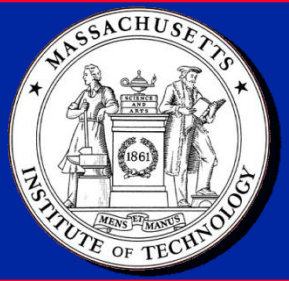
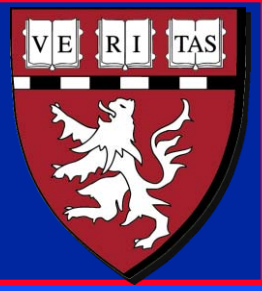


Massachusetts Institute of Technology
Harvard Medical School
Brigham and Women's Hospital
VA Boston Healthcare System



2.79J/3.96J/20.441/HST522J

REGENERATION OF JOINT TISSUES
Cartilage

M. Spector, Ph.D.

Knee Joint

Bone

Art. Cart.

Medical illustration removed due to copyright restrictions.

Meniscus **Ligament**

Bone

Total Knee Replacement Prosthesis

Co-Cr Alloy

Bone

Implant photo removed due to copyright restrictions.

Polyethylene

Bone

INTRAARTICULAR JOINT TISSUES

- What are the unique characteristics of the joint environment?
- Why don’t these tissues heal?
- How are such diverse functions met by only one structural protein - collagen?

INTRAARTICULAR ENVIRONMENT

- Synovial fluid
- High mechanical loads
- Low vascularity

JOINT TISSUES

Limitations to Healing

- Absence of a fibrin clot
  - Absent or low vascularity
  - Dissolution of clot in synovial fluid
- Cell migration restricted by matrix
- Low cell density
- Low mitotic activity
- Mechanical loading disrupts reparative tissue

TISSUES COMPRISING JOINTS

	Permanent Prosthesis	Regeneration Scaffold
Bone	Yes	Yes
Articular cartilage	No	Yes*
Meniscus	No	Yes*
Ligaments	No	Yes*
Synovium	No	No

* In the process of being developed

JOINT TISSUES

	Loading	Tissue Type	Cell Type	Round/ Lac.	Coll.	PG	Vasc.	
Art. Cart.	Comp.	Hyal. Cart.	Chond.	Yes	II	+++	0	0
Meniscus	C/T	Fibro-Cart.	Fibro-Chond.	Yes	I	0/+	0*	0
ACL	Tens.	Fibrous Tissue	Fibro-blast	No	I	0	0**	0

* Inner third
** Mid-substance

Several slides on structure of cartilage removed due to copyright restrictions. (Medical illustrations.)

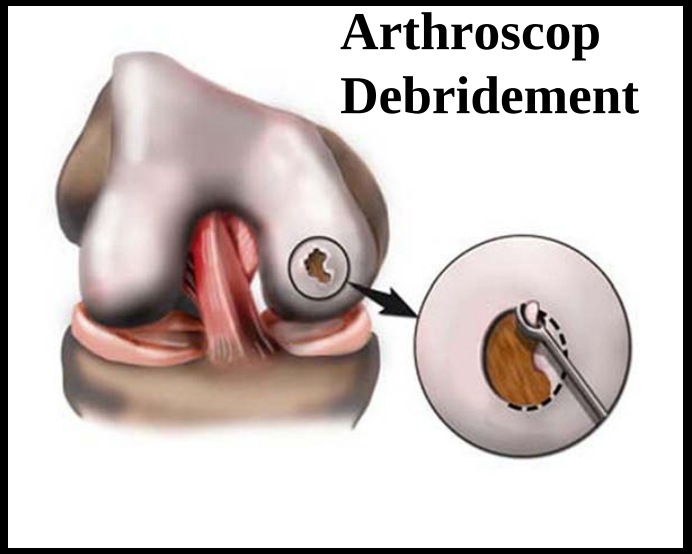


Figure by MIT OpenCourseWare.

"Micro-fracture"

Osteochondral Plug Autograft ("Mosaicplasty")

30 years

Current Clinical Practice

Autologous chondrocytes injected under a periosteal flap (Genzyme; "Carticel")

R

Future Clinical Practice
Implementing Tissue Engineering

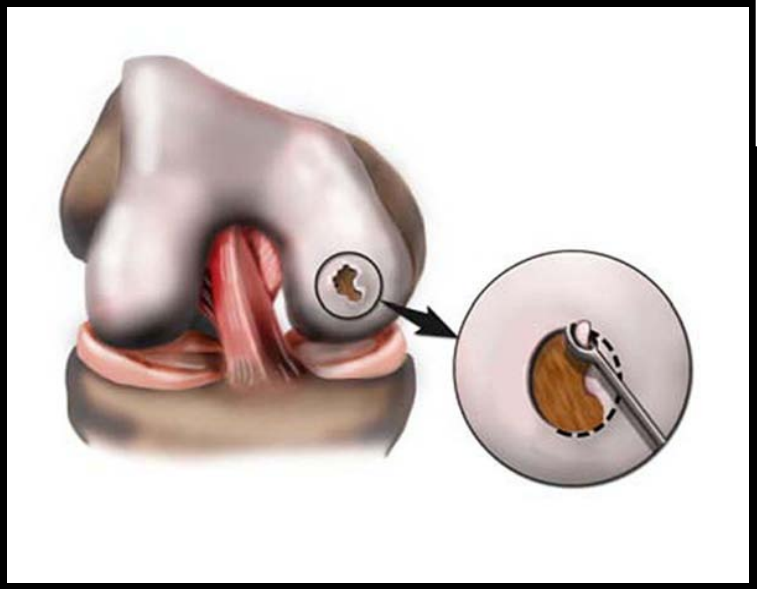
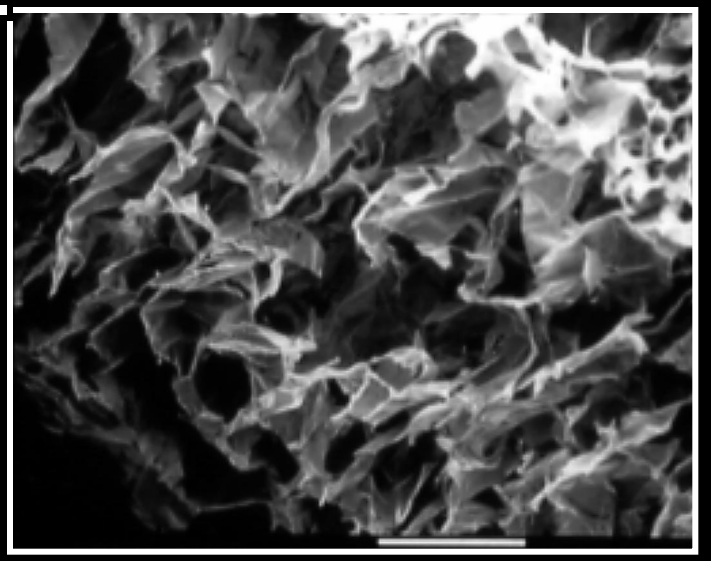


Figure by MIT OpenCourseWare.

Microfra

Implantation of a cell-seeded matrix



Implantation of the matrix alone, or supplemented with growth factors or genes for the GFs

Stem cells from bone marrow infiltrate the defect

TISSUE ENGINEERING

Cells

- Autologous, allogeneic, or xenogeneic
- Differentiated cell of the same tissue type or another tissue type, or stem cell

Autologous Chondrocyte Implantation

Image removed due to copyright restrictions.
Figure 1 in Brittberg, M., et al. "Treatment of Deep Cartilage Defects in the Knee with Autologous Chondrocyte Transplantation." *NEJM* 331, no. 14 (1994): 889-895.
http://content.nejm.org/cgi/content/abstract/331/14/889

This process has been commercialized by Genzyme (for ~$20,000).

M Brittberg, *et al.*, NEJM 33:889 (1994)

Collagen membrane to replace a periosteal tissue graft to contain injected autologous chondrocytes (grown in culture)

Image and embedded video removed due to copyright restrictions.

Autologous Chondrocyte Implantation

Image removed due to copyright restrictions.
Figure 4 in Brittberg, M., et al. "Treatment of Deep Cartilage Defects in the Knee with Autologous Chondrocyte Transplantation." *NEJM* 331, no. 14 (1994): 889-895.
http://content.nejm.org/cgi/content/abstract/331/14/889

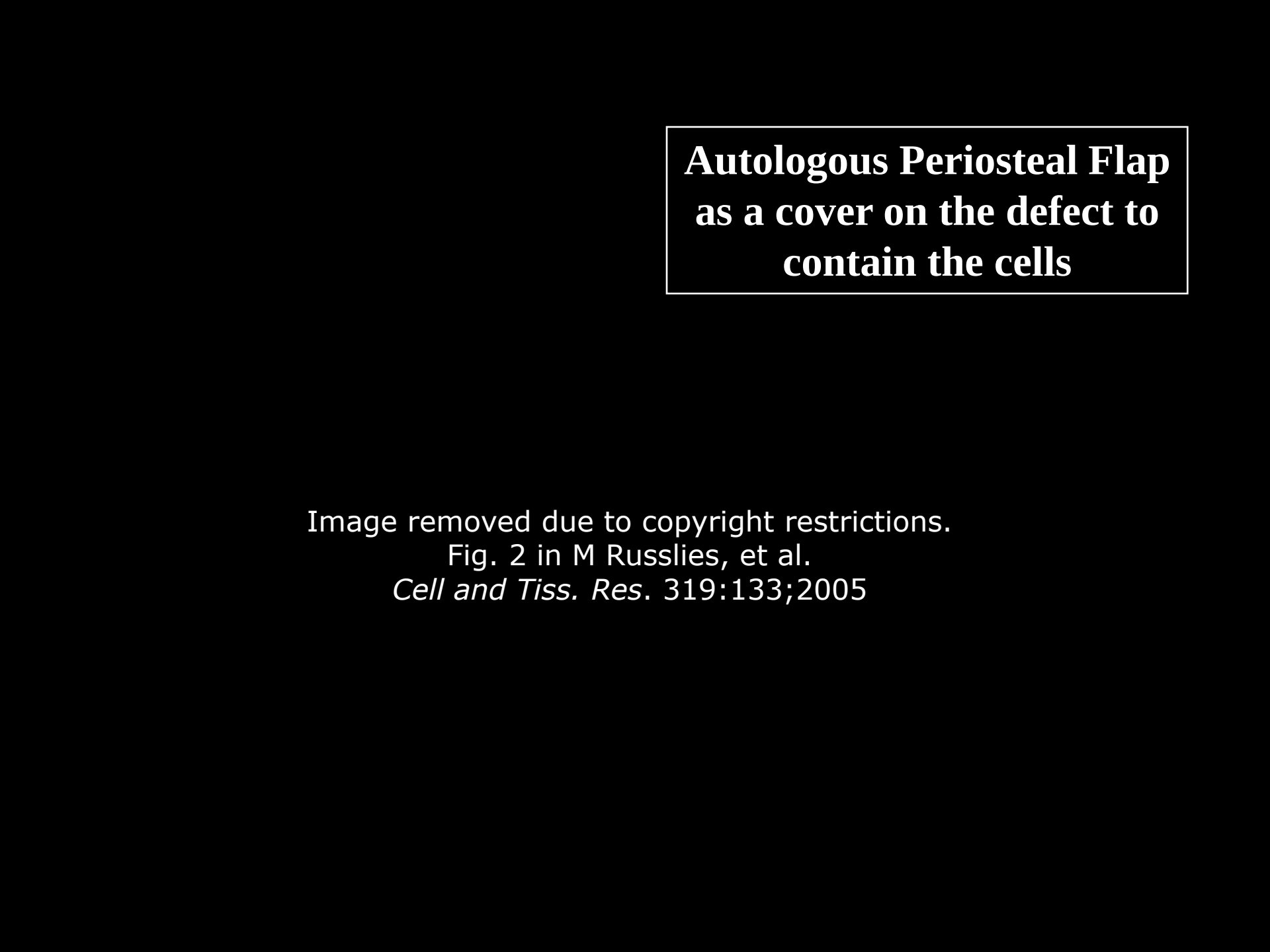
M Brittberg, *et al*., NEJM 33:889 (1994)

ROLES OF BIOMATERIALS IN TISSUE REGENERATION

Membranes

- Prevent the collapse and infiltration of surrounding tissue into the defect.
- Contain cells in a defect.
- Serve as a carrier for cells.

