CELIVION



The Art of Cellular Revival

Lifting skin’s potential. Redefining premium regeneration.







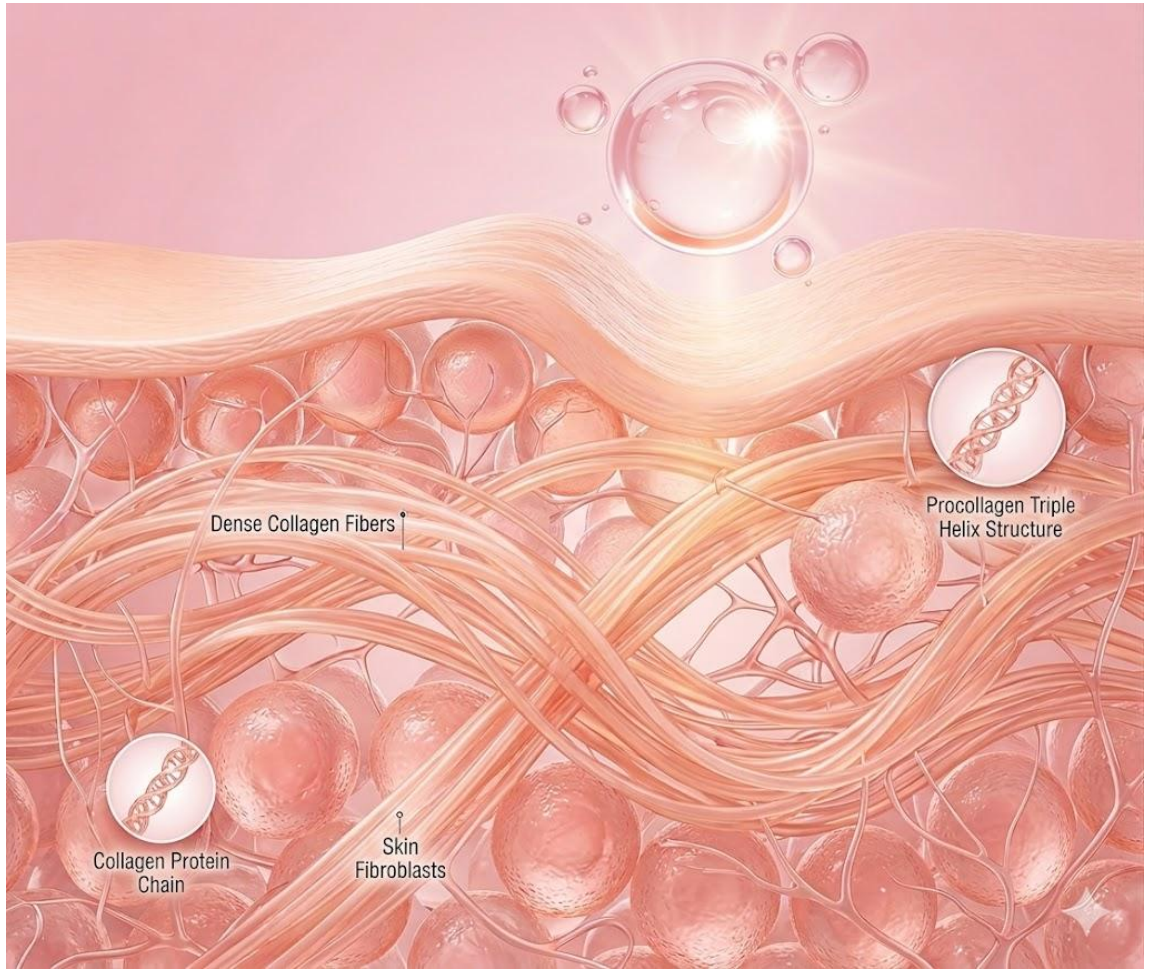
CELIVION

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Allogeneic Collagen Injection Market

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Collagen

Definition: Collagen is the most abundant protein in the human body and a biodegradable, natural biomaterial.

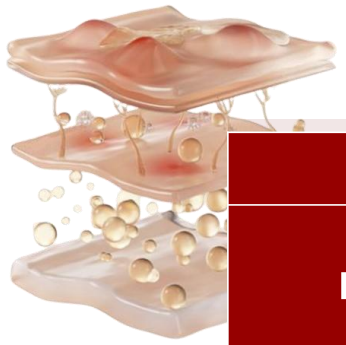
Composition: It constitutes 70% to 79% of the skin's dermal layer, making it essential for tissue regeneration.

Function: It acts as a 3D scaffold for cell growth and facilitates the transfer of growth factors and cytokines.

Clinical Advantage: Bio-derived collagen offers superior regeneration and resilience compared to synthetic fillers, making it ideal for regenerative treatments.

Allogeneic Collagen Injection Market

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Category	Allogeneic Collagen	Fillers (HA Series)	Exosomes
Biocompatibility	**Exceptional.** Matches human skin structure; minimal risk of biological rejection.	**Moderate.** Uses bio-components, but cross-linking agents may trigger sensitivity.	**Caution Required.** Cell-derived nature may cause immune or inflammatory reactions.
Safety Profile	Significantly low probability of immune responses or adverse side effects.	Potential for inflammation, swelling, or rare vascular complications.	Risk of localized allergic reactions or post-procedure inflammation.
Regenerative Mechanism	**Direct Regeneration.** Provides a structural scaffold and directly activates **fibroblasts**.	**Physical Filling.** Simply occupies space to provide immediate mechanical volume.	**Signal Induction.** Facilitates cell-to-cell signaling but lacks direct material supply.
Tissue Integration	**Fuses naturally** with skin tissue, ensuring high retention and stability.	Does not fuse; sits within the tissue and gradually degrades over time.	Absorbed or dissipated quickly after stimulating cellular activity.
Tactile Experience	**Naturally absorbed** for a soft, seamless touch indistinguishable from real skin.	Excellent for volume, feel like a foreign body or turn firm if overfilled.	Primarily improves skin texture; no significant change in physical feel.
Aesthetic Result	Delivers natural contours and high patient satisfaction without an "artificial" look.	Effective for dramatic shaping, but risks creating unnatural or uneven contours.	Focuses on overall skin health rather than structural or shape changes.

Allogeneic Collagen Injection Market

Superiority

Natural origin
Derived from human collagen, it has high skin affinity, is abs orbed into the body, and stimulates self-collagen productio n.

Regenerating effect
Expect long-term effects by inducing skin-based improvem ent rather than simple volume replenishment.

Compound beauty effect
It not only improves wrinkles, but also helps improve overall skin conditions such as skin texture, pigment, and elasticity.

Safety

No risk of allergies
It is an auto- or human-derived ingredient and has no risk of immune response.

No foreign body sensation
There is no feeling of foreign matter left in the body as it is n aturally absorbed after time after injection.

Minimize serious side effects
Fillers can cause serious side effects when injected with blo od vessels, but allogeneic collagen is naturally absorbed and has a low risk.



"Same homogeneous ECM family, but **different machining philosophy and preservation methods.**

For Celivion, it's not just about how much you put in

it focuses on how much "living structure" you put in

It's an allogeneic collagen family, but it's not just a volumetric agent

Low temperature process (Allo-PELT) ensures maximum ECM structure

Ultra-fine/uniform particle design reduces resulting deviation and sensitivity

Product designed to balance maintenance period + regeneration response

Allo-PELT Technology (Low temperature process ensures maximum ECM structure)

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Common allogeneic collagen involves heat or chemical processing during processing, which will inevitably cause some damage to the ECM structure.

Celivion uses Allo-PELT to **preserve ECM as circular as possible without thermal denaturation**."

- **Low temperature process**→ Minimize thermal denaturation
- **ECM Retention**→ Simple Volume X, Regeneration Environment O
- **The concept of adding a regenerative structure**, not injecting collagen

****Ultrafine/uniform particle design (clinical stability)**

Even with the same ECM, non-uniform particle size and structure can lead to greater post-procedure deviation or sensitivity, Celivion **is highly consistent and stable in its results** because **it selects and quantifies ultrafine particles at a uniform rate."**

- **Reduce the deviation** of the procedure
- **Manage risk for** sensitive aesthetic procedures
- **Predictable response** to repeat procedures

****Celivion** optimizes both **durability and regeneration** through a specialized particle structure, overcoming the typical trade-off between the two.

Manufacturing Process (hADM cell-free allogeneic dermal human cellular dermal matrix) CELIVION

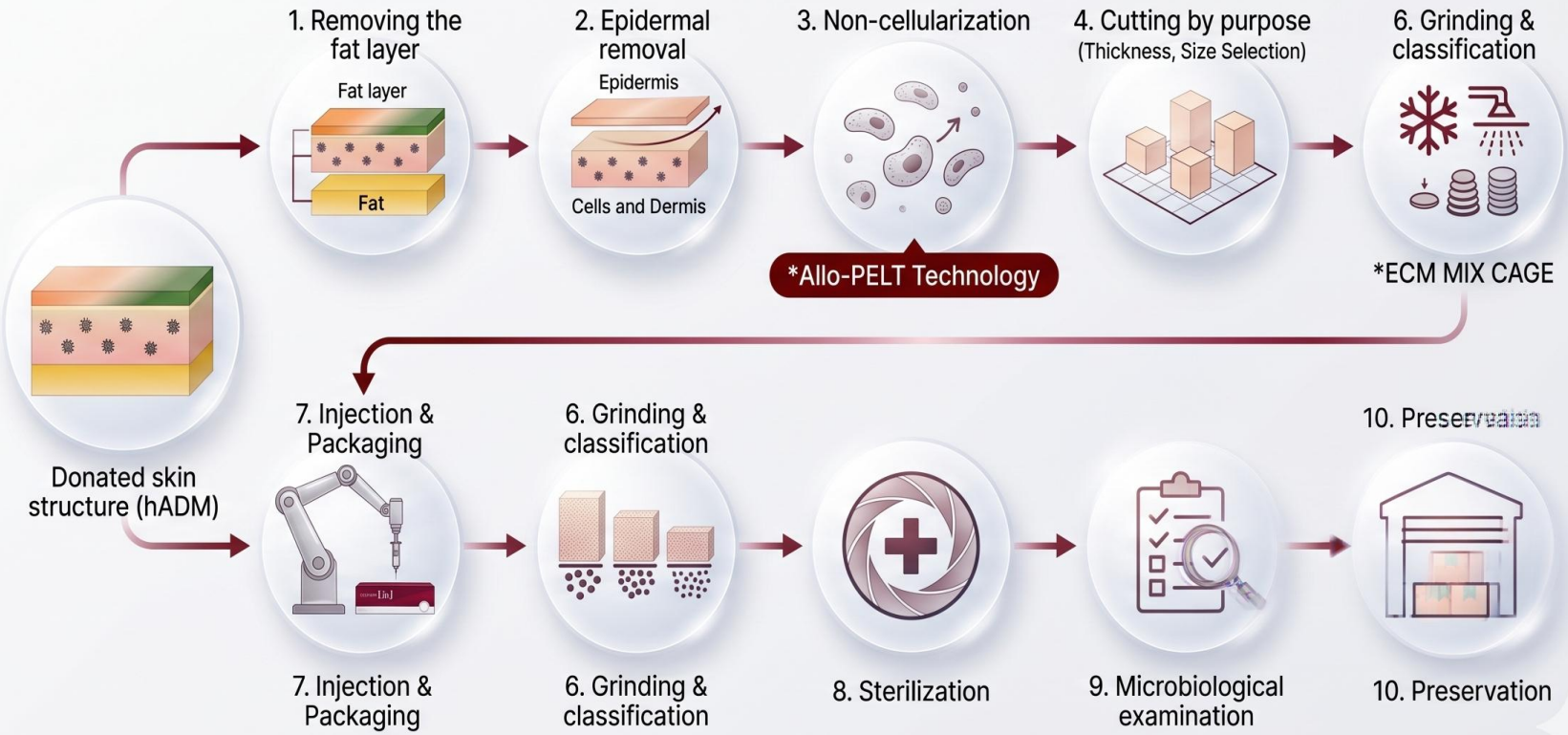
The Solution



Key Features

- High-Density Soft Tissue Support
- Allo-Pelt Technology
- 150 mg X 1 Syringe

10-Step hADM Processing (hADM)



*Specialized Allo-PELT Technology - Patent undisclosed

ADM processed with Allo-Pelt technology delivers high-density structural support for soft tissue.

