

Cell technologies for spinal fusion

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Abstract

For a successful spinal fusion to occur, several vital elements are necessary. They consist of the presence of the bone-forming cell (osteoblast) or its precursor, the appropriate biological signals directing bone synthesis, and a biocompatible scaffold on which the process can occur. The most critical of these components is the osteoblast or its precursor, the mesenchymal stem cell (MSC), both of which possess the ability to form bone. As a result, many current techniques attempt to maximize the benefits derived from harvesting the ready source of MSCs from bone marrow, while minimizing the associated complications. These cellular technologies seek to improve on the harvest and concentration of the MSCs or enhance their delivery and action. This review focuses on the terminology, historical underpinnings, and current research rationale and techniques and discusses the possible future of these technologies. © 2005 Elsevier Inc. All rights reserved.

Keywords:

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Introduction

Spinal fusion is a common procedure used in more than 200,000 cases per year in the United States [1]. The current standard for spinal fusion is autograft because of its immunogenetic compatibility, absence of disease transmission, biomechanical strength and osteoinductive properties. However, autologous graft harvesting has been associated with various complications [2–14]. Also, in cases requiring large fusion areas, such as revision spine surgery, the amount of autologous bone available is frequently insufficient.

The use of allograft has gained interest because it avoids many of the morbidities associated with the harvest of autograft. However, allograft is coupled with various drawbacks compared with autograft, such as risk of transmission of infection, poor osteoinductive properties, less osteogenic capabilities, delayed time to fusion and potential nonunion [15–18]. Moreover, it has been noted that tensile forces,

predominantly associated with posterior fusion, contribute to the increased incidence of nonunion in comparison to regions primarily subjected to compressive loads, as in anterior interbody fusions. Furthermore, allograft, more than autograft, is subjected to deleterious complications associated with such biomechanical factors [19,20]. In addition, various local and systemic factors may contribute to adverse outcomes of both autograft and allograft fusion material [21–33].

To address the various potential complications associated with autograft or allograft substrates, researchers are developing various cellular technologies to augment and potentially replace the use of autologous graft harvesting and enhance allogeneic properties. Recent investigations have focused on the role of the osteoprogenitor cells, specifically the multipotential mesenchymal stem cells (MSCs). It has been noted that a single mesenchymal-derived precursor has the potential to give rise to an adipocyte, osteoblast, or hematopoietic-supporting cell or to induce osteogenesis from mature osteoblasts [34,35]. Because these progenitor cells maintain the ability to differentiate and stimulate induction of key bone cells, they are an integral component in bone formation. Current techniques attempt to maximize the benefits derived from harvesting the ready source of osteoprogenitor cells from bone marrow.

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The purpose of this narrative review is to provide the reader with a basic review of current cellular techniques in spinal fusion. The focus of the paper is to explain pertinent terminology, review the historical perspective, explain current research rationale, provide examples of current techniques, and discuss the possible future of these technologies.

Terminology

To better understand the theory behind current bone graft techniques, it is important to understand the terminology. Bone graft can be any material that promotes bone growth and healing. Osteogenic materials are those that contain osteoprogenitor cells that can lay down a new bone matrix [36]. Osteoinductive materials are ones that provide signals necessary to induce differentiation of local MSCs into mature osteoblasts, whereas osteoconductive materials serve as a passive scaffolding to promote vascular invasion and bone apposition on its surface for new bone formation [36,37]. These three processes exist in spinal fusion, but vary in degrees and depend on the type of graft material (Table 1).

The primary bone-forming cell in the body is the osteoblast, and its precursor is the MSC. Bone formation occurs as the extracellular matrix, which is produced by the osteoblast, becomes mineralized. Osteoprogenitors refer to all the cell stages stemming from pluripotent MSCs up to the osteoblast. This naturally occurring differentiation process is regulated by a series of naturally occurring proteins, or growth factors, that eventually guide the MSC to form osteoblasts. In addition, the biology of spinal fusion is a complex process that entails the inflammatory, reparative and remodeling phases.

Historical perspective and background

The use of autologous cellular techniques for spinal fusion is not a recent concept. In 1911, Albee, in his groundbreaking paper, described a series of three patients with Pott's disease (tuberculosis of the spine) who underwent successful spinal stabilization with bone removed from the tibia and placed

between adjacent vertebra [38]. In that same year, Hibbs, independently described his attempts at surgically fusing the posterior spinal elements of young patients with spinal tuberculosis by using autologous bone taken from the iliac crest [39].

