Tackling the perplexing challenges of articular cartilage regeneration

An overview of this area’s unique issues, treatment methods, and our ECM-Loaded Allograft Technology.
Articular cartilage (from the Latin articularis) is the smooth, elastic, white cartilage tissue that covers the articular surfaces of bone ends (where they come together to form joints). Healthy cartilage helps absorb shock, and allows joints to move smoothly, and reduces friction.¹/²

Hyaline Cartilage: Translucent bluish-white tissue that forms the main component of the joint surface. When it is damaged, the joint surface may become rough, which can cause pain when bones move along it, make movement difficult, and lead to arthritis in the joint.¹

Articular Cartilage Damage:
- Occurs most often in young adults and is common in runners as well as in skiers, cyclists, and soccer players.
- Can be caused by injury, overuse, parts out of alignment, or muscle weakness as well as from normal wear-and-tear.

The Major Challenge:
Articular cartilage has a very limited capacity for self-repair (healing). Small damage does not repair itself and often worsens over time which can cause the onset of osteoarthritis.³

Arthroscopic Grading System for Cartilage Defects⁴

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>(normal) healthy cartilage</td>
</tr>
<tr>
<td>1</td>
<td>cartilage has a soft spot, blisters, or superficial wear</td>
</tr>
<tr>
<td>2</td>
<td>minor tears of less than one-half the thickness of the cartilage layer</td>
</tr>
<tr>
<td>3</td>
<td>lesions have deep crevices of more than one-half the thickness of the cartilage layer</td>
</tr>
<tr>
<td>4</td>
<td>the cartilage tear is full thickness and exposes the underlying subchondral bone</td>
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¹http://orthoinfo.aaos.org/topic.cfm?topic=a00422
²http://www.dartmouth-hitchcock.org/ortho/articular_cartilage_injury.html
³https://en.wikipedia.org/wiki/Articular_cartilage_damage
⁴The International Cartilage Repair Society
Chondral injuries (articulate cartilage injuries) - whether focal or diffuse - are particularly difficult to treat.

The nuances of cartilage structure and its natural environment limit its ability to self-repair:

- Cartilage is *aneural* and *avascular*: it lacks of nerves and blood supply, respectively.
- The osteochondral (articular cartilage (*chondro*), and the bone (*osteo*) underneath\(^2\)) environment demonstrates a highly-organized zonal architecture and limits cartilage’s ability to self-repair with restricted vascularization.\(^1\)

When articular cartilage does self-heal, it often does so incorrectly:

- Although cartilage is avascular, when damage spreads from the chondral defect to the subchondral bone (the bone below the cartilage that provides support for the cartilage of the articular surface), the bone's blood supply initiates a healing process in the defect.

This produces scar tissue comprised of a type of cartilage called *fibrocartilage*, which can fill in the articular cartilage defect, but varies significantly in structure from the original hyaline cartilage.

Fibrocartilage is much denser than hyaline cartilage and can’t withstand regular wear-and-tear like hyaline cartilage so is at a higher risk of breaking down.

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\(^1\) Articular Cartilage Repair of the Knee” Karen Hambly, www.cartilagehealth.com/acr.html

\(^2\) http://www.uwhealth.org/sports-medicine/clinic/osteochondral-injuries/10110

In the face of all of these challenges...

How then should we treat articular cartilage damage?

The Aim: Due to the shortcomings of fibrocartilage in the role of replacement articular cartilage, the goal of cartilage restoration procedures is to stimulate new hyaline cartilage growth to replicate the body’s original performance.

A Complex Solution:
Cartilage function requires the balanced interplay of hydration/lubrication and the ability to withstand compressive, tensile, and the other mechanical forces at play in the course of normal daily life.
Hence, tissue engineering efforts to repair cartilage necessarily must consider the cells, scaffold, and environment surrounding the injury.

Surgical techniques to repair damaged cartilage continue to evolve, but biological solutions, including cell-based therapies and stem cell-derived technologies, offer the promise of addressing the age-old (and often, age-related) need for effective approaches to cartilage repair and regeneration.

This article features an overview of several articular cartilage treatment technologies:
- Osteochondral Autograft Transfers / OsteoArticular Transfer System (OATS)
- Osteochondral Allograft Transplantation (OA)
- Autologous Chondrocyte Implantation (ACI)
- Allogeneic Juvenile Chondrocytes
- ECM-Loaded Allografts
  (the focus of Lattice Biologics’ current Next Generation Allograft research and development efforts)
OATS stands for **Osteochondral Autograft Transfers** or **OsteoArticular Transfer System**. OATS is most accurately described as **Osteochondral Autograft Resurfacing/Mosaicplasty**. ("Osteo-" is derived from the Greek word for bone (osteon), whereas "chondral" is derived from the Greek khondros, which refers to cartilage.\(^1\)

**Autografts** or **autologous grafts**: (auto, meaning self) tissues that are harvested from and transplanted within the same patient.

**Mosaicplasty**: procedure of implanting multiple small plugs in a pattern to fill a defect.

**OATS (Osteochondral Autograft Resurfacing/Mosaicplasty)**: treatment procedure for filling small defects (2-4 cm\(^2\)) with even smaller circular grafts (4-8 mm) of bone and cartilage which are harvested from the patient (usually from a non weight-bearing cartilage region) and transplanted in a mosaic pattern.

