ARTICULAR CARTILAGE ENGINEERING WITH AUTOLOGOUS CHONDROCYTE TRANSPLANTATION

A REVIEW OF RECENT DEVELOPMENTS

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Although several attempts to improve the repair of injured articular cartilage have recently been described[1-6], articular cartilage resurfacing remains a formidable challenge. Most current cartilage-repair methods depend on an introduction of chondrogenic cells into the defect area. Which cells are best to use and which donor tissue is best for harvesting the cells have yet to be determined. However, since chondrocytes are responsible for the unique features of articular cartilage, it seems rational to use truly committed chondrocytes to repair an articular cartilage defect.

In Gothenburg, Sweden, the experience with biological articular resurfacing dates back to the early 1980s. This research has been focused on the use of autologous articular chondrocytes[7-10] for the repair of focal articular cartilage defects, even though other chondrogenic cells are possible alternatives. The primary goal of the initial in vitro chondrocyte cell culture is to increase the number of cells in order to provide a sufficient number to fill a focal defect of articular cartilage. To accomplish this, chondrocytes are isolated from small slices of cartilage harvested arthroscopically from a minor weight-bearing area of the injured knee. The extracellular matrix is removed by enzymatic digestion, and the cells are then expanded in monolayer culture. Once a sufficient number of cells has been obtained, the chondrocytes are suspended in culture medium and are implanted into the cartilage defect with use of a periosteal patch over the defect as a method of cell containment.

The expansion of chondrocytes in vitro results in the selection of a limited number of chondrocyte progenitor clones, and the culture process allows the cells to dedifferentiate and revert to a fetal stage. Implantation of the cells into the defect initiates cell condensation and cartilage formation, which is similar to the mesenchymal condensation that occurs during limb formation.

Animal Experiments

Peterson et al.[7], in 1984, and Grande et al.[11], in 1989, presented their results on the effects of autologous chondrocyte transplantation on the healing of chondral defects that had not penetrated into the subchondral bone plate in rabbits. Defects treated with autologous chondrocyte transplantation had substantial formation of cartilage (82% of the area of the defect) compared with that in the untreated controls. Autoradiography of the repair cartilage showed labeled cells incorporated into the repair tissue[11]. Goldberg and Caplan[5] compared the implantation of committed chondrocytes to that of mesenchymal stem cells for the repair of full-thickness defects in the femoral condyles of adult rabbits. Both cell types elicited repair of the defects with tissue resembling hyaline cartilage. However, the mesenchymal stem-cell repair tissue more closely resembled hyaline cartilage than did the repair tissue from the committed chondrocytes. In a previous study[9], we compared periosteal grafts with and without chondrocytes in rabbit patellar chondral defects. One year following implantation, the periosteal grafts with the chondrocytes had resulted in an average repair area of 87% of the total area of the defect, compared with a repair area of 31% in the defects treated with the graft of periosteum alone. Histologic analysis demonstrated a significant difference between the two graft types ($p = 0.0015$), with the tissue produced by the chondrocytes and periosteal flap receiving a much higher histologic score than the defects treated with only the periosteal flap. Rahfoth et al.[12] transplanted allogeneic chondrocytes embedded in agarose gel into rabbit articular cartilage defects. Defect repair was analyzed for six to eighteen months. At eighteen months, a morphologically stable hyaline-like cartilage was present in 47% of the defects. To monitor the persistence and the phenotype of the implant chondrocytes in the repair tissue, Dell'Accio et al.[13] used fluorescent-labeled articular chondrocytes. Their data indicated that the implanted cells persisted in the defects for at least fourteen weeks, participated in the integration with the surrounding tissues, and became part of a repair tissue rich in type-II collagen and sulfated proteoglycans.

However, deterioration of the tissue quality as well as poor integration with the surrounding native cartilage at eighteen months has been described. Using a dog model, Breinan et al.[14] found that, at twelve to eighteen months after transplantation of autologous chondrocytes and periosteum, there was no difference in the repair compared with that following transplantation of periosteum alone. It should be pointed out that, in a substantial number of the defects, there had been penetration into subchondral bone during creation of the defect.

