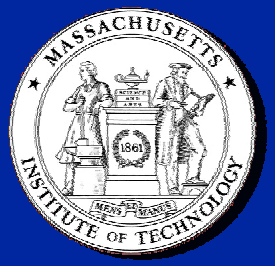
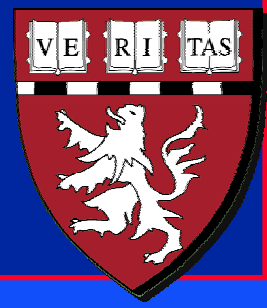


Massachusetts Institute of Technology
Harvard Medical School
Brigham and Women's/Massachusetts General Hosp.
VA Boston Healthcare System



2.79J/3.96J/BE.441/HST522J

BIOMATERIALS FOR JOINT REGENERATION-II

M. Spector, Ph.D. and I.V. Yannas, Ph.D.

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

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

JOINT TISSUES
REPARATIVE PROCEDURES

Art. Cart.	Microfracture, osteochondral plugs, articular chondrocyte implantation [Tiss. engr. cart.; Collagen matrices]
ACL	Tendon autografts
Meniscus	Suture, meniscal allografts [Collagen matrices]

JOINT TISSUES

	Loading	Tissue Type	Cell Type	Round/ Lac.	Coll.	PG	Vasc.	Heal.
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

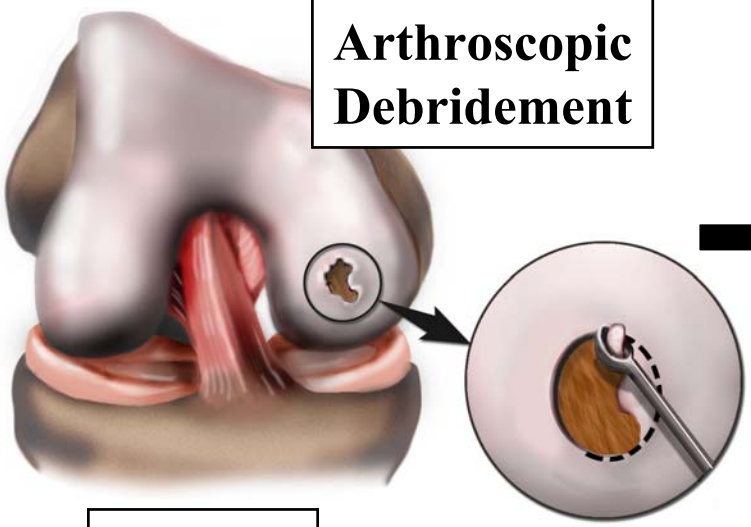
ARTICULAR CARTILAGE

Chondrocytes
Extracellular matrix

Water	66-78%
Organic material	22-34%
Proteoglycan	22-38%
Collagen type II	48-62%
Fibronectin & Other matrix proteins	05-15%

Human Knee from Patient with Rheumatoid Arthritis

Image removed due to copyright considerations.



Arthroscopic Debridement

30 years

Image source: OCW

"Microfracture"

Image removed due to copyright considerations

Image removed due to copyright considerations

Osteochondral Plug Autograft ("Mosaicplasty")

