



Industry News

Stem Cells in Orthopaedics: Myth, Miracle, or Something In-Between

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Forum Examines Stem Cells in Orthopaedics (AAOS 2014)

The ability of stem cells to divide and become more specialized cells—such as bone, blood, or muscle—makes them attractive agents in many areas of medicine. Additionally, the ability to harvest stem cells from an individual and reimplant them in the same individual, thus potentially reducing or eliminating the risk of infection, makes stem cell therapy appealing to both patients and physicians.

During Monday's AAOS *Now*-sponsored Forum on "**Stem Cells in Orthopaedics: Myth, Miracle, or Something In-Between**," an international group of clinicians, scientists, and regulators examined the research behind orthopaedic applications of stem cells and addressed the clinical and ethical issues surrounding the growth of this treatment option. Presenters covered areas ranging from basic science to stem cell use in regenerative medicine, nonunions and fractures, and spine and sports medicine.

What is a stem cell?

"Although there are many different definitions of a stem cell," said Pamela G. Robey, PhD, acting director of the National Institute of Health Stem Cell Unit in the National Institutes of Dental and Craniofacial Research, "all share two common characteristics: In the body, the offspring of a single cell are able to reconstitute a functional tissue, also called potency, and these cells are able to proliferate or renew themselves."

Dr. Robey began by discussing the development of stem cells. Totipotent cells develop from the fertilized egg and have the ability to divide and become all the different cells in an organism as well as the placental cells. Embryonic cells are pluripotent, meaning they can differentiate into various cell types. Multipotent fetal stem cells can develop into more than one cell type but are more limited than pluripotent cells.

One of the proven stem cell therapies, noted Dr. Robey, is the use of bone marrow stromal cells (BMSC) for tissue replacement in building bone within focal cavities. The use of stem cells in a systemic way to strengthen bone or replace cartilage, however, is still under study.

Regenerative medicine

According to Arnold I. Caplan, PhD, professor of biology and general medical science at Case Western Reserve University and founder and chief scientific officer of CellBank Technologies, “Every second, 15 million blood cells ‘drop dead’ in your body—and that keeps you alive. The source of those blood cells is bone marrow stem cells; without them, you die.”

Dr. Caplan noted that tissue engineering requires the ability to manage the development pathway of mesenchymal stem cells (MSCs). To date, he said, “no one can do that.” He also noted that the pericytes located on blood vessels detach and become MSCs in the presence of inflammation or injury. “These MSCs (which I call medicinal signaling cells) not only become the first line of defense against an auto-immune reaction by stopping an overaggressive immune response, they also make molecules that stop cells from dying from apoptosis.”

The business of regenerative medicine is growing, noted Dr. Caplan, as is the interest in using MSCs in a systemic way. He pointed out that approximately 385 clinical trials using MSCs are ongoing and more than 4,000 studies have been published. A phase II study has found that using MSCs to treat degenerative disk disease results in lower mean pain scores, reduced opioid use, and fewer surgical and nonsurgical interventions for persistent pain at 12 months.

Stem cells and bone

“I’m going to focus on adult stem cells,” said **Thomas A. Einhorn, MD**, chair of the department of orthopaedic surgery and professor of orthopaedic surgery, biochemistry, and biomedical engineering at Boston University. “These cells are taken from the bone marrow space and concentrated without any manipulation other than simple centrifugation. From the time the cell leaves the body until it returns is a maximum of about 20 minutes.”

Dr. Einhorn reported on research using autologous bone marrow grafting for nonunions. Because the research found a positive correlation between the number and concentration of colony-forming units (CFUs) and the volume of mineralized callus at 4 months, he began to apply the technique to treating nonunions. “We aspirate carefully,” he said, “and try not to draw any more than 5 ccs from one spot.” His technique adapts lessons learned from trauma surgeons and relies on continually reorienting the needle to reach new areas of the iliac crest.

