

The last step before you close is the first step in your patient's healing.

Finally, a next generation bioactive tissue.





A bioactive tissue matrix that reduces scar tissue formation and modulates inflammation with natural barrier properties to enhance healing.



## 

Since 2006, as the **premier leader** in regenerative medicine, **MiMedx** has been dedicated to advancing healing through innovative biomaterial products and bioimplants. To date, over **25** clinical and scientific papers have been **published** in peer-reviewed journals on our PURION<sup>®</sup> Processed amniotic membrane allografts. The company's **proprietary PURION Process** and its multi-layer grafts are covered by over **20 issued patents**, with more than 80 patents pending. PURION Processed allografts are **clinically effective** and more than **500,000 allografts** have been distributed to date with **no adverse reactions** attributed to our products.<sup>†</sup>

days.

### Proven cell proliferation in

AmnioFix stimulates human dermal fibroblasts (HDFs) and human mesenchymal stem cells (MSCs) to proliferate.<sup>1</sup>



MSC Proliferation in response to AmnioFix



cell numbe

AM189.002



There are **226** soluble **growth factors, cytokines,** and **chemokines** involved in soft tissue healing and modulation of inflammation contained in every AmnioFix amnion/chorion membrane allograft processed using the proprietary PURION<sup>®</sup> Process.<sup>1,4</sup>

All amniotic membrane products are **NOT equal**.

AmnioFix has **MORE** soluble growth factors and cytokine content than competitor single layer tissue repair products composed of amnion alone.<sup>2</sup>



In a study investigating the use of AmnioFix in reducing epidural fibrosis and facilitating dissection in revision spinal injury, **AmnioFix performed better** than other barriers previously utilized in revision surgery.<sup>3</sup>

Reduction in scar tissue and inflammation

No intraoperative or postoperative complications, including cerebrospinal leaks, wound infections or wound dehiscence.

# The AmnioFix Difference

## All amniotic membrane products are **NOT equal**.

AmnioFix allografts contain BOTH amnion and chorion layers

The chorion layer contains cytokines and chemokines which help regulate the inflammatory response

> Each AmnioFix graft contains approximately 20x more growth factors and cytokines than selected single layer grafts<sup>2</sup>

## Easy to use

**5 year shelf life** at ambient conditions; no special storage required Proprietary PURION® Process and its multi-layer grafts are covered by over **20 issued patents,** with more than **80 patents pending** 

**Over 500,000** allografts have been distributed with **NO** adverse reactions attributable to our products<sup>†</sup>

# AmnioFix® Don't close without it.

#### **TO FIND OUT MORE ABOUT AMNIOFIX:**

Please Call: **866.477.4219** Email: **customerservice@mimedx.com** Reimbursement Hotline: **855.882.8480** 

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† As of January 1, 2016

1. Data on file

Koob TJ, Lim JJ, Zabek N, Massee M, Cytokines in single layer amnion allografts compared to multilayer amnion/chorion allografts for wound healing. J Biomed Mater Res B Appl Biomater. 2014 Aug 30. doi: 10.1002/jbm.b.33265.
 Subach BR, Copay AG. The use of a dehydrated amnion/chorion membrane allograft in patients who subsequently undergo reexploration after posterior lumbar instrumentation. Adv Orthop. 2015;2015:501202.
 Koob TJ, et al. A Primer on Amniotic Membrane Regenerative Healing. 1st ed. Grand Rapids, MI: MiMedx/Color House Graphics. 2015.



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## An Amnion/Chorion Membrane Allograft

AmnioFix<sup>®</sup> is a bioactive tissue matrix composed of human amnion/chorion membrane for homologous use to modulate inflammation, reduce scar tissue formation, and enhance healing.





#### Modulates Inflammation Reduces Scar Tissue Formation Enhances Healing

#### **Growth Factors Present in AmnioFix**

There have been 226 different growth factors, specialized cytokines, and enzyme inhibitors identified in AmnioFix, including the following which are some of the most notable regulatory factors that help enhance healing:<sup>1-4</sup>

- Transforming Growth Factor Beta (TGF-B1) Promotes normal soft tissue healing and reduced scar formation
- Fibroblast Growth Factor (FGF) Promotes cellular proliferation and important for collagen matrix formation
- Platelet Derived Growth Factors (PDGF AA & BB) Promote cell proliferation in connective tissue and enhance soft tissue healing

Native Growth Factors Present	Relative Amount Determined by ELISA Assay (n=5)	Release Profile (n=5) • 24 hr incubation period at 4°C • Remaining in tissue
PDGF-AA	+++++	<u>13</u> % 87%
PDGF-BB	+	4% 96%
bFGF	++	<b>44</b> % <b>56</b> %
TGF-ß1	++	24% 76%
EGF	+	<b>63</b> % <b>37</b> %

Growth Factors contained in PURION® Processed dehydrated amnion/chorion membrane, relative amounts and release profile. Measured by ELISA testing unlysed and lysed tissue in suspension.

#### **Extracellular Components in AmnioFix**

The Extracellular Matrix of amniotic membrane is composed of three major classes of biomolecules:

- Structural proteins: collagen types I, III, IV, V and VII, and elastin
- Specialized proteins: fibronectin, TIMPs<sup>+</sup>, and laminins
- Proteoglycans: formed when GAGS are linked to core proteins

In addition to the properties of the growth factors present which modulate inflammation, AmnioFix can also stimulate native cells to upregulate their production of immunomodulatory factors.<sup>5</sup>

PURION<sup>®</sup> Processed dehydrated human amnion/chorion membrane (dHACM) contains extracellular matrix, stimulates multiple cell types to migrate and proliferate, and acts as a Stem Cell Magnet<sup>™</sup> drawing mesenchymal stem cells and hematopoietic stem cells from tissues to the site of injury.<sup>6</sup>

Recruited stem cells modulate the body's inflammatory response releasing their own growth factors, cytokines, and paracrine factors to begin the healing process.<sup>7</sup>

#### **PURION Process**

AmnioFix is processed using the proprietary PURION Process, a unique approach that provides an effective and easy to use allograft.

