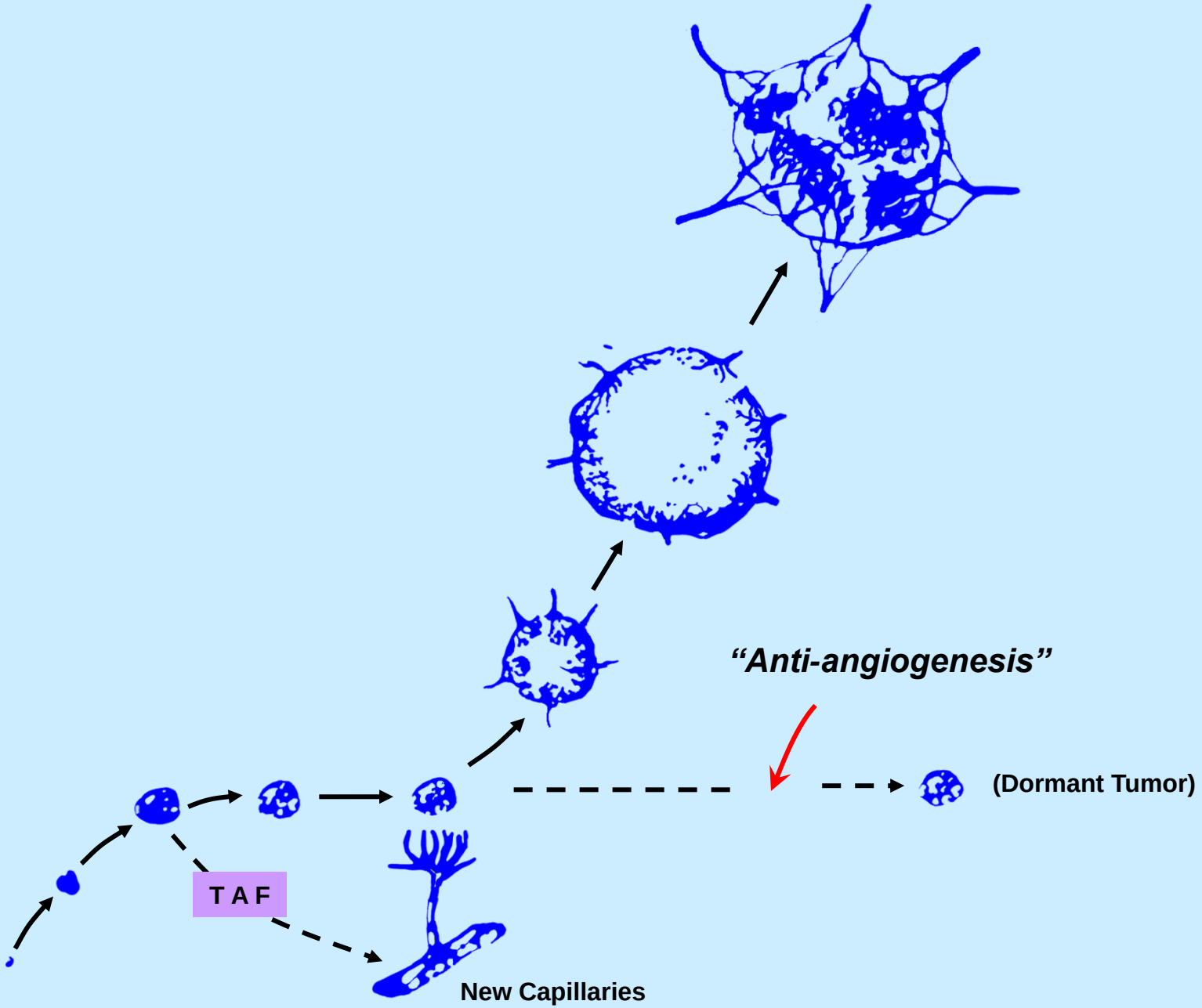
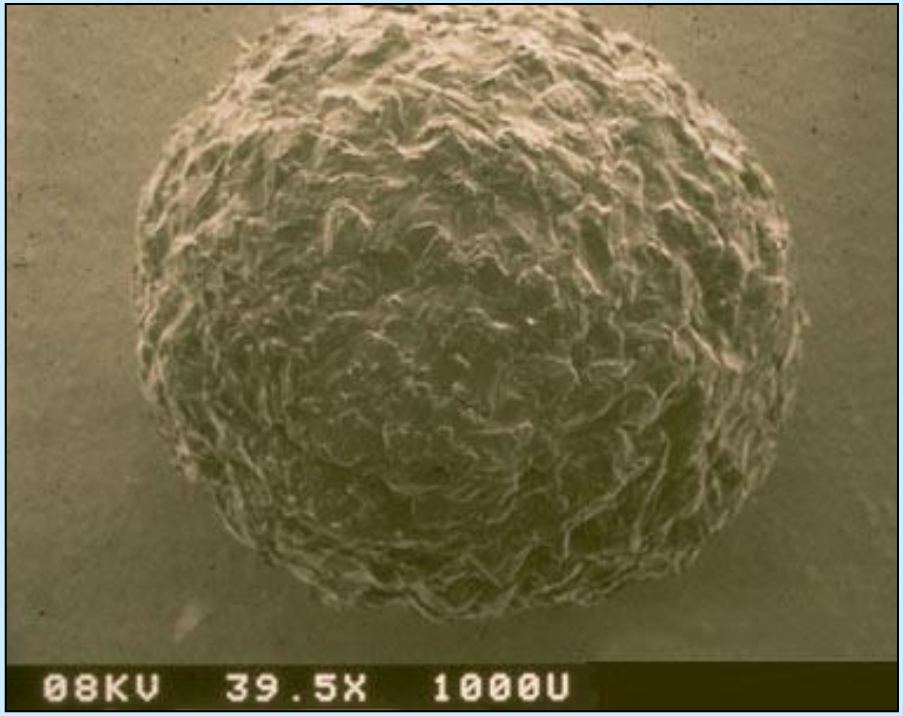
Exploring biomaterials, delivery systems, and tissue engineering

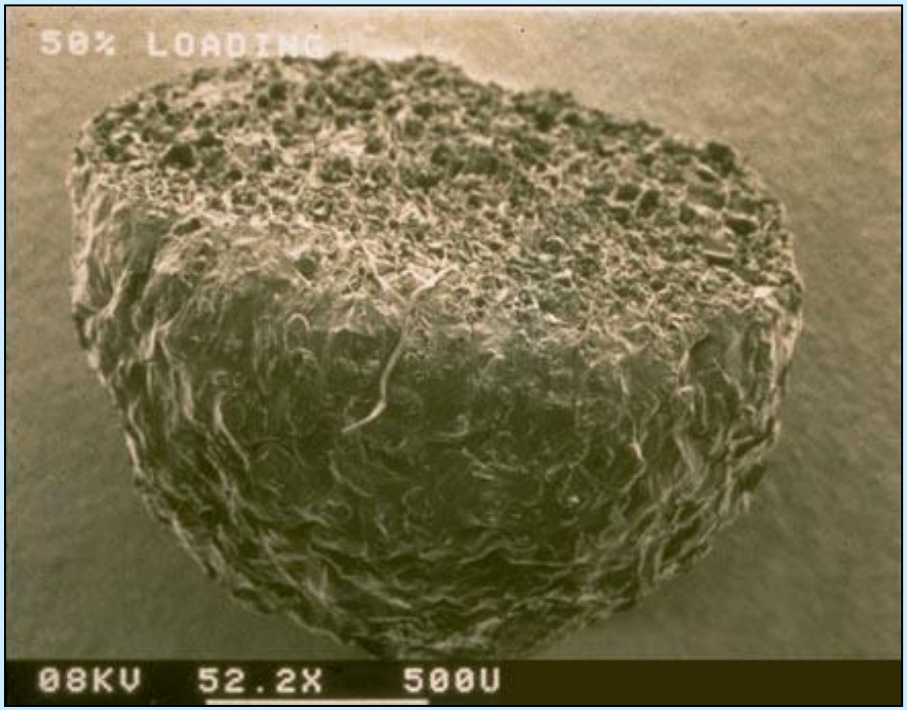
Dr. Robert S. Langer
David H. Koch Institute Professor
Massachusetts Institute of Technology

