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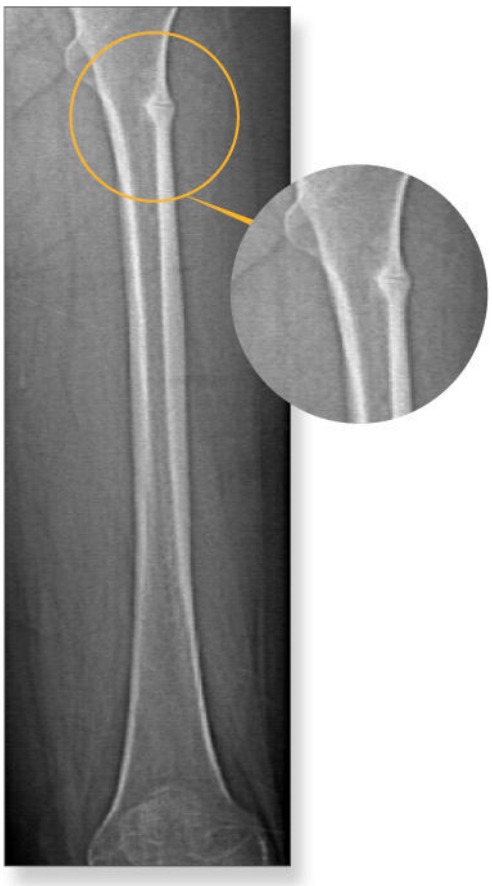

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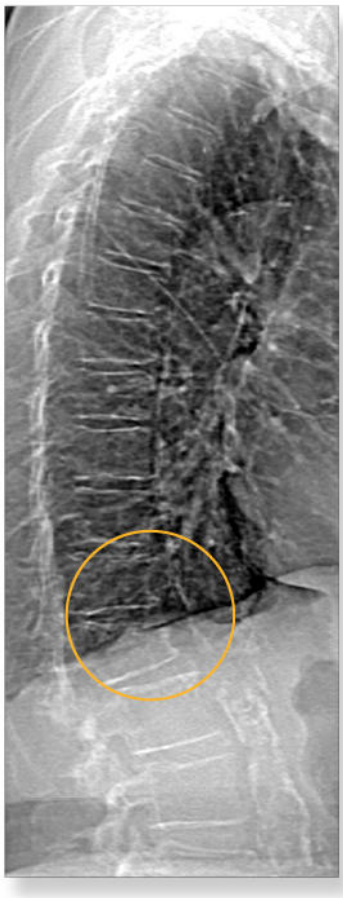

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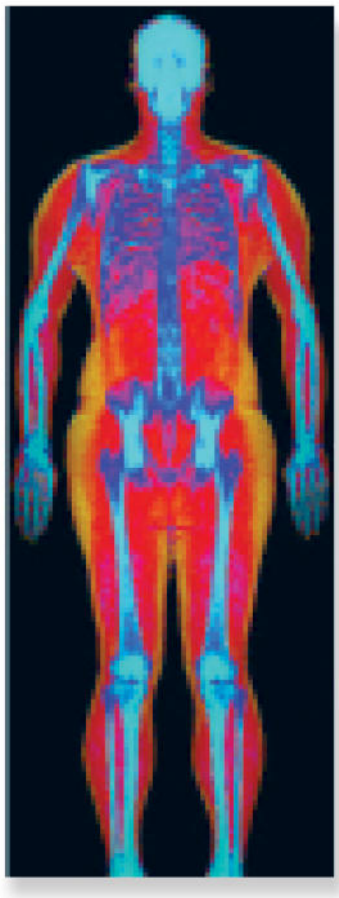

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TASK FORCE REPORT

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American Society for Bone and Mineral Research-Orthopaedic Research Society Joint Task Force Report on Cell-Based Therapies

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ABSTRACT

Cell-based therapies, defined here as the delivery of cells in vivo to treat disease, have recently gained increasing public attention as a potentially promising approach to restore structure and function to musculoskeletal tissues. Although cell-based therapy has the potential to improve the treatment of disorders of the musculoskeletal system, there is also the possibility of misuse and misrepresentation of the efficacy of such treatments. The medical literature contains anecdotal reports and research studies, along with web-based marketing and patient testimonials supporting cell-based therapy. Both the American Society for Bone and Mineral Research (ASBMR) and the Orthopaedic Research Society (ORS) are committed to ensuring that the potential of cell-based therapies is realized through rigorous, reproducible, and clinically meaningful scientific discovery. The two organizations convened a multidisciplinary and international Task Force composed of physicians, surgeons, and scientists who are recognized experts in the development and use of cell-based therapies. The Task Force was charged with defining the state-of-the art in cell-based therapies and identifying the gaps in knowledge and methodologies that should guide the research agenda. The efforts of this Task Force are designed to provide researchers and clinicians with a better understanding of the current state of the science and research needed to advance the study and use of cell-based therapies for skeletal tissues. The design and implementation of rigorous, thorough protocols will be critical to leveraging these innovative treatments and optimizing clinical and functional patient outcomes. In addition to providing specific recommendations and ethical considerations for preclinical and clinical investigations, this report concludes with an outline to

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address knowledge gaps in how to determine the cell autonomous and nonautonomous effects of a donor population used for bone regeneration.

KEY WORDS: ANIMAL MODELS; CELL/TISSUE SIGNALING, TRANSCRIPTION FACTORS; CELLS OF BONE; CLINICAL TRIALS; GENETIC RESEARCH

Executive Summary

Despite great advances in restorative surgeries involving prosthetic devices, there has been limited progress in the development of biological technologies for musculoskeletal repair. Cell-based therapies, defined here as the delivery of cells in vivo to treat disease, have recently gained increasing public attention as a potentially promising approach to restore structure and function to musculoskeletal tissues. Although cell-based therapy has the potential to improve the treatment of genetic, degenerative, inflammatory, and traumatic disorders of the musculoskeletal system, there is also the possibility of misuse and misrepresentation of the efficacy of such treatments. The medical literature contains anecdotal reports and research studies, along with web-based marketing and patient testimonials supporting cell-based therapy.

Both the American Society for Bone and Mineral Research (ASBMR) and the Orthopaedic Research Society (ORS) are committed to ensuring that the potential of cell-based therapies is realized through rigorous, reproducible, and clinically meaningful scientific discovery. In response, the two organizations convened a multidisciplinary and international Task Force composed of physicians, surgeons, and scientists who are recognized experts in the development and use of cell-based therapies. The Task Force charge was to define the state-of-the art in cell-based therapies and to identify the gaps in knowledge and methodologies that should guide the research agenda.

