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the voice of pain medicine

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Amniotic Fluid May be Safe and Effective Alternative to Hyaluronic Acid for Osteoarthritis Pain: Interim Results

March 19, 2015, NATIONAL HARBOR, Md. – An early snapshot of study outcomes suggests that the use of a processed amniotic fluid allograft may be safe and effective for the treatment of knee osteoarthritis (OA) as an alternative to hyaluronic acid (HA). Longer-lasting benefits with less risk of complications were reported today in a scientific poster presented at the 31st Annual Meeting of the American Academy of Pain Medicine.

"AmnioClear LCT is demonstrated in this study to offer pain and functional improvement that is greater at 13 weeks than at 30 days; thus it appears to offer longer-lasting relief at a higher level," said lead author Didier Demesmin, M.D., a pain management specialist with the University Pain Medicine Center in Somerset, N.J.

"It also demonstrated much lower incident of pain, swelling or inflammation compared to other injections," said Noreen Rana, M.P.H., research director at the center.

The most common form of knee arthritis is OA in which the cartilage wears away in a gradual process with pain that worsens over time, according the American Academy of Orthopaedic Surgeons (AAOS). Steroids, which may offer quick transient pain relief but are not recommended for repetitive use, and HA are standard alternatives to surgery. HA is a naturally occurring substance found in the synovial fluid, which lubricates the cartilage and reduces friction in the joint. The FDA approved HA knee injections starting in the 1990s, and they are frequently performed.

Yet the effects of HA decline after 7 weeks for a single injection or 12 weeks with multiple injections, the study authors said. Further, the Centers for Medicare and Medicaid Services (CMS) and AAOS have questioned the effectiveness of hyaluronic acid in the treatment of knee OA in patients over 65 and in the general population (Newberry et al, *AHRQ Technology Assessment, Draft*: Project ID: DJDTO913). In a 200-page Technical Assessment of HA in OA knees, CMS collaborated with the Agency for Healthcare Research and Quality to perform a meta analysis of the literature. They concluded that evidence was inconclusive to determine whether HA knee injections led to clinically meaningful improvement.

-More-

"Payer coverage has started to decline as a result of the AAOS recommendation, and many believe the CMS Tech Assessment will eventually cause further and more severe decline in HA coverage," Demesmin said.

As an alternative, investigators looked at amniotic fluid, noting its similarity to the synovial fluid in that both protect and lubricate the contents of a closed environment. Furthermore, the transplant of fetal membranes and fluid from one individual to another is not new and has been used to treat orthopedic conditions (Trelford et al, *Am J Obstet Gynecol* 1979;134(7):833-45). The cushioning action of amniotic fluid for the fetus is the same – "homologous," as the FDA terms it -- function in a recipient's knee, Demesmin said.

"This all-natural supplement alternative to synthetic treatments and the anti-inflammatory nature of amniotic fluid is precisely what painful OA knees need." Demesmin added that HA is FDA-cleared only for use in the knee, while the amniotic injection can be used in any synovial joint.

In this single-arm, prospective, multi-center, post-marketing study, a cohort of registry enrollees with a diagnosis of Grade 1, 2 or 3 OA and no recent HA, steroid or platelet-rich plasma injections were assessed for pain with the visual analogue scale (VAS) and the Western Ontario and McMaster Universities Arthritis Index (WOMAC) at baseline and at 30, 90 and 180 days. The registry was underwritten by Liventa Bioscience, which is based in West Conshohocken, Penn., and run under institutional review board guidance.

The interim report presented data from the first 15 of 23 investigative sites. Results observed in the first 170 amniotic fluid-treated patients showed their VAS and WOMAC scores improved an average of 68.1 percent (44mm) and 70.9 percent (812mm), respectively, at 30 days. Improvements increased at 90 days to 82 percent for WOMAC and 74 percent for VAS.

Like other commonly used surgical allografts, the amniotic fluid injection does not require pre-market approval, thus it is currently marketed and being used in clinics across the country. Liventa Bioscience elected to conduct a post-market (non-FDA) study to confirm efficacy and safety and to inform clinicians of expected outcomes, prior to a full market launch, which is taking place at the AAPM annual meeting. Additional studies, including randomized controlled trials, are planned.