#### **Immunologically Privileged**

Human amniotic membrane is considered immunoprivileged and has not been shown to elicit an immune response from recipients.<sup>8</sup>

#### **Ease of Use**

- Dehydrated for ease of use and application
- Five year shelf life at ambient conditions; no special storage required
- Over 500,000 allografts distributed with no adverse reactions attributed to our products<sup>††</sup>

#### Application

AmnioFix may be mixed with sterile saline. Refer to "Instructions for Use" included with product for full application instructions and recommendations.

#### Product Offering

Item Number	Size
AI-5020	20 mg
AI-5050	40 mg
AI-5125	100 mg
AI-5200	160 mg

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#### **Ordering Information**

Customer Service: 866.477.4219 Email: customerservice@mimedx.com www.amniofix.com

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8. Sherwood, Lauralee. Human Physiology, From Cells to Systems, 7th ed. Belmont, CA: Cengage Learning, 2010.



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<sup>†</sup> Tissue Inhibitors of Metalloproteinases

<sup>† †</sup> As of January 1, 2016

<sup>1.</sup> Koob TJ, Rennert R, Zabek N, Massee M, Lim JJ, Temenoff JS, Li WW, Gurtner G. Biological properties of dehydrated human amnion/chorion composite graft: implications for chronic wound healing. Int Wound J. 2013 Oct;10(5):493-500. 2. Koob TJ, Lim JJ, Massee M, Zabek N, Denozière G. Properties of dehydrated human amnion/chorion composite grafts: implications for wound repair and soft tissue regeneration. J Biomed Mater Res B Appl Biomater. 2014 Aug;102(6):1353-62. 3. Koob TJ, Lim JJ, Massee M, Zabek N, Rennert R, Gurtner G, Li WW. Angiogenic properties of dehydrated human amnion/chorion allografts: therapeutic potential for soft tissue regeneration. Vasc Cell. 2014 May 1;6:10.

<sup>4.</sup> Koob TJ, et al. A Primer on Amniotic Membrane Regenerative Healing. 1st ed. Grand Rapids, MI: MiMedx/Color House Graphics. 2015. 5. Massee M, Chinn K, Lei J, Lim JJ, Young CS, Koob TJ. Dehydrated human amnion/chorion membrane regulates stem cell activity in vitro. J Biomed Mater Res B Appl Biomater. 2015 Jul 14. doi:10.1002/jbm.b.33478. [Epub ahead of print] 6. Maan ZN, Rennert RC, Koob TJ, Januszyk M, Li WW, Gurtner GC. Cell recruitment by amnion chorion grafts promotes neovascularization. J Surg Res. 2015 Feb;193(2):953-62.

## SCIENTIFIC & CLINICAL MONOGRAPH



#### **AmnioFix® Product Description**

AmnioFix is a bioactive tissue matrix allograft composed of dehydrated human amnion/chorion membrane (dHACM) that preserves and contains multiple extracellular matrix proteins, growth factors, cytokines, and other specialty proteins. AmnioFix is intended for homologous use to reduce scar tissue formation, modulate inflammation, enhance surgical wound healing, and act as a barrier membrane. AmnioFix is processed through the proprietary PURION® process that protects the delicate scaffold during processing, leaving an intact collagen matrix. The result is a durable, bioactive allograft with natural barrier properties which may be stored at ambient conditions for up to 5 years. AmnioFix is available in sheet, particulate, and wrap configurations and in a variety of sizes to reduce wastage.



MiMedx<sup>®</sup> is a leading biopharmaceutical company developing and marketing regenerative and therapeutic biologics utilizing human placental tissue allografts and patent protected processes for multiple sectors of healthcare. The multitude of factors preserved in all MiMedx products, their inherent benefits, and the Company's rigorous safety standards provide the critical advantage and differentiation of MiMedx products.

#### **Amniotic Tissue: Source of Amnion and Chorion**

Amniotic membrane, or the amniotic sac, is composed of an inner layer called the amnion and an outer layer called the chorion. The amniotic sac is formed after conception during the fetal maturation process.<sup>5</sup> The chorionic plate is intertwined with the placenta and is often confused with the chorion membrane, which is part of the amniotic sac and does not integrate with maternal tissue (Figure 1).



The use of amniotic membrane in the clinical setting has a history spanning over 100 years. Amniotic membranes are composed principally of three types of material: structural collagen and extracellular matrix, intact cells and a large number of potent regenerative molecules. When the amniotic sac is processed for clinical use, the specific processing technique can affect the preservation of proteins like growth factors, cytokines and chemokines thus affecting the stimulus for host cells to migrate, infiltrate and engraft into the tissue. AmnioFix features both the amnion and chorion layers and, due to the proprietary PURION Process utilized to process the tissue, retains a substantial amount of growth factors to enhance healing. Growth factor signaling and recruitment are important for the natural soft tissue healing process (Figure 2), and have been shown to be amplified in the presence of PURION Processed dHACM.

#### FIGURE 2



#### Source Of Amniotic Tissue

Eligible placental tissue donors are living mothers that have delivered a live birth by scheduled Caesarean section. All tissues are recovered under full informed consent of the donor (mothers of the newborn children). All tissues recovered meet stringent specifications during donor screening and laboratory testing to reduce the risk of transmitting infectious disease. AmnioFix allografts are procured and processed in the United States according to standards and/or regulations established by the American Association of Tissue Banks (AATB) and the United States Food & Drug Administration (FDA). A thorough medical and social history of the donor is also obtained, and all screening tests are reviewed by the MiMedx Medical Director prior to release of the tissues. Only tissues from donors with acceptable test results, according to the standards of MiMedx Tissue Services, LLC, as well as the standards and/or regulations of all state and federal regulatory bodies, are released.

The listed communicable disease testing is performed by a laboratory registered with the FDA to perform donor testing and certified to perform such testing on human specimens in accordance with the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and 42 CFR part 493, or that has met equivalent requirements as determined by the Centers for Medicare and Medicaid Services (CMS).

