The Future of Cartilage Restoration

Nicholas A. Sgaglione, MD

INTRODUCTION

Recent advances in the approach to treating focal articular cartilage lesions have captured the interest of clinicians, patients, researchers, and industry. What was once seemingly "untreatable" is now the subject in basic science projects, novel technologies, surgical techniques, and outcomes investigations.[5-7,30,35,44,51,56] Moreover, the significance of treating symptomatic articular cartilage lesions has been heightened by the increase in athletic patients we treat and the media attention. This "captive audience" continues to grow as well as the increasing incidence and recognition of symptomatic chondral defects.[1,15,29,34] Our clinical responsibilities will also expand as our patient population ages and seeks to reduce degenerative disease risks while pursuing a more active lifestyle and increased fitness level. Several societal and medical trends have also been recognized and will continue to shape our approach to treating joint pathology. These include a greater emphasis on preemptive diagnosis, early intervention and prevention, less invasive surgery, biological approaches, accelerated recovery, and cost-effective treatments.

In the past ten years, numerous reports of viable biological methods to resurface symptomatic articular cartilage defects have become accepted within the mainstream of orthopedic practice including marrow stimulation procedures, osteochondral transplantation, and ex-vivo autologous chondrocyte implantation.[2,10,13,25,26,30,54,60,61] Other projects continue to be investigated and explored as improvements in biochemistry, tissue engineering, polymer science, and cell biology are realized. Challenges remain and controversies continue to arise within articular cartilage surgery, and despite clinical work and enormous progress, significant limitations remain as far as many of these available techniques are concerned. For the most part, many current surgical procedures remain at their inception and can be considered first-generation methods. Evolving technologies and novel biological treatment solutions for articular cartilage pathology hold great promise and most likely represent what may be seen in the future.[5-7,24,27,28,36,40,41,53,56]

This article reviews the future of treating symptomatic articular cartilage defects in the knee and defines the clinical challenge that we face in providing the clinician with a clearer view of how to sort out what to do, what not to do, and when to do it.[55]

WHERE ARE WE?

Several available surgical methods exist for treating symptomatic focal articular cartilage defects in the knee, including marrow stimulation and subchondral bone drilling, auto- and allograft osteochondral transplantation, and autologous chondrocyte implantation (ACI). All of these procedures may play a role in the approach to chondral pathology depending on lesion characteristics, clinical indications, patient profile, and surgeon preference.

Marrow stimulation techniques, including microfracture, can be performed arthroscopically and primarily at the time of an index surgical intervention. Using arthroscopic awls to perforate the subchondral bony base of a chondral defect can be technically easy to perform with little associated morbidity. Long-term reports of clinical success have been reported and a recently published controlled comparison 2-year follow-up study found similar outcomes in patients treated with microfracture compared to those treated with autologous chondrocyte implantation.[32,60,61] The glaring limitation to marrow stimulation

Dr Sgaglione is from the Department of Orthopedics, North Shore University Hospital, Great Neck, NY.

Reprint Requests: Nicholas A. Sgaglione, MD, Department of Orthopedics, North Shore University Hospital, 600 Northern Blvd, Great Neck, NY 11021.

methods such as microfracture is the tendency for the treatment to result in a fibrous tissue or fibrocartilagenous healing response.[20,38,42] Poole[48] agrees that fibrous tissue and any tissue response short of hyaline cartilage may not respond in a durable manner to joint forces and repetitive loading over time.

Osteochondral autograft transplantation can also be performed arthroscopically or using arthroscopically-assisted methods and at the time of an index intervention. This technique has been shown to result in viable plug transfer of hyaline tissue including a bone-based graft that securely anchors the press-fit replacement tissue.[2] Autograft transfer makes good sense as it provides a viable source of zoned hyaline tissue using a relatively less-invasive method with a short-term healing site profile. Several studies have reported on good intermediate-term success with this procedure.[4,25,26,45] The technique, however, can be challenging, in particular restoring the precise surface anatomy and condylar bevel or curvature.[3,25,33,62] Recent published reports indicate that technical issues such as graft size and harvest and insertion methods may contribute to less than optimal results. Problems with perimeter integration, surface fibrillation, cleft formation, gapping, and cyst formation may be greater than originally appreciated. In addition, larger lesions can be difficult to treat and gain access to, and the procedure is limited by the number of grafts that can be harvested along with the potential of harvest site morbidity.[17,18,21,25,33,56,59]

Osteochondral allograft transplantation represents an optimal method for transplanting hyaline tissue especially where more extensive lesions are treated using larger grafts without any associated harvest site issues. At least with salvage, the results of osteochondral allograft have been encouraging at long-term follow-up.[12,13,56,57] Despite this success, concerns remain regarding limitations in donor tissue availability, cost, disease transmission, and chondrocyte and tissue viability.[63,64]

Autologous chondrocyte implantation, which represents the first approved technology based on ex-vivo chondrocyte culturing and staged reimplantation has been reported to result in hyaline-like tissue with durable clinical results and survivorship at extended follow-up.[4,39,42,46,47,56] A more recent study, however, found in patients treated with ACI who underwent follow-up second look tissue biopsies, only 39% of the treated defects were noted to be filled with hyaline cartilage while 43% were filled with fibrocartilage, and 18% with no healing tissue response at all. These histological results were similar to a controlled comparison treatment study group who underwent microfracture.[32] Furthermore, ACI requires a two-staged procedure, the second of which includes an arthrotomy and the use of a periosteal patch to seal the cell-implanted lesion site. Periosteal harvesting is associated with more invasive intricate surgery and has been reported to result in postoperative morbidity related to hypertrophy, which may require subsequent surgical debridement.[39,56]

Current available surgical options have advantages and disadvantages and at times these treatment options may be associated with narrow or ill-defined indications. No current technique stands out as an optimal surgical method that predictably restores zoned hyaline cartilage using a cost-effective single-staged minimally invasive method that is applicable to most of the significantly sized lesions indicated for surgery. Clinical challenges and controversy therefore remain.

