

# ViviGen<sup>®</sup> Cellular Bone Matrix

The right cells. The right time. The right forms.

## Cell Types Involved in Bone Healing

Bone is a highly dynamic tissue and undergoes remodeling, which is a balance between the removal of old mineralized bone and the formation of new bone. As a result, bone is in a constant state of renewal. During the bone remodeling and repair processes, osteogenic cells are required to reach the defect site to directly participate in these processes<sup>2</sup>. Bone cells that are responsible for this remodeling process have very specific roles and functions.

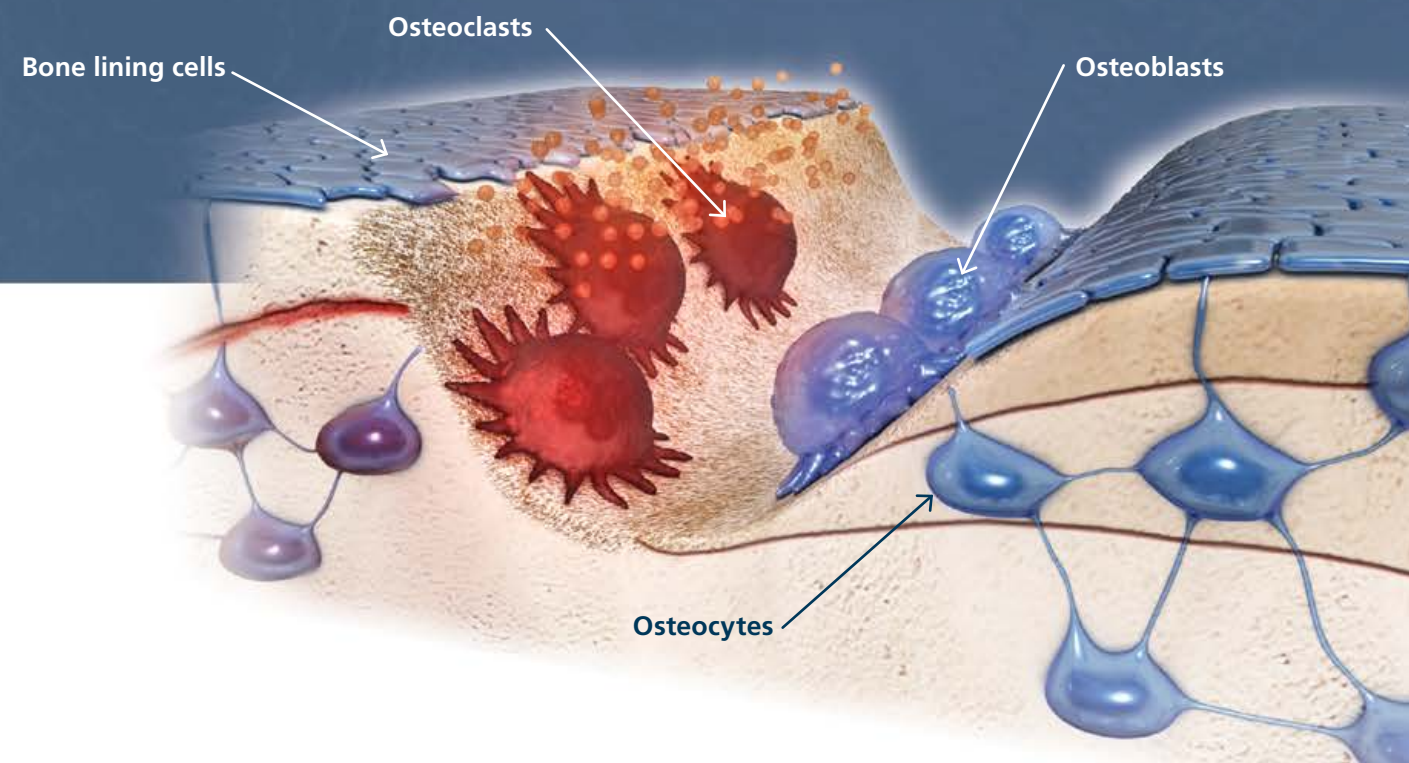
These include:

**Osteoblasts** are bone building cells. They secrete the collagen matrix and synthesize proteins such as osteopontin and osteocalcin that are involved in the mineralization of the matrix<sup>2,3</sup>. Osteoblasts can differentiate into osteocytes.

