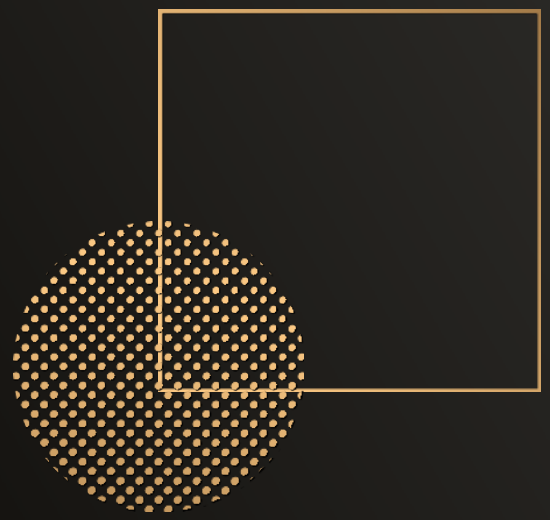
Exosomes

South Beach Symposium
Miami Beach, FL

February 6 - 8, 2024

Presented by Michael H. Gold, MD
Gold Skin Care Center
Tennessee Clinical Research Center
Nashville, TN 37215

Academic Appointments



01. Assistant Clinical Professor

- Department of Medicine, Division of Dermatology, Nashville, TN USA
- Vanderbilt University School of Medicine: 2006-2014
- Vanderbilt University School of Nursing: 2006-2020

02. Adjunct Assistant Professor

- Meharry Medical College: 2013 – Present
- School of Medicine, Nashville, TN

03. Visiting Professor of Dermatology

- Huashan Hospital, Fudan University (Shanghai Medical University), Shanghai, China
- The First Hospital of China Medical University, Shenyang, China:
- Guangdong Provincial People's Hospital, Guangzhou, Zhejiang

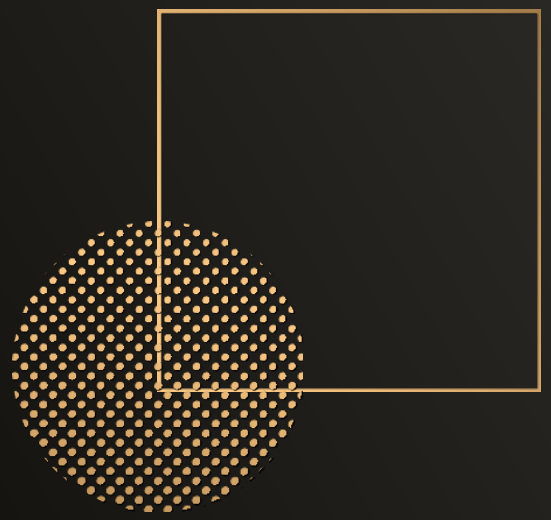
04. Visiting Professor of Plastic Surgery

- First People's Hospital of Foshan University, Guangdong, China
- The First Affiliated Hospital of Zhejiang University, Hangzhou, Zhejiang
- Rongjun Hospital, Jiaxing, China
- The People's Hospital of Hunan Province, Changsha, China

05.

- Editor-in-Chief – Journal of Cosmetic Dermatology – Wiley: 2016-Present
- Editor-in-Chief- Dermatological Reviews – Wiley: 2019 - Present

Conflict of Interest



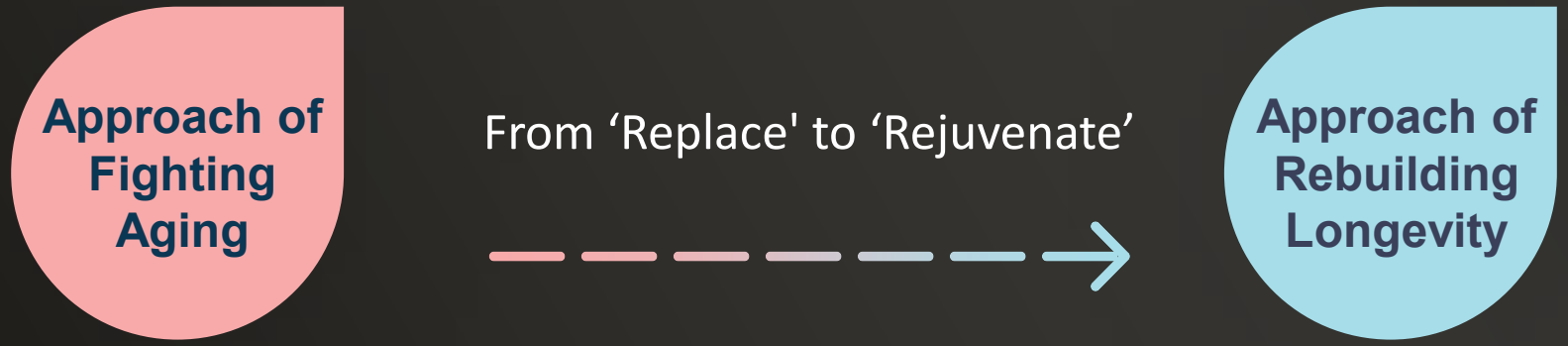
01. Consultant to many pharmaceutical, cosmeceutical, laser and energy-based device companies

02. Consultant, performs research and speaks on behalf of numerous pharmaceutical and medical device companies

03. For the benefit of this presentation, consultant, Investigator, Speaker for almost every company in this space

Topical Exosome Cosmeceuticals

Evolution in Regenerative Aesthetics



Slide Courtesy of Saranya Wyles, MD, PhD

MAYO CLINIC DEFINITION

Regenerative Medicine – (n.)

a branch of medicine that uses native and bioengineered cells, assistive devices, and engineering platforms to develop new treatments to heal tissues and organs **to restore form and function** lost to aging, disease, or damage

Slide Courtesy of Saranya Wyles, MD, PhD

Regenerative Skincare Technologies Derived From Human Fibroblasts: Growth Factors and Exosomes for Transformative Outcomes
Dermatol Surg. 2024 Nov 1;50(11S):S139-S144

Regenerative Skincare Technologies Derived From Human Fibroblasts: Growth Factors and Exosomes for Transformative Outcomes

Tsing Cheng, PhD,* Gail K. Naughton, PhD,† Elizabeth T. Makino, BS, CCRA, MBA,* Kuniko Kadoya, PhD,* and Prithwiraj Maitra, PhD*

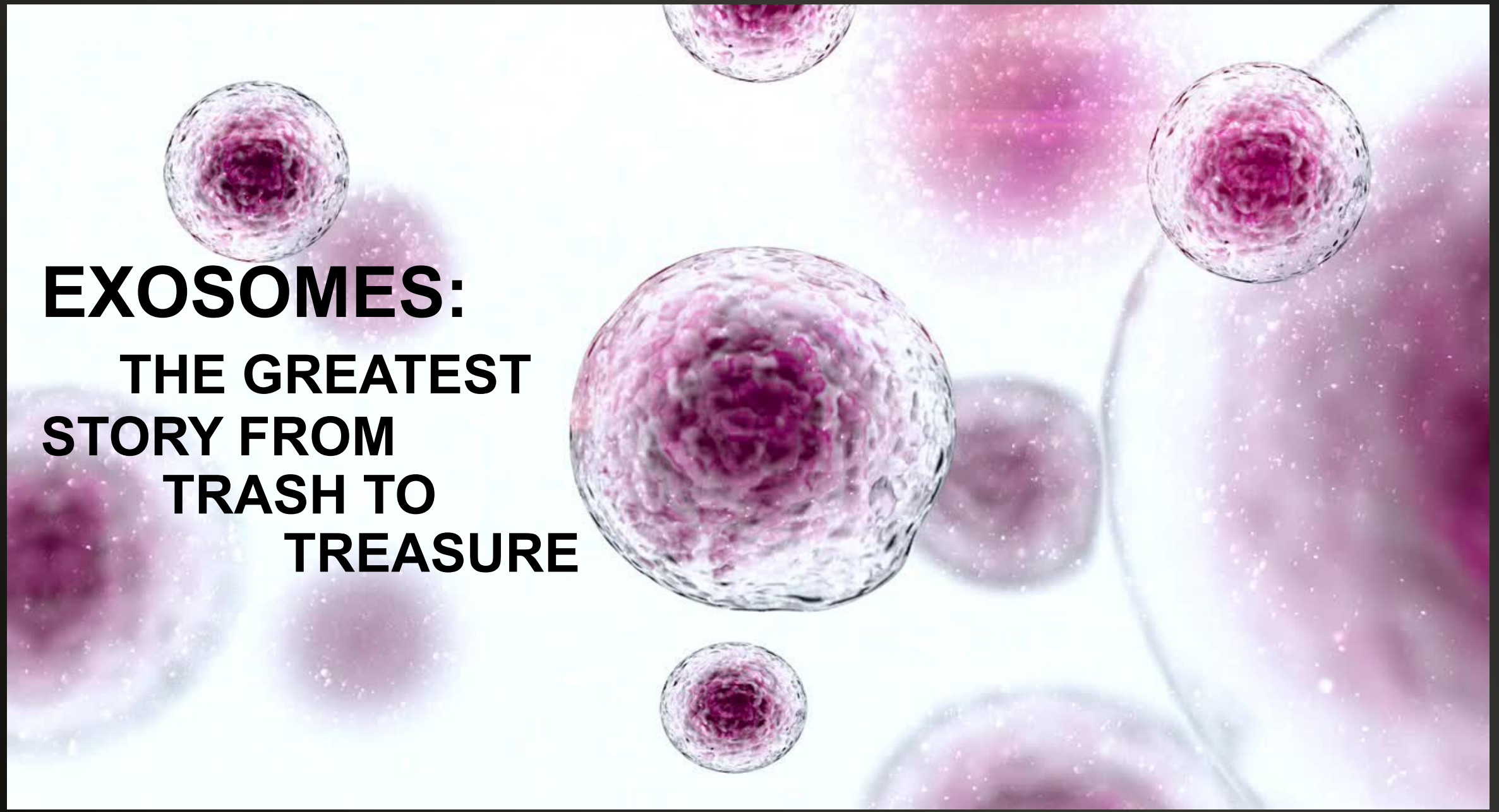
BACKGROUND Since the early 2000s, human fibroblast conditioned media (HFCM) has been used in topical growth factor skincare to support skin regeneration and skin rejuvenation. Human fibroblast conditioned media contains the fibroblast secretome including growth factors as well as exosomes. The potential benefits of topically applied exosomes are gaining interest in the medical aesthetic field.

OBJECTIVE This article aims to summarize the preclinical and clinical data available on regenerative HFCM-based topical skincare with a focus on studies investigating products applied to improve overall facial skin rejuvenation and/or after in-office cosmetic procedures. In addition, available data on fibroblast-derived exosomes will be covered.

METHODS A focused literature review was conducted to provide an overview of evidence on HFCM-based topical skincare.

RESULTS Human fibroblast conditioned media–based skincare significantly reduces signs of skin aging including photodamage, coarse lines and wrinkles, and sagging. After in-office cosmetic procedures, HFCM-based skincare can stimulate skin recovery and reduce downtime as well as provide skin quality benefits to enhance overall treatment outcomes. Application of purified exosomes from HFCM also demonstrated significant improvements in multiple skin aging parameters.

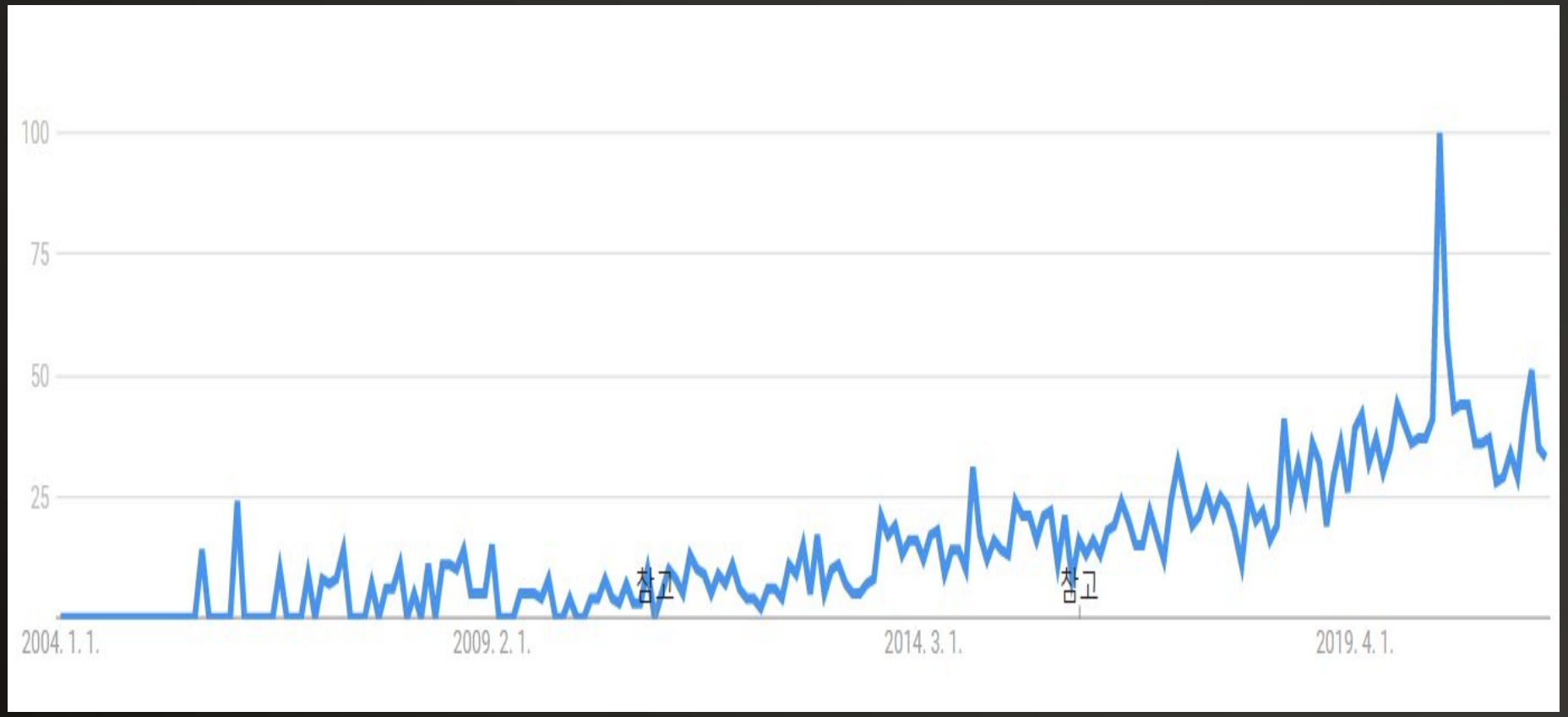
CONCLUSION Human fibroblast conditioned media combines naturally secreted fibroblast-derived growth factors and exosomes that stimulate skin regeneration and rejuvenation as evidenced by a variety of assays and assessments including in vitro preclinical studies, clinical investigator grading, instrumentation measurements, biopsy analyses, and patient-reported outcomes.



Slide Courtesy of Saranya Wyles, MD, PhD

Google Trend on Exosomes

Interest over Time on Google Trends: 10X increase for last 10 years



Source: Google Trends, https://bioinformant.com/exosomes/

Exosomes: Bigger than Botox (www.Elle.com)

Beauty > Makeup & Skincare 2023

Bigger Than Botox: The Newest Beauty Game Changer

Exosome therapy has dermatologists and plastic surgeons rethinking the future of aesthetics.

BY KATHLEEN HOU PUBLISHED: OCT 3, 2023

Botulinum toxin: 25,626 results
Exosome: 31,533 results

Many dermatologists have heard of exosome therapy from conferences and studies — and like many skin innovations, it's been available in South Korea for a few years. Young Woo Ro, MD, founder of the renowned Oracle dermatology clinic in Seoul, tells me he first heard of it in aesthetics about five years ago. In South Korea, exosomes are a common add-on to Fraxel or microneedling, where the microchannels help them get into deeper layers of the skin. Exosome skin boosters are another popular treatment, containing a cocktail of ingredients like hyaluronic acid, amino acids, collagen peptides, and glutathione, for additional "brightening, firming effects," says David Kim, MD, of Idriss Dermatology in New York City. He tells me that ASCE+ is a popular exosome product; the subtype SRLV is for skin and HRLV is for hair, and both contain exosomes derived from roses.

Source: https://www.elle.com/beauty/makeup-skin-care/a45324690/what-are-exosomes/

Exosomes in the World

LASER SKIN MEDICA

allure

Exosome Therapy Is Dermatologists' New Favorite Skin-Rejuvenation Treatment

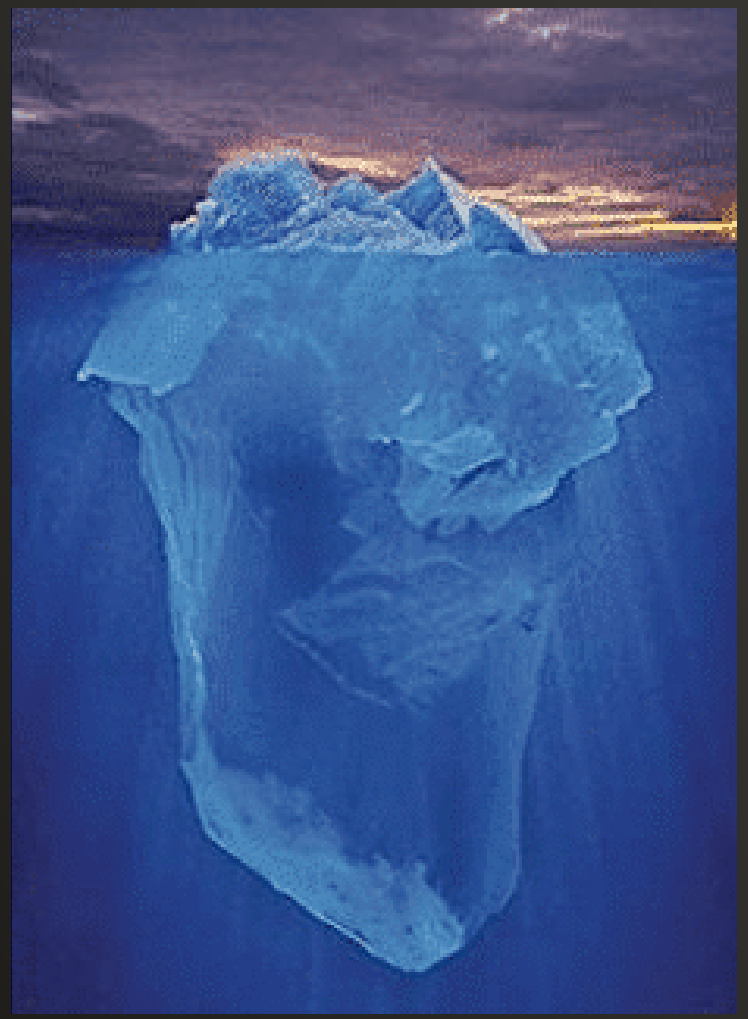
This popular K-beauty treatment is finding stateside success for its impressive calming, soothing, and brightening benefits.

What are exosomes?

Exosomes are nanoparticles released by nearly all cells in the human body, and skin cells have their very own kind of exosomes. They contain various lipids, proteins, amino acids, peptides, growth factors, and genetic material.

"They work by communicating and transmitting signals between cells," board-certified dermatologist Ramya Garlapati, MD, tells *Allure*. "You can think of them as messengers sending signals to unhealthy cells, triggering them to regenerate." In other words, exosomes prompt the body's natural healing process, says Eunice Park, MD, dual board-certified facial plastic and reconstructive surgeon in Syosset, New York.

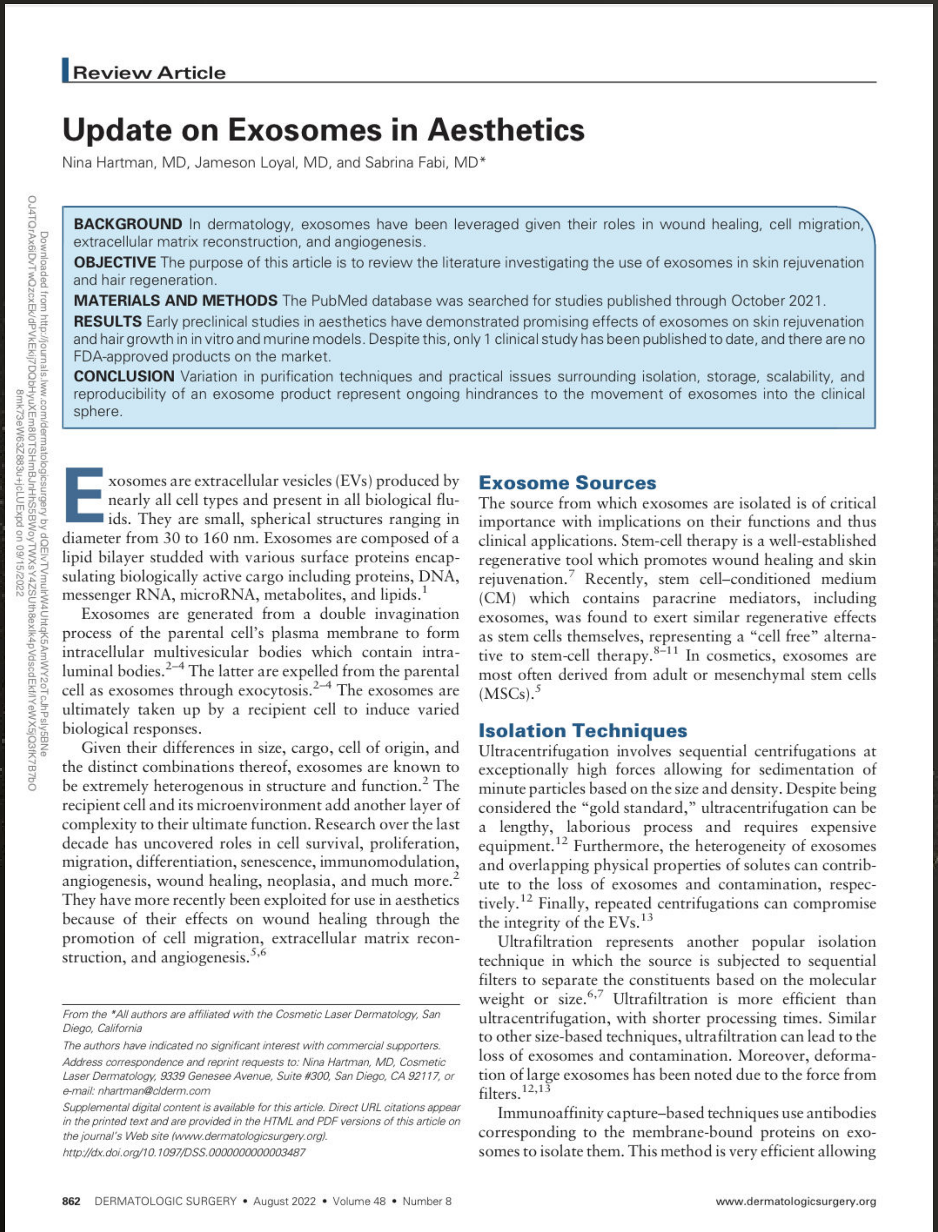
When used as an in-office skin-care treatment, exosomes are extracted from human stem cells and frozen to keep them as stable as possible, Dr. Peredo says. However, unlike actual stem cells, exosomes don't have a nucleus. They're just mRNA (similar to the COVID vaccine), so there's no possibility of an adverse graft-versus-host reaction, she adds.



