TECHNICAL MONOGRAPH

Exclusively foot & ankle
Paragon 28®

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THE MISSION OF PARAGON 28®

Our mission is to strategically build a company around the core principles that **drive innovation and quality.** Relentlessly working to advance the science behind foot and ankle surgery, Paragon 28 is passionate about and committed to:

- Blending different surgical philosophies from various global thought leaders to develop biomechanically and clinically relevant surgical solutions.
- A customer service based, dedicated, and highly-trained distribution network to the foot and ankle market.
- Meeting the needs of increasing pricing pressures and reimbursement while continuing to develop cutting-edge surgical implants.
- Creating complete surgeon-centric systems, specialty instruments, and next generation implants to solve real world issues faced by foot and ankle surgeons.
- Improving clinical outcomes through meaningful and unbiased research. We are ready to embrace research data regardless of marketing impact.

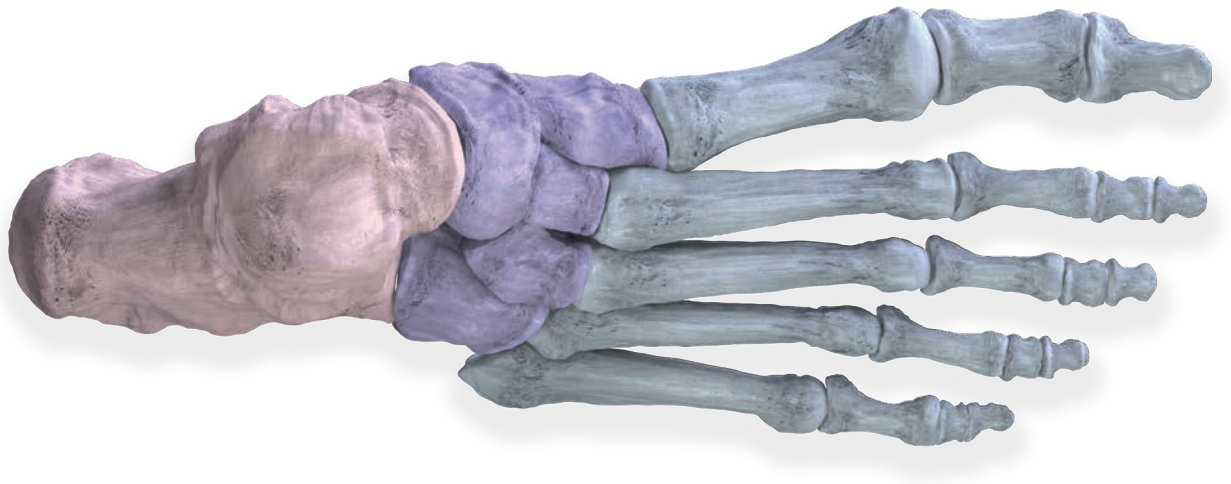
PARAGON 28 HISTORY

In 2010, Paragon 28 was established as an orthopedic foot and ankle company. The name “Paragon 28” was chosen to show that we are exclusively a foot and ankle company, with the “28” representing the number of bones in the foot. We will remain true to that vision. Paragon 28 was started as a small, family-based company and we have kept those core ideals as we have grown.

Our first product was the Monster® Screw System, followed by the Gorilla® Plating System. As we continue to add more products, we maintain a fine level of detail to every feature of every product we design. The goal is to give options to the foot and ankle surgeon, knowing there is more than one way to achieve a great result. We have listened to surgeons and will continue to do so in order to understand and address their specific needs.

SURGICAL RATIONALE FOR BONE GRAFTING

- Success of orthopedic surgical procedures, such as treating fractures, securing osteotomies, and spinal fusion, relies upon the formation of a solid bone fusion mass.
- Bone grafts play a critical role in the formation of a fusion mass. Autograft bone taken from the patient has long been accepted as the gold standard bone augmentation graft material for these procedures.
- Most commonly taken from the iliac crest, autograft contains osteogenic, osteoconductive, and osteoinductive elements essential for the formation of new bone.
- Autograft is readily available, low-cost, and presents no concerns with regard to tissue compatibility and disease transmission.
- Given its autologous source, autograft is, by definition, histocompatible and non-immunogenic.



