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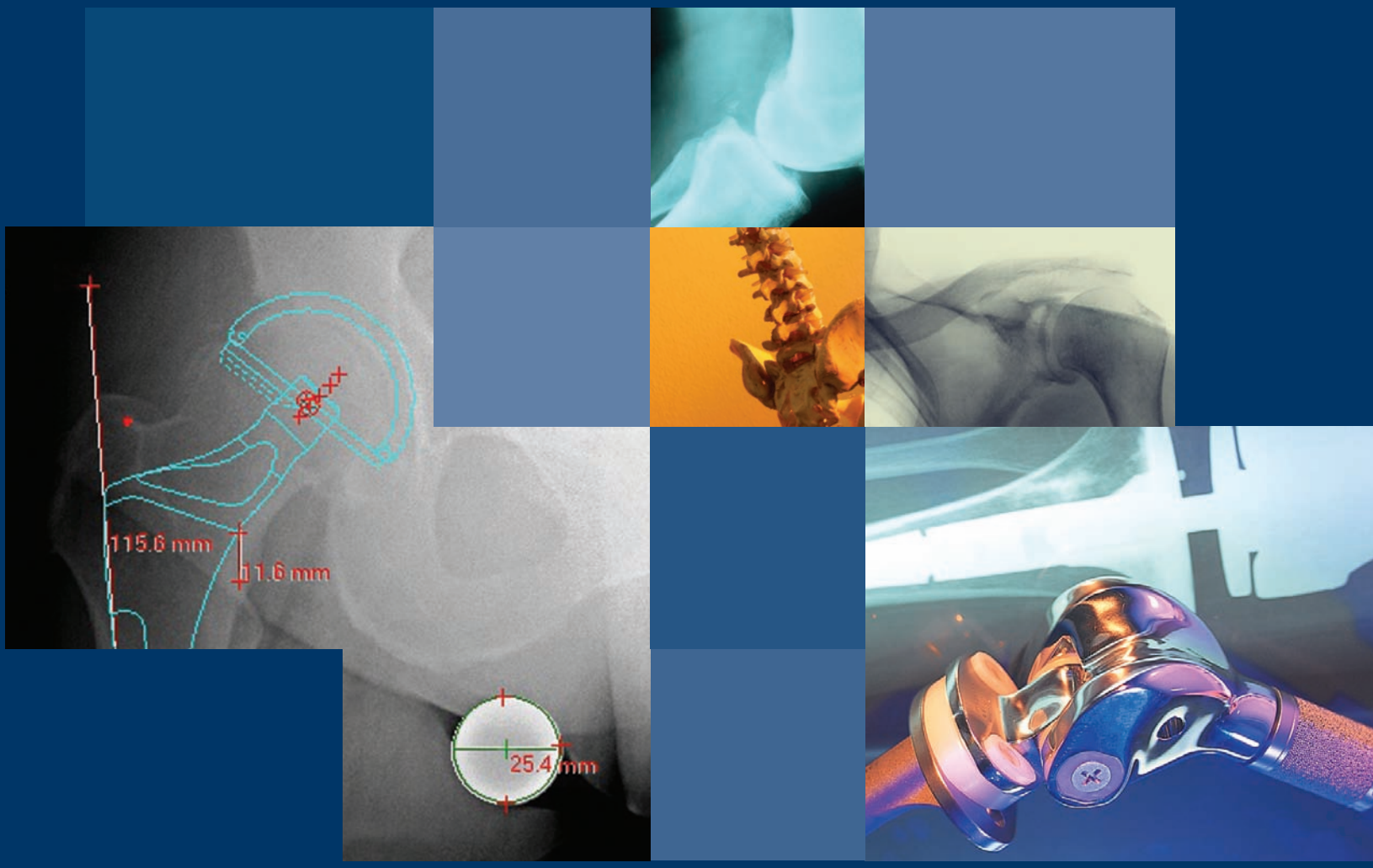

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SPORTS MEDICINE AND TRANSLATIONAL RESEARCH: SOLVING CLINICAL PROBLEMS IN THE SHOULDER AND KNEE THROUGH BASIC SCIENCE RESEARCH

Nicole A. Friel, MS; Brian J. Cole, MD, MBA

Author Affiliations – Departments of Orthopedic Surgery and Anatomy and Cell Biology, Rush University Medical Center, Chicago, Illinois.