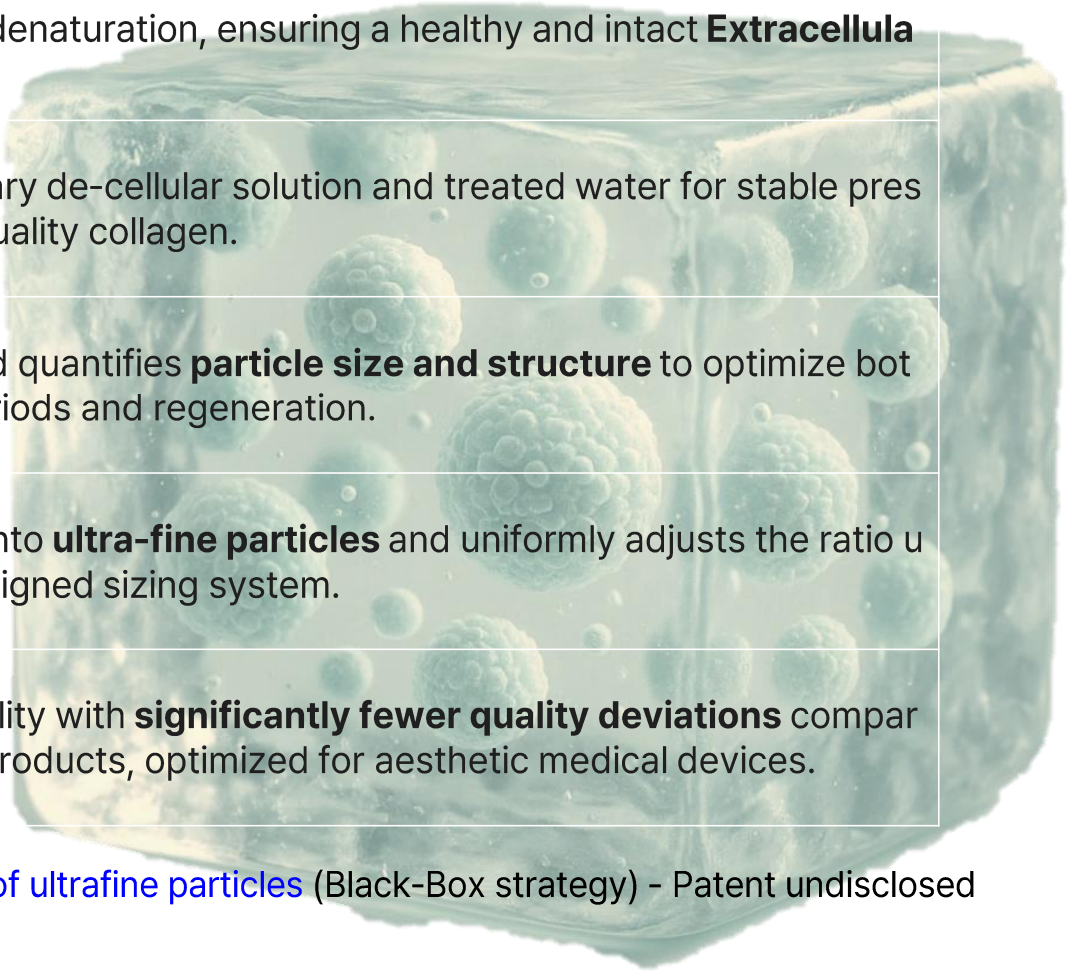
CELIVION LIN J - hADM SOLUTION

Allo - PELT Technology

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Preserved ECM at Low Temp. Processed

Category	Key Details	Benefits & Competitive Edge
Core Technology	**Low-Temperature Processing**	Prevents thermal denaturation, ensuring a healthy and intact **Extracellular Matrix (ECM)**.
Material Quality	**Pure Allogeneic Collagen**	Utilizes a proprietary de-cellular solution and treated water for stable preservation of high-quality collagen.
Precision Engineering	**Advanced Particle Design**	Precisely sorts and quantifies **particle size and structure** to optimize both maintenance periods and regeneration.
Proprietary System	**ECM Mix Cage**	Pulverizes tissue into **ultra-fine particles** and uniformly adjusts the ratio using a custom-designed sizing system.
Quality Standard	**Superior Consistency**	Ensures high stability with **significantly fewer quality deviations** compared to third-party products, optimized for aesthetic medical devices.



Allo - PELT Technology = Method of preserving ECM with uniform size and ratio of ultrafine particles (Black-Box strategy) - Patent undisclosed

Allo - PELT Technology

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Content Analysis of Skin Composition

Ingredients	Typical ADM criteria	Competitors	**Celivion**
Collagen	More than 70%	approx. 70~80%	**approx. 82.8 %**
Elastin	approx. 3 ~ 6 %	approx. 0.94~3%	**approx. 4.7%**
Elastin retention rate (Native Skin contrast)	-	approx. 70~80%	**approx. 85.6%**
GAGs (Glycosaminoglycans)	approx. 0.1 ~ 0.4 %	approx. 0.2~0.4%	**approx. 0.23%**

KMEDIhub 대구경북첨단의료산업진흥재단 Testing Institution: Kmedihub Preclinical Research Center

Allo - PELT Technology

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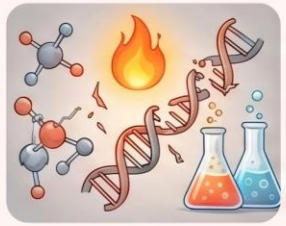
Quality Over Quantity: The Science of Healthy Collagen

The Risk of Standard Processing



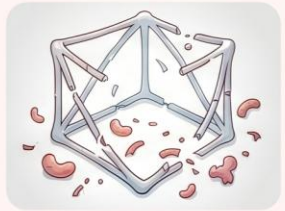
Quantity ≠ Quality

High collagen levels are ineffective if structural **deformation** has occurred.



Heat & Surfactant Damage

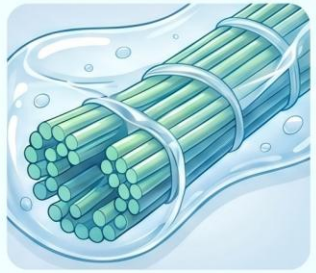
High temperatures and strong chemicals cause permanent structural deformation.



The Danger of Over-Processing

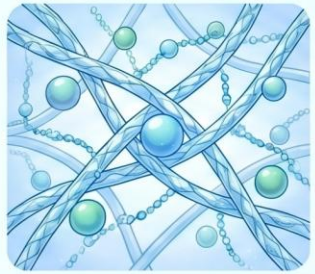
Excessive cell removal destroys signals (GAG/proteins) needed for regeneration.

The Celivion Solution



Low-Temperature Extraction

Minimizes structural deformation by avoiding heat-sensitive damage.



Preserved Regenerative Structures

Keeps the essential scaffolding intact for better cellular signal transmission.

Collagen = temperature sensitive material
(Structural deformation occurs when high temperatures or strong surfactants are used ↑)
In other words, levels can be high, but 'healthy collagen' can be damaged.

* In case of excessive cell removal, various substances required for regeneration are also responsible for transmitting signals and substances from the outside of the lost cell to the inside (GAG / protein / sugar components, etc.)

**Celivion minimizes collagen deformation through a low-temperature process,
in the direction of preserving the structures needed for regeneration around the cells together
It's a product that designed processing philosophy**

Surfactant residue not detected (0.004%)

Koptri
Korea Polymer Testing & Research Institute

www.polymer.co.kr
Test report No.: 25-01203
Page 2 / 2

TEST REPORT

표 1. 시료명 및 시료사진

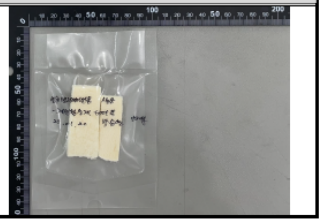
No.	의뢰자가 제공한 시료명	시험에 사용한 시료명	시료사진
1	ADM(Varidation)	Koptri 25-07-00909-1	

표 2. 시험방법 및 분석결과

시료명	시험항목	단위	시험방법	검출한계	시험결과
Koptri-25-07-00909-1	Triton X-100	%	HPLC-ELSD	0.004	불검출
		mg/kg		40	불검출

Note) a) 1 % = 10 000 mg/kg = 10 000 ppm
b) Koptri-BB-VI20-SW0,1-EA-DW10
c) HPLC-ELSD; High Performance Liquid Chromatography – Evaporative Light Scattering Detection
d) 불검출; 검출한계 미만
e) Triton X-100 (Cas 9036-19-5)

Relationship between Decellularization and Temperature

In general, high-temperature processes are advantageous for removing cells and lipids. However, high-temperature processes are likely to affect **collagen and ECM structure** at the same time and may be accompanied by structural degeneration risks.

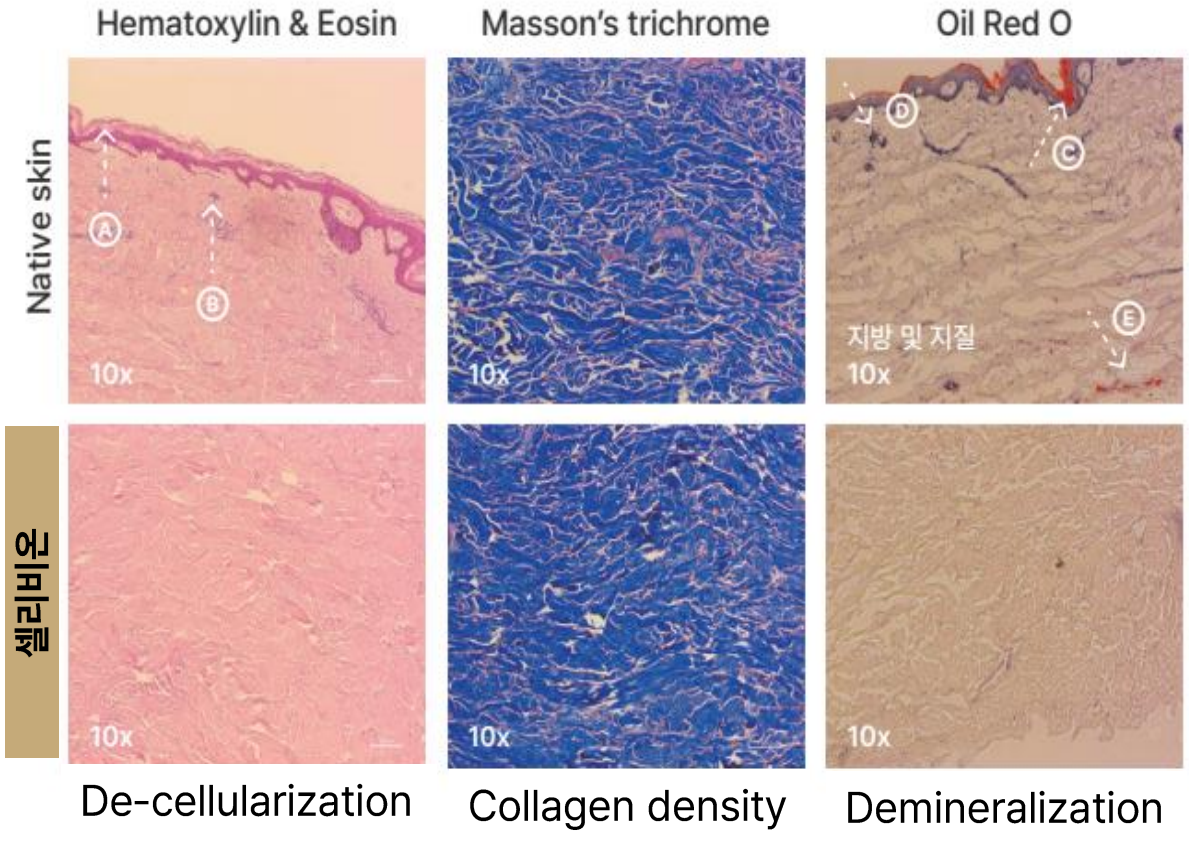
The Allo-PELT method overcomes the limitations of low temperature by gradually adjusting the low temperature conditions and **preserves healthy collagen and ECM structures** while efficient decellularization.

Residual amount and safety

Surfactant residue after the process is very low, **at 0.004%,** and is managed below the detection limit (substantially undetected level)
This is the result of a process design to **ensure a healthy ECM without leaving unnecessary ingredients**.

Allo - PELT Technology

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De-cellularization test

Safety & Biocompatibility

Celivion based on cell-free dermis was found to effectively remove cells and fat during processing, and the density of collagen remained stable after treatment.

In addition, it was verified that decellularization and de-cellularization were successfully achieved through tissue staining,

It is a human tissue product that has proven the safety and biocompatibility of the product as it was not detected in the results of the surfactant residual test.

KMEDIhub 대구경북첨단의료산업진흥재단 Testing agency: Kmedihub Preclinical Center

Superior Decellularization

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Safe DNA levels ADM Acellular Dermal Matrix (cellular dermis) An important indicator for the purity and safety of collagen products derived from the human body

* Safety threshold 50 ng/mg (the lower the value, the safer it is)

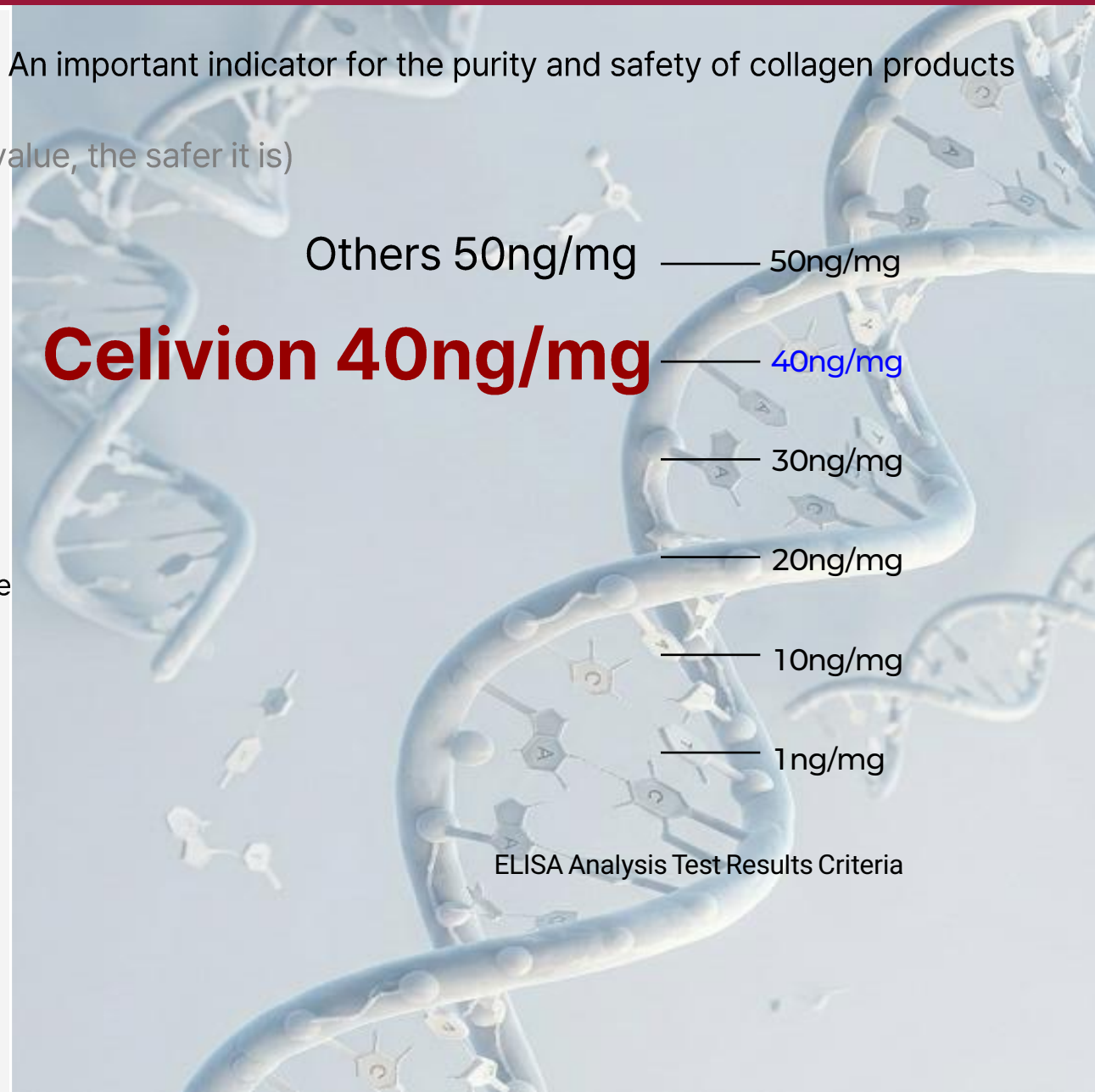
DNA levels' meaning

1. Degree of desaturation: Lower DNA levels mean better cell components are removed (reduce immune response and minimize rejection after transplantation)
2. Product purity: DNA is considered non-collagenic, to obtain high purity collagen

The removal of DNA, fat, cytoplasm, etc. is essential, and the lower the DNA level, the higher the purity and quality of collagen

3. Safety and biocompatibility: High DNA levels cause inflammatory or immune responses. Products with low DNA levels are biocompatible and effective for tissue regeneration

The mass of DNA in one cell is 6.6 pg, 10 ng = approximately 1,500 intracellular DNA mass, which contains more decellularization per cell (cell-free)
30mg X 1,500 cell = about 45,000 more cells decelled (sterilized) for 30mg products
There could be a difference of 150 mg X 1,500 cells = about 225,000 cell DNA compared to 150 mg products.



