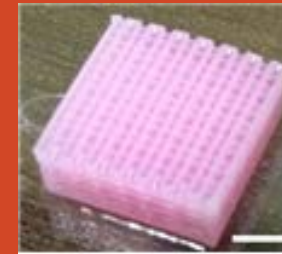
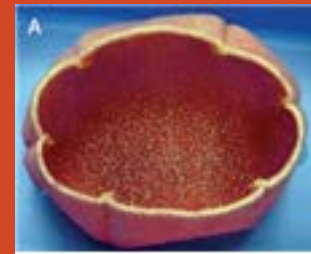
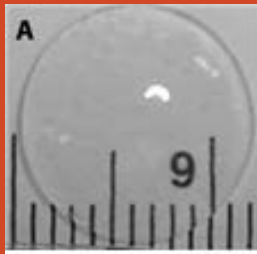


# Tissue Reconstruction & Integration

EunAh Lee, PhD



# Current Life Science Topics

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1. Fundamentals in Basic Biochemistry & Cell Biology
2. Introduction to Tissue Engineering & Regenerative Medicine
3. Developmental Tissue Reconstruction
4. Wound Healing & Regeneration
5. Natural Tissue Composition & Cell-ECM Interaction
6. Stem Cells & Cell-Based Therapy
7. Biomaterials
8. *Mid-Term Exam*
9. Mechano-transduction & Bioreactors
10. **Discussions on Tissue Reconstruction**
11. Regulation & Ethics
12. AI in Current Life Science
13. Machine Learning & Github
14. Deep Neural Network
15. Convolutional Neural Network
16. *Final Exam*

# Study Materials

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## Briefing & Discussion

- Macchirarini P 2008 Lancet (SJ)
- Alsberg E-2002 PNAS (JJ)
- Swisher SL 2015 Nat Comm (JM)

## Other Topics

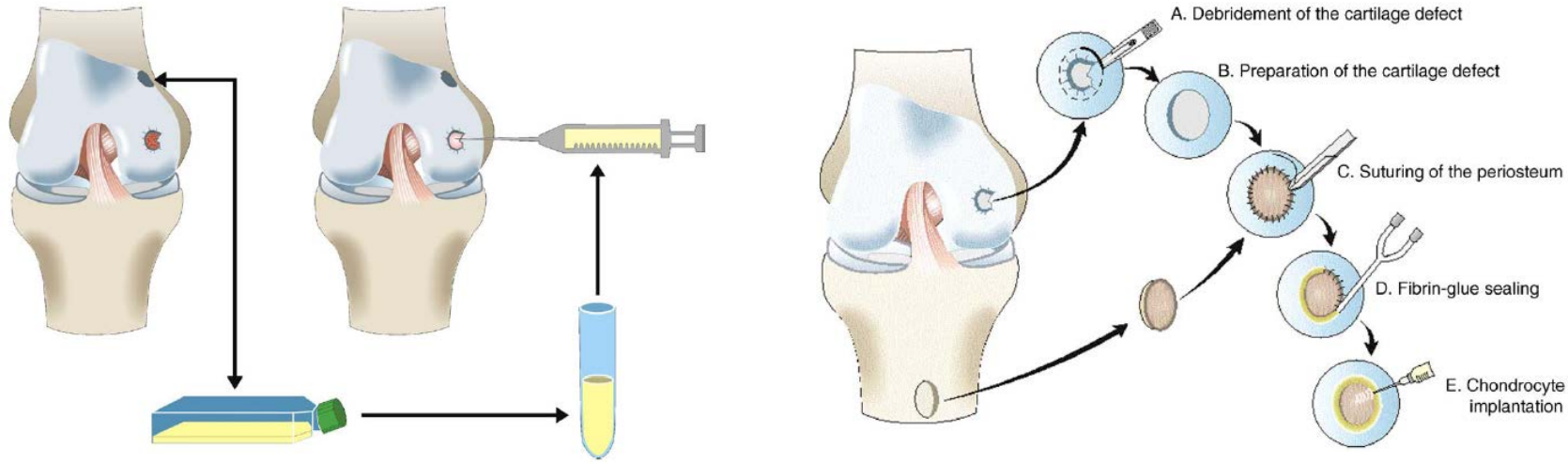
- Whole Organ Decellularization for Vascularized Liver Organoid
  - Baptista PM 2011 Hepatology
- Growth & Transplantation of Custom Vascularized Bone Graft
  - Warnke PH-2004 Lancet
- First Human Face Allograft
  - Devauchelle B-2006 Lancet
- Tissue Engineered Autologous Urethra & Bladder for Cystoplasty
  - Raya-Rivera A 2011 Lancet
  - Atala A 2006 Lancet
  - TED Lecture by Anthony Atala (2009)

# ACT (Autologous Chondrocyte Transplantation)

Marlovits S-2006 EJR

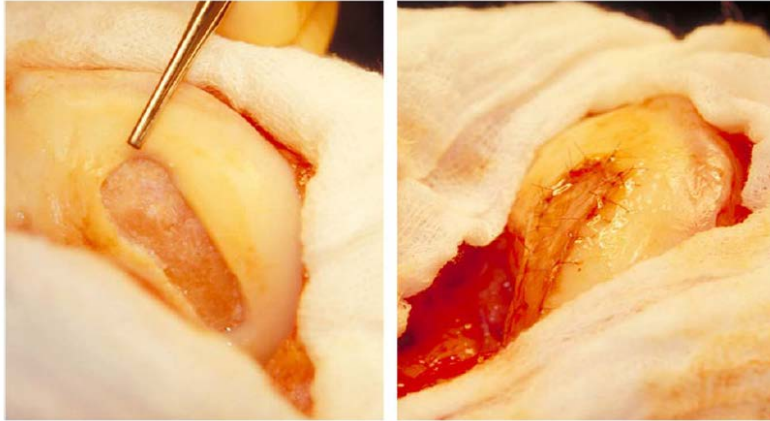
Kock L et al., 2010 Osteoarthritis & Cartilage