Corresponding Author – Brian J. Cole, MD, MBA, Departments of Orthopedic Surgery and Anatomy and Cell Biology, Rush University Medical Center, Chicago, IL 60612 (bcole@rushortho.com).

Introduction

This article provides an overview of multidisciplinary studies performed within the Department of Orthopedic Surgery at Rush University Medical Center to address clinical problems related to shoulder and knee surgery. In these studies, basic science research is used to address clinical issues with the goal of improving patient care.

The Shoulder

Arthroscopic rotator cuff repair is one of the procedures most commonly performed by sports medicine and upper extremity specialists. Advances in diagnoses, surgical techniques, minimally invasive surgery methods, and pain management are continuing to evolve.

Surgical techniques

The advent of the double-row suture anchor technique for rotator cuff repair is of interest as this technique may help either prevent failures of the rotator cuff to initially heal or decrease the re-tear rate. In order to better characterize this technique, we are performing laboratory studies on the supraspinatus tendon in human cadavers to evaluate the biomechanical strength of sutures in both the medial and lateral portions of torn and intact tendons. We are also examining the collagen fibril diameter at the medial and lateral tendon regions under transmission electron microscopy (TEM). A more complete understanding of the functional and architectural properties of regional collagen fibers may help facilitate surgical planning.

Preliminary findings[1] suggest that the medial row of torn supraspinatus tendons has biomechanical properties that are significantly better than those of the lateral row. This inferior mechanical response of the lateral tendon is consistent with clinical observations that tendon pathology and matrix degeneration initiate near the insertion site of the supraspinatus tendon.[2] The superior pullout resistance of the medial row may provide a strain-shielding effect for the lateral row following double-row repair.[3] Supporting the biomechanical findings from a structural basis, TEM results show larger collagen fibrils and greater fibril density of the medial supraspinatus tendon. These ultrastructural properties may explain the more robust matrix for resisting suture migration and thus support medial row repair. These ultrastructural and biomechanical results offer a scientific rationale for

double-row rotator cuff repair, which has been supported by our clinical outcomes as determined by second-look MRIs at 2-year follow-up.

Pain management

Rotator cuff repair results in significant postoperative pain, and several treatments have been used to solve this problem. Bupivacaine intra-articular continuous infusion pain pumps have been used successfully to reduce pain within the first few days after surgery. However, prolonged intra-articular infusion of local anesthetic is now a suspected cause of a rare, but devastating postoperative destruction of the articular cartilage of the glenohumeral joint. In a case series by Hansen et al,[4] continuous infusion of bupivacaine with a pain pump catheter was implicated as the cause of destructive glenohumeral chondrolysis. In addition to clinical reports of chondrolysis, studies have demonstrated chondrotoxic effects due to bupivacaine in an in vitro model using bovine chondrocyte cultures as well as osteochondral explants.[5,6]

These problems have led to 2 preclinical animal studies evaluating the use of anesthetics in the rabbit glenohumeral joint. Rabbits underwent unilateral supraspinatus transection and repair, and were assigned randomly to 1 of 3 groups to receive infusions of either saline, bupivacaine, or bupivacaine plus epinephrine over 48 hours into the glenohumeral joint. The study showed decreased cartilage cell viability at 1 week postoperatively, suggesting chondrotoxic effects of local anesthetics.[7] However, in a second study with a 3-month end point, there were no differences in chondrocyte number, suggesting that the 3-month period allowed for the cartilage to recover.[8] Overall, these studies tell us to proceed with caution when using prolonged intra-articular administration of local anesthetics in our patients.