Poster LB004 – Amniotic Fluid as a Homologue to Synovial Fluid: Interim Analysis of Prospective, Multi-Center Outcome Observational Cohort Registry of Amniotic Fluid Treatment for Osteoarthritis of the Knee

About AAPM

The American Academy of Pain Medicine is the premier medical association for pain physicians and their treatment teams with over 2,500 members. Now in its 32nd year of service, the Academy's mission is to optimize the health of patients in pain and eliminate pain as a major public health problem by advancing the practice and specialty of pain medicine through education, training, advocacy and research. Information is available on the Academy's website at www.painmed.org.

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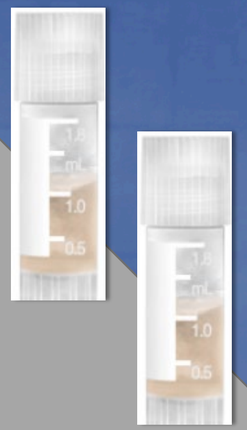
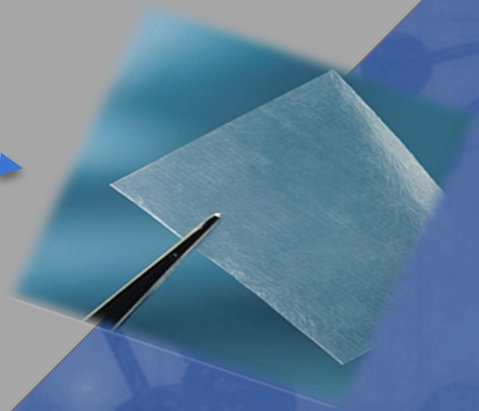
100% liquid allograft, rich in natural growth factors and cytokines, associated with tissue repair, replacement, and regeneration.



Dual-layer (Amnion/Amnion) dehydrated human amnion membrane (dHAM)



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Growth factors which stimulate cellular growth and differentiation

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Cellular Growth and Differentiation

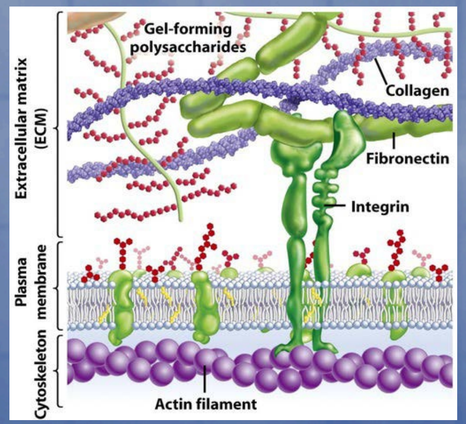
EGF

PDGF

TGF - β 1

Induces cell growth and differentiation

Induces cell proliferation



Induces cell proliferation; stimulated ECM production; promotes tissue remodeling

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Growth factors which stimulate new blood vessel formation (Angiogenesis)

b-FGF	Fibroblast Growth Factor - basic
ANG-2	Angiopoietin 2
VEGF	Vascular Endothelial Growth Factor

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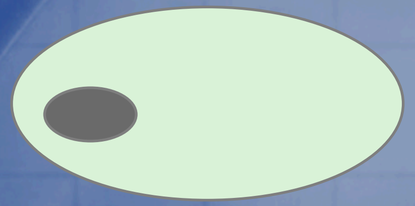
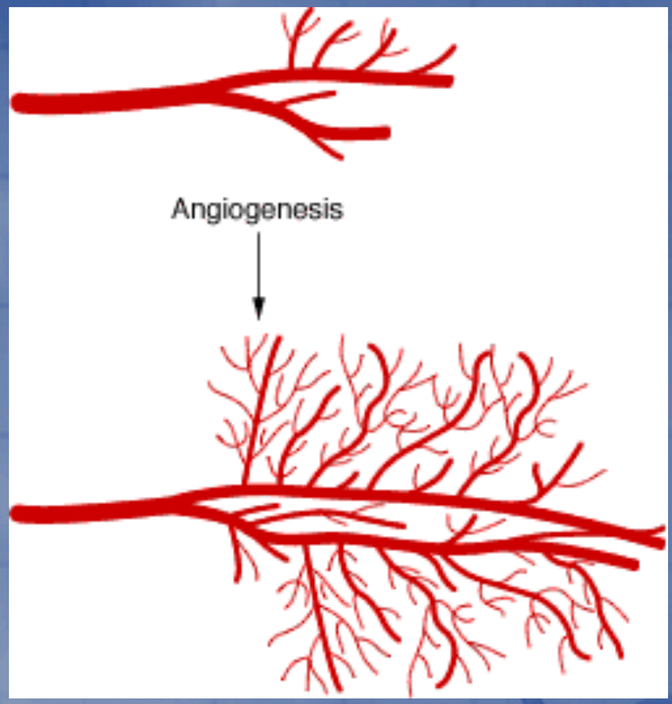
Angiogenesis