Current Clinical Practice

Image removed due to copyright considerations

Image removed due to copyright considerations

Total Knee Replacement

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

Future Clinical Practice
Implementing Tissue Engineering

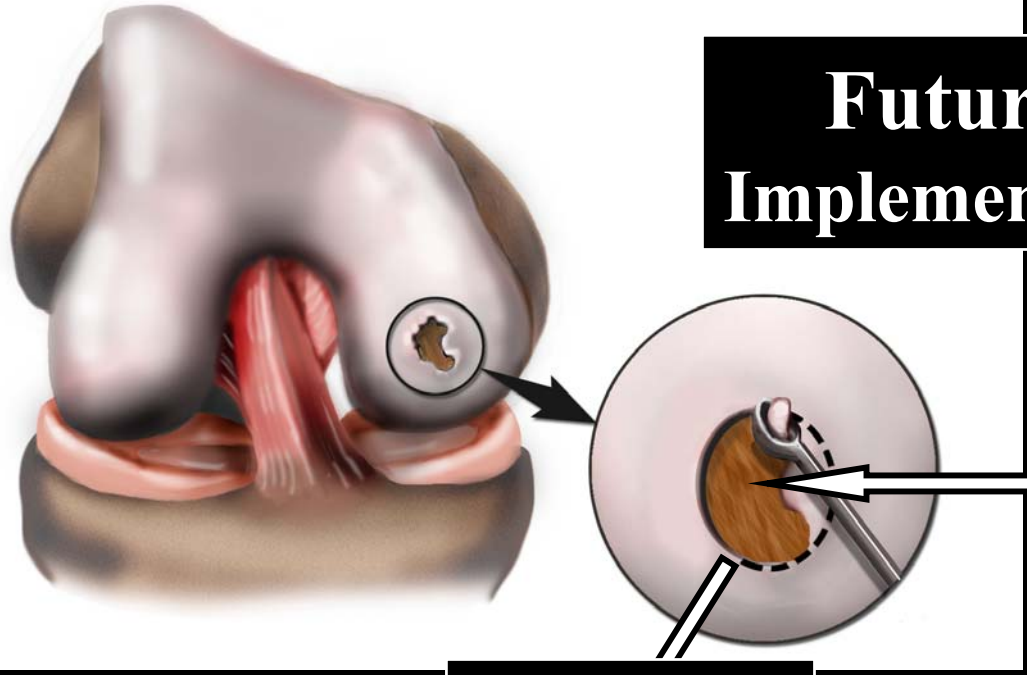


Image source: OCW

Implantation of a cell-seeded matrix

Image removed due to copyright considerations.

Microfracture

Image removed due to copyright considerations.

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

Stem cells from bone marrow infiltrate the defect

ELEMENTS FOR TISSUE ENGINEERING

Tissue Engineering Triad*

- CELLS
- MATRIX (INSOLUBLE REGULATOR)
  - Porous, absorbable biomaterials
- SOLUBLE REGULATORS
  - Cytokines (Growth Factors)

Environmental Factors

- Mechanical loading

* Used individually or in combination, but probably always best with a matrix (*i.e.*, with a biomaterial)

ARTICULAR CARTILAGE

Limits to Regeneration

- Avascular (and aneural)
- Relatively low cell density
- Cells of low mitotic activity
- Cells cannot freely migrate

