



# **Introduction of Collagen Matrix**

**The next generation of tissue regenerative technology.**

**CEO: DJ Hsieh**

**November 29, 2017**

# About CEO: DJ Hsieh

## Education

- Ph. D, Cell & Molecular Biology, SUNY at Buffalo

## Current Position

- CEO, ACRO Biomedical Co., Ltd.
- Adjunct Professor, National Kaohsiung Marine University
- Director of Academia-Industry Consortium for Southern Taiwan Science Park/  
Director of Taiwan Supercritical Fluid Association/Taiwan Biotechnology Industry Alliance/  
Supervisor of The Allied Association for Science Park Industries

## History

- CEO, Sunmax Biotechnology
- Deputy CEO, Institute for biotechnology and medicine industry (IBMI)
- Director of Business Development, Animal Technology Institute Taiwan
- CEO, PRIT Biotech
- Founder/CEO, Acrobio Investment Consulting Co. Ltd.
- Associate Professor, Kaohsiung Medical University

# Introduction of ACRO Biomedical

ACRO Biomedical was founded in June, 2014, and is positioning in developing and producing biomaterials for the applications in tissue engineering and regenerative medicine (TERM). Using its proprietary super critical CO<sub>2</sub> (SCCO<sub>2</sub>) technology to remove cells, fats and non-collagenous proteins in animal organs and tissues , while keeping the intact collagen scaffolds as the products for the high-end medical devices.

- In 2016, the world's first successful canine corneal transplantation was conducted.
- In the leading position in global tissue engineering with advance technique and complete product pipelines.
- In May 2017, received FDA 510K and TFDA class II medical device approval for Collagen Matrix product.
- In November 2017, received TFDA class II medical device approval for Bone Graft product.

<b>Company</b>	ACRO Biomedical Co., Ltd.
<b>Chairman</b>	Wang, Lu-Yen
<b>Factory Location</b>	3rd Fl., No. 57, Luke 2nd Rd., Lujhu Dist., Kaohsiung City 82151, Taiwan
<b>Established date</b>	June, 2014
<b>Paid-up Capital</b>	NTD 206.7 millions (~USD7M)
<b>Company positioning</b>	develop and produce medical devices for the use in tissue engineering and regenerative medicine
<b>Total employee</b>	25

# Milestones of ACRO Biomedical

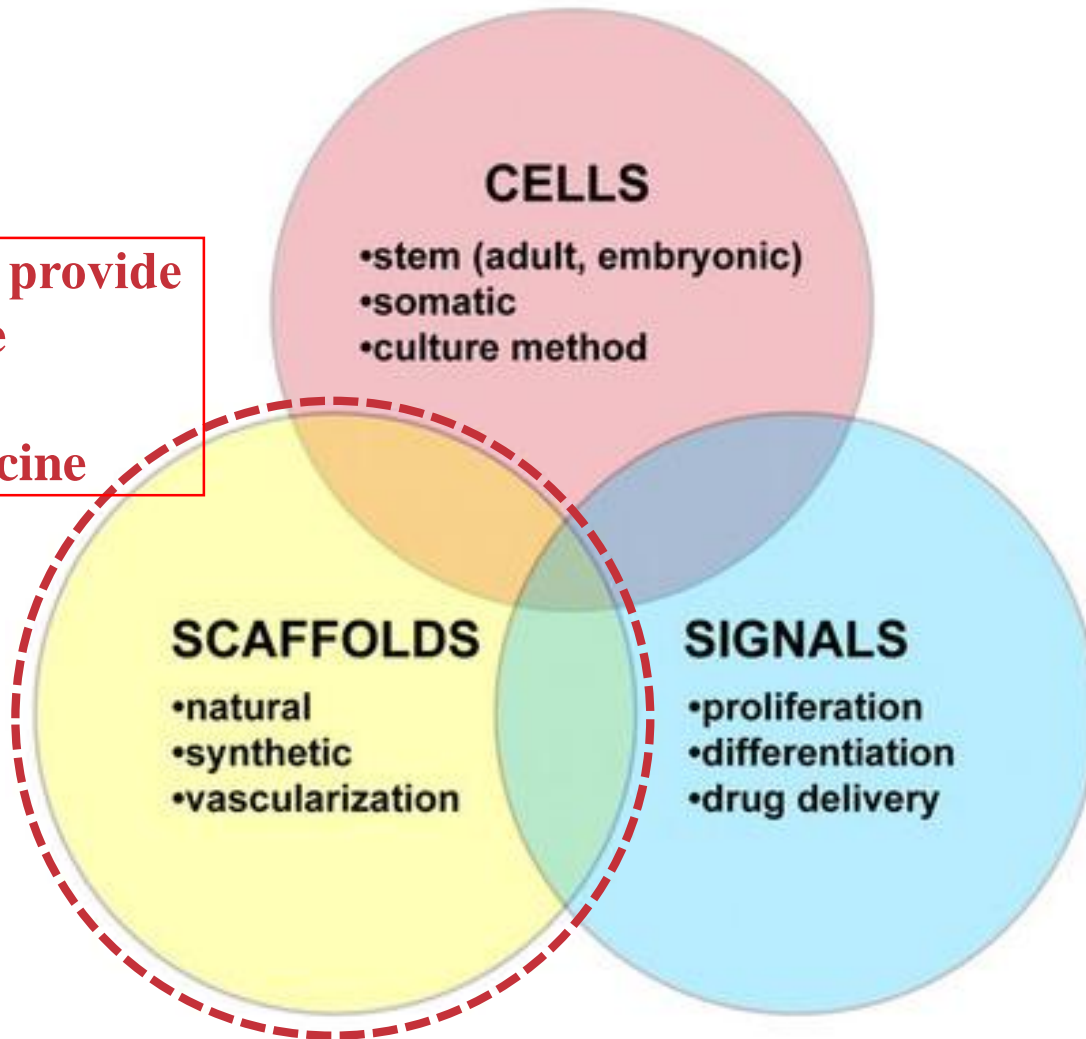
<b>June 2014</b>	Company established by a group of scientists, professors, doctors and angel investors
<b>July 2015</b>	Constructed GMP qualified factory in the Biotech area of Kaohsiung Science Park
<b>August 2015</b>	Acquired license for Manufacture and Sale of Therapeutic Medical Device Products
<b>May 2016</b>	Received International Management System Certificate- ISO13485
<b>June 2016</b>	Received GMP management system approval for medical device from Taiwan FDA
<b>June 2016</b>	Submitted product registration for TFDA Medical Device: Collagen Matrix
<b>August 2016</b>	Submitted product registration for USFDA Medical Device: Collagen Matrix
<b>September 2016</b>	Acquired licenses of 4 Class I Medical Device products from TFDA
<b>September 2016</b>	Launched ACRODERM skin care series products
<b>September 2016</b>	Conducted the world's first successful canine corneal transplantation
<b>November 2016</b>	Interviewed and broadcasted by Discovery Channel of cornea project and the case on corneal transplantation
<b>November 2016</b>	Qualified as the Emerging Biotech company by Ministry of Economic Affairs
<b>April 2017</b>	Acquired CE Mark licenses of 4 Class I Medical Device products

