BONE-GRAFT SUBSTITUTES: *FACTS, FICTIONS & APPLICATIONS*

AMERICAN ACADEMY OF ORTHOPAEDIC SURGEONS
70th Annual Meeting
February 5 - 9, 2003
New Orleans, Louisiana

COMMITTEE ON BIOLOGICAL IMPLANTS

Prepared by:

A. Seth Greenwald, D.Phil.(Oxon)
Scott D. Boden, M.D.
Victor M. Goldberg, M.D.
Yusuf Khan, M.S.
Cato T. Laurencin, M.D., Ph.D.
Randy N. Rosier, M.D.

Acknowledgements:

Exactech, Inc.
GenSci OrthoBiologics, Inc.
Interpore Cross International
Medtronic Sofamor Danek
Osteotech, Inc.
Regeneration Technolgies, Inc.
Stryker Biotech
Synthes USA
Wright Medical Technology, Inc.
Zimmer, Inc.

This material was first published, in slightly different form, in J Bone Joint Surg Am 83(Suppl. 2):98-103, 2001.

A REALITY CHECK

It is estimated that more than 500,000 bone-grafting procedures are performed annually in the United States, with approximately half of these procedures related to spine fusion. These numbers easily double on a global basis and indicate a shortage in the availability of musculoskeletal donor tissue traditionally used in these reconstructions. (Figure 1)

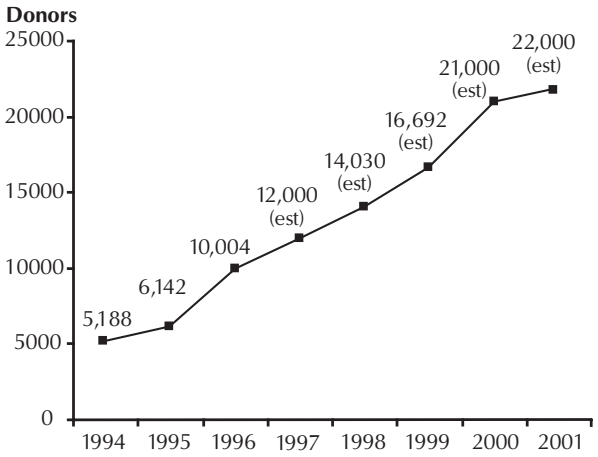


Figure 1: *U.S. trends in musculoskeletal tissue donors*
Source: United Network for Organ Sharing & MTF

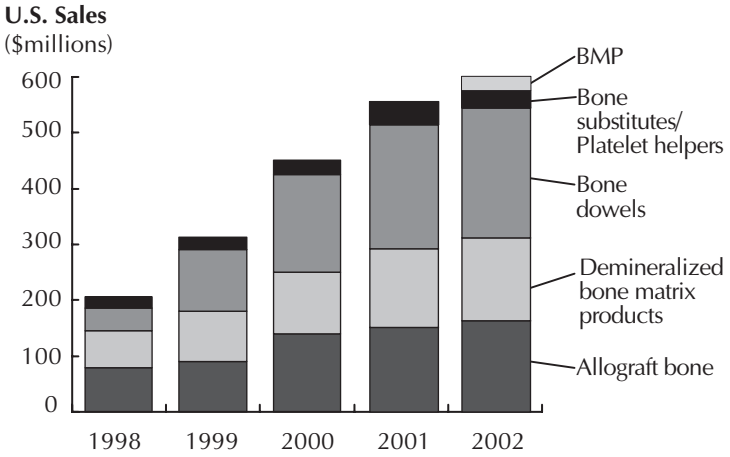


Figure 2: *U.S. sales of bone graft and bone substitutes*
Source: Orthopedic Network News, industry estimates

This reality has stimulated a proliferation of corporate interest in supplying what is seen as a growing market in bone-substitute materials. (Figure 2) These graft alternatives are subjected to varying degrees of regulatory scrutiny, and thus their true safety and effectiveness in patients may not be known prior to their use by orthopaedic surgeons. It is thus important to gain insight into this emerging class of bone-substitute alternatives.

THE PHYSIOLOGY OF BONE GRAFTING

The biology of bone grafts and their substitutes is appreciated from an understanding of the bone formation processes of *Osteogenesis*, *Osteoinduction* and *Osteoconduction*.

Graft Osteogenesis: The cellular elements within a donor graft, which survive transplantation and synthesize new bone at the recipient site.