Due to limitations in harvesting donor site material, this procedure is only used when the defects to be repaired are small or when less invasive methods (e.g. microfracture) have failed. Suitable defects for this procedure can arise from traumatic injury or chronic cartilage injuries, such as osteoarthritis.\(^1\)

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Osteochondral Allograft (allogeneic graft) (allo, meaning other) therapies are similar to the traditional OATS procedure; however, the donor tissue originates from another person, most notably, cadaveric tissue.

**Pro’s:** Area size: This method can be used for larger defects (>4 cm²) because donor tissue is available in greater quantity than it would be from the patient’s own body.

**Con’s:** Compatibility: This can be an issue, but surgeons and manufacturers take extra measures to match donor material to the patient (such, as to match knee or other joint size).

Limited freshness time window: There are also concerns with the freshness of the graft and viability of the tissue cells. Cartilage transplant must occur within two weeks post donor tissue recovery to preserve the cartilage cell viability.

Outcomes: Grafts are sutured to the site of injury using fibrous glue, but healing outcomes can be constrained by the viability and compatibility of the graft tissue.

Osteochondral Allograft transfer. A large cylindrical plug is harvested from a cadaveric femoral condyle and implanted in the matched position in the patient’s cartilage defect through an open approach.

Source: http://www.gamradtortho.com/conditions/KneeArticularCartilageRestoration.php
Autologous Chondrocyte Implantation is a cell-based therapy for repairing damaged cartilage.

The Process: involves harvesting cartilage cells from the patient, expanding the cells using laboratory culture, and then implanting the cells back into the patient through an open surgery underneath a patch sewn to the native cartilage.

Significant improvements have been made to the technique since its original description in 1994. These include the implantation of cartilage cells on matrices or scaffolds rather than underneath a patch.

Although Autologous Chondrocyte Implantation (ACI) has shown promise in repairing certain cartilage lesions, the approach still suffers from a number of limitations.

Limitations:
1) Donor site morbidity
2) Limited number of cells
3) Loss of phenotype during ex vivo expansion
5) Dramatic age-related decline in chondrogenic activity.

The Upside:

Regenerative Properties: Allogeneic juvenile chondrocytes (from <13-year-old donors) appear to superior to adult cells in their ability to regenerate cartilage.

Juvenile chondrocytes show superior cartilage production in vitro: 100x higher proteoglycan content and 100x and 700x higher collagen types II and IX.

Reduced Risk: Allogeneic juvenile chondrocytes grew faster than adult cells and did not stimulate lymphocyte proliferation, suggesting they pose little risk of immunologic incompatibility in adult hosts.1

Lasting Synthesis Capabilities: Studies of juvenile chondrocytes grown in the presence of adult chondrocytes (and/or adult cartilage fragments) demonstrate that they retain their ability to abundantly synthesize new cartilage in a pseudo “transplanted” adult environment.2

See sources on the following page.
Allogeneic juvenile chondrocytes are becoming a worthwhile option for repairing articular cartilage lesions of considerable size, that were once considered unlikely to heal from transplanted cell therapy approaches.

Current studies using “particulated juvenile articular cartilage allografts” appear to overcome previous obstacles to cartilage regeneration, such as limited engraftment and necrosis of transplant tissue. Additionally, new techniques, including cutting transplanted cartilage tissue before implanting, ostensibly enhances “filling” of the defect by allowing chondrocytes to escape from the matrix, migrate, multiply, and form new cartilage that integrates with the surrounding host tissues.³

Figure: Juvenile and adult chondrocytes cultured separately were compared after 6 weeks of incubation. Shown are typical Safranin-O stains (a cartilage stain) for proteoglyca and immunofluorescence stains for link protein, collagen type II. Vigorous cartilage matrix production was evident in the culture of juvenile cells, but not in the culture of adult cells.³

Although cell-based therapies offer a promising biological approach for treating cartilage defects, retaining cellular viability during expansion and implantation is never guaranteed. Lattice Biologics is developing ECM-Loaded Allograft Technology to increase the odds.

**ECM Benefits:**

- Provides mechanical support for cells and tissues.
- Integrates cells into tissues.
- Influences cell shape and movement, provokes responses from mechanical and chemical signaling pathways.
- Coordinates the behavior of different cells in tissues.

**Promising Therapies:** Current studies suggest that stem cell-derived extracellular matrix (ECM) may contain all of the instructive potential to create an optimal healing microenvironment.¹

**Differentiation:** Directed stem cell cultivation in vitro can be used to reconstruct the optimal ECM to favor cell proliferation and lineage-specific differentiation. *Proof-of-concept studies have already demonstrated the capacity for stem-cell secreted ECM to be transferable and influence newly-introduced stem cells.*²

**Activating the Body:** Application of ECM generated by this native tissue engineering approach to decellularized allograft material could reconstruct the regenerative niche in the body and support production of new tissue from the host’s own circulating stem cells.

Designing this type of customized hybrid biomaterials to create implantable cartilage-healing allografts utilizes stem cell technology without the regulatory hurdles or immunological risks associated with a cell-based approach.