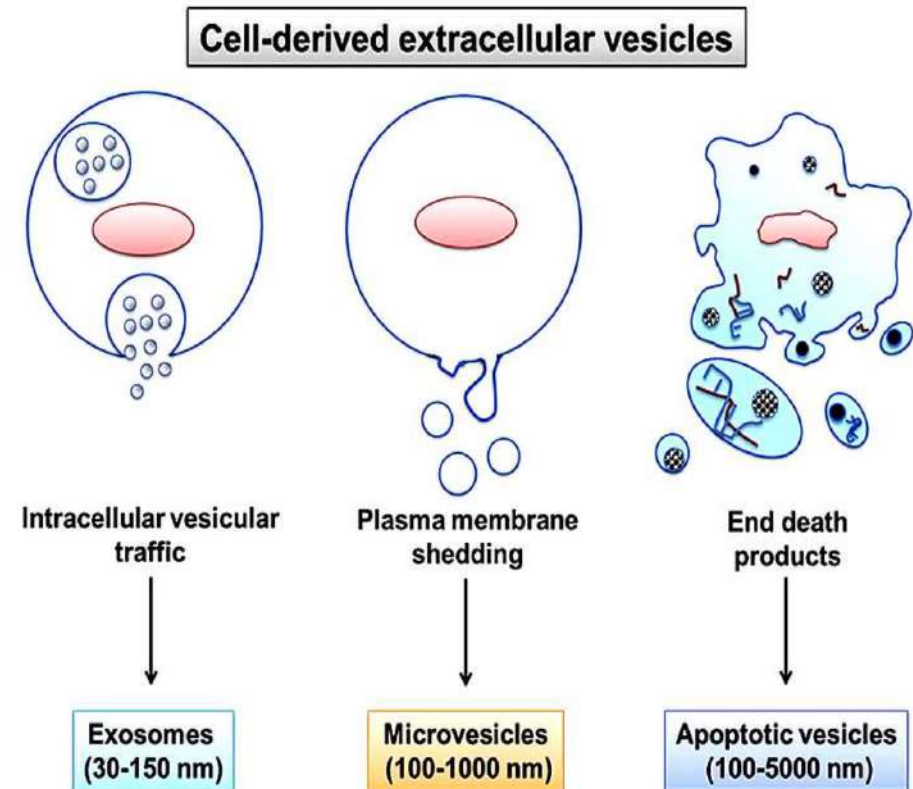


# Qué es un Exosoma?

Gabriel Buendía Bordera

## Vesículas extracelulares

- **Extracellular vesicles (EVs)** are membrane derived nanometer-sized vesicles.
- EVs are released by normal, diseased, and transformed cells *in vitro* and *in vivo*, and carry lipids, proteins, mRNAs, non-coding RNAs, and even DNA out of cells.
- Classification of extracellular vesicles according to the mechanism of generation.
  - Exosomes are generated intracellularly from multivesicular bodies.
  - Microvesicles are produced by budding from the extracellular membrane.
  - Apoptotic vesicles are released upon cell fragmentation during apoptotic cell death.

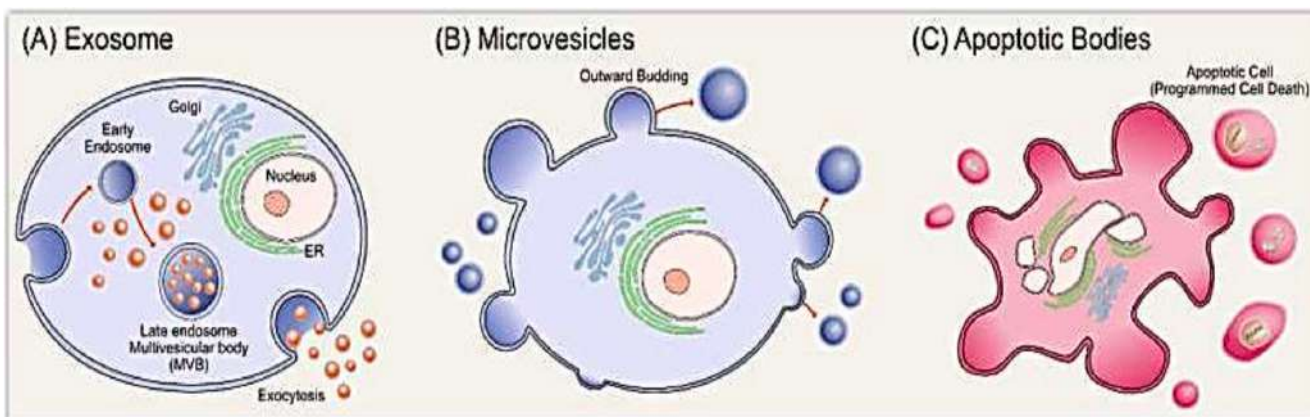


(Source: Devhare and Ray, 2018)

## Tipos de Vesículas extracelulares

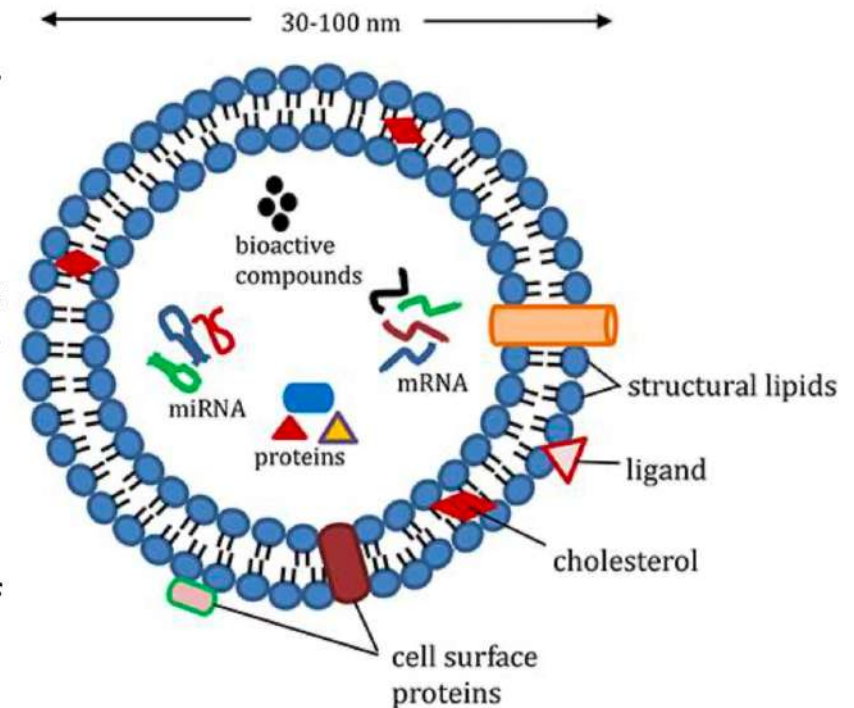
(Source: Edip and Peynircioğlu, 2015; Gurunathan *et al.* 2019)

Type	Size	Density	Biogenesis	Composition
Microvesicles	100-1000 nm	undefined	Budding of plasma membrane	Actin, tubulin, $\beta 1$ integrin, VAMP3*, miRNA*
Exosomes	50-100 nm	1.13-1.19 g/mL	Exocytosis of multivesicular bodies	Heat shock proteins, actin, tubulin, MHC molecules*, tetraspanins (CD63, CD81, CD82, CD9), miRNA, mRNA*
Apoptotic bodies	100-5000 nm	1.16-1.28 g/mL	Budding of plasma membrane during apoptosis	Annexin V, C3b*, thrombospondin, any cellular components
Retrovirus-like particles	90-100 nm	1.13-1.16 g/mL	Direct budding of plasma membrane	Retroviral proteins such as Gag*, cytoskeletal proteins, plasma membrane components



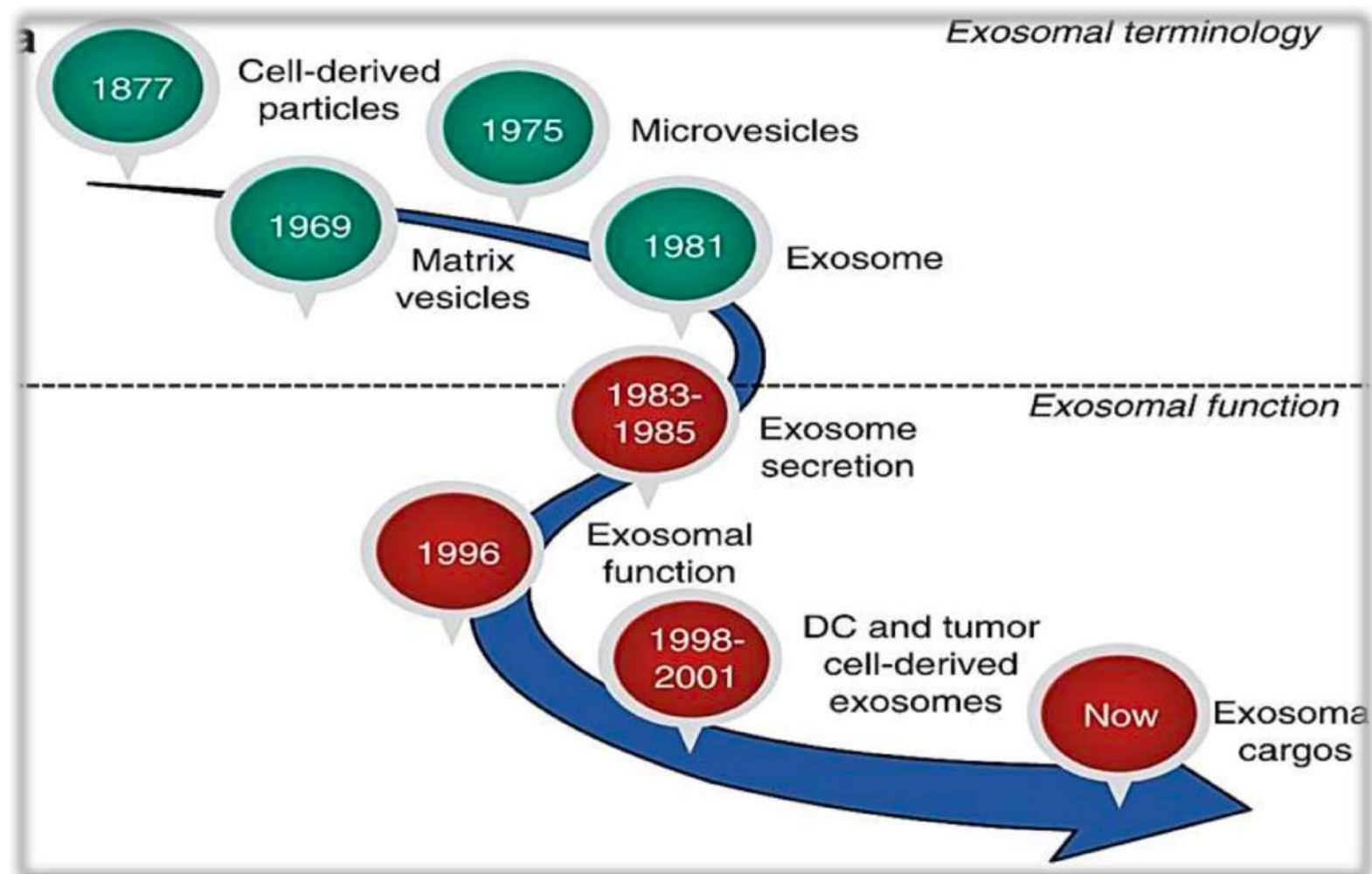
## Estructura del exosoma

- Exosomes are nano-sized small extracellular vesicles secreted by cells, carrying nucleic acids, proteins, lipids and other bioactive substances to play a role in the body's physiological and pathological processes.
- In 1986, Eberhard G. Trams and R.M. Johnstone first discovered a small vesicle with a membrane structure in the culture supernatant of red blood cells of sheep in vitro, and named it exosomes.
- Exosomes are single-membrane nano-sized vesicles with a diameter of ~30 to ~100nm with a topology similar to that of a cell.



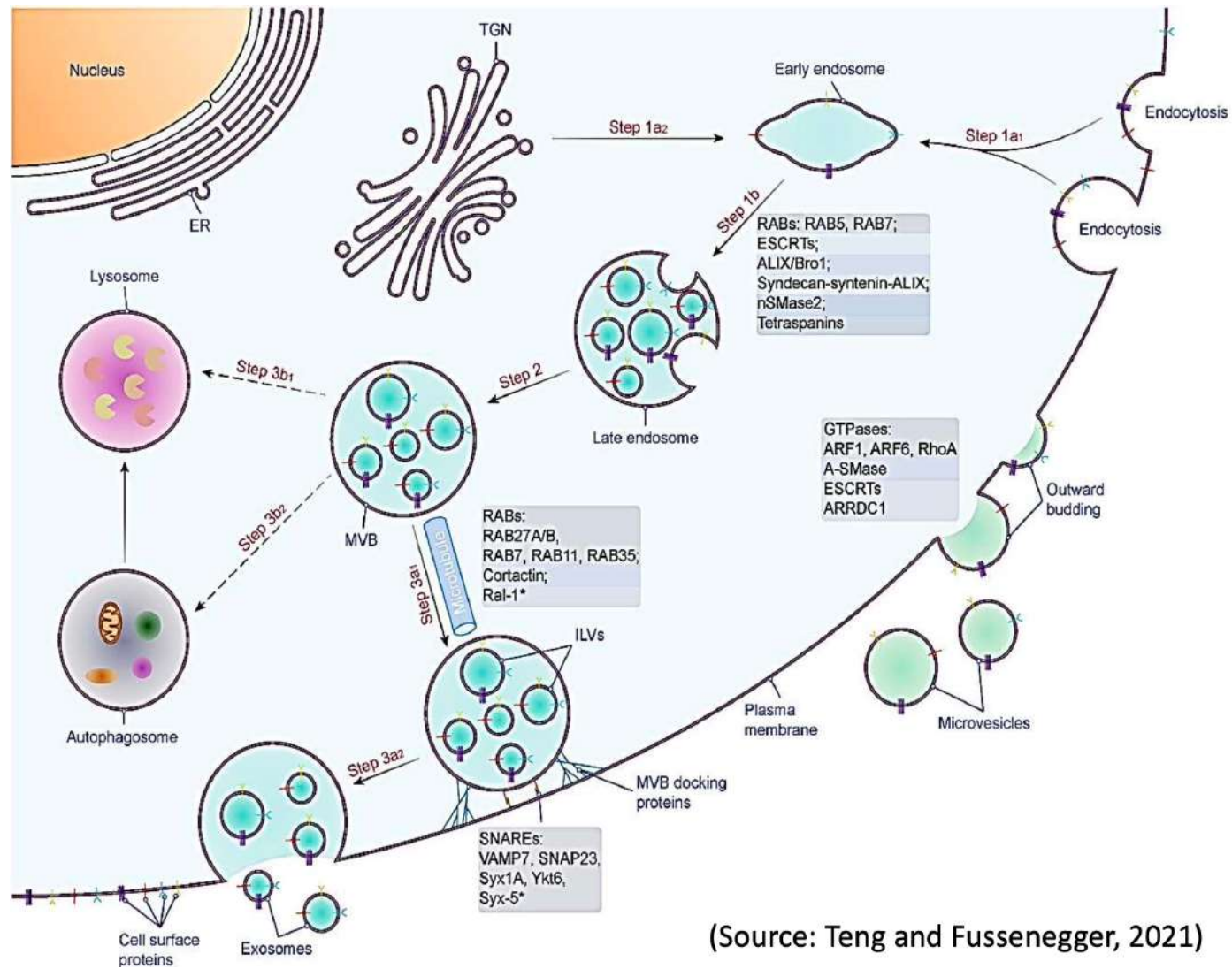
(Source: Akuma *et al.* 2019)

## Historia de la investigación



(Source : Gao *et al.* 2018)

## ¿ Cómo se genera un exosoma?

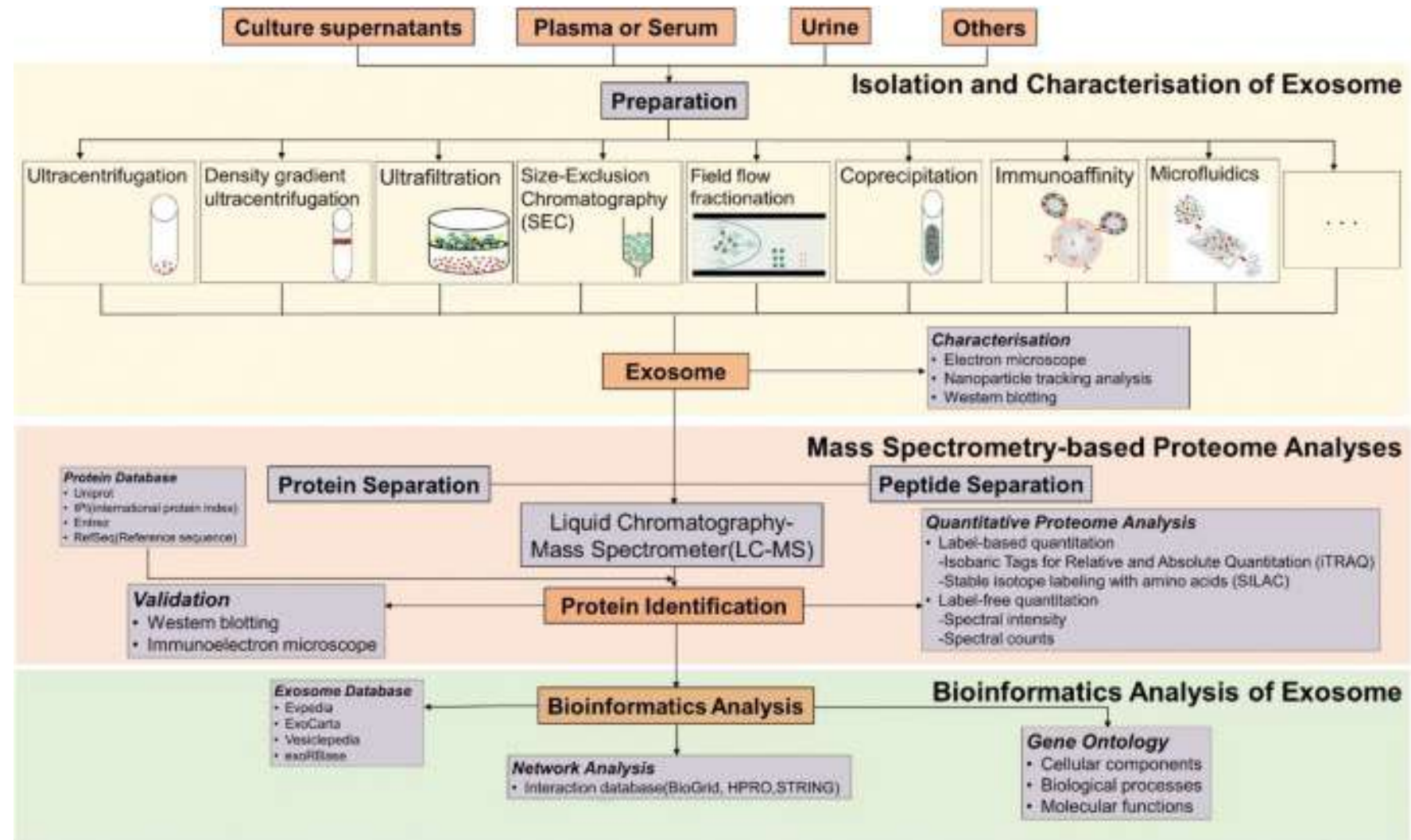


(Source: Teng and Fussenegger, 2021)

## Vesículas extracelulares

- Exosomes are of two types
  1. Natural exosomes
  2. Engineered exosomes
- **Natural exosomes** are divided into
  - ✓ Animal-derived exosomes: normal exosomes and tumor exosomes.
  - ✓ Plant-derived exosomes.
- **Engineered exosomes** are Engineering of targeted molecules on exosomes, where Targeting ligands on the surfaces of exosomes can also be engineered. The most commonly used technique is to insert the gene encoding the targeting proteins into the donor cells. The donor cells then secrete this protein in the exosomes.
- Almost all types of normal cells can produce exosomes, human umbilical vein endothelial cells, mesenchymal stem cells (MSC), nervous system cells such as schwann cells, astrocytes and neurons, by epithelial cells, by fibroblasts and adipocytes, as well as by cells of the immune and hematopoietic systems, where their secretion was first detected in particular by reticulocytes, B lymphocytes, T cells, platelets, mast cells, dendritic cells, natural killer (NK) cells and macrophages.

