HUMAN AMNIOTIC MEMBRANE GRAFTS TO ENHANCE HEALING

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Good Wound Care

"Treat the whole patient, not just the hole in the patient"

- Ensure adequate perfusion to wound site
- Address metabolic challenges (glucose / nutrition)
- Debride to bleeding tissue – "Cut the wound out of the patient"
- Assess patient's need for off-loading, compression, and/or negative pressure
- Address bio-burden, biofilms, and infection
- Create a moist healing environment with focus on moisture balance
- **Re-balance microscopic wound environment (homeostasis)**
  - **Wound healing mediators (cytokines and chemokines)**
  - **Inflammatory mediators**

CHRONIC WOUND TREATMENT PARADIGM

For years, leaving opportunities along the way for:

- *Major complications*
- *Increased costs*
- *Reduced QOL*
- *Increased chance of death*

Why Amniotic Membrane?

- **Barrier properties[1]**
- **Modulates inflammation[2]**
- **Reduces scar tissue formation[2]**
- **Immunologically privileged[3]**
- **Contains essential growth factors[4]**
- **Enhances wound healing[5]**

[1] Tao H, Fan H. Implantation of amniotic membrane to reduce post laminectomy epidural adhesions. Eur Spine J. 2009 Aug; 18(8):1202-12.
[2] Tseng SC, Li DQ, Ma X. Suppression of transforming growth factor-beta isoforms, TGF-beta receptor type II, and myofibroblast differentiation in cultured human corneal and limbal fibroblasts by amniotic membrane matrix. J Cell Physiol. 1999 Jun;179(3):325-35.
[3] Hao Y, Ma DH, Hwang DG, Kim WS, Zhang F. Identification of antiangiogenic and anti-inflammatory proteins in human amniotic membrane. Cornea. 2000 May;19(3):348-52.
[4] 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.
[5] Zelen CM, Serena TE, Denozière G, Fetterolf DE. A prospective randomized comparative parallel study of amniotic membrane wound graft in the management of diabetic foot ulcers. Int Wound J. 2013 Oct;10(5):502-7.

FDA Regulatory Classifications for Tissue & Cell Based Products

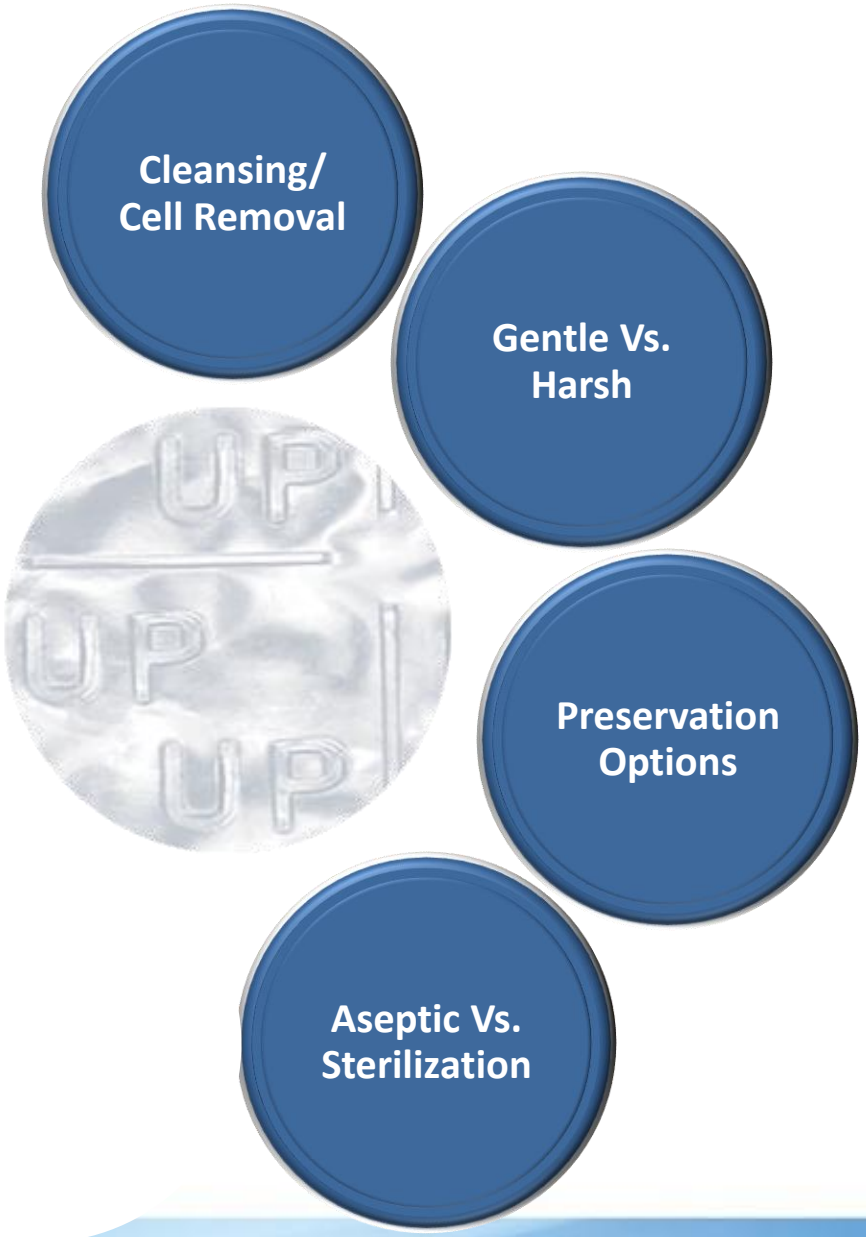
Classification	Category	Description
361 HCT/Ps (Human Cell Tissue/ Products)	Human Tissue (Allograft).	Minimally manipulated, intended for homologous use. No clearance or premarket approval required. Requires FDA Good Tissue Practices (GTP).
510(k) Clearance (351 HCT/Ps)	Medical Device (Example: decellularized human dermis, xenografts, collagen dressings, bone void filler).	Requires FDA Substantial Equivalence, shorter submission and less required verses PMA. Based on predicate device. Requires FDA Current Good Manufacturing Practice (cGMP).
Premarket Approval (PMA)	Medical Device (Example: human living skin substitutes, bone substitute).	Requires extensive FDA premarket approval process, including comprehensive clinical trials. Requires FDA Current Good Manufacturing Practice (cGMP).
Biologic License Application (BLA) (351 HCT/Ps)	Biological product (Example: Cell products, such as those containing hematopoietic progenitor cells, vaccines, and blood components).	Requires extensive FDA premarket approval process, including comprehensive preclinical and clinical trials. Requires compliance to FDA Current Good Manufacturing Practice (cGMP).
New Drug Application (NDA)	(Example: living stem cells non-autologous, second degree relative, or autologous stem cells that are expanded in the laboratory).	Requires extensive FDA premarket approval process, including comprehensive clinical trials. Requires FDA Current Good Manufacturing Practice (cGMP).

Placental Based Allografts

After Live Births

- Amniotic Fluid
- Amnion Membrane
- Chorion Membrane
- Umbilical Cord
- Placenta with Chorionic Plate

Tissue Processing



Step Process to Ensure Safety

Major Process Steps	Criteria that Ensures Tissue Safety
Donor Screening	Acceptable donor medical history approved by Medical Director
Infectious Disease Testing	Negative results for all FDA approved tests that includes HIV, Hepatitis B and C, Syphilis, and Human T-cell lymphotropic virus (HTLV)
Processing	A validated process with proven Bacterial/Spore reduction capabilities that range from 1.4 – 5.6 Logs
Terminal Sterilization of all grafts	Require a validated process per ISO 11137 standards providing at least a 10^{-6} SAL with irradiation dose monitoring linked to the release of every tissue distributed
Double sterile barrier product packaging	A validated process per FDA recognized ASTM D4169 standards that ensures sterility is maintained post distribution

Amniotic Membrane Grafts

Not All Amniotic Membrane Products Are the Same

Single Layer Grafts - Amnion

Decellularized (cells removed)

Biovance® (Celgene/Alliqua)

Cellular (non-living cells)

AmnioExcel® (BioD/DermaSciences)[1]

Neox® 100 (Amniox)

Cellular (living cells)

Grafix® Prime (Osiris Therapeutics)[2]

- Single Randomized Clinical Trial in DFUs

REFRENCE:

1. Snyder RJ, Shimozaki K, Tallis A, Kerzner M, Reyzelman A, Lintzeris D, Bell D, Rutan RL, Rosenblum B. A Prospective, Randomized, Multicenter, Controlled Evaluation of the Use of Dehydrated Amniotic Membrane Allograft Compared to Standard of Care for the Closure of Chronic Diabetic Foot Ulcers. *Wounds* 2016;28(3):70-77
2. Lavery LA, Fulmer J, Shebetka KA, Regulski M, Vayser D, Fried D, Kashefsky H, Owings TM, Nadarajah J; Grafix Diabetic Foot Ulcer Study Group. The efficacy and safety of Grafix(R) for the treatment of chronic diabetic foot ulcers: results of a multi-centre, controlled, randomised, blinded, clinical trial. Int Wound J. 2014 Oct;11(5):554-60.

Bilayer Grafts - Amnion/Chorion (dHACM)

Cellular (non-living cells)

AmnioFix® & EpiFix® (MiMedx) [3-8]

- Has completed randomized clinical trials in both DFUs and VLUs

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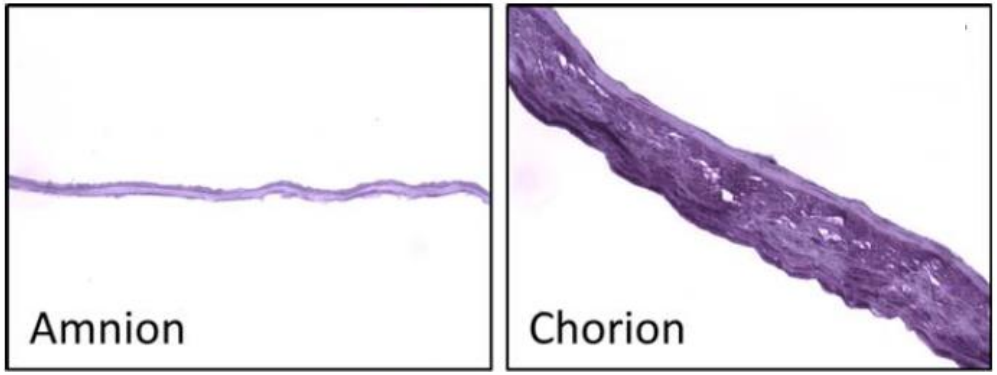
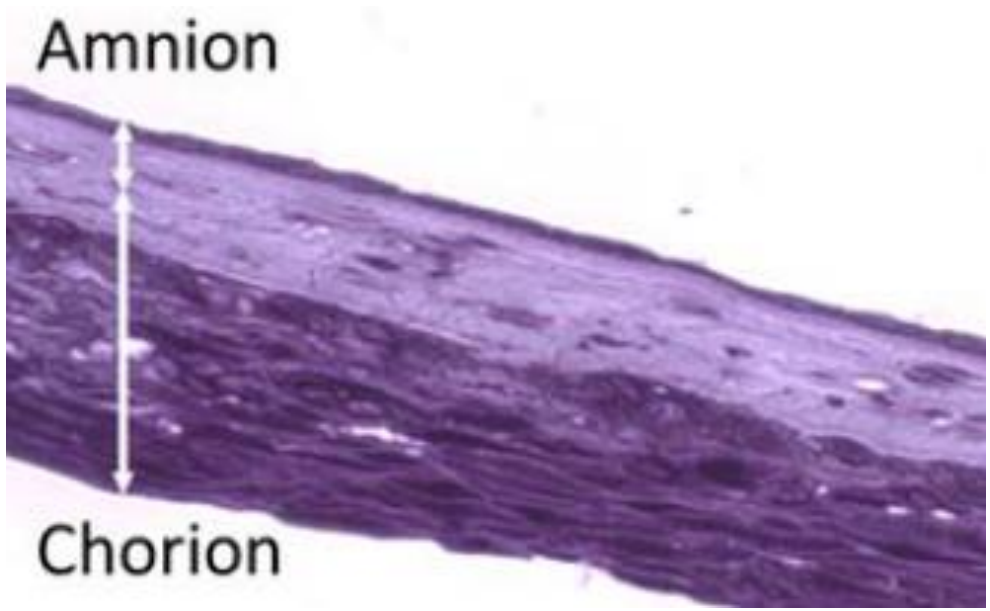
Dehydrated Human Amnion Chorion Membrane (dHACM)

Preserves:

Extracellular Matrix

- Structurally intact tissue
- Collagens I, III, IV, V, VII
- Elastin, Laminin, fibronectin, proteoglycans, and glycosaminoglycans
- Non-viable cells





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Evolution of Thinking

VS.

