CELLULAR BONE MATRIX

A PARAGON 28®
PRESERVE™ PRODUCT

V92™ CELLULAR BONE MATRIX

TECHNICAL MONOGRAPH

Exclusively foot & ankle Paragon 28®

V92® Overview

The V92 cellular bone matrices are viable allogeneic bone allografts containing viable bone-derived cells. Each V92 product contains the three key components that are ideal for bone formation:

1. An osteoconductive three-dimensional scaffold with cortical and cancellous components
2. A demineralized bone scaffold with osteoinductive potential, which provides exposure of signaling molecules and bone morphogenetic proteins[1]
3. Bone-derived cells to support osteogenic healing processes

The V92 product line is prepared with a novel DMSO-free cryoprotectant, which preserves an optimized viable cell component for osteogenic bone regeneration.

The V92 cellular bone matrices offer two (2) different bone scaffolding options to meet specific handling characteristics and surgeon preferences. These bone scaffolding options, in combination with the cell component, allow for two (2) final product configurations: V92 and V92-FC.

Key Features of V92® Product Line

- Two (2) unique scaffold blends for optimal handling characteristics: V92, V92-FC
- Proprietary, optimized bone microparticulate size range of 100-300 m.[8]
- Novel DMSO-free cryoprotectant, with no rinsing and decanting steps required prior to use.
- Average cell viability of the cell component exceeds 80% post-thaw.[12]
- Minimum of 150,000 viable cells per cc of allograft post-thaw.[12]
- Convenient handling and preparation in the OR, with total preparation time on the back table of less than 20 minutes.
- Four (4) hour working window for implantation after thaw without loss of cell viability.[12]
- Product shelf-life is two (2) years from date of processing when stored at -65°C or colder.

Bone Grafting

Bone grafting is a surgical procedure commonly used for treating fractures, or for securing a bony arthrodesis for a range of indications. Autograft has long been accepted as the gold standard graft material for these procedures because it possesses all three key properties needed for new bone growth: osteoconductivity to facilitate attachment and healing, osteoinductivity through bone stimulating growth factors that elute from the matrix, and osteogenic activity that provides a cellular component capable of responding with new bone formation. Given its autologous source, autograft is by definition histocompatible and non-immunogenic.

While autograft use typically results in high fusion rates, autograft also varies in both quality and quantity depending on the donor and site of harvest. Additional concerns associated with autograft harvest stem from concerns regarding increased surgical time, limited volume availability, surgical site morbidity, potential for blood loss, and infection.[2] In response to these challenges, a wide range of alternative allogeneic and synthetic graft materials have been made available to surgeons. One grafting material option of particular interest is a viable allogeneic bone graft that contains bone-derived cells.

Bone Structure and Regenerative Potential

Although marrow accounts for 4% of the human body weight, it serves a dual role by providing a structural component to cancellous bone. Spongy cancellous bone is much weaker than compact cortical bone, but its foam-like structure makes it a good energy-absorbing material, as demonstrated experimentally more than a century ago by Physick, and later asserted by Evans, Pedersen, and Lissner.[3] The presence of fat, marrow substance, and blood in the interstices of spongy bone enhances its energy-absorbing capacity by making it act like a quasi-hydrostatic system. The capacity of bone to absorb energy is one of its most important mechanical properties when it comes to fracture mechanics, as all physical injuries arise from the absorption of energy. Together, the cancellous spongy component of bone and the cellular marrow-filling component of bone are inextricable and both contribute to the energy loading capacities. Similarly, the V92 bone matrices were developed to support the composition and sustain the hydrostatic component of the grafting material by incorporating both a bone scaffold component and add a cellular component.

Several cell types have been identified within cancellous bone. Among those cell types capable of repair and regeneration, mesenchymal stem cells (MSCs) have been identified as a type of adult stem cell that retains the ability to self-renew and differentiate. MSCs are 'multipotent', meaning they can differentiate into more than one type of specialized cell of the body, but not all types. These cells can produce all tissues derived from the mesoderm, which include bone, cartilage, fat, muscle, and tendon. In the skeletal system, MSCs provide a foundation for differentiation into the osteogenic cells required for bone repair, remodeling and maturation. Under the appropriate conditions, MSCs differentiate into osteoblasts that subsequently make new bone.

An Alternative to Autograft

MSCs exhibit special immunological properties of biologic transparency. They do not stimulate allogeneic rejection and are not eliminated by the host immune response.[4] This lack of allogeneic reaction has been supported by in vitro studies as well as current clinical data for cellular bone matrices.[2] Recognizing the biologic and regenerative potential of MSCs, Paragon 28 has developed a stringent process for separating bone-derived cells from blood forming and immunogenic components, resulting in an allograft product that features a scaffold component and a cellular component. The imperative commitment of product development has been to achieve a bone allograft that provides both an inductive and conductive presence as a scaffold without sacrificing the viability of its cellular component. After processing, what remains is a viable cell component rich in MSCs optimized for osteogenic bone regeneration. These bone-derived cells, when recombined with the bone scaffold, provide a basis for tissue supplementation that carries the intentions of autograft without the complications attendant to its harvest.

V92 Cellular Bone Matrices: Viable Stem Cell Containing Bone Graft Substitute

After a stringent donor screening process, the cellular component of the V92 cellular bone matrices is collected from the vertebral body region of the donor [Figure 1], an area known to be rich in mesenchymal stem cells. Prior studies have reported that the highest concentration of mesenchymal stem cells is found in the pelvic girdle and vertebral body regions.[5] In addition, it has been reported that the quantity as well as the differentiation and regenerative potential of osteogenic MSCs decreases with age.[6,7] The donor criteria for the V92 cellular bone matrices is limited to donors between the ages of 15 and 55, younger than typical for allograft bone products. This specific age criteria, along with the vertebral body bone source, allow for maximum yield of viable bone-derived components.

