BIOVANCE®

Human Amniotic Membrane Allograft

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BIOVANCE® vs dehydrated Human Amnion/Chorion Membrane (dHACM)

The pure amniotic membrane allograft BIOVANCE supports tissue restoration in an orderly progression through wound healing

Background: Successful application of biomaterials for wound healing requires that these biomaterials contain components capable of promoting endogenous regeneration processes such as tissue remodeling and repair. Some of these biomaterials have demonstrated the ability to support wound closure;3,4 however, their mechanisms of action are not well known.

Description: This compilation of in vitro data presents findings demonstrating how BIOVANCE and dHACM affect and interact with the major cell types involved in wound healing.

INDICATIONS FOR USE
BIOVANCE is an allograft intended for use as a biological membrane covering that provides the extracellular matrix while supporting the repair of damaged tissue. As a barrier membrane, BIOVANCE is intended to protect the underlying tissue and preserve tissue plane boundaries with minimized adhesion or fibrotic scarring. Indications include, but are not limited to, surgical covering, wrap or barrier, application to partial- and full-thickness, acute and chronic wounds (such as, traumatic and complex wounds, burns, surgical and Mohs surgery sites; and diabetic, venous, arterial, pressure and other ulcers), including wounds with exposed tendon, muscle, bone or other vital structures.

WARNINGS
If a patient has an adverse reaction related to the use of BIOVANCE, immediately discontinue its use. BIOVANCE should not be used on clinically infected wounds.

PRECAUTIONS
BIOVANCE should not be used together with a collagenase product on the wound.

CONTRAINDICATIONS
BIOVANCE is contraindicated in patients with a known hyper-sensitivity to BIOVANCE.

For product information, product complaints, or adverse reaction reporting, call 1-844-963-2273.

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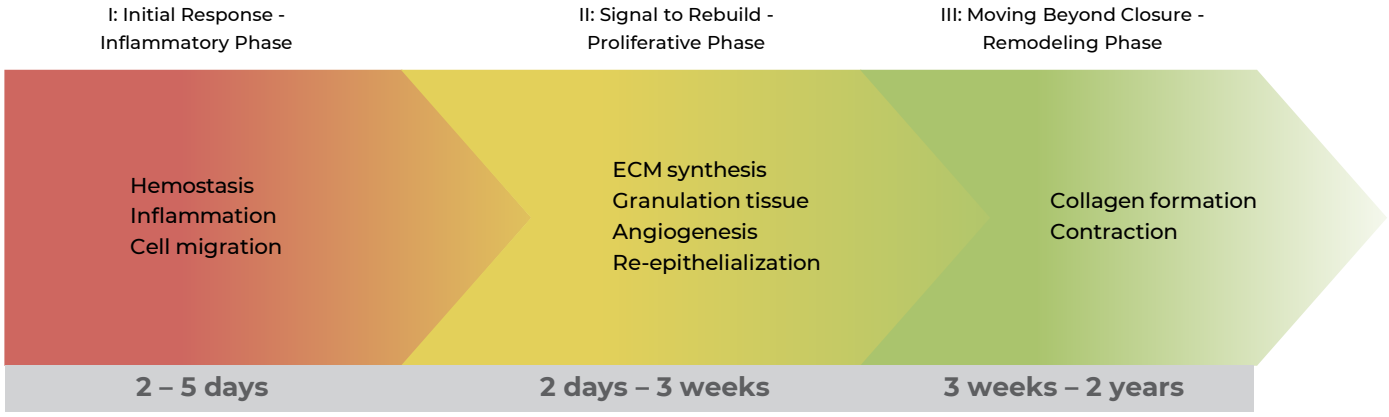
Wound healing: A predictable and orderly progression of phases[5]

In a healthy state, there is a predictable sequence of cells, growth factors, cytokine secretions, cell attachment and proliferation, angiogenesis, and Extracellular Matrix (ECM) production



- Platelets initiate wound healing through secretion of proteins
- Proteins signal the need for cleanup
- Macrophages clean the wound site

- Keratinocytes, endothelial cells, and fibroblasts vascularize new tissue and produce a protective epithelial layer
- Endothelial cells initiate angiogenesis and tissue repair