Blood vessel formation

FGF-b
ANG-2
VEGF



Stimulates new blood vessel formation



Growth factors which **stimulate** tissue remodeling

MMP-9

Matrix Metallopeptidase 9

Growth factors which **decrease** tissue remodeling

TIMP 1,2,3,4

Tissue inhibitor of Metalloproteinase 1,2,3,4

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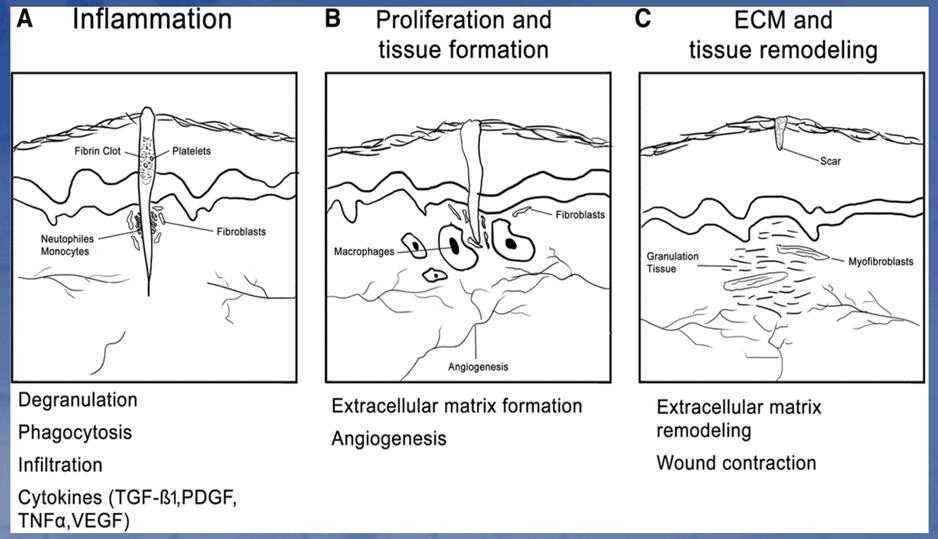
Regulation of Tissue Remodeling