Autologous Periosteal Flap as a cover on the defect to contain the cells

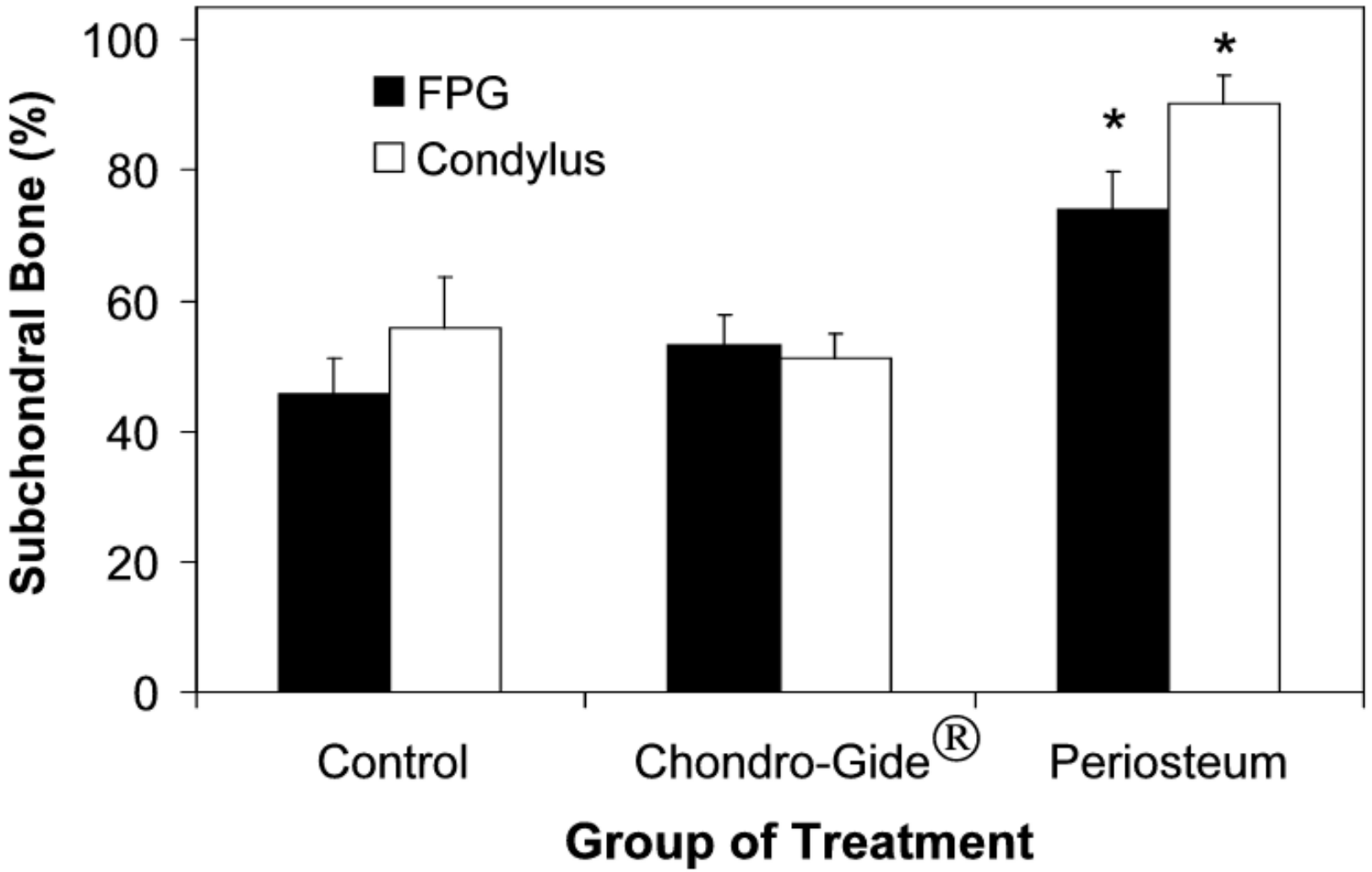


PERIOSTEUM STIMULATES SUBCHONDRAL BONE DENSIFICATION IN AUTOLOGOUS CHONDROCYTE TRANSPLANTATION IN SHEEP

Images removed due to copyright restrictions.
Fig. 3-Fig. 5 in M Russlies, et al.
Cell and Tiss. Res. 319:133;2005

Results also showed no difference in the make-up of the cartilaginous reparative.

M Russlies, *et al*., Cell and Tiss. Res. 319:133;2005



M Russlies, *et al.*, Cell and Tiss. Res. 319:133;2005

ROLES OF BIOMATERIALS IN TISSUE REGENERATION

Membranes

- Prevent the collapse and infiltration of surrounding tissue into the defect.
- Contain cells in a defect.
- Serve as a carrier for cells.

MATRIX-INDUCED AUTOLOGOUS CHONDROCYTE IMPLANTATION

MACI

The defect area is covered with tissue-engineered collagen membrane which is pre-loaded with autologous chondrocytes.

Future Clinical Practice
Implementing Tissue Engineering

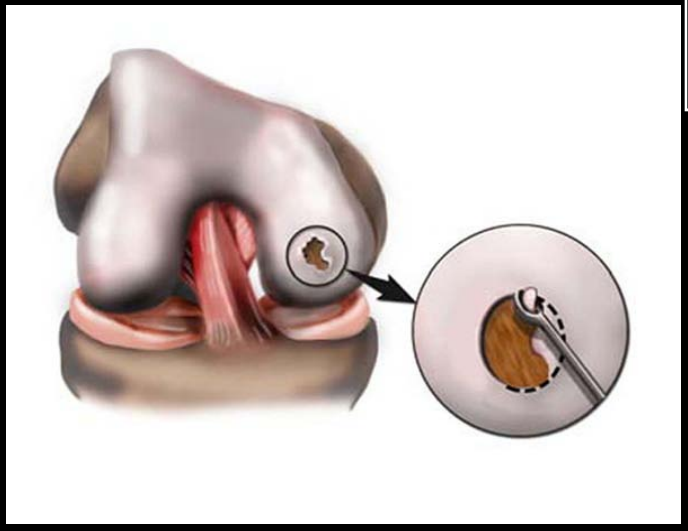
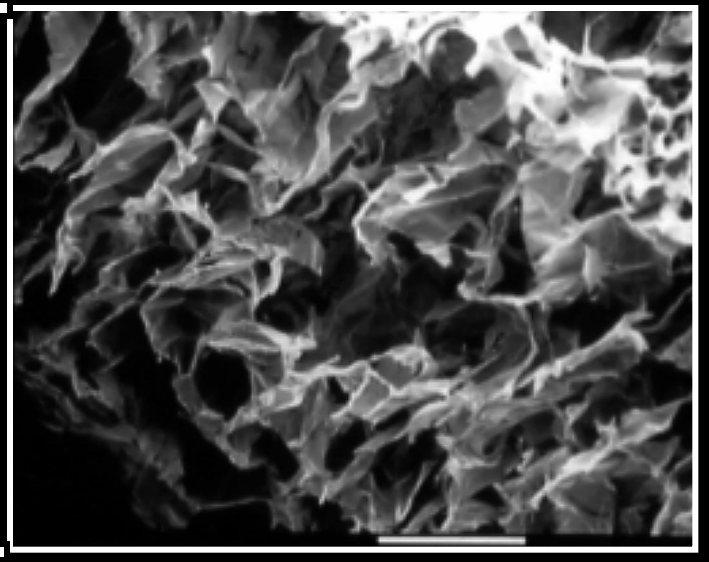


Figure by MIT OpenCourseWare.