TISSUE ENGINEERING

Cells

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

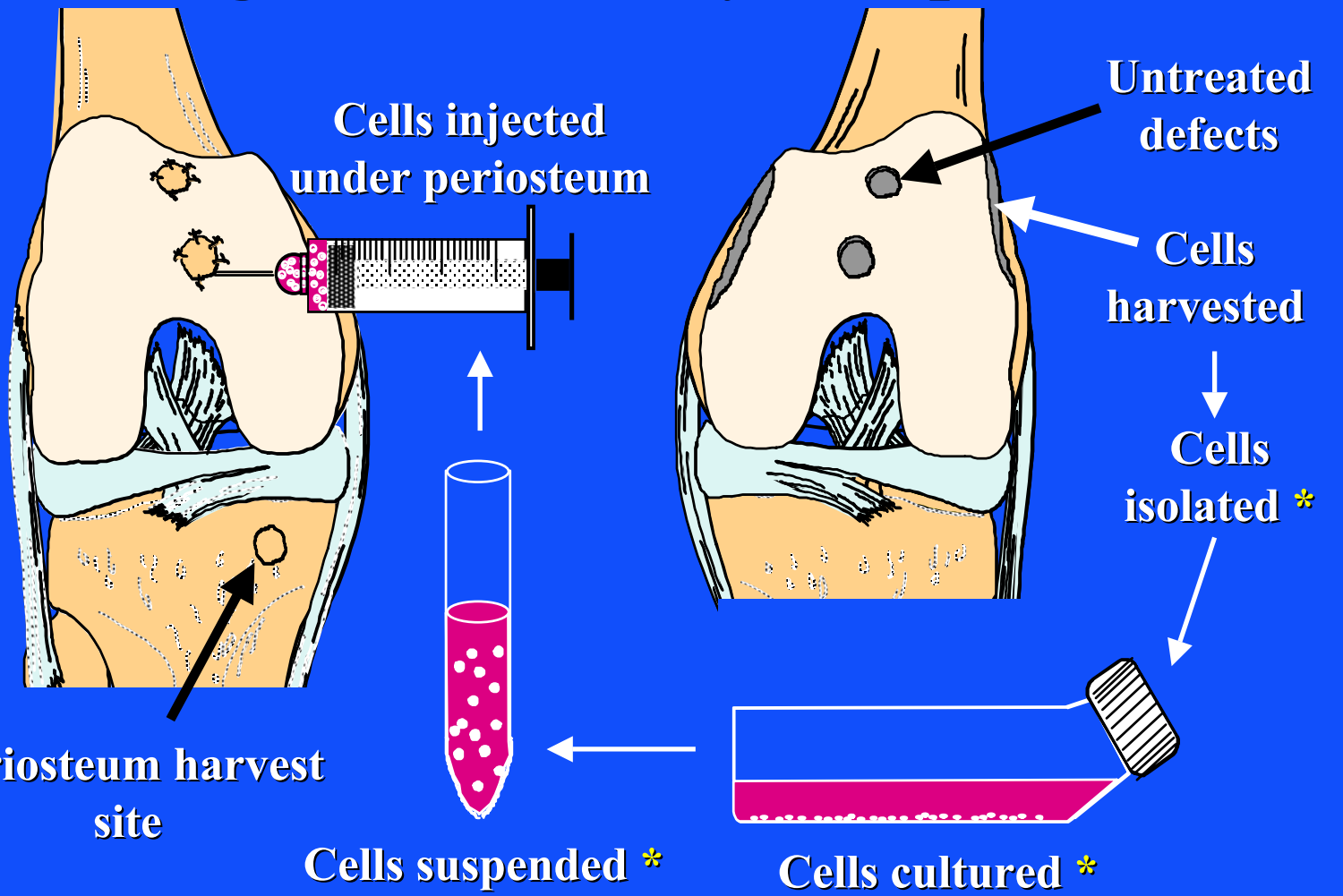
Autologous Chondrocyte Implantation

Image removed due to copyright considerations.

This process has been commercialized by Genzyme (for USD$11,500).

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

Canine Study
Autologous Chondrocyte Implantation



* by Genzyme Biosurgery

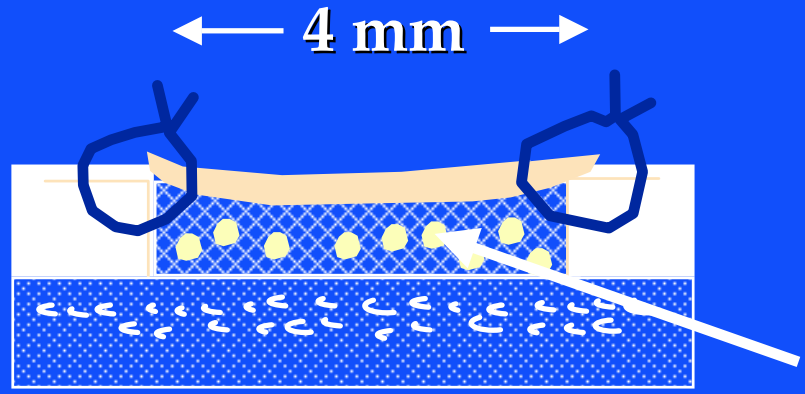
CELL-SEEDED COLLAGEN MATRICES

- Chondral defects (to the tidemark)

