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Quality & Research

# Stem Cell Therapy in Orthopaedics

Cell therapies have been used in a variety of medical specialties to restore function and improve the quality of life. In some cases, cell therapies have been life saving. For example, several cancers of the hematopoietic and lymphatic system are treated with autologous and allogeneic cell therapy via bone marrow transplantation.

In treating musculoskeletal disorders, cell therapy has been used mainly for bone grafting of skeletal defects, in the management of delayed unions and nonunions, to obtain spinal arthrodesis, in the treatment of osteonecrosis, and, more recently, for tissue engineering purposes.

Historically, the surgical reconstruction of bony defects has involved the use of medical implants or bone grafts. The advent of tissue engineering over the past few decades has generated considerable interest in exploiting the potential of cell-based therapy in orthopaedics. Although numerous 'pilot' studies and research projects have been conducted, definitive Level I studies are lacking. Several questions must be addressed about the use of cell-based therapies for a specific application.

This article examines the basics of cell therapy; a follow-up article next month will look at the clinical aspects of stem cell therapy in orthopaedics.

### Why use cells?

Since the discovery of bone morphogenetic protein by Marshall Urist, MD, scientists have tried to identify the appropriate balance of substances to stimulate osteogenesis. Although several proteins have been shown to be osteoinductive and osteoconductive, the tissue responses to these proteins are variable and influenced by the microenvironment, including the bony architecture. A cell, which produces multiple paracrine modulators, offers an alternative to attempting to identify a cocktail of substances to introduce into the cellular milieu.

### Which cells should be used?

Stem cells have the ability to recapitulate ontogeny and thereby differentiate into different cell types. Stem cells may be self-renewing (establishing a pool of stem cells) or progenitor cells. Stem cells are described as being totipotent, pluripotent, multipotent, or unipotent cells, depending on how many distinctive types of cells the stem cell can become.

The potential of a subset of stem cells reflects how close the cells' development is to embryogenesis. Embryonic stem cells are believed to have the greatest potential to develop into all of the different cell types, while adult stem cells are believed to be more limited. Somatic cells, ie, non–germ-cell cells, have also been studied as cells that are end-differentiated to the cell type of interest.

Understanding the specific clinical application for which the stem cells will be used also enters into the decision-making process. Stimulating fracture healing of cortical-cancellous bone is quite different from using bone graft to reconstruct a defect within trabecular bone created by dead or diseased bone. However, both circumstances involve complex mechanisms requiring different cell types, proteins, and structures to restore the anatomy of the region of interest.

Vasculogenesis is vital to the outcome of bone grafting procedures and, of course, osteogenesis is required to restore the bony structure. But whether using just one cell type—such as mesenchymal stem cells (MSCs)—will be sufficient to jump-start the process of healing is unclear. For this reason, using bone marrow aspirates containing multiple cell types and a cocktail of growth factors and other proteins has been advocated for bone grafting procedures. End-differentiated cells, such as chondrocytes, have also been

studied but may require additional
processing.

### Autogeneic vs allogeneic cells?

Autograft bone is generally accepted as the ‘gold standard’ with the potential for faster osteogenesis. But is this also true for autogeneic cells for cell-based therapy?

Autogeneic cells have the following advantages:

- Healing takes place at a faster rate with increased mechanical strength of the repaired tissue.
- No evidence of an adverse immunologic response has been noted

If bone marrow aspirate is used, mesenchymal, hematopoietic, and other progenitor cells will be present. But the limited availability of aspirate and cells at the time of harvesting of the cells may require that the cells be cultured until a sufficient number is available to reconstruct medium-to-large lesions.

Other factors to consider are the biologic variability among patients and the feasibility of using autogenous cells with a specific patient. The patient’s age or disease state may affect both the proliferative capacity and the functioning of donor cells.

Allogeneic cells have the following advantages:

- They can be screened for their proliferative and functional capacities.
- They can be controlled for age and disease.
- The number of available cells can be boosted.

Depending on the application, allogeneic cells can potentially be an “off-the-shelf” product, thereby increasing both the quantity and quality of cells available at the time of surgery.

Concerns have been raised about the potential immunogenicity of allogeneic cells. For example, graft-versus-host disease has developed in some bone marrow transplant patients, a complication not evident from animal studies conducted on syngeneic animals. However, little evidence exists on the immunologic consequences of bone graft in general and especially in those bone grafts that have been processed to retain the viability of mesenchymal

stem cells. Whether a subsequent immune reaction develops to or by these transplanted allogeneic cells during differentiation is unknown.

Cells can be introduced into the region of interest alone, with bone graft or bone graft substitute, or seeded onto a scaffold. The number of cells required will depend on the method of introduction, the number of cells retrieved, and the type of cell used. The rate of cellular proliferation depends on the cell type and patient factors (such as age or disease).

Generating enough MSCs for certain orthopaedic applications may take days to weeks. The scaffold chosen must be optimized for the biologic and mechanical environment for a specific application. It must also allow for a seamless boundary between implant and host (ie, incorporation of the graft. Numerous scaffolds have been studied; currently approved grafts) are for non–weight-bearing applications.

Although considerable research has focused on understanding the behavior of stem cells, animal studies are ultimately needed to transition this treatment option from the bench top to the bedside. Three different approaches have been used: calvarial, critical-sized, and segmental defects. Regardless of approach, these studies have demonstrated significantly more bone formation when cells are placed into a scaffold than when a scaffold alone is used.

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