Recently, using the previously established canine model for repair of articular cartilage defects, Lee et al.[15] evaluated the healing of chondral defects that extended only to the tidemark fifteen weeks after implantation of an autologous articular chondrocyte-seeded type-II collagen scaffold. The amount and composition of the repair tissue were compared with those in the study by Breinan et al.[14], who used the same animal model, with analysis of the following groups: defects implanted with an autologous chondrocyte-seeded collagen scaffold that had been cultured in vitro before implantation, defects implanted with autologous chondrocytes alone, and untreated defects. The percentages of tissue types filling the defects were evaluated histo-

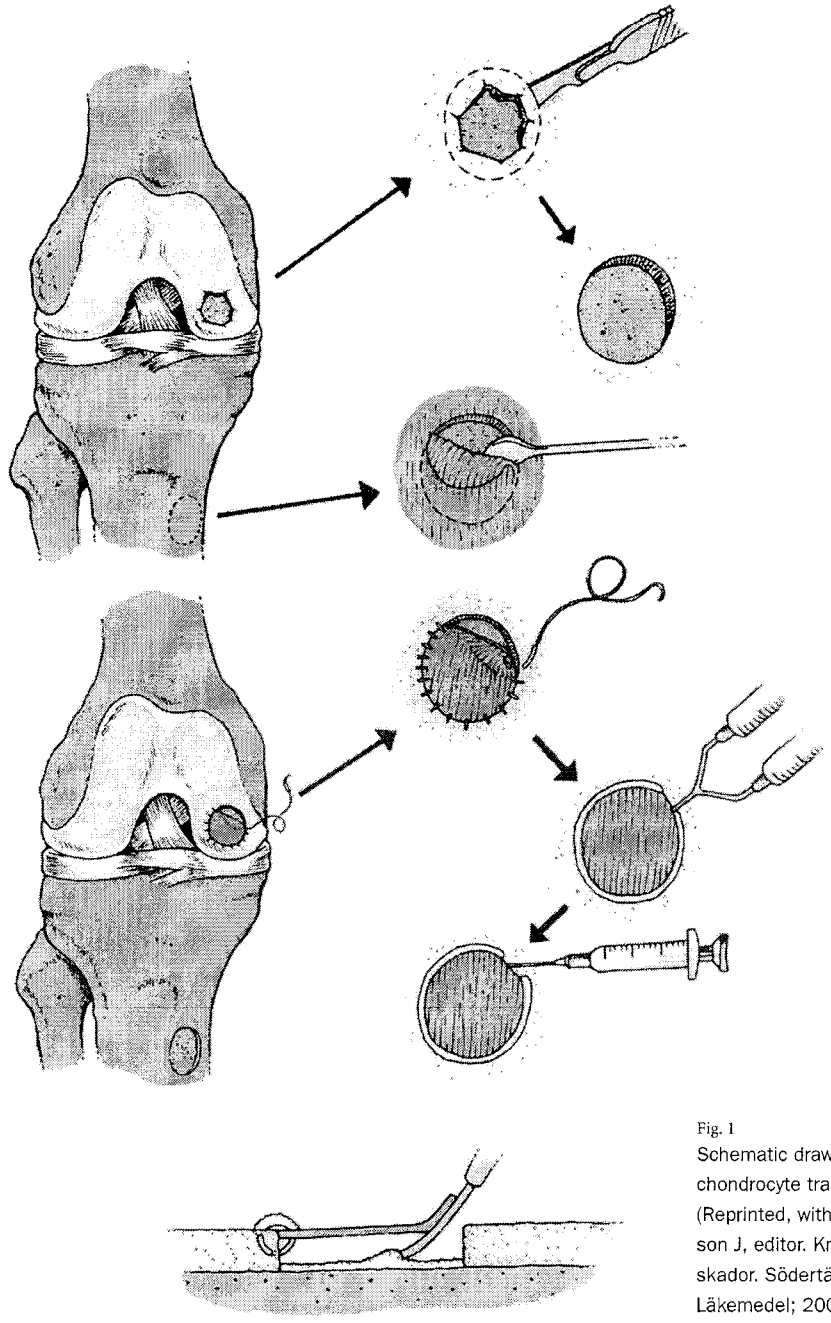

Fig. 1
Schematic drawing of the autologous chondrocyte transplantation technique. (Reprinted, with permission, from Karlsson J, editor. Knäledens sjukdomar och skador. Södertälje, Sweden: Astra Läkemedel; 2000. p 70.)

morphometrically, and the mechanical properties of the repair tissue were examined. The reparative tissue formed from the autologous chondrocyte-seeded collagen scaffolds filled 88% ± 6% of the cross-sectional area of the original defect, with hyaline cartilage accounting for 42% ± 10% (range, 7% to 67%) of the defect area. These values were greater than those reported previously for untreated defects and for defects implanted with a type-II collagen scaffold seeded with autologous chondrocytes that had not been cultured in vitro[7,9].