Images removed due to copyright considerations

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

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.*

Seeding of Collagen Matrices with CAC

Images removed due to copyright considerations

Collagen discs
9 mm diam x 3 mm thick

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

Image removed due to copyright considerations

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

Defects treated by autologous chondrocyte implantation, 6 months postoperative

Image removed due to copyright considerations

H. Breinan, *et al.*
J. Orthop. Res. 2001;19:282-292

1.5 mo. Fibrous tissue

Images removed due to copyright considerations

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

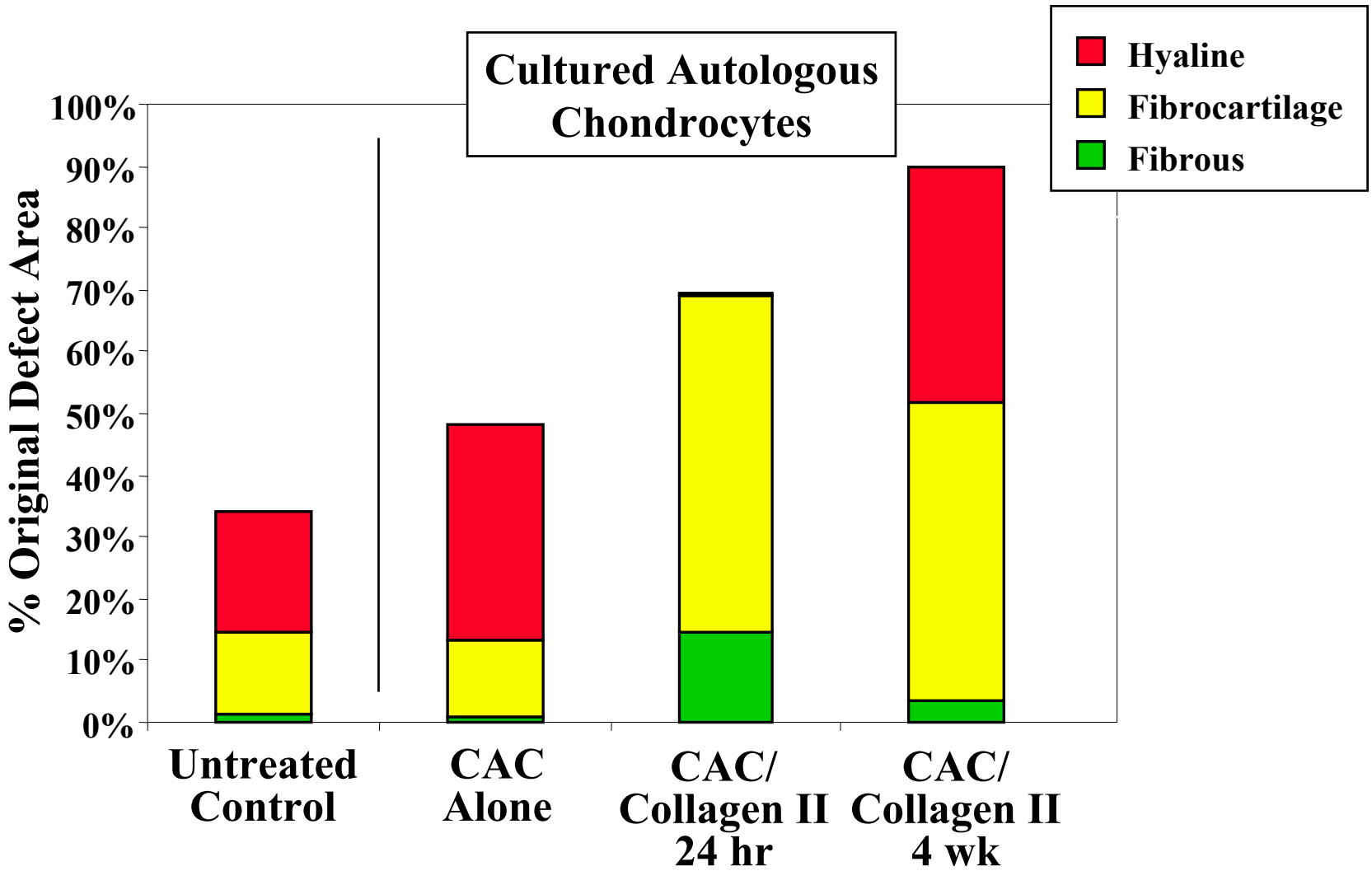
6 mo. Articular cartilage and fibrocartilage