## Técnicas de Aislamiento





## Vesículas extracelulares



# INTRODUCCION

ASCEplus SRLV

ASCE<sup>plus</sup>™

Advanced Skincare Complex from ExoCoBio

## Líder Mundial en la Industria de Exosomas – Competitividad de ExoCoBio

### Líder Mundial de Exosomas ; [ ExoCoBio Globalmente ]



**US** Fundada en 2016  
\$168.5M, Series A/B/C

**US** Fundada en 2008  
\$112M, Series A/B/C

**UK** Fundada en 2016  
\$59.5M, Series A/B



- Fuente: <https://bioinformant.com/top-exosome-companies>
- Basado en el tamaño financiero a partir de 2018



**KR** Fundada en 2017  
**\$46M**, Series A/B

- BioInformant, una compañía de noticias que se especializa en el campo de células madre/exosomas, seleccionó las 4 principales empresas de biotecnología de exosomas en todo el mundo, que incluyeron ExoCoBio
- **"ExoCoBio" fué la única compañía asiática seleccionada**

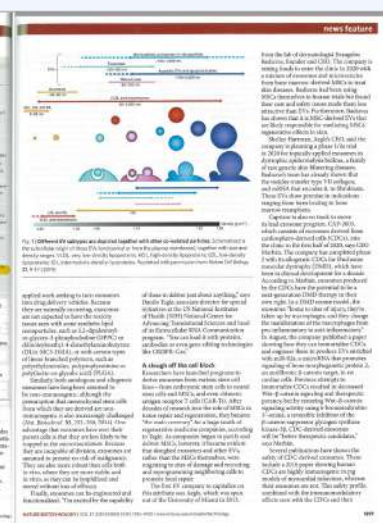
## Líder Mundial en la Industria de Exosomas – Competitividad de ExoCoBio

# Líder Mundial de Exosomas ; [ ExoCoBio Globalmente ]



news feature

Company name	Product	Indication	Expected EU (breakthrough) date	Lead PI product definition
Amgen (USA)	Amgen's first-in-class (FIC) anti-IL-17A antibody, secukinumab	Psoriasis and ankylosing spondylitis	2015	First-in-class anti-IL-17A antibody, secukinumab
Novartis (USA)	Novartis' first-in-class (FIC) anti-IL-17A antibody, ixekicimab	Psoriasis and ankylosing spondylitis	2015	First-in-class anti-IL-17A antibody, ixekicimab
Regeneron (USA)	Regeneron's first-in-class (FIC) anti-IL-17A antibody, brodalumab	Psoriasis and ankylosing spondylitis	2015	First-in-class anti-IL-17A antibody, brodalumab
Novartis (USA)	Novartis' first-in-class (FIC) anti-IL-17A antibody, ixekicimab	Psoriasis and ankylosing spondylitis	2015	First-in-class anti-IL-17A antibody, ixekicimab
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En la Revista científica de renombre mundial "Nature Biotechnology,"  
ExoCoBio fué la única compañía asiática citada

## Líder Mundial de Exosomas, ExoCoBio



La Primera Compañía Líder  
Cosmecéutica y Biofarmacéutica

» basada en Exosomas «

ExoCoBio investiga y desarrolla  
**estética de regeneración basada en exosomas  
y nuevos biofármacos de última generación**



> Vista aérea de la primera planta de fabricación y laboratorio de GMP de nuevos fármacos basados en exosomas del mundo (Osong)

Programado para completar la construcción a finales de 2022, la instalación está ubicada en una parcela de 71,000 pies cuadrados (6,596 m<sup>2</sup>) ocupada con un edificio de dos plantas con un área total de 42,000 pies cuadrados (3,902 m<sup>2</sup>). La instalación es donde la I+D y la fabricación de nuevos fármacos innovadores basados en exosomas se llevan a cabo simultáneamente, también cuenta con una línea de I+D y fabricación para los **exosomas de células madre ingenuas**, que ha estado desarrollando ExoCoBio, y el nuevo proyecto, los **exosomas modificados genéticamente**..

- Destacado en el medio de comunicación nacional BioSpectator News (2021.08.24)

## Contratos exclusivos de suministro y distribución con una empresas a nivel global con un importante conglomerado nacional

# BENEV

### Asociación exclusiva de suministro y distribución

BENEV, una empresa que lideró el mercado con MGF Serum Rejuvenecedor, un nombre familiar en productos de factor de crecimiento compuesto, destacó la excelencia de los exosomas.

**BENEV firmó un contrato exclusivo con ExoCoBio, y está realizando negocios y comercializando activamente con "ERC" y "ERC+" (Exosome Regenerative Complex), productos obtenidos de ExoCoBio como productos representativos de BENEV.**



- BENEV: Fundada en 2000 con sede en California, EE. UU., la empresa ofrece productos de marca exclusivos a profesionales del cuidado de la piel de todo el mundo.

# LG Chem

### Asociación exclusiva de suministro y distribución

Posteriormente, firmó un contrato de distribución nacional exclusiva en 2021 para la línea "ASCEplus", que fue seleccionada como la principal marca y tipo de producto en ascenso en el mercado como sucesora de la principal marca de relleno HA del mercado estético "YVOIRE".

**El contrato exclusivo con ExoCoBio está aumentando su cuota de mercado en el canal de la estética, y el marketing activo continúa con el producto de ExoCoBio como su producto principal.**





## Kim Kardashian reveals her favorite new beauty secret is a laser and light facial combination totaling \$1400

By Jarret Thomas Sackman and Christine Rendon For Dailymail.com  
01:45 21 Dec 2022, updated 02:03 12 Jan 2023



© Kim Kardashian Instagram

**Cutting edge: 'A serum of exosomes' was applied to Kim's flushed face after the treatment, helping to heal her skin by speeding cell turnover**

# IMCAS World Congress 2023 Program

**FOCUS ON S140, S141**

## Exosomes research

Room: Room 342 - Level 3

Date: Friday 27 January 2023 at 10:30 to 12:30

Format: FOCUS SESSION > lectures covering a major topic of the congress

### Chairs



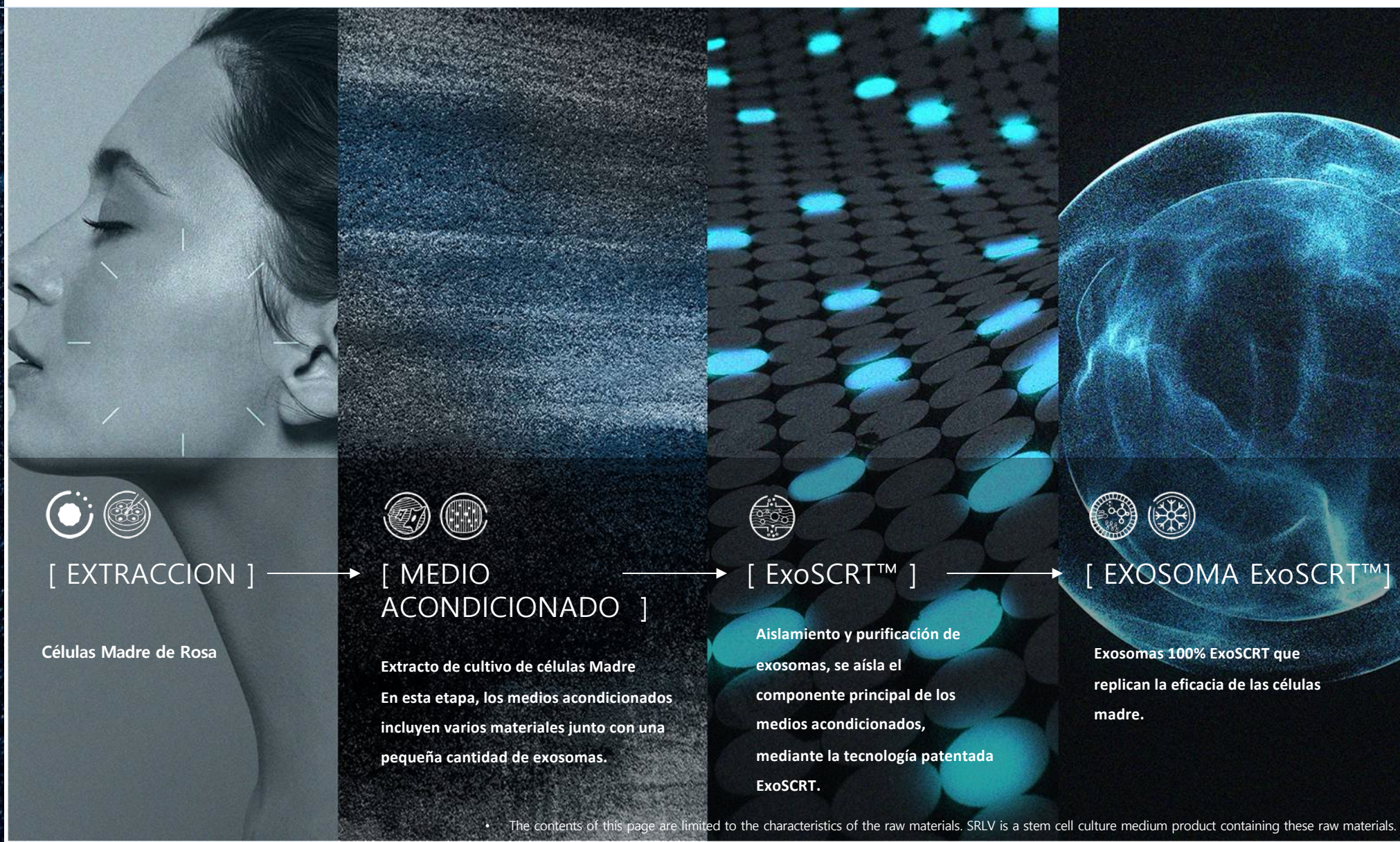
Hours	Speakers	Lecture title	Abstract
10:30	Prof Florence SABATIER	Extra cellular vesicles Characterization and Therapeutic Potential	
10:45	Dr Steven R COHEN	Introduction and pre-clinical science and early cases	
10:57	Dr Tunc TIRYAKI	Hybrisome to retinol in a 100 person study	
11:09	Dr Sabrina FABI	Update on Exosomes in Aesthetics	
11:21	Dr Young Seob LEE	Comparing the skin lifting effects of botulinum toxin and exosome with botulinum toxin	
11:33	Dr Diane Irvine DUNCAN	Improving your patient outcomes in your practice with exosomes (educational grant from Exocobio)	
11:45	Dr Atchima SUWANCHINDA	Ex vivo Exosome: future facial regeneration	



121504



## Exosoma ExoSCRT™ – Introducción



• The contents of this page are limited to the characteristics of the raw materials. SRLV is a stem cell culture medium product containing these raw materials.

## Exosoma ExoSCRT™ – Pautas

Tecnología Patentada

ExoSCRT™  
Exosoma

- Análisis de las características del exosoma según la Sociedad Internacional de Vesículas Extracelulares y el Ministerio de Seguridad de Alimentos y Medicamentos de Corea
- Confirmación del exosoma a través de un estricto control de calidad de acuerdo con las pautas de la Sociedad Internacional de Vesículas Extracelulares y el Ministerio de Seguridad de Alimentos y Medicamentos de Corea

### 1. ISEV

Identificación y Control de Calidad de Exosomas

Conforme a la norma

de ISEV

ISEV : Sociedad Internacional de Vesículas Extracelulares. Una institución científica internacional basada en la investigación de exosomas, microcélulas, tumores y otras secreciones de células.

The image shows two screenshots of the ISEV (International Society for Extracellular Vesicles) guidelines. The top screenshot is the 'MISEV 2014' editorial from the Journal of Extracellular Vesicles, titled 'Minimal experimental requirements for definition of extracellular vesicles and their functions: a position statement from the International Society for Extracellular Vesicles'. The bottom screenshot is the 'MISEV 2018 Update' from the same journal, titled 'Minimal information for studies of extracellular vesicles 2018 (MISEV2018): a position statement of the International Society for Extracellular Vesicles and update of the MISEV2014 guidelines'. Both documents list numerous authors and include an 'OPEN ACCESS' badge.

### 2. MFDS

Identificación y Control de Calidad de Exosomas

Conforme a las pautas

de las Instituciones

Gubernamentales

- Los contenidos de esta página se limitan a las características de las materias primas obtenidas a partir de un medio de cultivo de células madre que contiene estas materias primas.

The image shows four screenshots of the MFDS (Ministry of Food and Drug Safety) guidelines for 'Exosome-based Therapeutic Products' (세포외소포자체계 제품, 비임상 및 임상 평가 가이드라인). The first screenshot is the title page, dated 2018.12. The second screenshot is the '1. 적용 범위' (Scope of Application) section. The third screenshot is the '31 세포외소포자체계 생산을 위한 유통용량의 측정법' (Measurement method for distribution of extracellular vesicle system production). The fourth screenshot is the '32 세포외소포자체계 제조방법, 원리 및 설계, 특성분석' (Manufacturing method, principle and design, and characteristic analysis of extracellular vesicle system). The documents are in Korean and include various regulatory details.

## Exosoma ExoSCRT™ – Directrices

- ExoCoBio **produce Exosomas ExoSCRT™ de calidad** a través de 2 métodos de estandarización y 9 métodos de control de calidad **de acuerdo con los estándares de la sociedad internacional de vesículas extracelulares**

### 1. Estandarización de Exosomas

Método de Estandarización	MISEV 2018	MFDS Directrices	Ejemplo	ExoCoBio
Perfilado de Contenido	-1)	Si	Proteínas, RNAs, Lipidos	Si
Morfología	Si	Si	Electron microscope	Si

### 2. Control de Calidad de Exosomas

Método de Control de Calidad	MISEV 2018	MFDS Directrices	Ejemplo	ExoCoBio
Cuantificación	≥ 2 metodos	≥ 2 metodos	NTA Proteinas o lipidos	Si Si
Distribución de tamaño	Si	Si	NTA	Si
Identidad	Si	Si	CD9, CD63, CD81	Si
Pureza	Si	Si	Calnexina	Si
Ensayos de fuerza	Si	Si	Colágeno, proliferación, inmunomodulación, etc	Si
Pruebas de Mycoplasma <sup>4)</sup>	-1)	Si	Cultura directa, PCR	Si
Pruebas de Endotoxinast <sup>4)</sup>	-1)	Si	KTA, KCA, o análisis de coagulación	Si
Pruebas Esterilidad <sup>4)</sup>	-1)	Si	Cultura directa,	Si
Virus Test <sup>4)</sup>	-1)	Si	Método rápido	Si

- Los contenidos de esta página se limitan a las características de las materias primas. SRLV es un medio de cultivo de células madre que contiene estas materias primas.

<sup>1)</sup>-: not included since beyond the scope; <sup>ND</sup>2): not disclosed; <sup>UM</sup>3): unknown method; <sup>4)</sup>: performed for exosomes solution not for cells or other starting materials

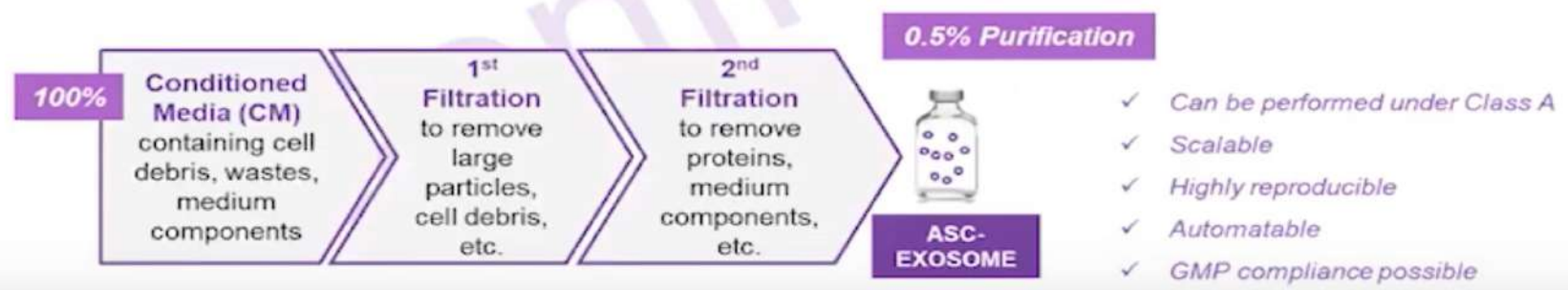
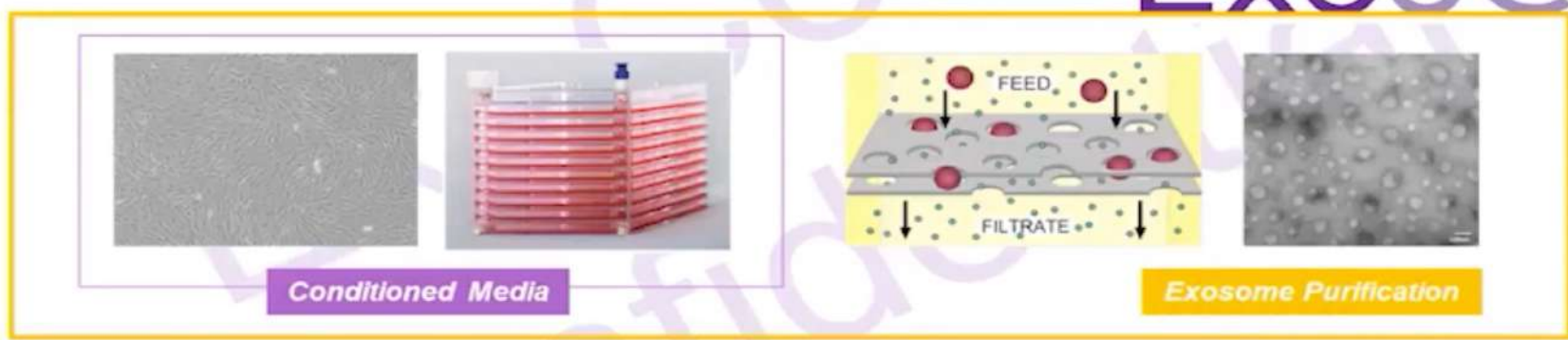
# ExoCoBio's ExoSCRT™ Purification Technology

## Exosome Purification Methods

ExoCoBio	Company					
	R	O	A	K	D	P
ExoSCRT™ (TFF-based)	Not disclosed	Not disclosed	Not disclosed	Not disclosed	Not disclosed	Centrifugation ?

- ExoCoBio's ExoSCRT™ Exosome Isolation Technology is based on the TFF which is the most ideal for industrial manufacturing of Exosomes (protected by patent #10-1895916).
- Total Protein: Conditioned media (100%) VS Exosome (0.5%)

# ExoSCRT

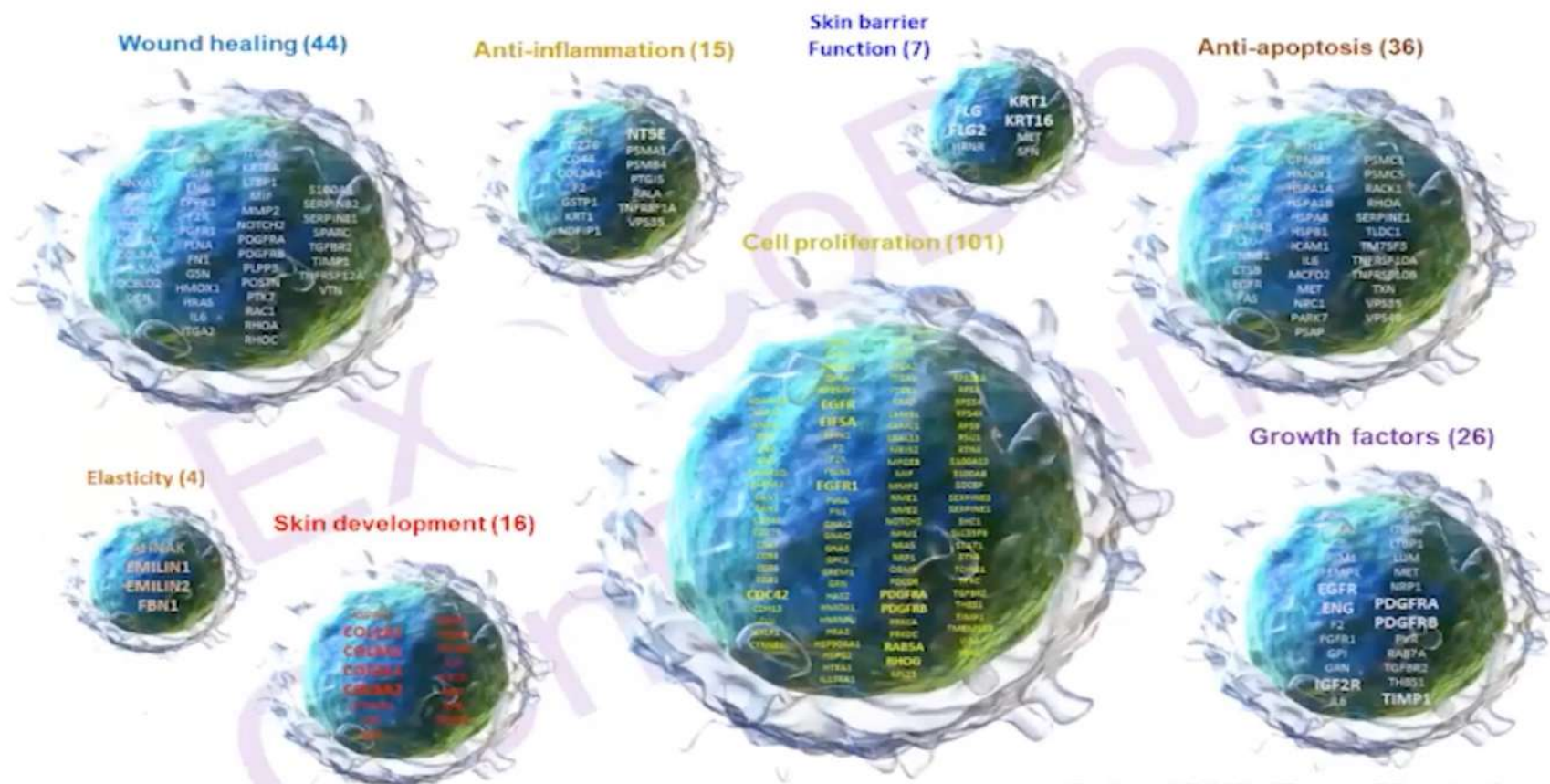


Strictly Confidential

ExoCoBio Webinar 2020.04

# Exosomal Protein Profiling

- ASC-Exosomes have about 1,050 proteins and 180 of them are functional for skin.
- Major expected functions are **cell proliferation, wound healing, anti-apoptosis & growth factors.**