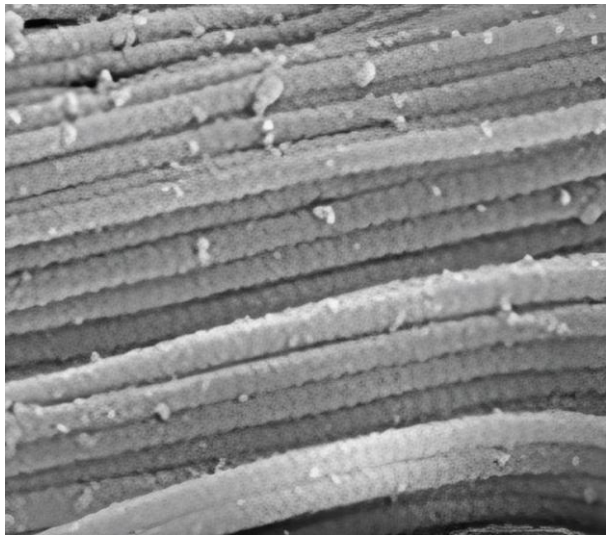
Superior Decellularization

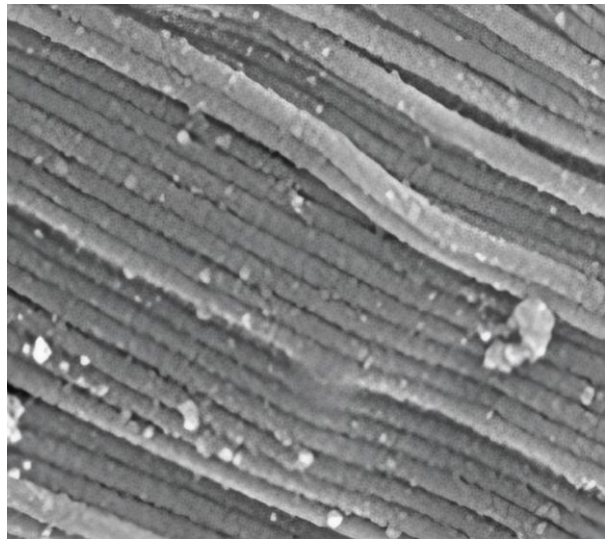
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Observation window of ECM's unique matrix structure and shape maintenance after processing

Meaning of SEM photo: Collagen bundles are arranged clearly and parallel after processing = It means maintaining collagen shape

Competitor A

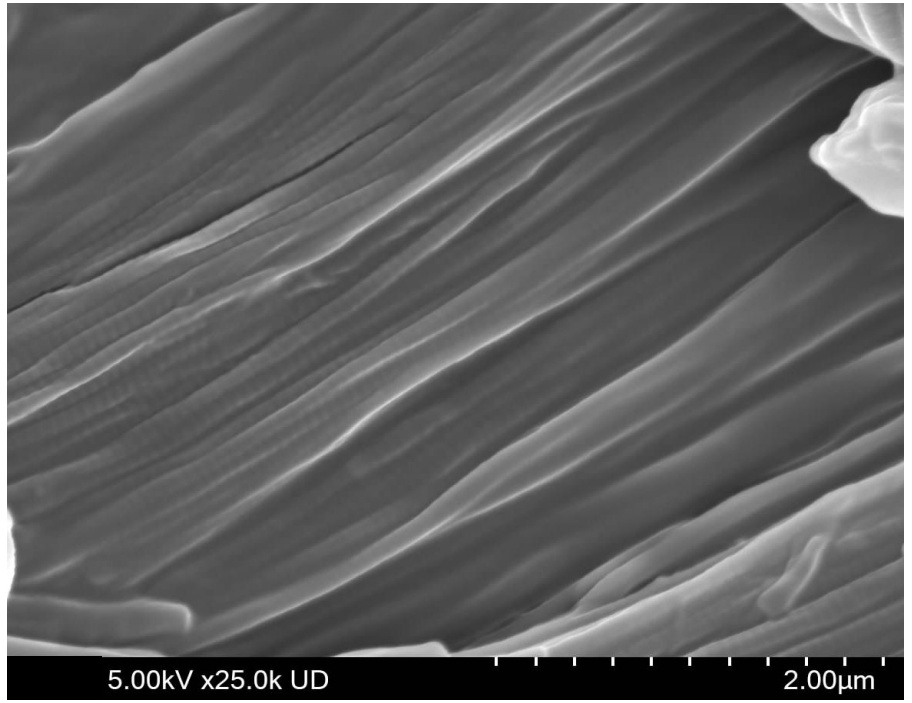




Main Purpose of PELT Construction : Maximum Preservation of ECM

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X 25000



Observe whether the fiber remains in shape

- Collagen-specific texture is well maintained
- Clear and parallel arrangement
- Keep each floor constant without any signs of breakage or crushing

SEM : Scanning Electron Microscope

Tester : KNU 경북대학교 | 공동실험실습관

Collagen Denaturation Test Post-Processing

CELIVION

Observation of Collagen Native Property Retention
FT-IR Analysis - Fourier Transform Infrared Spectroscopy

	Standard Deviation p2/p3	Average P2/P3
CELIVION	0.023	0.990
Competitor A	0.024	0.884

- P2 (1250–1220 cm^{-1}): Amide III band – Analysis of collagen triple helix structure (changes when the triple helix structure collapses).
- P3 (1450 cm^{-1}): A physical property index wavelength capable of quantifying collagen denaturation and cross-linking density.
- p2/p3 ratio: Denaturation (helix > random coil) – The closer the ratio is to 1, the less denaturation has occurred.

FT-IR: Fourier Transform Infrared Spectroscopy – A highly powerful tool for identifying the molecular structure and composition of substances.

시험기관 : KNU 경북대학교 공동실험실습관 (Testing Institution: KNU Kyungpook National University Center for Scientific Instruments)

Post-Processing Collagen Denaturation Test

CELVION

Observation of Collagen Native Property Retention
FT-IR Analysis - Fourier Transform Infrared Spectroscopy

Polímeros
ISSN 1678-5169 (Online)
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https://doi.org/10.1590/0104-1428.0091

Preparation and characterization of Chitosan/Collagen blends containing silver nanoparticles

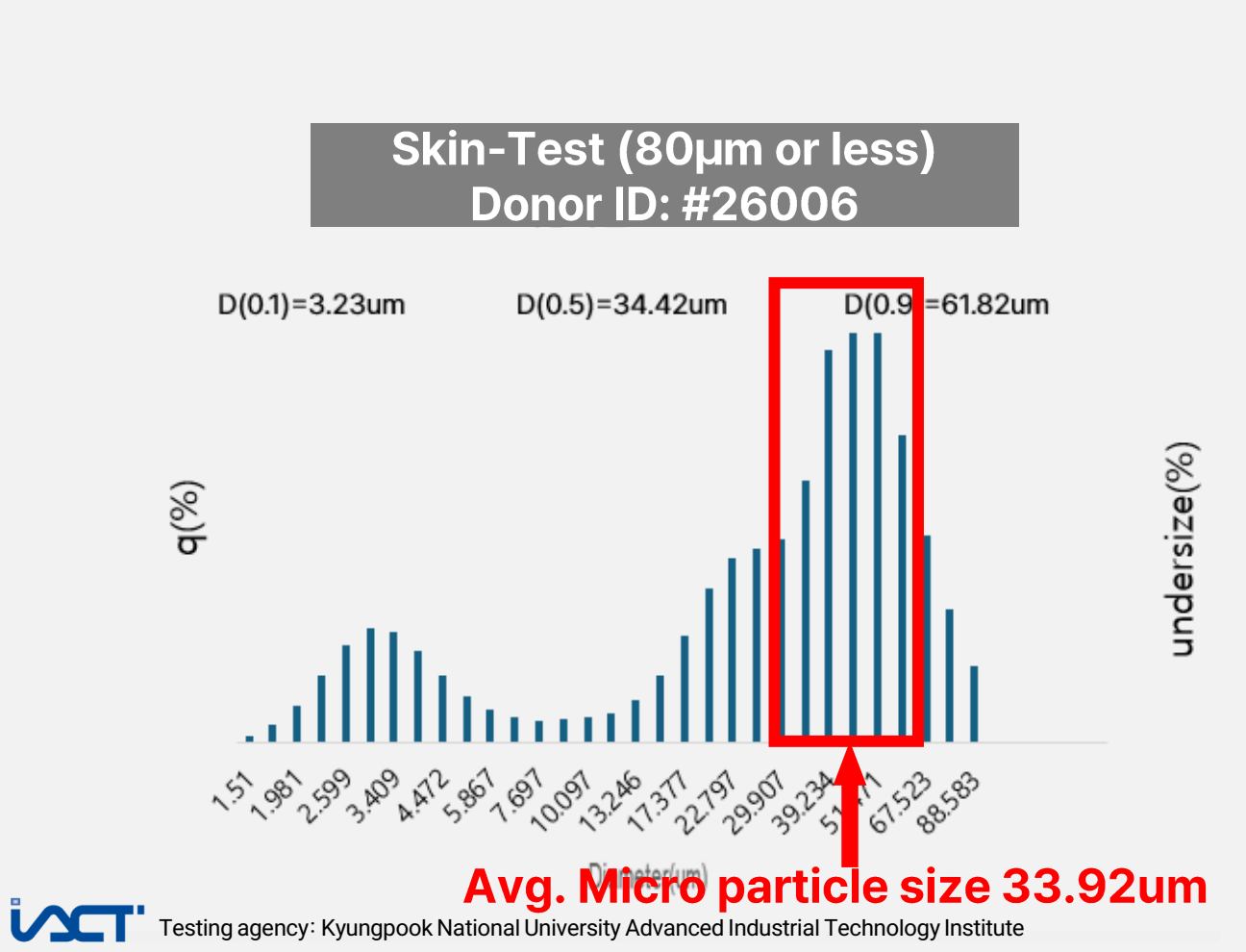
Jonacir Novaes[1], Eloi Alves da Silva Filho[1]*, Paulo Matheus Ferro Bernardo[1] and Enrique Ronald Yapuchura[2]

The integrity of the triple helix of the collagen can be evaluated by the ratio between the absorbance at 1235 and 1450 cm^{-1} [16]. That is an very important, since this three-dimensional collagen characteristic gives it important biological and mechanical properties[13]. The values of this ratio for the denatured collagen are about 0.5 and those of intact structures are about 1. For the samples in the proportion of 1:1, 1:2 and 1:3 chitosan/collagen, the ratios obtained were above of 1, but for the 3:1 proportion the value obtained was 0.46, which is indicative that the increase in the amount of chitosan in relation to the collagen destabilizes the triple helix of the protein structure of the collagen[17].

- The integrity of the collagen triple helix structure can be evaluated using the absorbance ratio of 1235 cm^{-1} (P2) / 1415 cm^{-1} (P3).
- A value of 0.5 or lower indicates denatured collagen, while the value for intact (undamaged) collagen is approximately 1.0.

Collagen Particle Size and Uniformity

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Particle size analysis

1. Particle size check through particle size analysis

Manufactured by the ultra-precise grinding process, the product consists of evenly distributed microparticles centered around about **33.92μm**, designed to suit the user's convenience and indications, naturally reconstructs in tissues when transplanted, and has higher regenerative retention than general materials.

The uniform particle size distribution directly affects the absorption rate/reduction of mixing stability/aggregation during the procedure.
In particular, the aggregation during the mixing process seems to be related to the **embossing (bulk surface) phenomenon** that may occur after injection.

Celivion is oriented towards reducing agglomeration during mixing and increasing surface stability after injection by designing particle sizes uniformly.

Collagen Particle Size and Uniformity

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In molecular performance, it's not about size — it's about intelligent design.

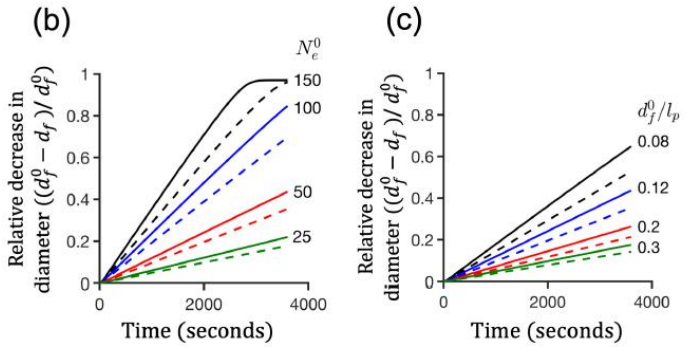


Figure 3: Degradation of single fibril. (a) Validation of the single fibril model with the experimental findings of Flynn et al. (2013). Relative decrease of fibril diameter $(d_f^0 - d_f)/d_f^0$ (or, the extent of degradation) with time for two cases: (b) fixed initial fibril diameter $d_f^0/l_p = 0.12$ and varying number of enzymes surrounding a fibril (N_e^0); (c) Varying d_f^0/l_p and fixed $N_e^0 = 50$. Here $l_p = 1$ µm is a nominal length scale. The length of the fibril is $\ell_f/l_p = 2$ in (b) and (c). The solid and dashed curves in (b) and (c) correspond to $k_+^c = 0.583\ \mathrm{s}^{-1}$ (Mallya et al., 1992) and $0.472\ \mathrm{s}^{-1}$ (Welgus et al., 1982), respectively.