1 Function

1 Growth Factor

Multi-Functions

200+ Bioactive Proteins

226 Natural Bioactive Proteins Preserved in PURION® Processed dHACM[1-4]

- Angiostatin
- Galectin-7
- TIMP-2
- IL-1 F10
- IGFBP-2
- FLRG
- IGFBP-6
- Pentraxin 3
- Resistin
- CA9
- OSM
- TRAIL
- Thrombospondin-5
- WISP-1
- S100A8
- RGM-B
- Marapsin
- PGRP-S
- Thrombospondin-2
- aFGF
- FABP2
- OPG
- Trappin-2
- Dkk-4
- Lipocalin-2
- Cystatin C
- FGF-9
- IL-1ra
- Leptin
- MCSF
- Cripto-1
- GASP-1
- TFPI
- GRO
- GDNF
- PIGF
- Eotaxin-2
- IGFBP-3
- Thyroglobulin
- OPN
- Furin
- DKK-1
- GROa
- PF4
- BMP-5
- Granulysin
- Galectin-1
- DAN
- IL-21
- Clusterin
- MIF
- GDF-15
- CEA
- MIP-1a
- CXCL16
- CNTF
- TPO
- Procalcitonin
- sFRP-3
- FGF-19
- PDGF-AA
- MCP-1
- Kallikrein 5
- PARC
- FGF-21
- VEGF
- IP-10
- NT-3
- IL-18
- IL-8
- IL-1 F8
- VEGF-D
- I-309
- Eotaxin
- ACE-2
- NSE
- PAI-1
- IL-1 F5
- IL-1 F7
- Gas 1
- CRP
- HGF
- 6Ckine
- EG-VEGF
- Cystatin B
- CHI3L1
- IL-17C
- SP-D
- uPA
- ANG-4
- Shh-N
- TSH
- Renin
- NT-4
- GASP-2
- ANGPTL3
- FGF-6
- NAP-2
- BDNF
- ST2
- IL-34
- BAFF
- EGF
- GH
- IGF-I
- BTC
- TGFb3
- MIP-1d
- Ck beta 8-1
- IL-12p40
- Adiponectin
- TSP-1
- Angiotensinogen
- Serpin A4
- Midkine
- TGFb1
- IL-1 F6
- Dkk-3
- IL-1 F9
- Osteoactivin
- DcR3
- Fractalkine
- LAP(TGFb1)
- IGF-2
- DLL1
- PDGF-BB
- Angiogenin
- Cystatin A
- BMP-7
- MBL
- Cystatin E M
- NOV
- Eotaxin-3
- PDGF-AB
- IL-33
- SDF-1b
- IL-6
- BMP-9
- LIGHT
- TNFb
- IL-1a
- NRG1-b1
- FGF-7
- IL-32 alpha
- IL-7
- HB-EGF
- Pref-1
- Follistatin-like 1
- gp130
- RBP4
- hCGb
- Legumain
- Prolactin
- bIG-H3
- RANTES
- WIF-1
- Galectin-3
- Follistatin
- APRIL
- Insulin
- IL-24
- CF XIV
- ULBP-1
- Chemerin
- C5a
- MIG
- IL-23
- IL-17B
- VEGF-C
- IL-6sR
- MIP-1b
- ENA-78
- IL-20
- TGFb2
- Lymphotactin
- AgRP
- TNFa
- I-TAC
- Flt-3L
- IL-1b
- G-CSF
- IL-2
- Fetuin A
- ANGPTL4
- IGFBP-5
- Adipsin
- TIMP-1
- LRIG3
- IGFBP-1
- BMP-2
- HAI-2
- CXCL14
- IGFBP-4
- FSH
- TRANCE
- TWEAK
- Galectin-9
- ADAMTS13
- ANG-2
- MCP-2
- IL-27
- HCC-1
- Kallikrein 14
- bFGF
- ANG-1
- IL-16
- IL-11
- BLC
- IL-17E
- TIMP-4
- IL-3
- Galectin-2
- SCF
- GCP-2
- GM-CSF
- Activin A
- IL-15
- IL-4

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Relative Growth Factor Amounts Between PURION® Processed Amnion and Chorion

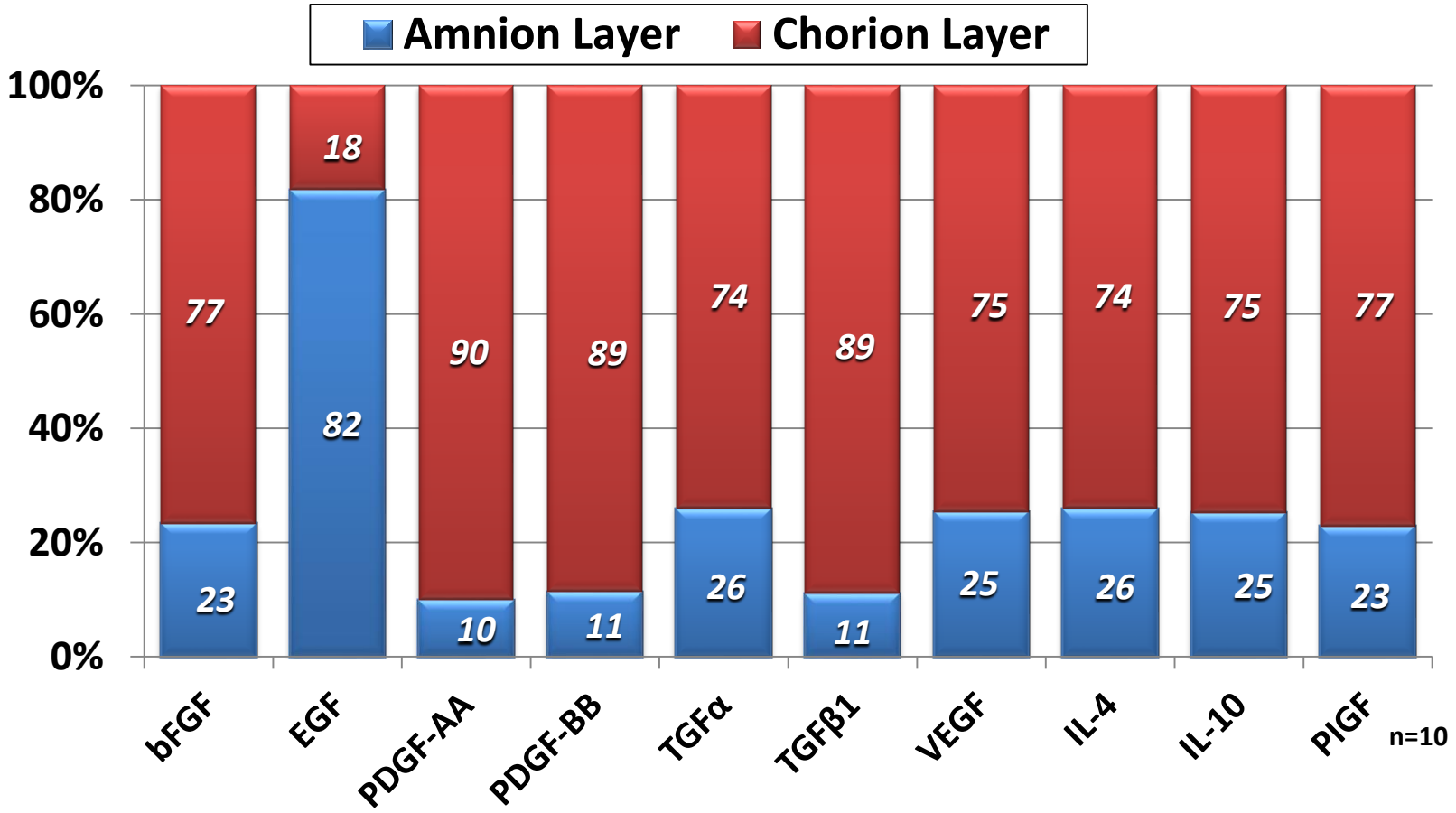
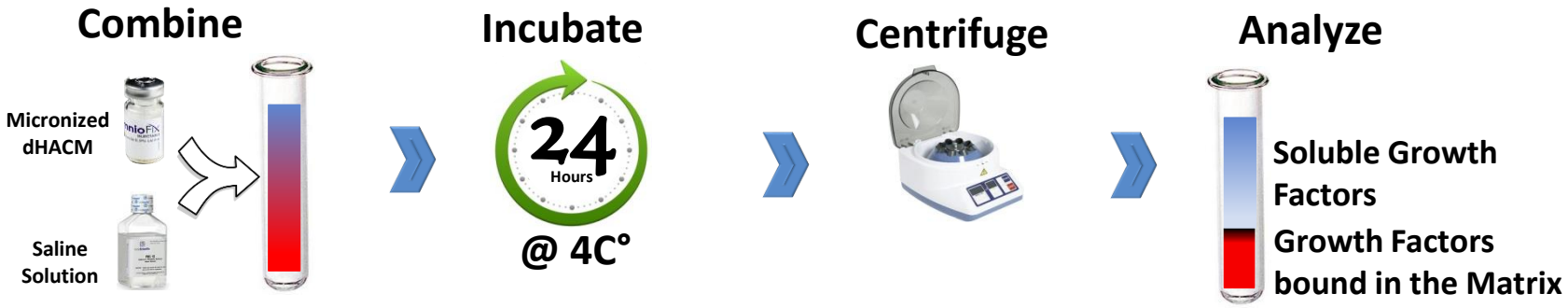


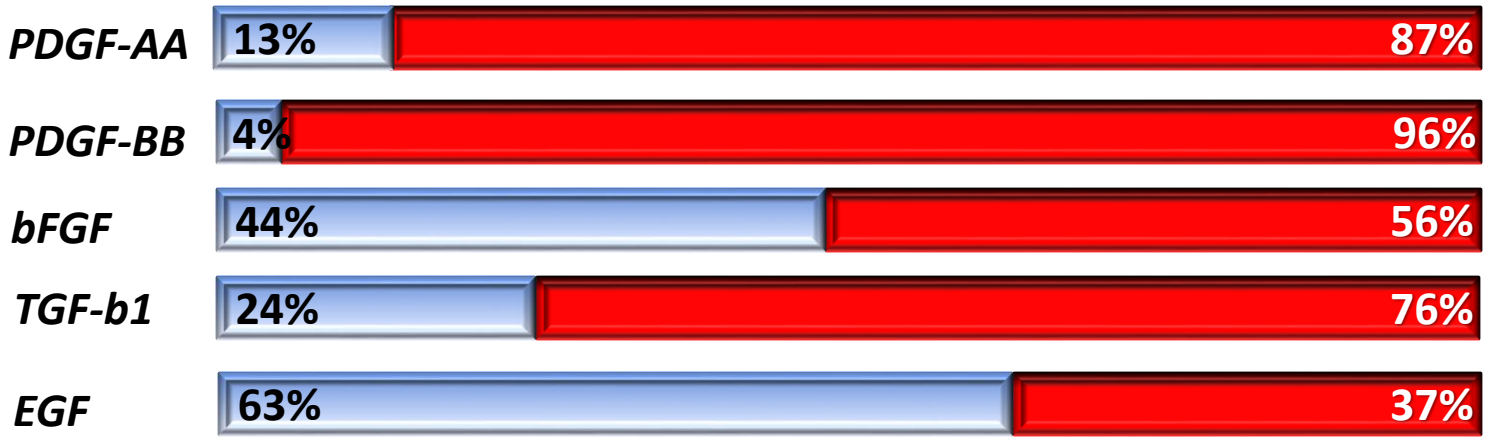
Chart adapted from Koob TJ, Lim JJ, Zabek N, Massee M. Cytokines in single layer amnion allografts compared to multilayer amnion/chorion allografts for wound healing. J Biomed Mater Res B Appl Biomater. 2015 Jul;103(5):1133-40.