# Autologous Chondrocyte Implantation (ACI)

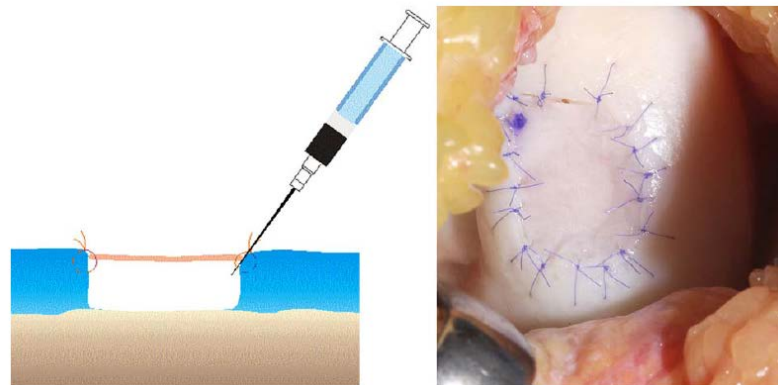


# Generations of ACI

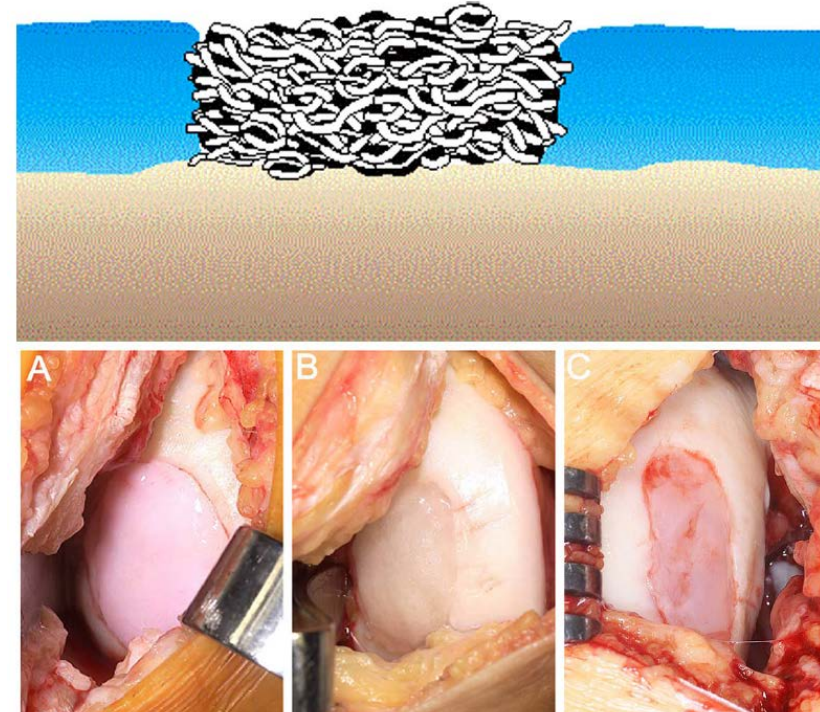
## 1<sup>st</sup> Generation



## 2<sup>nd</sup> Generation

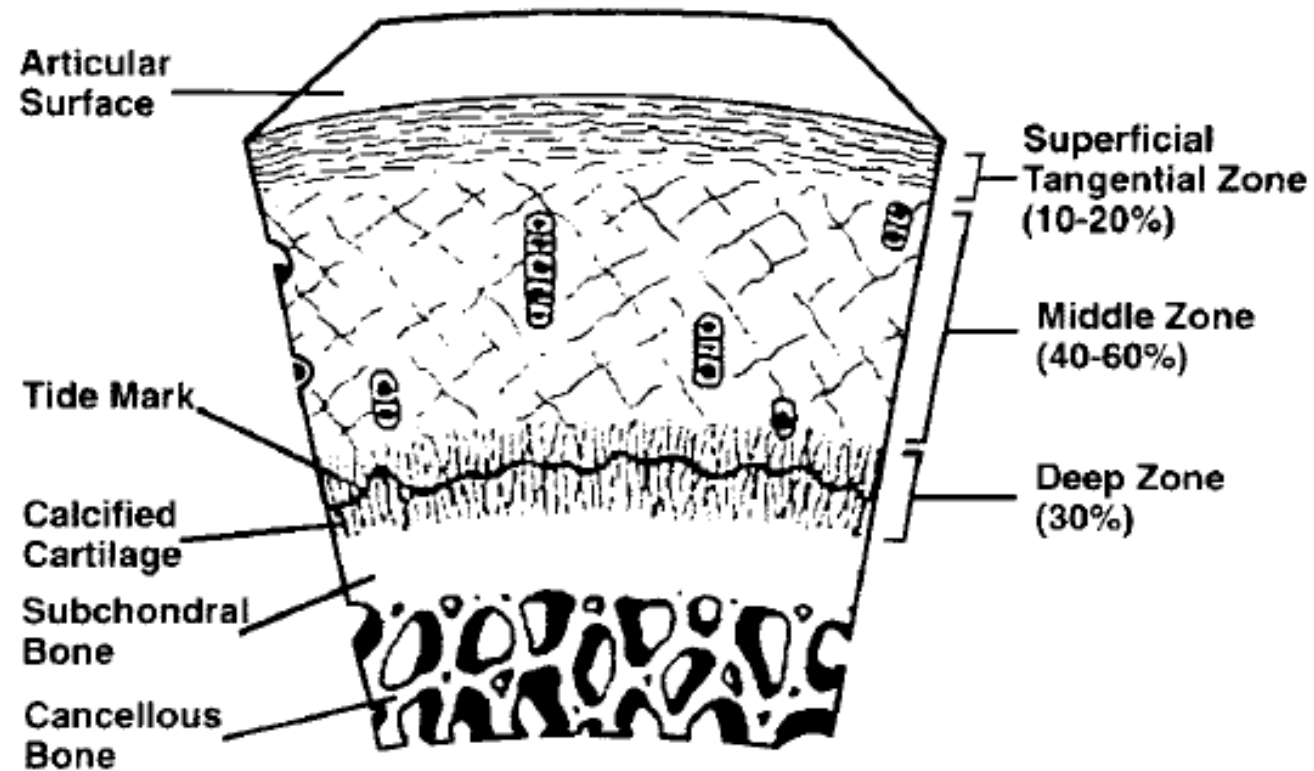


## 3<sup>rd</sup> Generation

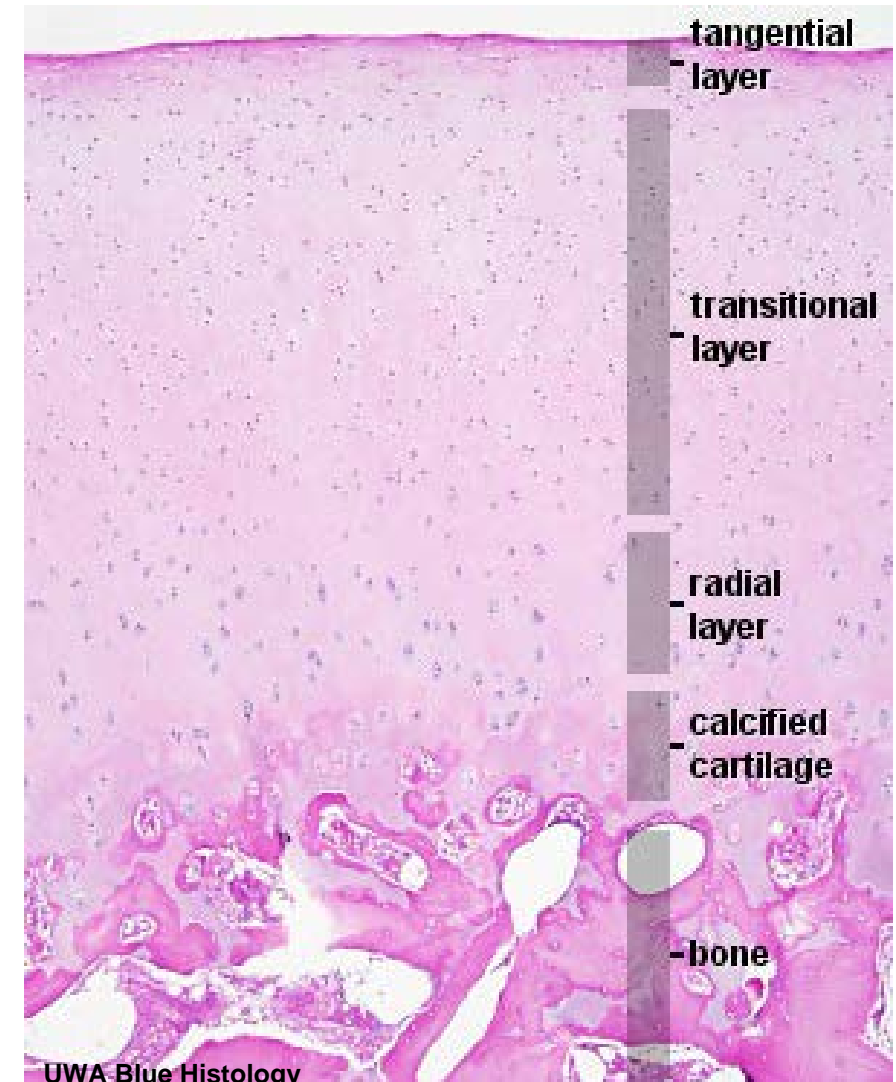




# Zonal Organization of Normal Articular Cartilage

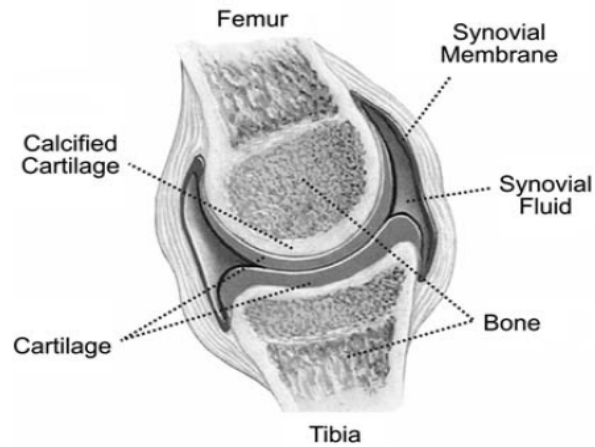


Mandelbaum BR et al., 1998

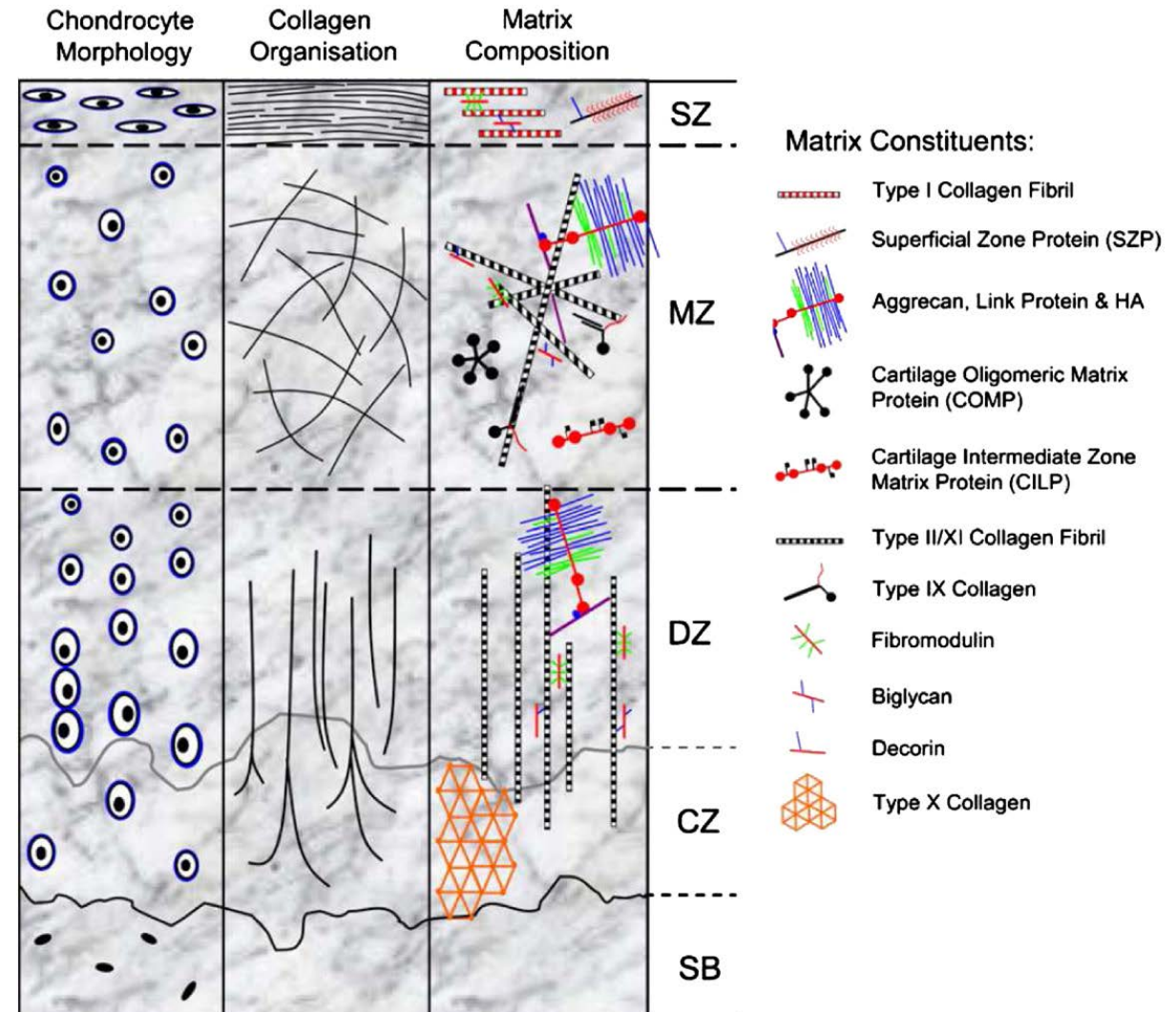


UWA Blue Histology

# Structure & ECM organization of Articular Cartilage



Schulz RM and Bader A 2007 Eur Biophys J



Hayes AJ 2007 J Histochemistry & Cytochemistry



# Challenges in Cartilage Tissue Engineering

## Cell Source & Expansion

## Proteoglycan/Collagen Content

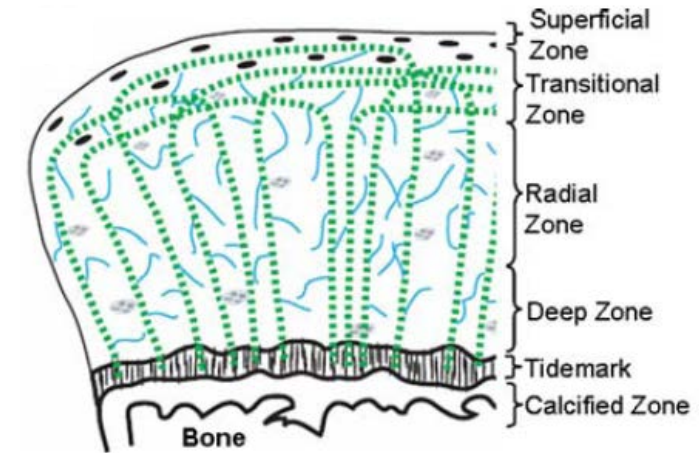
## Zonal organization

- Collagen alignment
- Reconstruction of Depth-dependent Structure

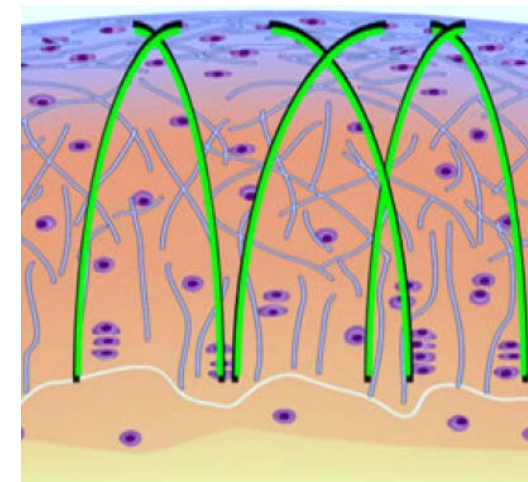
## Tissue Integration

## Monitoring of Chondrogenesis

- Non-destructive monitoring



Schulz RM and Bader A 2007 Eur Biophys J



Kock et al., 2011

# Engineering Cartilage with Zonal Structure

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## Cell-based methods

Kim et al., 2003; Waldman et al., 2003; Schuurman et al., 2009; Malda et al., 2010; Ng et al., 2005

## Scaffold-based methods

Woodfield et al., 2005

## Combination of cells & scaffolds

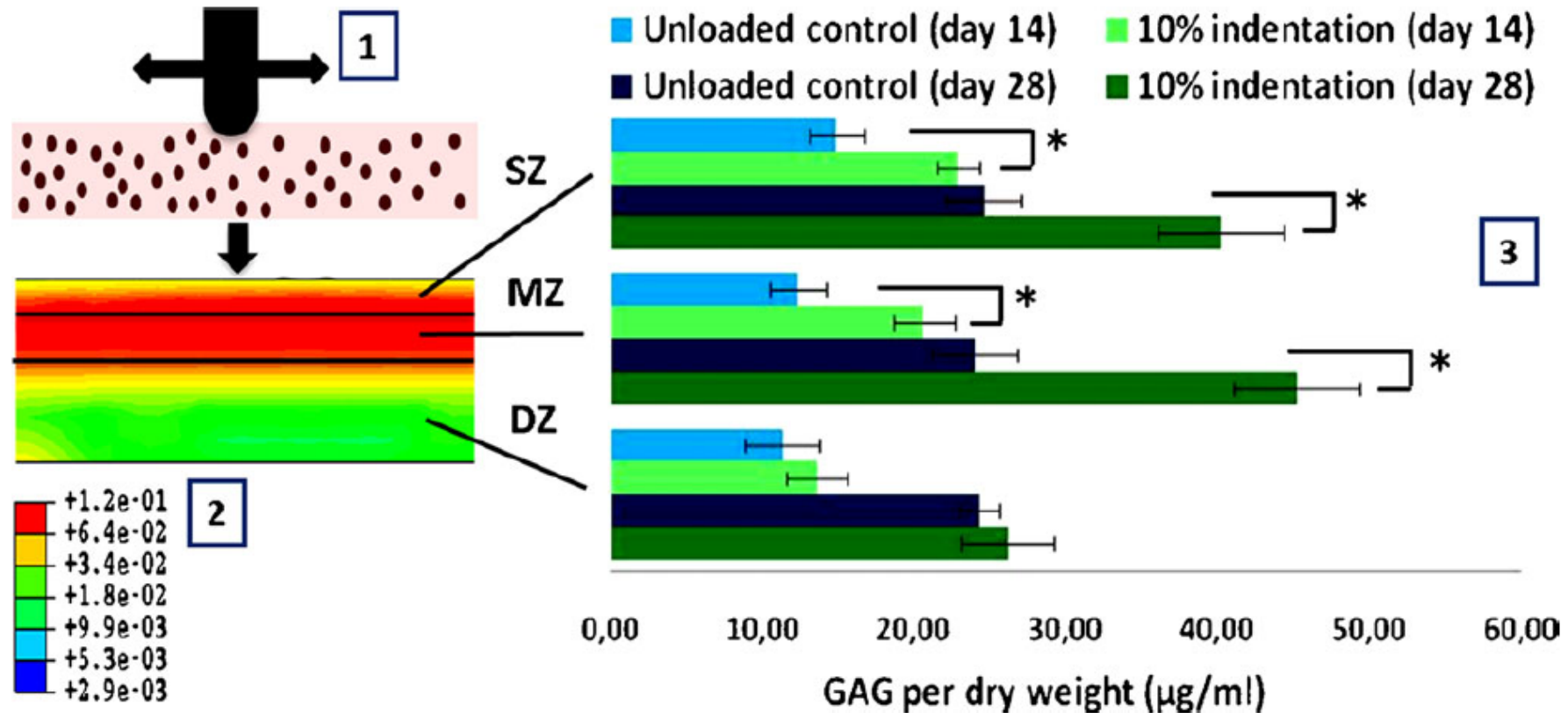
Nguyen et al., 2011a; Nguyen et al., 2011b

## Depth-dependent strain fields

Kock et al., 2010; Khoshgoftar et al., 2011



# Reconstruction of Zonal Distribution



Kock L et al., 2010 Osteoarthritis & Cartilage

# Tissue Integration

## ARTICLES

# Multifunctional chondroitin sulphate for cartilage tissue–biomaterial integration

DONG-AN WANG<sup>1,2</sup>, SHYNI VARGHESE<sup>1</sup>, BLANKA SHARMA<sup>1,3</sup>, IOSSIF STREHIN<sup>1</sup>, SARA FERMANIAN<sup>1,3</sup>, JUSTIN GORHAM<sup>4</sup>, D. HOWARD FAIRBROTHER<sup>4</sup>, BRETT CASCIO<sup>5</sup> AND JENNIFER H. ELISSEEFF<sup>1,5\*</sup>

<sup>1</sup>Department of Biomedical Engineering, Johns Hopkins University, Baltimore, Maryland 21218, USA

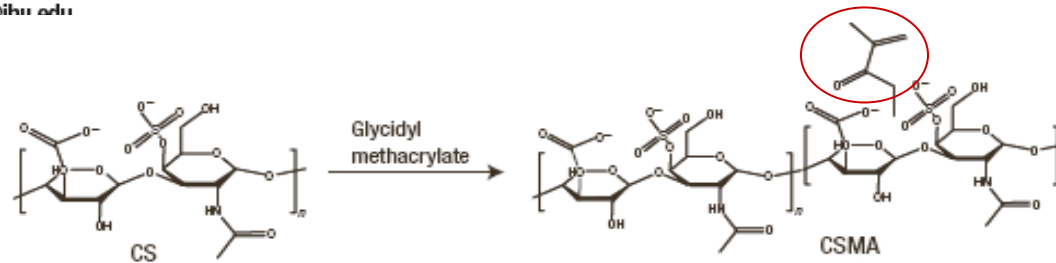
<sup>2</sup>Division of Bioengineering, School of Chemical and Biomedical Engineering, Nanyang Technological University, Singapore 637457

