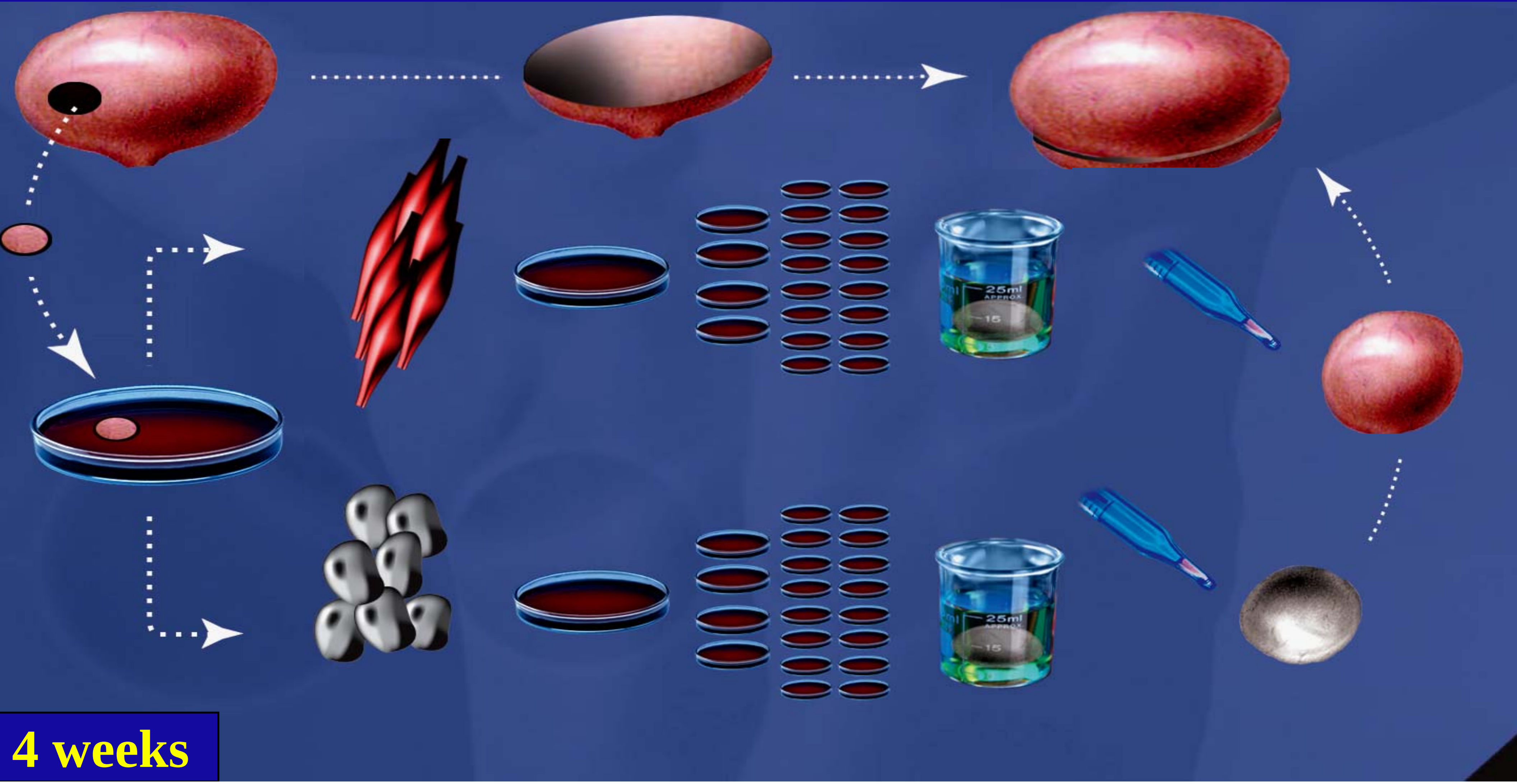
1 Month





Clinical Experience- 3 year follow-up in patients with engineered vaginas

Creation of the First Engineered Organ: Bladder



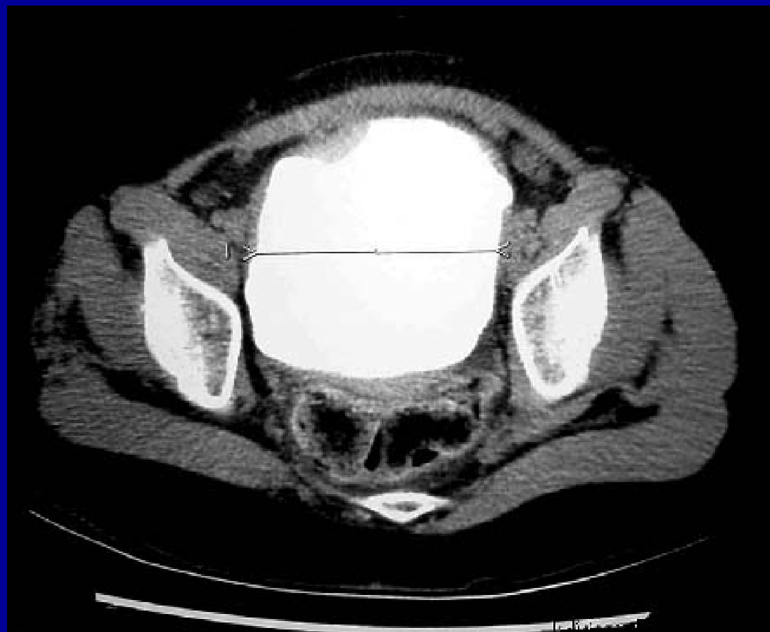
4 weeks

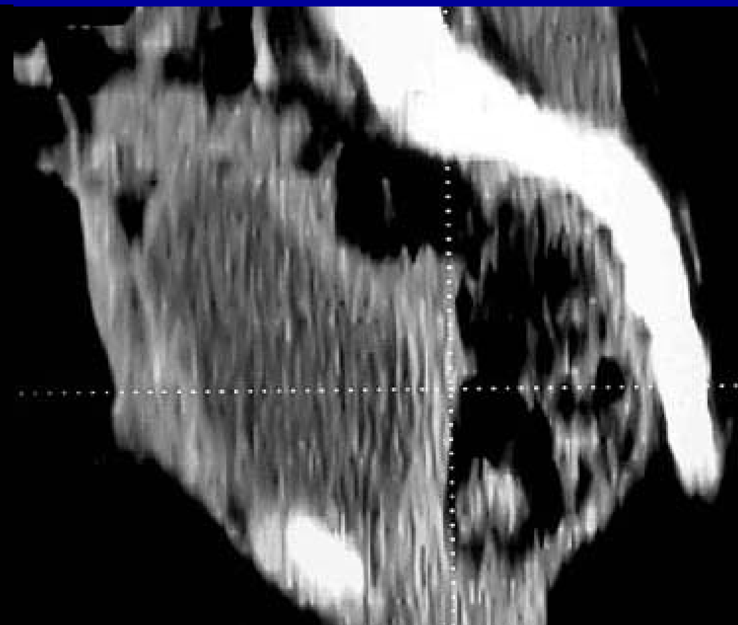
Oberpenning et al, 1999

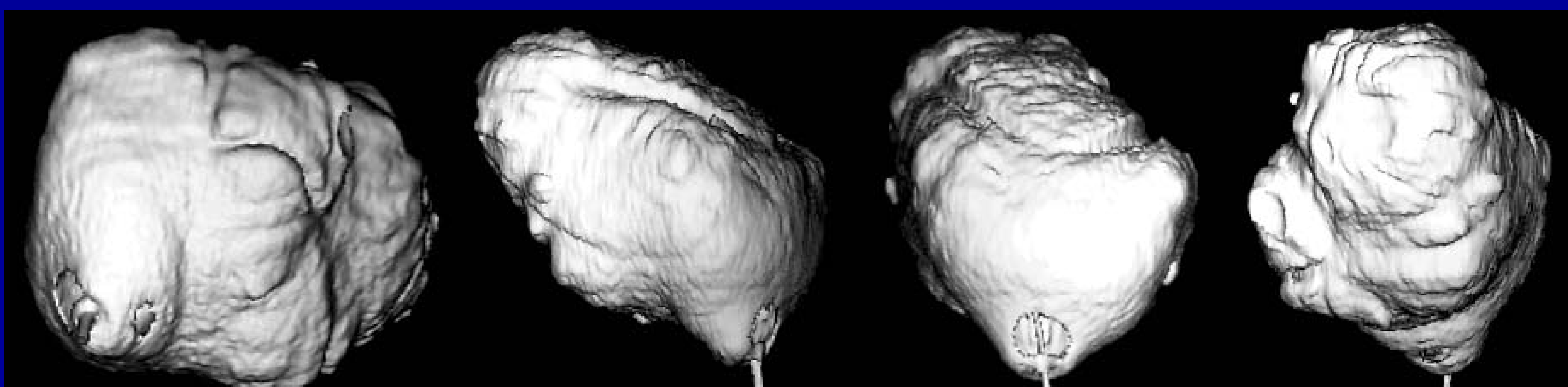
Clinical Studies

Patients with high pressure /low capacity bladders

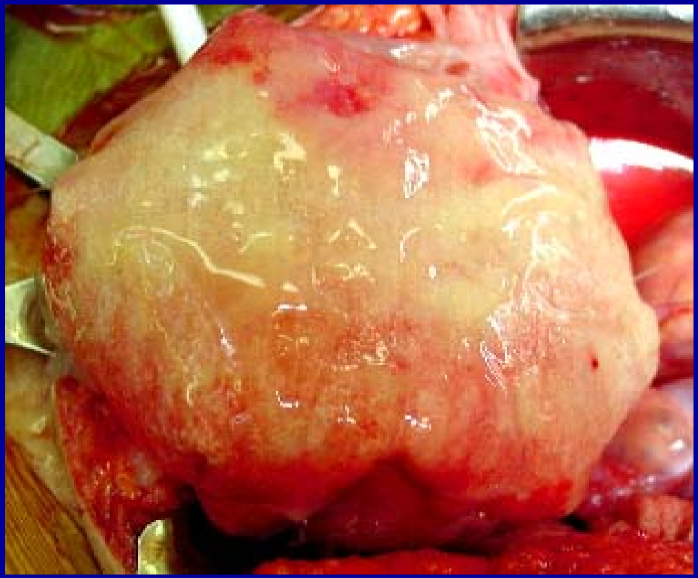
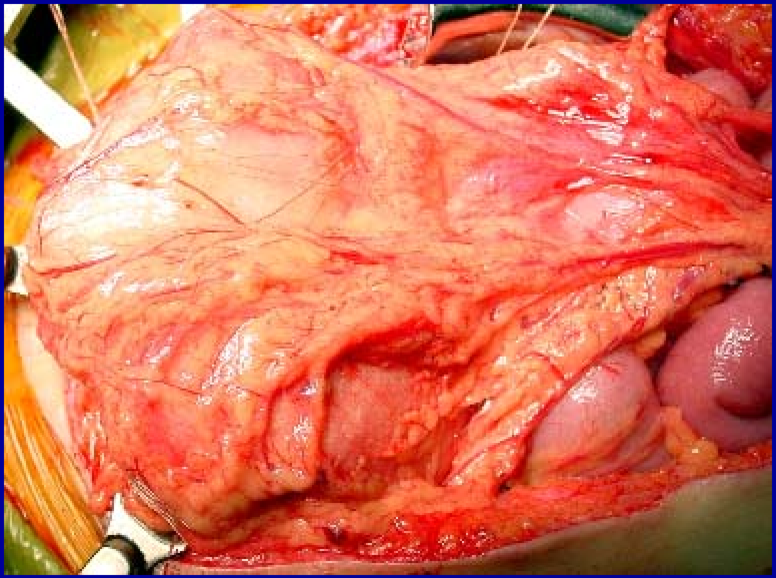
All failed medical therapy and were considered candidates for bladder reconstruction