CHALLENGES

The treatment of articular cartilage defects poses numerous significant challenges in comparison to treatment of fractures, muscle, and meniscal, or ligament injuries. One factor related to the challenge of surgically restoring chondral defects is the unique structural and functional characteristics of hyaline tissue. The ultrastructure of articular cartilage imparts properties that permit it to efficiently respond to variable compressive loading in a mobile, fluid-filled environment. This complex architecture has yet to be surgically reproduced in a predictable manner. Furthermore, variable lesion pathoetiologies including osteochondritis dissecans, chondral and osteochondral fractures, and early degenerative lesions limit the precise classification of articular defects and interpretation of surgical indications and treatment outcomes. Many case studies of chondral "lesions" are invalidly combined data sets of patients with variable pathological processes. The tendency for articular cartilage to respond to injury in a disordered manner limits the predictability of who may or may not express symptoms.

Shelbourne et al[58] recently found that in a 6- to 8-year follow-up of patients noted to have untreated Outerbridge grade-III or -IV chondral defects diagnosed at the time of anterior cruciate ligament (ACL) reconstruction, similar functional and overall clinical results were observed in patients with and without chondral pathology. This study, although retrospectively defined, shows that the natural history of certain articular cartilage defects in the knee is poorly understood. All chondral pathology may not progress to significantly symptomatic articular cartilage lesions.

Furthermore, such an unpredictable response to injury is compounded by the biolatency of chondrocytes, that is the unique metabolic response of chondrocytes. The biolatency may require more comprehensive and extended approach to outcomes assessments dictating that traditional outcome follow-up parameters be reconsidered prior to concluding whether a treatment is truly efficacious. Another challenge in analyzing articular cartilage

treatments is confounding pathology. Study designs are further potentially biased by the fact that chondral trauma frequently presents with other knee pathology (ACL and meniscal tears), making it difficult to determine which pathologic entity is responsible for which symptom and to what extent. Published reports of treatment outcomes that compare methodologies remain limited and controlled prospective longer-term literature, rare.[4,32]

TREATMENT GOALS

The treatment goals of articular cartilage defects in the knee must be defined to rigorously analyze current approaches and proposed solutions. Practically speaking, the "Holy Grail" as far as surgical treatment of chondral pathology is concerned, would be to replace a cartilage defect with hyaline tissue that integrates with native host tissue and functions durably under load and over time and most importantly provides an asymptomatic joint. The procedure should preferably be performed arthroscopically or using minimally invasive methods and be able to applied at an index point of service intervention to ensure a cost-effective single-staged surgery with minimal morbidity (Table 1).

TABLE 1
TRENDS IN THE APPROACH TO ARTICULAR CARTILAGE LESIONS

Biological treatment solutions
Noninvasive diagnostic imaging
Cost containment
Minimally invasive surgery
Accelerated rehabilitation

These goals can be outlined more conceptually according to three areas of consideration: tissue restoration and histological fill; biomechanical and functional response to joint loading; and clinical outcomes and specifically symptomatic resolution both over short term as well as over extended follow-up. Tissue restoration in the purest sense requires re-establishing zoned hyaline cartilage.[48] Zoned hyaline cartilage can be defined as a uniquely layered architecture and ultrastructure that incorporates specifically arranged chondrocytes distributed in an extracellular matrix including a fibrillar type II collagen meshwork and adjacent calcified zone and tidemark intimately interdigitated with the subchondral bone. The resurfacing of symptomatic articular defects more often (and particularly in cases of osteochondritis dissecans) requires treatment and re-establishment of the subchondral bone. Zoned hyaline cartilage maintains its exquisite functional characteristics because of its structural properties and distinct ratios and distribution of chondrocytes, extracellular matrix, and collagen. Because optimal loading and durable response to loading may not be achieved unless zoned hyaline cartilage is obtained, one of our goals should be more precise histomorphometric tissue.

Functional loading of articular cartilage is dependent on a highly complex interaction of extrinsic and intrinsic factors. Extrinsic factors include patient activity levels and functional demands placed on the knee as well as body mass index, lower extremity mechanical alignment, and associated degenerative joint disease processes, ligament patholaxity, and meniscal attrition (the same factors that tend to introduce confounding bias as far as clinical study results are concerned). Intrinsic factors include the site (condyle location, trochlea, patella, etc), size, perimeter (geometric characteristics of the shoulders of the lesion), and depth of the defect. In addition, the complex cascade of biochemical and catabolic enzymatic processes including cytokines and matrix metalloproteinases may also play a role in terms of intrinsic pathways. The more precise approach to articular cartilage defects in the future will most likely require consideration of site-specific treatments to address some of these factors and more precise control of catabolic processes in addition to anabolic enhancement.[7,10]

What remains confusing and controversial is the debate over how we determine clinical outcomes. Presumably, we measure outcome success by the elimination and absence of pretreatment symptoms such as site-specific pain, effusion, and catching. Over what period of time is success measured? Does success mean that there will be no progression to osteoarthritis or no progression during a certain time frame? Is such a "bridge" procedure adequate to temporize symptoms? Is clinical success good enough or do we demand specific tissue fill, and to what extent and with what type of tissue? Should we not also use mechanical measures to evaluate the repair tissue response to load? Are microindentation probes that quantitate the stiffness of the repair tissue in comparison to "normal" native host hyaline cartilage, a more true measure of success? Is tissue fill with hyaline cartilage assessed and measured arthroscopically or using newer noninvasive magnetic resonance imaging (MRI) technologies? Is the extent of tissue fill always clinically correlative with a durable response to loading and presumed symptom resolution? These unanswered questions need to be defined as we introduce more surgical techniques that must be effectively evaluated and precisely compared in a matched and controlled setting. In addition, treatment assessment must include controlled comparisons between specific surgical interventions and no treatment.