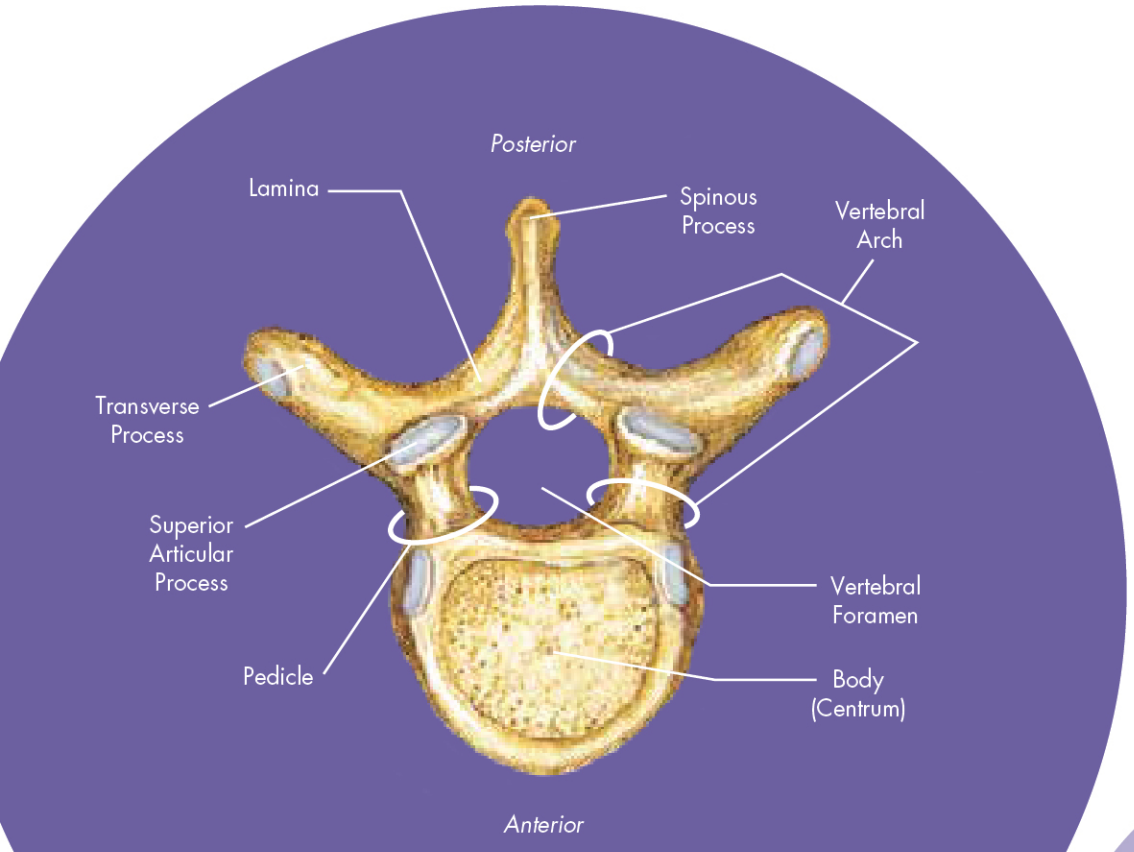


Figure 1 - Vertebral Body

Aseptic Tissue Processing

The V92 cellular bone matrices are minimally-manipulated, human cellular and allograft tissue products regulated by the FDA Center for Biologics Evaluation and Research. All four iterations in the V92 cellular bone matrix product line are processed in cGTP conditions at UMTB's state of the art manufacturing facility. UMTB has an impeccable record of quality that exemplifies its robust manufacturing processes where more than two million grafts distributed over 45 years of service have yielded no disease transmissions. The VIA allogeneic bone matrices are processed in an aseptic manner in ISO 5 (Class 100) clean rooms using procedures and screening criteria that meet the requirements of the American Association of Tissue Banks (AATB) [Figure 2]. Microbiological testing is performed before and after processing to ensure safety of the final product. Tissue is recovered and processed according to a strict timeline that includes recovery and processing within 24 and 120 hours post-mortem, respectively. Proprietary processes allow the isolation of a viable cell population and reduces exposure to contaminants that could stimulate an immune response. The measures taken throughout processing to ensure regulatory compliance and safety of final allograft product are implemented in an effort to continue the safety record UMTB has established over the last 45 years.

Figure 2 - ISO 5 (Class 100) clean rooms

Donor Criteria and Screening for Tissue Safety

Donor Testing:

- HIV-1 and 2 Antibody
- HIV-1 PCR Nucleic Acid Test
- Hepatitis B Surface Antigen
- Hepatitis B Core Antibody (IgG & IgM)
- Hepatitis B Virus Nucleic Acid Test (if applicable)
- Hepatitis C Virus Antibody
- Hepatitis C Nucleic Acid Test
- Human T-Lymphocytic Virus Antibody I/II (if applicable)
- Syphilis Rapid Plasma Reagin Screen or T.pallidum IgG Screen
- Cytomegalovirus (IgG & IgM)

Donor Screening:

- Medical and social history review
- Physical examination
- Medical record evaluation, including autopsy report (if performed)
- Licensed physician review of donor record

V92 Handling and Optimized Bone Scaffold Component

The V92 cellular bone matrices offer two (2) different bone scaffolding options to meet specific handling characteristics and surgeon preferences. These bone scaffolding options, in combination with the cell component, allow for two (2) final product configurations: V92, V92-FC.

V92 and V92-FC

The bone scaffold component of V92 and V92-FC combines a proprietary mixture of 100-300 µm demineralized cortical bone and mineralized cortical and cancellous bone. The demineralized bone component contains growth factors and has osteoinductive potential.1 The mineralized scaffold component is a balanced combination of cortical and cancellous bone optimized for bone formation. The microparticulate size range of 100-300 µm present in V92 and V92-FC induces simultaneous activity of osteoclasts and osteoblasts, allowing for active particles to undergo direct ossification [Figure 7].[8] The scaffold components are freeze-dried for superior induction of bone formation and biologic behavior.[9] Final preparation of the V92 microparticulate scaffold and cell mixture allows for tight packing of a defect with a cohesive wet sand consistency. Final preparation of the V92-FC microparticulate scaffold and cell mixture facilitates a biologic allograft that retains features consistent of a cohesive allograft with hydrophobic properties that resists lavage.

