

AlphaGRAFT[®]

CELLULAR BONE MATRIX



FACTORS • FUNCTION • FORMATION

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Improving Spinal Fusion

The AlphaGRAFT[®] Cellular Bone Matrix was designed to maintain cell viability and promote safe, reliable bone grafting. Optimize the fusion process with a graft powered by three key features:

FACTORS

HIGH GROWTH FACTOR CONTENT

Proprietary processing retains the native growth factors from bone lining cells, enriching the cortical bone fibers.

High amounts of osteoinductive, angiogenic, and proliferative growth factors are readily available in situ.¹

Enriched AlphaGRAFT CBM Fibers demonstrates a 6.3-fold increase in osteoinductive (OI) potential over demineralized bone fibers (not enriched) from the same donor.²

FUNCTION

VIABLE CELLS

Osmotic shock technology lyses hematopoietic cells and mineralized cancellous bone preserves osteoprogenitor cells that are resistant to lysing.

No decrease in cell viability was shown after thawing for grafts stored at -80C.³

Graft remains viable for 5 hours of working time after thaw prior to implantation.⁴

CRYOPROTECTANT AND SYRINGE PACKAGING

Packaging allows for rapid heat transfer homogeneously for all sizes of AlphaGRAFT CBM.

Rapid thawing (< 8 minutes)⁵ prevents ice crystals from forming intracellularly, thereby maintaining cell viability.

There is no need to rinse and decant the tissue prior to implantation.

FORMATION

NOVEL PROCESSING

High quality graft maintains a balance between cells and growth factors.

Patented process preserves growth factors found in donor tissue.

Validated processing leads to a graft with cells, signals, and scaffold.

FIBER-BASED

Cortical bone fibers provide exceptional handling properties.

The graft expands in situ and improves fill.

Cortical bone fibers provide a 3D interconnected network to promote cell proliferation and fusion.

SAFETY

Processing successfully removes immunogenic components from AlphaGRAFT CBM mitigating concerns of an immune response.^{6,7}

AlphaGRAFT CBM during processing is treated with gentamicin, vancomycin, and amphotericin b.

Each lot is tested for sterility using USP <71> standards.

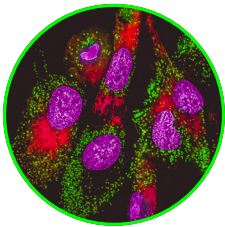


Complete Composition

AlphaGRAFT® CBM is composed of growth factor-enriched cortical bone fibers and natively occurring living cancellous bone particles containing various endogenous osteogenic cells, including mesenchymal stem cells. Proprietary processing creates a **balanced** cellular bone matrix that:

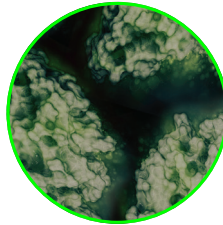
- Results in a viable cellular graft that thaws rapidly due to advanced cryopreservation techniques⁵ and allows for 5 hours of working time post-thaw;⁴
- Has high growth factor content¹ on the extracellular matrix of the cortical bone, making those factors available *in situ* to assist in tissue regeneration.

AlphaGRAFT CBM is an advanced cellular bone matrix that possesses all three of the essential components of bone remodeling:



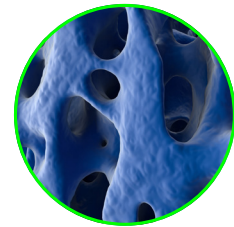
OSTEOGENESIS

Mineralized cancellous bone contains attached endogenous progenitor and bone cells. Cells are viable and active as confirmed by MTS assay.⁸



OSTEOINDUCTION

Validated processing of cortical bone leads to fibers with osteoinductive potential. Osteoinductive, angiogenic, and proliferative growth factor quantities are elevated over donor-matched controls due to novel proprietary processing techniques.¹



OSTEOCONDUCTION

AlphaGraft CBM contains mineralized cancellous bone combined with cortical bone fibers providing an environment that promotes cell attachment, proliferation, and tissue growth.