Task Force charges

The objective of this Task Force report is to provide guidance to investigators, clinicians, and the general public about the potential and challenges of cell-based therapies for both soft and mineralized skeletal structures. See Table 1 for the complete Task Force charges that informed development of this report and the recommendations included herein. Candidate sources of stem/progenitor cells are reviewed, and optimized experimental protocols for assessing their progenitor and healing properties in animal models are presented. The Task Force examined the diverse range of affected tissues to assess the current state of cell therapy and developed recommendations for investigators and observers regarding evidence of potential clinical efficacy of cell based therapy

Task Force review process

The ASBMR-ORS Task Force reviewed nearly 400 manuscripts in which cell-based therapies were used in animal models to promote tissue repair in musculoskeletal tissues. Outcomes were classified into five categories: (i) radiographic; (ii) histologic, including tissue organization and biochemical or molecular composition of resulting tissue; (iii) donor cell tracking; (iv) function of resulting tissue; and (v) non-target or systemic effects (Table 2). The overall judgment of how these outcomes were evaluated included:

1. Radiographic and histologic assessment: The methods of X-ray, micro–computed tomography (μCT), and magnetic resonance imaging were among the most widely used for outcome measures. Also widely used were histological methods that assessed the efficacy of cell-based therapy. However, histological methods primarily relied on non-quantifiable approaches (eg, hematoxylin and eosin staining) and often did not employ more rigorous analytical histomorphometric approaches. The use of more detailed analysis of the repair tissue using specialized staining, immunohistochemistry, or RNA expression assays, such as in situ hybridization, was less frequent and the utilization varied between tissues. When specific matrix components were assessed, only a limited number of protein markers were used, most commonly collagen types and aggrecan.
2. Functional criteria: Surprisingly, relatively few studies carefully considered functional criteria, such as the measurement of mechanical properties and pain. This may be partly due to the generally short duration of the studies and the challenge of defining function in different animal models. In addition, few manuscripts addressed non-target or systemic effects of treatment. Because transplanted cells, eg, mesenchymal stem/progenitor cells (MSCs) may have biological effects, such as influencing host immune-inflammatory responses,[1,2] it is essential that perturbations of immune function, and other non-target functions, be considered in future studies.

Table 1. ASBMR-ORS Task Force Charges

Task Force charge
1. Make recommendations for provisional case definitions of cell-based therapies, including cell sources and target tissues, so that subsequent studies will report using common language and avoid ambiguity due to the complexity of the cell preparatory steps.
2. Address the specific requirements of tissue type, anatomical site and location, underlying disease state, host (gender and/or age), and local environmental status.
3. Carefully review the current available information to assess what is known and what is not known regarding different cell-based therapies, cellular sources, and protocols for addressing specific target tissues. Specifically, the literature will be reviewed and characterized according to whether the evidence is based on in vitro, in vivo (ie, animal models), or clinical reports.
4. Review the available noninvasive diagnostic (eg, biomarkers) and imaging techniques for characterizing the outcome of cell-based therapies.
5. Identify the key questions that the scientific community should address, and recommend a research agenda to elucidate the best approaches for cell-based therapy.
6. Establish criteria for assessing potential biological and clinical efficacy, and develop guidelines appropriate for the claimed use of each cell-based therapy.

Table 2. Percentage of Studies That Measured Various Outcome Criteria

Outcome criteria	Bone	Cartilage	Disc	Meniscus	Tendon/ligament
Radiographic	64	40	70	20	26
Histological	81	78	92	76	82
Origin of cellular components	45	20	68	56	36
Tissue organization	41	58	74	84	85
Biochemical/molecular	21	56	50	32	62
Functional	26	42	18	36	13
Off-target tissue effects	11	0	2	44	15

All values are percentages.

3. Cell fate: Evaluation of cell fate is critical for assessing the efficacy of cell-based therapies. Despite its importance, few studies performed cell tracing or described the localization or persistence of donor cells in the host tissue. In studies where donor cell fate was followed, cells were tracked using a variety of techniques, including those using detectable transgene reporters encoding fluorescent proteins (ie, green fluorescent protein [GFP], red fluorescent protein [RFP]) or enzyme (LacZ) for direct detection of donor cells or species-specific markers/antigens in cases of xenogeneic transplantation.

Overview of Task Force findings and recommendations

Task Force recommendations are summarized in Table 3. Guidance for conducting preclinical and clinical studies of cell-based therapies is offered as a part of these recommendations (see Key Question 5, below). The Appendices A through F provide more details regarding publications related to cell based therapies in various musculoskeletal tissues and also detail supplementary information on how to determine the cell autonomous and non-autonomous effects of a donor population being used for bone regeneration.

Conclusions

The efforts of this Task Force are designed to provide researchers and clinicians with a better understanding of the current state of the science and research needed to advance the study and use of cell-based therapies for skeletal tissues. The design and implementation of rigorous, thorough protocols will be critical to leveraging these innovative treatments and optimizing clinical and functional patient outcomes. In addition to providing specific recommendations and ethical considerations for preclinical and clinical investigations, this report concludes with an outline to address knowledge gaps in how to determine the cell autonomous and non-autonomous effects of a donor population used for bone regeneration. Currently, there is no proof of efficacy of these treatments given the lack of rigorous clinical studies and randomized clinical trials, and that these therapies should thus be considered experimental.

Introduction

Bone, articular/hyaline cartilage, intervertebral disc, meniscus, tendon, and ligaments are all musculoskeletal tissues that function to provide mechanical support and permit locomotion. The support comes from highly organized extracellular matrices, including collagens, proteoglycans, and glycoproteins, intermixed with carbonate-rich apatite (in the case of bone and hypertrophic cartilage), that modulate the mechanical properties of the tissues. Among the musculoskeletal tissues, there is wide variability in terms of mechanical properties and function, the level of tissue oxygenation, cell turnover, and regenerative capacity. Loss of structure and function of musculoskeletal tissues is the principal cause of physical disability. Furthermore, this loss poses severe challenges to quality of life and presents heavy disease burden, particularly for the aged population.

Despite the great advances in restorative surgeries involving prosthetic devices, there has been limited progress in the development of biological technologies for musculoskeletal repair. Cell-based therapies have recently gained increasing public attention as a potentially promising approach to restore structure and function to musculoskeletal tissues. In fact, the technique of autologous chondrocyte implantation (ACI), developed two decades ago, which involves surgical implantation of a patient's own cartilage cells and chondrocytes to repair focal articular cartilage defects in the joint, is the earliest effective clinical cell therapy procedure that remains continuously practiced.[3] A recent entry is stem/progenitor cell–based therapy, which has captured the public's attention because of the possibility of supplying sufficient numbers of cells that can differentiate into skeletal cells and provide tissue-appropriate signals necessary for tissue regeneration.

Although cell-based therapy has potential to improve the treatment of genetic, degenerative, inflammatory, and traumatic disorders of the musculoskeletal system, there is also the possibility of misuse and misrepresentation of the efficacy of such treatments. The medical literature contains research studies and anecdotal reports and research studies, along with web-based marketing and patient testimonials supporting cell-based therapy.

- Both the ASBMR and ORS are committed to ensuring that the potential of cell-based therapies is realized through thorough, rigorous, reproducible, and clinically meaningful scientific discovery. In response, the two organizations convened a multidisciplinary and international Task Force composed of physicians, surgeons, and scientists who are recognized experts in the development and use of cell-based therapies. The task force leaders and members were selected by each society for their expertise. Individual subgroup members searched the PubMed database for studies published in English between years 1995 and 2019 related to the subject area, the studies were reviewed by the subgroup, and studies were included in the report if they provided information relevant to the study topic, and utilized good experimental design and technique. In completion of Appendices B through F (Bone, Cartilage, Disc, Meniscus, and Tendon and Ligament cell-based therapy articles), the Task Force performed a detailed search with inclusion of articles published through 2015.