What we know about Exosomes

And What is yet to be discovered

Photo Courtesy of Glynis Ablon, MD



Review Article

Update on Exosomes in Aesthetics

Nina Hartman, MD, Jameson Loyal, MD, and Sabrina Fabi, MD*

BACKGROUND In dermatology, exosomes have been leveraged given their roles in wound healing, cell migration, extracellular matrix reconstruction, and angiogenesis.

OBJECTIVE The purpose of this article is to review the literature investigating the use of exosomes in skin rejuvenation and hair regeneration.

MATERIALS AND METHODS The PubMed database was searched for studies published through October 2021.

RESULTS Early preclinical studies in aesthetics have demonstrated promising effects of exosomes on skin rejuvenation and hair growth in in vitro and murine models. Despite this, only 1 clinical study has been published to date, and there are no FDA-approved products on the market.

CONCLUSION Variation in purification techniques and practical issues surrounding isolation, storage, scalability, and reproducibility of an exosome product represent ongoing hindrances to the movement of exosomes into the clinical sphere.

Exosomes are extracellular vesicles (EVs) produced by nearly all cell types and present in all biological fluids. They are small, spherical structures ranging in diameter from 30 to 160 nm. Exosomes are composed of a lipid bilayer studded with various surface proteins encapsulating biologically active cargo including proteins, DNA, messenger RNA, microRNA, metabolites, and lipids.[1]

Exosomes are generated from a double invagination process of the parental cell's plasma membrane to form intracellular multivesicular bodies which contain intraluminal bodies.[2–4] The latter are expelled from the parental cell as exosomes through exocytosis.[2–4] The exosomes are ultimately taken up by a recipient cell to induce varied biological responses.

Given their differences in size, cargo, cell of origin, and the distinct combinations thereof, exosomes are known to be extremely heterogenous in structure and function.[2] The recipient cell and its microenvironment add another layer of complexity to their ultimate function. Research over the last decade has uncovered roles in cell survival, proliferation, migration, differentiation, senescence, immunomodulation, angiogenesis, wound healing, neoplasia, and much more.[2] They have more recently been exploited for use in aesthetics because of their effects on wound healing through the promotion of cell migration, extracellular matrix reconstruction, and angiogenesis.[5,6]

From the *All authors are affiliated with the Cosmetic Laser Dermatology, San Diego, California

The authors have indicated no significant interest with commercial supporters.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.dermatologicsurgery.org).

http://dx.doi.org/10.1097/DSS.0000000000003487

Exosome Sources

The source from which exosomes are isolated is of critical importance with implications on their functions and thus clinical applications. Stem-cell therapy is a well-established regenerative tool which promotes wound healing and skin rejuvenation.[7] Recently, stem cell–conditioned medium (CM) which contains paracrine mediators, including exosomes, was found to exert similar regenerative effects as stem cells themselves, representing a "cell free" alternative to stem-cell therapy.[8–11] In cosmetics, exosomes are most often derived from adult or mesenchymal stem cells (MSCs).[5]

Isolation Techniques

Ultracentrifugation involves sequential centrifugations at exceptionally high forces allowing for sedimentation of minute particles based on the size and density. Despite being considered the "gold standard," ultracentrifugation can be a lengthy, laborious process and requires expensive equipment.[12] Furthermore, the heterogeneity of exosomes and overlapping physical properties of solutes can contribute to the loss of exosomes and contamination, respectively.[12] Finally, repeated centrifugations can compromise the integrity of the EVs.[13]

Ultrafiltration represents another popular isolation technique in which the source is subjected to sequential filters to separate the constituents based on the molecular weight or size.[6,7] Ultrafiltration is more efficient than ultracentrifugation, with shorter processing times. Similar to other size-based techniques, ultrafiltration can lead to the loss of exosomes and contamination. Moreover, deformation of large exosomes has been noted due to the force from filters.[12,13]

Immunoaffinity capture–based techniques use antibodies corresponding to the membrane-bound proteins on exosomes to isolate them. This method is very efficient allowing

Exosomes in Aesthetics: A Growing Trend

Clinical Applications:

- Skin Remodeling
- Hyperpigmentation
- Scarring
- Alopecia

"Mesenchymal stem cell–derived exosomes have been established as hypoimmunogenic"

Hartman N, Loyal J, Fabi S. Update on Exosomes in Aesthetics. *Dermatol Surg*. 2022;48(8):862-865. doi:10.1097/DSS.0000000000003487

Role of Exosomes in Skin Diseases
J Cosmet Dermatol. 2022;21:3219–3225

REVIEW ARTICLE

JCD Journal of Cosmetic Dermatology WILEY

Role of exosomes in skin diseases

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Abstract

Background: Exosomes, as a family member of extracellular vesicles, are cell-secreted nanoscale structures that play pivotal roles in regulating physiological and pathophysiological processes of the skin. Exosomes induce communication between cells and are responsible for transporting cellular components such as microRNAs, mRNAs, DNA, lipids, metabolites, and cell-surface proteins. Numerous preclinical and clinical trials searched the contribution of exosomes to skin functions and disorders. Thus, exosomes are gaining increasing attention within investigational dermatology. In advance, stem-cell-derived exosomes were integrated into the functional cosmetics industry nominated as cell-free regenerative medicine.

Objective: This review aims to demonstrate the roles of exosomes in inflammatory skin disorders, stem cell, and tumor biology through a comprehensive evaluation of the diagnostic, prognostic, and therapeutic perspectives.

Methods: A comprehensive literature search was performed using electronic online databases "PubMed" and "Google Scholar" using key words "exosomes", "skin", "wound healing".

Conclusion: Exosomes are regarded as promising diagnostic and prognostic biomarkers for various skin diseases. Future prospects are repurposing exosomes to treat skin disorders, either as drug carriers or drugs themselves.

KEYWORDS
cancer, exosome, extracellular vesicle, inflammatory skin diseases, stem cell

Systematic Review of Exosome Treatment in Hair Restoration: Preliminary Evidence, Safety, and Future Directions
J Cosmet Dermatol. 2023;22:2424–2433

REVIEW ARTICLE

JCD Journal of Cosmetic Dermatology WILEY

Systematic review of exosome treatment in hair restoration: Preliminary evidence, safety, and future directions

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Abstract

Background: Exosomes are small extracellular vesicles with potential roles in modulating the hair growth cycle and are an emerging therapy for patients with alopecia. In recent years, researchers have made significant progress in deciphering the network of cellular interactions and signaling pathways mediated by the transfer of exosomes. This has opened the door to a wide range of potential therapeutic applications with an increasing focus on its application in precision medicine.

Aim: To evaluate current published evidence, both preclinical and clinical, on the use of exosomes for hair restoration.

Methods: In January 2023, a systematic search was conducted using PubMed, Embase, and the Cochrane Library. Records were identified, screened, and assessed for eligibility as per the PRISMA guideline.

Results: We identified 16 studies (15 preclinical and 1 clinical) showing varying degrees of efficacy using exosomes derived from sources including adipose-derived stem cells (ADSCs) and dermal papilla cells (DPCs). Applications of exosomes isolated from ADSCs (ADSC-Exo) and DPCs have shown early promising results in preclinical studies corroborated by results obtained from different model systems. Topical ADSC-Exo has been tried successfully in 39 androgenetic alopecia patients demonstrating significant increases in hair density and thickness. No significant adverse reactions associated with exosome treatment have been reported thus far.

Conclusions: Although current clinical evidence supporting the use of exosome treatment is limited, there is a growing body of evidence suggesting its therapeutic potential. Further studies are warranted to define its mechanism of action, optimize its delivery and efficacy, and to address important safety concerns.

KEYWORDS
alopecia, exosomes, hair, regenerative medicine

A Comprehensive Review of the Medical and Cosmetic Applications of Exosomes in Dermatology
J Cosmetic Dermatol. 2024;00:1-5

A comprehensive review of the medical and cosmetic applications of exosomes in dermatology

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Abstract

Background: Exosomes are a subset of extracellular vesicles that are released by all cell types and are theorized to play a crucial role in intercellular communication. Ranging from 40 to 160 nm in diameter, exosomes contain a variety of genetic materials including DNA, RNA, mRNA, metabolites, proteins, and lipids depending on their cellular origin.

Aim: Given that intercellular communication is abetted by the exchange of cellular components via exosomes, their applied use can have important implications for disease pathology and exosome-based therapeutics. We provide a comprehensive review of the current application of exosomes in medical (and skin) diseases and in cutaneous medical aesthetics.

Methods: A literature search was conducted on PubMed reviewing exosomes and their application in medical and aesthetic fields.

Results: While the therapeutic use of exosomes in the treatment of medical and cosmetic dermatological procedures is promising, it is also important to note that most studies implementing exosomes as therapeutic agents have been conducted in preclinical models, thus highlighting the need for additional studies and clinical trials. One more important note in the aesthetic world associated with exosomes is that in the United States, at the time of this writing, exosomes may only be topically applied and not injected into the skin, as is done in many countries worldwide.

Conclusion: There is a need for additional studies and clinical trials to evaluate the safety and therapeutic effect and safety of exosomes in medical and aesthetic fields.

KEYWORDS
exosome, extracellular vesicles, immunity, intercellular communication

Exosomes in Cosmetic Dermatology: A Review of Benefits and Challenges. J Drugs Dermatol. 2025 Jan 1;24(1):12-18.

Exosomes in Cosmetic Dermatology: A Review of Benefits and Challenges

Diala Haykal, Saranya Wyles, Lilit Garibyan, Hugues Cartier, Michael Gold

PMID: 39761139 DOI: 10.36849/JDD.8872

Abstract

Background: Exosomes are small extracellular vesicles (30-150 nm in size) that play a critical role in cellular communication, transporting proteins, lipids, and nucleic acids between cells. This literature review focuses on evaluating the potential benefits and limitations of exosomes in enhancing skin health and aesthetics through indications such as skin rejuvenation, hair restoration, and pigmentation disorders.

Methods: A thorough literature search was conducted on PubMed using specific MeSH, including "exosomes," "aesthetics," "cosmetic dermatology," "skin rejuvenation," "hair growth," and "wrinkle reduction." The search was limited to free-access studies published in various countries within the last ten years (2014-2024). As a result, a total of 56 relevant references were identified and reviewed to support the discussion.

Results: There are currently no US Food and Drug Administration (FDA) approved exosomes. This review highlights exosomes' potential in skin rejuvenation through extracellular matrix production and matrix metalloproteinases (MMP) inhibition, as well as in hair restoration by stimulating follicle cell activity and modulating inflammation. Despite these benefits, challenges remain, including inconsistent isolation methods, source variability, and the need for clinical trials to confirm long-term safety and efficacy. The regulatory landscape is evolving, and further research is essential to meet standards before exosomes can be broadly adopted in cosmetic dermatology.

Conclusion: While exosomes hold significant potential for non-invasive cosmetic dermatology, there are challenges that need to be addressed, including the standardization of exosome isolation and characterization, the establishment of safety profiles, and the conduct of extensive clinical trials. J Drugs Dermatol. 2025;24(1):12-18. doi:10.36849/JDD.8872.

Topical Exosome Cosmeceuticals

- Exosomes, as a family member of extracellular vesicles, are cell-secreted nanoscale structures that play pivotal roles in regulating physiological processes in the skin
- Exosomes induce communication between cells and are responsible for transporting cellular components such as microRNAs, mRNAs, DNA, lipids, metabolites, and cell-surface proteins
- Numerous preclinical and clinical trials search the contribution of exosomes to skin functions and disorders

Exosomes: the latest in regenerative aesthetics

Krishna S Vyas[1], Joely Kaufman[2], Girish S Munavalli[3], Kiran Robertson[4], Atta Behfar[5] & Saranya P Wyles*,[6]

Regenerative Medicine

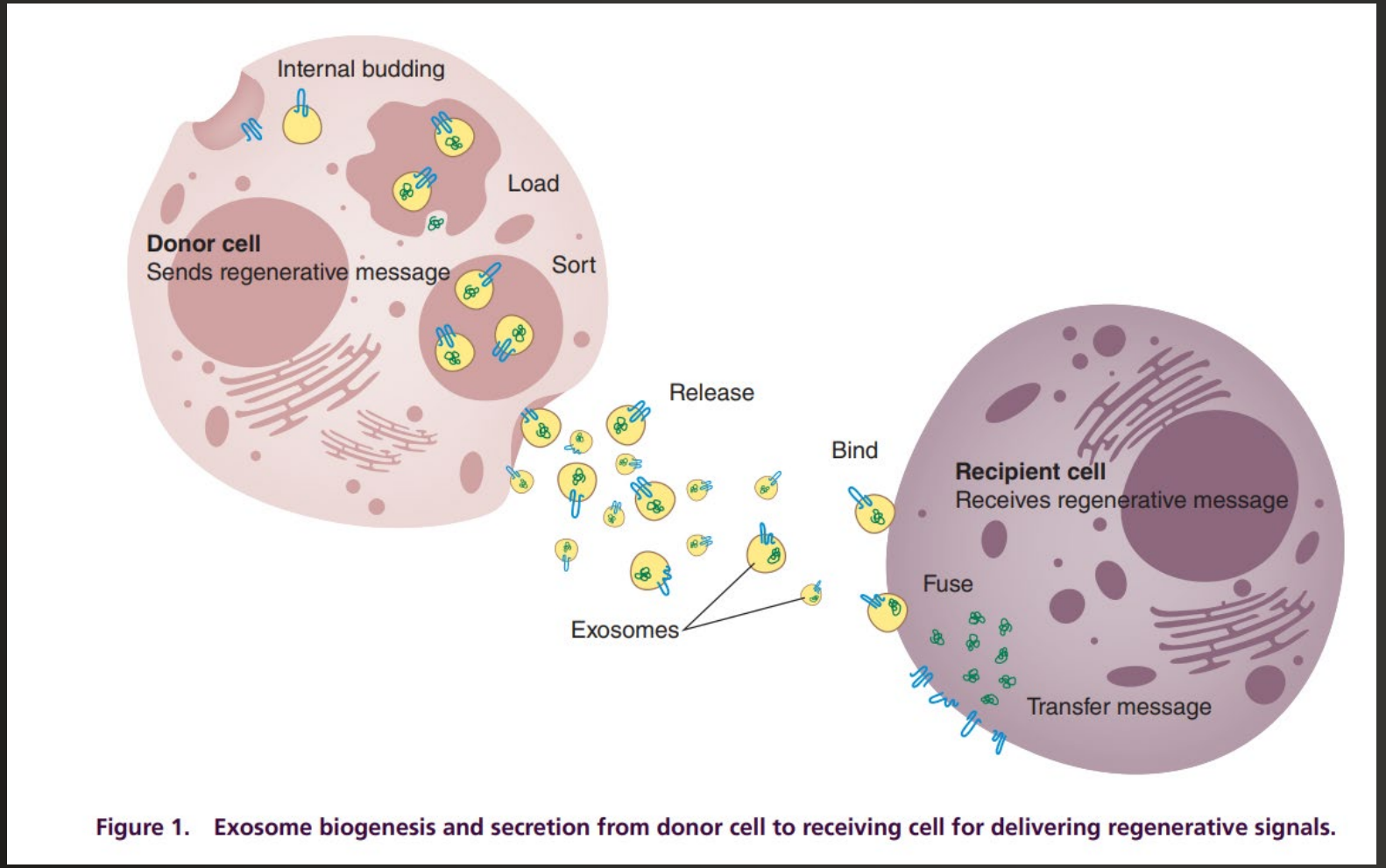


Figure 1. Exosome biogenesis and secretion from donor cell to receiving cell for delivering regenerative signals.

Slide Courtesy of Saranya Wyles, MD, PhD

Topical Exosome Cosmeceuticals

- Exosomes are gaining increasing attention within investigational dermatology
- In addition, stem-cell-derived exosomes are integrated into functional cosmeceuticals as cell-free regenerative medicine

Topical Exosome Cosmeceuticals

- Cellular communication is essential for the development and maintenance of the human body
- During the last decade, extracellular vesicles (EV) have emerged as a critical component of intercellular communication
- In addition to protein secretion into the extracellular space, all cells can interact with their neighboring counterparts by EVs
- EVs contain nucleic acid (DNA, mRNA, and miRNA) and specific repertoires of proteins and lipids, implicated as the “exosome cargo” revealing their “biological signatures”

Topical Exosome Cosmeceuticals

- EVs are classified into three groups regarding their size and formation
  - Exosomes: (30-150 nm)
  - Microvesicles (100-1000 nm)
  - Apoptotic bodies (>1000 nm)
- Microvesicles and apoptotic bodies are derived from the cellular membrane, whereas exosomes are generated at the endosomal membrane

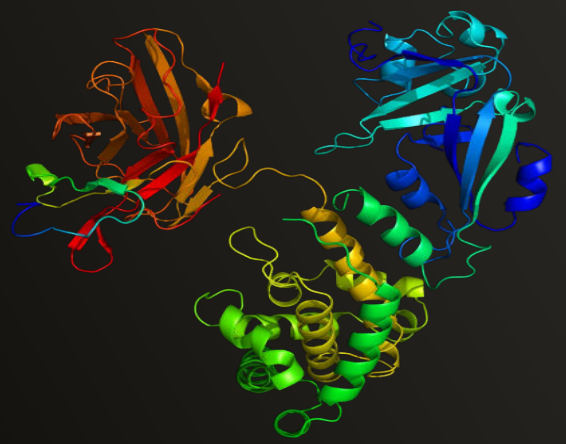
Components of Exosomes

• Micro RNA

• Stable protein bio-signals

• Manage inflammation and regeneration(enhance collagen and elastin synthesis)

• Used to enhance healing in aesthetic dermatological treatments



• Growth Factors

• Regulate gene expression

• Promote keratinocyte migration

• • Interact with messenger RNA

• • Re-epithelialization of skin in wound healing

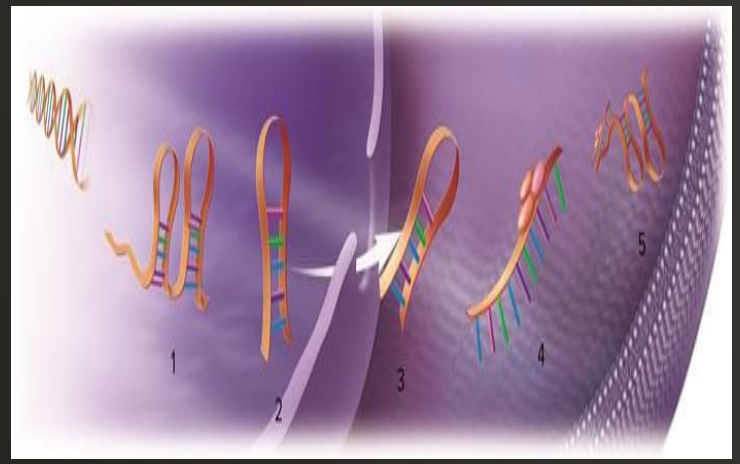


Photo Courtesy of Glynis Ablon, MD

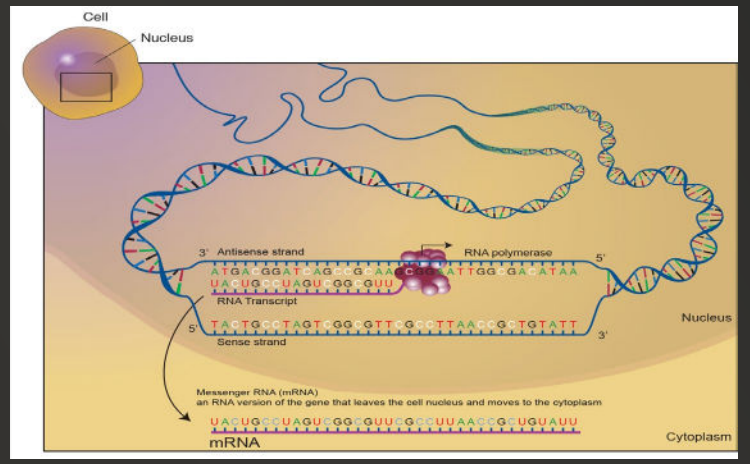
• Messenger RNA

• COVID Vaccine

• Cancer Research

• Key component of Exosomes

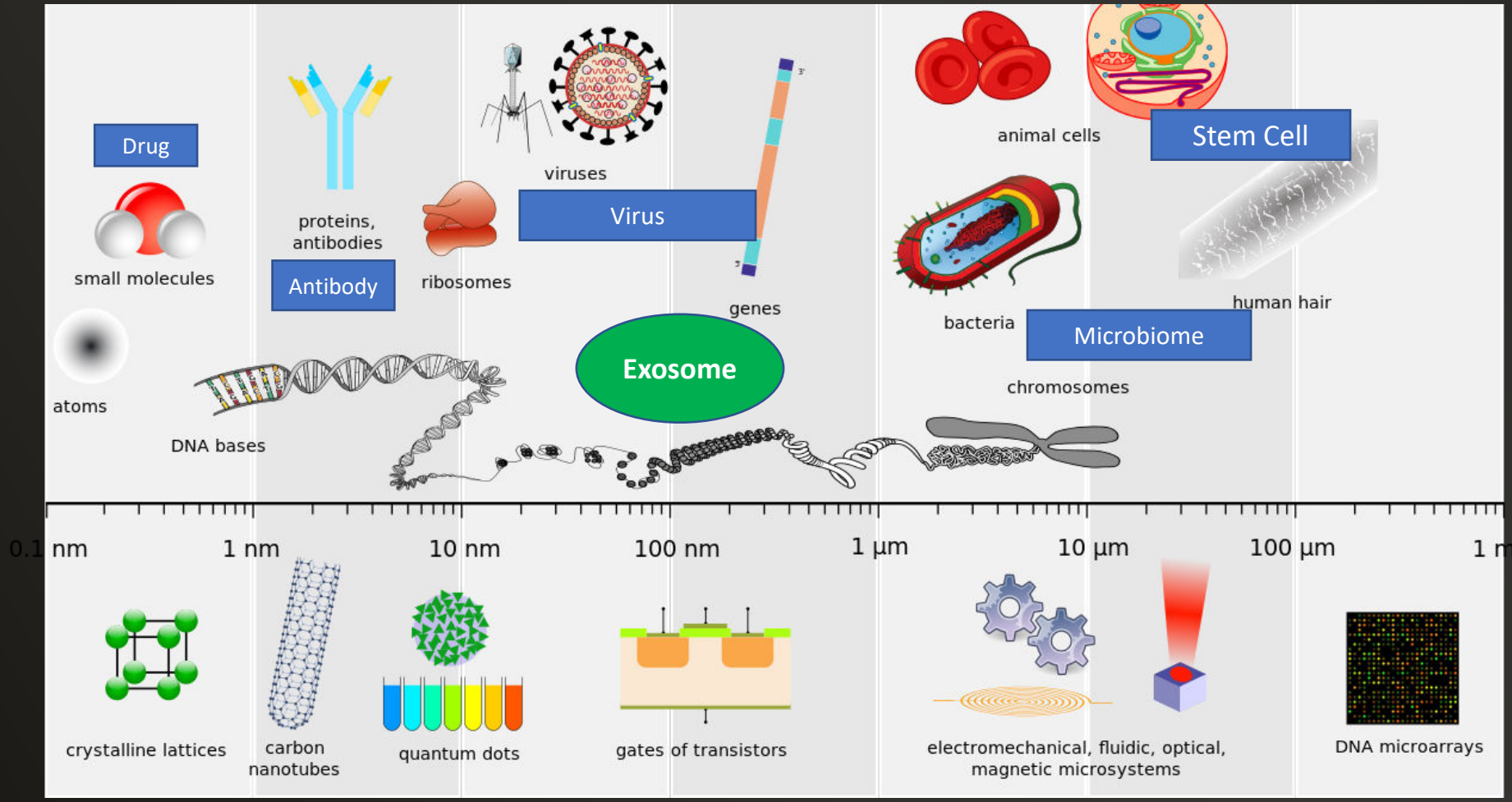
• Natural vs. Synthetic



Topical Exosome Cosmeceuticals

- EVs have been isolated in almost all body fluids, including blood, urine, saliva, breast milk, and are constitutively secreted
- Various resident skin cells and immune cells secrete exosomes
- Cellular stress or exposure to other cellular activation signals may alter the amount and secretion pattern of exosomes
- The same cell may produce various exosomes differing in their size and ingredient depending on the activation signal, including hypoxia, inflammatory signals, and expression of oncogenes
- The lipid bilayer of exosomes differs from the plasma membrane, making them resistant to degradation; improving their biologic activity