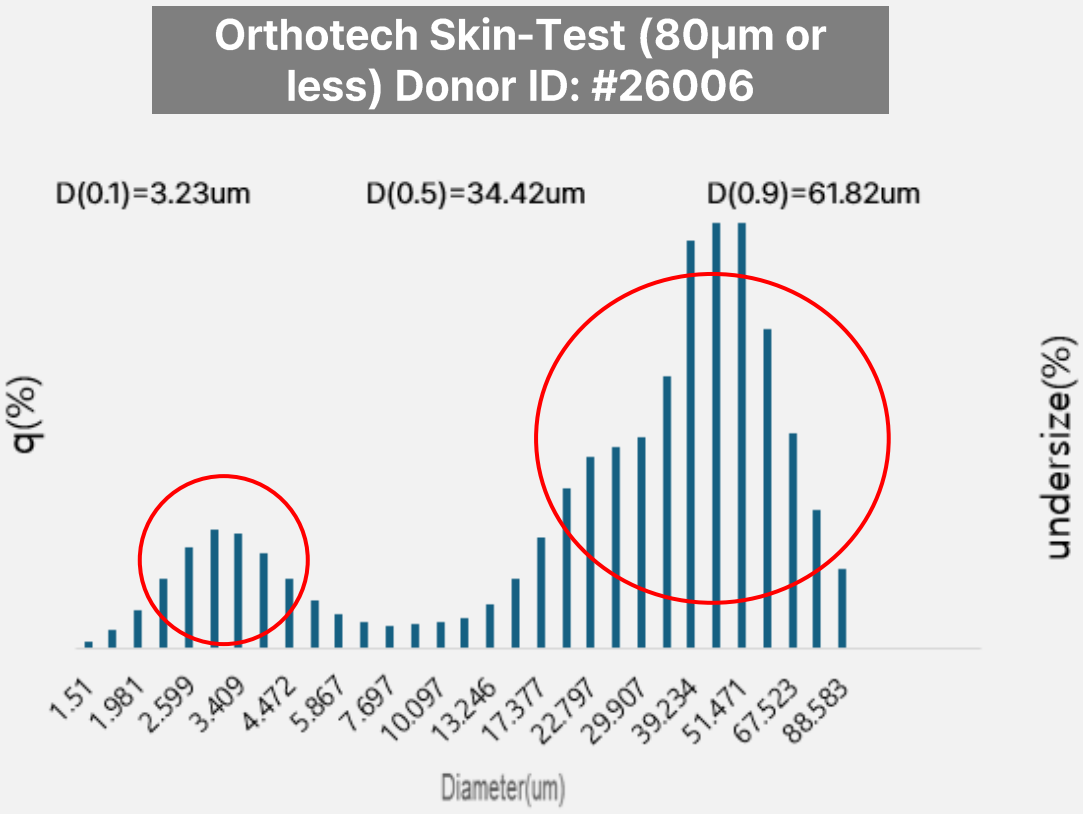
* Reference articles: Modeling collagen fibril degradation as a function of matrix microarchitecture

Some recognize that the larger the molecular size, the greater the effect. However, this is a simplified interpretation, which is not necessarily the case in terms of actual regeneration reactions and absorption rates.
This paper reports that smaller molecular sizes and thinner structures can lead to higher intratissue penetration and absorption efficiency.

ECM solution designed for absorption efficiency
What matters is how well it is absorbed and works in the tissue
Celivion has **uniformly designed thin, fine-structured collagen particles to consider absorption** and dispersion in tissues and has chosen a more efficient direction to drive the regenerative environment.
This is not a design that emphasizes quantity or size, but a medical design philosophy that prioritizes tissue reactivity and absorption efficiency.

Collagen Particle Size and Uniformity

CELVION



Testing agency: Kyungpook National University Advanced Industrial Technology Institute

Particle size analysis

2. Importance of Collagen Type Configuration

Having only large collagen particles or only small particles is not ideal. For optimal regenerative performance, collagen particles should be **evenly and uniformly distributed**. This balanced particle distribution improves the efficiency of attracting bioactive regenerative substances, leading to **enhanced absorption** and a more effective stimulation of the skin's regenerative response.

There are **28 types of collagen**, of which **Type I** constitutes the majority of the dermal structure, while **Type III** plays a key role in connecting and supporting the collagen network.

- **Type I:** Forms the primary structural framework of the skin
- **Type III:** Acts as a connective scaffold linking Type I fibers together

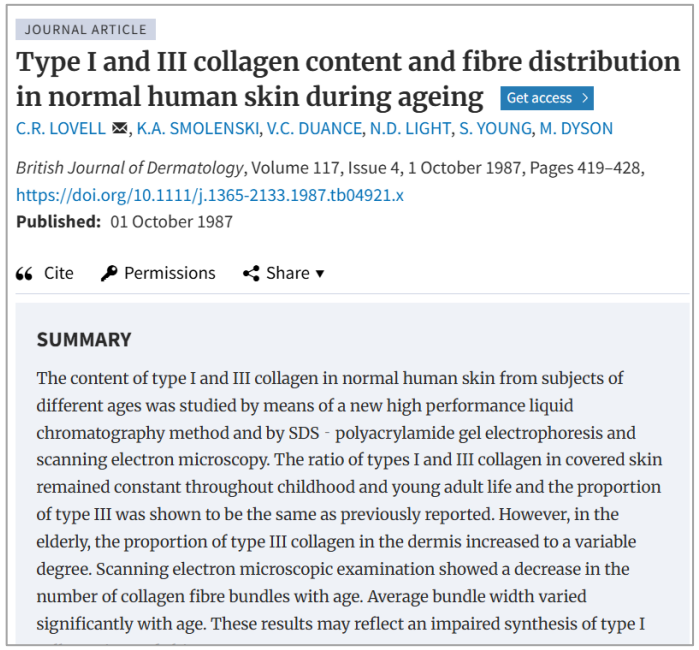
When **Type III collagen is present alongside Type I**, the collagen structure becomes more stable—similar to a formwork or scaffold—creating an environment that is more favorable for **elasticity recovery and tissue regeneration**.
This synergistic structural reinforcement is described as the **Taragrain Effect**.

Therefore, an advanced collagen formulation should not focus solely on increasing the proportion of Type I collagen but also ensure the **appropriate inclusion of Type III collagen** as a key design factor for enhanced regenerative performance.

Proportion of Collagen Types

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Ratio of Collagen Type I & III in Normal Adult Dermis



JOURNAL ARTICLE

Type I and III collagen content and fibre distribution in normal human skin during ageing Get access

C.R. LOVELL, K.A. SMOLENSKI, V.C. DUANCE, N.D. LIGHT, S. YOUNG, M. DYSON

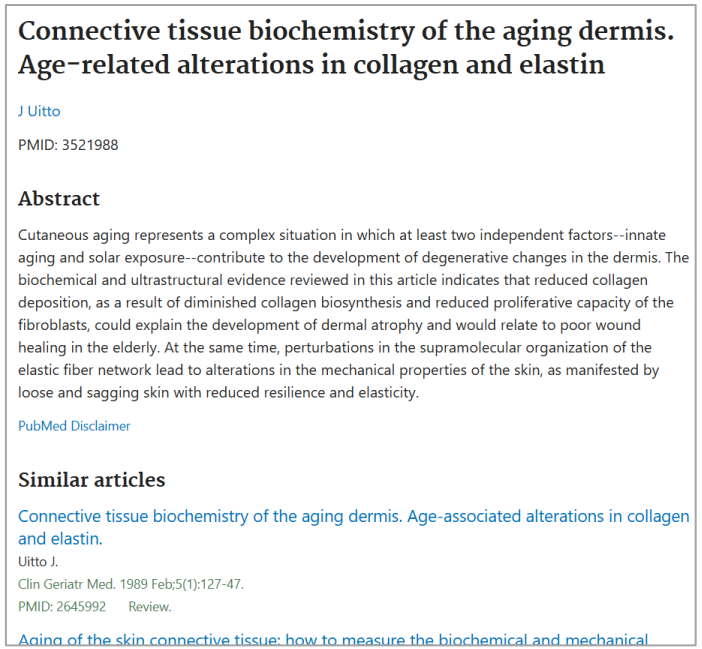
British Journal of Dermatology, Volume 117, Issue 4, 1 October 1987, Pages 419–428,
https://doi.org/10.1111/j.1365-2133.1987.tb04921.x
Published: 01 October 1987

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SUMMARY

The content of type I and III collagen in normal human skin from subjects of different ages was studied by means of a new high performance liquid chromatography method and by SDS - polyacrylamide gel electrophoresis and scanning electron microscopy. The ratio of types I and III collagen in covered skin remained constant throughout childhood and young adult life and the proportion of type III was shown to be the same as previously reported. However, in the elderly, the proportion of type III collagen in the dermis increased to a variable degree. Scanning electron microscopic examination showed a decrease in the number of collagen fibre bundles with age. Average bundle width varied significantly with age. These results may reflect an impaired synthesis of type I

Lovell CR et al., *Br J Dermatol* (1987)



Connective tissue biochemistry of the aging dermis. Age-related alterations in collagen and elastin

J Uitto

PMID: 3521988

Abstract

Cutaneous aging represents a complex situation in which at least two independent factors--innate aging and solar exposure--contribute to the development of degenerative changes in the dermis. The biochemical and ultrastructural evidence reviewed in this article indicates that reduced collagen deposition, as a result of diminished collagen biosynthesis and reduced proliferative capacity of the fibroblasts, could explain the development of dermal atrophy and would relate to poor wound healing in the elderly. At the same time, perturbations in the supramolecular organization of the elastic fiber network lead to alterations in the mechanical properties of the skin, as manifested by loose and sagging skin with reduced resilience and elasticity.

PubMed Disclaimer

Similar articles

Connective tissue biochemistry of the aging dermis. Age-associated alterations in collagen and elastin.
Uitto J.
Clin Geriatr Med. 1989 Feb;5(1):127-47.
PMID: 2645992 Review.

Aging of the skin connective tissue: how to measure the biochemical and mechanical

Cheng W et al., *African Journal of Biotechnology* (2011)

- Type I: Approx.80~85%
- Type III: Approx.10~20%
- I/III ratio: 4:1 ~ 5:1
- Proportions remain relatively stable throughout adulthood

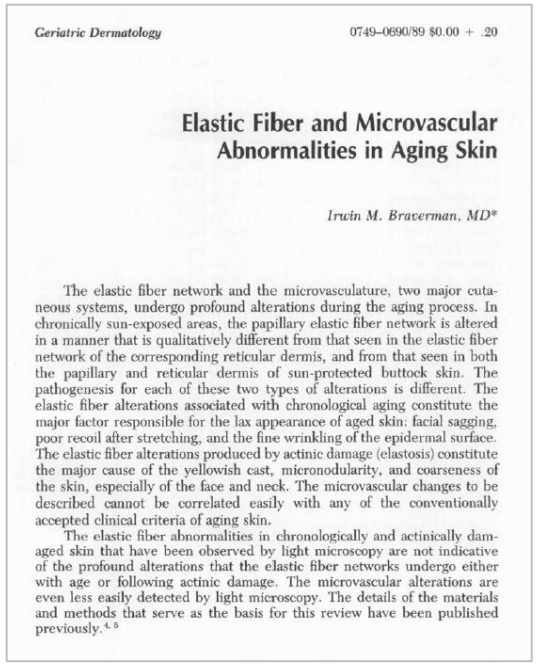
Strong adult dermis is a balanced structure of Type I dominance + Type III presence

Normal adult dermis has a balanced structure where Type I is dominant, but Type III coexists. CELIVION pursues a design philosophy that considers the structural preservation of the ECM, rather than focusing solely on collagen content.

Ratio of Collagen Types and Composition of ECM

CELIVION

Composition Ratio of Dermal ECM



Geriatric Dermatology 0749–0690/89 $0.00 + .20

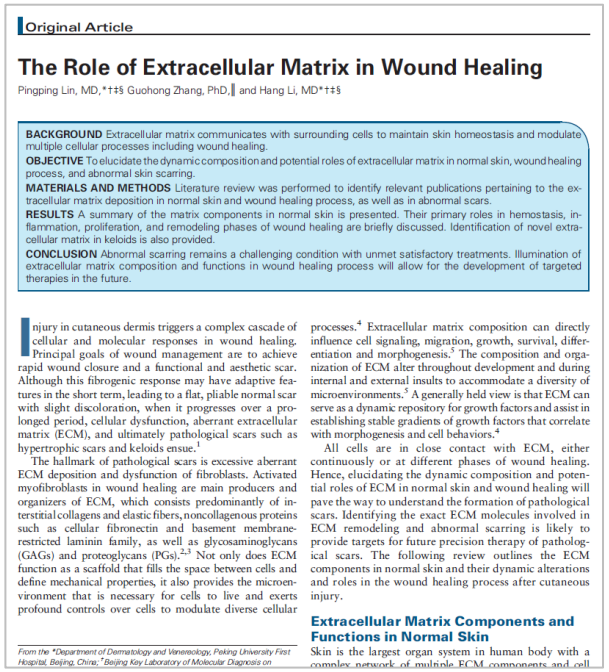
Elastic Fiber and Microvascular Abnormalities in Aging Skin

*Irwin M. Braverman, MD**

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The elastic fiber abnormalities in chronologically and actinically damaged skin that have been observed by light microscopy are not indicative of the profound alterations that the elastic fiber networks undergo either with age or following actinic damage. The microvascular alterations are even less easily detected by light microscopy. The details of the materials and methods that serve as the basis for this review have been published previously.[4,5]

Uitto J., *Clinics in Geriatric Medicine* (1989)



Original Article

The Role of Extracellular Matrix in Wound Healing

Pingping Lin, MD,*†‡§ Guohong Zhang, PhD,‖ and Hang Li, MD*†‡§

BACKGROUND Extracellular matrix communicates with surrounding cells to maintain skin homeostasis and modulate multiple cellular processes including wound healing.
OBJECTIVE To elucidate the dynamic composition and potential roles of extracellular matrix in normal skin, wound healing process, and abnormal skin scarring.
MATERIALS AND METHODS Literature review was performed to identify relevant publications pertaining to the extracellular matrix deposition in normal skin and wound healing process, as well as in abnormal scars.
RESULTS A summary of the matrix components in normal skin is presented. Their primary roles in hemostasis, inflammation, proliferation, and remodeling phases of wound healing are briefly discussed. Identification of novel extracellular matrix in keloids is also provided.
CONCLUSION Abnormal scarring remains a challenging condition with unmet satisfactory treatments. Illumination of extracellular matrix composition and functions in wound healing process will allow for the development of targeted therapies in the future.