**Osteoclasts** are bone removing cells. They are responsible for the absorption and removal of old bone.

**Osteocytes** are terminally differentiated osteoblasts that are entrapped in the mineralized matrix. They are able to send signals based on stress and strain felt within the bone to begin the remodeling process.

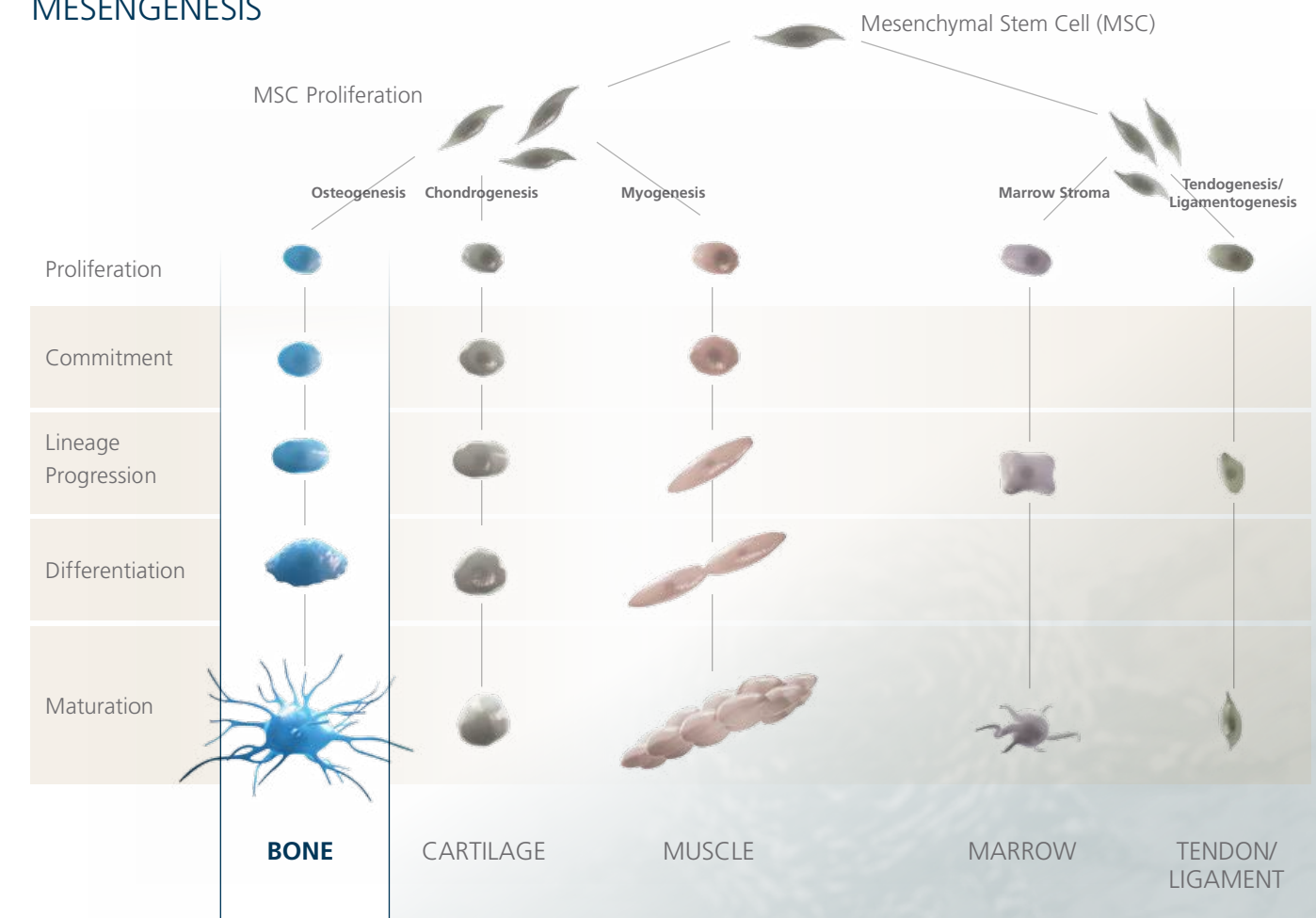
**Bone lining cells** are cells that line the surface of bone. They direct mineral uptake and release in bone.



## The Bone Cell Advantage

ViviGen® Cellular Bone Matrix represents a paradigm shift in the field of bone repair. A body of evidence has emerged supporting the fact that bone cells are the preferred cells for bone formation compared to undifferentiated Mesenchymal Stem Cells (MSCs), because they are fully differentiated and are committed solely to laying down bone matrix.