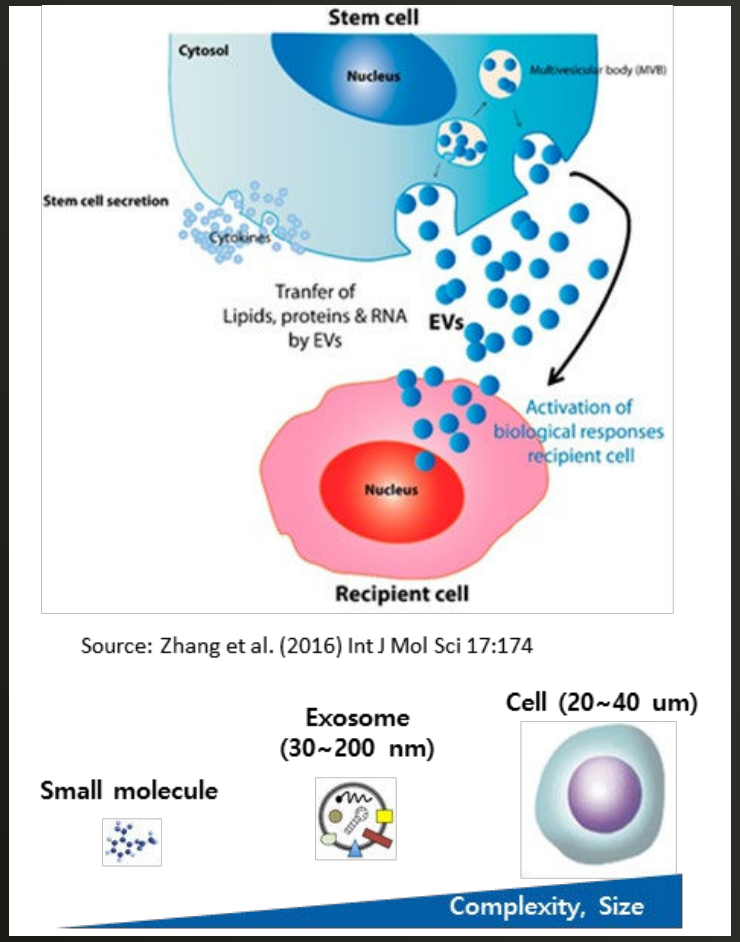
Exosome and Others

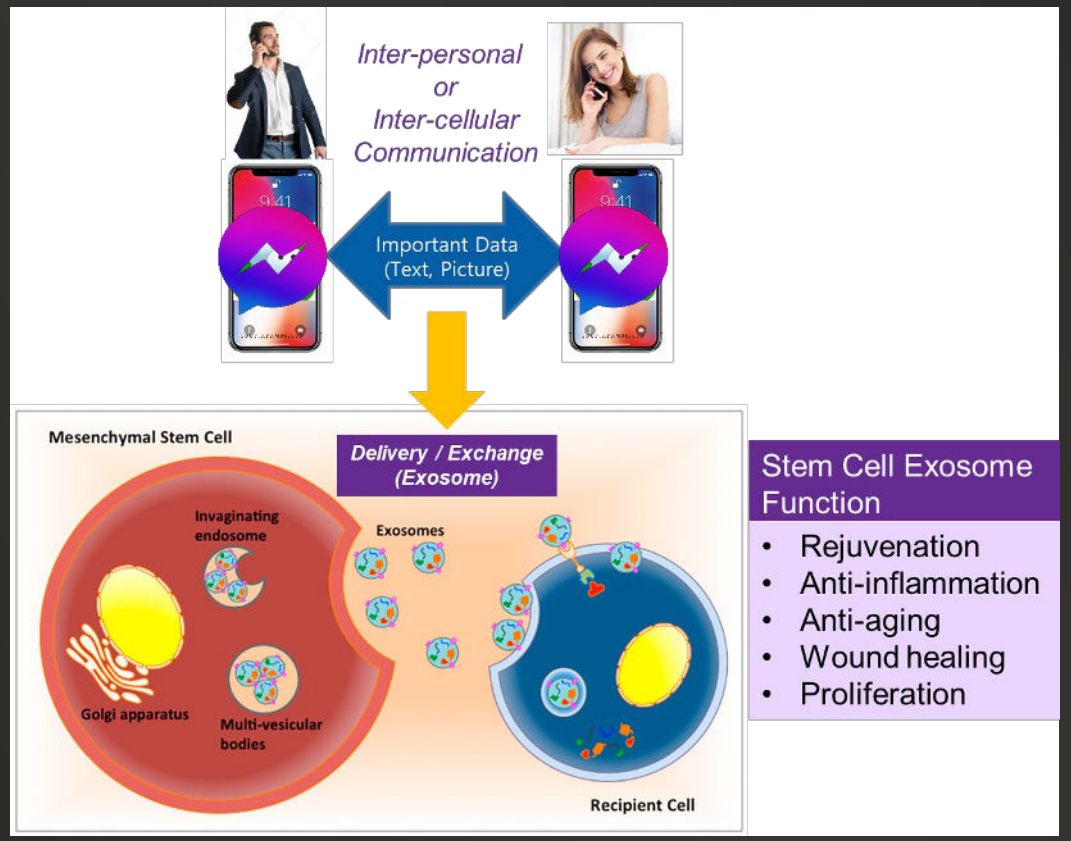


- **Exosomes are very new, in terms of 1) Size, 2) Complexity, 3) Research, 4) Production, & others.**

What are Exosomes?

- **The most important mechanism of cell-to-cell communication between our cells, delivering proteins, nucleic acids, and others.**
- **Avatar or ambassador of cells for "Cell-free Therapy"**





Topical Exosome Cosmeceuticals

- Exosomes attend essential roles in pathological and physiological conditions by manipulating cellular communication, eventually gene expression
- Two major translational insights explain the considerable attention they have gained:
  - First, the diagnostic and prognostic potential for biomonitoring purposes
  - Second, therapeutic repurposing, which is not readily available and appears on the horizon

Topical Exosome Cosmeceuticals

The US Food and Drug Administration (FDA) regulates regenerative medicine products. There continues to be broad marketing of unapproved products considered regenerative medicine therapies that are intended for the treatment or cure of a wide range of diseases or medical conditions. These products require FDA licensure/approval to be marketed to consumers. Before approval, these products require FDA oversight in a clinical trial. These unapproved products whether recovered from your own body or another person's body, include stem cells, stromal vascular fraction (fat-derived cells), umbilical cord blood and/or cord blood stem cells[1], amniotic fluid, Wharton's jelly, ortho-biologics, and exosomes. FDA has received reports of blindness, tumor formation, infections, and more, detailed below, due to the use of these unapproved products.

FDA U.S. FOOD & DRUG ADMINISTRATION

Public Safety Notification on Exosome Products

There are currently no FDA-approved exosome products. Certain clinics across the country, including some that manufacture or market violative "stem cell" products, are now also offering exosome products to patients. They deceive patients with unsubstantiated claims about the potential for these products to prevent, treat or cure various diseases or conditions. They may claim that they these products do not fall under the regulatory provisions for drugs and biological products – that is simply untrue. As a general matter, exosomes used to treat diseases and conditions in humans are regulated as drugs and biological products under the Public Health Service Act and the Federal Food Drug and Cosmetic Act and are subject to premarket review and approval requirements.

Slide Courtesy of Saranya Wyles, MD, PhD

Exosome Cell Sources

Umbilical Cord Mesenchymal Stem Cells-Exos	Adipose Derived Stem Cells-Exos	Bone Marrow Derived Stem Cell-Exos	Human Trophoblast-Exos	Plant derived Exos
• Skin rejuvenation • Human dermal fibroblast(HDF) migration and upregulation of collagen	•Cell proliferation and migration •Decrease ROS production and DNA damage	• Exosomes concentrate the natural function of a stem cell. • Regenerative for skin	• Superior regenerative capabilities • Prolif and migration of HDF • Increase collagen I and III, elastin • Decr MMP1,3	• Regenerative capacity • promote cellular growth with protective effects against inflammation, oxidation and stress. • Exosome like nano-vesicles

Photo Courtesy of Glynis Ablon, MD

5 THINGS YOU SHOULD ASK AN EXOSOME COMPANY

What is the cell of origin for your exosomes?

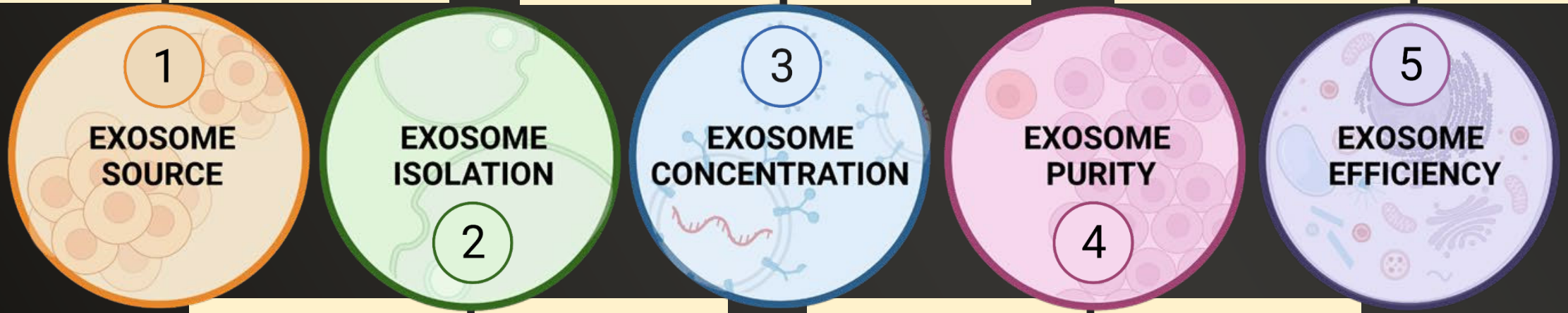
If cells, who are the donors and how are they screened?

How is the number of exosomes per vial determined?

What is the concentration?

What is the effect of exosomes with AND without combined device therapy?

How do their exosomes alone work (without device pairing)?



How are the exosomes manufactured or isolated from the cell source?

If high-speed spinning, how do they ensure that the structure is protected?

What is contained within the exosomes? How is the cargo validated?

Is the exosome quality and purity consistent from batch-to-batch?

Regulation of Exosomes as Biologic Medicines: Clin Transl Sci. 2024;17:e13904

Regulation of exosomes as biologic medicines: Regulatory challenges faced in exosome development and manufacturing processes

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Abstract

With advances in medical technology, extracellular vesicles, also known as exosomes, are gaining widespread attention because of their potential therapeutic applications. However, their regulatory landscape is complex and varies across countries because of their unique intracellular mechanisms of action. The diversity of manufacturing techniques renders their standardization challenging, leading to a fragmented regulatory landscape. The current global regulatory framework of exosomes can be broadly classified into two strategies: one involves elucidating constituent components within exosomes and the other involves examining the physiological repercussions of their secretion. When using exosomes as therapeutic agents, they should be governed similarly to biological medicinal products. Similar to biologics, exosomes have been analyzed to determine their particle size and protein composition. An exosome-based therapeutic agent should be clinically approved after understanding its molecular composition and structure and demonstrating its pharmacokinetics and therapeutic efficacy. However, demonstrating the pharmacokinetics and therapeutic efficacy of exosomes is challenging for regulatory agencies. This article reviews the technical characteristics of exosomes, analyzes the trends in regulatory laws in various countries, and discusses the chemistry, manufacturing, and control requirements of clinical applications.

Exosomes, as Delivery Vehicles, Possess Numerous Advantages: Clin Transl Sci. 2024;17:e13904

TABLE 1 Exosomes, as delivery vehicles, possess numerous advantages: Advantages of exosomes as delivery vehicles.

a. Natural targeting ability
b. Nonimmunogenicity
c. Nanoscale size and overcoming biological barriers
d. Blood-brain–barrier penetration
e. Oral drug formulation capability
f. Enhanced storage capability
g. Natural nanoparticle with reduced safety risks

Note: Modified from Exosomes as Carriers for Drug Delivery in Cancer Therapy Published on March 29, 2022. Surface modification of exosome membranes can be achieved through direct and indirect methods. Indirect modification refers to the engineering of exosome-releasing cells. Cell engineering methods include genetic engineering, metabolic engineering, and direct membrane engineering of parent cells.

Different Regulatory Standards for Exosomes
Clin Transl Sci. 2024;17:e13904

TABLE 2 Different regulatory standards for exosomes.

Country	USA	Europe	Japan	South Korea	Taiwan
Classification criteria	Contents of exosomes can affect physiological function		Based on how exosomes are obtained		
Regulatory unit	USFDA	EMA	MHLW & PMDA	MFDS	TFDA
Product classification	Mechanism of action (MOA) provides sufficient preclinical and clinical research data to demonstrate the safety and efficacy: Biomarkers for disease diagnosis or Therapeutic products[a]	Includes functional translated RNA (ATMP) Excludes functional translated RNA (Biologics)	Nonliving cell–containing medications	Drugs manufactured by isolating and purifying extracellular vesicles secreted by living cells	Derivatives included in regenerative medicine
Quality Control Point	cGMP Product Development Chemical Manufacture Control (CMC) Regulations to assure that the quality is built into the design and manufacturing process at every step	PIC/s GMP Regulation from the source of raw material production to the end of consumer use	PIC/s GMP Regulation from the source of raw material production to the end of consumer use	PIC/s GMP Regulation from the source of raw material production to the end of consumer use Guideline on Quality, Nonclinical, and Clinical Assessment of Extracellular Veside Therapeutic Products	PIC/s GMP Regulation from the source of raw material production to the end of consumer use Guiding principles for manufacturing control and development strategies for extracellular veside preparations (Draft)

Note: Regulatory standards for exosomes vary worldwide, depending on their characteristics. They are based on whether the exosome content can affect physiological functions in the USA and Europe and based on how they are obtained in Japan, South Korea, and Taiwan. These guidelines are intended to ensure that pharmaceutical products are consistently produced and controlled with high standards of quality, safety, and efficiency. This includes provisions for ensuring the proper documentation and traceability of pharmaceutical products throughout their lifecycle, from raw material procurement to distribution and use.

[a]Reference compilation: Cheng, K. & Kalluri, R. Guidelines for clinical translation and commercialization of extracellular vesicles and exosomes based therapeutics. *J. Extracell. Vesicles.* 2, 100029 (2023).

"Renewosomes™", not Stem Cells, promote soft tissue healing

- **Only** about **5-10%** of patients historically treated with stem cells have shown benefit
- Large studies have been performed to evaluate **inconsistent clinical efficacy** of stem cell therapy
- Successful patients received stem cells capable of releasing an **overabundance of regenerative exosomes**
- Established ***exosomes, not stem cells*** provide the necessary cues for tissue healing

Patented process to manufactu re and scale regenerative exoso mes termed ***Regenosomes™***

Exosomes can come from many sources

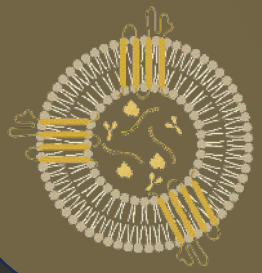
Platelet-derived exosomes are the latest advancement as they are uniquely designed for skin renewal

Platelets

Platelet-Rich Plasma (PRP) – (First Generation)

Renewing Exosomes – (Next Generation)

- **Release high volume of antioxidants and growth factor complex**
- **Calms tissue**
- **"Message" to help renew**



Renewosome™ technology in (plated)™ Skin Science

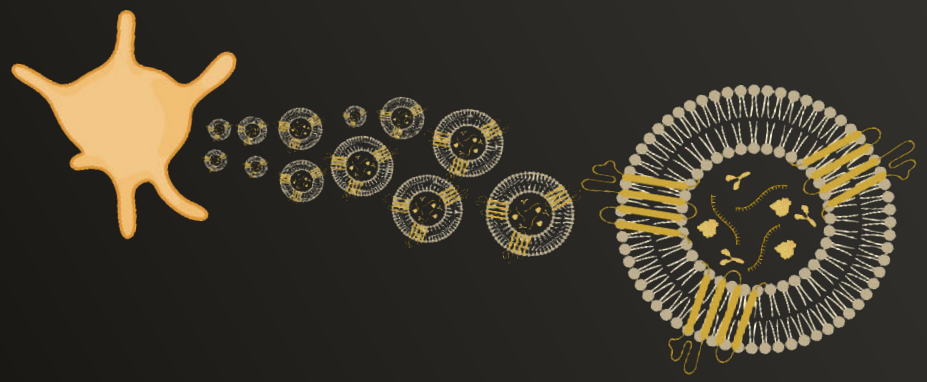
RION aesthetics

Exosome Concentration Matters

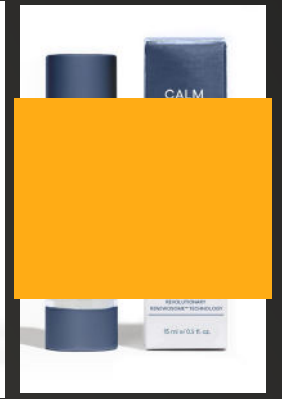
Platelets Yield High Concentration of Exosomes Compared to Other Sources

Platelet

Trillions of Exosomes



(plated)™ Skin Science Products



- Over 1 trillion exosomes in every bottle
- Up to 15 billion exosomes in every pump

Stem Cell-Derived Exosome Brands: Concentrations Range from 2.5 Billion – 10 Billion Per Bottle

Recent Studies Measuring Anti-Aging Impact

Data shows promising results as soon as 6-weeks, up to 6 months, and post-procedure use

POSH (Platelets on Skin Health) Study:
A Novel Antiaging Skin Care Regimen Containing **(plated)™ INTENSE**

- **56 Patients**
- **Average age: 54**

Sponsored by RION Aesthetics

POPPS (Platelets on Post-Procedure Skin) Study:
A Post-Laser Procedure Study Using **(plated)™ CALM**

- **18 Patients**
- **Comparing use of (plated)™ CALM to standard of care post laser (CO_2)**
- **Dr Steve Dayan, Chicago, IL**

Sponsored by RION Aesthetics

Efficacy and Tolerability of Topical Platelet Exosomes for Skin Rejuvenation Six-Week Results
Aesthet Surg J. 2022 Sep 14;42(10):1185-1193

Aesthetic Surgery Journal
2022, 1–9

https://doi.org/10.1093/asj/sjac149
www.aestheticsurgeryjournal.com
OXFORD
UNIVERSITY PRESS

Efficacy and Tolerability of Topical Platelet Exosomes for Skin Rejuvenation: Six-Week Results

Sydney L. Proffer, MD, MS; Christopher R. Paradise, PhD; Emily DeGrazia, BA; Yael Halaas, MD; K. Kay Durairaj, MD; Michael Somenek, MD; Angela Sivly, BS; Andrea J. Boon, MD; Atta Behfar, MD, PhD; and Saranya P. Wyles, MD, PhD

Abstract

Background: Exosomes are regenerative mediators for skin rejuvenation. Human platelet extract (HPE) is an allogeneic exosome product derived from US-sourced, leukocyte-reduced apheresed platelets with consistent purity and potency.

Objectives: The authors sought to better characterize the safety and tolerability of novel HPE (plated) Intensive Repair Serum (Rion Aesthetics, Rochester, MN) and its maximal effects on skin rejuvenation at 6 weeks.

Methods: This prospective, single-arm, non-randomized, longitudinal study investigated the safety and efficacy of HPE. Structured sub-analysis evaluated multifactorial improvement in skin health following standardized skin care regimen to determine the maximal effect. Evaluation at baseline and 6 weeks included participant questionnaires and photo documentation with VISIA-CR Generation 5 3D PRIMOS (Canfield Scientific Inc, Fairfield, NJ).

Results: VISIA-CR imaging yielded quantifiable and statistically significant improvements in overall skin health (skin health score). A greater score correlated to greater overall skin health, and there was a statistically significant mean delta improvement of 224.2 ± 112.8 (mean ± standard deviation, $P \leq 0.0001$) in skin health score at 6 weeks compared with baseline. This correlated to reduction in redness, wrinkles, and melanin production across all cosmetic units ($P = 0.005$, $P = 0.0023$, $P \leq 0.0001$, respectively) and significant improvements in luminosity and color evenness ($P \leq 0.001$).

Conclusions: A topically applied platelet-derived exosome product, HPE, induced normalization to skin health at 4 to 6 weeks with improved various clinical measures of facial photodamage and cutaneous aging. It is safe, well-tolerated, and well-liked by participants.