Note: Please refer to the V92 package inserts for complete allograft preparation instructions and any additional product information.

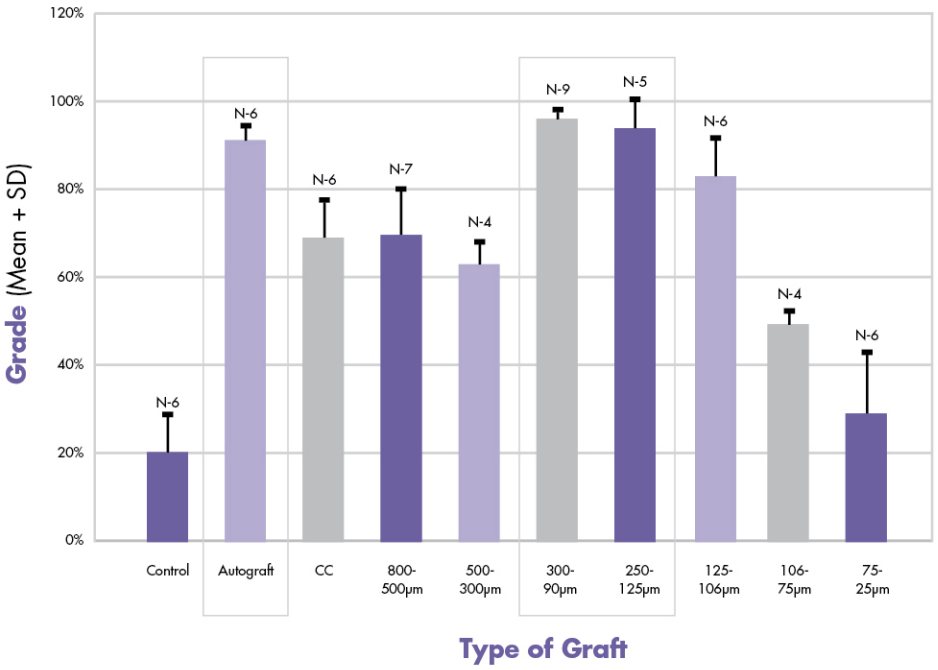


Figure 7 - Graphic representation showing the ability of 100-300µm allograft bone particles to induce bone formation in bone defects.

Novel Cryoprotectant to Maximize Cell Viability

The V92 cellular bone matrices utilize a novel, next-generation cryoprotectant for preservation of the cell component. I t is a non-toxic alternative to traditional DMSO-based cryopreservation media. Providing dependable cell identity and the ability to sustain cell viability post-thaw, this novel cryoprotectant affords advantages in cell characterization and final preparation to ensure minimal loss of viable bone-derived components.

Dimethyl sulfoxide (DMSO) is the most widely accepted cryoprotectant for cell preservation, in spite of concerns around its cytotoxicity and negative effect on cell differentiation.[10,11] Using a Neutral Red Uptake assay, the V92 cryoprotectant was evaluated in comparison with DMSO media samples of differing concentrations. In the testing, the components were determined to have a cytotoxic effect based on the ability to maintain L929 viability after 48-hour exposure to positive control conditions. Results show that the DMSO-free cryoprotectant samples have similar absorbance readings to the media positive control [Figure 8 and Figure 9]. In contrast, the DMSO media samples (at 2.5%, 5%, and 10% dilutions) resulted in significantly reduced populations of cells compared to the positive control. Therefore, the DMSO-free V92 cryoprotectant is not toxic to the cells and allows for optima cell health post-thaw.

Further evaluation of the cryoprotectant for V92 was also performed to ensure lack of an immune response. A Mixed Lymphocyte Reaction (MLR) assay was performed with representative V92 samples in co-culture with lymphocyte mitogens (PHA and LPS), which are designed to trigger cell division. Results demonstrate that when V92 cells were combined with PHA and LPS mitogens, there was no evidence to show that cell proliferation was stimulated. This indicates the absence of mature lymphocytes in the supernatant of V92 [Figure 10].

Along with preserving both viability and phenotypic potency, a controlled rate of cooling is implemented to minimize crystallization and prevent negative effects on the cells. The cell component is maintained in protective conditions at -65°C or colder with a product shelf-life of two (2) years from date of processing. Remaining on dry ice (-65°C or colder) from manufacturing through transfer to distribution, graft viability remains ready for use. The ability to combine the V92 scaffold components with the cells directly, without rinsing and decanting steps that could potentially damage the cell population, ensures minimal loss of viable bone-derived components. In addition, testing has shown the V92 products have a four (4) hour working window for implantation without loss of cell viability. Overall, the techniques used to preserve the cell component of V92 allow for consistent delivery of viable allograft to the patient.