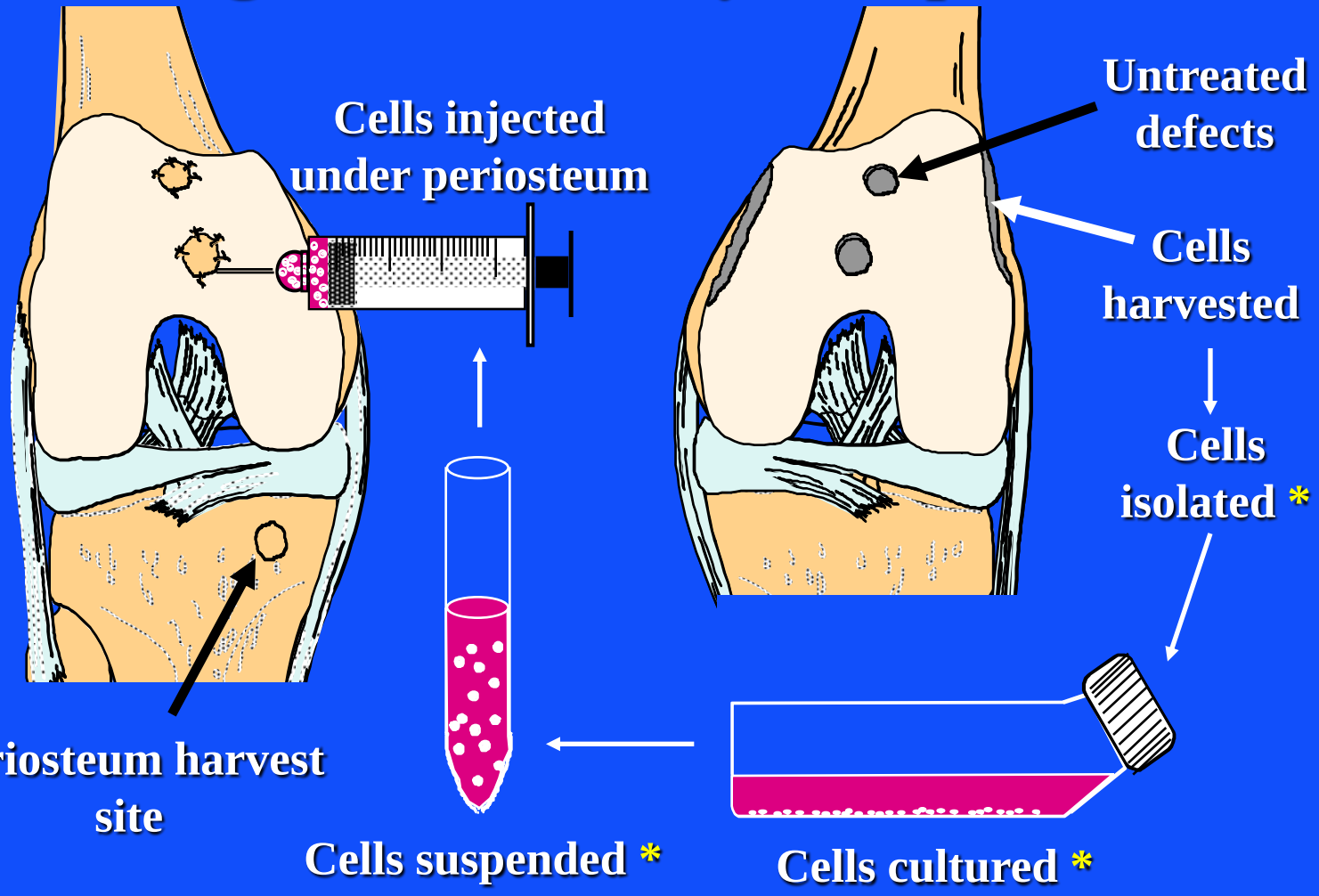
Implantation of a cell-seeded matrix



"Microfracture": Stem cells from bone marrow infiltrate the defect

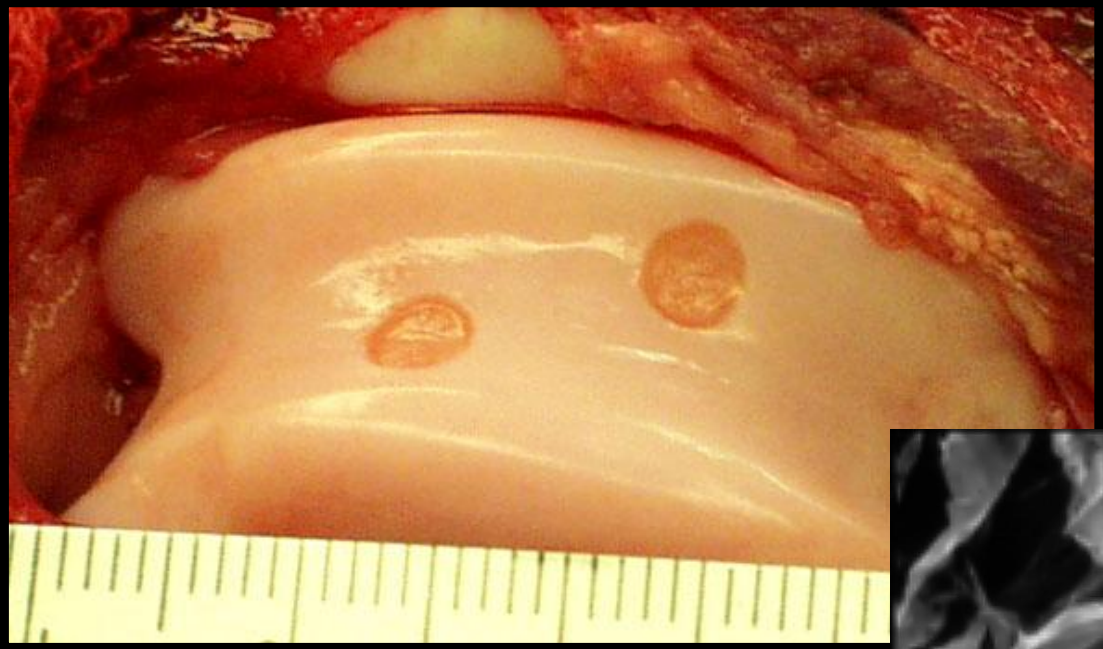
Implantation of the matrix alone, (or supplemented with growth factors or genes for the GFs)

Canine Study
Autologous Chondrocyte Implantation

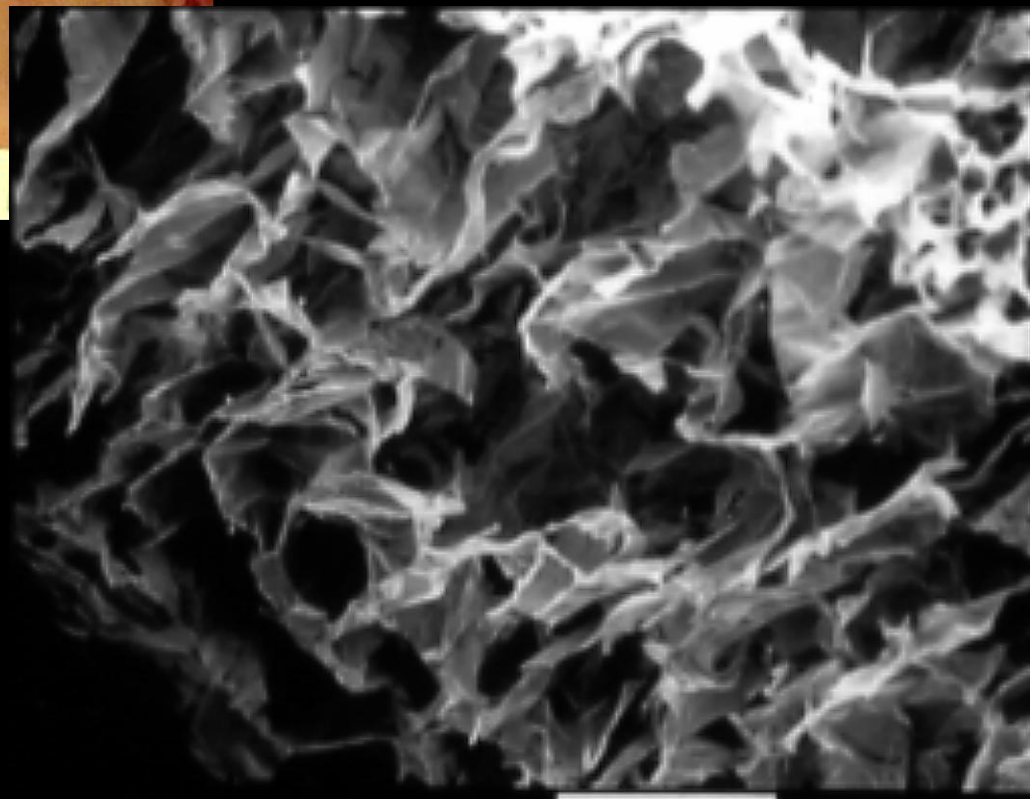


* by Genzyme Biosurgery

CELL-SEEDED COLLAGEN MATRICES



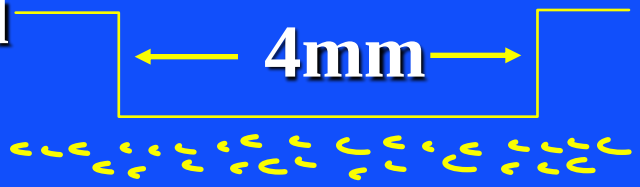
- **Chondral defects (to the tidemark)**



- **Type II (porcine) collagen scaffold**
- **Seeded with cultured autologous chondrocytes (CAC)**

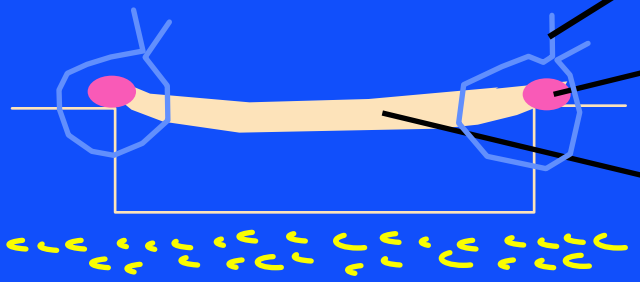
CANINE ACI STUDY
TREATMENT GROUPS

Empty Control
EC



Suture

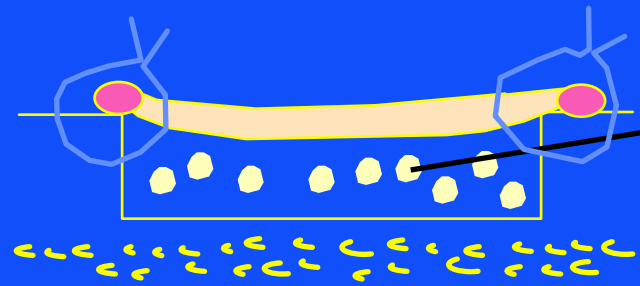
Periosteum
Alone
P



Fibrin Glue

Periosteum

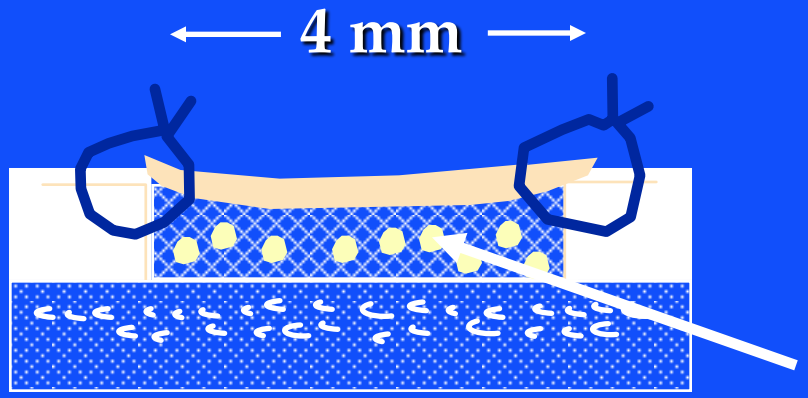
Cultured
Autologous
Chondrocytes
CAC



Autologous
Chondrocytes

H Breinan, et al, J. Bone Jt Surg 79-A:1439;1997

AUTOLOGOUS CHONDROCYTE-SEEDED COLLAGEN MATRIX



Chondrocyte-seeded type II collagen implant*

*** Cells seeded into the matrix 24 hours* and 4 weeks prior to implantation**

*** HA Breinan, *et al.* J . Orthop. Res. 2000;18:781-789 and C.R. Lee, *et al.* J. Orthop. Res. 2003;21:272-281**

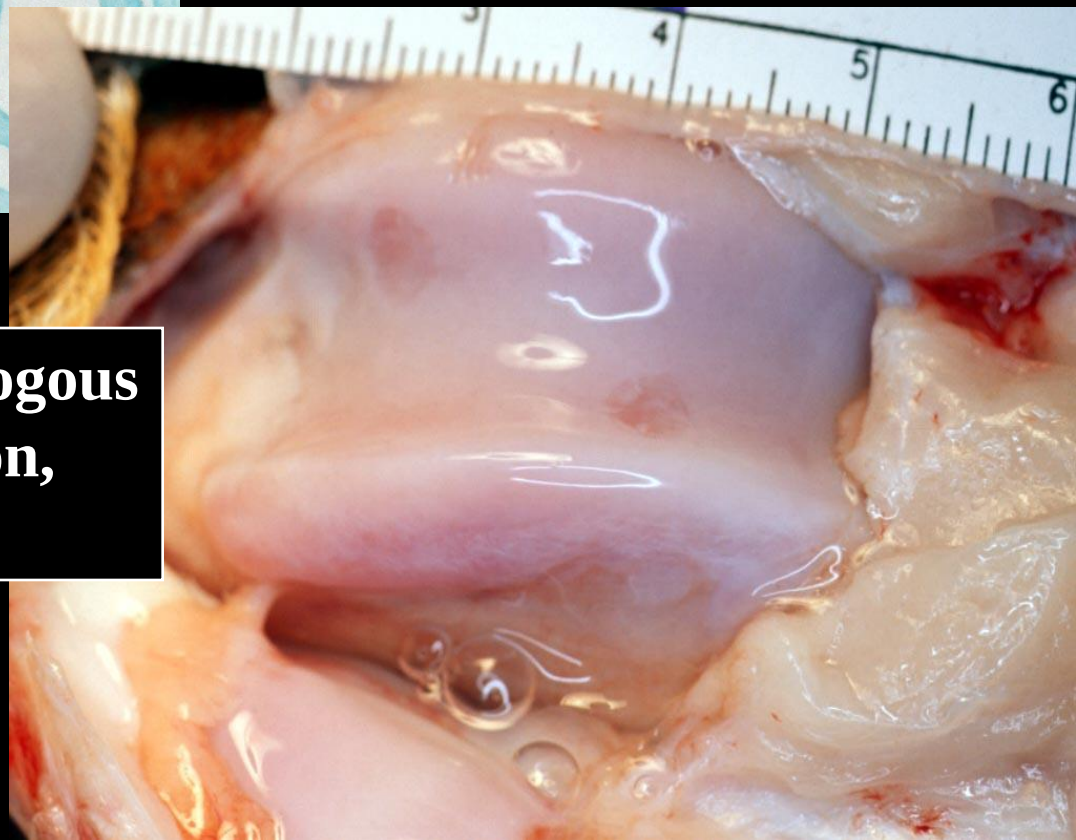
Seeding of Collagen Matrices with CAC

Diagram removed due to copyright restrictions.

Collagen discs
9 mm diam x 3 mm thick

CR Lee, *et al*, Biomat. 2001;22:3145.