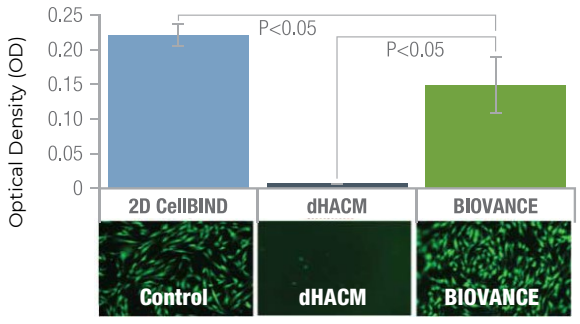
- Collagen maturation
- Capillary regression

BIOVANCE: A cell-friendly matrix[1]

Within 24 hours, fibroblasts and keratinocytes readily attached to BIOVANCE, but not dHACM[1]

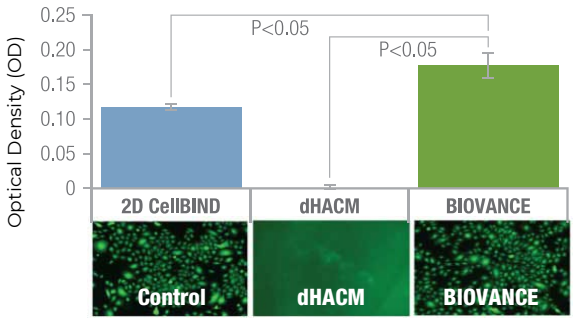
FIBROBLASTS

Fibroblast Attachment at 24 hrs (MTS Assay), n=3



KERATINOCYTES

Keratinocyte Attachment at 24 hrs (MTS Assay), n=3



- In *in vitro* data, BIOVANCE served as a natural scaffold with an intact basement membrane that supported a high level of fibroblast and keratinocyte attachment vs dHACM, which had no attachment of either cell type

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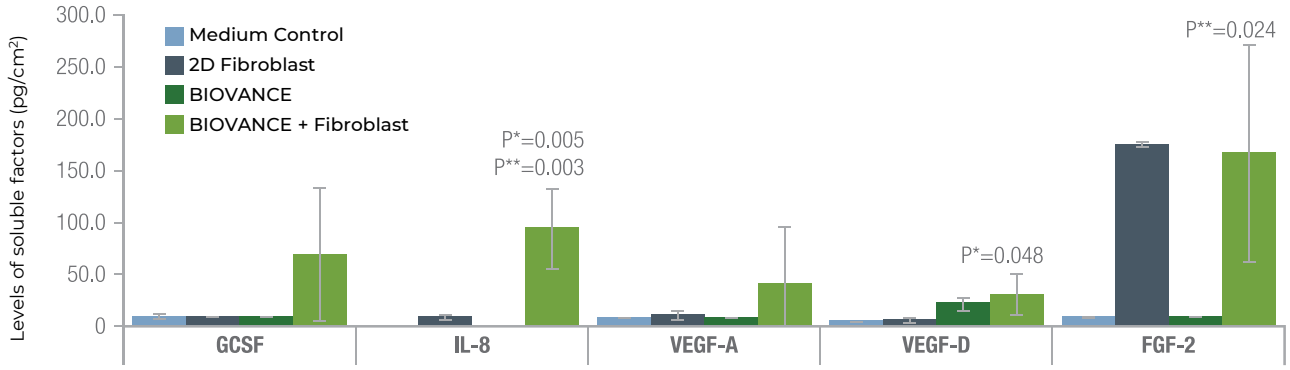
Fibroblasts that attach to and grow on BIOVANCE release growth factors in vitro that support wound closure[1]

Levels of selected growth factors produced by fibroblasts grown on BIOVANCE[1]