Growth Factor Release Profile for dHACM

Method



Results

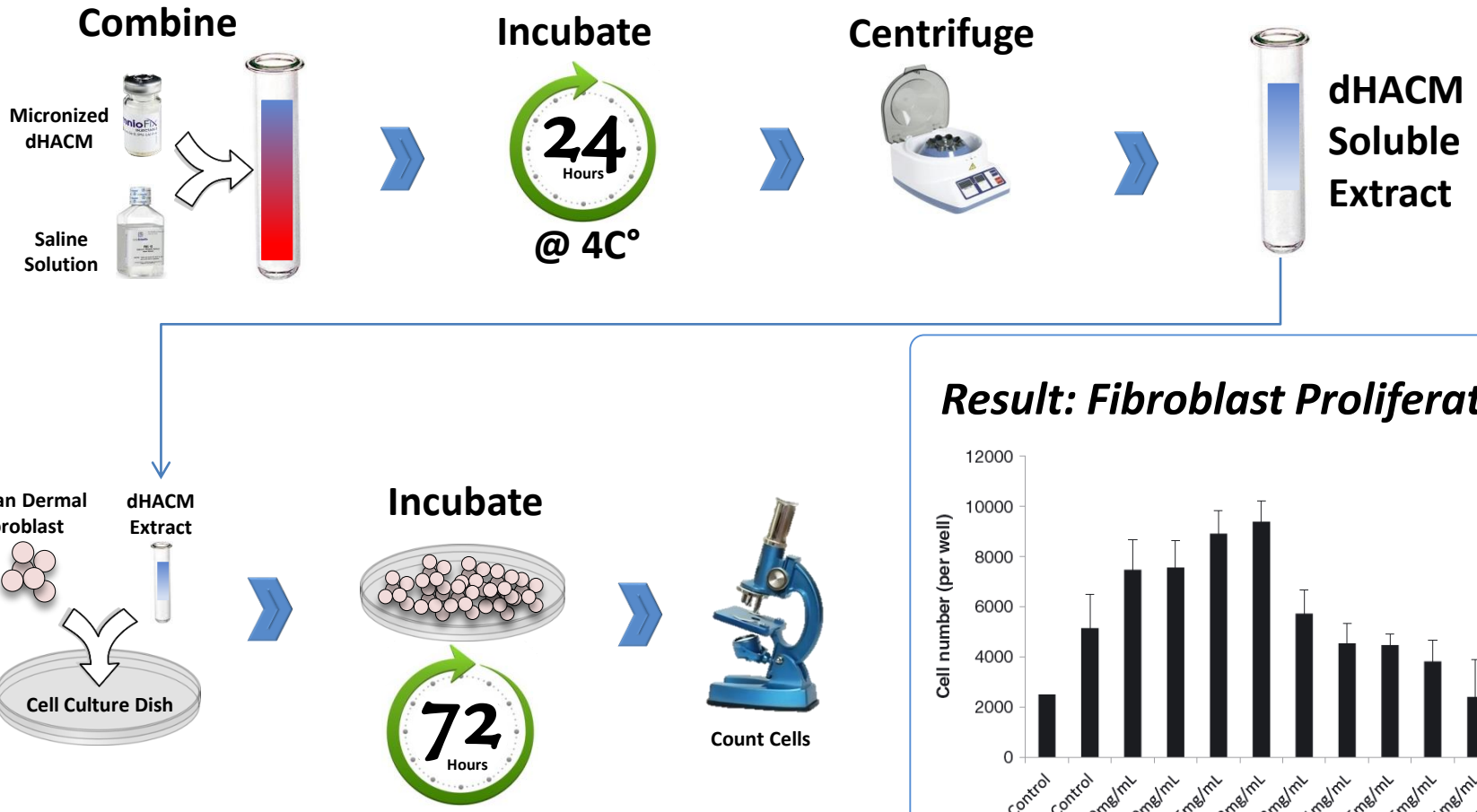


Determined by ELISA Assay (N=5)

Adapted from 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.

Effects of Extracts of dHACM on Adult Human Dermal Fibroblasts Proliferation

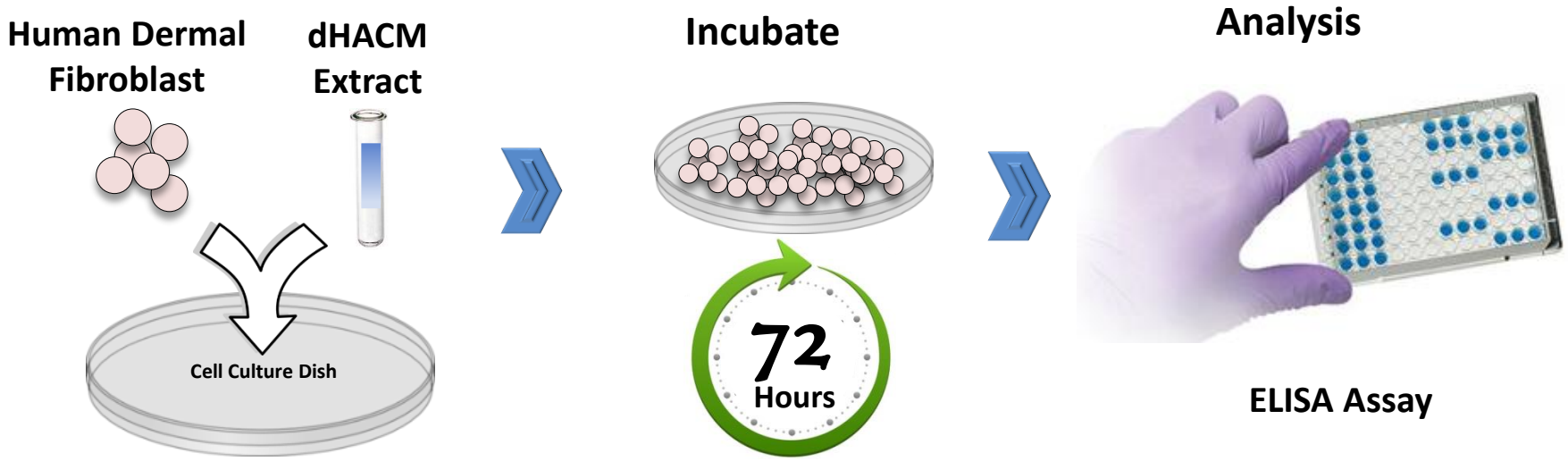
Method



Result: Fibroblast Proliferation

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.

dHACM Extracts Stimulate Growth Factor Production by Human Dermal Fibroblasts



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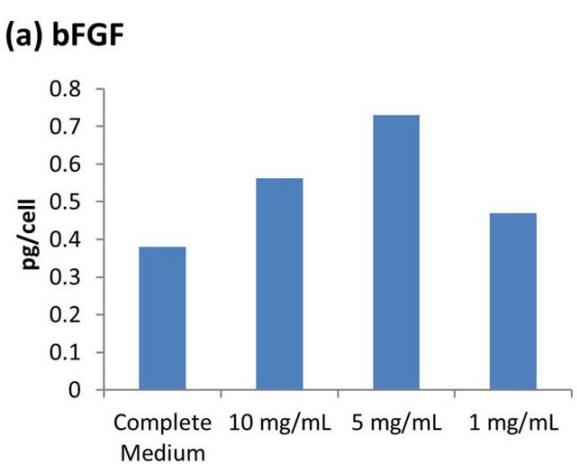
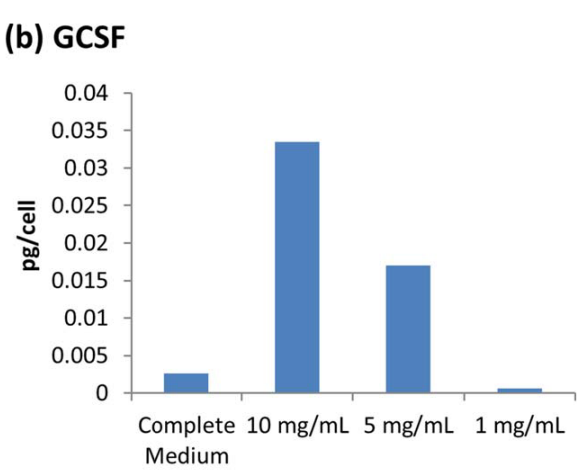
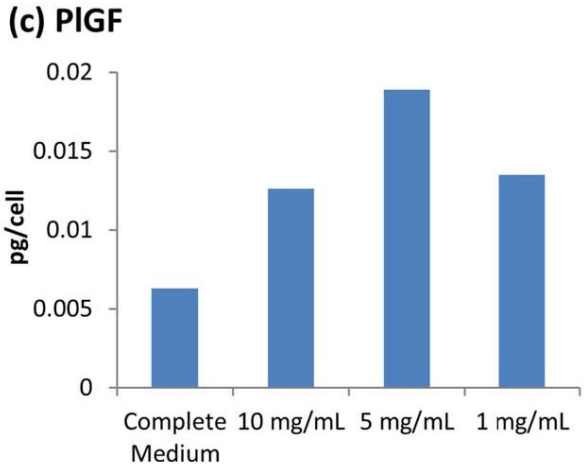
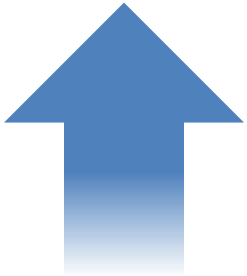






