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Advancing Regenerative Surgery in Orthopaedic Sports Medicine

The Critical Role of the Surgeon

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The constant desire to improve outcomes in orthopaedic sports medicine requires us to continuously consider the challenges faced in the surgical repair or reconstruction of soft tissue and cartilaginous injury. In many cases, surgical efforts targeted at restoring normal anatomy and functional status are ultimately impaired by the biological aspect of the natural history of these injuries, which acts as an obstacle to a satisfactory repair process after surgery. The clinical management of sports injuries and the delivery of appropriate surgical intervention are continuously evolving, and it is likely that the principles of regenerative medicine will have an increasing effect in this specialized field of orthopaedic practice going forward. Ongoing advances in arthroscopy and related surgical techniques should facilitate this process. In contrast to the concept of engineered replacement of entire tissues, it is probable that the earliest effect of regenerative strategies seen in clinical practice will involve biological augmentation of current operative techniques via a synergistic process that might be best considered “regenerative surgery.” This article provides an overview of the principles of regenerative surgery in cartilage repair and related areas of orthopaedic surgery sports medicine. The possibilities and challenges of a gradual yet potential paradigm shift in treatment through the increased use of biological augmentation are considered. The translational process and critical role to be played by the specialist surgeon are also addressed. We conclude that increased understanding of the potential and challenges of regenerative surgery should allow those specializing in orthopaedic surgery sports medicine to lead the way in advancing the frontiers of biological strategies to enhance modern clinical care in an evidence-based manner.

Keywords: sports medicine; cartilage repair; clinician-scientist; translational research

The practice of orthopaedic surgery sports medicine, and the associated demand for constantly improving patient outcomes with which it comes, demands of us to recognize that considerable challenges are still faced in the surgical repair or reconstruction of soft tissue and cartilaginous injury. In many cases, surgical efforts targeted at restoring normal anatomy and functional status are ultimately impaired by the biological aspect of the natural history of

these injuries, which acts as an obstacle to a satisfactory repair process after surgery. In an effort to deliver the best patient care we possibly can, it is likely that we can still find ways to further improve outcomes if we can influence this biological healing process in a favorable manner. The term “regenerative medicine” (RM) has been used in many contexts, but ultimately, it refers to the use of biological therapies to replace, repair, or promote the regeneration of diseased or damaged tissue.[§] It may have particular relevance in orthopaedic surgery sports medicine in view of the biological aspects of the conditions faced in the clinic and operating room. At the present time, there is a growing database of preclinical and early clinical evidence for the introduction of biological therapies into clinical practice, and it is reasonable to hope that we will ultimately be able to routinely harness such therapies to improve patient outcomes after surgical intervention.^{||} Safely taking advantage of the potential of such new treatment options that may be on the horizon is closely linked to the concept of translational research, the mechanisms by

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[§]References 2, 9, 19, 20, 29, 33, 39, 43, 49, 52, 54, 58, 60-63, 76, 78-80.

^{||}References 6, 13, 15, 21, 28, 31, 47, 51, 53, 59, 63, 66, 67.

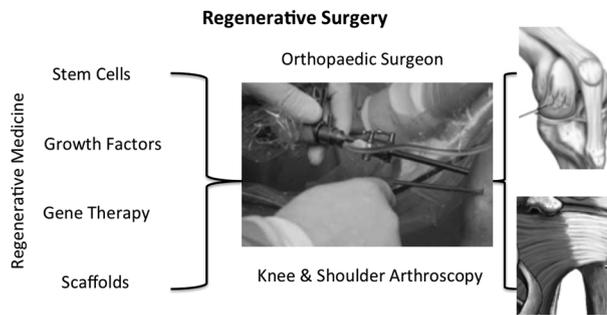


Figure 1. The surgeon provides a key link in safely translating the potential of laboratory regenerative medicine into augmented tissue repair in orthopaedic sports medicine regenerative surgery.

which we link science and surgery, the laboratory, and the patient. As surgeons, our goal is ultimately to restore our patients to a state of natural form and function through our surgical intervention. In translational research, the relevant questions are raised at the bedside by clinicians, investigated in the laboratory and clinical research units, before bringing a suitable form of intervention back to the bedside.

The term “regenerative surgery” (Figures 1 and 2), combining the concepts of orthopaedic surgery sports medicine and RM, is the one utilized in the remainder of this article. Herein, we provide important examples of how and why biological therapies might be applied in orthopaedic surgery sports medicine. Key clinical conditions of the knee and shoulder, alongside some difficulties faced in improving the outcomes from current treatment options, are considered. Significant issues regarding the role to be played by all surgeons in linking science and surgery are addressed, as is the need to also develop a larger number of active clinician-scientists and better infrastructural mechanisms for effective translation of laboratory research potential to practical improvements in the outcome from surgical intervention. The aim of this article is to outline the critical role of the surgeon and show that an increased understanding of the potential and challenges of this unfolding field should allow those specializing in orthopaedic sports medicine to lead the way in advancing the frontiers of biologically augmented intervention to enhance modern clinical care in an evidence-based manner.