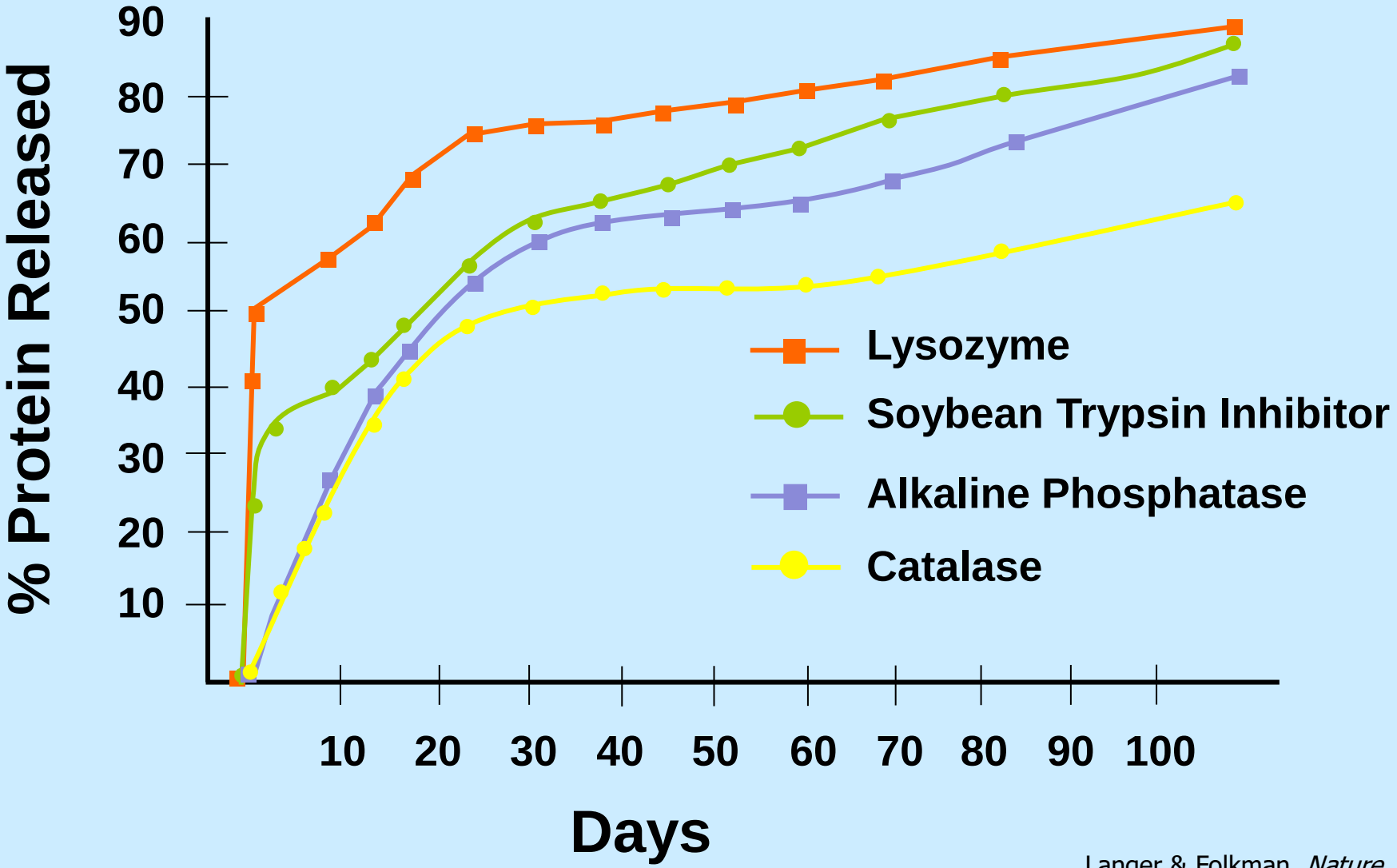

"Anti-angiogenesis"
(Dormant Tumor)
T A F
New Capillaries

"The use of polymer matrices for slow release systems has been virtually restricted to small molecules."

Chemical and Engineering News, 1977


08KV 39.5X 1000U


50% LOADING
08KV 52.2X 500U



Langer & Folkman, *Nature*, 1976

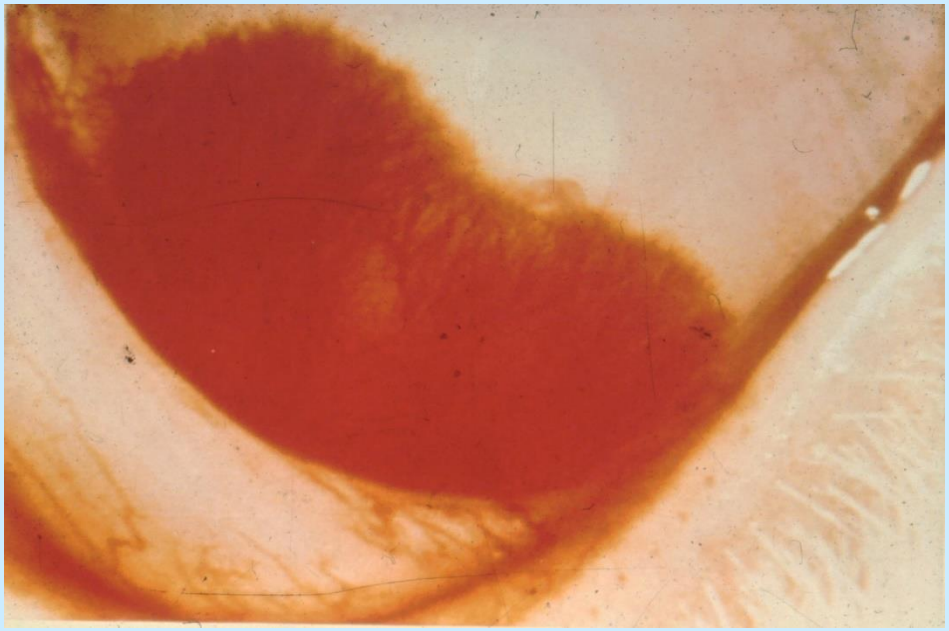
This approach will not work because

- Large molecules cannot slowly diffuse through solid polymers
- Organic solvents will denature peptides or proteins

"One evening, I went to a faculty dinner at a Chinese restaurant with Bob Langer and some senior MIT professors. A senior scientist sat quizzing us while smoking a cigar. When the older scientist heard Langer's concepts for polymeric drug delivery, he blew a cloud of smoke in Langer's face and said, 'You better start looking for another job.' I thought I was in a Fellini movie."

Professor Michael Marletta
CH and Annie Li Chair in the Molecular Biology of Diseases, University of California – Berkeley
Member, National Academy of Sciences

Rabbit corneal pocket assay



-CDI

+CDI

Langer et al, *Science*, 1976

Angiogenesis inhibitors approved for clinical use

Date Approved	Drug	Disease
February 2004	Avastin (Bevacizumab)	Colorectal Cancer
November 2004	Tarceva (Erlotinib)	Lung Cancer
December 2004	Macugen	Macular Degeneration
December 2005	Nexavar (Sorafenib)	Kidney Cancer
December 2005	Revlimid	Myelodysplastic Syndrome
January 2006	Sutent (Sunitinib)	Gastric (GIST), Kidney Cancer
June 2006	Lucentis	Macular Degeneration
May 2007	Torisel (CCI-779)	Kidney Cancer
November 2007	Nexavar (Sorafenib)	Hepatocellular Carcinoma
February 2008	Avastin	Breast Cancer
May 2009	Avastin	Glioblastoma
November 2010	Afinitor	Giant Cell Astrocytoma
April 2011	Zactima (Vandetanib)	Medullary Thyroid Cancer
May 2011	Sutent	Pancreatic Neuroendocrine Tumors
November 2011	Eylea (Aflibercept)	Macular Degeneration
January 2012	Axitinib (AG-013736)	Kidney Cancer
July 2012	Afinitor	Breast Cancer
September 2012	Eylea (Aflibercept)	Central Retinal Vein Occlusion
January 2013	Avastin	Metastatic Colorectal Cancer
February 2013	Pomalyst (Pomalidomide)	Multiple Myeloma
April 2014	Cyramza	Advanced Stomach Cancer
August 2014	Avastin (Bevacizumab)	Cervical Cancer
November 2014	Avastin	Recurrent Ovarian Cancer
December 2014	Cyramza (Ramucirumab)	Non-small Cell Lung Cancer
February 2015	Lucentis	Diabetic Retinopathy with DME
February 2015	Lenvima (Lenvatinib)	Thyroid Cancer
April 2017	Lucentis	Diabetic Retinopathy

"Generally the agent to be released is a relatively small molecule with a molecular weight no larger than a few hundred. One would not expect that macromolecules, e.g. proteins, could be released by such a technique because of their extremely small permeation rates through polymers. However, Folkman and Langer have reported some surprising results that clearly demonstrate the opposite."

-Stannett, Koros, Paul, Baker, Lonsdale, *Adv. Poly. Sci.*, 1979.

U.S. Patent 4,391,797: Folkman and Langer

- Two phase system
- 1st phase – polymer with water sorbtivity not greater than 50%
- 2nd phase – agglomerated macro-molecular material of MW at least 1000


Decapeptyl SR 11.25 mg
triptorelin
for injection
IPSEN
3-Month

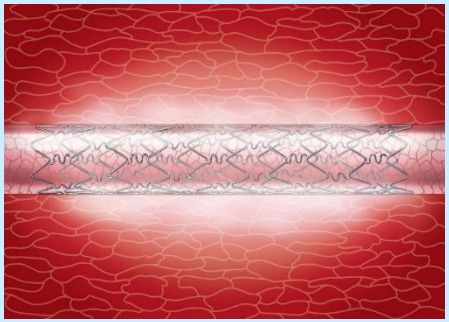

Vivitrol


NDC 65250-266-20
EXPAREL
(bupivacaine liposome injectable suspension)
1.3%
266 mg / 20 mL (13.3 mg/mL)
For Infiltration Only
Not For Any Other Route of Administration
STERILE
Rx Only


DILUENT FOR NUTROPIN
1.5 mL SINGLE USE
Contents: Each 1.5 mL contains
sodium salt; 1 mg/mL polysorbate
and sterile water for injection
pH 5.8-7.2. DO NOT FREEZE
Instructions for Use: See
manufactured for Genentech
AUX LOT: L03A9
NDC 50242-
Nutropin DEPOT
somatropin (rDNA origin) for
injectable suspension
13.5
Manufactured for:
Genentech, Inc.
So. San Francisco, CA
94080-4990