We have evaluated and treated a number of young patients with glenohumeral chondrolysis possibly related to the prolonged use of local anesthetic agents following shoulder surgery. We recently completed an analysis of patients treated with biologic shoulder reconstruction using osteochondral allografts for replacement of the humeral head often performed in association with soft-tissue interposition using a lateral meniscal allograft sewn to the periphery of the glenoid. This patient group has proven to be particularly challenging in terms of the pain and dysfunction that are present following the development of glenohumeral chondrolysis. While we are achieving clinical success in this area, we recognize that arthroplasty may still be the primary alternative for some of the most challenging cases. These results were presented at the 2009 Specialty Day of American Shoulder and Elbow Surgeons and the American Orthopaedic Society for Sports Medicine in Las Vegas

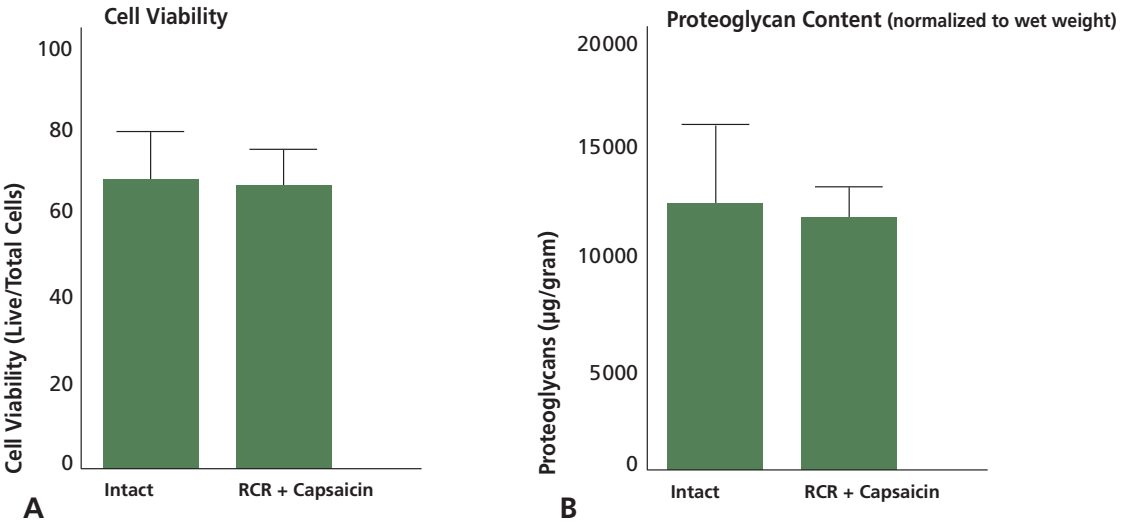

Figure 1. Cell viability **(A)** and proteoglycan content **(B)** at 1-week post-op for intact shoulders and shoulders with rotator cuff repair (RCR) and capsaicin. There were no significant differences between the intact and RCR/capsaicin groups for cell viability or proteoglycan content. Error bars denote standard deviation.

and will be published in the *American Journal of Sports Medicine*.[9,10]

The potential detrimental effects of local anesthetics have led to a search for an alternate intra-articular agent to achieve postoperative pain relief. The objective of a current study using a rabbit shoulder model is to evaluate the effect of a highly purified form of capsaicin on glenohumeral articular cartilage and rotator cuff tendon healing. If this one-time intra-articular injection can relieve pain without chondrotoxicity to the cartilage of the glenohumeral joint or impairment of rotator cuff tendon healing, this may provide an alternative for patients for postoperative pain management.

In preliminary results, cell viability and proteoglycan content of shoulders treated with capsaicin were similar to that of untreated shoulders, at the 1-week end point (Figure 1). Elevated proteoglycan synthesis at 1 week returned to normal at 18 weeks implying no long-term damage to chondrocytes or matrix. Failure strength of repaired shoulders, irrespective of treatment, was similar, suggesting no detrimental effects on the quality of tendon healing. The results indicate that a single injection of highly purified capsaicin into the glenohumeral joint does not induce a deleterious response with regard to cartilage matrix metabolism, cell viability, or rotator cuff healing and may potentially provide a safe alternative to manage postoperative pain.