THE RATIONALE AND POTENTIAL OF REGENERATIVE SURGERY IN SPORTS MEDICINE

Cartilage Repair

Cartilage surgery is fast becoming a specialized field of sports medicine practice of its own merit.^{9,29} Each month brings forth new literature addressing the unresolved and ongoing clinical problem, the outcome of treatments currently offered, and the potential of novel biological strategies for improved intervention. Regeneration of durable hyaline cartilage remains a frontier beyond our reach in

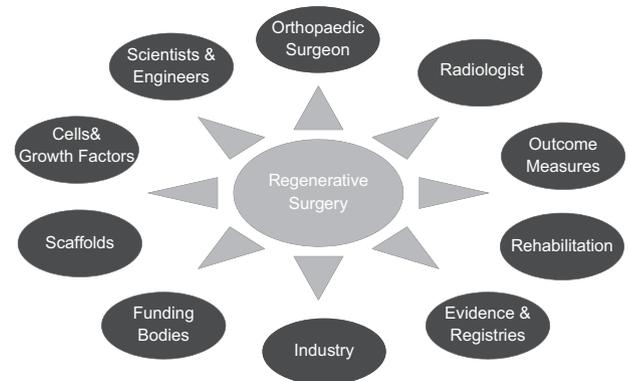


Figure 2. Diagrammatic representation of many of the key components making up a successful program in regenerative surgery. Collaboration and communication are crucial in this effort.

the operating room at present, but there are promising signs for the future. While it is difficult to be selective in terms of biological therapies that might ultimately help us deliver this to patients, if we focus on augmentation of current surgical strategies, we believe that 2 areas in particular represent the progress that may be made in this regard in the short to medium term: (1) application of growth factors and (2) stem cell (mesenchymal) therapy.^{6,39,62,69}

Fortier et al recently presented a comprehensive review of the use of growth factors in animal models²⁴ of cartilage repair and concluded that individual growth factors can enhance cartilage production and decrease catabolic activity. In particular, Fortier et al²⁴ identified BMP-7 as the gold-standard growth factor with the ability to decrease catabolic activity. In time, it is possible that both BMP-7 and other growth factors will be introduced to clinical practice either in isolation or possibly to augment microfracture, cellular transplantation strategies, and possibly even allograft or autograft osteochondral transplantation techniques. This can obviously positively affect the current operative options. From the clinician’s perspective, it will be necessary going forward to have a clinical awareness of these growth factor/gene therapy–related strategies of biological augmentation in cartilage repair as they move toward clearly defined surgical tools.

In terms of stem cell therapy, it is in the first instance helpful to have an understanding of the use of stem cell therapy as the “engine room” of regenerative strategies (Figure 3).³¹ While primary differentiated cells are routinely utilized in current clinical practice (eg, chondrocytes), stem cells have become the main cell source for laboratory tissue repair research because they meet several major cell therapy requirements that differentiated primary cells do not. They are defined by their self-renewal, differentiation capacity, and ability to proliferate in culture without loss of their potential to form tissue. Embryonic stem cells (ESCs) have the advantages of vast potential for multiplication and ability to regenerate many different types of tissue in a consistent manner. Despite this, we must be aware that there remain major

ethical and safety issues relating to the use of ESCs, and for now, their use will continue to be reserved for laboratory and preclinical study. At the current time, adult stem cell niches, and in particular mesenchymal stem cells (MSCs), would instead appear to have the strongest evidence to support their safe use as the next generation of cellular treatments in our field. Although they do not have the pluripotency of ESCs, MSCs are multipotent cells that can differentiate into a variety of cell types including osteoblasts, chondrocytes, and adipocytes. In addition to avoiding immune rejection, they are known to have both immunomodulatory and vasculogenic effects, which benefit tissue repair. Identifying specific markers for the isolation of cell subpopulations with higher chondrogenic potentials may enhance neocartilage formation. A number of preclinical studies provide preliminary data in regard to MSCs in cartilage, but recently published pilot results from a human study may be worthy of special mention here. In the study in question, Haleem et al³⁵ demonstrated feasibility and proof of principle that autologous culture-expanded MSCs in a platelet-rich fibrin glue (PRFG) as a scaffold may be used clinically to good effect in the treatment of full-thickness articular cartilage defects, particularly large-sized defects (>4 cm²). Platelet-rich fibrin glue successfully retained the cultured MSCs within the defects and provided them with a suitable environment to synthesize a cartilaginous matrix with the gross appearance of hyaline cartilage. This study used standardized clinical outcome scores to assess the results of this treatment modality and magnetic resonance imaging (MRI) for assessment and follow-up of the repair. The positive 1-year clinical outcomes in this study, limited by follow-up and control, further support randomized controlled clinical trials of this treatment modality with larger numbers of patients and longer follow-up periods. This is potentially a very exciting concept as the key tools involved utilize endogenous substances and have been extensively investigated individually before being combined as an overall treatment strategy to be taken to clinical trial. The idea of “facilitated endogenous repair” was previously introduced by Evans et al²¹ and is a mechanism we can relate to as surgeons in an effort to move science to surgery in this manner.