SURGIFLO


Floseal




Hydureon


LUPRON
DEPOT

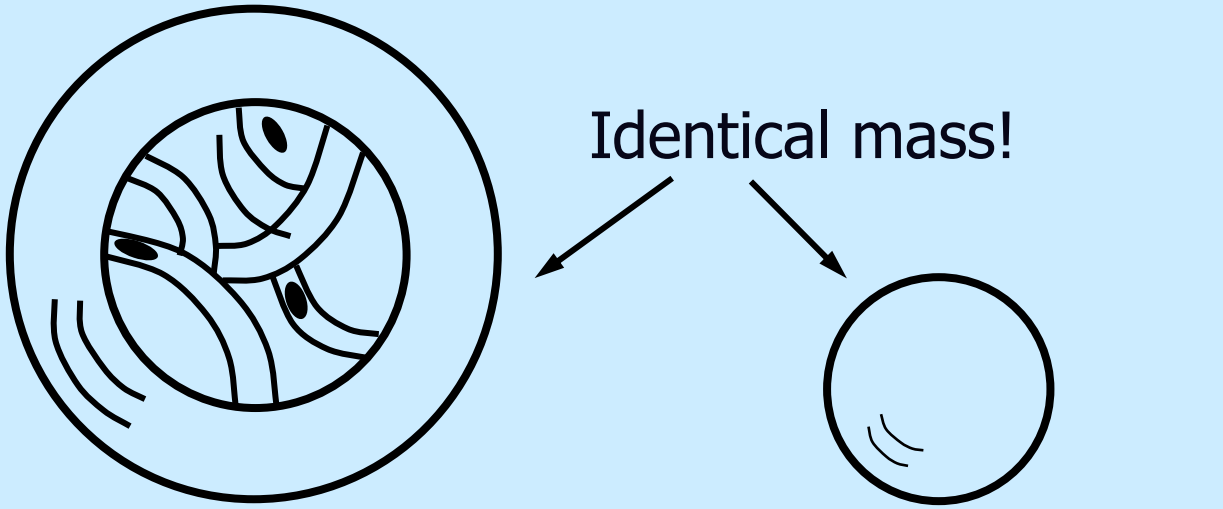

50 mg
37.5 mg
25 mg
RisperdalCONSTA
risperidone
DOSE PACK CONTENTS:


GLIADEL Wafer
(polifeprosan 20 with
carmustine implant)
7.7 mg carmustine/wafer
Contents:
8 wafers, individually packaged


Zoladex 3-month
10.8 mg
10.8 mg goserelin

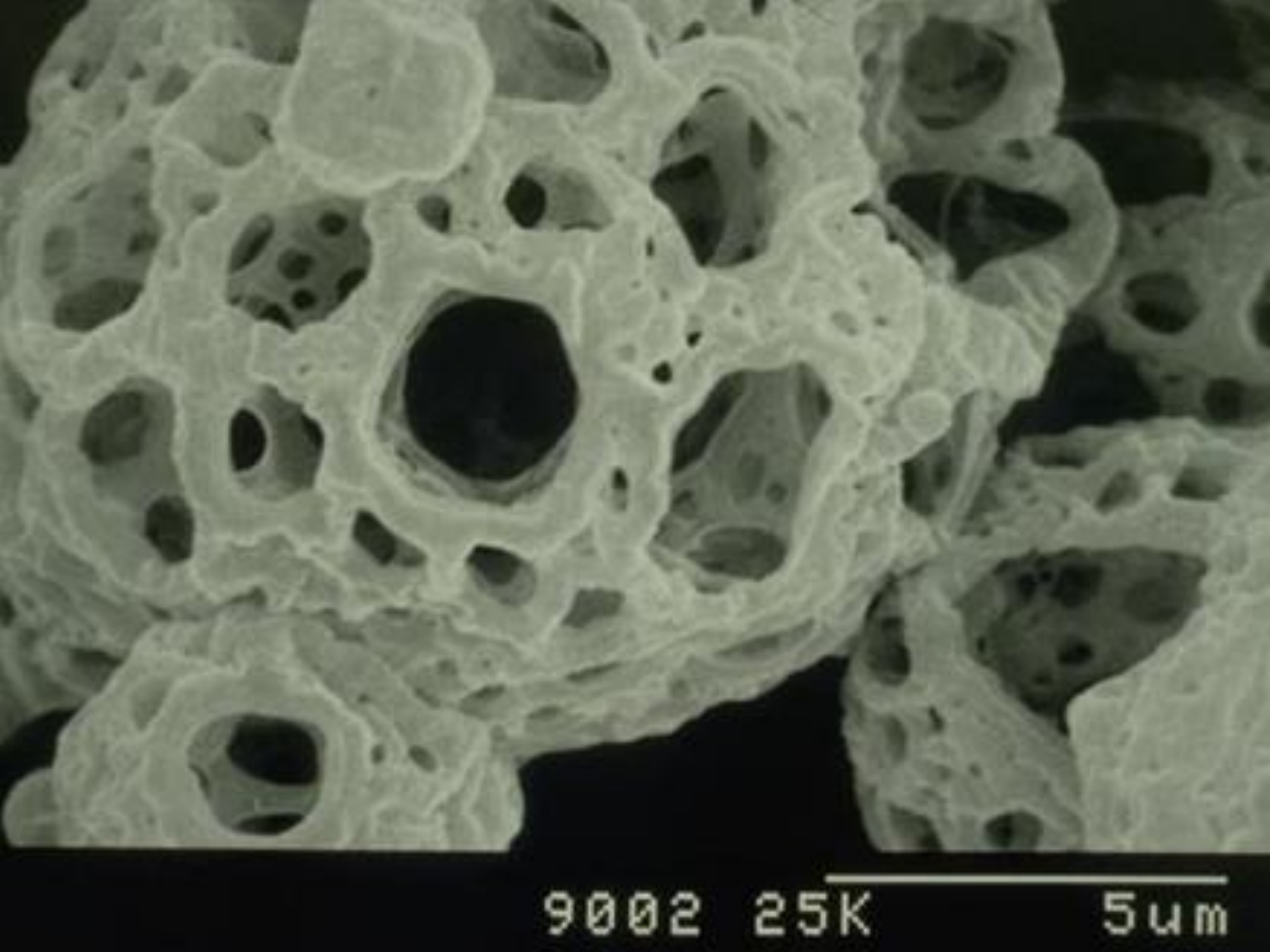
Advantages of porous aerosols for inhalation therapy