Chondral defect immediately postoperative. Arrow shows perforation of calcified cartilage and subchondral bone (SCB)

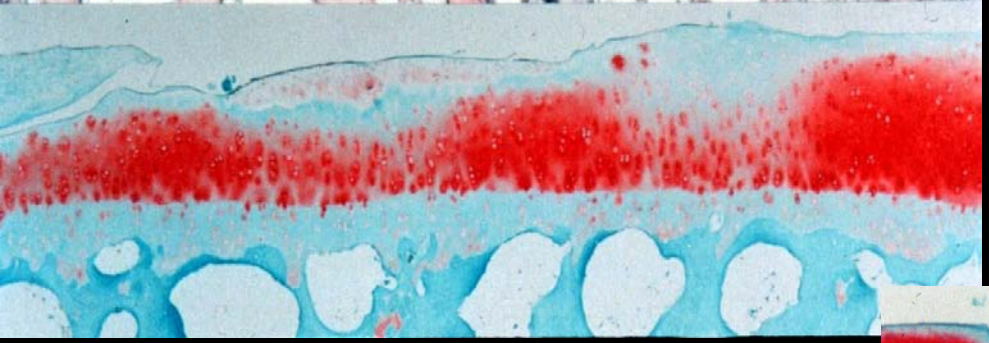


Defects treated by autologous chondrocyte implantation, 6 months postoperative

See H. Breinan, M. Spector *et al*. J. Orthop. Res. 2001;19:482-492

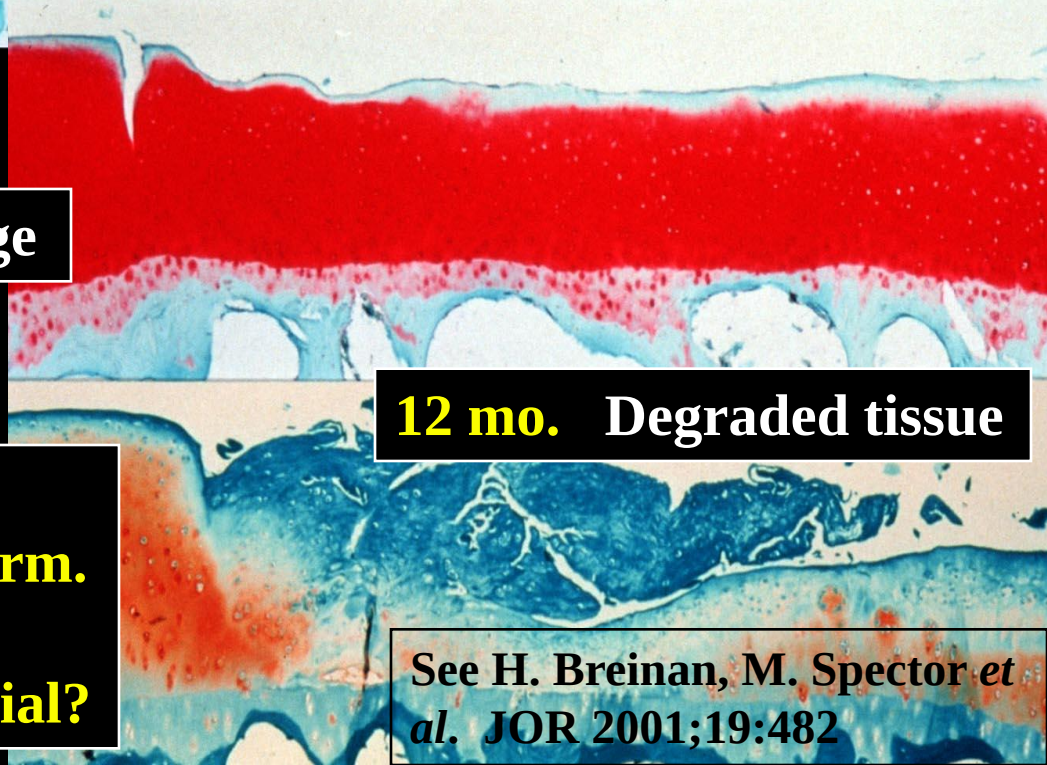
AUTOLOGOUS CHONDROCYTE IMPLANTATION

1.5 mo. Fibrous tissue



3 mo. Hyaline cartilage (some articular cartilage), fibrocartilage, and fibrous tissue

6 mo. Art. cart. and fibrocartilage

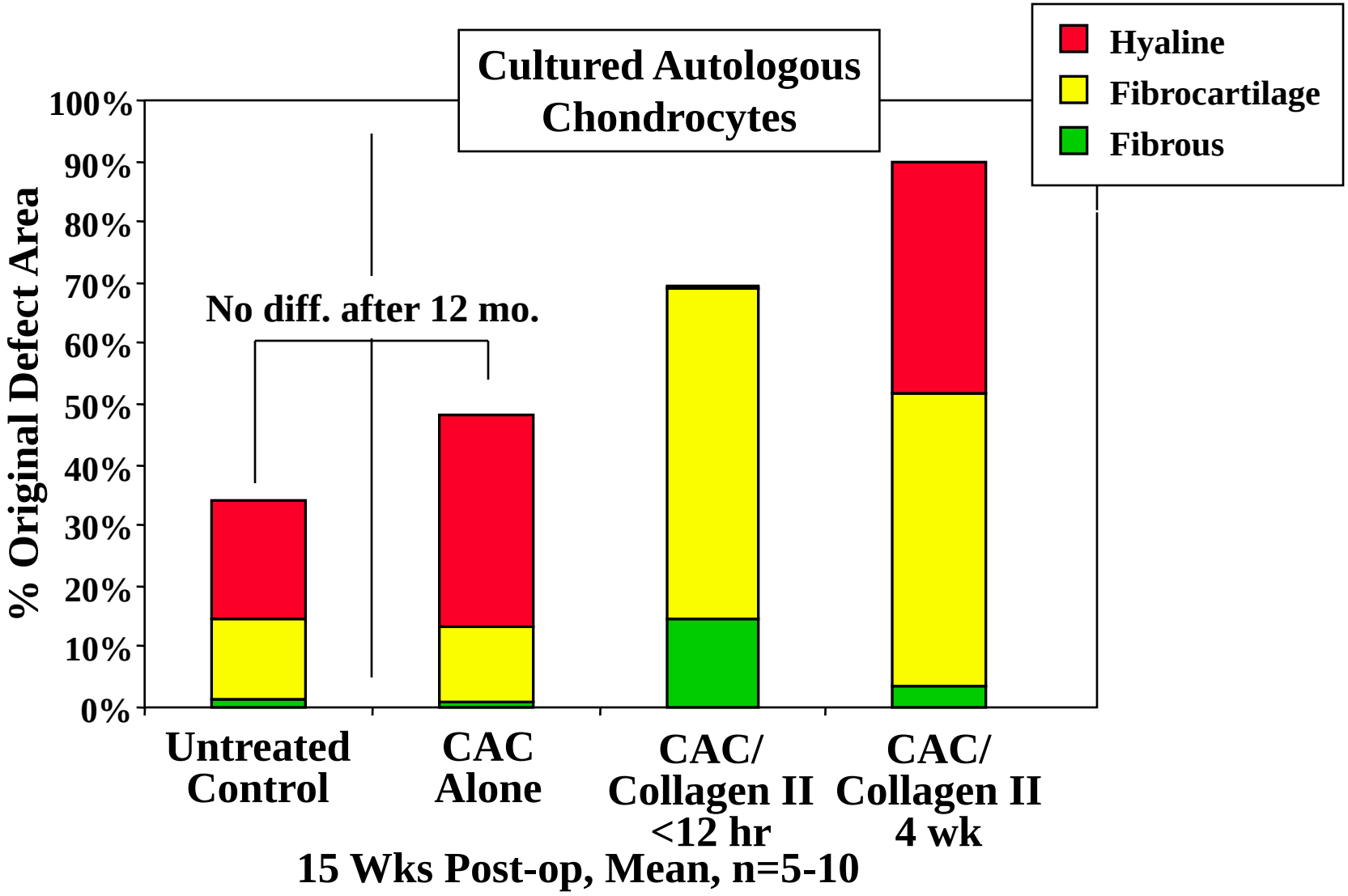


12 mo. Degraded tissue

Tissue that formed after 3 and 6 months did not function longer term. Is the problem a lack of fill or the tissue types comprising the material?

See H. Breinan, M. Spector *et al.* JOR 2001;19:482

Implantation of Cells Alone or in a Type II Collagen Matrix

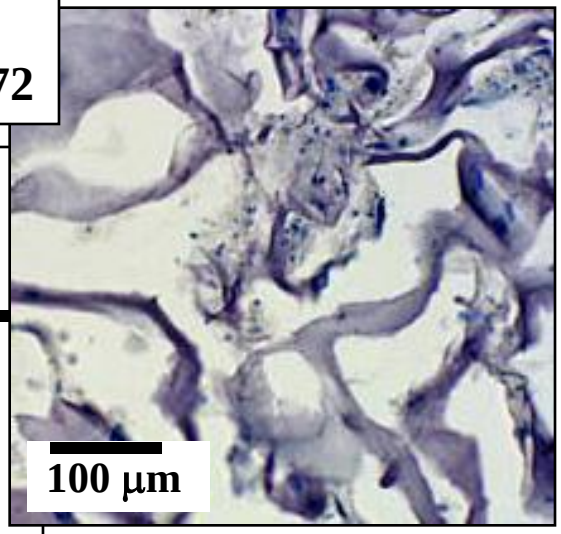


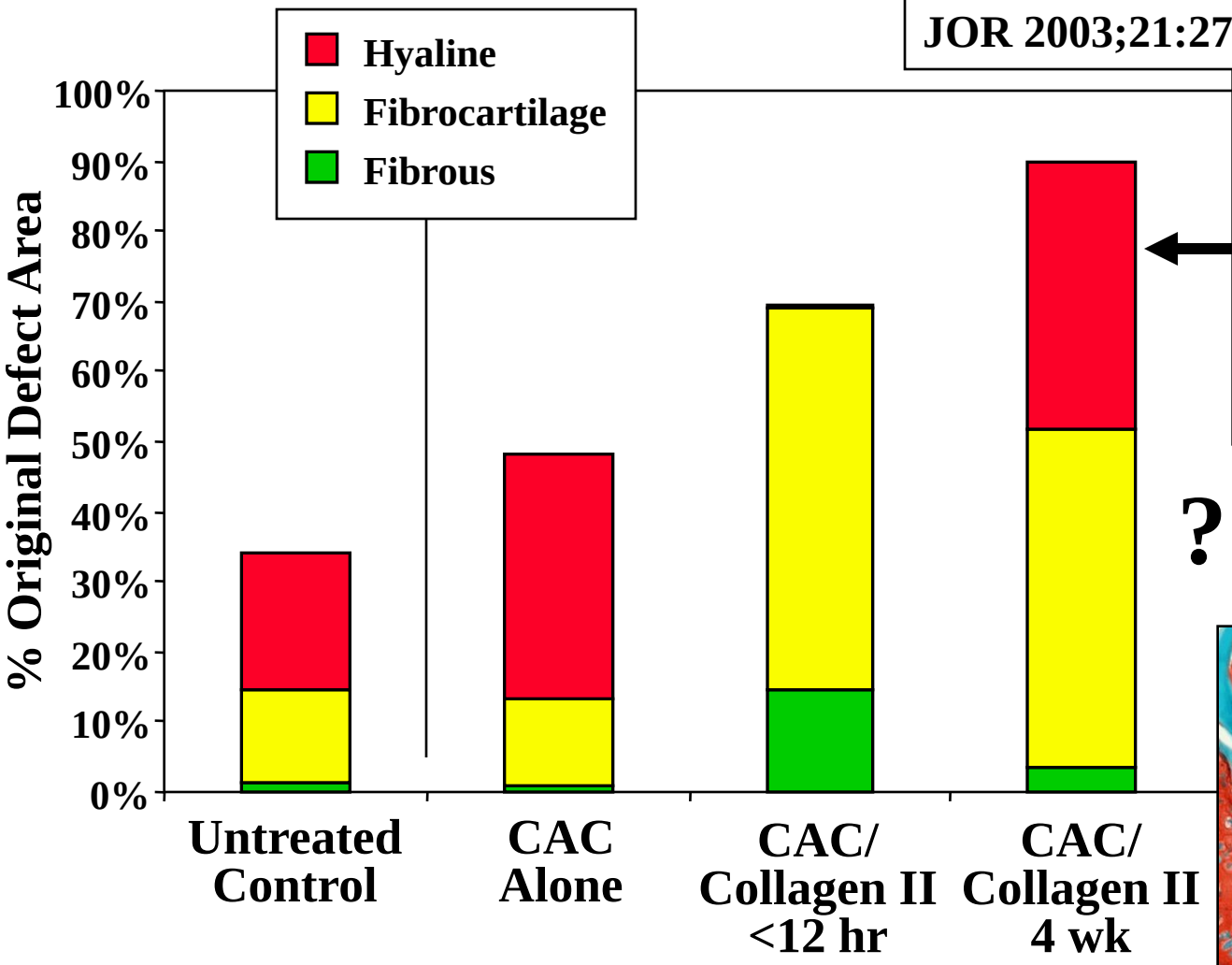
HA Breinan, *et al*. J . Orthop. Res. 2000;18:781-789
and C.R. Lee, *et al*. J. Orthop. Res. 2003;21:272-281

