

OraGEN[®]

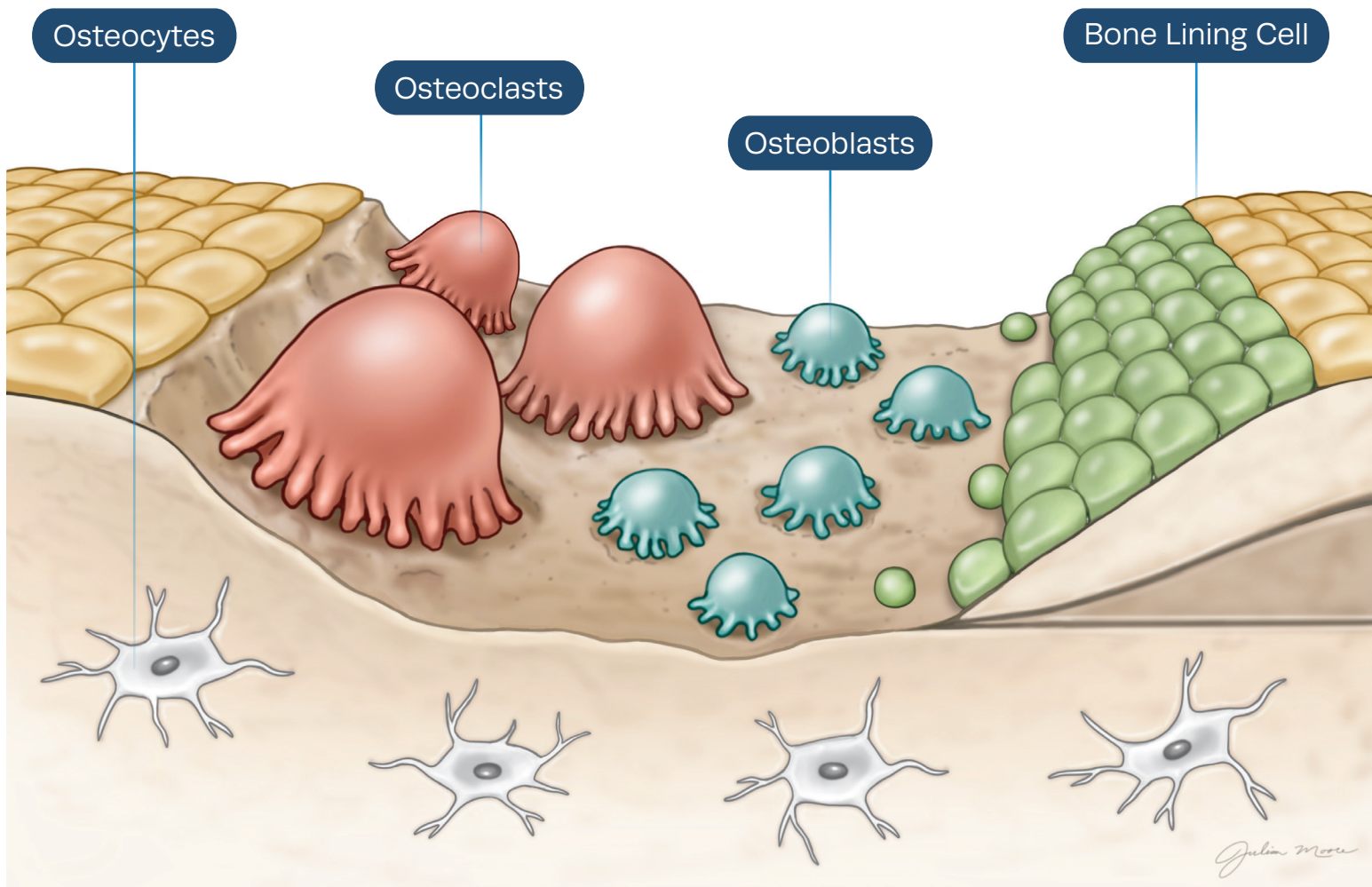
Cellular Bone Matrix



SALVIN[®]

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 bone remodeling and repair, osteogenic cells are required to reach the defect site to directly participate in these processes.² Bone cells that are responsible for this remodeling process have very specific roles and functions.