TRENDS

More recently, several trends in orthopedics and medicine in general have been recognized and appear to be driving the development of newer treatment methods and

TABLE 2
GOALS FOR TREATMENT OF FOCAL ARTICULAR CARTILAGE DEFECTS

Zoned hyaline cartilage
Minimally invasive approach
Single-staged "point of service" index intervention
Cost-effective treatment
Clinically successful in short term and durable over longer term
Chondroprotection

cutting edge technologies. One significant trend is the increasing emphasis on biological approaches and solutions. Prosthetic arthroplasty has enjoyed considerable success over the past 35 years, yet limitations exist and the perfect artificial joint has not been found. Durability issues, need for revision, and morbidity related to materials wear and breakdown as well as aseptic loosening continue to remain a problem. These limitations will be of greater concern as patient life expectancies continue to increase.

Another important trend is the increasing improvements in noninvasive imaging of articular cartilage. Specific magnetic resonance techniques including high-resolution moderate TE fast spin-echo, fat suppressed 3-D spoiled gradient echo sequencing, delayed gadolinium-enhanced MRI of cartilage, and T2-collagen mapping have been reported. They all represent evolving and potentially significantly more accurate and precise methods to diagnose and define articular cartilage pathology, tissue repair response, and clinically correlative validation of symptoms, outcomes, and lesion resurfacing.[8,9,49] In the future, we anticipate being able to fully scan a joint and know the precise status of all articular surfaces both preemptively and immediately following injury and following surgical treatment.

An additional trend is the considerable and increasing concern for cost-effective medical intervention. This has become a significant reality as government and third-party insurers regulate health-care spending and cap certain procedures as well as seek to define clinical treatment guidelines.

Another trend is the increased emphasis on minimally-invasive procedures, which have captured the imagination of patients even when certain miniaturized techniques can represent technology beyond reason. Patients will continue to demand less painful surgical procedures, therefore less-invasive interventions will continue to evolve. Furthermore, as patients seek minimally-invasive alternatives to traditional procedures, they in part expect faster healing, quicker recoveries, and "accelerated rehabilitation protocols." These demands are magnified by the media as well as patients and physicians alike and can at times contribute to unrealistic expectations regarding the manipulation of healing and biology. These trends of biological solutions, noninvasive imaging, cost containment, demand for minimally-invasive procedures, and accelerated recovery may continue to drive or at least impact future consideration of articular cartilage treatments (Table 2).

WHAT LIES AHEAD?

The biological resurfacing of focal chondral lesions can be approached using several methods including repair, regeneration, or replacement.[44] Repair, by definition can be considered a staged injury response mechanism that may be completed in a shorter defined time period. Regeneration defines a more lengthy process that tends to require a more extended maturation phase or recapitulation of the developmental cascade. Replacement would be defined by the use of a biological prosthesis or porous polymer. Of the current available treatments, marrow stimulation or microfracture represents a process of promoting tissue repair, while ACI could be considered a first generation regeneration technique while osteochondral transplantation may be considered biological replacement.

Whether repair, regeneration, or replacement techniques are followed, several key components would be essential to optimize the production of new articular cartilage tissue. One would be a chondroprogenitor cell source for replication, biologic turnover, and most importantly matrix production. The methodology used for targeting the chondroprogenitor cell line may vary and can include treatments that directly affect the native cells and tissue (ie, using an exogenous bioactive polypeptide injected or applied to the lesion intra-articularly). Another method may include transplantation of the chondroprogenitors onto a scaffold from an exogenous but autogenous source either locally or distant or from a separate allogeneic site. The cell line may also be treated in an ex-vivo manner to "activate" the cells to produce a more robust extracellular matrix. Finally, an expanded and fully formed tissue may be transplanted after potential exogenous treatments either with bioactive factors or extrinsic biomechanical or biophysical stimulation (ie, using a bioreactor in which in vitro cyclic compressive stimulation is applied to expanded tissue cultures to induce a more exuberant cellular response and extracellular matrix production).[52] The requirements for successful hyaline tissue production as far as chondroprogenitor lines are concerned would include cellular proliferation, differentiation, phenotypic expansion, perimeter and deep integration, and tissue maturation. A selected cell line would be expanded to proliferate and phenotypically express chondrocytic functions to produce extracellular matrix and

