rhPDGF-BB/β-TCP

TECHNOLOGY OVERVIEW

AUGMENT®
Bone Graft

THE **FIRST** AND **ONLY**
PROVEN ALTERNATIVE TO
AUTOGRAFT IN ANKLE AND
HINDFOOT ARTHRODESIS

WRIGHT
FOCUSED EXCELLENCE

AUGMENT®
Bone Graft

THE **FIRST** AND **ONLY** PROVEN ALTERNATIVE TO AUTOGRAFT IN ANKLE AND HINDFOOT ARTHRODESIS

A Better Way.

Proven

Level 1 evidence of safety and effectiveness as a replacement to autograft in the largest F&A clinical trial ever conducted

Unique

The only biologic product specifically engineered, proven, and approved for ankle and hindfoot fusions

Labeled

Class III combination product specifically proven in, and labeled for, ankle and hindfoot arthrodesis via a rigorous PMA regulatory pathway

Safe

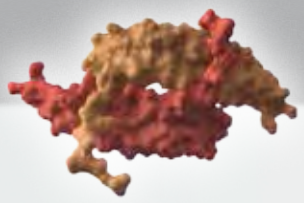
Proven safe through multiple clinical trials and successful commercial use since 2009 in Canada and 2011 in Australia and New Zealand, while eliminating the proven risks, morbidities, and costs associated with autograft harvest

Ankle arthrodesis patient treated with AUGMENT® Bone Graft

AUGMENT® Bone Graft should be placed in direct contact with well-vascularized bone.

rhPDGF-BB Solution

Recombinant Human Platelet Derived Growth Factor-BB (3ml)



Bioengineered version of a key human growth factor

Highly purified with consistent biological activity

Triggers the wound healing/bone repair cascade via three key actions:

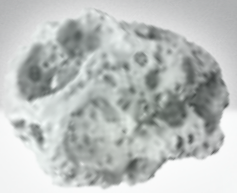
CHEMOTAXIS
Attracts bone forming cells

MITOGENESIS
Stimulates bone forming cells to multiply

ANGIOGENESIS
Promotes the formation of new blood vessels in the bone healing environment

β-TCP Granules

Beta Tricalcium Phosphate (3cc)



Osteomimetic scaffold with long history of orthopedic use

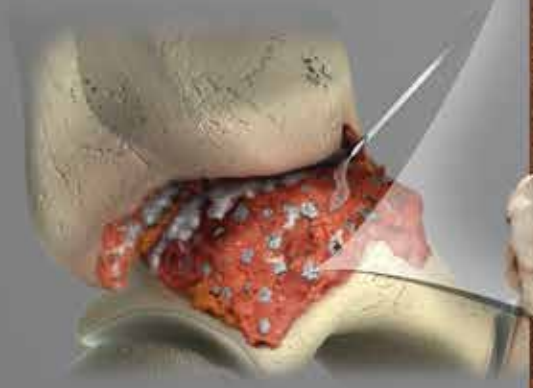
Delivers rhPDGF-BB to healing environment

Provides an osteoconductive matrix

Preserves space for bone formation

Resorbs and replaced with bone as site heals

AUGMENT® Bone Graft Works in a Unique Way to Stimulate Three Key Processes of Early Bone Healing.



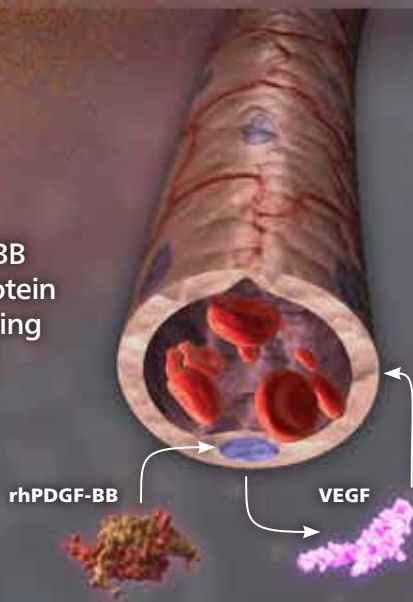
Following preparation of the bone surfaces, the surgeon implants AUGMENT® Bone Graft into the fusion site. The rhPDGF-BB releases from the β-TCP, forming a concentration gradient as it migrates throughout the local environment.