Images removed due to copyright considerations

12 mo. Degraded tissue, fibrocartilage and fibrous tissue

H. Breinan, *et al.*
J. Orthop. Res. 2001;19:282-292

Summary of Results: Canine Model



15 Wks Post-op, Mean, n=6

Future Clinical Practice
Implementing Tissue Engineering

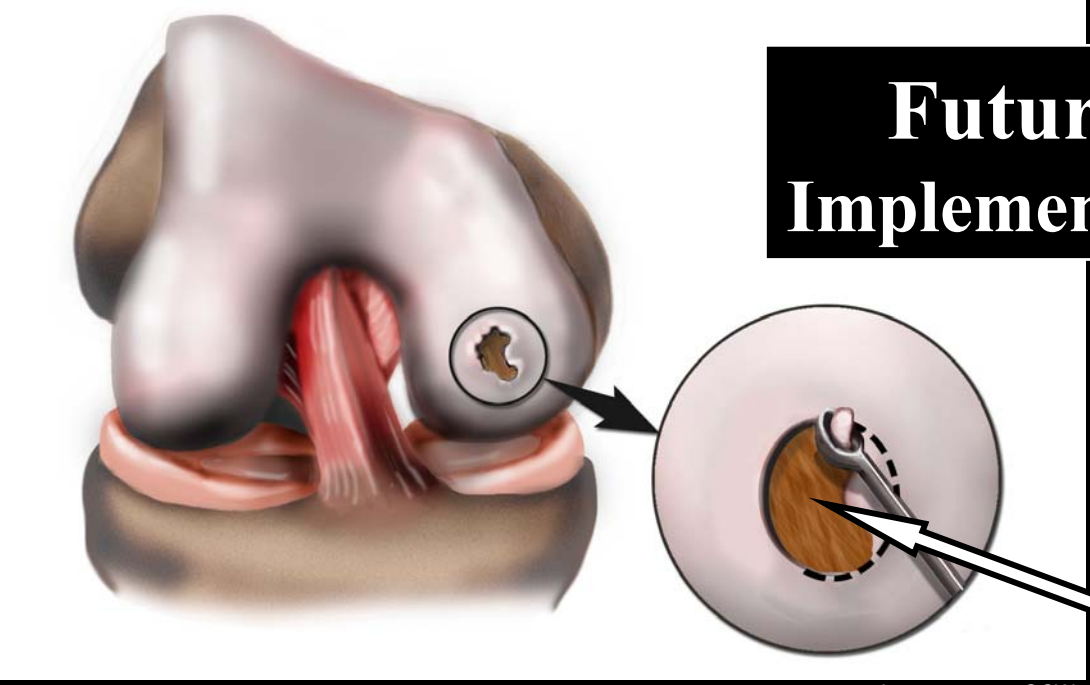


Image source: OCW

Implantation of a **cell-seeded matrix**

Image removed due to copyright considerations.

Image removed due to copyright considerations.