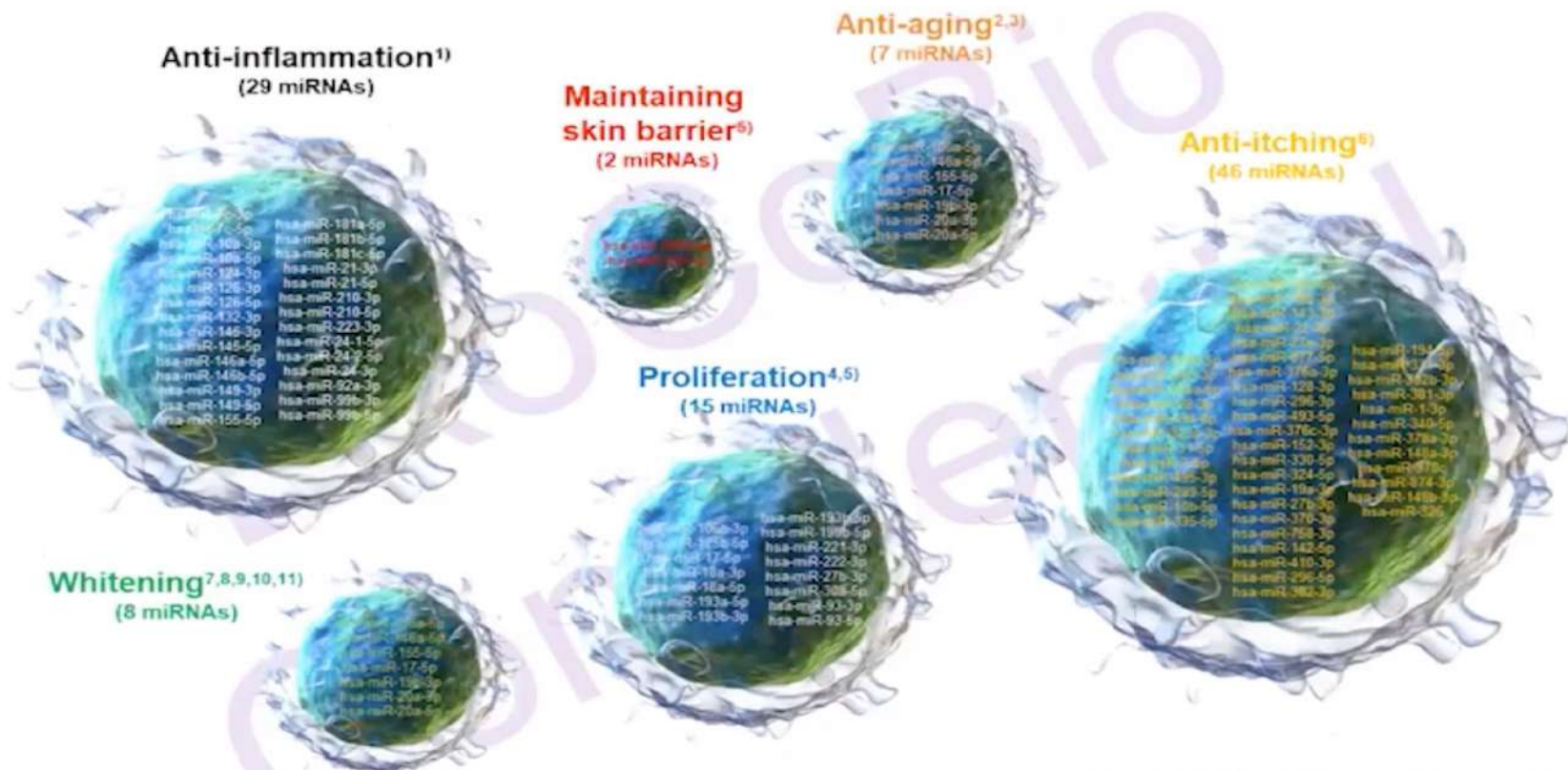
Source: ExoCoBio, unpublished data

1) Front Immunol. 2018; 25:9-1377  
 2) Ageing Res Rev. 2014; 17:9-15  
 3) Aging Cell. 2010; 9:291-6  
 4) Non-coding RNA Investig. 2018; 2:28  
 5) Physiol Genomics. 2011; 43:543-556  
 6) ExoCoBio prediction  
 7) Domest Anim Endocrinol. 2010; 38:200-9  
 8) RNA Biol. 2014 Jun 1; 11: 732-741.  
 9) J Invest Dermatol. 2013; 133:201-9  
 10) J Invest Dermatol. 2014; 134:2846-2849  
 11) Int. J. Mol. Sci. 2015; 16:10921-10933

Source: ExoCoBio, unpublished data

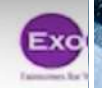
# Exosomal miRNA Profiling

- ASC-Exosomes are found to have about 600 miRNA and 100 of them are functional for skin.
- Major expected functions are **anti-itching, anti-inflammation & proliferation**.



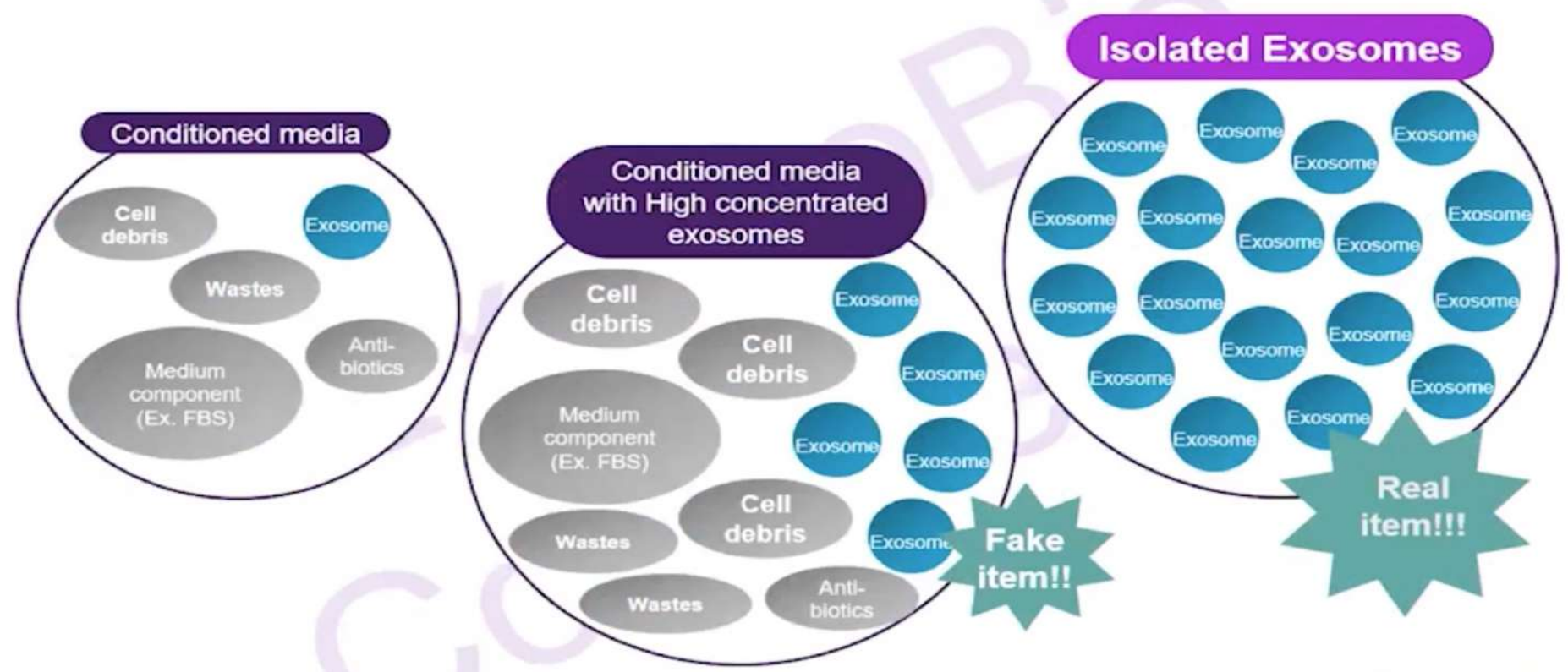
Source: ExoCoBio, unpublished data

1) *Front Immunol*, 2018, 25:9-1377  
 2) *Ageing Res Rev*, 2014, 17:9-15  
 3) *Ageing Cell*, 2010, 9:291-6  
 4) *Non-coding RNA Investig*, 2018, 2:28  
 5) *Physiol Genomics*, 2011, 43:543-556  
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 7) *Domest Anim Endocrinol*, 2010, 38:200-9  
 8) *RNA Biol*, 2014, Jun 1, 11: 732-741  
 9) *J Invest Dermatol*, 2013, 133:201-9  
 10) *J Invest Dermatol*, 2014, 134:2846-2849  
 11) *Int J Mol Sci*, 2015, 16:10921-10933



# Exosome VS Stem Cell Conditioned Media (CM)

- Protein amount: 100% VS 0.5%
- **No culture reagents, no wastes, no antibiotics**
- Anti-inflammation or immuno-modulation



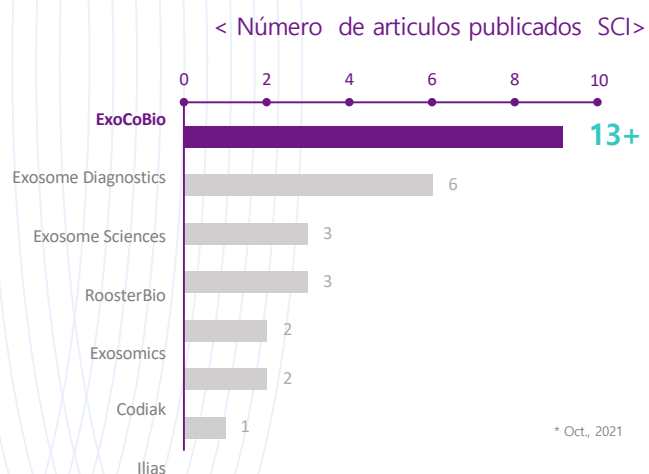
## I+D de ExoCoBio – Estado Actual

# Fondo de Exosoma ; [Sólida Base Científica]

ExoCoBio desarrolla **medicina regenerativa basada en exosomas y nueva biomedicina** con una sólida base científica.

### 1. El mayor número de publicaciones

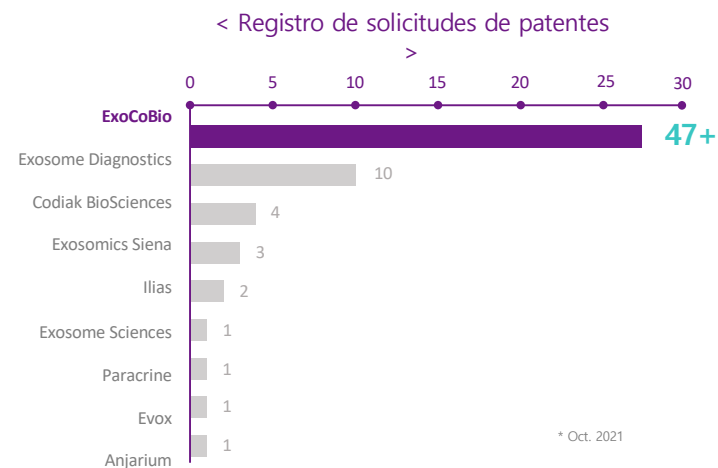
Entre 26 compañías de Exosomas



Fuente: análisis interno de ExoCoBio basado en la afiliación del autor correspondiente  
<https://bioinformant.com/exosome-therapeutics-diagnostics/>

### 2. El mayor número de patentes

Entre 26 compañías de Exosomas



\*Incluyendo la patente con licencia exclusiva  
Fuente : Análisis interno de ExoCoBio| <https://bioinformant.com/exosome-therapeutics-diagnostics/>

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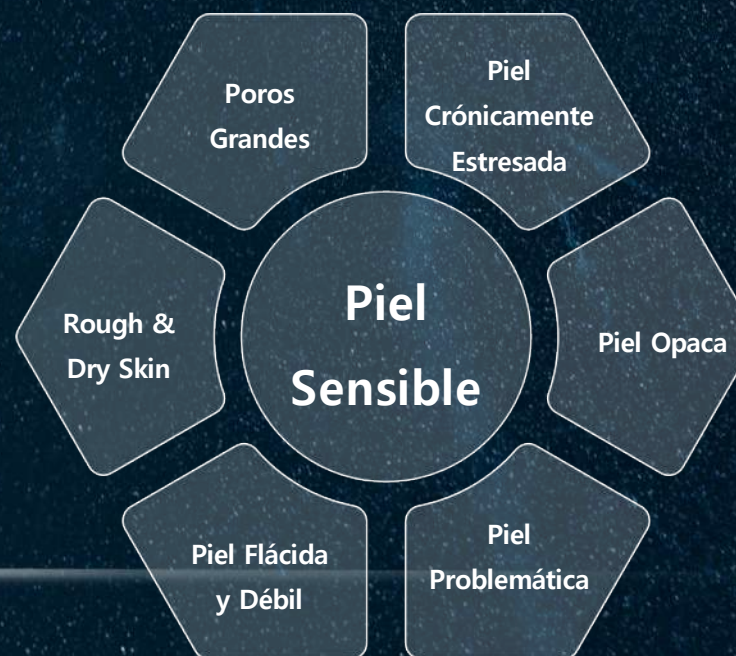
## I+D de ExoCoBio – Publicaciones

No.	Publicación	Contenido
1	<b>(Primera publicación a nivel mundial)</b> Los exosomas derivados de células madre mesenquimales derivadas de tejido adiposo humano alivian la dermatitis atópica (2018.07.)	<ul style="list-style-type: none"> <li>Eficacia de exosomas derivados de células madre adiposas para mejorar la dermatitis atópica</li> <li>Se ha confirmado la posibilidad de que Exosomas ExoSCRT™ funcione como cura para la dermatitis atópica</li> </ul>
2	<b>(Primera publicación a nivel mundial)</b> Los exosomas de células madre mesenquimales derivadas de tejido adiposo humano promueven la reparación de la barrera epidérmica al inducir la síntesis de novo de ceramidas en la dermatitis atópica(2020.03.)	<ul style="list-style-type: none"> <li>Eficacia de los exosomas derivados de células madre adiposas en la regeneración de la barrera cutánea</li> <li>Unido a la investigación con el primer investigador mundial de barrera cutánea: Peter M. Elias (UCSD) y su equipo</li> </ul>
3	<b>(Primera publicación a nivel mundial)</b> Tratamiento combinado con exosomas derivados de células madre de tejido adiposo humano y láser de CO2 fraccionado para cicatrices de acné: estudio prospectivo, doble ciego, aleatorizado y de cara dividida de 12 semanas (2020.10.)	<ul style="list-style-type: none"> <li>Estudio clínico sobre exosomas derivados de células madre adiposas: curación de cicatrices de acné</li> <li>La posibilidad de Exosomas ExoSCRT™ como una cura innovadora para las cicatrices del acné</li> </ul>
4	<b>(Primera publicación a nivel mundial)</b> Evaluación toxicológica de exosomas derivados de células madre/estromales mesenquimales derivadas de tejido adiposo humano(2020.05.)	<ul style="list-style-type: none"> <li>Seguridad de la aplicación cutánea de exosomas derivados de células madre adiposas por primera vez</li> </ul>
5	Exosomas derivados de células madre/estromales mesenquimales para terapias inmunomoduladoras y regeneración de la piel (2020.05.)	<ul style="list-style-type: none"> <li>Perspectiva de la eficacia del exosoma de células madre en la regeneración / inmunomodulación de la piel</li> <li>Introducción de la tecnología de ExoCoBio (ExoSCRT™) / producto (ASCE™ y ASCEplus™)</li> </ul>
6	Eficacia de exosomas derivados de células madre/estromales derivadas de tejido adiposo humano para aclarar la piel: un estudio prospectivo, de cara dividida, aleatorizado y controlado con placebo (2021.11.)	<ul style="list-style-type: none"> <li>Eficacia del exosoma derivado de células madre adiposas para aumentar la luminosidad.</li> <li>Estudio clínico con evaluación aleatorizada, doble ciego y de cara dividida</li> </ul>
7	Aislamiento reproducible a gran escala de exosomas de células madre/estromales mesenquimales derivadas de tejido adiposo y su aplicación en la lesión renal aguda (2020.07.)	<ul style="list-style-type: none"> <li>Efecto positivo del exosoma derivado de células madre adiposas en la recuperación del riñón dañado por LRA</li> </ul>
8	Avances en Análisis de Biodistribución de Exosomas por Imágenes Moleculares(2020.01.)	<ul style="list-style-type: none"> <li>Una revisión y perspectiva de los avances en el análisis de la biodistribución de exosomas</li> </ul>
9	Exosomas derivados de células madre mesenquimales derivadas de tejido adiposo humano para el tratamiento del enrojecimiento facial relacionado con dupilumab en pacientes con dermatitis atópica (2021.04.)	<ul style="list-style-type: none"> <li>Ensayo clínico sobre la eficacia de ExoSCRT™ como tratamiento del enrojecimiento facial relacionado con dupilumab, un producto para pacientes con dermatitis atópica</li> </ul>



• The contents of this page are limited to the characteristics of the raw materials. SRLV is a stem cell culture medium product containing these raw materials.

## Solución Diferenciada Triple A+ Para varios problemas de piel



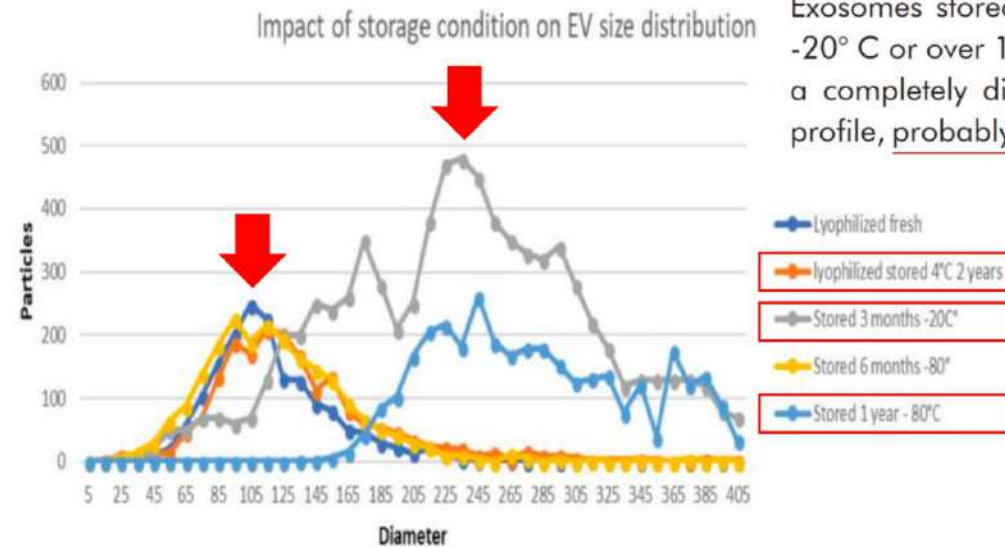
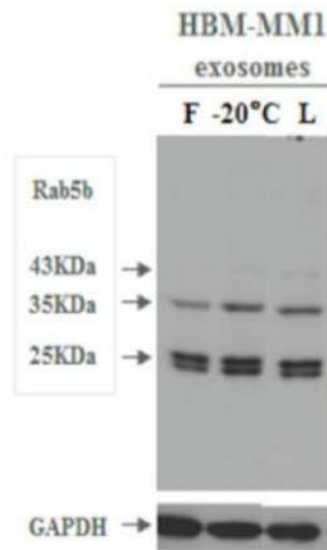
## Ventajas de la liofilización

- Lyophilization is the best way to keep the potency and particle size.

### Advantages of Lyophilized Exosomes (Source: HansaBioMed)

- Easy to reconstitute
- Easy to ship and store (+4°C)
- Long term storage stability (up to 36 months)
- Better performances than competitors (liquid formulations)

Lyophilization does not substantially affect EV particle size distribution or biomarker expression compared to other storage methods (Fig 1, 2). Exosomes stored for over 3 months at -20° C or over 1 year at -80° C showed a completely different size distribution profile, probably due to EV aggregation.



1. Fresh (F), frozen (-20°C) and lyophilized ...

2. Particle size distribution chart of Exosomes stored lyophilized or frozen.

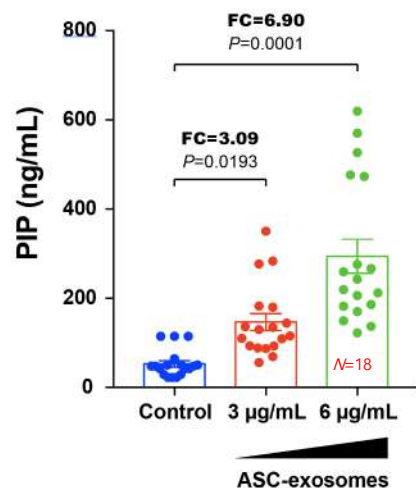
## Exosoma ExoSRT™: Eficacia (piel)

- Aumenta el colágeno en 7 capas, la elastina en 3 capas y la proliferación celular en un 80 % como máximo

### Síntesis de Colágeno Mejorada

[ Aumento en la síntesis de Colágeno ]

7 Capas max.

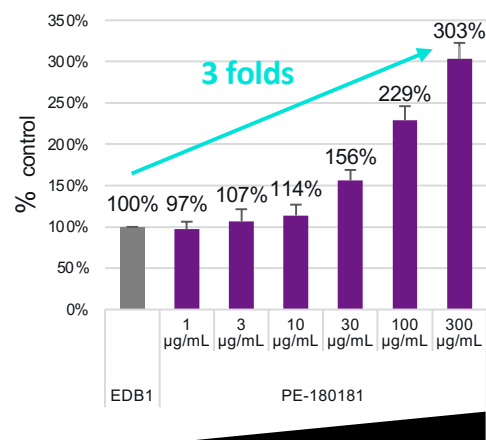


### Aumento de Elastina

[ Aumento en la Elastina ]

3 Capas max.

Cell: HDF (Passage 9)  
Number: 5x10<sup>4</sup> cells / 24 well plate  
Time: 72 h, Supernatant



### Proliferación de células de fibroblastos humanos

[Proliferación de Fibroblastos]

80% max.