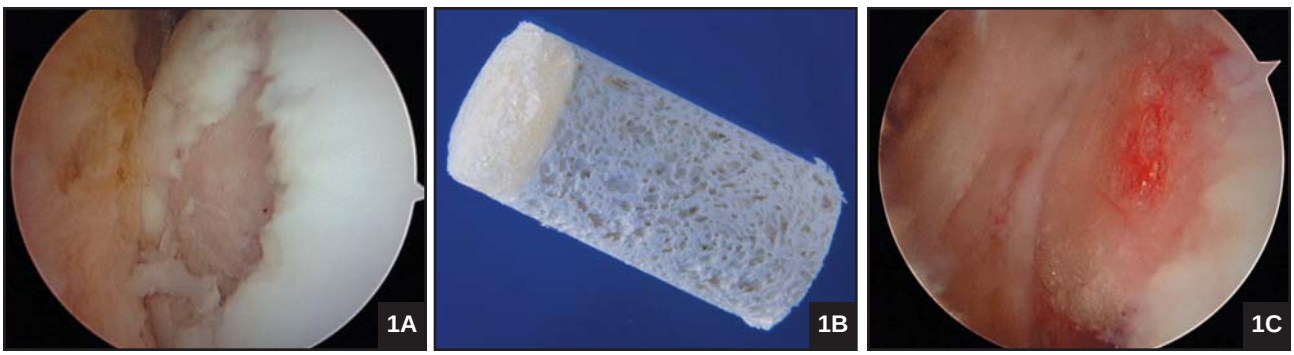

Figure 1. Osteochondral fracture of lateral femoral condyle that measures 20×25×8 mm (A). 10×17-mm intra-articular bilayered (polylactide-glycolide surface/calcium sulfate base) bone graft substitute (B). Post insertion arthroscopic view of the resurfaced chondral defect (C).

proteoglycan macromolecules that more expeditiously impart optimal biomechanical function.[40]

Sources of chondroprogenitor cell lines include mesenchymal stem cells and immature or juvenile chondrocytes as well as differentiated chondrocytes (as used in ACI). Several sources of stem cells exist including those from bone marrow elements as well as muscle, dermal, adipose, and periosteal tissue. Furthermore, autogenous versus allogeneic cell lines may be selected depending on availability, cost effectiveness, and compatibility. The advantages of using autogenous cell lines and tissue include reduced cost and negligible disease transmission and immunologic issues while the advantages of allogeneic sources include availability and reduced harvest site issues and morbidity.[5,10,14,16,56,63]

Regeneration of new tissue also would require a porous scaffold to act as a delivery vehicle for the selected chondroprogenitors and to provide a unique 3-dimensional structure within a focal defect that is to be treated. A matrix or scaffold would provide surface structure to facilitate cell migration, attachment and stability, and porosity or void volume to allow for cell expansion, angiogenesis (where applicable), and tissue maturation to proceed in a stable manner.[24,40] The immature composite tissue would initially require an organizational architecture and temporary load sharing during the potentially lengthy proliferative and maturation phases of repair and regeneration. The tissue construct including the scaffold would require attachment to the underlying bone tissue and adjacent native articular cartilage. Numerous scaffolds have been reported and continue to evolve as novel biomaterials and polymers are developed. Scaffolds may purely be biological in nature (collagen, hyaluronate, alginate, submucosal xenograft, and dermal allografts) while others are mineral-based (tricalcium phosphate, hydroxyapatite, and calcium sulfate) while still others are carbohydrate-based (polylactide, polyglycolide, and polycaprolactone). Scaffolds comprised of hybridized composites and copolymers of each category are commonly reported.[16,22,40,65] Recently, acellular mineral-based/carbohydrate composite polymer scaffolds were released for use in filling intra-articular bony defect and osteochondral fractures (OsteoBiologics, Inc, San Antonio, Tex) (Figure 1).

Advancing new tissue regeneration also includes the use of bioactive factors, which may be used to amplify cell expansion, strengthen phenotype, improve extracellular matrix production, and simultaneously reduce cell breakdown and catabolic degradation. These complex proteins can be classified according to their actions as anabolic agents or morphogens and growth factors that function to amplify chondrocyte phenotype and differentiation, improve the quality of the matrix expression, and thereby produce a purer and more optimal and durable hyaline tissue. Other bioactive proteins can be classified as catabolic inhibitors, which act to control and limit degradative processes, tissue breakdown, and cell death or apoptosis. Bioactive polypeptides can have numerous functions, and in addition may act on adjacent host tissue as mitogens and chemotactic agents that permit manipulation and control of biological processes including healing, repair and regeneration.[10,19,24,37,53] Delivery of bioactive growth factors remains an issue. Questions remain regarding whether they should be introduced directly at the treatment site in-vivo or indirectly using ex-vivo methodologies or whether they should be impregnated within a scaffold and be carrier-based. The use of gene-modified cell-based therapies may hold the answer as chondroprogenitor cell lines may be modified in the laboratory using candidate genes that encode for selected morphogenic proteins that enhance healing. Those tissue engineered cell lines can then be delivered to the treatment site to amplify and promote healing and regeneration.