In 1945, R.D. Owen discovered, during his experiments, a lifelong blood chimerism between twin cows, which eventually led to the first description of the stem cell [40]. Through the years, the concept of a stem cell has been expanded and refined. By 1988, M.E. Owen [41] and Friedenstein et al. [42–44] noted that these precursor cells, known as MSCs, existed in the bone marrow and had the ability to differentiate into a variety of cell lines, including bone.

Such discoveries prompted research into the potential use of MSCs in bone healing. Basic science studies in animals have clearly shown the role of these multipotential cells in bone healing in various models of long bones [45–47]. Furthermore, the clinical use of autologous bone marrow injections has been successful in tibial nonunions [48]. However, research on bone marrow aspiration (BMA) techniques in spinal fusion models has not been as clear. Using a rabbit model, Curylo et al. [49] showed that when used to augment a posterolateral fusion, bone marrow aspirate resulted in a greater fusion mass when compared with controls. The researchers concluded that in cases in which an adequate quantity of autogenous bone graft is not available, the addition of bone marrow may facilitate greater bone formation and a successful fusion. In a study that compared the efficacy of mixed and cloned marrow cells alone in a rat spine model, by Cui et al. [50] found increased bone formation and more successful fusions in the specimens that received the cloned osteoprogenitor cells rather than the mixed marrow population. Muschler et al. [51] attempted to determine whether the biologic milieu of a bone marrow clot could significantly improve the efficacy of posterior spinal fusion in a canine model. Using union scores, computed tomography scans and mechanical testing, those researchers concluded that the addition of a simple concentration of cells from the bone marrow or the delivery of an increased number of cells in a graft site was not enough to achieve solid spinal fusion.

Table 1

Properties of various bone graft substrates

Grafting material	Osteoconduction	Osteoinduction	Osteoprogenitor cells	Immunogenicity	Donor-site morbidity	Immediate torque strength
Cancellous autologous graft	++++	++	+++	–	+	–
Cortical autologous graft	+	+/-	+/-	–	+	++
Fresh allograft	+	+/-	–	++	–	++
Frozen allograft	+	+/-	–	+	–	++
Freeze-dried allograft	+	+/-	–	+/-	–	+
Ceramics	+	–	–	–	–	+/-
Demineralized Bone matrix	+	++	–	–	–	–
Bone marrow	–	+/-	++	–	–	–
Particulate ceramic with bone marrow	++	+/-	++	–	–	–

+ = weak positive role; ++ = more positive role; +++ = strong positive role; ++++ = strongest positive role; – = no role; +/- = may play a role. (© 1995 American Academy of Orthopaedic Surgeons. Reprinted with permission from Gazdag AR, Lane JM, Glaser D, Forster RA. Alternatives to autogenous bone graft: efficacy and indications. J Am Acad Orthop Surg 1995;3:1–8.

These studies highlight some of the challenges associated with the use of BMA for spinal fusions. They suggest that, if used alone, iliac crest BMA, although potentially effective as an augment or graft extender, is likely ineffective as a bone graft substitute. As a result, newer techniques have been developed to improve the harvest and concentration or to enhance the delivery and action of the MSCs.

Cellular techniques

The ability to obtain a solid spinal arthrodesis depends on several factors. One important variable under the control of the surgeon is careful operative technique. Clinically, the cellular components for a spinal fusion can come from various sites. Anteriorly, perforation of the superior and inferior end plates allows the rich multipotential MSCs present within the vertebral body to “flow” into the site of the interbody fusion and thereby provide a source of osteogenic cells. Similarly, posteriorly and posterolaterally, meticulous decortication of the bony elements exposes cancellous raw surfaces that provide a site for fusion “attachment” but also are a source of local stem cells. Furthermore, the overlying periosteum and surrounding muscles are sources of osteogenic cell materials. Although these techniques provide a source of osteogenic cells, they are limited. As a result, supplemental bone grafting has become commonplace in spinal fusions.

