## NanoBone® as an Alternative to Infuse®, Cellular Allografts, and Other Graft Types

NanoBone represents the intersection between nanotechnology and biological healing response. Physical processes are at work on the cellular level. Knowledge of physics (on the nano-scale) is essential for a good understanding of these cellular processes. To be able to understand the basis of health and disease, knowledge of both physics and molecular biology is essential.

The inventor of NanoBone, Prof. Dr. Thomas Gerber has spent a career studying nanotechnology as it relates to biology and evaluating bone graft substitute options. Professor Gerber is the former chair of Nanostructured Materials at the University of Rostock Physics Institute in Germany.

*Current options for bone grafting include:*

1. Autograft (the traditional "gold standard") that provides osteoconductive, osteoinductive, and osteogenic properties
2. Human-derived allograft tissue
3. Synthetic materials that are designed to be added to autograft to increase the volume of graft material
4. Genetically engineered proteins, e.g., recombinant human bone morphogenetic protein (Infuse® by Medtronic)
5. Cell-containing allograft products (e.g., Trinity Evolution® by Orthofix, Osteocel® by NuVasive, Bio$^4$ ™ by Stryker)

Each of these options can be effective but come with well-documented side effects and have premium prices. Cell-containing allograft product options are derived from human bone, so their activity can be variable and supporting clinical data is sparse.

Traditional synthetic bone grafts are osteoconductive, that is, they behave as scaffolds in which the patient's bone grows around and through microscopic pores in the material. These are primarily designed to be used in combination with surgically harvested autograft to increase the total volume of graft available. Synthetic bone graft substitutes do offer the safety of not transmitting infection or disease.

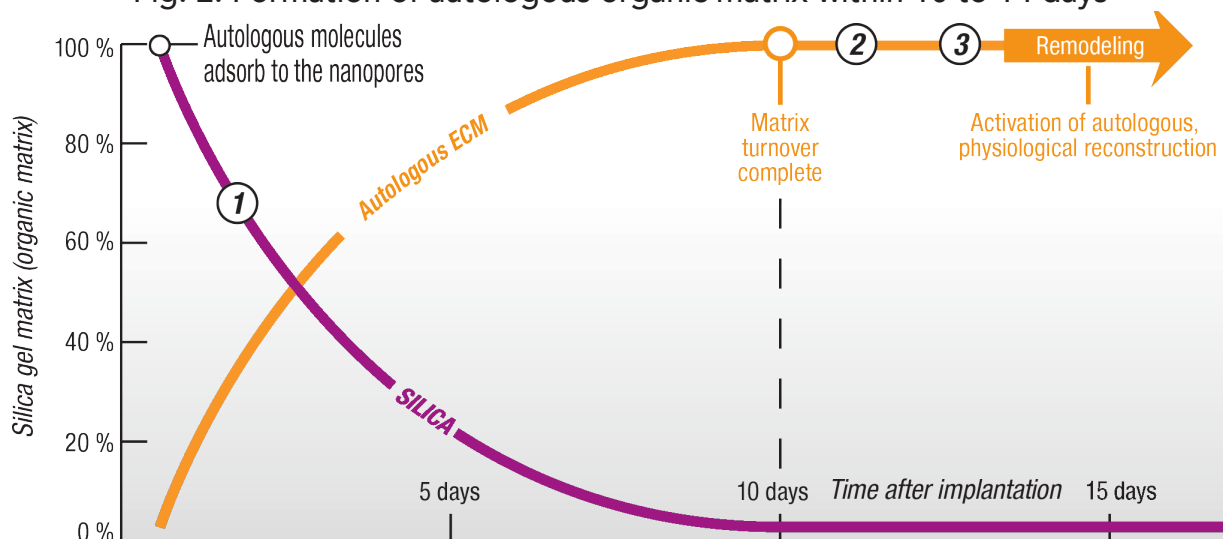
NanoBone Bone Graft is a recent nanotechnology option designed as a standalone grafting material able to harness the body's own capacity to heal bone. Based on years of scientific research and over 100,000 clinical cases, the FDA has cleared NanoBone for use as a standalone graft due to its ability to create a bone forming environment within 10-14 days that replicates the architecture and chemistry found in natural bone.

Fig. 1. NanoBone consist of nanocrystals of hydroxyapatite, the same mineral as bone, and an amorphous silica matrix.

NanoBone consists of nanocrystals of hydroxyapatite (HA), the same size, chemistry, morphology as in human bone, dispersed in an amorphous silica gel matrix (ASG). These nanocrystals are not bound to one another and autologous proteins adsorb rapidly to the surface.

The matrix that holds the HA nanocrystals in place is highly nanoporous with an extremely large internal surface area (forty-times the surface area of other calcium phosphate putties) for binding autologous growth factors, including BMP-2, that are critical for new bone formation. ASG is also very hydrophilic and releases silicon dioxide, which triggers angiogenesis, enhancing the differentiation of bone forming cells, and stimulating new bone formation.