The recent recognition of a novel cellular niche, induced pluripotent stem cells (iPSCs), should also be mentioned here. In 2006, it was shown that mouse embryonic and adult fibroblasts acquire properties similar to those of ESCs after retrovirally introducing genes encoding for transcription factors.⁶⁵ Their discovery provides another alternative cell source for cartilage tissue engineering, which is free from ethical controversies associated with ESCs but with similar pluripotency that may ultimately result in greater efficacy than MSC use. The biology underlying the reprogramming mechanism of iPSCs remains poorly understood at present, but iPSCs may eventually prove to be one of the most exciting cellular options on the horizon in sports surgery. An important next step will be to identify ways of assessing which iPSC lines are sufficiently reprogrammed and safe to use for therapeutic applications. The approach of generating patient-specific pluripotent cells will possibly transform our work in sports medicine in many ways. As these tools become

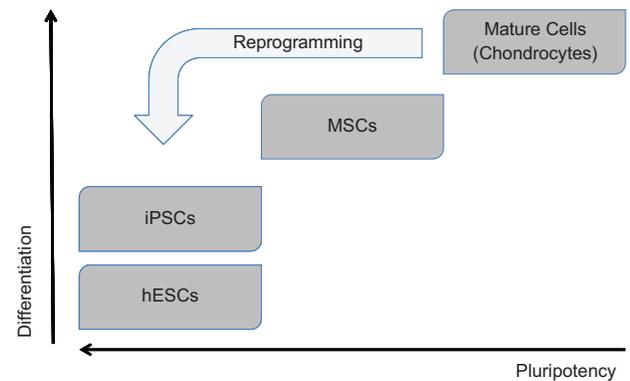


Figure 3. Diagram demonstrating the relationships/differences between various commonly considered cell types in terms of potency and differentiation. It is now believed any cell in the body can be reprogrammed back to a cell containing the multipotentiality traditionally only associated with embryonic stem cells. hESCs, human embryonic stem cells; iPSCs, induced pluripotent stem cells; MSCs, mesenchymal stem cells.

available for clinical evaluation, it will be helpful for surgeons and scientists alike to consider their role.

Finally, in this section, we must consider scaffolds and related structures.^{5,30,32,44,85} While we have outlined that the philosophy of RM might be shifting away from trying to recapitulate every detail of living tissues toward exploiting the essential interactions that allow the body to maintain homeostasis and repair tissues, it is likely that scaffolds still have a role to play. Their use in experimental and clinical studies will continue to facilitate precise understanding of underlying molecular, cellular, and environmental interactions in addition to contributing to the bioengineering capabilities to re-create these interactions on the appropriate spatiotemporal scales. Natural and synthetic polymers, inorganic materials, and their composites have all been formulated into porous scaffolds, nanofibrous membranes, microparticles, and hydrogels for use in the treatment of sports medicine conditions. Some of the benefits of synthetic polymeric biomaterials are that they have reproducible mechanical and chemical properties, are easily fabricated into different shapes and sizes, can degrade by hydrolysis, and are useful for preclinical evaluation. However, there is some concern that they may lack functional chemical groups for cellular binding. There has therefore been some interest in adding functional groups to nondegradable synthetic graft surfaces in the hopes of enabling tissue growth and avoiding poor tissue integration, foreign body immune responses, and high failure rates. Another concern is that synthetic polymers may release acidic by-products or unnatural polyesters into the bloodstream during degradation. For these reasons, there also remains considerable interest in the application of natural, protein-based fiber materials as scaffolds. Regardless of which material is used, one of the key factors in effective application of scaffolds in tissue engineering is the optimization of cell-biomaterial interactions, particularly in terms of the ability of cells to adhere, proliferate,

and secrete matrix onto the scaffold. Incorporating biological signals in 3 dimensions can induce desired cell fate and tissue regeneration, and subtle changes may have profound effects on cellular responses. Naturally derived materials contain inherent signals for chondrogenesis, and culturing stem cells on cartilage-derived matrix can promote chondrogenic differentiation in the absence of exogenous growth factors. Grafting biomimetic signals such as GAGs, proteins, or short peptides onto 3-dimensional synthetic scaffolds can also influence cell proliferation and differentiation. We also know that zonal organization in scaffolds may be important. Cartilage tissue demonstrates significant variance in cell phenotype, composition, and matrix organization along the depth of the tissue. This reflects different biomechanical and functional requirements of different zones. Re-creating the zonal variations in engineered cartilage tissue may be beneficial for functionality and long-term stability of the engineered tissue. In addition to this, we now understand that mechanical stimulation also plays a role in the biological process. Increased collaboration by specialist sports surgeons with biomaterial specialists may facilitate further advances in this field.

