One of the main sources of back pain is clinical spinal instability.1 This pain often originates at the motion segments of the spine or intervertebral discs. The resultant back pain is often treated with the surgical stabilization of a painful spine segment. Instrumentation provides an immediate stabilization of the spine segment, while bone grafts facilitate a biologic response to promote the formation of new bone. The formation of new bone permanently fuses the spine segments. Once fusion occurs, mechanical loads are transferred from the instrumentation to the fused spine segment. If fusion does not occur, the instrumentation will remain subject to mechanical loads and may eventually fail due to metal fatigue.2 Furthermore, continued motion in a painful spine segment is likely to remain a source of pain.

Bone grafts are utilized as either scaffolding for osteogenesis (bone formation) or stimulation of bone growth in a desired area. Recently, there has been an increased emphasis on incorporating biologic therapies in bone-forming grafts.

The mechanisms of actions of bone grafts fall into three general types:

- **Osteogenesis**: The bone graft contains bone-forming cells (osteoblasts). Bone harvested from a person’s iliac crest is typically used and contains osteoblasts. Local bone removed at the surgical site is a convenient source of graft, but generally contains cortical bone with much fewer osteoblasts.

- **Osteoconduction**: The graft material acts as a scaffold onto which bone cells can attach, grow, divide, and migrate. Osteoblasts work much better when they have a scaffold or matrix for attachment.

- **Osteoinduction**: The bone graft contains chemicals that attract primitive stem cells and immature bone cells, then promote the proliferation and differentiation of these cells into bone-forming cells.

Grafts may be classified according to their composition and mechanism of actions.

- **Bone**: Grafts made of bone are osteoconductive and may be osteogenic if they contain bone-forming cells.
  - Autografts: patient’s own bone (iliac crest or local bone)
  - Allografts: donor bone (cadavers or tissue bank)
  - Demineralized bone matrix (DBM): human-derived bone powder is demineralized, leaving only the organic bone matrix
  - Mineralized allograft: cortical/cancellous bone chips are chopped-up pieces of bone
  - Xenograft: mineralized cortical granules of bone derived from another species (most commonly cows and pigs).

- **Ceramics**: Ceramics are synthetic materials manufactured so that each ceramic granule mimics human cancellous bone. Ceramics are primarily osteoconductive. Common ceramic materials are:
  - Hydroxyapatite (HA)
  - Tricalcium Phosphate (TCP)
  - Biphasic Calcium Phosphate (HA:TCP)
  - Calcium Sulfate

- **Cell-signaling materials**: Cell-signaling materials are osteoinductive.
  - Bone Morphogenetic Proteins (BMPs) are proteins present in small quantities within bone. It would require hundreds of kilograms of bone to extract milligram quantities of BMP. Researchers were able to produce these proteins in large quantities through the use of recombinant DNA technology. BMPs promote the migration of primitive stem cells and immature bone cells, their proliferation, and their differentiation into bone-forming cells.
  - i-FACTOR Biologic Bone Graft combines a unique anorganic bone mineral (ABM) and small peptide (P-15) that acts as an attachment factor for specific integrins on osteogenic cells.

Historically, bone harvested from the iliac crest has been the graft of choice in spine surgery. However, its effectiveness depends on the patient’s bone quality.
Furthermore, the added surgical procedure required to harvest bone from the iliac crest may lead to increased morbidity, blood loss, injury to local nerves, damage to blood and lymphatic vessels, infection, disturbances in gait, prolonged hospitalization, and protracted recuperative time.3

In 2006, the FDA approved the use of bone morphogenetic proteins (BMPs) in spinal fusion. BMPs are members of the TGF β superfamily of biological molecules. BMP molecules share a similar structure and amino acid sequence at the carboxyl terminal region. Different BMPs are not interchangeable, though some such as BMP-2 and BMP-4 show significant homology. Through signal transduction, BMP receptors effect the mobilization of members of the SMAD family of proteins which are associated with bone development.4 BMPs interact with bone morphogenetic protein receptors (BMPRs) on the cell surface. This initiates a cascade of events that can facilitate bone formation. BMPs may be active at multiple points throughout this cascade. First, BMPs induce cell migration to the site of administration. Osteoprogenitor cells, osteoblasts, and mesenchymal stem cells respond to the chemotactic signal. Mesenchymal stem cells are undifferentiated and can produce several connective tissue cells including cartilage-producing chondrocytes and bone-producing osteoblasts. The proliferative response may be enhanced by molecular signals released by cells at the injury site. BMPs affect undifferentiated cells but do not appear to have a cell-specific effect on mature differentiated cells.5 (Figure 1)