Clinical Research

Autologous cells expanded in vitro and combined with periosteum were first implanted in articular cartilage defects of patients in 1987[8]. This first generation of chondrocyte transplantation procedures was initially termed autologous chondrocyte transplantation. Today, the technique is called either autologous chondrocyte transplantation or autologous chondrocyte implantation. Implantation consists of an arthrotomy, preparation of the defect, harvest of a periosteal flap, fixation of the periosteal flap to the defect, securing a watertight seal with fibrin glue, implanting the chondrocytes, and wound closure (Fig. 1).

The surgical technique for autologous chondrocyte implantation has been extensively described in several reports[8,16-20]. The steps include an initial arthroscopic harvest of cartilage, isolation of chondrocytes by enzymatic digestion, and growth of the cells in cell culture to obtain twenty to fifty times the initial number of cells. To determine the amount of cartilage needed to be harvested, biopsy specimens from 1000 patients were studied in our laboratory. The mean weight of the biopsy tissue was 280 mg (range, 4 to 1700 mg). The mean cell density, in specimens from 500 patients, was 2600 cells/mg of biopsy tissue.

When chondrocytes are grown as cartilage explants, there is a linear relationship between their biosynthetic activity and the number of seeded chondrocytes; thus, the number of cells in the initial explant is important[21]. However, the number of cells that is needed for clinical implantation of the chondrocytes either as a suspension or in a scaffold has not been studied sufficiently. LeBaron and Athanasiou[22] noted that polylactide-polyglycolide scaffolds seeded with a density of <10 million cells/mL resulted in the formation of very little cartilage. They noted that seeding at high cell densities seemed desirable[22]. Puelacher et al.[23] observed that seeding scaffolds at a cell density ranging from 20 to 100 million cells/mL resulted in the formation of cartilage when the scaffold was implanted subcutaneously into nude mice. In the clinical setting today, the aim is to transplant at a cell density of 30×10^6 cells/mL.

Cartilage Injuries Are Seldom an Isolated Entity

It is seldom that an isolated cartilage injury is the sole cause of symptoms and disability. Satisfactory results should not be expected from any cartilage repair method unless coexisting knee disorders are considered and addressed. Biomechanical malalignment and ligamentous insufficiency can lead to excessive overloading that may negatively affect the grafted area. Therefore, it is crucial that any associated pathological condition of the knee that is responsible for or contributing to the chondral defect be identified and corrected before or in conjunction with the implantation of the cells. Concomitant disorders can be treated before or at the same time as the autologous chondrocyte transplantation.

As much larger defects are now being repaired, it has also become important to protect the repair tissue. Even if a patient with a large defect does not have major malalignment, it might be wise to use an unloader brace or even to perform an unloading osteotomy. Repairs that are not protected may have a good appearance at two years, but high loads on the repair area may cause progressive matrix thinning that ultimately leads to destruction of the repair.

Ligament insufficiency may produce excessive shear forces in the knee, which may jeopardize the induced repair tissue. If performed concomitantly, anterior cruciate ligament reconstruction should precede autologous chondrocyte implantation and may be performed in a standard fashion with the desired technique of the surgeon and patient. Regardless of the technique that is used, it is beneficial to wait for final fixation until the autologous chondrocyte transplantaion procedure is completed. There is very little modification to the anterior cruciate ligament rehabilitation protocols needed because the anterior cruciate ligament is more limiting and is the overriding guidance postoperatively.

The lack of a meniscus protecting the cartilage area places additional load on the grafted area. When a patient has had a subtotal or total meniscectomy, a meniscal transplantation may be considered. A meniscal implant also may reduce the forces in the involved compartment and help to protect the repair tissue. When meniscal transplantation is performed in combination with an autologous chondrocyte transplantation, the meniscal transplant should be placed and secured before completion of the autologous chondrocyte transplantation.