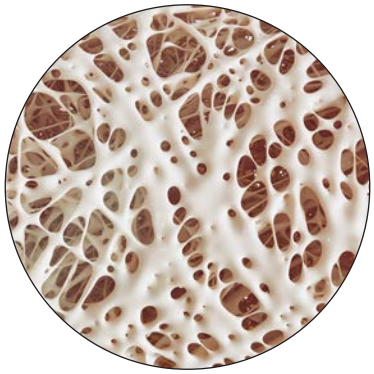
HINDFOOT **MIDFOOT** **FOREFOOT**

BONE GRAFTING CLINICAL CHALLENGES

While autograft use typically results in high fusion rates, it also varies in both quality and quantity depending on the donor and site of harvest. Autograft quality is influenced by age, metabolic abnormalities, and smoking.[1] Additional concerns associated with autograft harvest include increased surgical time, limited volume availability, surgical site morbidity, potential for blood loss, and infection.[2-5] In response to these challenges, a wide range of alternative bone graft substitutes, graft extenders, and osteologic materials, such as allogeneic and synthetic graft materials, have been developed and made available to surgeons. Allogeneic grafts are bone sourced from human donors.

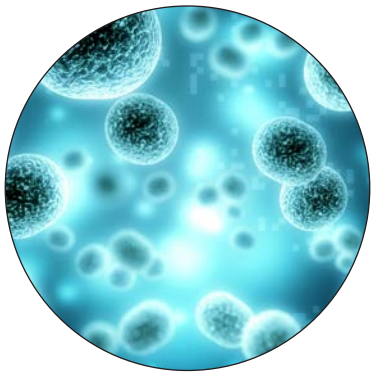
ALTERNATIVE BONE GRAFT OPTIONS

In a quest to find alternatives to autograft to support the clinical need for bone grafts many have turned to allograft as the next best solution. Ideally, a bone graft alternative to autograft would contain the three key elements of bone formation and mimic the composition of native bone.



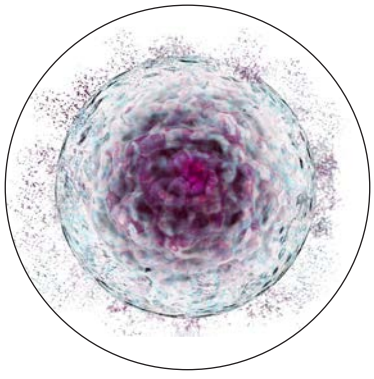
OSTEOCONDUCTIVE

Allograft bone represents a natural three-dimensional osteoconductive alternative with cortical and/or cancellous components if care is given to the processing of the product.



OSTEOINDUCTIVE

Demineralization of cortical bone exposes endogenous growth factors that may provide an osteoinductive potential in the allograft tissue.[6]



OSTEOGENIC

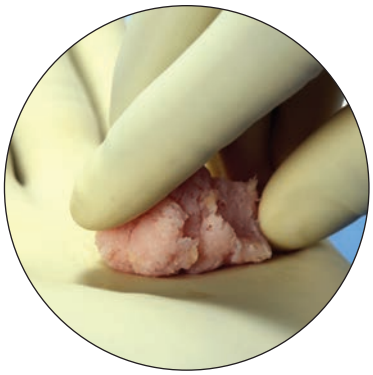
Viable bone matrices (VBMs) are allogeneic bone grafts containing endogenous live cells to support the osteogenic process.

V92-FC+™ VIABLE ALLOGENEIC BONE SCAFFOLD PRODUCT INFORMATION

V92-FC+™ is a viable allograft with an average of 1.5 million cells/cc of allograft packaged in a convenient syringe which thaws quickly and retains viability for four hours post thaw to accommodate clinical needs. The excellent handling characteristics of the allograft provide the surgeon with many opportunities of clinical placement, from packing and shaping to easy administration through a 6 mm bone funnel. The allograft provides the three key elements of bone formation. The foundation is an osteoconductive and osteoinductive bone scaffold composed of cancellous chips and demineralized cortical fibers to deliver a 100% human-derived product that mimics the structure of native bone. V92-FC+™ utilizes a novel cryoprotectant for preservation of the cell component that is DMSO-free, so there is no need to rinse or decant during the preparation of the product..