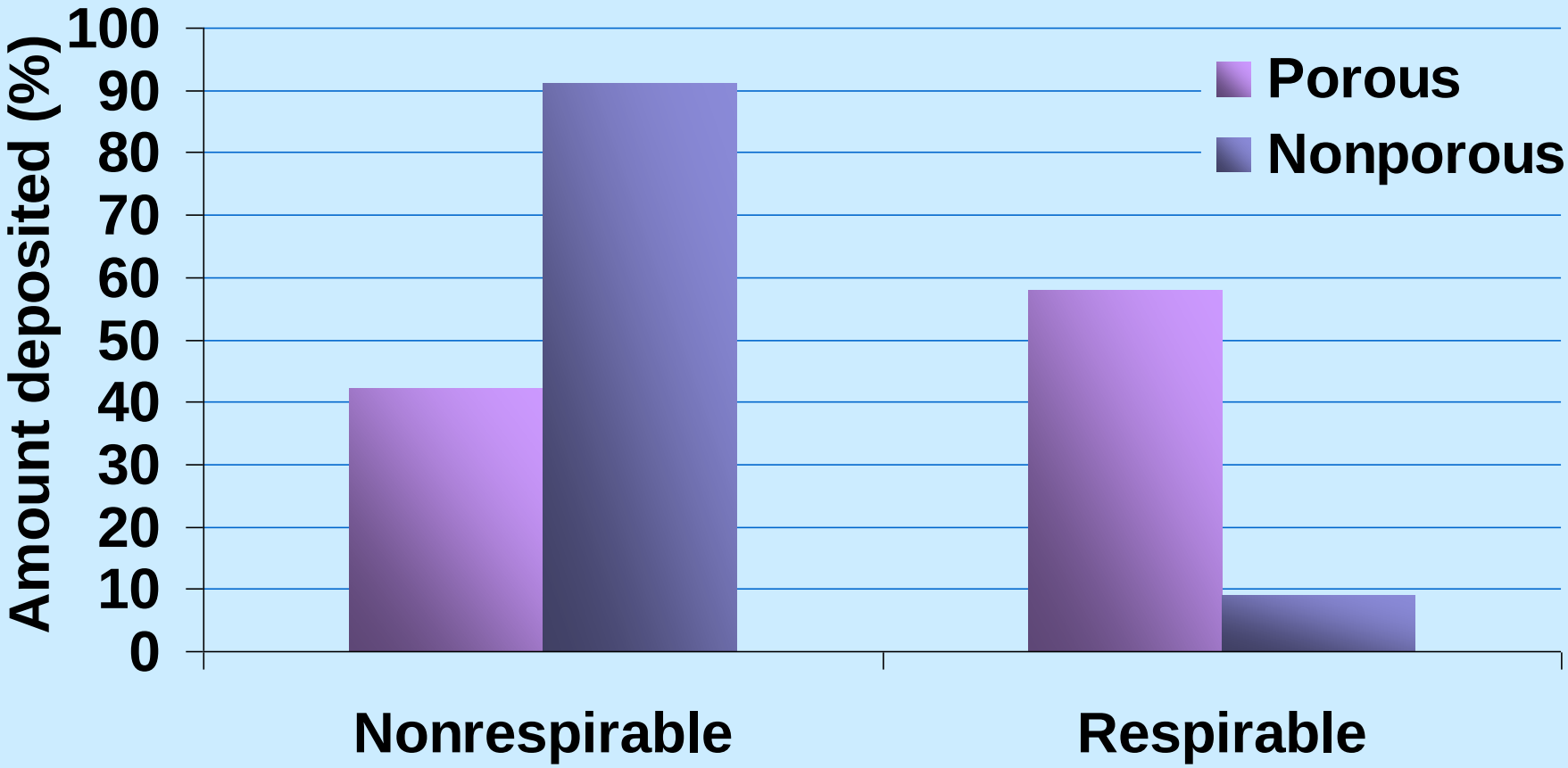
Optimal size for deep lung deposition

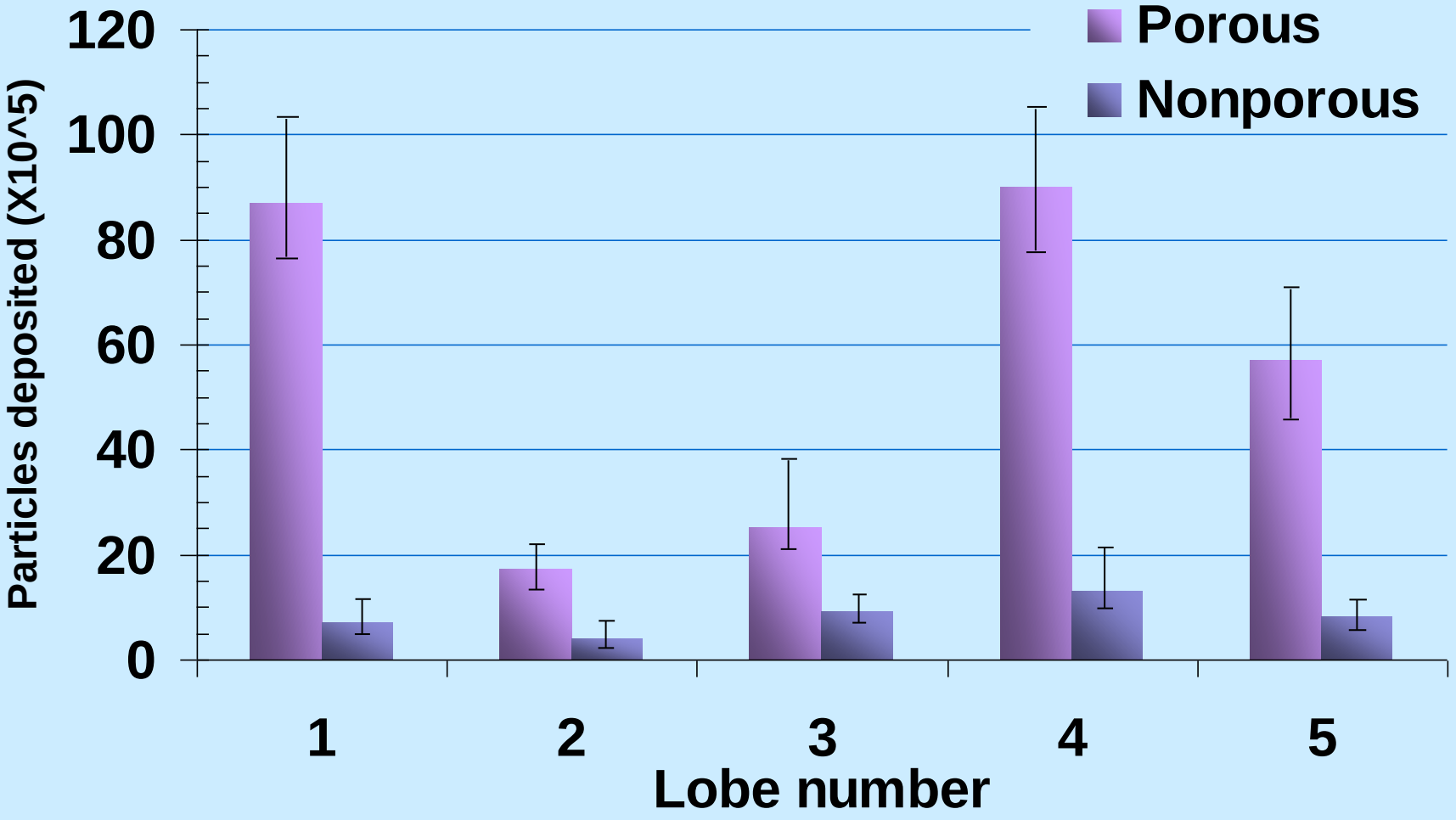


Advantages of large size for therapeutic aerosols

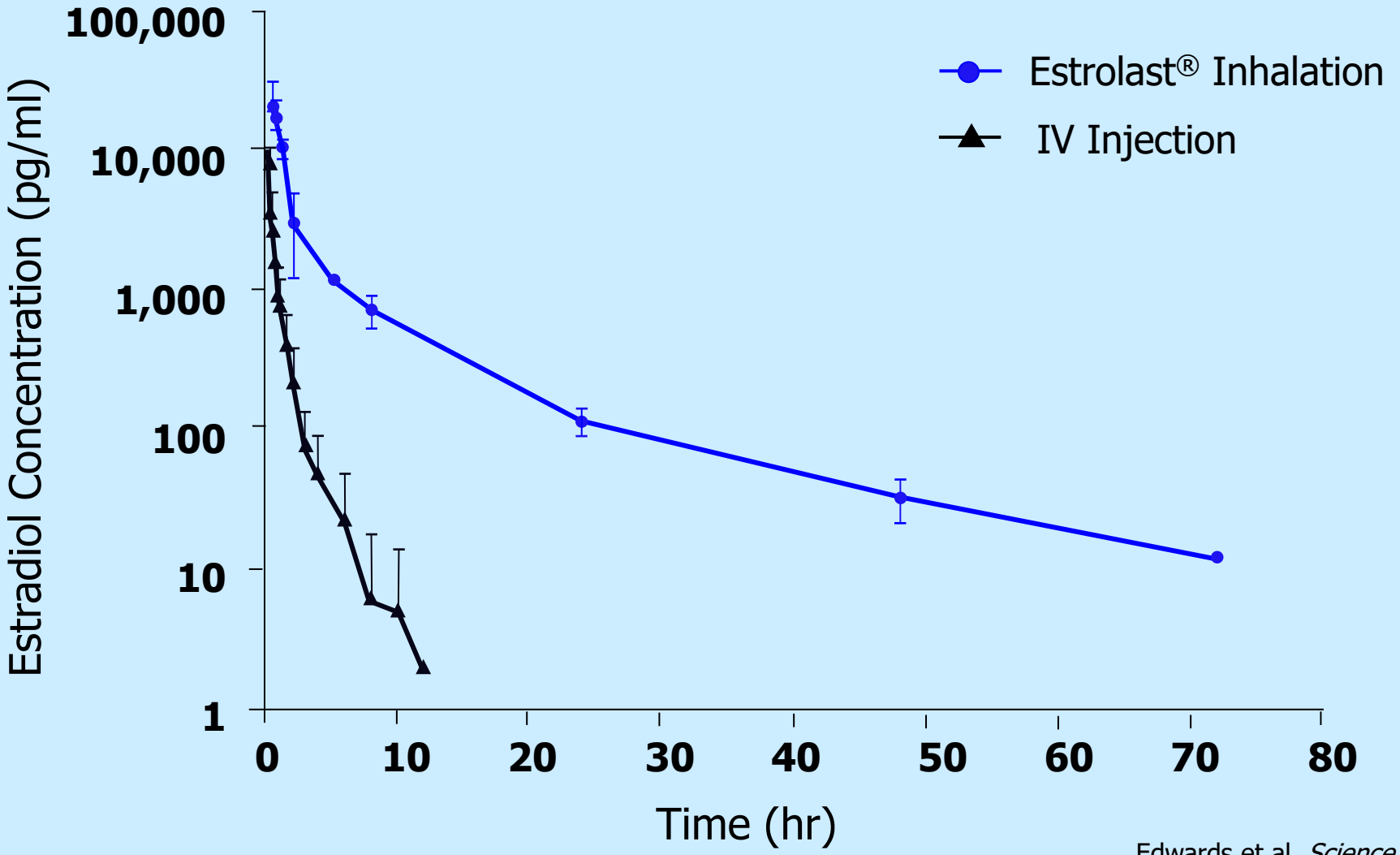
- Easier aerosolization and flowability
- Less prone to phagocytosis


9002 25K
5um


Amount deposited (%)
100
90
80
70
60
50
40
30
20
10
0
Porous
Nonporous
Nonrespirable
Respirable


Porous
Nonporous
Particles deposited (X10^5)
120
100
80
60
40
20
0
1
2
3
4
5
Lobe number