Meniscal Repair

Many of the same principles apply in meniscal injury.^{5,26,36,45,55,73,82} Approximately 1.5 million knee arthroscopies are performed each year in the United States, and approximately 750,000 of these involve a meniscal procedure, usually debridement. We now know that the natural history of partial or complete meniscectomy demands of us the need to consider repair rather than debridement as our default management of these injuries. Removal of this important anatomic structure eventually leads to degenerative changes of the articular cartilage and subsequent clinical symptoms.⁸¹ These degenerative changes are the result of increased peak stresses on the articular cartilage because of a decreased contact area in the meniscectomized compartment of the knee.⁸² The cartilage volume loss after meniscectomy is estimated at 4% per year and is more pronounced in the lateral compartment than in the medial compartment (because of the convex femoral condyle articulating on a convex lateral tibial plateau).⁸² These findings have substantially influenced our therapeutic approach to this condition. Total meniscectomy has now almost been completely abandoned in favor of partial meniscectomy and meniscus-repairing procedures. Both procedures have the theoretical advantage of being more protective to the articular cartilage. However, difficulties do remain. We know, for example, that there is still a failure rate of healing of up to 20% or more with current surgical repair techniques.⁸² In addition to this, the recent MOON (Multi-center Orthopaedic Outcomes Network) cohort study has also demonstrated that only 30% of medial meniscal tears and 10% of lateral meniscal tears are amenable for repair.²² It is therefore clear that novel solutions are required to provide treatment options for the vast majority of patients with such injuries. Again, it is likely that augmented repair has a major role to play as the endeavor to

engineer total meniscal replacements remains a more long-term target. This potential for biological augmentation of surgical repair needs to be investigated in more detail and ultimately refined to clearly define arthroscopic or minimally invasive surgical techniques. Microfracture of the intercondylar notch, use of platelet-rich plasma, fibrin plugs, and others are at present employed by a number of specialists in the field, and it should be possible to build on these concepts going forward.²⁶ Another tool worth considering may be to promote the homing in of administered supportive cells (eg, MSCs), or cells released through microfracture, for example, through identification of injury markers or epitopes on the menisci to which antibody-labeled cells may bind. This concept is being explored in our laboratory at present, having previously been suggested in terms of repair of articular cartilage by Poole et al.⁶⁸ However, it must be noted that a comprehensive understanding of the basic biology of meniscal injury has not yet been achieved, and this may act as an obstacle to improved intervention. A literature search for this article found evidence of much ongoing work toward treatment strategies but a lack of exploration of the background processes and impediments to repair. This must improve if we are to adequately treat meniscal injury with satisfactory efficacy. The likelihood of success will be increased, however, by combining the questions of the surgeon with the basic investigative potential of the laboratory.

Shoulder Surgery: The Rotator Cuff

Regenerative surgery has also a major role to play in the area of shoulder surgery.^{42,43} Despite the prevalence of rotator cuff injury, for example, and the myriad surgical repair techniques available, the inability of the rotator cuff to heal back to the insertion site on the humerus after repair is a significant clinical problem. The attachment of tendon to bone presents a great challenge in engineering because a soft compliant material (tendon) attaches to a stiff (bone) material. A high level of stress accumulates at the interface because of the difference in stiffness of the 2 materials. This problem is solved by the presence of a unique transitional tissue at the interface, which in the normal state can effectively transfer the stress from tendon to bone and vice versa through its gradual change in structure, composition, and mechanical behavior. Surgical reattachment of separated tendon and bone often fails and presents difficulty for tendon-to-bone healing because of the lack of regeneration of this specialized structure. Instead, rotator cuff healing occurs by reactive scar formation rather than regeneration of a histologically normal insertion site. The overall structure, composition, and organization of a normal insertion site do not regenerate. Specifically, the zone of calcified cartilage does not reform. The poor healing response likely relates to insufficient expression of genes that direct formation of the complex structure and composition of the insertion site. Clinical studies have shown radiographic failures at the repair site at 2 years in anywhere from 11% to 95% of patients, depending on the size and chronicity of the tear, presence of fatty infiltration, and the age and general health status

of the patient. Although patients with retears or failed healing may have pain relief, these studies show that they have inferior functional results when compared with patients with healed repairs. Given the related abnormalities in the cellular and molecular signals in the healing environment, attention has turned to methods to augment the biological response after rotator cuff repair. Further consideration by surgeons of the need to address the biological processes of the injury and healing process that follows surgical repair may lead to improved healing rates and functional results over that seen with current standard reattachment procedures alone. For example, we and others have recently shown that biological augmentation of acutely injured rotator cuffs with scleraxis-transduced MSCs or osteoconductive Ca-P matrix at the tendon-bone repair site is associated with improved outcomes in the early postoperative period after rotator cuff repair in small animal models.^{34,46,47} However, these are just examples of the work being done in this field, and further studies are needed to determine if these types of approaches remain safe and effective in larger models and ultimately in patients. There are important limitations in knowledge that currently limit the clinical application of various biological approaches to augment rotator cuff tendon healing. Much more information is required to understand the role of inflammatory cells and mediators in the healing process. It is likely that signals produced by inflammatory cells soon after surgical repair play an important role in the initiation and regulation of the healing process; however, further information is required to identify how these signals control healing. One of the most important limitations in current knowledge relates to the effect of mechanical load on tendon-to-bone healing. There is currently very little information available about the effect of timing, magnitude, and type of mechanical load on tendon-to-bone healing. These studies do, however, demonstrate the potential effect that biological augmentation may have on clinical practice as we seek to improve outcomes from shoulder surgery. In addition, these studies on enhancing attachment at the tendon-bone interface will have significant implications for other surgical strategies, where there is a focus on this phenomenon including that of cruciate ligament reconstruction and related surgery.²⁸