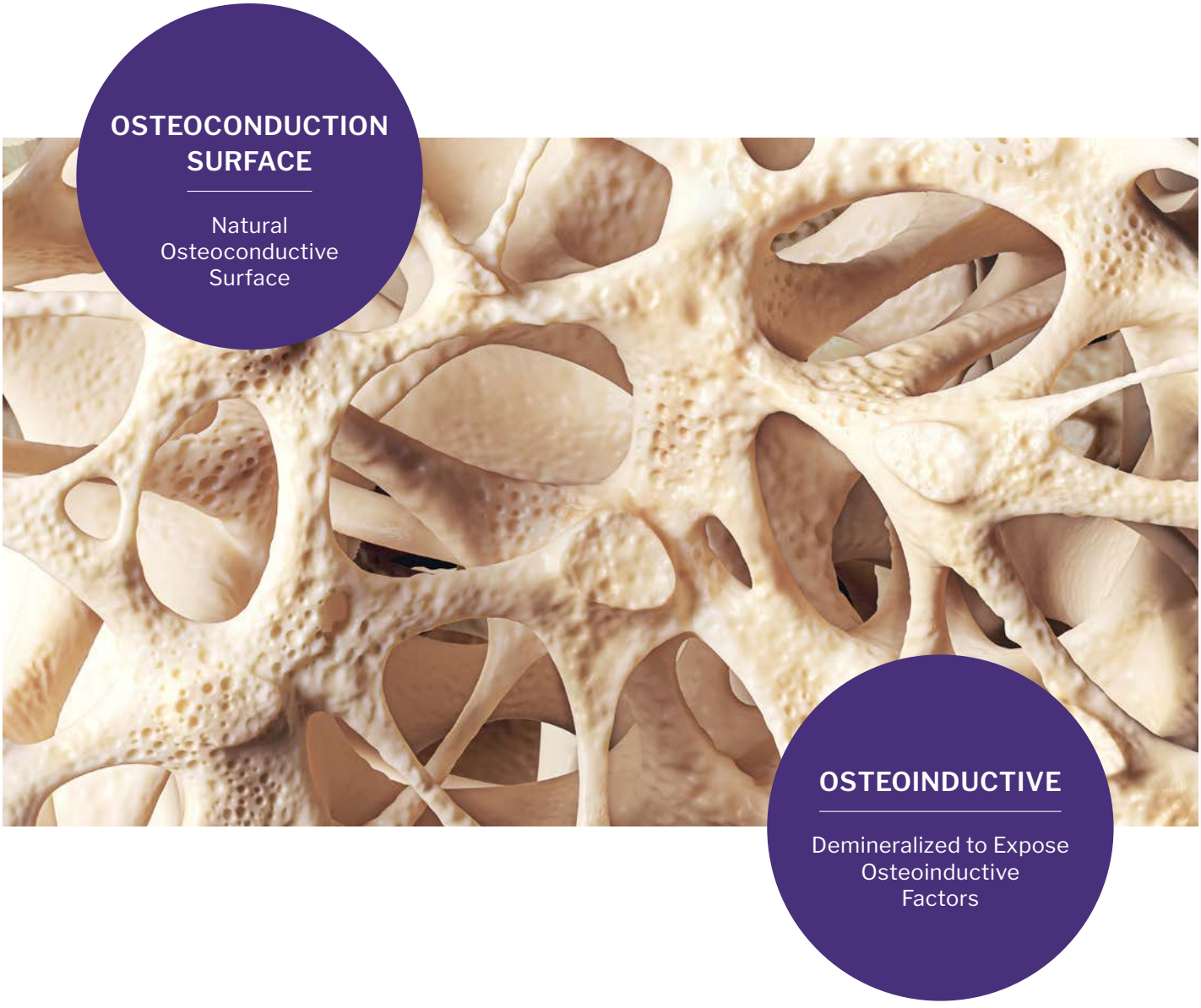
KEY FEATURES AND BENEFITS

- Thaws in under 15 minutes
- Viable for four hours-post thaw
- No need to rinse or decant—V92-FC+™ preserves native bone cells in a DMSO-free cryoprotectant
- Packaged in an easy-to-use syringe
- Easily administered through a 6 mm bone funnel