Growth Factor Production



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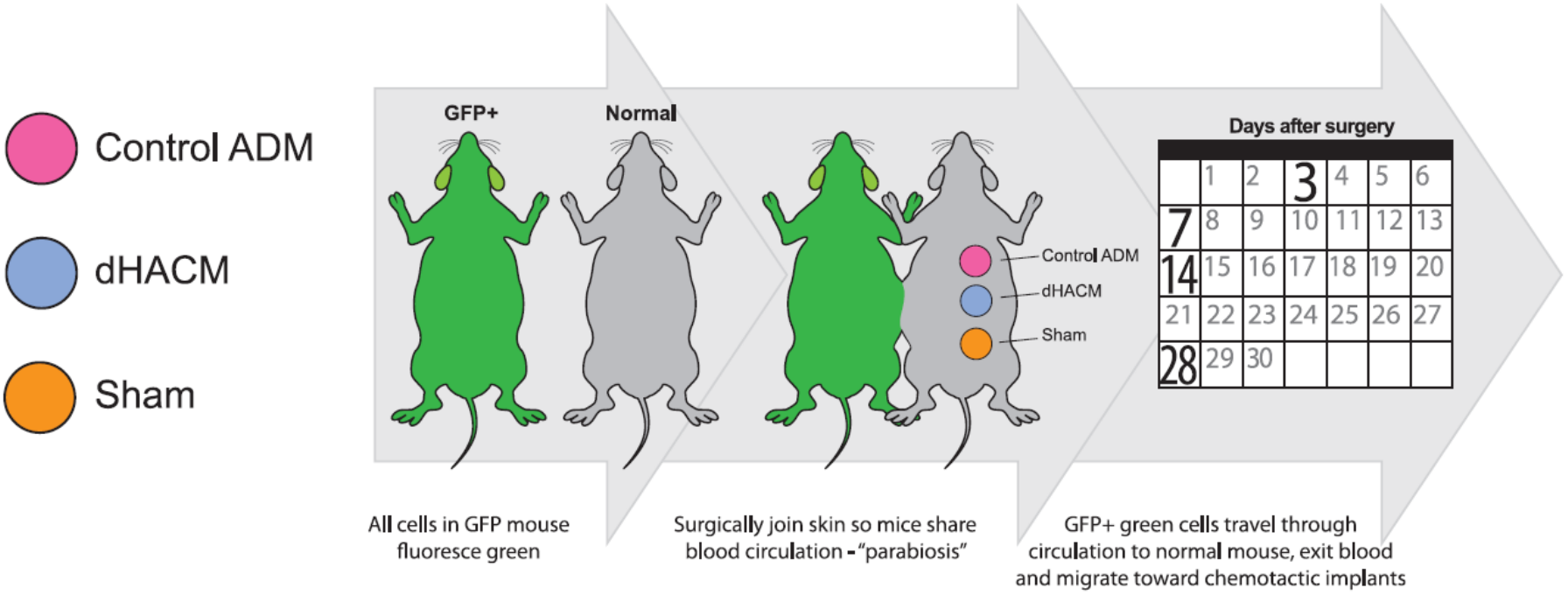
dHACM Recruits of Circulating Hematopoietic Stem Cells



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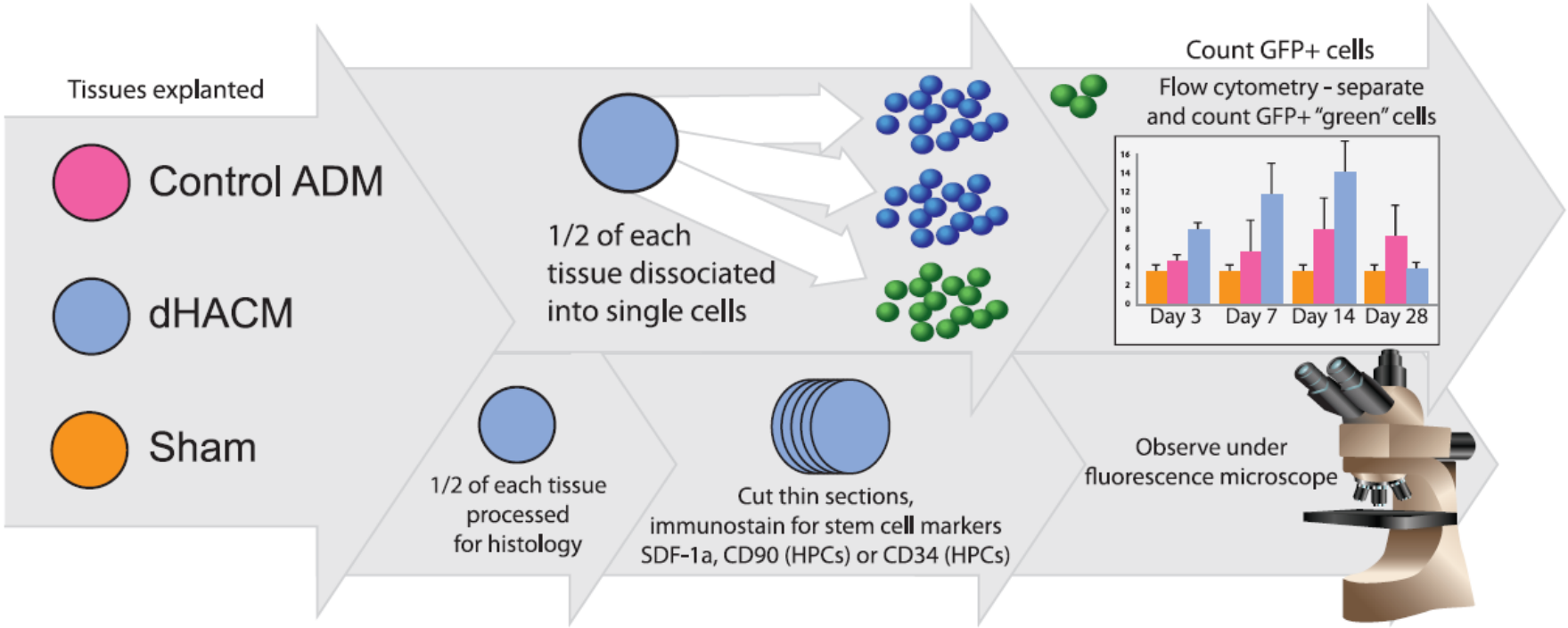
dHACM Recruits of Circulating Hematopoietic Stem Cells



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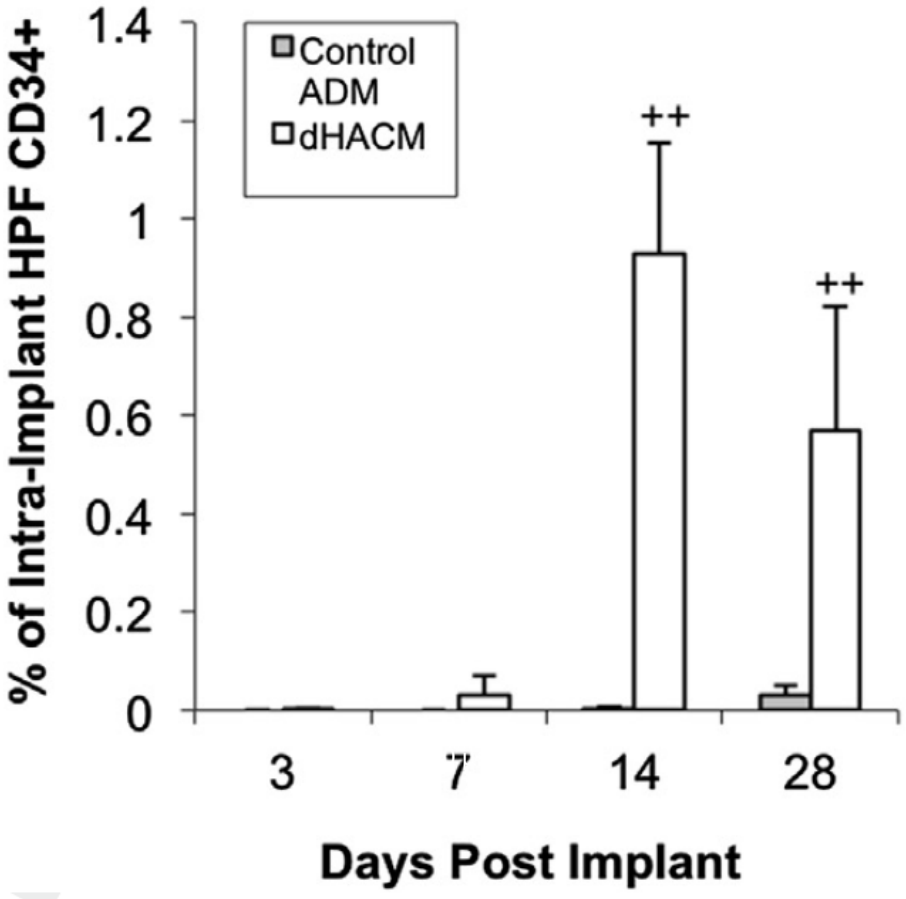
Intra-implant CD34 + progenitor cell engraftment was increased in the dHACM group compared with control



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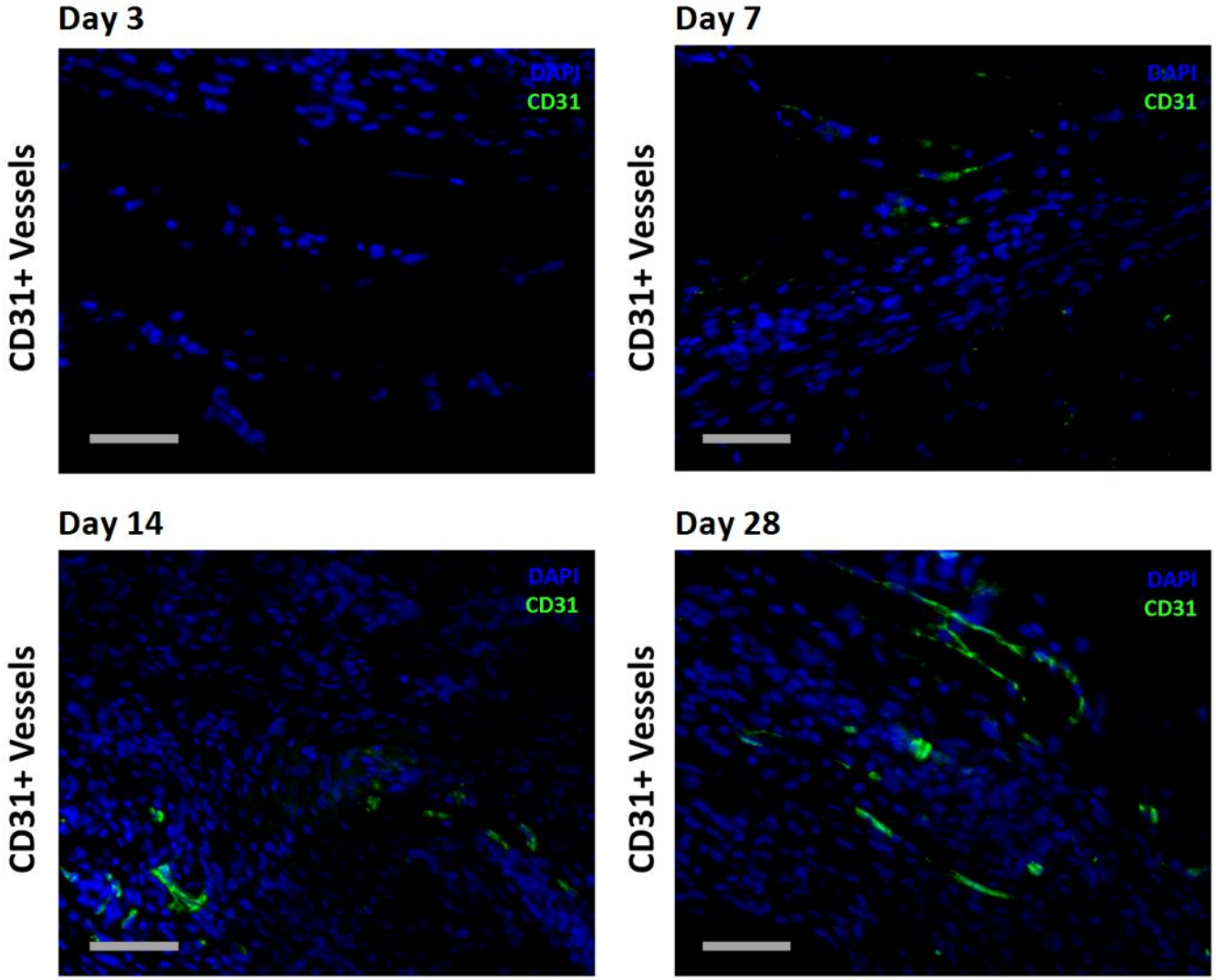
Promotion of Angiogenesis within the dHACM Graft in an Ischemic *in vivo* Model