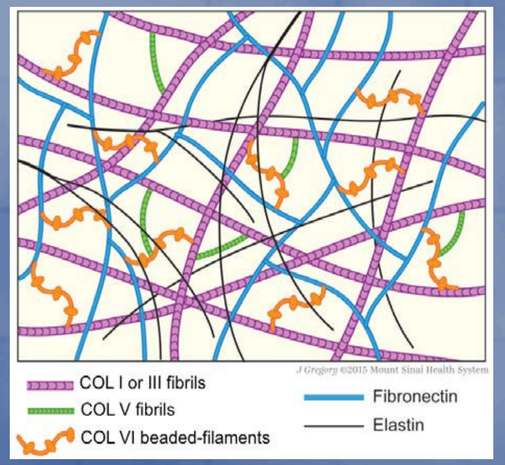
MMP-9

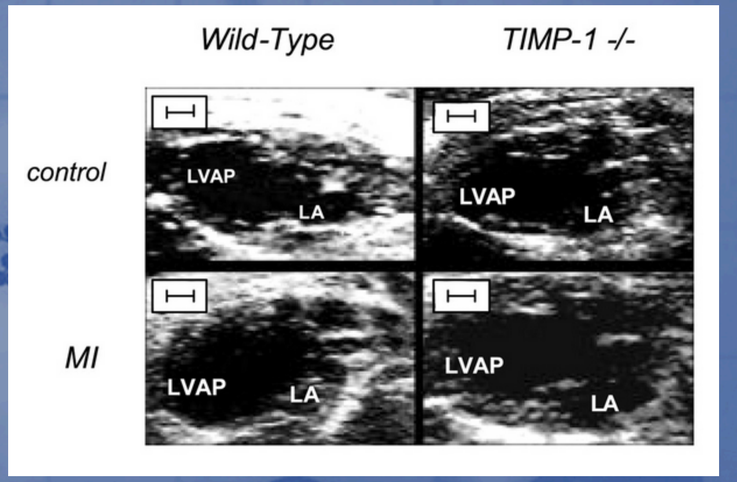
TIMP 1,2,3,4

Stimulates tissue remodeling

Helps to regulate appropriate tissue remodeling







Growth factors which have anti-inflammatory activity

IL - 10

Interleukin 10

IL-1RA

Interleukin -1 receptor antagonist

Growth factors which have antimicrobial activity

MPO

Myeloperoxidase

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Fluid Flow™

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Fluid Flow™

Protein Analysis

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Memo: Evaluation of Sterilized Amniotic Fluid Samples

Introduction

The purpose of this study was to evaluate the growth factor content present within amniotic fluid samples provided by Bone Bank Allografts (BBA). These fluid samples consist of Amniotic fluid that has been sterile filtered, sterilized, and then stored at ambient temperature.

Methods

Growth Factor and Cytokine Analysis

Growth factor and cytokine content from ambient sterile fluid samples from 3 donors was determined through the HI 8-1/2 S3 Raybiotech custom proteomics microarray kit according to the manufacturer's instructions (RayBiotech, Narcross GA). Each sample was assessed in duplicate, requiring 100 µl- per well within the array.

Angiogenic Growth Factors	Regenerative Growth Factors	Immune Modulating Cytokines	Osteogenic & Chondrogenic Growth Factors
Acidic Fibroblast Growth Factor (aFGF)	Adiponectin (APN)	Tissue Necrosis Factor Alpha (TNFa)	Bone Morphogenetic Protein 6 (BMP-6)
Angiopoietin (ANG)	Epidermal Growth Factor (EGF)	Interleukin-4 (IL-4)	Bone Morphogenetic Protein 7 (BMP-7)
Angiopoietin-2 (ANG-2)	Galectin-7 (GAL)	Interleukin-6 (IL-6)	Fetuin A (FET)
Basic Fibroblast Growth Factor (bFGF)	Hepatocyte Growth Factor (HGF)	Interleukin-8 (IL-8)	Osteoprotegerin (OPG)
Endocrine gland-derived vascular endothelial growth factor (EG-VEGF)	insulin-like growth factor-binding protein 1 (IGFBP-1)	Interleukin-1 family member 5/ Interleukin 36 receptor antagonist (IL-1F5)	Osteopontin (OPN)
Platelet Derived Growth Factor AA (PDGF-AA)	Insulin-like growth factor-binding protein 5 (IGFBP-5)	Interleukin 1 receptor antagonist (IL-1ra)	
Platelet Derived Growth Factor AA (PDGF-BB)	Insulin-like Growth Factor-I (IGF-I)	Interleukin 10 (IL-10)	
Placenta Growth Factor (PIGF)	Insulin-like Growth Factor-2 (IGF-II)	Tissue Inhibitor of Metalloproteinase 1 (TIMP-1)	
stromal cell-derived factor 1 (SDF-1)	Transforming growth factor alpha (TGF-a)	Tissue Inhibitor of Metalloproteinase 2 (TIMP-2)	
Thrombospondin 1 (TSP-1)	Transforming growth factor beta 1 (TGF-ß1)	Tissue Inhibitor of Metalloproteinase 4 (TIMP-4)	
Vascular Endothelial Growth Factor (VEGF)	Transforming growth factor beta 1 (TGF-ß3)		
Vascular Endothelial Growth Factor D (VEGF-D)			
Angiopoietin-like 4 (APL4)			

Table 1: Description of growth factor categories.

Results

Proteomic evaluation of fluid samples revealed high concentrations of multiple growth factors including TSP-1 , HGF, IGFBP-5, IGF-1/2, TGFa, and TGF-ß3, IL-1F5, TIMP-2, BMP-7, Fetuin A, and OPN (shown below).

Fluid Flow™: Product Pricing

Fluid Flow™ (cc)	Q-Code Invoice Price	Rebate (40%) Price
0.5	$1,000	$600
1.0	$2,000	$1,200
2.0	$4,000	$2,400

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Thank You!

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