IMPROVING TRANSLATION FROM SCIENCE TO SURGERY: THE ROLE OF THE SURGEON AND THE SYSTEM

The potential of regenerative surgery to aid our patients is clear. Although we may some day be able to think about these options for augmentation as routinely as we do standard surgical procedures themselves, at present, there is clearly a problem that much of the knowledge emanating from the laboratory does not translate to the operating room.^{40,49} The National Institutes of Health (NIH) funded nearly \$15 billion of basic science research in 2009, and it might be reasonable to hope that this investment would soon bring returns in terms of improved clinical outcomes in the near future. Unfortunately, current statistics indicate

that less than 25% of highly promising biomedical discoveries result in a published randomized clinical trial, and less than 10% are established in clinical practice within 20 years.¹⁷ Regardless of the reasons cited for this phenomenon—regulatory, structural, economic, or motivational—the result is the same: we are not reaping the full benefits of our investment in research. Addressing this issue in the clinical community is by no means an easy task, given the immense surgical demand current workloads place on clinicians. While enormous amounts of new basic science knowledge are available, efforts toward translation have not been able to keep pace.⁵⁶ Our current deficit has previously been labeled the “valley of death,” and neither basic researchers, busy with discoveries, nor surgeons, busy with patients, appear keen to venture there.¹⁰ The causes of this are likely multifactorial, but it is our responsibility to consider the role of the surgeon because we can undoubtedly make a difference, given the link we form between the laboratory and the patient. Given the ever-growing sophistication of our scientific knowledge and the additional new laboratory discoveries that are likely in the future, it should be an important part of our training and practice to engage with this process.

The surgical personality, which is inherently impatient with the status quo, may actually be of significant importance in leaping the current hurdles that are part of the translational process. Spindler and Dunn have recently outlined the potential benefits in a transition from the traditional bench-to bedside approach to a more applicable bedside-to-bench approach.^{22,77} This should interest us as clinicians because the multistep process proposed in their model develops first from the need to treat a human condition. In practical terms, this refers to the surgeon playing the initial role in identifying modifiable predictors of important clinical outcomes that are amenable to regenerative surgery (eg, a meniscal tear). The second part of the process they propose involves piloting the proposed solution to establish proof of concept and reproducibility in a translational model. Third is to perform comparative and safety studies in a larger animal experiment over a longer time period (ie, translational model). The fourth stage involves a pilot study in a small group of humans to confirm evidence of effect and safety. Fifth is an efficacy trial, either a randomized trial or a human cohort. Sixth and finally, we must consider post-market surveillance for safety in a large human cohort. The surgeon can ultimately play a major role in most of these phases, moving from the current position of often being an interested spectator from outside the field of play. Spindler and Dunn⁷⁷ also note that to establish clear targets for biologically enhanced intervention, there is a clearly defined need for funding the study of large prospective cohorts for major orthopaedic conditions by the NIH, analogous to the Framingham study on cardiovascular disease. Such studies would facilitate the accurate identification of further proven modifiable predictors on which further laboratory and clinical research should be focused. Surgeons are in a strong position to drive the demand for this to happen.

While the individual clinical surgeon can play a major role as outlined above, ultimately, the large-scale translation of scientific knowledge to surgical care requires greater attention to specialized infrastructure and

TABLE 1
Fields in Which the Sports Medicine Specialist Requires Specialized Training
If They Are to Act as a Clinician-Scientist in Bridging the Gap Between Operating Room and Laboratory^a

Field	Tools and Skills Needed
Biomedical research	Comprehensive knowledge of field; ability for solid benchwork and appropriate study design
Intellectual property	Access to experts in development and protection; understanding of the process, strategies, and importance of intellectual property; knowledge of patents
Funding	Knowledge of funding sources; ability to negotiate with institutional, governmental, and industrial partners
Regulatory agencies	Knowledge of national and international regulations and bodies; ability to navigate through system and processes
Legal issues	Knowledge of intellectual property laws, patient rights, investigator rights, and legal framework between startups, academia, and industry
Ethical issues	Awareness of patient rights, animal rights, medical and research ethics, university and clinical institutional regulations, and regulatory body regulations
Communication skills	Ability to speak to various types of audience, prepare manuscripts, interact with digital media, and build relationships between various departments and institutes
Preclinical testing	Knowledge of regulatory requirements before clinical testing; ability to evaluate viability of standard operating procedures and strategically optimize resources
Trial design	Knowledge of process, challenges, and concerns; ability for critical thinking skills to overcome hurdles; ability for developing protocols and forging collaboration
Fundamental skills	Networking, team building, communication, strategic thinking, and problem solving

^aSuch individuals require extended training and dedicated mentorship to be successful.