The donor is screened for:

HIV-1&2 Plus 0 Antibody	HTLV-1&2 Antibody	Hepatitis B Core Antibody	Hepatitis C Antibody	Hepatitis B Virus (Nucleic Acid Test (NAT))
HIV Type 1 (Nucleic Acid Test (NAT))	Syphilis (Serologic Test)	Hepatitis B Surface Antigen	Hepatitis C Virus (Nucleic Acid Test (NAT))	West Nile Virus (Nucleic Acid Test (NAT))*

\*WNV NAT screening conducted on donors based on exposure risk per FDA Guidance for Industry.

#### The U.S. Pharmacopeia Monograph<sup>7</sup>

The United States Pharmacopeia (USP) and the National Formulary (NF) are the public pharmacopeial standards for drug substances, dosage forms, compounded preparations, excipients, dietary supplements, and medical devices. MiMedx dHACM (AmnioFix) is the first amnion/chorion dehydrated membrane to be described in a USP monograph for amniotic membrane allografts.

#### **The PURION Process**

The PURION process is a patented process which safely and gently cleans the tissue, including the separation of the placental tissues, cleansing, reassembling of the amnion and chorion layers, and gentle tissue dehydration. The PURION process removes blood components while protecting the intricate extracellular matrix (ECM) of the amnion and chorion membrane, leaving intact cells and the extracellular matrix. When dehydration is complete, the graft is cut to multiple clinically-specific sizes, packaged and sterilized, yielding an allograft that can be stored at ambient temperatures for up to 5 years. The PURION process retains the nonviable cells and pericellular matrix in the tissue after processing.



#### **Terminal Sterilization**

MiMedx amniotic tissue membrane allografts, processed using the Company's PURION process, utilize terminal sterilization as an essential part of the process. This proprietary processing technology provides the MiMedx amniotic membrane allografts with their unique capabilities to retain the factors that are critical for clinical efficacy, provide ease of use by the physician, and offer the capacity to be stored at ambient conditions with a five year shelf life.

The terminal sterilization conducted by MiMedx is a validated process in conformance with the International Organization for Standardization ("ISO") standard ISO 11137 "Sterilization of Healthcare Products." Conformance with this ISO standard requires a demanding Sterility Assurance Level ("SAL") 10<sup>-6</sup>, which corresponds to the assurance that there is a probability of less than 1 in 1,000,000 units being non-sterile. To further enhance the safety of its amniotic products, the MiMedx proprietary processing methodology employs aseptic processing techniques in addition to terminal sterilization.

MiMedx has been processing its amniotic products based on the regulations and guidance issued by both the FDA and the American Association of Tissue Banks ("AATB") standards and guidance on donor eligibility and screening to reduce the risk of disease transmission via human tissues.

MiMedx's PURION process and low dose terminal sterilization have demonstrated that the product retains its biological activity critical to wound healing. Scientific studies have specifically examined the impact of irradiation on bioactivity by testing samples of dHACM pre- and post-sterilization. Terminal sterilization did not impact the biological activity of PURION processed amniotic membrane, which promoted similar levels of human dermal fibroblast and mesenchymal stem cell proliferation as pre-sterilization tissues.<sup>8</sup> Additionally, the maintenance of bioactivity and the ability to promote the subsequent healing cascade have been scientifically proven for MiMedx's products in multiple clinical trials and peer-reviewed, published papers. Therefore, the PURION process offers an ideal balance of both patient safety and clinical efficacy.

#### No Immune Response

The amnion and chorion layers of human amniotic membrane serve as the principle tissue separation between mother and child. The layers do not have vascularity nor do they present clinically relevant amounts of antigens that the mother or child would react with during pregnancy.<sup>9</sup> This enables the PURION processed dHACM tissue transplants to take place without the need to match blood types or other indicators that would cause a rejection. Amniotic membrane tissues are ideal for transplantation as they have been found to be immunologically privileged and do not require decellularization.

#### Packaging

All PURION processed amniotic membrane allografts are dehydrated and packaged utilizing aseptic technique into an inner peel pouch and sealed with an outer peel pouch system within a clean manufacturing environment. Based upon validations, each graft has been effectively sterilized using irradiation. The outer peel pouch is NOT considered sterile. The inner pouch, which contains the graft, is considered sterile unless the pouches are damaged or compromised, in which case the product should be returned to MiMedx.

#### **AmnioFix Configurations**

**Amniotic Membrane Allograft:** This amnion/chorion configuration is delivered as a dry sheet and is embossed, which enables the user to identify the correct orientation prior to application of the graft. In its dry state and prior to hydration, the allograft may be cut with sharp scissors to the appropriate size required. The allograft can then be placed on the surgical site, using the orientation of the "UP" embossment lettering as a guide. Proper orientation of the allograft can be noted when the embossment nomenclature reads correctly from left to right. The allograft can

then be hydrated while on the surgical site with sterile saline solution. AmnioFix is available in multiple sizes and is designed for single use in a single patient.

**Amniotic Membrane Wrap Allograft:** This amnion/chorion configuration is delivered as a dry sheet and embossed. AmnioFix Wrap differs from the traditional AmnioFix sheet membrane in that the layers of the membrane are arranged to provide two less-adherent sides to allow for gliding on both contact surfaces. When the allograft is placed surgically around a nerve or tendon, the AmnioFix Wrap provides a gliding surface in the repaired area, acts as a barrier membrane and reduces the formation of scar tissue. The AmnioFix Wrap can be stitched to itself for ease of use, as determined by surgeon preference.

**Amniotic Membrane Injectable:** This amnion/chorion configuration is delivered as a micronized powder that can be reconstituted with sterile saline to form an injection. Dry application of AmnioFix Injectable is also possible by removing the top of the vial and applying the powder onto the treatment area. If utilization as a paste is desired, the product may be transferred into a sterile cup and mixed with single drops of saline until the desired consistency is achieved.