Pharmacokinetic profile of estrolast



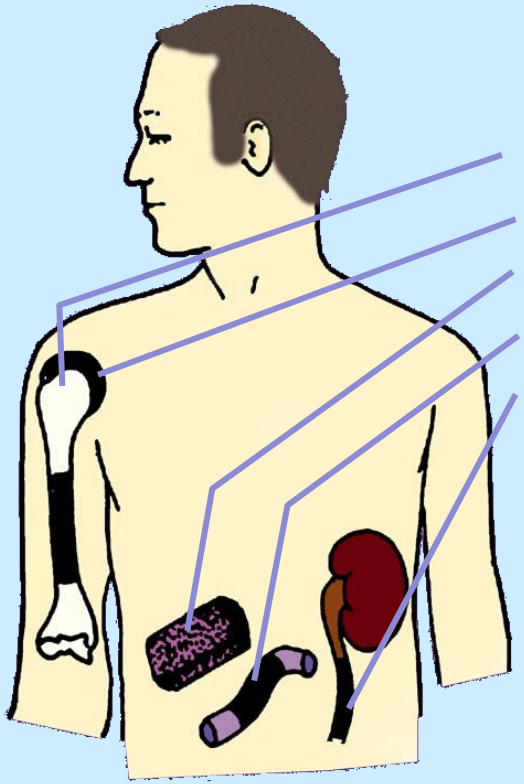
Edwards et al, *Science*, 1997

Cells
Osteoblasts
Chondrocytes
Hepatocytes
Enterocytes
Urothelial cells

Biodegradable polymer scaffold

***In vitro* tissue**

***In vivo* implantation**

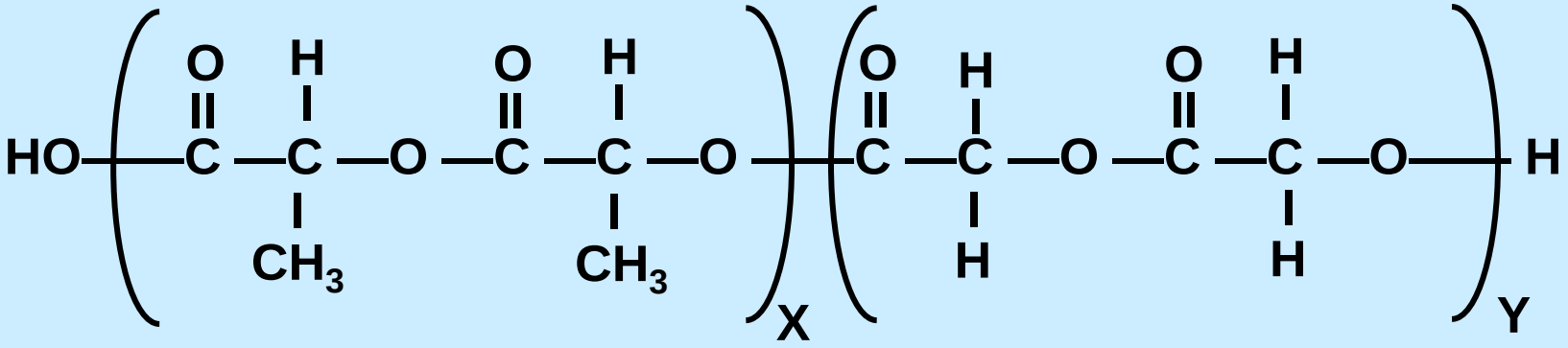


New

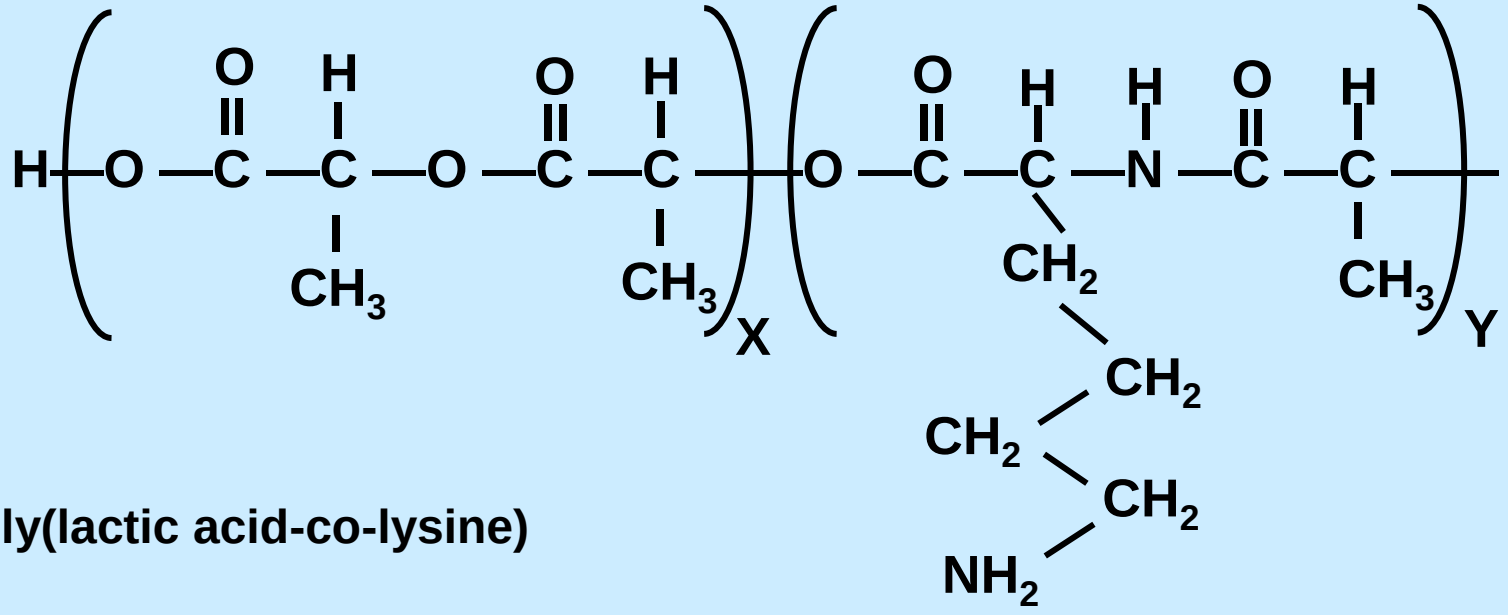
Bone
Cartilage
Liver
Intestine
Ureter

Langer, R. and Vacanti, J., Tissue engineering, *Science*, 260: 920, 1993 (> 6,100 c

Polymer comparison



Poly(lactic acid-co-glycolic acid)



Poly(lactic acid-co-lysine)