COMPONENT	CONTENT (VOL. %)
Cortical bone fibers	30 - 50%
Mineralized cancellous bone	50 - 70%
Average osteogenic cells	175,000 viable cells per cc ⁸
DMSO-free cryoprotectant*	

*Note: the cryoprotectant does not add volume to AlphaGRAFT CBM. The cryoprotectant resides in the interstitial spaces and/or is absorbed by the cortical bone fibers and/or mineralized cancellous bone.





Balanced Approach

While other cellular bone matrices may focus solely on growth or thaw time, AlphaGRAFT® CBM aims to address all the prerequisites for optimal bone healing. This includes osteoconductive matrices, osteoinductive factors, and osteogenic cells. This unique graft maintains a critical balance between cells and growth factors in the graft material.

- Proprietary processing involves osmotically lysing bone marrow cells in the cancellous bone to enrich it with cells resistant to lysing.
- Growth factors are extracted from the lysed cells and then delivered along with the cortical bone fibers.

VIABLE CELLS

Mineralized Cancellous
Mesenchymal Stem Cells

GROWTH FACTORS

Cortical Bone Fibers
Intracellular and Extracellular
Growth Factors

Cell Viability

ACCURATE CELL MEASUREMENT

RAPID THAWING

CRYOPROTECTANT

THE ALPHAGRAFT DIFFERENCE:

Cell viability is measured using MTS proliferation assay, which is performed on end product. The MTS reagent can penetrate tissue to reach cells that may not be liberated via enzymatic digestion.

Cell viability is 94.84% of original value after 3 years.⁹

All sized units thaw in less than 8 minutes at room temperature.⁵

Open-bore syringe packaging and DMSO-free cryoprotectant allow for efficient heat transfer homogeneously for all sizes of AlphaGRAFT CBM.

AlphaGRAFT CBM is DMSO-free and is cryopreserved with a minimal amount of cryopreservative that does not add volume to the graft.

This eliminates the need to rinse and decant the tissue prior to implantation.

OTHER CBMS:

Traditionally CBMs use excessive enzymatic digestion and manual measurement techniques that require optimization for accurate testing.

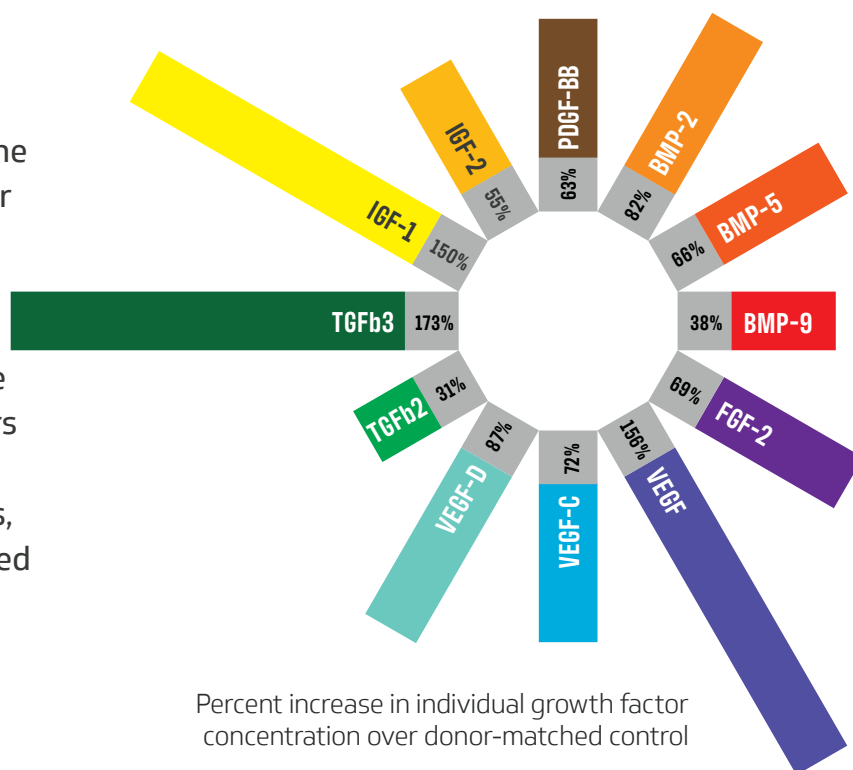
Other CBMs primarily use jar or vial packaging that slows the thawing process.^{10,11}

DMSO, used in other CBMs, has a higher freezing temperature than water, thus requiring more heat to thaw.