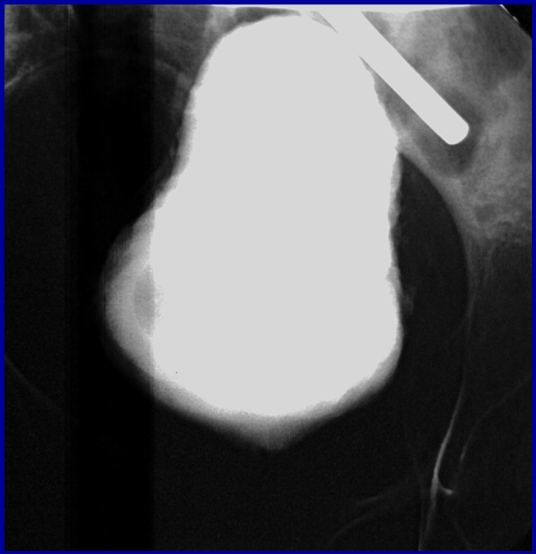




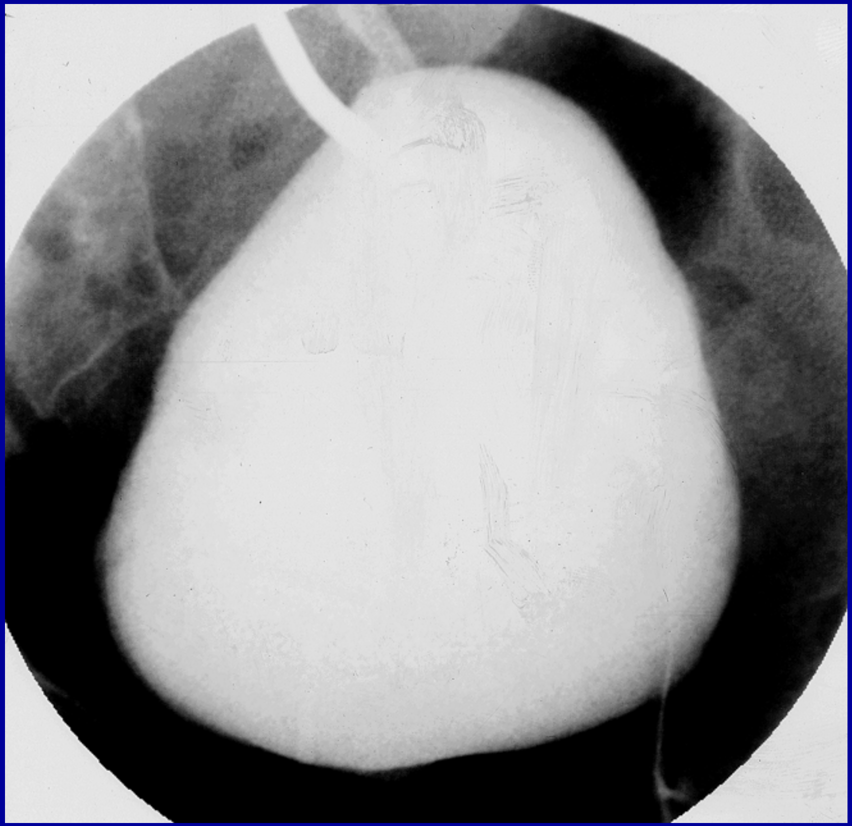


Pre-Op

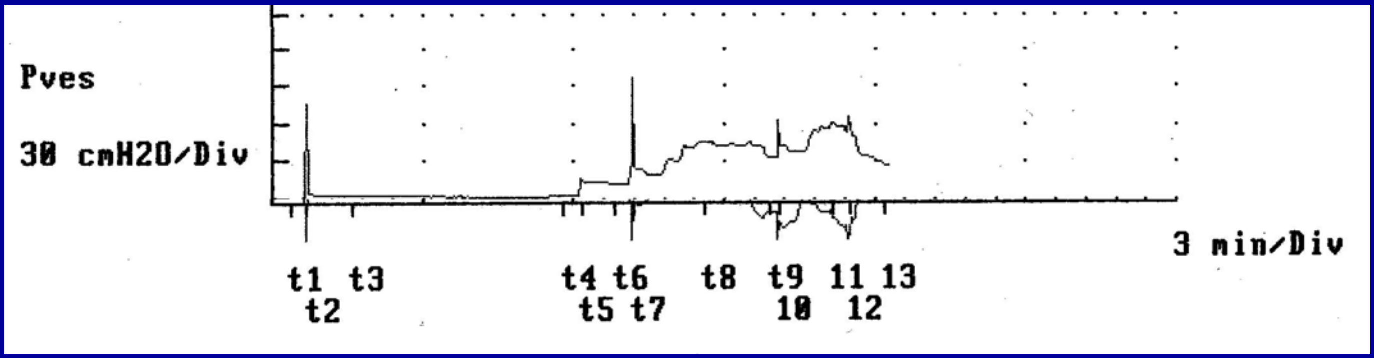


Post-Op (6 Mo.)

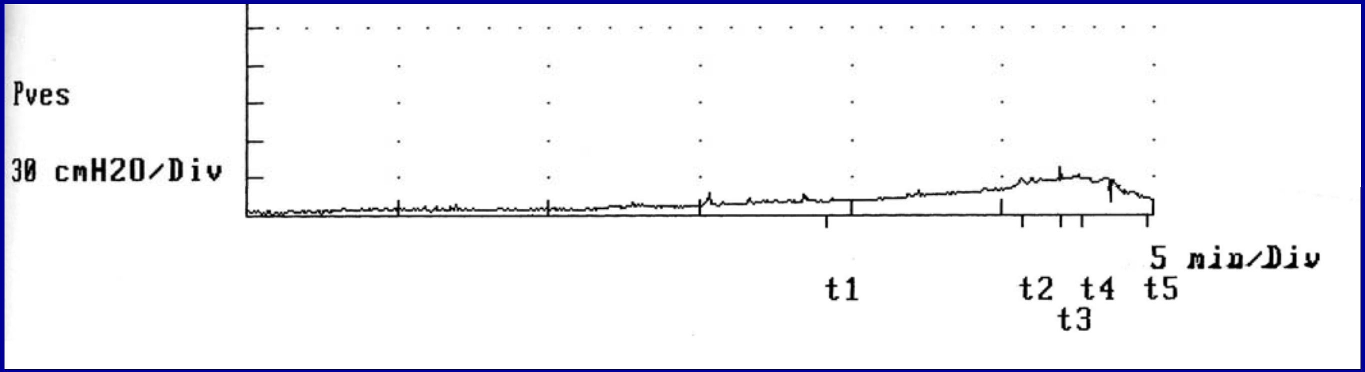


Urodynamic Studies

Pre-Op.



Post-Op.