Platelet-derived exosomes for Anti-aging POSH Study-platelets on skin health

- + 56 subjects (8 males, 48 females 40-80 y.o) enrolled mild-moderate facial wrinkles, moderate global fine lines
- + 6 weeks used specified skincare regimen including gentle cleanser, moisturizing sunscreen, night
- moisturizer and test serum twice daily
- + Photo documentation Visia CR Generation 5 3D Primos baseline and 6 weeks
  - + Wrinkle fractional area
  - + Erythema fractional area
  - + Brow spot fractional area
  - + Luminosity score
  - + Color evenness
- + Traditional photography Blinded board-certified plastic surgeons evaluated images
  - + 10 point modified-Griffiths scale
- + Subject self-assessment for improvement

Proffer SL, et al. Aesth Surg J. 2022;42(10):1185-1193

Results

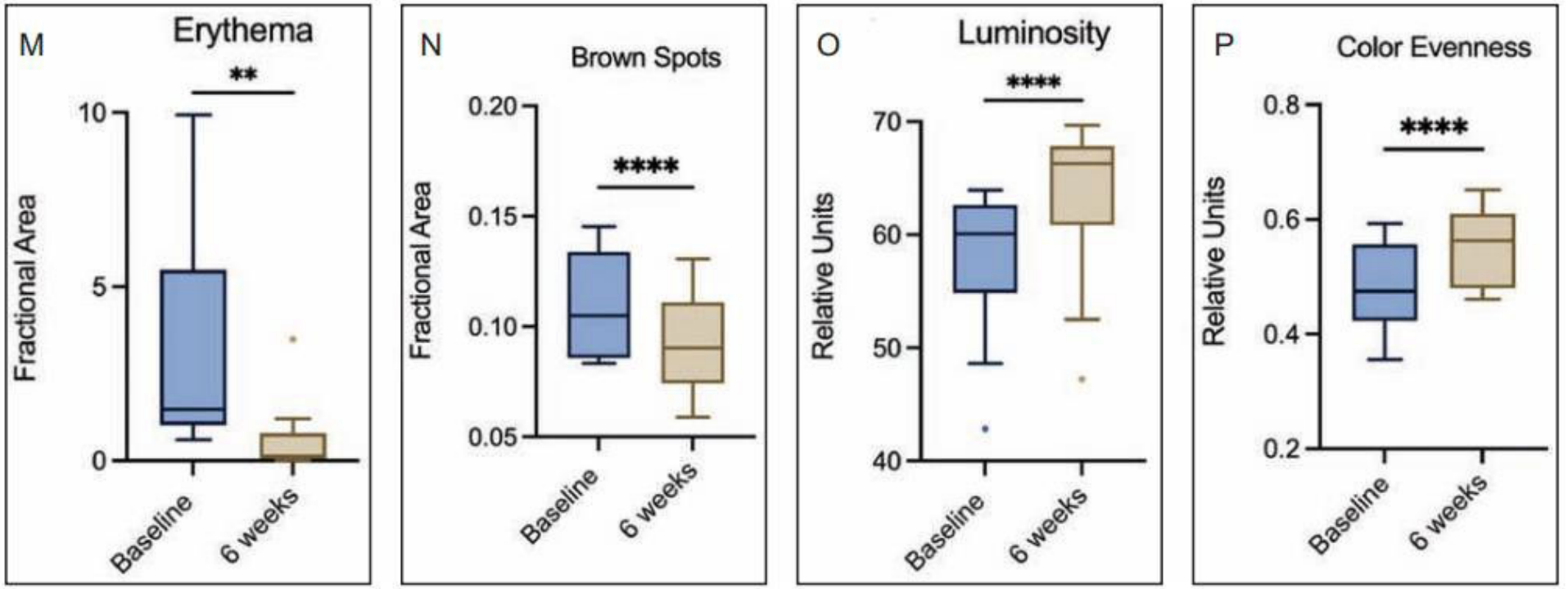
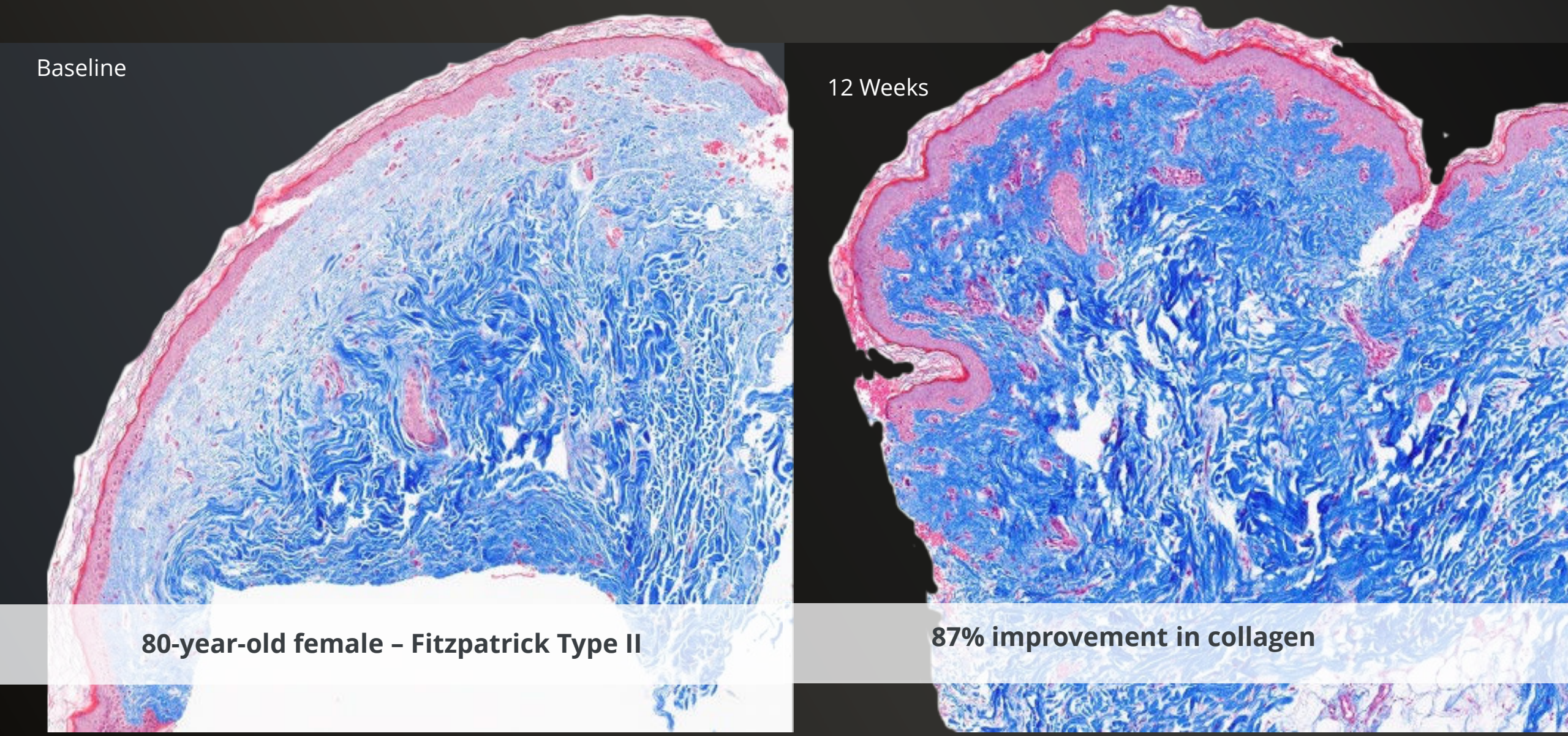


Figure 1. Continued.

To determine maximal skin health induction effect, the top-quartile responders were graphed examining the mean delta reduction in erythema fractional area (M), brown spot fractional area (N), and mean delta improvement in luminosity (relative units) (O) and color evenness (relative units) (P) at baseline and 6 weeks. Asterisks were considered statistically significant (****$P < 0.0001$, ***$P < 0.001$, **$P < 0.01$, *$P < 0.05$, ns = $P > 0.05$).

Proffer SL, et al. Aesth Surg J. 2022;42(10):1185-1193

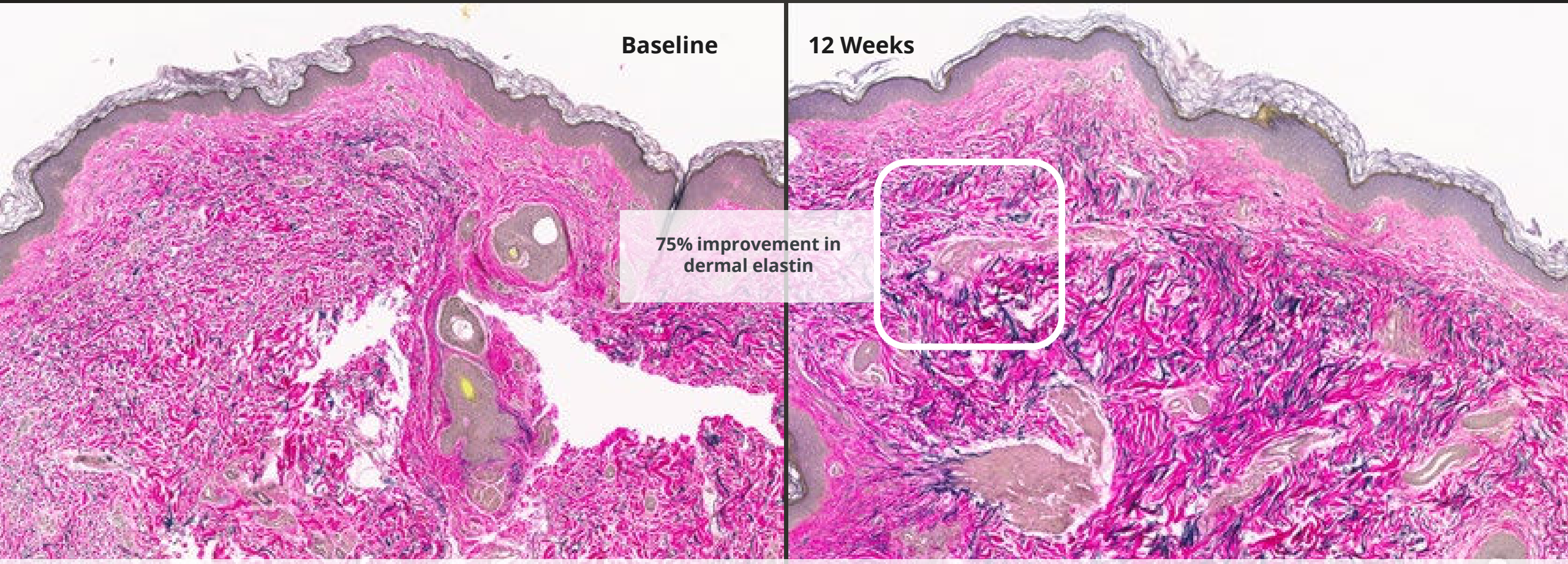
Masson’s Trichrome - Collagen



80-year-old female – Fitzpatrick Type II

87% improvement in collagen

Verhoeff-Van Gieson - Elastin

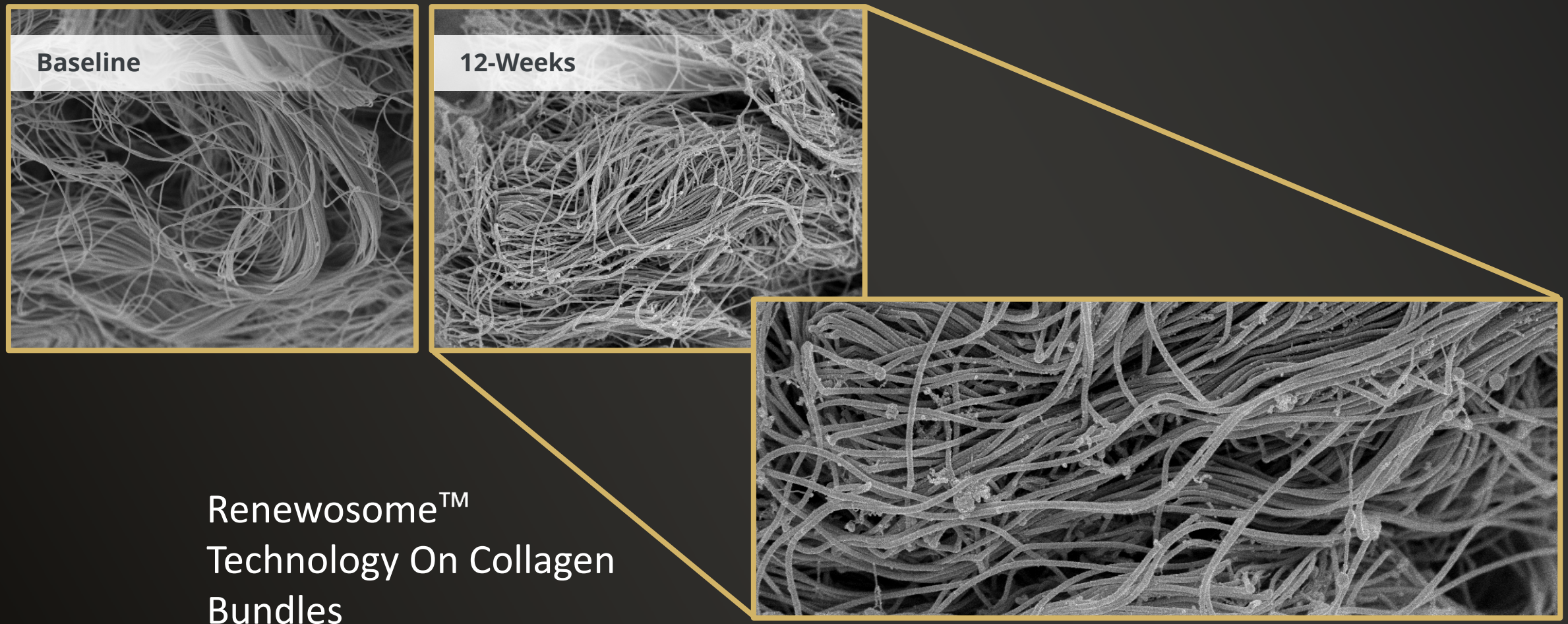


59-year-old female – Fitzpatrick Type II

50% improvement in elastin in reticular dermis (mid-dermis)

Electron Microscopy Collagen

Inner Arm Biopsy



Renewosome™ Technology On Collagen Bundles

RION aesthetics

Conclusion: Platelets Hold the Power to Renew

POSH Study Summary with (plated)™ INTENSE

6- month safety results

- No allergic reaction with repetitive treatment

12-week Improvement

- Improvement across wide variety of visible signs of aging
- Helps support natural production in collagen and elastin
- Reduction in cellular senescence burden ($p<0.01$)

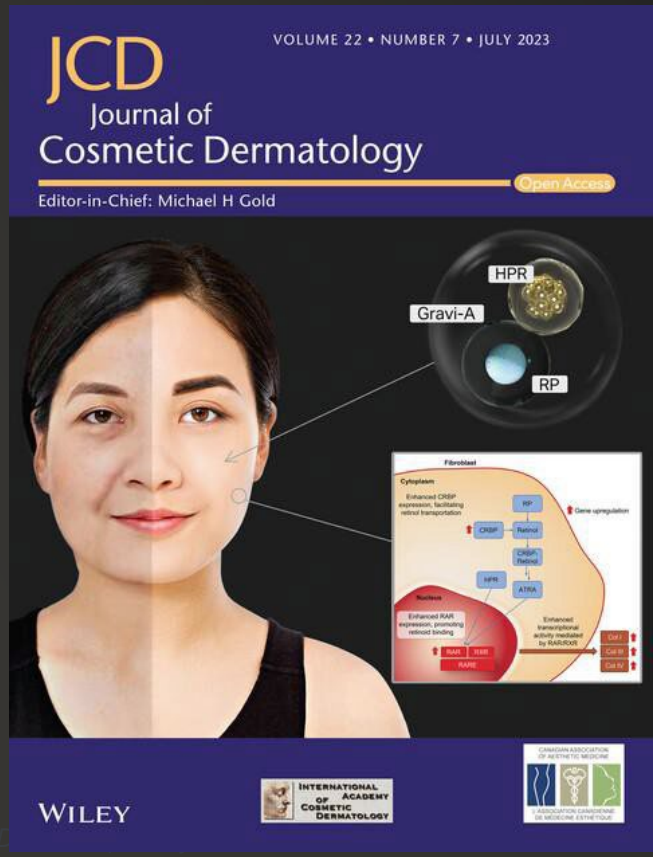
CLINICAL STUDY – SKIN RECOVERY

JDD 2023;22(9):2464 - DATA SHOWS PROMISING RESULTS AS EARLY AS 5 DAYS

Safety and Efficacy of Human Platelet Extract (HPE) in Skin Recovery after Fractional CO_2 Laser Resurfacing of the Face

A Randomized, Controlled, Evaluator-Blinded Pilot Study conducted by Steven Dayan, M.D.

- 18 patients, randomized to use exos or silicone gel post-procedure
- Age range: 32-77 years old
- Post-Fractionated CO2 laser followed by topical human platelet extract applied 3X daily for 30 days after CO_2 laser



Dermatology

Study sponsored by Rion Aesthetics, Inc.

Results

- +Statistically significant improvement
  - +Less crusting on day 10 compared to control
  - +Less downtime in the first 14 days
  - +Brighter skin at day 14
  - +More youthful looking skin day 14 and 30

Dayan S, et al. JDD 2023;22(9):2464

Safety and Efficacy of Human Platelet Extract in Skin Recovery After Fractional CO2 Laser Resurfacing of the Face: A Randomized, Controlled, Evaluator-Blinded Pilot Study

J Cosmet Dermatol. 2023;00:1–7

Safety and efficacy of human platelet extract in skin recovery after fractional CO_2 laser resurfacing of the face: A randomized, controlled, evaluator-blinded pilot study

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[4]Boulder Biostatistics, Steamboat Springs, Colorado, USA
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[6]Mayo Clinic, Rochester, Minnesota, USA

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Steven Dayan, DeNova Research, Chicago, IL, USA.
Email: sdayan@drdayan.com

Funding information
Rion Aesthetics

Abstract

Background: Fractional carbon dioxide (CO_2) laser resurfacing is used successfully for facial rejuvenation. Post procedure skincare is a variable that influences downtime caused by pain/tenderness, erythema, crusting, and bruising.

Aims: The primary objective of this pilot study was to demonstrate the benefits of human platelet extract (HPE) (plated)™ CALM Serum, a new topical cosmetic product, following fractionated CO_2 ablative laser resurfacing treatment to the entire face versus standard of care.

Methods: In a single-center, randomized, evaluator-blinded pilot study, a total of 18 subjects were randomized into two groups, CO_2 facial resurfacing followed by post-procedural standard of care (Stratacel silicone gel) or CO_2 facial resurfacing with the addition of HPE renewosomes in the CALM Serum.

Results: CALM Serum demonstrated statistically significant less crusting at Day 10 compared to the control group ($p=0.0193$) with less downtime in the first 14 days ($p=0.03$). Subjects treated with CALM Serum had statistically significant brighter appearing skin at 14 days ($p=0.007$) and more youthful looking skin on Days 14 and 30 ($p=0.003$ and 0.04, respectively).

Conclusions: This study demonstrates that Renewosome™ technology provides statistically significant post-laser clinical recovery over silicone gel for reducing crusting, and downtime. Subjects reported less diary days of symptoms of pain/tenderness, redness, crusting/flaking, bruising, and itching in the first 14 days compared to the control group. CALM also demonstrated statistically significant improvements in brighter and more youthful appearing skin. CALM is safe and well tolerated.

KEYWORDS
fractional CO_2 laser, human platelet extract, skin rejuvenation

Effect of Topical Human Platelet Extract (HPE) for Facial Skin Rejuvenation: A Histological Study of Collagen and Elastin
J Drugs Dermatol. 2024 Sep 1;23(9):735-740.

Effect of Topical Human Platelet Extract (HPE) for Facial Skin Rejuvenation: A Histological Study of Collagen and Elastin

Saranya P. Wyles MD PhD,[a] Sydney L. Proffer MD MS,[a] Patricia Farris MD,[b] Lindsey Randall BS,[c] Matthew L. Hillestad PhD,[d] Mary P. Lupo MD,[e] Atta Behfar MD PhD[d]

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ABSTRACT

Background: Regenerative aesthetics has garnered significant attention. In this toolkit, exosomes are small extracellular vesicles derived from various sources such as platelets.

Objective: To characterize the cosmetic effect and tolerability of topical human platelet-derived extract (HPE), Intense Serum (Rion Aesthetics, Inc., Rochester, MN), on facial skin rejuvenation after 12 weeks of twice daily use without any confounding aesthetic procedures.

Materials and Methods: This prospective, single-arm, non-randomized, evaluator-blinded clinical study evaluated subjects at baseline and 12 weeks using participant questionnaires and photo-documentation with Canfield VISIA-CR 3D PRIMOS. The histological evaluation included Masson's Trichrome for collagen and Verhoeff-Van Gieson staining for elastin. Electron microscopy characterized collagen bundle thickness.

Results: Fifty-six participants (mean age: 54 years old) were enrolled. Following topical HPE use, 87.3% of subjects reported improvement in facial skin aging including sustained pigment reduction and improvement in luminosity and color evenness at 12 weeks ($P \leq 0.001$). Histology revealed a significant increase in collagen fibril thickness at 12 weeks ($P \leq 0.0001$). No serious adverse effects.

Conclusion: This study demonstrates improvement in facial skin health after topical HPE use, supported by collagen and elastin formation in the dermis. The product is well-tolerated, and participants were satisfied with the overall cosmetic outcome.

J Drugs Dermatol. 2024;23(9):735-740. doi:10.36849/JDD.8162

HAIR Serum

Our platelet-derived exosomes create an environment to:

- Prolong anagen phase of hair growth cycle
- Promote elongation of hair follicles
- Support scalp health

Hair Serum Ingredients

Platelet-Derived Exosomes

- Contributes to cell proliferation in hair follicle
- Supports the body's natural production of collagen and elastin

Biotin

- Helps to promote stronger hair and prevents it from becoming weak and brittle

Arginine

- Reduces dihydrotestosterone (DHT) androgen levels without increasing testosterone outputs

Carnosine

- Excellent antioxidant properties
- Helps reduce the damage from free radicals

Sea Moss

- Delivers natural ingredients such as Citrulline-Arginine (a dipeptide) that delays catagen phase and maintains most hair in anagen phase, thus supports hair growth and hair elongation

Hyaluronic Acid

- Improves appearance of hair thickness, fullness

Turmeric

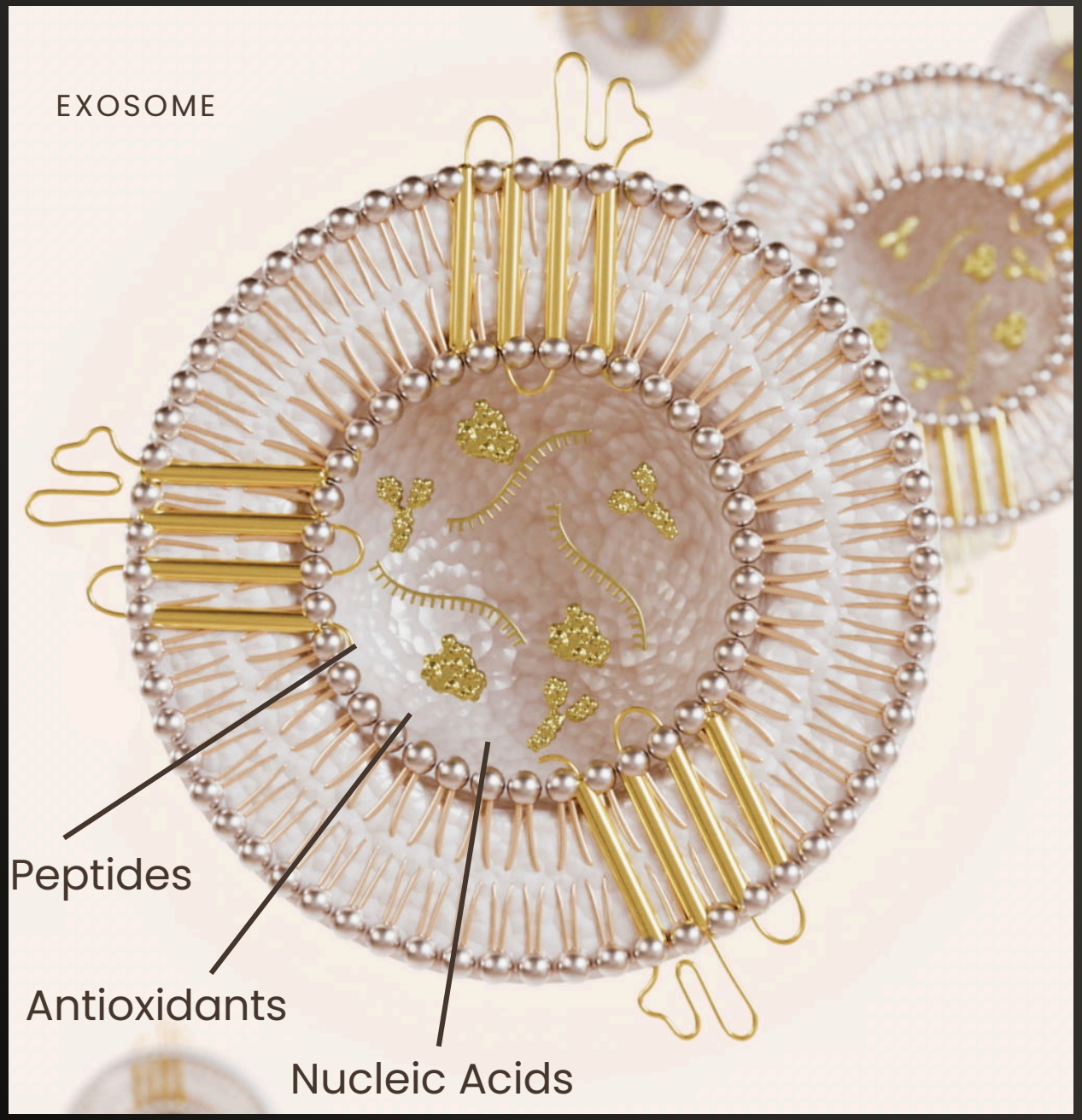
- Anti-inflammatory properties
- Regulate hair growth
- Decreases levels of DHT

Lindera Strychnifolia Root Extract

- An Asian shrub that contains sesquiterpenes, polyphenols and lignans that are meant to act positively on hair density
- Provides a protection of hair health by acting on scalp microbiota

Greyverse™

- It offers an unprecedented efficient solution to prevent, stop, and reverse this inevitable sign of aging.