# Milestones of ACRO Biomedical

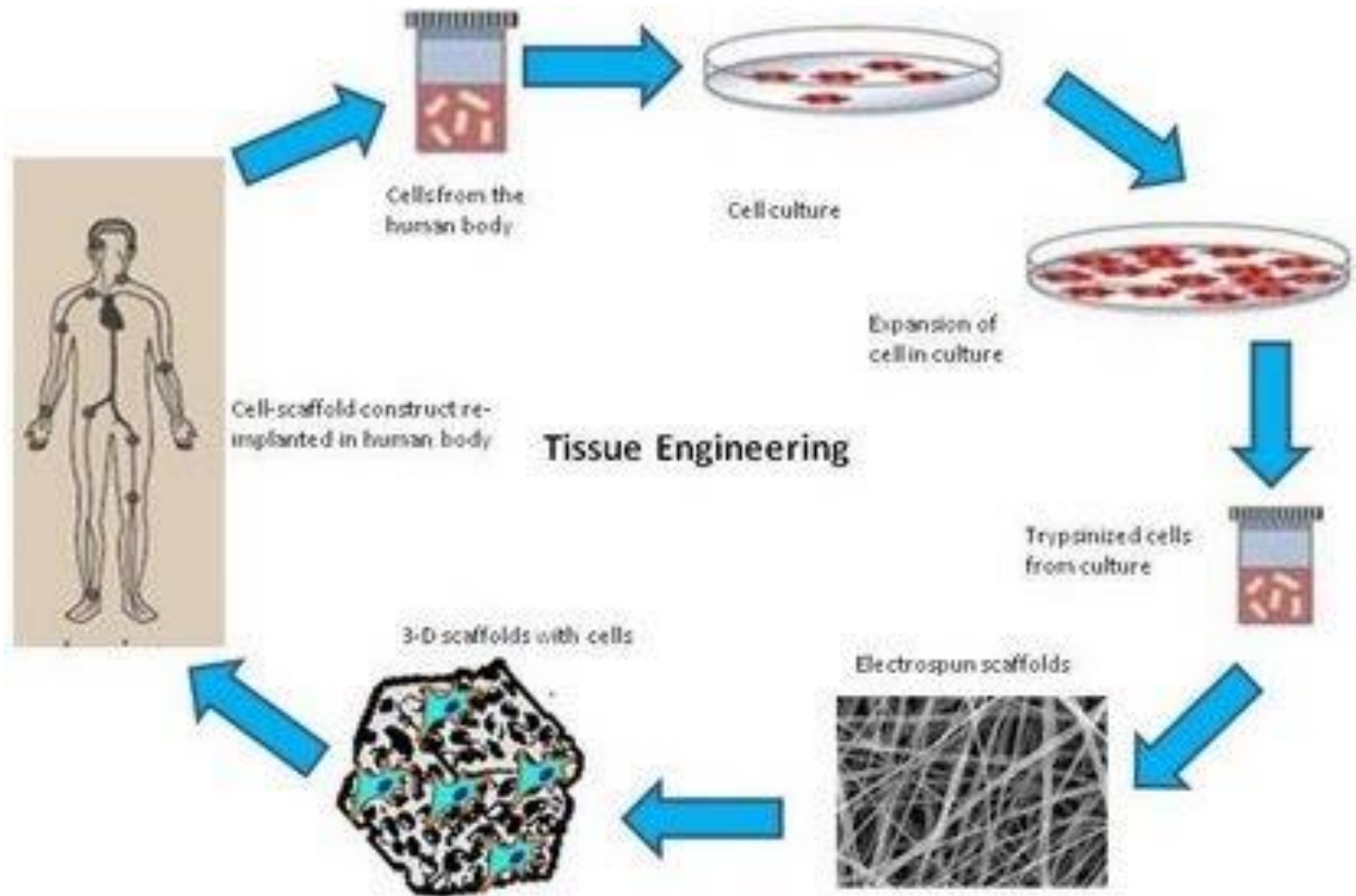
<b>April 2017</b>	Submit product registration for TFDA Medical Device: Bone Graft, 6/1 submit to USFDA
<b>May 2017</b>	5/10 received FDA510K for Collagen Matrix product
<b>May 2017</b>	5/16 received TFDA class II Medical Device approval for Collagen Matrix product
<b>Sept. 2017</b>	Initiate IRB-approved human clinical test in Kaohsiung Veteran General Hospital for Collagen Matrix product.
<b>October 2017</b>	Sign distribution agreement for Collagen Matrix Taiwan market with Jinglun Incorporation.
<b>October 2017</b>	Submit product registration for TFDA Medical Device: Dental Bone Graft, 6/1 submit to USFDA
<b>November 2017</b>	License out Collagen Ophthalmic Matrix to Oculus BioMed for Australian/New Zealand market
<b>November 2017</b>	11/8 receive TFDA approval for class II medical device Bone Graft product.
<b>November 2017</b>	Receive National Innovation Award for Collagen Ophthalmic Matrix product.

# Three Elements for TERM

ACRO's products provide scaffolds for tissue engineering and regenerative medicine



# Tissue Engineering



# Important Features of Scaffolds

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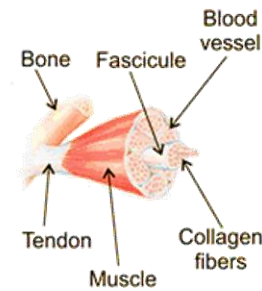
1. Biocompatibility
2. Biodegradability
3. Mechanical properties
4. Scaffold architecture
5. Manufacturing technology
6. Choices of biomaterial



# Collagen Scaffolds

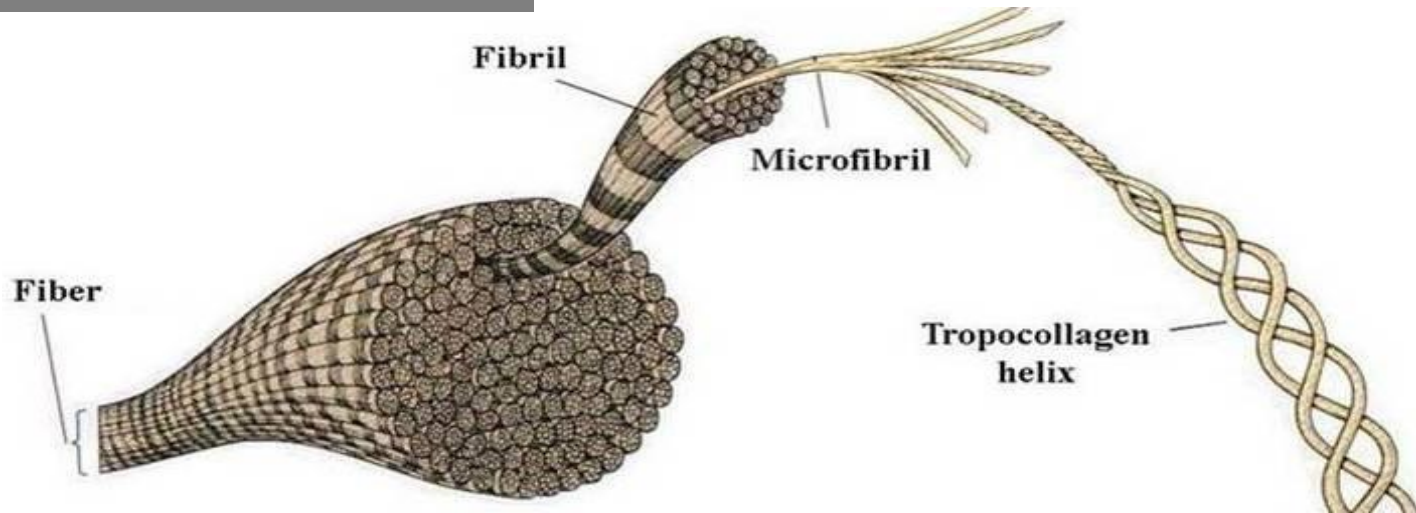
## Collagen

- Collagen makes up **25~35 %** of the total amount of proteins in human body.
- Collagen can be found almost everywhere in the body, such as skin, bone, cartilage, ligament, muscles and connective tissue.
- Scientists refer collagen as the glue that holds the body together.



# Collagen: Triple-helix Structure

## Collagen Structure



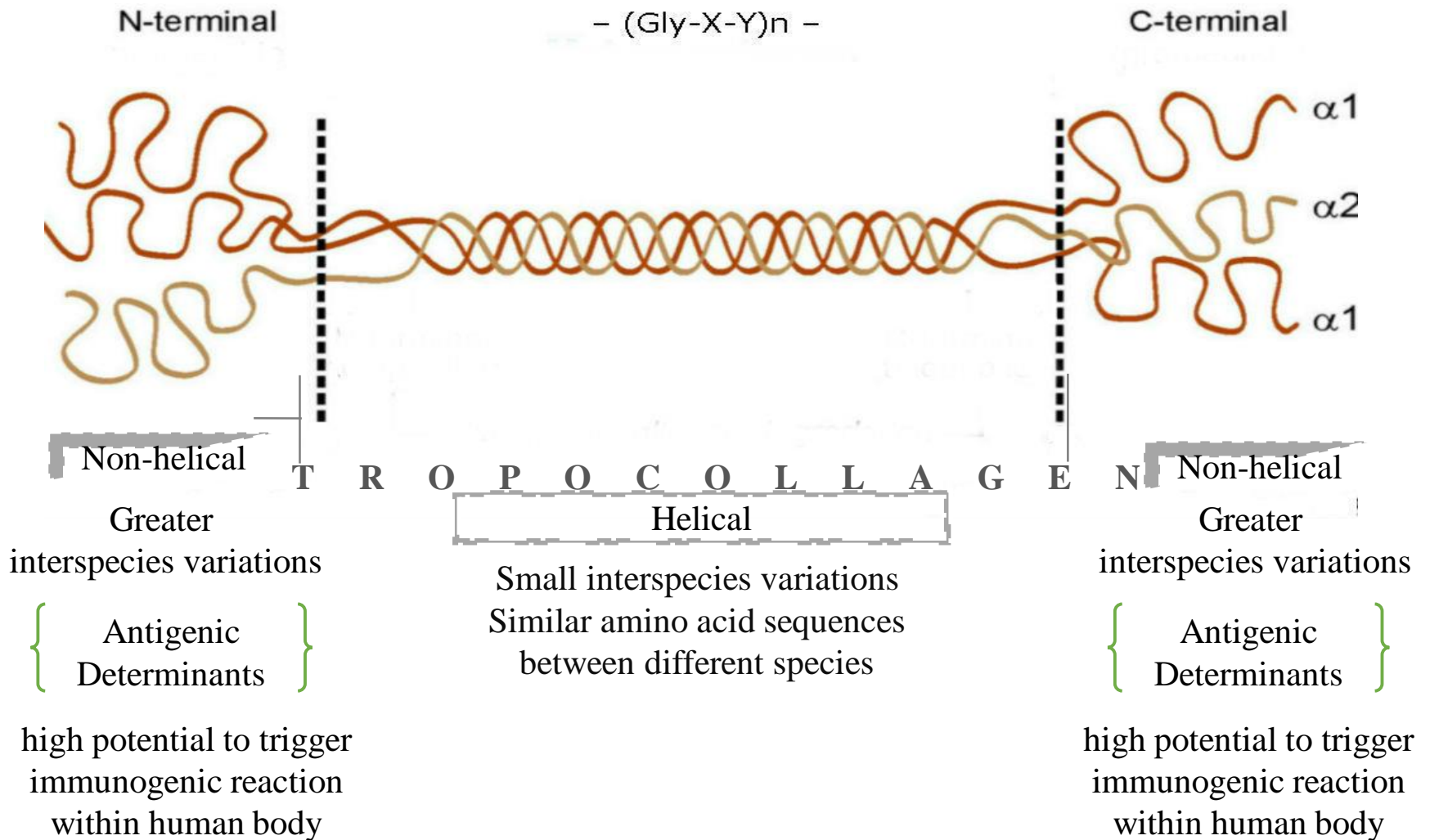
Hydroxyproline and lysine of polypeptide bond with enzymes to aid cross-linking, forming **Fiber from Fibril**.