Graft Osteoinduction: New bone realized through the active recruitment of host mesenchymal stem cells from the surrounding tissue, which differentiate into bone-forming osteoblasts. This process is facilitated by the presence of growth factors within the graft, principally bone morphogenetic proteins (BMPs).

Graft Osteoconduction: The facilitation of blood-vessel incursion and new-bone formation into a defined passive trellis structure.

All bone graft and bone-graft-substitute materials can be described through these processes.

BONE AUTOGRAFTS

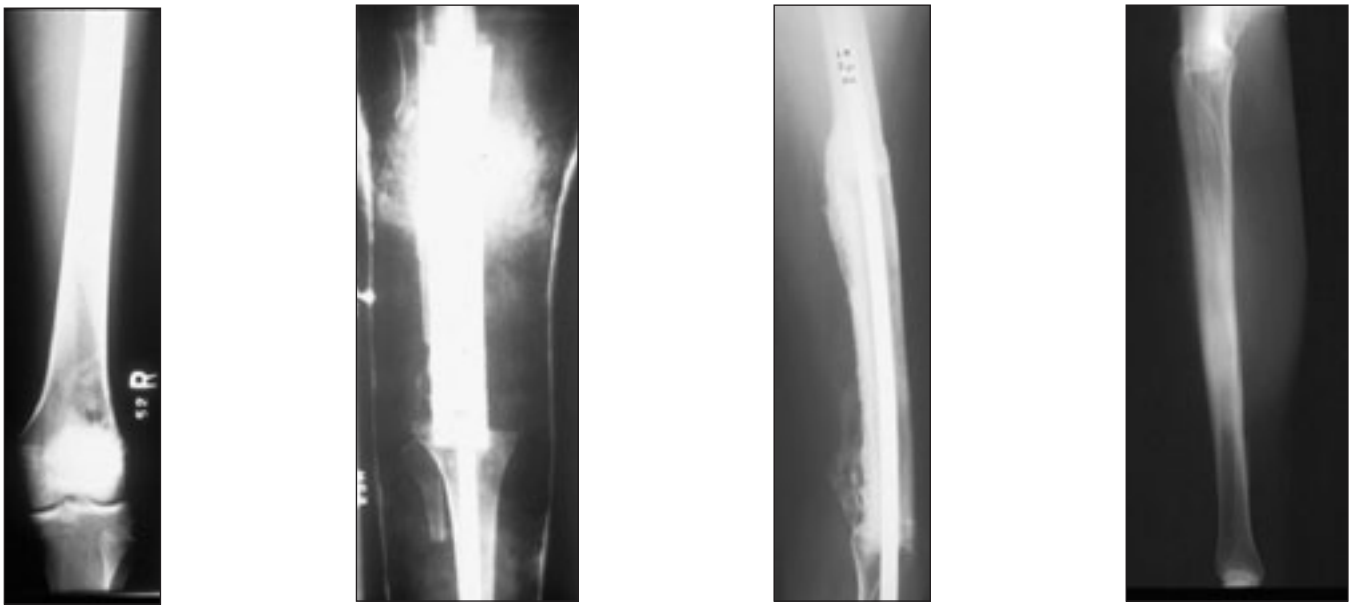
Fresh autogenous cancellous and, to a lesser degree, cortical bone are benchmark graft materials that allograft and bone substitutes attempt to match in *in vivo* performance. They incorporate all of the above properties, are harvested at both primary and secondary surgical sites, and have no associated risk of viral transmission. Furthermore, they offer structural support to implanted devices and, ultimately, become mechanically efficient structures as they are incorporated into surrounding bone through creeping substitution. The availability of autografts is, however, limited and harvest is often associated with donor-site morbidity.