Bone Healing & Remodeling

Osteoblasts

Bone building cells that secrete the collagen matrix and synthesize proteins such as osteopontin and osteocalcin and are involved in the mineralization of the matrix.^{2,3} Osteoblasts can develop into osteocytes.⁴

Osteoclasts

Bone cells responsible for the absorption and removal of old bone.⁴

Osteocytes

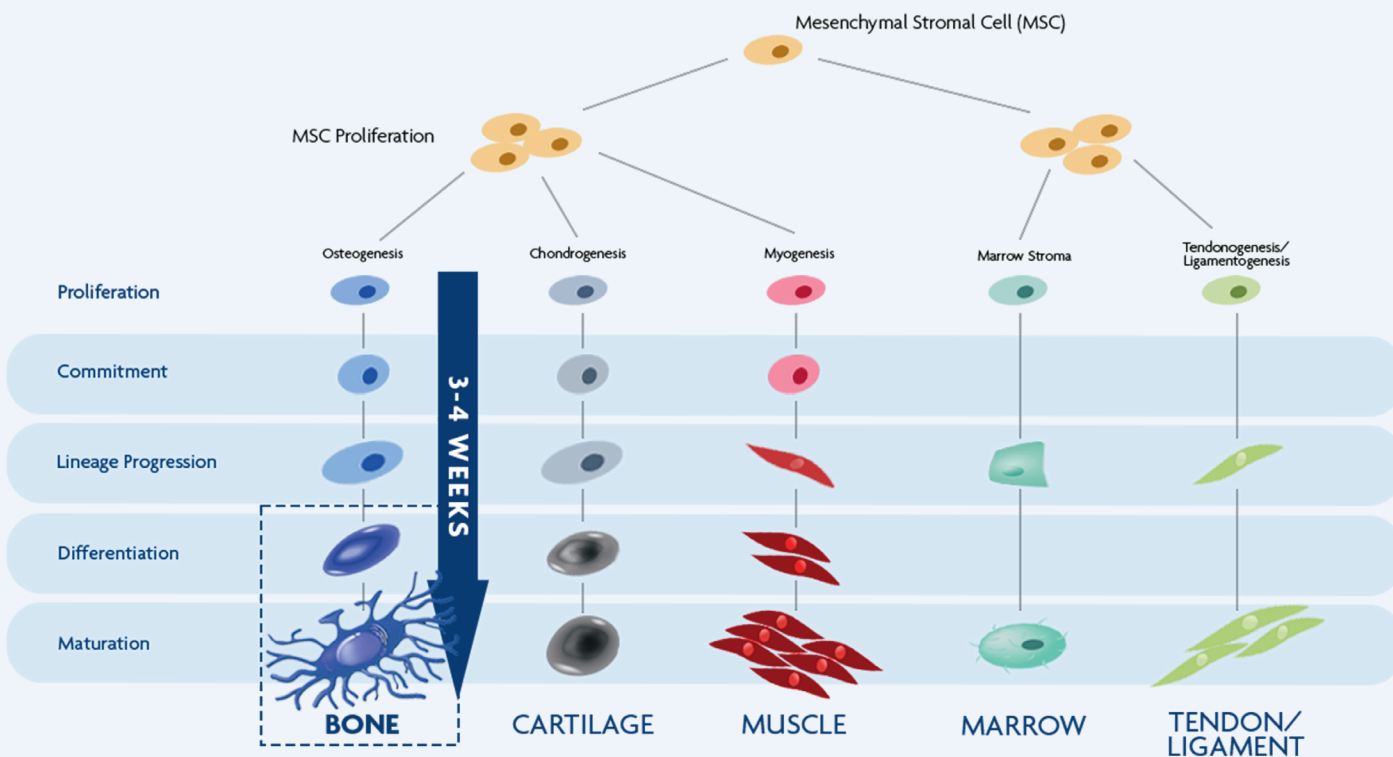
Terminally differentiated osteoblasts that are entrapped in the mineralized matrix. They are able to send signals based on stress and strain felt within the bone to begin the remodeling process.⁴

Bone lining cells

Cells that line the surface of bone that direct mineral uptake and release in bone.⁴

The Bone Cell Advantage

OraGen® 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.^{5,6} **Unlike MSCs, which require 2–4 weeks to differentiate into osteoblasts through the process of mesengensis, OraGen delivers lineage-committed osteogenic cells at the time of implantation.**



Pre-Clinical Studies Suggest Bone Cells†:

