Emerging technologies: What is the future of cartilage restoration?

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Abstract
Introduction
Injury to articular cartilage injury is a common and challenging diagnosis, often resulting in substantial morbidity for patients. A treatment strategy typically includes simple debridement, microfracture, osteochondral autograft or allograft transplantation or cell-based therapy such as autologous chondrocyte implantation. We review cell-based cartilage repair technologies currently in the early phases of clinical application and highlight the promise and limitations in this rapidly advancing area of musculoskeletal medicine.

Conclusion
Cartilage restoration is a field that is currently growing at a fast pace. We reviewed new cartilage restoration technologies; many of these have shown promise but have relatively limited long-term outcome data to guide clinicians. Future research will help improve our understanding, and more effective techniques can become available.

Introduction
Despite substantial progress on basic science and clinical fronts over the last few decades, articular cartilage injury remains an enormous challenge for musculoskeletal physicians. The diagnosis is unfortunately quite common—in a review of over 25,000 knee arthroscopies performed over a 15-year period, the incidence of chondral lesions was noted to be 60%6. Chondral injuries often cause substantial morbidity for patients, including significant time lost from work and sport. Furthermore, while the natural history of the various types of chondral lesions is not yet fully understood, a long-term concern is development of progressive degenerative joint disease. The disease burden for both patients and physicians is large, and given the complexity of the issues involved, treatment dilemmas often exist.

Algorithms for operative treatment of symptomatic chondral lesions vary, but guidelines for choosing between currently available treatments have been offered15. These include evaluation and treatment of any associated joint pathologies including systemic disorders, limb malalignment, meniscal deficiency and ligamentous instability. A thorough assessment of the size, thickness and location of the chondral lesion is also required. Based on lesion and patient characteristics, a treatment strategy is chosen. In current practice, this typically includes one of the following options: simple debridement, microfracture, osteochondral autograft or allograft transplantation or cell-based therapy such as autologous chondrocyte implantation (ACI).

Each of these strategies has relative merits and limitations, but no currently available technique meets all requirements for an ‘ideal’ treatment option. As described by Gomoll and Farr; an ideal cartilage repair technique would be (1) cost-efficient, (2) easily available or of-the-shelf, (3) implantable through a single-stage, minimally invasive technique, (4) produce physiologically stratified, fully integrated (basilar and marginal) hyaline repair tissue and (5) allow for quick return to activity.6 While current options—with varying degrees of efficacy—may ameliorate symptoms, the broader goal of restoring a durable, smooth, hyaline tissue that effectively transmits shear and compressive loads from the cartilage to the bone remains elusive7. A recapitulation of the multilayered nature of hyaline cartilage, including the normal bone–cartilage interface, appears to be fundamental to this endeavor7.

The goal of this critical review is to provide an overview of cell-based cartilage repair technologies currently in the early phases of clinical application and highlight the promise and limitations in this rapidly advancing area of musculoskeletal medicine.

Discussion
Restoration techniques based on chondrocyte transplantation
ACI
ACI (Sanofi Bioservices, Cambridge, MA) was the first technique developed to treat chondral defects with chondrocyte transplantation. ACI was pioneered in Sweden in the mid-1980s and was the subject of a landmark clinical report by Peterson and Brittberg in 19944. The technology received FDA approval for use in the United States in 19956. The concept involves a two-stage procedure in which a small sample of healthy, articular cartilage is biopsied and undergoes enzymatic digestion followed by cultivation and expansion of chondrocytes in a laboratory setting over a several week period. The resulting cell culture is treated with trypsin and placed in liquid suspension...
for implantation at a second-stage surgery. The cellular implantation requires an open surgery in which the chondral lesion is carefully prepared and a periosteal (or collagen) patch is sutured in place over the lesion to create a watertight seal. The cellular suspension is then delivered into the lesion bed below the patch. By implanting expanded chondrocytes into the lesion, the goal is to ultimately fill the defect with a mature hyaline-like cartilage, with wear and load transmission properties more closely approximating native cartilage.