Multiple Microfibril are lined parallelly to form **Fibril**.

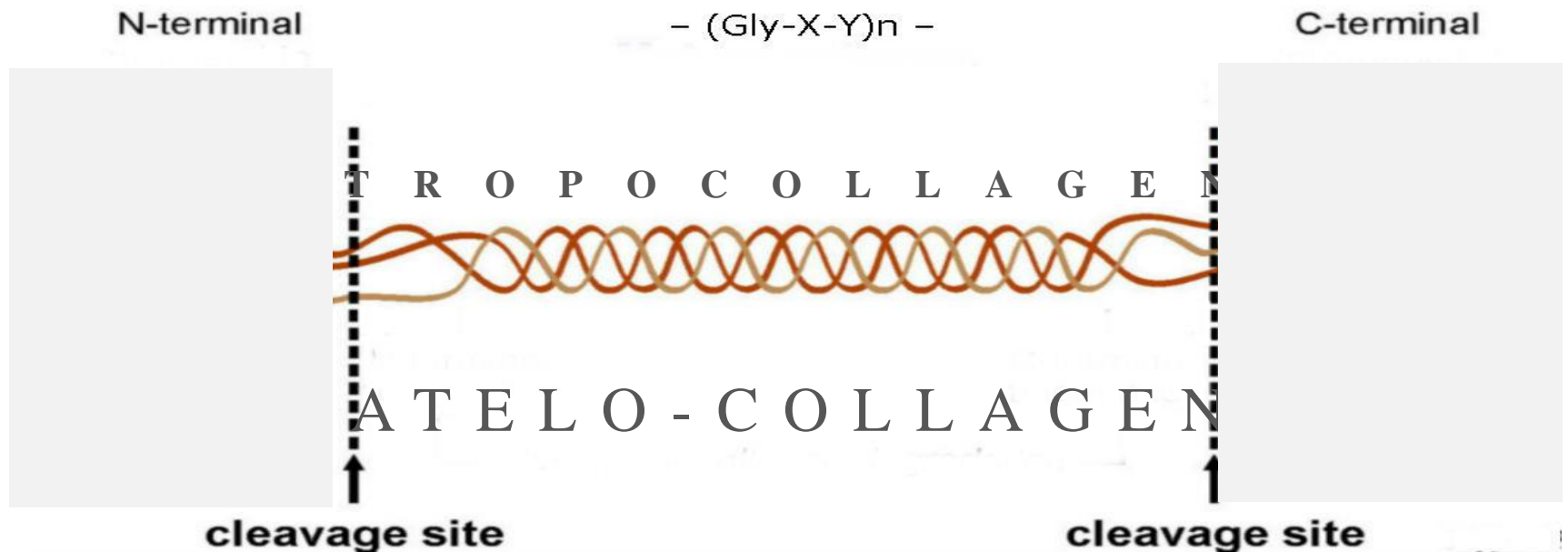
Multiple Tropocollagen molecules accumulated to form **Microfibril**.

Collagen is the most abundant protein in human body which forms different structures with specific mechanical strength or flexible web-like structure.

# Collagen Structure



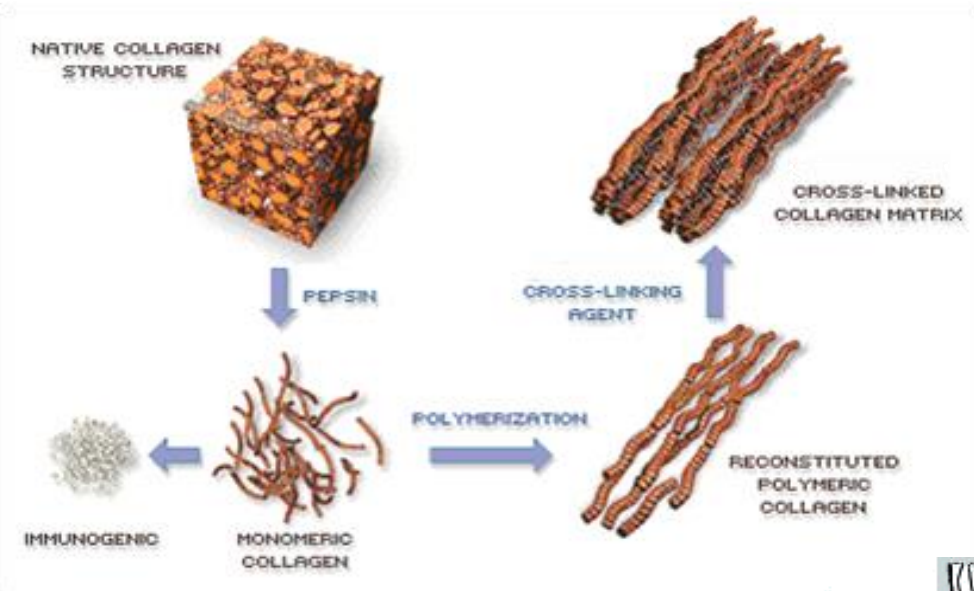
# Atelocollagen



comparable to human collagen  
with smaller concern over immunogenic  
reaction.

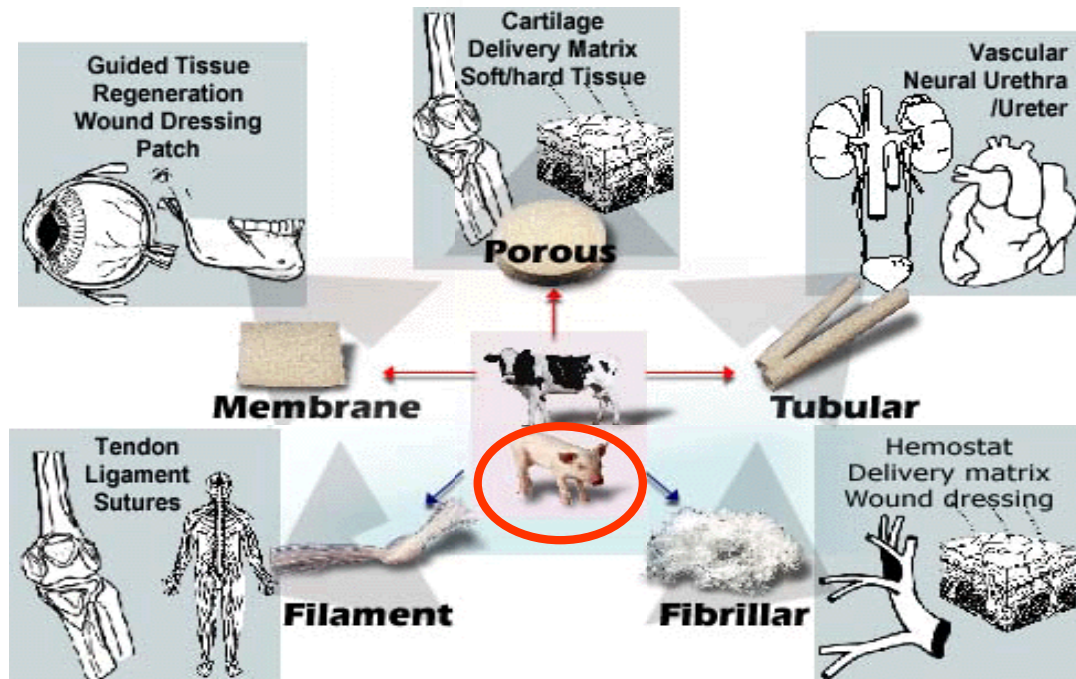


# Traditional Process



The loose collagen is reconstructed using chemical cross-linking agents

Products made by traditional process



# Disadvantages of Traditional Processed Collagen

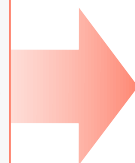
## Other processes to make decellularized collagen scaffolds

Strong Acids

Strong Alkali

SDS

Organic Solvents



1

Time, space and money consuming

2

Atelocollagen can be easily bio-degraded, so it's hard to reach the time length requirement of the product.

3

C-Terminal and N-Terminal are hard to be removed completely, and the residues would cause allergic reaction.

4

Most of the chemical cross linking agents are carcinogens, and often cause allergic reaction.

5

Reconstruction of collagen cannot duplicate the porosity and mechanical strength of natural collagen scaffold.