Despite promising preclinical work, clinical applications are limited by control, dosing, half-life, safety, and cost issues. This technology awaits more definitive bioas-

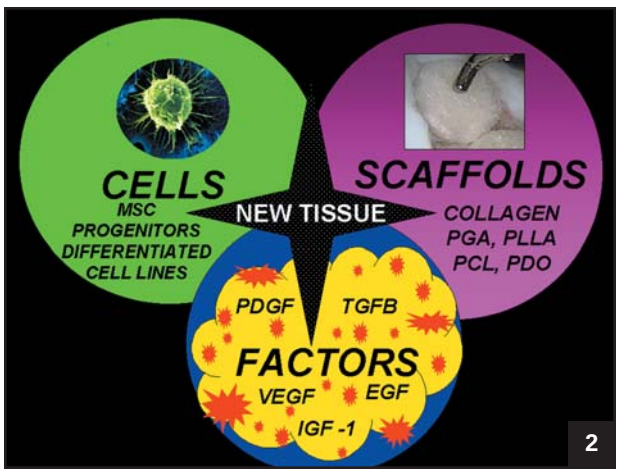

Figure 2. Schematic of required cell source, scaffold, and bioactive factors for tissue regeneration. Abbreviations: EGF=epidermal growth factor, IGF-1=insulin-like growth factor, MSC=mesenchymal stem cells, PCL=polycaprolactone, PDGF=platelet-derived growth factor, PDO=polydiaxanone, PGA=polyglycolic acid, PLLA=polylactic acid, TGFB=transforming growth factor, and VEGF=vascular endothelial growth factor.

says for documentation of specific growth factor presence, concentration, stability, expression, and effective action. The recent reports of platelet-rich plasma have stimulated interest in the potential for a "one stop," intraoperative, cost-effective practical method for introducing and capturing "growth factors" within an operating room setting. The use of concentrated autogenous platelet-rich plasma theoretically loaded with growth factors may play a role in the treatment of a drilled chondral defect to amplify the "superclot" that forms. The use of "ready-to-mix" concentrates of the patient's blood products prepared at the time of the surgical procedure may represent the first example of the introduction of clinically practical application of bioactive factors to the surgical site. In addition, centrifuged and intraoperatively-prepared platelet-rich plasma may also be used with biocompatible scaffolds to "seed" the acellular constructs. However, much work is needed to validate this emerging biotechnology both in basic science laboratory assays as well as evidenced-based clinical efficacy and safety trials.

The requirements for successful tissue repair mechanisms include cells, scaffold, and bioactive factors, however each part of the equation must be coordinated and balanced to ultimately produce a zoned hyaline structure that can intimately integrate within the surrounding native tissue (Figure 2).

FUTURE APPROACHES

Next Generation Cell-Based Therapies

The new generation of cell-based therapies used for implanting ex-vivo expanded autogenous chondrocytes and novel scaffolds has been clinically reported on in Europe. Elimination of periosteal patch requirements has reduced the invasiveness of the procedure and increased the potential for arthroscopic application and theoretically reduced the incidence of periosteal hypertrophy-associated complications. Several resorbable scaffolds have been used including extracellular xenograft collagen membranes or esterified nonwoven hyaluronic acid matrices that function as platforms for ex-vivo impregnation of the autogenous chondrocytes. These membrane or matrix associated autologous chondrocyte implantations methods and hyaluronic acid-based scaffolds (Hyalograft C / Hyaff 11) provide the potential to implant a 3-dimensional chondrocyte-seeded construct that can either be press-fit into the chondral defect or attached using minimally-invasive suturing techniques, bioadhesives, or bioabsorbable anchors. They have several advantages over first generation ACI techniques and although initial clinical data appears encouraging, these methods are currently not approved by the Food and Drug Administration for clinical use in the United States.[11,43]

Another novel cell-based technology that has successfully completed preclinical testing in a porcine animal model in the United States, is based on a technique that uses autologous chondrocytes that are seeded onto a bovine collagen sponge (NeoCart Histogenics, Malden, Mass). The 3-dimensional construct is then statically cultured ex-vivo and expanded and then placed in a computerized cyclic hydrostatic loading chamber using a nutrient-rich perfusate and controlled low oxygen and gas environment. Exposure to biophysical stimuli using external bioreactor technology has been shown to promote better-defined chondrogenic phenotype and robust extracellular matrix with greater potential for successful hyaline tissue expansion and perimeter integration. On completion of the 6-week laboratory treatment, the mature construct is then implanted into the chondral defect using a mini-arthrotomy or potentially arthroscopic technique and held in place using a proprietary bioadhesive. This methodology is currently undergoing a phase I clinical trial (Kusanagi, personal communication, 2004).

The use of juvenile allogeneic chondrogenic precursor cells that can be cultured and expanded ex-vivo using scaffold-independent methodology to produce cartilaginous tissue is currently under preclinical large animal model investigation. Less differentiated, immature chondrogenic cell lines have been shown to result in a more zoned and higher "quality" hyaline tissue response and possibly more optimal functional construct that may remodel more appropriately and respond to load more optimally (Huckle, personal communication, 2003).

Gene-Modified Tissue Engineering

The enormous potential of gene-modified therapy and tissue engineering has generated significant interest in all

of medicine but particularly in orthopedics. The ability to manipulate articular cartilage tissue repair or generating tissue is an exciting concept. Gene therapy may be defined as the ability through gene transfer to deliver a therapeutic protein to a target cell or tissue to induce that cell or tissue to engage in repair or regeneration and guide healing. Various approaches may be taken using human recombinant gene models.[5,22,27,31,40]

One approach may include the selection of a candidate gene that selectively codes for expression of a specific therapeutic protein that would presumably contribute to articular cartilage repair or regeneration by acting on chondroprogenitor cells. The gene would then be introduced into a selected target cell line, which may be a chondrocyte or stem cell that would then be manufactured and express the therapeutic protein. Introduction of the candidate gene and encoding DNA into the selected target cell could be performed using viral transfection or nonviral methods and using ex-vivo or in-vivo techniques. After the gene has transduced the target cell, it would then function as a source of the therapeutic protein or bioactive factors, which on their release, would presumably result in a higher quality structural repair tissue. Mechanisms to control the process would need to be programmed into the sequence using genes for promoters, cell line purification and phenotype expression, timing and dosing of the protein production, and shutting it down ("suicide genes").