#### **AmnioFix: A Bioactive Tissue Matrix Allograft**

AmnioFix is a bioactive tissue matrix that contains intact, non-living cells. There are a multitude of growth factors and cytokines contained within PURION processed tissue allografts, and these allografts have been shown to promote human fibroblast and microvascular endothelial cell proliferation *in vitro*.<sup>2,10,11</sup> The cellular signals contained in the tissue upregulate the production of angiogenic factors, and they recruit and promote engraftment of endogenous progenitor cells, including mesenchymal and hematopoietic stem cells, likely via stromal cell-derived factor 1 (SDF-1) and other growth factors. This indicates that angiogenesis could be a contributing mode of action for AmnioFix activity, and that the bioactive nature causes the surrounding cells to respond by upregulating biosynthesis of growth factors to promote healing.<sup>12</sup>

FIGURE 3 Micrograph of Hematoxylin and Eosin (H&E) stained cross section of AmnioFix, with cell nuclei.

Amnion Structural Proteins – Collagen I, III, IV Cell-binding Domains – Fibronectin, Collagen V, VII Growth Factor Binding – Proteoglycans, Laminin **Chorion** Structural Proteins – Collagen I, III, IV; Elastin Fibers Cell-binding Domains – Fibronectin, Collagen V, VII Growth Factor Binding – Proteoglycans, Laminin



Within AmnioFix, non-viable cells are preserved, resulting in an allograft that is bioactive and structurally intact (Figure 3). The intact extracellular matrix contains Collagens I, III, IV, V and VII, as well as laminin, fibronectin, and proteoglycans. These components, including cytokines, chemokines and growth factors active within the tissue, are instrumental to both the structural integrity of the allograft as well as the biological activity that is preserved.

There have been 285 regulatory proteins including growth factors, specialized cytokines, and enzyme inhibitors identified in AmnioFix to date.<sup>1-3</sup> The following are some of the most notable regulatory factors that help enhance healing:

- Transforming Growth Factor Beta (TGF- $\beta$ ) Promotes normal soft tissue healing and reduced scar formation
- Fibroblast Growth Factor (FGF) Promotes cellular proliferation and important for collagen matrix formation
- Platelet Derived Growth Factors (PDGF AA & BB) Promote cell proliferation in connective tissue and enhance soft tissue healing

#### **SCIENTIFIC EVIDENCE**

#### **Growth Factors Known To Regulate Soft Tissue Healing**

The following list of growth factors and cytokines are known to be present within AmnioFix including some of the most notable: transforming growth factors alpha and beta (TGF- $\alpha$ & $\beta$ ), basic fibroblast growth factor (bFGF), platelet derived growth factors (PDGF AA & BB), and vascular endothelial growth factor (VEGF).<sup>10,11</sup> The growth factors have been quantified and converted to a (+) rating system to provide relative amounts present in the tissue.

<b>REGULATORS OF SOFT TISSUE HEALING IN AMNIOFIX<sup>2,10,11</sup></b>			
Abbreviation	Cytokine	Function	Content
Ang	Angiogenin	Stimulates migration, proliferation, and vessel formation by endothelial and smooth muscle cells	++++
Ang-2	Angiopoietin-2	Regulates neovascularization in conjunction with angiopoeitin-1 and VEGF	+++
bFGF	Basic Fibroblast Growth Factor	Heparin-binding protein with broad mitogenic activity; Potent stimulator of angiogenesis	+++
BMP-5	Bone Morphogenetic Protein 5	Plays a role in bone and cartilage development	+++
BDNF	Brain-Derived Neurotrophic Factor	Supports the growth, differentiation, and survival of neurons	+++
EG-VEGF	Endocrine Gland-Derived Vascular Endothe- lial Growth Factor	Stimulates endothelial cell migration, proliferation, and survival; Potent stimulator of angiogenesis	++++
EGF	Epidermal Growth Factor	Stimulates proliferation, differentiation, and survival in numerous cell types, including epithelial cells	+++
FGF-4	Fibroblast Growth Factor 4	Broad mitogenic and cell survival activity	++++
KGF; FGF-7	Keratinocyte Growth Factor	Promotes proliferation and migration of epithelial cells and keratinocytes	++++
GH	Growth Hormone	Stimulates body growth through IGF-1 production, involved in anabolic activity	+++
HB-EGF	Heparin Binding EGF-Like Growth Factor	Causes keratinocytes and fibroblasts to migrate to the wound and proliferate; Promotes angiogenesis	++
HGF	Hepatocyte Growth Factor	Regulates cell growth, cell motility, and morphogenesis in epithelial cells; Important in angiogenesis	++++
IGF-I	Insulin-Like Growth Factor 1	Stimulates body growth through broad mitogenic activity	+++
IGFBP-1	Insulin-Like Growth Factor Binding Protein 1	Binds and stabilizes IGF-1 as a carrier protein; Alters interactions with surface receptors	+++++
IGFBP-2	Insulin-Like Growth Factor Binding Protein 2	Binds and stabilizes IGF-1 as a carrier protein; Alters interactions with surface receptors	+++++
IGFBP-3	Insulin-Like Growth Factor Binding Protein 3	Binds and stabilizes IGF-1 as a carrier protein; Alters interactions with surface receptors	+++++
IGFBP-4	Insulin-Like Growth Factor Binding Protein 4	Binds and stabilizes IGF-1 as a carrier protein; Alters interactions with surface receptors	+++++
IGFBP-6	Insulin-Like Growth Factor Binding Protein 6	Binds and stabilizes IGF-1 as a carrier protein; Alters interactions with surface receptors	+++++
β-NGF	Beta Nerve Growth Factor	Important for growth, maintenance, and survival of neurons	++
PIGF	Placental Growth Factor	Stimulates proliferation and migration of endothelial cells; Potent stimulator of angiogenesis	+++
PDGF-AA	Platelet-Derived Growth Factor AA	Stimulates proliferation, migration, and angiogenesis	++++
PDGF-BB	Platelet-Derived Growth Factor BB	Stimulates proliferation, migration, and angiogenesis	++++
TGF-a	Transforming Growth Factor Alpha	Stimulates proliferation and migration of keratinocytes; Potent stimulator of angiogenesis	++
TGF-β1	Transforming Growth Factor Beta 1	Controls proliferation, differentiation, and apoptosis of numerous cell types	++++
VEGF	Vascular Endothelial Growth Factor	Stimulates endothelial cell migration and activation; Potent stimulator of angiogenesis	+++
TIMP-1	Tissue Inhibitor of Metalloproteinase 1	Binds and inactivates a number of matrix metalloproteinases (MMPs)	+++++
TIMP-2	Tissue Inhibitor of Metalloproteinase 2	Binds and inactivates a number of matrix metalloproteinases (MMPs)	+++++
TIMP-4	Tissue Inhibitor of Metalloproteinase 4	Binds and inactivates a number of matrix metalloproteinases (MMPs)	++++