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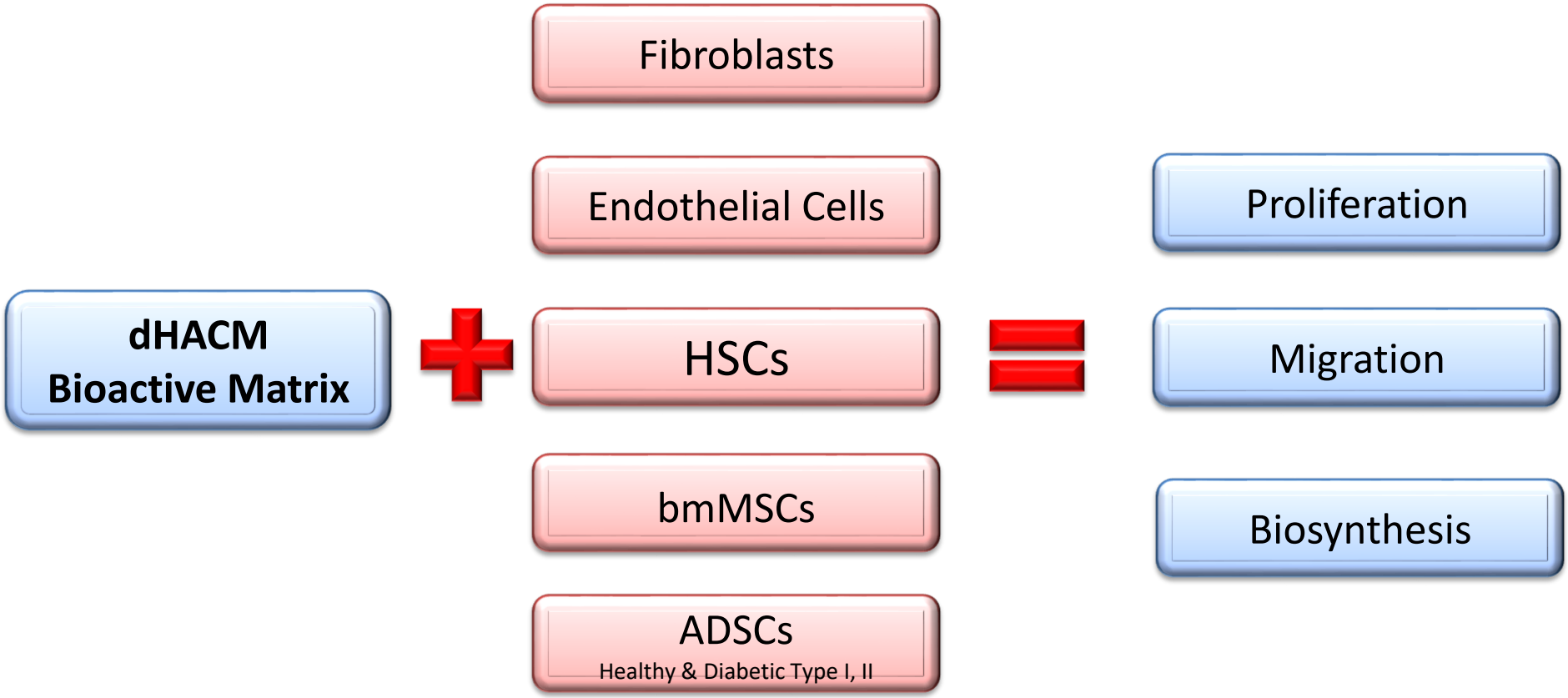
Biological Activity of PURION® Processed dHACM[1-8]



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DIABETIC FOOT ULCER STUDIES

Comparative Review of Advanced Biologically Active Skin Substitutes

Diabetic Foot Ulcer - Level I Clinical Evidence

Product	N=	Complete Healing at		
		4 weeks	*6 Weeks*	*12 Weeks*
EpiFix[1] (dHACM)	100	85%*	95%*	97%*
Grafix[2]	97	15%†	37%†	62%*
Apligraf[3]	208	20%	45%	56%*
Dermagraft[4]	245	11%†	23%†	30%*
AmnioExcel[5‡]	21	-	33%*	-

* ≤ 0.05
† not reported - estimated
‡ Intent to treat study

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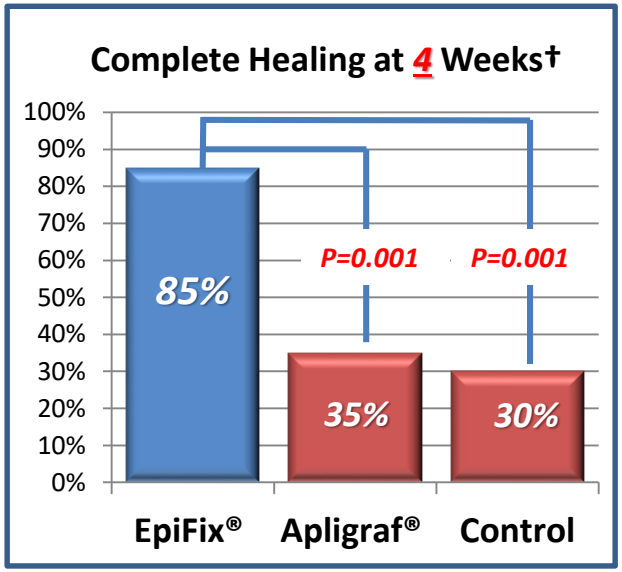
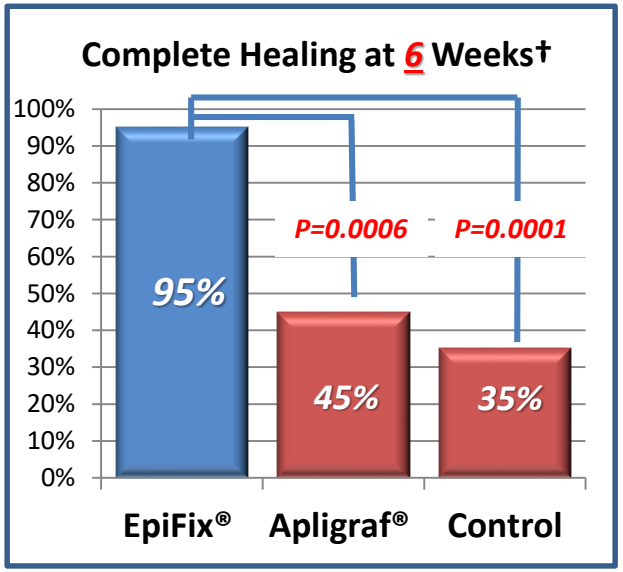
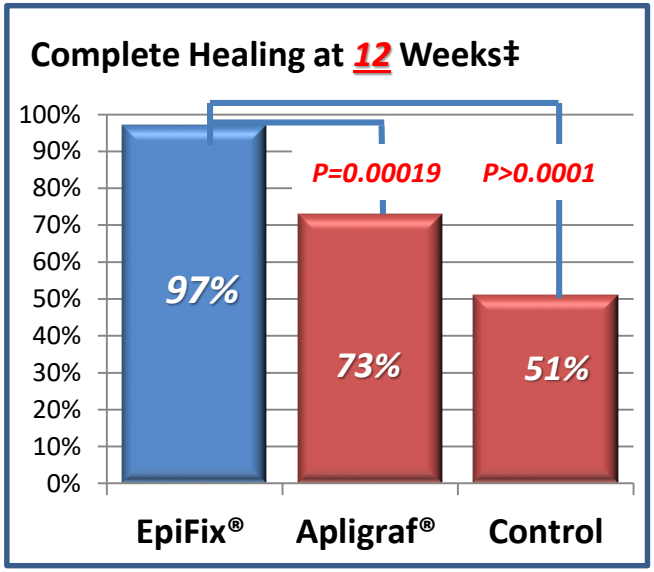
Multi-Center Comparative Effectiveness Study of Healing DFUs Using EpiFix®, Apligraf®, and Standard Care

DFU Trial Showed Superiority of EpiFix® over both Apligraf® and Standard Care for Complete Healing at 4, 6 and 12 Weeks



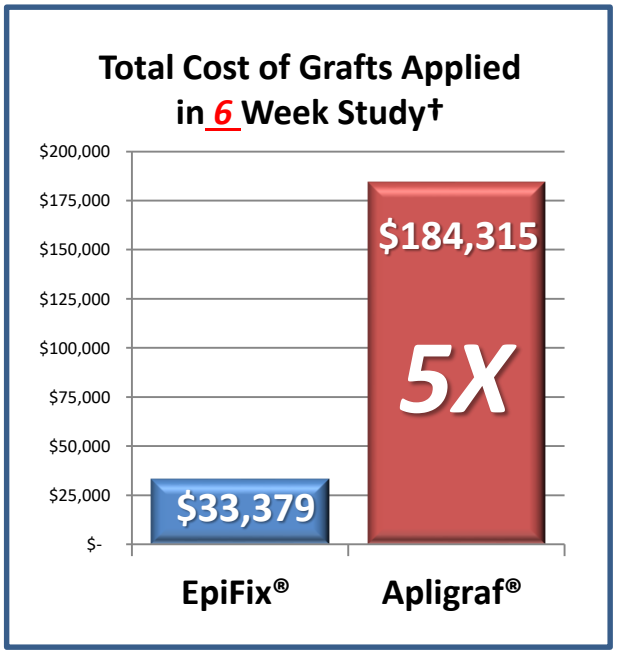


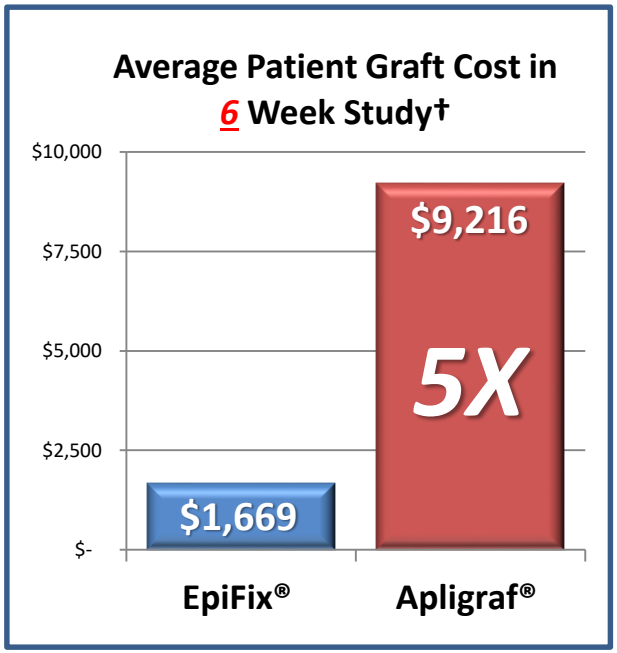


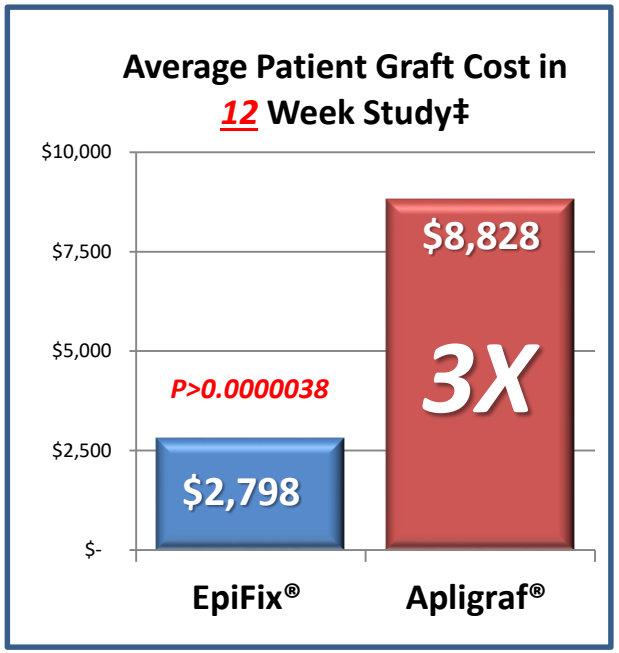
† Zelen CM, Gould L, Serena TE, Carter MJ, Keller J, Li WW. A prospective, randomised, controlled, multi-centre comparative effectiveness study of healing using dehydrated human amnion/chorion membrane allograft, bioengineered skin substitute or standard of care for treatment of chronic lower extremity diabetic ulcers. Int Wound J. 2015 Dec;12(6):724-32.