20KV 121X 100U 1873 V-HEPTA

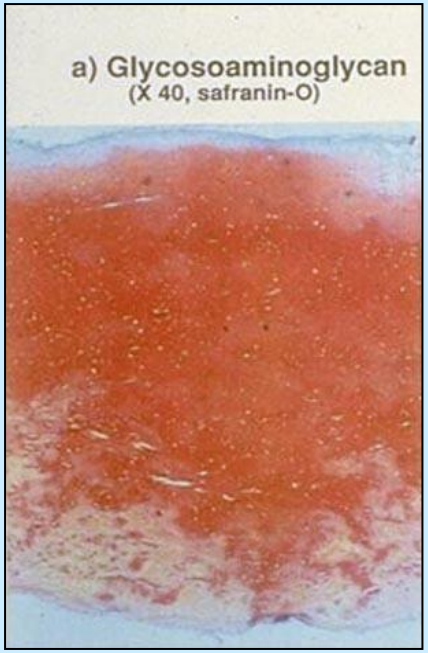
3D tissue engineering

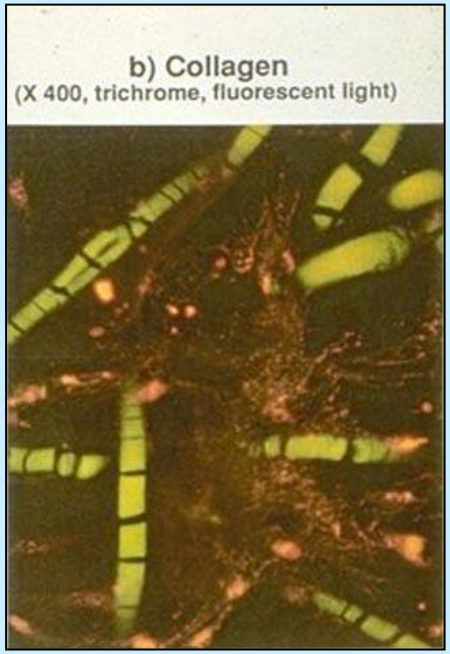
BEFORE
cell seeding

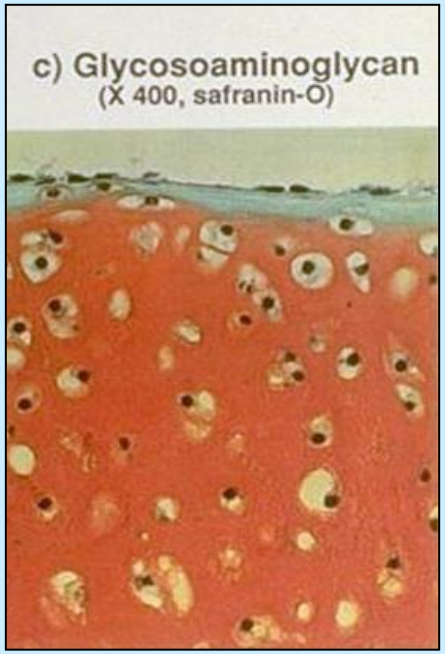
AFTER
2 weeks in culture

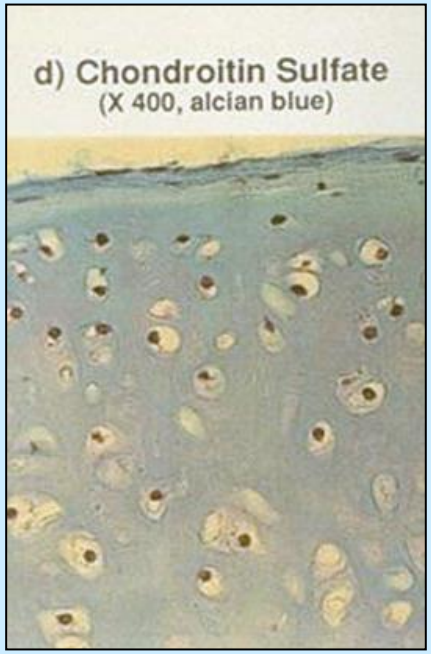
Cartilage

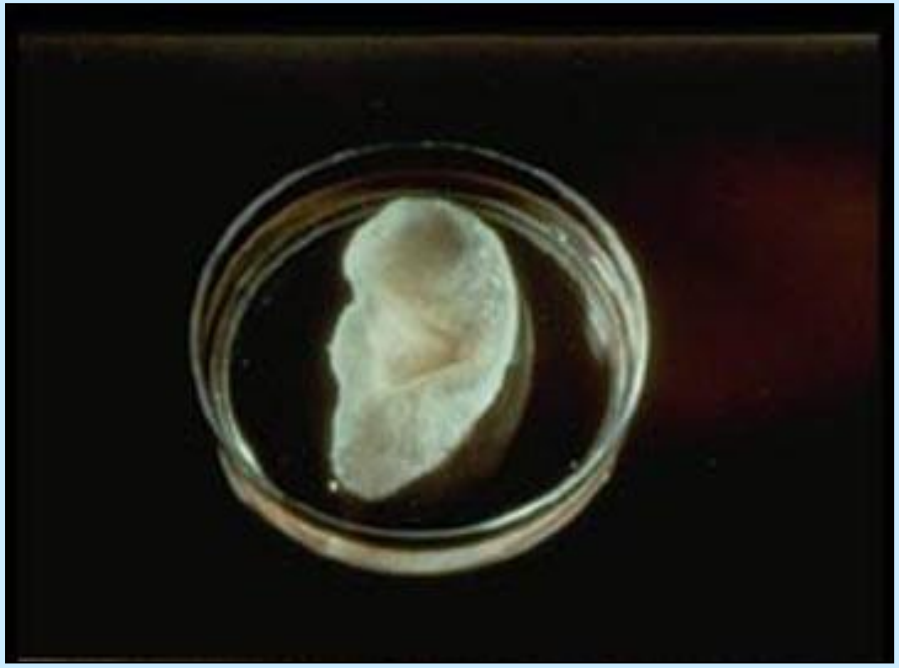

0
1
2

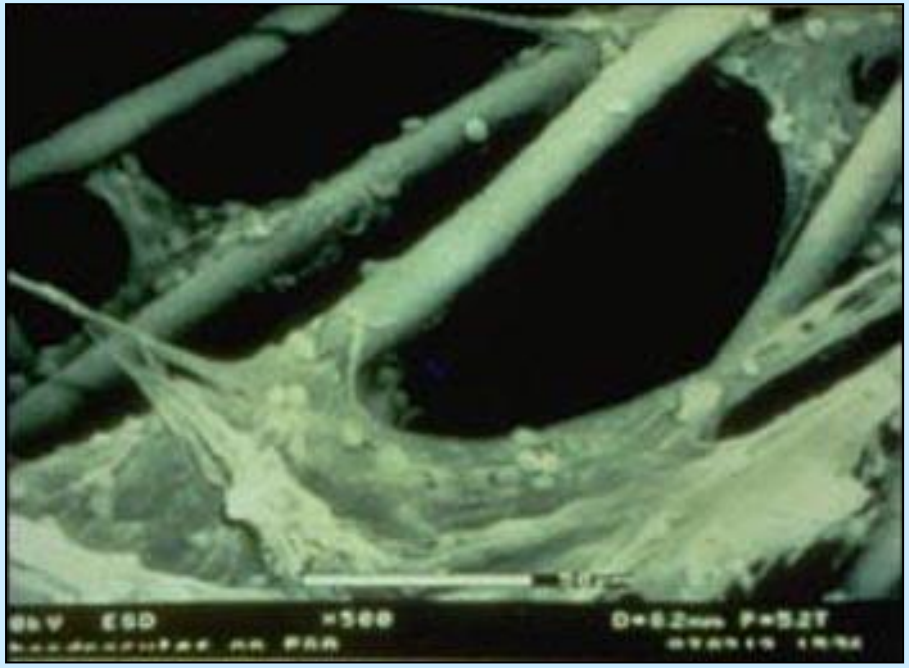

a) Glycosoaminoglycan
(X 40, safranin-O)


b) Collagen
(X 400, trichrome, fluorescent light)


c) Glycosoaminoglycan
(X 400, safranin-O)


d) Chondroitin Sulfate
(X 400, alcian blue)



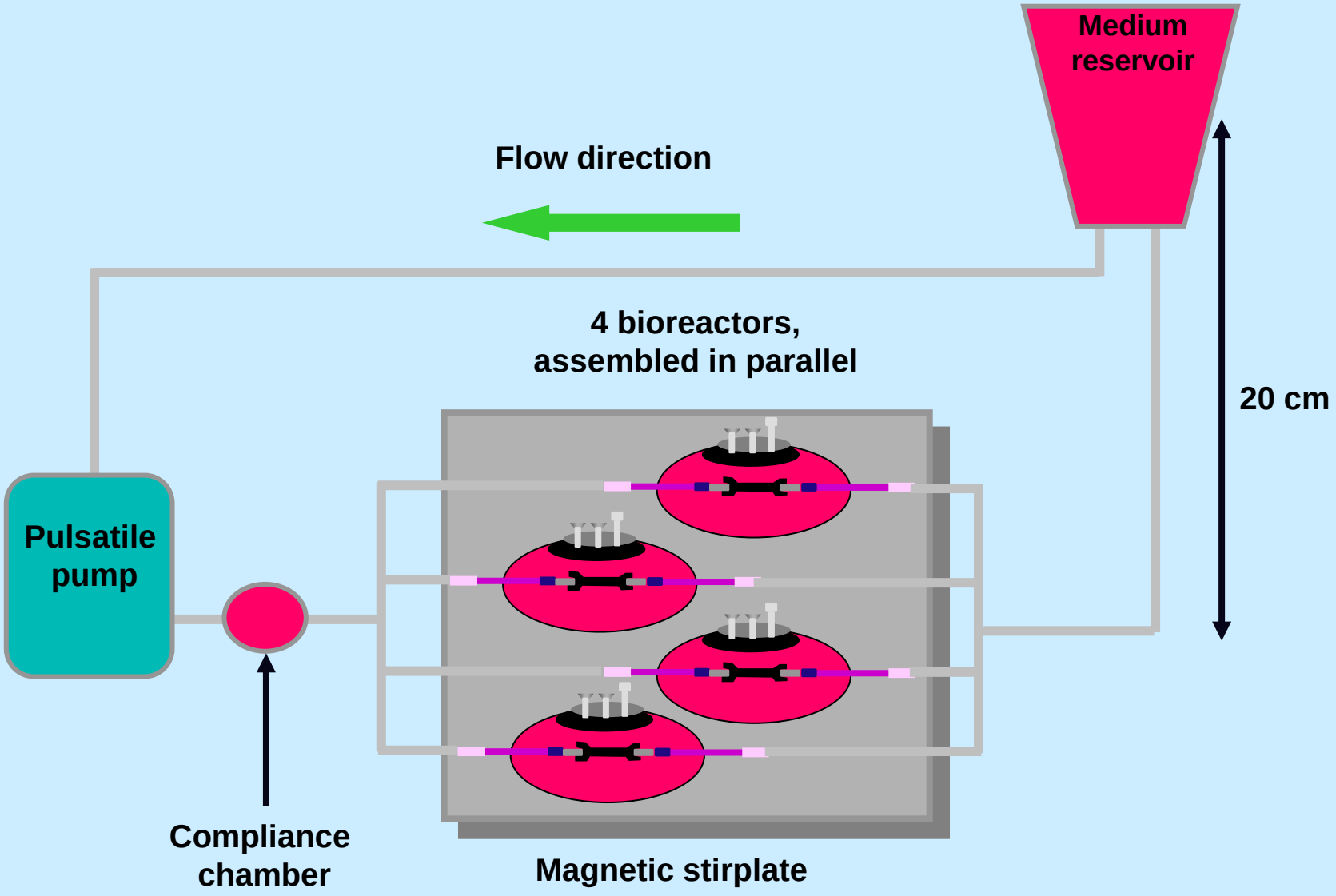

ESD
×500

Blood vessels


0
1
2
3
4

System

- Modified poly glycolic acid (PGA) tubes
- 8 weeks SMC culture, then EC
- Bio-Reactors – Pulsatile radial stress

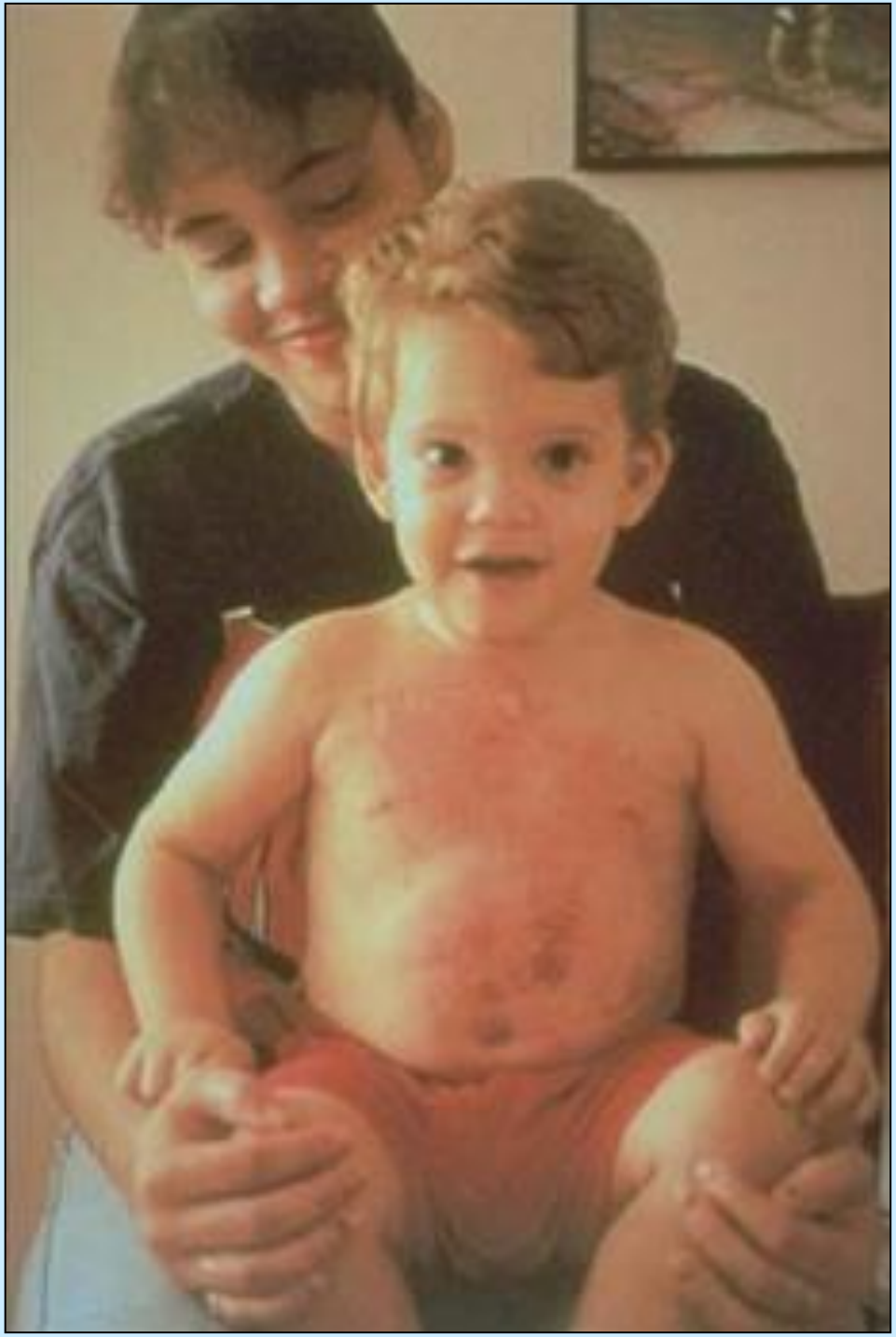

Medium reservoir
Flow direction
4 bioreactors, assembled in parallel
20 cm
Pulsatile pump
Compliance chamber
Magnetic stirplate