<sup>3</sup>Cartilix, Inc., Foster City, California 94404, USA

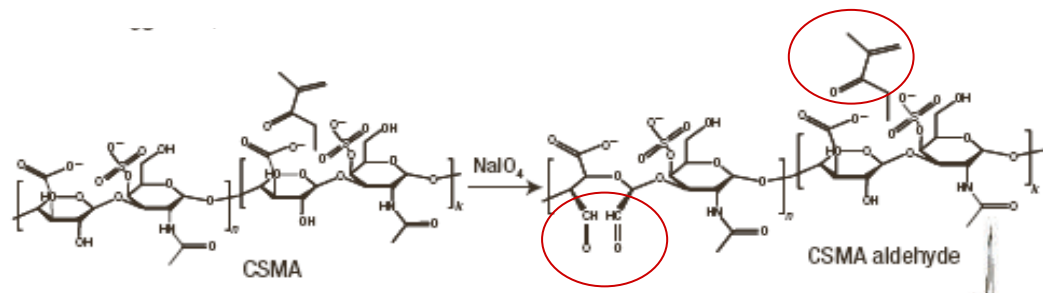
<sup>4</sup>Department of Chemistry, Johns Hopkins University, Baltimore, Maryland 21218, USA

<sup>5</sup>Department of Orthopedics, Johns Hopkins Medical School, Baltimore, Maryland 21218, USA

\*e-mail: jhe@jhmi.edu



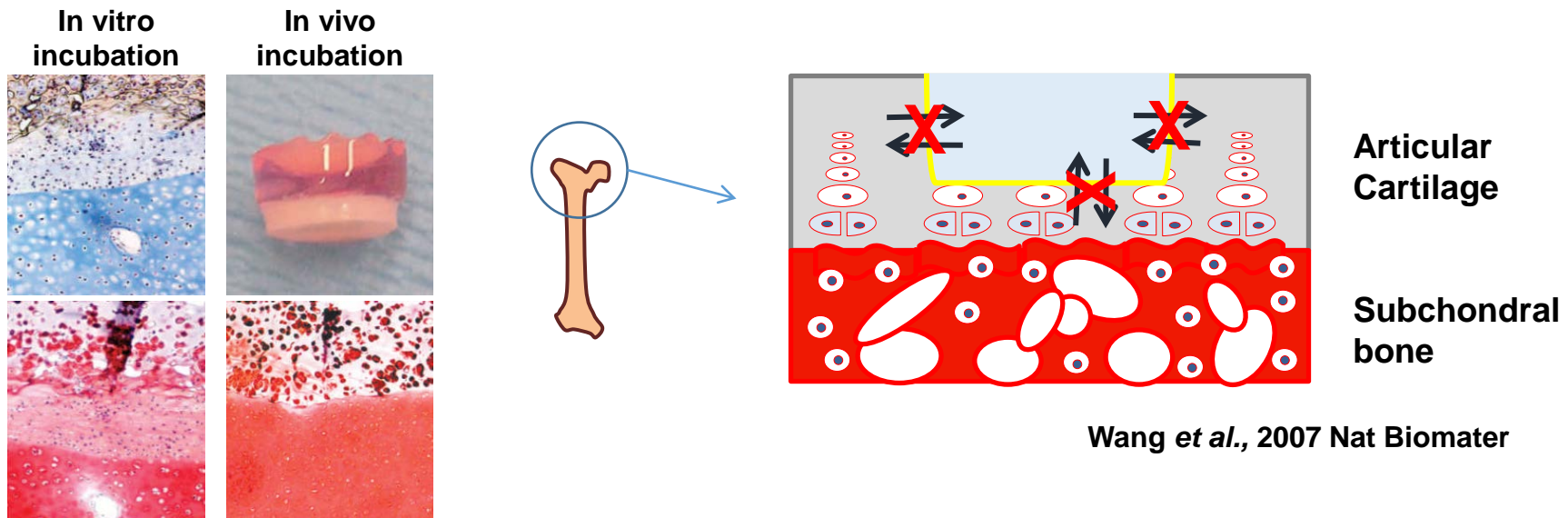
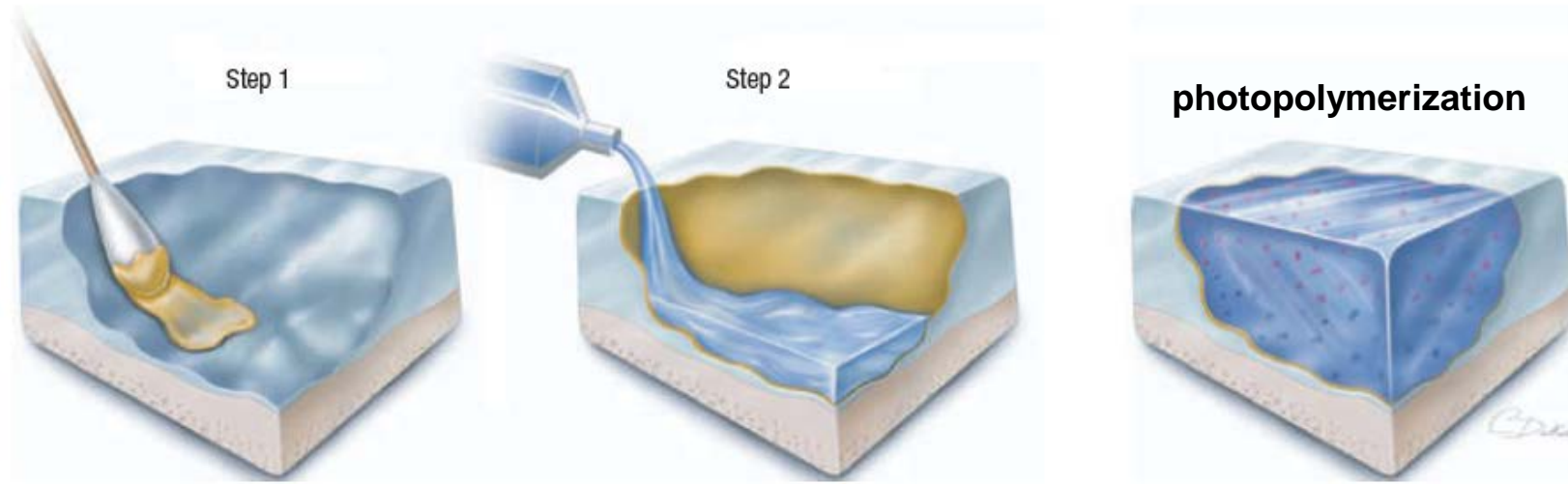
**Metacrylated chondroitin sulfate**  
(yield= 12%)  
- polymerize via a radical mechanism



**Aldehyde-grafted chondroitin sulfate**  
(yield= 70%)  
-conjugates with amines  
via a Schiff-base reaction



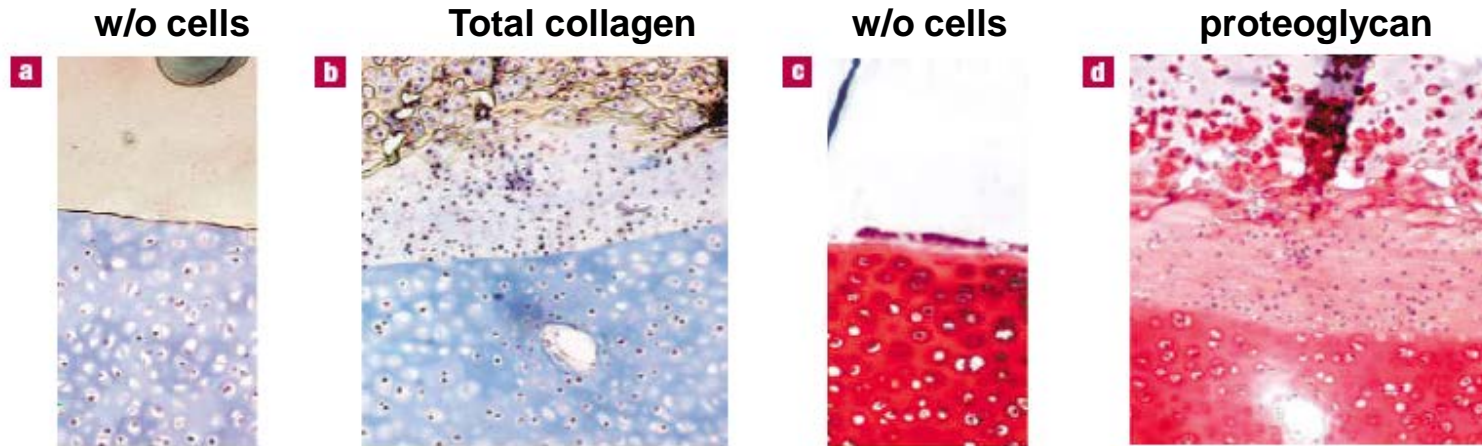
# Demerits of Paste-Type Adhesives



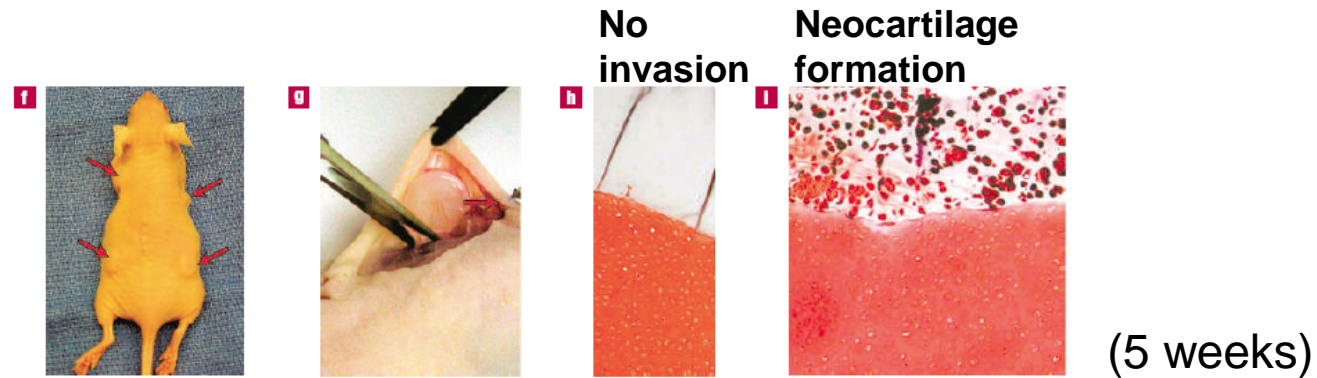
Wang et al., 2007 Nat Biomater

# Tissue Integration vs Tissue Insulation

*In vitro*  
incubation



*In vivo*  
incubation

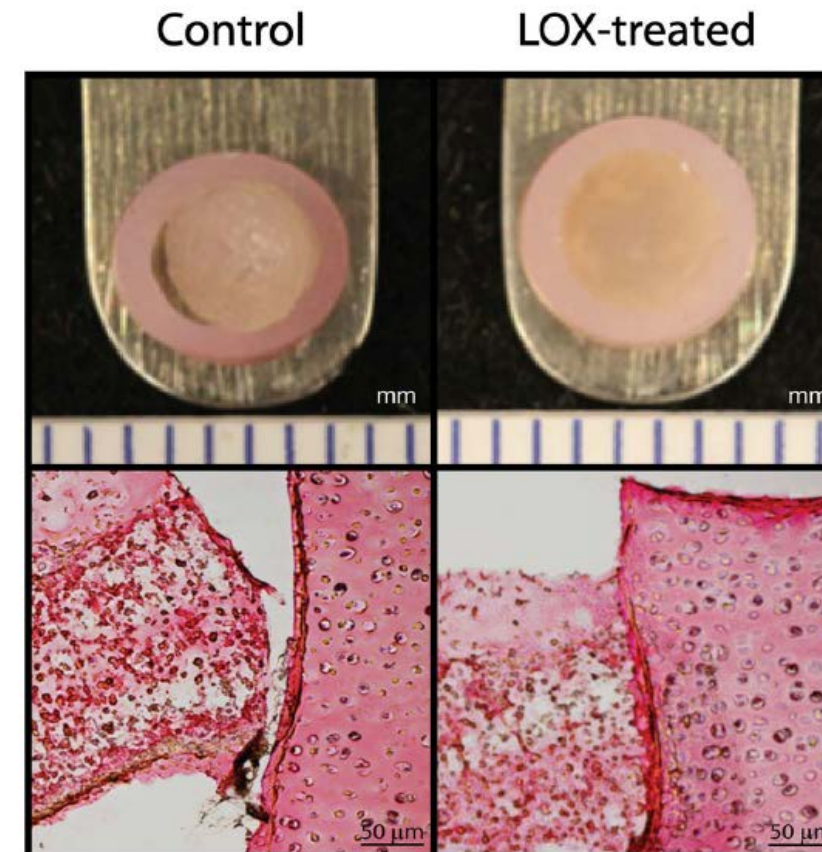
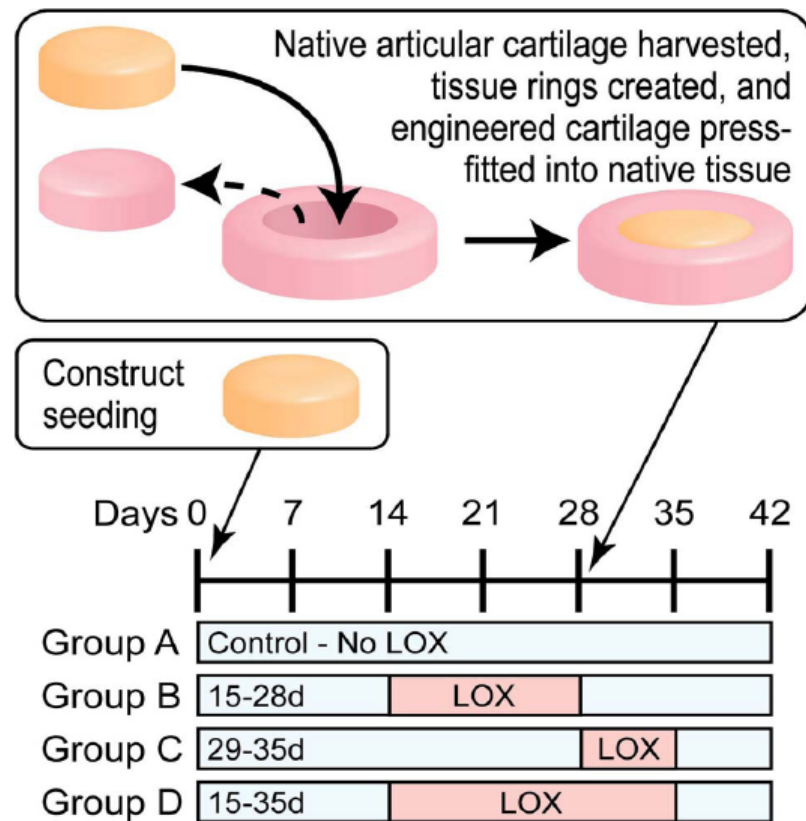