Each task force was asked to review all published studies in English published between years 1995 and 2019. This report reflects the findings and recommendations of the Task Force in

Table 3. Summary of Findings and Recommendations From the ASBMR-ORS Task Force

Key question	Primary findings and recommendations
1. What is the current knowledge of limitations of cell-based therapies according to cellular source?	• Pluripotent stem/progenitor cells present unique challenges in terms of differentiation efficacy (compared to multipotent stem/progenitor cells) and in terms of safety. Further standardization and research into safety methods are needed before these models can be better leveraged for clinical use. • Connective tissue–specific stem/progenitor cells require better justification and nomenclature in order to differentiate the source of the progenitor population used for a particular cell therapy. • Markers for human and murine BMSCs are currently too nonspecific and nonexclusive. • The extent to which non-skeletal–derived MSCs contribute to the production of functional skeletal tissues remains to be determined.
2. What is the current knowledge of the therapeutic utility of cell-derived products based on cellular source?	• The efficacy of platelet-rich plasma is not yet established, but evidence exists supporting its use in bone regeneration, cartilage repair, osteoarthritis treatment, and tendon/ligament and meniscal repair. • Animal models using cell-derived conditioned medium preparations have demonstrated a benefit in healing skeletal tissues, but human studies are lacking and the efficacy of conditioned medium preparations remains unclear. • EVs derived from cells may mediate intracellular communication and thereby affect repair and disease processes.
3. What is the current knowledge of tissue-specific animal models of cell-based therapies?	• Mice are commonly used to study cell-based therapies for osteoporosis, osteogenesis imperfecta, fracture healing, and ectopic bone formation. Findings usually require replication in larger animals before being studied in clinical protocols. • For cartilage models, larger animals—including horses, dogs, goats, and sheep—are preferable to rodents and rabbits, although rabbit models are frequently used. • Rabbits and rats are commonly used in intervertebral disc disease and injury models, but larger animals such as sheep and dogs are preferable due to better generalizability to humans. • Sheep, pigs, and primates are useful in models of meniscus healing because they possess knee joint anatomy similar to humans, but these models still have certain limitations (eg, differences in biped versus quadruped meniscus and cartilage contact mechanics). • Rabbit and rodent models are convenient to study stem/progenitor cell therapies for acute tendon injury and repair. However, larger animal models (ie, horse, pig, dog, and sheep) may better meet FDA guidelines for demonstrating the efficacy of cell-based therapies and delivery devices in humans. The suitability of an animal mode for tendon/ligament repair will depend on the tissue being examined and the objectives of the study.
4. What are the Task Force–recommended criteria for interpreting a cell-based regenerative experiment?	• Success should be measured by the ability of cell-based therapies to regenerate or repair degenerated or injured tissue, decrease pain, and restore structure, mechanical properties, and function. • Interventions must be compared to vehicle control using validated outcome measures that include both functional and pain assessments. • Studies should consider cell autonomous and non–cell autonomous mechanisms of influence of cell-based therapies.
5. What are the Task Force recommendations for preclinical and clinical studies of cell-based therapies?	Recommendations for preclinical studies • The Task Force found no preferred, standardized animal model for preclinical studies of cell-based therapies. Both large-animal and small-animal models have deficiencies and either singly and in combination fail to reproduce the biomechanics or biology seen in humans. • The Task Force recommends animal models be chosen based on size and anatomical considerations as well as protocol design and objectives, including cost, technical challenges, use of both autologous and allogeneic cells, potential complications related to immune

(Continues)

Table 3. Continued

	rejection, and the degree to which the model mimics human anatomy and disease. • The optimal preclinical approach would be to initiate studies in small animals that focus on cellular, molecular, functional outcomes, mechanical properties, and genetic characterization, and, if these models provide proof of principle, perform follow-up trials in larger, more clinically relevant animals if indicated. • Immune reactions in animals should be considered when assessing reparative potential in humans. • A combination of evidence from in vitro and large and small animal in vivo studies may be needed to obtain FDA clearance. • Interpretation of the role of donor stem/progenitor cells in tissue repair is critical. • More research is needed investigating cell-based therapies in various mesenchymal tissues as well as noninvasive assessments of tissue composition, structure, and function. • Centralized data resources, such as the NIH-supported National Swine Resource and Research Center, can play a valuable role in advancing this line of research. Recommendations for clinical studies • The study methodology must be of the highest quality, including the use of appropriate design, blinding, techniques to prevent bias, validated quantitative outcome measures, and appropriate statistical techniques. • Development and use of noninvasive measures of human tissue composition, structure, and mechanical function is essential. • Patient-reported outcome measures are sensitive and valuable tools to assess functional improvement, tissue structure, pain, and quality of life. Research and clinical ethical considerations • All animal studies should be conducted with strict adherence to ethical guidelines and with approval from an Institutional Animal Care and Use Committee Review Board. • Although cell-based therapies may seem appealing due to their novelty and innovativeness, patients should be clearly informed that little data exists in either larger-animal preclinical studies or randomized clinical trials to support the use of cell-based therapies. However, cell-based therapies thus far appear to be generally safe and well-tolerated. • Patients also should be made aware that use of these therapies is often "off label" and unlikely to be reimbursed by medical insurance. • For patients to truly give informed consent, a neutral or second-opinion physician should be consulted to explain the benefits and potential risks for patients regarding receiving or not receiving the treatment. • Given the lack of rigorous evidence, the Task Force cannot currently recommend local or systemic stem/progenitor cell therapy for skeletal tissue repair and regeneration and encourage clinical trials for treatment protocols to receive FDA approval.

BMSC = bone marrow stromal cell; MSC = mesenchymal stem/progenitor cell; EV = extracellular vesicle; FDA = U.S. Food and Drug Administration; NIH = National Institutes of Health.

response to its charge of defining the state of the art in cell-based therapies and identifying the gaps in knowledge and methodologies that should guide the research agenda.

Key Question 1: What Is the Current Knowledge of Limitations of Cell-Based Therapies According to Cellular Source?

- Pluripotent stem/progenitor cells present unique challenges in terms of differentiation efficacy (compared to multipotent stem/progenitor cells) and in terms of safety. Therapeutic use of these cells in clinical practice is not recommended until further standardization and safety validation.
- Connective tissue-specific stem/progenitor cells require additional justification and nomenclature in order to differentiate the source of the progenitor population used for a particular cell therapy.
- Markers for human and murine bone marrow stromal cells (BMSCs) are currently too nonspecific and nonexclusive.
- It is unclear the extent to which non–skeletal-tissue–derived MSCs are useful in producing functional skeletal tissues.

Stem/progenitor cells

Based on the fact that virtually all tissues undergo renewal, albeit at highly variable rates, enduring tissue regeneration depends on the presence of a subset of tissue-specific stem/progenitor cells within a given population that can fuel tissue renewal. Hence, considerable effort has been focused on identifying cell sources that have the ability to maintain tissue homeostasis, including musculoskeletal tissues.[4] Stem/progenitor cells in mammals can be divided into two broad categories: pluripotent stem/progenitor cells and postnatal stem/progenitor cells from various sources (see https://stemcells.nih.gov/info/basics/1.htm for more information).

