What’s New in Surgical Restoration of Articular Cartilage

Paul R. Fleissner Jr. M.D.
Clinical Professor of Orthopaedics NEOMED
Crystal Clinic Orthopaedic Center
Akron, Ohio

Articular Cartilage

- Allows Nearly Frictionless Motion
- Lubrication of Joint
- Transmits & Distributes Forces

Articular Cartilage Composition

- Water (65 – 80 %)
- Collagen Type II (10 – 20 %)
- Aggrecan (5 %)
Articular Cartilage

- Avascular
- Aneural
- No Lymphatics

Because of this, articular cartilage has a limited capacity for intrinsic healing and repair.

Is This True???
Mechanism of Injury - Typically Trauma

- Rotational force in direct trauma is the most common cause of injury
- In most cases, injury is in weight-bearing area of articular cartilage
- Usually in the medial compartment (4X – lateral side)
- More often seen with other traumatic injuries to the knee, such as ligamentous or meniscal damage
Goals of Cartilage Repair

- Restore smooth articular cartilage surface
- Relieve patient's symptoms and improve function
- Match biomechanical and biochemical properties of normal hyaline cartilage
- Prevent or slow progression of focal chondral injury to end-stage arthritis

Standard of Care in the U.S.
The objective of Microfracture is to bring marrow–derived stem cells into the lesion to create a repair tissue.

Articular Chondrocytes are not the primary repair cell.
Microfracture repair tissue is predominantly fibrocartilage (Type I collagen).
Repair tissue often lacks long-term durability, since it does not have the appropriate mechanical or biological properties.
Repair tissue begins to deteriorate after about 1 year.
Objective of ACI is to deliver viable chondrocytes to regenerate cartilage tissue in a lesion.

- Two surgical procedures are required: a harvesting surgery and an implantation surgery following cell culture for cell count expansion.
- Suture fixation of membrane is technically demanding.
- High cost (~$25,000)
Objective of OATS/Mosaicplasty technique is to restore the articulating surface with a more or less normal osteochondral structure.

Harvest site morbidity can be extensive, especially with mosaicplasty.

Procedure can be technically demanding.

Repair tissue in the spaces between plugs is fibrocartilage.
OSTEOCHONDRAL ALLOGRAFT

- Indicated for Lesions too Large for OATS or ACI
- Indicated for Lesions that are NOT Contained

Emerging Competitive Products

Juvenile Cartilage

- Particulated Juvenile Cartilage
- 1 Month shelf life
- $4,500 per unit
- Refrigerated Product
 Freeze-Dried Cartilage

- Augment to Microfracture
- Mix with PRP and Seal with Fibrin Glue
- Collagen mostly Type II
Allograft Disc

- Cartilage Bone Disc
- Frozen Product
- Two year shelf life
- Cut to Size
- $5,000 per piece
What's New???

One Step Stem Cell Procedure

- Use Bone Marrow Concentrate for Stem Cells
- With or Without Membrane
- Covered with Tisseel
One Step Stem Cell Procedure

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One Step Stem Cell Procedure
Cartilage Processor

- Point-of-Care Cartilage Autograft Processor

Cartilage Processor

- Conveniently Powered by Surgical Drill

Cartilage Processor

- Precision in Size Reduction and Separation
Cartilage Processor

- Rapid Increase in Surface Area and Chondrocyte Exposure

Cartilage Processor

- Creates autologous cartilage particles smaller than 1mm in size
- Can produce a volume of cartilage graft sufficient to apply to a 4cm squared defect
- Graft produced in 2 minutes
- Utilizes standard surgical drill
- Maintains a high degree of cell viability & bioactivity
- Sterile, disposable

One Year Post-op
Viable Allograft Cartilage

- Allograft cartilage particles <1mm
- Provides viable chondrocytes capable of migrating, proliferating and producing neocartilage tissue matrix components
- Enzyme exposure during processing to improve diffusion of factors and increase chondrocyte exposure
- Cryopreserved to increase shelf life
Scientific Rationale

What is driving this sudden appearance of viable cell allograft products?