**Cytokines Found In AmnioFix** Some of the known specialized cytokines and proteins found in PURION Processed dHACM known to regulate inflammation include: Interleukin I receptor antagonist (IL-1ra), Interleukin 4 (IL-4) and Interleukin 10 (IL-10), which may be contributing factors to the immunologically privileged properties of the tissue.<sup>2,10,11</sup>

REGULATORS OF INFLAMMATION IN AMNIOFIX <sup>2,10,11</sup>			
Abbreviation	Cytokine	Function	Content
GCSF	Granulocyte Colony-Stimulating Factor	Stimulates the proliferation, differentiation, survival, and activation of neutrophils	++
GM-CSF	Granulocyte Macrophage Colony-Stimulating Factor	Stimulates production of granulocytes and monocytes	+
GDF-15	Growth Differentiation Factor 15	Regulates inflammatory and apoptotic pathways in injured tissues	++++
IFNγ	Interferon Gamma	Activator of macrophages	++
IL-1a	Interleukin 1 Alpha	Activates lymphocyte proliferation; Induces fibroblast proliferation	+++
IL-1β	Interleukin 1 Beta	Involved in lymphocyte proliferation, differentiation, and apoptosis	+++
IL-1ra	Interleukin 1 Receptor Antagonist	Antagonist of IL-1 signaling	++++
IL-4	Interleukin 4	Stimulates proliferation of activated B cells and T cells	++
IL-5	Interleukin 5	Regulates eosinophil growth and activation; Stimulates B cell growth; Increases immunoglobulin secretion	++
IL-6	Interleukin 6	Stimulates production of neutrophils and growth of B cells	+++
IL-7	Interleukin 7	Stimulates proliferation, maturation, and survival of B cells, T cells, and natural killer cells	++
IL-10	Interleukin 10	Enhances B cell survival, proliferation, and antibody production	++
IL-12p40	Interleukin 12 p40	Subunit of IL-12p70; Can act as IL-12 antagonist	+++
IL-12p70	Interleukin 12 p70	Stimulates growth and differentiation of T cells and natural killer cells	+
IL-15	Interleukin 15	Stimulates proliferation of T lymphocytes; Induces proliferation of natural killer cells	++
IL-17	Interleukin 17	Increases chemokine production	++
MCSF	Macrophage Colony-Stimulating Factor	Involved in proliferation, differentiation, and survival of monocytes and macrophages	++
OPG	Osteoprotegerin	Soluble decoy receptor that inhibits osteoclast activation	++++
Abbreviation	Chemokine	Function	Content
BLC	B Lymphocyte Chemoattractant (CXCL13)	Selectively chemotactic for B lymphocytes	+++
Eotaxin-2	Eotaxin 2	Induces chemotaxis in eosinophils and T lymphocytes	++
I-309	Chemokine Ligand 1 (CCL1)	Recruits monocytes, natural killer cells, and immature B cells and dendritic cells	+++
IL-8	Interleukin 8	Induces chemotaxis in neutrophils and other granulocytes	++
IL-16	Interleukin 16	Chemoattractant for CD4+ cells, including T cells, monocytes, eosinophils, and dendritic cells	+++
MCP-1	Monocyte Chemotactic Protein 1 (CCL2)	Recruits monocytes, memory T cells, and dendritic cells	++++
MIG	Monokine Induced by Gamma Interferon (CXCL9)	Chemoattractant for T cells	++++
MIP-1a	Macrophage Inflammatory Protein 1 Alpha (CCL3)	Chemotactic for neutrophils and monocytes	+++
MIP-1β	Macrophage Inflammatory Protein 1 Beta (CCL4)	Chemoattractant for natural killer cells and monocytes	+++
MIP-1d	Macrophage Inflammatory Protein 1D (MIP-5, CCL15)	Chemoattractant for neutrophils, monocytes, and lymphocytes	+++
RANTES	Regulated on Activation, Normal T-cell Expressed and Secreted (CCL5)	Chemotactic for T cells, eosinophils, and basophils	++++

#### **The Power of Chorion**

An important consideration is how the growth factors interact with one another to promote healing. Amnion and chorion contain different amounts and types of the various growth factors. The PURION process and resultant multi-layer grafts are covered by over 40 patents, and more than 1,000,000 grafts have been distributed to date. In addition, reviews of published literature fail to demonstrate that "Chorion-free" provides any clinical advantage, or that chorion has been shown to elicit an immune response.

The chorion layer is four to five times thicker and contains more growth factors as a result (Figure 4). PURION processed dHACM allografts include the chorion layer due to the substantial contribution of ECM, growth factors and cytokines within this layer.



AmnioFix contains approximately 20 times more chemokines and cytokines than selected competitive products comprised of amnion alone (Figure 5).



#### **Growth Factor Release Profile**

PURION processed dehydrated amnion/chorion membrane (dHACM) was micronized and rehydrated with neutral saline, then incubated for 24 hours at 4°C and centrifuged for ten minutes to create a supernatant liquid and solid material pellet. The supernatant liquid was tested for PDGF-AA, PDGF-BB, b-FGF, TGF-β1 and EGF using ELISA protocols. The relative percentage of each growth factor that was extracted in neutral saline compared to that remaining in the tissue is shown in the following chart (Figure 6).<sup>10</sup>

Native Growth Factors Present	Relative Amount Determined by ELISA Assay (n=5)	Release Profil 24 hr incubatior Remaining in Tig	e (n=5) n period at 4°C ssue
PDGF-AA	+++++	13%	87%
PDGF-BB	+	<b>4</b> %	96%
bFGF	++	44%	56%
TGF-β1	++	24%	76%
EGF	+	63%	37%

The release profile shows the percentage of growth factors from PURION processed dHACM released into the neutral saline. As the remaining solid is remodeled over time, it has been proposed that the growth factors still bound into the extracellular matrix are released into the surrounding tissue, providing a continual release of growth factors during the tissue regeneration process (Figure 7).