Pluripotent stem cells (embryonic stem cells) and induced pluripotent stem cells

Embryonic stem cells (ESCs) are pluripotent stem cells derived experimentally by extraction from the inner cell mass of an early-stage embryo, the blastocyst, whereas postnatal stem/progenitor cells are found in different organs and tissues. Pluripotency refers to the potential of a stem cell to differentiate into cells of all three germ layers—endoderm, mesoderm, and ectoderm. In addition to ESCs, induced pluripotent stem cells (iPSCs) can be generated from adult somatic cells by reprogramming with essential pluripotency transcription factors by a variety of methods and are nearly identical to ESCs.

Because of their highly uncommitted state, pluripotent ESCs and iPSCs present more challenges in terms of being induced to differentiate into a specific musculoskeletal cell type compared to multipotent stem/progenitor cells, such as postnatal stem/progenitor cells. Osteogenic differentiation provides an example. There have been a number of reports on the differentiation of human ESCs (hESCs) and iPSCs into osteogenic cells through the formation of embryoid bodies, spontaneous differentiation, indirect co-culture with osteogenic cells, treatment with conditioned medium generated by osteogenic cells, or use of various schemes for direct osteogenic differentiation.[5] However, for the most part, the results have relied on in vitro differentiation assays that may not reflect capabilities in vivo, and results from limited studies involving in vivo transplantation are not conclusive.[6–9] Furthermore, most studies use ectopic transplantation sites rather than sites within an injured skeletal tissue that would better mimic a clinical scenario. The lack of differentiation into a functional tissue is likely because these cells have not undergone a developmental process that commits them to a particular lineage.[10] Thus, there is the issue of differentiation efficacy. Another concern is safety, such as (i) the potential for tumor formation, and (ii) the potential for immunological rejection when allogeneic ESCs or iPSCs are introduced in vivo.[11] More standardization and safer methods are clearly needed to bring pluripotent stem cells into clinical use.

Connective tissue–specific stem/progenitor cells

BMSCs are non-hematopoietic adherent cells first identified and characterized by Friedenstein[12] A subset of BMSCs are skeletal progenitor cells that differentiate into cartilage, bone, hematopoiesis-supportive stroma, and marrow adipocytes based on rigorous clonal and differentiation assays performed in vivo (bone, fat) and in vitro (cartilage). However, the original concept of a tissue-specific stem/progenitor cell for bone, was later altered to include other mesodermal derivatives such as muscle, tendon, and ligament, and BMSC terminology was altered so that these cells are considered synonymous with MSCs. A better justification and nomenclature of stem/progenitor cells from other connective tissue sources need to be developed to clearly differentiate the source of a progenitor population used for a particular cell therapy.

A number of markers of BMSCs have been identified (such as CD73, CD90, CD105, and CD146, along with lack of expression of CD11b, CD14, CD19, CD34, CD45, and HLA-DR).[13] However, the markers used are neither specific nor exclusive, because they are also expressed in many adherent fibroblastic cell populations. Although such "markers" have been utilized to identify cells derived from periosteum, synovium, dental pulp, and periodontal ligament cells (tissues associated with the skeleton) that are very similar to BMSCs and are capable of differentiating into cartilage, bone, and fat in vitro,[14] it should be noted that these various cell types are not identical in their in vivo differentiation capacity.[15–18] Furthermore, the standard in vitro assays used to claim "tri-lineage" differentiation are often not predictive of in vivo differentiation capacity.[19] Whether and how these differences may have arisen from their different native tissue microenvironment needs to be examined.

In the last several years, lineage tracing studies have identified a self-renewing multipotent cell population called the skeletal stem cell (SCC) present in bone tissue of humans (PDPN+, CD146–, CD73+, and CD164+) and mice (Tie2–, integrin AlphaV+, Thy–, 6C3–, CD105–, and CD200+) that has differentiation restricted to the osteoblast, chondrocyte, and stromal cell lineage, and not adipocytes. In both mice and humans, these cells, when implanted into the renal capsule form ectopic bone and cartilage, and the cells support marrow formation. The SCC population is expanded in culture by BMP-2 and in vivo by bone fracture.[20–22] Another study identified a rare population of Gremlin 1+ (Grem1+) cells in the metaphysis and tissues adjacent to the growth plate in mice. Similar to the SCC population, Grem1+ cells are BMP-2 responsive, self-renewing, and formed bone, cartilage, and stromal tissues, with limited adipocyte differentiation. During development and aging, the Grem1+ population generates articular and growth plate cartilage, and is found in periosteum, osteoblasts, and osteocytes. Like SCC, the Grem1+ cells expand in fractures. Moreover, Grem1+ cells transplanted into fractures engraft, self-renew, and form osteoblasts, and Grem1+ cells can be harvested and re-expanded. The elimination of Grem1+ cells in developing mice results in reduced bone mass.[23]

Thus, there is a rare self-renewing SCC population in bone that is separate from the bone sinusoids that does not strictly meet the definition of an MSC, because it lacks capacity for adipocyte differentiation The SCC is necessary for development of bone and cartilage, maintenance of the adult skeleton, and bone repair. These approaches show the utility of cell lineage tracing in defining progenitor cell populations in vivo. However, the manner in which these rare cell populations are applicable for a cell-based therapy approach remains to be determined. Similarly, it is unclear whether an analogous tissue lineage–restricted stem cell is present in other musculoskeletal tissues, such as tendon, ligament, or disc.

Nonskeletal tissue–derived MSCs

MSC-like cells obtained from nonskeletal sources (eg, muscle, cord blood, Wharton's jelly, dermal, adipose, and amniotic fluid MSCs) have also been promoted as another source of progenitors for cell therapy of skeletal tissues.[24,25] However, many of the cells used in these studies were pretreated with chondrogenic/osteogenic

factors, and whether these nonskeletal cells produce functional bone and associated tissues, or whether they induce local cells to undergo a repair process in vivo,[26,27] is not known.

Perivascular stromal cells from various tissues have stem cell characteristics and differentiate into osteoblasts, chondrocytes, and adipocytes. In bone marrow, cell lineage studies show that LepR+ perivascular cells located around both arterioles and sinusoids account for nearly all of the fibroblastic colony-forming unit (CFU-F) in bone marrow. Lineage tracing shows that LepR+ perivascular cells are the major source of bone and adipocytes in bone marrow in adult mice. Moreover, they are involved in the regeneration of bone marrow following radiation and participate in fracture healing.[28] Perivascular cells isolated from fat, muscle, pancreas, skin, lung, brain, eye, gut, bone marrow, and umbilical cord are NG2+, CD146+, PDGF-R beta+, and alpha SMA+.[29] These cells are multipotent and differentiate into osteoblasts, chondrocytes, and adipocytes. In addition, a Gli1+ stromal cell population present in the adventitial layer of arteries has stem cell characteristics. Gli1+ cells differentiate into osteoblasts and are responsible for the vascular calcifications that occur in atherosclerosis and in chronic kidney disease.[30] Thus, perivascular stromal cells, as well as adventitial cells, are a key source of MSCs in nonskeletal tissue–derived tissues. These cells have been used in animal models in cell-based therapy approaches.[31–35]

Differentiated skeletal cells

Fully committed cells associated with the skeleton, such as osteoblasts, chondrocytes, and tenocytes, have limited ability to self-renew. However, they may be considered therapeutically useful in situations where there is low tissue turnover. ACI, which uses culture-expanded autologous chondrocytes harvested from the less weight-bearing articular cartilage of the joint, has shown efficacy in the repair of focal cartilage defects.[3] It is, however, generally acknowledged that the cultured chondrocytes undergo dedifferentiation and/or hypertrophy in vitro, thus compromising the quality of the regenerate cartilage, which is often more fibrous in nature or sometimes undergoes overgrowth and/or calcification. Also, currently ACI procedures are recommended only in young patients and exclude older adults (≥45 years old),[36–38] because this age group has a higher susceptibility to degenerative joint diseases.