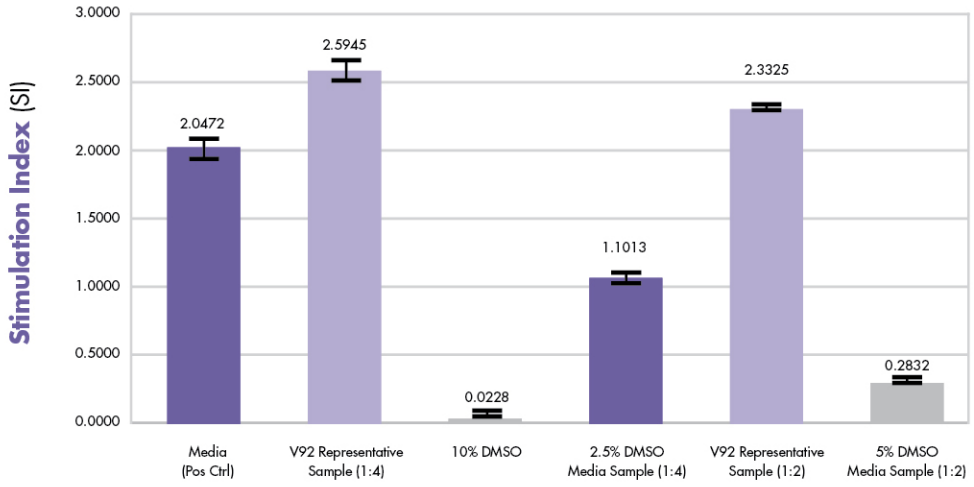


Figure 8 - 48-hour cytotoxicity results performed on L929 cells after exposure to EMEM/10% FBS (positive control), the V92 representative formulation 1:4, the V92 representative formulation 1:2, 2.5% DMSO, 5% DMSO, 10% DMSO, and no cells (negative control). L929 cells are a standard and accepted surrogate cell line for cell culturing purposes.

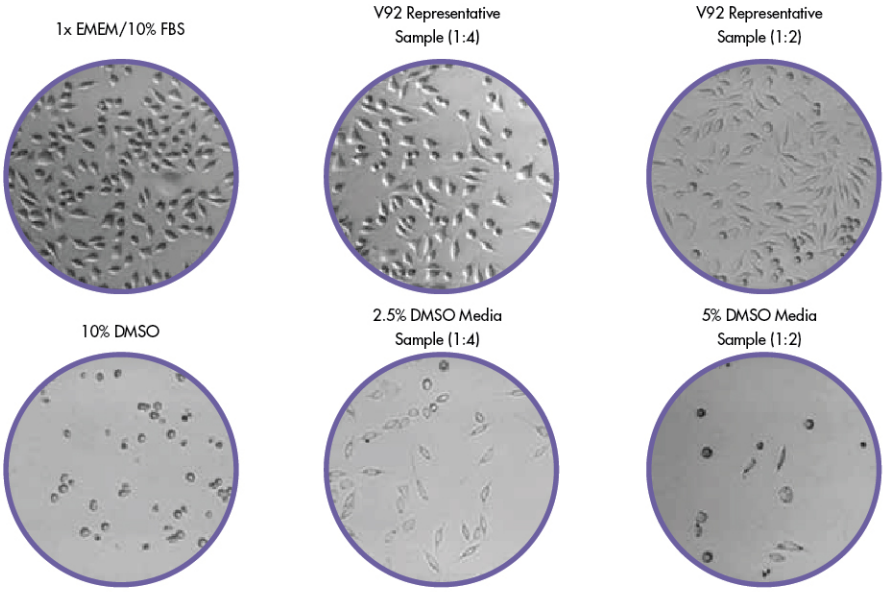
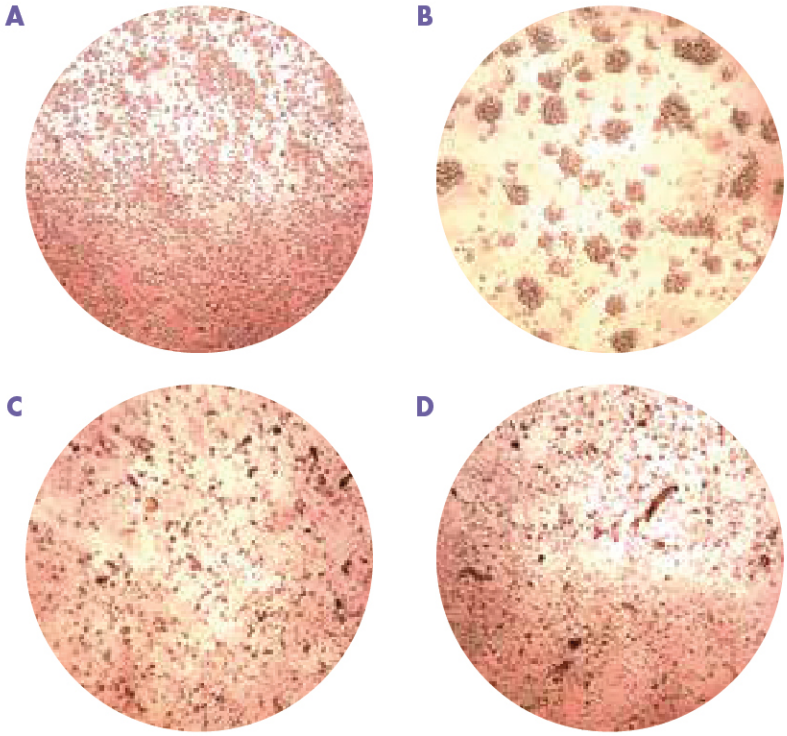


Figure 9 - Live imaging of L929 cells using 20X objective lens after 48-hour exposure to EMEM/10%FBS (positive control), the V92 representative formulation 1:4, the V92 representative formulation 1:2, 2.5% DMSO, 5% DMSO, 10% DMSO, and no cells (negative control). L929 cells are a standard and accepted surrogate cell line for cell culturing purposes.

Figure 10 - PBMCs and VIA supernatant response to 2-day PHA and LPS treatment A: PBMCs only, B: PBMCs response to PHA (LPS stimulation), C: Test Cells in PHA, D: Test Cells in LPS. 100X magnification.



Cell Component and Quality Control Testing

Viable osteogenic cells are a key component of the V92 cellular bone matrix. The process for optimal cell selection begins with a detailed donor screening process, and continues through spinal tissue collection and processing, all the way through to cryopreservation. The bone separation process uses proprietary cell extraction methods designed to yield an optimal cell population for bone repair [Figure 11].