‡ Zelen CM, Serena TE, Gould L, Le L, Carter MJ, Keller J, Li WW. Treatment of chronic diabetic lower extremity ulcers with advanced therapies: a prospective, randomised, controlled, multi-centre comparative study examining clinical efficacy and cost. Int Wound J. 2015 Dec 23. doi: 10.1111/iwj.12566. [Epub ahead of print]

Multi-Center Comparative Effectiveness Study of Healing DFUs Using EpiFix®, Apligraf®, and Standard Care







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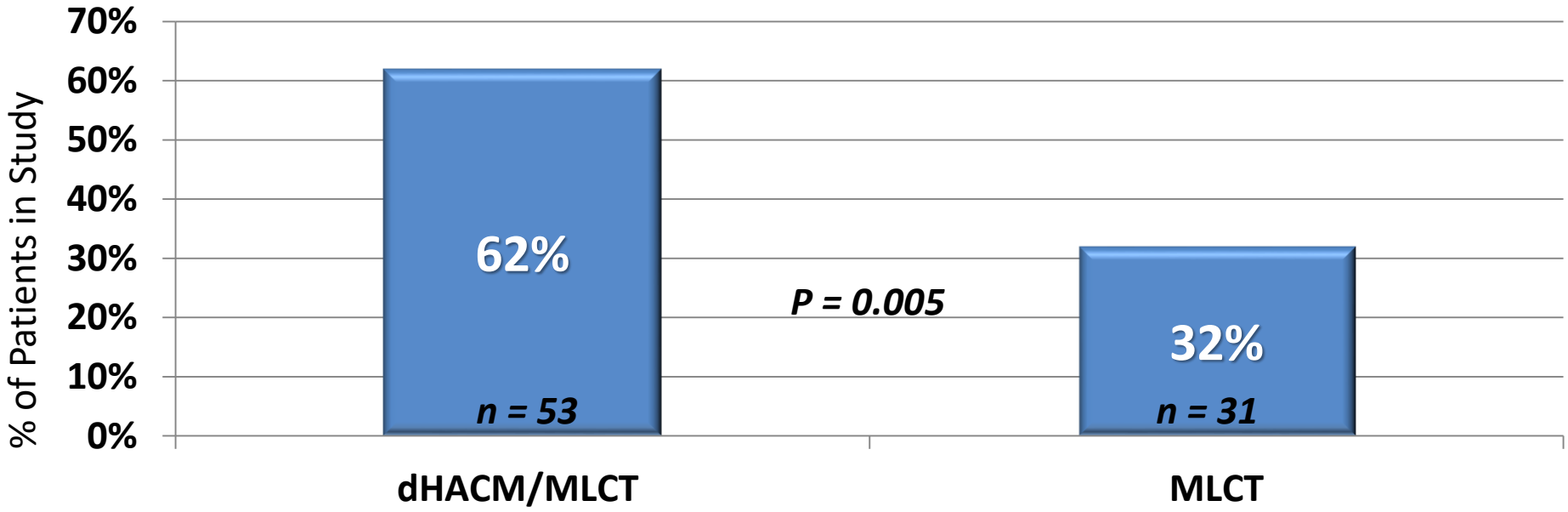
VENOUS LEG ULCER STUDIES

Multi-Center, Randomized, Controlled, Venous Leg Ulcer Trial

(n = 84)

≥ 40% Wound Area Closure of Venous Leg Ulcers in 4 Weeks



PAIN Observation measured: EpiFix® showed a reduction in pain in 79.5% of the patients that received EpiFix® compared to 52.4% patients receiving only MLCT.

Serena TE, Carter MJ, Le LT, Sabo MJ, DiMarco DT; EpiFix VLU Study Group. A multicenter, randomized, controlled clinical trial evaluating the use of dehydrated human amnion/chorion membrane allografts and multilayer compression therapy vs. multilayer compression therapy alone in the treatment of venous leg ulcers. Wound Repair Regen. 2014 Nov-Dec;22(6):688-93.

Comparative Review of Advanced Biologically Active Skin Substitutes

Venous Leg Ulcers - Level I Clinical Evidence

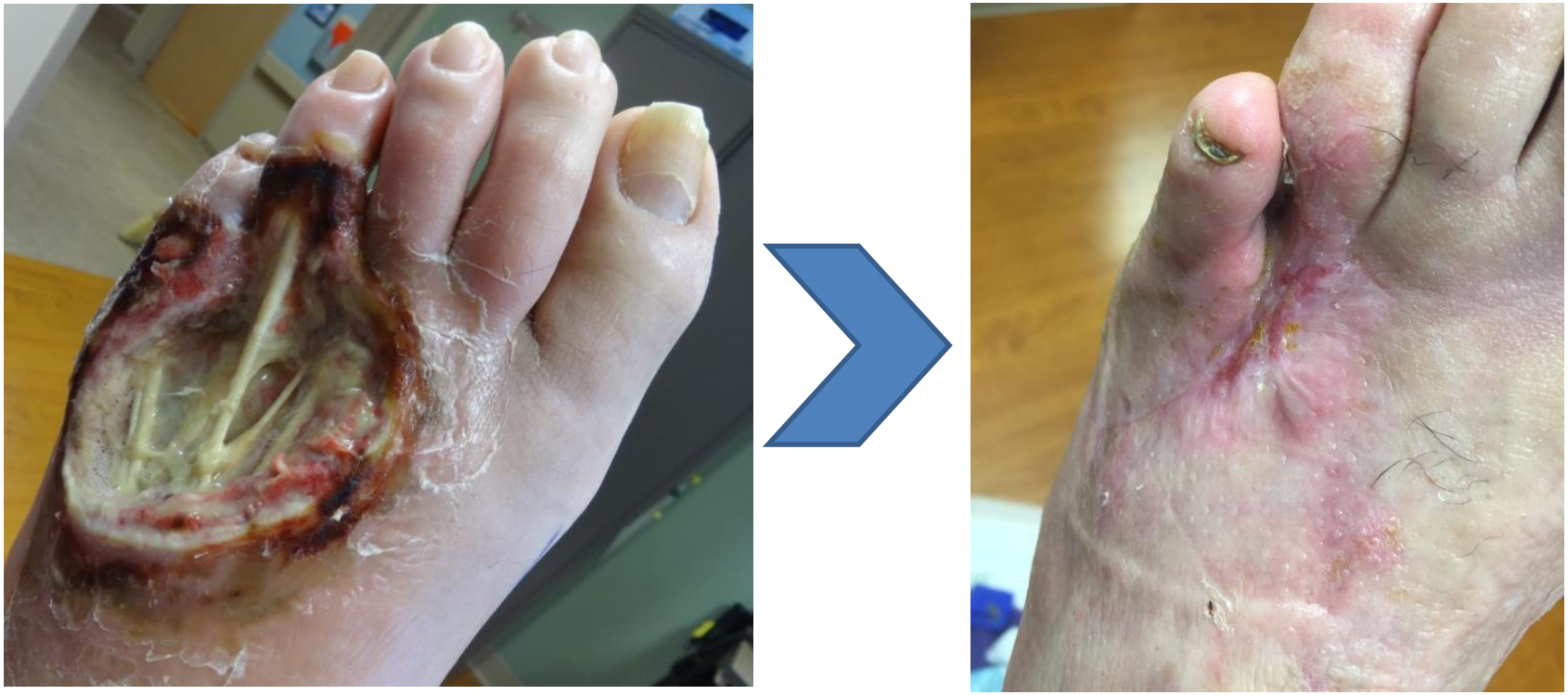
Product	N=	Complete Healing at				
		4 weeks	*8 Weeks*	*12 Weeks*	*16 Weeks*	*24 Weeks*
EpiFix[1] ongoing	36	17%	33%	58%	72%	-
Control[1]	37	11%	24%	41%	46%	-
Apligraf[2]	140	9%	29%	37%*	-	57%*
Control[2]	110	5%	19%	24%	-	40%
Dermagraft[3]	274	-	-	-	73%	-
Control[3]	263	-	-	-	67%	-

Note: Apligraf, Dermagraft, and EpiFix studies are independent of one another * ≤ 0.05

1. Shareholder Call Presentation. http://phx.corporate-ir.net/phoenix.zhtml?c=213465&p=irol-eventDetails&EventId=5250680. (as of 3/27/2017)
2. Atillasoy E. The Safety and Efficacy of Graftskin (Apligraf) in the Treatment of Venous Leg Ulcers: A Multicenter, Randomized, Controlled Clinical Trial. *Wounds*. 2000; 12(5 Suppl A):20A-26A.
3. https://clinicaltrials.gov/ct2/show/results/NCT00909870?sect=X01256#all (as of 3/27/2017)

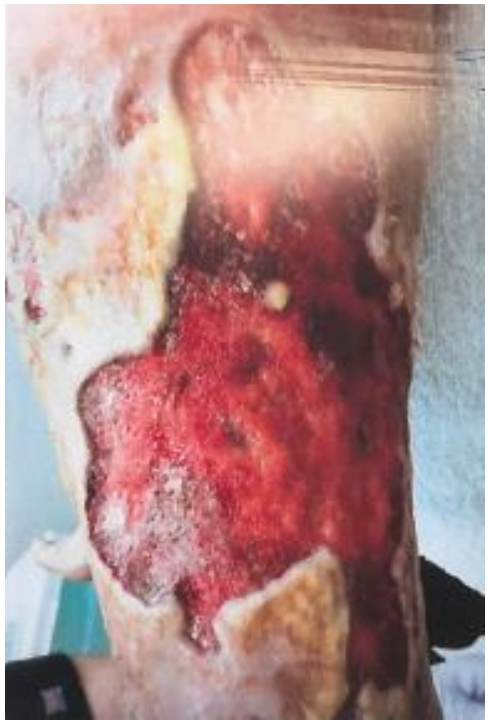
COMPLEX WOUND CASE EXAMPLES

Complex Wounds: Exposed Bone/Tendon

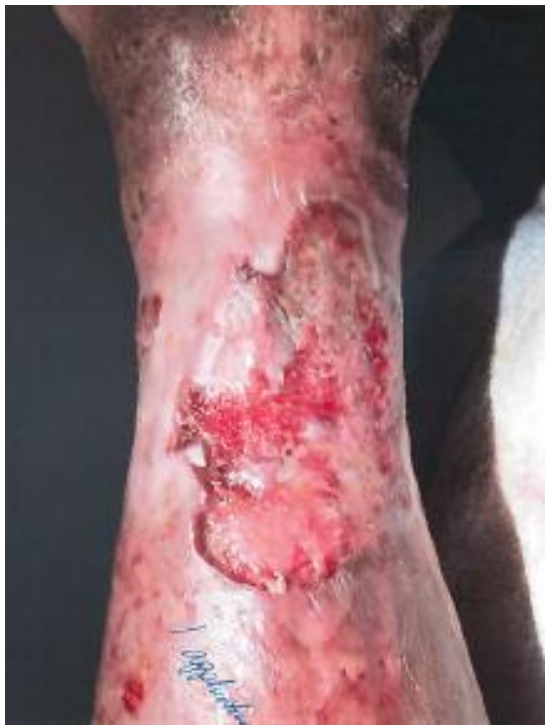


dHACM has been used for both primary closure and as an important adjunct in the treatment of complex wounds.