Key Question 2: What Is the Current Knowledge About the Therapeutic Utility of Cell-Derived Products Based on Cellular Sources?

- The efficacy of platelet-rich plasma is not yet established, but evidence exists supporting its use in bone regeneration, cartilage repair, osteoarthritis treatment, and tendon/ligament and meniscal repair.
- Animal models using cell-derived conditioned medium preparations have shown a benefit in healing skeletal tissues, but human studies are lacking and the efficacy of conditioned medium preparations remains unclear.
- Extracellular vesicles derived from cells may mediate intracellular communication and thereby affect repair and disease processes.

There are many examples of cell therapy in which positive outcomes were observed without evidence of the donor cells within the repair field. This is particularly true in experiments in which the treating cells were administered systemically. It is now well established that when administered systemically, skeletal progenitor cells do not efficiently or stably home to a target tissue.[39,40] Consequently, some successful outcomes are attributed to factors transiently produced by the donor cells that influence a successful host reparative response.[39,41] This cellular process is classified as a donor cell–nonautonomous effect in that the long-term presence of the donor cells is not required because they did not participate directly in the repair process. If these factors could be identified, they could be used directly without the need for supplying the producing cells. Some of the candidate factors that have been investigated include platelet-rich plasma, conditioned medium, and extracellular vesicles (EVs).[42]

Platelet-rich plasma

Derived from megakaryocytes, platelets contain a long list of (approximately 300) growth factors, such as platelet-derived growth factor, transforming growth factor beta, and vascular endothelial growth factor, and others such as cytokines, coagulation factors, fibrinolytic factors and proteins, proteases, antiproteinases, and lipids. Upon platelet activation, eg, as a result of tissue injury, these factors are released for acute repair but are unlikely to have sustained activity or localization. Consequently, there are efforts to develop preparations, such as platelet-rich plasma (PRP) gels or PRP combined with other biological materials such as demineralized bone matrix or cells, to extend the biological activity of PRP.[43] PRP has been used in a number of clinical settings for bone regeneration[44] cartilage repair,[45] treatment of osteoarthritis,[46] and tendon/ligament and meniscal repair.[47] However, the biological action of PRP, eg, in regulating differentiation of multipotent MSCs,[48] remains unclear. In addition, the efficacy of PRP in the repair of hard tissues has yet to be established, in view of the wide variability in methods and measures of the studies that have been conducted.

Conditioned medium

Cells from connective tissues (including skeletal tissues) secrete a broad array of growth factors, cytokines, and other biologically active factors. It has been suggested that conditioned medium can exert a beneficial effect on healing of skeletal tissues based on paracrine, immunomodulatory, and immunosuppressive effects that encourage local cells to begin the repair process. A large number of animal studies[49] and one human study[50] have used this approach to treat injured skeletal tissues; however, efficacy of this type of therapy remains unestablished.

EVs

Perhaps the first description of EVs (eg, exosomes, ectosomes, microvesicles, microparticles) in the literature comes from the finding of matrix vesicles in cartilage.[51] EVs, first termed microparticles, have since been detected in many bodily fluids. It is now thought that in culture, virtually all cell types release some sort of EV, formed by different processes and of varying size. Results derived from the use of conditioned medium may be due to the presence of EVs in addition to other factors. EVs are proposed to mediate intercellular communications and have been implicated in repair and disease processes by virtue of the cargo that they carry, which may include proteins, biofactors, and RNAs, including specific miRNAs, among others.[52,53]

Key Question 3: What Is the Current Knowledge About Tissue-Specific Animal Models of Cell-Based Therapies?

- Mice are commonly used to study cell-based therapies for osteoporosis, osteogenesis imperfecta, fracture healing, and ectopic bone formation. Findings usually require replication in larger, more clinically relevant animals before being studied in clinical protocols.
- For cartilage models, larger animals—including dogs, goats, and sheep—are preferable to rodents and rabbits, although rabbit models are frequently used. Horse models have unique benefits but are costly and have large housing-space demands.
- Rabbits and rats are commonly used in intervertebral disc disease and injury models, but larger animals such as sheep and dogs are preferable because of better generalizability to humans.
- Sheep, goats, pigs, and primates are useful in models of meniscus healing because they possess knee joint anatomy similar to humans, but these models still have certain limitations (eg, differences in biped versus quadruped meniscus and cartilage contact mechanics).
- Rabbit and rodent models are convenient to study stem/progenitor cell therapies for acute tendon injury and repair. However, larger animal models (ie, horse, pig, dog, and sheep) may better meet US Food and Drug Administration (FDA) guidelines for demonstrating the efficacy of cell-based therapies and delivery devices in humans. The suitability of an animal model for tendon/ligament repair will depend on the tissue being examined and the objectives of the study.

Bone

Mice are commonly used to study cell-based therapies (eg, BMSCs, adipose-derived stromal cells) in models of osteoporosis, osteogenesis imperfecta, fracture healing, and ectopic bone formation (subcutaneous or intramuscular). Mice allow genetic approaches and have a high tolerance to xenograft engraftment. Humanized mice permit modeling of human cell activity and function. The reviewers recommend that the animal model yield convincing evidence with regard to bone architecture and mechanical properties. Impactful studies should clearly define the changes associated with cell therapy and the mechanism of cell involvement in the regenerative process.

A disadvantage of mice is that confirmation of findings typically requires subsequent experimentation in a larger animal model which more closely mimics the structure and mechanical features of human tissues prior to consideration for use in clinical trials. The rat is also an inexpensive small-animal model, and because it is relatively larger, it may have some advantages for mechanical testing. Gene-editing technologies are now being applied to the rat to provide genetic models that previously were only available in the mouse. Successful outcome should then be tested in larger animal models.

The models of bone disease/injury identified in the review included calvarial defects (46 studies), fracture (seven studies), heterotopic ossification (intramuscular, three studies), heterotopic ossification (subcutaneous, 38 studies), long-bone cortical defect (drill, 13 studies), long-bone segment (acute repair, 28 studies), long-bone segment (chronic repair, three studies), osteoporosis (nine studies), or other (heterotopic, two studies) (Appendix B).

Cartilage

Rabbits and rats were the most commonly used animals among the 49 preclinical studies that examined cell-based therapies for the regeneration of articular cartilage (Table 4). Rabbit models were the most frequently used. Rabbits are widely available, are relatively low-cost, have simple handling requirements, and have a robust base of literature for comparison.[56] However, there are several disadvantages inherent in rabbit studies. Pure chondral lesions are difficult to create in the thin cartilage of this species. Also, researchers need to consider the potential for a natural healing response given the smaller size of cartilage defects (<3 mm)[3] and the difference in mechanical loading in the rabbit knee relative to humans. Although rodents are widely used to screen new biomaterials and cell-laden constructs, the use of rodents for articular implants is less practical because of their very thin articular cartilage.[57,58] Furthermore, unlike larger animals, rodent growth plates remain open during adulthood. The epiphysis is therefore more highly vascularized, a feature that may contribute to more robust intrinsic cartilage repair.