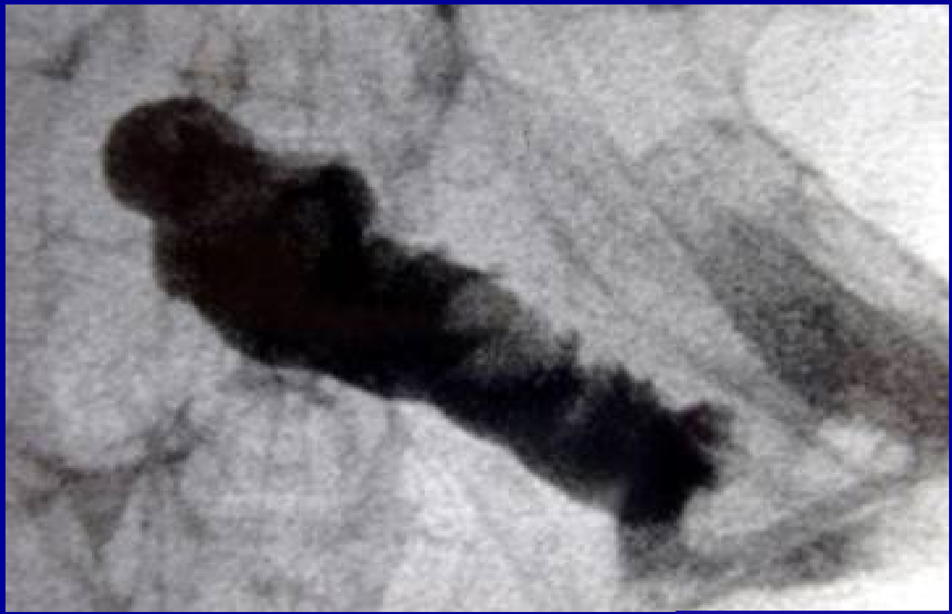
<u>Clinical Experience</u>

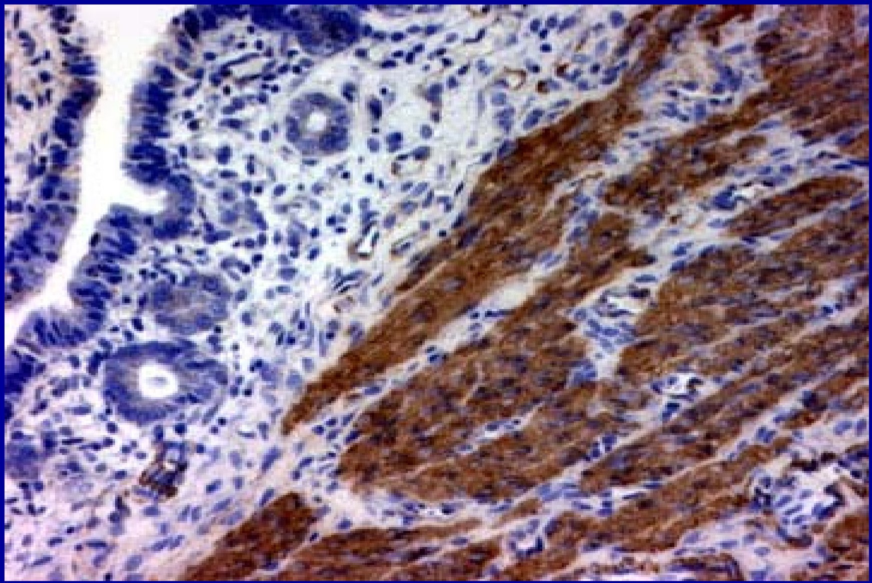
3 protocols

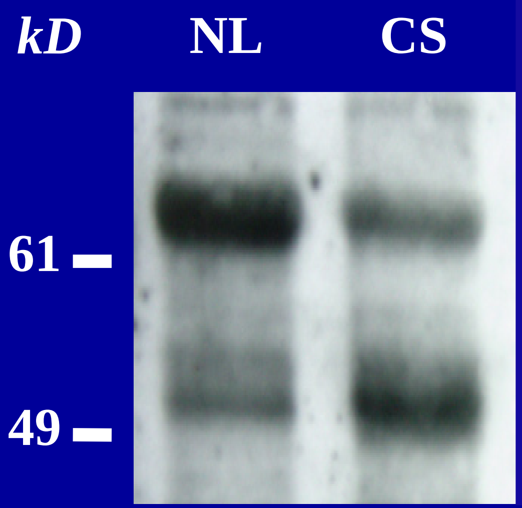
5 year follow-up

The Lancet, April 06

UTERUS



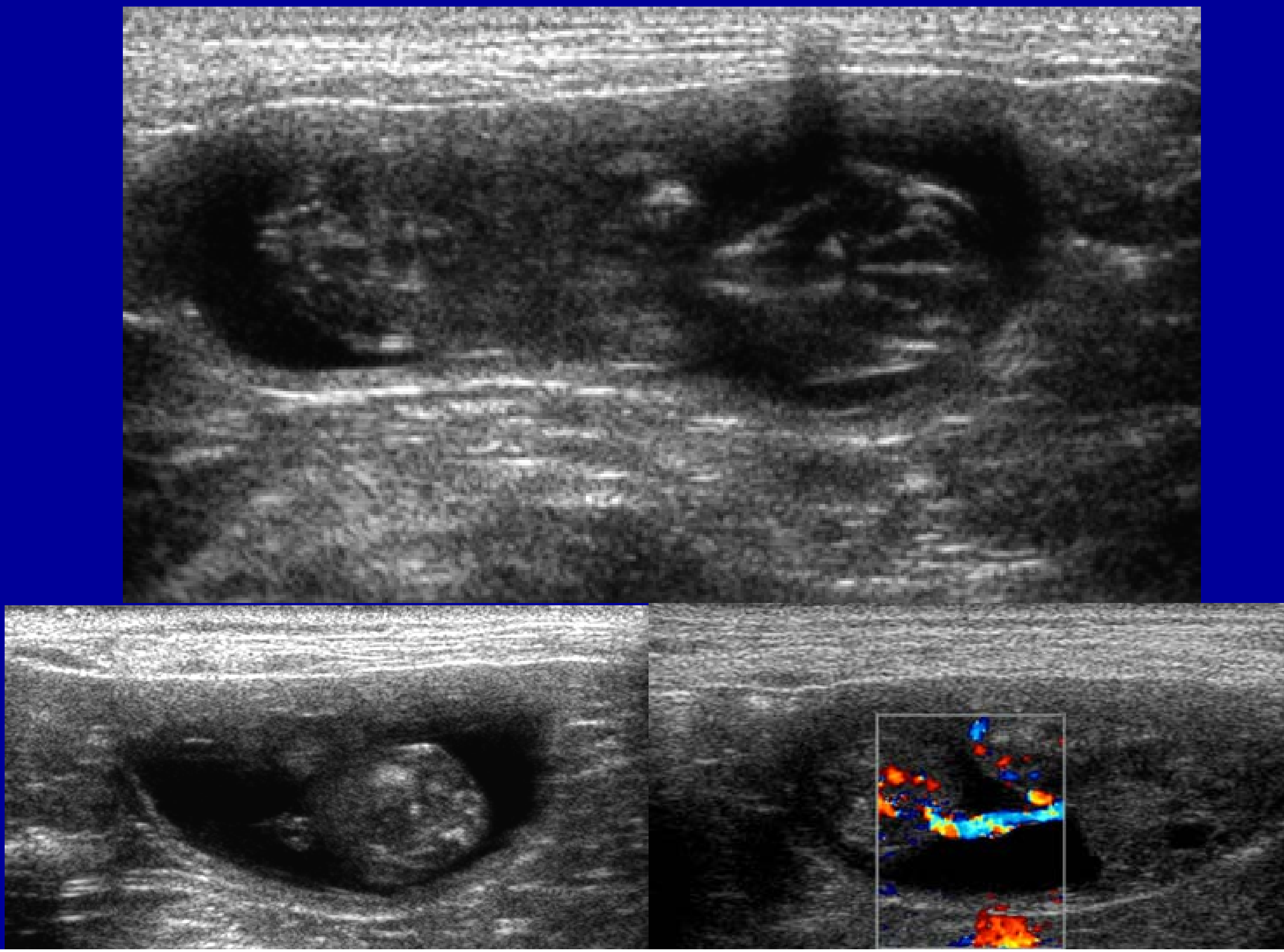




Estrogen receptor B

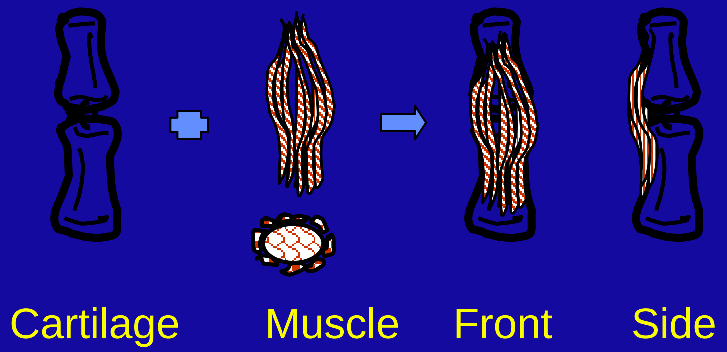
Fetus in Tissue Engineered Uterus

Near-term

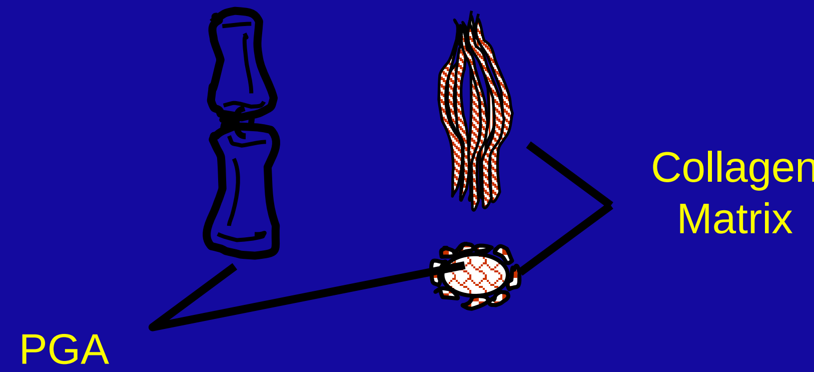


Engineering of the Digit

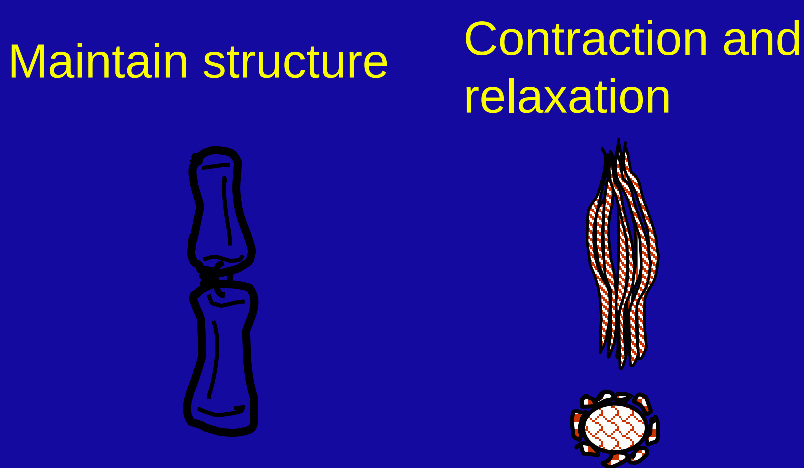
Scaffold Configuration for Digits



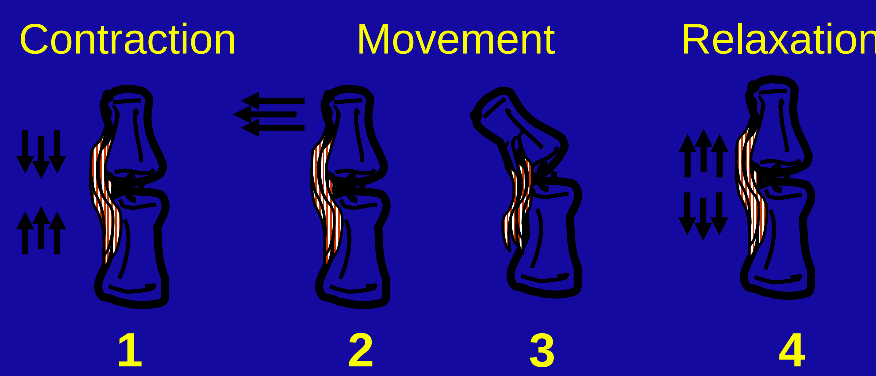
Scaffold Composition



Functional Components

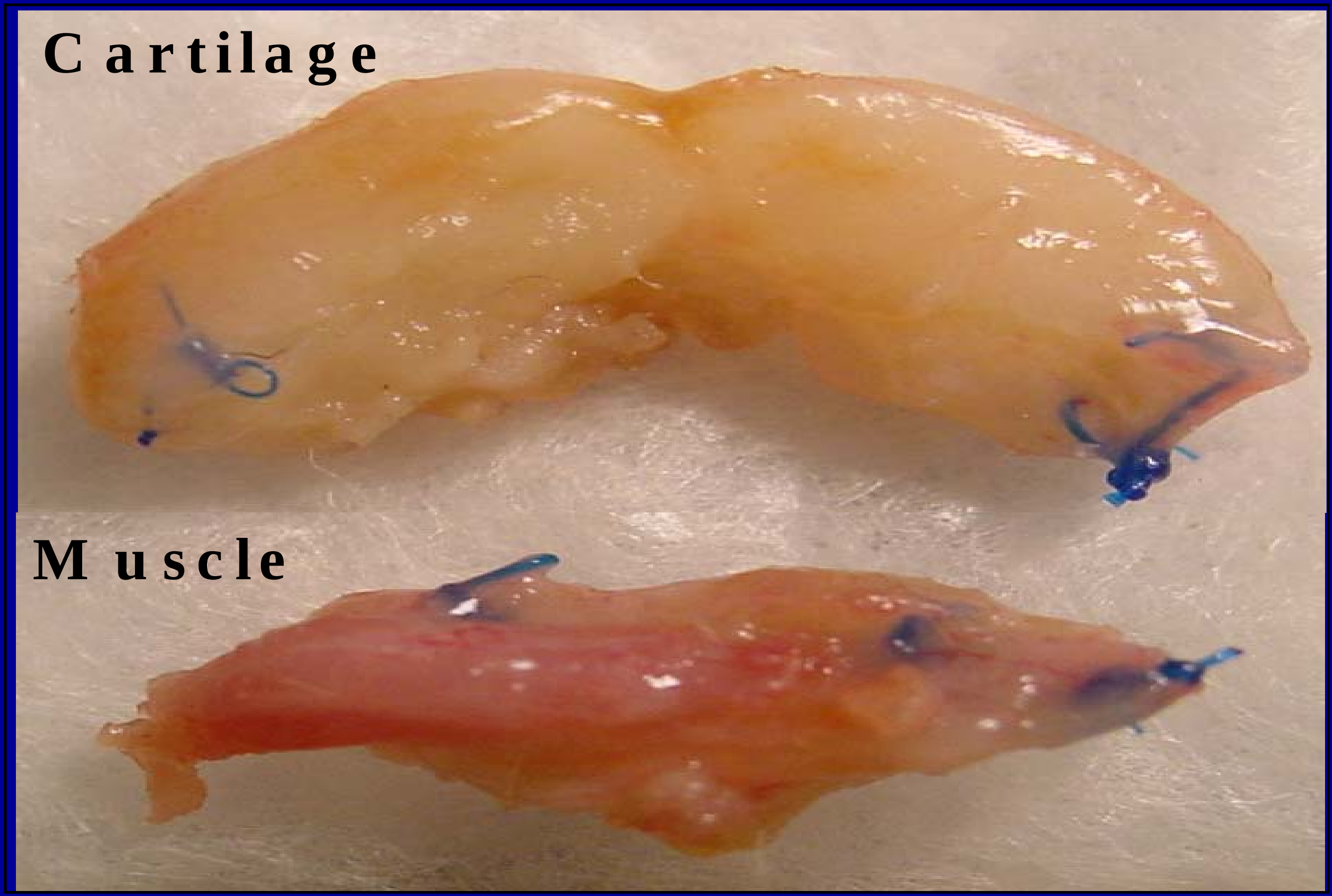


Muscle Function and Digit Movement



Engineered Digit

Cartilage and muscle composite tissue



Steve Badylak, MD, PhD, DVM
Material-Induced Regeneration

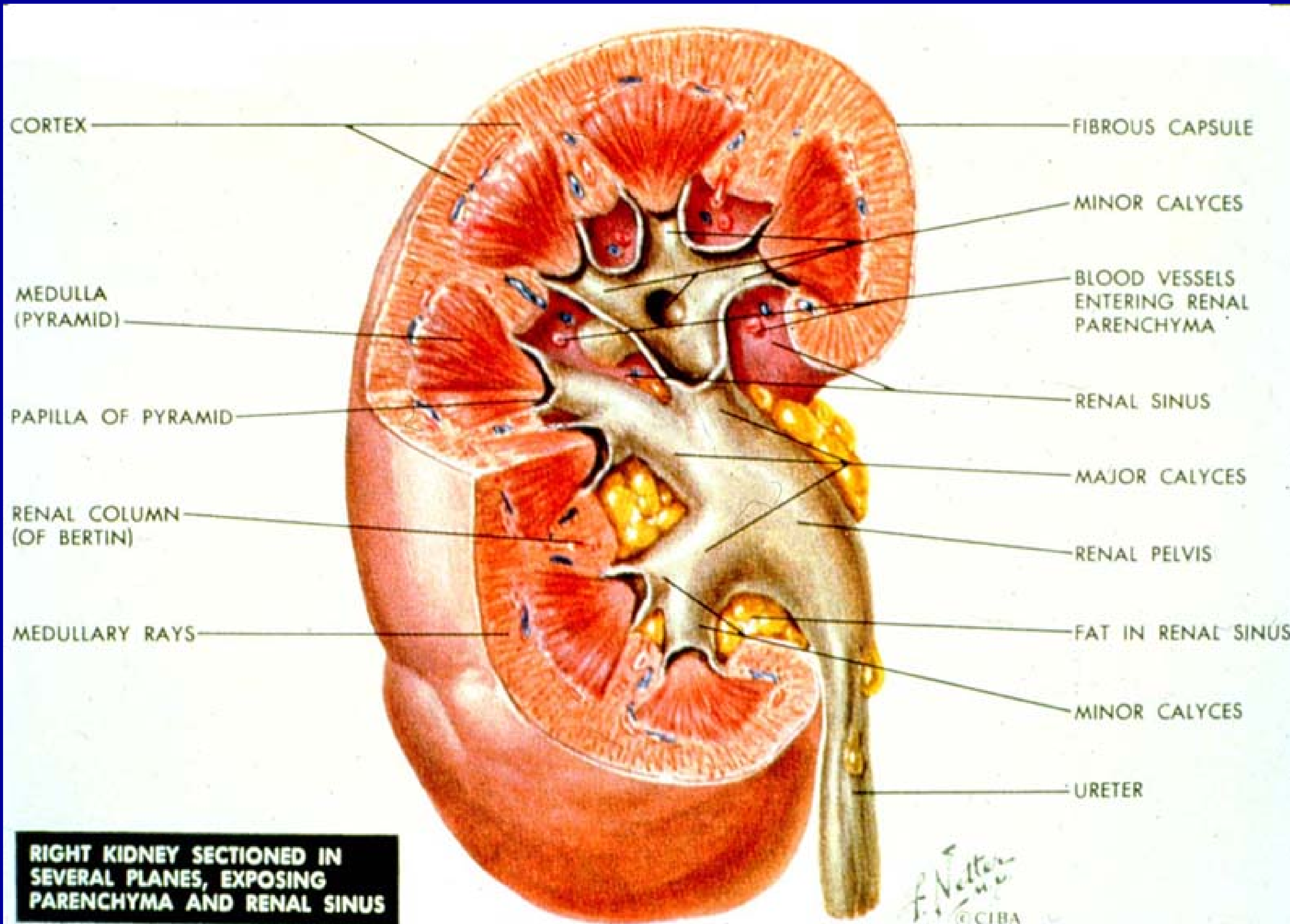
Commercially available product

FDA approved

Fingertip Regeneration in 78-year-old man

Fingertip Regeneration in 78-year-old man

