

# Overview of Existing Cartilage Repair Technology

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**Abstract:** Currently, autologous chondrocyte implantation and osteochondral grafting bridge the gap between palliation of cartilage injury and resurfacing via arthroplasty. Emerging technologies seek to advance first generation techniques and accomplish several goals including predictable outcomes, cost-effective technology, single-stage procedures, and creation of durable repair tissue. The biologic pipeline represents a variety of technologies including synthetics, scaffolds, cell therapy, and cell-infused matrices. Synthetic constructs, an alternative to biologic repair, resurface a focal chondral defect rather than the entire joint surface. Scaffolds are cell-free constructs designed as a biologic “net” to augment marrow stimulation techniques. Minced cartilage technology uses stabilized autologous or allogeneic fragments in 1-stage transplantation. Second and third generation cell-based methods include alternative membranes, chondrocyte seeding, and culturing onto scaffolds. Despite the promising early results of these products, significant technical obstacles remain along with unknown long-term durability. The vast array of developing technologies has exceptional promise and the potential to revolutionize the cartilage treatment algorithm within the next decade.

**Key Words:** cartilage, repair, synthetic, scaffold, minced cartilage, second generation, third generation

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Focal chondral defects have been noted in up to 63% of patients undergoing arthroscopy of the knee.<sup>1</sup> Although a majority are silent, symptomatic lesions result in significant morbidity and present a complex treatment scenario. Current decision-making, on the basis of defect geometry and patient characteristics, progresses linearly from palliative to reparative to restorative options.<sup>2</sup> Cartilage restoration through osteochondral allografting or autologous chondrocyte implantation (ACI) has proven efficacy, but technical and biologic limitations to these procedures exist. A plethora of emerging technologies and associated techniques have been described to advance the first generation of cartilage repair and restoration techniques to help minimize complications with several goals in mind including predictable clinical

and functional outcomes, efficient surgical techniques, cost-effective technology, low-morbidity single-stage procedures, and the creation of durable cartilage repair tissue.

First generation cartilage restoration techniques have focused on the use of allograft and autologous cell 2-stage implantation procedures. ACI addresses 2 important aspects of cartilage repair strategy: the use of autogenous cells and the potential to regenerate hyaline-like tissue. Symptom improvement and durability of ACI has been demonstrated in multiple studies investigating its application in the knee,<sup>3–5</sup> with additional infrequent application to the humeral head<sup>6</sup> and talus.<sup>7,8</sup> The potential to create hyaline cartilage is touted, although second-look biopsies often reveal fibrocartilage or mixed hyaline and fibrocartilage tissue.<sup>4,9,10</sup> Limitations of ACI include the necessity of 2 procedures, relatively long recovery periods, and slow tissue maturation derived from the implanted chondrocytes. Common adverse effects reported to the US Food and Drug Administration (FDA) are failure, delamination, and tissue hypertrophy, which have resulted in a reoperation frequency of approximately 15% to 30%.<sup>11</sup> Apart from mechanical symptoms, morbidity of the anteromedial tibial periosteal donor site is occasionally problematic.

Osteochondral allografting resurfaces focal chondral defects with mature hyaline cartilage. Good to excellent results are reported in over 70% of femoral condyle transplants with long-term follow-up.<sup>12,13</sup> Patellofemoral use is limited owing to difficulty in achieving adequate contour matching and fixation techniques. Incorporation of graft borders into the surrounding native tissue does not often occur and frequently fissures persist. Technical considerations, including fresh tissue preservation methodology, graft handling, and impaction procedures have serious implications on graft viability.<sup>14</sup> Concerns about graft sterility, supply constraints, and cost are also limiting factors to increasing the use of osteochondral allografts.

Currently, ACI and osteochondral grafting bridge the gap between palliation of cartilage injury (ie, debridement) and resurfacing via joint arthroplasty. Because the natural history of articular cartilage lesions when asymptomatic remains largely unknown, a general consensus exists that most can be relatively ignored and treated with proper patient education regarding the development of relevant symptoms related to these defects. That being said, there are certain defects and scenarios that pose legitimate threats to the long-term health of the knee joint. These include patients who have

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undergone subtotal meniscectomy (especially lateral) and associated ipsilateral malalignment in association with a known chondral defect. As the relative invasiveness and resource intensity of any single procedure decreases and the clinical outcomes become more predictable, it is likely that the decision to treat even the asymptomatic incidental defect may lead to increased utilization of available options. Domestically, greater than 400,000 cartilage related-procedures, including debridement (more than 200,000), marrow-stimulating techniques (more than 25,000), ACI (about 1500) and osteochondral auto (more than 1000), and allografting (about 1500) were performed in the year 2007 with an estimated market value of between 50 and 60 million dollars. Estimates of knee arthroplasties are 350,000 per year, with an expectation to increase owing to population growth and increased longevity. Individuals tend to remain active longer, increasing the need for durable alternatives to arthroplasty. The potential market for advanced cartilage therapies is forecasted at 500,000 procedures with a value of \$1.5 billion.