OPTIMIZED BONE SCAFFOLD

V92-FC+™ provides an osteoconductive bone scaffold composed of mineralized cancellous bone along with demineralized cortical fibers. Bone fibers offer superior osteoconductivity when compared to powder due to the increased ability for cells to migrate along fibers, creating "cellular highways" for bone formation.[7] Additionally, interconnected cortical fibers provide moldable handling so that the product stays in place where implanted, even in the presence of blood flow and irrigation. The demineralized cortical fibers also offer an osteoinductive benefit.[8] Cancellous chips provide additional structure to the mix, providing bone-to-bone contact for the implanted graft. Together the cancellous bone and demineralized cortical fibers mimic the particulate structure of native bone.



VIABLE CELLS

V92-FC+™ delivers an average of 1.5 million cells/cc of allograft with a 92% viability at four hours post-thaw. The industry-best quantity of viable cells is made possible by proprietary Integrity Processing™ developed through 50+ years of focus on process improvements and the novel DMSO-Free cryoprotectant.

Cell Characterization

Multiple assays have been conducted to verify the cell viability as well as characterize the endogenous cell population in the V92FC+™ product.

A fluorescence assay showed the live cells attached to the cancellous bone particles; green cells are alive and red fluorescence indicates a dead cell. The photo in Figure 1 demonstrates the presence of live cells in V92-FC+™ and indicates a good overall cell viability.

Cell viability was also demonstrated through a migration assay, in which the cancellous bone was plated and incubated for up to four weeks at 37°C in a 5% CO_2, 5% O_2 incubator. Colony formation, shown in Figure 2, was observed during this incubation period and demonstrates the overall health of the attached cells.

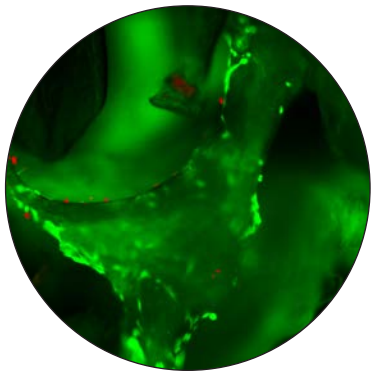


Figure 1: Fluorescent Microscopy photo

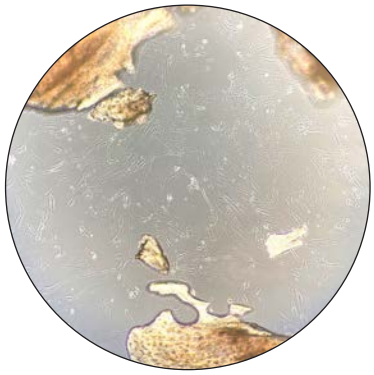


Figure 2: Brightfield Microscopy Photo

Progenitor Potential

Cell characterization was conducted with flow cytometry to analyze surface markers. Marker analysis showed high expression of known progenitor cell surface markers, such as CD44, CD73, CD90, and CD105, CD166. This analysis also showed low expression of hematopoietic progenitor markers of CD34 and CD45.[6]

	V92-FC+™ Cellular Component
CD44	+++
CD73	+++
CD90	+++
CD166	+++
CD105	+++
CD34	–
CD45	–

+++	Expression between 80–100%
++	Expression between 60–80%
+	Expression between 40–60%
–	Expression lower or equal to 5%

Figure 3: Surface Marker Expression

Osteoprogenitor Activity

An Alkaline-Phosphatase (ALP) assay demonstrated the ability of the V92-FC+™ cells to differentiate under physiologically relevant conditions toward osteoprogenitors with enhanced ALP activity. Cells isolated from V92-FC+™ were plated and incubated for four weeks at 37°C in a 5%CO_2, 5%O_2 incubator in basal or osteogenic media. ALP staining was significantly higher in osteogenic media, indicating the cells could differentiate into an osteoblastic lineage.

