Key Points

- Biologic strategies to promote bone healing can generally be classified as cellular, growth factors, or scaffolds.
- Emerging BMP products will be targeted at the veterinary market.
- A variety of biologic scaffolds are in wide use as graft extenders or supplements.
- Cell-based strategies are still in early development, but once refined could greatly increase the options for augmenting fracture healing.

In 1668 Dutch surgeon Job van Meekeren recorded the first bone xenotransplant. He described the use of canine calvarium to repair a defect in the skull of a Russian noble, caused by a sword impact. The success of the procedure was a mixed blessing, as the church later excommunicated the nobleman for having been defiled by the canine xenograft. Over the past 350 years (primarily the last 20), there has been dramatic growth in the number of orthobiologics available in the marketplace. Their global revenue in 2012 is projected to exceed $3.5 billion USD, and new products are continually being developed. A number of these products are targeted at the veterinary market, and a majority of the products approved for human use have their experimental roots in animal models. In order to safely and appropriately utilize these therapeutics, it is important that veterinarians understand the science behind their development and mechanisms of action.

Fracture healing is a complex interaction of molecular, cellular, and mechanical events. The three essential components for new bone formation are 1) bone-producing cells, 2) a mechanical scaffold that supports bone growth, and 3) biologic signals for bone production. The primary bone-producing cell is the osteoblast. This cell is derived through a series of steps from its precursor, the mesenchymal stem cell. Osteoblasts attached to the scaffold produce extracellular matrix, which undergoes mineralization into bone. Mechanical, molecular, and nutritional signals influence the rate and distribution of new bone production by osteoblasts. These signals include such factors as gravity and the stress of weightbearing, growth factors, and tissue oxygen tension. Autogenous bone graft can aid bone formation by supplementing all three of the necessary factors for bone formation: viable osteoblasts (osteogenesis), intact scaffold (osteocduction), and functional growth factors (osteoinduction). The search for bone graft alternatives in human medicine is driven largely by the high morbidity associated with autograft donor sites. This is not generally reported in veterinary medicine. However, enhancement of bone healing and bone graft alternatives are useful in the case of large bone defects, arthrodesis, spinal fusion, nonunion, arthroplasty, or when patient factors negatively affect bone healing.

Orthobiology is the incorporation of biology and biochemistry in development of bone and soft tissue replacement materials for skeletal and tissue healing. In the case of fracture healing, an ideal orthobiologic would accelerate fracture union, strengthen native repairs, facilitate healing of critical-size defects/non-unions, and decrease patient morbidity. It would have the capability of osteogenesis, osteocduction, and osteoinduction. We can categorize orthobiologics by identifying the strategy by which they promote bone growth—cells, scaffolds, or growth factors.
Cells

The mesenchymal stem cell (MSC) is integral to the process of fracture healing, however its mechanisms remain somewhat unclear. It is not known whether MSC’s ultimately become functional cells within regenerated bone, whether they facilitate bone regeneration primarily through expression of growth factors, or if both processes occur. The traditional source of mesenchymal stem cells is bone marrow autograft. Relatively fewer MSC are present in bone marrow aspirate- probably less than 0.01% of nucleated cells. Higher concentrations of stem cells have been obtained for clinical therapeutics from three sources: culture-expanded bone marrow-derived MSC, bone marrow concentrate, and adipose-derived stromal vascular fraction cells. Cells obtained with these techniques have been used to treat tendon, ligament, and cartilage injuries in dogs and horses. No clinical studies have examined the use of stem cells to augment fracture repair in animals. Experimental studies have successfully healed critical-sized bone defects in animal models using culture-expanded autologous and allogeneic MSC, as well as concentrated MSC via intra-operative selective cell retention techniques. The FDA has approved a system for concentration of MSC from bone marrow aspirate using selective cell retention. However, its use for treatment of fractures/nonunions has not been published.

Growth Factors

As understanding of fracture healing has improved, several critical proteins that regulate this intricate process have been identified. The bone morphogenetic protein (BMP) family is the most widely studied of these molecules. The osteoinductive capacity of BMP’s was first identified in the 1960’s, when bone was produced in a heterotopic site by implantation of BMP in a mouse muscle pouch. Two of these proteins, BMP-2 and BMP-7 have been licensed for clinical use in people for ten years. BMP-2 and 7 are labeled for use in spinal fusions, open tibia fractures, non-union long bone fractures, and certain maxillofacial applications; they are used in many off-label applications as well (as many as 85% of cases may be off-label). Clinical use of rhBMP-2 in non-unions and segmental defects in dogs and cats has been described in several case series. Recently, a multi-center, controlled, randomized, blinded clinical trial of an rhBMP-2 formulation in dogs was completed. The study examined the effect of rhBMP-2 on healing of naturally-occurring diaphyseal fractures. The study group showed a significant reduction in time to radiographic fracture union as compared with the control group. This product has been granted marketing approval in Europe as of early 2012. Clinical use of BMP’s in veterinary patients will undoubtedly increase. However, concern over adverse events (primarily heterotopic bone formation and inflammation) in human patients reminds us to proceed with caution when expanding use in animals.

Other growth factors, such as transforming growth factor-B, insulin-like growth factor-1, vascular endothelial growth factor and fibroblast growth factor, are currently under investigation or in clinical use to augment bone healing. Many of these molecules are found in relatively high concentration in platelet-rich plasma (PRP), a product of autologous blood. PRP is currently used for clinical treatment of bone and soft tissue injuries, although evidence of its efficacy is somewhat mixed.

Scaffolds

While they lack osteogenic properties and have reduced or non-existant osteoinductive potential as compared to bone autograft, scaffold biomaterials play an important role in fracture healing. Demineralized bone matrix and collagen are used primarily as graft extenders or
delivery platforms for growth factors. In addition to being available as DBM, allogeneic bone can be purchased as cortico/cancellous chips, cortical grafts, and whole bone segments. Clinical reports of allograft use in dogs have demonstrated effective graft incorporation into native bone. The creation of veterinary bone banks over the past 15 years has made purchase and use of bone allograft a reality for any practice. Frozen and freeze-dried formulations are available for most products.

Today, autogenous bone graft remains the only single substance that provides osteogenesis, osteoinduction, and osteoconduction to a healing fracture. Autograft remains the gold standard for bone transplantation. With the increasing number of orthobiologic options for enhancing fracture healing, this may change. In all likelihood, the most promising bone substitute will arise as a composite graft material, combining MSC, growth factors, and scaffold.

References