1. Chemotaxis

Mesenchymal Stem Cells (MSCs) are attracted to the fusion site by the increased concentration of rhPDGF-BB in the local environment. MSCs move toward the rhPDGF-BB concentration from bleeding bone, muscle, and the periosteum to infiltrate the implant.

3. Angiogenesis

In parallel with the effects of rhPDGF-BB in the bone formation cascade, the protein also promotes angiogenesis by increasing vascular endothelial cell, pericyte, and smooth muscle responses.



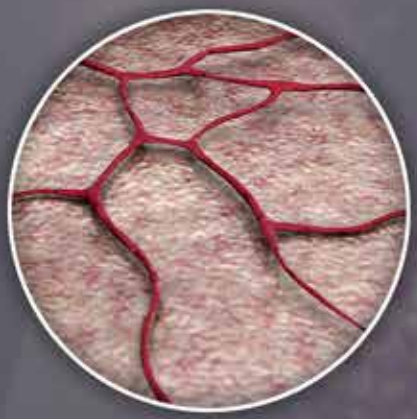
Completion of the Bone Formation Process

Once the colony of MSCs has divided repeatedly, native bone morphogenetic proteins (BMPs) secreted from the local bony environment induce the MSCs to mature into osteoblasts. These mature, bone forming cells will then lay down new bone to create a continuous scaffold, fusing the bone surfaces.

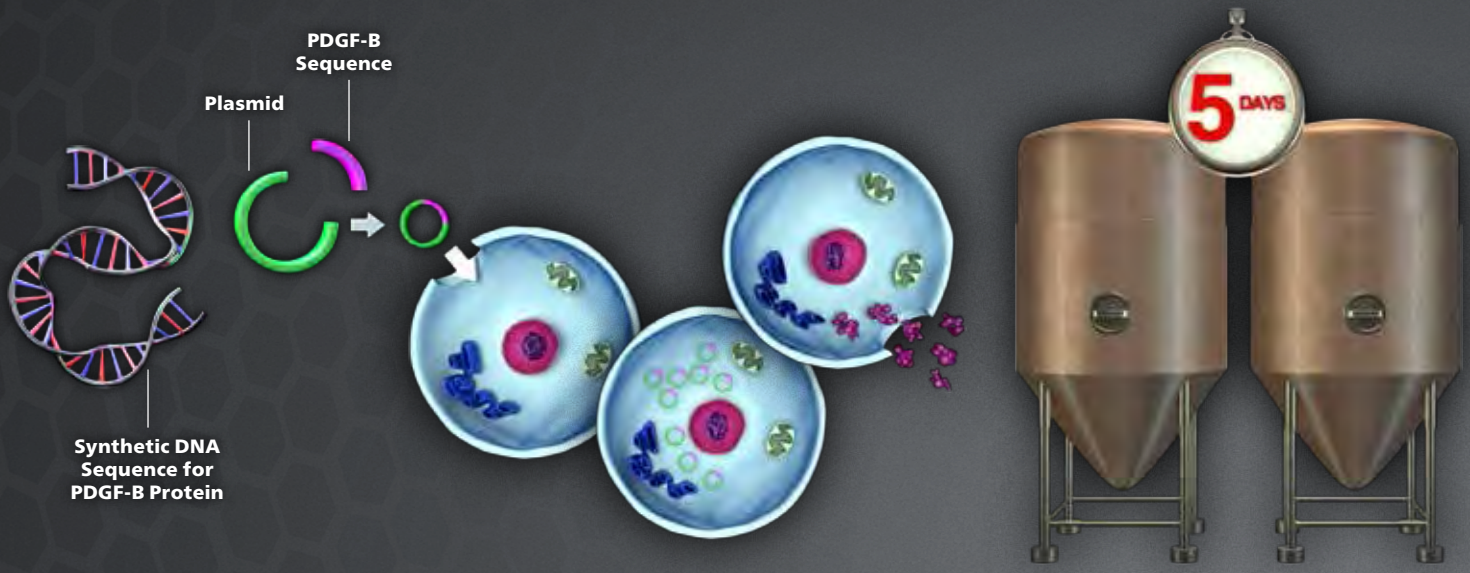
2. Mitogenesis

MSCs are stimulated to divide and proliferate in the presence of the higher concentration of rhPDGF-BB within the graft site.