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

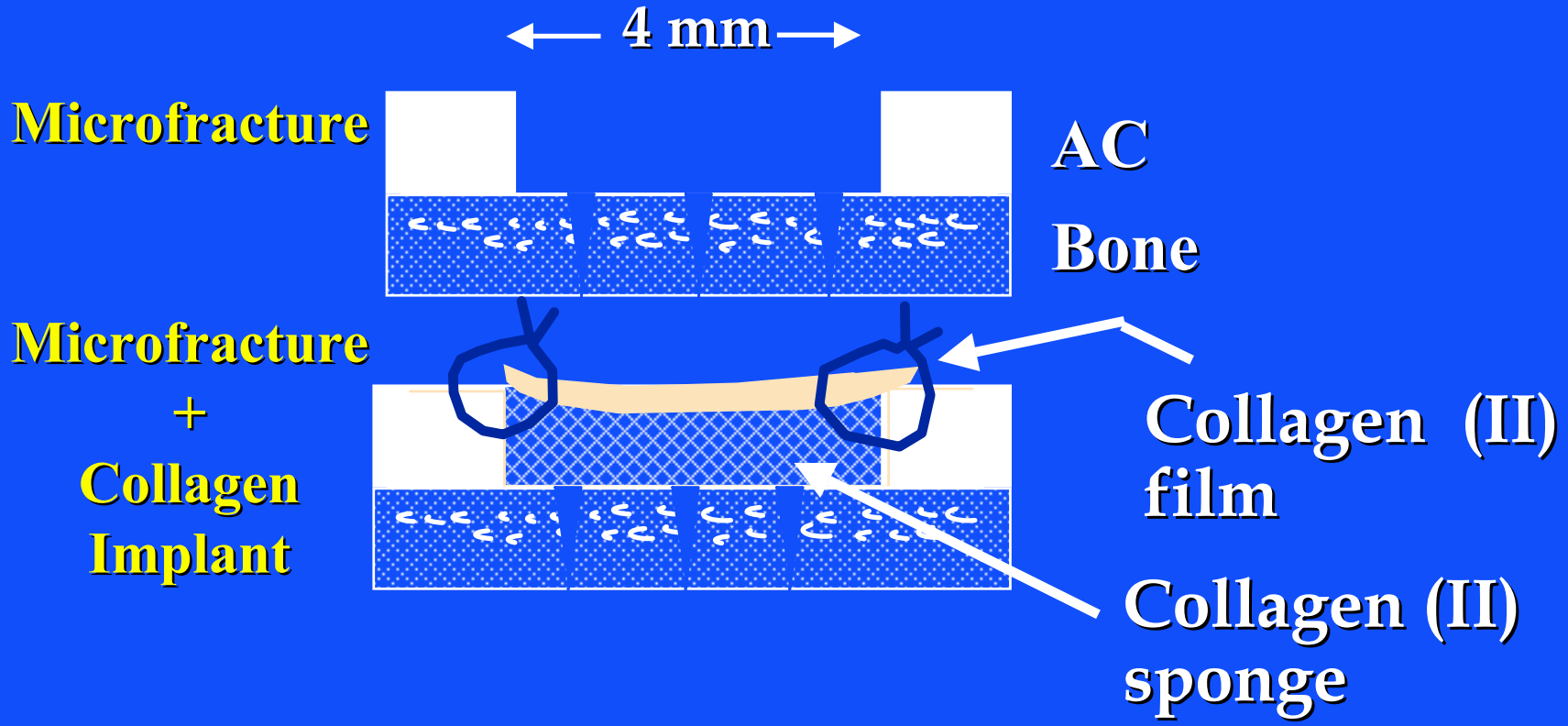
"Microfracture":
Stem cells from bone marrow infiltrate the defect