# Induced Collagen Cross-Links Enhance Cartilage Integration

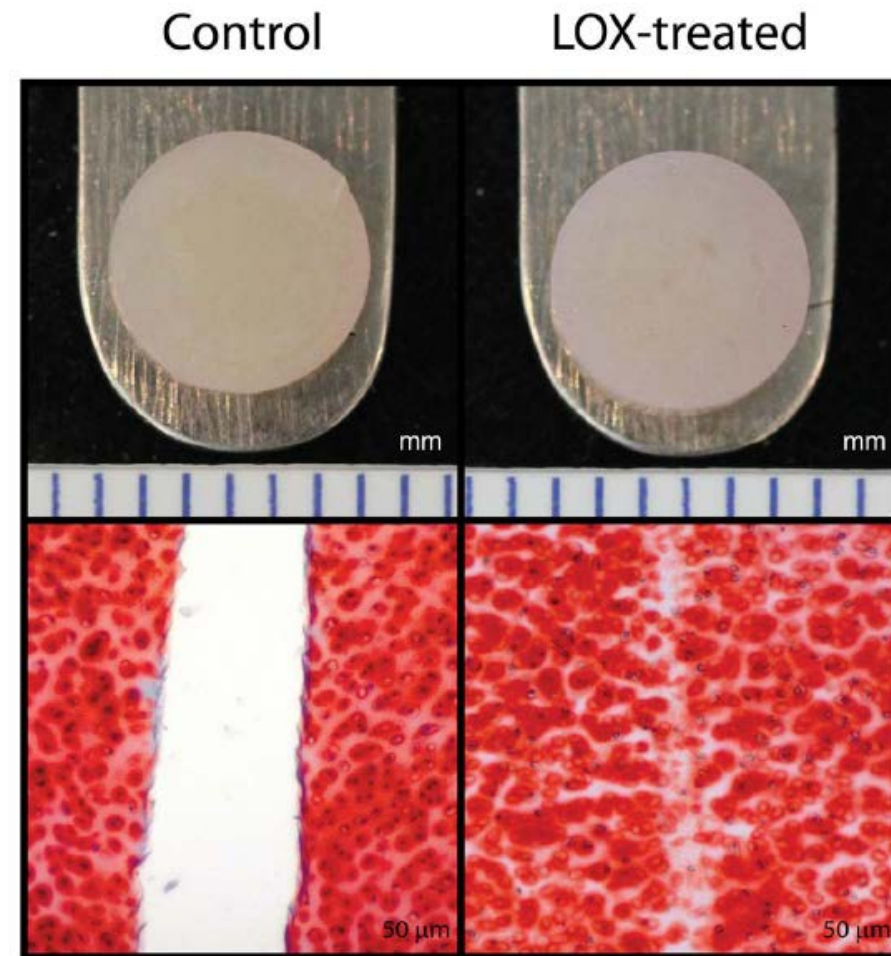
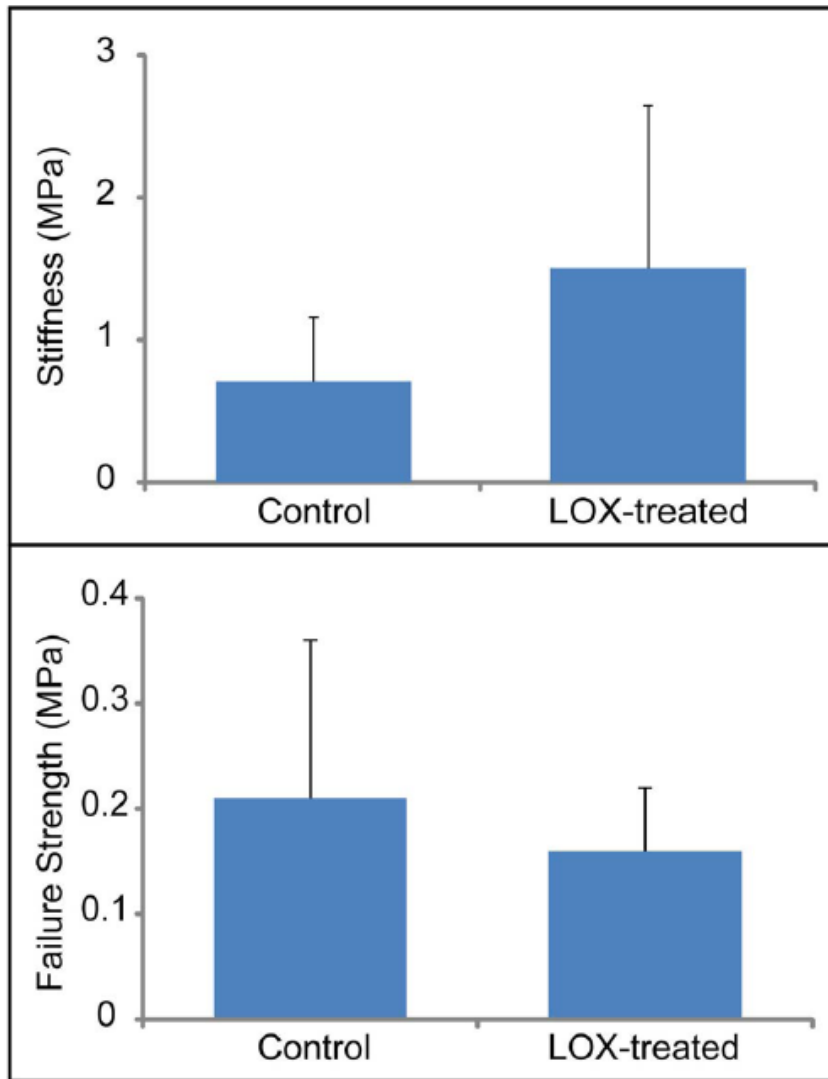
Athens AA 2013 PLoSOne

Aristos A. Athens<sup>1,2</sup>, Eleftherios A. Makris<sup>1,3</sup>, Jerry C. Hu<sup>1\*</sup>

**1** Department of Biomedical Engineering, University of California Davis, Davis, California, United States of America, **2** Davis Senior High School, Davis, California, United States of America, **3** Department of Orthopedic Surgery and Musculoskeletal Trauma, University of Thessaly (BIOMED), Larisa, Greece







## **INTERLEUKIN-1 $\beta$ ENHANCES CARTILAGE-TO-CARTILAGE INTEGRATION**

I.M. Khan<sup>1,\*</sup>, L.G. Gonzalez<sup>2</sup>, L. Francis<sup>3</sup>, R.S. Conlan<sup>3</sup>, S.J. Gilbert<sup>1</sup>, SK Singhrao<sup>1</sup>, D. Burdon<sup>4</sup>, A.P. Hollander<sup>5</sup>,  
V.C. Duance<sup>1</sup> and C.W. Archer<sup>1</sup>

### **Intrinsic barriers to integration**

- **Avascular & hypocellular nature of articular cartilage**
- **Limited migration of chondrocytes or SCs**
- **ECM is inhibitory for cell migration**

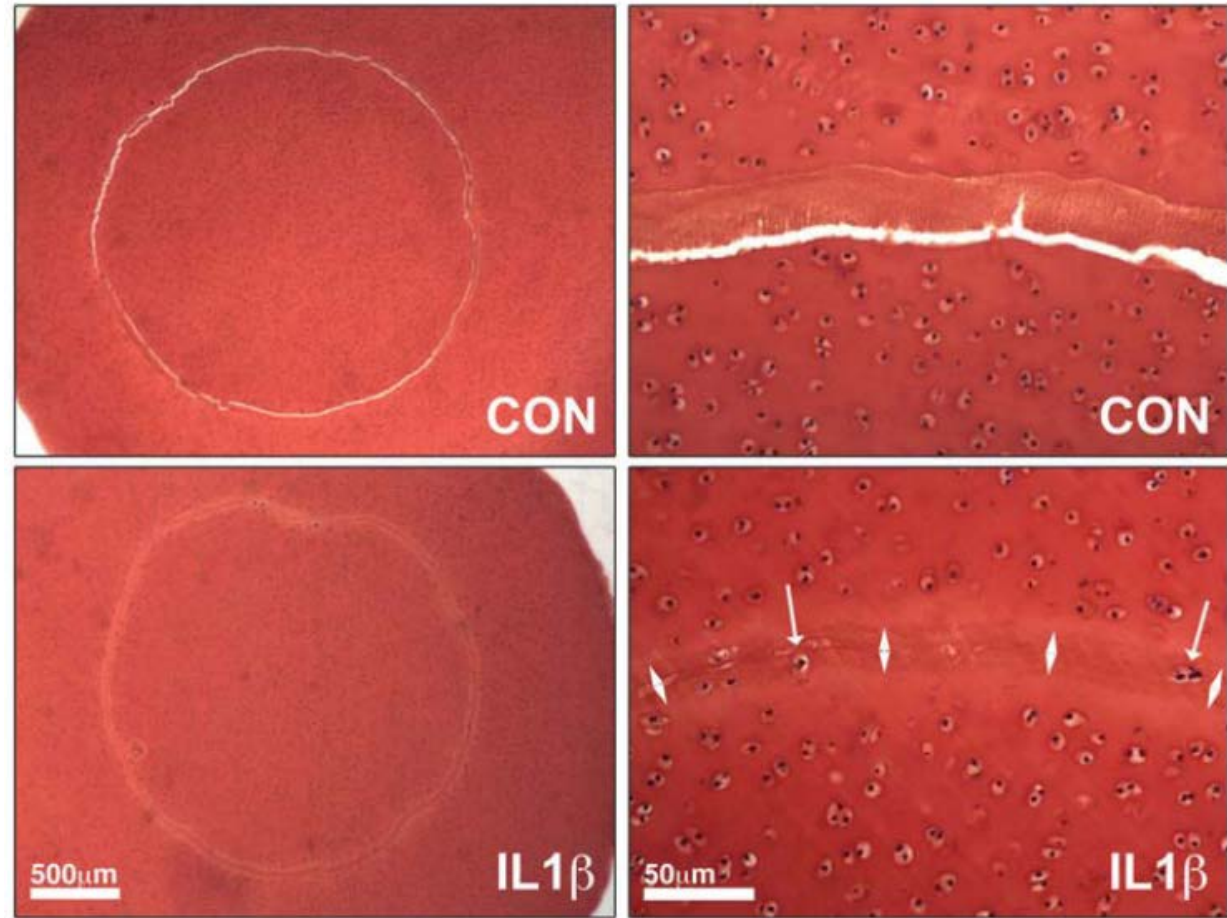
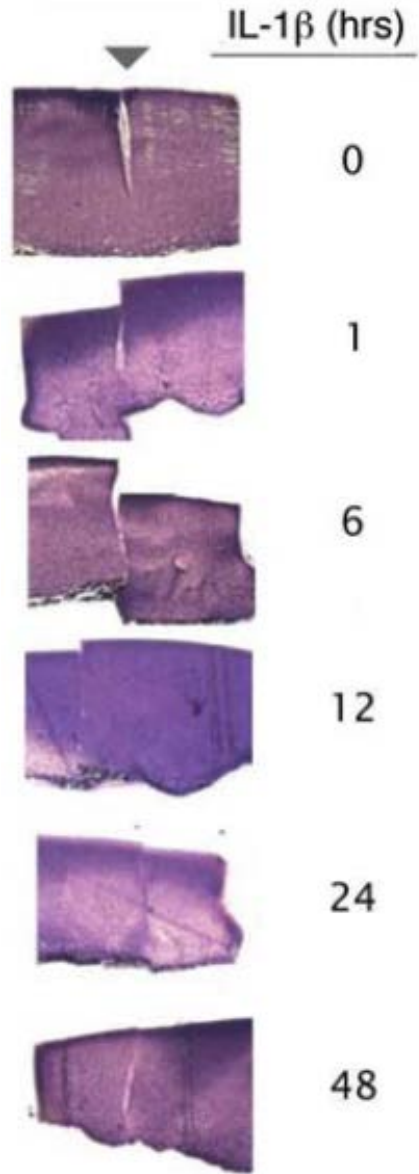
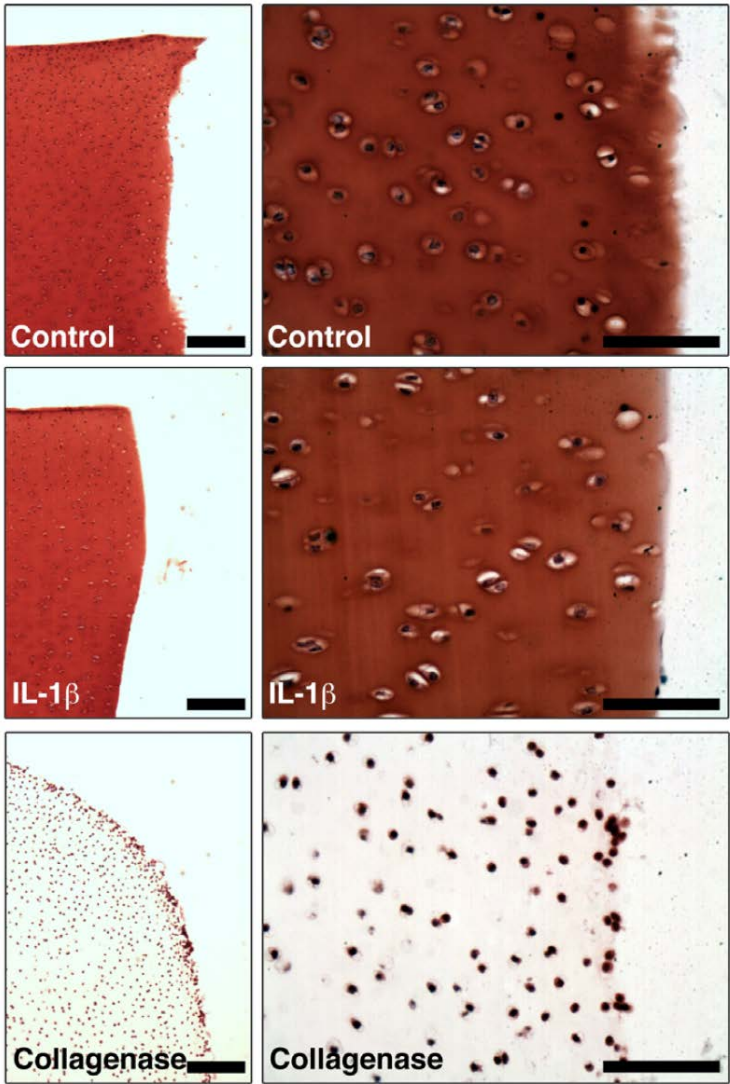
### **Strategy: IL-1 $\beta$ (well-characterized catabolic cytokine)**