Currently, a clinical trial has been launched investigating the use of P-15, an amino acid peptide, in cervical fusion. i-FACTOR™ (Cerapedics, Broomfield, CO) is a peptide-enhanced bone graft that utilizes a unique small peptide (P-15™) intended to stimulate the natural bone healing process. It combines anorganic bone mineral (ABM) and P-15 to act together as an attachment factor for specific integrins on osteogenic cells. (Figure 2)
The first step in the bone formation process is cell attachment. Osteogenic precursor cells bind to P-15 via their α2β1 integrins, which are signaling receptors. i-FACTOR bone graft is placed in a bony defect in the presence of bleeding bone, an environment rich with osteogenic cells. It is intended to increase the opportunity for cell binding in the fusion site by making an abundance of P-15 available to osteogenic precursor cells, potentially resulting in enhanced cell attachment. Osteogenic cells contain α2β1 integrins that act as signaling receptors, allowing cells to attach to P-15. Cell binding between P-15 and α2β1 integrins is intended to initiate natural signaling of mechanical and chemical information within the cell and the extracellular matrix, contributing to the production of specific growth factors, cytokines, and bone morphogenetic proteins (BMPs) and ultimately, leading to new bone formation. i-FACTOR is designed to stimulate a healing response only in the presence of bone-forming cells. This novel mechanism of action is intended to enhance the body’s natural bone healing process.

P-15 Small Peptide- i-FACTOR technology is based on the biological activity resulting from a synthetically derived form of a 15-amino acid peptide found in type I human collagen. Type I human collagen is the primary organic component found in autograft bone. This 15-amino acid peptide is responsible for the attachment and proliferation of osteogenic cells. These cells attach to the synthetic P-15 part of i-FACTOR in a similar way they would attach to type I collagen.

- Anorganic Bone Mineral (ABM) provides the optimal surface for irreversible electrostatic binding of P-15. ABM is a naturally porous bone scaffold with a physiological rate of resorption, resulting in a substrate favorable to osteogenic cell growth and formation.

**Figure 3.** P-15: A synthetic fifteen amino acid polypeptide that mimics the cell-binding of Type 1 human collagen and is responsible for osteogenic cell attachment via α2β1 integrins which activates the body’s production of BMPs and growth factors. Image courtesy of Cerapedics, Inc.
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• Hydrogel Carrier- i-FACTOR Putty uses carboxymethylcellulose (CMC), an inert and biocompatible hydrogel, to aid in the handling and placement of the ABM/P-15 particles at the graft site.

i-FACTOR bone graft received the CE Mark, a regulatory conformity marking for products on the European market, in late 2008. It has been utilized clinically in over 10,000 spine, trauma, and orthopedic surgeries worldwide. Currently, i-FACTOR bone graft is commercially available in both a Putty and Flex (flexible strip) form in more than 20 countries outside the United States. i-FACTOR bone graft is currently being evaluated in the United States (FDA) as part of an Investigational Device Exemption (IDE) clinical study in the cervical spine and is not available for sale in the US.

A study of the early fusion rates and the rate of graft-related complications during an ALIF was performed comparing autograft, i-FACTOR (P-15) and Infuse (rhBMP). Over 24 months, data was collected from 95 consecutive ALIF implants in 75 patients (57 single level, 16 double level and 2 three level surgeries). Of these, 10 were Infuse (rh-BMP), 10 were autograft (iliac crest bone) and 75 were i-FACTOR (P-15). Outcomes were assessed based on standard cut coronal CT scans and graft-associated complications. Based upon 3 month data, all groups demonstrated excellent early fusion rates with bony bridging occurring faster in Infuse and i-FACTOR patients. At the 3 month point, 3 out of 10 autograft patients suffered from significant graft site pain; 1 out of 10 BMP patients had a clinical complication; none of the 45 iFACTOR patients had a clinical complication, though graft migration was noted. The study data will have to be analyzed after longer term follow-up to draw clinically relevant conclusions from the study; however, the three month data is very promising.

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Dr. Martin’s research interests include neuroimmunology, virology and immunology. He is engaged in collaborative research through SRF, with the Medical University of South Carolina Children’s Hospital, geared toward the development of neuroprotective and neuroregenerative compounds for the treatment of nerve pathology. Dr. Martin’s current research collaborations include research initiatives to apply stem cell therapy for tissue preservation, the development of regenerative therapies for intervertebral discs, and the development of novel methods of enhancing bone fusion.

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Dr. Copay studies the outcomes of surgical and non-surgical spine treatments. She published several articles on the outcomes of spine fusion. She has ongoing research projects concerning the effectiveness of new spine technologies and the long-term outcomes of surgical treatments.