Canine Model Microfracture

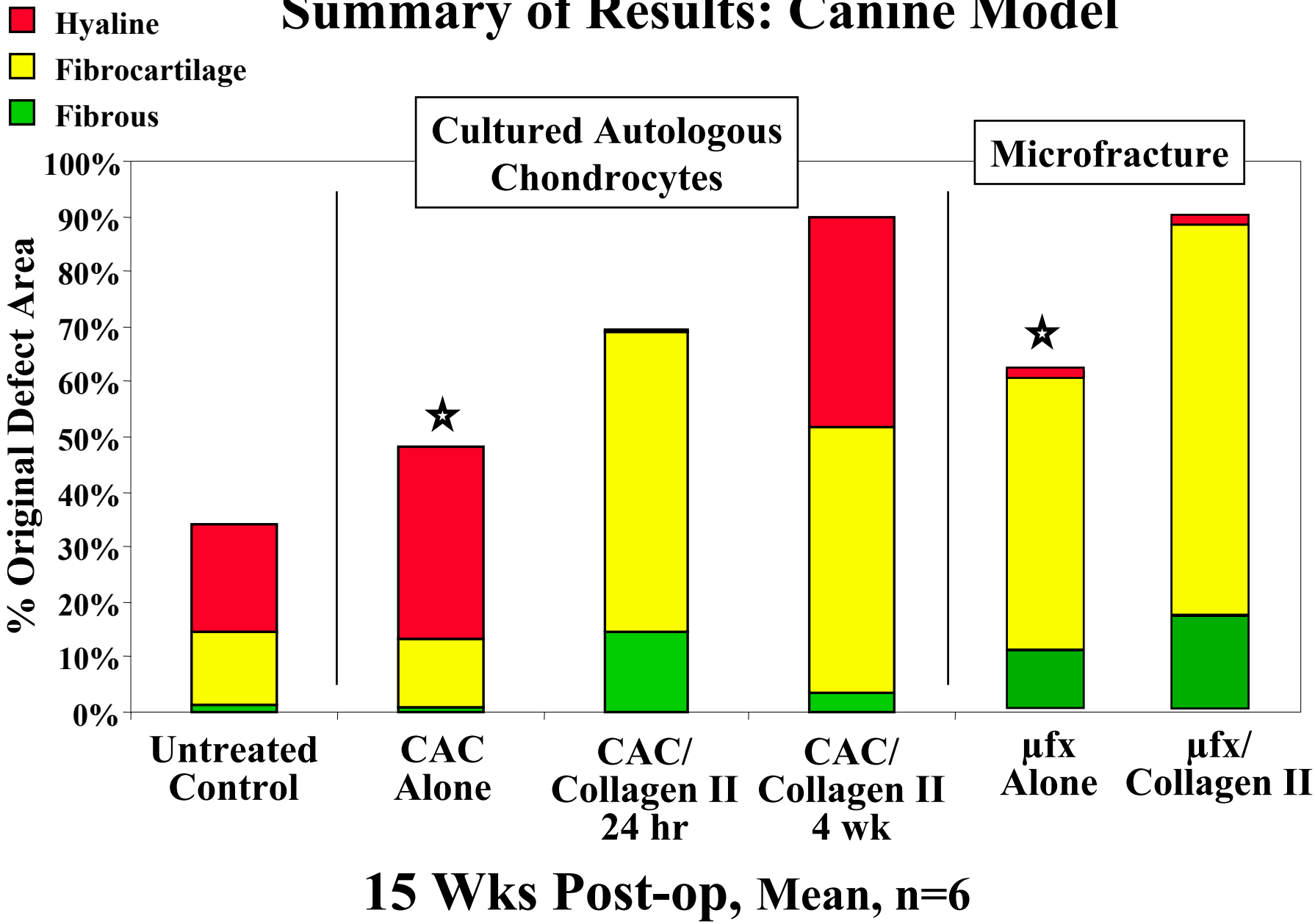
Images removed due to copyright considerations

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

CANINE MICROFRACTURE STUDY TREATMENT GROUPS



Summary of Results: Canine Model



15 Wks Post-op, Mean, n=6

☆ Procedures currently used

JOINT TISSUES

	Loading	Tissue Type	Cell Type	Round/ Lac.	Coll.	PG	Vasc.	
Heal. 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