Since its introduction, ACI has gained widespread acceptance as a viable cartilage repair strategy. In addition, generally favourable clinical results have been reported in numerous studies, and ACI remains a valuable tool for many cartilage restoration surgeons. However, there are limitations to the technique. These include the overall cost of the procedure, the two-stage surgical technique, lengthy and intensive rehabilitation and complications attendant to an extensive surgical procedure. This has limited the widespread use of ACI.

To address some of these potential problems and limitations with the original ACI method, numerous variations on the original concept have been developed in the past decade. As tissue engineering capabilities have become increasingly sophisticated, much interest has focused on developing scaffolds that accommodate autologous chondrocytes and promote their growth in a supportive three-dimensional environment, thereby creating an implantable tissue with properties more closely approximating hyaline cartilage.

**Emerging cartilage restoration technologies—two-stage techniques**

Matrix-induced ACI (MACI) MACI (Sanofi Biovernas) is a second-generation ACI technique that involves the use of a porcine-derived type I/III collagen carrier matrix. Like ACI, the technique requires a two-stage surgical procedure, with initial harvest of a cartilage sample, followed by expansion in culture for several weeks. The cells are then seeded on the collagen matrix and cultured for an additional 3 days. The collagen patch can then be implanted with either an arthroscopic or open technique. Additionally, it can be secured in place with fibrin glue, rather than suture as in the original ACI technique. Although it is available in Europe, MACI is not yet FDA approved in the United States and is currently undergoing a phase 3 multicentre clinical trial in Europe. A number of case series have reported initial results with MACI, and three recent studies have been published with MACI versus osteochondral autograft, ACI with collagen membrane and microfracture. In all three studies, MACI showed improved clinical results over the alternative restorative techniques.

**Hyalograft C**

Hyalograft C (Fidia Advanced Biopolymers Laboratories, Padova, Italy) is a tissue engineered scaffold (Figure 1), whose main component – HYAFF11 – is an esterified derivative of hyaluronic acid (HA) and is a prominent component of normal cartilage matrix. A cartilage sample is obtained from an initial arthroscopy, and the chondrocytes are harvested and seeded onto the HA scaffold. This scaffold is comprised of a network of 20-micron thick fibres. It is believed that the scaffold promotes matrix production and limits dedifferentiation of cells expressing the chondrocyte phenotype. The graft can be implanted arthroscopically with application of gentle pressure to allow fit into the lesion bed. The scaffold is designed to take advantage of the natural adhesive properties of the complex sugars in the matrix and allows for implantation without adjunctive fixation (Figure 2). A number of case series evaluating hyalograft C have been conducted, including most recently a seven-year follow study of 62 patients, which showed maintenance of statistically improved International Knee Documentation Committee (IKDC) scores and reported an 11% failure rate.

**BioSeed C**

BioSeed C (BioTissue Technologies GmbH, Freiburg, Germany) is a synthetic scaffold in clinical use in Europe since 2001 (Figure 3). The polymer scaffold contains fibrin, polyactic/polyglycolic acid [polyglactin, Vicryl (Ethicon GmbH, Norderstedt, Germany)] and polydioxanone. Autologous chondrocytes are harvested and embedded in the fibrin and cultured. At a second stage, the graft material is fitted into the chondral defect and secured at each corner with resorbable sutures via an anchor-knot technique. The fixation technique is felt to work well even for partially uncontained defects. Four-year follow-up data on a cohort of 52 patients with BioSeed C implants showed improved Lysholm, Knee Injury and Osteoarthritis Outcome Score (KOOS), and IKDC scores and magnetic resonance imaging (MRI) documentation of moderate to complete defect fill in 43 of 44 patients.

**NeoCart**

After initial arthroscopic cartilage biopsy, the NeoCart technique (Histogenics, Waltham, MA) requires seeding of autologous chondrocytes in a bovine-derived three-dimensional type I collagen honeycomb matrix (Figure 4). The chondrocyte-embedded matrix is then cultured in a bioreactor, which creates an environment of variable hydrostatic pressure and low oxygen tension, to simulate intra-articular conditions. The resulting tissue has been shown to contain glycosaminoglycan and a favourable ratio of...
## Table 1  Characteristics of selected scaffolds used in emerging cartilage restoration techniques