Control Negativo      1% Suplementos de crecimiento

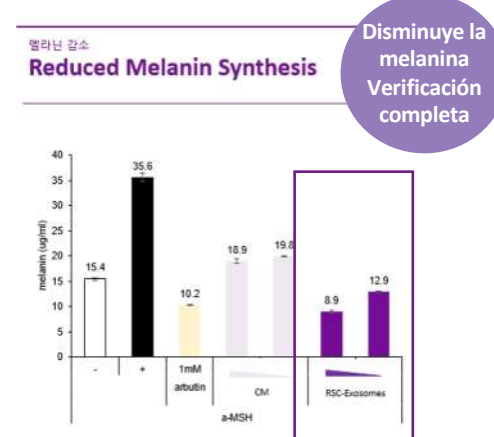
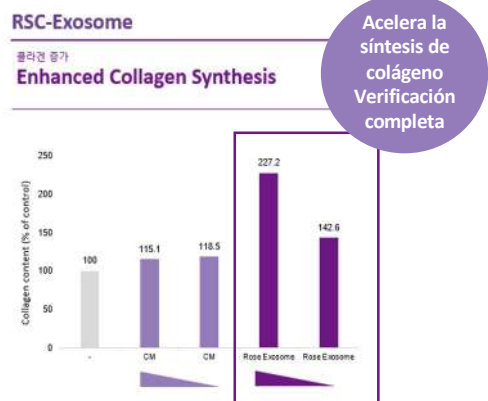


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## Funciones Fuertes- Exosomas de Células Madre de Rosa

# Efecto Iluminador Mejorado de Exosomas de Células Madre de Rosas

- Patente para aceleración de síntesis de colágeno y brillo (Suprime la síntesis de melanina) / Posee 2 patentes en total
- El primer producto del mundo que contiene "exosomas derivados de células madre vegetales" en lugar de un medio de cultivo celular derivado de células madre vegetales



Nombre de la patente y resumen de contenidos	Nombre de la patente y resumen de contenidos
<ul style="list-style-type: none"> <li>(exosoma de células madre de rosa) Una composición cosmética que comprende un exosoma derivado de la célula madre de rosa como ingrediente activo. * Registro No. KR 10-2058444 (2019. 12. 17)</li> <li>Fibroblastos de piel humana a partir de exosomas obtenidos a partir de medio de cultivo de células madre de rosas mediante purificación por separación- <b>Patente por su efecto acelerador de la síntesis de colágeno</b></li> </ul>	<ul style="list-style-type: none"> <li>Compuesto cosmético iluminador que incluye el exosoma derivado de células madre de rosa como ingrediente activo * Registration Number 10-2261434 (2021. 06. 01)</li> <li>Exosomas obtenidos a partir de medio de cultivo de células madre de rosa mediante purificación por separación - <b>Patente por su efecto aclarante de la piel</b></li> <li>(Reduce la melanina)</li> </ul>

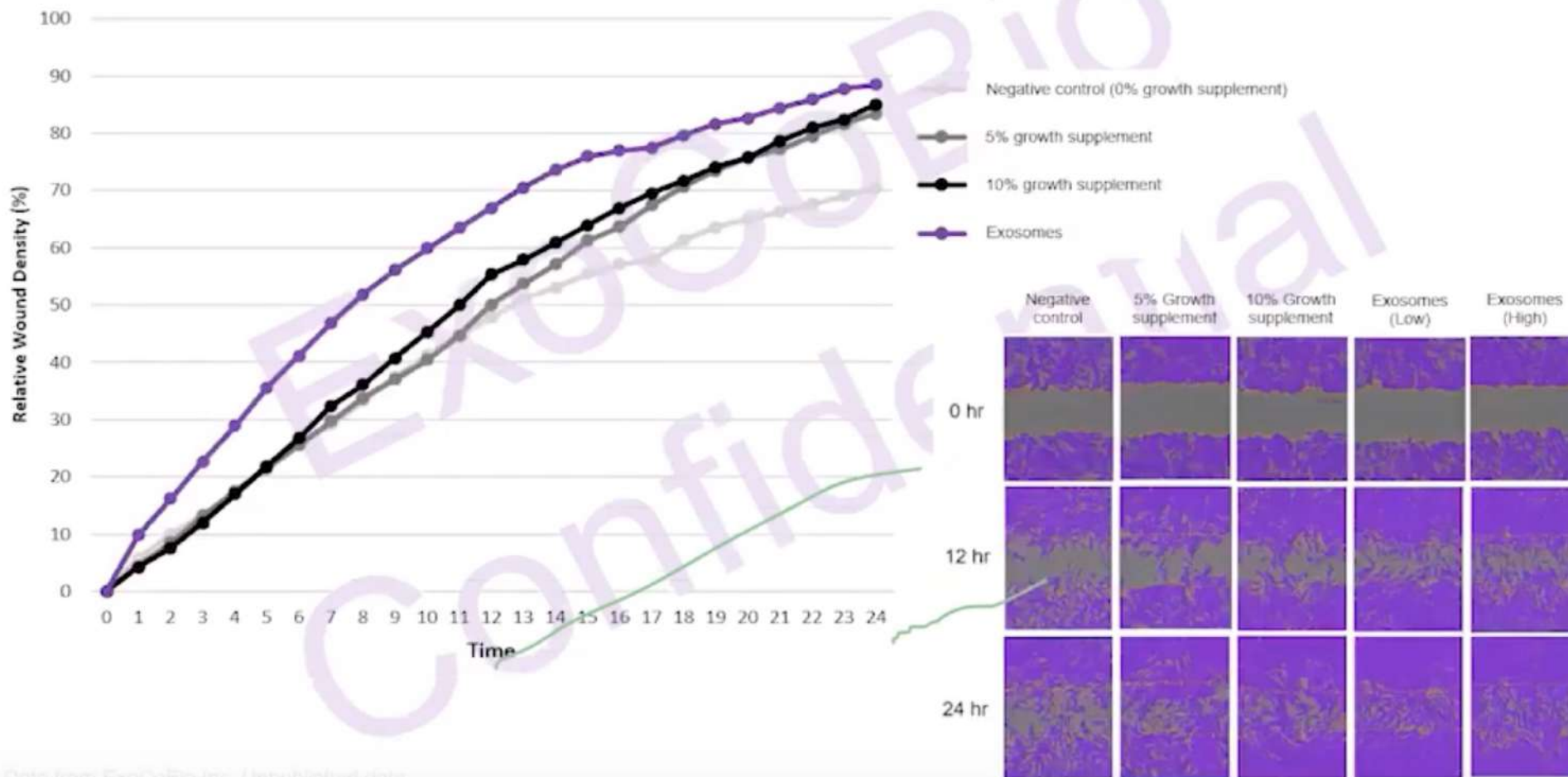
Se agrega un efecto de brillo para mejorar los efectos existentes.  
conocido por muchos usuarios anteriores de ASCEplus SRLV



※ Not feasible to include text notation regarding whitening effect (Not an ingredient tested on function)  
• The contents of this page are limited to the characteristics of the raw materials. SRLV is a stem cell culture medium product containing these raw materials.

- ASC-Exosomes increase the migration of human dermal fibroblast cells (HDF)

### Enhanced Migration (Wound Healing) of HDF by ASC-Exosomes



Data from ExoCoBio Inc. Unpublished data

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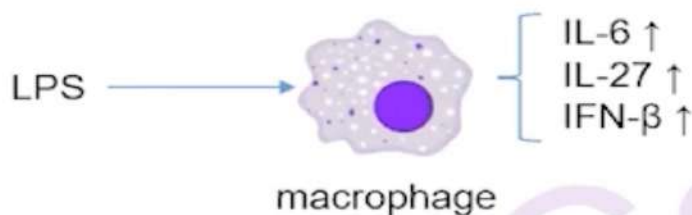
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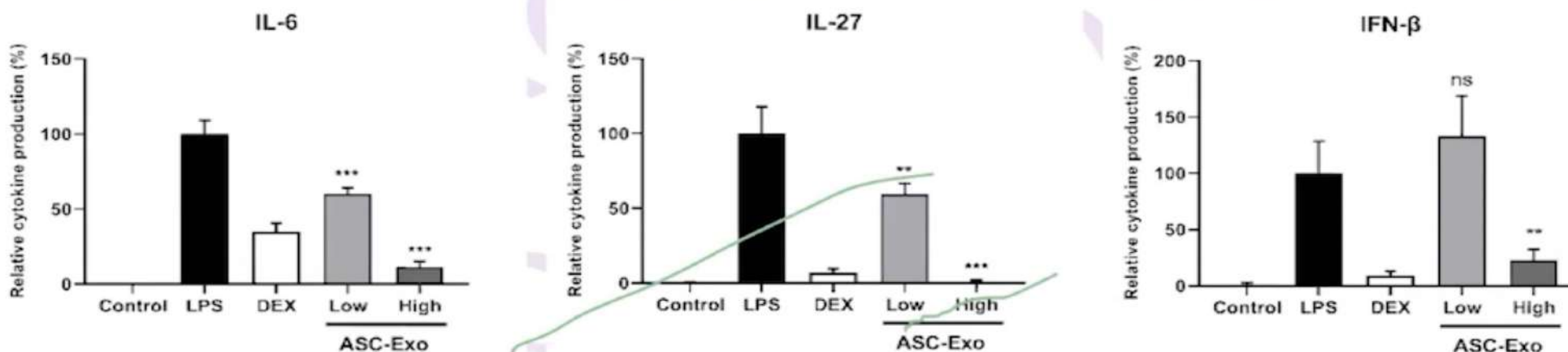
## Anti-inflammation by ASC-Exosomes(1)

ASC-Exosomes reduce the cytokine production in LPS-stimulated murine macrophages in a dose-dependent manner

- LPS stimulates macrophage to secrete IL-6, IL-27, & IFN- $\beta$



- However, pre-treatment of ASC-Exosomes inhibit LPS-induced secretion of IL-6, IL-27, & IFN- $\beta$ .



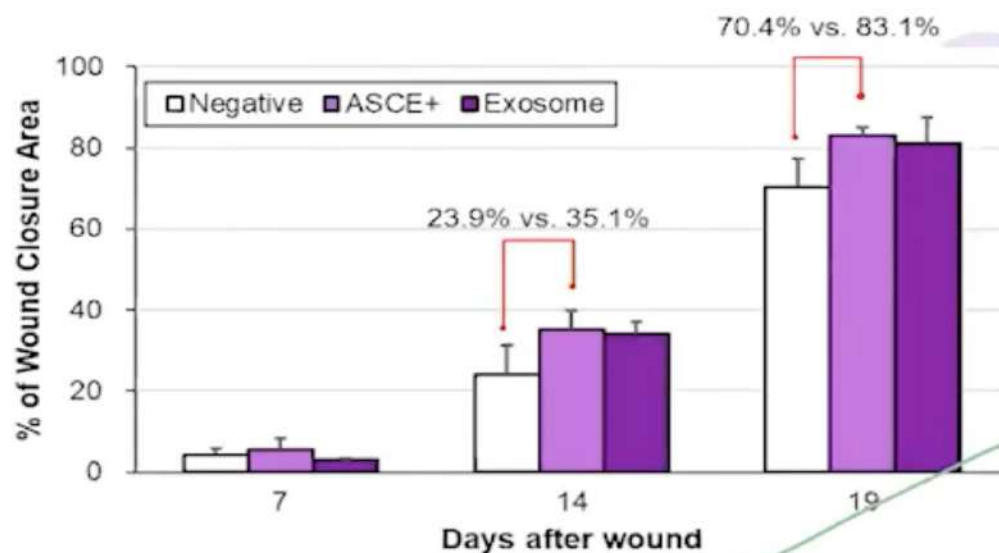
LPS: lipopolysaccharide, bacterial toxin inducing inflammation  
 DEX: dexamethasone, a steroid drug with anti-inflammatory effect  
 Low:  $6.0 \times 10^9$  particles/mL  
 High:  $2.0 \times 10^{11}$  particles/mL

Data from ExoCoBio Inc.  
 Ha et al. (2020) *Regulatory Toxicology & Pharmacology*, Under revision.

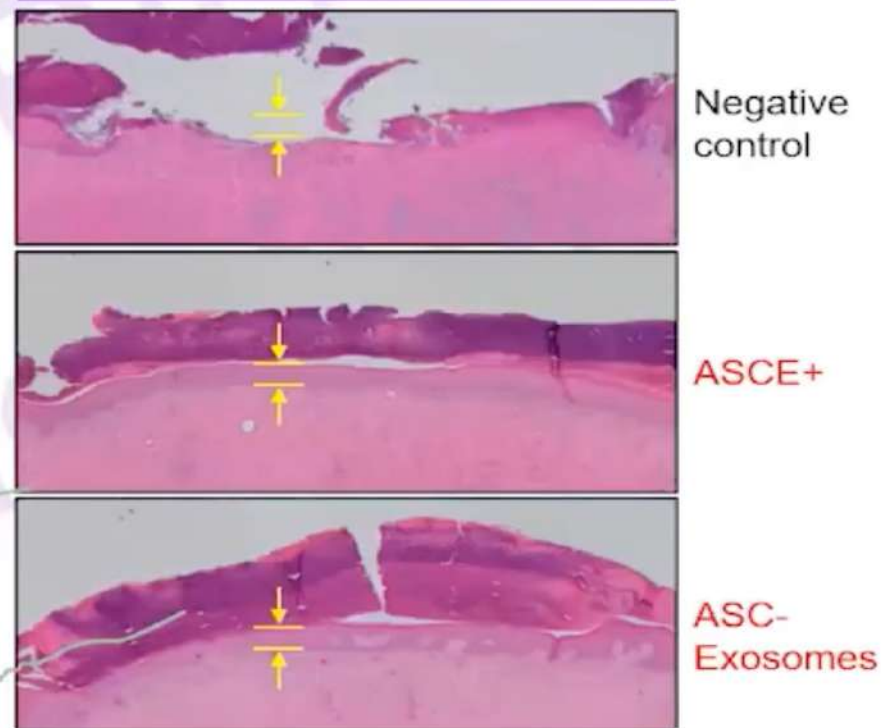
## Wound Healing by ASC-Exosomes(2)

- ASC-Exosome and ASCE+ enhanced the wound closure of wound and the re-epithelization of skin in pig skin incision model.

### Increased Wound Closure by ASCE+



### Re-epithelization of Skin by ASCE+



Data from ExoCoBio Inc. Unpublished data.



# Studies of ASC-EXOSOME on AD in Animal Models

World first exosome therapeutic for atopic dermatitis

- Efficacy in multiple animal models

## Complementary Animal Models

### Model 1: Inflammatory Model

- Animal: NC/Nga mouse
- AD Inducer: house dust mite antigen
- Route: SC & IV
- Frequency & Duration: 3 times/week x 4 weeks

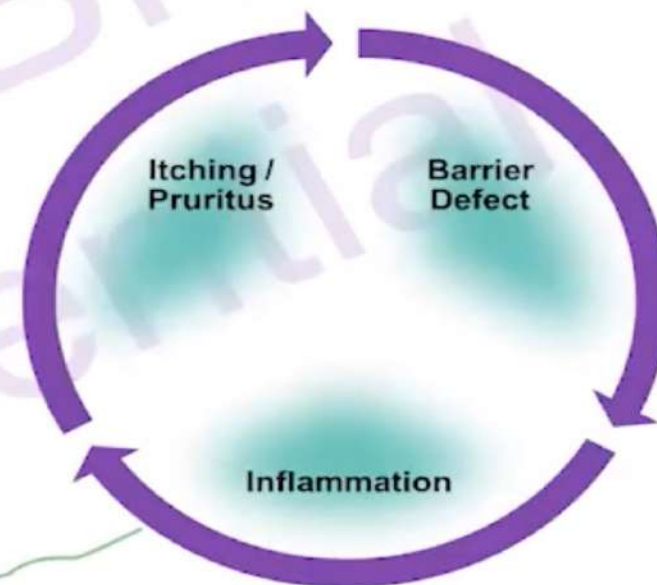
### Model 2: Skin Barrier Disruption Model

- Animal: SKH-1 mouse
- Barrier disruption by a chemical
- Route: SC
- Frequency & Duration: 3 times/week x 4 weeks

### Model 3: Spontaneous AD Model

- Animal: Shetland sheepdog
- AD Inducer: natural
- Route: SC
- Frequency & Duration: 12 times over 5 weeks

## Vicious Cycle of Atopic Dermatitis



# Therapeutic Effects of ASC-Exosomes on AD – Inflammatory Model (1)

## World first exosome therapeutic for atopic dermatitis

### Effects on severe case

- Reduced clinical scores, skin thickness, infiltration of inflammatory cells such as mast cells and IDECs

## Reference

Choi et al. Stem Cell Research & Therapy (2019) 10:187  
https://doi.org/10.1186/s13287-019-0269-3

Stem Cell Research & Therapy

LETTER Open Access

Exosomes derived from human adipose tissue-derived mesenchymal stem cells alleviate atopic dermatitis

Byoung Seung Cho, Jin Ock Kim, Dae Hyun Ha and Yong Woon Yi

**Abstract**  
Exosomes are nano-sized vesicles (30–200 nm) constantly released by almost all cells. The ability of exosomes to travel between cells and deliver their cargo, which includes lipids, proteins, and nucleic acids, makes them an appealing cell-free therapy option to treat multiple diseases. Here, we investigated for the first time whether human adipose tissue-derived mesenchymal stem cell-derived exosomes (ASC-exosomes) can ameliorate atopic dermatitis (AD) in an in vivo mouse model. When injected either intravenously (IV) or subcutaneously (SC) into NC/Nga mice treated with house dust mite antigen, ASC-exosomes were found to induce pathological symptoms such as clinical score, the levels of serum IgE, the number of eosinophils in blood, and the infiltration of mast cells, CD86+, and CD206+ cells in skin lesions. ASC-exosomes also significantly reduced mRNA expression of various inflammatory cytokines such as interleukin (IL)-4, IL-23, IL-31, and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) in AD skin lesions of NC/Nga mice. Taken together, these results suggest that ASC-exosomes can be a novel promising cell-free therapeutic modality for AD treatment.

**Keywords:** Exosome, Adipose tissue-derived mesenchymal stem cells, Atopic dermatitis, Inflammation

**Introduction**  
Since current treatment options for atopic dermatitis (AD) are limited and have potentially harmful side effects, there are urgent needs to develop novel therapies that are safe and efficacious [1]. Several biologics targeting pro-inflammatory cytokines are currently under development and dupilumab, a dual inhibitor of IL-4 and IL-13, was recently approved by the US FDA for treating adults with moderate to severe AD [1]. Although long-term follow-up study is needed to determine late side effects of dupilumab [1], its efficacy indicates that multiple targeting is a plausible way to treat AD [2].

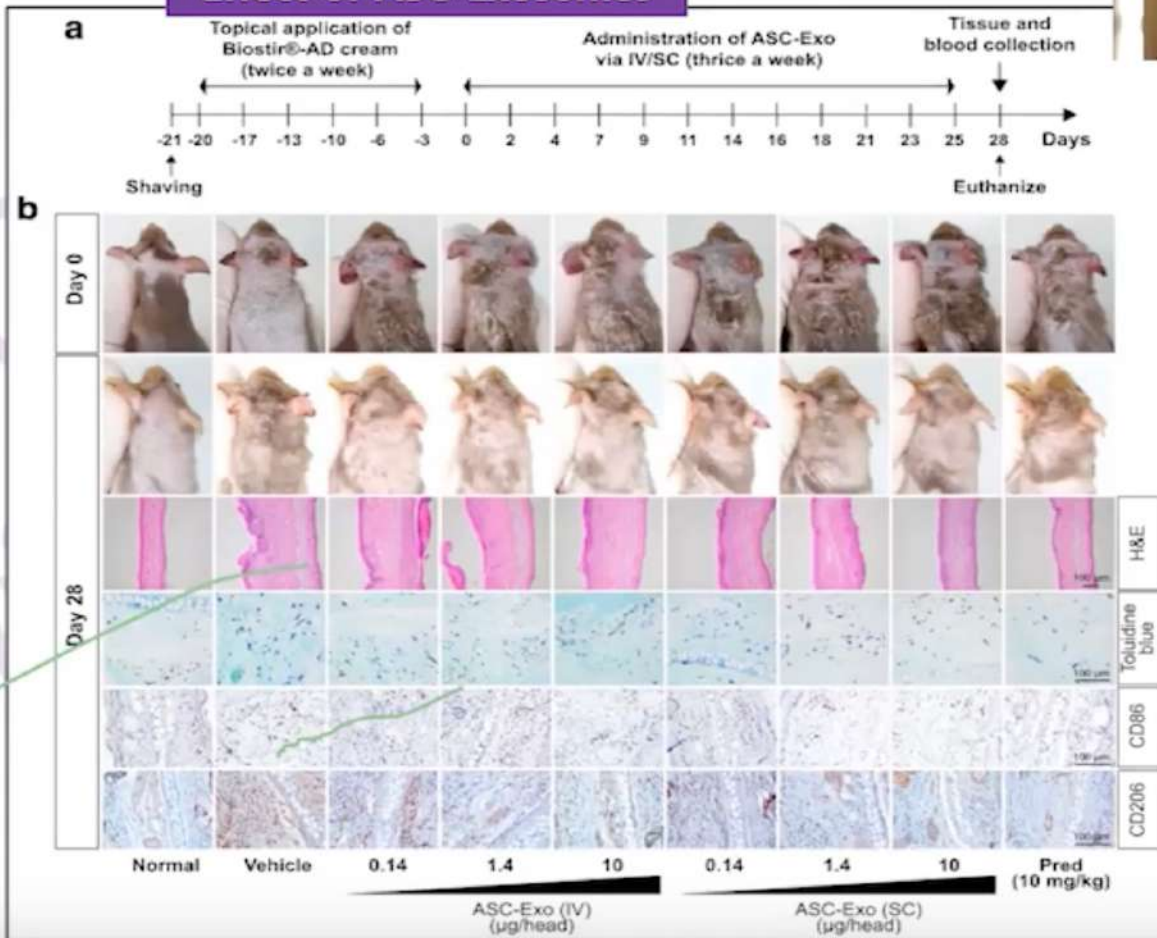
Several studies have demonstrated that the allergic progress in AD could be suppressed by mesenchymal stem cells (MSCs) derived from human umbilical cord blood (UCB-MSC), bone marrow (BM-MSC), or adipose tissue (ASC) by modulating multiple targets [3]. However, therapeutic use of MSCs has several drawbacks, such as poor engraftment efficiency, potential tumor formation, unwanted immune responses, non-specific differentiation, short half life, and the difficulty of quality control before administration [4].