0
1
2

Characteristics

- 50% collagen
- Rupture strengths > 2000 mg Hg
- Suture retention – Strengths up to 90g
- Demonstrates contractile responses to serotonin, endothelin-1, and prostaglandin F2α

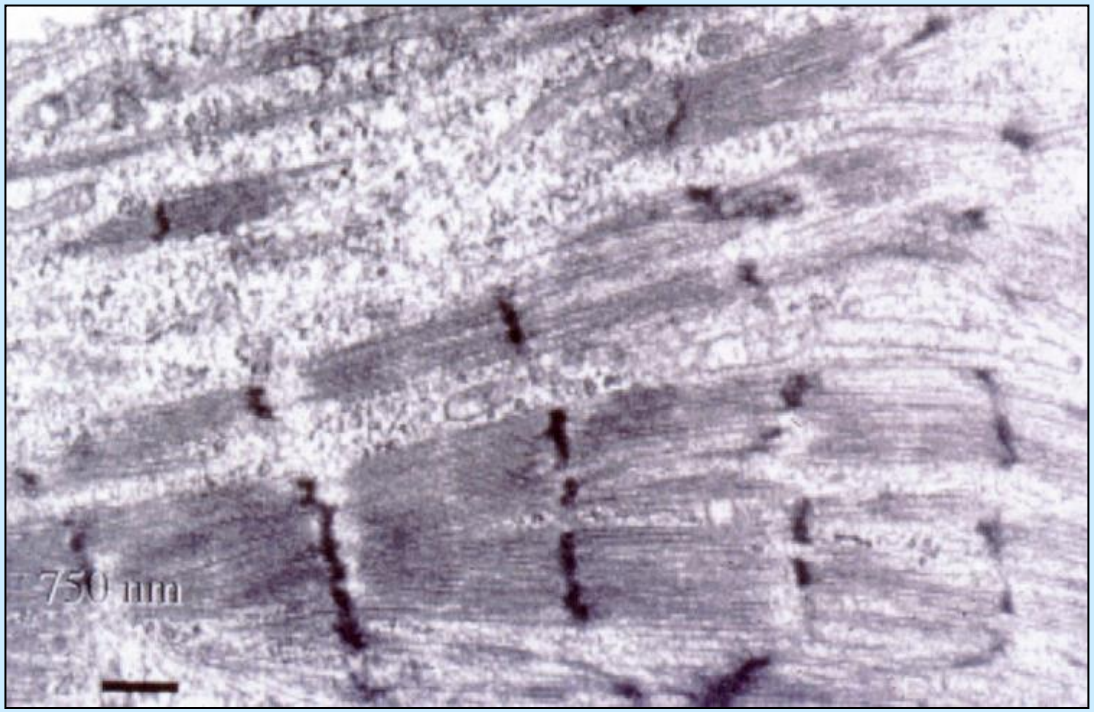
Skin



Heart

Cardiac specific ultrastructure

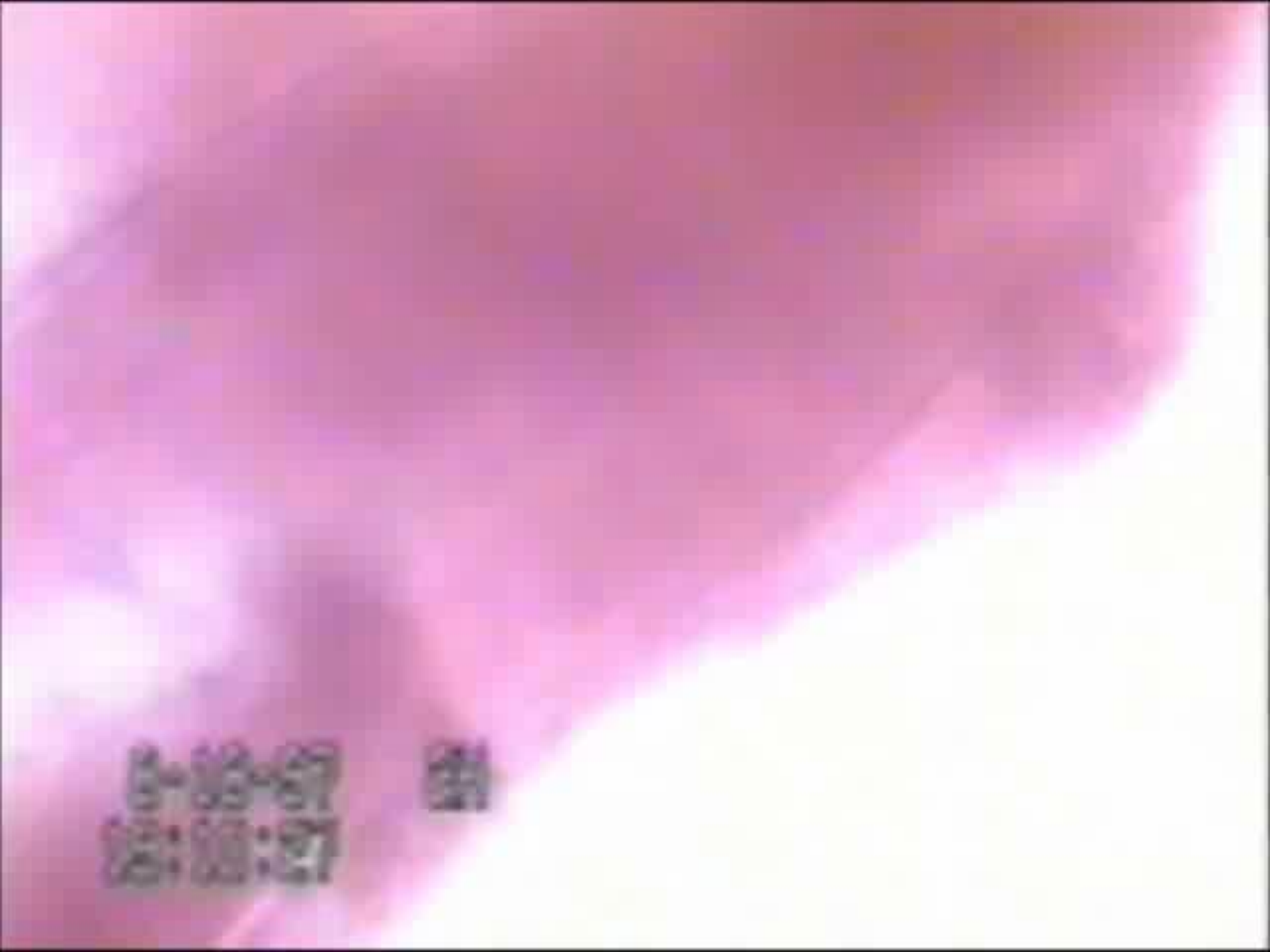
Sarcomeres



Intercalated Disc

Transmission Electron Micrographs

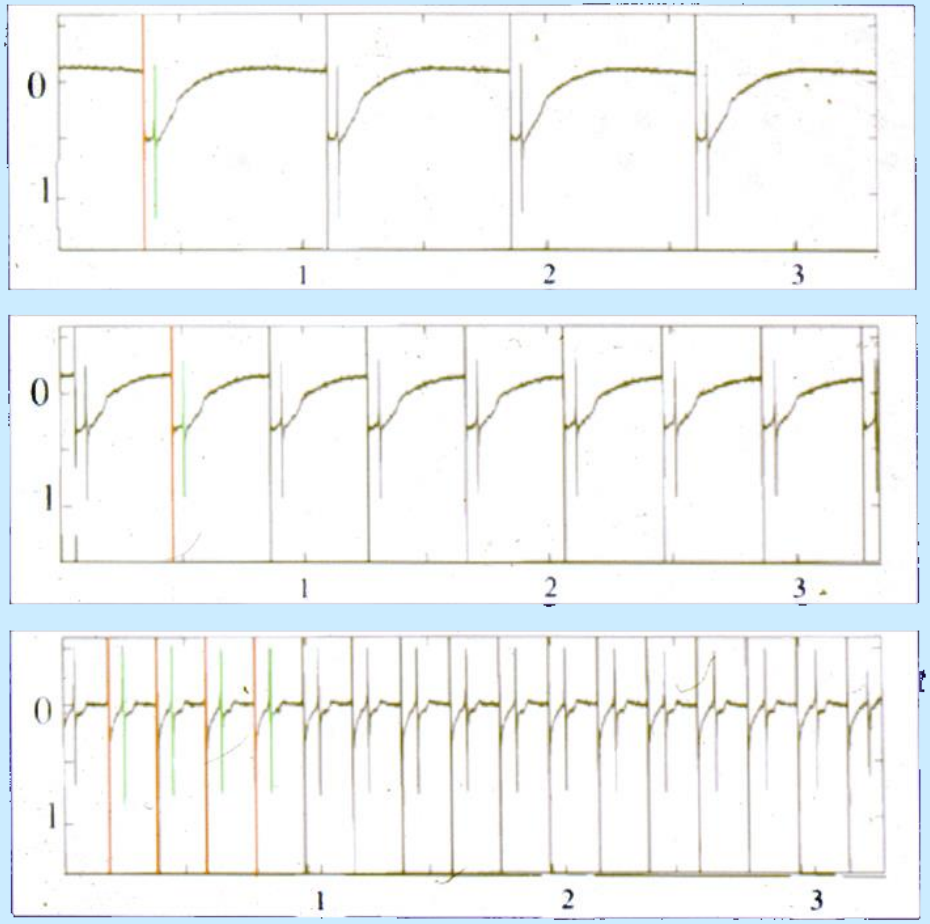
Bursac et al. AJP, 1999



Construct contractility

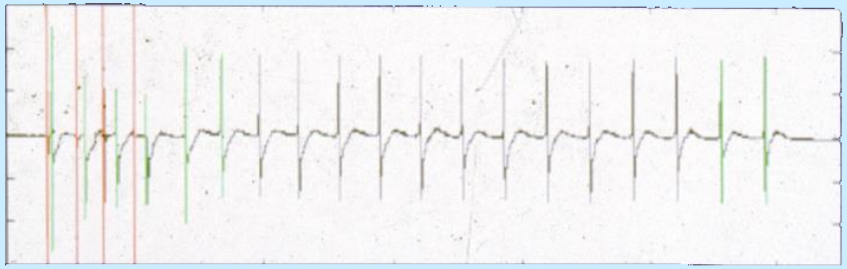
Simulation → Tissue Response

Paced Rates: 80, 150 and 300 bpm



Time (s)