During cell processing, characterization of each donor lot assures that cell viability will exceed 80% before proceeding to cryopreservation. Additionally, prior to release for distribution, each production lot of cell components is subjected to a 30-day post-cryopreservation Quality Control test. Average cell viability exceeds 80% on samples tested to date, and a minimum of 150,000 viable cells per cc of final allograft is required from every donor lot.[11] Altogether, this product qualification testing helps assure a consistently high number of viable bone-derived components that are combined with our optimized bone scaffolds prior to implantation.

Figure 11 - Final Cell Component Vials

Mixed Lymphocyte Reaction Testing

Mesenchymal stem cells are known to be immune privileged cells because they lack MHC class II antigens and prevent T cell proliferation.4 To ensure complete safety of the V92 cell components, a mixed lymphocyte reaction (MLR) assay was performed to assess the potential for activation of T-cell proliferation. In a standard MLR assay, a population of responder cells is co-cultured with a population of stimulator cells. If the stimulator cells are non-immunogenic, the population of responder cells will not proliferate.

In the MLR assay performed on V92, freshly isolated peripheral blood mononuclear cells (PBMCs) were used as the primary responder cells. Cell samples from three different donors of V92 were used as the stimulator cell populations. PBMC responder cells treated with Phytohemaglutinin (PHA), a mitogen that triggers cell division, were used as the positive control. Freshly isolated PBMCs alone were used as the negative control.

After co-culture of the PBMCs and V92 test samples for 4 days, the stimulation indices (SI) showed a range from 1.02 to 1.35 [Figure 12]. This range indicates very low stimulation when compared to the negative control. By contrast, the SI for the positive control human allogeneic 2-way MLR was significantly greater with a SI of 3.84 (p 0.00008). These results suggest that the responder T lymphocytes and dendritic antigen presenting cells in the human PBMC responder population are not reacting to the different histocompatibility antigens on the VIA test cells. Therefore, the results indicate the lack of a significant immune response in the V92 product, further ensuring the safety of the final allograft product for implantation into the patient.

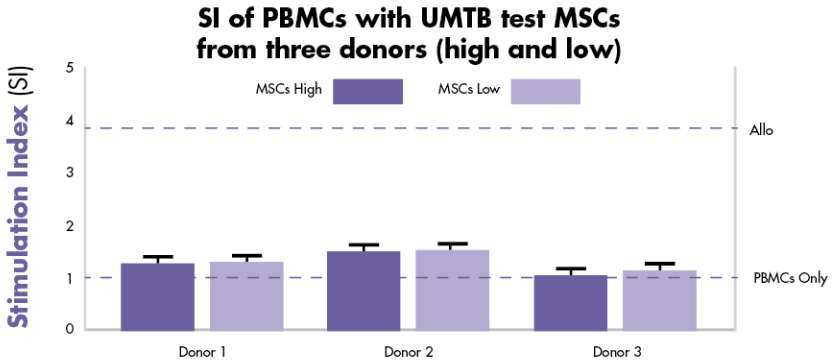


Figure 12 - Stimulation index calculated from BrdU ELISA ABS450 relative to PBMCs. Dotted line at SI 3.84 represents response of positive 2-way allogeneic MLR response. Dotted line at 1.00 represents response of the negative control. Stimulation indices for test samples range from 1.02 to 1.35.

Flow Cytometry Analysis

Cells from post-cryopreservation samples of V92 are evaluated for their expression of certain cell surface markers. Flow cytometry analysis is performed using an Attune NxT flow cytometer system (Invitrogen). Utilizing fluorescent antibodies, the cells are stained with CD73, CD90, CD45, and GlycoA to evaluate MSC content. The cells are stained with SSEA-4 to analyze MIAMI cell content and stained with CD15 to assess the presence of pluripotent cells. Lastly, CD45 and CD34 stains are performed to confirm the lack of hematopoietic cells.

Figure 13 below depicts a summary of the post-cryopreservation cell characterization using flow cytometry analysis. The "+" denotes the expression of the cell surface marker, and "-" denotes little to no expression of the cell surface marker. The additional "++" and "+++" correspond to increased expression of cell surface markers relative to the other surface markers.

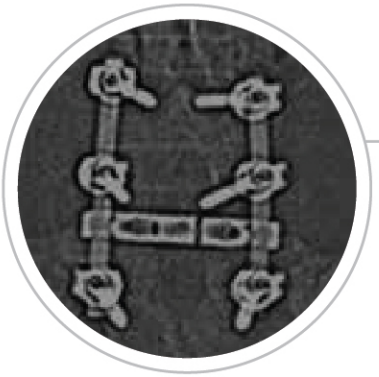
High expression of MIAMI cells is evidenced by increased expression of SSEA-4, the hallmark cell surface marker of this cell population. High expression of CD73 and CD90 confirms the presence of a robust cell population replete with mesenchymal stem cells. Furthermore, testing shows greatly increased expression of CD15, a cluster of differentiation biomarker characteristic of pluripotent cells.12 Altogether, the flow cytometry results demonstrate a highly regenerative cell population for osteogenic bone regeneration. In addition to confirming stem cell content, this flow cytometry protocol is designed to validate our donor selection criteria, vertebral bone source, and processing methods so that a safe product can be delivered to the patient.

Cell Surface Marker	Cell Type	Expression
CD73	MSCs	+.
CD90	MSCs	+
SSEA-4	MSCs, MIAMI Cells	++
CD15	Pluripotent Cells	+++
CD45	Hemapoietic Stem Cells	–
GlycoA	Red Blood Cells	–
CD34	Hemapoietic Stem Cells	–

Figure 13 - Post-Cryopreservation Cell Characterization with Flow Cytometry.