- Remain at the defect site longer⁵, directly participate in the bone formation process and deposit a higher quality of bone compared to MSCs.⁶
- Secrete chemotactic factors such as IGF-1, which may play a major role in recruitment of osteoblasts during bone formation.^{7,8}
- Secrete cytokines to stimulate angiogenesis⁷ and work in concert to facilitate further MSC differentiation.⁹
- Maintain viability, proliferation potential and osteoblastic function later in life compared to an MSC.¹⁰⁻¹³

†Pre-clinical data may not be predictive of human clinical results

THREE KEY PROPERTIES OF ORAGEN

1 CELLS

Osteogenic (Viable Cells)

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

2 SCAFFOLD

Osteoconductive (Corticocancellous Chips)

Provide a natural scaffold for cell attachment, migration and proliferation¹

3 SIGNALS

Osteoinductive (Demineralized Bone)

A patented demineralization process exposes natural growth factors within the bone matrix that recruit host cells and stimulate bone forming activity¹

OraGen is a 361 Human Cells, Tissues and Cellular-based Product 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.¹

Safety

At LifeNet Health, we take immense pride in our safety record spanning more than 40 years. We hold the longest continuous accreditation from the American Association of Tissue Banks (AATB) and have implemented a comprehensive range of measures to ensure the safety of our allograft bio-implants. This includes stringent donor screening methods and release criteria.

To secure suitable donors, we maintain an extensive network of recovery partners. As a leading, federally designated Organ Procurement Organization, we only accept donors from federally designated Organ Procurement Organizations and qualified tissue recovery partners. These partners are regularly audited to ensure their recovery processes meet current FDA regulations, AATB standards, and our own stringent guidelines.

Donor Criteria

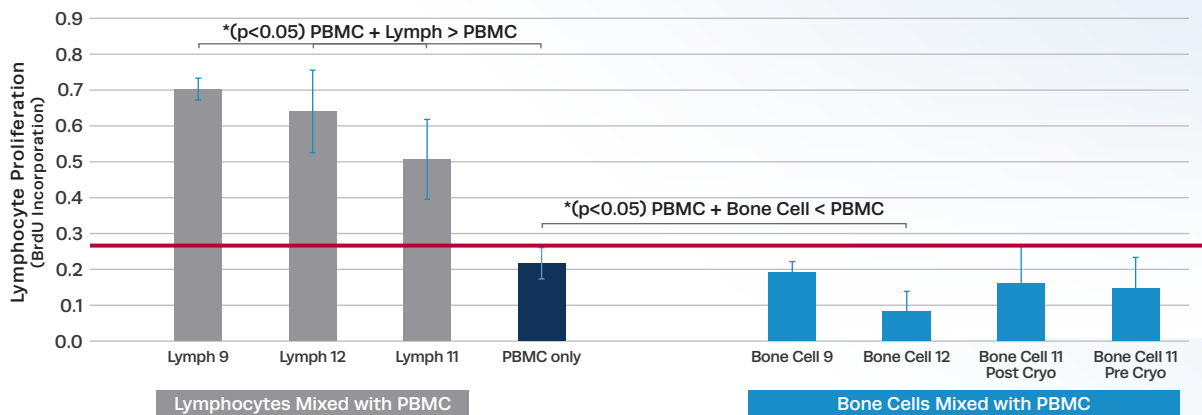
Every donor for OraGen must meet LifeNet Health's strict medical and behavioral risks assessment in addition to microbial and serological testing.

Aseptic Processing

LifeNet Health utilizes aseptic techniques in ISO certified clean rooms. Each lot of final product is tested for sterility per USP <71>.

OraGen Cells are Non-Immunogenic¹

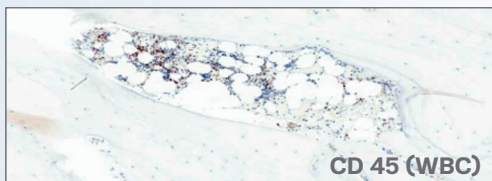
Mixed Lymphocyte Reaction Study¹



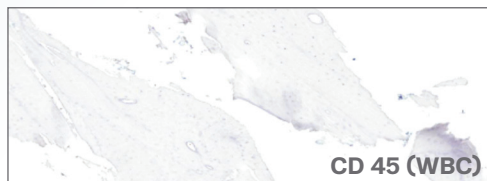
Mixed lymphocyte reaction. Lymphocytes from OraGen donors were combined with PBMC to elicit an immune reaction (grey bars). OraGen derived bone cells from the same donors were mixed with PBMC (light blue bars). PBMC alone was used as a negative control (dark blue bar).