Collagen structure is loose due to the absence of C-Terminal and N-Terminal; thus in the traditional process, chemical cross linking agents are used to strengthen the structure

# Proprietary Technology

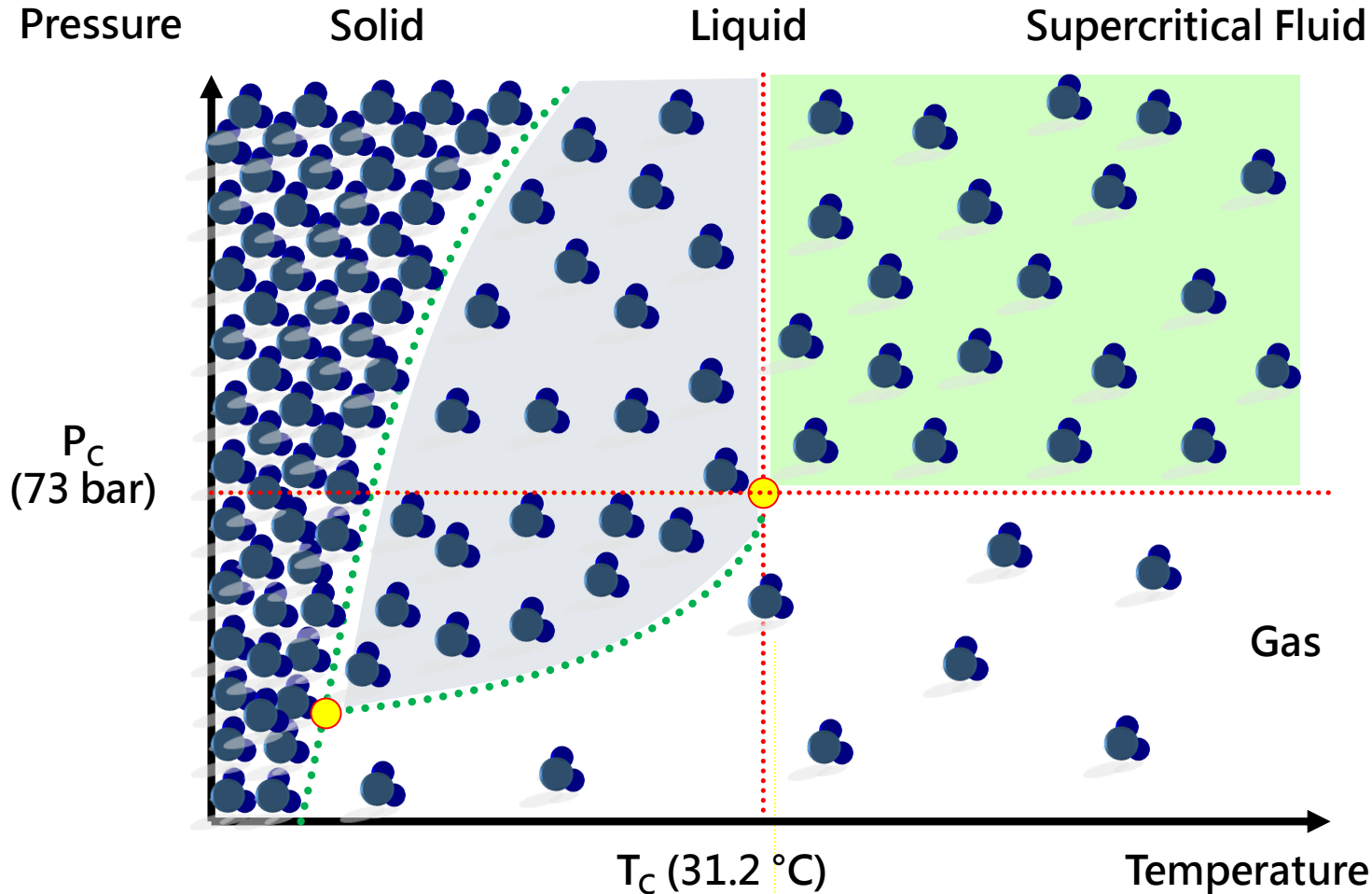
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The Proprietary Technology- **Supercritical CO<sub>2</sub>** is used to remove cells, fats and other substances in animal organs and tissues, while keeping the undiminished **collagen scaffolds** as the product for the high-end medical devices.

**Minimum Manipulation!!**



# Phase diagram of CO<sub>2</sub>



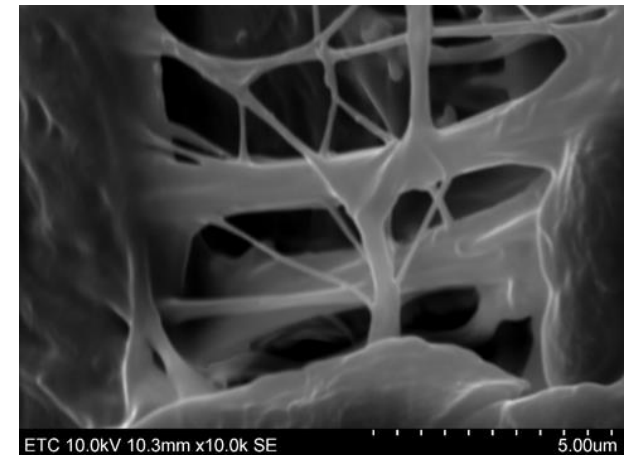
- Variability of Density,
- Lower viscosity than liquids,
- High Diffusivity,
- "Tunable" Solvation



# Critical Factors of scCO<sub>2</sub> Technology

Temperature/Pressure/Speed/  
Static-Dynamic Extraction/  
Cycle Times and Duration

Collagen structures  
after scCO<sub>2</sub> process



- Easy and low cost
- High efficiency and safe
- Sterilization and virus deactivation
- Green (no pollution) and can be applied to different organs and tissues

# Core Technology- Supercritical CO<sub>2</sub>




## Medical Devices

### Supercritical CO<sub>2</sub>

SPF Pig



5000-5L Supercritical CO<sub>2</sub> Extraction System

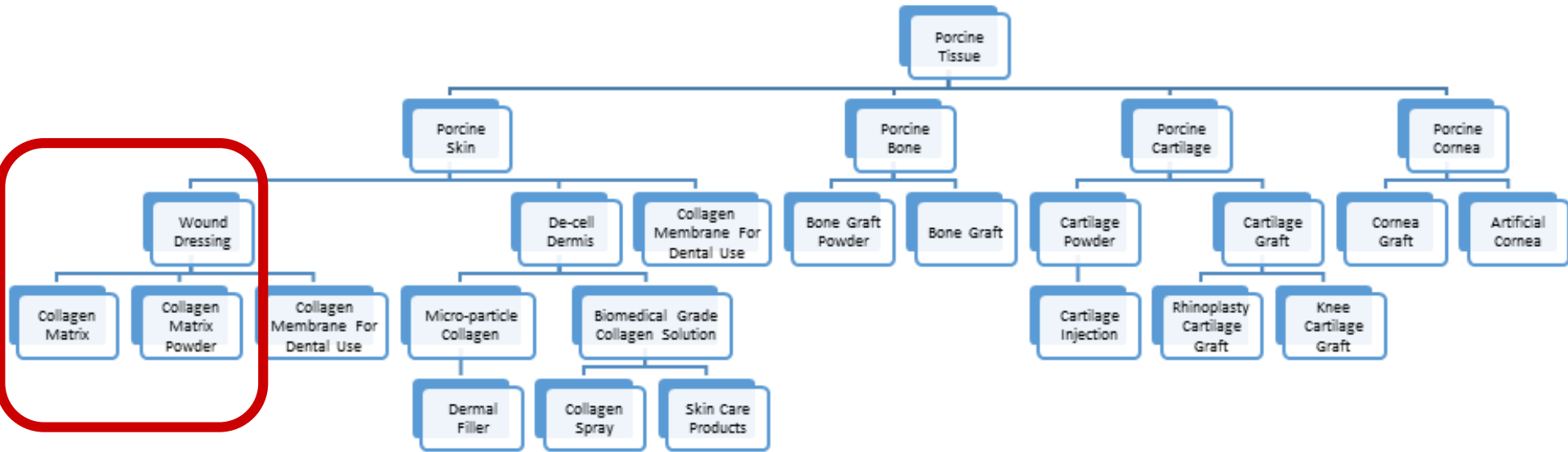
Item	Use	Picture
Bone Graft for Dental Use	Augmentation or reconstructive treatment of the alveolar ridge	
Collagen Membrane for Dental Use	Barrier between soft and hard tissue	
Bone Graft	Bone filler for bony voids or gaps	
Collagen Matrix	Wound Dressing for ulcers and wounds	
Collagen Ophthalmic Matrix/Artificial Cornea	Matrix for reconstructing corneal structure	
Dermal Filler	Injected filler to reduce or eliminate wrinkles	
Spinal Cord	Biomaterial for spinal trauma repair	

# Product Category

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- **Wound Care:** Collagen Matrix, Collagen Matrix Powder, Collagen Membrane, Scar Spray, Scar Care Dressing, External Aesthetic Restoration Prothesis
- **Orthopedics:** Bone Graft (granule, cube, bullet shape)
- **Dentistry:** Bone Graft and Collagen Membrane
- **Ophthalmology:** Collagen Ophthalmic Matrix, Collagen Biocornea
- **Aesthetic Medicine:** Collagen Dermal Filler
- **Medical Devices for Companion Animals**
- **Others:** Atelocollagen, Skin Care Products, Research Materials

# Collagen Matrix and Collagen Matrix Powder



# Product Description

## Product Name

ABCcolla<sup>®</sup> Collagen Matrix

TFDA: Class II; I. 4018

FDA Product Code : KGN ◦



## TFDA Spec

- |               |               |
|---------------|---------------|
| ■ 1 cm x 2 cm | ■ 1" x 2"     |
| ■ 2 cm x 2 cm | ■ 1.5" x 1.5" |
| ■ 2 cm x 3 cm | ■ 1" x 1.5"   |
| ■ 3 cm x 4 cm | ■ 1.5" x 2"   |
| ■ 5 cm x 5 cm | ■ 2" x 2"     |