- **Enzymatic removal of proteoglycan (trypsin, collagenase, chondroitinase...)**
- **Shifting metabolic state anabolism -> catabolism**
  - **Increased proteoglycan turnover & Disruption of collagen network**

### **IL-1 $\beta$**

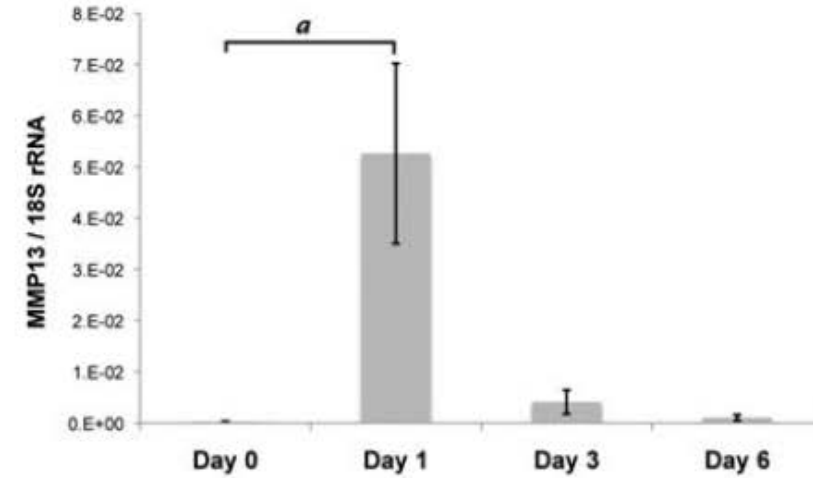
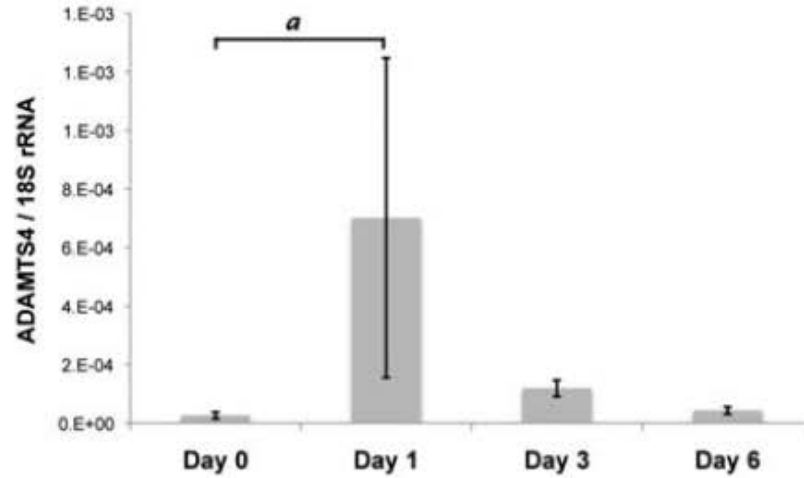
- **Expressed by activated synoviocytes, mono-nuclear cells, chondrocytes**
- **In an animal study, injected IL-1  $\beta$  induced inflammation, joint swelling, and degradation of collagen and PG**





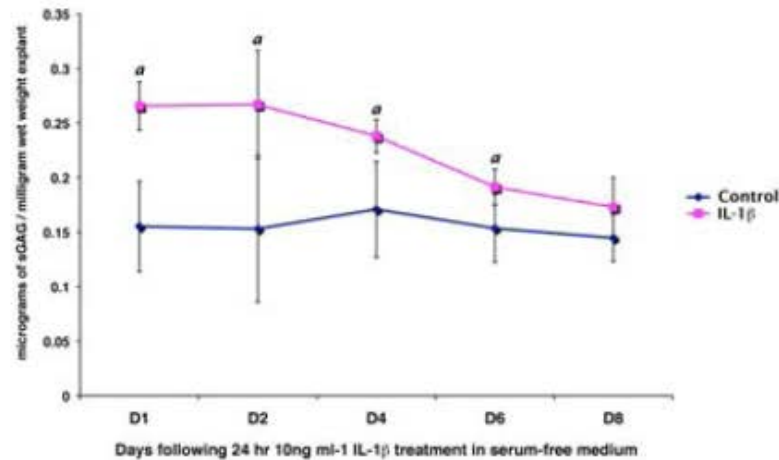
## ADAMTS4 & MMP13 : Catabolism-related genes (proteinases)

**a**

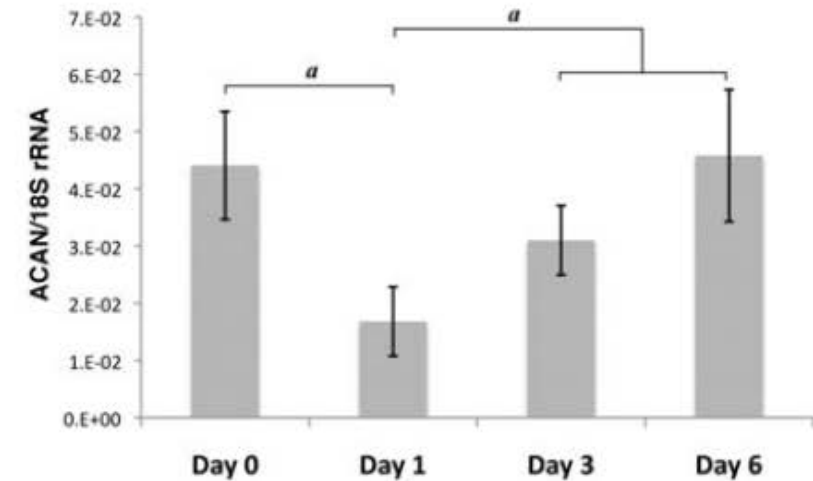


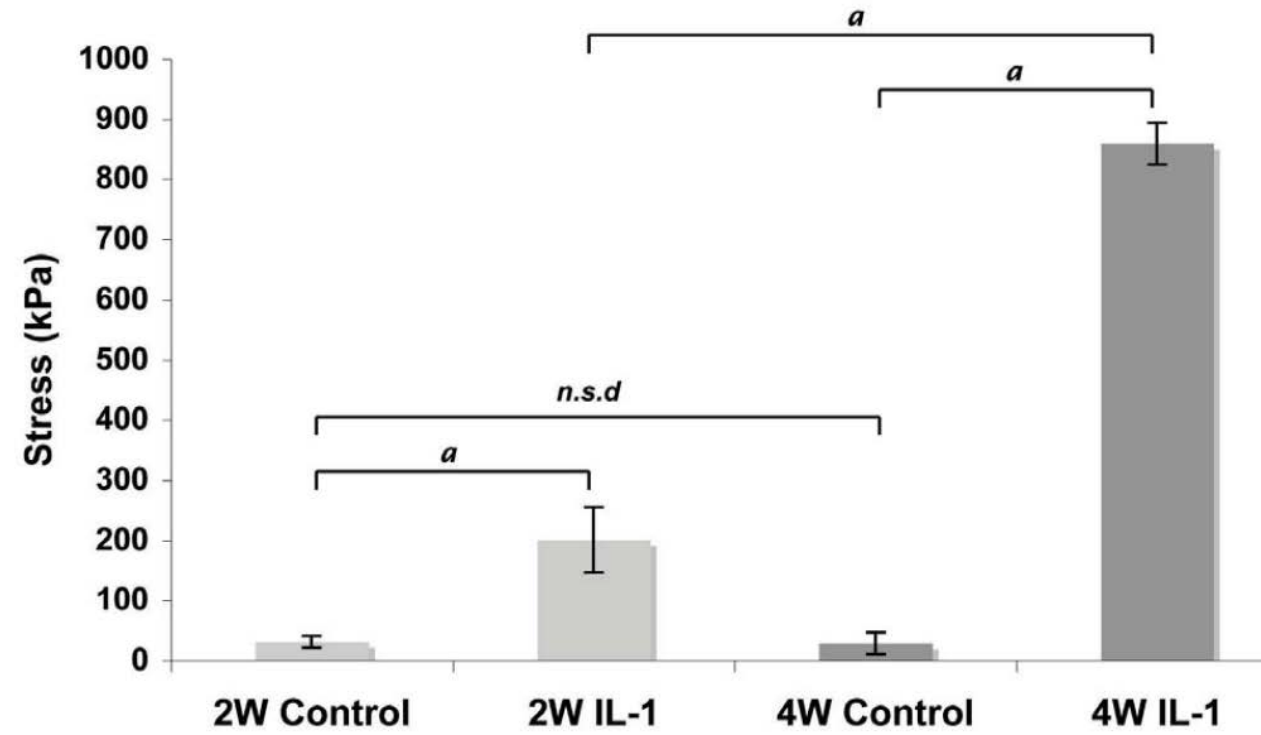
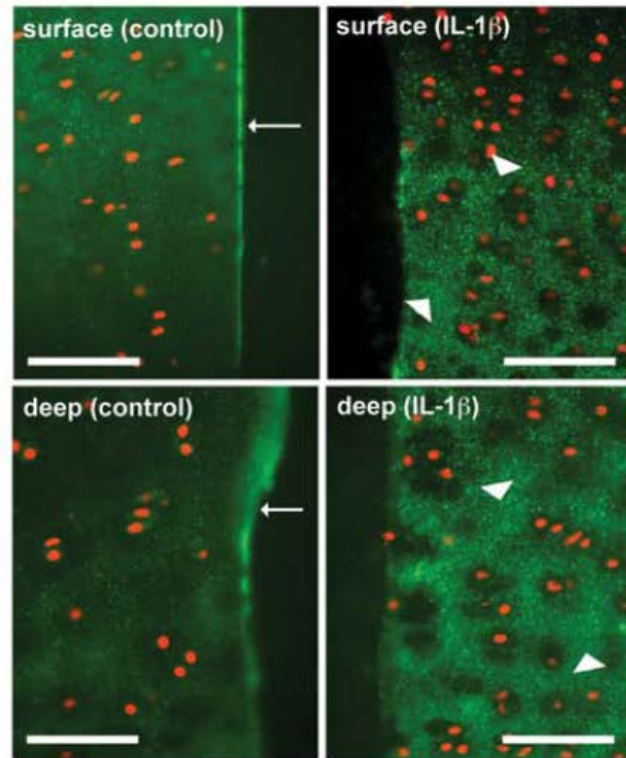
**b**

### Soluble GAGs in the media



### Aggrecan expression







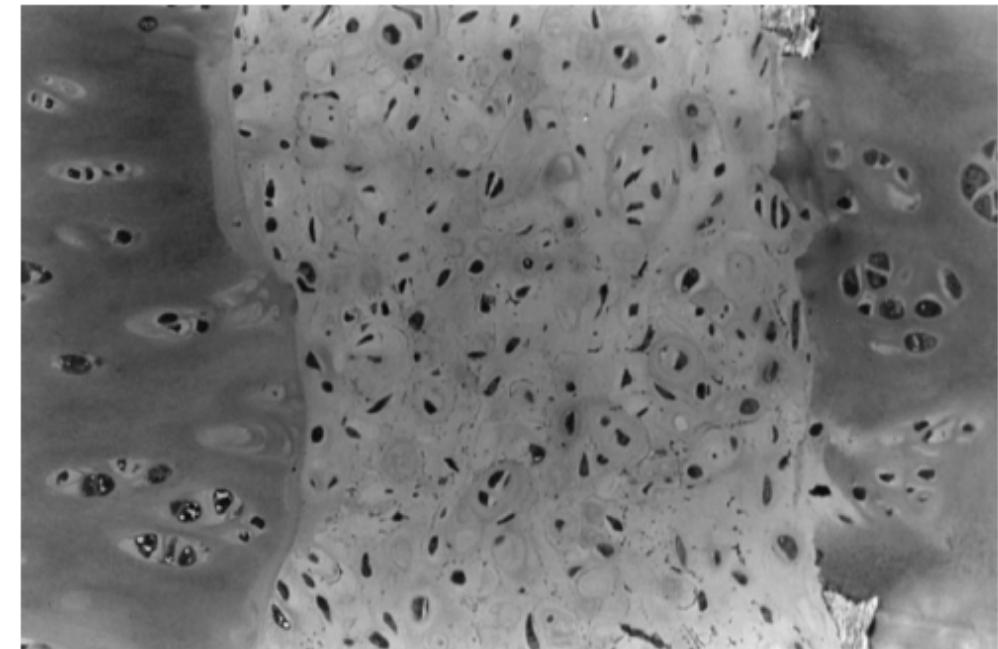
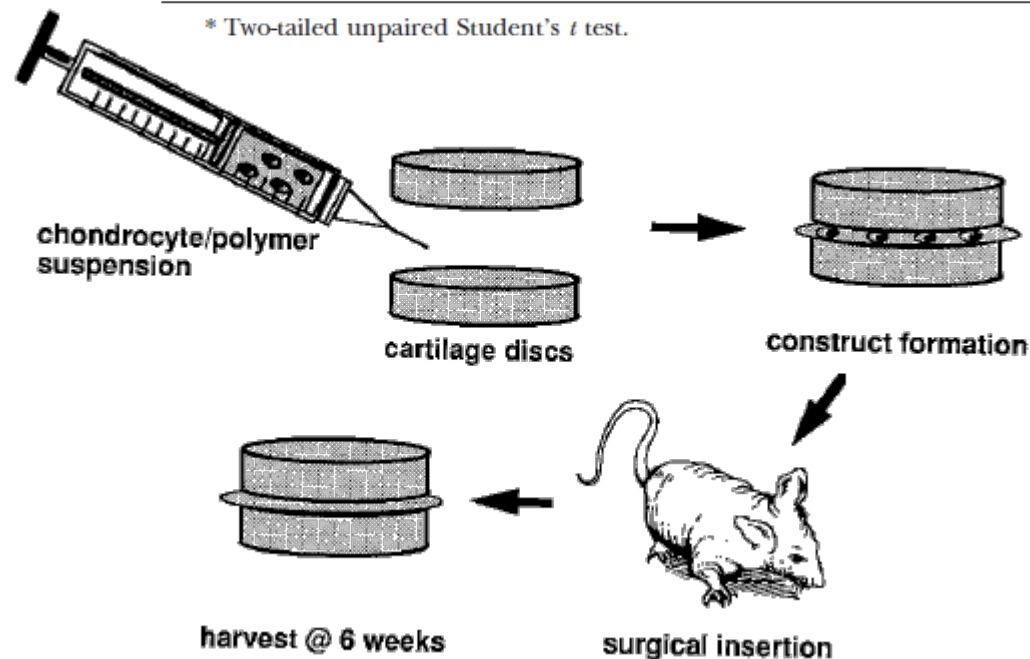
# Adhesion of Tissue-Engineered Cartilage to Native Cartilage

Silverman RP - 2000 Plast Reconstr Surg

Ronald P. Silverman, M.D., Lawrence Bonasser, Ph.D., David Passaretti, M.D.,  
Mark A. Randolph, M.A.S., and Michael J. Yaremchuk, M.D.