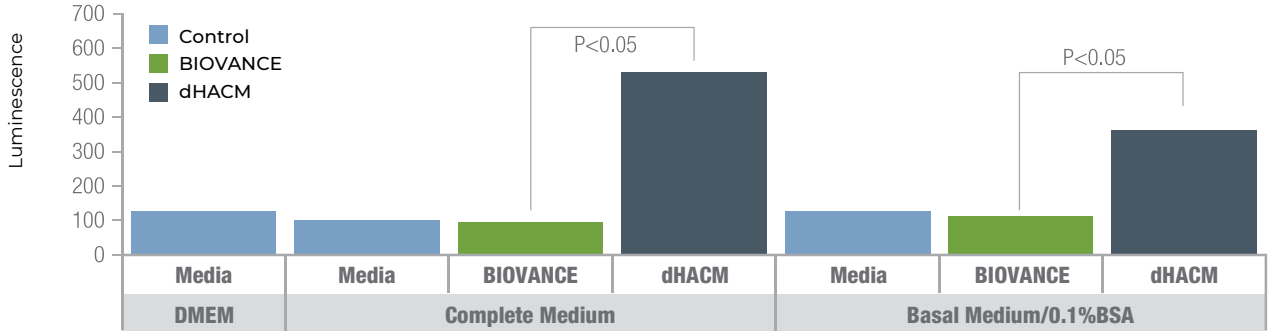


- Growth factors, among other key molecules released by attached fibroblasts, may support key events in wound healing such as cell survival, wound closure, and angiogenic blood vessel formation
- Once growth factors were released, measured cell metabolic activity showed the revival of senescent endothelial cells and keratinocytes

In vitro study demonstrated dHACM stimulated cell death at 24 hours[1]

dHACM extract caused fibroblast apoptosis at 4 hours and eventual cell death within 24 hours[1]

Levels of Apoptosis at 4 hrs Cell Culture in "Extract," n=3



BIOVANCE contains limited amounts of soluble extracellular matrix proteins and virtually no cytokines, while dHACM demonstrated an overwhelming variety[1,2]

- Extracts of BIOVANCE supported cell attachment, proliferation, and production of insoluble fibronectin network
- Extracts of BIOVANCE did not contain any components that were deleterious to cell survival
- Despite the presence of a variety of growth factors and cytokines, the extracts of dHACM contained biochemical components that caused cell apoptosis at 4 hours, followed by eventual cell death at 24 hours

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"Our body knows what it needs, when it needs it, and how much it needs to heal a wound."
- T. Treadwell MD, SAWC Meeting, May 2, 2015

- Wound healing is a methodical, organized process dependent upon a predictable sequence of events
- Too much interference or inappropriate signaling can cause chaos or senescence, damaging wound healing progress[6]

Benchtop study findings:

BIOVANCE helps the body restore the natural wound healing processes

- Offers pure human amniotic tissue with an intact basement membrane
- Serves as a cell-friendly structure for fibroblast and keratinocyte attachment within hours
- Cell attachment is a natural stimulus for the orderly release of growth factors and cytokines
- The released growth factors and cytokines activated starved (senescent) cells

dHACM may present obstacles in the wound healing process

- Fibroblast and keratinocyte attachment not observed within 24 hours
- dHACM provides a variety and quantity of growth factors and cytokines to the wound upon application, which may disrupt the wound healing process
- dHACM extract was associated with fibroblast apoptosis at 4 hours and cell death at 24 hours

In vitro data demonstrated BIOVANCE pure amniotic membrane allograft supports the orderly progression of wound healing that is lost in a chronic wound state. BIOVANCE supports tissue restoration.

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1. Bhatia M, Pereira M, Rana H, Stout B, Lewis C, Abramson S. The mechanism of cell interaction and response on decellularized human amniotic membrane: Implications in wound healing. *Wounds.* 2007;19(8):207-217. 2. Koob TJ, Lim JJ, Zabek N, Massee M. Cytokines in single layer amnion allografts compared to multilayer amnion/chorion allografts for wound healing. *Journal of Biomedical Materials Research Part B: Applied Biomaterials.* 2015;103(5):1133–1140. 3. Zelen CM, Gould L, Serena TE, Carter MJ, Keller J, Li WW. A prospective, randomised, controlled, multi-centre comparative effectiveness study of healing using dehydrated human amnion/chorion membrane allograft, bioengineered skin substitute or standard of care for treatment of chronic lower extremity diabetic ulcers. *Int Wound J.* 2015;12(6):724-732. doi:10.1111/iwj.12395 4. Wilcox JR, Carter MJ, Covington S. Frequency of debridements and time to heal: A retrospective cohort study of 312 744 wounds. JAMA dermatology. 2013;149(9):1050-1058. doi:10.1001/jamadermatol.2013.4960 5. Akbik D, Ghadiri M, Chrzanowski W, Rohanizadeh R. Curcumin as a wound healing agent. *Life Sci.* 2014;116(1):1-7. doi:10.1016/j.lfs.2014.08.016 6. SAWC Spring 2015 Meeting Presentation: The Progenerative Power of Amnion: The Science and the Clinical Experience for BIOVANCE® Human Amniotic Membrane Allograft, Mohit Bhatia, PhD.

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