Recent projects have centered on the introduction of genes coding for chondrogenic morphogens including insulin-like growth factor (IGF-1), platelet-derived growth factor, basic fibroblast growth factor, transforming growth factor-beta (TGF-B) including the bone morphogenetic proteins (BMP-2, 4, and 7).[19,22,27,36,41,53] Evolving study has now also included work on bioactive peptides that act on levels "upstream" in the neochondrogenesis pathway in an attempt to recapitulate events that may occur ontologically in earlier stages of cartilage regeneration. By selecting out embryonic pathways and reproducing progenitor cell mechanisms, neochondrogenesis may be more efficiently replicated and possibly controlled. Recent experiments in a New Zealand rabbit model have used pluripotent periosteum and muscle-derived mesenchymal stem cells as target cells and several candidate genes that encode for BMP-7, IGF-1 and the sonic hedgehog protein.[19,36,37] Both BMP-7 and IGF-1 have been shown to improve the quality of the expressed chondral tissue through stimulation of proteoglycan synthesis and proliferation of chondrocytes while the sonic hedgehog protein is part of a family of polypeptide regulators that function "upstream" of the traditional chondrocyte-regulating growth factors (TGF-B). The sonic hedgehog protein acts on the signal for initial patterning of chondrocytes that may allow for more control of chondrocyte precursor cell proliferation particularly if stem cell lines are used.[50] Initial experiments have included repair constructs for chondral defects using these gene-modified approaches, and encouraging laboratory results have been observed with the resultant hyaline cartilage constructs noted to have superior characteristics in comparison to untreated controls. Continued work is progressing to improve repair tissue and subchondral bone integration as well as to ensure a more viable zoned repair tissue.

LIMITATIONS

Despite the rapid developments in finding a solution for treating articular cartilage pathology, many limitations still exist. The extrapolation of laboratory and bench-top results to the clinical setting remains indefinable. Difficulty still exists in transferring projects that have realized success in the smaller animal model to a viable larger animal experimental model that more optimally replicates human clinical trials. Problems exist with obtaining site-specific zonal hyaline tissue that predictably integrates with the subchondral bone and surrounding normal native tissues. Bioactive factor applications remain elusive and in some respect a clinical "leap of faith." Their safety, dosing, control, and cost effectiveness remain questionable. The use of gene-modified protocol, stem cells, and bioactive factors is still in its infancy. Tremendous hurdles remain as we face increasingly stringent government regulatory issues, politically-charged legalities, and media-driven public safety concerns. Most importantly, a need for cost-effective interventions exists that are equally practical and acceptable to clinicians and patients.

CONCLUSION

Efforts to find a more successful treatment approach to symptomatic focal articular cartilage pathology will continue to evolve and be shaped by basic science and clinical energies. The increased emphasis on biological approaches to surgery has contributed to an exciting time in which molecular biologists, bioengineers, polymer chemists, and clinical orthopedists, are working to find solutions. The future holds promise, and although many rapid advances and progress have been realized, more work still needs to be done.

Many unanswered questions and many unsolved problems will remain until a reproducible and more predictable methodology is realized. Connective tissue progenitor cell lines, allogeneic tissue, novel biocompatible scaffolds, and bioactive factors will play a role as work in these areas expands. Our targets must be realistic and practical goals must be considered. The quest for valid data analysis, evidenced-based controlled clinical studies, and interpretations must be encouraged and continued to

be scrutinized. We are moving in the right direction of cartilage restoration, however more work remains.