- Existing technologies
  - High cost (ACI)
  - Technically difficult (OATS)
  - Patient improvements degrade over time and bridges may be burned (MFx)
- The regulatory hurdle for products needing FDA approval is high
- New science has challenged conventional wisdom regarding cartilage tissue, cartilage grafting, and cryopreservation

Scientific Rationale

- The conventional notion
  - Cartilage is a structural, non-dynamic tissue in which chondrocytes are “trapped”.
  - Limited regenerative capacity – as if chondrocytes are not looking for something to do, they’re looking for a reason to die
  - This conclusion seems reasonable given that lesions on articular surfaces are not expected to heal, but rather to progress to chronic degeneration
Scientific Rationale

- The historically dominant cartilage repair technologies are consistent with the conventional notion
  - Debridement/Chondroplasty
    - Clean up and smooth out the articular surface to improve sliding, while disturbing the chondrocytes as little as possible
  - ACI (autologous chondrocyte implantation)
    - Liberate the chondrocytes entirely from their pericellular “prison”, so they can proliferate, migrate, regenerate
  - Microfracture (marrow stimulation)
    - Get the chondrocytes out of the way entirely, and let stem cells do the work
  - OATS
    - Replace the articular surface with undisturbed, fully formed articular cartilage; no need for the chondrocytes to do anything

Scientific Rationale

- The new paradigm
  - Cartilage tissue is suitable for void filling and provides scaffolding and growth factors
  - Chondrocytes are capable of migrating, proliferating, and producing neo-cartilage tissue matrix components

If you…
  - Position the chondrocytes near the tissue surface (or vice versa)
    - Reduces the distance needed to migrate out of the tissue, and increases exposure to external stimulating factors
  - Provide progenitor cells and/or growth factors (BMAC, PRP) as part of the surgical technique
    - To provide additional stimulus for neo-cartilage matrix component (e.g., GAG) production by chondrocytes

Cartilage Processor

- Following Particulation:
  - Chondrocyte Viability Remains high
  - Chondrocytes Can Produce Matrix Components
  - Chondrocytes Can Proliferate and Occupy the New Matrix
Scientific Rationale

- Chondrocyte viability remains >90%
  - Qualitative Live/Dead Assay (Green = live cell)

SEM showing cells at fragment surface

Scientific Rationale

- Chondrocyte viability remains >90%
  - Quantitative cell viability assay

![Bar chart showing cell viability](chart.png)

Scientific Rationale

- Chondrocytes produce matrix components
  - Quantitative GAG assay during 4 weeks culture

![Bar chart showing GAG assay](chart2.png)
Scientific Rationale

- Chondrocytes proliferate and occupy new matrix
  - Fluorescent microscopy showing chondrocyte outgrowth and particle fusion

Viable Allograft Cartilage

- The enzyme exposure process...
  - Promotes earlier, more robust chondrocyte bioactivity

Following cryopreservation...
  - The chondrocytes rapidly recover to bioactivity levels comparable to non-cryopreserved fresh allograft tissue

Viable cartilage allograft...
  - Is immunologically safe to implant

Scientific Rationale

- Enzyme exposure process
  - Improves chondrocyte outgrowth from the fragments
  - Improves particle fusion

- Cryopreservation
  - Chondrocytes demonstrate robust outgrowth from fragments following cryopreservation
  - Outgrowth from enzyme exposed tissue occurs faster than from non-exposed tissue (both cryopreserved)
  - Bioactivity of cryopreserved tissue is low initially after thawing, but rapidly recovers
**Scientific Rationale**

Outgrowth results with human tissue

![Images of untreated and treated cartilage fragments](image)

- Untreated and treated human cartilage fragments embedded in fibrin glue.
  - (A) Untreated cartilage fragment - t0.
  - (B) Untreated cartilage fragment - 6 wk of culture.
  - (C) Treated cartilage fragment - t0.
  - (D) Treated cartilage fragment - 6 wk of culture.
  - The f corresponds to fibrin. The arrow shows cellular outgrowth.

**Scientific Rationale**

Cryopreservation can be utilized to increase the shelf life of enzyme-exposed allograft tissue.

![Images of cryopreserved and non-cryopreserved cartilage fragments](image)

- Chondrocytes demonstrate robust outgrowth from enzyme-treated fragments following cryopreservation.

**Scientific Rationale**

Human cartilage fragments can be cryopreserved up to at least 6 months and still demonstrate robust outgrowth and matrix production similar to non-cryopreserved cartilage.

![Images of cryopreserved and non-cryopreserved cartilage fragments](image)

- Histological section of adult human cartilage fragments stained with H&E.
  - (A) Fresh fragments - uncultured.
  - (B) Fresh fragments - 8 weeks of culture.
  - (C) 12 weeks cryopreserved - 8 weeks of culture.
  - (D) 24 weeks cryopreserved - 8 weeks of culture.
Where Do We Go From Here?

Maybe Cartilage Is Repairable?

Chondral Fracture
Bioscaffolds & Gene Therapy

MACI
- FDA approval in November

MACI
- Two stage procedure
- Very Expensive
- Failures difficult to convert to other procedures