With regard to the use of stem cells in treating osteonecrosis of the femoral head, Dr. Einhorn reported on his prospective case series of patients with stage 1 or stage 2 osteonecrosis. Among the patients available for follow-up at one year, 75 percent had significant symptomatic improvement, did not require any further surgical intervention, and exhibited no further collapse.

“But the home run is treating osteoarthritis (OA),” he said. He cited an equine study using bone marrow aspirate concentrate to treat extensive (15 mm) full-thickness defects created in the lateral trochlear ridge of the femur in 12 horses. At 8 months, results showed increased fill of the defects and improved integration of repair tissue with surrounding cartilage. A more recent study on human patients who

received partial medial meniscectomy and were treated with adult MSCs found no ectopic tissue or clinically important safety issues and a significant increase in meniscal volume. In addition, “patients with osteoarthritic changes who received MSCs experienced a significant reduction in pain compared with controls.”

Cartilage repair and regeneration

Farshid Guilak, PhD, Laszlo Ormandy Professor and vice-chair of the departments of orthopaedic surgery, biomedical engineering, and mechanical engineering and materials science at Duke University Medical Center, addressed the use of stem cells to treat OA and delay total joint replacement. He noted the challenges in treating OA with tissue engineering as well as possible approaches to solving those challenges.

For example, Dr. Guilak noted that current scaffolds do not possess adequate mechanical properties. “Gels are excellent for keeping the cells alive, but they have the properties of Jello; they don’t hold up to load very well. Nonwoven fibrous polymers are also great for growing cells, but don’t have the right mechanical properties. Recently, improvements have been made in the types of materials available. Two-dimensional woven scaffolds, however, are limited in thickness, so we are developing a three-dimensional weaving to make bioscaffolds that have the strength of fibers, the flexibility of a textile, are porous, and defined in their architecture.”

Molded scaffolds that deliver both cells and growth factors may be used to develop constructs for whole joint resurfacing, noted Dr. Guilak, but optimal scaffold and cell sources remain to be determined.

Spine and sports

According to **Wellington Hsu, MD**, professor of orthopaedic surgery and director of research at the NMH Musculoskeletal Institute, Northwestern University Feinberg School of Medicine, the number of different tissues in the spine presents several opportunities for the use of biologics such as stem cells. However, efficacy, safety, cost, and regulatory issues must be considered.

“These cells are all powerful,” said Dr. Hsu, “but they have so many different pathways that you really have to control one pathway to get the results you’re looking for. Although MSCs can form any number of mesodermal tissues, you have to be able to block the rest of them to get bone.”

The market for stem cell products is strong and expected to triple in the next six years. However, regulatory and legal issues may present issues for both manufacturers and researchers.

Scott A. Rodeo, MD, co-chief, sports medicine and shoulder service, at the Hospital for Special Surgery and professor, orthopaedic surgery, at Weill Cornell Medical College, addressed the use of cell-based therapies for tendon and tissue injuries in sports medicine. “Cells alone don’t do much,” he noted, pointing out that the delivery vehicle (scaffold) and the addition of transcription and growth factors may enhance cell-based approaches.

Dr. Rodeo also reported that various options for “cell-based” therapy are available, beyond just stromal cells from marrow or adipose tissue. These include adult differentiated cells (skin, tendon), intrinsic cell niches, and allogeneic and placental cells.

Practical concerns

Forum participants also addressed practical concerns such as issues of cost and availability (Dr. Einhorn); safety, culture, and storage (Koen Bos, MD, PhD, Erasmus University, The Netherlands); and regulatory issues (Celia Witten, MD, PhD, director of the office of cellular, tissue and gene therapy at the U.S. Food and Drug Administration’s Center for Biologics Evaluation and Research). In-depth reports on these concerns as well as on the topics covered in this article will appear throughout the year in *AAOS Now*.

Details of the authors’ disclosure as submitted to the Orthopaedic Disclosure Program can be accessed electronically at www.aaos.org/disclosure