supportive mechanisms carefully developed for this purpose. This starts with the need for increased formal scientific training and support of a subset of surgeons to lead this translational process as clinician-scientists (Table 1).[¶] Such individuals can have a major effect within the practice of sports medicine surgery, in particular given the dual scientific and clinical components that underlie impediments to improving the outcome of current surgical procedures. Brand and Hannafin⁸ have previously addressed “the environment of the successful clinician-scientist” and concluded that the clinical demands placed on such individuals continue to be a major impediment. This should be a big concern in our community as the future of our profession and development of skilled surgeons capable of integrating biology into surgery may be negatively affected if we do not give dual clinical and scientific pursuits the attention they require. Mentorship is the key component predicting any individual’s future success in this field. The development and support of individuals conducting dual surgical and scientific activities within orthopaedic specialty groups, academic departments, residency, and orthopaedic sports medicine fellowship programs might be the single biggest leap we can make within the field of sports medicine and regenerative surgery at the present time. For medical schools, teaching hospitals, university heads, and department chairmen, the challenge is to create a more attractive and supportive academic culture that not only attracts and trains but also actively nurtures and sustains clinical and translational surgeon-scientists. This is supported by a report by the Association of American Medical Colleges calling on the leadership of academic medical centers to reaffirm translational and clinical research as a core

mission and to promote training programs for clinician-scientists that provide protected time for trainees and dedicated time for capable mentors.^{3,16} These principles are equally valid in the context of regenerative surgery and orthopaedic sports medicine. In many ways, we have a big head start, given the immense interest students, residents, and fellows show in orthopaedic surgery and sports medicine. Many of these individuals participate in basic and clinical research during training, and most appear excited and challenged by the opportunities to combine clinical and research activities to a varying degree. This is most often seen where adequate structures for project training, funding, and mentorship are in place. Ultimately, however, if we do not address the need for an increased number of orthopaedic surgery sports medicine clinician-scientists, we may continue to produce a substantial volume of encouraging, but ultimately repetitive, preclinical data in small animals without translating these findings into pivotal clinical trials.⁵²

THE NEED FOR ADEQUATE FUNDING

Funding is another matter that requires our attention and is an area where everyone in the field can play a role. This relates to funding of both the basic laboratory research that will underpin our clinical practice in regenerative surgery and also of the infrastructure, which will house and protect the principles that will underpin translation of laboratory findings to safe clinical practice. We must insist on adequate resources being made available to capitalize on the immense scientific discoveries of the past couple of decades and simultaneously ensure funding is spent in a way that will ultimately enhance patient care. At a national level, the NIH has promoted the development of a new

[¶]References 1, 3, 7, 8, 12, 18, 23, 37, 38, 41, 42, 70, 71, 83, 84.

discipline of clinical and translational science with the foundation of the Clinical and Translational Science Awards (CTSAs) in 2005. These grants were created to stimulate progress from scientific innovation to health improvement and will have an estimated \$500 million annual budget by 2012.¹⁷ The members of the CTSA consortium serve as a magnet that concentrates basic, translational, and clinical investigators; community clinicians; clinical practices; networks; professional societies; and industry to facilitate the development of new professional interactions, programs, and research projects.⁶⁴ It is essential that we highlight to such bodies the potential that we believe regenerative surgery can play in clinical sports medicine practice in an effort to capitalize on the funding that may be available to assist in the development of biological tools for surgery. Our input may also help these consortia to successfully achieve funding to continue their activities in the next round in an effort to bridge the gap between discovery and clinical testing so that more efficient translation of promising discoveries may take place. Academic departments in orthopaedic surgery sports medicine ultimately will carry much of the responsibility of ensuring that this happens. Those institutes and departments that do make careful and well-planned investments in people and facilities can maintain high-quality research productivity and, when positioned with the correct intellectual capital, can create innovative business opportunities in addition to seeking support through traditional federal, state, and extramural and intramural structures.

In addition to communicating with standard national grant and funding agencies, it may be important at this time of financial constraint and fiscal policy overhaul that we also establish direct communication with our local, state, and government representatives. The patients we treat and the conditions with which they present should represent a core part of the mandate on which representatives are elected and work for on behalf of the community. In addition to being advocates for our patients, we can also emphasize the social and economic benefits of adequate investment in this area. It is important that we communicate that the work being done should be seen as an asset rather than a liability; for this to be seen through to fruition, however, will require an honest and intense application to the process by both clinicians and scientists together, and thus, we must also play our part to ensure a long-term return for everyone involved.

PROMOTING EVIDENCE-BASED SURGERY

Although the timeline remains unclear, it is reasonable to believe we will eventually make the progress required in the process of developing novel clinical treatment options for the introduction to clinical practice. With this will come the need to practice evidence-based intervention.^{13,14,48,50,60} Our patients, hospitals, regulatory bodies, and insurance providers will insist on this being the case. In the case of regenerative surgery, treatment to be used in humans should logically undergo a scrutiny of evidence before widespread application. It would seem appropriate

that high-quality confirmatory evidence about safety and efficacy from randomized trials be obtained prior to patient application. The recent emergence of platelet-rich plasma (PRP) as a treatment strategy in many forms of musculoskeletal injury, often without due consideration of its merits in an individual case, may offer an example of how this process is sometimes not used most effectively. Foster et al²⁵ have previously evaluated the use of PRP and note that although there are numerous basic science studies, animal studies, and small case reports regarding PRP-related products, there are only a few controlled clinical studies that provide a high level of medical evidence regarding its potential benefits. The number of participants in the studies is typically small, and the majority of studies are underpowered. They emphasize to us the need to assess the evidence in the literature that supports safety and efficacy. We must extend this way of thinking to all biological strategies. While the attitude of "what harm might it do?" may not be catastrophic with PRP, the potential effect of getting it wrong with stem cells or genes encoding for various growth factors should be reason enough to ensure an evidence-based approach for all future treatments.