<table>
<thead>
<tr>
<th>Product name</th>
<th>Scaffold type</th>
<th>Adjunct with MFx?</th>
<th>Trials</th>
<th>Cell free?</th>
</tr>
</thead>
<tbody>
<tr>
<td>NeoCart (Histiogensics Corporation, Waltham, MA)</td>
<td>Protein based (bovine-type I collagen)</td>
<td>No</td>
<td>• Phase II studies complete&lt;br&gt;• Ongoing phase III study</td>
<td>No&lt;br&gt;Harvested chondrocytes grown into collagen and secured via bioadhesive</td>
</tr>
<tr>
<td>CaRes-1S (Arthro-Kinetics, Esslingen, Germany)</td>
<td>Protein based (rat-tail type I collagen)</td>
<td>No</td>
<td>• Animal trials&lt;br&gt;• Case study of 15 humans&lt;br&gt;• No comparative human trials to date</td>
<td>Yes&lt;br&gt;Shown in animal studies to have equivalent repair tissue compared to cellular technique</td>
</tr>
<tr>
<td>Hyalograft C (Fidia Advanced Biopolymers, Abano Terme, Italy)</td>
<td>Carbohydrate based (HYAFF 11-esterified derivative of hyaluronate)</td>
<td>No</td>
<td>• Improved patient outcomes in clinical studies&lt;br&gt;• Multiple comparative studies with MFx showing improved results at 5 years</td>
<td>No&lt;br&gt;Combined with autologous articular chondrocytes&lt;br&gt;Advantage over ACI is less invasive procedure</td>
</tr>
<tr>
<td>Cartipatch (Tissue Bank of France)</td>
<td>Carbohydrate based (Agarose-alginate)</td>
<td>No</td>
<td>• Phase II multicentre study showed significant improvements&lt;br&gt;• Two phase III trials comparing mosaicplasty and MFx on-going in Europe, Asia and Middle East</td>
<td>No&lt;br&gt;Autologous chondrocytes implanted into the 3D scaffold. 3D scaffold thought to improve stability and ease of surgical handling</td>
</tr>
<tr>
<td>BST-CarGel (biosynotech, Quebec, Canada)</td>
<td>Combined scaffold (polysaccharide chitosan and an aqueous glycerol phosphate buffer)</td>
<td>Yes</td>
<td>• Phase II clinical trials show improved WOMAC scores for pain, stiffness and function&lt;br&gt;• Phase III randomized multicentre study comparing with MFx alone is complete but data not published to date</td>
<td>Yes&lt;br&gt;Scaffold is inserted in one step to an area that has been prepared using bone marrow stimulation techniques</td>
</tr>
<tr>
<td>Bioseed C (BioTissue Technologies GmbH)</td>
<td>Combined scaffold (fibrin glue combined with a copolymer of PGA, PLA and PDS)</td>
<td>No</td>
<td>• Phase III trials comparing with ACI alone showed improved outcome scores and comparable outcome levels&lt;br&gt;• Caution in that ACI-only group had larger defect and longer follow-up</td>
<td>No&lt;br&gt;Harvested autologous chondrocytes are implanted onto the 3D scaffold</td>
</tr>
</tbody>
</table>
Combined scaffold (polymor-
erization of homologous fibrinogen and recombinant hyaluronan)  No  Phase II clinical trial versus MFX on-going in United States and Israel  No  Cartilage biopsy with high chondrogenic potential placed in recombinant FGF-2 prior to seeding 3D scaffold  Applied via miniarthrotomy and sealed with fibrin glue

Chondro-Gide  Combined scaffold (bilayered collagen membrane)  Yes  Can also be used in characterized chondrocyte implantation  • Outcome score improvement with adjunct to CCI  • Positive clinical improvement and MRI improvement when used as adjunct to MFX  • No current studies to compare long-term results of ACI or versus MFX alone  Both acellular and cellular techniques  Can be used in two-step process as an adjunct to injected chondrocytes or as a one-step adjunct to microfracture in a technique known as autologous matrix-induced chondrogenesis

BioCart II  BioCart II (ProChon BioTech, Rehovot, Israel) is a two-stage autologous chondrocyte technique that utilizes autologous serum with additional growth factors to expand the chondrocytes and seed them onto a fibrin/HA-based scaffold (Figure 5)28. The scaffold has a three-dimensional open pore design, which promotes chondrocyte growth. A recent case series reported on 31 patients at an average of 17-month follow-up and demonstrated significantly improved IKDC scores as well as MRI T2-mapping values29.