Traditionally CBMs have equal volume of cryoprotectant as the graft itself, requiring more energy and time to thaw.

Growth Factor Content

AlphaGRAFT® CBM is processed using a novel patented process that preserves the growth factor content found in the donor tissue. The intracellular & extracellular growth factors are harvested together during the processing and are delivered with the extracellular matrix (ECM) of the cortical bone fibers. These growth factors are then readily available *in situ* to assist in tissue regeneration. Unlike other CBMs, these critical growth factors are quantified at high levels in AlphaGRAFT CBM in comparison to donor-matched control.¹



BMPs

BMPs are osteoinductive and induce bone formation by differentiating mesenchymal stem cells into osteoblasts.

FGFs

FGFs induce angiogenesis by increasing osteoblast proliferation and are a potent stimulant for cartilage formation.

IGFs

IGFs stimulate osteoblast proliferation and bone matrix synthesis. IGFs also stimulate osteoclasts.

PDGF

PDGF is a key regulator in tissue repair and stimulates bone cell proliferation and angiogenesis.

TGF-b

TGF-b induces proliferation and differentiation of bone by differentiating osteoprogenitor cells and by regulating proliferation and extracellular matrix synthesis.

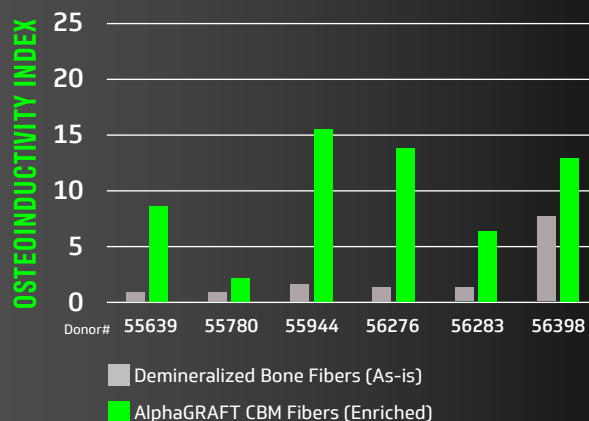
VEGF

VEGF regulates proliferation and survival of endothelial cells through nutrient supply from newly formed blood vessels.

Osteoinductive (OI) Potential

Active bone morphogenic proteins in DBM can stimulate osteogenic differentiation of pre-myoblasts by inducing alkaline phosphatase (ALP) activity.¹² *In vitro* assay quantifies the ALP activity which is then converted into an osteoinductive index (OI) score.

The enrichment process used for AlphaGRAFT CBM Fibers results in a graft that demonstrates a **6.3-fold increase** in OI over demineralized bone fibers (not enriched) from the same donor.²



Patient Safety

As with all ATEC Spine surgical solutions, patient safety is a top priority.

ATEC Spine is proud to partner with DCI Donor Services (DCIDS), an industry-leading allograft provider setting the standards in tissue quality and safety. DCIDS Tissue Bank's robust quality systems are built into every stage of allograft production starting with stringent donor screening, eligibility determination, and release criteria. Quality standards are established to meet or exceed the regulations and guidelines of the U.S. Food and Drug Administration, the American Association of Tissue Banks, and individual state health departments.

AlphaGRAFT® CBM Is Not Immunogenic

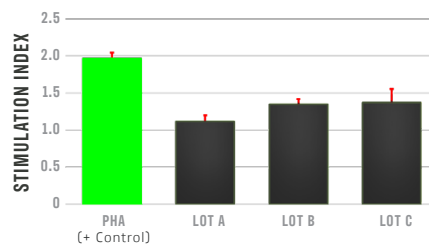
AlphaGRAFT CBM's cell enrichment process results in removal of immunogenic components, mitigating concerns for immune response. Processing of AlphaGRAFT CBM is performed using aseptic techniques wherein the tissue is soaked in an antibacterial solution to minimize bioburden level.