Exosomes are nanovesicles (30–200 nm) released by almost all cells and found in all body fluids [4]. Exosomes deliver their cargo (proteins, lipids, and nucleic acids) from originating cells to recipient cells. Growing evidence suggests that exosomes derived from stem cells could be a promising alternative to cell-based therapy because exosomes would avoid most of the problems associated with cell-based therapy while recapitulating the therapeutic efficacy of stem cells [4]. For example, exosomes have no risk of tumor formation as they cannot replicate. They also can be sterilized by filtration and have a longer shelf-life than cells themselves. Being much smaller than stem cells, exosomes easily circulate through the body and reach sites of injury. In addition, long-term repetitive administration of exosomes does not elicit toxicity [5]. Here, we for the first time investigated the therapeutic effect of exosomes derived from human ASC (ASC-exosomes) on AD in a mouse model.

© Correspondence: yiwon@skku.ac.kr  
Seoul City Science Institute #315, Seoul City, Inc., 222, Nongno, 19 Gwanak-gu, Seoul 01510, Korea

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## Effect of ASC-Exosomes



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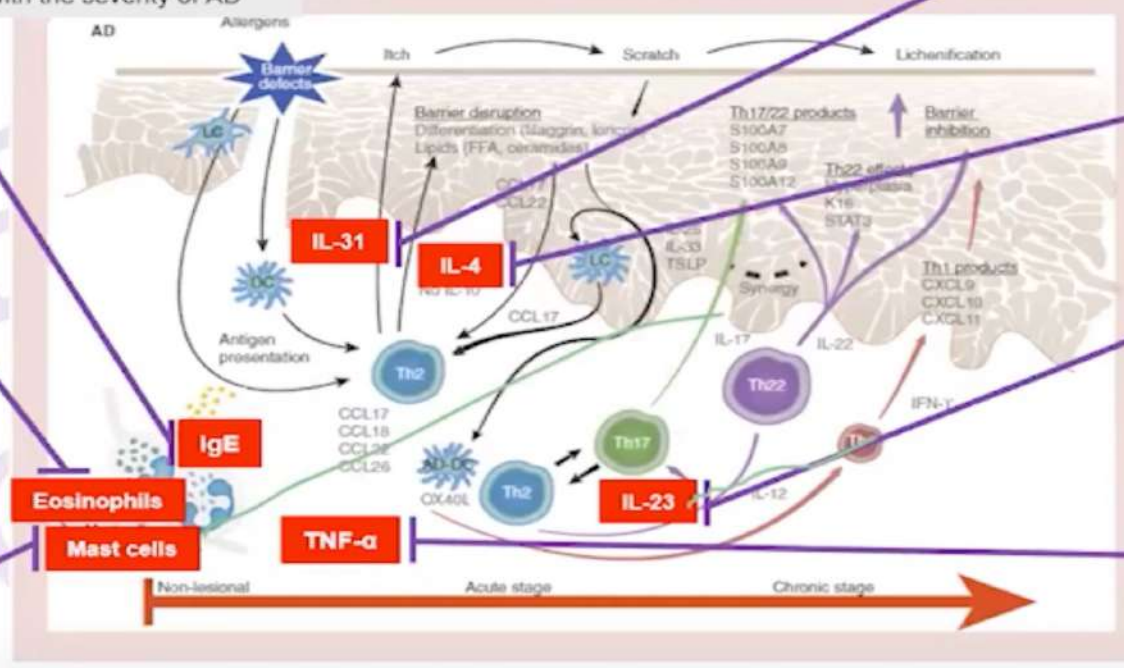
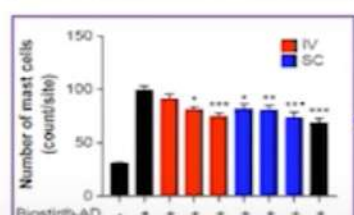
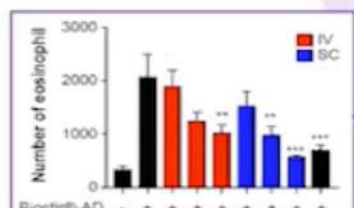
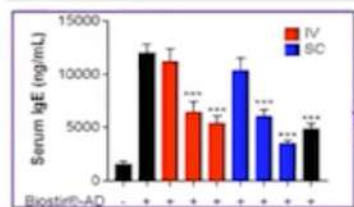
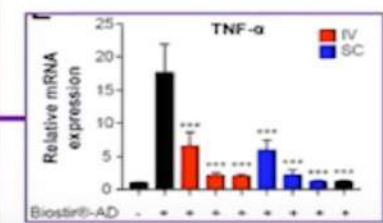
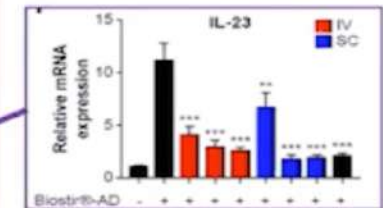
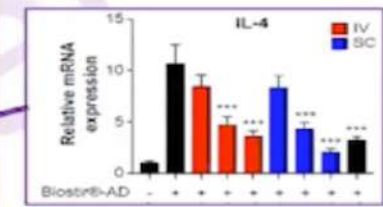
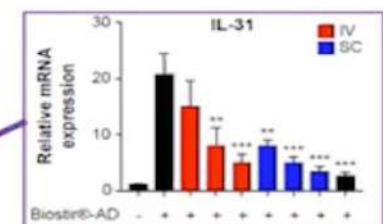
# Therapeutic Effects of ASC-Exosomes on Atopic Dermatitis

## World first exosome therapeutic for atopic dermatitis

- Reduced the mRNA expression of multiple inflammatory cytokines

Potential Target	Function
IgE	<ul style="list-style-type: none"> <li>Main cause of AD</li> <li>Activating mast cells &amp; eosinophils</li> </ul>
IL-31	<ul style="list-style-type: none"> <li>Produced by Th2 &amp; mast cells</li> <li>Influencing class switch to IgE</li> <li>Recruiting inflammatory cells</li> <li>Correlated with the severity of AD</li> </ul>
TNF- $\alpha$	<ul style="list-style-type: none"> <li>Produced mainly by macrophages</li> <li>Correlated with the severity of AD</li> </ul>

Potential Target	Function
IL-4	<ul style="list-style-type: none"> <li>Polarizing naïve CD4+ T cells to Th2</li> <li>Initiating class switch to IgE</li> <li>Activating chemotaxis of eosinophils</li> </ul>
IL-23	<ul style="list-style-type: none"> <li>Induces IFN-<math>\gamma</math></li> <li>Induces the differentiation of naïve CD4+ T cells into highly pathogenic helper T cells (Th17/ThIL-17)</li> </ul>



Source: Cho et al., Stem Cell Res & Ther 2018;9:187.

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# Skin Barrier Re-construction by ASC-Exosomes (1)

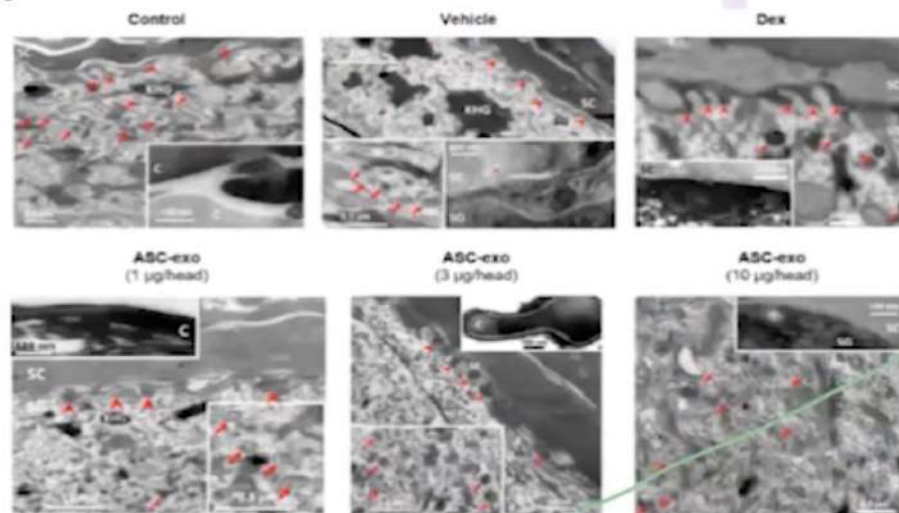


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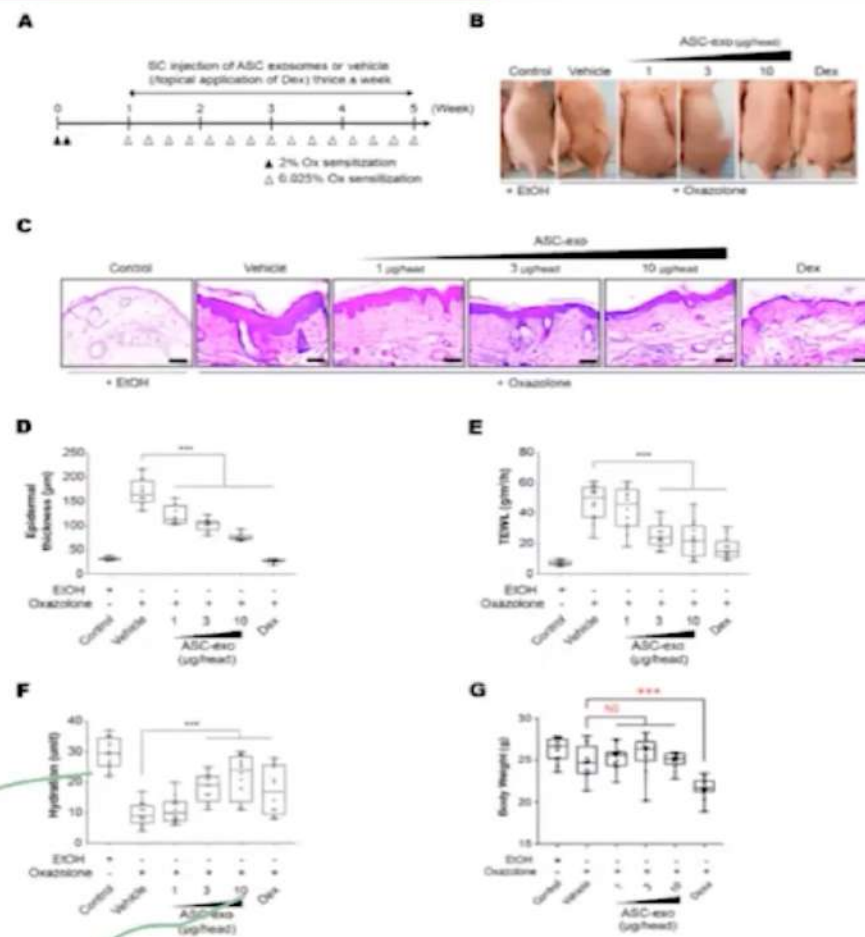
## Exosomes from Human Adipose Tissue-Derived Mesenchymal Stem Cells Promote Epidermal Barrier Repair by Inducing de Novo Synthesis of Ceramides in Atopic Dermatitis

Kyong-Oh Shin <sup>1,2</sup>, Dae Hyun Ha <sup>1,2</sup>, Jin Ock Kim <sup>1,2</sup>, Debra A. Crumrine <sup>3</sup>, Jason M. Meyer <sup>3</sup>, Joan S. Wakefield <sup>3</sup>, Yerin Lee <sup>3</sup>, Bogyong Kim <sup>3</sup>, Sungeun Kim <sup>3</sup>, Hyun-keun Kim <sup>3</sup>, Joon Lee <sup>3</sup>, Hyuck Hoon Kwon <sup>3</sup>, Gyeong-Hun Park <sup>3</sup>, Jun Ho Lee <sup>3</sup>, Jihye Lim <sup>3</sup>, Sejeong Park <sup>3</sup>, Peter M. Elias <sup>3</sup>, Kyungho Park <sup>1,2</sup>, Yong Weon Yi <sup>1,2</sup> and Byong Seung Cho <sup>1,2</sup>

Received: 20 January 2020; Accepted: 09 March 2020; Published: 10 March 2020

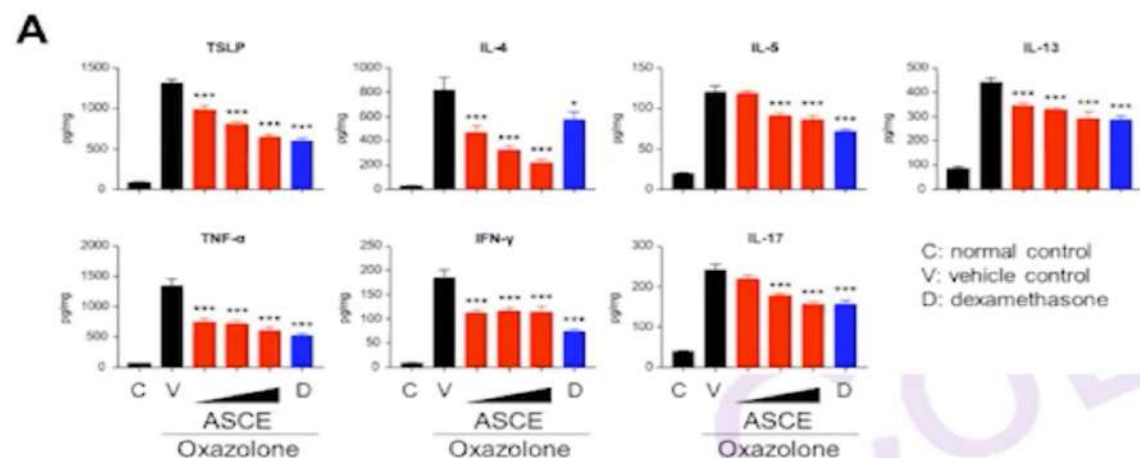


**Figure 6.** ASC-exosomes restore oxazole-induced defects in the lamellar secretory system. Electron micrographs of epidermis. Inserts show high magnification of lamellar bodies and/or processed lamellar lipids as indicated. Note that lamellar bodies are more abundant at the SG-SC interface in the ASC-exosomes treated group compared with the vehicle and dexamethasone groups. KHG: keratohyaline granules, C: corneocyte, arrows: lamellar bodies, arrow heads: lipid secretion points, \*: lipid phase separation (indicating incomplete processing). Scale bar: 100 nm.



**Figure 3.** ASC-exosomes improve atopic dermatitis (AD) induced by repeated exposure to Ox. (A) Schematic diagram of the study protocol. The first two days 2% Ox was applied, before leaving 5 days for recovery. Dexamethasone was topically applied thrice a week as a positive control. (B) Representative dorsal skin photographs of each treatment group showing comparison of AD-like skin lesions (C) Representative images of hematoxylin and eosin (H&E)-stained epidermal histological sections from dorsal skin of mice from different treatment groups showing thickness of epidermis.

# Skin Barrier Re-construction by ASC-Exosomes (3)

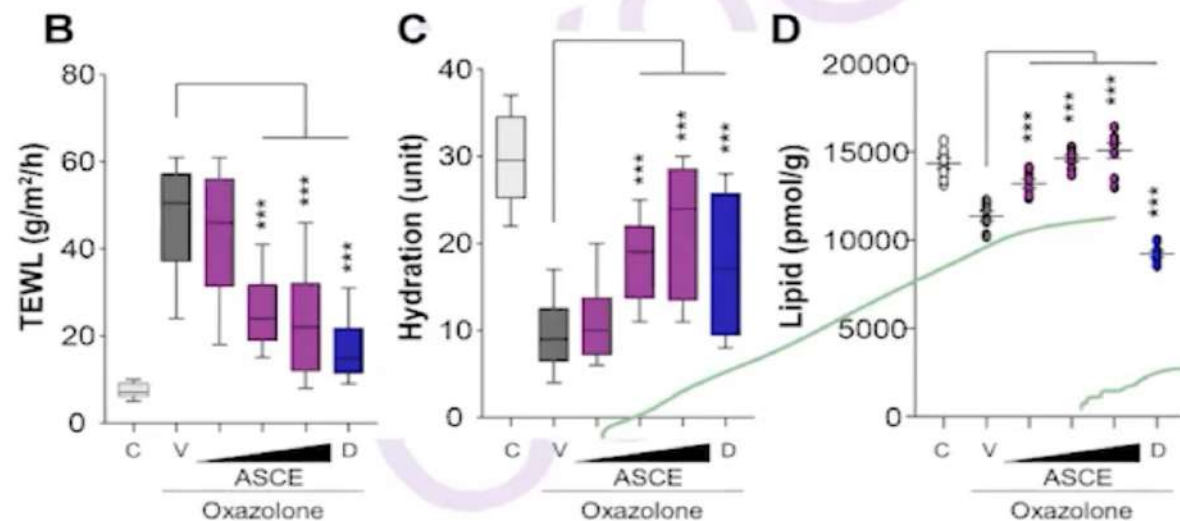


**ASC-Exosomes improve epidermal barrier function impaired by repeated oxazolone challenges.**

(A) ASC-Exosomes reduce the level of multiple inflammatory cytokines in AD-like lesion.

Effects of ASC-EXOSOME on (B) trans-epidermal water loss (TEWL), (C) stratum corneum (SC) hydration, and (D) lipid synthesis.

Error bars depict the SEM. \*\*\* $P < 0.001$  vs vehicle. Dex, dexamethasone.



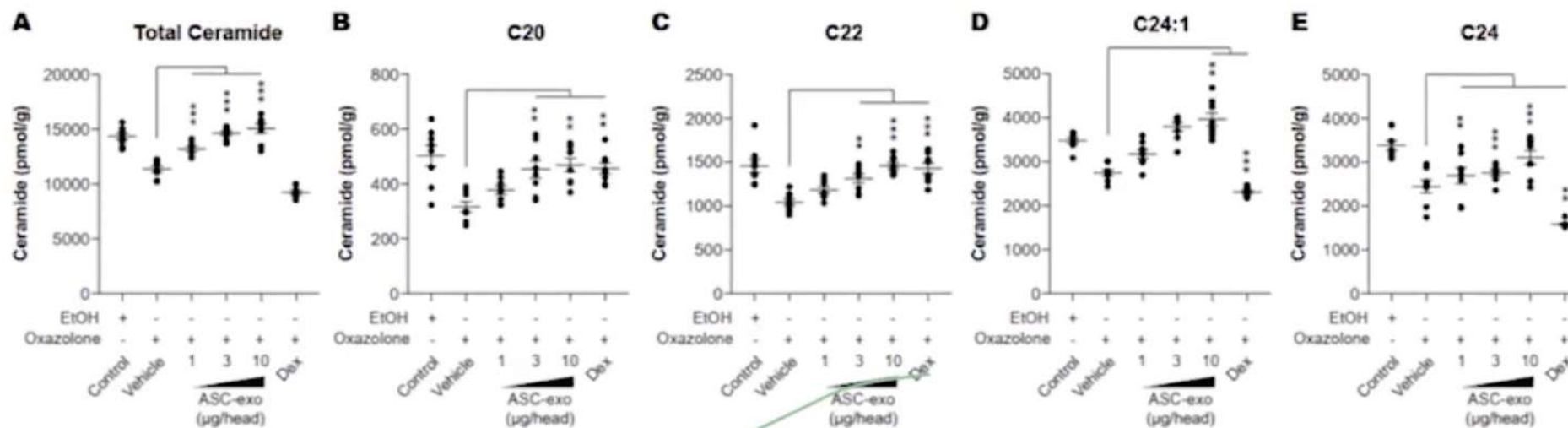
Data from ExoCoBio Inc.  
Ha et al. (2020) *Cells* 9:680.

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## Skin Barrier Re-construction by ASC-Exosomes (2)

- ASC-Exosomes, for the first time in the world, were proved to **increase the amount of the key lipids such as ceramides & dihydroceramides**
- However, the steroid was found to have little or no effects on the amount of lipids and sphingoid bases



Data from ExoCoBio Inc.  
Ha et al. (2020) *Cells* 9:680.

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# ASC-Exosomes on AD – Natural AD

- Spontaneous atopic dermatitis on Shetland Sheepdog (9-year old)
- 12 times SC injection over 5 weeks
- **Symptoms were improved as early as 3 days after first injection**
- **No rebound has been observed after last injection**
- **Increased vitality & body weight (13 → 16 kg)**
- **Other medications were stopped after exosome injection**



Shetland Sheepdog  
(9-year old)

50 days after last Inj.



Before Injection



3 days after 1<sup>st</sup> Inj.



544 days after last Inj. (Aug 17, 2019)



Data from ExoCoBio Inc. Unpublished data.