BONE ALLOGRAFTS

The advantages of bone allograft harvested from cadaver sources include its ready availability in various shapes and sizes, avoidance of the need to sacrifice host structures and no donor-site morbidity. Bone allografts are distributed through regional tissue banks. Still, the grafts are not without controversy, particularly regarding their association with the transmission of infectious agents, a concern virtually eliminated through tissue-processing and sterilization. However, both freezing and irradiation modify the processes of graft incorporation and affect structural strength. A comparison of the properties of allograft and autograft bone is shown in Figure 3. Often, in complex surgical reconstructions, these materials are used in tandem with implants and fixation devices. (Figure 4)

Bone Graft	*Structural Strength*	*Osteo-Conduction*	*Osteo-Induction*	*Osteogenesis*
Autograft				
Cancellous	No	+++	+++	+++
Cortical	+++	++	++	++
Allograft				
Cancellous				
Frozen	No	++	+	No
Freeze-Dry	No	++	+	No
Cortical				
Frozen	+++	+	No	No
Freeze-Dry	+	+	No	No
Demineralized Allogeneic Cancellous Chips	No	+	++	No

Figure 3: *Comparative properties of bone grafts*



(a) *(b)* *(c)* *(d)*

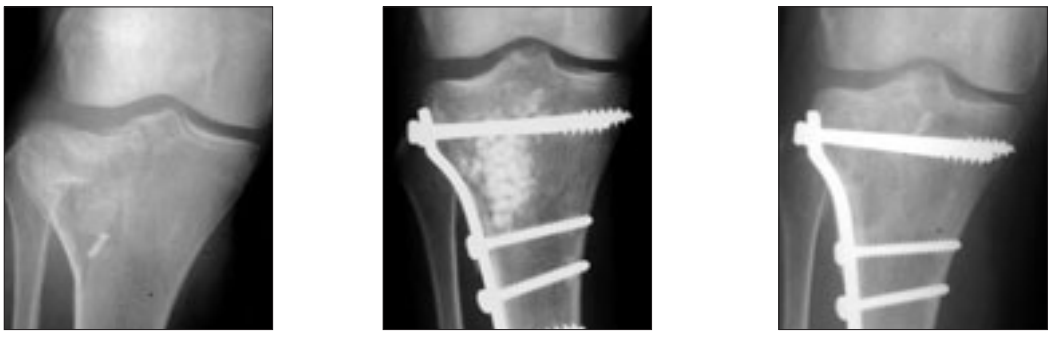
Figure 4: *(a) A 17-year old patient with osteosarcoma of the distal part of the femur with no extraosseous extension or metastatic disease. Following chemotherapy, (b) limb salvage with wide resection was performed. Femoral reconstruction with the use of an autogenous cortical fibular graft, iliac crest bone chips, morselized cancellous autograft and structural allograft combined with internal fixation. (c) Graft incorporation and remodeling are seen at 3 years. (d) Limb restoration is noted at 10 years following resection. (The intramedullary rod was removed at 5 years.)*

BONE GRAFT SUBSTITUTES

The ideal bone-graft substitute is biocompatible, bioresorbable, osteoconductive, osteoinductive, structurally similar to bone, easy to use and cost-effective. Within these parameters a growing number of bone alternatives are commercially available for orthopaedic applications, including reconstruction of cavitary bone deficiency and augmentation in situations of segmental bone loss and interbody spine fusion. They are variable in their composition and their claimed mechanisms of action. Figure 5 shows a sampling of bone-graft substitute materials. Those containing growth factors in their composition inclusive of rhBMP-2 and rhBMP-7 (OP-1) demonstrate osteoinduction in clinical application, while the remainder are predominantly osteoconductive in their claims. All offer minimal structural integrity. A series of case examples demonstrate their mechanisms of action through the healing process. (Figures 6, 7 and 8)