The Knee

Focal chondral defects of the knee can be treated with a wide array of cartilage restoration techniques. Current repair techniques include debridement, marrow stimulation, osteochondral grafting (autograft and allograft), and autologous chondrocyte implantation. In general, good or excellent results are achieved in 75% of appropriately indicated patients who present with symptomatic cartilage problems.[11-13] Clearly, there is significant room for the development of new cartilage repair technologies and improvement of existing technologies.

Allograft tissue handling

Allograft tissue, among its many benefits, offers challenges. The process of donor recruitment, tissue procurement, anatomic manipulation, infectious disease screening, and sterilization increases costs and complicates the timeline for graft use. Traditionally, osteochondral allografts are implanted fresh within 7 days following only a brief period of storage at 4°C. Cooling graft tissue has the advantage of extending graft availability post harvest. However, there is concern that prolonged cooling of the tissue will decrease chondrocyte viability and thus lead to worse clinical outcomes.

To evaluate this theory, we looked at whole, intact canine osteochondral materials exposed to cold preservation (4°C) for 14, 21, or 28 days.[14] Cell viability was greater than 95% at 14 days, 75% to 98% at 21 days, and 65% to 90% at 28 days (Figure 2). Sulfate incorporation was also suppressed in samples stored for longer periods. Despite these variations, there were no significant differences between the groups. Thus, the data provided evidence that osteochondral plugs can be obtained from intact femoral condyles that have been in cold preservation for up to 28 days and tissue banking protocols for osteochondral allograft materials have changed accordingly.

In a subsequent study, the reversibility of metabolic suppression in cold-preserved cartilage was assessed. Using articular cartilage explants, it was determined that abrupt warming of the cartilaginous tissue is

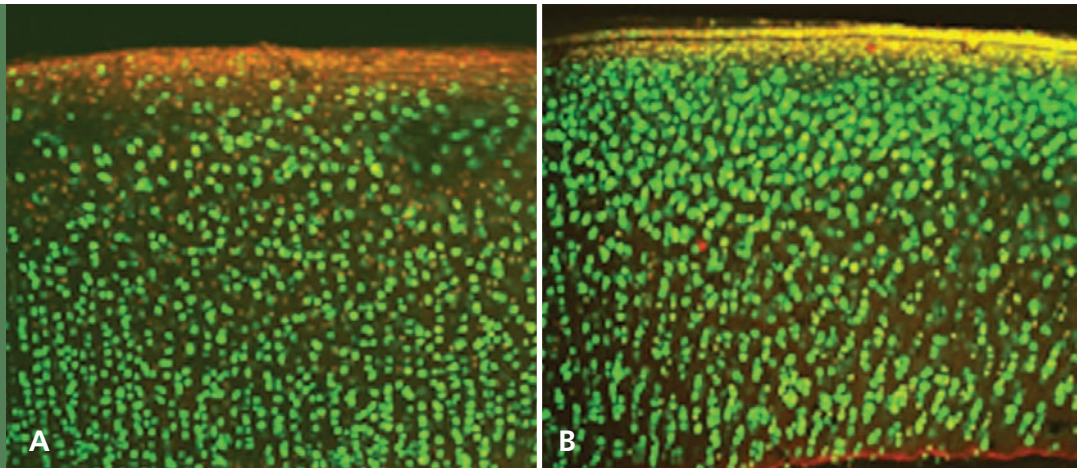

Figure 2. Cell viability in **(A)** fresh cartilage (cell viability 95%-100%) and **(B)** osteochondral allograft tissue cold preserved for 28 days (cell viability 65%-90%).

associated with proteoglycan suppression and increased nitric oxide production. However, we were able to partially reverse metabolic suppression of cold-preserved osteochondral allograft materials with gradual warming. Clinically, our findings have led to changes in the way we handle osteochondral allograft tissue. For example, prior to implantation we now soak the osteochondral allograft in cold saline rather than room-temperature solutions.