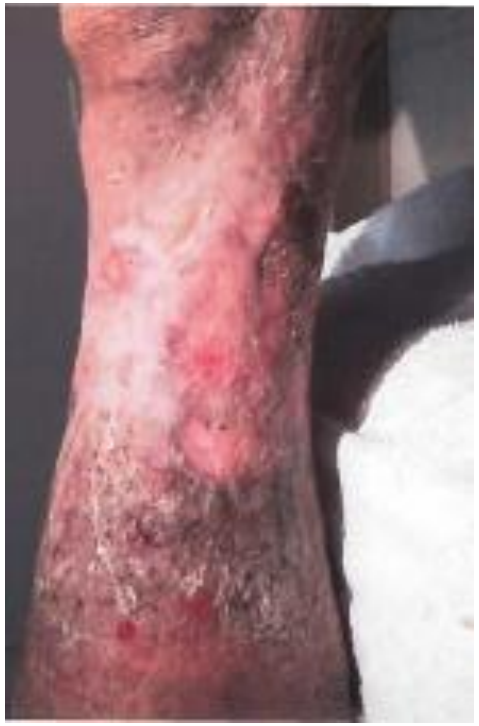
VLU Wound Healing



Initial Wound,
Pretreatment and first application of dHACM
Mid-Feb 2015
Wound 25x19cm
(475cm^2)

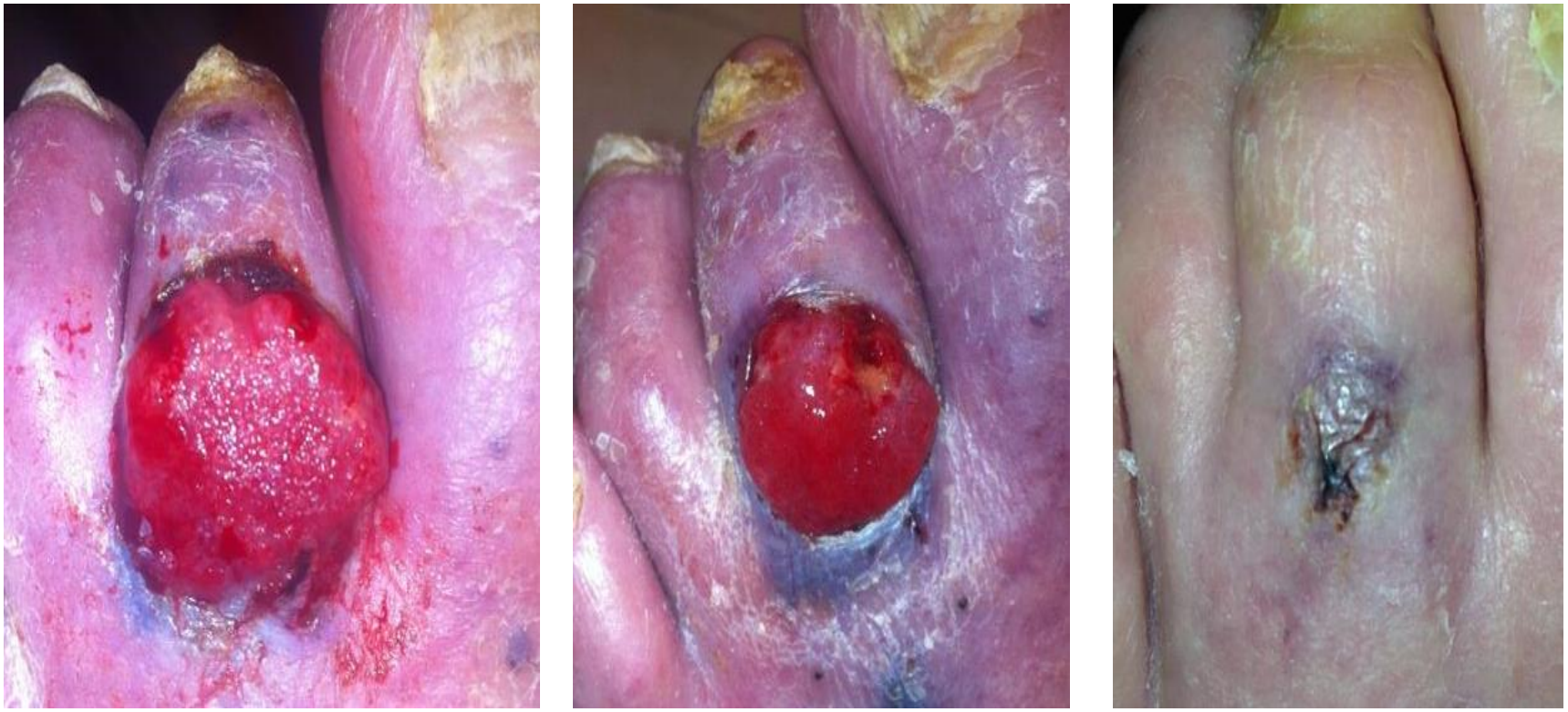


Pre-debridement and Second Application of dHACM
4/7/2015
Wound < 100 cm^2



Week of 4/13/2015
Healed

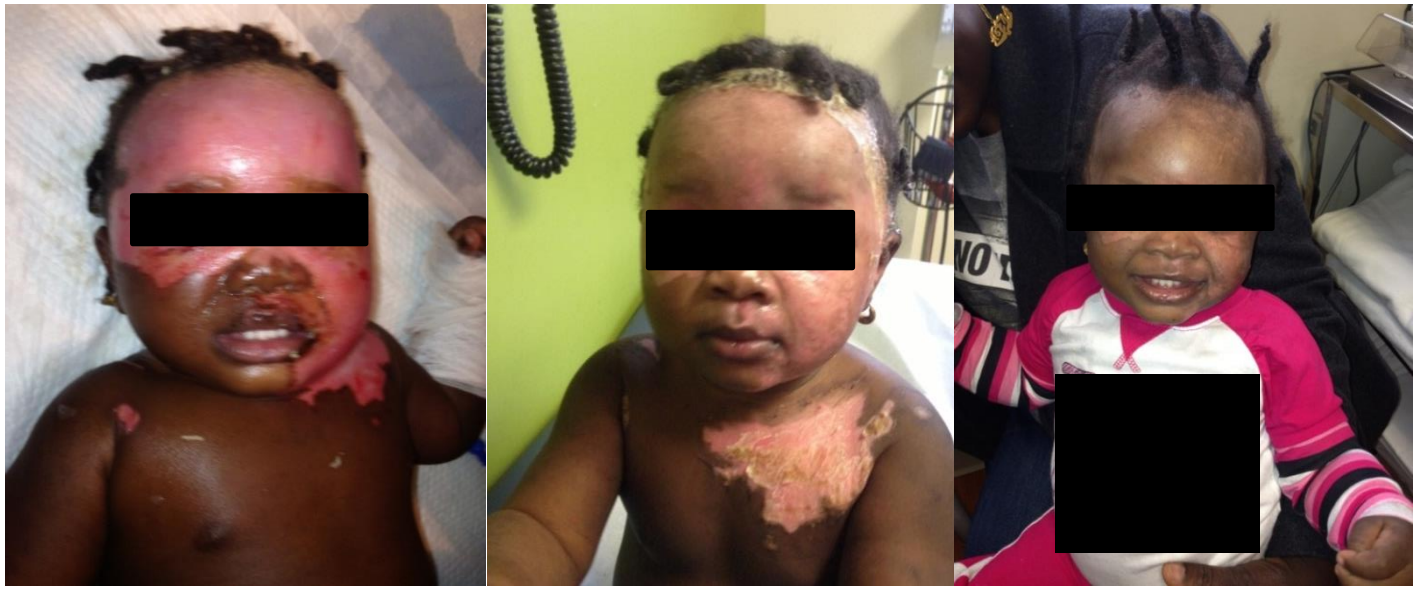
Hypergranulation



Hypergranular wound to 2nd PIPJ; Closed with 5 applications of dHACM sheet in 5 weeks

Pediatric Partial-Thickness Burn

- Toddler presented with a partial-thickness, typical scald burn on the face and head
- dHACM was applied, and the patient's pain resolved quickly after covering the raw nerve endings in the burn; the patient returned home the day after application
- Returned one week later for follow-up; the pain was managed and the burn was healing well at that point
- At 3 to 4 weeks after the application, the patient was getting some pigment back in the skin and showed no signs of future scarring



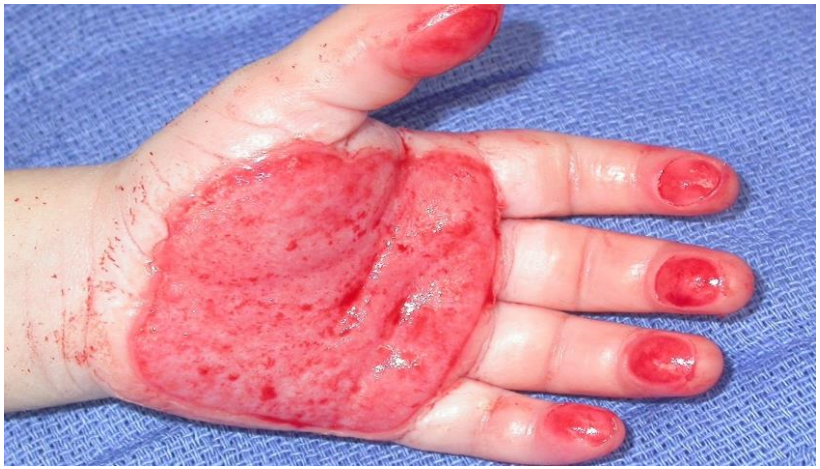
Day 1

Week 1
Post dHACM application

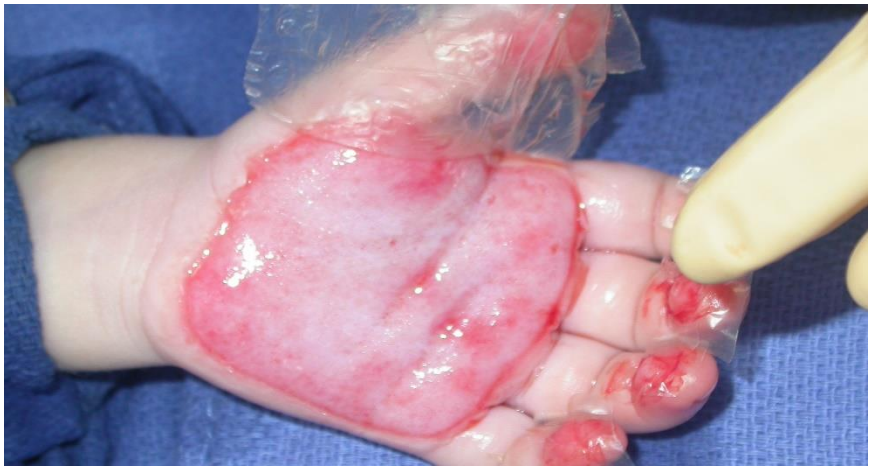
Week 4
Regaining pigment, no signs of scarring