Biostructural and technical considerations play an important role in developing the optimal cartilage repair solution. The optimal technique should be simple, single-stage, and cost-effective with a high rate of success and few associated complications. The ideal construct would contain both a scaffold and optimized chondrocytes potentially incorporating growth factors either at the time of graft creation or as an adjunct to the implantation process. Over 20 products are currently within the biologic pipeline from discovery to phase 3 trials. These innovations represent a variety of technologies including joint resurfacing, synthetic scaffolds, cell therapy, and cell-infused matrices that all seek to emerge as an ideal solution for the treatment of symptomatic chondral defects. Notably, despite the need for these resurfacing solutions, none are dedicated toward the treatment of overt osteoarthritis with ultrastructural and morphologic changes to the subchondral bone and tibio-femoral architecture.

## SYNTHETICS

Synthetic constructs, an alternative to biologic repair, resurface a focal chondral defect rather than the entire joint surface. If feasible, these products would be widely available and cost-effective, with minimal concern for disease transmission compared with allogenic procedures. Implantation would be single-staged and minimally invasive technique completed either arthroscopically or through a miniarthrotomy and quadriceps sparing approach. Developmental considerations include the material properties, osteoconductivity and chondroconductivity, fixation, and biotolerability. The cylinder must be able to withstand weight-bearing forces in confined compression and recreate a low friction, durable surface. Most synthetic constructs have adequate biomechanical properties when placed in a confined environment, but lack an interface that is conducive to tissue ingrowth and replacement. Research in arthroplasty component

loosening confirms the delicate nature of the implant-bone interface.

Frictional wear debris and micromotion are main contributors to osteolysis and periprosthetic inflammation.<sup>15</sup> Synthetic cartilage constructs are considered medical devices and several are currently in the developmental pipeline. They typically follow a device approval pathway through the FDA as class II or class III medical device where they may be required to undergo a formal prospective randomized comparative study for noninferiority or even superiority relative to existing technology. SaluCartilage (Salumedica, Smyrna, GA) is composed of a polyvinyl alcohol-hydrogel. It is available in diameters from 6 to 15 mm and implantable using an osteochondral-type press-fit technique. A cohort of patients, average age 56 years, had significant increases in the Lysholm II and Tegner scores at 2 years without evidence of osteolysis or loosening.<sup>16</sup> An investigation by Falez and Sciarretta had positive outcomes in 13 of 15 at 1 year with 1 case of dislodgement and 1 case of loosening.<sup>17</sup> Currently, SaluCartilage is CE-marked in the European Union and gathering data on long-term follow-up with no formal application at the time of this writing to the FDA status.

The ABS ChondroCushion (Advanced Bio-Surfaces, Minnetonka, MN) plug technology consists of a series of various size cylinders made from biocompatible polyurethane. The design involves copolymerizing a soft durometer polyurethane to a hard durometer polyurethane. The hard durometer portion has a series of circumferential barbs that provide a firm press-fit into the prepared bone layer of an osteochondral lesion. The soft durometer portion of the implant fills the cartilaginous portion of the osteochondral lesion and provides support for the surrounding articular cartilage and a smooth low friction surface for the opposite articulating cartilage. Unpublished preclinical research has demonstrated preservation of the structure and function of the cartilage surrounding the implant and the cartilage on the opposite articulating surface. The data will be submitted to the FDA and most likely will be considered as a medical device requiring further clinical study.

Carticept Medical Inc (Alpharetta, GA) is developing a poly (vinyl alcohol) hydrogel as a cartilage replacement therapy for full thickness chondral defects. The material is optimized to closely resemble the wear, strength, and coefficient of friction properties of human articular cartilage. A proprietary patterning technology is applied to the bone contact side of the hydrogel to induce bone ingrowth, to initiate long-term fixation of the implant. Small and large animal studies have shown promising results with the implant. Carticept Medical will compile the results and final data to submit for approval for an initial US clinical trial.