# Clinical Cases (US)

## BENEV, USA



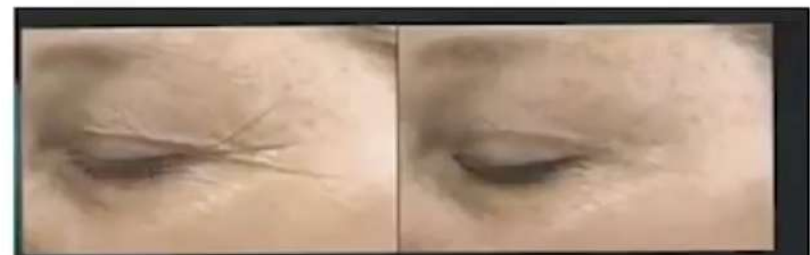
SENSITIVE SKIN

CALM SKIN



PROBLEM SKIN

CLEAR SKIN



AGING SKIN

FIRM SKIN



DULL  
& DEHYDRATED SKIN

RADIANT  
HYDRATED SKIN



UNEVEN TEXTURE  
& ENLARGED PORES

SMOOTH SKIN  
MINIMIZED PORES

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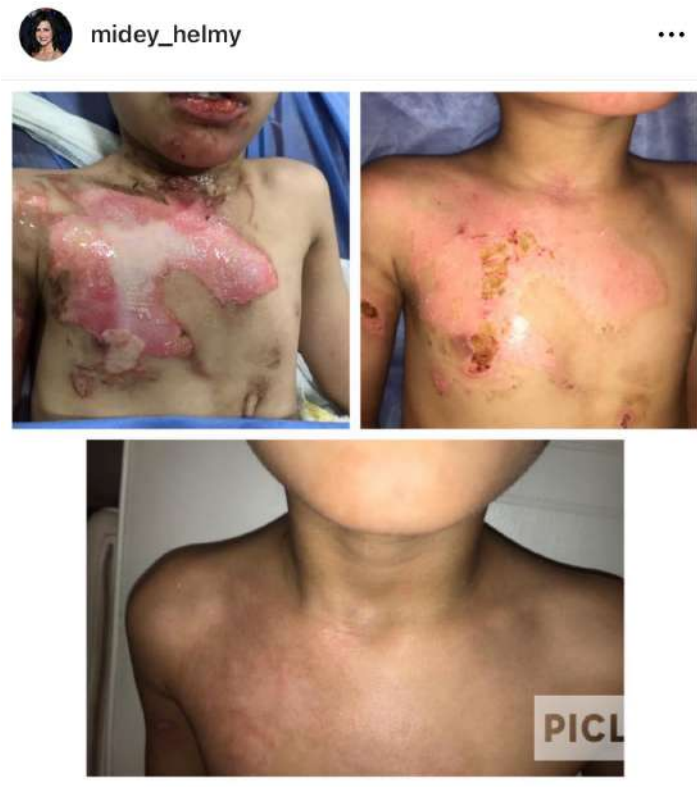
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## Ejemplos de regeneración



87 Me gusta  
midey\_helmy Birthday fun went wrong. Treatment using ASCE dermal signaling kit in 5 days.  
@exosome\_regen\_med\_aesthetics



86 Me gusta  
midey\_helmy One week, second degree burn #wound #healing #burn #maxillofacial #cosmetics #beauty #no\_scars

A dual synergy product through perfect harmony of  
**EXOCAPSULE** and **W-FORMULA**  
for faster wound healing and strong anti-pigmentation ingredients

Crystal of active ingredients

### Lyophilized capsule

[ No. 1 | EXO CAPSULE ]

2.5  
billions

- ExoSCRT® Exosomes
- Rose Stem Cell Exosomes



Optimal synergy formula

### Balm Solution

[ No. 2 | W-FORMULA ]

- Tranexamic acid
- Madecassoside
- D-panthenol
- Niacinamide

Efficacy specific to  
post care

Freeze drying

Fresh Mix immediately  
before use

Proved effect of  
ExoSCRT® exosomes

Patented exosome  
technology



# Testimonial

[ US ]

## Radiation Burns

- Radiation-induced burn with bleeding, blistering, & pain
- 2 treatments per day for 1 week
- Source: Diane Duncan MD, FACS (US)



### Lisa

- Breast cancer survivor
- Radiation-treated patient

"As soon as we applied the EXOBALM, the pain was gone. It was amazing that it didn't burn. My skin was not burning"

"(...) after that I just used the EXOBALM exclusively. It was blessing and I would absolutely recommend it to anybody that is going through something like that, because it is extraordinary."

"엑소밤을 바르자마자 통증이 사라졌습니다. 제 피부가 더 이상 화끈거리지 않아 놀라웠어요."

그 뒤로 저는 엑소밤만을 단독으로 사용했습니다. 엑소밤을 만난 건 축복이었고, 같은 문제를 겪고 있는 모두에게 적극 추천할 것입니다."

< Before >



< After >



# Testimonial

[ UK ]

## Superficial Burns

- RF needling superficial burns
- 2 topical treatments per day for 1 week
- Source: Shameema Damree MD (UK)



< Before >

< After >



< Before >

< After >



Shameema Damree MD, UK

“We have successfully treated this patient for superficial burns and achieved excellent healing, prevented any scarring and treated hyperpigmentation also with ASCE+ EXOBALM.”

“ASCE+ 엑소밤의 우수한 상처치유 효능으로 표재성 화상을 성공적으로 치료하고, 흉터와 색소침착을 예방했습니다.”



Courtesy of: Rosario Blas, MD, FPDS, FAAD

- 92/F bedridden, with recurrent painful bed sores 3-5 days' duration.
- Co-morbid: hypertensive, dyslipidemia, mild dementia.
- Treatment: Simple topical application of ExoCoBio ASCE+ SRLV 3x/day into each wound.
- No pain that evening, patient was able to sleep well.
- 2<sup>nd</sup> photo: after 7 days of treatment



Courtesy of: Elaine Co, MD, MBA and Rosario Blas, MD, FPDS, FAAD  
Philippines



- 69/M Exfoliative Dermatitis of 2 months' duration, secondary to "natural, herbal" oils applied.
- Was being treated with other medications like oral antihistamines, Oral antibiotics, emollients, hypoallergenic skin care products and mid-potency topical steroids. Minimal improvement, quality of life impaired due to intense prickly itching.
- 2<sup>nd</sup> photo was taken 20 minutes after one in-clinic simple application of ExoCoBio ASCE+ SRLV: marked improvement of skin quality and zero itching. Improvement continued with that single topical application of SRLV and home use simple commercially available moisturizers.

# INTRODUCCION

ASCEplus HRLV

# ASCE<sup>plus</sup>

Advanced Skincare Complex from ExoCoBio

ASCEplus HRLV < Problemas Capilares >

# Scalp Care | HRLV



“  
”

## Problemas Capilares que requieren HRLV

- 1  Aquellos que **no están satisfechos** con su tratamiento capilar actual
- 2  Aquellos a los que preocupa su **debilitamiento Capilar**
- 3  Aquellos a los que preocupa los **problemas de su cuero cabelludo**
- 4  Aquellos que quieren un **cabello y un cuero cabelludo saludable**

La descripción en esta página se limita a las características de las materias primas de HRLV. HRLV es un medio acondicionado con células madre que contiene estas materias primas.



## ASCEplus HRLV < Introducción >

“Polvo Liofilizado para maximizar el efecto del procedimiento”

La fuerte vitalidad de la  
Rosa de Damasco

Tecnología de Investigación  
por la empresa de Exosomas  
ExoCoBio

Sinergia de los ingredientes  
activos optimizando su efecto  
para el cabello

Sin Conservantes

Utiliza varios  
Ingredientes Activos

### ASCEplus HRLV

[ Polvo Liofilizado ]



Spec. 20 mg X 5 Vials

#### Células Madre de la Rosa

10 factores de crecimiento para  
el cabello: Noggin, FGF, SCF, TMB4, etc

30 tipos de nutrientes para el cabello:  
Biotina, Cobre Tripéptidos, etc.

30 tipos de miRNA antiinflamatorios del cuero cabelludo:  
miR 231, miR 835, miR 391, miR 100, etc.

Optimizado para mejorar el entorno capilar, como la producción de cabello en zonas altamente despobladas, **permitiendo un nivel más alto de cuidado del cabello y del cuero cabelludo.**

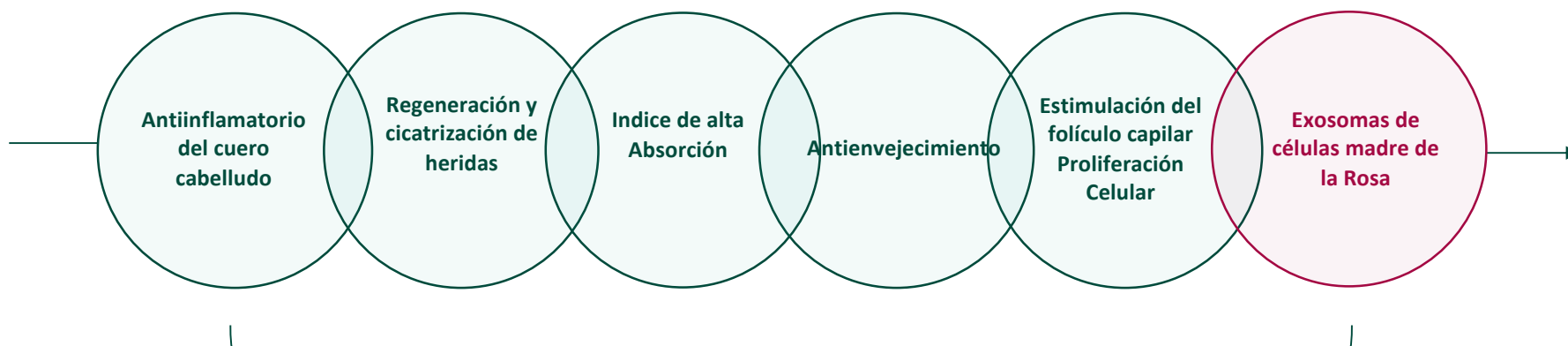
Patente KR 10-2209294 / KR 10-2265875

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## ASCEplus HRLV <Principales Efectos del Producto>

Nivel Premium de cuidado para el entorno capilar

# ASCEplus HRLV



Equilibra el entorno del cabello dañado al brindar los efectos activos a toda la capa del cuero cabelludo con la excelente tasa de absorción de HRLV.

**Proporciona una solución premium para el cuidado del cuero cabelludo que lleva la salud de tu cabello al siguiente nivel.**

- La descripción en esta página se limita a las características de las materias primas de HRLV. HRLV es un medio acondicionado con células madre que contiene estas materias primas.

## ASCEplus HRLV < Efectos – Cuero Cabelludo >

De la Epidermis a la Dermis

Satisface todas las necesidades de cada capa del cuero cabelludo y proporciona el entorno apropiado para la mejora fundamental

### Epidermis

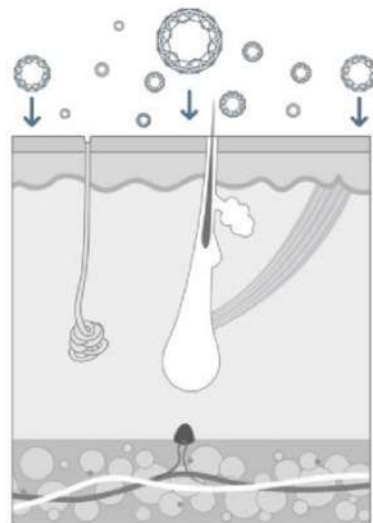
Los Lípidos abundantes fortalecen la barrera

### Dermis

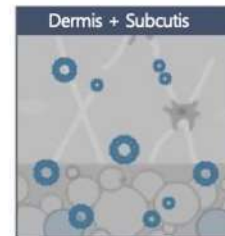
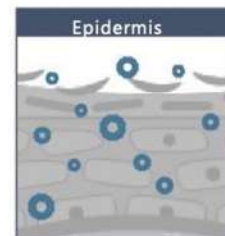
Aumento de la Dermis por proliferación de

### Subcutis

Aumento de la fuerza, estimulando el tejido graso.



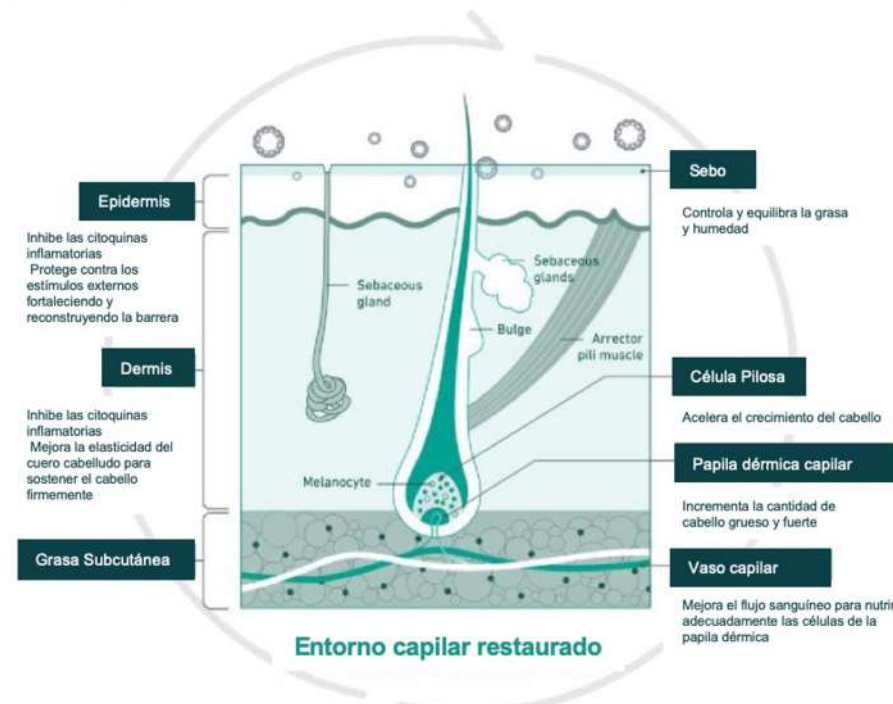
Entorno del cabello dañado



ASCE+ HRLV

- Inhibe las citoquinas inflamatorias
- Protege contra los estímulos externos fortaleciendo y reconstruyendo la barrera

- Inhibe las citoquinas inflamatorias
- Mejora la elasticidad del cuero cabelludo para sostener el cabello firmemente



Entorno capilar restaurado

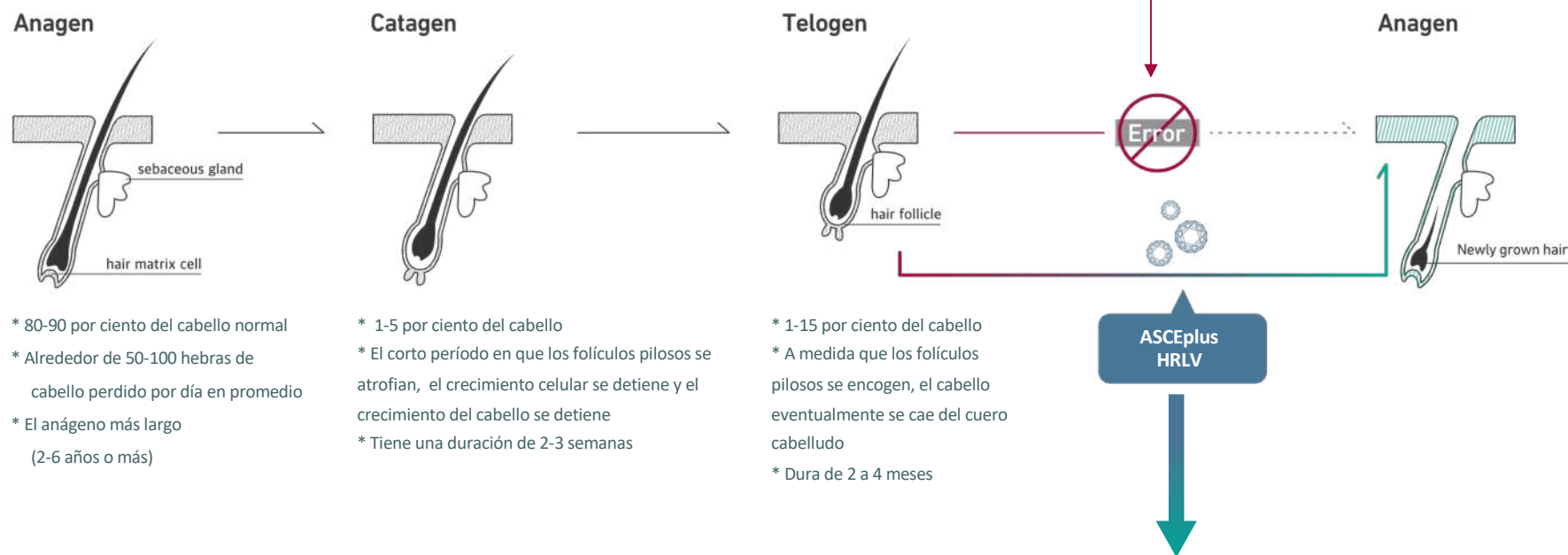
- La descripción en esta página se limita a las características de las materias primas de HRLV. HRLV es un medio acondicionado con células madre que contiene estas materias primas.

## ASCEplus HRLV <Efecto- 1. Cabello>

### Ciclo del Cabello ; [Ciclo del cabello - Ciclo de crecimiento del cabello]

\* La condición en la que el ciclo del cabello (ciclo de crecimiento del cabello) se ralentiza y se debilita y no crece cabello en el área donde debería haberlo

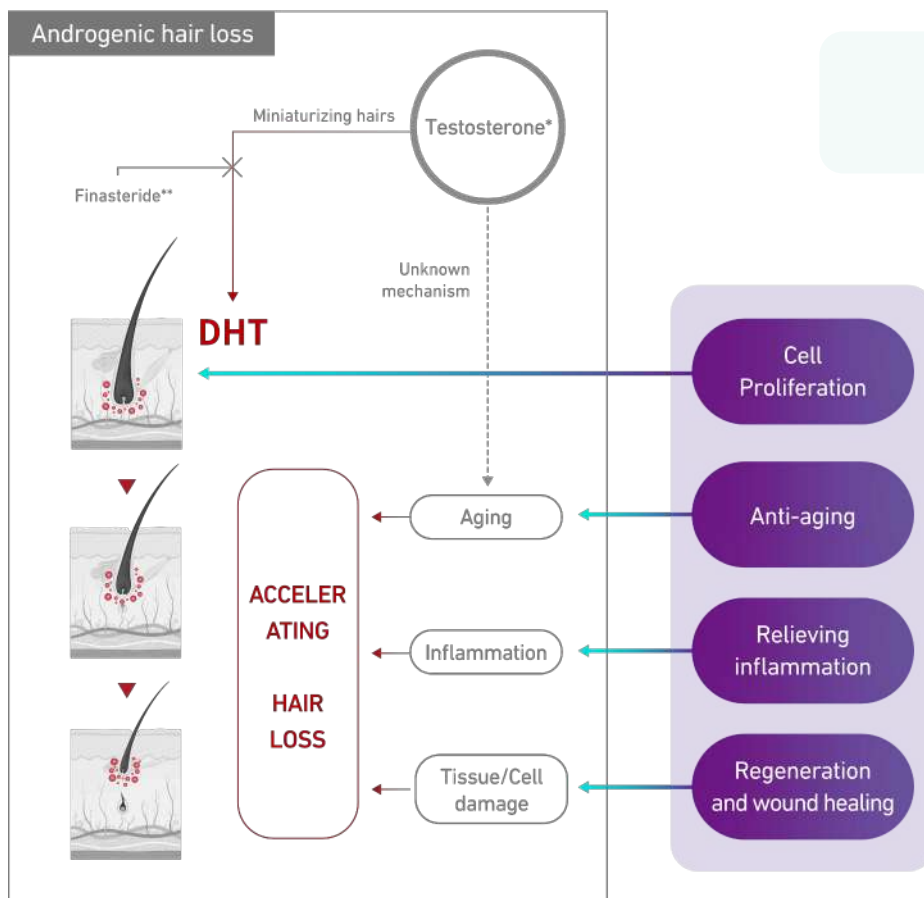
\* Síntomas en los que el anágeno se acorta y el telógeno se alarga, lo que provoca debilitamiento, cabello opaco y pérdida de cabello.



Normalice el ciclo de su cabello a través del cuidado premium de HRLV que cubre todas las capas del cuero cabelludo

• La descripción en esta página se limita a las características de las materias primas de HRLV. HRLV es un medio acondicionado con células madre que contiene estas materias primas.

## ASCEplus HRLV <Principales Efectos del Producto>



Con la perfecta sinergia de ASCE y HRLV,  
**previene y frena la caída del cabello.**

Efectos	Factores de crecimiento y Proteínas	miRNAs
<b>Folículo capilar/ Estimulación de Proliferación celular</b>	<ul style="list-style-type: none"> <li>~100 proteínas</li> <li>HF promoción: Wnt/<math>\beta</math>-catenin, EGFR</li> <li>Proliferación: Caveolina 1 2, CDC42, DDR2, GFFR2, etc</li> </ul>	<ul style="list-style-type: none"> <li>15 miRNAs</li> <li>miR 100, miR 25, etc</li> </ul>
<b>Antienvejecimiento</b>	<ul style="list-style-type: none"> <li>~30 proteínas</li> <li>PRDX1, PRDX6, HSP90AA1, LMNA, etc</li> </ul>	<ul style="list-style-type: none"> <li>9 miRNAs</li> <li>miR 229, miR 385, miR 203, etc</li> </ul>
<b>Antiinflamatorio</b>	<ul style="list-style-type: none"> <li>~15 proteínas</li> <li>APOE, GSTP1, TNFRSF1A, etc</li> </ul>	<ul style="list-style-type: none"> <li>~30 miRNAs</li> <li>miR let-7b, miR 231, miR 835, miR 391, etc</li> </ul>
<b>Regenerador y Cicatrizante de heridas</b>	<ul style="list-style-type: none"> <li>~40 proteínas</li> <li>Caveolina 1, Colágeno Tipo I, Colágeno Tipo III, EGFR, FGFR1, etc</li> </ul>	<ul style="list-style-type: none"> <li>miR 431, miR 455</li> </ul>
<b>Alto nivel de absorción</b>	<ul style="list-style-type: none"> <li>CD44</li> </ul>	

\*Testosterona Es un tipo de hormona masculina asociada con la alopecia masculina.

\*\*Finasteride Tratamiento anticáida que evita que la testosterona, una hormona masculina, se transforme en otra hormona masculina (DHT)

Source: ExoCoBio, unpublished data

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## Hagamos un poco de biología molecular...

Wnt/ $\beta$ -catenin: The Wnt signaling pathways are a group of signal transduction pathways which begin with proteins that pass signals into a cell through cell surface receptors. The name Wnt is a portmanteau created from the names Wingless and Int-1. **Wnt signaling pathways use either nearby cell-cell communication (paracrine) or same-cell communication (autocrine).** They are highly evolutionarily conserved in animals, which means they are similar across animal species from fruit flies to humans.