Osteochondral Injuries and Osteochondritis Dissecans

Osteochondral lesions of up to 8 mm in depth have been shown to heal well clinically after autologous chondrocyte transplantation alone[24]. However, bone-grafting is recommended for osteochondral defects of more than 8 to 10 mm in depth. Bone-grafting can be done at the time of arthroscopic evaluation and the harvest of the cartilage. Alternately, a one-stage procedure consisting of autologous chondrocyte transplantation in combination with bone-grafting can be performed as a so-called sandwich technique. With that technique, the bone defect is filled with bone graft, periosteum is sutured on top of the bone graft at the level of the subchondral bone plate, a second layer of periosteum is placed over the cartilage defect, and the chondrocytes are then placed between the layers of periosteum.

Additional Suggestions Regarding Operative Technique

A chondral defect that extends into the intercondylar notch is an example of an uncontained chondral defect that does not have a cartilage wall on one side to which the periosteal graft

TABLE I Results Two to Ten Years After Autologous Chondrocyte Transplantation for Lesions of the Femoral Condyle or Osteochondritis Dissecans

Lesion	No.	Mean Duration of Follow-up *(yr)*	Mean Age at Treatment *(yr)*	Mean Defect Size (Range) *(cm²)*
Femoral condyle	57	4.0	32.9	4.2 (1.3-12)
Osteochondritis dissecans	58	5.6	26.4	5.7 (1.5-12)
Femoral condyle + anterior cruciate ligament	27	4.3	30.3	3.9 (1.5-14)

*Of the patients who had had one to several previous anterior cruciate ligament reconstructions before a new anterior cruciate ligament reconstruction in combination with autologous chondrocyte transplantation, 63% had subjective improvement. †Of the patients who were treated with a combination of an autologous chondrocyte transplantation and anterior cruciate ligament reconstruction performed for the first time, 85% felt that they had improvement. ‡According to the objective assessment, 74% of all patients were considered to have improvement.

can be sutured. In such a case, the periosteal graft can be sutured to the intercondylar synovium. A cartilage defect on the peripheral border of the femoral condyle also lacks a peripheral cartilage margin. There are two recommended options for periosteal fixation in such a situation. One is to use drill holes to secure the sutures, and the other is to use mini-suture anchors. The procedure can also be combined with other procedures to form a hybrid technique. For example, mosaicplasty can be performed simultaneously to reconstruct the missing wall—i.e., the uncontained part of the lesion[20]. Bone-marrow-stimulation techniques such as drilling, microfracturing, and carbon fiber implantation might also be combined with autologous chondrocyte transplantation, especially on the posterior femoral condyles and the posterior surface of the tibial plateau.

Rehabilitation

Rehabilitation should be based on the patient's status and needs, the size and location of the lesion, and any additional surgical procedures that have been performed.

Continuous passive motion and a program of gradually increasing weight-bearing should be the initial steps of the rehabilitation process. Postoperatively, the use of continuous passive motion normally starts on the first day and continues while the patient stays in the hospital (for two or three days). A gradual increase in the range of motion with a goal of 0° to 70° of flexion is desirable, but flexion should not extend beyond 70° in order to avoid disturbing the arthrotomy wound.

Protection of the repair tissue from excessive intra-articular forces is critical during the early postoperative period. Twisting, rotational, and shearing forces should be avoided. The increase of weight-bearing to full weight-bearing and normal walking should be gradual. From the start, pain determines the level of weight-bearing by patients with a small, well-contained lesion.

Beginning in the second week, a progressive closed-chain exercise program with light resistance is started. Open-chain knee-strengthening can be introduced at approximately twelve weeks, but running is not advised until nine to ten months after the grafting. High-level activities are begun at about twelve to fifteen months.

Isometric quadriceps and hamstrings strengthening should be introduced early and should be progressively advanced to resisted exercises.

Rehabilitation after treatment of a patellar or trochlear lesion requires special considerations. Contact pressure at the patellofemoral articulation is maximized between 40° and 70° of knee flexion, and thus this arc should be avoided during active knee flexion until the graft is mature enough to withstand shear stresses. In addition, patients should not be allowed to perform open-chain extensions during the first ten to twelve weeks following repair of a patellar or trochlear lesion. Continuous passive motion is encouraged. If the defect is large, use of an unloader brace should be considered.

Complications

The few complications associated with autologous chondrocyte transplantation are those normally seen with arthrotomies; they include postoperative stiffness, venous thromboembolism, and postoperative infection. Complications directly related to the graft are uncommon[25].