	Constructs with Neocartilage ( <i>n</i> = 10)	Controls ( <i>n</i> = 6)	<i>p</i> *
Modulus (MPa)	Mean $\pm$ SD 0.74 $\pm$ 0.22	Mean $\pm$ SD 0.21 $\pm$ 0.074	0.000108
Tensile strength (MPa)	0.065 $\pm$ 0.024	0.0099 $\pm$ 0.0097	0.000185
Failure strain (%)	0.17 $\pm$ 0.061	0.040 $\pm$ 0.026	0.000178
Fracture energy (J)	0.00049 $\pm$ 0.00032	3.1E-05 $\pm$ 5.4E-05	0.003584

\* Two-tailed unpaired Student's *t* test.

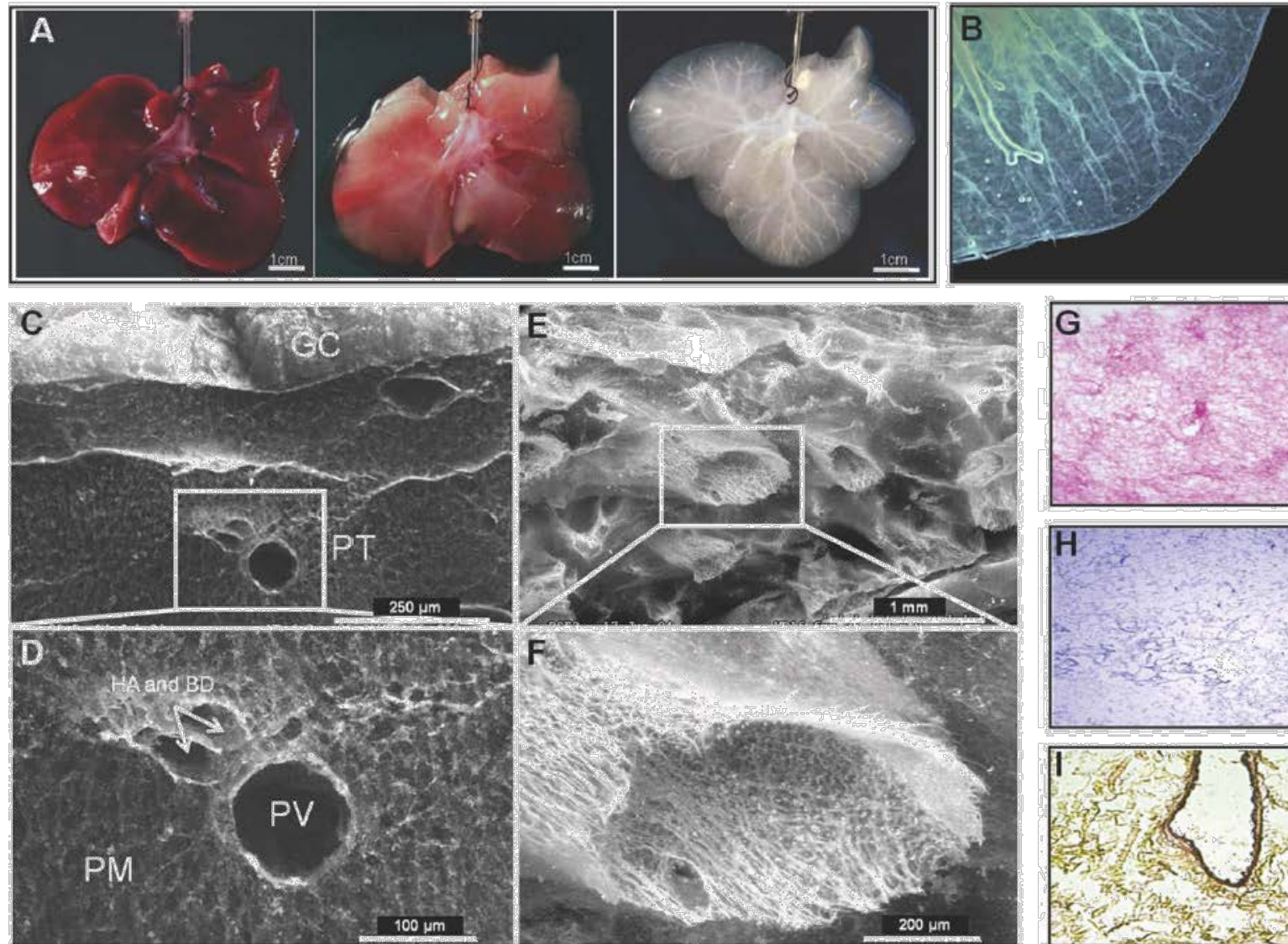


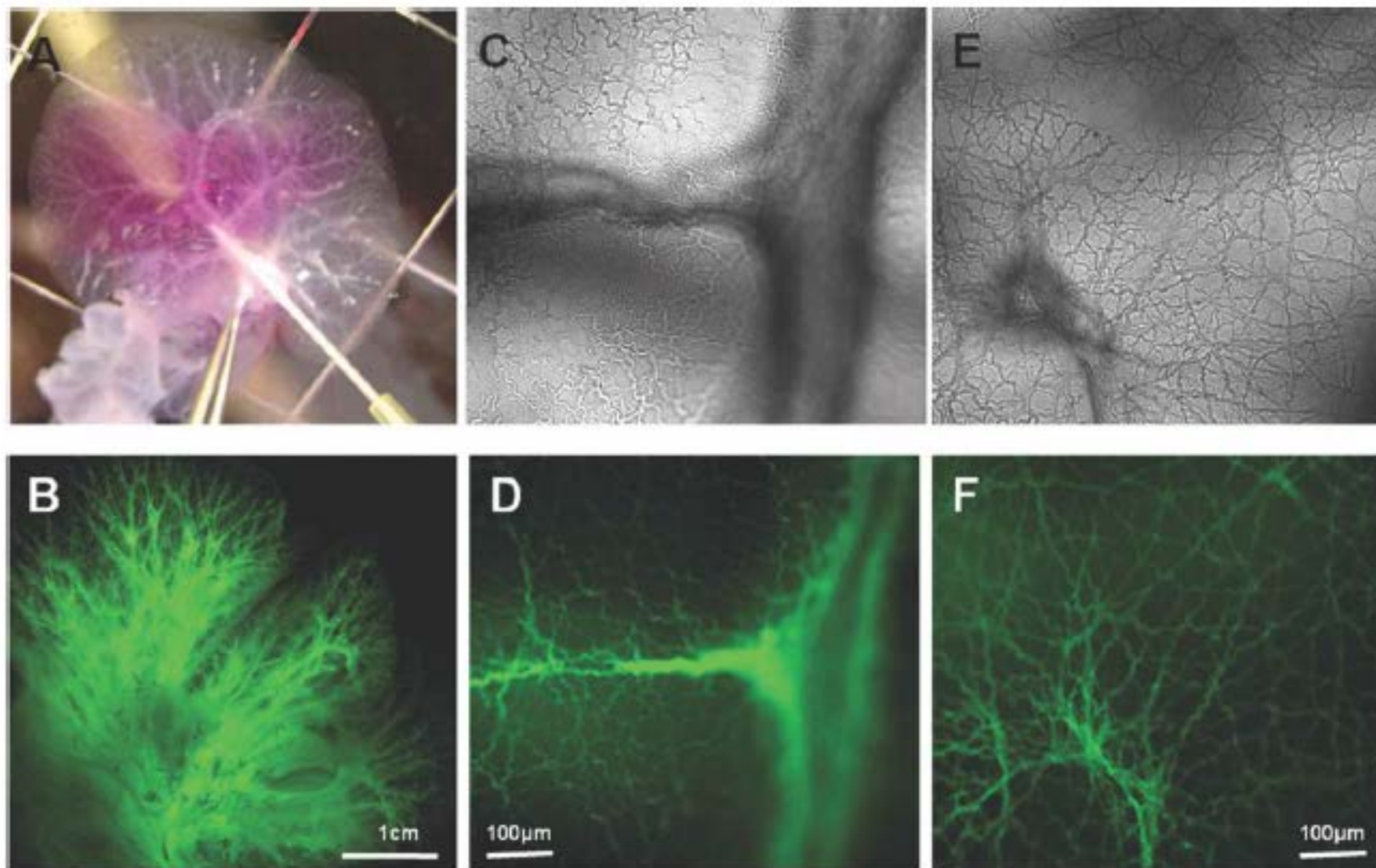
# Whole Organ Decellularization for Vascularized Liver Organoid

Baptista PM 2011 Hepatology



# Whole Organ Decellularization - Liver



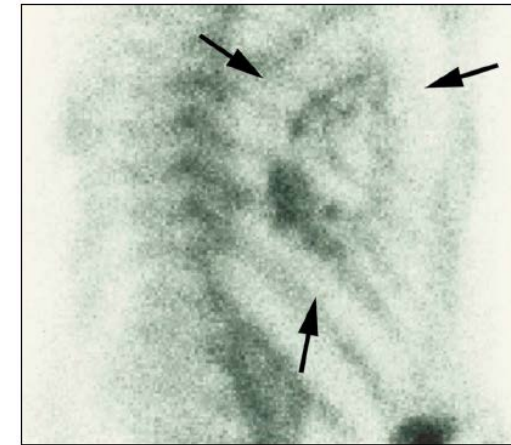
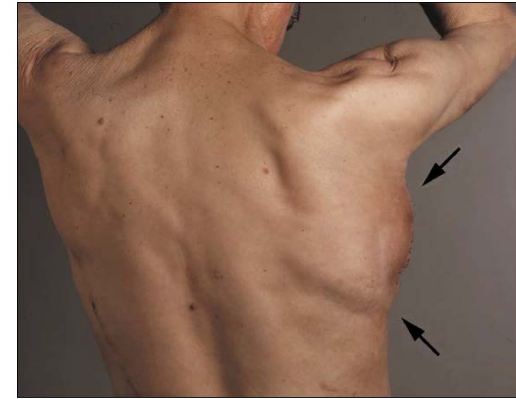
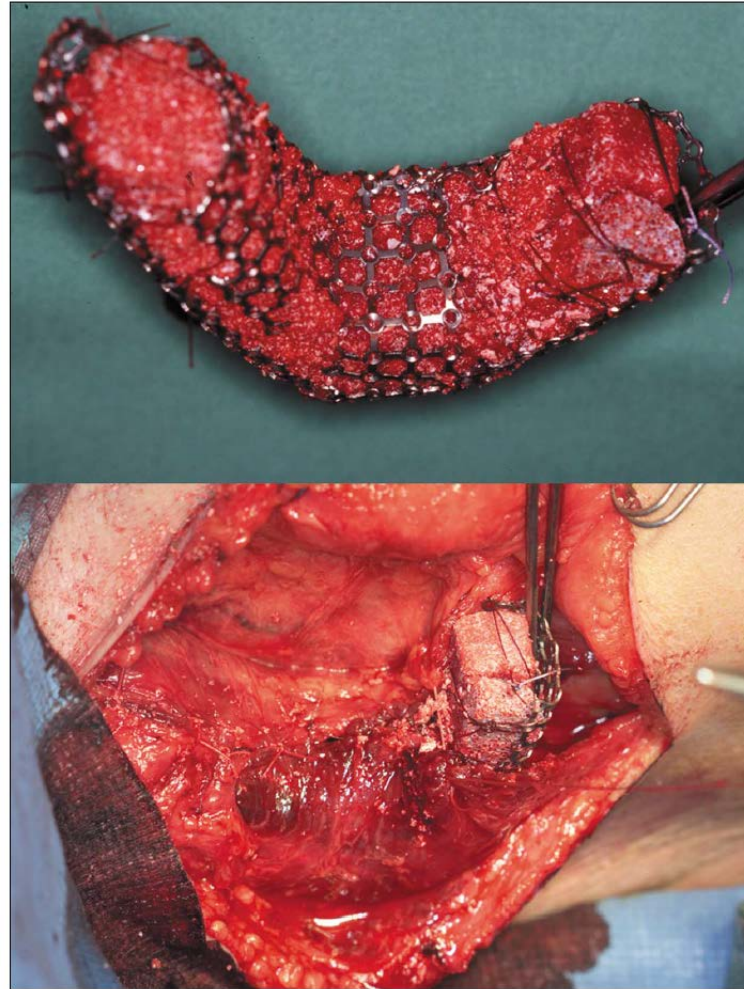
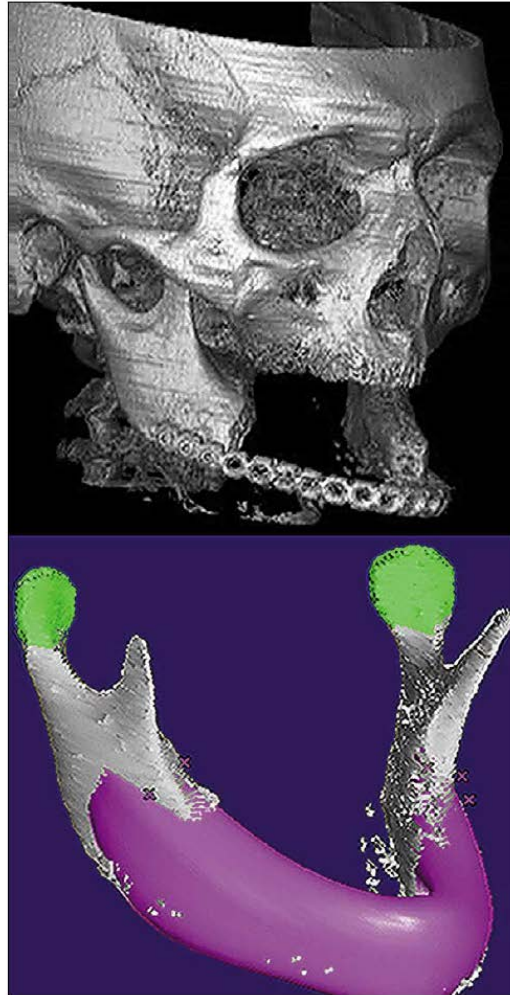