Currently, two principal cellular options are in routine use for spinal fusions: autologous bone graft and marrow-based grafts. The use of autologous bone graft can be separated into either local autograft or iliac crest bone graft (ICBG). Autologous bone graft harvested from the iliac crest is considered the standard. Marrow-based grafts include a wide range of techniques that predominantly focus on collecting and preparing the cellular elements of the bone marrow through various aspiration techniques.

Autologous bone graft

Autologous ICBG is considered the ideal graft source because it contains all the key elements necessary to achieve a solid spinal fusion (Table 1). Perhaps the most vital of the components are the living cells, which are the osteoprogenitors that provide the machinery necessary to drive the bone metabolic process. These osteoprogenitor cells also include MSCs and are capable of direct osteosynthesis without any additional elements from the surrounding environment. In addition, there is an osteoinductive component that exists either directly from growth factors already present from the harvested material or indirectly from the synthesis of these proteins by the living osteogenic cells themselves. Finally, in cases in which the autologous iliac crest harvest includes cancellous or corticocancellous bone, this bone provides the physical scaffolding that orients the cells and provides access to the stimulatory signals.

The advantages of autologous ICBG should be balanced against the known complications, which include chronic

pain, hypersensitivity, increased blood loss, increased operative time, deep infection, vascular and neural injuries and poor cosmetic results [2–14]. Furthermore, limited supply can be problematic for patients undergoing procedures that require large graft volumes or in revision cases. As a result, in some cases, the use of local bone graft may be considered.

Like ICBG, local autograft also carries the key elements necessary for a spinal fusion. However, as has been shown, it does not possess the same level of biologic activity as iliac crest autograft as a result of its poor cellularity. Furthermore, the availability of local bone is usually limited and is frequently insufficient in quantity to be used alone.

Bone marrow-based grafts

The second cellular technique focuses on bone marrow-based grafts. The central theme behind these techniques is to maximize the benefits of the autologous bone graft while minimizing potential complications. This class of techniques is based on obtaining and using the cells and stimulatory signals present in the bone marrow for potentiating spinal fusions, typically through BMA [52]. Autologous bone marrow has intrinsic osteogenic potential because of the presence of osteoprogenitor cells and, when delivered in an appropriate matrix, can contribute substantially to bone formation at the grafted site.

The bone marrow is typically obtained through a percutaneous or limited open incision using a needle aspiration technique. Iliac crest bone marrow contains the highest percentage of osteogenic cells and osteoinductive factors available; therefore, it is the aspiration site of choice [52,53]. The aspiration can be performed from either an anterior or a posterior approach, depending on the position of the patient and the surgical procedure being performed.

Although the aspirate obtained is highly cellular, it contains both hematopoietic and mesenchymal cell lineages. Both are involved in bone formation, but only the mesenchymal lineage includes the osteoprogenitor cells, which are directly responsible for bone formation. Unfortunately, the mesenchymal lineage comprises only a small fraction of the cellular elements in bone marrow and may be present as only 1 MSC per 100,000 cells [54].

The presence of these osteoprogenitor cells can be confirmed by several methods. One technique is to determine the number of alkaline phosphatase-positive colony-forming units (CFU-ALPs) that occur when bone marrow cells are plated in vitro. As each stem cell begins to proliferate, it begins forming individual colonies of cells; those colonies that produce alkaline phosphatase are considered to have osteogenic cells and are therefore osteoprogenitors.

Using such methods to identify osteoprogenitor cells, researchers have investigated the effects of various factors on bone marrow cellularity. Studies suggest that a patient's age, sex, smoking habit, corticosteroid use, alcohol abuse and aging can alter the bone marrow composition and the osteoblastic progenitor cell pool within the bone marrow [55–58].

Although many of these factors are not under the direct control of the surgeon, the aspiration volume obtained at the time of the bone marrow harvest is under such control. In a study by Muschler et al. [55], the researchers evaluated the number of nucleated osteoblast progenitor cells that were obtained with different volumes of aspiration. Bone marrow samples were obtained from the anterior iliac crest of 32 patients without systemic disease. The researchers found that larger volume aspirations decreased the concentration of nucleated osteoblast progenitor cells because of dilution of the bone marrow sample with peripheral blood. An increase in the aspiration volume from 1 to 4 mL caused a decrease of approximately 50% in the final concentration of CFU-ALPs. As a result, the researchers recommended that aspiration volume should be limited to 2 mL or less to maximize cellular yield. Therefore, after the aspiration of 2 mL bone marrow, the needle should either be advanced further or be redirected before obtaining the second 2-mL aliquot [55]. Moreover, although 20% to 25% of the cellular variability seen during repeat aspirates was due to variations within the same patient, the researchers believed that nearly 60% to 70% of the variations were related to variability between subjects. This variability further supports the findings that the number of nucleated cells available for harvest vary significantly from one individual to another [55]. Patient age also has been shown to affect the quality of the bone marrow from patient to patient, with decreasing cellularity with increasing age [59,60].