Engineering of Ears


CORTEX
MEDULLA
(PYRAMID)
PAPILLA OF PYRAMID
RENAL COLUMN
(OF BERTIN)
MEDULLARY RAYS
FIBROUS CAPSULE
MINOR CALYCES
BLOOD VESSELS
ENTERING RENAL
PARENCHYMA
RENAL SINUS
MAJOR CALYCES
RENAL PELVIS
FAT IN RENAL SINUS
MINOR CALYCES
URETER
RIGHT KIDNEY SECTIONED IN
SEVERAL PLANES, EXPOSING
PARENCHYMA AND RENAL SINUS
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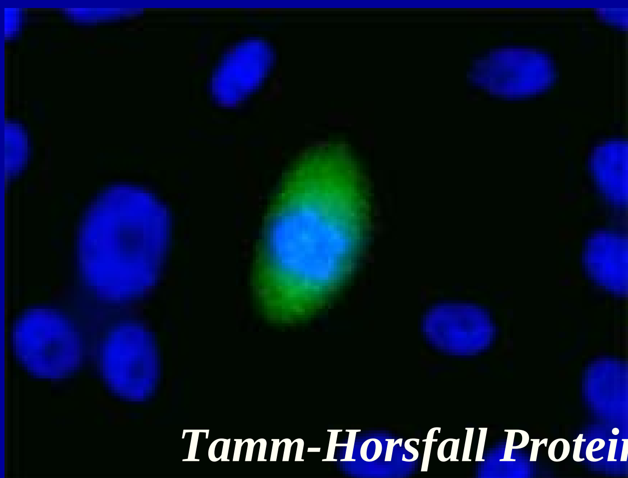
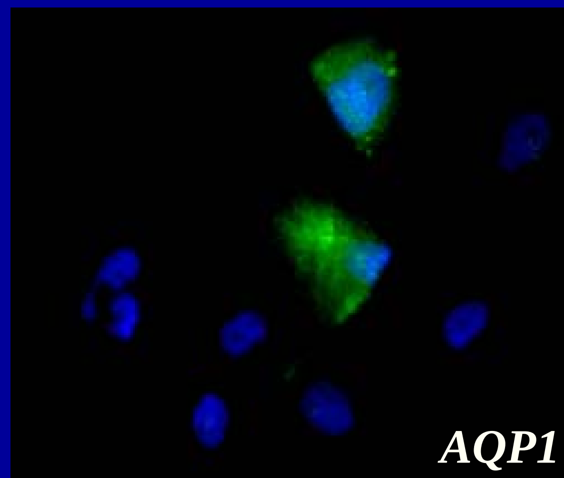
<u>Renal Cells</u>

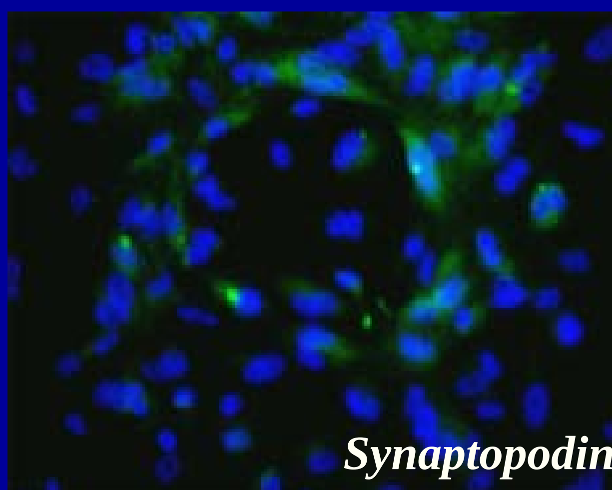


Tamm-Horsfall Protein

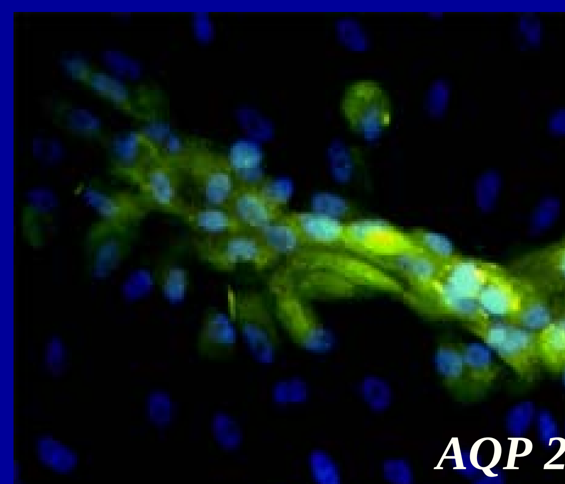


AQP1

Von Willebrand factor

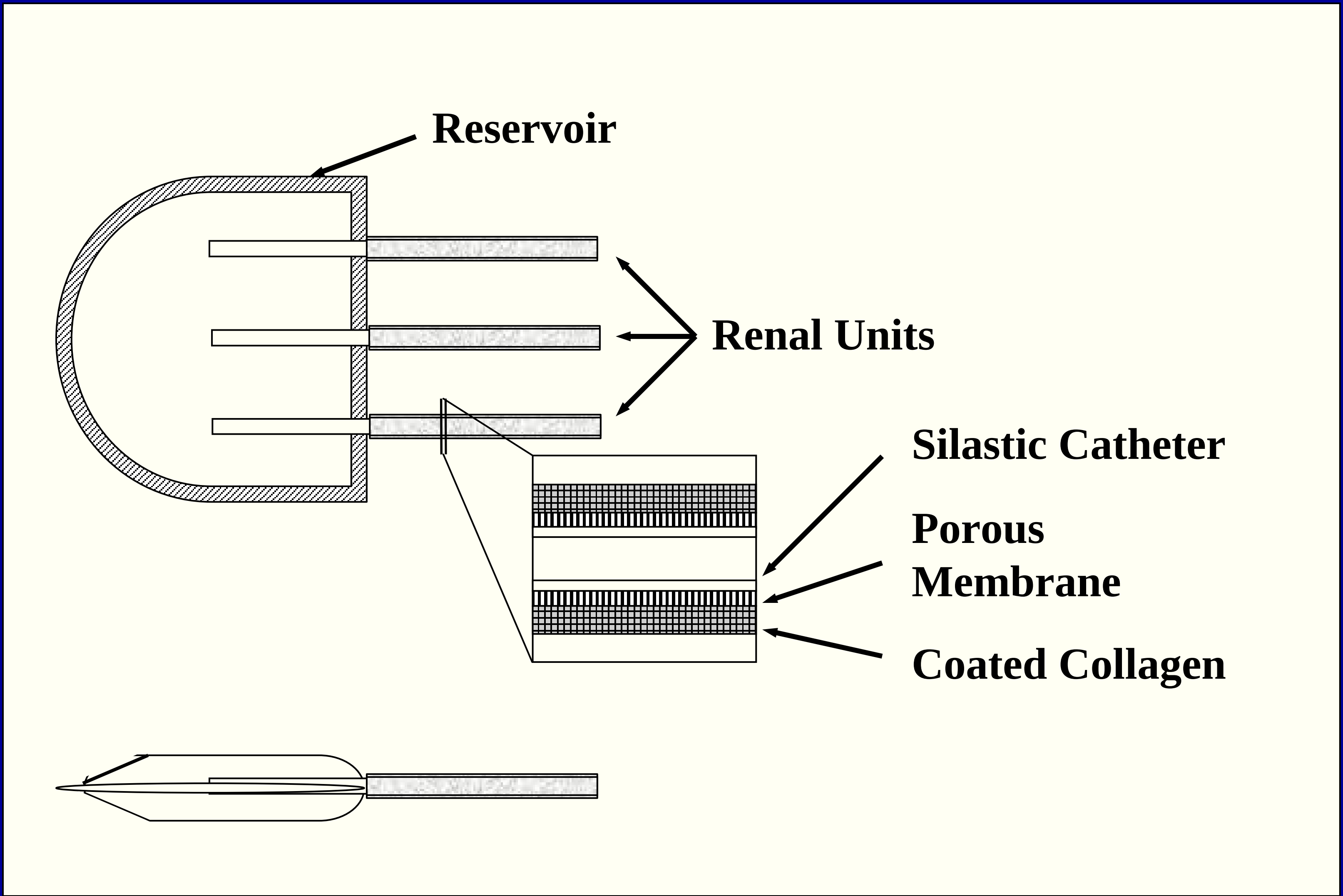


Synaptopodin



AQP 2

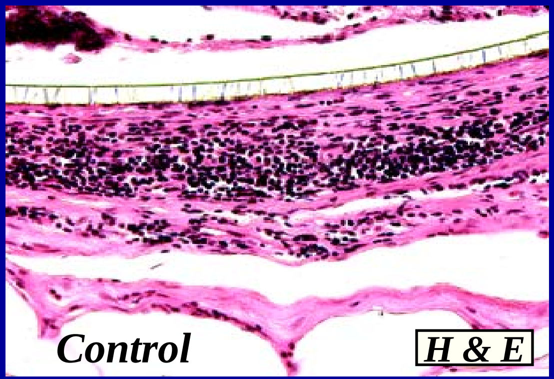
Renal Device

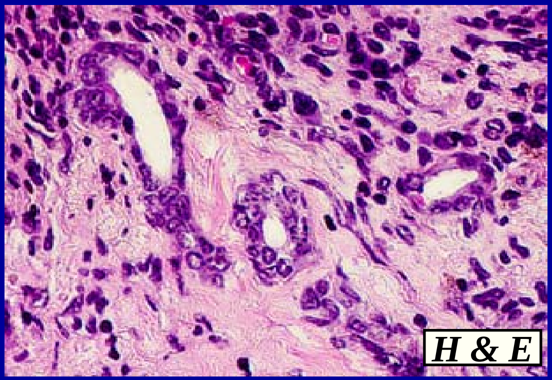


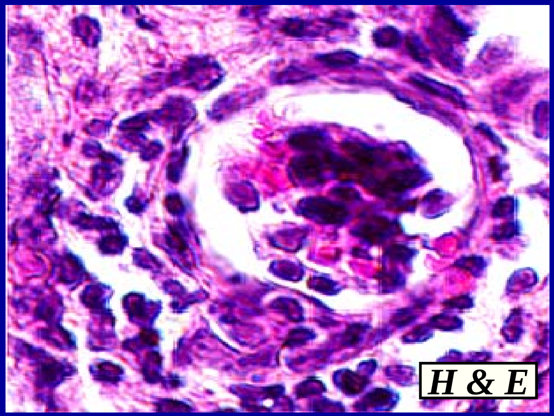
Retrieved Renal Units

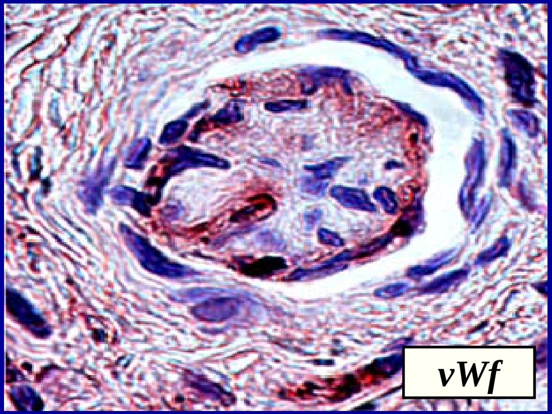
Cloned Cells | **Allogeneic Cells** | **Unseeded**