Conclusion: A cell-seeded matrix is better than the current method of ACI

Summary of Results: Canine Model

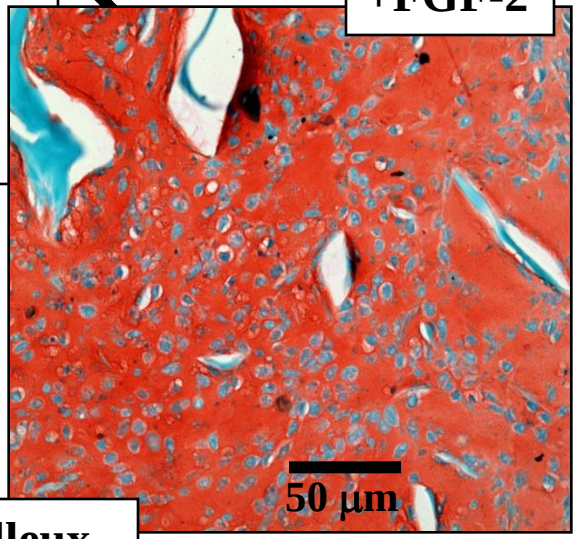
CR Lee, *et al.*
JOR 2003;21:272





?

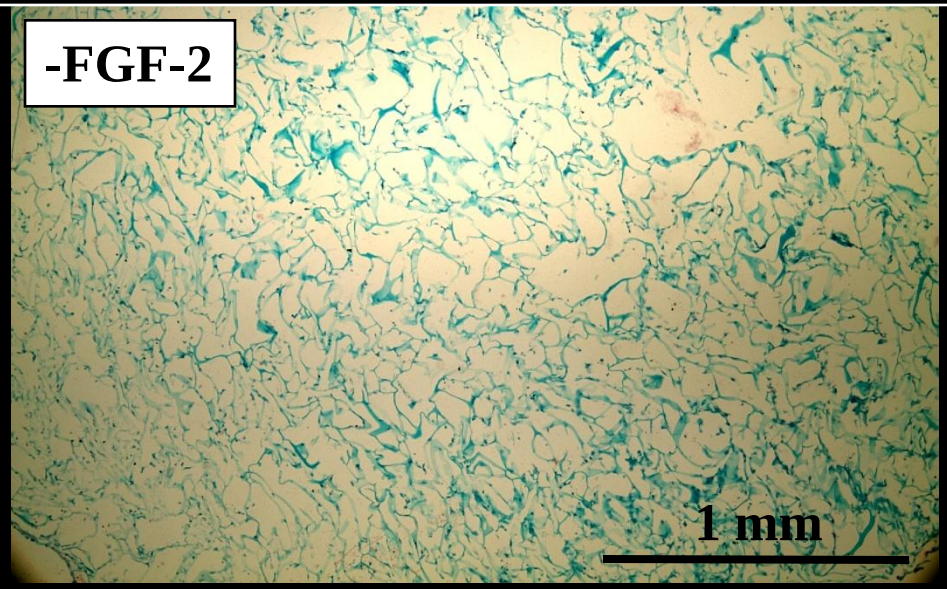
+FGF-2

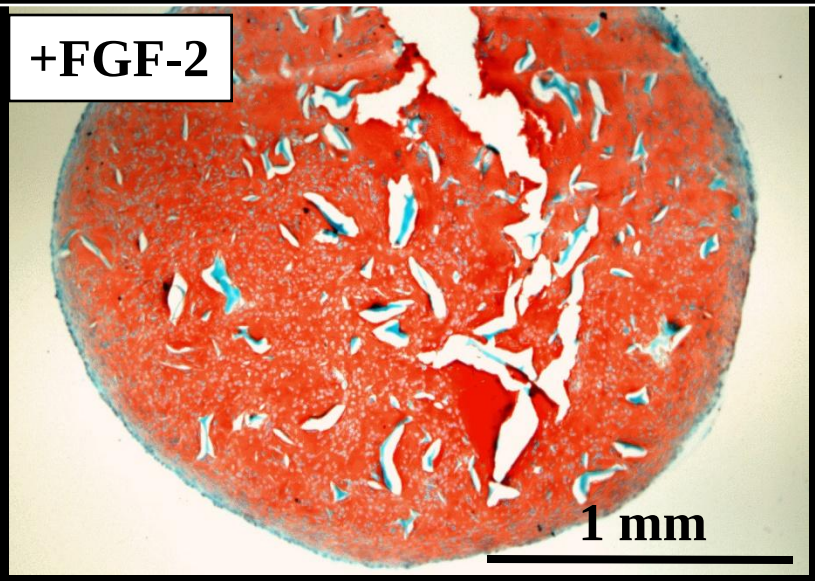


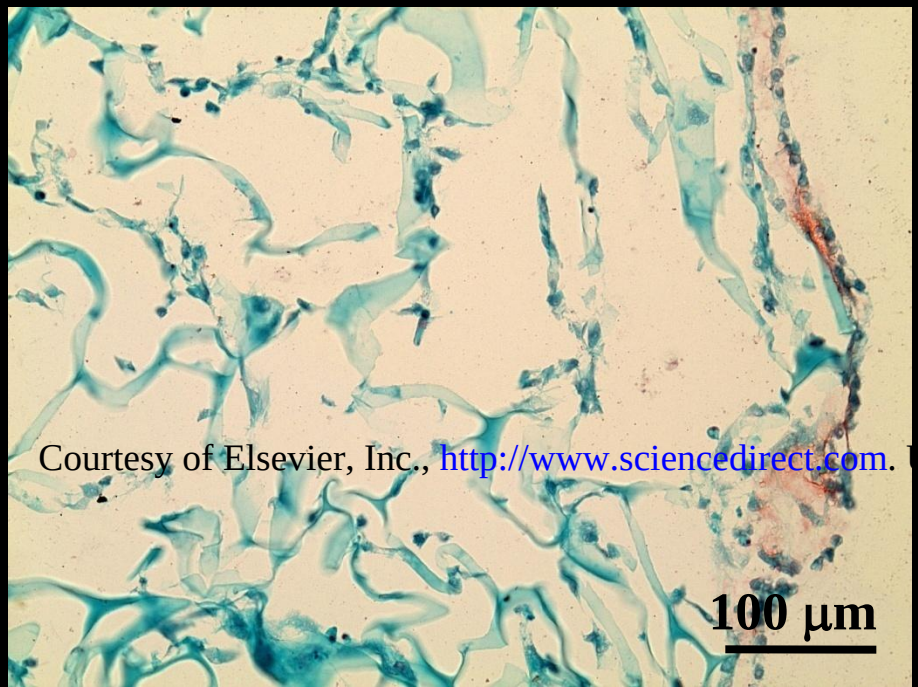
N. Veilleux

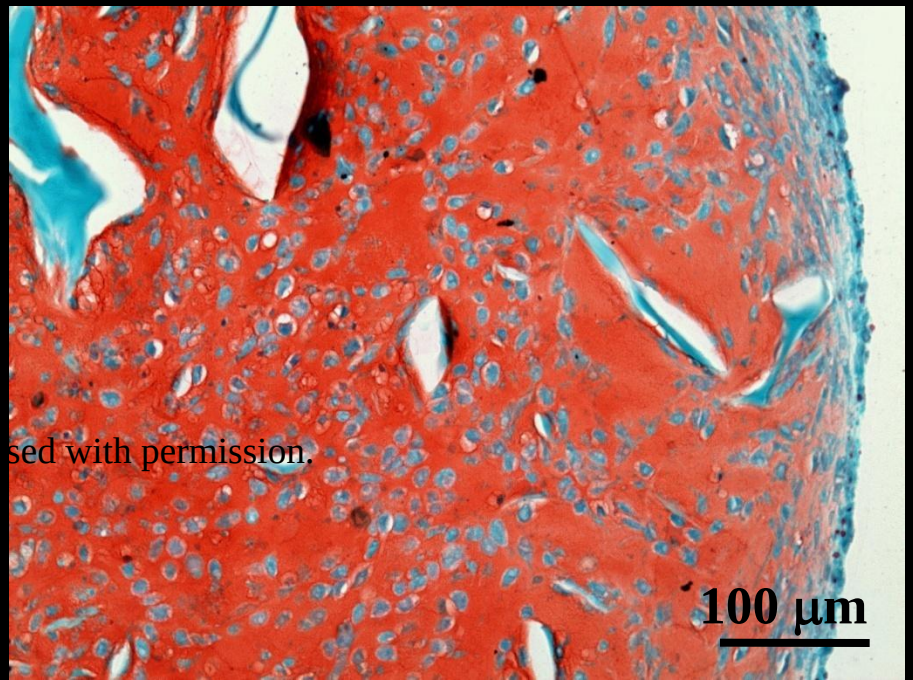
15 Wks Post-op, Mean, n=5-10

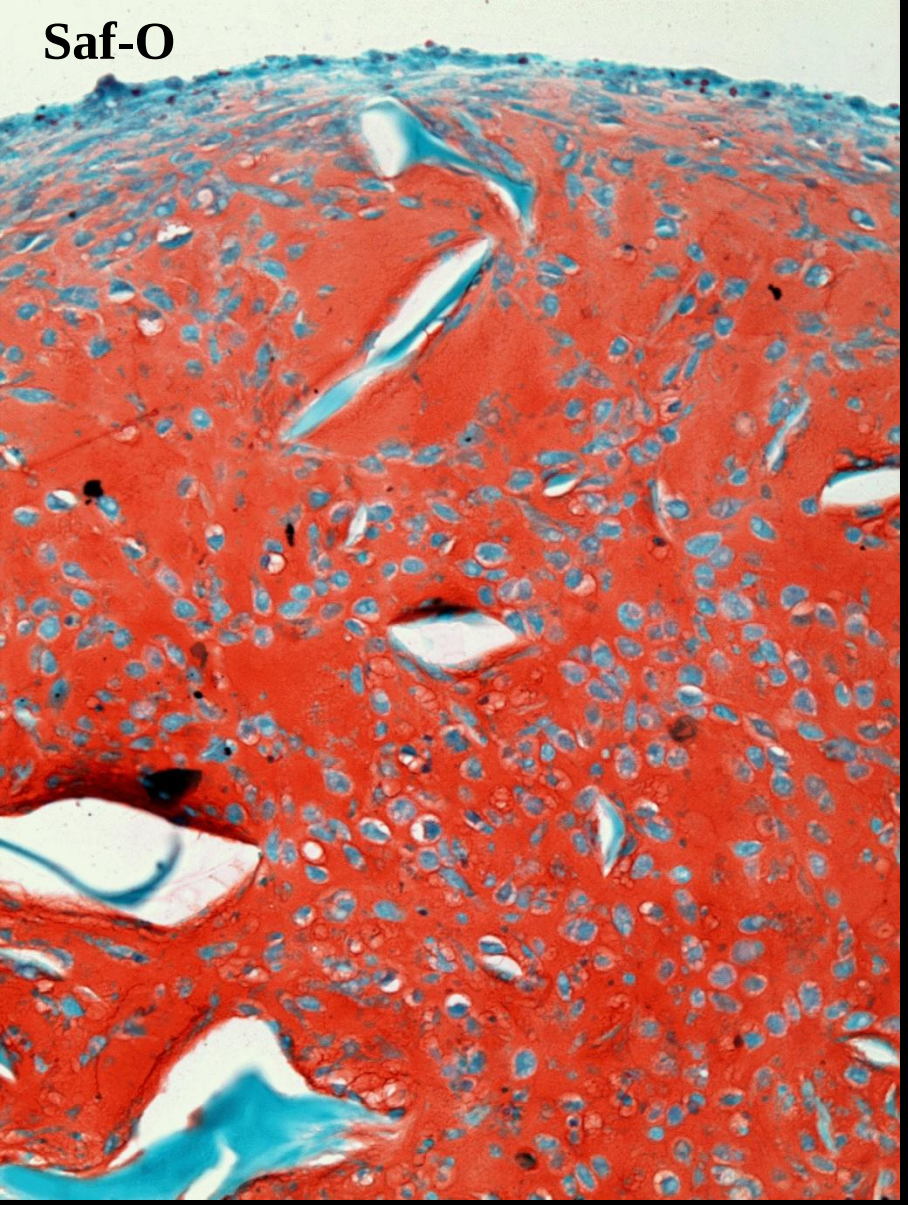