#### FIGURE 7 The time release properties of bFGF, PDGF-AA, and TGF-β1<sup>13</sup>

Elution of growth factors over 96 h into normal saline. bFGF, PDGF-AA, and TGF- $\beta$ 1 eluted out from dHACM in 0.9% saline at 37°C. After an initial release of these growth factors, the rate of release declined, and significant amounts of these growth factors were not released into saline after 96 h. Collagenase digestion of the tissue released the remaining bound growth factors from the tissue. The trend line illustrates the means for five replicate samples at each time point.



#### **Growth Factor Activity**

One property of AmnioFix that is important for healing and soft tissue repair is the stimulation of human cells to proliferate in response to the soluble growth factor and cytokine molecules released from the product. Human fibroblasts are important for secreting angiogenic growth factors and new tissue matrix deposition, while human mesenchymal stem cells (MSCs) are needed to modulate the local immune response at sites of injury and restore homeostasis.

*In vitro* cell-based assays were conducted to measure human dermal fibroblast and MSC proliferation in response to AmnioFix over the course of 3 days, and the results are shown below (Figure 8).<sup>14</sup>

#### FIGURE 8 Human cellular proliferation in response to soluble factor extracts of AmnioFix.

A) Human dermal fibroblasts (HDF), B) Human mesenchymal stem cells (MSC). \*p<0.05 versus basal medium controls. Concentrations of AmnioFix extracts tested are shown on the X-axis of each graph.



The data show that extracts of soluble factors from AmnioFix stimulate human dermal fibroblasts (HDFs) and MSCs in cell culture to proliferate to a significantly greater level (p<0.05) than basal medium controls. The samples cultured in complete medium represent the near optimal growth conditions for the respective cells, and at higher concentrations of AmnioFix extract, HDFs and MSCs approached or exceeded the cell numbers in the complete treatment groups.

#### **Effects On Mesenchymal Stem Cell Migration**

The effects of PURION processed dHACM on mesenchymal stem cell (MSC) and hematopoietic stem cell (HSC) migration were demonstrated *in vivo* using a parabiosis mouse model.<sup>12</sup> In this model, one green mouse genetically engineered to have stem cells containing green fluorescent protein (GFP) was conjoined (shared circulation) with a wild type or normal mouse (Figure 9).



The GFP mouse acted as a stem cell donor to the wild type mouse when the latter was implanted subcutaneously with PURION processed dHACM. Results showed that the PURION processed dHACM induced greater recruitment of engrafted GFP+ cells inside the implant when compared to the sham implant and an acellular bovine dermis (PriMatrix<sup>®</sup>, TEI Biosciences, Boston, MA) control (listed as Control ADM) (Figure 10). This research supports the hypothesis that AmnioFix could attract endogenous stem cells to engraft into the surgical site.



PURION processed dHACM contains extracellular matrix, stimulates multiple cell types to migrate and proliferate, and draws mesenchymal stem cells and hematopoietic stem cells from tissues to the site of injury. These stem cells then release their own growth factors, cytokines and paracrine factors to help modulate the body's inflammatory response and begin the healing process (Figure 11).

#### FIGURE 11

Effects of dehydrated human amnion/chorion tissue allografts (dHACM) on mesenchymal stem cell recruitment. Figure used with permission.<sup>6</sup>



#### AmnioFix Inhibits Protease Activity<sup>3</sup>

Multiplex and single-factor ELISAs were utilized to identify cytokines and regulatory proteins (nmol/mg of tissue) in AmnioFix (Figure 12). Of the factors identified, 46.7% were classified as tissue growth factors that can promote wound healing, including IGFBP-3, PIGF, PDGF-AA, TGF- $\beta$ 1, and VEGF. Protease inhibitors such as tissue inhibitor of metalloproteinase 1 (TIMP-1), TIMP-2, alpha-2-macroglobulin ( $\alpha$ 2M), and alpha-1 antitrypsin (A1AT) accounted for 46.3% of the identified factors; whereas matrix metalloproteinases (MMPs) such as MMP-2, MMP-8, and MMP-9 comprised only 1.7% of the detected molecules. Even though MMPs were present in dHACM tissues, inhibitors of MMPs overwhelmingly outnumbered the MMP enzymes by an overall molar ratio of 28:1. Protease activity assays also revealed that the MMPs in the tissue exist primarily either in their latent proenzyme forms or complexed with inhibitors.



#### AmnioFix Promotes Hyaluronic Acid Production by Synoviocytes<sup>15</sup>

Human synoviocytes were cultured in the presence of AmnioFix extracts, either at 1 or 10 mg/mL. Basal medium in the absence of serum and complete medium supplemented with 10% serum acted as negative and positive controls, respectively. After 3 days of treatment with AmnioFix, hyaluronic acid content in the culture medium was determined by ELISA. AmnioFix increased hyaluronic acid concentration after 3 days compared to basal and complete medium, indicating that AmnioFix promoted production of hyaluronic acid by human synoviocytes (Figure 13).

#### FIGURE 13

Production of hyaluronic acid by human synoviocytes in response to AmnioFix after 3 days. Synoviocytes were treated with 1 or 10 mg/mL of AmnioFix extract. Basal and complete medium acted as negative and positive controls, respectively.



#### AmnioFix Is Biocompatible and Naturally Resorbs In Vivo14

To examine biocompatibility and bioresorption of AmnioFix *in vivo*, AmnioFix was implanted subcutaneously in normal, immune competent rats and tracked for up to 97 days. The implants were resected at 1, 7, 14, 22, 42, and 97 days after implantation, and the specimens were analyzed histologically by an independent board certified histopathologist for biocompatibility and bioresorption (Figure 14). AmnioFix underwent steady bioresorption with decreasing amounts of material present at the implant sites over time. AmnioFix was also biocompatible with minimal encapsulation observed after 97 days.