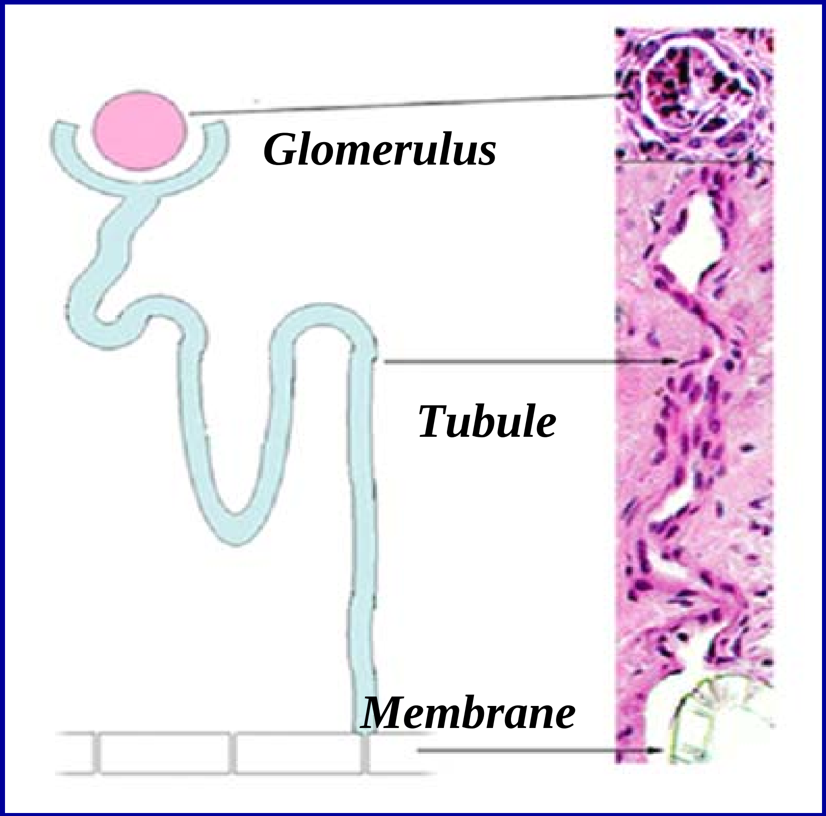
Retrieved Renal Tissues

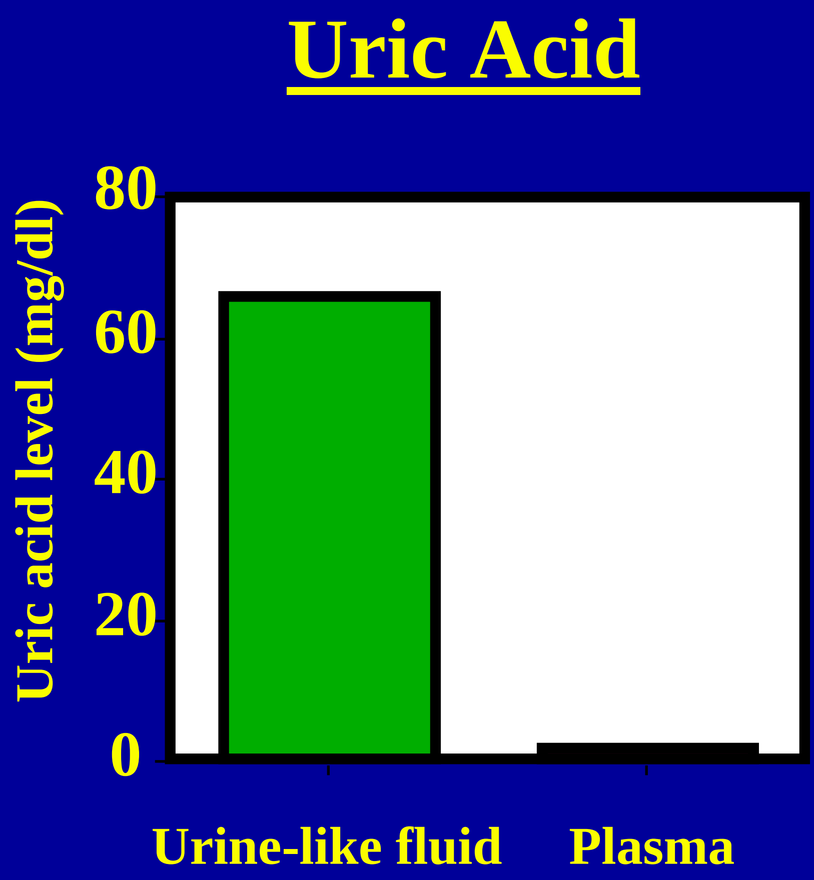


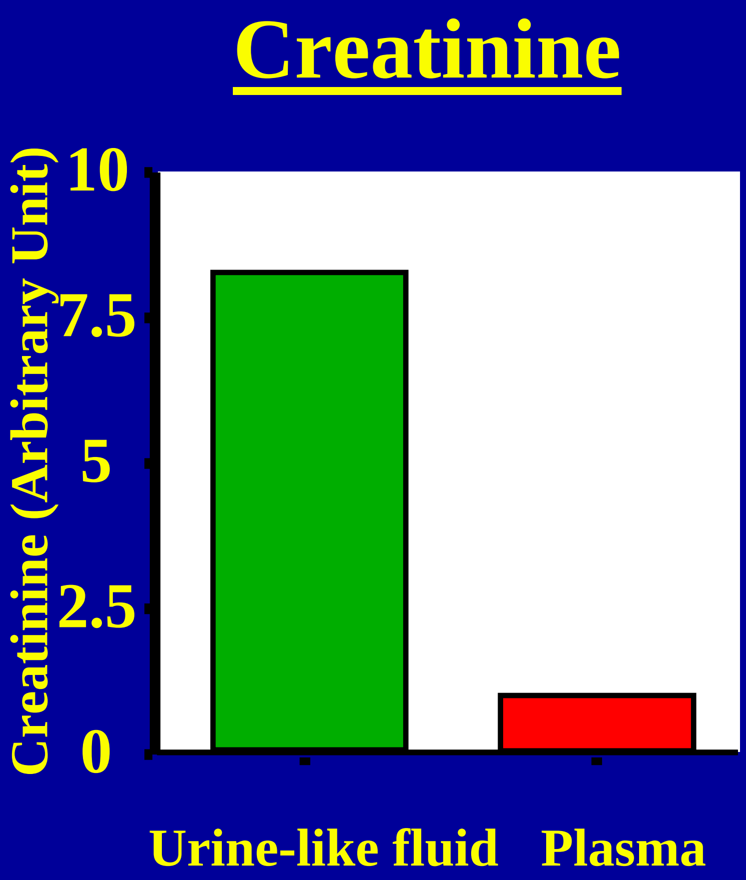


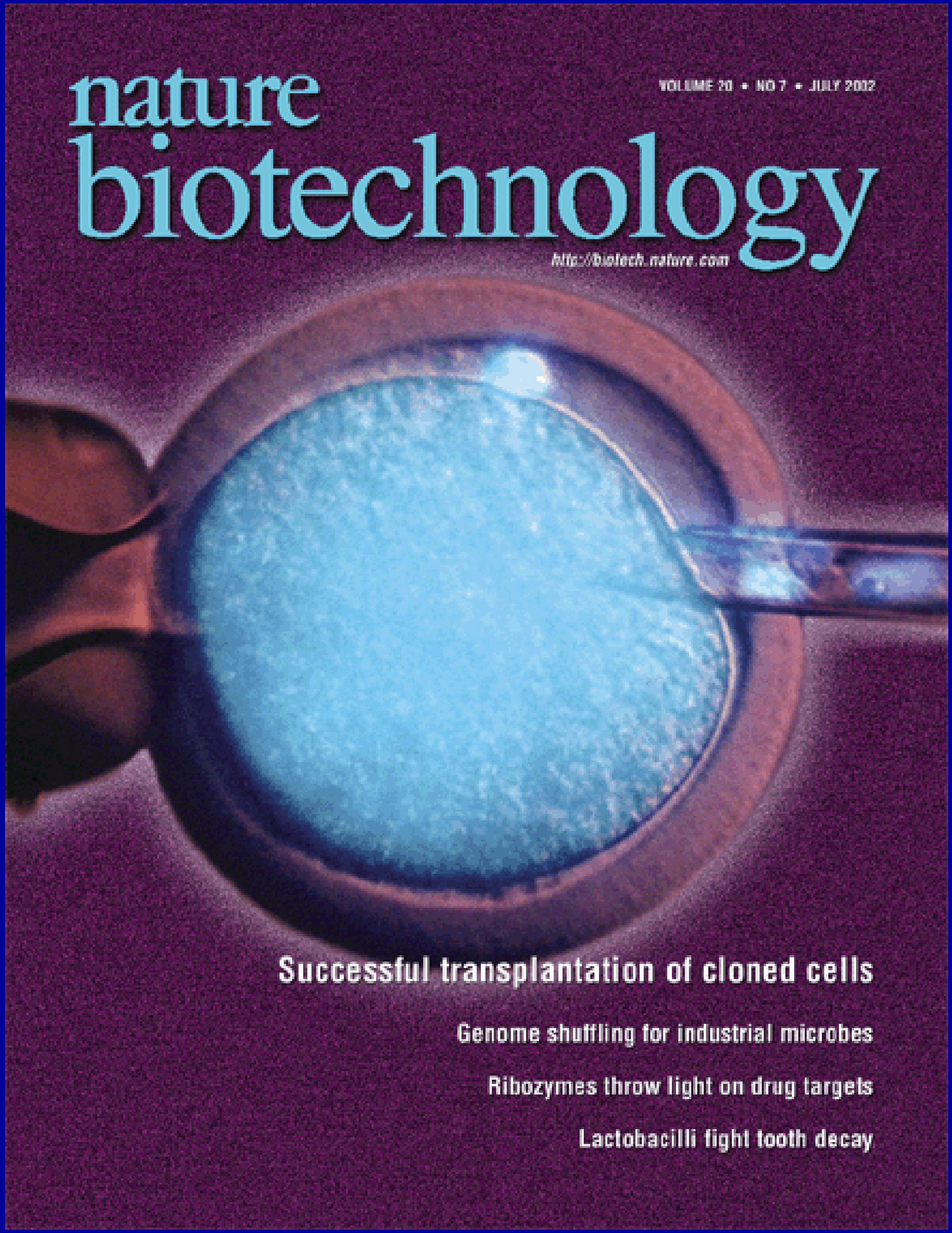







Uric Acid
Uric acid level (mg/dl)
80
60
40
20
0
Urine-like fluid
Plasma


Creatinine
Creatinine (Arbitrary Unit)
10
7.5
5
2.5
0
Urine-like fluid
Plasma


nature
biotechnology
VOLUME 20 • NO 7 • JULY 2002
http://biotech.nature.com
Successful transplantation of cloned cells
Genome shuffling for industrial microbes
Ribozymes throw light on drug targets
Lactobacilli fight tooth decay

CELL THERAPY

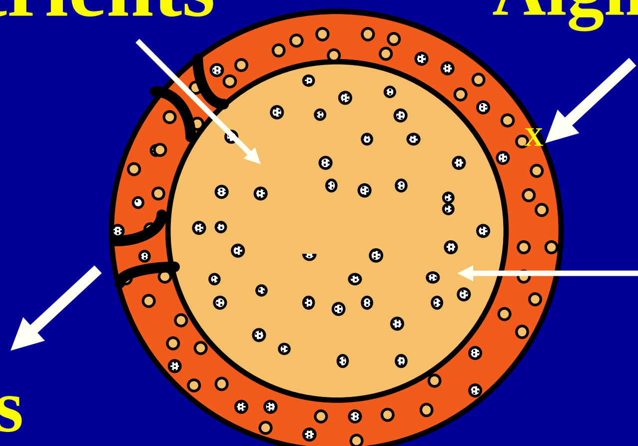
Injectable Cells for Therapy

Cartilage cells : FDA phase II and III multicenter clinical trials, 110 patients, 10 centers, 5 year follow-up

Muscle cells: Phase 1 FDA trial, 32 patients, single Injection, 80% success at 3 and 12 months, 5 year follow-up

Empty Microcapsules

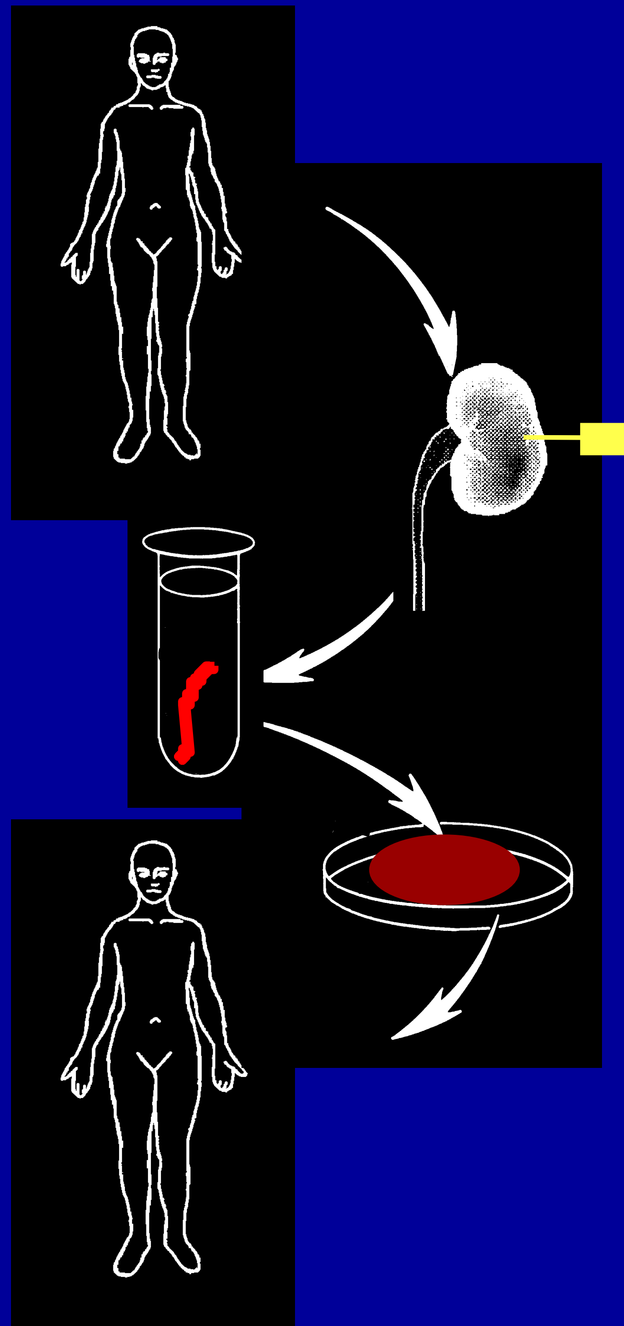
Encapsulated Cells



Applications for Engineered Cell

Tumor therapy
- **Endostatin**
- **Others**

Excretion of proteins/ hormones
- **Menopause (estrogen)**
- **Diabetes (insulin)**
- **Parkinson's (L-Dopa)**
- **Testosterone**



<u>Stem Cells</u>

A stem cell can become any cell and it can create any tissue or organ

Only 2 pluripotent stem cell types described to date:

- **Embryonic stem cells**
- **Adult bone marrow stem cells**

Pluripotent stem cells: only 2 identified to date

Embryonic stem cells

Pro: very high replicative potential

Con: Malignant potential, issues with rejection, ethical issues

Adult bone marrow stem cells:

Pro: low malignant potential, can be used without rejection

Con: very low replicative potential

Amniocentesis: amniotic fluid that bathes the fetus in the womb during pregnancy

Placenta: the tissue in the womb that houses the baby

Amniotic fluid and placental tissue: Possible source for stem cells?