# Growth & Transplantation of Custom Vascularized Bone Graft

Warnke PH-2004 Lancet



# Custom Vascularized Bone Graft



Warnke PH-2004 Lancet



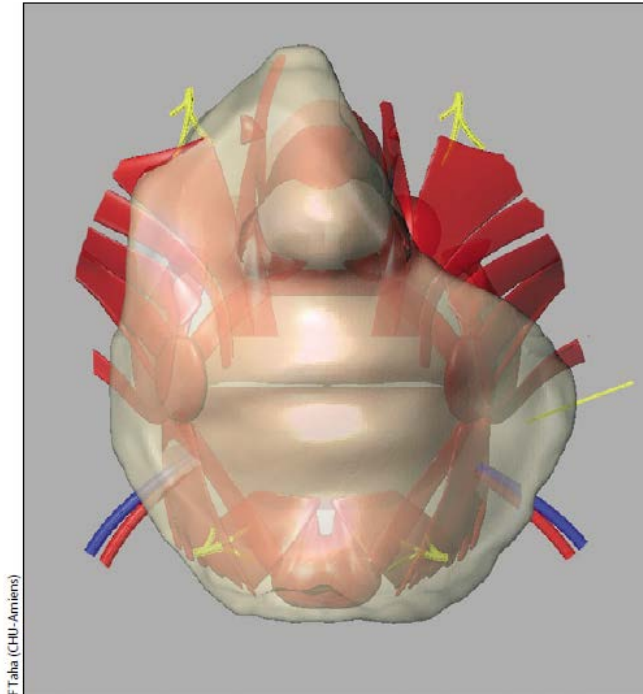
Warnke PH-2004 Lancet



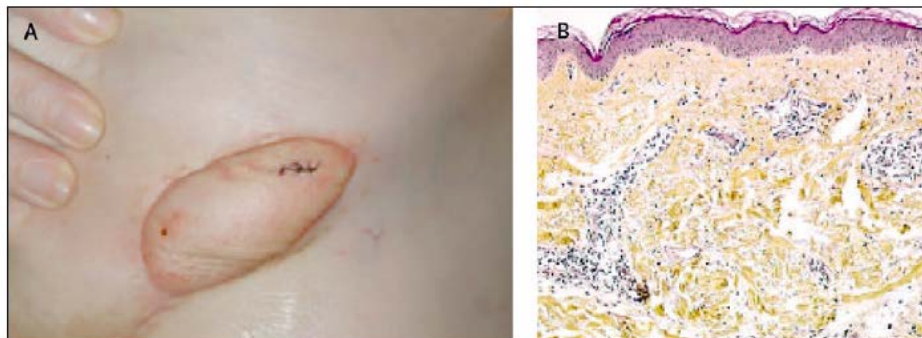
# First Human Face Allograft

Devauchelle B-2006 Lancet

# The First Human Face Allograft



FTaba (CHU-Amiens)



Devauchelle B-2006 Lancet

# Medication for Immune-suppressive Effect

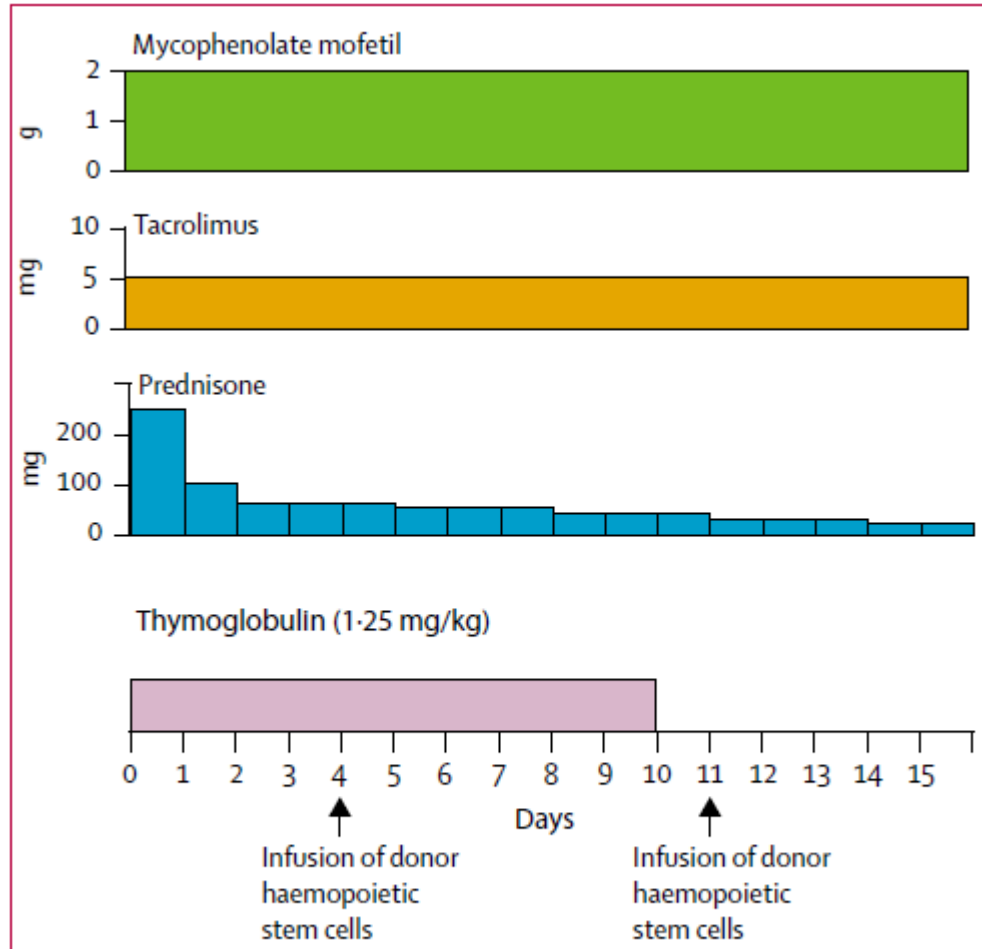


Figure 3: Immunosuppressive treatment during first 2 weeks after surgery, with two stem-cell infusions

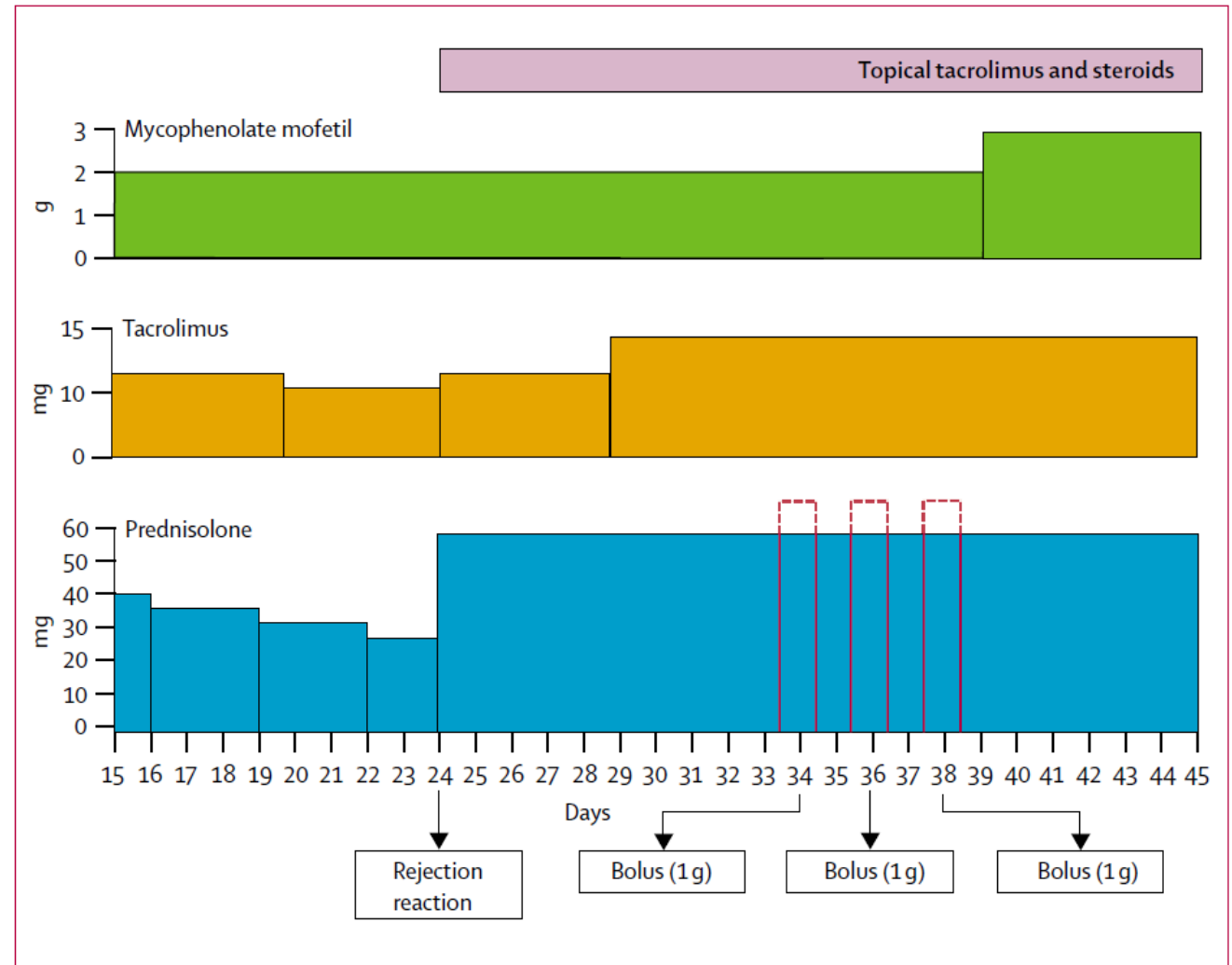


Figure 6: Immunosuppressive treatment between days 15 and 45

# 세계 첫 안면이식 프랑스 여성, 수술 11년 만에 암 으로 사망



2016.09.07 KBS NEWS

2005년 세계에서 처음으로 안면 이식 수술을 받은 프랑스 여성이 수술 11년 만인 지난 4월 사망한 것으로 뒤늦게 알려졌다.

프랑스 일간지 르 피가로는 6일(현지시간) 세계 최초로 안면 이식 수술을 받은 이자벨 디누아르가 지난 4월 22일 49세로 숨졌다고 밝혔다.

보도에 따르면, 디누아르는 지난해 이식 거부반응이 일어나 입술 일부를 이용할 수 없게 됐다. 또 수술 후 이식된 부분의 거부반응을 없애기 위해 복용한 약 때문에 몸 두 군데에서 암도 발병했다.

디누아르는 이식 거부반응을 없애기 위해 강한 면역 억제제 처방을 받아왔다. BBC 방송은 이 때문에 신체 면역력이 떨어져서 결국 암으로 목숨을 잃었다고 전했다.

디누아르의 이식 수술과 치료를 담당한 아미앵 병원도 디누아르의 사망 사실을 확인했지만, 병원 측은 가족의 사생활 보호를 위해 이를 발표하지 않은 것으로 알려졌다.

아미앵 병원은 디누아르가 오랜 투병 끝에 사망했다고 밝혔지만, 구체적인 사망 원인은 공개하지 않았다.

디누아르는 2005년 5월 개인적인 일을 잊고자 수면제를 먹고 잠들었다가 자신의 애완견에게 얼굴 아랫부분을 물어뜯겼다. 이 사고로 그녀의 코와 입술이 없어지고 잇몸과 아래턱이 모두 드러나는 상해를 당했다.

당시 아미앵 병원 의사들은 그녀의 상처가 너무 심해서 일반적인 얼굴 재건 수술이 아닌, 안면 이식 수술을 선택했다.

그녀는 그해 11월 뇌사 상태 환자의 얼굴을 떼어내 자신의 얼굴에 부분 이식하는 수술을 세계 최초로 받았다.

디누아르는 수술 3개월 후 TV 앞에서 서서 "수술로 나도 다른 사람처럼 얼굴을 갖게 됐다. 보통 생활을 할 수 있을 것"이라며 "거울을 볼 때 나와 안면 기증자가 섞인 모습이 보인다. 기증자는 언제나 나와 함께 있다"고 말했다.

그녀의 수술 이후 미국, 스페인, 터키, 중국, 폴란드 등에서 총 30여 건의 안면 이식 수술이 시행됐다.