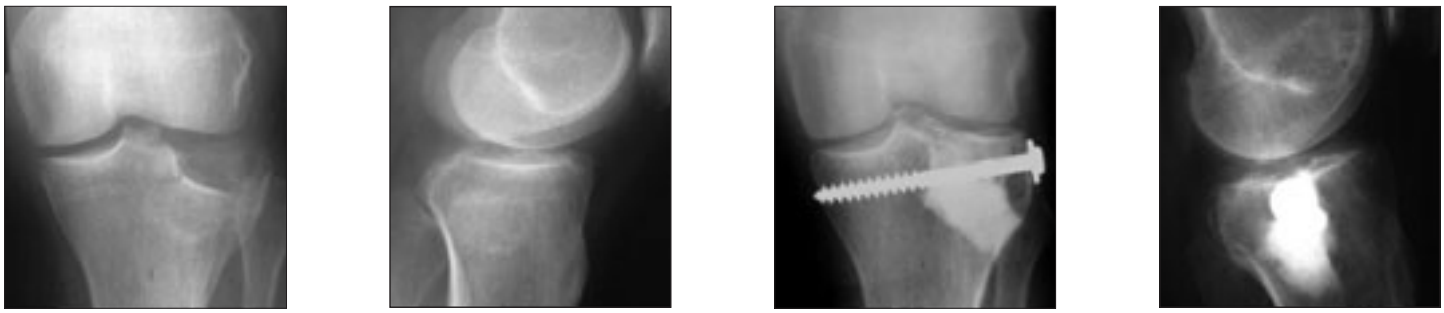
Company	Commercially available product	Composition	Commercially available forms	Claimed mechanisms of action	Burdens of proof	FDA status
Exactech, Inc.	Opteform®	DBM and cortical cancellous chips in gelatin carrier	Formable putty in circular disks or syringeable cylinders	• Osteoconduction • Bioresorbable • Limited osteoinduction	• Human studies • Case reports • Animal studies • Every lot tested *in vivo* for osteoinduction	• 510(k) clearance required • Regulatory discretion currently permits sale
	Optefil™	DBM suspended in gelatin carrier	Injectable bone paste or powdered form	• Osteoconduction • Bioresorbable • Limited osteoinduction	• Human studies • Case reports • Animal studies • Every lot tested *in vivo* for osteoinduction	• 510(k) clearance required • Regulatory discretion currently permits sale
GenSci OrthoBiologics	OrthoBlast™	Heat sensitive copolymer with cancellous bone chips and DBM	Injectable paste or putty	• Osteoconduction • Bioresorbable • Limited osteoinduction	• Case reports • Animal studies • Cell culture	• 510(k) clearance required • Regulatory discretion currently permits sale
	DynaGraft®	Heat sensitive copolymer with DBM	Injectable gel, matrix or putty	• Osteoconduction • Bioresorbable • Limited osteoinduction	• Human studies • Case reports • Animal studies • Cell culture	• 510(k) clearance required • Regulatory discretion currently permits sale
Interpore Cross International	ProOsteon® 500R	Coral HA composite	Granular or block	• Osteoconduction • Bioresorbable	• Human studies • Case reports • Animal studies	• 510(k) cleared
Medtronic Sofamor Danek	InFuse™	rhBMP-2 protein with absorbable collagen sponge	Freeze-dried powder and sponge in several sizes	• Bioresorbable sponge • Osteoinduction	• Human studies • Animal studies	• PMA approved for fusion with spinal cage
MTF/Synthes	DBX®	DBM in a sodium hyaluronate carrier	Injectable paste, putty and corticocancellous mix	• Osteoconduction • Bioresorbable • Limited osteoinduction	• Human studies • Case reports • Animal studies	• 510(k) clearance required • Regulatory discretion currently permits sale
Osteotech	Grafton®	DBM combined with Glycerol	Pellets, plugs, formable putty and injectable gel	• Osteoconduction • Bioresorbable • Limited osteoinduction	• Human studies • Case reports • Animal studies	• 510(k) clearance required • Regulatory discretion currently permits sale
Regeneration Technologies	OSTEOFIL®/ REGENAFIL®	DBM combined with non-toxic natural gelatin carrier	Injectable paste, injectable putty, strips and blocks with cortical cancellous chips	• Osteoconduction • Bioresorbable • Limited osteoinduction	• Human studies • Case reports • Animal studies • Every lot tested *in vivo* for osteoinduction	• 510(k) clearance required • Regulatory discretion currently permits sale
Stryker Biotech	OP-1 Implant	rhBMP-7 with type 1 bone collagen	Lyophilized powder reconstituted to form wet paste	• Resorbable collagen scaffold • Osteoinduction	• Human studies • Animal studies	• HDE approval for long bone nonunions
Synthes	Norian® SRS®	Calcium phosphate	Injectable paste	• Osteoconduction • Bioresorbable • Compressive strength: 50 MPa	• Human studies • Case reports • Animal studies	• 510(k) cleared
	Calceon® 6	Calcium sulfate	Pellets	• Osteoconduction • Bioresorbable	• Animal studies	• 510(k) cleared
Wright Medical Technology	OSTEOSET®	Surgical grade calcium sulfate	Various sized pellets	• Osteoconduction • Bioresorbable	• Human studies • Case reports • Animal studies	• 510(k) cleared
	AlloMatrix™	DBM with surgical grade calcium sulfate powder	Injectable or formable putty	• Osteoconduction • Bioresorbable • Limited osteoinduction	• Case reports • Animal studies • Cell culture	• 510(k) clearance required • Regulatory discretion currently permits sale
Zimmer	Collagraft™	Mixture of hydroxyapatite, tricalcium phosphate and bovine collagen	Strip configurations	• Osteoconduction • Bioresorbable • Limited osteoinduction when mixed with bone marrow	• Human studies • Case reports • Animal studies • Cell culture	• PMA approved