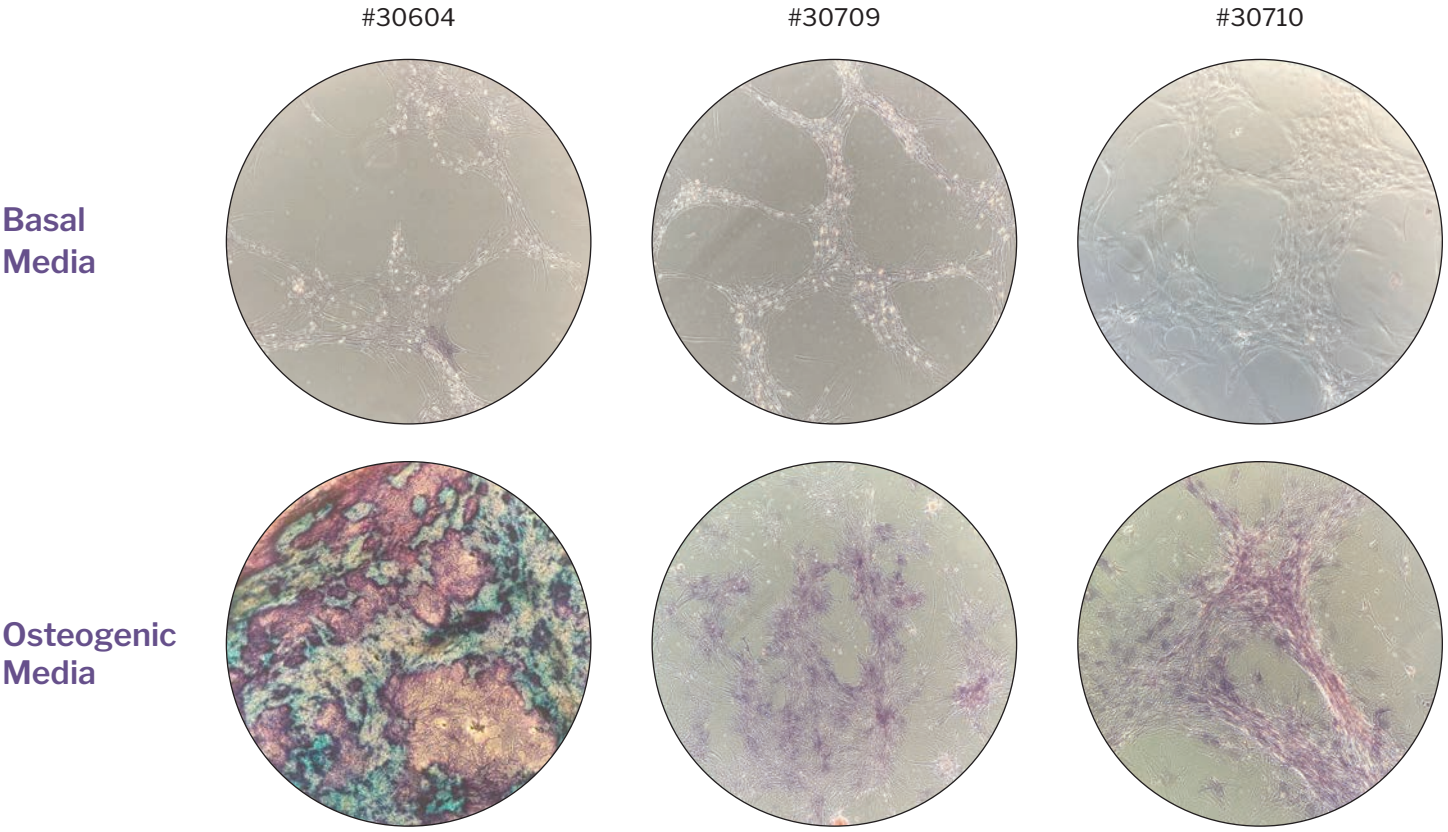


Figure 4: Alkaline-Phosphatase Expression

Summary

V92-FC+™ viable allogeneic bone scaffold is composed of demineralized bone fibers and viable endogenous cells attached to cancellous bone preserved using the DMSO-Free, non-cytotoxic cryoprotectant. Taken together, the studies done to characterize the endogenous cells in V92-FC+™ bone matrix support the following conclusions:

- Attached cells on the cancellous bone are viable
- Those cells positively express markers linked to progenitor cells, such as CD44, CD73, CD90, CD105, and CD166
- Those cells can, under physiologically relevant conditions, differentiate toward osteoblastic lineage