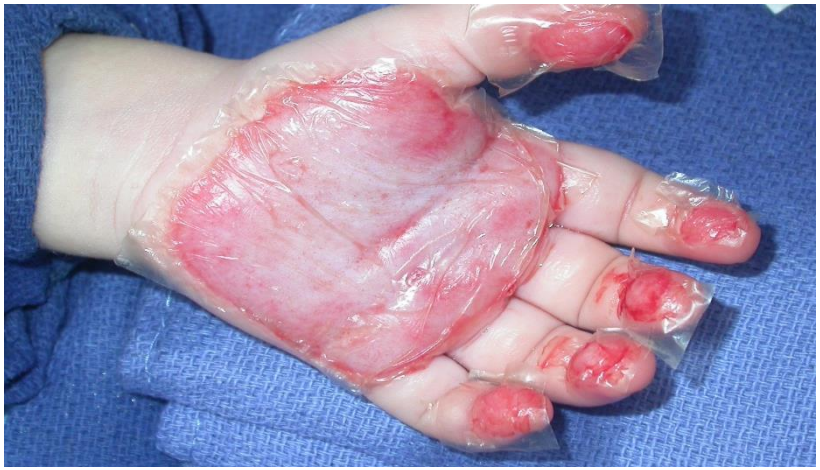
4 year old contact burn

Presentation

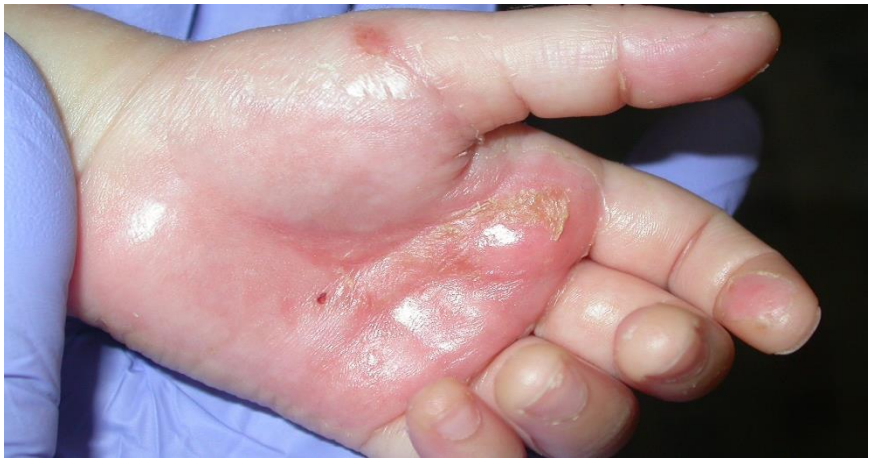


dHACM Application



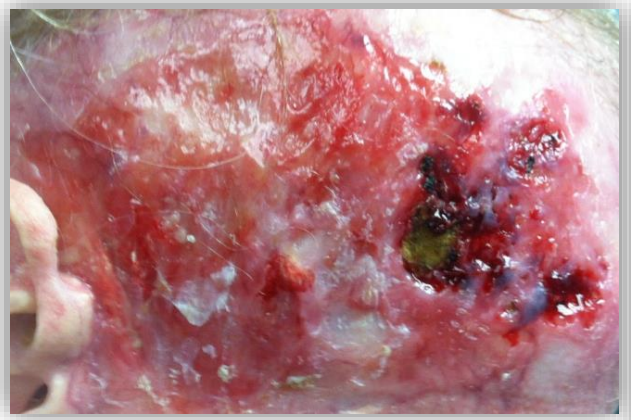


dHACM in place

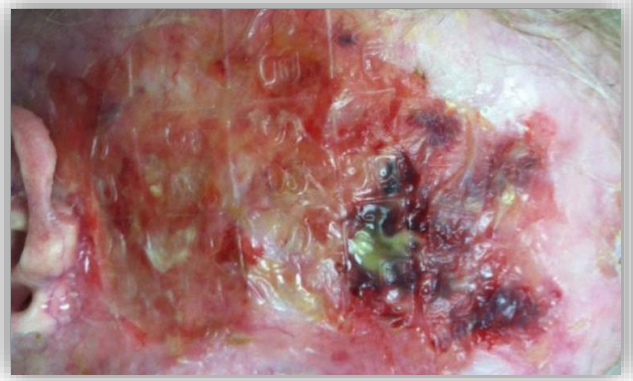


2 weeks after dHACM Application

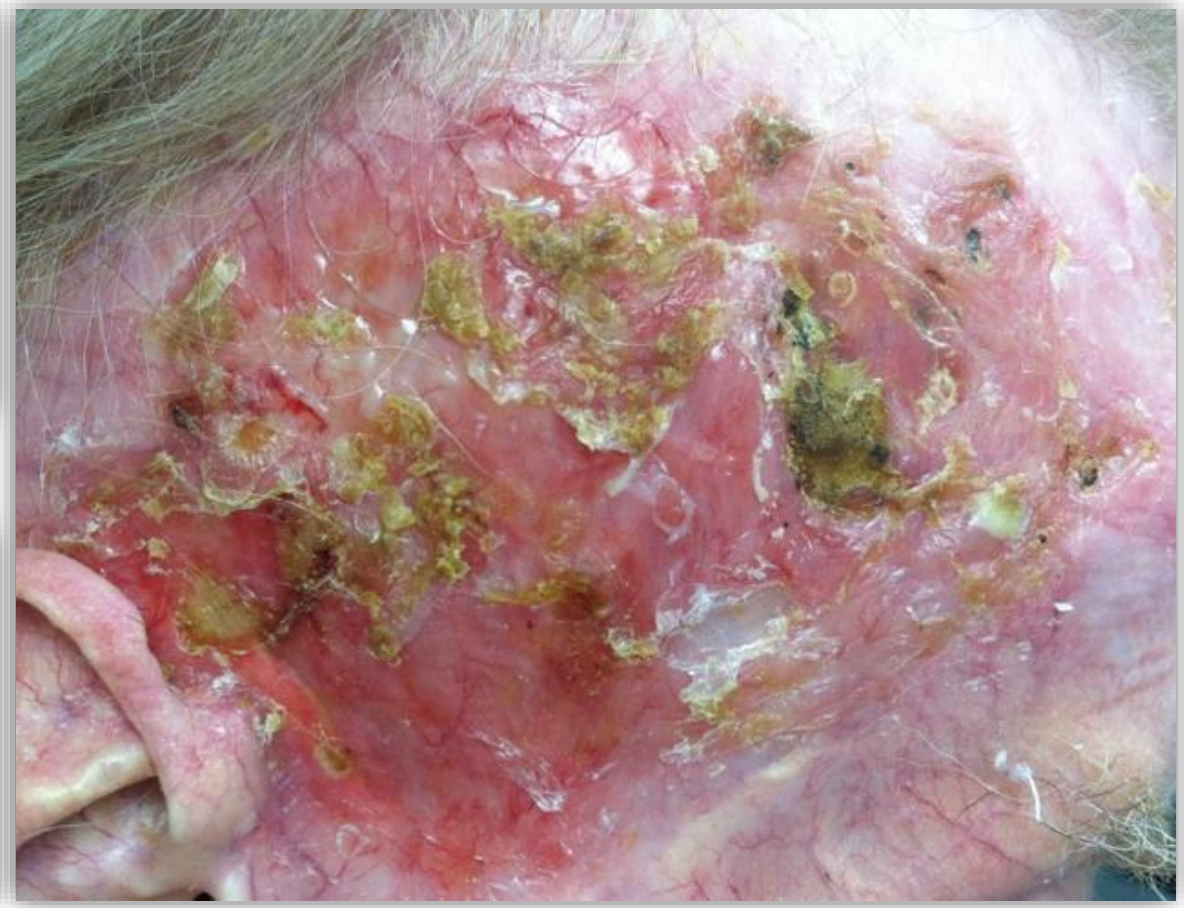
Radiation Dermatitis



Dermagraft® and Oasis® treatments failed, then dHACM was applied

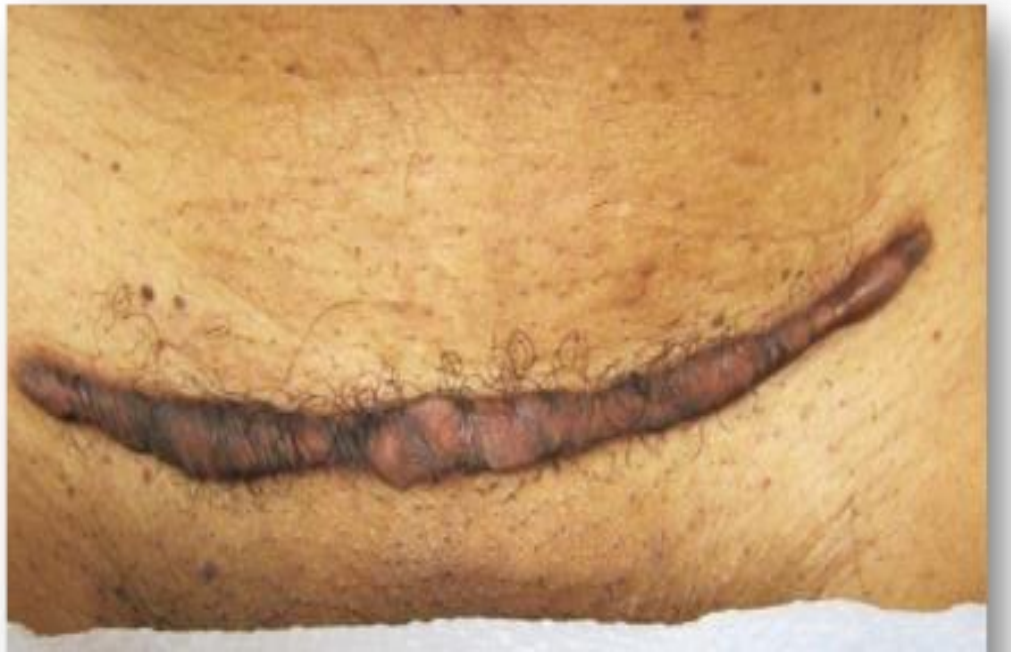


One dHACM graft applied to the surface of the wound



Week 1 Post application of dHACM

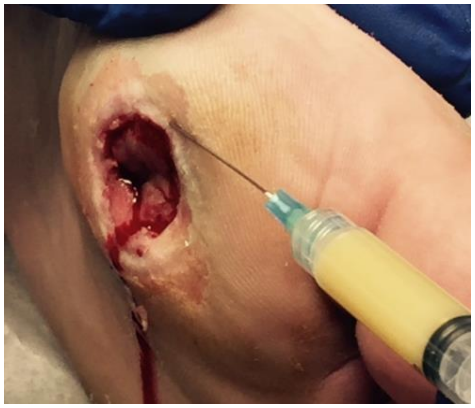
Keloid Scar Revision



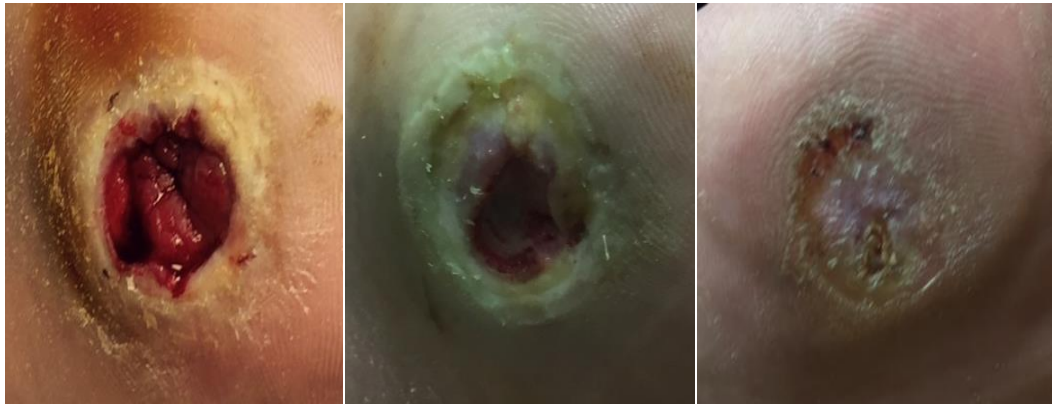
Pre-Op

1 Year
Post-scar revision using dHACM on 1/3 portion of original scar

Injection of dHACM Micronized and saline



Injection of dHACM Micronized and saline



2 weeks post injection

6 weeks post injection

12 weeks post injection

THANK YOU