These newly formed blood vessels support the formation of bone by supplying oxygen & nutrients, carrying additional cells and signals to the healing environment, and eliminating local waste.



Manufacturing a Recombinant Therapeutic



Synthetic DNA Construct

Using gene splicing techniques, the DNA sequence corresponding to the human polypeptide PDGF-B is obtained and inserted into a larger DNA construct called a plasmid.

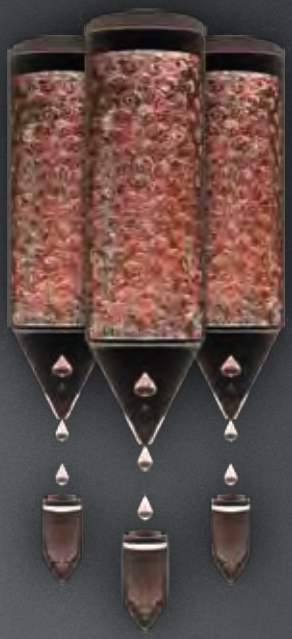
Yeast Cell Transformation

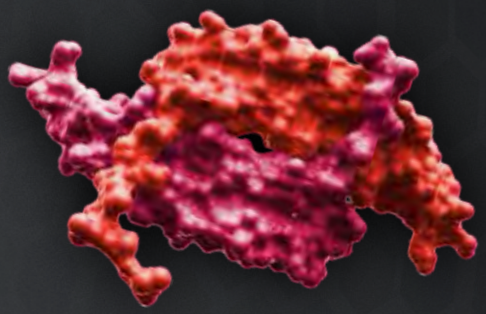
Plasmids are inserted into a yeast cell through a process called transformation. As these cells are cultured, the PDGF-B polypeptide is expressed and dimerizes, forming biologically active PDGF-BB, which is then secreted.

rhPDGF-BB Production

To produce sufficient quantities of the protein, the transformed yeast cells are cultured in large-scale fermenters, which provide an environmentally controlled environment.

The yeast cells undergo rapid cellular division, arriving at high cell density by 5 days. The cells produce additional copies of the synthetic DNA sequence, which are then used to code for the rhPDGF-BB protein. The rhPDGF-BB protein is secreted by the yeast cells into the medium.





rhPDGF-BB

Purification and Cross-Linking

The rhPDGF-BB is then purified from the culture medium by running chromatography columns, separating the molecule from the other medium components.

The resultant protein has the same chemical structure, three-dimensional conformation, cross-linking, and receptor affinity as the native human protein.

Sterility Assurance and Formulation

The purified protein is combined with sodium acetate solution to provide a consistent pH and concentration of 0.3mg/mL. The resultant solution is then double micro-filtered to ensure purity and sterility.*

*Well-established and validated sterilization method that avoids any use of radiation or other protein damaging processes.

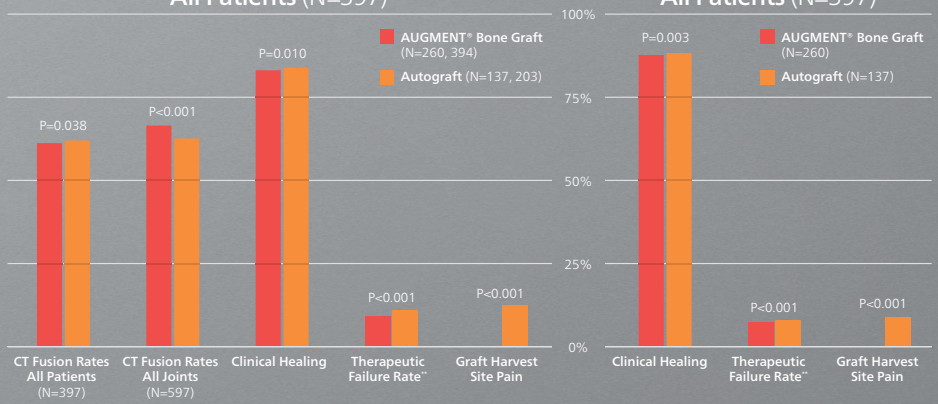
Proven as a safe and effective alternative to autograft, in the largest foot & ankle clinical trial in history.