Fig. 2. Formation of autologous organic matrix within 10 to 14 days




Over a period of 10-14 days, the silica gel matrix is replaced by an autologous organic matrix that is osteogenic. This 'rapid osteogenesis' is the foundation of NanoBone technology. Once this organic matrix is in place, the normal process of cell-mediated bone formation and resorption proceeds. The hydroxyapatite nanocrystals are immediately available to these cells for incorporation into new bone. In clinical cases, healing can occur in as little as eight (8) weeks[1]. NanoBone is fully integrated into newly formed bone and is actively remodeling by three (3) months.[2]

NanoBone SBX Putty uses a Poloxamer carrier that has been modified to improve handling, specifically to be more adhesive to hold the bone graft in place during and after surgery. NanoBone QD contains NanoBone SBX Putty in a minimally-invasive applicator and is designed for controlled and precise placement of NanoBone. NanoBone is radiolucent and appears similar to the patient's own bone on X-ray. This facilitates viewing the operative site and observing new bone formation postoperatively. In various clinical cases, NanoBone is completely converted to autologous bone.

NanoBone is commercially available and has been used successfully for more than ten years in the US and Europe in over 100,000 clinical cases (see below for example). These cases show rapid, consistent clinical and radiographic healing with virtually no complications.

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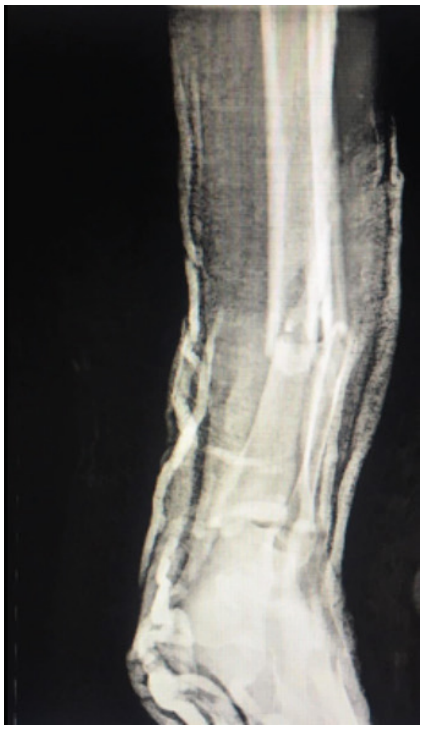
1 Ortega, G. Using Nanotechnology as stand-alone bone grafting in open fracture bone defects and nonunions, Orthopaedic Trauma Association Annual Meeting, #1043, 2020.

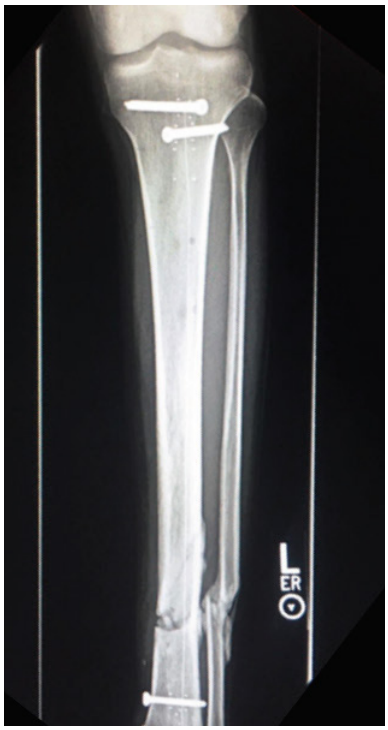
2 Dau, M., et. al., In vivo comparison of a granular and putty form of a sintered and a non-sintered silica-enhanced hydroxyapatite bone substitute material, J. Biomat Appl 34(6): 864-874, 2020.

In a recent prospective study of trauma cases, bone healing with NanoBone used as a standalone BGS (without autograft, bone marrow aspirate, or blood) was comparable to the gold standard autograft with a lower overall complication rate.[3] This is the same standard that Infuse® Bone Graft used to secure FDA clearance and is in contrast to cellular allografts, which are not regulated by the FDA and are not required to demonstrate equivalency to autograft.

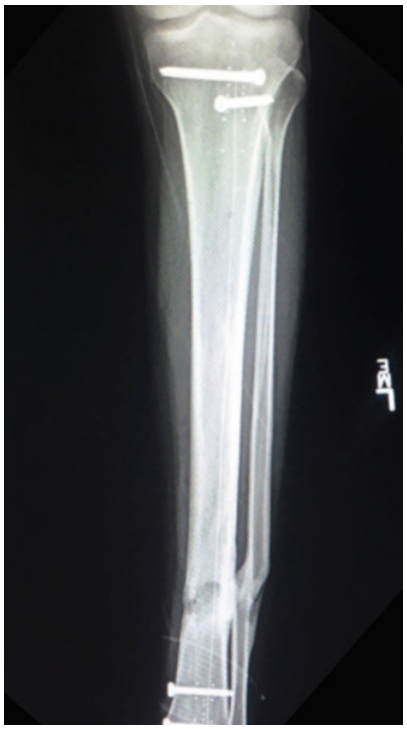
Fig 3. Pre- and postoperative radiograph images in open tibial fracture with bony defect in non-union treated with NanoBone[4]



Initial Injury



Prior to application of NanoBone



Healed tibia 3 months after application of NanoBone

3 Kienast, B., et. al., Nanostructured synthetic bone replacement material for the treatment of bone defects, Trauma und Berufskrankheit, 18(4):308-318, 2016.

4 Ortega, G., Application of nanocrystalline hydroxyapatite (NanoBone® Bone Graft) in an open tibial fracture with bony defect.



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