In a study by Hernigou et al. [61], the researchers aspirated and compared the bone marrow from the nonunion site of a spinal fusion with the samples taken from the iliac crest of the same patient or from a group of bone marrow donor patients. The researchers found that the bone marrow of the nonunion site contained lower amounts of progenitor cells and, surprisingly, that the progenitor cells in the iliac crests of the same patients with pseudarthrosis also were low compared with a control population of bone marrow donors.

It is important to note that the effectiveness of any bone graft depends on the graft's cellular make-up. Therefore, disadvantages to the routine use of marrow-based grafts include the inconsistent results obtained from aspiration techniques, the low osteoprogenitor content obtained from small aspiration contents, and the lack of a structural scaffold. To address these actual and potential deficiencies, researchers are developing newer technologies that concentrate the bone-forming cells and osteoinductive proteins through either cellular retention or cellular expanding techniques. At this time, although direct clinical evidence demonstrating the efficacy of these technologies for spinal fusion is lacking, early basic science and laboratory findings are encouraging [51,55,109].

In cellular retention (Cellec; DePuy Spine, Raynham, MA), a substrate is designed to possess specific characteristics and biocompatibility that increase the chance of the cellular elements adhering onto the substrate. Matrix geometry, biocompatibility, and rate of bone marrow flow through the substrate are a few factors that can affect the ultimate yield in

this technique. The processing method builds on the natural "attachment" tendency of bone-forming cells. Relying on the principle of an affinity column, the technology facilitates the retention of osteoprogenitor cells within the matrix, while discouraging retention of other non-bone-forming cells. The obvious advantages of selective cellular retention include the ability to increase the mesenchymal cell lineage by identifying certain matrix-specific receptors present on these cells, while providing an osteoconductive scaffold [51,55,109].

Although bone marrow is known to contain pluripotent progenitor cells, the number of cells in such an environment is considered low. To increase the number of the osteogenic cells obtained from the bone marrow aspirate, the method of "cellular expanding" has been developed. In this technique, the cells from the bone marrow aspirate are cultured in vitro for several weeks. Theoretically, this technique has the potential of producing an unlimited number of bone-producing cells for use in that patient. Disadvantages include the need for two separate procedures, cost, and availability of sophisticated instrumentation, techniques, and personnel [110–113]. Currently, this technology is not in routine use in spinal fusions.

Biologic stimuli

The complex process of bone formation can be affected by a variety of biologic signals, including mechanical loads and electromagnetic and chemical factors. Theoretically, the application of various biologic signals involved with bone formation can affect spinal fusions. One area of intensive investigation is the role of osteoinductive proteins, specifically growth factors in enhancing cellular technologies in spinal fusion.

The ability for osteoinductive proteins to differentiate precursor cells into bone was first noted by Urist in 1965 when he discovered in a rat model the induction of new endochondral bone formation at ectopic sites from isolated bone inductive extract taken from adult bone [62]. This seminal work brought attention to the presence of bone morphogenetic proteins (BMPs) and their role in bone formation. Since the 1960s, approximately 20 BMPs have been identified. BMPs are considered multifunctional cytokines that belong to the 43-member transforming growth factor β superfamily. Throughout the ensuing years, studies have shown that BMPs are involved in the formation of ectopic bone, chondroblasts and visceral development [63–66]. More specifically, various studies have highlighted the potential of BMPs in the treatment of nonunions of the femur [67] and tibia [68] as well as segmental long-bone defects [69,70]. Because of their derived amino acid sequence, BMPs are further divided into groups [63,71,72]. In essence, BMPs possess the ability to enhance osteoinduction and act as both a chemotactic agent and a growth and differentiating factor.