MIXED LYMPHOCYTE REACTION (MLR) STUDY⁶

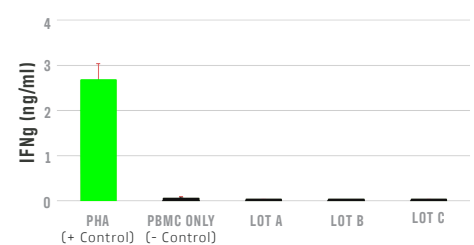
AlphaGRAFT CBM donors had less PBMC proliferation in comparison to PHA (positive control), which is a measuring stick for an immunogenic material in this model.

AlphaGRAFT CBM donors did not increase interferon γ , a well-known mediator of immune response and an activator of macrophages.

PBMC ACTIVATION



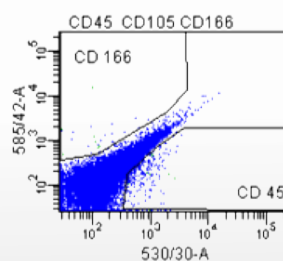
IFN γ PRODUCTION



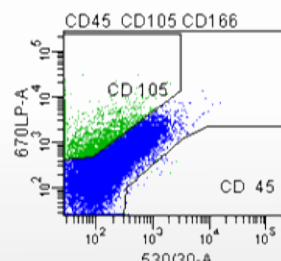
SURFACE MARKER ANALYSIS USING FLOW CYTOMETRY⁷

Surface markers were chosen to confirm presence or absence of certain cell types within the AlphaGRAFT CBM:

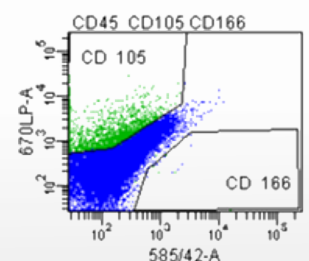
- CD45 is expressed on all hematopoietic cells except for platelets and erythrocytes.
- CD105 is a well-known surface marker for various mesenchymal stem cells.
- CD166 is used to evaluate presence of T- cells and cancer cells.



POPULATION	#EVENTS	%PARENT
CD 45	759	1.0
CD 166	82	0.1



POPULATION	#EVENTS	%PARENT
CD 45	73	0.1
CD 105	5,763	7.8



POPULATION	#EVENTS	%PARENT
CD 166	62	0.1
CD 105	6,300	8.5

RESULTS

AlphaGRAFT CBM is >99.0% free of CD45 positive cells, suggesting that the processing reduces the number of potentially immunogenic cells from the bone marrow, thereby reducing the risk of eliciting an immune response.

AlphaGRAFT CBM is >99.9% free of CD166 positive cells, suggesting that the processing reduces the number of potential T-cells and cancer-causing cells from the bone marrow, thereby, reducing the risk of eliciting an immune response.

Cells positive for CD105 show the presence of mesenchymal stem cells that are known to differentiate into bone-forming cells and to take part in bone regeneration.

Competitive Comparison

FEATURES*	AlphaGRAFT® CBM (ATEC Spine)	Osteocel® Pro (NuVasive)	Trinity ELITE® (Orthofix)	Bio4® (Stryker)	Vivigen® Formable (Depuy)
Cells	✓	✓	✓	✓	✓
Fiber-based	✓	✗ 10	✓ 13	✗ 15	✓ 17
Enriched with Osteoinductive Growth Factors	✓	✗ ^	✗ ^	✗ ^	✗ ^
Enriched with Angiogenic Growth Factors	✓	✗ ^	✗ ^	✓ 15	✗ ^
Enriched with Proliferative Growth Factors	✓	✗ ^	✗ ^	✗ ^	✗ ^
DMSO-free	✓	✗ 10	✗ 11	✓ 16	✗ 18
Antibiotic-treated	✓	✓ 10	✗ 14	✓ 15	✓ 18
Thaw-time <10 minutes	✓	✗ 10	✗ 11	✗ 15	✓ 17

* The data presented for competitor products is collated from information publicly available online (websites, brochures, IFU etc).

^ The data suggests osteoinductive potential but there was no mention of enrichment with growth factors.

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