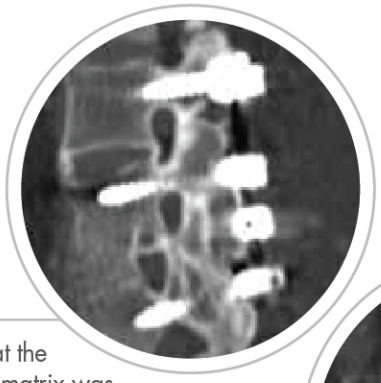
Case 1: Lateral Lumbar Spine Fusion

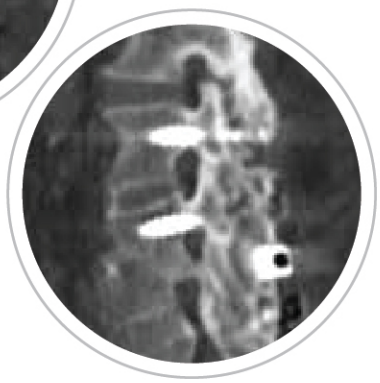
A 53-year-old female with a history of adjacent segment disease and facet arthrosis at the L3-L4 level following an L4-S1 spinal fusion with pedicular fixation.



Preoperative Imaging

Preoperative CT scan demonstrated severe bilateral facet arthropathy with calcification of the ligamentum flavum resulting in thecal sac compression and severe central canal stenosis.

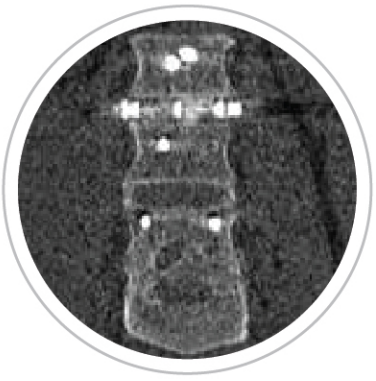




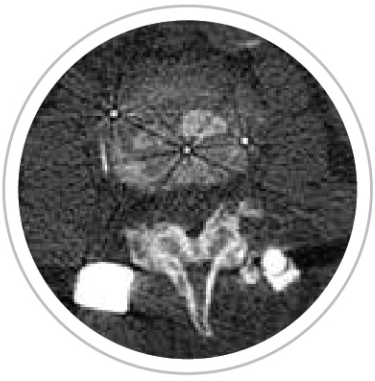
Procedure

A lateral lumbar interbody fusion was performed at the L3-L4 level to extend the fusion. V92 cellular bone matrix was packed into the dual chambers of the interbody device prior to insertion. Following device insertion, posterior pedicle screw fixation was used for additional lumbar stabilization with a combination of ceramic bone graft substitute and V92, along with patient bone marrow concentrate.

Sagittal



Coronal



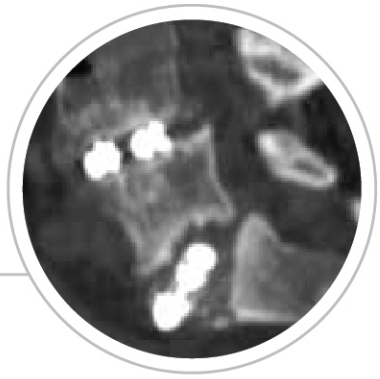
Axial

Six-Month CT Scan Assessment

Bone fusion with mineralization of the graft material across the disc space in the interbody implant chambers, with very robust bone strongly present in the most proximal chamber of the device. No evidence of osteolysis, heterotopic bone or graft site inflammation.

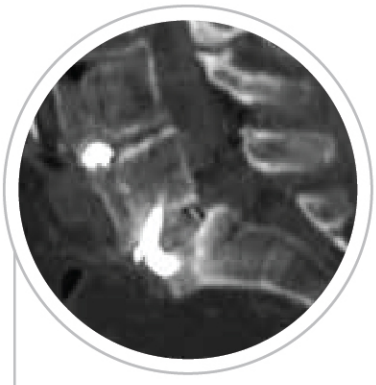
Case 2: Anterior Lumbar Spinal Fusion

A 78-year-old female presented with a history of back pain and left leg pain and prior lumbar fusion surgery at L4-L5 and L5-S1 levels. Patient fell approximately five months after surgery. Pseudoarthrosis, pedicular fixation loosening, and bony neural foraminal stenosis were present at the L5-S1 level. Trace antero-listhesis of L5 on S1 was also noted.

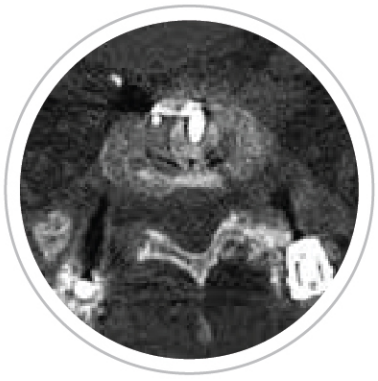


Procedure

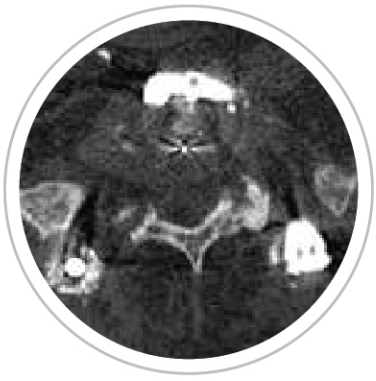
An anterior lumbar interbody fusion with supplemental anterior plating device was performed at the L5-S1 level. V92 cellular bone matrix was packed into the central chamber of the interbody device prior to insertion. Additional V92 was packed around the device after insertion. Following device insertion, posterior pedicle screw fixation was used for additional lumbar stabilization with a ceramic bone graft substitute with patient bone marrow concentrate.