## FDA Spec

- |               |                |               |
|---------------|----------------|---------------|
| ■ 1 cm x 2 cm | ■ 1 cm x 5 cm  | ■ 1" x 2"     |
| ■ 2 cm x 2 cm | ■ 2 cm x 5 cm  | ■ 1.5" x 1.5" |
| ■ 2 cm x 3 cm | ■ 3 cm x 5 cm  | ■ 1" x 1.5"   |
| ■ 3 cm x 4 cm | ■ 3 cm x 10 cm | ■ 1.5" x 2"   |
| ■ 5 cm x 5 cm | ■ 5 cm x 10 cm | ■ 2" x 2"     |

# About ABCcolla® Collagen Matrix

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## **Description**

**The Collagen Matrix is the decellularized porcine hide, and consists mainly type I collagen.**

## **Features of the Collagen Matrix**

- 1. Intact collagen scaffolds for wound healing and tissue regeneration**
- 2. Biocompatible and self-absorbable**
- 3. Absorb exudates and keep the wound bed moisture**
- 4. For use: rehydrate before applying to the wound**

# Physicochemical Properties

	Item	Criteria	Result
1	Collagen Source	Porcine dermis	
2	Trace impurities	<50 ppm (ASTM F1185)	PASS
3	Residual DNA	< 50 ng/mg sample	PASS
4	Sterilization	Gamma Irradiation, SAL <10 <sup>-6</sup>	PASS
5	Collagen content	>500 ug/mg	PASS
6	Absorbency	>12 g/100 cm <sup>2</sup>	PASS
7	Endotoxin	<20 ED/device	PASS

# Biocompatibility Test

Regulation	Item	Result
ISO 10993-5	Cytotoxicity	PASS
ISO 10993-10	Sensitization	PASS
ISO 10993-10	Irritation or Intracutaneous Reactivity	PASS
ISO 10993-11	Acute Systemic Toxicity	PASS
<USP> 151	Material-Mediated Pyrogenicity	PASS
ISO 10993-11	Subchronic Toxicity	PASS
ISO 10993-3	Genotoxicity (Ames, MLA)	PASS
ISO 10993-6	Implantation	PASS
ISO 10993-4	Hemocompatibility	PASS
USP38-NF33 <85>	Endotoxin Test	PASS
ICH Q5A	Virus Inactivation Study	PASS

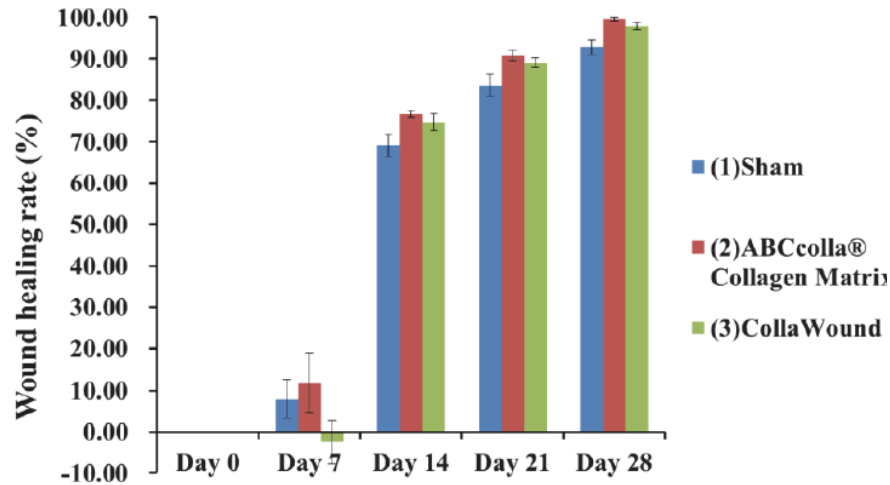


# Viral Reduction Test

Viral Reduction Test	Viral Reduction Factor ( $\log_{10}$ )			
	BPIV	PRV	Reovirus 3	PPV
Value	$\geq 9.336$	$\geq 9.980$	$\geq 8.399$	$\geq 13.172$

- The result of the viral reduction test of all four viruses passes the standard: ( $\log_{10}$ )  $\geq 6$  logs, which is regulated by ICH Q5A.

# Animal Performance Test



The result indicated that the wound healing rate is similar but slightly faster than the predicate device.



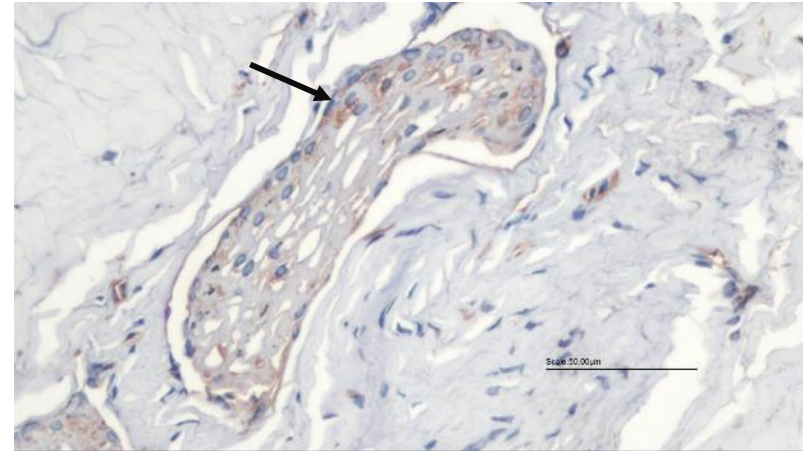
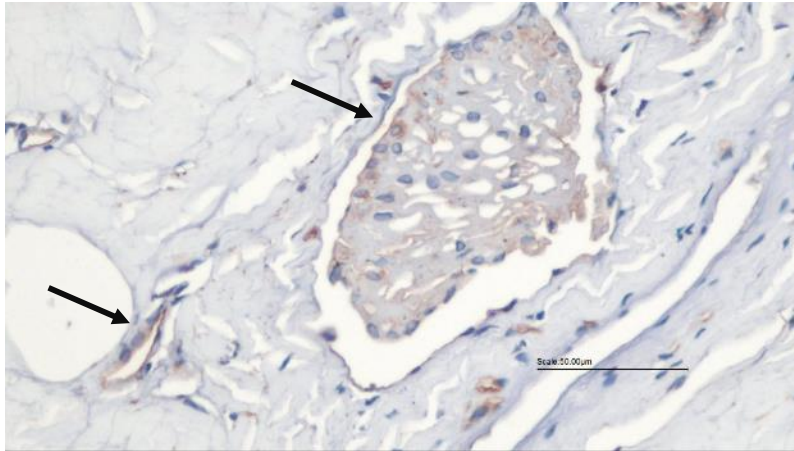
Wound healing process on pig.

The result showed better wound healing and had less scar formation.

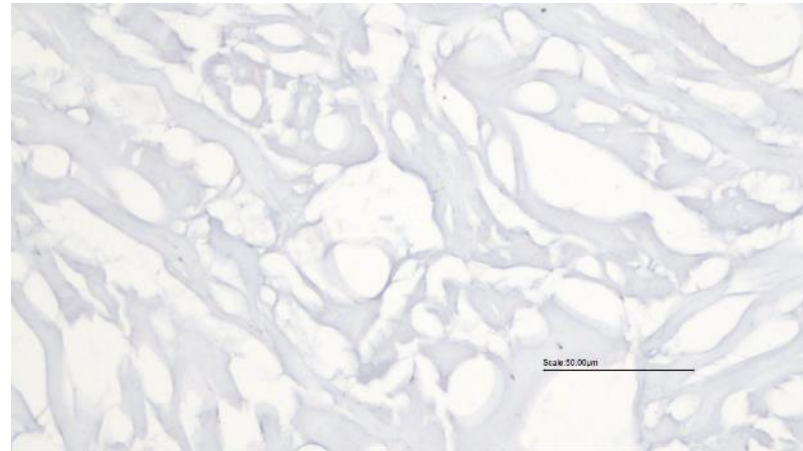
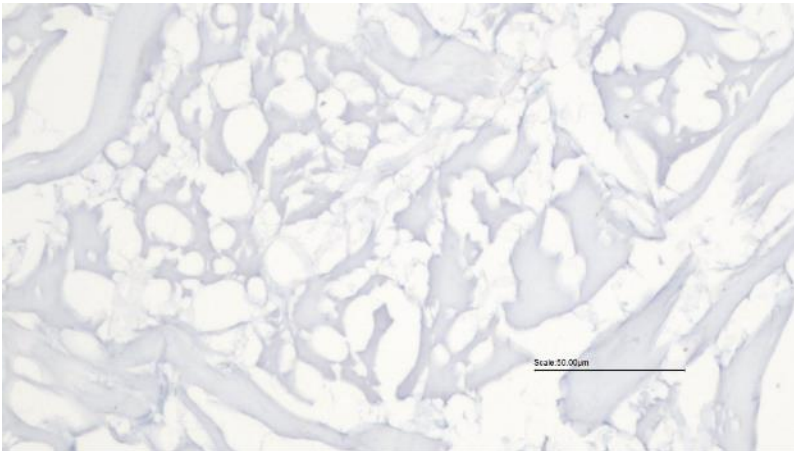
# No Immunogenic Protein