Injury in cutaneous dermis triggers a complex cascade of cellular and molecular responses in wound healing. Principal goals of wound management are to achieve rapid wound closure and a functional and aesthetic scar. Although this fibrogenic response may have adaptive features in the short term, leading to a flat, pliable normal scar with slight discoloration, when it progresses over a prolonged period, cellular dysfunction, aberrant extracellular matrix (ECM), and ultimately pathological scars such as hypertrophic scars and keloids ensue.[1]

The hallmark of pathological scars is excessive aberrant ECM deposition and dysfunction of fibroblasts. Activated myofibroblasts in wound healing are main producers and organizers of ECM, which consists predominantly of interstitial collagens and elastic fibers, noncollagenous proteins such as cellular fibronectin and basement membrane-restricted laminin family, as well as glycosaminoglycans (GAGs) and proteoglycans (PGs).[2,3] Not only does ECM function as a scaffold that fills the space between cells and define mechanical properties, it also provides the microenvironment that is necessary for cells to live and exerts profound controls over cells to modulate diverse cellular processes.[4] Extracellular matrix composition can directly influence cell signaling, migration, growth, survival, differentiation and morphogenesis.[5] The composition and organization of ECM alter throughout development and during internal and external insults to accommodate a diversity of microenvironments.[5] A generally held view is that ECM can serve as a dynamic repository for growth factors and assist in establishing stable gradients of growth factors that correlate with morphogenesis and cell behaviors.[4]

All cells are in close contact with ECM, either continuously or at different phases of wound healing. Hence, elucidating the dynamic composition and potential roles of ECM in normal skin and wound healing will pave the way to understand the formation of pathological scars. Identifying the exact ECM molecules involved in ECM remodeling and abnormal scarring is likely to provide targets for future precision therapy of pathological scars. The following review outlines the ECM components in normal skin and their dynamic alterations and roles in the wound healing process after cutaneous injury.

Extracellular Matrix Components and Functions in Normal Skin

Skin is the largest organ system in human body with a complex network of multiple ECM components and cell

*From the *Department of Dermatology and Venereology, Peking University First Hospital, Beijing, China; †Beijing Key Laboratory of Molecular Diagnosis on*

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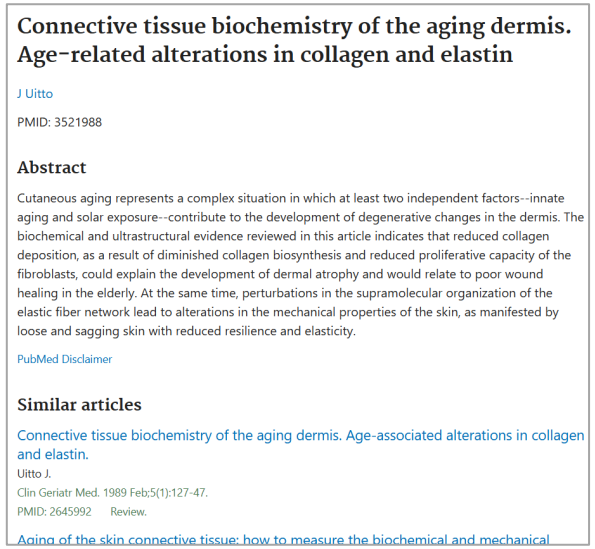
- Collagen: 70–80% of dermal dry weight
- Elastin: 2–4%
- GAG/Proteoglycan: Present in small amounts, yet key to moisture retention
- **ECM is a "Network Structure," not collagen alone**

Although 70–80% of the dermis consists of collagen, ECM is a network formed together with elastin and GAG.
Celivion offers an ECM structure-focused solution that considers the regenerative environment, rather than a collagen-only approach.

Ratio of Collagen Types and ECM Components

CELIVION

Changes in Type I/III Ratio According to Aging



Connective tissue biochemistry of the aging dermis. Age-related alterations in collagen and elastin

J Uitto

PMID: 3521988

Abstract

Cutaneous aging represents a complex situation in which at least two independent factors--innate aging and solar exposure--contribute to the development of degenerative changes in the dermis. The biochemical and ultrastructural evidence reviewed in this article indicates that reduced collagen deposition, as a result of diminished collagen biosynthesis and reduced proliferative capacity of the fibroblasts, could explain the development of dermal atrophy and would relate to poor wound healing in the elderly. At the same time, perturbations in the supramolecular organization of the elastic fiber network lead to alterations in the mechanical properties of the skin, as manifested by loose and sagging skin with reduced resilience and elasticity.

PubMed Disclaimer

Similar articles

Connective tissue biochemistry of the aging dermis. Age-associated alterations in collagen and elastin.

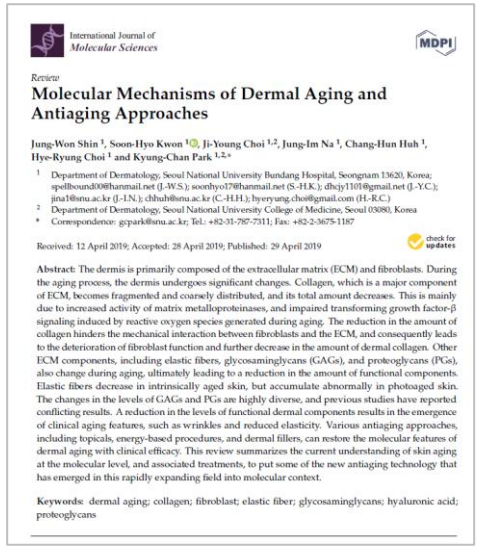
Uitto J.

Clin Geriatr Med. 1989 Feb;5(1):127-47.

PMID: 2645992 Review.

Aging of the skin connective tissue: how to measure the biochemical and mechanical

연령별 I/III 비율 비교



International Journal of Molecular Sciences

MDPI

Review

Molecular Mechanisms of Dermal Aging and Antiaging Approaches

Jung-Won Shin [1], Soon-Hyo Kwon [1], Ji-Young Choi [1,2], Jung-Im Na [1], Chang-Hun Huh [1], Hye-Ryung Choi [1] and Kyung-Chan Park [1,2,*]

1 Department of Dermatology, Seoul National University Bundang Hospital, Seongnam 13620, Korea; spellbound008@hanmail.net (J.-W.S.); soonhyo17@hanmail.net (S.-H.K.); dhcjy1101@gmail.net (J.-Y.C.); jina1@snu.ac.kr (J.-I.N.); chhuh@snu.ac.kr (C.-H.H.); hyeryung.choi@gmail.com (H.-R.C.)

2 Department of Dermatology, Seoul National University College of Medicine, Seoul 03080, Korea

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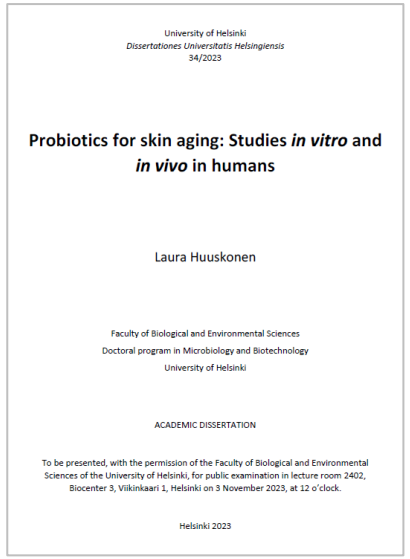
Received: 12 April 2019; Accepted: 28 April 2019; Published: 29 April 2019

check for updates

Abstract: The dermis is primarily composed of the extracellular matrix (ECM) and fibroblasts. During the aging process, the dermis undergoes significant changes. Collagen, which is a major component of ECM, becomes fragmented and coarsely distributed, and its total amount decreases. This is mainly due to increased activity of matrix metalloproteinases, and impaired transforming growth factor-β signaling induced by reactive oxygen species generated during aging. The reduction in the amount of collagen hinders the mechanical interaction between fibroblasts and the ECM, and consequently leads to the deterioration of fibroblast function and further decrease in the amount of dermal collagen. Other ECM components, including elastic fibers, glycosaminglycans (GAGs), and proteoglycans (PGs), also change during aging, ultimately leading to a reduction in the amount of functional components. Elastic fibers decrease in intrinsically aged skin, but accumulate abnormally in photoaged skin. The changes in the levels of GAGs and PGs are highly diverse, and previous studies have reported conflicting results. A reduction in the levels of functional dermal components results in the emergence of clinical aging features, such as wrinkles and reduced elasticity. Various antiaging approaches, including topicals, energy-based procedures, and dermal fillers, can restore the molecular features of dermal aging with clinical efficacy. This review summarizes the current understanding of skin aging at the molecular level, and associated treatments, to put some of the new antiaging technology that has emerged in this rapidly expanding field into molecular context.

Keywords: dermal aging; collagen; fibroblast; elastic fiber; glycosaminglycans; hyaluronic acid; proteoglycans

Molecular Mechanisms of Dermal Aging



University of Helsinki

Dissertationes Universitatis Helsingiensis

34/2023

Probiotics for skin aging: Studies *in vitro* and *in vivo* in humans

Laura Huuskonen

Faculty of Biological and Environmental Sciences

Doctoral program in Microbiology and Biotechnology

University of Helsinki

ACADEMIC DISSERTATION

To be presented, with the permission of the Faculty of Biological and Environmental Sciences of the University of Helsinki, for public examination in lecture room 2402, Biocenter 3, Viikinkaari 1, Helsinki on 3 November 2023, at 12 o'clock.

Helsinki 2023

Probiotics for skin aging
(연령별 콜라겐 변화)

- Fetus: I/III ≈ 1:1 (High Type III content)
- Adult: Increase in I/III (Type I dominance)
- Aging Skin: Decrease in Type III, worsening ratio imbalance
- Total collagen amount decreases by approximately 1% annually

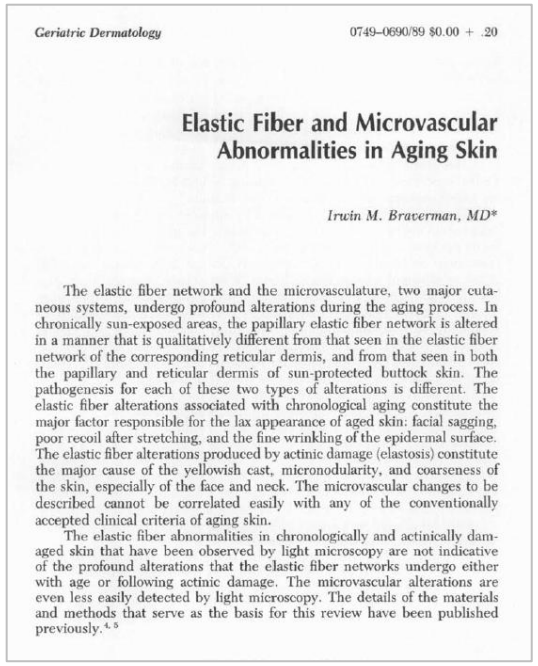
•The key to aging is not simply "collagen reduction," but the **decrease of Type III collagen and the resulting structural imbalance.**

Aging begins not only with the reduction of total collagen but also with the loss of Type III collagen and structural imbalance.
CELIVION approaches this based on the standard of 'structural balance' rather than just 'quantity'.

Ratio of Collagen Types and ECM Components

CELIVION

Composition of Dermal ECM



Geriatric Dermatology 0749–0690/89 $0.00 + .20

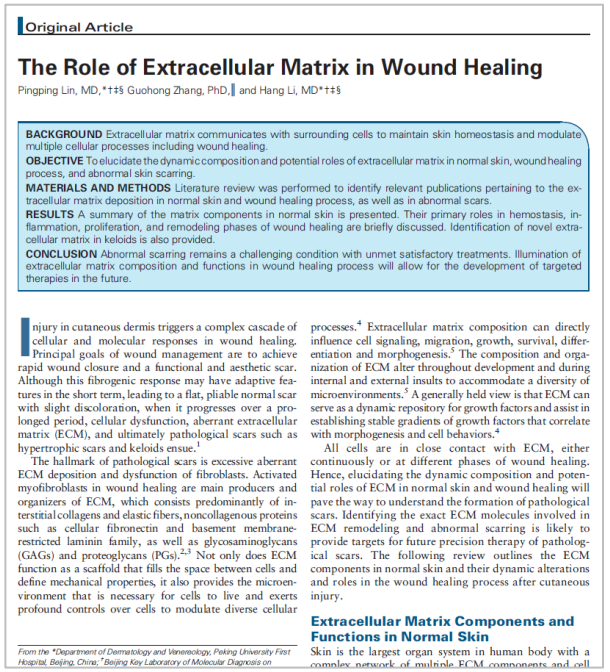
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The Role of Extracellular Matrix in Wound Healing

- Collagen: 70–80% of dermal dry weight
- Elastin: 2–4%
- GAG/Proteoglycan: Present in small amounts, but key to maintaining hydration
- ECM is a "Network Structure," not collagen alone
- ECM is not just a mass of collagen; it is a structural network of Collagen + Elastin + GAGs.