Sagittal



Axial



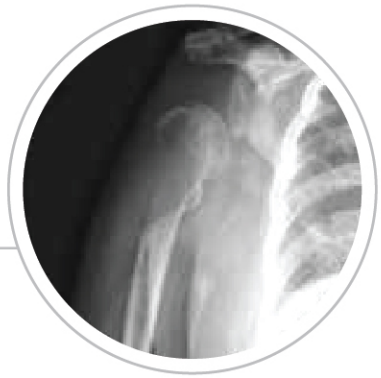
Axial

Six-Month CT Scan Assessment

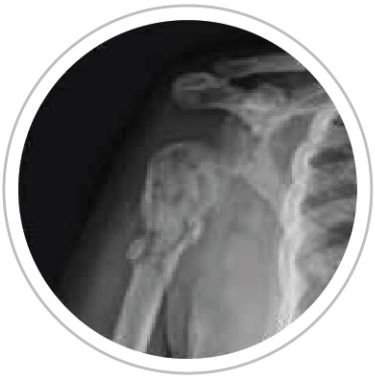
Bony fusion was evident across the interbody space with mineralization of the graft material within the interbody implant. Robust bone mineral present not only within the central chamber of the device but also lateral to the device. No evidence of osteolysis, heterotopic bone or graft site inflammation was present.

Case 3: Extremity Case

A 53-year-old male presented with intractable pain from a lytic lesion of the right proximal humerus.



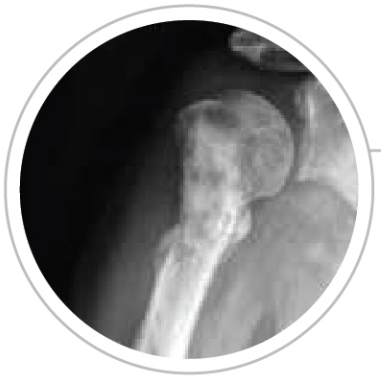
Preoperative Imaging



Two-Week Postoperative Image

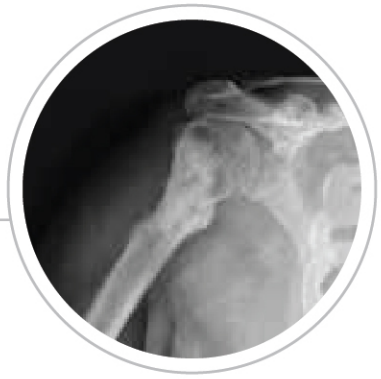
Procedure

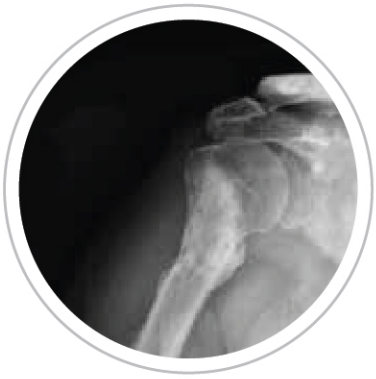
V92 cellular bone matrix and allograft morselized cortical bone chips were packed into the lesion site.



10-Week X-Ray

Bone graft consolidation is apparent with mineralization of the graft material at the fracture site. There is healing and filling of the defect. No evidence of osteophyte formation or graft site inflammation or seroma.



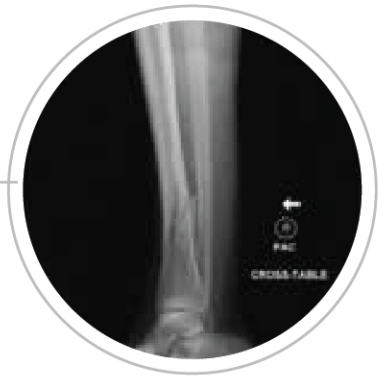


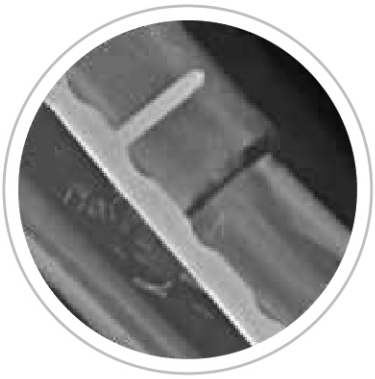
One-Year Postoperative Images

Bone graft is fully incorporated and the defect has been filled. Normal usage of the shoulder has been restored.

Case 4: Allograft Host-Junction Site Fracture - Revision

A 38-year-old male with pathologic fracture through a low grade osteosarcoma (image below) was referred after sustaining a fracture during a skiing trip. Fracture due to inadequate fixation of the graft and a substantial fracture gap in the proximal allograft-host junction site.

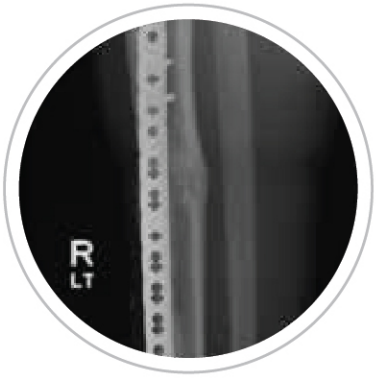




Procedure

Initially, the bone was resected along with adjacent soft tissue. Reconstruction was performed using an intercalary cortical allograft and vascularized fibula that was stabilized with a distal tibial locking plate. Later, due to persistent pain and radiographic non-union at the proximal allograft junction, surgery was recommended using V92 cellular bone matrix.

The fibrous interface at the non-union site was debrided and a high-speed burr was used to create a bleeding surface on the host bone interface. A cortical non-locking screw was placed to engage the allograft and provide sufficient purchase and stability. The defect was then packed with the V92.



Radiographic Assesment

Radiographically, bone formation at the interface of the allograft was robust with periosteal bridging between the native bone and the allograft at 5 and 10 month assessment. The vigorous regenerative response with the cellular graft accommodated a more assertive return to function, which further stimulated bone modeling. There was no evidence of heterotopic bone at the graft placement site and osteogenic activity aligned with dynamic loading.