REFERENCES

1. Aroen A, Loken S, Heir S, Alvik E, Ekeland A, Granlund OG, Engebretsen L. Articular cartilage lesions in 993 consecutive knee arthroscopies. *Am J Sports Med*. 2004;32:211-215.
2. Barber FA, Chow JC. Arthroscopic osteochondral transplantation: Histologic results. *Arthroscopy*. 2001;17:832-835.
3. Bartz R, Kamaric E, Noble P, Lintner D, Bocell J. Topographic matching of selected donor and recipient sites for osteochondral autografting of the articular surface of the femoral condyles. *Am J Sports Med.* 2001;29:207-212.
4. Bentley G, Biant LC, Carrington RW, et al. Autologous chondrocyte implantation was superior to mosaicplasty for repair of articular cartilage defects in the knee. *J Bone Joint Surg Br.* 2003;85:223-230.
5. Bruder S. Current and emerging technologies in orthopaedic tissue engineering. *Clin Orthop*. 1999;376(suppl):S406-S409.
6. Buckwalter JA. Integration of science into orthopaedic practice: implications for solving the problem of articular cartilage repair. *J Bone Joint Surg Am*. 2003;85(suppl 2):1-7.
7. Buckwalter JA, Mankin HJ. Articular cartilage: degeneration and osteoarthrosis, repair, regeneration, and transplantation. *Instr Course Lect*. 1998;47:477-486.
8. Burstein D, Gray M. New MRI techniques for imaging cartilage. *J Bone Joint Surg Am.* 2003;85(suppl 2):70-77.
9. Burstein D, Gray M. Potential of molecular imaging of cartilage. *Sports Med Arthros Rev*. 2003;11:182-191.
10. Chen FS, Frenkel SR, DiCesare PE. Repair of articular cartilage defects, I: treatment options. *Am J Orthop*. 1999;2:88-96.
11. Cherubino P, Ronga M, Grassi F, Bulgheroni P. Autologous chondrocyte implantation with a collagen membrane. *J Orthop Surg*. 2002;1:169-177.
12. Chu CR, Convery FR, Akeson WH, Meyers M, Amiel D. Articular cartilage transplantation. Clinical results in the knee. *Clin Orthop*. 1999;360:159-168.
13. Convery RF, Akeson WH, Meyers MH. The operative technique of fresh osteochondral allografting of the knee. *Operative Techniques in Orthopaedics*. 1997;7:340-344.
14. Cook S, Salkeld S, Popich-Patron L, Ryaby J, Jone D, Barrack R. Improved cartilage repair after treatment with low-intensity pulsed ultrasound. *Clin Orthop*. 2001;391(suppl):S231-243.
15. Curl WW, Krome J, Gorgon ES, Rushing J, Smith BP, Poehling GG. Cartilage injuries: a review of 31,516 knee arthroscopies. *Arthroscopy*. 1997;13:456-460.
16. Diduch DR, Jordan LC, Mierisch CM, Balian G. Marrow stromal cells embedded in alginate for repair of osteochondral defects. *Arthroscopy*. 2000;16:571-577.
17. Duchow J, Hess T, Kohn D. Primary stability of press-fit–implanted osteochondral grafts. Influence of graft size, repeated insertion, and harvesting technique. *Am J Sports Med.* 2000;28:24-27.
18. Evans PJ, Miniaci A, Hurtig MB. Manual punch versus power harvesting of osteochondral grafts. *Arthroscopy*. 2004;20:306-310.
19. Fortier LA, Balkman CE, Sandell LJ, Ratcliffe A, Nixon AJ. Insulin-like growth factor-I gene expression patterns during spontaneous repair of acute articular cartilage injury. *J Orthop Res*. 2000;19:720-728.
20. Frisbie DD, Oxford JT, Southwood L, et al. Early events in cartilage repair after subchondral bone microfracture. *Clin Orthop.* 2003;407:215-227.
21. Garretson RB III, Katolik LI, Verma N, Beck P, Bach BR, Cole BJ. Contact pressure at osteochondral donor sites in the patellofemoral joint. *Am J Sports Med.* 2004;32:967-974.
22. Grande D, Mason J, Dines D. Stem cells as platforms for delivery of genes to enhance cartilage repair. *J Bone Joint Surg Am.* 2003;85(suppl 2):111-116.
23. Grande DA, Breidbart AS, Mason J, Paulino C, Laser J, Schwartz RE. Cartilage tissue engineering: current limitations and solutions. *Clin Orthop*. 1999;367(suppl):S176-S185.
24. Grande DA, Halberstadt C, Naughton G, Schwartz R, Manji R. Evaluation of matrix scaffolds for tissue engineering of articular cartilage grafts. *J Biomed Mater Res.* 1997;34:211-220.
25. Hand CJ, Lobo J, White L, Miniaci A. Osteochondral autograft resurfacing. *Sports Med Arthros Rev.* 2003;11:245-263.
26. Hangody L, Fules P. Autologous osteochondral mosaicplasty for the treatment of full thickness defects of weight-bearing joints: ten years of experimental and clinical experience. *J Bone Joint Surg Am.* 2003;85(suppl 2):25-32.
27. Hannallah D, Peterson B, Lieberman JR, Fu FH, Huard J. Gene therapy in orthopaedic surgery. *Instr Course Lect.* 2003;52:753-768.
28. Hickey DG, Frenkel SR, Di Cesare PE. Clinical applications of growth factors for articular cartilage repair. *Am J Orthop.* 2003;2:70-76.
29. Hjelle K, Solheim E, Strand T, Muri R, Brittberg M. Articular cartilage defects in 1,000 knee arthroscopies. *Arthroscopy*. 2002;18:730-734.
30. Jackson DW, Scheer MJ, Simon TM. Cartilage substitutes: overview of basic science and treatment options. *J Am Acad Ortho Surg.* 2001;9:37-52.
31. Jackson DW, Simon TM. Tissue engineering principles in orthopaedic surgery. *Clin Orthop.* 1999;367(suppl):S31-S45.
32. Knutsen G, Engebretsen L, Ludvigsen TC, et al. Autologous chondrocyte implantation compared with microfracture in the knee. A randomized trial. *J Bone Joint Surg Am.* 2004;86:455-464.
33. Koh J, Wirsing K, Lautenschlager E, Zhang LO. The effect of graft height mismatch on contact pressures following osteochondral grafting; a biomechanical study. *Am J Sports Med.* 2004;32:317-320.
34. Mafulli N, Binfield PM, King JB. Articular cartilage lesions in the symptomatic anterior cruciate ligament-deficient knee. *Arthroscopy*. 2003;19:685-690.
35. Mandelbaum BR, Browne JE, Fu F, et al. Current concepts on articular cartilage lesions of the knee. *Am J Sports Med.* 1998;26:853-861.
36. Mason JM, Brietbart AS, Barcia M, Porti D, Pergolizzi RG, Grande DA. Cartilage and bone regeneration using gene-enhanced tissue engineering. *Clin Orthop*. 2000;379(suppl):S171-S178.
37. Mason JM, Grande DA, Barcia M, Grant R, Pergolizzi RG, Brietbart AS. Expression of human bone morphogenic protein 7 in primary rabbit periosteal cells: potential utility in gene therapy for osteochondral repair. *Gene Ther.* 1998;5:1098-1104.