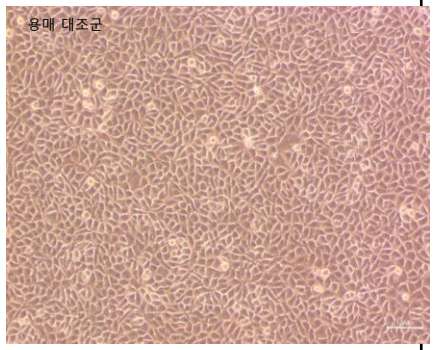
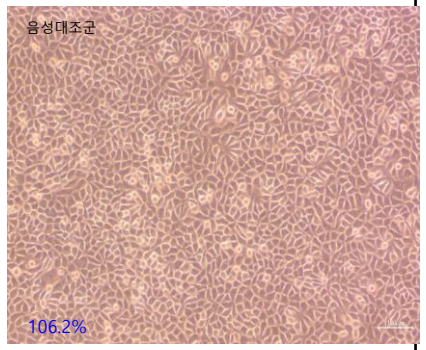
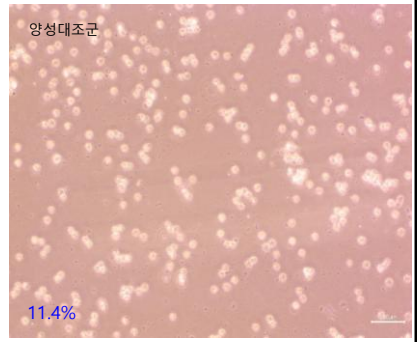
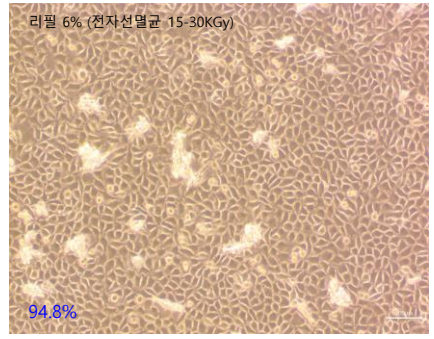
CELIVION provides an **ECM structure-focused solution** that considers the regenerative environment, rather than an approach focused solely on collagen.

While 70–80% of the dermis is composed of collagen, the ECM is a network formed together with elastin and GAGs. CELIVION provides an ECM structure-focused solution that considers the regenerative environment, rather than an approach focused solely on collagen.

Results of Cytotoxicity Test (In Vitro Cytotoxicity Test)

CELIVION

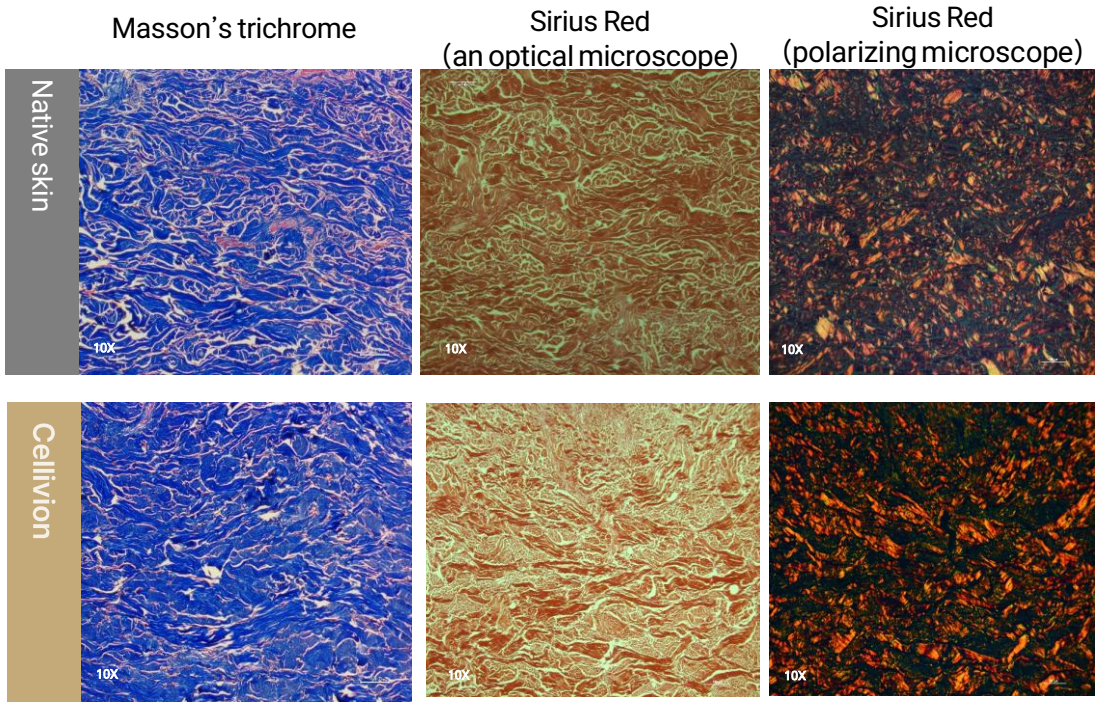
In Vitro Cytotoxicity Test

Group	MEM Medium	Negative Control	Positive Control	CELIVION
Test Results	100.0 %	106.2 %	11.4 %	94.8 %
✔ Test Methods • Cytotoxicity - Extraction Test Method • ISO 10993-12 (Method by KTR (Certified Testing Institute)) • Extraction Time: 24 hours • Test Temperature: 37°C • Rotation Speed: 120 rpm • Cell Line: L929 cells • Incubation Time: 48 hours				

The donor of CELIVION products, processed to remove **immunogenic factors**, demonstrates high cell viability and **exhibits biocompatibility**.

Collagen Particle Size and Uniformity

CELIVION



Collagen density and type analysis:

Tissue staining (static analysis)

Masson's trichrome

: Check the density of collagen (observation of changes before and after processing)

- Blue : Full collagen fiber dyeing (assessment of fiber distribution and density)
- Red : Muscle, cytoplasm, collagen degeneration - red expression

Sirius Red : Staining Collagen Fiber / Check Collagen Type

- General Microscope: Collagen – Red
- Polarization Microscope:

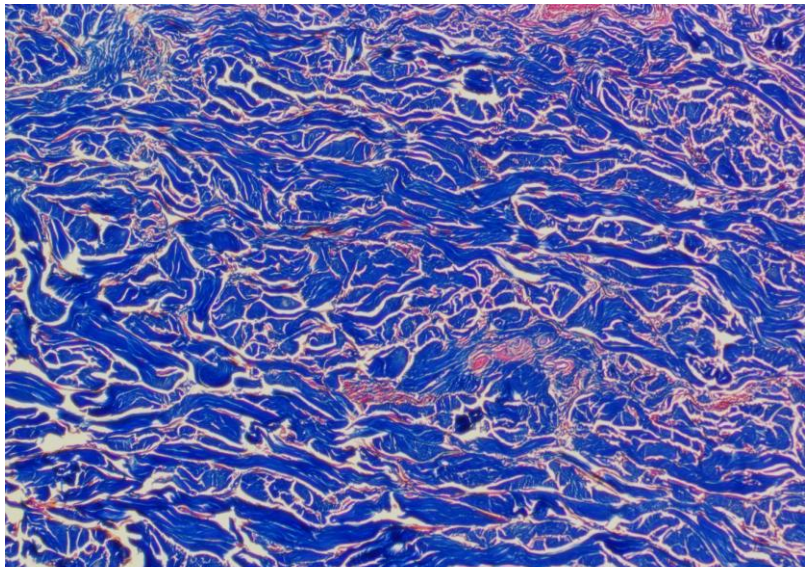
Collagen type I – Yellow/Orange *Large Conservation

Collagen type III – Maintaining the proper line for green skin flexibility/resilience

** Collagen type I: Collagen (80-90%) most present in the dermal layer of the skin = Skin strength and structural support

Collagen type III: Mainly present in skin, blood vessels, internal organs, etc. along with type I = Provides flexibility and elasticity

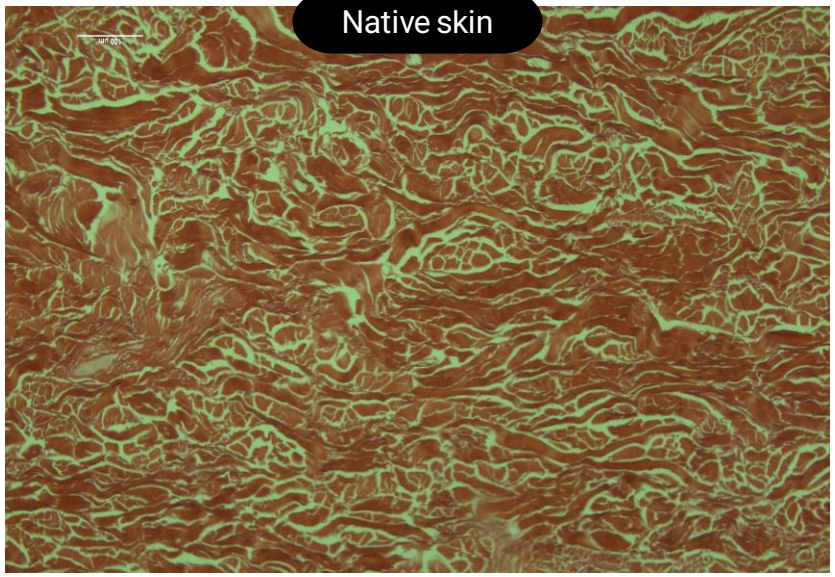
KMEDIhub 대구경북첨단의료산업진흥재단 Testing agency: Kmedihub Preclinical Center



Masson's trichrome

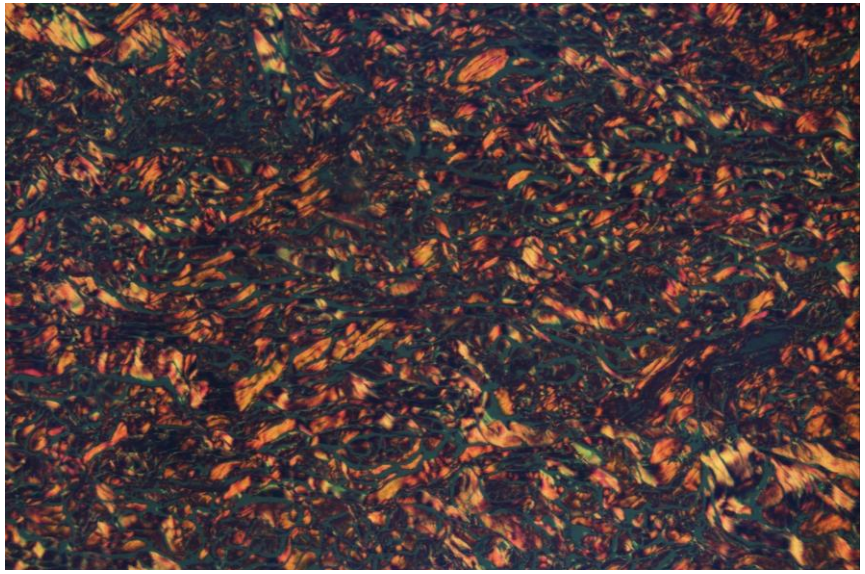
①Increased blue collagen density ▲

②decreased red cytopathic degeneration ▼



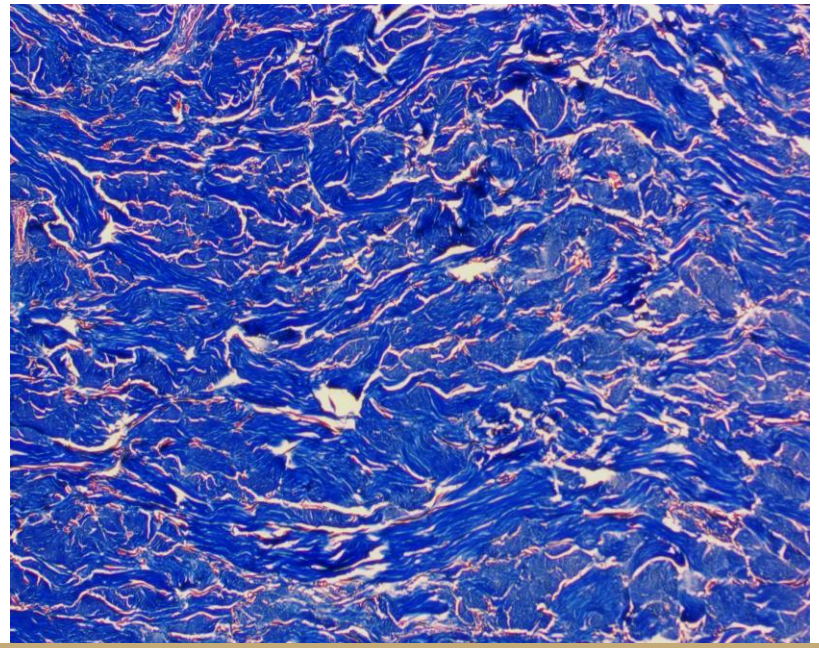
Sirius Red (an optical microscope)

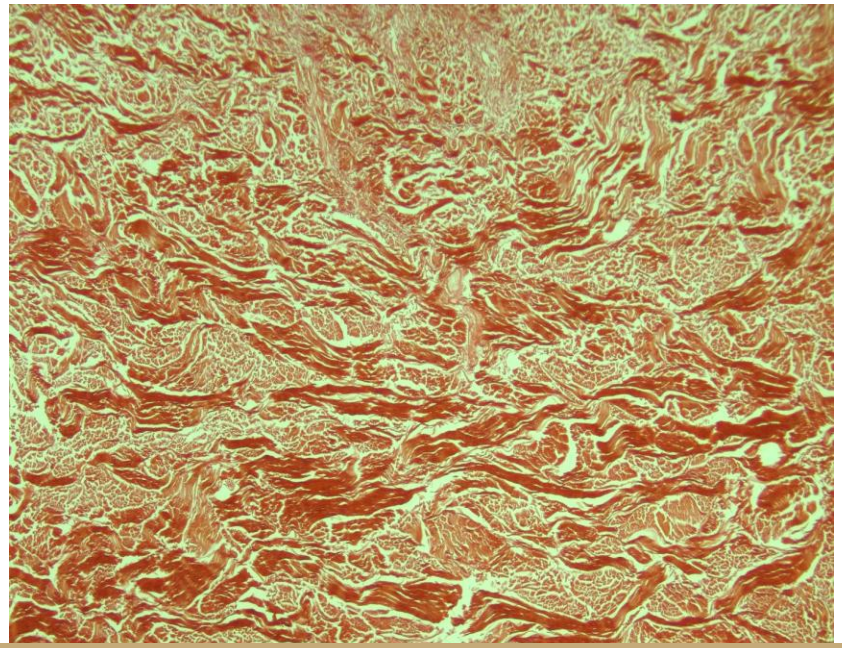
Red Collagen Uniform Distribution and Maintenance