### MESENGENESIS



### Pre-Clinical Studies Suggest Bone Cells

- Remain at the defect site longer<sup>4</sup>, directly participate in the bone formation process and deposit a higher quality of bone than MSCs<sup>5</sup>
- Secrete chemotactic factors such as IGF-1, which may play a major role in recruitment of osteoblasts during bone formation<sup>6,7</sup>
- Secrete cytokines to stimulate angiogenesis<sup>8</sup> and work in concert to facilitate further MSC differentiation<sup>8</sup>
- Maintain viability, proliferation potential and osteoblastic function later in life compared to an MSC<sup>9,10,11,12</sup>

## 3 Key Components of ViviGen

ViviGen contains the elements necessary for bone formation<sup>1</sup>

### 1 Viable Cells (Osteogenic)

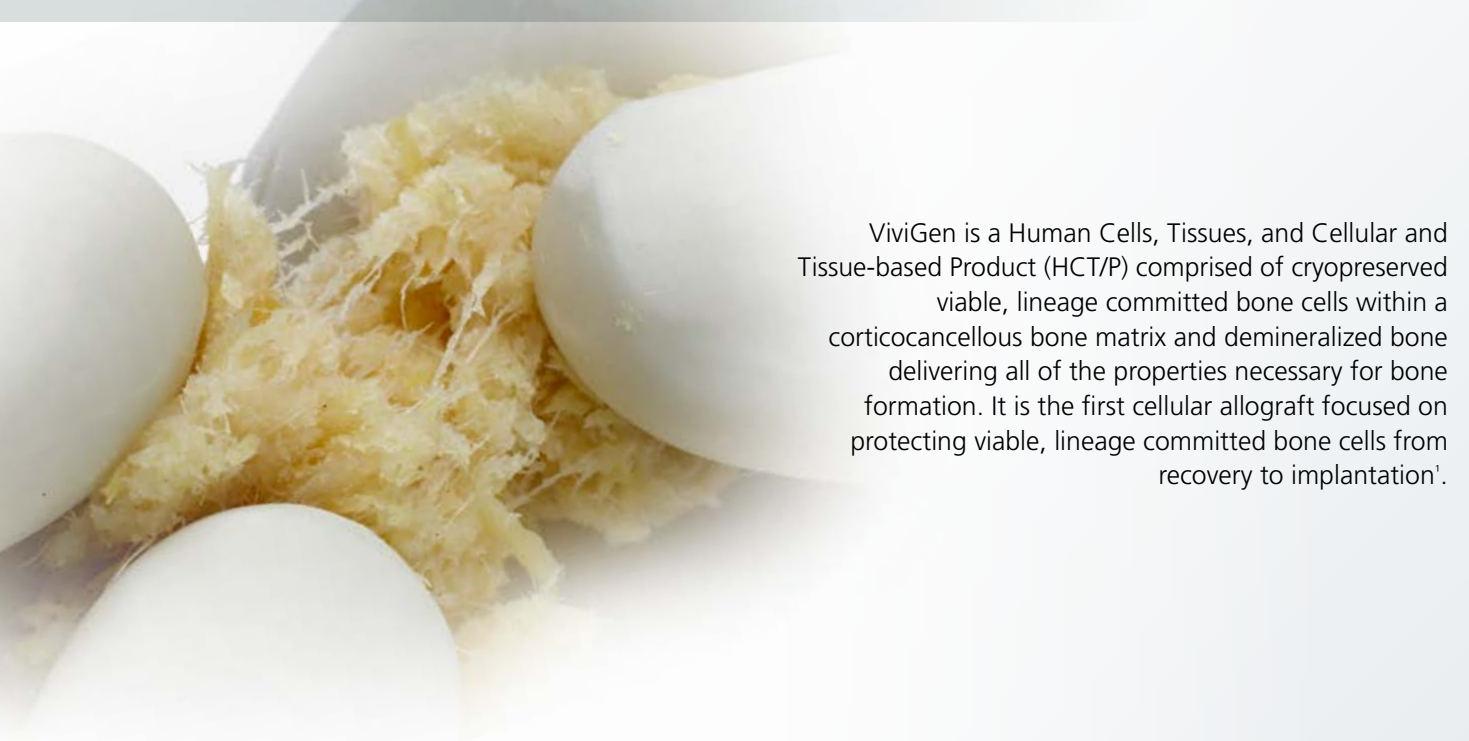
The processing of ViviGen removes bone marrow components including Mesenchymal Stem Cells while retaining the desirable bone cells (osteoblasts, osteocytes and bone lining cells)<sup>1</sup>