Frequently Asked Questions (FAQ)

1. What are the V92 cellular bone matrices?

The V92 cellular bone matrices are allogeneic bone matrix products containing viable bone-derived cells. Each V92 product contains the three key components ideal for bone formation: an osteoconductive matrix, a demineralized matrix component with osteoinductive potential, and osteogenic cells. The V92 cellular bone matrices are safe and non-immunogenic and provide an ideal alternative to autograft in a variety of orthopaedic and spine applications.

2. What is the donor screening criteria for V92?

The V92 products are recovered from qualified tissue donors between the ages of 15 and 55 that meet strict testing and screening criteria for safety. This testing and screening includes medical and social history, physical examination, medical record review, and serology testing. All results are reviewed by the Medical Director and all tissue must be deemed suitable for transplantation.

3. How are the VIA products processed to ensure safety?

The V92 products are processed under aseptic conditions in class 100 clean rooms using procedures that meet the requirements of the American Association of Tissue Banks (AATB). Microbiological testing during and after processing ensures safety of the final product. Lastly, mixed lymphocyte reaction testing is performed to confirm that the cell components do not illicit an immune response.

4. What is the regulatory classification of V92?

The V92 products are regulated by the Food and Drug Administration (FDA) Center for Biologics Evaluation and Research. The V92 products are also recovered and processed according to the guidelines set forth by the American Association of Tissue Banks (AATB).

5. What are the storage requirements and shelf life of V92?

The shelf-life of the VIA products is two (2) years from date of processing when stored at -65 C or colder.

6. What are the indications for use of the V92 products?

V92 and V92-FC are each intended for the treatment of musculoskeletal defects as a bone void filler.

7. What Quality Control measures are performed for lot release?

During cell processing, characterization of each donor lot assures that cell viability will exceed 80% before proceeding to cryopreservation. Additionally, prior to release for distribution, each production lot of cell components is subjected to a 30-day post-cryopreservation Quality Control test. Average cell viability exceeds 80% on samples tested to date, and a minimum of 150,000 viable cells per cc of final allograft is required from every donor lot.[12] Altogether, this product qualification testing helps assure a consistently high number of viable bone-derived components that are combined with our optimized bone scaffolds prior to implantation.

8. How are the cells in V92 protected during cryopreservation?

A novel, DMSO-free cryoprotectant is used in the cell component to protect the cells during freezing. A controlled rate of cooling is implemented to minimize crystallization and prevent negative effects on cells. The cell component is maintained in protective conditions at -65°C or colder until the product is shipped, allowing graft viability to be sustained until ready for use.

9. What is the preparation protocol for the V92 products?

The V92 products are easily prepared in the OR, with total preparation time on the back table being less than 20 minutes. The cryopreservation technique allows for the V92 scaffold components and cells to be combined directly, without rinsing and decanting steps that could potentially damage the cell population. The V92 products have a four (4) hour working window for implantation after thaw without loss of cell viability. (Note: Please refer to the V92 package inserts for complete allograft preparation instructions)

10. What are the different handling options available for V92?

The V92 cellular bone matrices offer four (4) different bone scaffolding options with specific handling characteristics to meet surgeon preferences.

V92

- Components:
  1. Bone microparticulate jar,
  2. Cell vial
- Final handling: Cohesive, wet sand consistency

V92-FC

- Components:
  1. Bone microparticulate jar,
  2. Bone gel jair
  3. Cell vial
- Final handling: Moldable, paste consistency

References

1. Gruskin, E., et al., Demineralized Bone Matrix in Bone Repair, History and Use. Advanced Drug Delivery Reviews, 2012. 64: 1063-1077.
2. Grabowski, G. and R.N. Robertson, Bone allograft with mesenchymal stem cells: a critical review of the literature. Hard Tissue, 2013. 2(2).
3. Evans, F. G., H. E. Pedersen, and H. R. Lissner, The role of tensile stress in the mechanism of femoral fractures, J. Bone Joint Surg., 33A: 485-501, 1951
4. Ryan, J.M., et al., Mesenchymal stem cells avoid allogeneic rejection. Journal of Inflammation, 2005. 8(2): p. 11.
5. McLain, R.F., et al., Aspiration of osteoprogenitor cells for augmenting spinal fusion: comparison of progenitor cell concentrations from the vertebral body and iliac crest. Journal of Bone and Joint Surgery, 2005. 87-A(12): p. 2655-2661.
6. D'ippolito, G., et al., Age related osteogenic potential of mesenchymal stromal cells from human vertebral bone marrow. Journal of Bone and Mineral Research, 1999. 14: p. 1115-1122.
7. Sethe, S., A. Scutt, and A. Stolzing, Aging of mesenchymal stem cells. Ageing Research Reviews, 2006. 5: p. 91-116.
8. Malinin, T.I., et al., Particulate Bone Allograft Incorporation In Regeneration of Osseous Defects; Importance of Particle Sizes. The Open Orthopaedics Journal, 2007. 1: p. 19-24.
9. Malinin, T. and H.T. Temple. Comparison of frozen and freeze-dried particulate bone allografts. Cryobiology, 2007. 55: p. 167-170.
10. Renzi, S., et al., Mesenchymal stromal cell cryopreservation. Biopreservation and Biobanking, 2012. 10(3): p. 276-281.
11. Asghar, W., et al., Preserving human cells for regenerative, reproductive, and transfusion medicine. Biotechnology Journal, 2014. 9: p. 895-903.
12. Data on file at Paragon 28.

Acknowledgments

Clinical cases provided by the following surgeons:
Case 1 & 2: Dr. William C. Tally, Athens Orthopaedic Group, Athens, GA
Case 3 & 4: Dr. H. Thomas Temple, University of Miami & Nova Southeastern University

For more information on V92™ please contact:

Paragon 28, Inc.
14445 Grasslands Dr.
Englewood, CO 80112, U.S.A.
855.786.2828
www.paragon28.com

Processed by: UMTB
An AATB Accredited Tissue Bank
P01-TM-0003 RevB