Technology

Proprietary platelet-derived exosomes

Platelet key pathways for hair:

Wnt/β-catenin	PI3K-AKT

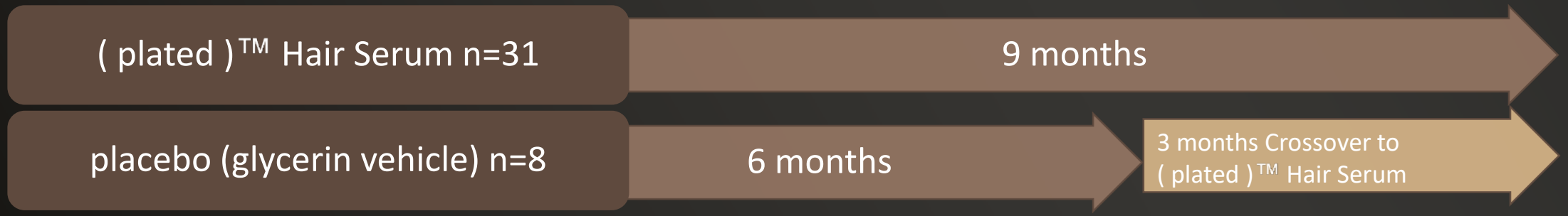
- ☑ Prolongs active growth phase
- ☑ Helps transition from telogen phase → anagen phase
- ☑ Signals hair follicle regeneration
- ☑ Enhances cell communication, boosting epidermal & dermal signaling to hair follicles

Clinical Study: Randomized, Double-Blind, Placebo-Controlled Study of (plated)™ Hair Serum

Dr. Rod Rohrich – Dallas Plastic Surgery Institute

Participants were randomized to apply either (plated)™ Hair Serum for 9 months or topical placebo (glycerin vehicle) for 6 months with the option to cross over to (plated)™ Hair Serum at 6 months for an additional 3 months

- Follow-up visits were at months 1, 3, 6 and 9

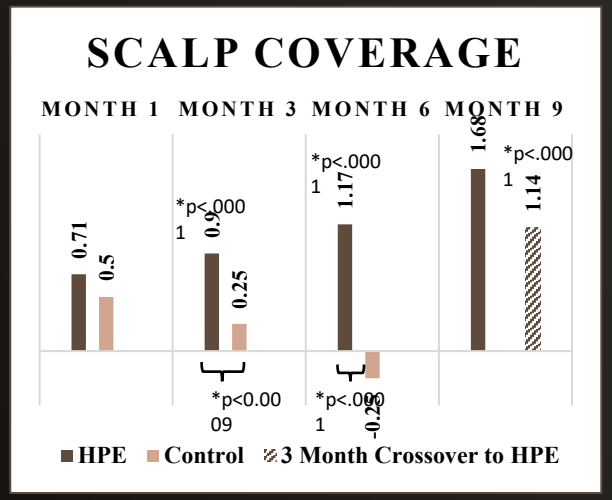


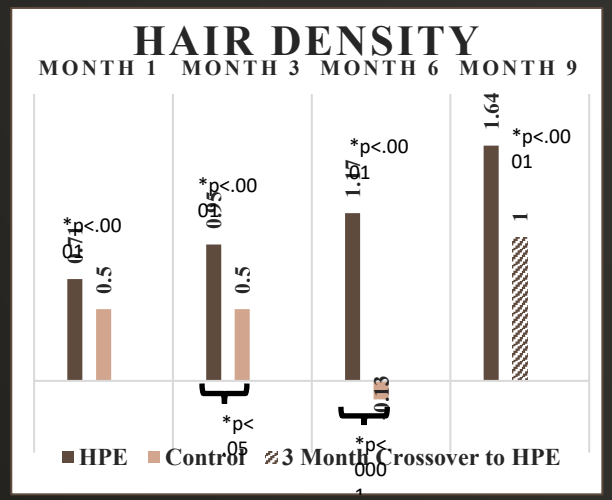
- Participants applied 1 dropper full of product to 8 areas and massage into the scalp (center part, front, crown, left and right parietal areas, back, and close to ears on both sides)

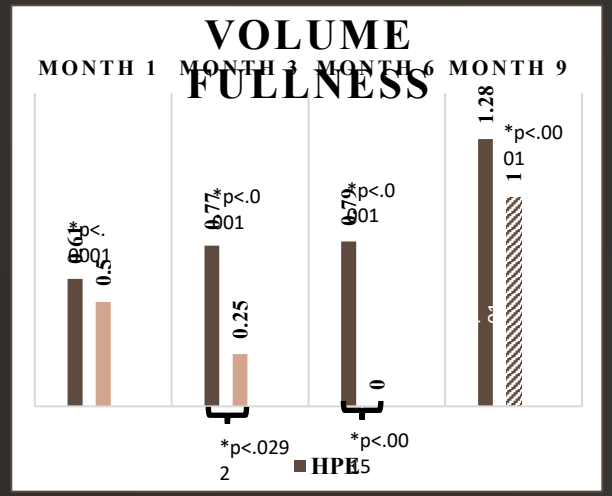
Clinical Results: Blinded Evaluator

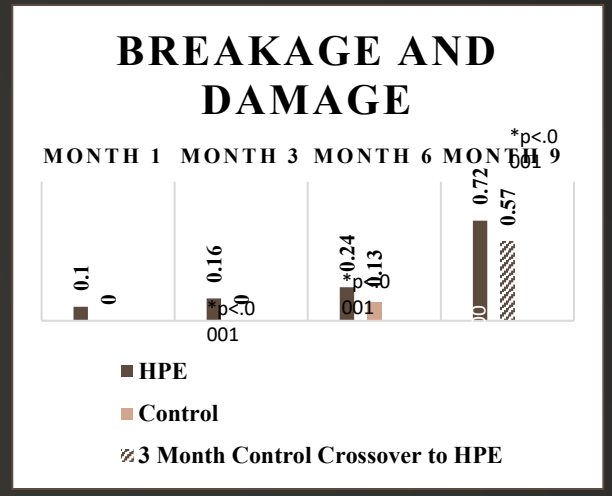
Significant Improvements over the Placebo Group, at 3 and 6 Months
*HPE = proprietary platelet-derived exosomes

- Participants in the HPE group had a statistically significant improvement as graded by the blinded evaluator at all follow-up time points over the course of the study except breakage and damage at Month 1
- The HPE group had statistically significant improvements over the control group at Months 3 and 6 for Scalp Coverage, Volume Fullness, and Density
- The Control group only had statistical improvements in hair appearance at months 3 and 6. Once the participants crossed over to HPE for 3 months after 6 months on control, all hair assessments were improved



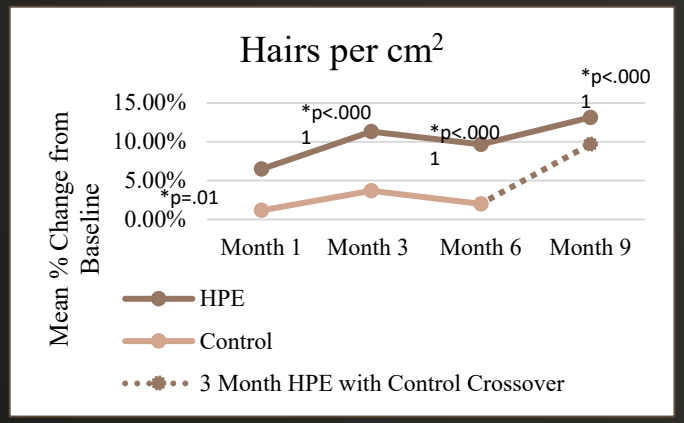


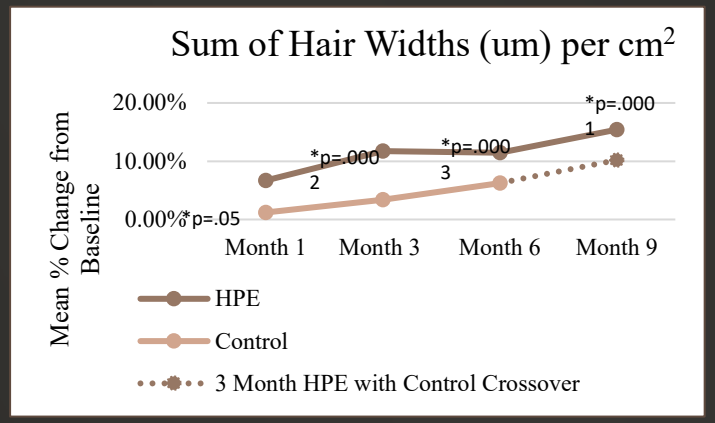


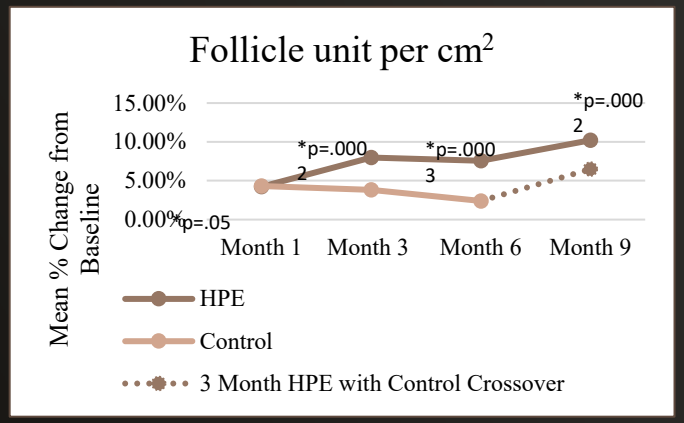


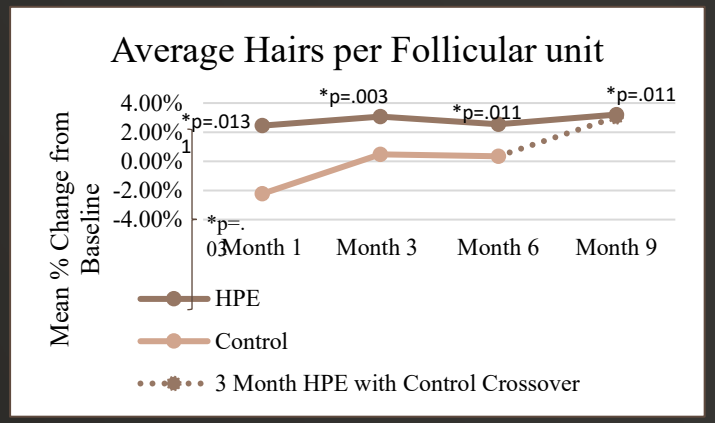
Clinical Study Results: Hair Trichoscopy

Statistically significant changes from baseline across 4 different measurements within the HPE Group



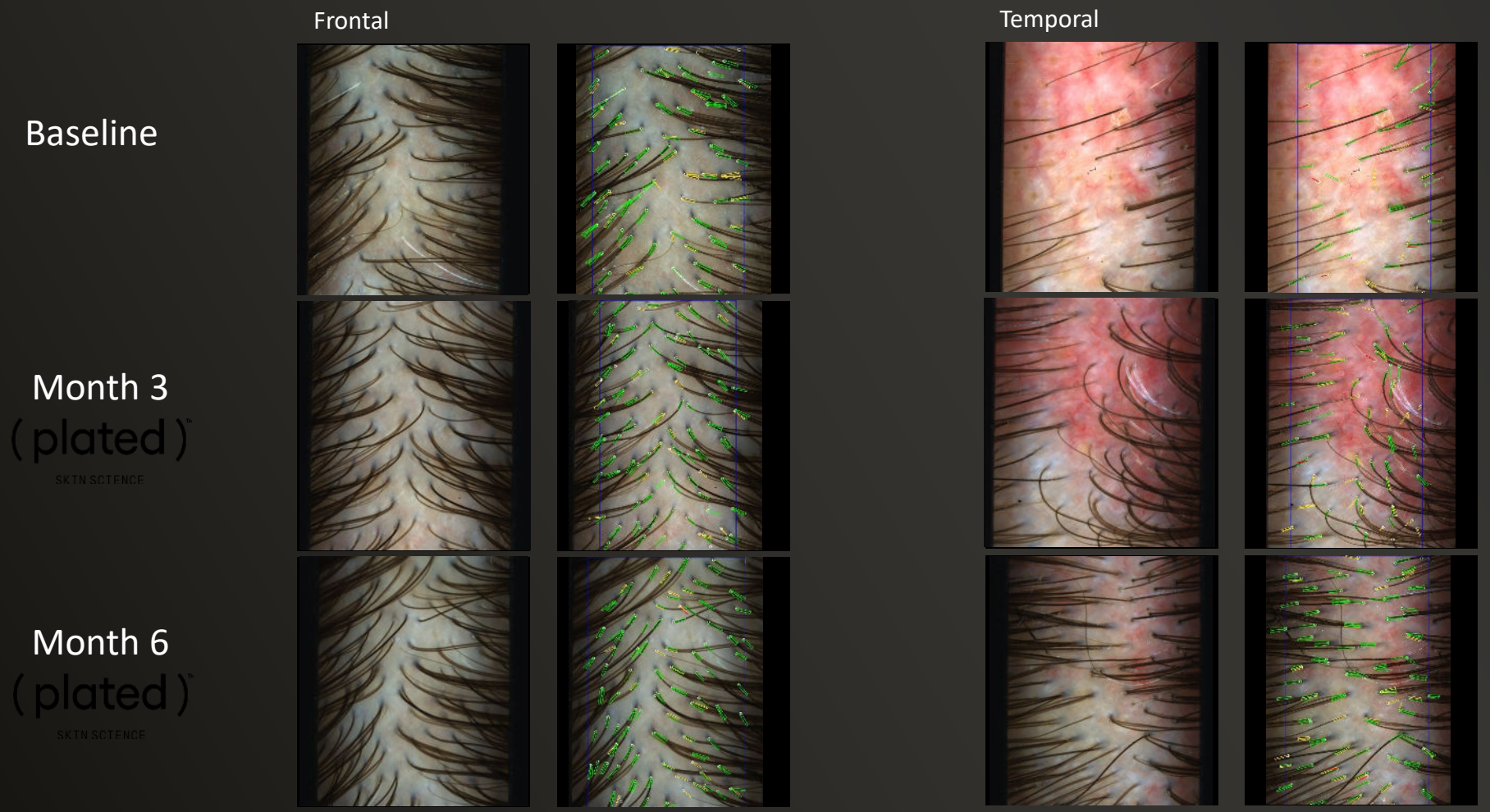






Clinical Study Results: Hair Trichoscopy

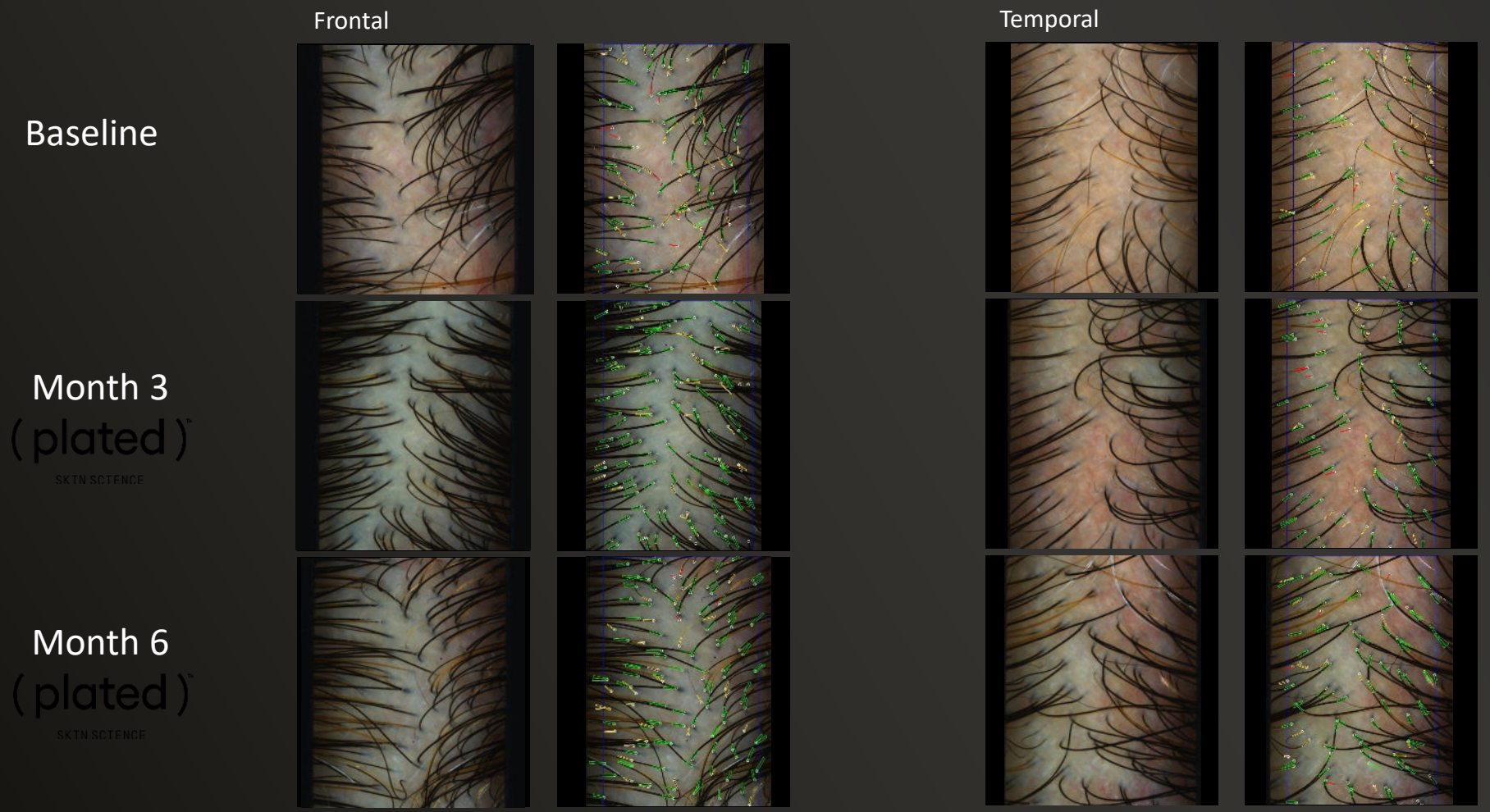
Statistically Significant changes from baseline across:
Hairs per cm^2 - Hair Width - Follicular Unit per cm^2 - Avg Hairs per Follicular Unit



Male Participant - Age 55, views from the HairMetrix®

Clinical Study Results: Hair Trichoscopy

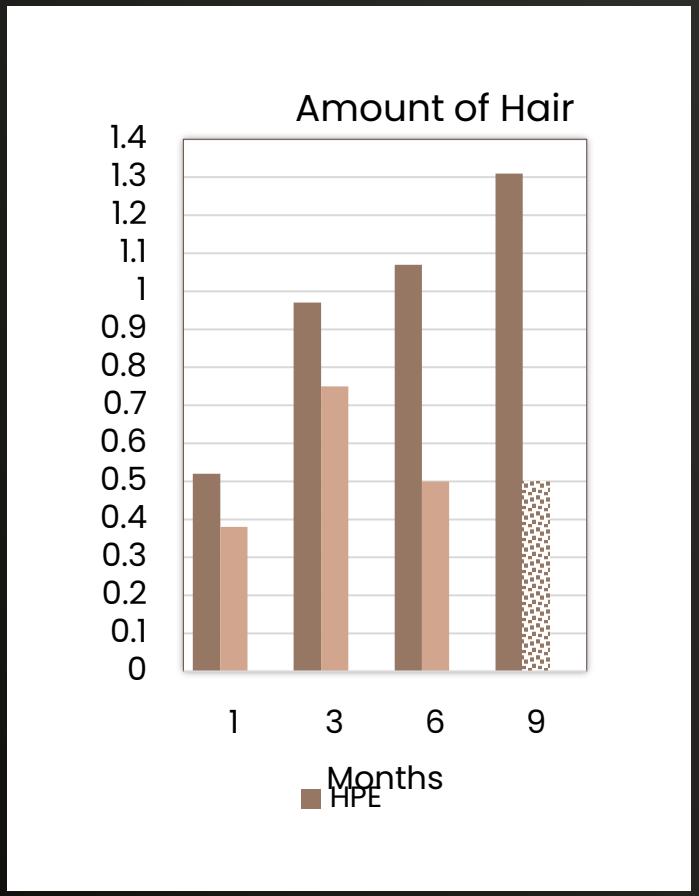
Statistically Significant changes from baseline across:
Hairs per cm^2 - Hair Width - Follicular Unit per cm^2 - Avg Hairs per Follicular Unit