## Alpha-gal stain

Porcine tissue

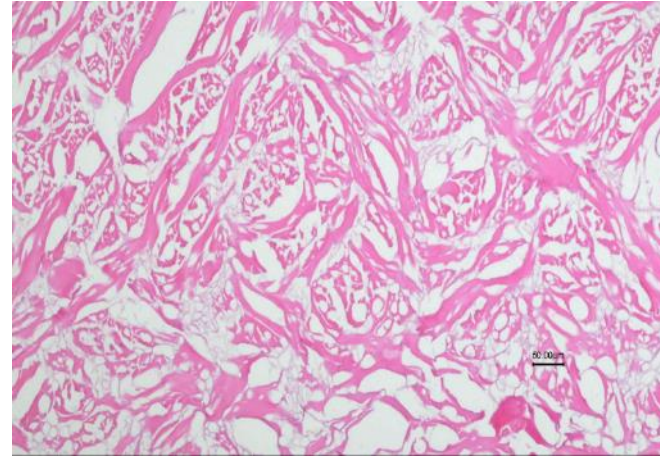
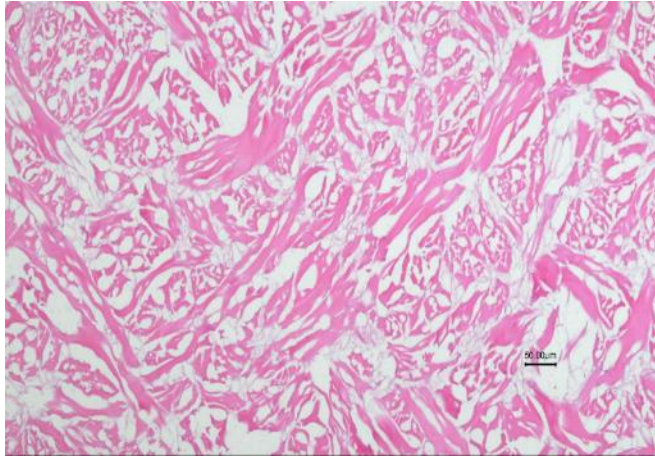


Collagen Matrix

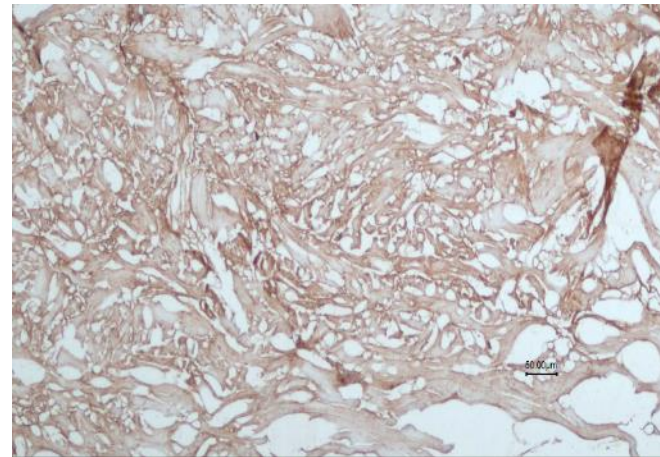
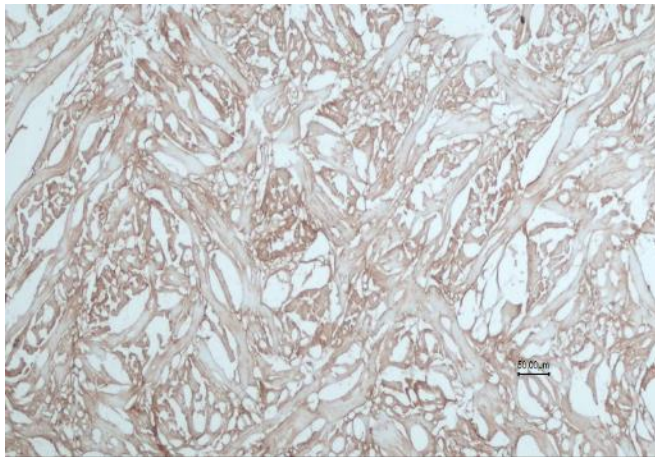


# H&E

**H&E stain**

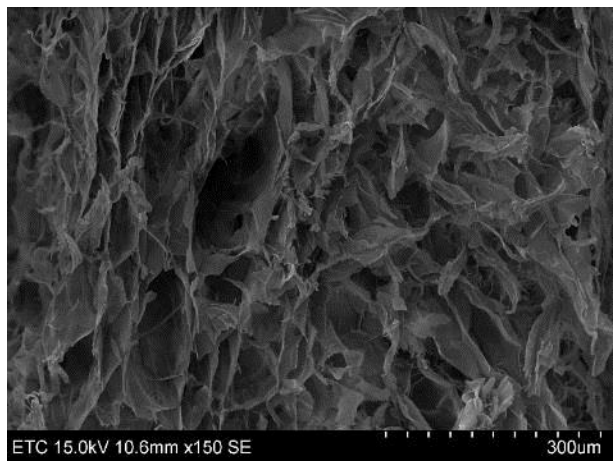
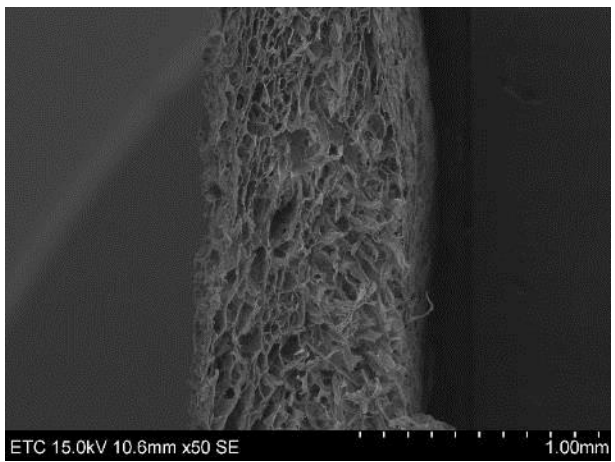


**Type I collagen stain**

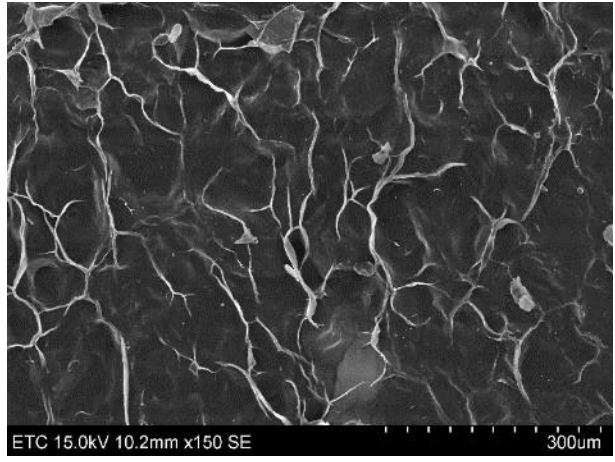
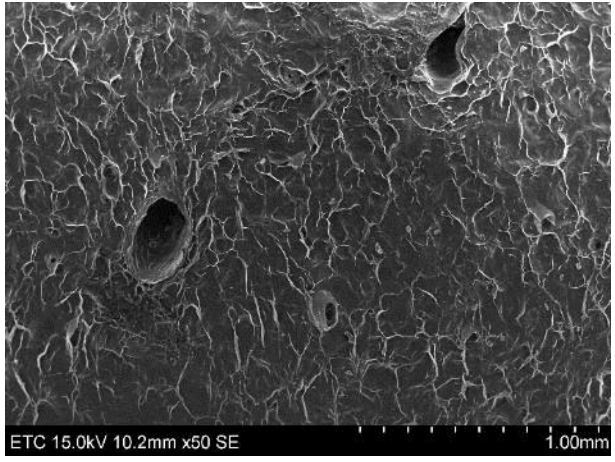