NOVEL CRYOPROTECTANT

Proper preservation of viable allografts requires strict adherence to recovery and processing protocols. To manufacture V92-FC+™, viable endogenous bone cells are collected from the donor and then preserved with the use of a novel DMSO-free cryoprotectant, which uses an extracellular protective coating on the cell to prevent crack propagation and membrane lysis[6] (Figure 5). Other viable bone matrix products on the market use DMSO as a cryoprotectant, which penetrates the cell and prevents crystal formation from within. At room temperature, DMSO-based cryoprotectants raise concerns about cytotoxicity and negative effects on cell differentiation.[9–11]

The novel cryoprotectant technology provides distinct advantages over DMSO-based cryoprotectant technology used in competitive products. As an added bonus, it does not require the multiple rinsing and decanting steps of DMSO-based cryoprotectants. Rinsing steps can diminish both the cell viability and the inherent regenerative properties of allografts.

The novel cryoprotectant provides a surgical procedure advantage over other cryoprotectants containing DMSO. Allografts treated with this cryoprotectant experience minimal cell loss and retain, on average, over 92% cell viability after thaw[6]. The cryoprotectant also allows for usage up to four hours after thawing and V92-FC+™ allografts can be stored for up to one year at or below -65°C.

Novel Cryoprotectant

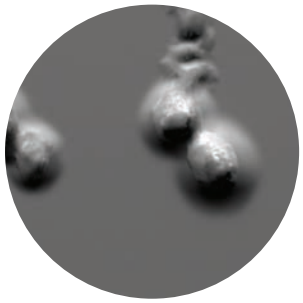


Figure 5*: *Cells protected with DMSO-free cryoprotectant to prevent crystalline damage (previously frozen) *Image captured by scanning electron microscope SEM*

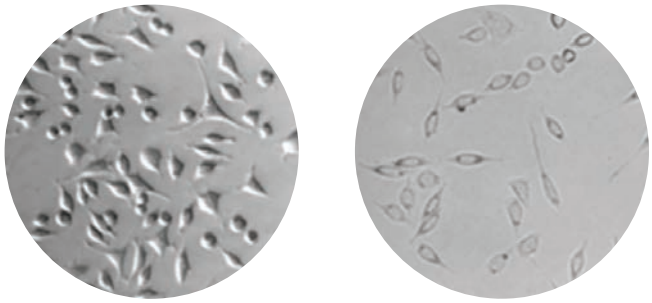


Figure 6: *Cytotoxicity assay showing higher number of viable cells in media containing up to 10% DMSO-free cryoprotectant (left) compared to media containing 2.5% DMSO (right), after 48 hours incubation*

V92-FC+™ SAFETY PROFILE

V92-FC+™ viable allogeneic bone scaffold is recovered from qualified tissue donors that meet strict testing and screening criteria for safety. V92-FC+™ has also been subjected to a mixed lymphocyte reaction (MLR) assay to ensure that the allograft does not stimulate an immune response.

A MLR assay is performed to assess the potential for activation of T-cell proliferation. Peripheral blood mononuclear cells (PBMCs) are isolated from multiple donors. Freshly isolated PBMCs from one donor (Negative Human Control) are used as the primary responder cells. Co-culture with cryopreserved PBMCs from a separate donor are used as control (Positive Human Control). V92-FC+™ cells are co-cultured with the primary responder cells, freshly isolated PBMCs, to see if they elicit an immunogenic response through the increase in expression of interferon gamma (IFN-y). Product from four representative donors are depicted as Donors 1–4.

The methodology follows standard protocols. Once the cells are treated and added to the 96-well culture plate, the plate is incubated for four days at 37° C with 5% CO_2 and >95% humidity. On day four, the supernatant is removed for IFN-y cytokine analysis.