Conclusions

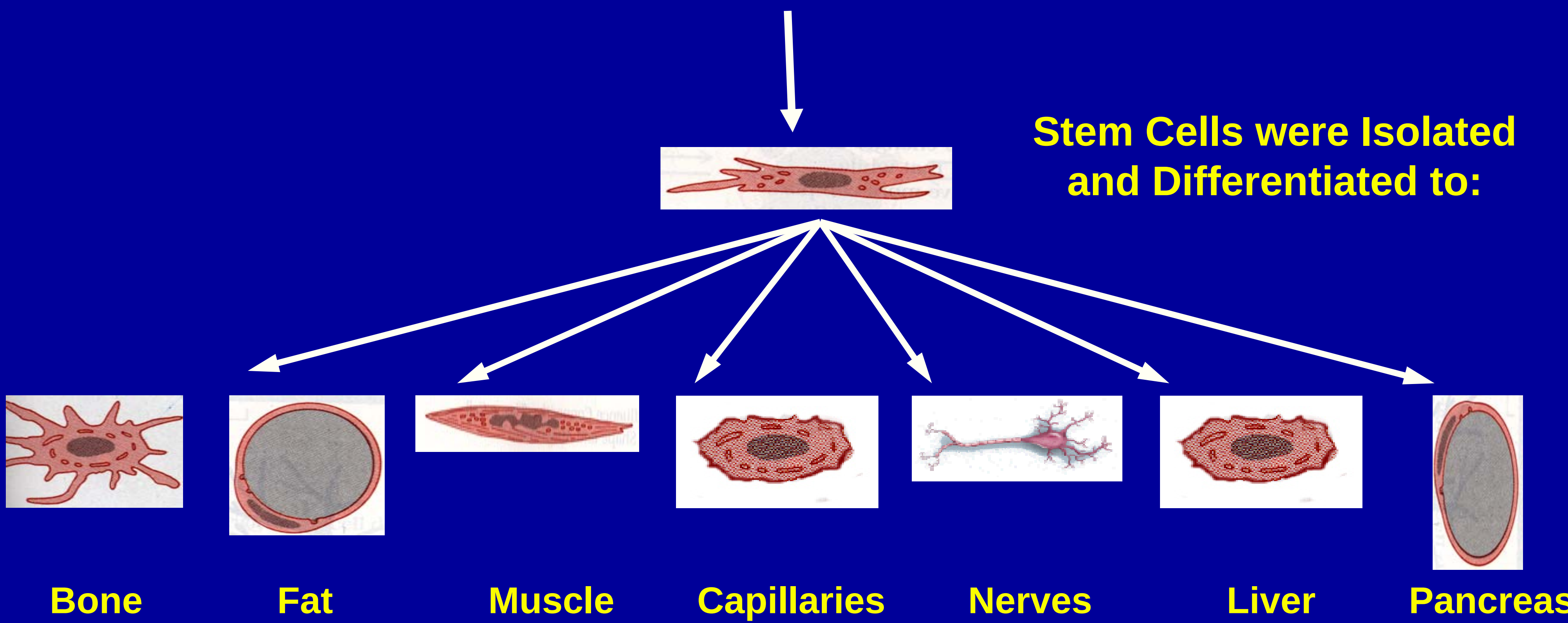
A new cell class is described, derived from amniotic fluid and placental tissue obtained during pregnancy or at the time of birth.

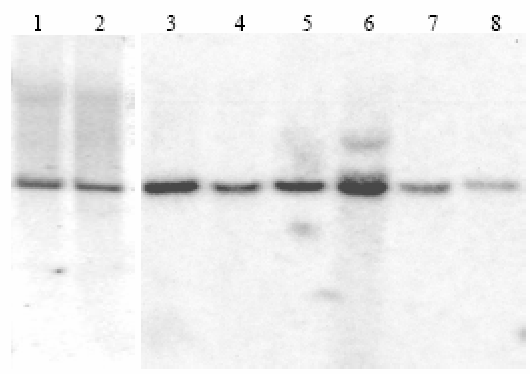
This system avoids the malignant potential and ethical concerns surrounding the use of embryonic stem cells

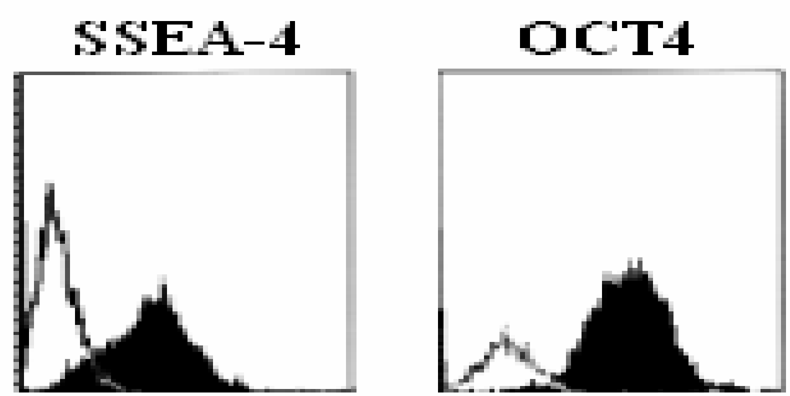
The stem cells can be rapidly expanded to large quantities sufficient for clinical translation, thus avoiding the limitations of adult bone marrow stem cells,

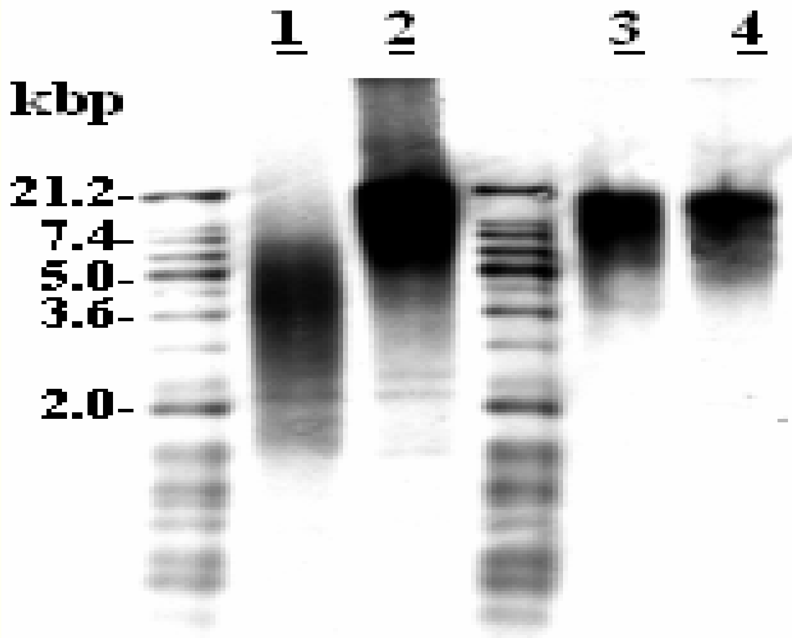
The stem cells could be stored at the time of birth for future "self" use, thus avoiding rejection

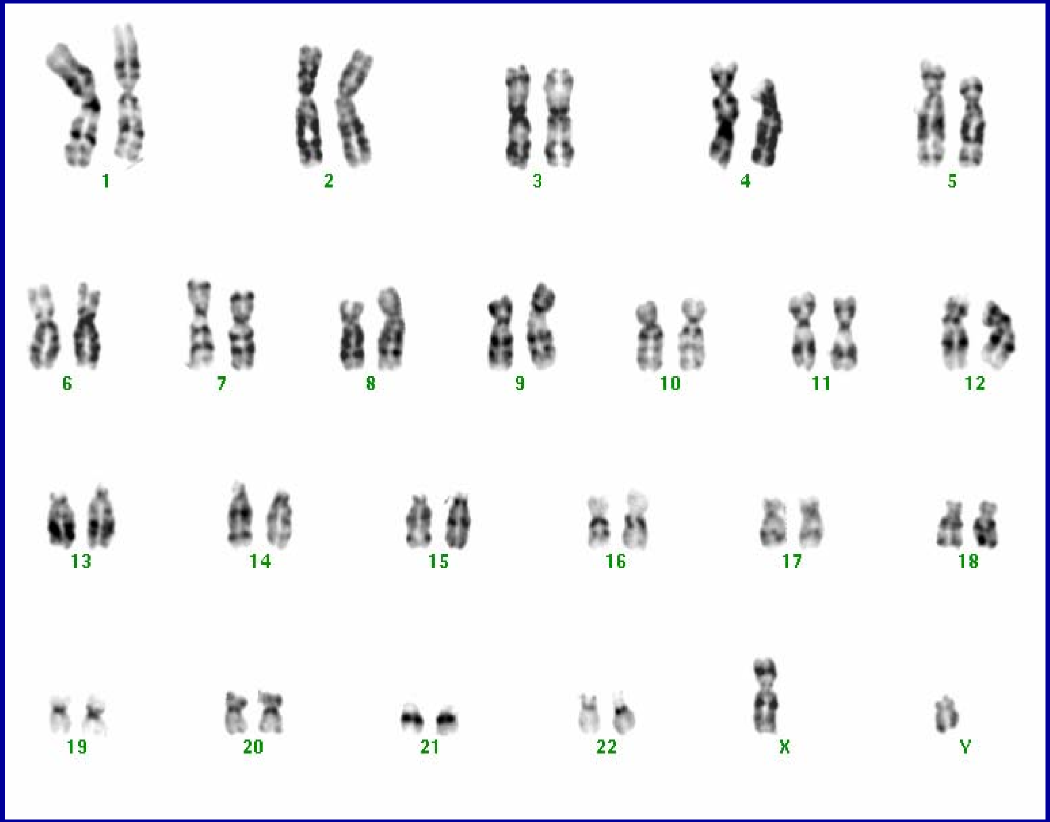
400 Human Amniotic Fluid and Placental Samples (10 - 40 wks)