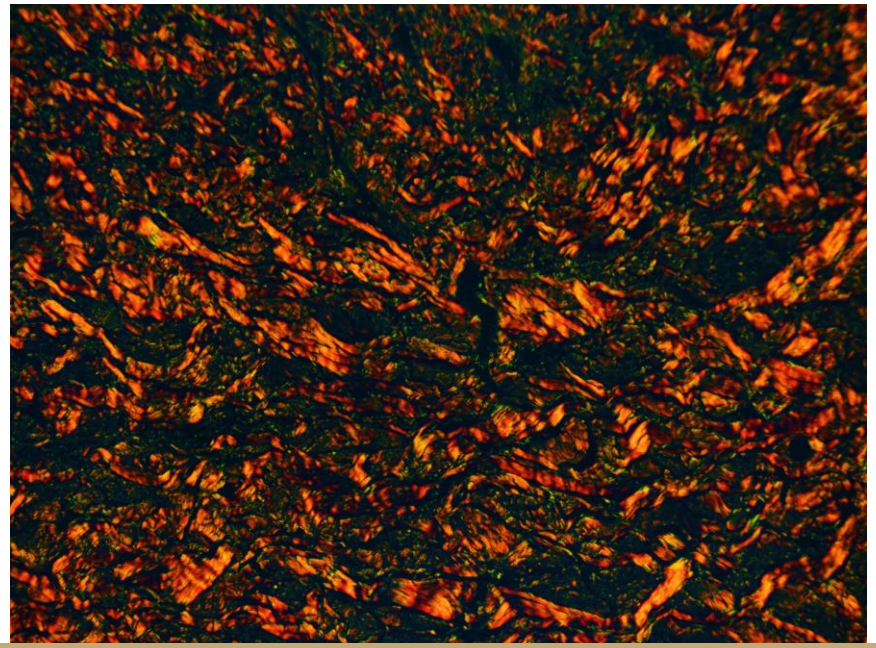


Sirius Red (polarizing microscope)

Collagen Type I Average 80-90% Retention (Yellow/Orange)
→ Strength/Structure Support
Collagen type III Preservation of Appropriate Line (Green)







Permit for establishment of a human tissue bank

■ 인체조직안전에 관한 규칙 [별지 제2호서식]

조직은행설립허가증

허가번호	제 336 호		
조직은행의 명칭	(주)바이오비쥬		
조직은행의 주소	경기도 하남시 하남대로 947 A동 15층 일부(풍산동, 하남테크노밸리U1 CENTER)		
대표자 성명	양준호	생년월일	1970 년 12 월 08 일
조직은행의 장 성명	김영제	생년월일	1983 년 01 월 19 일
의료관리자 성명	김기호	면허증별/면허번호	의사/제 7344 호
조직은행 유형	조직수입업자		
조직은행 업무구분	보관, 분배, 수입		
조직취급품목	뼈, 연골, 근막, 피부		
허가유효기간	2026 년 02 월 26 일 부터 2029 년 02 월 25 일 까지		

「인체조직안전 및 관리 등에 관한 법률」 제13조제1항 전단 및 제14조제2항과 「인체조직안전에 관한 규칙」 제5조제3항 및 제8조제1항에 따라 위와 같이 허가합니다.

2026 년 02 월 26 일

경인지방식품의약품안전청장



Safety

CELIVION

Serological Testing 10 types & HBV-NAT

Test	KFDA	FDA	KATB	AATB	Celivion
HIV 1 / 2 Ab	●	●	●	●	●
HCV Ab	●	●	●	●	●
HBsAg	●	●	●	●	●
STS(RPR)	●	●	●	●	●
HTLV	-	-	●	●	●
HIV NAT(PCR)	-	-	-	●	●
HCV NAT(PCR)	-	-	-	●	●
HBcAb	-	-	-	●	●
HBsAb	-	-	-	-	●
HBV-NAT	-	-	-	-	●

Celivion 10 types of TEST FINISHED

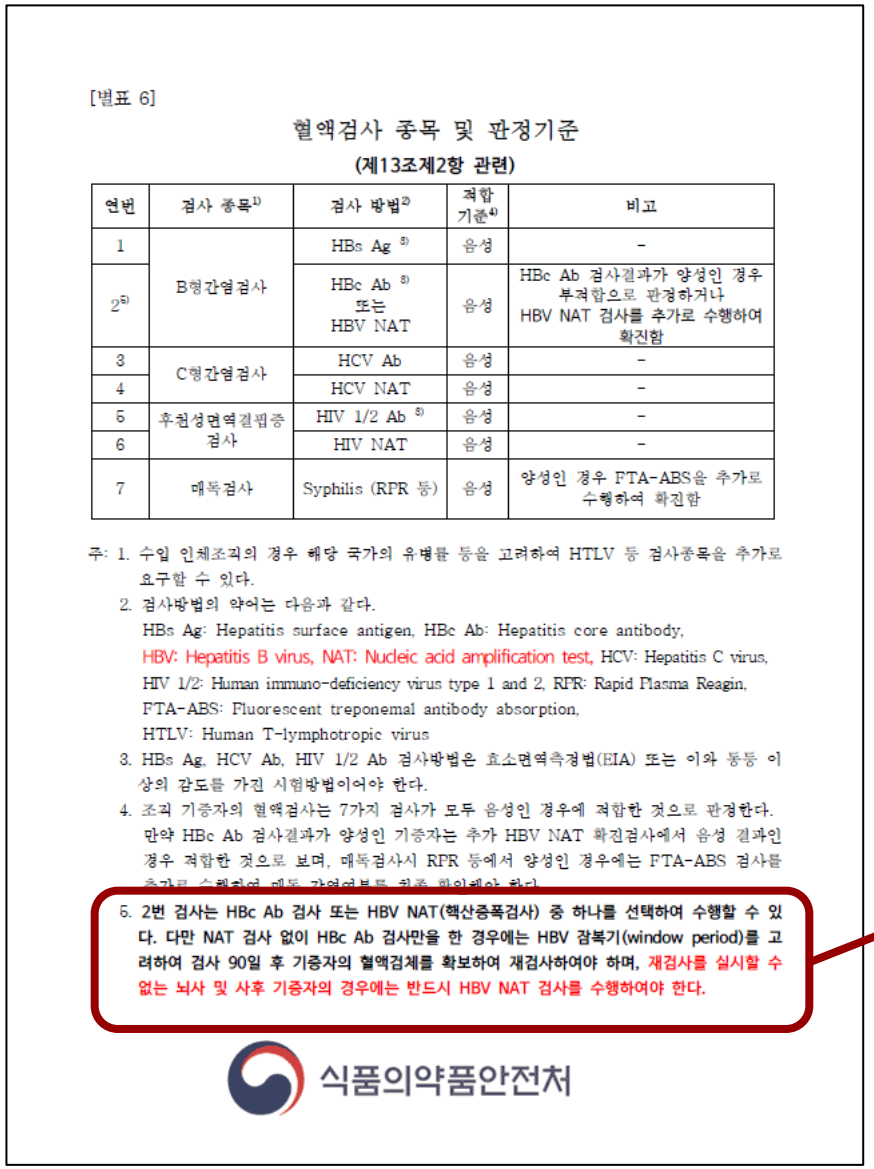
Our allogeneic collagen is distributed only as a donor in accordance with *AATB's management standards, extracting more safer collagen.
*Federation of American Organized Banks

Separate human tissue manufacturing facilities and strict quality standards

With over 20 years of experience as human tissue managers and researchers, we maintain excellent quality.

Regular safety systems and constant quality verification
Safety is very high compared to other companies.

HBV-NAT TEST Additional Nucleic Acid Amplification Test
(HBV: Hepatitis B virus, NAT: Nucleic acid amplification test)



[별표 6]

혈액검사 종목 및 판정기준

(제13조제2항 관련)

연번	검사 종목[1]	검사 방법[2]	적합 기준[4]	비고
1	B형간염검사	HBs Ag [3]	음성	-
2[5]		HBc Ab [3] 또는 HBV NAT	음성	HBc Ab 검사결과가 양성인 경우 부적합으로 판정하거나 HBV NAT 검사를 추가로 수행하여 확진함
3	C형간염검사	HCV Ab	음성	-
4		HCV NAT	음성	-
5	후천성면역결핍증 검사	HIV 1/2 Ab [3]	음성	-
6		HIV NAT	음성	-
7	매독검사	Syphilis (RPR 등)	음성	양성인 경우 FTA-ABS을 추가로 수행하여 확진함

주: 1. 수입 인체조직의 경우 해당 국가의 유병률 등을 고려하여 HTLV 등 검사종목을 추가로 요구할 수 있다.

2. 검사방법의 약어는 다음과 같다.
HBs Ag: Hepatitis surface antigen, HBc Ab: Hepatitis core antibody,
HBV: Hepatitis B virus, NAT: Nucleic acid amplification test, HCV: Hepatitis C virus,
HIV 1/2: Human immuno-deficiency virus type 1 and 2, RPR: Rapid Plasma Reagin,
FTA-ABS: Fluorescent treponemal antibody absorption,
HTLV: Human T-lymphotropic virus

3. HBs Ag, HCV Ab, HIV 1/2 Ab 검사방법은 효소면역측정법(EIA) 또는 이와 동등 이상의 감도를 가진 시험방법이어야 한다.

4. 조직 기증자의 혈액검사는 7가지 검사가 모두 음성인 경우에 적합한 것으로 판정한다. 만약 HBc Ab 검사결과가 양성인 기증자는 추가 HBV NAT 확진검사에서 음성 결과인 경우 적합한 것으로 보며, 매독검사시 RPR 등에서 양성인 경우에는 FTA-ABS 검사를 추가로 수행하여 매독 감염여부를 최종 확인해야 한다.

5. 2번 검사는 HBc Ab 검사 또는 HBV NAT(핵산증폭검사) 중 하나를 선택하여 수행할 수 있다. 다만 NAT 검사 없이 HBc Ab 검사만을 한 경우에는 HBV 잠복기(window period)를 고려하여 검사 90일 후 기증자의 혈액검체를 확보하여 재검사하여야 하며, 재검사를 실시할 수 없는 뇌사 및 사후 기증자의 경우에는 반드시 HBV NAT 검사를 수행하여야 한다.

식품의약품안전처

Celivion Safety System

HBV-NAT TEST

Nucleic Acid Amplification Test for Type B Infection
(HBV: Hepatitis B virus, NAT: Nucleic acid amplification test)

Regulations on tissue bank permission and human tissue safety management, etc

Article 13(2) Blood test items and criteria for judgment

"Test No. 2 may be performed by selecting either the HBc Ab test or the HBV NAT (Nucleic Acid Test). However, if only the HBc Ab test is conducted without the NAT, a follow-up test must be performed by securing the donor's blood sample 90 days later, accounting for the HBV window period. In cases of brain-dead or deceased donors where a follow-up test is not possible, the HBV NAT must be performed mandatory."