Obtaining relevant and repeatable preclinical data is a key element in the product development cycle that aims to bring new and improved treatments to the clinic.³³ A randomized controlled trial is the gold standard of evidence for the introduction of new medical devices or interventions. A pivotal case series may be an acceptable substitute for the randomized controlled trial when the efficacy of the control is well defined, the new intervention has low risk, and/or the alternatives are suboptimal. For this process to work, it is essential that all clinicians involved in such surgery engage with this process of continuous evaluation. There may be an argument to be made that all novel biological treatments should be part of a larger multi-institutional study where data are collated between individual surgeons and institutes. However, given the number of variables in individual practice and surgical intervention for any given patient, this will not be easy to achieve. Further discussion on this topic is warranted in the orthopaedic sports medicine community.

PRECLINICAL EVIDENCE: SURGICAL COLLABORATION IN ANIMAL MODELS

It has been noted above and elsewhere that advances in clinical practice often have their roots in basic science investigations that provide the proof of principle of the treatment concept in question. The previous section deals with our ultimate need to practice evidence-based surgery at a clinical level. However, if these concepts are to become reality, they first must be tested in translational animal models to confirm both safety and efficacy. The need to identify appropriate translational models in regenerative repair is therefore of critical importance and worthy of particular consideration here. Chu et al, Arnoczky et al, and Sah and Ratcliffe have previously addressed this issue separately in terms of articular cartilage, the meniscus, and

RM in general, and readers are referred to these texts for comprehensive coverage of this important issue.^{4,11,72} There are many animal models that are used in meniscal and articular cartilage defect research. Large animal models such as the goat or the horse may more closely resemble the human than smaller animal models such as rodents or rabbits. However, it is usually not fiscally feasible or practical to conduct initial experiments in larger species. Therefore, it is generally well accepted to choose a small animal model for initial lines of investigation. However, final preclinical evaluation of a clinical strategy for repair or reconstruction technique may require confirmation in a large animal model before trials in humans.

One can appreciate that various animal models offer distinct advantages and disadvantages for studying regenerative repair strategies. While a nonhuman primate shoulder, for example, may offer more anatomic, biomechanical, and immunological similarities to humans than other animals, cost and management issues make use of this model impractical. It is readily apparent that no one animal model reproduces all of the features of the human injury condition regardless of the clinical condition being evaluated. All animals differ from humans in terms of the biomechanical use of their joints. As well, because no animal is immunologically identical to the human, a possible adverse immunological response to an RM therapy in human patients may not be predicted from animal studies. However, while scientists may play the leading role in selecting animal models for preclinical testing, it does not make sense for this process to be ignored by surgeons. Practicing clinicians may have a major effect here, both in terms of relating the model to the clinical condition as it presents in a human joint and also in terms of refining the proposed surgical strategy for repair. This may involve actually going through the procedure in a research setting as it might be done in a human, keeping in mind surgical principles that we know can influence outcomes unrelated to the actual therapy itself that is being evaluated. Fully qualified surgeons will be required to generate satisfactory evidence as it is not enough that this be conducted solely by surgical residents or fellows. Despite their best intentions, orthopaedic trainees may have little experience of the real world of clinical arthroscopy and technical issues commonly faced and understood by experienced surgeons. While such individuals may have more time for such endeavors, it is likely that a guiding hand at the early stages of both research design and actual intervention will enhance the likelihood of generating accurate and clinically relevant data with this work.

IMAGING AND OUTCOME MEASURES

Key challenges exist in assessing the functional performance of regenerative therapies. Specifically, this involves a current lack of meaningful assessment tools, something again the expert clinician can help develop. This may start with consideration of the role of medical imaging and the need for closer collaboration of specialized surgeons with radiologists and scientists. The effect of improved

diagnostic imaging may start with the earlier identification of an abnormality where biological approaches are more likely to be efficacious. For example, current treatments of acute knee trauma focus primarily on the meniscus, ligament, and tendon, whereas articular cartilage injuries are often not apparent shortly after injury. Only at the end stage of cartilage disease are radiographic changes evident, and even then, the patient's subjective pain assessment and knee function are poorly correlated with the results of diagnostic imaging.⁸² Functional MRI and optical coherence tomography (OCT) are being studied, and in time, it is likely we will be able to utilize the information provided by these methods in the early time period after injury to affect the natural history of an untreated lesion. Magnetic resonance imaging can semi-quantitatively assess cartilage morphological characteristics and quantitatively evaluate regional cartilage volume and thickness.²⁷ Other cartilage parameters including cartilage quality, cartilage surface smoothness, cartilage coverage, and distribution of change can also be evaluated. Progress made in MRI technology in the past few years allows longitudinal studies of human knee cartilage morphology with enough accuracy to follow the disease-caused changes and also evaluate the therapeutic effects of chondroprotective drugs. For cartilage repair patients, future studies will be needed to determine whether MRI is prognostic of clinical outcome and can replace arthroscopic biopsy for monitoring repair tissue histology. In animal experimental settings, high-field strength MRI can noninvasively provide detailed images of joints and can be used to carry out *in vivo* longitudinal follow-ups in the same animals and track the disease as well as see how it responds to potential treatments. There are also several MRI methods that may allow the evaluation of the glycosaminoglycan matrix or collagen network of articular cartilage and may be the most sensitive method for the detection of early changes. These techniques need to be further explored and validated. With the development of new therapies in sports medicine in general, MRI will play an important role in the diagnosis, staging, and evaluation of the effectiveness of these therapies. Surgeons can help guide this process from a clinical perspective.