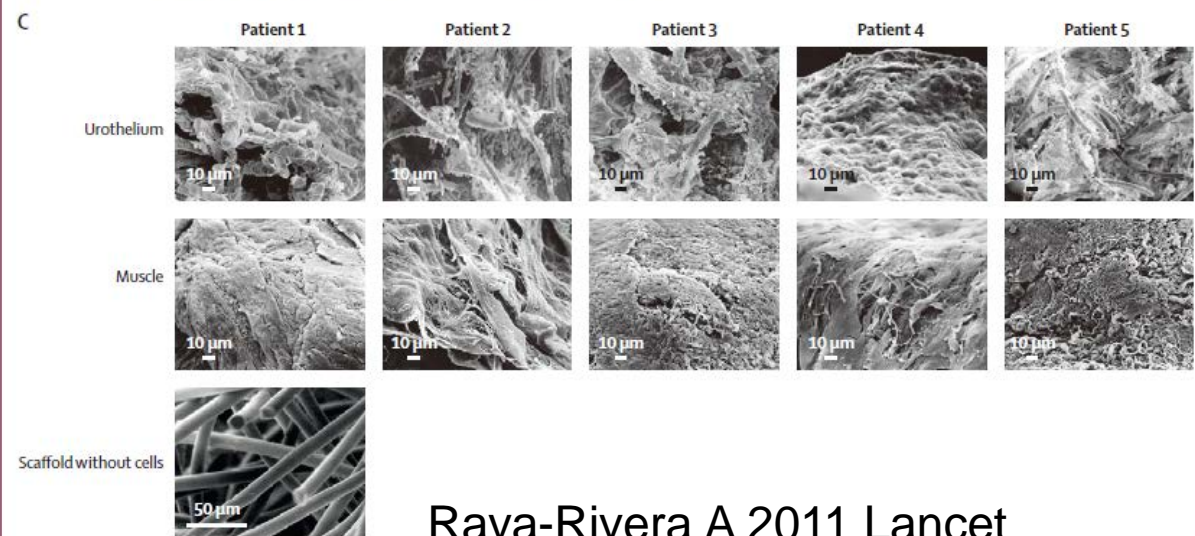
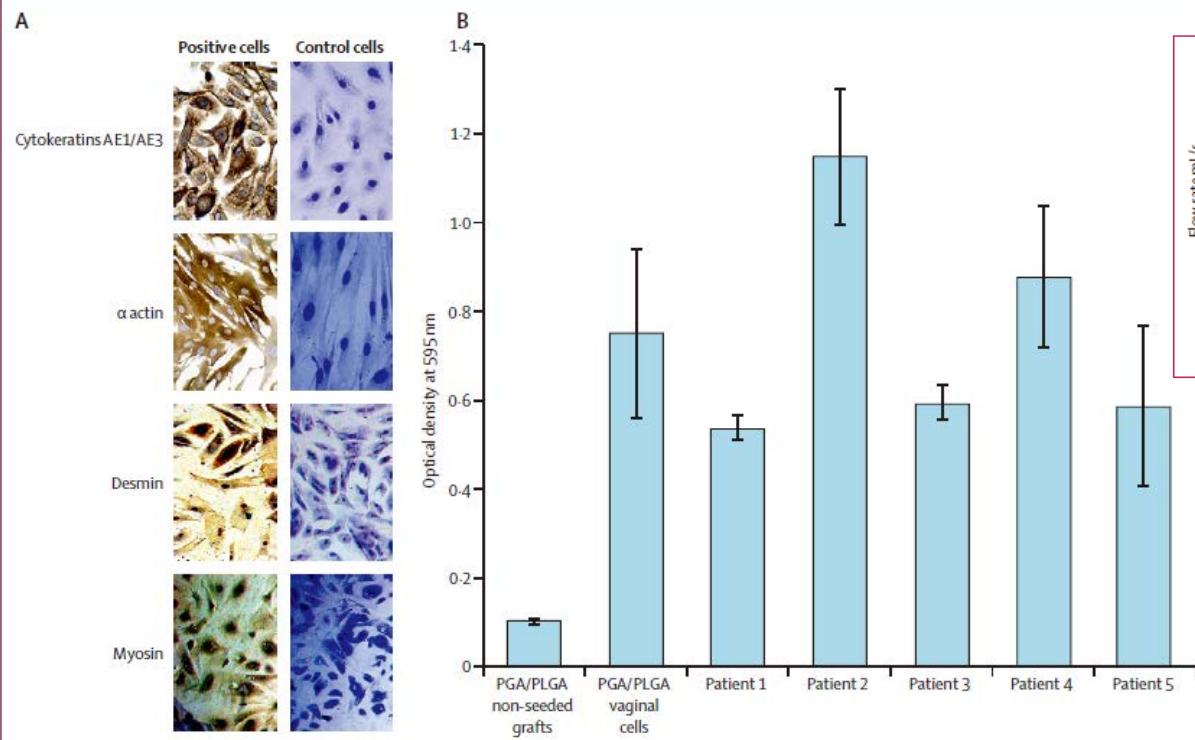
# Tissue Engineered Autologous Urethra & Bladder for Cystoplasty

Raya-Rivera A 2011 Lancet

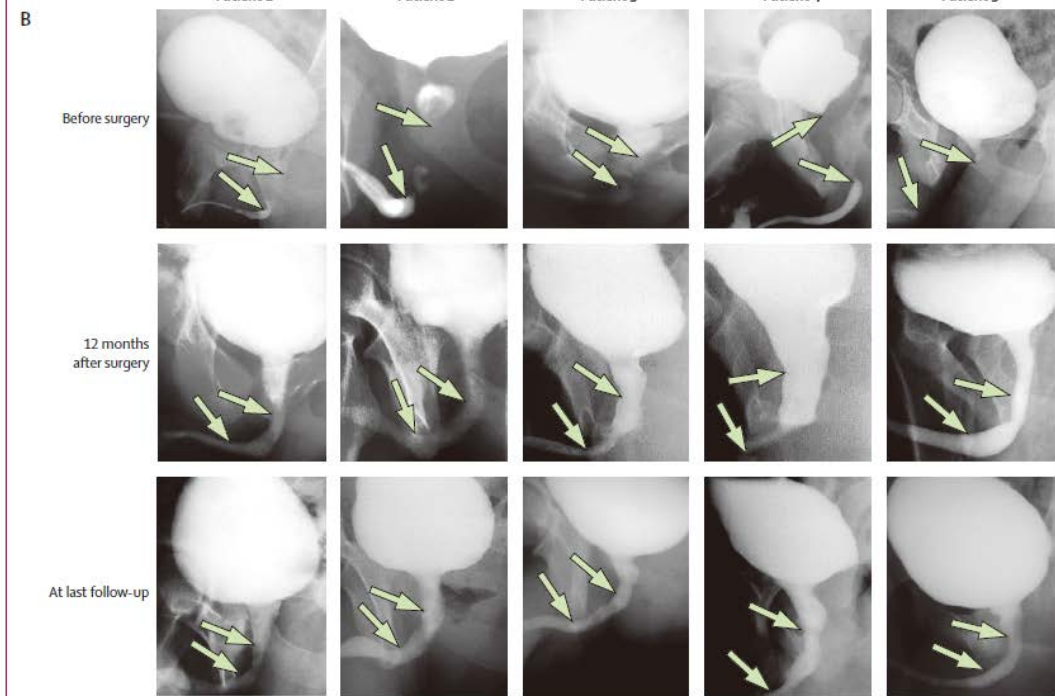
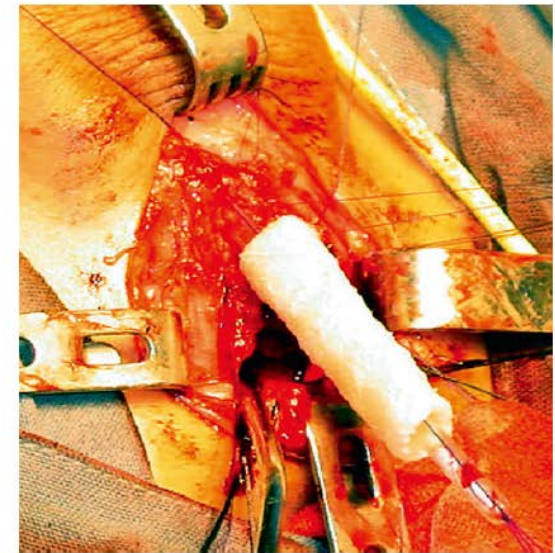
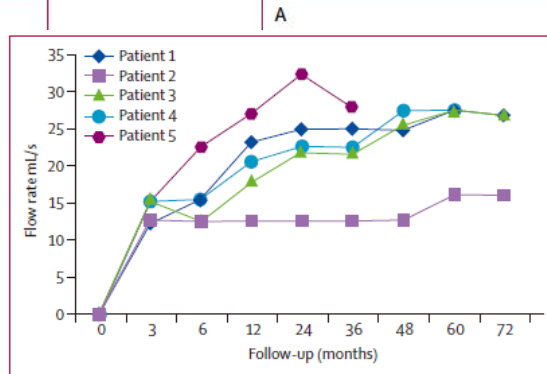
Atala A 2006 Lancet

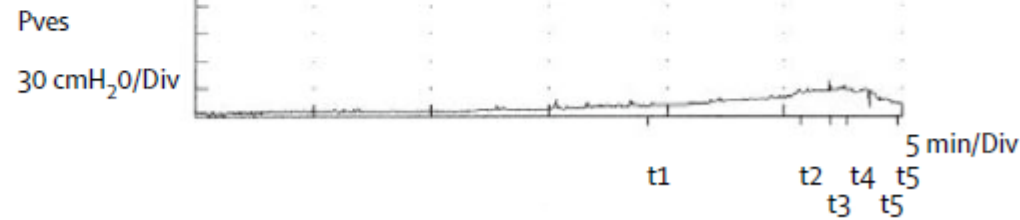
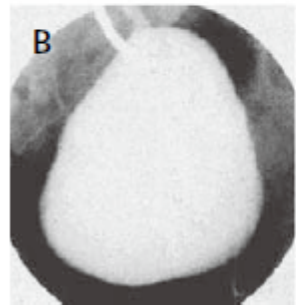
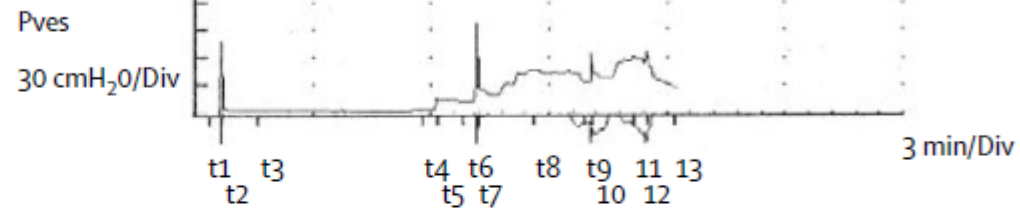
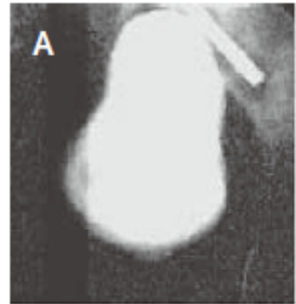
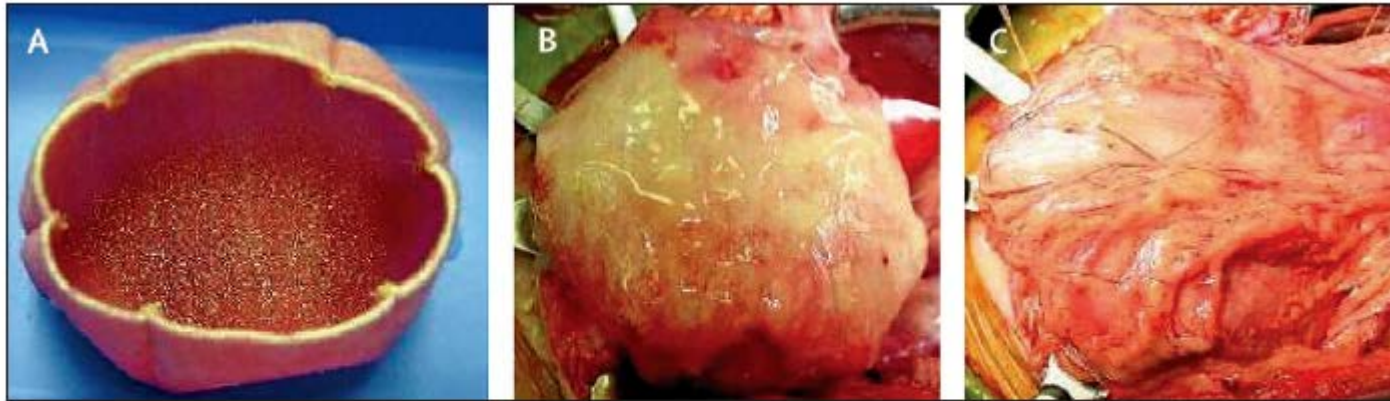
TED Lecture by Anthony Atala (2009)





Raya-Rivera A 2011 Lancet





	Patient (implant type)						
	1 (C)	2 (C)	3 (C)	4 (C+O)	5 (PC+O)	6 (PC+O)	7 (PC+O)
<b>Preoperative</b>							
Capacity (mL)	187	335	50	438	201	139	100
Leak point pressure (cm H <sub>2</sub> O)	55	45	38	42	51	67	82
Compliance (cm H <sub>2</sub> O/mL)	3.4	7.4	1.3	10.4	3.9	2.1	1.2
<b>3-12 months postoperative</b>							
Capacity (mL)	128	..	90	700	245	190	150
Leak point pressure (cm H <sub>2</sub> O)	45	..	35	30	30	45	40
Compliance (cm H <sub>2</sub> O/mL)	2.8	..	2.6	23.3	8.2	4.2	3.8
<b>13-24 months postoperative</b>							
Capacity (mL)	128	366	60	..	..	180	130
Leak point pressure (cm H <sub>2</sub> O)	48	18	54	..	..	44	40
Compliance (cm H <sub>2</sub> O/mL)	2.7	20.3	1.1	..	..	4.1	3.3
<b>25-36 months postoperative</b>							
Capacity (mL)	162	..	..	456	250	..	150
Leak point pressure (cm H <sub>2</sub> O)	45	..	..	42	25	..	43
Compliance (cm H <sub>2</sub> O/mL)	3.6	..	..	10.9	10	..	3.5
<b>37-48 months postoperative</b>							
Capacity (mL)	..	..	63	..	..	..	..
Leak point pressure (cm H <sub>2</sub> O)	..	..	36	..	..	..	..
Compliance (cm H <sub>2</sub> O/mL)	..	..	1.8	..	..	..	..
<b>49-61 months postoperative</b>							
Capacity (mL)	..	..	78	450	309	480	..
Leak point pressure (cm H <sub>2</sub> O)	..	..	45	18	24	47	..
Compliance (cm H <sub>2</sub> O/mL)	..	..	1.7	18	13	10.2	..

C=collagen. C+O=collagen plus omental wrap. PC+O=composite collagen-PGA plus omental wrap.

**Table: Preoperative and postoperative urodynamic findings**

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# EOD