Receptor function that entails signal transduction for BMP cellular osteoinduction is vital and consists of three types of receptors: type I, type II, and type III. However, type I and type II receptors appear to play a crucial role in BMP signaling and binding, particularly with their interaction with various Smad intracellular molecules that are integral in the osteoinduction process [73–75]. However, the type of Smad activation largely depends on the type of BMP ligand and receptor.

Various recombinant techniques have been developed to produce BMPs and evaluate their bone-forming role *in vivo* in animal studies. The process of recombinant BMP technology entails identification of the desired structure from bone extracts by bovine bone. Thereafter, a human complementary DNA (cDNA) sequence is ascertained by oligonucleotide probes, and the cDNA clone is then spliced into a viral expression vector and inserted into a carrier cell by transference. To date, largely recombinant human BMP-2 and recombinant human BMP-7 have been investigated in various animal models and have shown promising results with bone formation, high fusion rates, or both [76–85]. Human studies with BMPs have also been promising in their use of various surgical spine procedures. Overall, the application of BMPs has noted an increase in fusion rate and time to fusion in comparison to autologous ICBG or allograft substrates as well as with the presence of instrumentation [86–89].

Investigation of BMPs has shown that they can initiate the process of bone formation *de novo*. However, a certain hierarchical model entailing the bone formation capabilities of various BMPs has been suggested. According to Cheng et al. [35], BMP-2, -6 and -9 are more apt to induce osteogenesis from lineage-specific differentiation of progenitor cells than are other BMPs. Moreover, the researchers suggested that to optimize bone regeneration a coupling of various BMPs may enhance osteogenic activity. However, several studies have noted concern with overgrowth of bone formation, proper carrier and other safety considerations intrinsic to BMP use [90–92].

Osteoconductive scaffolds

Because scaffolds do not contain osteogenic cells or intrinsic biologic signals, they have no capacity on their own to create bone for spinal fusions. However, the importance of an effective osteoconductive scaffolding should not be underestimated. If designed correctly, osteoconductive scaffolds provide both the framework for the migration and attachment of surrounding osteogenic cells and the environment necessary for the synthesis of the extracellular matrix.

Currently, allograft is the most commonly used osteoconductive scaffold. It is typically used with autograft, as an extender or mixed with bone marrow aspirates to provide the necessary osteogenic and osteoinductive factors. However, because of the intensive preservation and preparation

treatment that it frequently undergoes, allograft can be expensive, and the diminished mechanical and biologic properties resulting from the processing can produce varied clinical results (Table 1). Other reported concerns include the risk of bacterial contamination, viral transmission and immunogenicity [15–18]. However, proper graft processing and preservation techniques can minimize potential immunogenetic-related complications and the risk of disease or infection transmission. Engineered osteoconductive materials, such as ceramics that include tricalcium phosphates, calcium carbonate and hydroxyapatite, may help address these issues, but, to date, their reported use alone for spinal fusions is limited [93].

Researchers are developing newer composite scaffoldings that are designed specifically to act as carriers for the osteogenic cells and simultaneously act as a delivery system for bioactive elements. They are designed to maintain a specific three-dimensional structure that can serve as an osteoconductive matrix for bone-forming cells and to be biocompatible while maintaining the ability to be biodegraded. The removal of the scaffold is important to minimize the effects of residual carrier on the biomechanical properties of the fusion, but this process must be carefully controlled. The rate of matrix resorption must match the expected rate of progressive bone replacement at the fusion site, while limiting the inflammatory process that occurs during this resorption process.

Collagen provides a physical and chemical environment that is favorable to bone regeneration. When introduced to the various scaffolds, collagen can substantially enhance the handling characteristics of the scaffold, thereby increasing its ability to act as a delivery system. These newer composite scaffolds provide physical resistance to tension and shear and show increased retention of the material of interest by resisting loss secondary to irrigation, local bleeding and physical displacement.

The combination of osteoconductive matrices with osteoinductive growth factors and osteogenic cells may potentially surpass the functionality of autograft and allograft. Thus, composite grafts comprise the most rapidly expanding category of autograft substitutes.