Impaction force for osteochondral grafts

Osteochondral autografts and allografts require mechanical force for proper graft placement into the defect site; however, the force applied during impaction compromises the tissue. In a controlled laboratory study, we aimed to determine the optimal impaction force and number of hits to seat the graft while minimizing cartilage damage.[15,16]

Osteochondral explants, harvested from fresh bovine trochleas, were exposed to a series of consistent impact loads delivered by a pneumatically driven device (Figure 3). Loads were delivered such that higher impaction forces received fewer hits and lower impaction forces received more hits in order to keep the impulse consistent. After we analyzed the plugs for cell viability, analyzed the histology by safranin O and picrosirius red, and assessed the release of sulfated glycosaminoglycans and nitric oxide, the results showed that impacted plugs had significantly lower cell viability than nonimpacted plugs. Also, a dose-response relationship in loss of cell viability with respect to load magnitude was seen, suggesting that greater impaction loads may cause more damage to the cartilage.

We can conclude that impaction loading parameters have a direct effect on the viability of the cartilage in the graft tissue. Optimal loading parameters for surgical impaction of osteochondral grafts use lower load magnitudes and a greater number of hits to ensure proper fit. Surgeons incorporating these loading parameters should see better clinical outcomes since the graft tissue will be compromised less when it is seated into the defect site. Several instrumentation companies have used this information to redesign the tolerances between the donor and recipient sockets to minimize the chances of chondral damage during insertion. In addition, these results may lead to consideration of further options to maintain cartilage during impaction, including pro-anabolic and anti-apoptotic interventions as well as surgical tools that can deliver impaction loads at preset parameters.

Engineered cartilage constructs

Biologic techniques allow for incorporation of native or donor tissue to fill small and large defects alike. One new option for treatment of chondral defects is a cartilage construct that may provide a biomechanically stable, hyaline-like cartilage tissue that avoids donor site morbidity and graft availability, limiting factors of osteochondral autografting and allografting, respectively. DeNovo ET (Zimmer, Inc, Warsaw, Indiana) is a scaffold-free construct generated from juvenile chondrocytes. Graft fixation into a defect is difficult given the fragility of the graft and the need for incorporation into surrounding tissue.

In a goat study completed in our lab, fibrin sealant was evaluated for fixation of the cartilage constructs in surgically created full-thickness chondral defects of the medial femoral condyle and trochlea.[17] At 24 weeks following surgery, the results showed that the use of fibrin glue provides reasonable success of graft fixation within a well-shouldered full-thickness cartilage defect (Figure 4). The results of this animal study

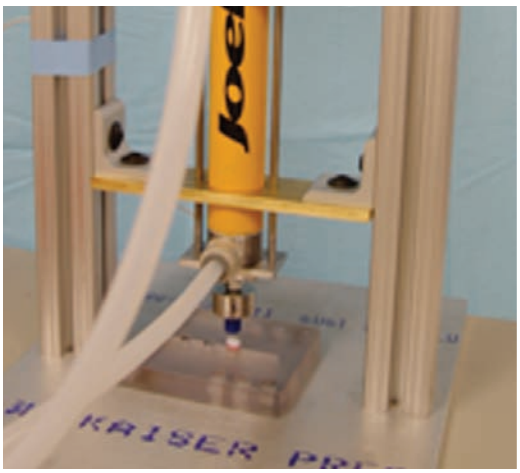

Figure 3

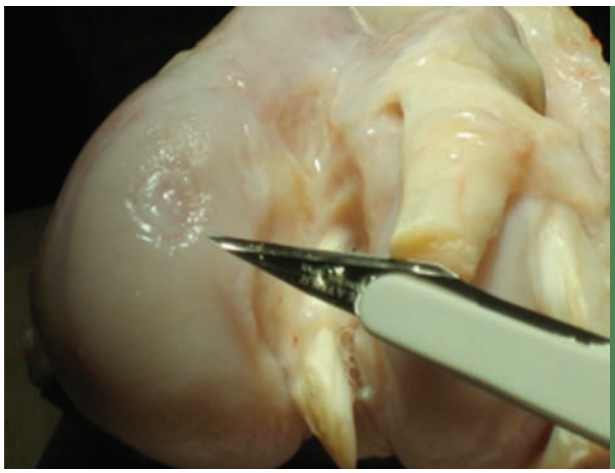

Figure 4

Figure 3. Pneumatic impaction device (SmartImpactor, Chicago, Illinois) used to deliver consistent loads and loading rates to the osteochondral grafts in the impaction study.