P2 Canine Chondrocytes in Type II Collagen Scaffold (carbodiimide x-linked), 2weeks in culture, Safranin-O Stain for GAG (N. Veilleux, M. Spector)

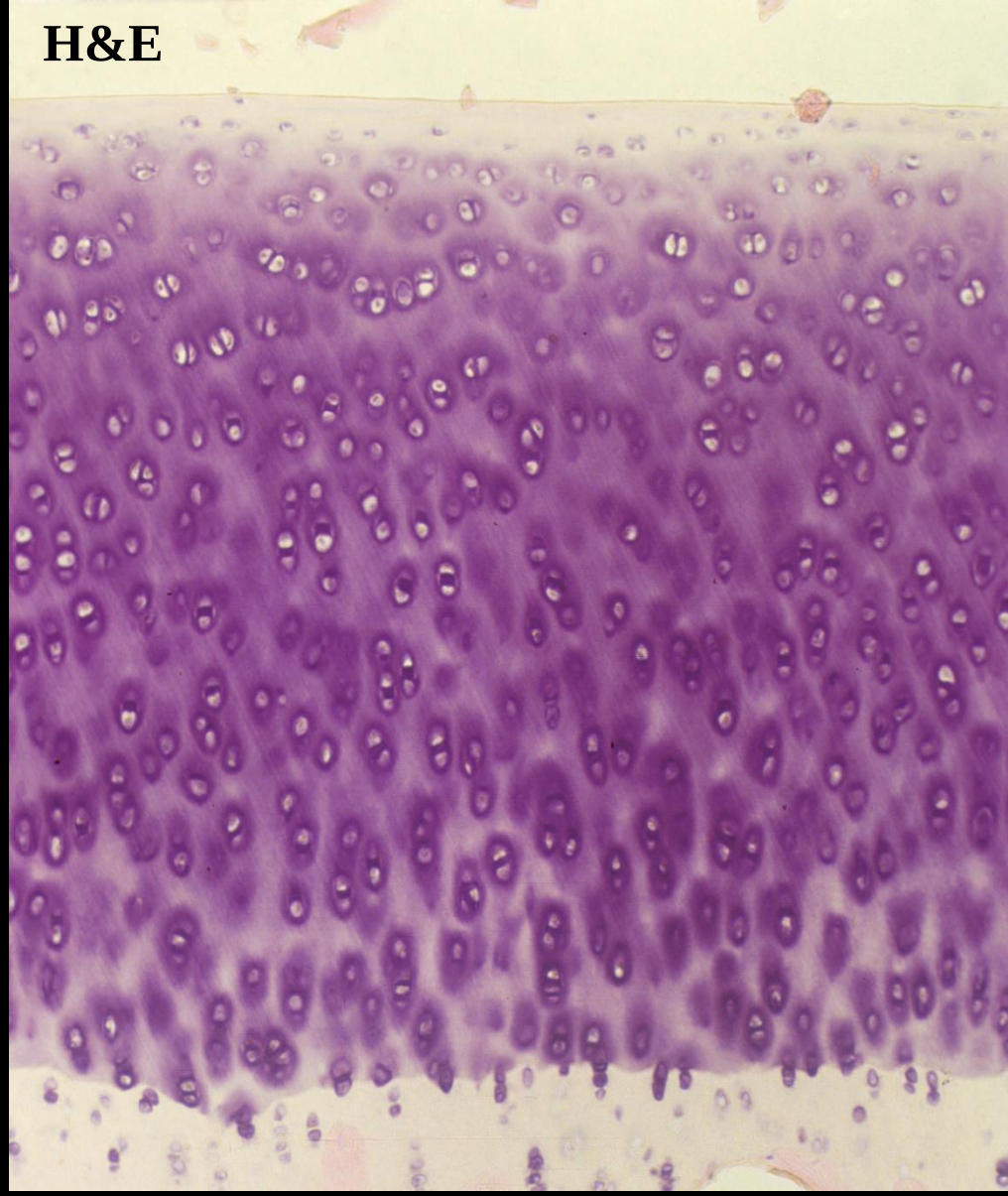








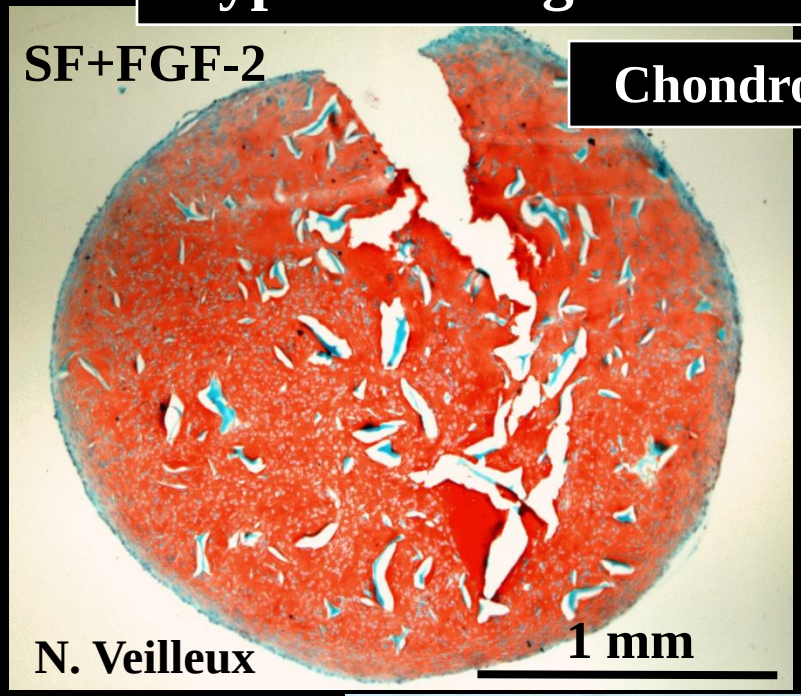




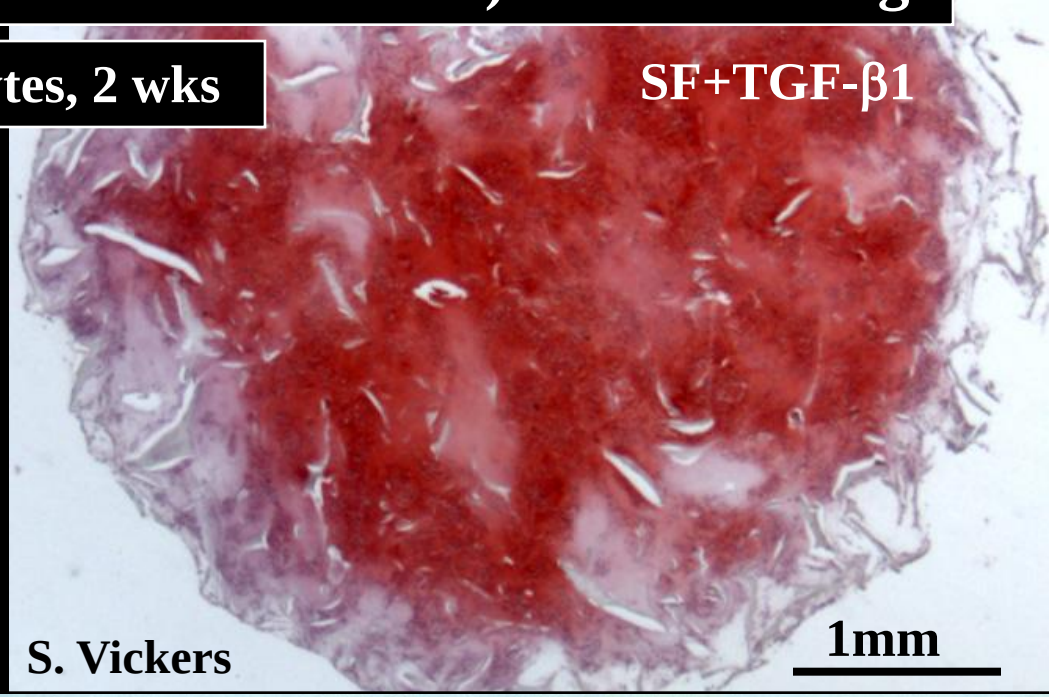
P2 Canine Chondrocyte-Seeded Type II Collagen (CD x-linked), 2w +FGF-2

Normal Canine Articular Cartilage

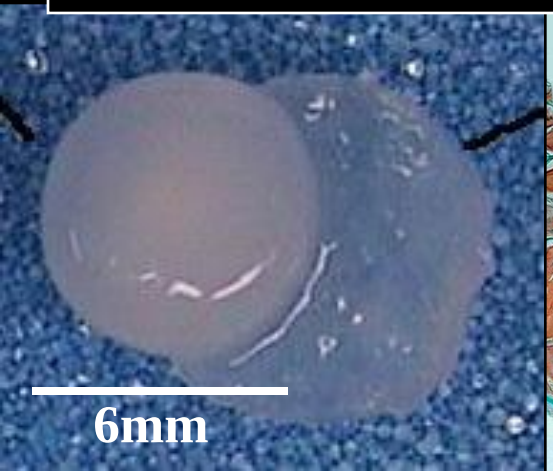
Type II Collagen-GAG (Carbodiimide X-L) Saf O staining