Future directions

Currently, bone marrow still remains the most reliable source for providing MSCs. However, studies suggest that a variety of other locations in the body, including adipose tissue, periosteum and muscle, also contain stem cells capable of osteogenic differentiation [34]. In regard to adipose-stromal cells, studies suggest that these cells are more than space fillers and can function as both osteoblastic and hematopoietic lineages that, under appropriate conditions, can dedifferentiate and return to the status of an uncommitted stromal stem cell [34,94,95]. The advantage of the use of adipose-stromal cells is their ease of access, and in most

cases, abundant quantity. Currently, in selected labs, researchers are studying the feasibility of multipotential adipocyte-stromal cells as a possible source for osteogenic cells in spinal fusion.

Aside from bone marrow cells, a variety of other cell types have been used to induce bone formation. Breitbart et al. [96] showed bone healing using cultured periosteal cells transduced retrovirally with the *BMP7* gene, whereas Lee et al. [97] showed that muscle-derived cells transduced with BMP-2 could heal critically sized bone defects in mice.

As research continues, more and more biologic signals are being identified each day that show properties in differentiating the bone-forming process. For example, other growth factors that have potential include platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF). VEGF may show promise in the management of pseudarthrosis and delayed unions by increasing the vascular supply to the site of interest [24].

PDGF can enhance bone healing by providing stimulatory signals at various stages of bone healing and can be obtained by concentrating the plasma component of peripheral blood drawn directly from the patient, creating a platelet-rich plasma (PRP) that has elevated concentrations of autologous PDGF and other growth factors. Regardless of the method used to concentrate the platelets, the resulting suspension contains increased growth factors proportional to the increased platelet count [98–100]. Newer techniques allow the PRP to be collected and concentrated from whole blood obtained either during surgery or immediately before surgery (Symphony; DePuy Spine).

Tissue engineering continues to provide newer and more advanced methods for developing osteoconductive carriers. The combination of growth factors within a bioengineered scaffolding provides the opportunity to create an activated matrix, which serves as a vehicle for the delivery of the osteogenic cell. A more sophisticated method focuses on transducing MSCs with a therapeutic gene [101–105]. This technique of gene transfer represents the next step in the evolution of therapies in promoting spinal fusion. As is the case with direct application of BMPs on the fusion site, proteins of interest by gene therapy may be delivered by adenoviral vectors, retroviral vectors or ex transduced cells. In essence, the process of gene therapy in spinal fusion allows for the introduction of certain genetic sequences within the cell that can manufacture a specific therapeutic protein. Theoretically, one or more genes encoding for an osteoinductive protein can be transferred into the spinal fusion site, allowing the transduced cells to secrete the proteins extracellularly. In this case, both the multipotential cell and the surrounding tissue can be modulated by the osteoinductive effects of the growth factors produced by the transduced cell. In these situations, the cells act as the “vehicle” to deliver the therapeutic gene of interest. Several studies that use gene therapy techniques to enhance fusion in various animal models have shown promise, but further studies are still warranted to substantiate their safety and

their various inherent dynamics for use in humans [97,102,106–108].

Summary

Currently the use of autologous ICBG for spinal fusion remains the standard. However, because of the complications associated with traditional open techniques for harvesting bone graft, newer alternatives are being investigated. Current cellular technologies focus predominantly on percutaneous aspiration-based techniques that attempt to obtain the cellular component of the bone marrow, specifically the MSCs, in a less invasive manner. The benefits of these techniques are the ability to obtain both osteogenic cells and osteoinductive factors with decreased morbidity. Although evidence suggesting the use of bone-marrow clot as a potential graft augment is limited, there is little evidence to support its use alone as a graft substitute.

The use of bone-marrow clot is likely multifactorial, including variable bone marrow cellularity among individuals and the lack of an effective osteoconductive carrier. To address these issues, researchers are using newer technologies to concentrate the harvested osteogenic cells and osteoinductive factors to potentiate their bone-forming properties while placing them onto a bioengineered matrix that can act as an osteoconductive carrier. Early studies show some promise that these techniques may have potential as bone graft substitutes.

The future of cellular technologies in spinal fusion is continually evolving. Alternatives to bone marrow as a source for MSCs may include adipose tissue and periosteum. Furthermore, new osteoinductive biologic signals are being discovered daily and are being evaluated for use in spinal fusions and in pseudarthroses repairs. Ultimately, it is likely that these cells and critical factors therein will be placed within bioengineered carriers designed specifically to mimic the tissue properties of bone while matching the rate of matrix resorption with bone formation. Finally, gene therapy, although in its infancy for spinal fusion, holds early promise.

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