## SCAFFOLDS

Scaffolds are designed to be chondroconductive or osteoconductive. They are implanted as cell-free constructs typically as a 3-dimensional construct into

osteocondral defects or by themselves often in liquid form to augment marrow stimulation techniques. Scaffolds are both cost-effective and time efficient, require a single-stage procedure, and avoid the use of allogenic tissue and expensive cell-based technology. Though the application is similar to synthetics, scaffolds have been developed to permit ingrowth, resorption, and replacement to form a biologic “net” to maintain the appropriate biologic environment to foster cartilage repair. As an adjunct to existing technology (ie, microfracture), the resorption profile should parallel the formation of native cartilage or cartilage replacement tissue.

Several scaffolds are being investigated as adjuncts to microfracture or used in isolation to fill an osteochondral defect. The regulatory pathway ranges from consideration of a scaffold as a device or a biologic. Those that are considered devices are often fast-tracked to market by limiting their labeled application as back-fill for an osteochondral defect rather than being used primarily to treat weight-bearing chondral or osteochondral lesions. In addition, some scaffolds are actually designed to “mimic” the layered anatomy of the osteochondral organ by making subtle changes to their material composition at their surface relative to the portion of the device that will sit within the subchondral bone.

The TrueFit Plug (OsteoBiologics/Smith & Nephew, Andover, MA) is a poly[D,L-lactide]/glycolide and calcium sulfate polymer marketed as a bone void filler that degrades over 6 to 9 months. Most commonly, the plug is used for “back-filling” trochlear donor sites for the Osteochondral Autograft Transplantation procedure. The TrueFit plug has Investigational Drug Exemption/Premarket Approval (IDE/PMA) from the FDA for this purpose and there is emerging experience investigating the off-label usage in weight-bearing femoral condyle lesions.

Examples of scaffolds that are anticipated to be used as adjuncts to microfracture include BST CarGel (BioSyntech, Quebec, Canada) and Gelrin C (Regentis, Haifa, Israel). Hydrogel scaffolds may prove useful as an adjunct to marrow-stimulation techniques, functioning to stabilize the fibrin clot and retain mesenchymal stem cells.

BST-CarGel is a chitosan-glycerol phosphate-based scaffold whose active component is a polyglucosamine thrombogenic polysaccharide. Peripheral whole blood is added immediately before implantation resulting in adhesion and polymerization of the construct. In sheep, CarGel-augmented microfracture had increased cells and collagen resulting in a more hyalinelike fill when compared with microfracture alone.<sup>18</sup> In rabbits, the chitosan-glycerol phosphate implants resulted in better integration and a more hyalinelike tissue than subchondral drilling alone.<sup>19</sup> BST-CarGel is currently in phase 3 trials in Canada and phase 2 trials in the United States.

GelrinC is a photopolymerizable PEGylated fibrinogen liquid that transforms into a hydrogel that precisely controlled degradation kinetics determined by the extent of PEGylation [ie, the degree of conjugation of polyethylene glycol (PEG) to denatured, reduced

fibrinogen chains making up the hydrogel network]. Preformed hydrogel implants are applicable for standard uses<sup>20</sup>; otherwise the liquid is polymerized in vivo with ultraviolet light to create a custom implant, contiguous with the cartilage defect margins. In vitro, GelrinC exhibits innate chondrogenic and osteoconductive potential, while being nonimmunogenic. Implantation in an ovine model demonstrates type II collagen and proteoglycans in defects containing the hydrogel, whereas empty defects had fibrocartilage and scar formation.<sup>21</sup> Gelrin C is in preclinical stages of investigation.

Both hydrogels will likely be considered as a class III medical device and require a formal IDE/PMA. Ongoing challenges with scaffolding include maintenance within the defect, controlling the rate of degradation, and promoting tissue maturation. This is rapidly emerging area of cartilage repair with a number of products in the developmental pipeline.

Chondromimetic (Orthomimetics, Cambridge, UK) is a porous biphasic scaffold with articular cartilage-like and subchondral-like layers. The construct, composed of calcium phosphate, collagen, and glycosaminoglycans, is designed as a scaffold that can be placed within a contained osteochondral defect. The structure provides a significant surface area for cell adhesion and facilitates remodeling. Chondromimetic implants in a caprine model demonstrated increased chondral and osseous fill of the defect when compared with empty defects at 12 weeks.<sup>22</sup>

Chrysalin (OrthoLogic, Tempe, AZ) is a synthetic peptide corresponding to a receptor-binding domain of human thrombin. It activates a cascade of healing and tissue repair; however, does not initiate the clotting pathway. Chrysalin gel constructs for cartilage repair are in preclinical evaluation, though application improved the healing of diabetic foot ulcers in a phase 1/2 trial.<sup>23</sup> At present, OrthoLogic is pursuing partnerships to further market Chrysalin-based technology.