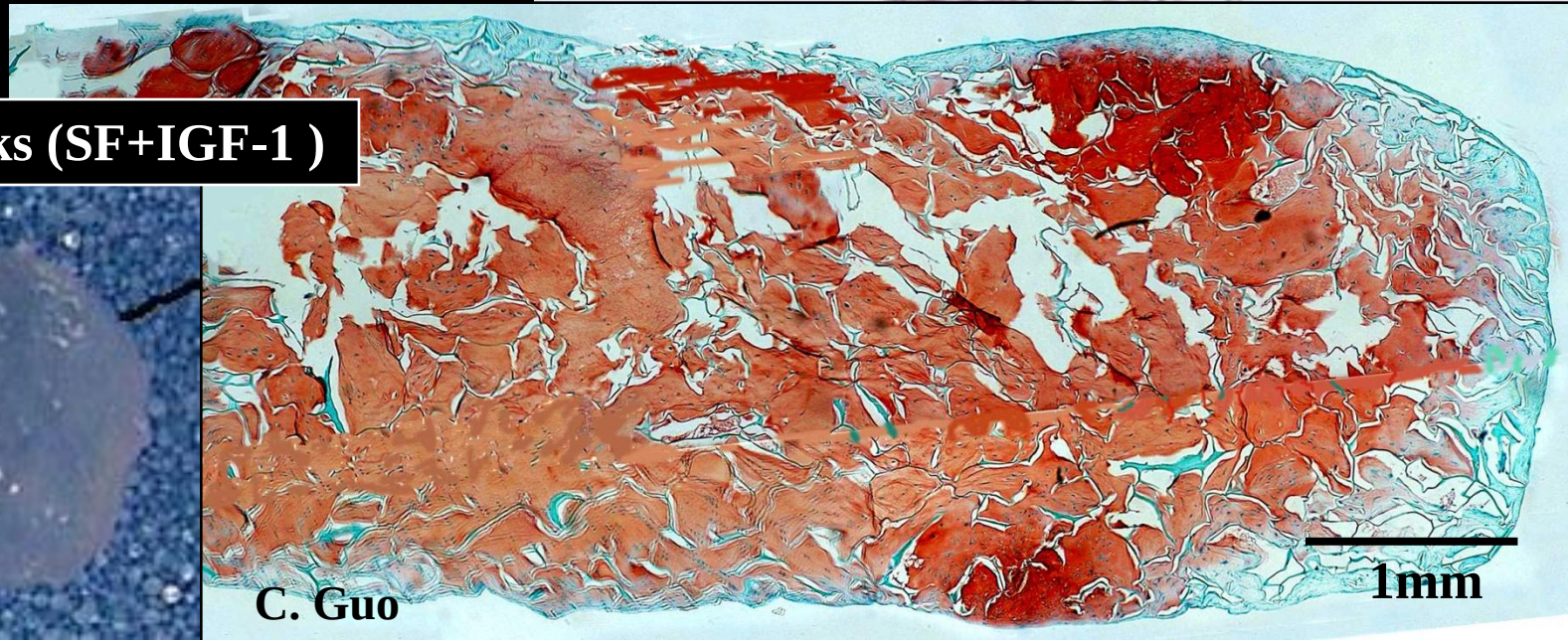


Chondrocytes, 2 wks



MSCs, 3 wks (SF+IGF-1)





Future Clinical Practice
Implementing Tissue Engineering

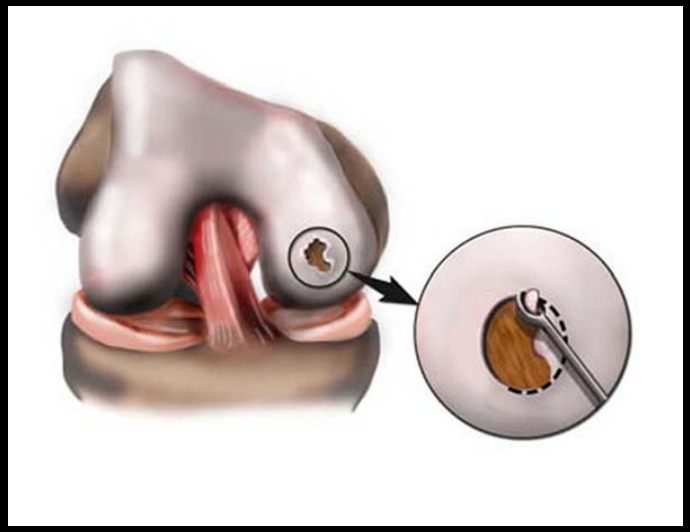
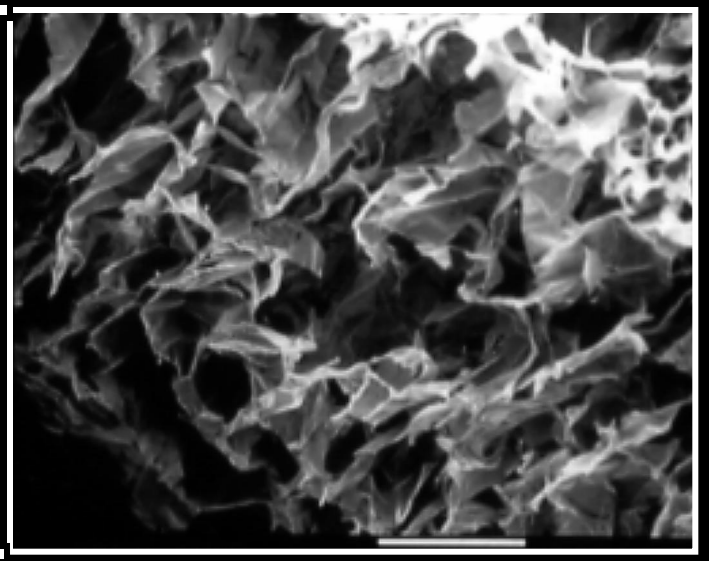


Figure by MIT OpenCourseWare.

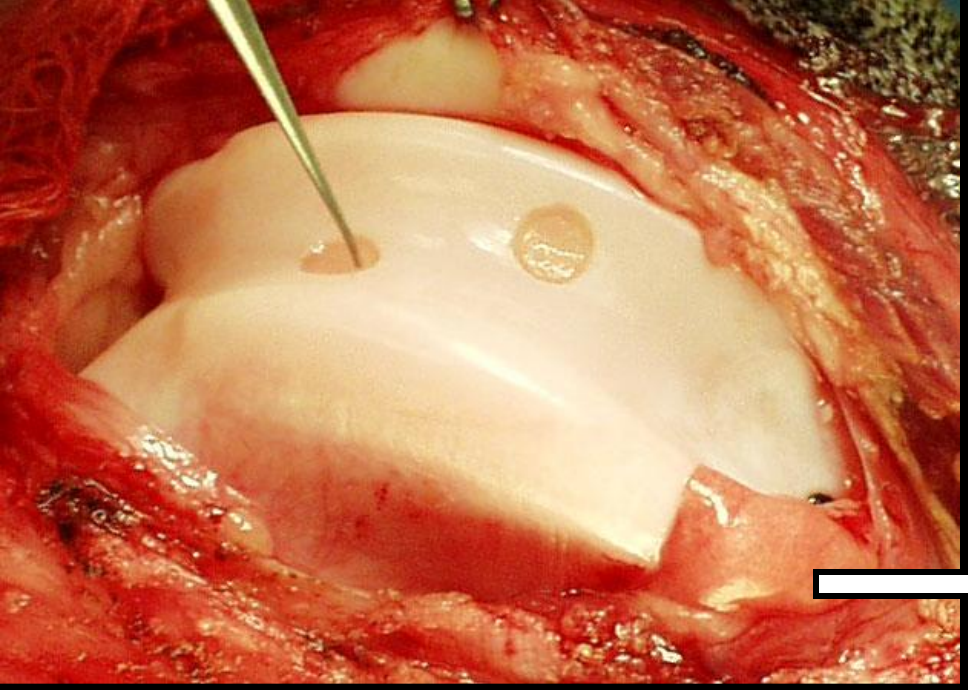
Implantation of a cell-seeded matrix

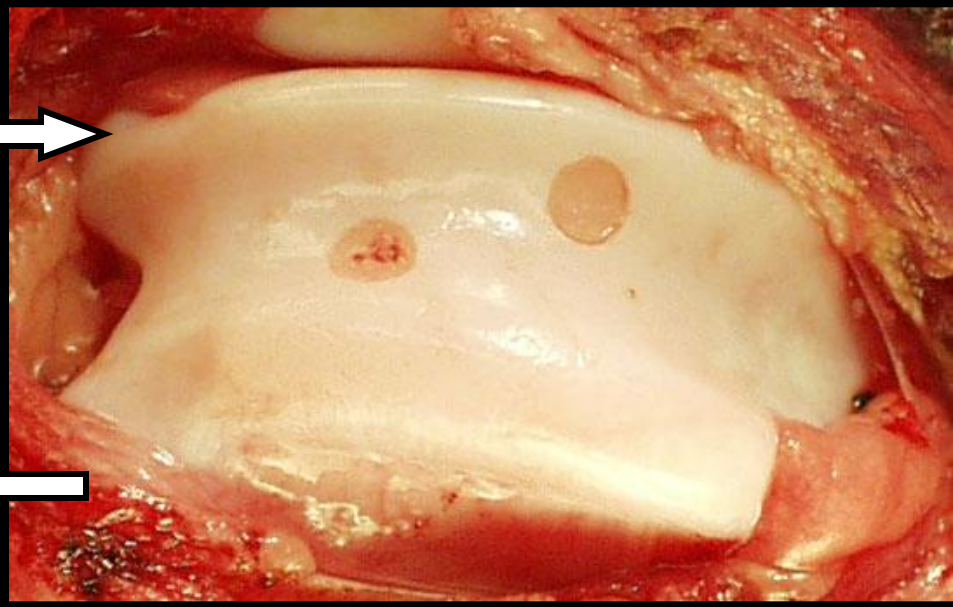


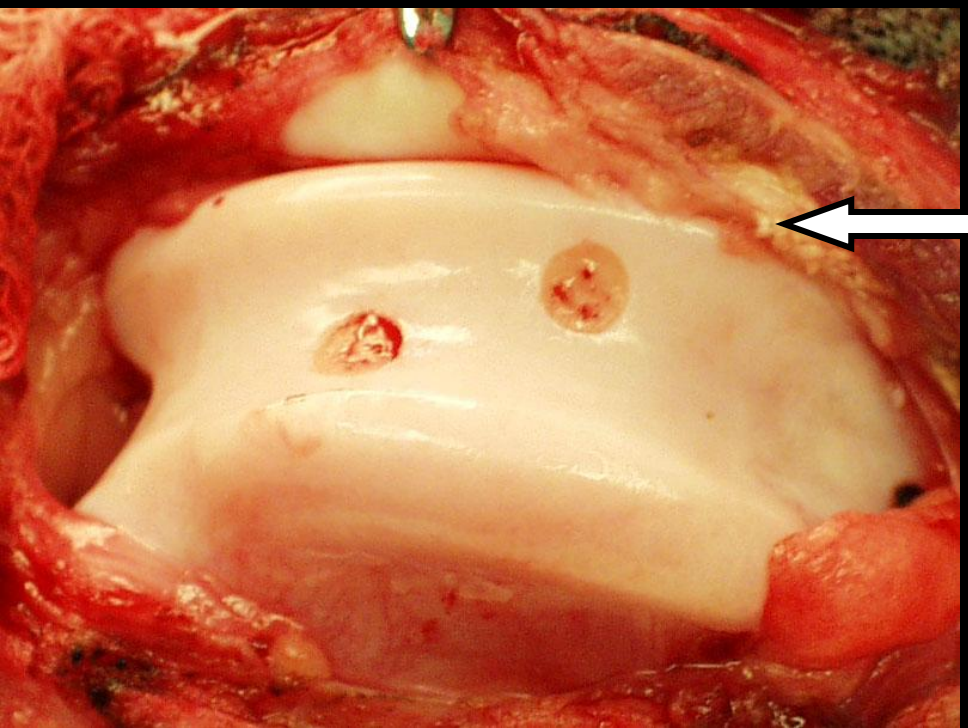
"Microfracture": Stem cells from bone marrow infiltrate the defect

Implantation of the matrix alone, (or supplemented with growth factors or genes for the GFs)