### 2 Corticocancellous Chips (Osteoconductive)

Provide a natural scaffold for cell attachment, migration and proliferation

### 3 Demineralized Bone (Osteoinductive)

A patented demineralization process exposes natural growth factors within the bone matrix that recruit host cells and stimulate bone forming activity



ViviGen is a Human Cells, Tissues, and Cellular and Tissue-based Product (HCT/P) comprised of cryopreserved viable, lineage committed bone cells within a corticocancellous bone matrix and demineralized bone delivering all of the properties necessary for bone formation. It is the first cellular allograft focused on protecting viable, lineage committed bone cells from recovery to implantation<sup>1</sup>.

## The Right Forms

A comprehensive solution to meet surgeons' clinical needs

ViviGen contains osteoinductive, demineralized bone particulate.

This particulate allows the graft to be placed into a contained void.



ViviGen Formable™ Cellular Bone Matrix contains osteoinductive, precision-machined, demineralized fibers.

These demineralized fibers provide a putty like consistency allowing the graft to be shaped and molded.



ViviGen and ViviGen Formable provide the same advantages with alternative formulations to meet surgeons' clinical needs.

## The Right Cells

### In Vitro Assays

#### ViviGen Bone Cells are Viable

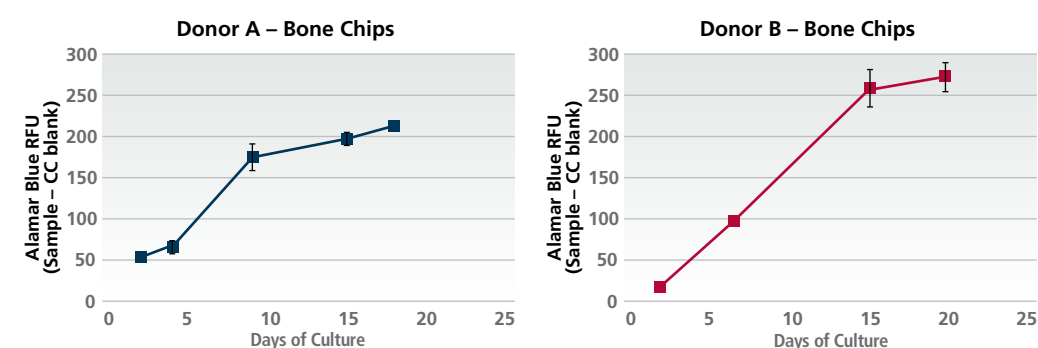
The ViviGen derived cells were able to migrate from the bone chips and attach to the culture plate, demonstrating that they survived the freezing and thawing process<sup>1</sup>.

#### ViviGen Bone Cells are able to Proliferate

Assays that can demonstrate the proliferation potential of cells are the ultimate test of viability, since they test cell function and not just membrane integrity. Results show that ViviGen cells not only survived cryopreservation and processing, but can also proliferate over time<sup>1</sup>.



Representative picture of cell migration, attachment, and growth of ViviGen derived cells.



Representative ViviGen bone matrix from 2 different donors were thawed and tested for growth potential by the Alamar blue assay. ViviGen derived bone cells proliferate over time.

#### ViviGen is Osteogenic<sup>1</sup>

ViviGen derived cells were analyzed to assess their capacity to generate bone. A substantial deposition of calcium was seen in the ViviGen cells as early as day 7. When allowed to differentiate to 14 - 21 days, extensive matrix deposits were evident by their positive red staining for calcium in the entire well<sup>1</sup>. In contrast, the comparative control of human bone marrow mesenchymal stem cells (hMSCs) were found to begin the deposition of extracellular calcium however, they detached from the culture wells after 21 days. No additional calcium deposition was found compared to those on day 14<sup>1</sup>.



Osteogenic capacity of ViviGen derived cells from two donors post processing, cryopreservation and thawing. Cells were allowed to grow until 75-85% confluent and then exposed to osteogenic media. Cells were then fixed at 7, 14, or 21 days and stained for calcium deposits with alizarin red. Human bone marrow mesenchymal stem cells (hMSCs, Lonza) were used as a comparative control.