CaReS  CaReS (Ars Arthro, Esslingen, Germany) utilizes a three-dimensional hydrogel based on rat-tail-derived type I collagen to promote growth of harvested autologous chondrocytes. The chondrocyte-gel mixture is cultured with autologous serum for 2 weeks and is then implanted into the chondral defect and secured with fibrin glue. The three-dimensional framework is believed to decrease the potential for chondrocyte dedifferentiation29. In addition, the hydrogel can be manufactured to meet surgeon-requested size specifications, and due to its water content it can be moulded intra-operatively to conform to the unique shape of each lesion. A multicentre case series reported on 116 patients treated with CaReS with average follow-up of 30 months and showed substantially improved IKDC, SF-36 and pain scores29.

Cartipatch  Cartipatch (Tissue Bank of France, Lyon, France) also uses a three-dimensional hydrogel scaffold for treating chondral defects. In this case, the hydrogel scaffold is comprised of a novel agarose-alginate mixture. The technique requires two stages, with initial harvest of a cartilage sample, culture of the chondrocytes with autologous serum, suspension of the cells in agarose-alginate and a second surgery with implantation of the chondrocyte-impregnated hydrogel into the defect via a miniarthrotomy30. The size of the hydrogel plug can be manufactured to meet the size requirements of the defect being treated. The hydrogel plug is manufactured to a predetermined diameter, and at implantation the lesion is drilled to a depth of 4 mm and a diameter corresponding to the size of the implant. The implant is then press-fit into the defect without adjunctive fixation. A multicentre case series of 17 patients with 2-year outcome data has been reported for Cartipatch30. The series demonstrated significantly improved IKDC scores over baseline. In addition, biopsies of the lesion were available in 13 patients—in eight of these, hyaline-like tissue was found at the site of the implantation.
Emerging cartilage restoration technologies—one-stage techniques

**Cartilage autograft implantation system (CAIS)**

CAIS (Depuy Mitek, Raynham, MA) involves arthroscopic harvest of healthy cartilage tissue, followed by mechanical digestion of the cartilage with a specialized instrument to create 1 to 2 mm chondral fragments. The fragments are secured to a synthetic scaffold (comprised of a 35% polycaprolactone, 65% polyglycolic acid copolymer and polydioxanone mesh) with fibrin glue. The scaffold is trimmed to the desired size and shape and implanted via a miniarthroscopy into the defect, with the chondral fragments facing the subchondral bone and then secured with two or more bioabsorbable staples. Initial results of a prospective randomized trial of CAIS versus microfracture followed 29 patients at 2-year follow up. The CAIS group showed statistically improved outcomes for IKDC and KOOS but no difference in SF-36 compared with the microfracture group. MRI data revealed increased number of intralesional osteophytes in the microfracture group. Clinical trials of CAIS are on-going in the United States (no longer enrolling patients) and Singapore (actively enrolling).

**DeNovo**

DeNovo NT (Natural Tissue) Graft (Zimmer, Inc, Warsaw, IN) consists of allogenic cartilage tissue obtained from juvenile human donor joints. The graft is minced into small pieces and implanted in a single stage into a chondral lesion and secured with fibrin glue. Juvenile donor cartilage is chosen based on the concept that juvenile chondrocytes have greater capacity for cell multiplication and anabolic activity than adult chondrocytes. The juvenile minced cartilage graft is considered allograft tissue and is therefore not formally regulated by the FDA. DeNovo NT is currently being studied in several on-going postmarket trials.

DeNovo ET (Engineered Tissue) (ISTO, St. Louis, MO) like DeNovo NT is derived from juvenile human donor cartilage; however, the ET product undergoes expansion in culture to produce a hyaline-like graft that can be trimmed to size and implanted with fibrin glue.