One specific complication, periosteal hypertrophy, usually occurs at seven to nine months. Patients complain of catching and localized pain, and arthroscopy may reveal substantial hypertrophy. The hypertrophy is normally controlled by trimming the graft to the level of the surrounding cartilage with a motorized shaver. Low-radiofrequency energy should not be used, as it could harm the surrounding cartilage[26,27]. Detachment of the repair tissue may also occur[25]. Partial detachment is managed by trimming the area, resecting the loose parts, and stimulating the area between the graft and the normal cartilage by subchondral microfracturing or drilling to induce interpositional tissue ingrowth. Total delamination is uncommon, but it may be seen in osteoarthritic patients with poor surrounding cartilage or in deep osteochondral lesions[25].

Outcomes

In Sweden, autologous chondrocyte transplantation combined with a periosteal graft has been used in approximately 1200 patients since October 1987, and, worldwide, variants of autologous chondrocyte transplantation or implantation have

TABLE I *(continued)*

Previous Operations	Percentage with Subjective/Objective Improvement	No. of Results			
		Excellent	Good	Fair	Poor
58 in 29 patients	89%/89.5%	33	18	4	2
96 in 48 patients	91%/93%	31	22	4	1
55 in 27 patients	63%*, 85%†/74%‡	9	11	6	1

now been tried in approximately 10,000 patients.

In patients with a small acute defect, autologous chondrocyte transplantation is mostly employed after other techniques have been tried, and failed, for six months. Autologous chondrocyte transplantation and an osteochondral graft (up to 4 cm^2) may be used immediately for large acute defects, as such large defects are difficult to resurface with other procedures.

In a clinical evaluation of 244 patients followed for two to ten years, subjective and objective improvement was seen in a large number of patients with a femoral condylar lesion or osteochondritis dissecans (Table I). The percentage of good to excellent results was high (84% to 90%) for patients with different types of single femoral condylar lesions, whereas it was lower (mean, 74%) for those with other types of lesions (Table II).

The increased difficulty involved with combined treatment (anterior cruciate ligament reconstruction and autologous chondrocyte transplantation) compared with autologous chondrocyte transplantation alone is reflected in the lower percentage of patients with combined treatment who had improvement, especially when they had had several anterior cruciate ligament reconstructions before the autologous chondrocyte transplantation procedure.

To study the long-term durability of autologous chondrocyte transplantation, sixty-one patients were followed for five to eleven years (mean, 7.4 years) after the surgery. At two years, fifty of the sixty-one patients had a good or excellent result, whereas, at the five to eleven-year evaluation, fifty-one of the sixty-one patients had such a result. The total failure rate was 16% (ten of sixty-one) at a mean of 7.4 years. All failures of autologous chondrocyte transplantation occurred in the first two years, so a high percentage of the patients who had a good to excellent result at two years had such a result at the time of long-term follow-up as well[16-19,32].

Most reports on the use of autologous chondrocyte transplantation at other centers have shown similar results, with a high number of patients with improvement.

A comprehensive analysis of autologous chondrocyte transplantation was recently presented[28]. The authors suggested that no definite conclusions can be drawn about the clinical effectiveness of the procedure and that it should be regarded as experimental. It has also been suggested that autologous chondrocyte transplantation needs to be compared with other cartilage repair procedures in randomized trials[29].

Knutsen et al.[30] studied eighty patients who had symptomatic focal cartilage lesions of the femoral condyles measuring 2 to 10 cm^2. The patients were treated at four hospitals and were randomized into two groups: those treated with autologous chondrocyte transplantation and those treated with microfracture. They were followed at twelve and twenty-four months. The authors found that, at one year, the outcomes were slightly, but not significantly, better in the patients treated with microfracture than they were in the patients treated with autologous chondrocyte transplantation, but both groups had acceptable short-term clinical results.

Horas et al.[31] performed a prospective clinical study to investigate the two-year outcomes in forty patients in whom a single focal articular cartilage lesion of the femoral condyle had been randomly treated with either transplantation of an autologous osteochondral cylinder or implantation of autologous chondrocytes. Both treatments decreased symptoms.

TABLE II Results Two to Ten Years After Autologous Chondrocyte Transplantation for Patellar, Multiple, and Trochlear Lesions

Lesion	No.	Percentage with Subjective Improvement	No. of Results			
			Excellent	Good	Fair	Poor
Patellar	32	72%	8	14	4	6
Multiple	58	76%	17	27	11	3
Trochlear	12	66%	2	5	5	0

However, the improvement provided by the autologous chondrocyte implantation lagged behind that provided by the osteochondral cylinder transplantation. Histologically, the defects treated with autologous chondrocyte implantation were primarily filled with fibrocartilage, whereas the osteochondral cylinder transplants retained their hyaline character, although there was a persistent gap and lack of integration between the transplant and the surrounding articular cartilage. The authors noted that their study included only a small number of patients, a relatively short (two-year) follow-up, and no control group.