# Collagen Matrix- SEM

Vertical section

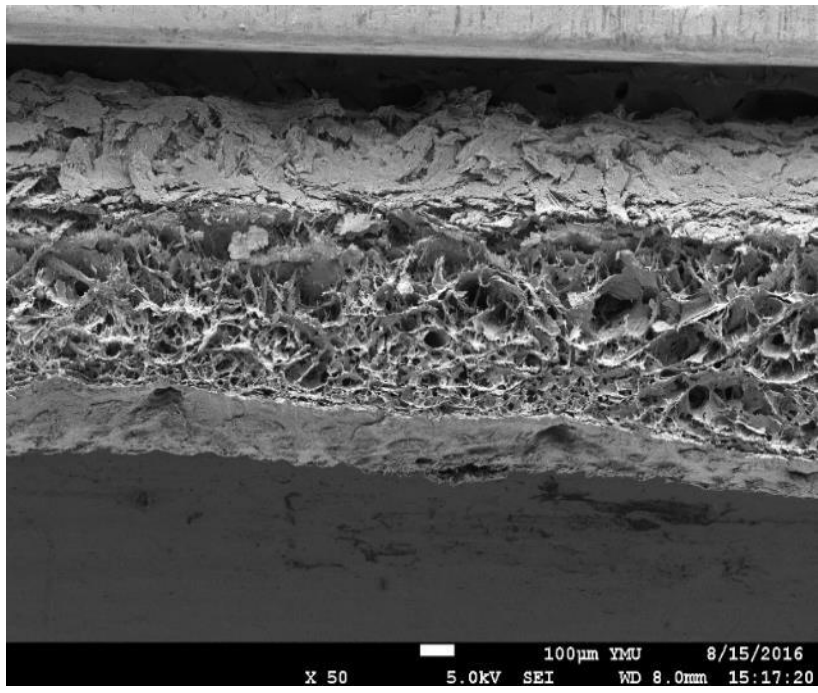


Surface

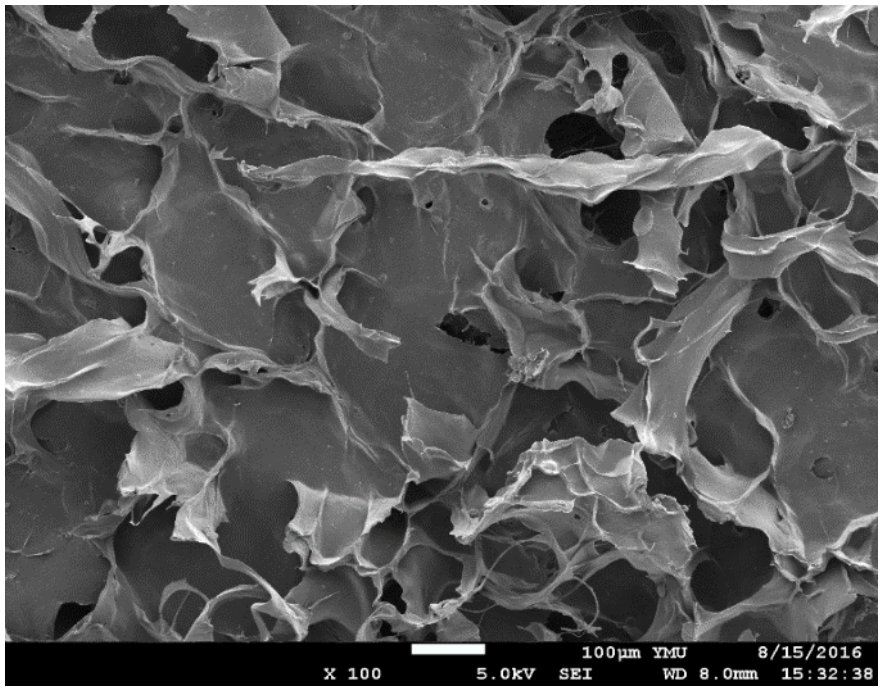


# Collagen Matrix- SEM

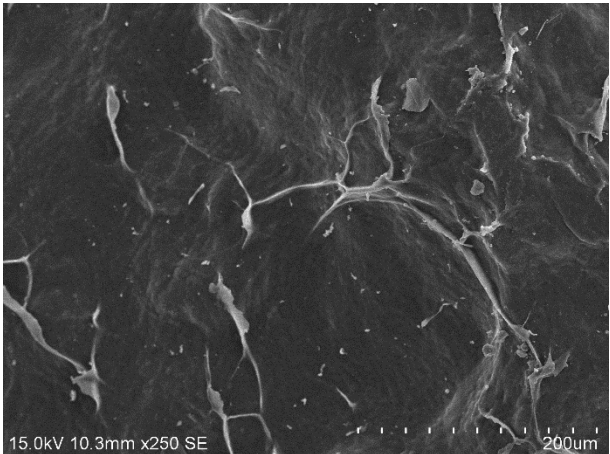
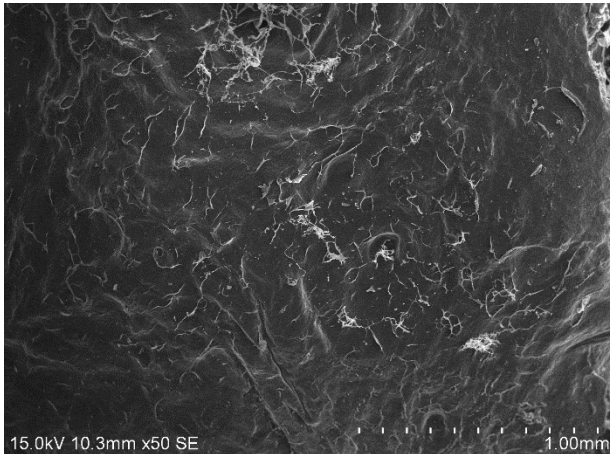
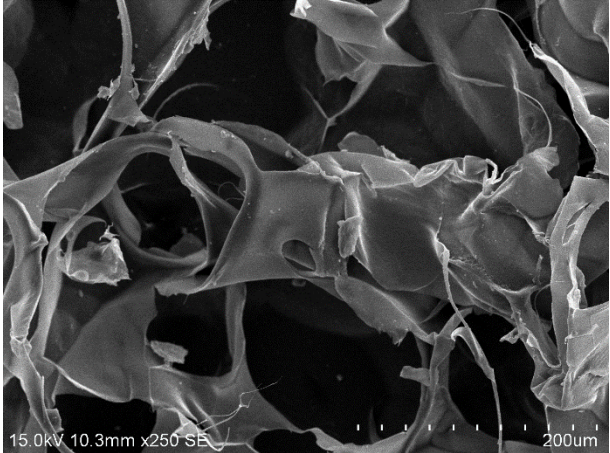
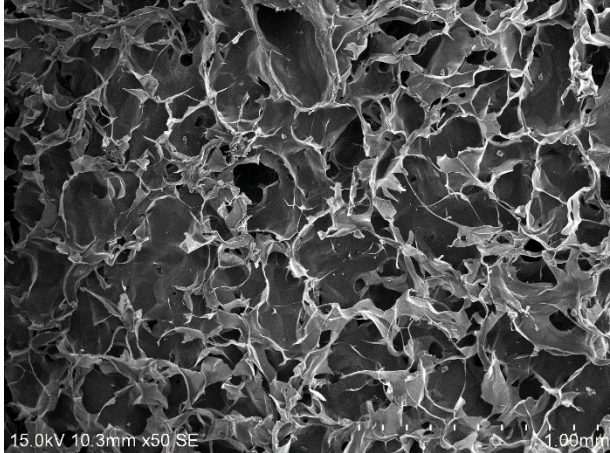
Vertical section