**Autologous matrix-induced chondrogenesis (AMIC)**

AMIC is a novel approach to cartilage restoration that combines microfracture with a porcine-derived collagen type I/III patch (Chondro-Gide, Geistlich Pharma AG, Wolhusen, Switzerland). In contrast to other techniques that have been discussed, no allogenic or autologous chondrocytes are implanted into the defect. In theory, the application of the collagen patch overtop of the microfracture bed can stabilize the clot and provide an enhanced three-dimensional framework for cell growth and expansion. In addition, AMIC has the advantage of being a one-stage procedure. The technique requires preparation of the collagen patch overtop of the microfracture bed, and it is currently under clinical trial.

**CAIS**

CAIS (Depuy Mitek, Raynham, MA) involves arthroscopic harvest of healthy cartilage tissue, followed by mechanical digestion of the cartilage with a specialized instrument to create 1 to 2 mm chondral fragments. The fragments are secured to a synthetic scaffold (comprised of a 35% polycaprolactone, 65% polyglycolic acid copolymer and polydioxanone mesh) with fibrin glue. The scaffold is trimmed to the desired size and shape and implanted via a miniarthroscopy into the defect, with the chondral fragments facing the subchondral bone and then secured with two or more bioabsorbable staples. Initial results of a prospective randomized trial of CAIS versus microfracture followed 29 patients at 2-year follow up. The CAIS group showed statistically improved outcomes for IKDC and KOOS but no difference in SF-36 compared with the microfracture group. MRI data revealed increased number of intralesional osteophytes in the microfracture group.

Clinical trials of CAIS are on-going in the United States (no longer enrolling patients) and Singapore (actively enrolling).
Technologies, Plymouth, MA), activated with an enzyme (Batroxobin, Plateltex S.R.O., Bratislava, Slovakia) to produce a sticky clot and implanted into the chondral defect. The defect is then covered with a collagen-type I/III patch (Chondro-Gide). A case series of 15 patients treated with this technique has been reported. This showed significantly improved VAS, SF-36, KOOS, IKDC, Tegner, Marx and Lysholm scores at 2-year follow-up. MRI data revealed complete fill of the defect in 12 of 15 patients. Histologic analysis of three biopsy specimens revealed tissue with a mixture of hyaline and fibrocartilage.

**Conclusion**

Cartilage restoration is a vast field currently experiencing rapid growth. The scope of the clinical problem of chondral injury is large, and there is a clear need for new technologies with wide availability, simple application and efficacious, lasting clinical results. We have reviewed some of the cartilage restoration technologies currently emerging in clinical practice. While many of these technologies show significant promise, in most cases, there is a paucity of high-level, long-term outcome data to guide clinicians. Future research will clarify the picture greatly. However, at this point, an ideal cartilage restoration technique is not yet available.

**Conflict of interests**

David C. Flanigan, MD, is a consultant for Sanofi and Smith and Nephew.

**Abbreviations list**

ACI, autologous chondrocyte implantation; AMIC, autologous matrix-induced chondrogenesis; BMAC, bone marrow aspirate concentrate; CAIS, cartilage autograft implantation system; HA, hyaluronic acid; IKDC, International Knee Documentation Committee; KOOS, Knee Injury and Osteoarthritis Outcome Score; MRI, magnetic resonance imaging; VAS, visual analogue scale.

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Figure 3: BioSeed C scaffold seeded with $2 \times 10^6$ autologous chondrocytes. (a). Vicryl sutures are then placed at every corner to serve as a pulley (b). The sutures are then fixed transosseously using 1.7-mm k-wires in an inside-out technique (c). The graft as a result fits smoothly into the defect (d). The graft is now securely fixed via a press-fit technique (e). Reprinted with permission from Erggelet C, Kreuz PC, Mrosek EH, Schagemann JC, Lahm A, Ducommun PP, Ossendorf C. Autologous chondrocyte implantation versus ACI using 3D-bioresorbable graft for the treatment of large full-thickness cartilage lesions of the knee. Arch Orthop Trauma Surg. 2010 Aug;130(8):957–64.

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Figure 4: (a) NeoCart implant. (b) NeoCart implanted in situ viewed via miniarthroscopy. Reprinted with permission from Crawford DC, Heveran CM, Cannon WD, Foo LF, Potter HG. An autologous cartilage tissue implant NeoCart for treatment of grade III chondral injury to the distal femur: Prospective clinical safety trial at 2 years. Am J Sports Med. 2009 Jul;37(7):1334–43.