Figure 5: *Summary of typical bone-graft substitutes that are commercially available*



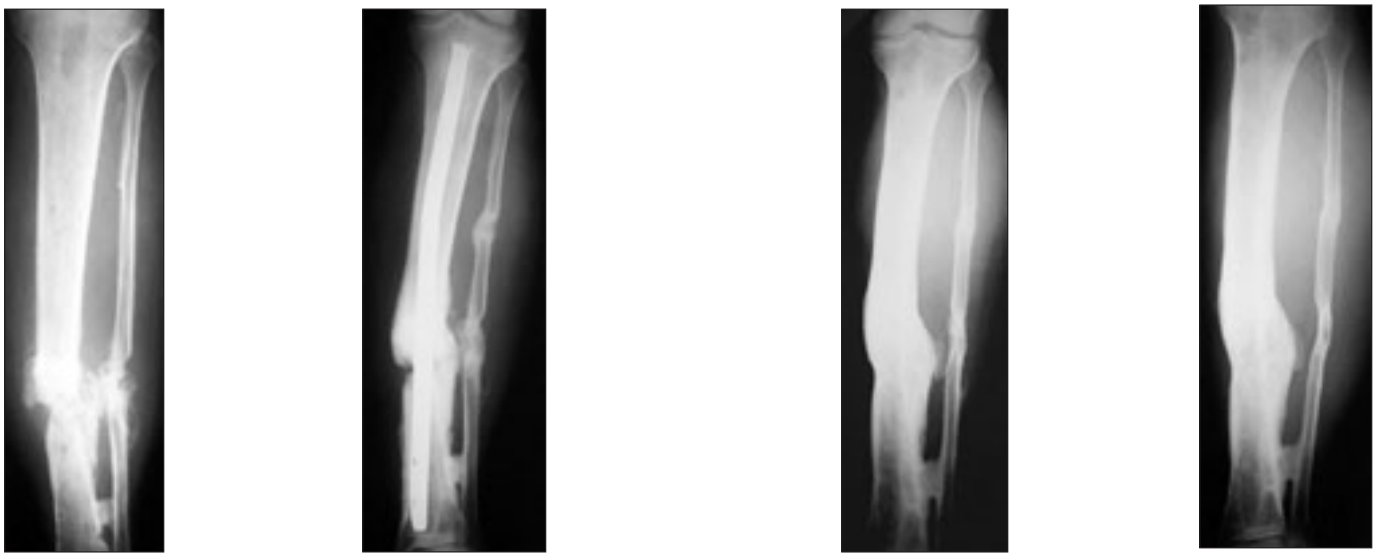
(a) *(b)* *(c)*

Figure 6: *(a) A 60-year old female with a comminuted depressed fracture of the lateral tibial plateau. (b) Three weeks after ORIF with filling of the resulting defect with OSTEOSET® (Wright Medical Technology, Inc., Arlington, TN) pellets. (c) At 7 months post-op, restoration of trabecular bone with complete dissolution of the graft material is noted.*



(a) (b)

Figure 7: *(a) AP and Lateral radiographs, 67-year old female with depressed fracture of the lateral tibial plateau. (b) AP and Lateral radiographs 12 months after ORIF with filling the defect with Norian® SRS® (Synthes USA, Paoli, PA). No loss of reduction of the plateau surface is noted, fracture completely healed.*



(a) (b) (c) (d)

Figure 8: *(a) A 23-year old male with an open, comminuted, grade II fracture of the left tibia. Prior treatments included autograft, skin flap and multiple irrigation and debridement to treat infection. Amputation was scheduled after failure of these treatments. (b) Six months following treatment with IM rod fixation and OP-1 Implant (Stryker Biotech, Hopkinton, MA). He was full weight bearing and pain free 9 months post-operative. (c) Five years post-operative. (d) Ten years post-operative.*

BURDEN OF PROOF

It is reasonable to assume that not all bone-substitute products will perform analogously. Thus, a quandary of choice confronts the orthopaedic surgeon. As a first principle, it is important to appreciate that different healing environments (e.g., a metaphyseal defect, a long-bone fracture, an interbody spine fusion, or a posterolateral spine fusion) have different levels of difficulty in forming new bone. For example, a metaphyseal defect will permit the successful use of many purely osteoconductive materials. In contrast, a posterolateral spine fusion will not succeed if purely osteoconductive materials are used as a stand-alone substitute. Thus, validation of any bone-graft substitute in one clinical site may not necessarily predict its performance in another location.