Figure 4. Engineered cartilage construct with successful femoral condyle retainment.

hold promise for future use of DeNovo ET grafts to treat human cartilage lesions. At Rush, we completed a phase 1 FDA study in 2007 and are embarking on a pivotal phase 3 study anticipated to begin patient enrollment toward the last quarter of 2009.

Minced cartilage

Many focal cartilage defects can be effectively treated with autologous chondrocyte implantation, a 2-step procedure requiring cartilage harvest at the index surgery, cell expansion, and subsequent reimplantation. In an effort to provide easier surgical delivery of autologous chondrocytes to repair chondral defects, minced cartilage may be an option. In this single-stage option, cartilage tissue, either processed intraoperatively (autologous) and loaded onto a scaffold or processed in advance (allogeneic) and available "on the shelf," can treat chondral defects.

In the lab, cartilage was harvested from both human and bovine trochleas, minced into small fragments (approximately 1 mm^3), loaded onto polyglycolic acid/polylactic acid (PGA/PLA) nonwoven felt or polyglycolic acid/polycaprolactone (PGA/PCL) foam reinforced with polydioxanone (PDS), and cultured.[18] The samples of minced cartilage with scaffold were then implanted into severe combined immunodeficient mice for 4 weeks to assess chondrocyte migration and growth (Figure 5). The study showed an inverse relationship between cartilage fragment size and amount of outgrowth (smaller size, more chondral growth), and the highest level of cellular activity was localized at the edge of the minced cartilage.

Further, we tested the effectiveness of the minced cartilage on goat specimens. A 7-mm trochlear defect was created and randomly assigned to 1 of 3 treatment options: no treatment (empty), scaffold alone, and scaffold with minced autologous cartilage fragments.[18] All treatments generated tissue in the defect. However, the scaffold with minced fragments demonstrated hyaline-like cartilage with better congruency, more intense staining for proteoglycans, a zonal structure, and a higher ratio of type 2 to type 1 collagen. At Rush, we completed a phase 1 FDA clinical study in 2007 and are now enrolling patients in a phase 3 multicenter study that will offer a prospective comparison of this Cartilage Autograft Implantation System to microfracture (DePuy Mitek, Inc, Raynham, Massachusetts).

Conclusion

These are just a few examples of how we at Rush University Medical Center have taken a multidisciplinary approach to real clinical problems related the treatment of shoulder and knee injuries. Taking the office to the laboratory and back has provided several opportunities to improve patient care.

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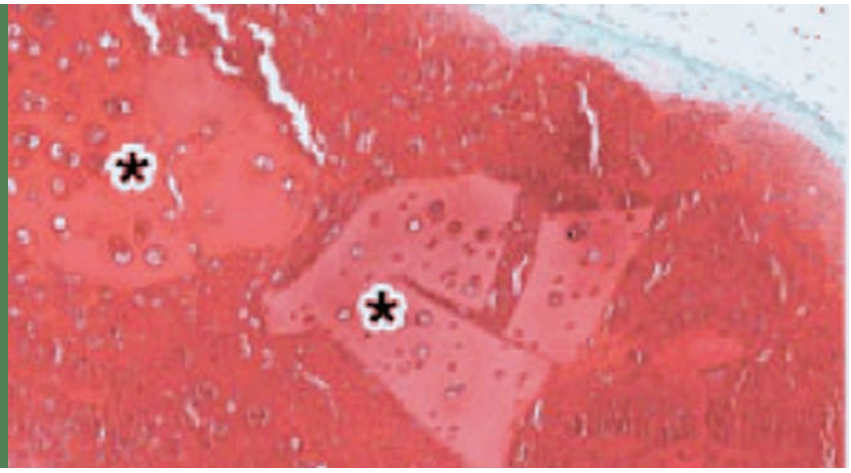

Figure 5. Safranin O stain of a bovine construct from a severe combined immunodeficient mouse with a cartilage-loaded scaffold, 4 weeks post operation. Asterisks denote original cartilage fragments.

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