Considering clinical relevance, a larger animal model is preferred to approximate the area and thickness of articular cartilage in the human.[59] Full-thickness cartilage defects can be created without damage to the subchondral plate in dogs.[60] However, the dog is rarely used for cartilage repair[61] because its status as a companion animal makes it a less attractive option. Goats and sheep are frequently used in cartilage repair models because the knee joints are large enough to create lesions as large as those treated in patients. The larger defect size and thicker cartilage layer permit biochemical assays of cartilage repair tissue as well as biomechanical testing.[62]

Domestic pigs, minipigs, goats, and sheep, although more expensive, are attractive because of the thicker articular cartilage that more closely mimics the human joint.[63] The main advantages of the horse model are the large joint size and thick articular cartilage layer with easy arthroscopic joint access, as well as the actual clinical need in equine veterinary care.[64,65] Horses can be monitored with respect to the clinical pain response to cartilage repair. A second-look arthroscopy with biopsy is usually the cornerstone of equine studies, allowing assessment of repair progression. However, specialized facilities and care are usually required, and thus this model is often used for late-stage development and pivotal studies.

In our review of 49 preclinical studies of cell-based therapy to promote cartilage repair, two used horses, six used sheep, 15 used rabbits, 10 used rats, six used goats, eight used pigs, one used dogs, and two used mice (Appendix C). Most of the models used an osteochondral defect model (42 studies). Five other studies used a partial-thickness cartilage-defect model, whereas two others used a model of global osteoarthritis from either injury (anterior cruciate ligament [ACL] and medial meniscectomy) or from chemically-induced osteoarthritis.

A total of 14 human studies were identified that examined cell-based therapy for articular cartilage repair. Because ACI therapy is already an FDA-approved procedure, studies using articular chondrocytes as a cell source were not included. All of the studies included full-thickness osteochondral defects. Bone marrow aspirate was the most common source of cells (10 studies) followed by peripheral blood–derived progenitors. One study each used either nasal chondrocytes or synovial progenitor cells.

Table 4. Individual Characteristics for Tissue Repair

Tissue	Indications for treatment	Structural repair goals
Bone	• Augmentation of standard therapies including: ○ Non-union fractures. ○ Delayed-union fractures. ○ Joint or spine fusions or to augment bone formation in osteonecrosis or osteoporosis. • May be used in combination with matrix products to augment the healing of bone defects.	• Mechanical stability across the fracture/defect site. • Union of the fracture/defect at the anatomical site via presence of a cortical bridge or outer cortical shell. • Properly aligned bone after healing. • Bone mineral density is appropriate for the area.
Cartilage	• Individuals who are experiencing chronic joint pain. • Augmentation of standard therapies, including repair of damaged or degenerated cartilage tissue. • May be used to augment osteoarthritis therapy.	• Mechanical stability of the joint. • Normal and painless range of motion.
Disc	• Individuals who are experiencing chronic low back pain (greater than 6 months) not responding to conservative therapy, excluding those with spondylolisthesis.	• Sufficient strength to support painless weight bearing. • Provide structural stability between vertebral bodies and protect spinal canal and nerve roots.
Meniscus	Augmentation of standard therapies including: • Enhancing or enabling repair of tears with poor potential healing capacity, including those with marginal vascularity, meniscus revision surgeries, meniscal tissue with intrinsic degenerative changes, or meniscal tears in older patients. • Replacement of seriously damaged menisci with engineered meniscal constructs populated with endogenous and/or transplanted stem/progenitor cells. • Repair/regeneration of horizontal cleavage tears found in degenerative meniscus tissue.	• Restoration of full knee range of motion. • Absence of joint line tenderness. • Absence of pain reproduction with provocative maneuvers such as rotation. • Absence of joint effusion. • Restoration of the mechanical function of the meniscus in sharing load transmission across the tibiofemoral joint. • Enhanced joint stability.
Tendon/ligament	• Improving the repair and reconstruction of injured tendons and ligaments. • Modulating inflammation associated with chronic tendinopathies.[54] • Facilitating tendon-graft or ligament-graft integration in reconstructive surgeries. • Promoting graftless ligament repair by inducing the native ligament tissue to regenerate.[55] • Development of artificial tendon and ligament for grafting.	• Full restoration of passive and active range of motion. • Stability of the joint. • Absence of inflammation. • Return to daily activities and sports. • Restoration of force transmission from muscle to bone or tendon, or the stabilization of a diarthrodial joint or ligament. • Improved range of motion and joint stability.

In 6 studies, mesenchymal progenitor cells from bone marrow (four studies), synovium (one study), and nasal cartilage (one study) were expanded in cell cultures prior to delivery into the joint.

Each of the papers was scored according to whether the study assessed the following features in the context of cartilage repair: radiographic criteria, histology, origin of the cell-tissue organization, biochemical criteria, functional outcomes, fate of the transplanted cells, and non-target tissue effects. Each criterion was scored as 0 (not examined); 1 (superficial analysis); or 2 (detailed analysis). A range of scores was identified, but consistently show higher scores in the preclinical models. All of the human studies had level of evidence 3 or 4, and analysis was limited because of the morbidity associated with tissue procurement in humans.

Intervertebral disc

Although there are murine genetic models of intervertebral disc disease, they often lack normal disc formation or develop severe structural alterations during development and thus have not been extensively used to study the role of cell-based therapies for disc regeneration.[66] The small size of mouse and rat discs compared to human discs limits their use in the assessment of disc repair methodologies, because nutrient diffusion is not fully evaluated. In addition, the morphology of the rodent disc differs somewhat from humans. Although rabbits and guinea pigs are larger, their discs are still several-fold smaller than human discs, and the tissues do not experience the same degree of loading. In comparison, larger, quadruped animals such as sheep have intravertebral discs that are closer in size and loading to those of humans.

Cell-based therapy for disc repair has been reported in at least 50 studies. Animals utilized include sheep (one study), dogs (five studies), rabbits (19 studies), minipigs (four studies), rats (10 studies), and mice (seven studies) (Appendix D). Models of disease occurring through either natural means (ie, aging as in human disc degeneration) or induced by removing various amounts of nucleus pulposus (NP) tissue (nucleotomy; the majority of animal studies), removal of herniated tissue (at the time of discectomy, two human studies), stab injuries to the annulus fibrosis with or without removal of NP tissue (two studies), or removal of a whole disc (three studies). Most studies tested treatment in the acute injury setting, but in three studies, cell therapy was used at 4, 6, or 12 weeks postinjury in dogs.[67–69] Chondrodystrophic canines

have been used, but whether these animals had developed premature degenerative disc disease at the time of implant evaluation was not specified.

Meniscus

Rabbits (43%) and rodents (16%) have been frequently used in studies that evaluate the underlying biological and molecular mechanisms of meniscus healing. Rabbits have also been used for preliminary analyses of new stem-cell or progenitor-cell therapy and tissue engineering approaches for the treatment of meniscal injury. Rabbits are less expensive than larger animal models and allow for the use of the larger group sample sizes that are necessary for more comprehensive outcome measures including histology, biochemical and molecular analyses of the repair tissue, and biomechanical testing.

