EDITORIAL

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Much-Needed Clarification and Guidance on Cell-Based Therapies for Musculoskeletal Disorders

Within the last 30 years, there have been many advancements within the field of stem cell biology, and controversies regarding their clinical implementation make the joint American Society for Bone and Mineral Research (ASBMR) and the Orthopaedic Research Society (ORS) Task Force by O'Keefe and colleagues especially timely.[1] Early descriptions of "the mesenchymal stem cell" by Friedenstein[2] and colleagues and later by Caplan[3] characterized these progenitors as a nonhematopoietic cell expanded by in vitro culture with the ability to self-renew and differentiate along multiple lineages. Since then, our understanding and ability to isolate pure populations of tissue-resident stem cells has allowed for the more accurate determination of key cellular signaling pathways.[4,5] The ability to induce pluripotency creating induced pluripotent stem cells (iPSCs) has further opened the door for use of progenitor cells in disease modeling, drug discovery, and regenerative strategies.[6] Finally, postnatal tissues such as bone marrow, periosteum, fat, brain, skin, and umbilical cord blood have been shown to harbor tissue resident progenitor cells, such as the skeletal stem cell,[5] with significant promise for potential clinical application.[7]

The present report broaches five main subjects: 1) limitations of cell-based therapies according to their cellular source (encompassing iPSCs, embryonic stem cells [ESCs], bone marrow stromal cells [BMSCs], skeletal stem cells [SSCs], nonskeletal-derived mesenchymal stem cells [MSCs], and differentiated skeletal cells); 2) utility of cell-derived products based on cellular source (encompassing platelet-rich plasma [PRP], conditioned medium, and extracellular vesicles [EV]); 3) tissue-specific animal models of cell-based therapies (focusing on bone, cartilage, intervertebral disc [IVD], meniscus, and tendon/ligament); 4) criteria for interpreting cell-based regenerative experiments; and 5) recommendations for preclinical and clinical cell-based therapies (preclinical animal models and human clinical trials).

The Task Force report bridges basic science and clinical practice. The ability for researchers to understand the clinical relevance and the practicing physician to understand the basic science will undoubtedly improve research outcomes and clinical practice. The Task Force report also allows for a more uniform understanding and improved ability to compare research outcomes by ensuring that key stakeholders involved in preclinical and clinical trials are aware of the recommendations. Of note, the Task Force report recommends that before Federal Drug Agency (FDA) approval there should be reproducibility across multiple institutions through shared collaboration and communication.

The structure given by this Task Force report will allow for governing bodies and regulatory authorities to evaluate clinical trial proposals and inform practicing surgeons about the fundamental principles behind stem cell therapies. Specifically, clear FDA guidelines can better direct rigorously controlled clinical trials with the goal of defining for clinicians the effectiveness of cell-based therapies for various indications. Importantly, the Task Force report specifically states that it "cannot support the current application of stem/progenitor cell therapy, whether administered locally or systemically, until the treatment protocols have obtained FDA approval." The dangers of unregulated purported "stem cell" therapies marketed to the uninformed public is a real threat to patient health.[8] By providing this Task Force report to surgeons and physicians, patients will also be better informed of the realistic potential of stem cell therapies and made aware of the expected outcomes.

With more than 100 new stem cell business websites appearing per year from 2014 to 2016, the ability for regulatory bodies such as the FDA to keep up with the rapidly expanding US direct-to-consumer stem cell industry is challenging.[9] And although the FDA currently regulates transplant of organs, including heart, lung, and kidney, far less regulation exists for purported stem cell transplantation with the transfer of fat. These so-called stem cell therapies, commonly performed for skin rejuvenation or joint disability, are not based on well-controlled clinical trials, yet vague promises of benefit are given to patients in exchange for remuneration. Fortunately, recent injunctions on multiple stem cell treatment centers taken by the federal court acting on behalf of the FDA show promise that recommendations and information given in Task Force reports such as this can provide stricter definition and regulation of stem cell therapies.[10] By providing more rigorous criteria for stem cell therapies using human cell and tissue-based products (HCTP), false advertising of unproven cellular therapies will be reduced. Furthermore, wide adoption of these Task Force recommendations and increased awareness by the public may also prompt reduction in medical tourism outside of the United States, thereby minimizing pitfalls of less reputable, poorly regulated stem cell therapy clinics.

Overall, the Task Force report is a timely contribution to the literature providing clarity and uniformity in an expanding discipline that remains largely unregulated. In light of the Task Force recommendations, the ability to better define and regulate this burgeoning industry allows for positive advancement toward the safe and efficacious use of stem cells. Most importantly, maintaining and updating the joint Task Force recommendations will provide

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scientists, surgeons, and physicians practicing within the field of cell-based regenerative medicine guidance to ensure, above all else, that patient safety is upheld.

Disclosures

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