A second principle is to seek the highest burden of proof reported from preclinical studies to justify the use of an osteoinductive graft material or the choice of one brand over another. Whether it is more difficult to make bone in humans than it is in cell-culture or rodent models, with a progressive hierarchy of difficulty in more complex species, has not been clearly determined. Only human trials can determine the efficacy of bone-graft substitutes in humans as well as their site-specific effectiveness.

BURDEN OF PROOF (Cont'd.)

A third principle requiring burden of proof specifically pertains to products that are not subjected to high levels of regulatory scrutiny, such as demineralized bone matrix (DBM) or platelet gels containing "autologous growth factors". Such products are considered to involve minimal manipulation of cells or tissue and are thus regulated as tissue rather than as devices, unless they are configured with an additive and then require 510(k) clearance. As a result, there is no standardized level of proof of safety and effectiveness required before these products are marketed and are used in patients. While these products may satisfy the technical definition of *"minimal manipulation"*, there is a risk that they will not produce the expected results in humans when there has been little or no testing in relevant animal models.

FUTURE

Recent FDA approvals include the use of rhBMP-2 for assisted spinal fusion and rhBMP-7 (OP-1) as an autograft substitute for tibial non-unions. The FDA Orthopaedic Device Advisory Panel has also recommended extending the indication for rhBMP-2, in conjunction with a collagen sponge, for the treatment of long bone fractures. These clinical applications demonstrate impressive osteoinductive capacity and pave the way for broader clinical applications. Their methods of administration include direct placement in the surgical site, but results have been more promising when the growth factors have been administered in combination with substrates to facilitate timed-release delivery and/or provide a material scaffold for bone formation. FDA regulatory imperatives will continue to determine their availability. Their cost/benefit ratio will ultimately influence clinical use.

Further advances in tissue-engineering, "the integration of the biological, physical and engineering sciences", will create new carrier constructs that regenerate and restore tissue to its functional state. These constructs are likely to encompass additional families of growth factors, evolving biological scaffolds and incorporation of mesenchymal stem cells. Ultimately, the development of *ex vivo* bioreactors capable of bone manufacture with the appropriate biomechanical cues will provide tissue-engineered constructs for direct use in the skeletal system.

TAKE HOME MESSAGE

- The increasing number of bone-grafting procedures performed annually in the U.S. has created a shortage of cadaver allograft material and a need to increase musculoskeletal tissue donation.
- This has stimulated corporate interest in developing and supplying a rapidly expanding number of bone substitutes, the makeup of which includes natural, synthetic, human and animal-derived materials.
- Fresh autogenous cancellous and, to a lesser degree, cortical bone are the benchmark graft materials that, ideally both allograft and bone substitutes should match in *in vivo* performance. Their shortcomings include limited availability and donor-site morbidity.
- The advantages of allograft bone include availability in various sizes and shapes as well as avoidance of host-structure sacrifice and donor-site morbidity. Tissue-processing, however, modifies graft incorporation as well as structural strength. Transmission of infection, particularly the human immunodeficiency virus (HIV) has been virtually eliminated as a concern.
- The ideal bone-graft substitute is biocompatible, bioresorbable, osteoconductive, osteoinductive, structurally similar to bone, easy to use and cost-effective. Currently marketed products are variable in their composition and their claimed mechanisms of action. It is reasonable that not all bone-substitute products will perform the same.
- Recent FDA approvals for specific uses of recombinant human growth factors (rhBMP-2 and rhBMP-7 (OP-1)) are based on demonstrated osteoinductive capacity in human trials. Other applications will likely emerge.
- A quandary of choice confronts the orthopaedic surgeon. *Caveat emptor*! Selection should be based on reasoned *burdens of proof*. These include examination of the product claims and whether they are supported by preclinical and human studies in site-specific locations where they are to be utilized in surgery.