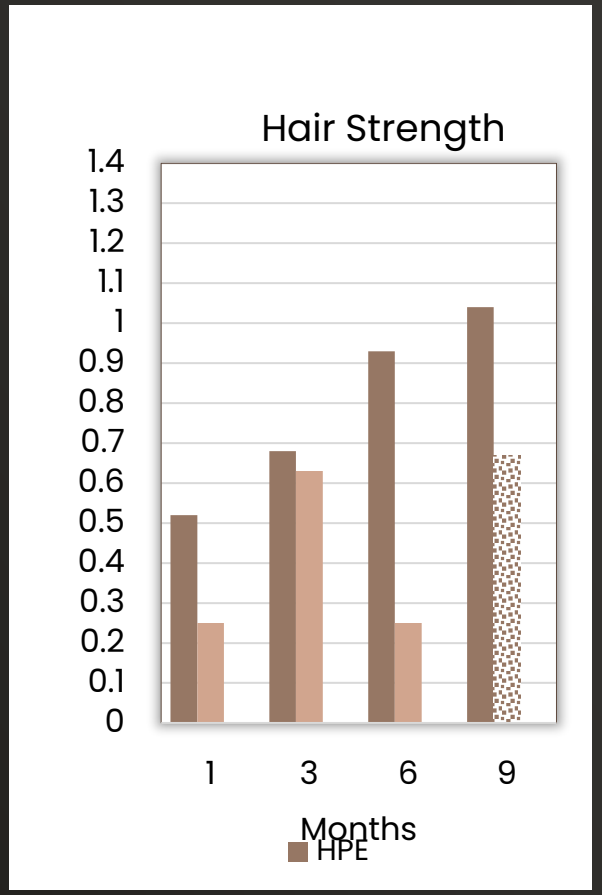


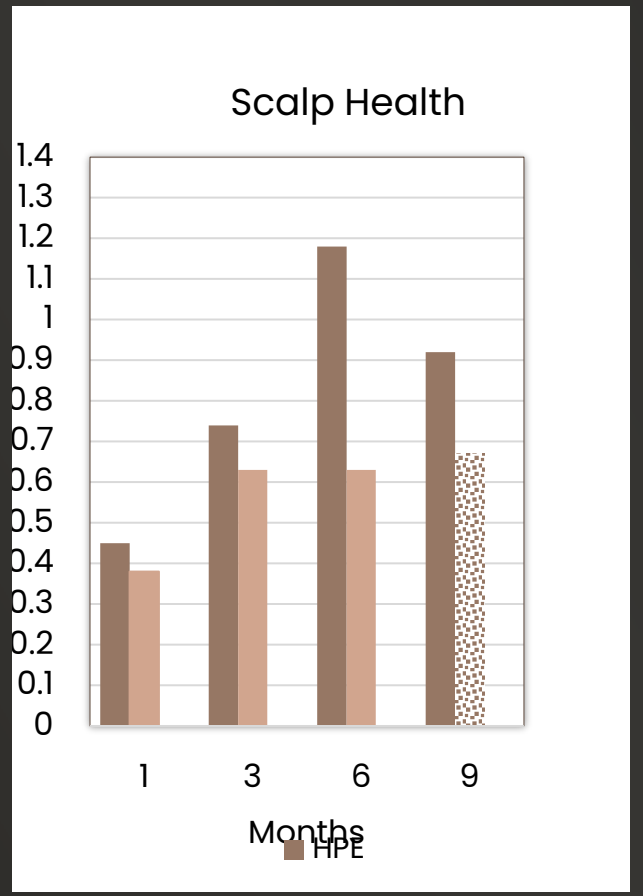
Female Participant - Age 50, views from the HairMetrix®

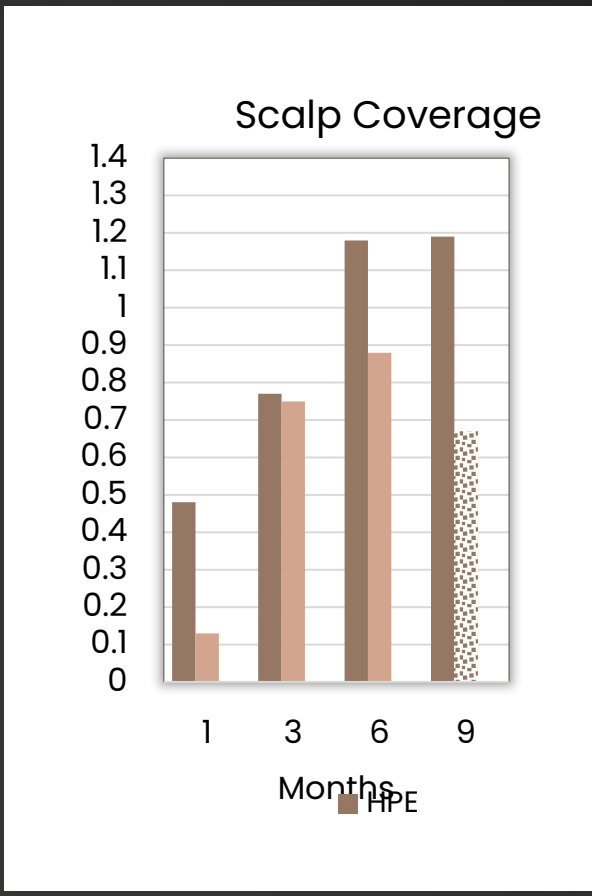
Clinical Study: Blinded Participant Assessments

Participants using (plated)™ Hair Serum graded significant improvements from baseline in hair assessments at all follow-up time points





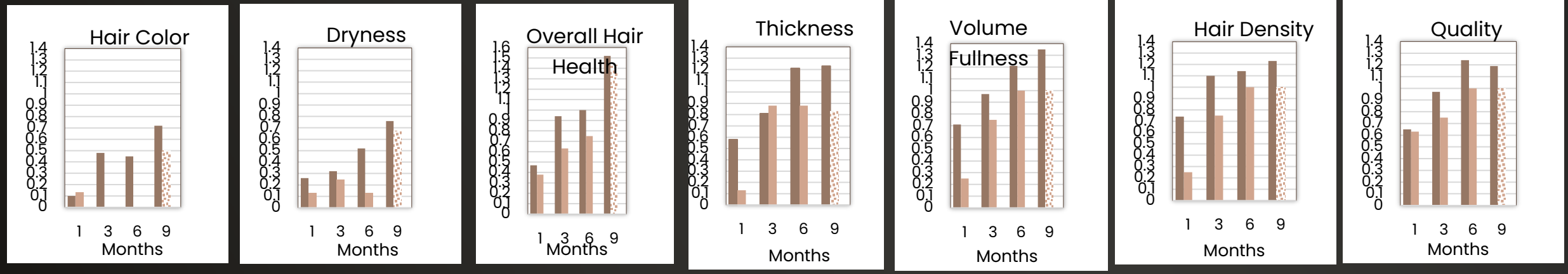




Mean Improvement from Baseline

Clinical Study: Blinded Participant Assessments

Participants using (plated)™ Hair Serum graded significant improvements from baseline in hair assessments at all follow-up time points



Mean Improvement from Baseline

Clinical Study Summary

→ 96% of participants showed improvements to hair appearance at 9 months

→ 100% of participants showed improvements to scalp coverage at 9 months

→ 96% of participants showed improvements to volume/fullness at 9 months

All from Blind Evaluator Ratings

Leverage the power of
platelet-derived exosomes for
Fuller, Stronger, Thicker-looking Hair

Topical Platelet Exosomes Reduce Senescence Signaling in Human Skin: An Exploratory Prospective Trial
Dermatol Surg. 2024 Nov 1;50(11S):S160-S165

Topical Platelet Exosomes Reduce Senescence Signaling in Human Skin: An Exploratory Prospective Trial

Saranya P. Wyles, MD, PhD,*† Grace T. Yu, BSc,‡ Michael Gold, MD,§ and Atta Behfar, MD, PhD†||

BACKGROUND Cellular senescence, an irreversible cell cycle arrest with secretory phenotype, is a hallmark of skin aging. Regenerative exosome-based approaches, such as topical human platelet extract (HPE), are emerging to target age-related skin dysfunction.

OBJECTIVE To evaluate the cellular and molecular effects of topical HPE for skin rejuvenation after 12 weeks of twice daily use.

METHODS Skin biopsies were obtained for histological evaluation of senescence markers, $p16^{INK4a}$ and $p21^{CIP1/WAF1}$. Telomere-associated foci, coassociation of telomeres, and DNA damage marker, γH2AX, were assessed. RNA sequencing evaluated senescence associated secretory phenotype (SASP) and extracellular matrix pathways.

RESULTS $p16^{INK4a}$ and $p21^{CIP1/WAF1}$ staining in senescent skin cells revealed low and high expression subgroups that did not correspond to chronological age. Topical HPE significantly reduced high $p16^{INK4a}$ cells in the dermis ($p = .02$). There was also a decrease in telomere damage after topical HPE ($p = .03$). In patients with high senescent cells at baseline, there was a 40% reduction in proinflammatory SASP. Extracellular matrix remodeling pathways, including collagen and elastic fibers, were up-regulated.

CONCLUSION Topical HPE, applied on intact skin, reduced senescence signaling and senescence-associated telomere damage after 12 weeks of twice daily use, targeting a path for skin longevity or healthy skin aging.

Safety in Exosomes

K N O W W H O Y O U A R E W O R K I N G W I T H

- Does your Exosome company have longevity?
- Are there published, clinical results?
- What safety testing is done? Is there genotoxicity testing results?
- Where are the Exosomes formulated? Are they in a certified laboratory?

SOURCING

CELL SOURCE COMPARISON

KNOW YOUR CELL SOURCE

UMBILICAL CORD MESENCHYMAL STEM CELLS-EXOS

- Skin rejuvenation
- Human dermal fibroblast (HDF) migration and upregulation of collagen

ADIPOSE DERIVED STEM CELLS-EXOS

- Cell proliferation and migration
- Decrease ROS production and DNA damage

BONE MARROW DERIVED STEM CELL-EXOS

- Exosomes concentrate the natural function of a stem cell
- Most regenerative for skin

PLANT EXOS

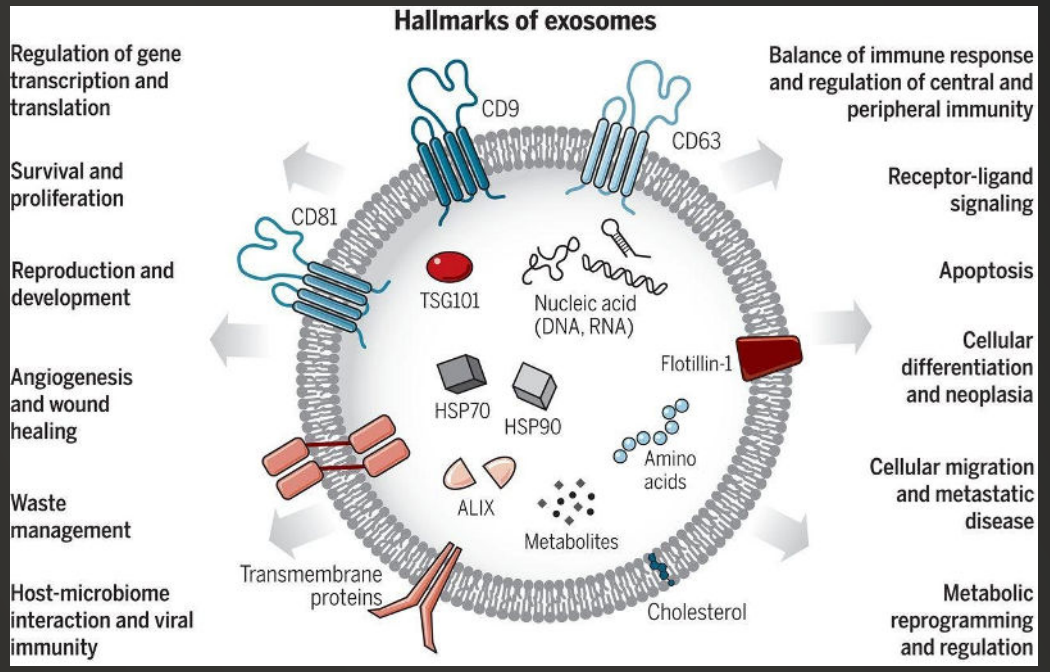
- Contain plant proteins
- Non-human
- Generally viewed as safer than human exosomes
- Likely to contain unique antioxidants & phytochemicals

AnteAGE MD®
Growth Factors & Cytokines

Hybrid Cell Source Advantage

B O N E M A R R O W + U M B I L I C A L M S C s

the only brand that combines Bone Marrow Mesenchymal Stem Cell exosomes with Umbilical Mesenchymal Stem Cell exosomes, giving you the optimal exosome treatment solution. Studies show that this combination is most effective for anti-aging, regeneration and repair.



Hair Exosomes

K E Y I N G R E D I E N T S

Wnt Specific Exosome

This highly complex formula specific exosomes are designed to selectively target WNT signaling up-regulation while also controlling inflammation and regeneration.

✓ WNT signaling activation

Shikimic Acid (SA)

SA is a biochemical metabolite in plants and microorganisms. A 2019 Korean study found that SA significantly prolonged the anagen phase giving hair more opportunity to grow.

✓ Prolonged anagen

Azelaic Acid

Azelaic acid is a naturally occurring by-product of the metabolism of yeast with anti-inflammatory and antioxidant properties. It has been used in hair loss treatments due to its ability to block the production of DHT.

✓ DHT Inhibitor

Caffeine

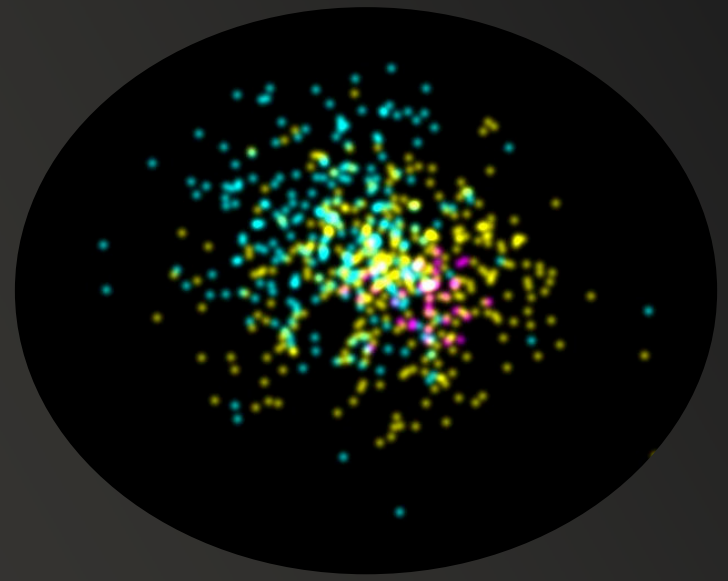
Caffeine has long been used to stimulate hair growth. Caffeine works as a DHT inhibitor; promoting hair growth and prolonging the anagen phase. The boost in energy your hair cells get when exposed to caffeine drives cellular activation and proliferation .

✓ Anti-Inflammatory

SOURCING

LOOKING INTO THE FUTURE

BIOMIMETIC EXOSOMES



BIOSOMES™

- No need for human cells
- Results are comparable human derived sources
- Removes any ethical concerns
- Contain recombinant human proteins
- Non-human derived
- Specific / targeted and customizable
- Replicate the function and beneficial effects of exosomes
- Sterile, endotoxin free, genotoxicity safe

Biosomes Treatment

By leveraging world-wide learnings and breakthroughs in exosome science, state-of-the-art technology that gives you the regenerative power of exosomes, with biomimetic capabilities that are familiar to your body.

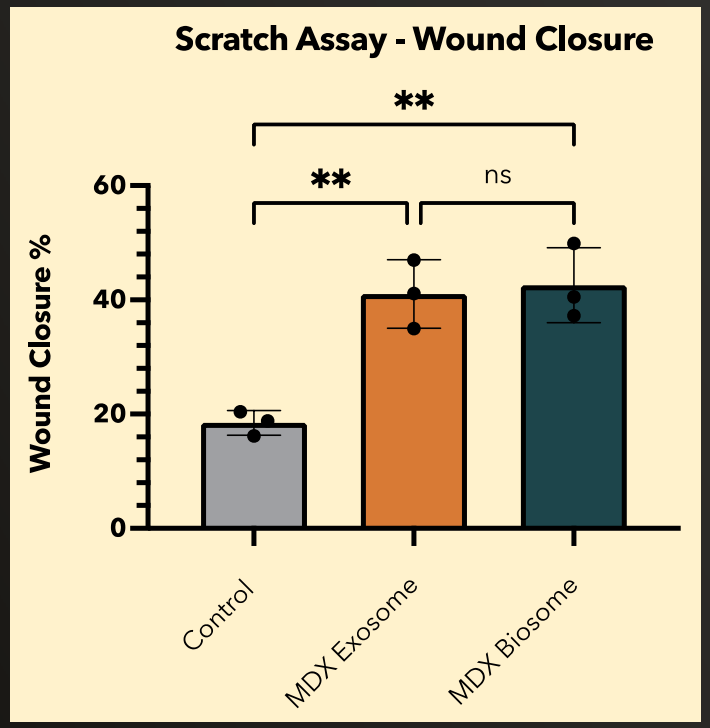
S C I E N C E B E H I N D B I O S O M E S

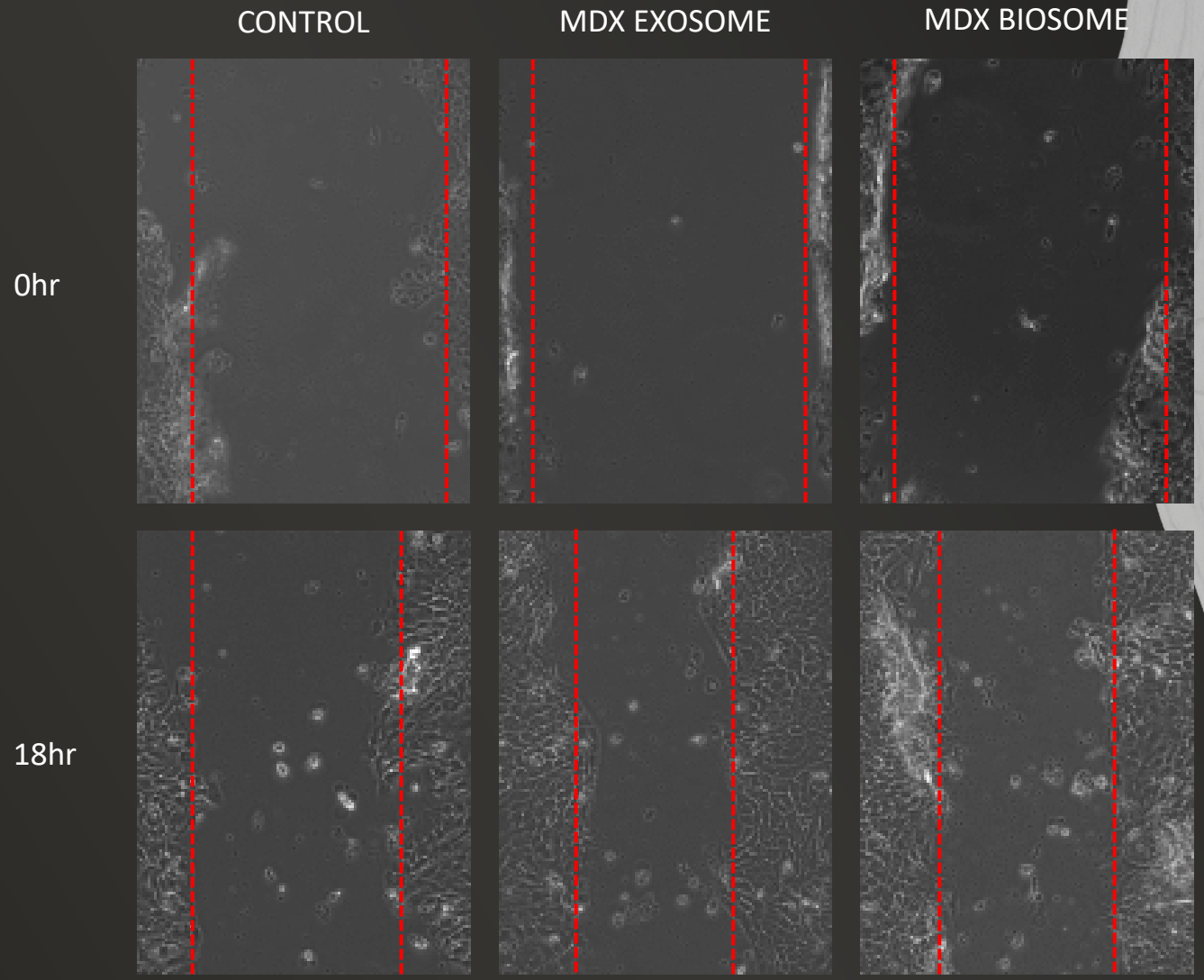
- Reproducing exosomes using synthetic lipid chemistry = Biosomes™
- Identifying the most abundant lipids in Exosomes
- Identifying the most abundant, functional and beneficial proteins found within exosomes
- Combine into one nanoparticle

NOT AVAILABLE IN THE MARKET AT THIS TIME-
BY THE END OF 2025

In Application

IN VITRO FUNCTION

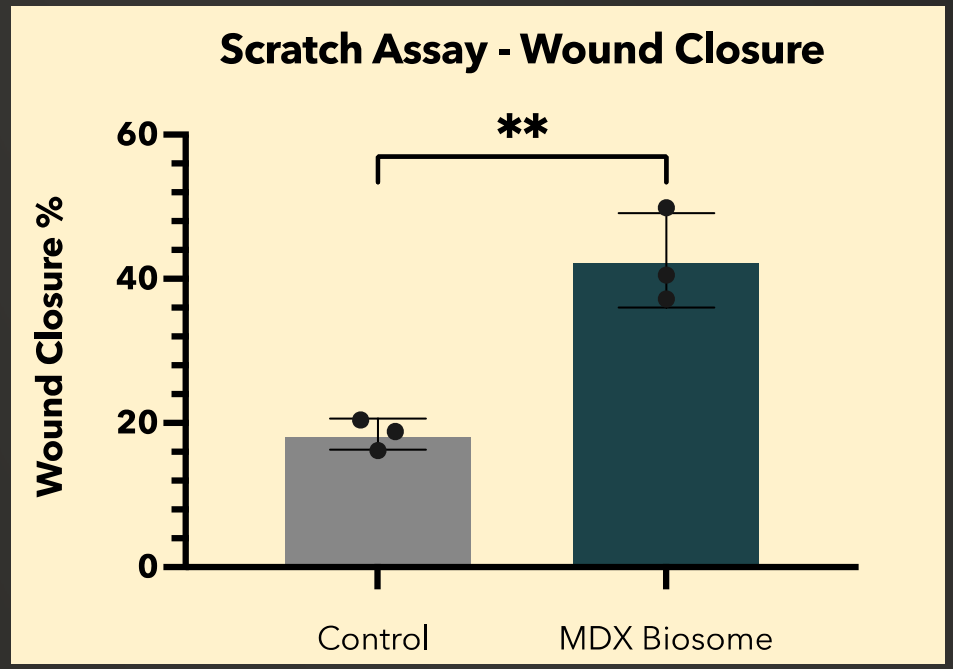




In Application

IN VITRO FUNCTION

200% Increase Wound Healing Potential



Biosomes Treatment

REASON TO BELIEVE

- Reproducing 15 Years in the Making: AnteAGE is a trusted brand
- Clinical Results: Proven efficacy
- Emphasis on Safety: Genotoxicity testing
- Biosomes have emerged by taking what we have learned from exosome science and applying this knowledge to a synthetic, non-human derived aesthetic treatment option

KEY BENEFITS

- Faster Results
- More Targeted
- Less Downtime
- Biomimetic Technology
- Equally as effective as a human derived exosome
- Truly Regenerative

Biosomes Treatment

KEY BENEFITS

	Biosomes	Alternative
Functional components	Contain recombinant human proteins	Plant or animal protein Antioxidants
Reproducibility	Manufactured according to strict SOPs. Reduced batch to batch variability	High variability between plant or animal sources
Specificity	Can decide exactly what IS or IS NOT included in each nanoparticle. We control the process	Natural nanoparticles that incorporate what is best for the source (animal or plant) and not what is best for you
Safety	No DNA, RNA or animal products	May contain animal or plant DNA, diseases and contamination
AnteAGE	Over a decade of scientific expertise in understanding growth factors in topical cosmetics	Companies joining the ‘hype’ of stem cell cosmetics

Biosomes Treatment

KEY TALKING POINTS

- Consistency in every vial
- 25 billion pure Biosomes per treatment for maximum results
- Growth factors chosen with precision. Every vial contains the best in anti-aging and regenerative product every time
- Biosomes do not need human cells to produce, therefore eliminating ethical and safety worries
- Safe for all skin types
- Can be safely combined with any aesthetic treatment without contraindication concerns

Exosomes in Both Treatment Solutions and Homecare

- Biosome technology has led to incorporation of the power of Exosomes into daily skincare
- Lipid nanoparticle technology can preserve these nanoparticles for a viable and effective product for use everyday, at home.