Canine Model Microfracture

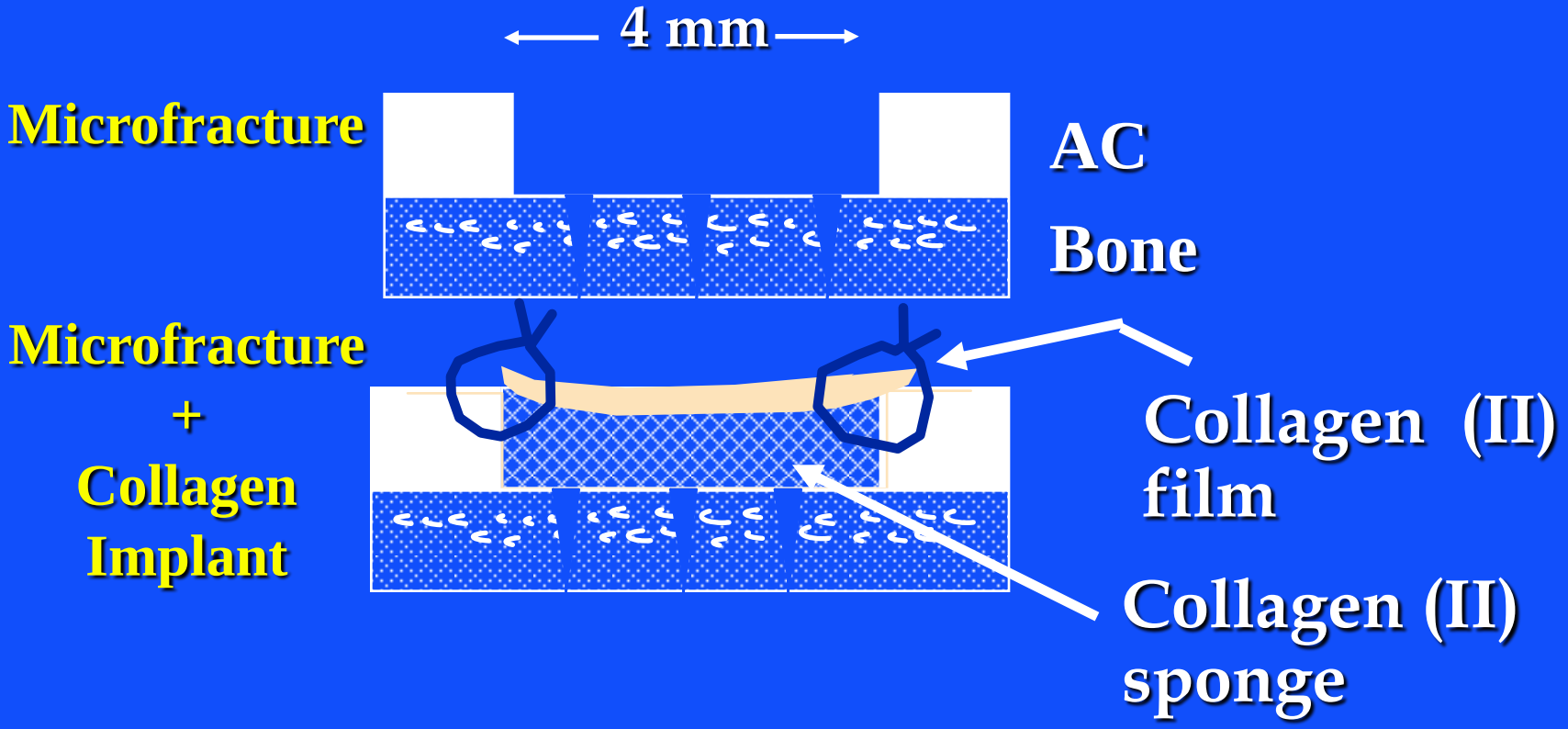






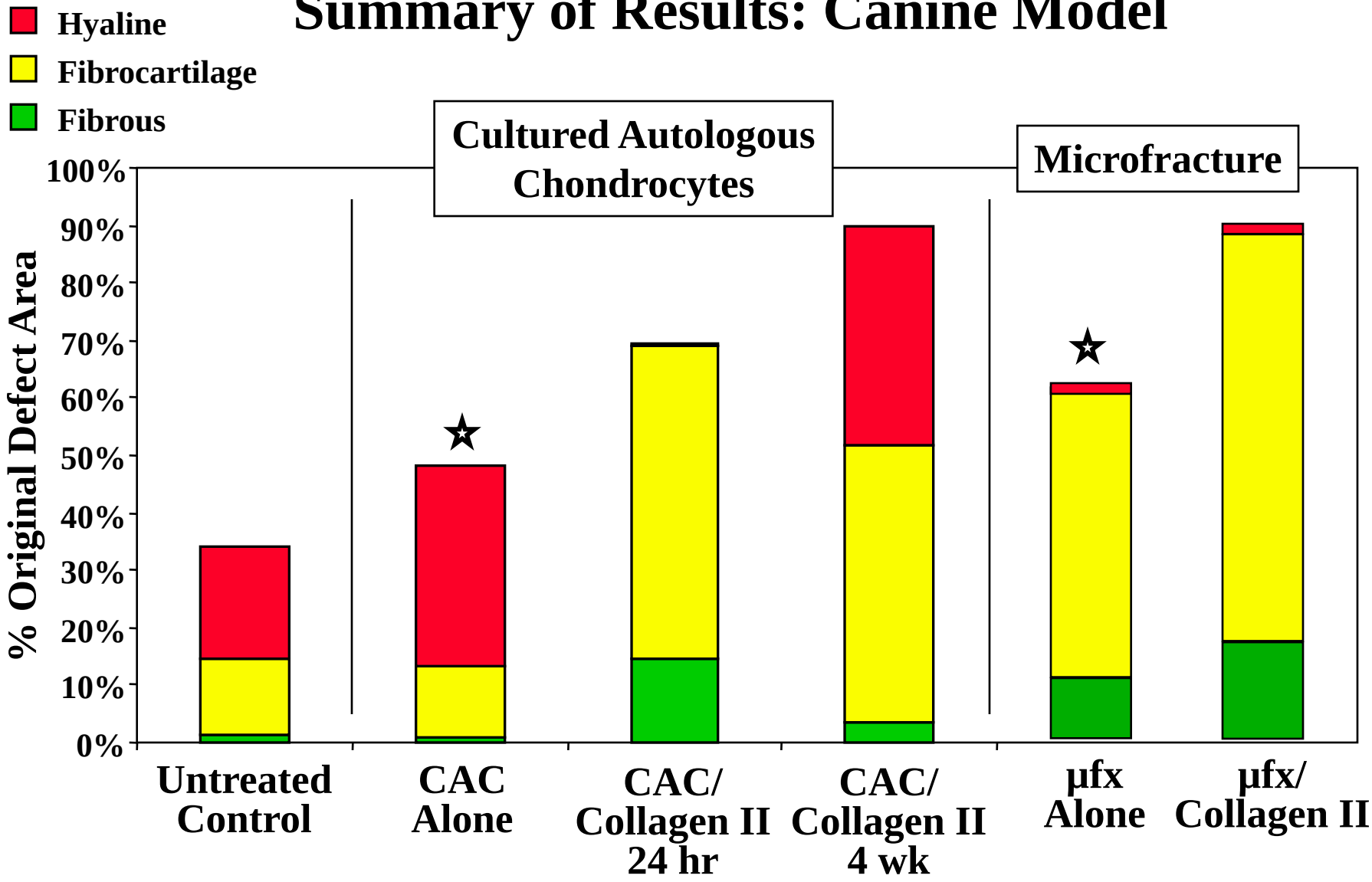
See HA Breinan, M. Spector *et al.*
J . Orthop. Res. 2000;18:781-789

CANINE MICROFRACTURE STUDY TREATMENT GROUPS



* HA Breinan, *et al.* J . Orthop. Res. 2000;18:781-789

Summary of Results: Canine Model



15 Wks Post-op, Mean, n=6

★ Procedures currently used

Autologous Matrix Induced Chondrogenesis

AMIC

The microfracture-treated defect is covered with a collagen membrane.

Several slides removed due to copyright restrictions.

- Medical illustrations of knee joint, with focus on cartilage surfaces and ligaments.
- Meniscus collagen architecture (cutaway diagram)
- Mechanical force analysis for femoral and tibial surfaces.
- Directional properties of meniscus (stress vs. strain graph)
- Histology photos of meniscus tissues: vascularity, fibrochondrocytes, Transmission Electron Microscopy and Polarized Light Microscopy
- Diagram of typical meniscal tear patterns, and arthroscopic view of a complex posterior horn meniscal tear (see http://www.orthoassociates.com/SP11B39/)

Regeneration of Meniscal Cartilage with Use of a Collagen Scaffold. Prelim. Data

K Stone, *et al*., J. Bone Jt. Surg. 79-A:1770-1777;1997

- **Collagen scaffold as a template for the regeneration of meniscal cartilage**
- **10 patients in a clinical feasibility trial (FDA-approved)**
  - **The goal of the study was to evaluate the implantability and safety of the scaffold as well as its ability to support tissue ingrowth.**
  - **The study based on *in vitro* and *in vivo* investigations in dogs that demonstrated cellular ingrowth and tissue regeneration through the scaffold.**
  - **Nine patients remained in the study for at least thirty-six months.**

Photograph of the collagen meniscal implant.

Images removed due to copyright restrictions.

Scanning electron micrograph of a cross section of the collagen meniscal implant.

K Stone, *et al*., J. Bone Jt. Surg. 79-A:1770-1777;1997

The sizes and shapes of the meniscal lesions as well as the menisci after placement of the collagen meniscal implant.

Photo removed due to copyright restrictions.

K Stone, *et al*., J. Bone Jt. Surg. 79-A:1770-1777;1997

Drawings showing insertion and suturing of the collagen meniscal implant.

Two drawings removed due to copyright restrictions.

K Stone, *et al*., J. Bone Jt. Surg. 79-A:1770-1777;1997

Several slides removed due to copyright restrictions.
Figures and captions from Rodkey, W., et al. "A Clinical Study of Collagen Meniscus Implants to Restore the Injured Meniscus." *Clinical Orthopaedics and Related Research* 367 (October 1999): S281-S292.

W. Rodkey, *et al.*, CORR 367S:281;1999

Regeneration of Meniscal Cartilage with Use of a Collagen Scaffold. Prelim. Data

K Stone, *et al*., J. Bone Jt. Surg. 79-A:1770-1777;1997

- **The collagen scaffold was implantable and safe over 3-yrs.**
- **Histologically, it supported regeneration of tissue in meniscal defects of various sizes.**
- **No adverse immunological reactions were noted.**
- **At 3 or 6 months after implantation, gross and histological evaluation revealed newly formed tissue replacing the implant as it was resorbed.**

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- At 3 yrs., the 9 pts. reported a decrease in symptoms.
- A scale assigned 1 point for strenuous activity and 5 points for an inability to perform sports activity
  - The average score was 1.5 points before the injury
  - 3.0 points after the injury and before the operation
  - 2.4 points at six months postoperatively
  - 2.2 points at twelve months
  - 2.0 points at twenty-four months
  - 1.9 points at thirty-six months.
- Scale assigned 0 points for no pain and 3 points for severe pain
  - The average pain score was 2.2 points preoperatively
  - 0.6 point 3- yrs. postoperatively.

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- One patient, who had had a repair of a bucket-handle tear of the medial meniscus and augmentation with the collagen scaffold, had retearing of the cartilage nineteen months after implantation. Another patient had debridement because of an irregular area of regeneration at the scaffold-meniscus interface twenty-one months after implantation.
- Magnetic resonance imaging scans demonstrated progressive maturation of the signal within the regenerated meniscus at three, six, twelve, and thirty-six months. These findings suggest that regeneration of meniscal cartilage through a collagen scaffold is possible. Additional studies are needed to determine long-term efficacy.

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- **Collagen scaffold as a template for the regeneration of meniscal cartilage**
- **10 patients in a clinical feasibility trial (FDA-approved)**
  - **The goal of the study was to evaluate the implantability and safety of the scaffold as well as its ability to support tissue ingrowth.**
  - **The study based on *in vitro* and *in vivo* investigations in dogs that demonstrated cellular ingrowth and tissue regeneration through the scaffold.**
  - **Nine patients remained in the study for at least thirty-six months.**

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