#### FIGURE 14

Biocompatibility and bioresorption of AmnioFix in a rat subcutaneous implant model. AmnioFix implants are marked by red asterisks (\*), while the native tissue is marked by blue asterisks (\*).



#### AmnioFix Protects Cartilage from Degradation In Vivo<sup>16</sup>

A medial meniscal transection (MMT) model was used to induce osteoarthritis (OA) in rat knee joints. Twenty four hours post-surgery, AmnioFix or saline was injected intra-articularly into the rat joint. Microstructural changes in the tibial articular cartilage were assessed histologically and using equilibrium partitioning of an ionic contrast agent micro computed tomography (EPIC-µCT) after 21 days post-surgery (Figure 15). Treated joints showed the presence of AmnioFix in the synovium up to 21 days post-surgery, and development of cartilage lesions at 21 days was prevented and the number of partial erosions was significantly reduced by treatment with AmnioFix. EPIC-µCT analysis quantitatively showed that AmnioFix treatment significantly reduced the occurrence of cartilage defects including erosion and lesions. These results suggest that AmnioFix Injectable is rapidly sequestered in the synovial membrane following intra-articular injection and attenuates cartilage degradation in a rat OA model.

#### FIGURE 15

Effect of AmnioFix in a rat medial meniscal transection (MMT) model of osteoarthritis. (A) Representative images of tibial cartilage by safranin 0 histology and equilibrium partitioning of an ionic contrast agent micro computed tomography (EPIC- $\mu$ CT). Black arrows indicate defects in cartilage surface. Arrow heads indicate healthy, full-thickness cartilage. (B) Average number of erosions was significantly reduced and no lesions were observed in AmnioFix treated joints, compared to saline control joints. \* indicates significant difference compared with saline control (p<0.05).



#### **CLINICAL DATA**

#### **Amniotic Membrane Clinical Benefit**

The application of amniotic membrane in a variety of clinical settings dates back more than one hundred years. This use is documented in multiple textbook chapters and more than 300 articles. A growing body of literature has evolved surrounding the various applications of PURION processed amniotic membrane allografts for a broad range of therapies, including treatments in wounds, orthopedics, neurosurgery, dermatology, otorhinolaryngology and more.

AmnioFix has been shown to be safe and effective for use clinically in surgical indications. It was used as a barrier to reduce scarring in the epidural space following transforaminal lumbar interbody fusion (TLIF) in the spine, based upon observations reported from a series of 5 case studies.<sup>17</sup> Implantation of AmnioFix in the epidural space during fusion procedures, and subsequent re-exploration of the treated space, resulted in 4/5 cases having easily detachable tissue, improved disability, mental and back pain scores with no intra-operative or post-operative complications. The results suggest that AmnioFix had favorable effects on epidural fibrosis and was well tolerated.

#### **AmnioFix Clinical Case Examples**

The following case examples illustrate some of the potential clinical applications of AmnioFix within multiple surgical procedures to help modulate inflammation, reduce scar tissue formation and enhance healing.

#### PATELLAR TENDON RUPTURE REPAIR

72-year-old male patient with a history of knee chondromalacia and meniscal tear presented with a full-thickness patellar tendon rupture. The patient was at risk for poor healing due to age, pre-existing osteoarthritis, and extensive proximal and distal tearing of the tendon. AmnioFix was placed directly over the repair site to enhance healing and minimize scar tissue formation. At 3 months post-op, the patient returned to full activity and regained full extension and strength in his knee.



Figure 1 Pre-operative MRI image showing proximal rupture (partial) of the patellar tendon.



Figure 2 MRI image showing full-thickness rupture of the patellar tendon, distally from the tibial tubercle.



**Figure 3** MRI image confirming severe patellofemoral osteoarthritis and rupture of the distal patellar tendon.



Figure 4 Pre-operative MRI image showing patella alta secondary to full-thickness patellar tendon rupture with severe interstitial degeneration of the ruptured patellar tendon.

#### TOTAL SHOULDER REPAIR

43-year-old male patient with a history of traumatic injury to his shoulder (6 shoulder surgeries) presented with chronic pain and osteoarthritis of the glenohumeral joint, as well as significant scarring throughout the shoulder capsular tissues. The patient underwent total shoulder repair, and AmnioFix was placed under the deltoid, on the superior aspect of the rotator cuff and at the proximal humerus, below the deltoid. On post-op day 4, the patient was noted to have good range of motion and was using his arm in a very normal, functional manner. He was able to discontinue physical therapy after three weeks.



#### ACL RECONSTRUCTION

32-year-old male patient presented with chronic ACL instability resulting from a football injury incurred 17 years prior. The patient underwent an ACL reconstruction using a Bone-Tendon-Bone graft from the contralateral knee. After harvesting patellar tendon for the autograft, a 2 cm x 3 cm AmnioFix graft was placed under the remaining patellar tendon to enhance healing of the defect and to prevent adhesions to the anterior tibia from developing. At 9 months post-op, the knee was stable. The patient's surgical repair was successful, and he was able to return to playing sports.



#### ACL RECONSTRUCTION & PATELLAR TENDON REPAIR

28-year-old female patient presented with a grade III ACL tear sustained while skiing. She was also diagnosed with a concurrent tear of the lateral patellar tendon at its proximal attachment. She underwent surgical reconstruction of the left knee approximately three months after her injury, which included endoscopic reconstruction of the ACL utilizing an Achilles tendon allograft wrapped with AmnioFix and repair of the partial tear of the lateral patellar tendon augmented by use of an AmnioFix allograft. At approximately four months post-op, a light jogging and swimming program was initiated, and at approximately eight months post-op, the patient was discharged from care, as she had excellent progress and recovery.



Figure 1 MRI images showing grade III rupture of the anterior cruciate ligament.



Figure 2 Achilles tendon allograft used for reconstruction of the ACL with AmnioFix wrap of the allograft.



Figure 3 Anatomical ACL reconstruction using augmented allograft wrapped with AmnioFix.