Surface



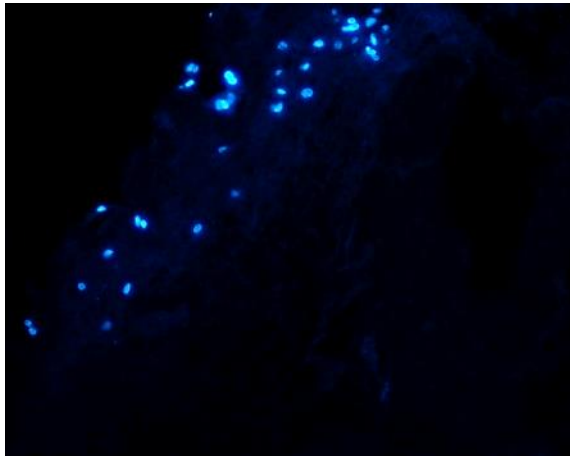
# Collagen Matrix- SEM



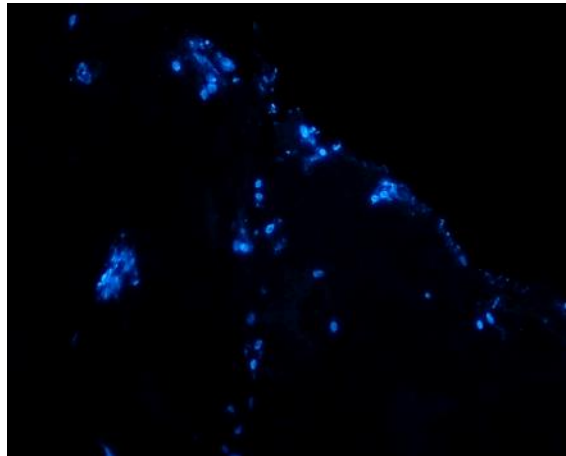
# Cells cultured on the Matrix

## DAPI- HSF cell

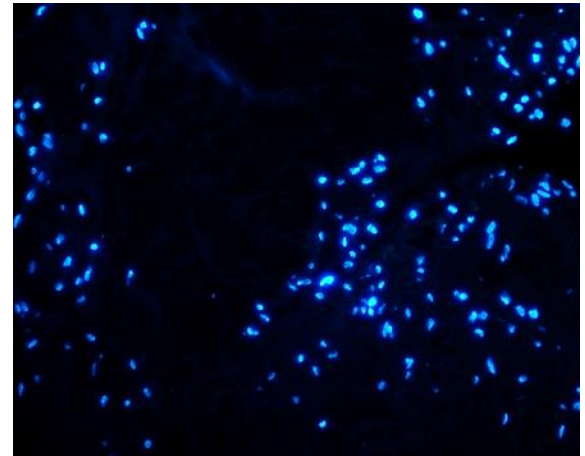
7 days



14 days



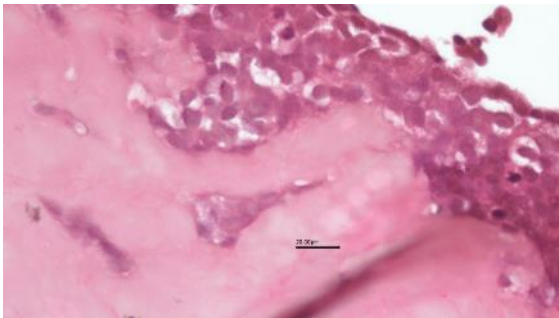
21 days



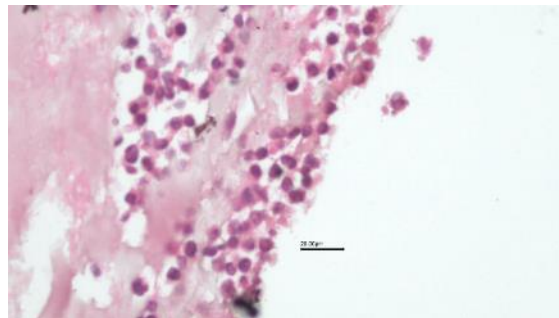


# Cell Proliferation- 3T3 cells

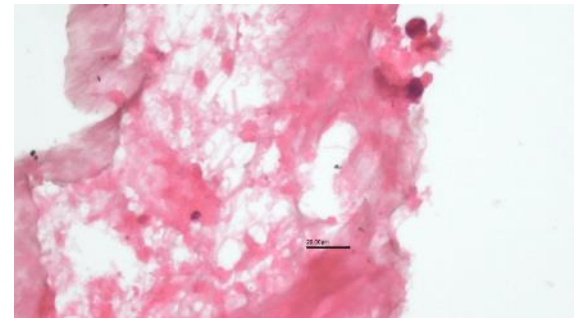
7 days




14 days




21 days



# TFDA Certificate (May 16, 2017)


  
**衛生福利部醫療器材許可證**  
 衛部醫器製字第 005730 號


  
 Ministry of Health and Welfare

中文名稱：亞比斯·可拉膠原蛋白敷料  
 英文名稱：ABCcolla Collagen Matrix  
 類別：第I類：一般及特別材料等敷料 廠商名稱：亞米生醫股份有限公司  
 規格：詳如中文仿單核定本 製造廠名稱：亞米生醫股份有限公司  
 製造廠地址：南部科學工業區高雄市中  
 行區路科二路 37 號 3 樓

效能：詳如中文仿單核定本  
 處方：空白

前項醫療器材經本部審核與藥事法之規定相符並准予申請許可證  
 衛生福利部部長

  
 陳時中

  
 衛生福利部

發證日期 106 年 05 月 16 日  
 有效日期 111 年 05 月 16 日

檢 查 日 期				
年	月	日	年	月
日	日	日	年	月
日	日	日	年	月

MF006926

# FDA510K, K162348



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
10903 New Hampshire Avenue  
Document Control Center - WO66-G609  
Silver Spring, MD 20993-0002

May 10, 2017

Acro Biomedical Co., Ltd

Dar-Jen Hsieh

CEO

3f., No.57, Luke 2nd Rd, Lujhu Dist.

Kaohsiung City, 82151 TW

Re: K162348

Trade/Device Name: ABCcolla Collagen Matrix

Regulatory Class: Unclassified

Product Code: KGN

Dated: April 10, 2017

Received: April 10, 2017

# Indication (USFDA)

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The Matrix is intended for the management of wounds including:

- Partial and full thickness wounds
- Venous ulcers
- Pressure ulcers
- Diabetic ulcers
- Tunnels/undermined wounds
- Surgical wounds
- Trauma wounds
- First and second-degree burns
- Draining wounds

# ABCcolla<sup>®</sup> Collagen Matrix Case Reports

Patient was injured by Forklift truck: Severe traumatic wound and bone fracture  
Wound Size 12cm x 8 cm

Day 0: Severe wound site



After debridement, observe the wound site



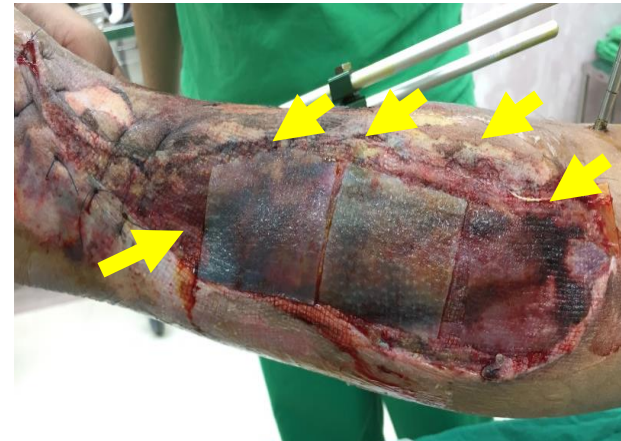
Day 3: No infection



Day 3: Attached ABCcolla<sup>®</sup> Collagen Matrix to accelerate wound healing process.



Day 8:  
5 days after applying ABCcolla<sup>®</sup> Collagen Matrix to the wound, the majority of the matrix was degrade, and as the arrows show, the tissues had grown and started to heal.



# Wound from removing the skin for the self skin grafting

## Wound size: 15cmX20cm

Day 0:

The Collagen Matrix was applied to the wound made by removing patient's skin for the skin grafting.



Day 7:

7 days after applying the matrix to the wound, the matrix was completely self-absorbed, and the wound site was almost fully recovered with no scar formation.

# ABCcolla<sup>®</sup> Collagen Matrix Case Reports

**Day 1 (Sep. 19):** Apply ABCcolla<sup>®</sup> Collagen Matrix to the wound on the arm, and artificial skin (X brand) to upper arm and back of the hand for the comparison.



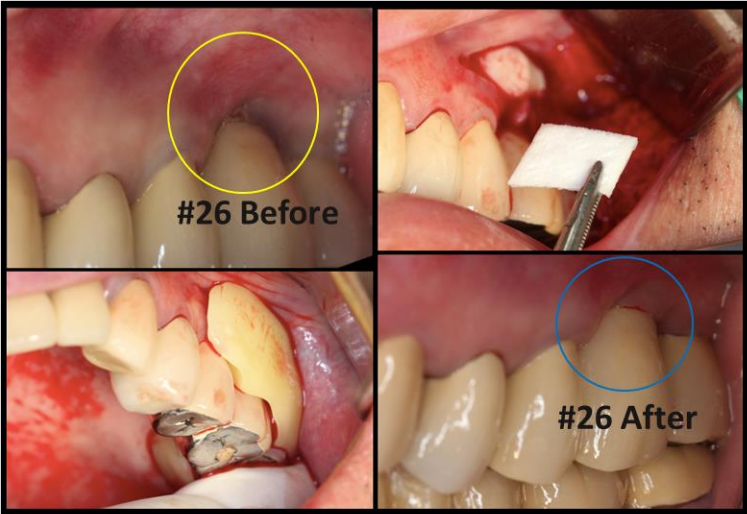
**Day 7:** Wound covered with ABCcolla Collagen Matrix had recovered well with no more exudates, while the site using artificial skin (X brand) are still wet, and the wound site was injured when changing the covered material.



# ABCcolla Collagen Matrix used for Soft Tissue Augmentation



After 14 Days



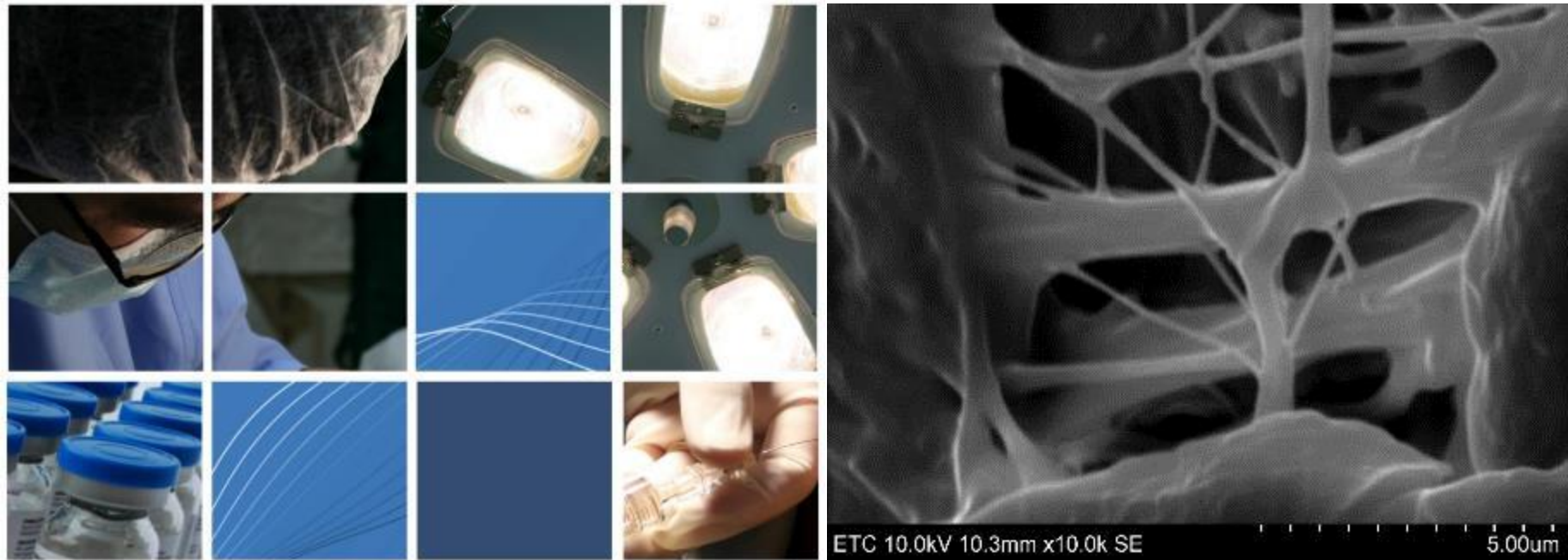


# Other Possible Application

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Other than trauma wounds, ulcers, and soft tissue augmentation, this Collagen Matrix can also be applied to

- Tendon Repair
- Phalloplasty
- Breast Reconstruction
- Partial mastectomy
- Meninges (for brain surgery)



# THANK YOU