International Journal of  
*Molecular Sciences*



*Review*

### Targeting Wnt/ $\beta$ -Catenin Pathway for Developing Therapies for Hair Loss

Bu Young Choi

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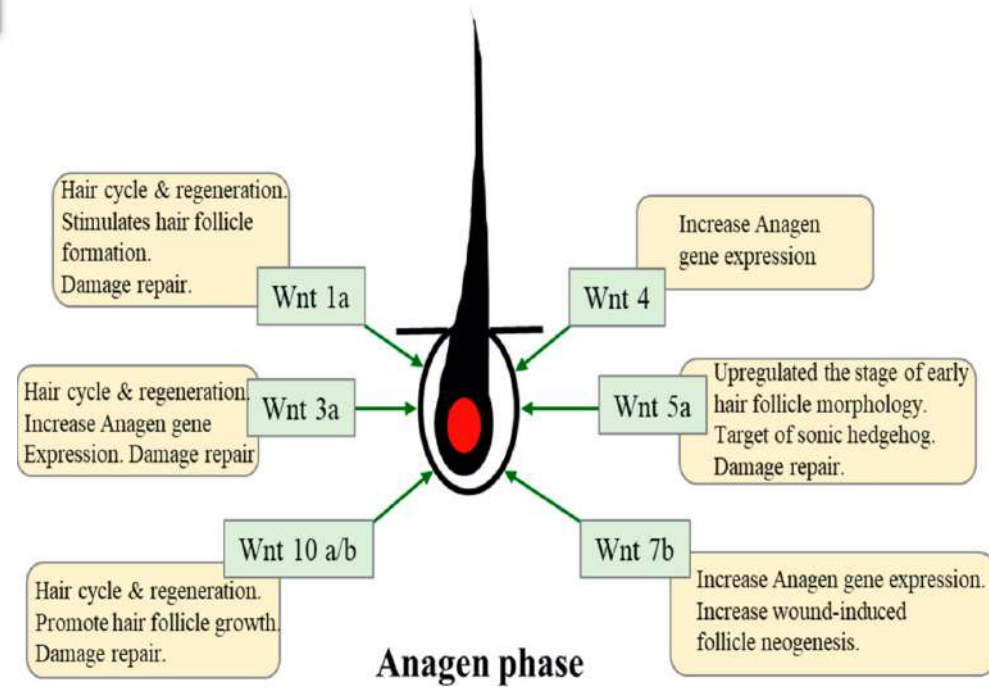
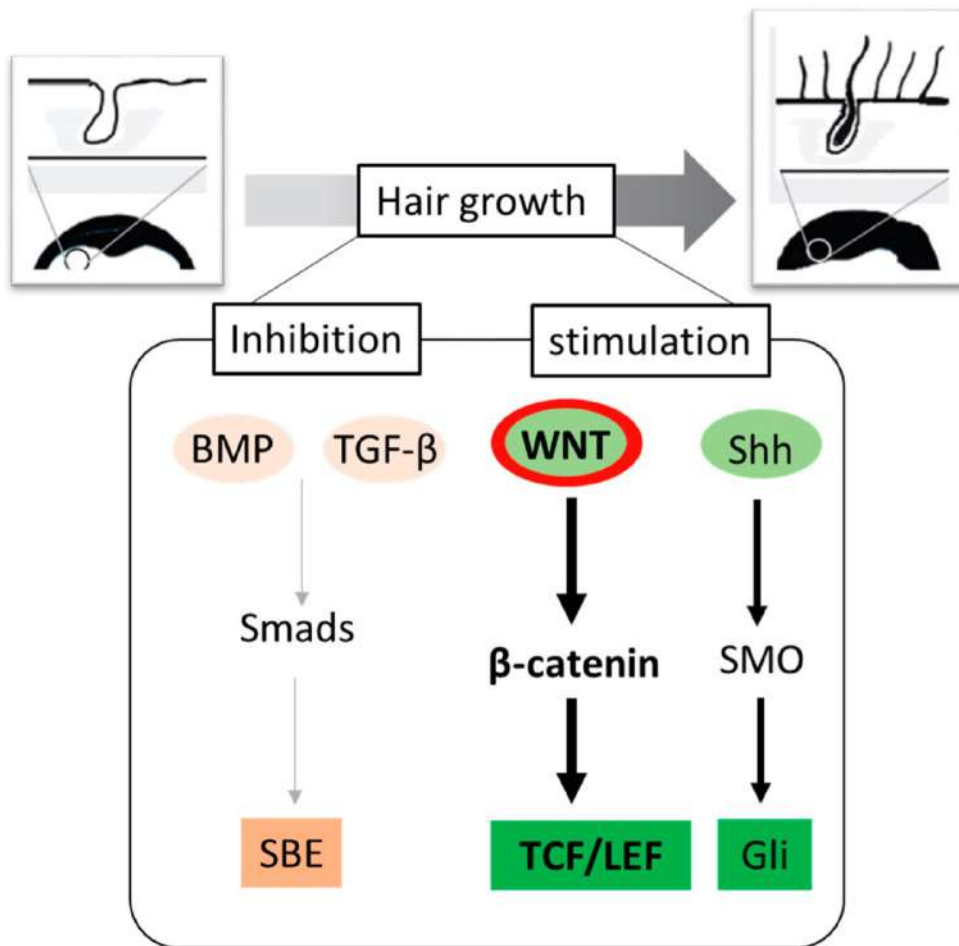
Received: 1 July 2020; Accepted: 10 July 2020; Published: 12 July 2020



**Abstract:** Persistent hair loss is a major cause of psychological distress and compromised quality of life in millions of people worldwide. Remarkable progress has been made in understanding the molecular basis of hair loss and identifying valid intracellular targets for designing effective therapies for hair loss treatment. Whereas a variety of growth factors and signaling pathways have been implicated in hair cycling process, the activation of Wnt/ $\beta$ -catenin signaling plays a central role in hair follicle regeneration. Several plant-derived chemicals have been reported to promote hair growth by activating Wnt/ $\beta$ -catenin signaling in various in vitro and in vivo studies. This mini-review sheds light on the role of Wnt/ $\beta$ -catenin in promoting hair growth and the current progress in designing hair loss therapies by targeting this signaling pathway.

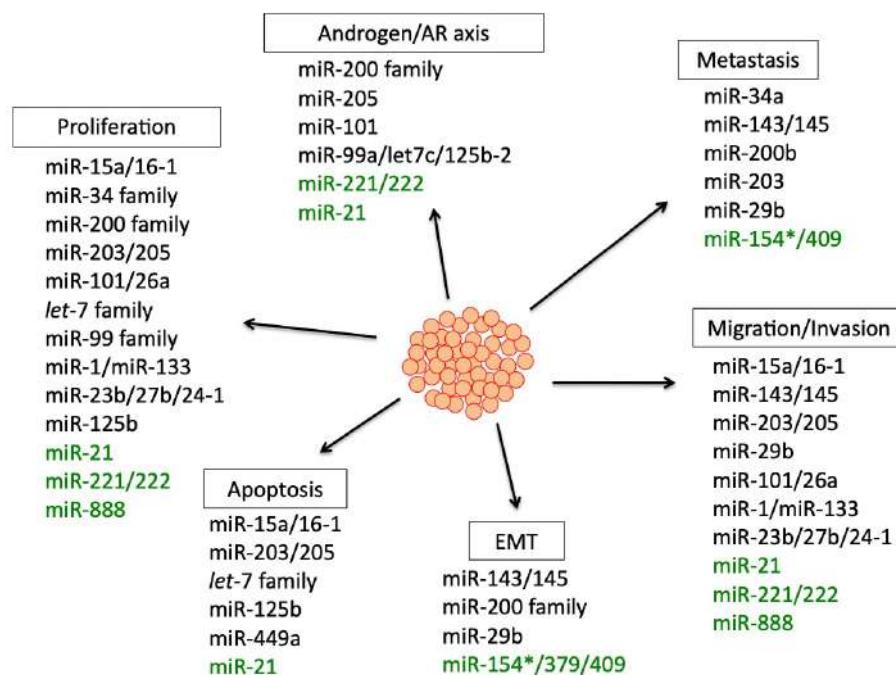
**Keywords:** hair loss; Wnt/ $\beta$ -catenin signaling

### Hagamos un poco de biología molecular...



## Hagamos un poco de biología molecular...

miR 100: The miR-99 family (miR-99a, miR-99b, and miR-100) is hypothesized to act as tumor suppressors in the prostate and family members are noted to be downregulated in advanced prostate cancer cell lines (C4-2 and WPE1-NB26) relative to less-aggressive cell lines (LNCaP and RWPE-1) and decreased in human prostate adenocarcinomas compared to nonmalignant tissue.



**Figure 12.2** *MicroRNAs associated with prostate cancer progression.* MicroRNAs play multiple roles during cancer progression in both negative (black) and positive (green) ways to modulate processes such as tumor proliferation, apoptosis, migration/invasion, epithelial to mesenchymal transition, metastasis, and androgen response in the prostate.



## Estado de la I+D relacionada (Documentación externa)

### 1. Acelera el crecimiento del cabello

Se confirmó que miR-100 de ReNcell-NV (nanocitos derivados de células neuroeléctricas) activa el mecanismo Wnt/ $\beta$ -catenina y tiene un efecto positivo en el crecimiento del cabello.

- miR-100 favorece la actividad de  $\beta$ -catenina
- Wnt/ $\beta$ -catenina: cuando la señal de Wnt se activa como una proteína de señalización entre las células foliculares y las células epiteliales que desempeña un papel importante en la formación de folículos, conduce a la producción de  $\beta$ -catenina y la formación de folículos.

Cuando se excluyó miR-100 (anti-miR-100), se redujo la actividad de  $\beta$ -catenina y se confirmó que HRLV contenía miR-100, el mismo ARNm, también

Cao et al. / Nanobiotechnol (2021) 19:20  
https://doi.org/10.1186/s12951-020-00573-5

Journal of Nanobiotechnology

RESEARCH Open Access

### Neural progenitor cell-derived nanovesicles promote hair follicle growth via miR-100

Lei Cao<sup>1†</sup>, Tian Tian<sup>2†</sup>, Yuanbo Huang<sup>3†</sup>, Shiqin Tao<sup>4</sup>, Xiaohong Zhu<sup>4</sup>, Mifang Yang<sup>4</sup>, Jing Gu<sup>1</sup>, Guangdong Feng<sup>1</sup>, Yinni Ma<sup>1</sup>, Ruihan Ke<sup>1</sup>, Wenrong Xu<sup>2</sup> and Lei Wang<sup>1\*</sup>

**Abstract**  
**Background:** Accumulating evidence shows that mesenchymal stem cell-derived extracellular vesicles (EVs) hold great promise to promote hair growth. However, large scale production of EVs is still a challenge. Recently, exosome-mimetic nanovesicles (NV) prepared by extruding cells have emerged as an alternative strategy for clinical scale production. Here, ReNcell-NV (ReNV) cells, a neural progenitor cell line was serially extruded to produce NV.  
**Results:** ReNV NV were found to promote dermal papilla cell (DPC) proliferation. In addition, in a mouse model of cyclosporin induced hair regeneration, ReNV NV were injected subcutaneously, resulting in an acceleration of hair follicle (HF) cycling transition at the site. The underlying mechanism was indicated to be the activation of Wnt/ $\beta$ -catenin signaling pathway. Furthermore, miR-100 was revealed to be abundant in ReNV NV and significantly up-regulated in DPCs receiving ReNV NV treatment. miR-100 inhibition verified its important role in ReNV NV-induced  $\beta$ -catenin signaling activation.  
**Conclusion:** These results provide an alternative agent to EVs and suggest a strategy for hair growth therapy.  
**Keywords:** Hair growth, Nanovesicles, Extracellular vesicles

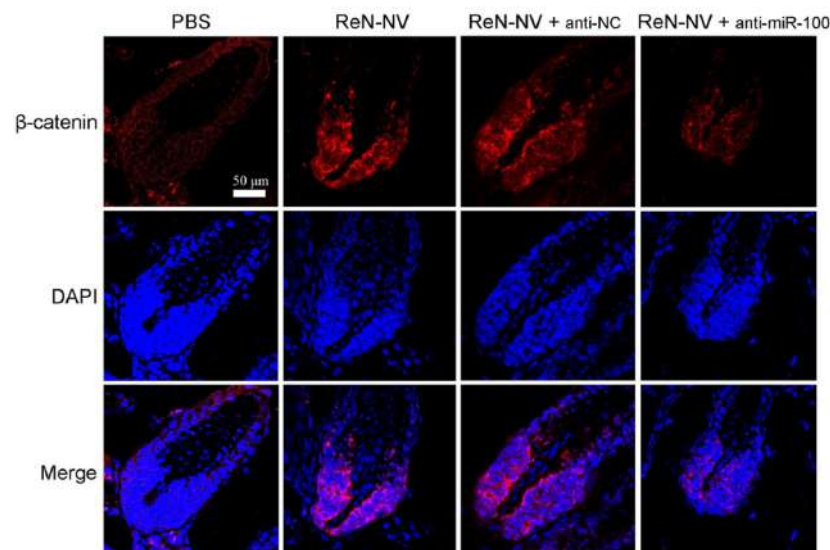
**Background**  
 Hair loss, characterized by shorter anagen and longer telogen phases of hair follicles (HF), is a common medical problem which may cause both cosmetic and psychological problems. Minoxidil, finasteride, platelet-rich plasma (PRP), low-level laser therapy (LLLT), stem cell therapy, and HF transplantation are current treatment approaches. Unfortunately, all of these treatments have limitations. According to previous studies, minoxidil may cause high rate of adverse effects, such as burning or pruritus at the application site, allergic contact dermatitis [1] and cardiovascular effects [2]. Finasteride was associated with rare complications of decreased libido [3], gynecomastia [4] and psychologic impairments [5]. LLLT may bring about adverse events including dry skin, pruritus, and scalp tenderness [6]. PRP has the limitation of no consensus regarding exact concentration, dosing parameters, depth of injection and usually leads to pain and erythema [7]. Stem cell therapy has not been approved and studies are being carried out to concern its safety, efficacy and accessibility [8]. HF transplantation is costly and there is a shortage of donor hair follicles [9]. Therefore, there is a high demand to explore new approaches for alopecia.

HF, which contains both epithelial and mesenchymal compartment, is a complicated organ which undergoes cycles of growth (anagen), regression (catagen), quiescence (telogen) and regeneration [10]. Epithelial-mesenchymal interactions play a critical role during HF development. Dermal papilla cells (DPCs), one

**Footnote:** \*Correspondence: wangl@163.com; ybwang@jnu.edu.cn; leiwang@jnu.edu.cn  
 †Lei Cao, Tian Tian and Yuanbo Huang contributed equally to this work.  
<sup>1</sup>Department of Dermatology, The Affiliated Wuxi No. 2 People's Hospital of Nanjing Medical University, Wuxi 214002, Jiangsu, China  
<sup>2</sup>Department of Dermatology, The Affiliated Wuxi People's Hospital of Nanjing Medical University, Wuxi 214002, Jiangsu, China  
 Full list of author information is available at the end of the article

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Fuente: Lei Cao, las nanovesículas derivadas de células progenitoras neurales promueven el crecimiento del folículo piloso a través de miR-100, J Nanobiotechnol (2021) 19:20



Rojo\*: imagen de inmunofluorescencia de  $\beta$ -catenin  
Azul\*: Núcleo celular

\*Tinción DAPI: método de tinción DAPI, tinción de cromosomas de células y observación con un microscopio de fluorescencia.

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## Hagamos un poco de biología molecular...

**PRDX1:** This gene encodes a member of the peroxiredoxin family of antioxidant enzymes, which reduce hydrogen peroxide and alkyl hydroperoxides. The encoded protein may play an antioxidant protective role in cells, and may contribute to the antiviral activity of CD8(+) T-cells. This protein may have a proliferative effect and play a role in cancer development or progression. Three transcript variants encoding the same protein have been identified for this gene.

**PRDX6:** The protein encoded by this gene is a member of the thiol-specific antioxidant protein family. This protein is a bifunctional enzyme with two distinct active sites. It is involved in redox regulation of the cell; it can reduce H<sub>2</sub>O<sub>2</sub> and short chain organic, fatty acid, and phospholipid hydroperoxides. It may play a role in the regulation of phospholipid turnover as well as in protection against oxidative injury.



### Journal of Investigative Dermatology

Volume 137, Issue 2, February 2017, Pages 295-304



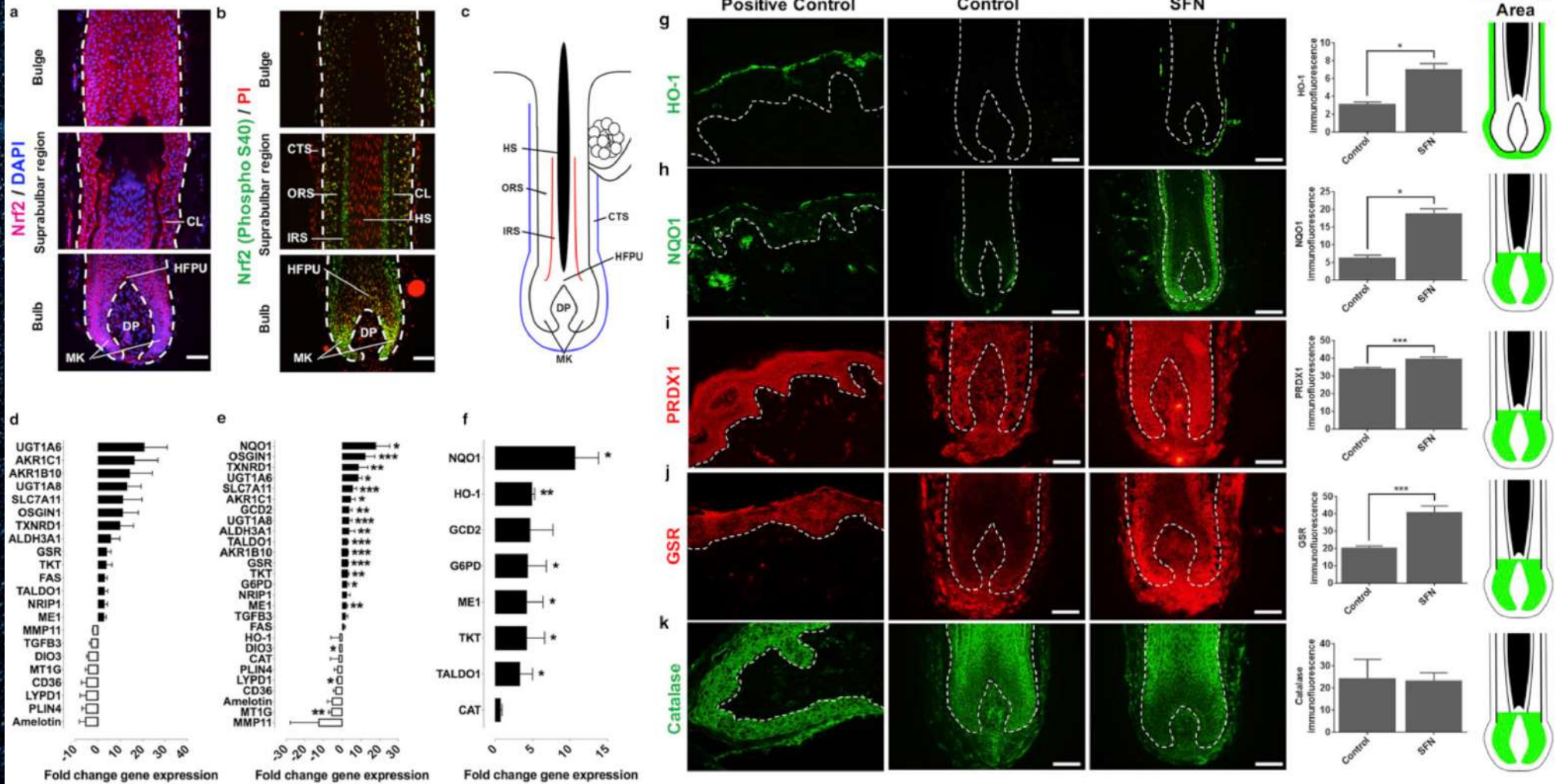
Original Article

Appendages

## Oxidative Damage Control in a Human (Mini-) Organ: Nrf2 Activation Protects against Oxidative Stress-Induced Hair Growth Inhibition

[Iain S. Haslam](#)<sup>1,2</sup>  , [Laura Jadkauskaite](#)<sup>1</sup>, [Imre Lőrinc Szabó](#)<sup>3</sup>, [Selma Staeger](#)<sup>1</sup>, [Jasper Hesebeck-Brinckmann](#)<sup>1</sup>, [Gail Jenkins](#)<sup>4</sup>, [Ranjit K. Bhogal](#)<sup>4</sup>, [Fei-Ling Lim](#)<sup>4</sup>, [Nilofer Farjo](#)<sup>5</sup>, [Bessam Farjo](#)<sup>5</sup>, [Tamás Bíró](#)<sup>3</sup>, [Matthias Schäfer](#)<sup>6</sup>, [Ralf Paus](#)<sup>1</sup>  

## Hagamos un poco de biología molecular...



## Hagamos un poco de biología molecular...

miR let-7b: The lethal-7 (let-7) gene was first discovered in the nematode as a key developmental regulator and became one of the first two known microRNAs (the other one is lin-4). Soon, let-7 was found in fruit fly, and identified as the first known human miRNA by a BLAST (basic local alignment search tool) research. The mature form of let-7 family members is highly conserved across species.

The let-7 family has a lot more members in vertebrates than in *C.elegans* and *Drosophila*. The sequences, expression timing, as well as genomic clustering of these miRNAs members are all conserved across species. The direct role of let-7 family in vertebrate development has not been clearly shown as in less complex organisms, yet the expression pattern of let-7 family is indeed temporal during developmental processes. Given that the expression levels of let-7 members are significantly low in human cancers and cancer stem cells, the major function of let-7 genes may be to promote terminal differentiation in development and tumor suppression.