No impact from COVID

All particles contain only beneficial proteins

Sterile

Highly customizable for specific applications

Exact composition always known

0% chance of containing DNA

Established technology - Vaccines

Endotoxin free

Engineered to minimize lot-lot variation

Validated

BiosomesP

Formulated for stability

Contain recombinant human protein

Developed based on the worldwide growing understanding of exosome science

Engineered to minimize lot-lot variation

Genotoxicity safe

Next generation technology
Growth Factors → Exosome → Biosome

The same lipid bi-layer membrane found in exosomes

Functionally tested

10 Questions to Ask an Exosome Innovator

1	2	3	4	5
Investment	**GMP Manufacturing**	**Publication**	**Patent**	**Efficacy Safety**
$80M Since 2017	ExoGMP™ $31M ExoSCRT™	29 10 more expected	72 9 US patents	1.6M clinical cases (50+ countries)

6	7	8	9	10
Source	**Quality/Purity**	**Stability**	**Registration**	**Customers**
ASC-Exo/ Plant/Others The most potent The most anti-inflammatory The closest to skin	4 Master Cell Banks TFF & QC/QA	Lyophilization (2-3 years)	US PCPC/ICID EU CPNP	15K clinics/providers (50+ countries)

9 Questions to Ask an Exosome Company

1. **Investment (R&D/Mfg)**
   $80M
   (Since 2017)

2. **GMP Manufacturing**
   ExoGMP™($31M)
   ExoSCRT™

3. **Publication**
   18
   (3 more expected)

4. **Patent**
   56+ (8 US patents)
   (110+ applications)

5. **Efficacy Safety**
   1.1M cases worldwide

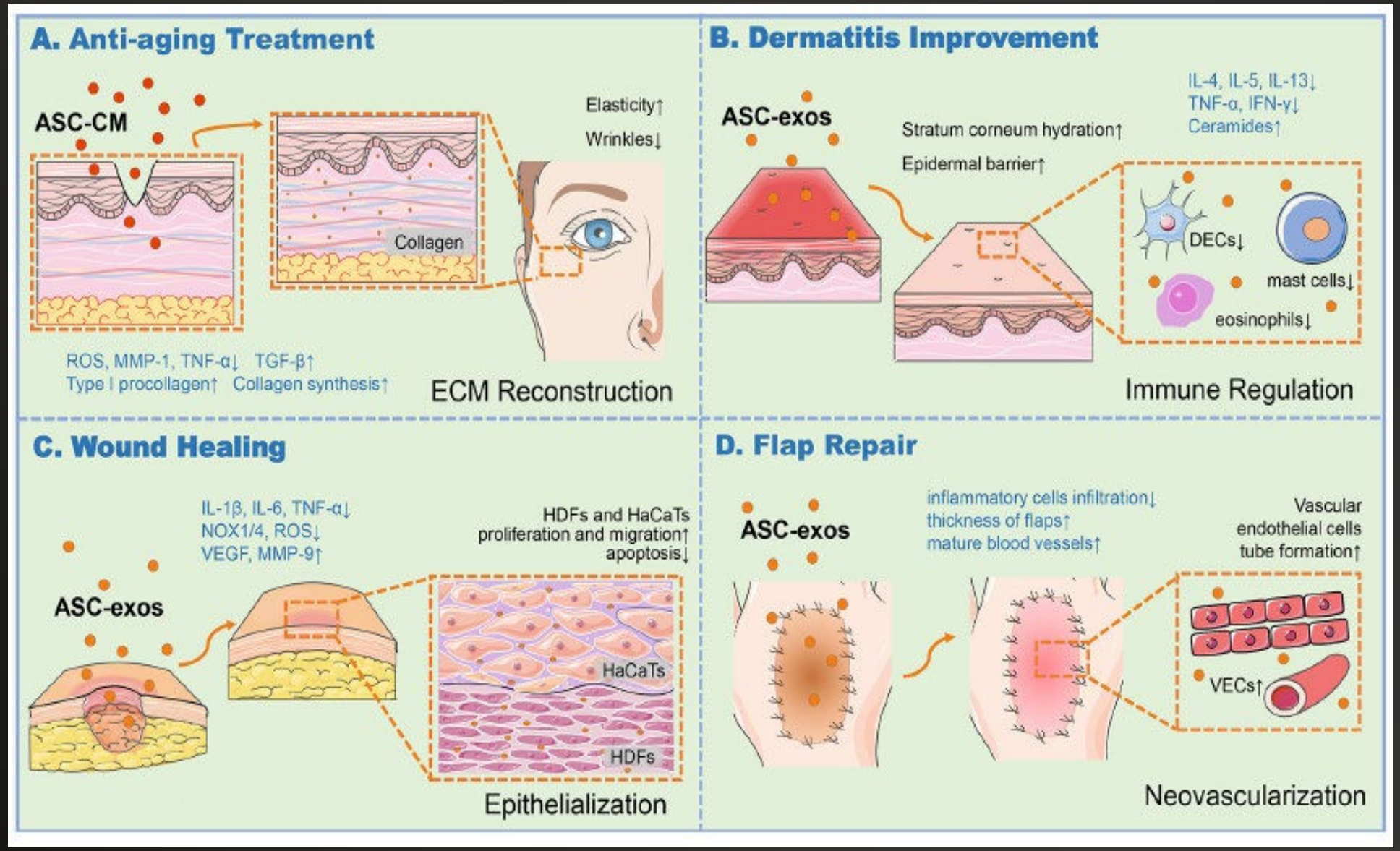
6. **Source**
   ASC-Exo/Plant/Others
   The most potent
   The most anti-inflammatory
   The closest to skin

7. **Purity**
   4 Master Cell Banks
   TFF & QC/QA

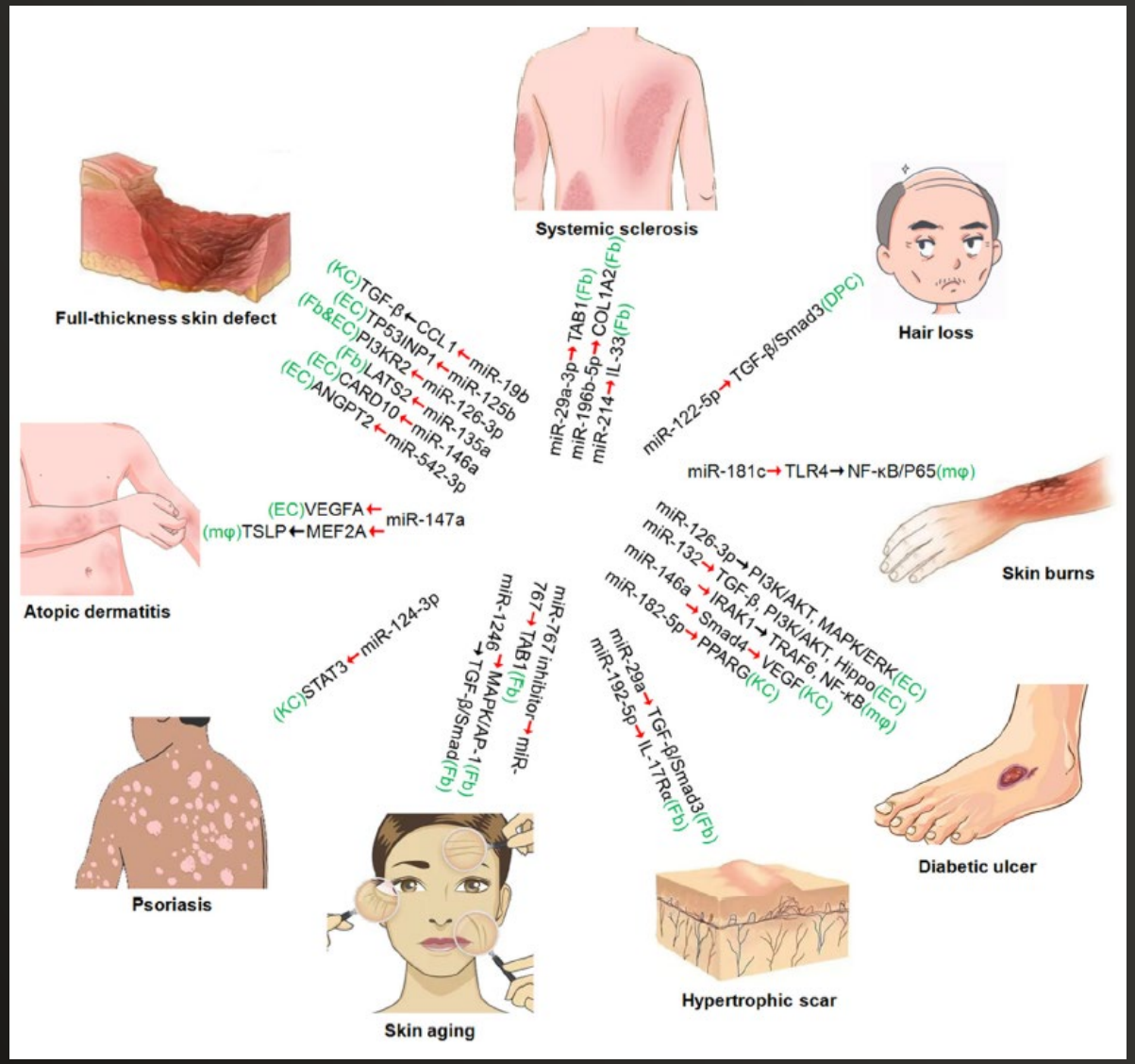
8. **Stability**
   Lyophilization
   (2-3 years)

9. **Registration**
   US PCPC/ICID
   EU CPNP

Exosomes in Skin-related Applications



Exosomal microRNA-Based therapies for skin diseases



- Twenty-one exosomal microRNA-based therapies for nine skin diseases.
- The red arrow in the figure represents targeted binding, the black arrow represents activation, and the green brackets represent the type of effector cells.
- miR, microRNA; Fb, fibroblasts; DPC, dermal papilla cell; m4, macrophage; EC, endothelial cell; KC, keratinocyte.

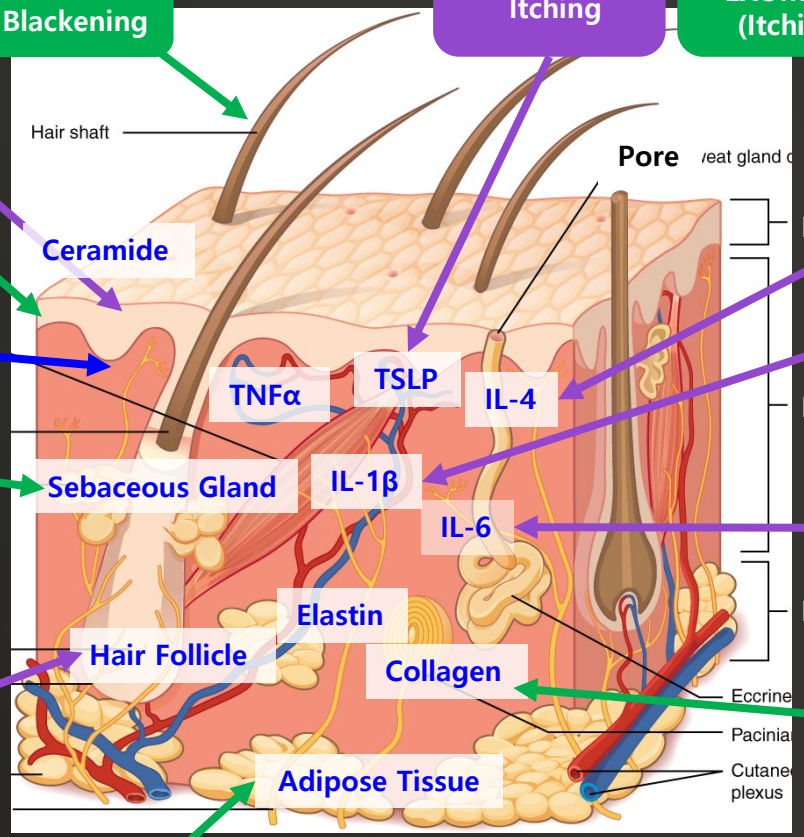
Source: Regenerative Therapy 25 (2024) 101-112

Comprehensive Patent Portfolio

- **55+ Patents (Medicine and/or aesthetics)**
- Naïve, conditioned or engineered
- Skin & hair
- Regeneration & anti-inflammation
- Human, plant, or microbial exosomes/EVs

Medicine or Medical Aesthetics

Aesthetics



Hair Blackening

Itching

EXOMAGE (Itching)

Celltweet (Itching)

Skin Barrier Reconstruction

Transdermal delivery

Wound Healing

Sebum reduction

Hair loss

Vexosome

Dermatitis

Anti-inflammation

EXOMAGE (Dermatitis)

Acne

Rose

Edelweiss

Galactomyces

Exosome & PDRN

Exosome Filler

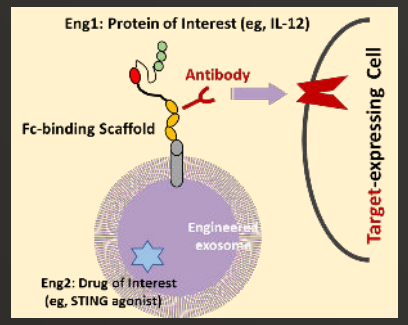
5 Types of Exosomes/Extracellular Vesicles (EV)

Patent No. KR 10-1895916

Human

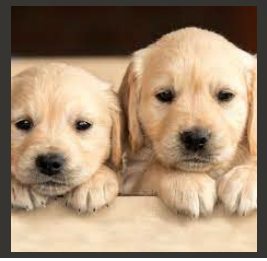
Plant

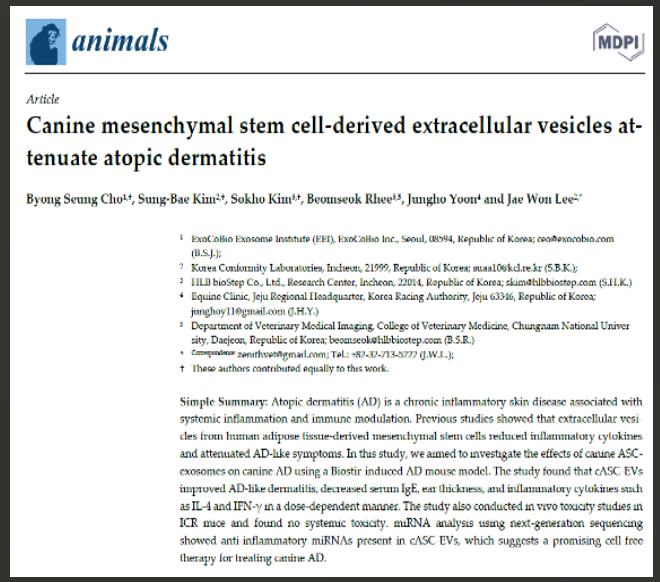
Microbe



Engineered
(Drug delivery)

Animal





animals

MDPI

Article

Canine mesenchymal stem cell-derived extracellular vesicles attenuate atopic dermatitis

Byong Seung Cho[1,†], Sung-Bae Kim[2,†], Sokho Kim[3,†], Beomseok Rhee[3,†], Jungho Yoon[4] and Jae Won Lee[2,*]

[1] ExoCoBio Exosome Institute (EEI), ExoCoBio Inc., Seoul, 08594, Republic of Korea; ceo@exocobio.com (B.S.J.);
[2] Korea Conformity Laboratories, Incheon, 21999, Republic of Korea; susa106@kcl.re.kr (S.B.K.);
[3] HLB bioStep Co., Ltd., Research Center, Incheon, 22014, Republic of Korea; skim@hlbbiostep.com (S.H.K.)
[4] Equine Clinic, Jeju Regional Headquarter, Korea Racing Authority, Jeju 63346, Republic of Korea; junghoy11@gmail.com (J.H.Y.)
[5] Department of Veterinary Medical Imaging, College of Veterinary Medicine, Chungnam National University, Daejeon, Republic of Korea; beomseok@hlbbiostep.com (B.S.R.)
* Correspondence: zenithvet@gmail.com; Tel.: +82-32-713-5777 (J.W.L.);
† These authors contributed equally to this work.

Simple Summary: Atopic dermatitis (AD) is a chronic inflammatory skin disease associated with systemic inflammation and immune modulation. Previous studies showed that extracellular vesicles from human adipose tissue-derived mesenchymal stem cells reduced inflammatory cytokines and attenuated AD-like symptoms. In this study, we aimed to investigate the effects of canine ASC-exosomes on canine AD using a Biostir induced AD mouse model. The study found that cASC EVs improved AD-like dermatitis, decreased serum IgE, ear thickness, and inflammatory cytokines such as IL-4 and IFN-γ in a dose-dependent manner. The study also conducted in vivo toxicity studies in ICR mice and found no systemic toxicity. miRNA analysis using next-generation sequencing showed anti inflammatory miRNAs present in cASC EVs, which suggests a promising cell free therapy for treating canine AD.

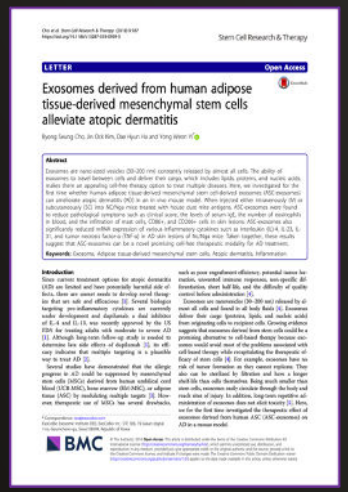
Exosome Regenerative Complex

- Exosome Regenerative Complex and Exosome Regenerative Complex + are post care " topical use" cosmetic solutions. The isolated and purified exosomes in both products have been accepted by the PCPC, and International Cosmetic Ingredient Nomenclature Committee (INC), and the name 'Human Adipose Stromal Cell Exosomes' was given and published in the International Cosmetic Ingredient Dictionary and Handbook, known as INCI book. There are at this time no other cosmetic INCI name(s) assigned to exosome products in the market prior to this accomplishment. These products are not drug products. They are not intended to prevent, treat or cure diseases or medical conditions. They are not intended to be injected or delivered intravenously.