75% of patients had risk factors for poor healing, including smoking history, prior surgery, diabetes, and obesity.

AUGMENT® Bone Graft was also shown to eliminate the cost and morbidity of harvesting autograft, while providing equivalent improvements in clinical outcomes.

Both treatment groups were compared at 24 weeks and 52 weeks for multiple criteria, as shown here.

Pivotal Trial Results†‡



† DiGiovanni C, *et al.* Recombinant human platelet-derived growth factor-BB and beta-tricalcium phosphate (rhPDGF-BB/β-TCP): An alternative to autogenous bone graft. *J Bone Joint Surg Am.* 2013; 95: 1184-92.

‡ FDA did not base its approval of AUGMENT® Bone Graft on radiologic findings from the pivotal study, but instead relied on clinical outcomes.

* All P values are for non-inferiority, except for graft harvest site pain, which is for superiority.

** Therapeutic failure rate was defined as delayed union or nonunion requiring surgery or further therapeutic intervention.

Brief Summary of Important Product Information

Indications for Use

AUGMENT® Bone Graft is indicated for use as an alternative to autograft in arthrodesis (i.e., surgical fusion procedures) of the ankle (tibiotalar joint) and/or hindfoot (including subtalar, talonavicular, and calcaneocuboid joints, alone or in combination), due to osteoarthritis, post-traumatic arthritis, rheumatoid arthritis, psoriatic arthritis, avascular necrosis, joint instability, joint deformity, congenital defect, or joint arthropathy in patients with preoperative or intraoperative evidence indicating the need for supplemental graft material.

Contraindications

AUGMENT® Bone Graft should not:

- be used in patients who have a known hypersensitivity to any of the components of the product or are allergic to yeast-derived products.
- be used in patients with active cancer.
- be used in patients who are skeletally immature (<18 years of age or no radiographic evidence of closure of epiphyses).
- be used in pregnant women. The potential effects of rhPDGF-BB on the human fetus have not been evaluated.
- be implanted in patients with an active infection at the operative site.
- be used in situations where soft tissue coverage is not achievable.
- be used in patients with metabolic disorders known to adversely affect the skeleton (e.g. renal osteodystrophy or hypercalcemia), other than primary osteoporosis or diabetes.
- be used as a substitute for structural graft.

Warnings

As with all therapeutic recombinant proteins, there is a potential for immune responses to be generated to the rhPDGF-BB component of AUGMENT® Bone Graft. The immune response to rhPDGF-BB was evaluated in two pilot and one pivotal studies for ankle and hindfoot arthrodesis procedures. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to AUGMENT® Bone Graft with the incidence of antibodies to other products may be misleading.

Women of childbearing potential should avoid becoming pregnant for one year following treatment with AUGMENT® Bone Graft. The implantation of rhPDGF-BB in women and the influence of their development of anti-PDGF-BB antibodies, with or without neutralizing activity, on human fetal development are not known.

The safety and effectiveness of AUGMENT® Bone Graft in nursing mothers has not been established. It is not known if rhPDGF-BB is excreted in human milk.

The safety and effectiveness of AUGMENT® Bone Graft has not been established in anatomical locations other than the ankle or hindfoot, or when combined with autologous bone or other bone grafting materials.

The safety and effectiveness of repeat applications of AUGMENT® Bone Graft have not been established.

The safety and effectiveness of AUGMENT® Bone Graft in pediatric patients below the age of 18 years have not been established.

AUGMENT® Bone Graft does not have any biomechanical strength and must be used in conjunction with standard orthopedic hardware to achieve rigid fixation.

The β-TCP component is radiopaque, which must be considered when evaluating radiographs for the assessment of bridging bone. The radiopacity may also mask underlying pathological conditions. Over time, the β-TCP is intended to be resorbed at the fusion site and replaced by new bone. Under such circumstances, it would typically be indistinguishable from surrounding bone.

Part No.	Description	Volume
K20003010	AUGMENT® Bone Graft	3cc

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