## MINCED CARTILAGE

The use of minced cartilage either with a scaffold or in combination with fibrin glue as a carrier is currently in the early phases of clinical utilization. In this single-stage option, cartilage tissue is either processed intraoperatively and loaded onto a scaffold (autologous) or processed in advance (allogeneic) and available “on-the-shelf.” The cartilage fragments are a source of viable chondrocytes that migrate into the surrounding scaffold or fibrin glue carrier and produce matrix and collagen. The Cartilage Autograft Implantation System (CAIS; DePuy Mitek, Raynham, MA) involves an instrument that harvests cartilage and distributes the autologous cartilage fragments homogeneously onto a 3-dimensional polyglycolide/polycaprolactone scaffold, which is secured within the defect with resorbable polydioxanone (PDS) staples. Cartilage is harvested from several nonweight-bearing locations resulting in minimal donor site morbidity. Studies in murine, caprine, and equine models exhibit chondrocyte outgrowth and cartilage formation. The

regenerated tissues demonstrate higher proteoglycan levels and expression of cartilage markers, such as collagen type II, indicative of better repair tissue quality.<sup>24</sup> A pilot phase I IDE/PMA clinical trial for CAIS will be completed in October, 2008, and a larger pivotal clinical trial is expected to begin in the summer of 2008.

DeNovo Natural Tissue (NT) graft (Zimmer, Warsaw, IN/ISTO, St Louis, MO) uses allogeneic juvenile cartilage secured with a fibrin adhesive. This was developed under the premise that cells from younger individuals have a higher anabolic capacity and potential for expansion when compared with adult tissue. However, as with any allogeneic tissue, concerns of donor-recipient disease transmission require strict screening protocols and may limit supply. Local cloning and matrix reformation were observed in an equine model after implantation. Marketing of the DeNovo NT graft is centered on the premise that this is "minimally manipulated tissue" and does not require the premarketing approval from the FDA. The DeNovo NT graft is in a postlaunch clinical study.

## SECOND GENERATION CELL BASED

Improvements on the original ACI (Genzyme Biosurgery, Cambridge, MA) technique initially described by Brittberg et al<sup>25</sup> in the year 1994 include alternative membranes and chondrocyte selection. The use of a type I/III collagen patch (Chondro-Gide, Geistlich Biomaterials, Wolhusen, Switzerland) avoids the complications associated with periosteal harvest and hypertrophy. Chondro-Gide, a porcine-derived bilayer, is approved in Europe with a reported reoperation rate of 8% or less.<sup>26,27</sup> The membrane is 2 layers: an open weave facilitating invasion and attachment plus a compact barrier surface. ChondroCelect (Tigenix Inc, Leuven, Belgium) is a proprietary genetic marker technology to optimize the chondrocyte population expanded in culture. A randomized clinical trial of ChondroCelect versus microfracture demonstrated similar clinical outcomes at 1 year; however, structural regeneration was better in the biopsies of the characterized chondrocyte implantation.<sup>28</sup> Though currently being evaluated in phase 3 international studies, a randomized trial comparing ChondroCelect with standard ACI has not been completed. This selection process is unavailable in the United States.

Synthetic coverings have evolved into biologic scaffolds that are seeded with autogenous cells. Fixation is achieved with sutures, fibrin glue, or other proprietary biologic adhesives and is technically easier than traditional ACI. Despite seeding cells onto a matrix, these constructs do not completely recreate the 3-dimensional structure of cartilage. Matrix-induced autologous chondrocyte implant (MACI; Genzyme Biosurgery, Cambridge, MA) contains cultured autologous chondrocytes, which are seeded onto a type I/III porcine collagen matrix 3 to 4 days before implantation. Consistent expression of aggrecan, type II collagen, and S-100 were observed in sequential biopsies with 75% hyalinelike

tissue at 6 months.<sup>29</sup> MACI compared with collagen-covered ACI in a randomized study had similar results with 66% rated good to excellent by the International Cartilage Repair Society scale.<sup>30</sup>