Sheep (8%), pigs (8%), and primates (4%) have been used as large animal models to study meniscus healing. These animals possess knee joints similar in size to the human knee, enabling testing of implants that could be used in humans. However, unlike humans, these animals are quadrupeds with obvious differences in meniscus and cartilage contact mechanics when compared to humans. There is also an inability to control postoperative weight-bearing in most large animal models.

For meniscus, the majority of models used were local acute injury (19 studies). Chronic injury studies (four studies) were also examined. Most meniscus models evaluate tissue formation in a punch defect, although linear tear models have also been used (Appendix E).

Tendon/ligament

Smaller animal models, including rabbits[70–81] and rodents (rats and mice),[12,82–97] have been used to evaluate the effectiveness of stem-cell/progenitor-cell therapies in acute tendon injury and repair. Early-stage studies and anatomical considerations might necessitate the use of smaller animals, such as in the case of rotator cuff repair, where the rat is a commonly used model because it resembles the human shoulder anatomy.[98] Furthermore, if the objective is to track the fate of implanted cells and to mechanistically evaluate their contributions to the repair tissue, rodent models (rats and especially mice) have the distinct advantage of the availability of reporter gene models (eg, GFP, RFP, mTmG, nTnG) and genetic models of conditional gene deletion.

Large animal models, including equine,[99–102] ovine,[100,103] swine,[104,105] and canine,[106,107] might better meet the FDA's preference for demonstrating efficacy of cellular therapies and delivery devices prior to human approval. The suitability of an animal model for tendon/ligament repair depends on the tissue being examined and the objectives of the study. For example, the canine model is commonly used to study flexor tendon repair because of the ability to simulate zone II injuries, reproduce clinical protocols of multistrand suture repair, and implement physical therapy.[106,107] Similar arguments can be made in favor of using large animals (eg, pigs) for evaluating cellular therapies in ACL repair and reconstruction.[104]

For tendon/ligament, various acute injury and repair models have been examined, including flexor tendon,[72,73,99–101,105–107] rotator cuff tendon,[83–86] Achilles tendon,[12,75,81,89,91,95,103] patellar tendon,[70,71,74,76–80,87,88,94,96,97] and ACL.[92,93,104] Furthermore, a number of equine studies have focused on veterinary clinical applications of autologous stem/progenitor cells to treat chronic overuse injury of the superficial digital flexor tendon in racehorses using ultrasound-guided intratendinous injections[99–102] (Appendix F).

Key Question 4: What Are the Task Force–Recommended Criteria for Interpreting a Cell-Based Regenerative Experiment?

- Success should be measured by the ability of cell-based therapies to regenerate or repair degenerated or injured tissue and to restore functioning.
- Interventions must be compared to vehicle control using validated outcome measures that include functional and pain assessments.
- Studies should consider cell autonomous and non–cell autonomous mechanisms of influence of cell-based therapies.

Understanding the role of donor cells in the repair process will provide specific information on the mechanism of action and the basis for therapeutic product development. The measure of success of cell-based therapies is the ability of the intervention to result in regeneration or repair of degenerated or injured tissue with restoration of structure, mechanical properties, and function. A key aspect is comparison to a vehicle control using validated outcome measurements that include functional assessment and evaluation of pain.

There are two major mechanisms through which cell-based therapies may influence the regenerative or reparative process, and both are equally relevant. These mechanisms are (i) cell autonomous and (ii) non–cell autonomous. In cell-autonomous therapies, the delivered cells have a therapeutic effect in part through being incorporated in the regenerating tissue and participating directly in the repair process. In non–cell autonomous therapies, the cells secrete factors, such as growth factors, cytokines, extracellular vesicles, or other regulatory signals, that influence the behavior of the host cell population in a manner that leads to tissue repair or regeneration. This can occur by their acting directly on host tissue–specific progenitor cells or can be indirect by influencing other processes such as vascularization or regulation of the immune response. It should be recognized that cell-based therapies which demonstrate a cell autonomous mechanism may additionally also act in a non–cell autonomous manner at the same time.

Key Question 5: What Are the Task Force Recommendations for Preclinical and Clinical Studies of Cell-Based Therapies?

Recommendations for preclinical studies

- The Task Force found no preferred, standardized animal model for preclinical studies of cell-based therapies.
- The Task Force recommends animal models be chosen based on size and anatomical considerations as well as protocol design and objectives, including cost, technical challenges, use of both autologous and allogeneic cells, potential complications related to immune rejection, and the degree to which the model mimics human anatomy and disease.
- The optimal preclinical approach would be to initiate studies in small animals that focus on cellular, molecular, functional outcomes, mechanical properties, and genetic characterization, and, if these models provide proof of principle, perform follow-up trials in larger, more clinically relevant animals if indicated.
- Immune reactions in animals should be considered when assessing the potential for use in humans.

- A combination of evidence from in vitro and large and small animal in vivo studies may be needed to obtain FDA clearance.
- Interpretation of the role of donor stem/progenitor cells in tissue repair is critical.
- More research is needed investigating cell-based therapies in various mesenchymal tissues as well as noninvasive assessments of tissue composition, structure, and function.
- Large-animal models are essential but are limited by expenses and technical demand. Centralized data resources, such as the NIH-supported National Swine Resource and Research Center (http://www.nsrrc.missouri.edu/index.asp), can play a valuable role in advancing this line of research.

Recommendations for clinical studies

- Study methodology must be of the highest quality, including the use of appropriate design, blinding, techniques to prevent bias, validated outcome measures, and appropriate statistical techniques.
- Development and use of noninvasive measures of human tissue composition, structure, and mechanical function is essential.
- Patient-reported outcome measures (PROMs) are sensitive and valuable tools to assess functional improvement, pain, and quality of life.

Research and clinical ethical considerations

- All animal studies should be conducted with strict adherence to ethical guidelines and with approval from the appropriate institutional animal care and use committee.
- Although these treatments may seem appealing because of their novelty and innovation, patients should be clearly informed that little data exists in either larger-animal preclinical studies or randomized clinical trials to support the use of cell-based therapies. However, cell-based therapies thus far appear to be safe and well-tolerated.
- Patients also should be made aware that use of these therapies is often "off label" and unlikely to be reimbursed by medical insurance.
- For patients to truly give informed consent, a neutral or second-opinion physician should be consulted to explain the benefits and potential risks of the patient receiving or not receiving the treatment.
- Given the lack of rigorous evidence, the Task Force cannot currently recommend local or systemic stem-cell/progenitor-cell therapy for skeletal tissue repair and regeneration.

Preclinical animal models

Overall, the reviewers found no preferred, standard animal model for a preclinical study. Thus, the Task Force recommends that, in addition to size and anatomical considerations, the choice of the animal model should thoughtfully consider other aspects of the study objectives and design, including the cost, technical challenges, the potential to use both autologous and allogeneic cells, and the degree to which the model mimics human disease.