Safety

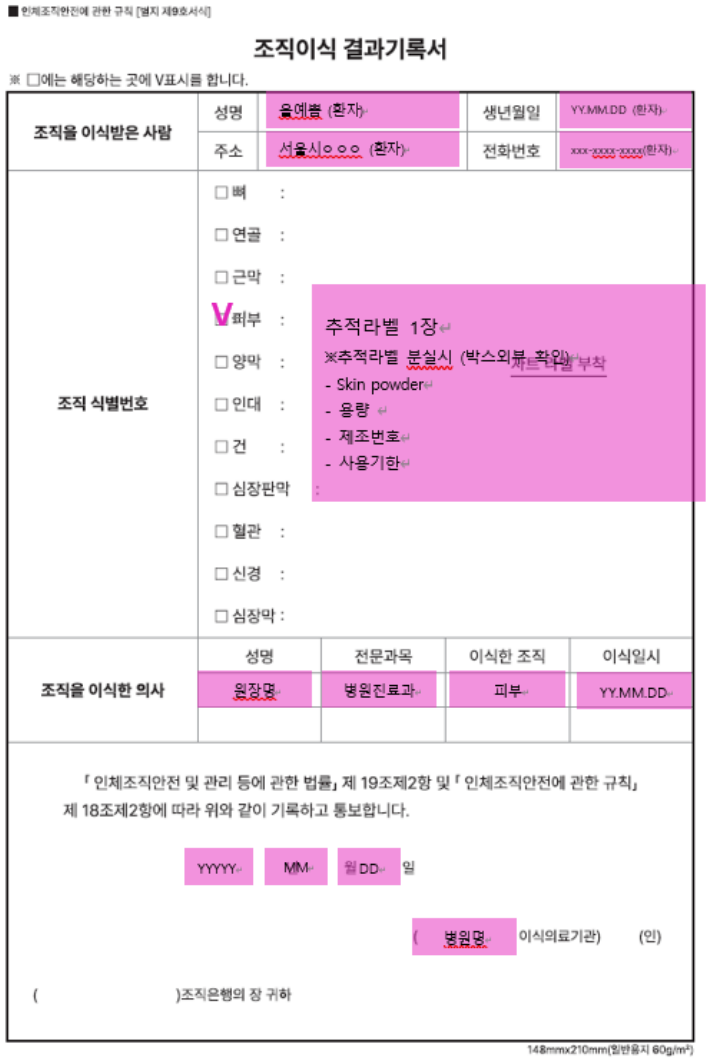
CELVION

Related articles

No.	Title	Content	Sources
1	Acellular Dermal Matrix Augmentation Significantly Increases Ultimate Load to Failure of Pectoralis Major Tendon Repair: A Biomechanical Study(2020)	**A. partial thickness RCT - ADM vs atelocollagen injection Comparison** Biomechanical studies have found that ADM is used as a reinforcement during thoracic tendon rupture surgery to increase the maximum rupture load at the surgical site by about 57%, suggesting that ADM can improve the strength and stability of tendon reconstruction surgery.	https://pubmed.ncbi.nlm.nih.gov/31859037/
2	USE of Injectable Acellular Dermal Matrix Combined with Negative Pressure Wound Therapy in Open Diabetic Foot Amputation(2022)	**A. Full-thickness RCT - ADM 1ml vs atelocollagen 1ml (3%) injection comparison** Injective ADM and negative pressure wound treatment were applied in combination to patients who underwent amputation for diabetic foot ulcers, and as a result, the wound healing period was shortened, the need for skin transplantation was reduced, and the number of dressing replacements was reduced compared to the NPWT alone.	https://pubmed.ncbi.nlm.nih.gov/35404696/
3	Successful Treatment of a Large Coccygeal Pressure Ulcer Using Injectable Acellular Dermal Matrix(2021)	**A. Large rotator cuff tear repairs injection ADM matrix (sheet type, GraftJacket product)** We successfully treated a large osteoclastic compression ulcer using injectable ADM and confirmed that the re-epithelialization of the wound was almost complete.	https://www.jwmr.org/journal/view.php?doi=10.22467/jwmr.2021.01683
4	Early Experience on Injectable Micronized Putty Type Human-Derived Acellular Dermal Matrix for Diabetic Foot Wounds(2024)	**A. Lateral epicondylitis (tennis elbow) chronic tendinosis injection leukocyte-rich + PRP (LRPRP) usage case report** Allogeneic decellular dermis is processed into fine powder and applied to diabetic footwound as an injection type. Single-step treatment, minimal pain, rapid granulation tissue formation and re-epithelialization effect were confirmed.	https://pubmed.ncbi.nlm.nih.gov/39800362/
5	Injection of an allodermal matrix and leukocyte-rich platelet-rich plasma mixture improved the tendon integrity in cases of full-thickness common extensor tendon tears of the elbow(2024)	**A. Use ADM + (MSC + PRP) in a baseball player's ulnar collateral ligament (UCL) surgery** Two patients with complete layer common extensor tendon rupture were treated with a mixture of injectable allogeneic decellular dermis (ADM) and leukocyte-rich platelet-rich plasma (LR-PRP). One year post-treatment follow-up revealed improved structural integrity of the proposal on MRI and ultrasound examination as well as decreased pain and improved function. It is a new non-surgical treatment that goes beyond simple pain relief to tissue reconstruction.	https://pubmed.ncbi.nlm.nih.gov/39705487/
6	Evaluation of Paste-Type Micronized Acellular Dermal Matrix for Soft Tissue Augmentation(2022)	**A. 18 cadaveric study** **B. Pectoralis Major Tendon Repair , load test** It was manufactured in gel form and treated like an injectable filler in the face and subcutaneous fat-deficient areas, and applied to the soft tissue depressions, scars or depressions of the face and body. After the procedure, the volume improvement was confirmed, and the duration was relatively recorded, and it was confirmed that it was stably absorbed into the tissue without any immune response or side effects.	https://pubmed.ncbi.nlm.nih.gov/36042026/

Human Tissue Management Guide

CELVION



■ 인체조직안전에 관한 규칙 [별지 제9호서식]

조직이식 결과기록서

※ □에는 해당하는 곳에 V표시를 합니다.

조직을 이식받은 사람	성명	윤예빛 (환자)	생년월일	YY.MM.DD (환자)
	주소	서울시ㅇㅇㅇ (환자)	전화번호	xxx-xxxx-xxxx(환자)
조직 식별번호	□뼈 : □연골 : □근막 : V피부 : □양막 : □인대 : □건 : □심장판막 : □혈관 : □신경 : □심장막 :	추적라벨 1장 ※추적라벨 분실시 (박스외부 확인) - Skin powder - 용량 - 제조번호 - 사용기한		
조직을 이식한 의사	성명	전문과목	이식한 조직	이식일시
	원장명	병원진료과	피부	YY.MM.DD

「인체조직안전 및 관리 등에 관한 법률」 제 19조제2항 및 「인체조직안전에 관한 규칙」 제 18조제2항에 따라 위와 같이 기록하고 통보합니다.

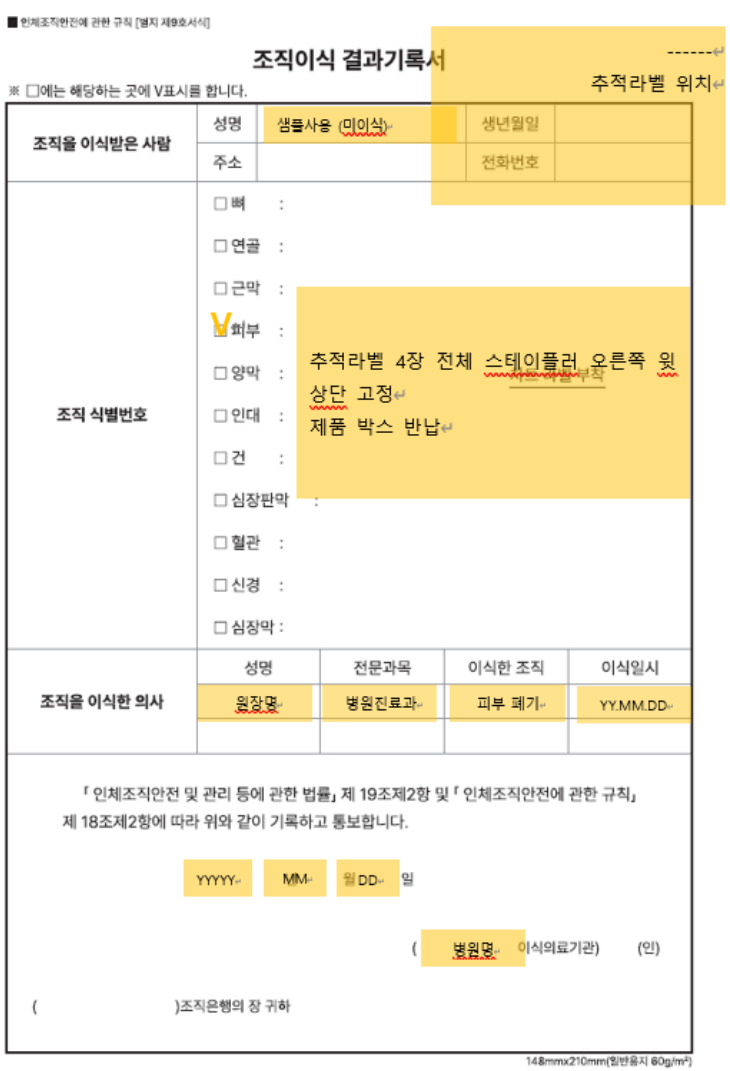
YYYY 년 MM 월 DD 일

(병원명 이식의료기관) (인)

( )조직은행의 장 귀하

148mmx210mm(일반용지 60g/m²)

At the time of patient transplantation



■ 인체조직안전에 관한 규칙 [별지 제9호서식]

조직이식 결과기록서

추적라벨 위치

※ □에는 해당하는 곳에 V표시를 합니다.

조직을 이식받은 사람	성명	샘플사용 (미이식)	생년월일	
	주소		전화번호	
조직 식별번호	□뼈 : □연골 : □근막 : V피부 : □양막 : □인대 : □건 : □심장판막 : □혈관 : □신경 : □심장막 :	추적라벨 4장 전체 스테이플러 오른쪽 윗 상단 고정 제품 박스 반납		
조직을 이식한 의사	성명	전문과목	이식한 조직	이식일시
	원장명	병원진료과	피부 폐기	YY.MM.DD

「인체조직안전 및 관리 등에 관한 법률」 제 19조제2항 및 「인체조직안전에 관한 규칙」 제 18조제2항에 따라 위와 같이 기록하고 통보합니다.

YYYY 년 MM 월 DD 일

(병원명 이식의료기관) (인)

( )조직은행의 장 귀하

148mmx210mm(일반용지 60g/m²)

When dispose product (without using)

1. **Name, date of birth, address, and contact information of the patient who received the tissue.**
2. **Accurately state the information on the tissue used for transplantation (remove one chart label attached to this implant package and attach it to the identification number column of the tissue transplant result record).**
3. **Name, medical department, transplanted tissue, and date and time of transplantation of the transplanted doctor.**
4. **Statement of the report date, the seal of the transplant medical institution and the signature of the doctor.**

* In accordance with the Human Tissue Act, the contents of the tissue transplant must be recorded and the "Tissue Transplantation Results Record" must be submitted within **one month from the date of transplantation**.

1. What kind of product is Celivion?

Human-derived cell-free allogeneic dermis (hADM) is processed into a uniform size and ratio of ultrafine particles,
It is an **allogeneic dermis** processed into a hydrated/non-hydrated formulation.

2. What is the Accellular Dermal Matrix (hADM), and what is the difference between collagen?

hADM removes only cells from the human dermis and preserves **collagen** and **extracellular matrix (ECM),**
It has excellent vascularization, cell infiltration, and mechanical strength, making it suitable for long-term tissue regeneration.
Collagen is a **single-component protein biomaterial** that functions as structural support and persistence that can be supplemented.

3. Are allogeneic dermal products safe for medical use?

Celivion manufacturers are processing high-quality and safe human tissue products with official approval from the Ministry of Food and Drug Safety as a human tissue bank.
Celivion also added **HBV-NAT tests to the 9 Serological Tests** stipulated in the Human Tissue Act
We are strengthening the safety evaluation of the product by conducting a total of 10 inspections.

**Article 13 of the Human Tissue Act: Regulations on Tissue Bank Permission and Human Tissue Safety Management, **HBV-NAT Test: Hepatitis B virus DNA detection test in blood

4. Compared to competitors L and M's products, what are the technical advantages?

Celivion is a product that applies tissue suitability research technology based on ECM and collagen components, and the manufacturing and processing process has its own technical difference called the **"Allo-PELT method"**. The difference in this processing method greatly affects the content of the product and the securing of high purity.

**The Allo-PELT method is a step-by-step low-temperature circulation system-based decellular processing technology developed to preserve components such as ECM and collagen in the homogeneous dermis as much as possible with the Preserved ECM at Low Temperature Processing.

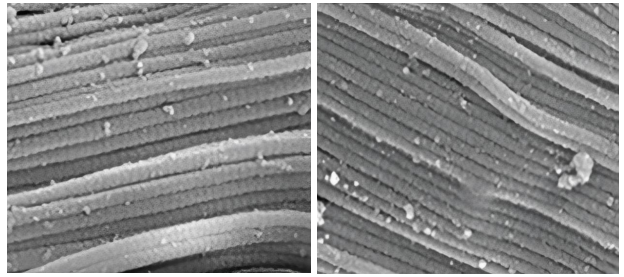
The Allo-PELT method does not use acetic acid, an acidic substance, or pepsin, a proteolytic enzyme, and is designed to maintain and preserve components such as ECM, collagen, and elastin as much as possible in a healthy state without damage. (We would like to inform you that the details of the process are not disclosed to protect our own technology.)

5. Why is 'low temperature' important in human tissue and biomaterial processing?

ECM is a key three-dimensional structure that determines tissue shape, strength, and regeneration with extracellular substrates, and is the basic framework of biological tissues composed of collagen, elastin, and glycoproteins. The preservation of healthy and pure ECM and collagen is a key factor in determining the performance of biomaterials.

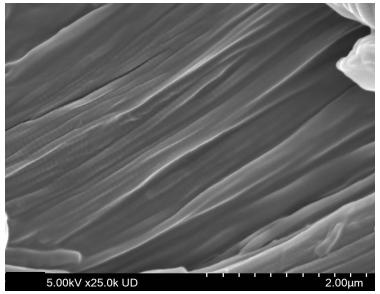
In particular, the low-temperature processing method is advantageous for preserving these key ingredients and maintaining high purity, making it more effective in regenerating the skin and maintaining elasticity..

Competitor A



Observation of ECM-specific matrix structure and shape maintenance after processing

Celivion



X 25000

Main Purpose of PELT Construction : Maximum Preservation of ECM

6. What is the meaning and significance of 'DNA figures'?

By measuring the total amount of chromosomal DNA in the cell's nucleus, **it is a measure of how well the decellularization process of human tissue has been processed.**

** DNA numerical value ▲ Decellularization process progresses well, resulting in excellent tissue regeneration and biocompatibility ▼ High purity, stability, and biocompatibility of products

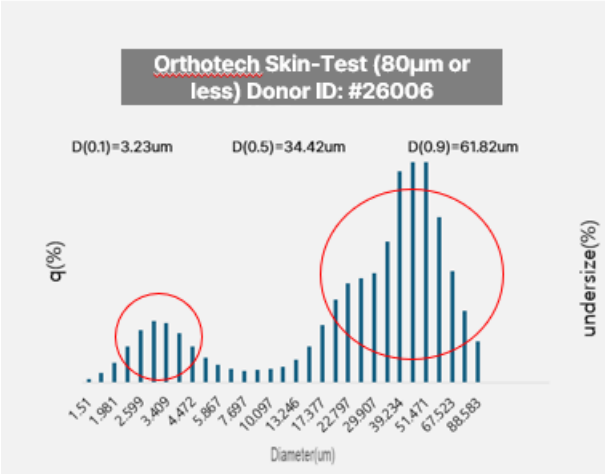
Generally, the safety threshold after processing human tissue products is 50 ng/mg and the level of celivion is 40 ng/mg, which minimizes inflammatory and immune responses. ** Approximately 1,500 DNA units of 10ng cells.



7. ' Why is 'particle size' important?

The more uniform and finer the particle size, the more naturally it is distributed and fused within the tissue, affecting post-transplant regeneration efficiency and retention.

Celivion has the highest proportion of particles with a size of avg. **33.92** μm, and its uniformity is high, **so there is little agglomeration and precipitation even when mixed with other components.**



8. Please tell me about the collagen composition.

Collagen exists in a variety of ways, from Type I to Type IV. Type I collagen is the most common component of the dermis,

It is most suitable for skin regeneration and dermal reconstruction because it has strength, support, and cell affinity. Collagen is very vulnerable to thermal degeneration,

The allo-PELT method, a low-temperature process, contains a large amount of **healthy and pure Type I collagen, and Type III is also properly mixed to form a more robust scaffold.**

9. Is it possible to mix and use it in parallel with other ingredients?

When mixed with crosslinked HA, **immediate synergy effects** such as volume, water supply, and anti-aging can be expected. (HA, PN, PLLA, NaCl, etc.)

10. What are the reasons for using allogeneic collagen and the adverse reactions after the procedure?

Allogeneic collagen has the advantage of low risk of developing an immune response, promoting auto-collagen production, and naturally absorbing it.

After the procedure, common injection reactions such as temporary swelling, flushing, and bruising may occur.

11. What kind of procedure or area do you usually apply it to?

For cosmetic purposes, it is effectively used in a variety of ways, including skin boosters, wrinkle improvements, and filler replacements.

ex) nasolabial folds / creases around the eyes / acne scars / forehead wrinkles / neck wrinkles / back of hand wrinkles / nose volume, etc