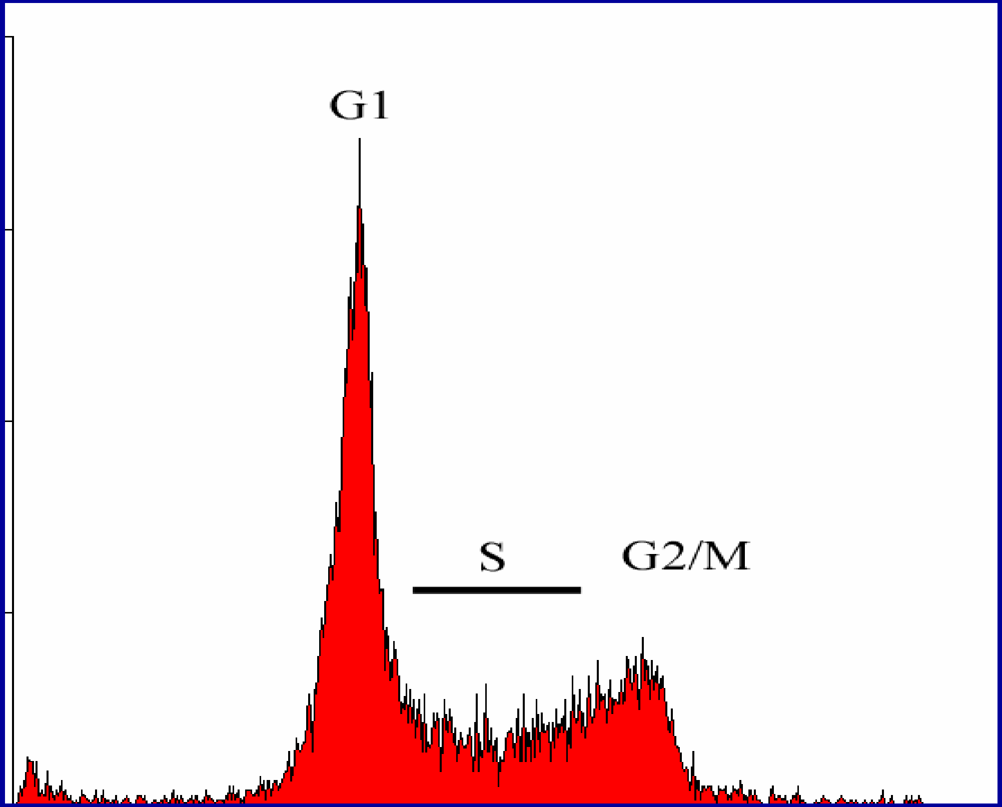



1 2 3 4 5 6 7 8

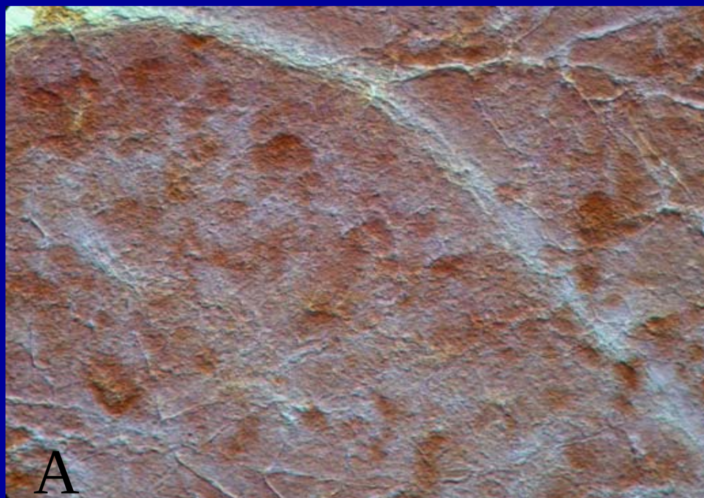

SSEA-4
OCT4


1 2 3 4
kbp
21.2-
7.4-
5.0-
3.6-
2.0-

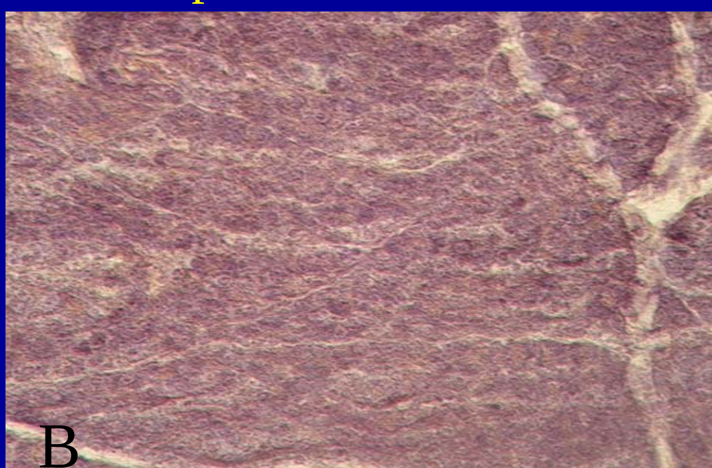

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
X
Y


G1
S
G2/M

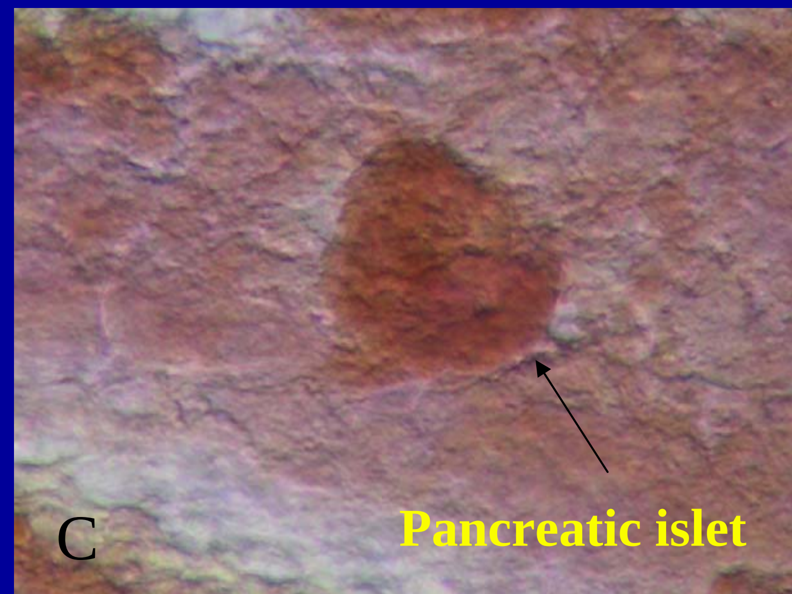
Pancreatic islets repaired after stem cell injection: insulin immuno staining



Normal pancreas

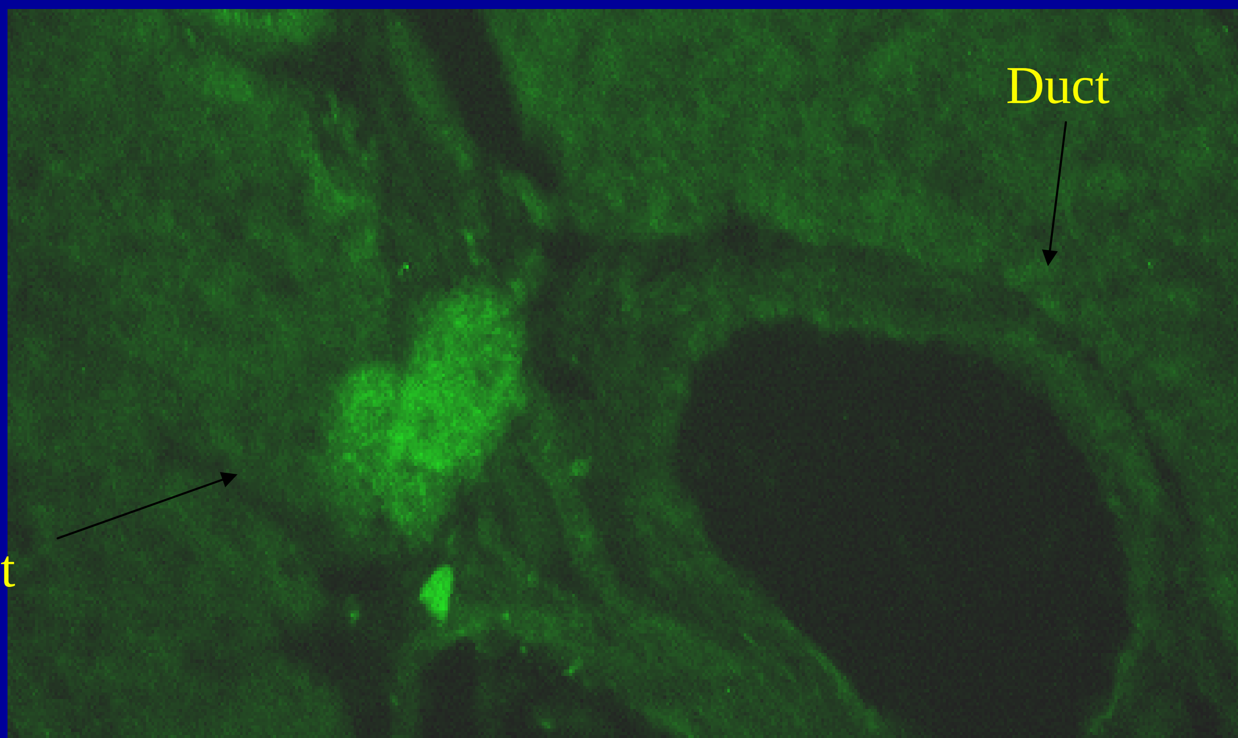


After STZ injection (28 d)



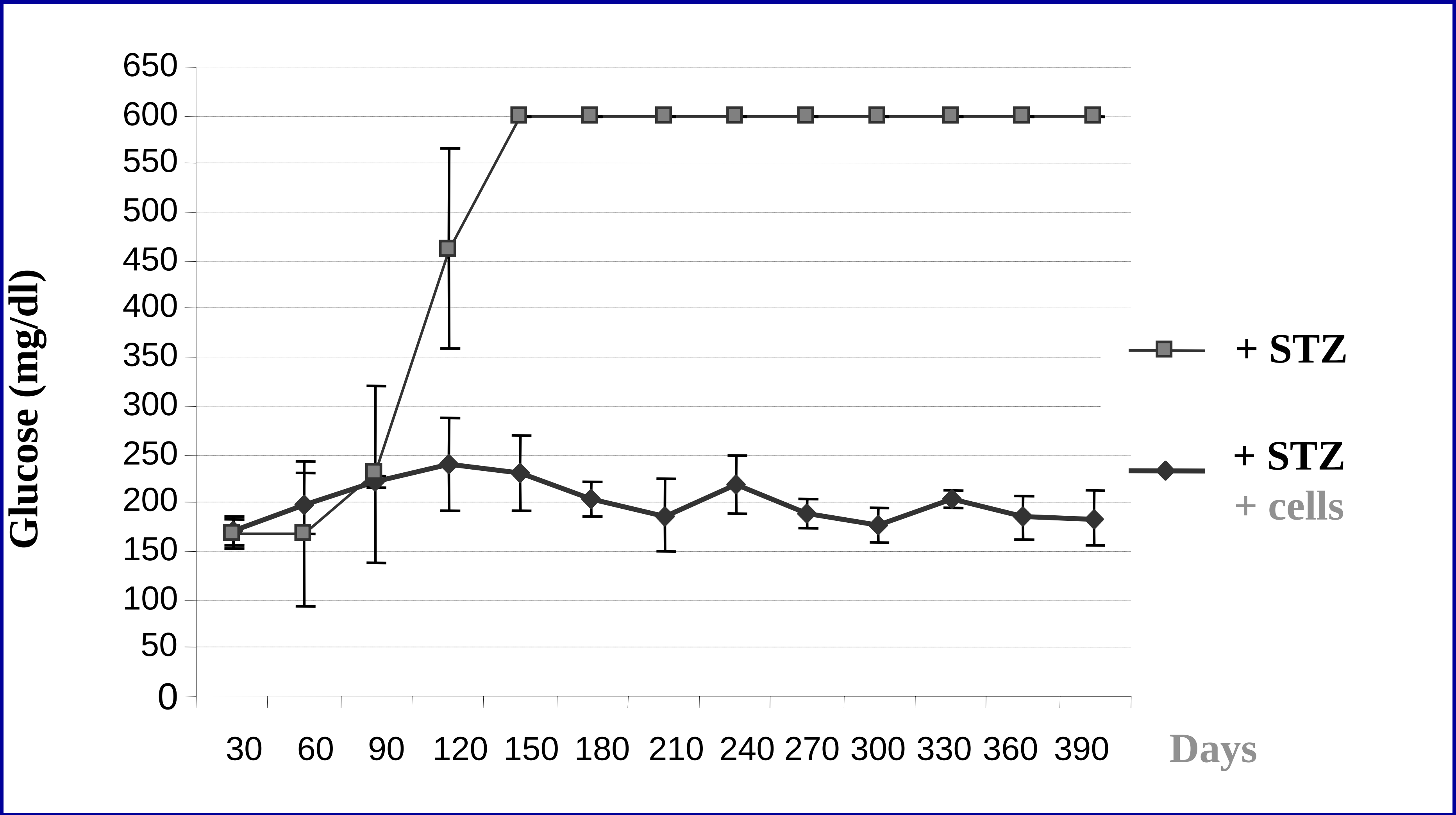
After cell injection (28 d)

Presence of MAFC (FITC-HA)