Publications

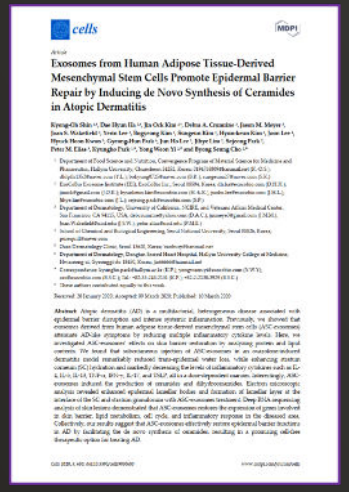
Year	Title	Journal	Impact Factor
July, 2018	**(Atopic Dermatitis)** Exosomes derived from human adipose tissue-derived mesenchymal stem cells alleviate atopic dermatitis	*Stem Cell Research & Therapy*	5.116
Jan, 2020	**(Biodistribution)** Advanced in analysis of biodistribution of exosomes by molecular imaging	*International Journal of Molecular Sciences*	4.556
Mar, 2020	**(Skin Barrier)** Exosomes from human adipose tissue-derived mesenchymal stem cells promote epidermal barrier repair by inducing de novo synthesis of ceramides in atopic dermatitis	*Cells*	4.336
May, 2020	**(Skin Regeneration)** Mesenchymal stem cell-derived exosomes for immunomodulatory therapeutics and skin regeneration	*Cells*	4.336
Jun, 2020	**(Safety Profiling)** Toxicological evaluation of exosomes derived from human adipose tissue-derived mesenchymal stem/stromal cells	*Regulatory Toxicology and Pharmacology*	2.652

Atopic Dermatitis (*Stem Cell Res. Ther.*)



Biodistribution (*Int. J. Mol. Sci.*)

Skin Barrier (*Cells*)



Skin Regeneration (*Cells*)

Safety Profiling (*Regul. Toxicol. Pharmacol*)

Publications

Year	Title	Journal	Impact Factor
Jul, 2020	**(TFF-AKI)** Reproducible large-scale isolation of exosomes from adipose tissue-derived mesenchymal stem/stromal cells and their application in acute kidney injury	*International Journal of Molecular Sciences*	4.556
In Press	**(Acne Scar)** Skin Brightening Efficacy by Exosomes Derived from Human Adipose Tissue-derived Stem/Stromal Cells: A Prospective, Split-face, Randomized Controlled Study	*Acta Dermato-Venereologica*	3.692
Under Revision	**(Skin Brightening)** Skin Brightening Efficacy by Exosomes Derived from Human Adipose Tissue-derived Stem/Stromal Cells: A Prospective, Split-face, Randomized Controlled Study	*Cosmetics*	(2.8)

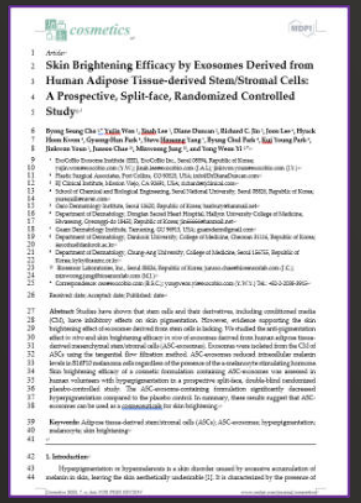
TFF – AKI (*Int. J. Mol. Sci.*)


Reproducible Large-Scale Isolation of Exosomes from Adipose Tissue-Derived Mesenchymal Stem/Stromal Cells and Their Application in Acute Kidney Injury

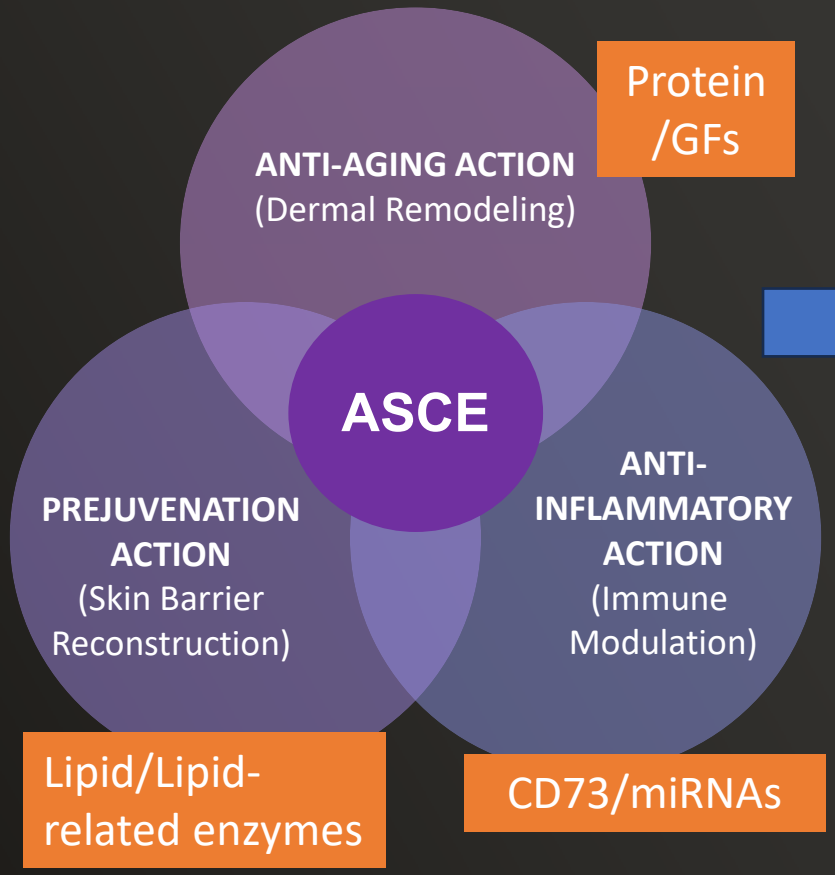
Acne Scar (*Acta Derm. Venereol.*)

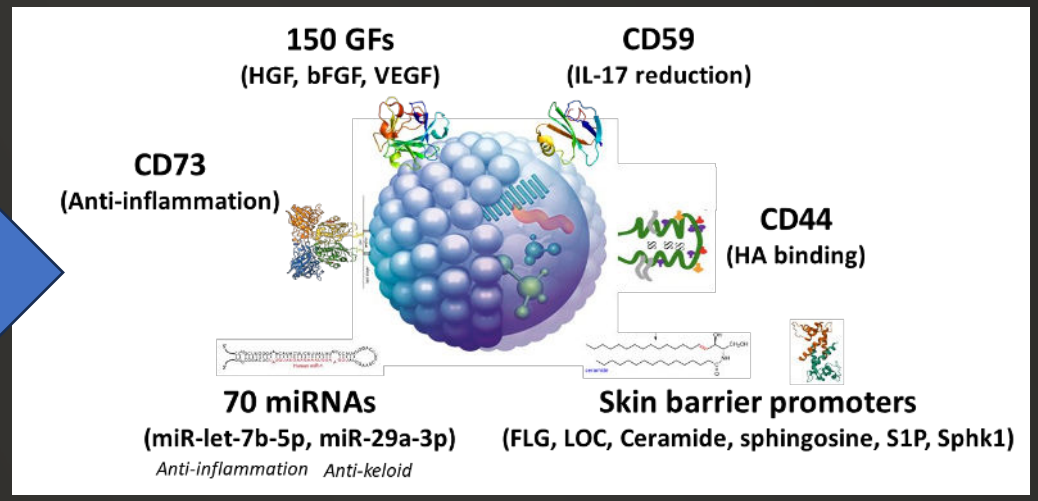

Combination Treatment with Human Adipose Tissue Stem Cell-derived Exosomes and Fractional CO_2 Laser for Acne Scars: A 12-week Prospective, Double-blind, Randomized, Split-face Study

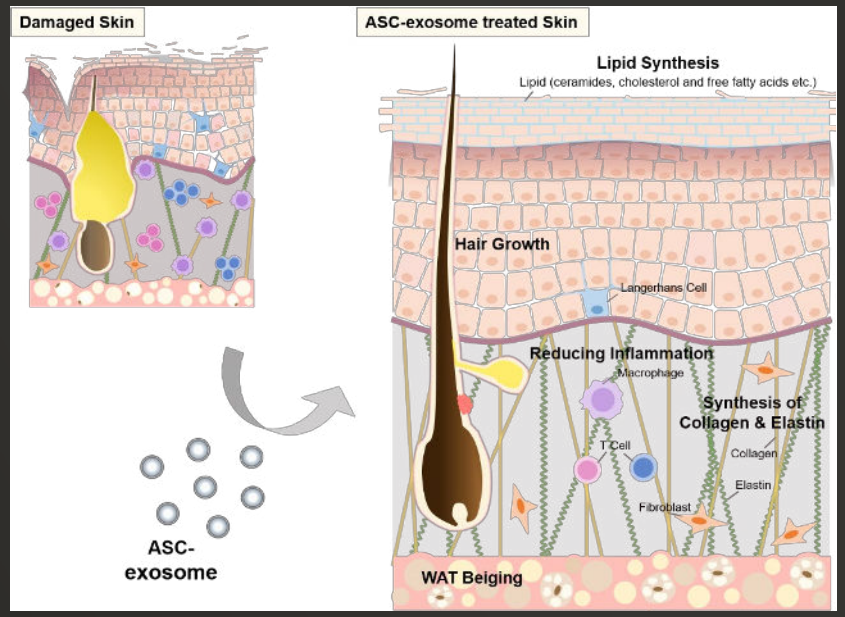
Skin Brightening (*Cosmetics*)


Skin Brightening Efficacy by Exosomes Derived from Human Adipose Tissue-derived Stem/Stromal Cells: A Prospective, Split-face, Randomized Controlled Study

New Paradigm







EXOSOMES TOPICAL APPLICATION

The World's First Exosome-based Double-blind Study

ActaDV

INVESTIGATIVE REPORT

Combination Treatment with Human Adipose Tissue Stem Cell-derived Exosomes and Fractional CO_2 Laser for Acne Scars: A 12-week Prospective, Double-blind, Randomized, Split-face Study

Hyuck Hoon KWON[1], Steven Hoseong YANG[2], Joon LEE[1], Byung Cheol PARK[3], Kui Young PARK[4], Jae Yoon JUNG[1], Youin BAE[5] and Gyeong-Hun PARK[5]

[1]Oaro Dermatology Institute, Seoul, Republic of Korea, [2]Guam Dermatology Institute, Guam, USA, [3]Department of Dermatology, Dankook University, College of Medicine, Cheonan, [4]Department of Dermatology, Chung-Ang University, College of Medicine, Seoul, and [5]Department of Dermatology, Dongtan Sacred Heart Hospital, Hallym University College of Medicine, Hwaseong, Republic of Korea

A variety of applications of human adipose tissue stem cell-derived exosomes have been suggested as novel

tient, one side of the face was treated with adipose tissue stem cell-derived exosomes gel and the other side was treated with control gel. Adipose tissue stem cell-derived exosomes-treated sides had achieved a significantly greater improvement than the control sides at the final follow-up visit (percentage reduction in

SIGNIFICANCE

able responses, a shorter recovery time, and fewer side-effects. The combined use of adipose tissue stem cell-derived exosomes with resurfacing devices could provide synergistic effects on the efficacy and safety of atrophic acne scar treatments.

But still clinical necessity for better efficacy & shortened post-treatment downtime is needed for these procedures !

Received: 12 July 2022 | Revised: 24 May 2023 | Accepted: 2 June 2023

DOI: 10.1111/jocd.15872

JCD Journal of Cosmetic Dermatology

WILEY

ORIGINAL ARTICLE

Efficacy of combined treatment with human adipose tissue stem cell-derived exosome-containing solution and microneedling for facial skin aging: A 12-week prospective, randomized, split-face study

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Exosome for Dupilumab Facial Redness (DFR)

Publication 1: KY Park et al., 2021, https://doi.org/10.1111/jocd.14153, Journal of Cosmetic Dermatology

Publication 2: KY Park et al., 2023, https://doi.org/10.1080/09546634.2023.2220444, Journal of Dermatological Treatment

Pub2: ASCE to Treat Dupilumab Facial Redness (DFR)

Adipose-derived stem cell exosomes for treatment of dupilumab-related facial redness in patients with atopic dermatitis

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ABSTRACT

Background: Dupilumab facial redness (DFR) is a side effect of dupilumab treatment that has only been recently reported. We previously reported on two patients with DFR who were successfully treated with a topical formulation containing human adipose tissue-derived mesenchymal stem cell-derived exosomes (ASCEs).

Objectives: The study aimed to evaluate the efficacy and safety of ASCEs in DFR.

Participants and methods: We performed 12-week prospective study at single center. Twenty adult atopic dermatitis patients diagnosed with DFR were enrolled. They were treated with a topical application of the exosome formulation every week for five consecutive weeks.

Results: After exosome treatment, both the average investigator global assessment score and clinical erythema assessment scale scores decreased. 19 patients (95%) were satisfied with the treatment. Compared to baseline, erythema index at week 4 were decreased by 31, 27, 13, and 25 units on the forehead, chin, right and left cheek respectively. The analysis of stratum corneum samples revealed the expression of IL-1α and human thymic stromal lymphopoietin was suppressed after exosome treatment, whereas filaggrin and vascular endothelial growth factor expression increased.

Conclusions: This study suggests topical formulation containing ASCEs can alleviate DFR by downregulating local inflammation and restoring skin barrier function.

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KEYWORDS
Atopic dermatitis; dupilumab; dupilumab facial redness; exosome; filaggrin; inflammation

Source: J Dermatolog Treat. 2023 Dec;34(1):2220444. doi: 10.1080/09546634.2023.2220444.

White Hair (Poliosis)

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poliosis with hair dye or wear a hat, headscarf, bandana, or wig.

If you really struggle to adjust to your poliosis, your doctor might suggest a support group where you can connect with other people who also have poliosis and other conditions that cause it.

Can White Hair from Poliosis Turn Dark Again?

White hair from poliosis, though, won't retur to your natural color again. It's caused by a lack of pigment and pigment cells, which leads to permanent color loss.

If your c
your doc

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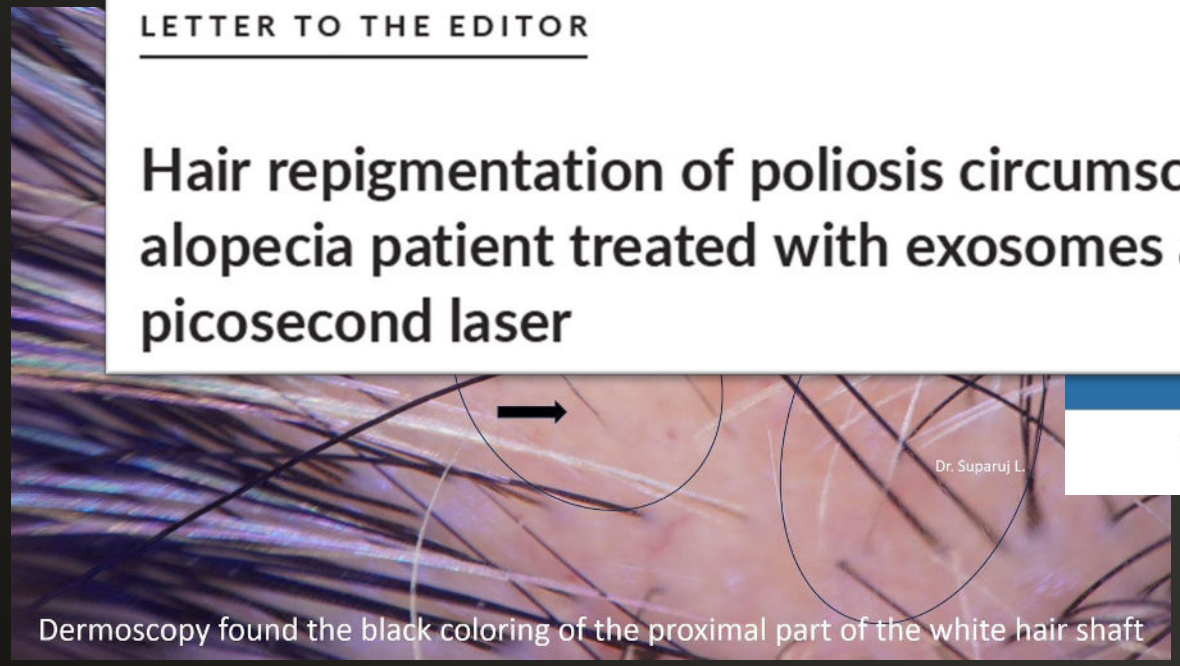
JCD Journal of Cosmetic Dermatology
WILEY

LETTER TO THE EDITOR

Hair repigmentation of poliosis circumscripta in androgenetic alopecia patient treated with exosomes and fractional picosecond laser

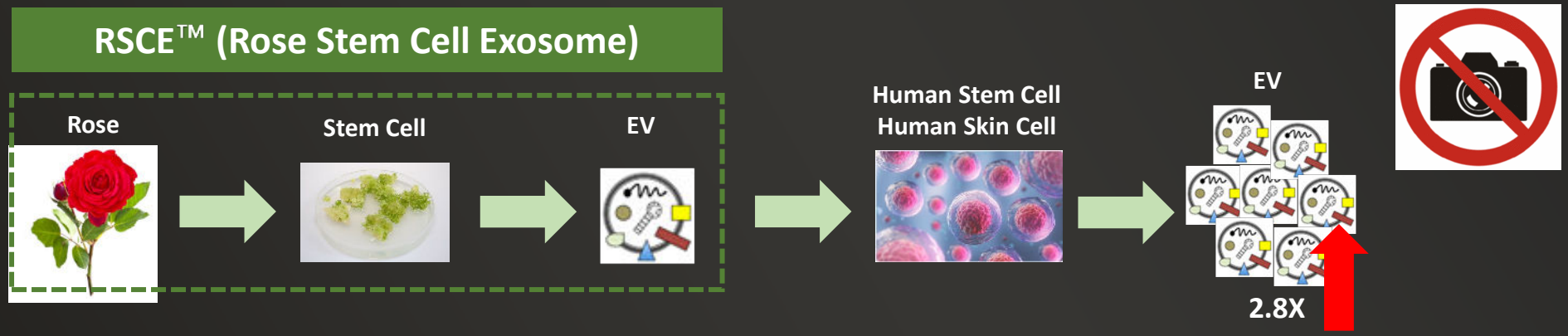


Dermoscopy found the black coloring of the proximal part of the white hair shaft

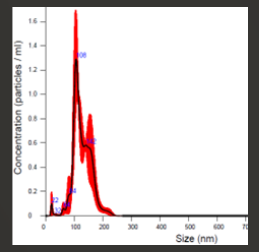
Source: Dr. Suparuj Lueangarun (Thailand)

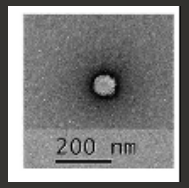
Rose Stem Cell Extracellular Vesicles

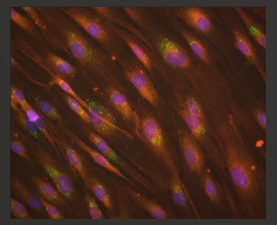
New Exosomes derived from Rose Stem Cells (Callus)

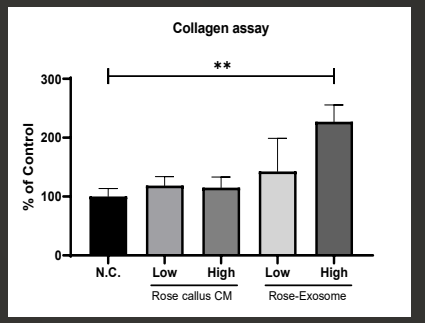


1. Rose stem cells are releasing their EVs or exosomes into conditioned media during callus culture.
2. The size & shape are very similar to human stem cell-derived exosomes.
3. RSCEs are effective in human dermal fibroblasts' proliferation, anti-inflammation, and collagen production (Patented).
4. RSCE can reduce the melanin synthesis of mouse melanoma cell line B16F10 (Patented).
5. Surprisingly, miRNAs of RSCE are mostly de novo sequences. Only 27 miRNAs are matching with human sequences. The top 5 miRNAs are all related to cellular proliferation or housekeeping.
6. Most importantly, RSCE was found to stimulate the EV release of human skin/stem cells (Patent pending).









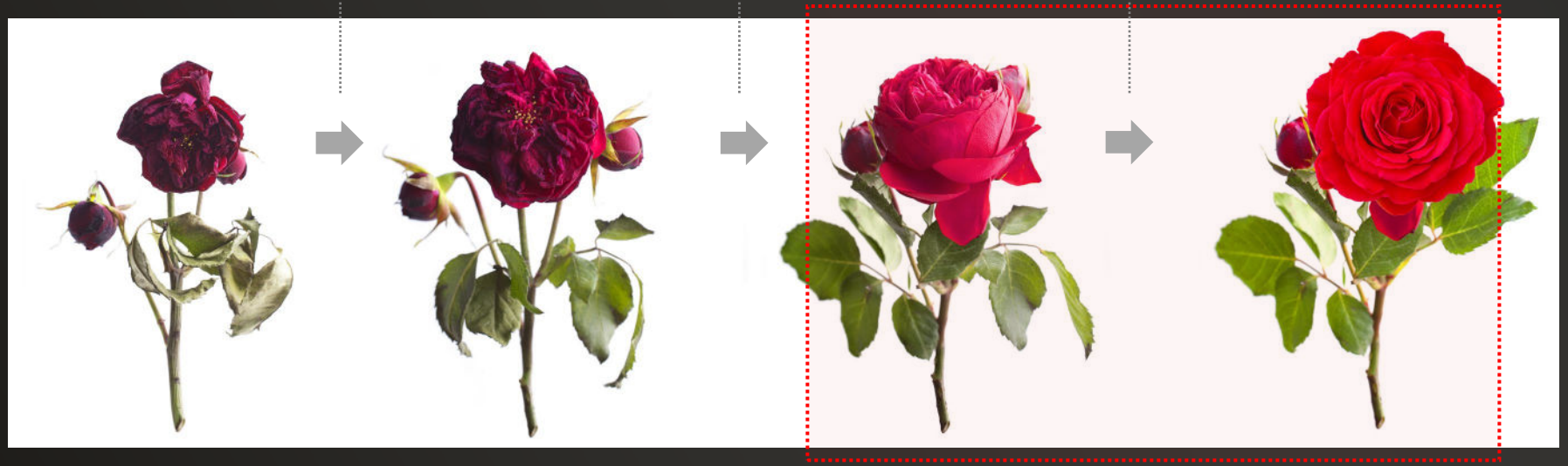
Source: ExoCoBio (To be published)

A New Wave OF Medical Aesthetics

VOLUME
REPLACEMENT
REPOSITIONING

SKIN
FIRMING
TIGHTENING

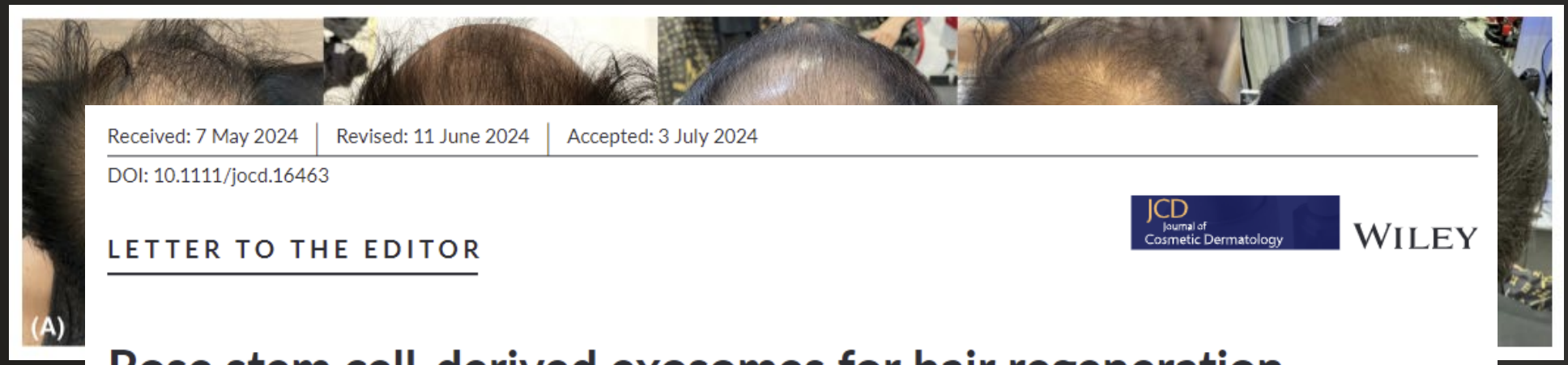
SKIN
Regeneration
Anti-inflammation



Courtesy: Dr. HS Choi, Piena Clinic (Seoul, South Korea)

Clinical Cases: Topical Exosome + Electroporation

- 54-year-old healthy male diagnosed with male pattern AGA
- Hamilton-NorwoodScale V, with no signs of inflammation or scarring
- The electroporation treatment lasted 15 min and was repeated every 3 weeks for a total of 12 sessions.



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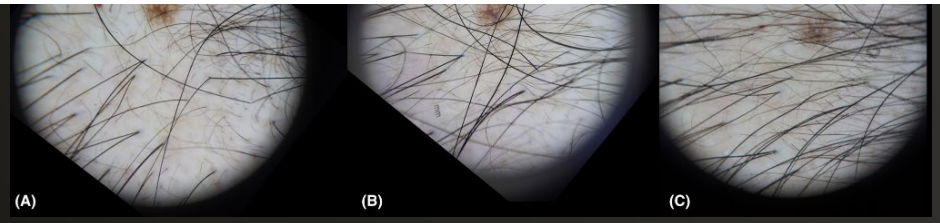
LETTER TO THE EDITOR

Rose stem cell-derived exosomes for hair regeneration enhancement via noninvasive electroporation in androgenetic alopecia



(A) Baseline, (B) After the 6th treatment, and (C) After the 12th treatment

Applying exosomes to the balding scalp area (A), followed by noninvasive electroporation (B) in AGA treatment.

Topical Exosome Cosmeceuticals

- Topical Exosome Cosmeceuticals are a growing part of regenerative medicine
- Source is important
- Clinical studies are critical
- More information will come our way to further define how best to use them and for what aesthetic conditions
- And FDA guidance is critical