## The Right Time

### Processing Time is Important



- Donor recovery and processing time directly affects cell viability<sup>13</sup>.
- ViviGen is recovered, processed, and placed into cryopreservation within 72 hours<sup>1</sup>.
- ViviGen is cryopreserved 24 hours faster than competitive cellular allografts<sup>14</sup>.

#### Rapid Thawing is Crucial for Cell Viability<sup>13</sup>

The thin walls of the ViviGen pouch allow for an efficient energy transfer resulting in a thaw time of less than 5 minutes for all sizes. This rapid thaw prevents ice crystals from forming intracellularly, ultimately maintaining cell viability.



THAWING TIME



## The Right Forms

### A Comprehensive Solution to Meet Surgeons' Clinical Needs

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## Safety

LifeNet Health prides themselves on their safety record over the last 30+ years. They hold the longest continuous accreditation from the American Association of Tissue Banks, and have a comprehensive range of measures in place to validate the safety of their allograft bio-implants; this includes stringent donor screening methods and release criteria. To obtain suitable donors, LifeNet Health maintains an extensive network of recovery partners. Additionally, LifeNet Health is a leading, federally designated Organ Procurement Organization. LifeNet Health only accepts donors from federally designated Organ Procurement Organizations and qualified tissue recovery partners. These partners are regularly audited to document that their recovery process meets current FDA regulations, AATB standards and LifeNet Health's own stringent guidelines.

### Donor Criteria

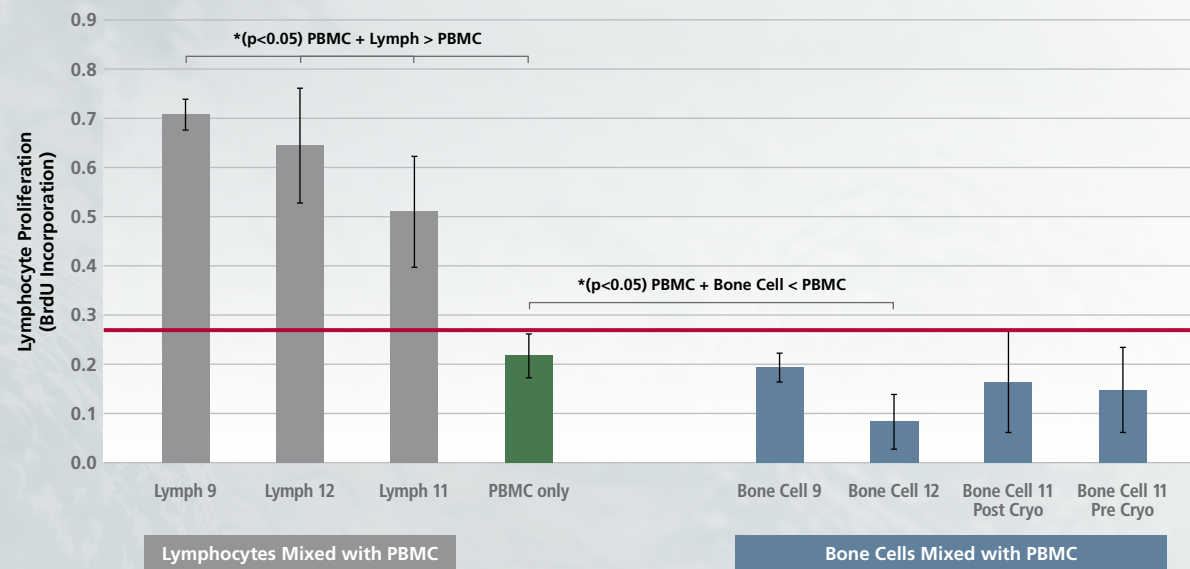
Every donor for ViviGen must meet LifeNet Health's strict medical and behavioral risks assessment in addition to microbial and serological testing.

### Aseptic Processing

LifeNet Health utilizes aseptic techniques in ISO certified clean rooms. Each lot of final product is tested for sterility.

## ViviGen Cells are Non-Immunogenic<sup>1</sup>

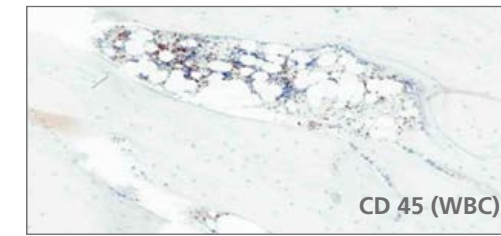
### Mixed Lymphocyte Reaction Study<sup>1,13</sup>



Mixed lymphocyte reaction. Lymphocytes from ViviGen donors were combined with PBMC to elicit an immune reaction (grey bars). ViviGen derived bone cells from the same donors were mixed with PBMC (blue bars). PBMC alone was used as a negative control (green bar).