The Cartilage Regeneration System, CaReS (Arthro Kinetics, Esslingen, Germany) uses a type I collagen matrix to support fresh autologous chondrocytes, which perform better than cells passaged in culture.<sup>31</sup> Good to excellent results in 78.6% of patients and a significant increase in International Knee Documentation Committee (IKDC) scores are reported at 2 years in patellofemoral constructs.<sup>32</sup> Complete defects filling and isointense magnetic resonance imaging signal occur (signifying healing) in 83.5% and 92.3% of patients, respectively, at 2 years after surgery.<sup>33</sup>

Hyalograft C (Fidia Advanced Biopolymers, Abano Terma, Italy) implants autologous cells onto an esterified hyaluronic acid scaffold. The use of Hyalograft C is demonstrated to regenerate normal cartilage both arthroscopically and by magnetic resonance imaging in greater than 75% of patients.<sup>34-36</sup> MACI and Hyalograft C remain unavailable in the US market pending completion of the Investigational New Drug/Biologic License Application (IND/BLA). Arthro Kinetics, (CaReS) has initiated the IND/BLA process and is currently in phase I clinical trials.

## THIRD GENERATION CELL BASED

The next iteration of cell-based technology involves the generation of 3-dimensional cartilage constructs. Autogenous or allogeneic cells are treated in vitro to induce cell proliferation and production of extracellular matrix. These structures are simple to implant through small incisions or entirely arthroscopically and will use biologic adhesives (ie, fibrin glue) for fixation. The DeNovo Engineered Tissue (ET) graft (Zimmer, Warsaw, IN/ISTO, St Louis, MO) is generated from juvenile cartilage cells processed under optimized biologic conditions. The tissue is hyalinelike and implantable in a single-stage procedure.

Neocart (Histogenics, Waltham, MA) technology creates a cartilage implant from a traditional articular cartilage biopsy. A 3-dimensional bovine collagen matrix supports the autologous cells during processing in a hydrostatic bioreactor, which provides optimal conditions for proliferation and matrix generation. Construct development takes 6 weeks at which point the finalized unit is trimmed to match the defect and secured with a biologic adhesive. Phase I evaluation of Neocart demonstrated full range of motion, decreased pain, and increased IKDC scores 15 months after implantation.<sup>37</sup> Currently, both the DeNovo ET graft and Neocart are in clinical trials and need to obtain BLA approvals from the FDA for marketing that is likely to take several years.

## CONCLUSIONS

The field of cartilage repair is rapidly advancing with new products and biotechnologies to address the

treatment of focal chondral defects. These constructs, designed to supplement or improve upon existing techniques, have unique profiles that could potentially fill the voids in current cartilage defect treatment algorithms (Table 1). Though nonbiologic replacements continue to be investigated, significant technical considerations will probably limit their usefulness and widespread implementation in the very young and active patient. The synthetic niche may be most appropriate for older patients who are at the lower age limit of arthroplasty and seek to delay the procedure for several years. The utilization of scaffolds as an adjunct to marrow stimulation techniques may offer an important improvement over current outcomes. Both scaffolding and cell-based technologies for cartilage repair need to prove efficacy over standard microfracture techniques, and optimally remain logistically simple, a single-stage procedure associated with low risk and complications while remaining cost-effective and efficacious. The concept of using minced tissue as a cell source is attractive as it provides a novel intraoperative approach for cartilage repair. However, only a long-term randomized clinical study will determine whether any of these approaches becomes a therapeutic reality.

Second-generation cell-based technology may offer a reduced complication rate normally associated with periosteum and a procedure that is technically easier to perform. The outcomes, however, are unlikely to be substantially better than first-generation ACI techniques. Third-generation cell-based technology—essentially the creation of an ex vivo chondral autograft—remains one of the ideal goals in the field of cartilage repair. Mature tissue might offer the advantage of shorter rehabilitation times and shorten the time to achieve clinical efficacy. In addition, less-invasive implantation techniques will likely be used. Despite the promising early results of these products, significant technical obstacles remain in terms of arthroscopically preparing the chondral defect, initial fixation techniques, subchondral and edge integration, and the unknown outcomes related to long-term durability. The vast array of developing technologies has exceptional promise and has the potential to revolutionize the current cartilage treatment algorithms within the next decade. Despite a highly optimistic scope of emerging

technologies, we will continue to remain challenged by the relatively young, active patient who has developed subchondral change and overt structural changes associated with osteoarthritis.

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**TABLE 1.** Traits of Cartilage Repair Technology

	Single Stage Procedure	3-Dimensional Structure	Formation of Hyaline Cartilage
Synthetics	+	+	–
Scaffolds	+	+	±
Minced cartilage	+	+	+
Second generation cell based	–	±	+
Third generation cell based	±	+	+

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