Tachyarrhythmia



0 **3** **6**

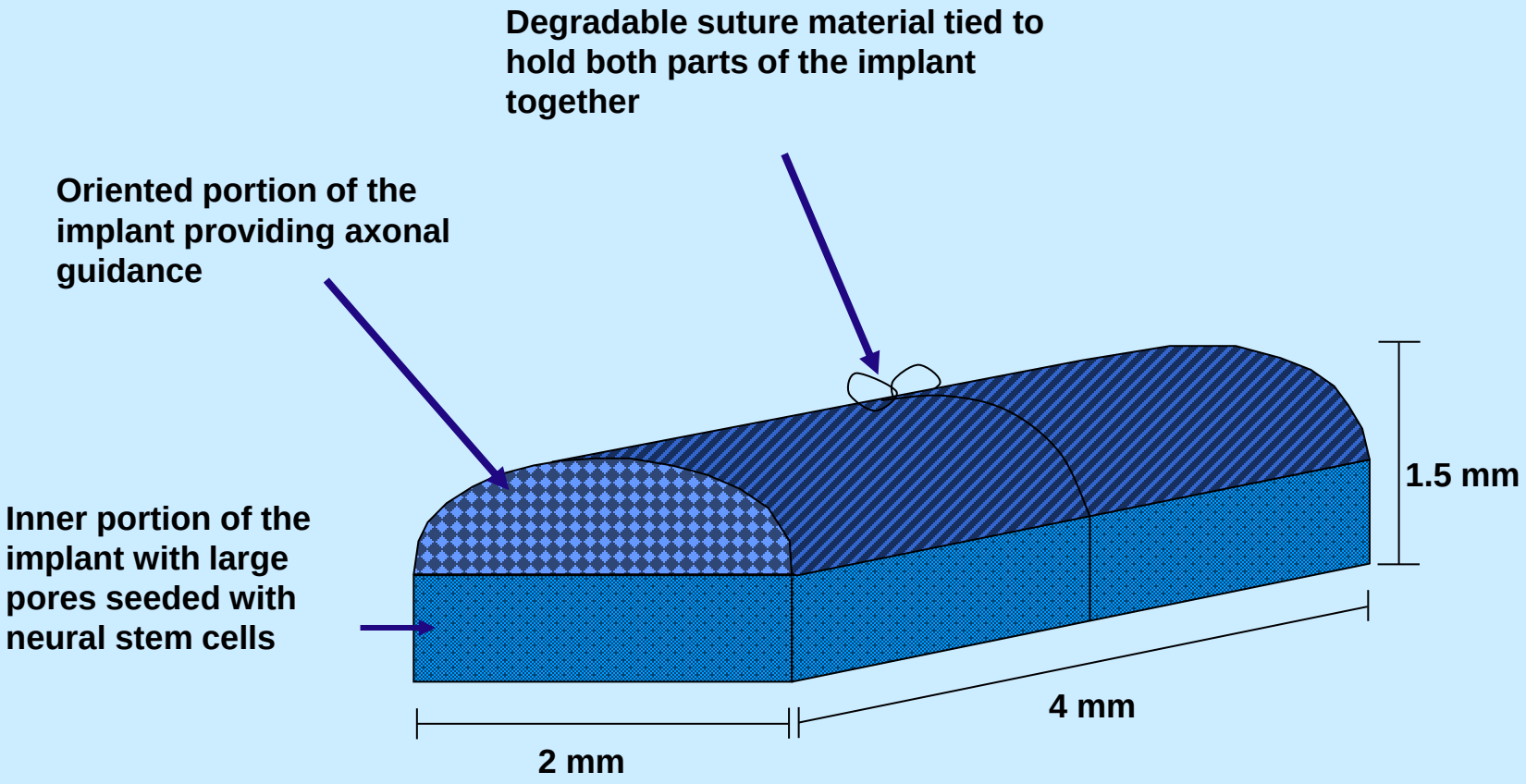
Conduction Block

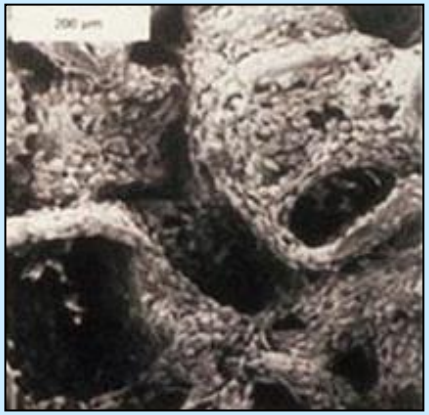
1 2 3 4 5

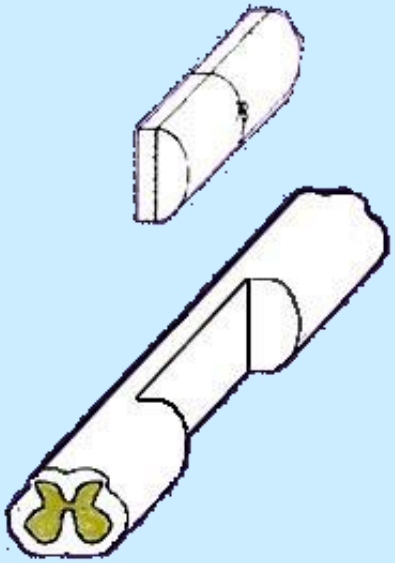
0 **Time (s)** **3**

Bursac et al. AJP 1999

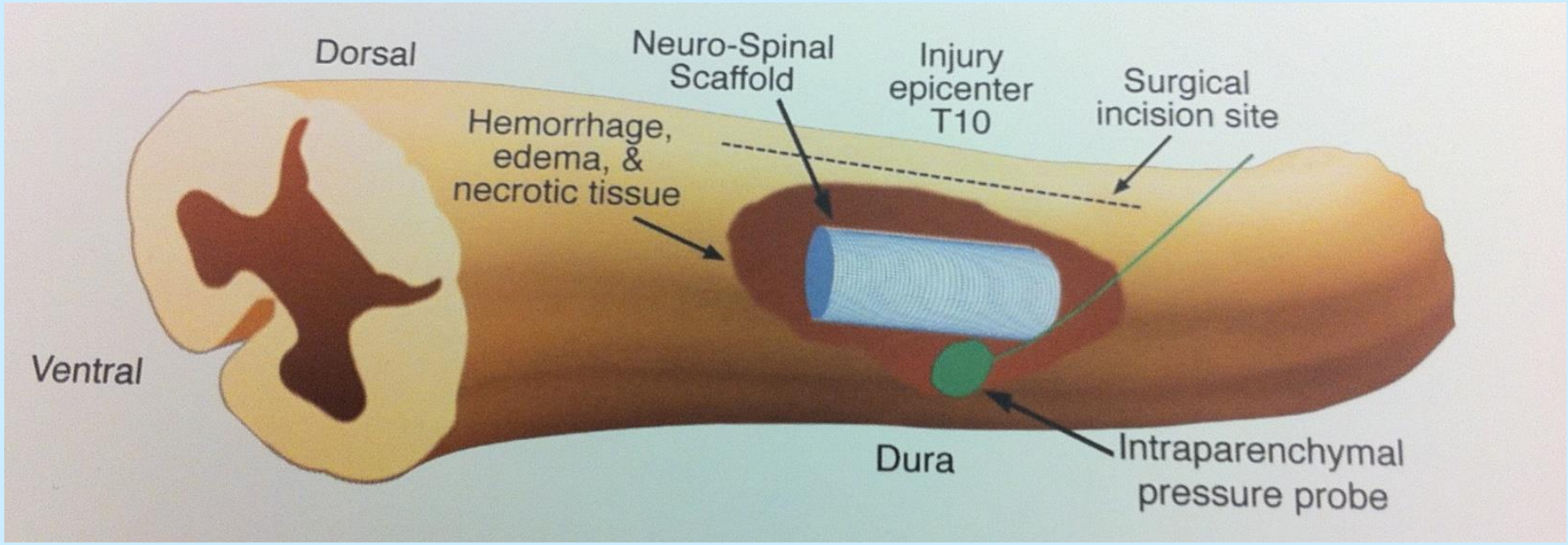
Spinal cord


Degradable suture material tied to hold both parts of the implant together
Oriented portion of the implant providing axonal guidance
Inner portion of the implant with large pores seeded with neural stem cells
1.5 mm
4 mm
2 mm






100 µm


Dorsal
Neuro-Spinal Scaffold
Injury epicenter T10
Surgical incision site
Hemorrhage, edema, & necrotic tissue
Ventral
Dura
Intraparenchymal pressure probe

Three months – First patient

- **No adverse events**
- **Active movement of hip flexors**
- **Palpable contractions of knee extensors**
- **Regained bowel function**
- **Improved bladder function**


EXIT