Lymphocytes from ViviGen donors were combined with peripheral blood mononuclear cells (PBMC) to illicit an immune reaction. As expected, lymphocytes stimulated a statistically significant proliferative response from the non-matched PBMCs. ViviGen derived bone cells from the same donors were also mixed with PBMC resulting in no proliferation. This illustrates the absence of an immune response from the ViviGen derived bone cells<sup>1</sup>.

## ViviGen Processing Removes Marrow Components<sup>1</sup>



Marrow components present pre-processing



Marrow components removed post-processing, cryopreservation and thawing

Staining for CD45, a type I transmembrane protein present on all hematopoietic cells, confirmed the presence of hematopoietic cells in the bone matrix prior to processing. Post processing, cryopreservation and thawing, marrow components including CD45 positive cells were absent, which confirmed the marrow components were negligible. This demonstrates the processing reduces the number of potentially immunogenic cells from the bone marrow, also reducing the risk of eliciting an immune response.<sup>1</sup>

## Features and Benefits

FEATURES	BENEFITS
<b>Osteogenic</b>	Contains viable, lineage committed bone cells that are able to proliferate in vitro post cryopreservation and thaw
<b>Osteoconductive</b>	Contains corticocancellous chips that provide a natural scaffold for cell attachment, cell migration and cell proliferation
<b>Osteoinductive</b>	Demineralization of the cortical bone exposes the natural growth factors within the matrix
<b>Safety</b>	Every lot is aseptically processed and all final product is tested for sterility using USP <71> standards
<b>Packaging</b>	The rapid heat transfer not only allows for all sizes to thaw in less than 5 minutes, but is also vital for cell viability
<b>Processing Time</b>	ViviGen reaches cryopreservation within 72 hours maximizing cell viability 24 hours sooner than competitive products
<b>Maximized Cell Viability</b>	The processing of ViviGen is focused on protecting viable, lineage committed bone cells from recovery to implantation <sup>1</sup>
<b>Multiple forms</b>	ViviGen and ViviGen Formable provide a comprehensive solution to meet surgeons' clinical needs

# Ordering

	ITEM NUMBER	DESCRIPTION
<b>ViviGen</b>	BL-1500-001	1cc
	BL-1500-002	5cc
	BL-1500-003	10cc
	BL-1500-004	15cc
<b>ViviGen Formable</b>	BL-1600-001	Small
	BL-1600-002	Medium
	BL-1600-003	Large
	BL-1600-004	X-Large



All Vivigen orders are placed with LifeNet Health directly by phone:  
1-888-847-7831, fax:1-888-847-7832 or email: [orders@lifenethealth.org](mailto:orders@lifenethealth.org).  
Business hours are Monday through Friday, from 7am to 7pm EST.

## Shipping

### Free Next-Day Delivery

Vivigen is shipped for next day delivery by 10:30am free of charge.  
Next day early AM is also available upon request.

1. Data on file LifeNet Health DHF 12-008, DHF 15-001
  2. Dirckx N, Van Hul M, Maes C. Osteoblast recruitment to sites of bone formation in skeletal development, homeostasis, and regeneration. Birth Defects Res C Embryo Today. 2013 Sep;99(3):170-91.
  3. Rupani A, Balint R, Cartmell SH. Osteoblasts and their applications in bone tissue engineering. Cell Health and Cytoskeleton 2012;4:49-61.
  4. Biomaterials 31 (2010) 242-249
  5. J Tissue Engineering & Regenerative Medicine 5 (2011) 831-844
  6. Biomaterials 32 (2011) 8150-8160
  7. Bone 43 (2008) 869-895
  8. European Cell and Materials 23 (2012) 13-27
  9. J. Orthopaedic. Research. 8 (1990), 234-237
  10. Bone 25 (1999), 667-673
  11. J. Orthopaedic. Research. 22 (2004), 30-38.
  12. Biochem. J. 333 (1998), 787-794.
  13. Human Reproduction vol.3 no.6 pp. 795-802, 1988
  14. Trinity Evolution® Product Brochure
- Findings from an in vitro assay are not always predictive of human clinical results.



[www.depuyssynthes.com](http://www.depuyssynthes.com)

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