Lymphocytes from OraGen 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. OraGen 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 OraGen derived bone cells¹.**

OraGen Processing Removes Marrow Components¹



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.¹**

THE RIGHT CELLS

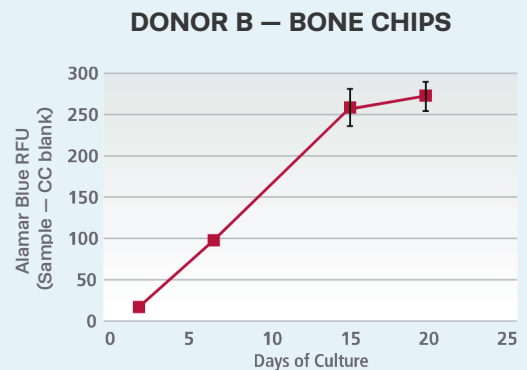
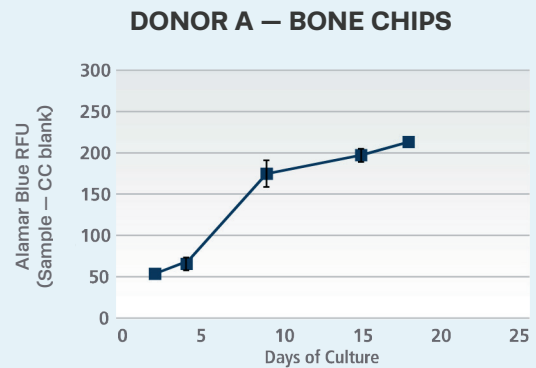
In Vitro Assay

OraGen Bone Cells are Viable

The OraGen 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.¹

OraGen 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 OraGen cells not only survived cryopreservation and processing, but can also proliferate over time.¹



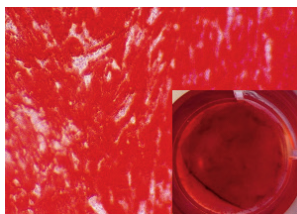
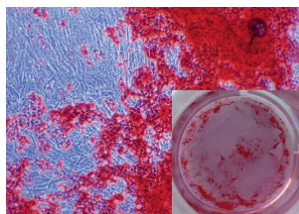
Representative OraGen Bone Matrix from 2 different donors were thawed and tested for growth potential by the Alamar blue assay. OraGen derived bone cells proliferate over time.

OraGen is Osteogenic¹

OraGen derived cells were analyzed to assess their capacity to generate bone. **A substantial deposition of calcium mineral deposits was seen in the OraGen 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.¹ 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 14.¹

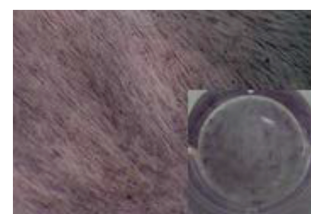
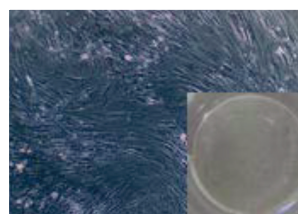
DAY 7

DAY 14



DAY 7

DAY 14



Osteogenic capacity of OraGen 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 5. Human bone marrow mesenchymal stem cells (hMSCs, Lonza) were used as a comparative control.

Clinically Meaningful Advantages

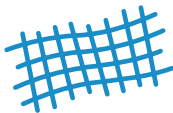
FEATURES

BENEFITS



Osteogenic

Native, viable, lineage-committed bone cells within the corticocancellous chips are able to proliferate *in vitro* post cryopreservation and thaw.¹



Osteoconductive

Corticocancellous chips that provide a natural scaffold for cell attachment, cell migration and cell proliferation.¹



Osteoinductive Potential

Demineralization of the cortical bone exposes the natural growth factors within the matrix.¹



Safety

Every lot is aseptically processed and all final product is tested for sterility using USP <71>.



Packaging

The rapid heat transfer not only allows for all sizes to thaw in less than 5 minutes, but is also vital for cell viability.¹



Processing Time

OraGen reaches cryopreservation within 72 hours maximizing cell viability.¹



Maximized Cell Viability

The processing of OraGen is focused on protecting viable, lineage committed bone cells from recovery to implantation.¹

TWO SIZES

Flexibility to treat
large or small, challenging
dental bone defects.



Instructions for Use available at LifeNetHealth.org/IFU

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