Pancreatic Islet

Control of Glucose Levels after Stem Cell Injection Long Term

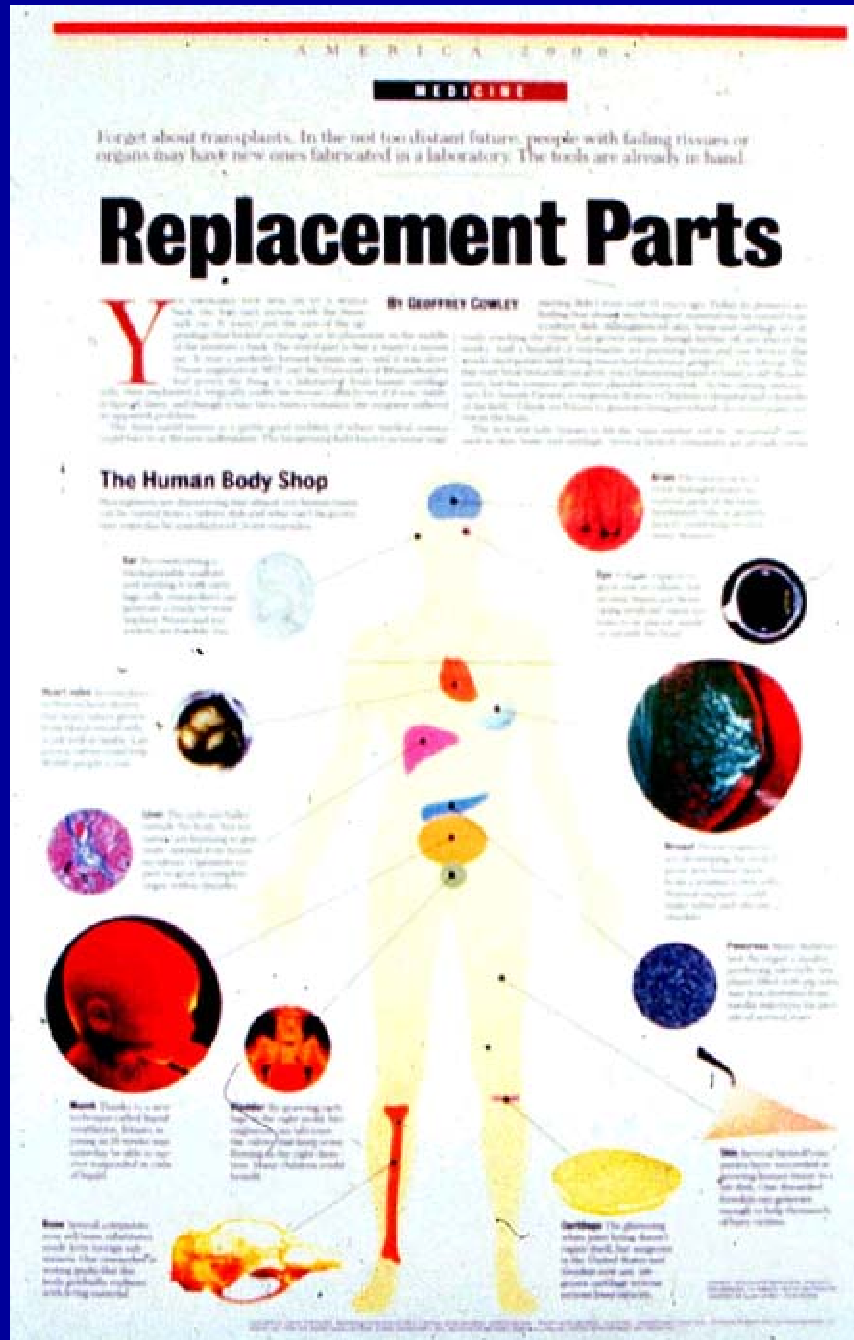


Amniotic fluid and placental tissue obtained during pregnancy may be an alternate source for obtaining human stem cells

This system would avoid the rejection, malignancy, and cell expansion concerns surrounding the use of current stem cells

The stem cells could be stored for future "self" use

P DeCopppi, G Bartsch Jr, M Siddiqui, L Perin, C Koh, J Hipp[2], J Knutson, A Milanesi, D Dello, P Baptista, JW Lee, S Hodges



AMERICA 2000

MEDICINE

Forget about transplants. In the not too distant future, people with failing tissues or organs may have new ones fabricated in a laboratory. The tools are already in hand.

Replacement Parts

BY GEOFFREY COWLEY

The Human Body Shop

Cell Types Grown at the Wake Forest Institute for Regenerative Medicine

- Heart
- Kidney
- Esophagus
- Bladder
- Sm/Sk Muscle
- Cartilage
- Urethra
- Vessels
- Salivary glands
- Trachea
- Bone
- Breast
- Lung
- Retina
- Uterus
- Nerve
- Liver
- Pancreas

Engineering of Tissues and Organs

Hollow tubes -> Hollow organs -> Solid Organs

Urology : Bladder - 9 years ; Urethra – 7 years; Penis- in progress

Gynecology: Uterus - 7 years; Vagina - 5 years

Vascular: Blood Vessels - 5 years; Heart Valves – in progress

Respiratory: Trachea – in progress

Orthopedic: Cartilage, Bone, Skeletal Muscle, Digits

Nephrology: Kidney-in progress

--All Required Integration--

Some of the work in this presentation was performed by over 300 researchers across a 16 year time span:

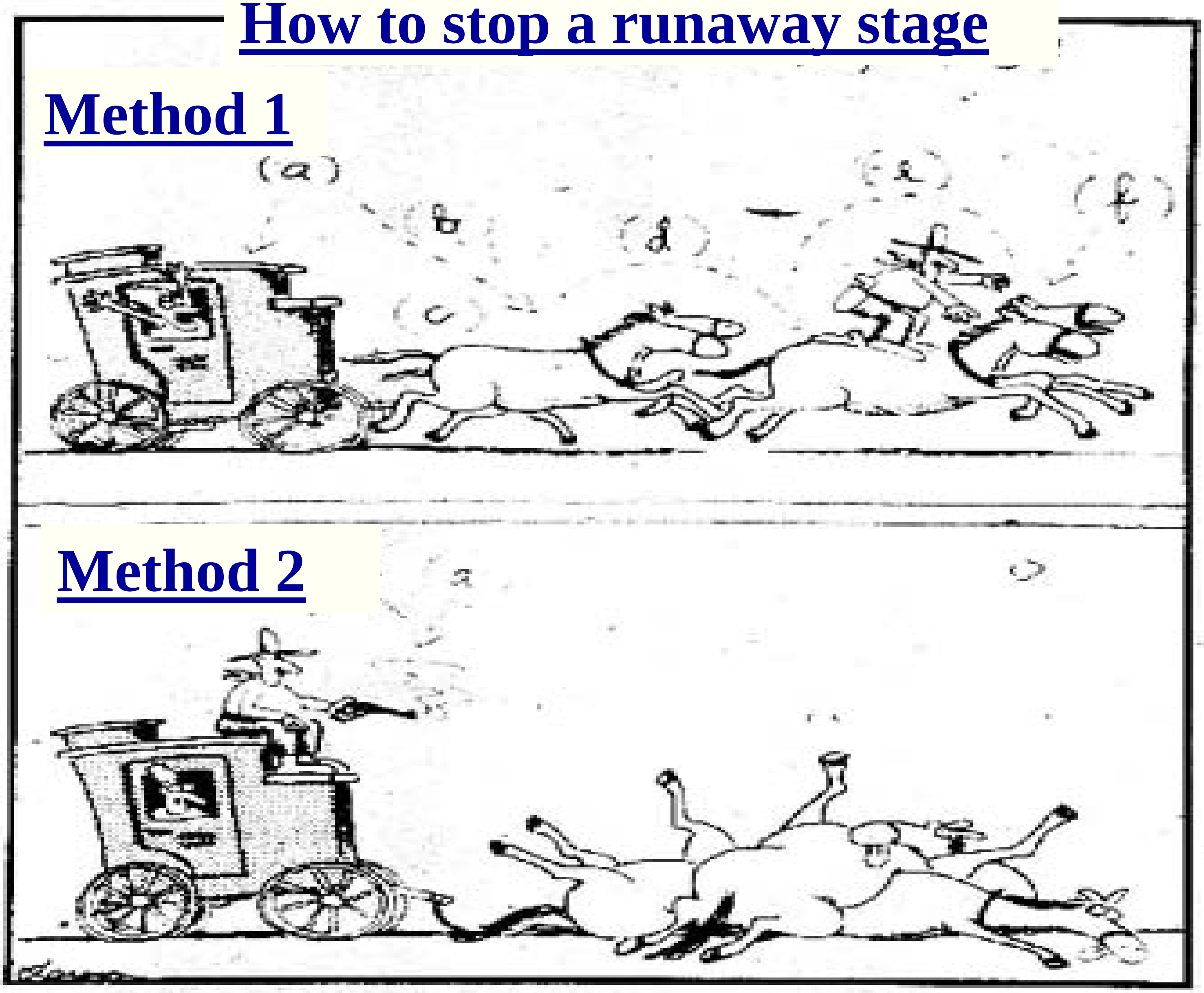
Growth factor biology (molecular biologists)
Cell growth and expansion (cell biologists)
Biomaterial production (material scientists)
Cell-Biomaterial interactions (bio-engineers)
Small & large animal models (physiologists, biochemists, veterinarians)
Clinical trials (physicians, epidemiologists, statisticians, regulatory specialists)

************MULTI-DISCIPLINARY TEAM************

How to stop a runaway stage

Method 1

Method 2



From the book *Guide to Western Stuff*

The medical means to achieve full tissue and organ restoration in those suffering combat casualties are within our reach

Additional effort and resources are needed to expand the current state of the field of regenerative medicine so all tissues and organs can be created and delivered to soldiers with combat casualties

The Army Institute for Regenerative will be formed in 2007 order to accelerate clinical translation by the U.S. Army Medical Research and Materiel Command

Colonel Robert Vandre
Dr. Frazier Glenn
General Eric Schoomaker

Wake Forest Institute for Regenerative Medicine

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Colin Bishop
George Christ
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James J. Yoo
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Ann Immekus
Ben Watts
Callie Crider
Cathy Mathis

Cesar Santos
Chanda Turner
Chris Sullivan
Cindy Andrews
Cindy Montgomery
Cindy Whetzel
Daniel Eberli
Dawn Delo
Diane Mann
Don Massey
Dong Joon Lee
Elana McNeill
Emily Crafton
Fernanda Egydio
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Hazem Osman
Helen Kincaid
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Jason Hipp
Jennifer Hipp
Jian-Ming Zhu
Jie Liu
Jim Jordan
Joel Berry
Joel Stitzel
Kian Mostafavi
Kineka Hull
Koudy Williams
Lars Bochmann
Masood Machingal
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Shirin Zare
So-Young Chun
Steve Schultz
Tamer AbouShawreb
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Tiffany King
Toshi Machiguchi
Vamsey Bobba
Yagna Jarajapu
Randy Geary

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NIH: HLBI

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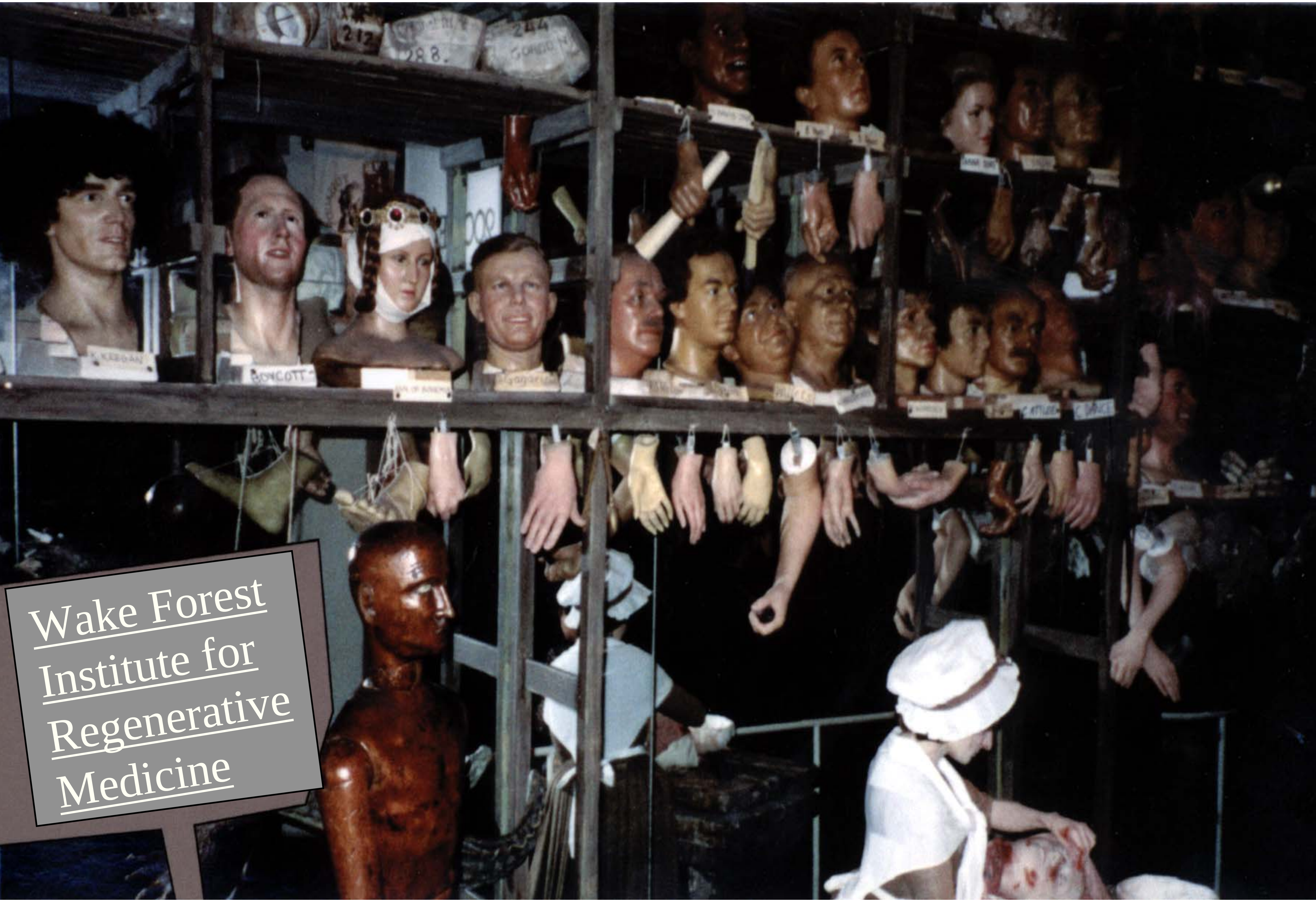
Muscular Dystrophy Association

The Crown Foundation

The Frase Foundation

Juvenile Diabetes Research Foundation

Howard Hughes Medical Research Foundation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Regenerative
Medicine