Bentley et al.[32] studied 100 patients (mean age, 31.3 years; range, sixteen to forty-nine years) with symptomatic chondral and osteochondral lesions of the knee that were suitable for cartilage repair. The patients were randomized to undergo either autologous chondrocyte transplantation (fifty-eight patients) or mosaicplasty (forty-two patients). Most lesions were post-traumatic, and the mean size of the defects was 4.66 cm^2. The mean duration of symptoms was 7.2 years, and the mean number of previous operations, excluding arthroscopy, was 1.5. The mean duration of follow-up was nineteen months (range, twelve to twenty-six months). Functional assessment with use of the modified Cincinnati and Stanmore scores and objective clinical assessment showed the rate of excellent or good results to be 88% after autologous chondrocyte transplantation compared with 69% after mosaicplasty. Arthroscopy at one year demonstrated an excellent or good repair in 82% of the autologous chondrocyte transplantation procedures and in 34% of the mosaicplasties. All five patellar mosaicplasties failed. This prospective, randomized clinical trial showed substantial superiority of autologous chondrocyte transplantation over mosaicplasty for the repair of articular defects in the knee.

Discussion

The long-term results presented in this article confirm our initial belief that treatment with autologous chondrocyte transplantation results in a durable repair for the majority of patients. They also demonstrate the importance of the two-year postoperative status as an indication of the long-term outcome of this treatment. Patients who have returned to activities of daily living and sports by two years after the autologous chondrocyte transplantation are able to continue these activities over the long term. Most grafts that fail do so within the first two years after the implantation.

The ankle, shoulder, elbow, hip, and wrist[33-38] have been treated with autologous chondrocyte transplantation in smaller numbers of patients. With the development of arthroscopic techniques[39,40], autologous chondrocyte transplantation will probably be used with increased frequency in these smaller joints. Periosteal hypertrophy could become a problem in smaller joints. The use of resorbable membranes instead of periosteum may be an important alternative to minimize the risk of hypertrophy in these joints.

As the chondrogenic effect of the periosteum declines drastically with age[41], the stimulatory effect of the periosteum might only be relevant in younger patients. Periosteum alone could be used to treat younger patients, but the combination of chondrocytes and periosteum may better be reserved for older patients.

The first generation of autologous chondrocyte transplantation involved the combination of two chondrogenic factors: the implanted suspension of chondrocytes and the cambium cells of the periosteum. This procedure has certain disadvantages, including the potential leakage of cells from defects, the dedifferentiation of cellular phenotype as the cells have been grown in monolayer before implantation, the uneven distribution of cells, and the substantial risk of periosteal hypertrophy. The technology for autologous chondrocyte transplantation needs to be improved, and there is now a search for new biomaterials with which to secure the cells in the defect area and enhance their proliferation and differentiation. Resorbable membranes, such as Chondro-Gide (a type-I/type-III collagen membrane; Geistlich Biomaterials, Pharma AG, Wolhausen, Switzerland), are a possible alternative to the periosteum[42,43], and the clinical results with that membrane seem promising. Similarly good short-term results have also been reported with the hyaluronan-based biodegradable polymer scaffold HYAFF-11 (Fida Advanced Biopolymers, Abano Terme, Italy)[44,45]. Our own experience has been with polyhydroxybutyrate, a patch used for cardiac surgery[46], which is of interest because it is resorbed about one year postoperatively. Also, Ethisorb (Ethicon, Norderstedt, Germany), a scaffold comprising polyglactin 910/poly-p-dioxanone, has been used in sheep with trochlear defects. The cartilage defects were repaired, but biopsies from many animals showed vascular ingrowth in the defects, even though the bone space was not opened and the repairs involved only femoral condyle lesions.

Tissue engineering is a field of biomedicine that is growing rapidly, and cell biologists, engineers, and surgeons have to work closely together to reduce the gap between where the cartilage repair technology is today and where we want it to be. This interdisciplinary repair technology may be named *biomedical surgery,* and its novel instruments include embryonal stem cells, pluripotent mesenchymal stem cells, morphogens, smart biomaterials, and gene transfers, which the different researchers should try to make into a biological well-tuned orchestra. ■

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