An optimal experimental approach to evaluating stem/progenitor cells for enhancing musculoskeletal tissue repair/regeneration would be to initiate studies in small animals that focus on cellular, molecular, functional, and mechanical outcome measures, and allow the examination of genetic factors influencing regeneration. Once these models provide proof of principle for the utility of a specific cell population in augmentation of repair, additional investigation would be completed in larger animals that more closely model the anatomical size and weight-bearing characteristics of human skeletal tissues. Subsequent successful outcomes in large-animal models, with inclusion of appropriate safety and efficacy profiles, would identify prime candidates for human clinical trials.

In studies where the reparative potential of human cells is assessed, immune reaction in the animal model is a challenge. Human cells are sometimes assessed in less-optimal models, including immunodeficient nude rat models or larger animals with drug-mediated immunosuppression, conditions that may influence the repair process. Still, with regard to immunological considerations of the efficacy of allogeneic progenitor cell therapy, mouse models of selective depletion of a subpopulation of T cells[108] or pig models of genetically manipulated major histocompatibility complex (ie, swine leukocyte antigen)[109] can be particularly useful.

The FDA will require clear and unequivocal evidence for the cellular basis of stem/progenitor–based therapies for musculoskeletal tissue repair. A combination of models will provide support for cell-based therapeutics, including in vitro three-dimensional models of tissue regeneration/tissue chip models,[110] small-animal models; and large-animal models. Fundamental requirements for adequate interpretation of cell-based therapies include the ability to: (i) track the donor cell population; (ii) determine cellular fate and differentiation; and (iii) define the role of the cell population in restoring a stable and mechanically functional tissue. (Additional information about determining cell fate can be found in Appendix A).

Interpretation of the role of donor stem/progenitor cells in the repair process is critical. Persistence of donor-derived cells during the repair should preferably be observed, although non–cell autonomous mediation of therapeutic effects must also be considered. Donor cells may undergo terminal differentiation and remain in the tissue as mature cells or may have a critical early and more transient role in driving the repair process. Cell-based therapy should be investigated in relevant models across the various mesenchymal tissues. Because mesenchymal tissues (ie, bone, cartilage, tendon, ligament, and disc) each require unique mechanical properties, the model should permit assessment of whether an appropriately functioning tissue forms. There is a need for the development of additional in vitro and in vivo models, as well as computational approaches. In particular, noninvasive assessments of tissue composition, structure, and function need further development as specific cell-based therapies are extended to human trials.

Large-animal models, although essential, are expensive and technically demanding. Large-animal studies are currently limited to autologous-based experiments, in which markers distinguishing host from donor are limited. The NIH-supported National Swine Resource and Research Center, a large-animal resource, has been developed. The center can provide pig lines with GFP reporters and also has pigs with genetic backgrounds similar to the mouse NSG.NOG strain. Successful results from studies using human progenitor cells in the mouse could transition to the immunocompromised pig as a route to FDA-approved clinical trials of a cell-based therapy.

Human clinical trials

Appropriate assessment of cell-based therapies in human studies will require appropriate study design, including the use of appropriate controls, blinding and elimination of investigator bias, appropriate validated outcome measures, and rigorous statistical analysis. Because of the difficulty and/or morbidity associated with

harvesting tissues from human subjects, the development and use of sensitive, noninvasive measures of tissue composition, structure, and mechanical function is essential.

In humans, sensitive, validated PROMs will provide a powerful tool to assess functional improvement. PROMs utilize patient-based assessments of their own functional status and perception of pain. Many validated outcome measures are now commonly used to assess the efficacy of various medical and surgical therapies. For upper extremities, functional outcome measures include grip strength and assessment of arm, shoulder, and hand function (ie, Disabilities of the Arm, Shoulder, and Hand [DASH] score) based on questionnaires. Lower-extremity fracture functional assessments could include the Timed Up and Go Test or the Lower Extremity Functional Scale. The Harris Hip Score and the 36-item Short Form Survey (SF-36) can measure hip and lower-extremity PROMs of function. Finally, functional criteria to assess the success of a spinal fusion could include the Oswestry Disability Index or the SF-12 or SF-36. Through a Common Fund initiative, the NIH developed a comprehensive PROM system called PROMIS that uses computer-adapted testing and thus has increased efficiency and sensitivity. This is being increasingly adopted as a PROM for patients with musculoskeletal disease.

The primary clinical goals of cell therapies are to treat symptoms, especially pain and instability, and to allow for return of normal function of the targeted tissue. Success can be defined as: (i) improvements in pain and/or physical function; (ii) a durable response (years); and (iii) a return of structural support or joint mobility that permits movement. Structural repair is a secondary outcome, implying that the tissue repair or implanted tissue has value to the degree which it permits painless function. The individual characteristics and properties necessary for regeneration are specific to the various musculoskeletal tissues (Table 4).

For therapeutic product development, strong preclinical evidence in model organisms on healing and function is an absolute requirement for the initiation of randomized clinical trials, which involve objective clinical outcome and follow-up measurements. Rigorous, scientifically based understanding of the mechanism of action is ultimately required to justify the therapeutic application of cell-based therapy. It is noteworthy that adult stem/progenitor cell therapy, which is often being practiced in an unregulated, non-standardized manner, has recently resulted in several highly publicized studies. To ensure safety and enhance efficacy, adult stem-cell therapy should be practiced only in a regulated and standardized manner. In addition, clinical trials submitted for publication should adhere to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) or Consolidated Standards of Reporting Trials (CONSORT) guidelines[1].

Ethical considerations

Animal studies

Animal studies should be conducted with strict adherence to ethical principles. The NIH provides guidelines (http://grants.nih.gov/grants/olaw/links.htm) and experiments should be approved by institutional animal use committees.

Cell-based therapy in humans

Currently, there is widespread use of cell-based therapeutics, often "off-label," in the clinical setting. The use of "stem/progenitor cells" to improve tissue healing has a distinct appeal to patients, because it suggests cutting-edge science with the potential to regenerate lost or damaged tissues. When combined with the reality that existing treatment options are often suboptimal for many soft-tissue injuries and that many patients seeking treatment are frequently relatively young and desirous of returning to an active lifestyle, an environment has been created in which patients are vulnerable and will seek such stem/progenitor cell treatments. However, although great potential exists for the use of cell-based approaches to improve tissue healing and regeneration, the reality is that current data for the use of cell-based therapies for augmentation of tissue healing is highly variable.[111,112]

Given this significant limitation, it is imperative that patients are informed that there exists little high-level animal model or randomized clinical trial data to support the use of stem/progenitor cell-based approaches for tissue healing. It should also be communicated to patients that use of these treatment approaches are most often off-label, and that the treating facility often has a financial incentive to perform a stem/progenitor cell procedure which is unlikely to be covered by standard medical insurance. At the same time, however, autologous therapies appear to be generally safe and well-tolerated, although their effectiveness is often largely based on testimonial evidence. Given this confluence of issues, it is critical that a neutral or second-opinion physician is consulted, such that truly informed consent may be provided. In the absence of these ethical considerations, the Task Force cannot support the current application of stem/progenitor cell therapy, whether administered locally or systemically, until the treatment protocols have obtained FDA approval.

[1] Clinical data utilizing these recommendations is not currently available and assessing efficacy is not possible at this time. Refer to the following FDA websites: https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm; https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm; and https://www.fda.gov/CombinationProducts/default.htm.

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