The potential effect of stem cell therapy to underpin regenerative approaches has been outlined earlier. Following the fate of these cells in the human body will be important. Techniques for stem cell labeling are now well established for preclinical studies. The most promising methods, such as iron oxide stem cell labeling, are currently hindered by issues related to concerns about the stem cell label becoming dissociated from the exogenously labeled stem cell, an issue that plagues most direct labeling techniques.²⁷ However, these techniques still offer a method for determining the immediate success of stem cell delivery even if serial inspection of stem cell persistence may be impaired. Reporter gene imaging offers the only noninvasive means to determine stem cell viability. Whereas reporter gene expression is often short lived, this may alleviate concerns about long-term expression of a foreign protein or enzyme. Microencapsulation techniques offer a method for radiographic tracking of stem cells.

Thus, these techniques may not only provide the means to study the conflicting responses of individual patients but also to tailor therapies for each patient to enable an optimal response to treatment.

Surgical instruments and intraoperative techniques are also evolving, and their further development can be driven by problems highlighted by specialists in the field. Spahn et al^{74,75} recently reported in this journal that the differences they found in interobserver evaluation in real-time arthroscopic cartilage grading demonstrate that subjective grading is not satisfactory. They noted that mechanical tests to grade cartilage damage are limited by the instruments used and by the ability to access all areas of cartilage within a joint. Better methods to diagnose cartilage injury or degeneration are therefore needed if regenerative surgery is to have the effect that ongoing research suggests it should. As an example, the Spahn et al⁷⁵ study used a near-infrared (NIR) spectroscopy system that was found to have a good interobserver correlation. Thus, this method and others could develop into a precise method of measuring cartilage lesions in the future, but it is likely that making this progress will need ongoing input by specialist surgeons in the field. In another interesting study, McCarty et al⁵⁷ also recently reported on an arthroscopic device to assess articular cartilage defects and treatment with a hydrogel. The device described allows for a quantitative assessment of the fluid pressurization ability of articular cartilage that can be used in the arthroscopic setting to complement and extend current diagnostic tools. It is likely that experienced arthroscopic surgeons can help refine such devices in cartilage surgery while assisting in their development for the evaluation of other forms of regenerative knee and shoulder surgery discussed above. It is unlikely that developing a deep understanding of biological processes and their modification will appeal to all surgeons alike. Focusing on engineering principles and surgical tools may be more attractive to others while being equally important in this developing field.

Finally, a key point of safe and effective surgical practice involves patient follow-up with carefully chosen clinical assessment tools at various time points following intervention. The outcome of any surgical procedure should be important to both patient and surgeon alike. However, we as a profession, with some notable exceptions, have been slow to understand what information to record, how best to collect and safely store it, and how best to use this valuable information. A major problem in sports medicine remains the lack of appropriate assessment methods to evaluate the efficacy of intervention. While multiple scoring systems are available for most conditions, their interobserver reliability is often questionable. In addition, the concerns and priorities of the patient and surgeon may differ. Furthermore, it is essential to remember that scoring systems are not valid when used in a modified form, and their use in this fashion should be discouraged. Finally, establishing national databases in sports medicine in the United States and in other countries around the world should remain a priority of surgeons. As funding becomes tighter, it will be difficult to ensure this happens,

but as noted earlier, clinicians must act as advocates for the patient regardless of any economic circumstances that prevail. The emergence of regenerative surgery and biological augmentation will demand of us that we apply ourselves to this task again, developing robust clinical measures that will indicate the effectiveness or otherwise of such an intervention. Use of improved and validated outcome scoring systems may considerably improve the exchange of information necessary for advances in our field and allow us to bring our specialty to the highest level we can.

CONCLUSION

Regenerative surgery holds great promise for orthopaedic sports medicine, but its introduction must be safe, effective, efficient, economical, and practical for widespread clinical use. In this complex and rapidly changing environment, both academically and more clinically oriented surgeons must take leadership roles to guide the development of regenerative approaches to soft tissue and cartilaginous injury while also acting as stewards to help surgical patients navigate the increasingly complex environment as it unfolds. As we develop novel surgical techniques and increase our arthroscopic expertise, we will serve our patients well by engaging with coexisting scientific efforts to understand the pathology we face, the biological strategies with which we may intervene, and the safe and effective surgical translation of future biological therapies and augments to everyday practice. Clinical trials and evidence-based practice must continue to underpin the clinical management of all conditions we treat. Developing our understanding of the potential and challenges of regenerative surgery should allow those specializing in orthopaedic sports medicine to lead the way in advancing the frontiers of biologically augmented approaches to modern clinical care.

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