38. Menche DS, Frenkel SR, Blair B, et al. A comparison of abrasion burr arthroplasty and subchondral drilling in the treatment of full-thickness cartilage lesions in the rabbit. *Arthroscopy.* 1996;12:280-286.
39. Minas T, Peterson L. Advanced techniques in autologous chondrocyte transplantation. *Clin Sports Med.* 1999;18:13-44.
40. Muschler GF, Nakamoto C, Griffith LG. Engineering principles of clinical cell-based tissue engineering. *J Bone Joint Surg Am.* 2004;86:1541-1558.
41. Musgrave DS, Fu FH, Huard J. Gene therapy and tissue engineering in orthopaedic surgery. *J Am Acad Orthop Surg.* 2002;10:6-15.
42. Nehrer S, Spector M, Minas T. Histologic analysis of tissue after failed cartilage repair procedures. *Clin Orthop.* 1999;365:149-162.
43. Nettles DL, Vail TP, Morgan MT, Grinstaff MW, Setton LA. Photocrosslinkable hyaluron as a scaffold for articular cartilage repair. *Ann Biomed Eng.* 2004;32:391-397.
44. O'Driscoll S. The healing and regeneration of articular cartilage. *J Bone Joint Surg Am.* 1998;80:1795-1812.
45. Pearce SG, Hurtig MB, Clarnette R, Kalra M, Cowan B, Miniaci A. An investigation of 2 techniques for optimizing joint surface congruency using multiple cylindrical osteochondral autografts. *Arthroscopy*. 2001;17:50-55.
46. Peterson L, Brittberg M, Kiviranta I, Akerlund E, Lindahl A. Autologous chondrocyte transplantation: biomechanics and long-term durability. *Am J Sports Med.* 2002;30:2-12.
47. Peterson L, Minas T, Brittberg M, Lindahl A. Treatment of osteochondritis dissecans of the knee with autologous chondrocyte transplantation: results at two to ten years. *J Bone Joint Surg Am.* 2003;85(suppl 2):17-24.
48. Poole AR. What type of cartilage repair are we attempting to attain? *J Bone Joint Surg Am*. 2003;85(suppl 2): 40- 44.
49. Potter HG, Linklater JM, Allen AA, Hannafin JA, Haas SB. Magnetic resonance imaging of articular cartilage in the knee: an evaluation with use of fast-spin-echo imaging. *J Bone Surg Am.* 1998;80:1276-1284.
50. Riddle RD, Johnson RL, Laufer E, Tabin C. Sonic hedgehog mediates the polarizing activity of the ZPA. *Cell*. 1993;75:1401-1416.
51. Sandell LJ, Silva MJ. What's new in orthopaedic research. *J Bone Joint Surg Am.* 2001;83:1117-1124.
52. Schreiber R, Ilten-Kirby B, Dunkelman N, et al. Repair of osteochondral defects with allogeneic tissue engineered cartilage implants. *Clin Orthop.* 1999;367(suppl):382-395.
53. Sellars RS, Zhang R, Glasson S, et al. Repair of articular cartilage defects one year after treatment with recombinant human bone morphogenetic protein-2 (rhBMP-2). *J Bone Joint Surg Am.* 2000;82:151-160.
54. Sgaglione N. Decision-making and approach to articular cartilage surgery. *Sports Med Arthros Rev.* 2003;11:192-201.
55. Sgaglione N. The biological treatment of focal articular cartilage lesions in the knee: future trends? *Arthroscopy*. 2003;19:154-160.
56. Sgaglione NA, Miniaci A, Gillogly SD, Carter TR. Update on advanced surgical techniques in the treatment of traumatic focal articular cartilage lesions of the knee. *Arthroscopy*. 2002;18(2 suppl):9-32.
57. Shasha N, Krywulak S, Backstein D, Pressman A, Gross AE. Long-term follow -up of fresh tibial osteochondral allografts for failed tibial plateau fractures. *J Bone Joint Surg Am.* 2003;85(suppl 2):33-39.
58. Shelbourne KD, Jari S, Gray T. Outcome of untreated traumatic articular cartilage defects of the knee. *J Bone Joint Surg Am.* 2003;85(suppl 2):8-16.
59. Simonian PT, Sussman PS, Wickiewicz TL, Paletta GA, Warren RF. Contact pressures at osteochondral donor sites in the knee. *Am J Sports Med.* 1998;26:491-494.
60. Steadman JR, Briggs KK, Rodrigo JJ, Kocher MS, Gill TJ, Rodkey WG. Outcomes of microfracture for traumatic chondral defects of the knee: average 11-year follow-up. *Arthroscopy*. 2003;19:477-484.
61. Steadman JR, Miller B, Karas S, Schlegel T, Briggs K, Hawkins R. The microfracture technique in the treatment of full-thickness chondral lesions of the knee in National Football League players. *J Knee Surg.* 2003;16:83-86.
62. Terukina M, Fujioka H, Yoshiya S, et al. Analysis of the thickness and curvature of articular cartilage of the femoral condyle. *Arthroscopy*. 2003;19:969-973.
63. Tomford WW. Transmission of disease through transplantation of musculoskeletal allografts. *J Bone Joint Surg Am.* 1995;77:1742-1754.
64. Vangsness CT, Garcia IA, Mills CR, Kainer MA, Roberts MR, Moore TM. Allograft transplantation in the knee: tissue regulation, procurement, processing and sterilization. *Am J Sports Med*. 2003;31:474-481.
65. Warren SM, Sylvester K, Chen CM, Hedrick MH, Longaker MT. New directions in bioabsorbable technology. *Orthopedics*. 2002;25(suppl):s1201-s1210.