#### ARTHROSCOPIC ROTATOR CUFF REPAIR

61-year-old male patient with a history of hypertension, coronary heart disease, non-insulin dependent diabetes, and asthma presented with a non-displaced proximal humerus fracture and a ruptured supraspinatus tendon. The patient underwent arthroscopic rotator cuff repair. After surgical repair, AmnioFix was injected into the repair site to enhance healing of the tendon. At first post-op visit, excellent, near normal passive range of motion was noted, with a VAS pain scale rating of 2/10. At seven weeks post-op, the patient returned with a pain scale rating of 0/10. The patient experienced a return to function and full strength regained in his rotator cuff.



Figures 1 & 2 Ruptured and retracted supraspinatus tendon



Figures 3 & 4 BridgeFix double-row rotator cuff repair



Figure 5 Injection of AmnioFix into rotator cuff repair

40-year-old female patient, who is a professional golf coach, presented with 6 months of progressive pain involving the great toe; an X-ray of the foot revealed osteoarthritis of the great toe. The patient underwent an ultrasound-guided injection of 40 mg of AmnioFix into the first MTP joint. At 2 months post-injection, the patient was virtually pain-free in the great toe and had returned successfully to playing and coaching golf.



#### Figure 1

Plain X-ray of the foot demonstrating mild to moderate arthritis of the great toe. Metatarsophalangeal (MTP) joint arthritis is present at the first ray as indicated by the yellow arrows. Joint space narrowing and subchondral sclerosis are present. Other joint spaces in the foot are preserved.



#### Figure 2

Ultrasound of the great toe MTP joint is an optimal way to guide injection. The joint space is shown in the middle of the screen, at the level of the dotted line. To the left and right, the bright regions show the bony margins of the joint. The far left discontinuity in the bony cortex represents a small bone spur. Yellow arrow indicates the optimal approach to the joint space for injection. The black region indicates joint fluid and is intra-articular. 64-year-old male patient and refinery worker who fell and sustained multiple orthopedic injuries, including a high grade subacute/chronic tear of the distal triceps. Due to the nature of the other injuries, an MRI of the triceps was performed approximately one month following the injury, revealing a high grade partial tear of the long head of the triceps tendon, microtearing and intervening granulation tissue involving the midline lateral, superficial, and intrasubstance fibers of the distal triceps. The deep fibers of the triceps tendon at the level of the injury were preserved. There was subacute and chronic Grade II partial tearing of the intrasubstance portion of the common extensor tendon. The patient had weakness in extension and his right elbow lacked power in extension. Approximately four and a half months following the initial injury, the patient underwent right elbow debridement of scar tissue and repair of torn triceps tendon. AmnioFix was applied to augment the repair, to encourage healing and minimize scar tissue formation.

The patient was seen approximately two weeks post-operatively. Healing was progressing as expected and he has followed post-operative instructions to remain in a sling. His exam shows that the incision is fully healed, and has range of motion from minus 5° to 105° with full pronation and supination. His triceps repair appears to be intact, as is his distal neurovascular exam. He has good mobility. He began gentle range of motion exercises, without weight and continued used of the sling for an additional six weeks, with physical therapy for twelve weeks. This 64-year-old patient with a right elbow high grade triceps tear was able to return to full activity and regained full extension and strength in his elbow after surgical repair augmented with AmnioFix.



Figure 1 Intraoperative picture of torn triceps tendon showing repair.





Repair of triceps tendon with AmnioFix applied to the repair site.

#### SUMMARY

The use of human amniotic membrane over the past 100 years has generated substantial data in multiple areas of medicine. Relevant immuno-histochemisty, ELISA, cell migration and proliferation studies conducted by MiMedx and independent laboratories have made significant contributions to this knowledge base. It is clear that the patent-protected PURION process produces a minimally manipulated and carefully preserved amniotic tissue that contains essential growth factors and extracellular matrix within the membrane. This sterilized PURION processed dHACM provides an easy to use allograft for multiple surgical intended uses with a 5 year shelf life at ambient conditions. Many of the key components present in natural amniotic membrane are preserved during the gentle PURION process, which accounts for the advantageous clinical properties observed when the allografts are used in the clinical applications described to modulate inflammation, reduce scar tissue formation, and enhance healing.



The multitude of factors preserved in all MiMedx products, their inherent benefits, and the Company's rigorous safety standards provide the critical advantage and differentiation of the MiMedx products.



#### About MiMedx:

MiMedx is a leading biopharmaceutical company developing and marketing regenerative biologics utilizing human placental tissue allografts and proprietary processes for multiple sectors of healthcare. *"Innovations in Regenerative Medicine"* is the framework behind our mission to give physicians products and tissues to help the body heal itself. We process the human amniotic membrane utilizing our proprietary PURION process, to produce a safe and effective implant. MiMedx proprietary processing methodology employs aseptic processing techniques in addition to terminal sterilization. MiMedx is the leading supplier of placental tissue allografts, having supplied over 1,000,000 allografts to date for application in the Wound Care, Burn, Surgical, Orthopedic, Spine, Sports Medicine, Ophthalmic and Dental sectors of healthcare.<sup>†</sup>



#### AmnioFix Product Offerings

#### AmnioFix

ltem Number	Size
APS-5160	16 mm disk
APS-5230	2 cm x 3 cm sheet
AAS-5330	3 cm x 3 cm sheet
APS-5260	2 cm x 6 cm sheet
APS-5440	4 cm x 4 cm sheet
AAS-5460	4 cm x 6 cm sheet
APS-5212	2 cm x 12 cm sheet
APS-5616	6 cm x 16 cm sheet
APS-5290	9 cm x 20 cm sheet

#### AmnioFix Sports Med

Item Number	Size
ASM-5050	20 mg
ASM-5040	40 mg
ASM-5100	100 mg

#### AmnioFix Wrap

ltem Number	Size
TN-5220	2 cm x 2 cm sheet
TN-5240	2 cm x 4 cm sheet
TN-5460	4 cm x 6 cm sheet

#### AmnioFix Injectable

Item Number	Size
AI-5020	20 mg
AI-5050	40 mg
AI-5125	100 mg
AI-5200	160 mg

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† As of August 1, 2018



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