The Evolution of Calcium Phosphates for Orthopedic Applications: Optimization of the Osteoconductive Scaffold

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Introduction: Over 500,000 bone grafting procedures are performed in the U.S. each year. Autograft, the patient's own bone tissue, usually taken from the Iliac Crest, is considered the gold standard for these procedures. There are, however, several disadvantages to using autogenous tissue, the first of which is an inherently limited quantity. Harvesting the bone also requires increased operating time and creates the potential for various complications which can lead to longer recovery times, prolonged disability and even chronic pain [Turner J.A. JAMA 1992 (268)(7):907-911]. The high cost and additional risks associated with autograft have led medical researchers to search for an alternative.

Bone Generation and Maintenance: There are three essential elements which are necessary to facilitate the generation of new bone tissue: an optimized scaffold for osteoconduction, signals or growth factors for osteoinduction and progenitor cells for osteogenesis. Historically, too much emphasis has been placed on signal and not enough attention paid to the physical properties of the scaffold. An effective bone graft substitute needs to provide for all three of these requirements.

The History of Calcium Salts: Plaster of Paris, calcium sulfate dehydrate, was the first bone substitute to be reported in scientific literature in 1892. No real progress was made, however, until the apatitic nature of the inorganic component of bone was established in 1951 using electron microscopy. Triple calcium phosphate, now known as tricalcium phosphate (TCP), was shown to stimulate bony union in rabbit radii in 1920 [Albee and Morrison Ann. Surg. 71:32-39 1920]. 50 years later the United States Army Institute of Dental Research had similar success when they initiated a program to study the effect of porous tricalcium phosphate ceramic to repair avulsive trauma wounds [Bhaskar, Cutright, et al Oral Surg 31:282-340 1971].

Later, in an effort to increase the initial strength of calcium phosphates injectable calcium phosphate cements (CPC) were developed. The initial compressive strength of the hardened cements is similar to that of cancellous bone (55 MPa) but CPC is not highly porous, which leads to inefficient resorption.

The Evolution of the Vitoss® Scaffold: In the development of Vitoss® (Orthovita, Inc. Malvern, PA) priorities shifted to encouraging the rapid replacement of the scaffold with new bone. A 1995 study comparing β-TCPs of 3 different porosities revealed the importance of structure. In a cervical goat model β-TCP scaffolds with higher porosity led to a substantially higher fusion rate [Toth, J.M. Spine 20: 2203-2210]. Most commercial scaffolds were only around 35-50% porous, with pores ranging from 100-300µm.

Considering that Human cancellous bone is more than 80% porous. Vitoss scaffold was engineered to have an open, interconnected porosity of 90% with pore sizes ranging from 1µm to 1,000µm.

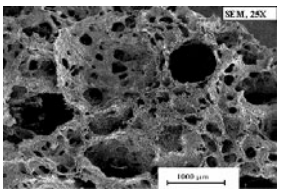

Figure 1: SEM of the 90% porous Vitoss scaffold with pore sizes ranging from 1-1,000µm

Methods: Vitoss was investigated in in-vitro cell culture as well as preclinical testing including athymic rat, rabbit, canine and primate models. The results of selected studies are presented. Vitoss has also been used for a broad range of clinical applications in the spine, pelvis and extremities since receiving FDA clearance in 2000.

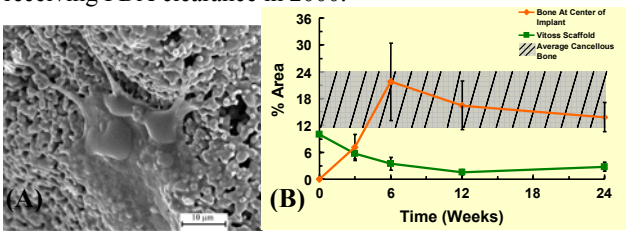

Figure 2: .(A) SEM of a rat osteoblast spreading within Vitoss scaffold in culture.(B) Quantitative histomorphometry results from a canine study(drill defect in proximal humeral metaphysis). At 12 weeks Vitoss is 86% resorbed and bone has returned to the center of the defect.

Discussion: Vitoss is an ideal scaffold because of the size distribution of its interconnected pores. This broad size range supports all of the biological processes associated with healing: Haversian bone ingrowth, revascularization, cell penetration and seeding and fluid, nutrient and oxygen flow. The porosity and nano-particulate nature of the β-TCP crystal phase in Vitoss allow it to resorb at a clinically relevant rate, matching the rate of new bone ingrowth (see figure 2B).

The chemistry and structure of the Vitoss scaffold are optimized for osteoconduction. The capillarity provided by the micropores gives Vitoss the ability to quickly absorb bone marrow and blood for osteoinduction and the macropores and nanoparticle technology promote osteoblast seeding and osteogenesis.

Conclusion: Vitoss®, an ultra porous, ultra low density, synthetic scaffold of beta tri-calcium phosphate (β-TCP) is the result of over 100 years of product evolution. Past research in the field has overlooked the importance of the physical structure of the scaffold. Vitoss, the first β-TCP cleared by the Food and Drug Administration (FDA), is composed of a material similar to those studied 100 years ago but the structure has been fine tuned to provide the ideal foundation for the regeneration of bone.