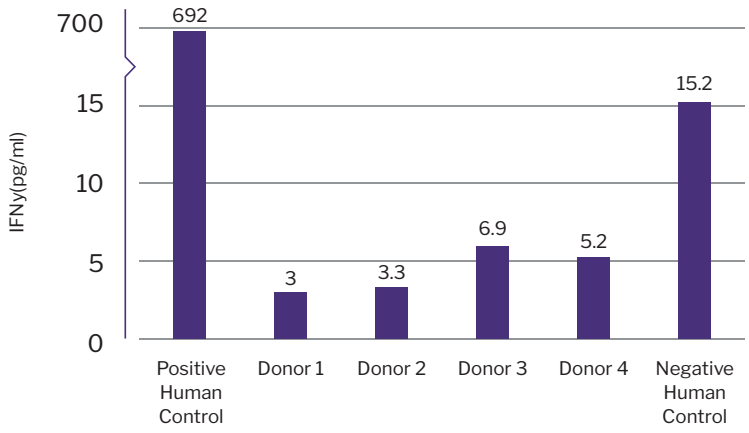


Figure 7: *Because the test samples (Donors 1–4) did not stimulate a significant response compared to the negative control, the MLR assays demonstrated that the V92-FC+™ viable allogeneic bone scaffold is not immunogenic and does not stimulate an immune response.*

QUALITY AND SAFETY

Donor Recovery and Processing

V92-FC+™ viable allogeneic bone scaffold is recovered from qualified tissue donors that meet strict testing and screening criteria for safety. This testing 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.

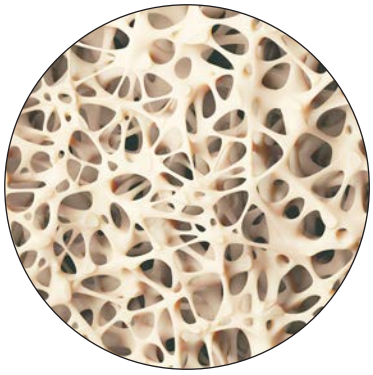
Donor Criteria and Screening for Tissue Safety Donor

TEST	SYMBOL
Cytomegalovirus*	CMV Ab (IgG & IgM)
Human Immunodeficiency Virus (HIV)	
HIV-1/2 Plus O Antibodies	HIV-1/2 Plus O Ab
Nucleic Acid Test for HIV-1 RNA	HIV-1 NAT
Hepatitis B Virus (HBV)	
HBV Surface Antigen	HBsAg
HBV Core Antibody (IgG & IgM)	HBcAb
Nucleic Acid Test for HBV DNA	HBV NAT
Hepatitis C Virus (HCV)	
HCV Antibody	HCVAb
Nucleic Acid Test for HCV RNA	HCV NAT
Human T Cell Lymphotropic Virus I/II*	
HTLV-I/II Antibody	HTLV-I/II-Ab
Syphilis**	
Rapid Plasma Reagin Screen	RPR
T. Pallidum	IgG

**A donor with a reactive result for the CMV or HTLV-I/II Antibody test is cleared for transplantation use only when the result from a confirmatory assay is nonreactive.*

***A donor whose blood specimen is unsuitable for the non-treponemal screening assay, such as the RPR test, or with a reactive result from the non-treponemal screening assay, is cleared for transplantation only when the result from the treponemal-specific (confirmatory) assay is nonreactive.*

1



RECOVERY <24 hours

- All allograft products begin with the gift of donated tissue
- Stringent donor selection criteria and screening for tissue safety

2

INTEGRITY PROCESSING <120 hours

- Unique and proprietary method that preserves the endogenous growth factors and viable cells
- Validated aseptic process
- 50+ years of integrity processing, with routine optimization

3

PACKAGING <6 hours

- Patented, unique, non-DMSO cryopreservation
- Thaws rapidly in under 15 minutes
- Packaged in an easy-to-use-syringe

FINAL PRODUCT: V92-FC+™

- Excellent handling characteristics
- Product can be easily administered through a bone funnel

ORDERING INFORMATION

CODE	DESCRIPTION
P01-V92-0102	V92-FC+™ Bone Matrix, 1.0cc
P01-V92-0252	V92-FC+™, Bone Matrix, 2.5cc
P01-V92-0502	V92-FC+™, Bone Matrix, 5.0cc
P01-V92-1002	V92-FC+™, Bone Matrix, 10.0cc

To learn more or to speak to a specialist, please call (855) 786-2828 or email info@paragon28.com.

NOTES:

Paragon 28® has used reasonable efforts to provide accurate and complete information herein, but this information should not be construed as providing clinical advice, dictating reimbursement policy, or as a substitute for the judgment of a health care provider. It is the health care provider's responsibility to determine the appropriate treatment, codes, charges for services, and use of modifiers for services rendered and to submit coverage or reimbursement-related documentation.

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