*Review*

### Perspectives on miRNAs Targeting DKK1 for Developing Hair Regeneration Therapy

Dimitri Papukashvili <sup>†</sup>, Nino Rcheulishvili <sup>†</sup>, Cong Liu, Fengfei Xie, Deependra Tyagi, Yunjiao He <sup>\*</sup> and Peng George Wang <sup>\*†</sup>

School of Medicine, Southern University of Science and Technology, Shenzhen 518000, China; dimitri@sustech.edu.cn (D.P.); nino@sustech.edu.cn (N.R.); 11930799@mail.sustech.edu.cn (C.L.); xieff@mail.sustech.edu.cn (F.X.); deependrat@sustech.edu.cn (D.T.)


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Tel.: +86-135-3765-7996 (Y.H.); +86-0755-8801-5584 (P.G.W.)

<sup>†</sup> These authors contributed equally to this work.

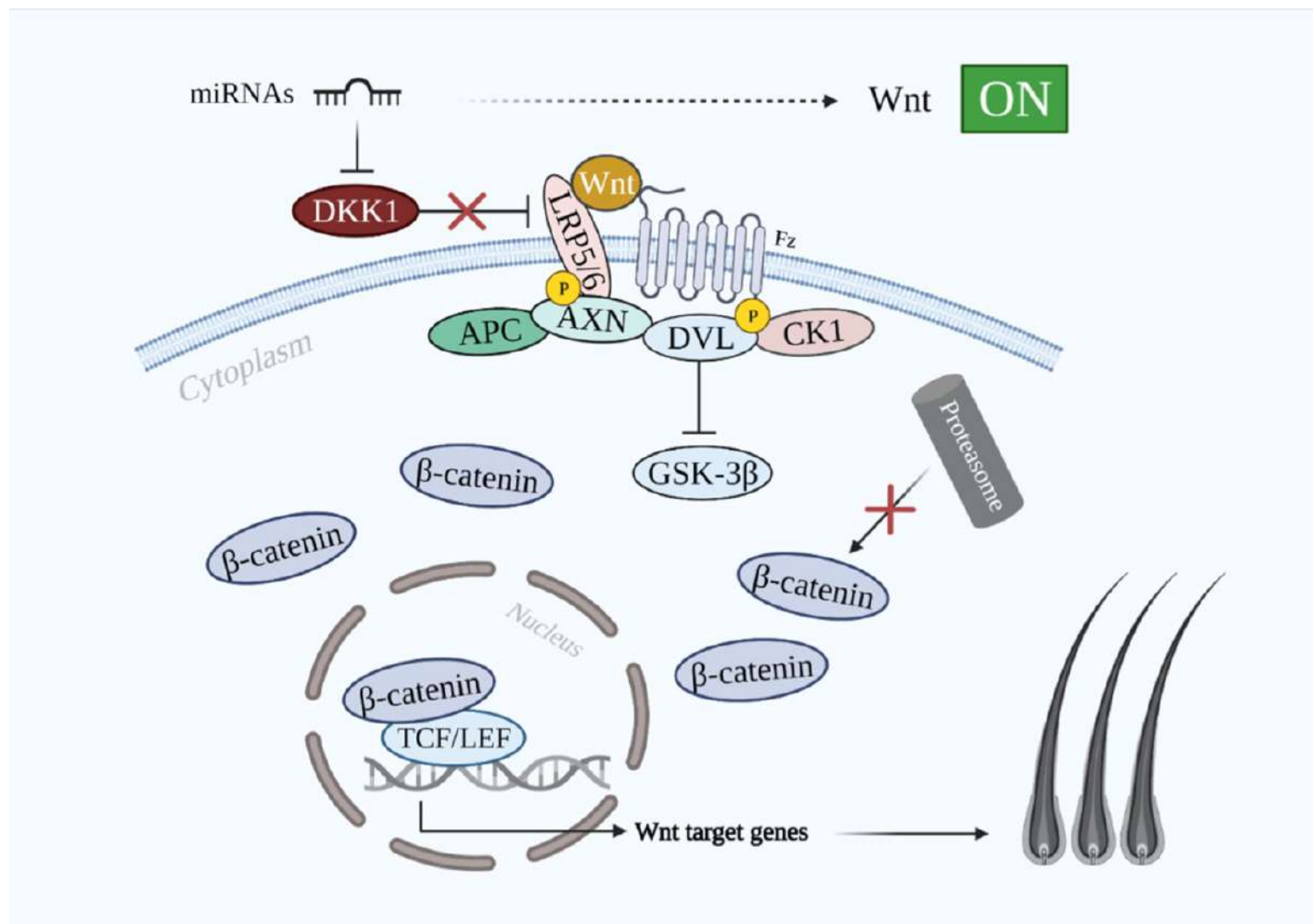
**Abstract:** Androgenetic alopecia (AGA) remains an unsolved problem for the well-being of humankind, although multiple important involvements in hair growth have been discovered. Up until now, there is no ideal therapy in clinical practice in terms of efficacy and safety. Ultimately, there is a strong need for developing a feasible remedy for preventing and treating AGA. The Wnt/ $\beta$ -catenin signaling pathway is critical in hair restoration. Thus, AGA treatment via modulating this pathway is rational, although challenging. Dickkopf-related protein 1 (DKK1) is distinctly identified as an inhibitor of canonical Wnt/ $\beta$ -catenin signaling. Thus, in order to stimulate the Wnt/ $\beta$ -catenin signaling pathway, inhibition of DKK1 is greatly demanding. Studying DKK1-targeting microRNAs (miRNAs) involved in the Wnt/ $\beta$ -catenin signaling pathway may lay the groundwork for the promotion of hair growth. Bearing in mind that DKK1 inhibition in the balding scalp of AGA certainly makes sense, this review sheds light on the perspectives of miRNA-mediated hair growth for treating AGA via regulating DKK1 and, eventually, modulating Wnt/ $\beta$ -catenin signaling. Consequently, certain miRNAs regulating the Wnt/ $\beta$ -catenin signaling pathway via DKK1 inhibition might represent attractive candidates for further studies focusing on promoting hair growth and AGA therapy.

**Keywords:** miRNA; AGA; DKK1; Wnt/ $\beta$ -catenin; hair

**Citation:** Papukashvili, D.; Rcheulishvili, N.; Liu, C.; Xie, F.; Tyagi, D.; Hu, Y.; Wang, P.G. Perspectives on miRNAs Targeting DKK1 for Developing Hair Regeneration Therapy. *Cells* **2021**, *10*, 2957. <https://doi.org/10.3390/cells10112957>

 check for updates

### Hagamos un poco de biología molecular...



## Hagamos un poco de biología molecular...

CD44: The CD44 antigen is a cell-surface glycoprotein involved in cell–cell interactions, cell adhesion and migration. In humans, the CD44 antigen is encoded by the CD44 gene on chromosome 11. CD44 has been referred to as HCAM (homing cell adhesion molecule), Pgp-1 (phagocytic glycoprotein-1), Hermes antigen, lymphocyte homing receptor, ECM-III, and HUTCH-1.

*J Cutan Pathol 1994; 229-232  
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**Journal of  
Cutaneous Pathology**  
ISSN 0303-6987

## CD44 expression in alopecia areata and androgenetic alopecia

CD44 is a widely distributed cell surface protein thought to be involved in multiple steps of normal immune cell function, including T-cell activation, and in cellular adhesion where it mediates cell attachment to hyaluronate. In normal skin, CD44 is found by immunohistochemical means to be primarily in eccrine coil cells. In this study, we have looked at the expression of CD44 in normal scalp and in two different hair disorders, androgenetic alopecia and alopecia areata. In normal scalp and androgenetic alopecia, CD44 was found in its normal distribution in eccrine coil cells. In scalp of 30 patients with alopecia areata, there was no expression of this glycoprotein. Patients were also assessed pre and post treatment for their alopecia areata, and even though they had no significant hair regrowth, 2 patients regained expression of CD44, indicating a variable expression of this protein in the alopecia areata disease process. The absence of CD44 expression in alopecia areata-affected scalp may give further information regarding the pathogenesis of this disease.

Sawaya ME, Bakshandeh H, Hordinsky MK, Penneys NS. CD44 expression in alopecia areata and androgenetic alopecia. *J Cutan Pathol* 1994; 21: 229–232. © Munksgaard 1994.

**Marty E. Sawaya\***,  
**Haleh Bakshandeh,**  
**Maria K. Hordinsky\*\* and**  
**Neal S. Penneys\*\*\*.**

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\*\*Department of Dermatology, University of  
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100277, Gainesville, FL 32610-0277, USA

Accepted January 11, 1994

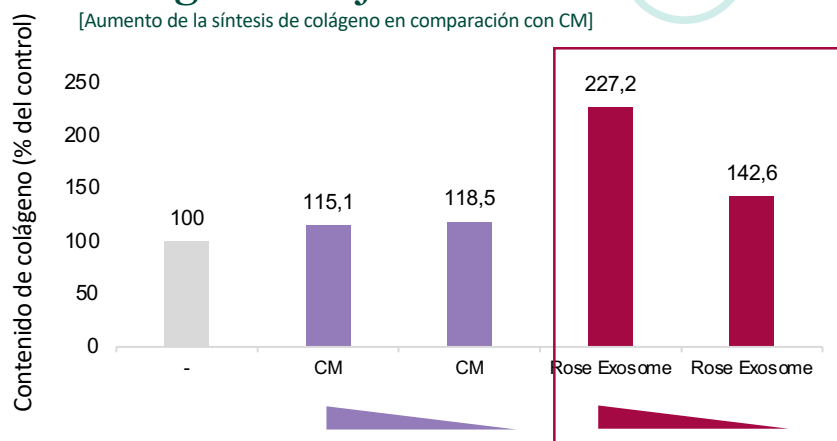
## ASCEplus HRLV <Efecto – Cuero cabelludo. Exosoma de células madre de rosas>

El ingrediente patentado “Exosoma de células madre de rosas” se completó con la tecnología de la firma global de investigación de exosomas ExoCoBio.

Los poderosos efectos de la “Rosa de Damasco,” llamada la reina de las rosas, son liofilizados y entregados al cuero cabelludo

### Síntesis de Colágeno Mejorada

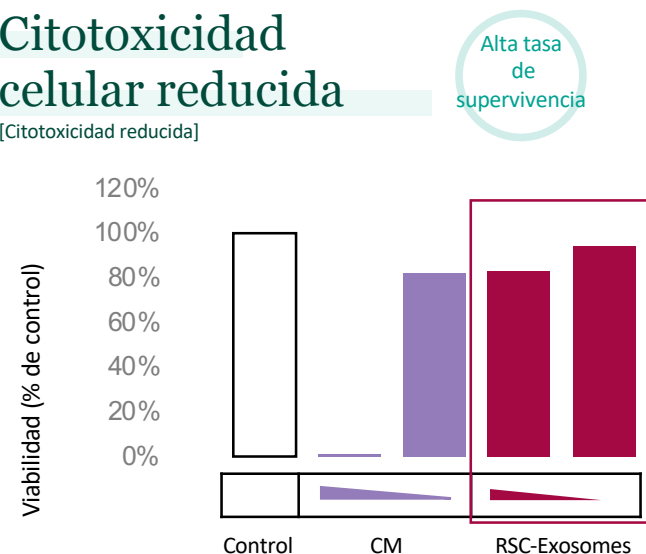
[Aumento de la síntesis de colágeno en comparación con CM]



CM : Medios acondicionados con células madre de rosas

### Citotoxicidad celular reducida

[Citotoxicidad reducida]



Nº Registro. (Fecha de Registro)	Nombre de la Patente	Resumen
10-2058444 (December 09, 2019)	(Exosoma de células madre de rosas) Un compuesto cosmético que incluye el exosoma derivado de células madre de rosas como ingrediente activo	El exosoma separado de los medios acondicionados con células madre de rosas se patentó para promover la síntesis de colágeno de fibroblastos de piel humana.

• La descripción en esta página se limita a las características de las materias primas de HRLV. HRLV es un medio acondicionado con células madre que contiene estas materias primas.

## ASCEplus HRLV <Efecto - 2. Cabello. Antienvjecimiento de la célula de la papila dérmica humana>

Cuando se irradia UVB a las células de la papila dérmica humana para inducir el envejecimiento, se confirma que el envejecimiento se previene hasta en un 45 % después del **tratamiento con medios acondicionados con células madre que contienen Exosomas (antes y después del tratamiento).**

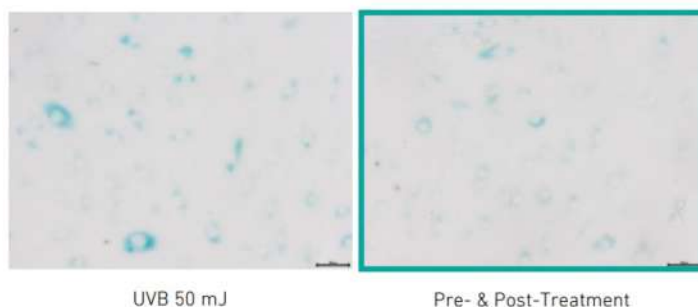
### Célula de papila dérmica de cabello humano

Hasta **45%**

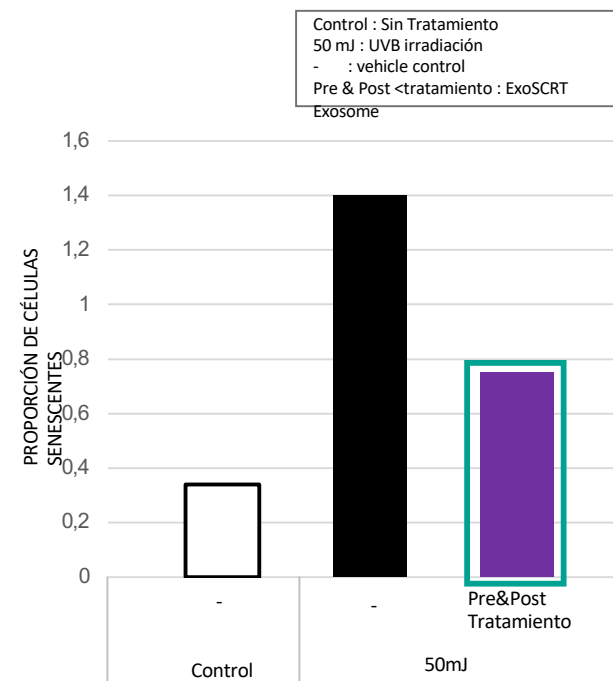
### Protección contra la senescencia

[ Anti-envejecimiento de las células de la papila dérmica ]

[  $\beta$ -gal staining assay ]



\*Ensayo de tinción de  $\beta$ -gal: método de prueba para verificar  $\beta$ -gal, una sustancia indicadora generada cuando las células envejecen, mediante tinción azul



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## ASCEplus HRLV <Efecto – 3. Cabello. Prevención del Blanqueamiento del Cabello>

Después de tratar con medio enriquecido con células madre que contenían exosomas,

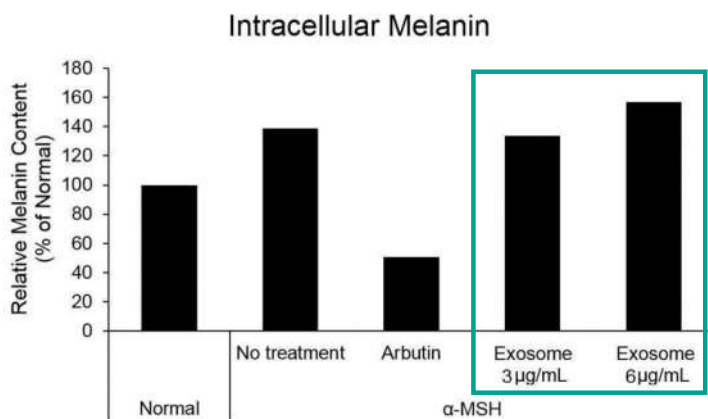
Se confirmó que los exosomas son efectivos para aumentar la síntesis de melanina y secretar melanina al exterior para promover el ennegrecimiento del cabello y prevenir el cabello canoso

### Estimular el cabello y prevenir el blanqueamiento del cabello.

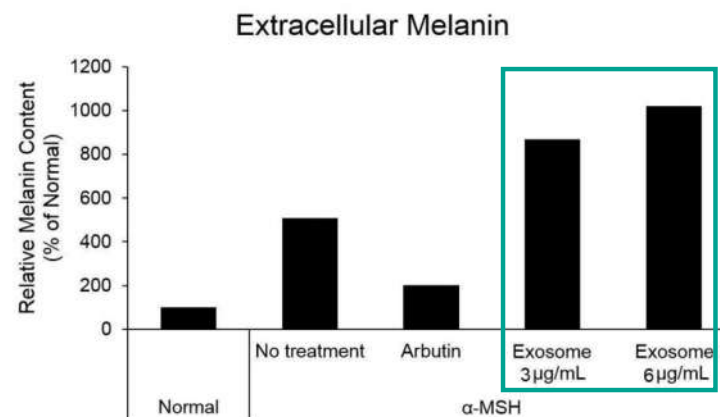
[Promover el ennegrecimiento del cabello / Prevenir el blanqueamiento del cabello]

\* Patente KR 10-2265875

α-MSH : α-Hormona estimulante de melanocitos  
Normal : no α-MSH  
Arbutin: Supresión de la producción de células de melanina  
Sin tratamiento: grupo de control tratado solo con α-MSH



\* Melanina intracelular: se confirmó que la melanina acumulada dentro de las células del melanoma aumentó significativamente.



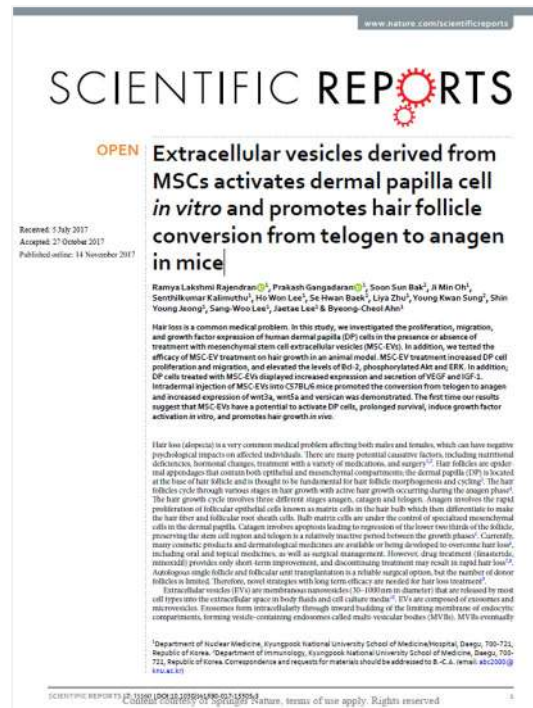
\* Melanina extracelular: se confirmó que aumentó la cantidad de melanina liberada por las células de melanoma.

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## Estado de la I+D relacionada (Documentación externa)

### 2. Promueve el cambio del ciclo capilar

MSC-EV (vesículas extracelulares del lóbulo medio) activa las células DP (células de la papila cervical) para promover la transición del ciclo del cabello del período de descanso al período de crecimiento para promover el crecimiento del cabello.



Fuente: Ramya Lakshmi Rajendran et al, Las vesículas extracelulares derivadas de MSC activan las células de la papila dérmica in vitro y promueven la conversión del folículo piloso de telógeno a anágeno en ratones, Scientific Reports 7: 15560

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### Algunos de los resultados iniciales (by Dr. De Felipe)



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### ASCEplus HRLV <Diferencias de SRLV>



Producto	HRLV ( Vial liofilizado para el rejuvenecimiento del cabello)	SRLV (Vial liofilizado para el rejuvenecimiento de la piel )
Objetivo	<ul style="list-style-type: none"> <li>Un producto capilar para profesionales que mejora la raíz del cabello y el cuero cabelludo</li> </ul>	<ul style="list-style-type: none"> <li>Un producto para profesionales de la piel que mejora la base de la piel.</li> </ul>
Especificación	<ul style="list-style-type: none"> <li>Formulación 1: Polvo liofilizado 20 mg x 5 viales</li> </ul>	<ul style="list-style-type: none"> <li>Formulación 1: Polvo liofilizado 20 mg x 5 viales</li> <li>Formulación 2: Diluyente 5,0 ml X 5 viales</li> </ul>
Ingrediente común	<ul style="list-style-type: none"> <li>Vesículas extracelulares de rosa damasco (exosoma de células madre de rosa)</li> </ul>	<ul style="list-style-type: none"> <li>Vesículas extracelulares de rosa damasco (exosoma de células madre de rosa)</li> </ul>
Principales Ingredientes Básicos	<ul style="list-style-type: none"> <li>Factores de crecimiento y péptidos relacionados con el cabello, etc.</li> <li>Una combinación de ingredientes activos optimizados para el cuidado del cuero cabelludo y el cabello</li> <li>Noggin, biotina, péptido de cobre, etc.</li> </ul>	<ul style="list-style-type: none"> <li>Factores de crecimiento, péptidos e ingredientes activos relacionados con la piel</li> <li>Una combinación de ingredientes activos optimizados para el cuidado de la piel</li> </ul>
Puntos de Diferencia	<ul style="list-style-type: none"> <li>Efectos de regeneración y antiinflamatorios en la piel probados por el SRLV existente</li> <li>Efectos multifuncionales en problemas complejos del cuero cabelludo y el cabello, como la normalización de los ciclos capilares y el entorno del cabello.</li> <li>Solución capilar premium de nueva generación que se puede aplicar a diversas indicaciones, como la pérdida de cabello androgénica, la pérdida de cabello inflamatoria, la pérdida de cabello circular y la pérdida de cabello femenina.</li> </ul>	<ul style="list-style-type: none"> <li>Aplicable a problemas complejos de la piel.</li> <li>(piel envejecida, piel inflamada, poros dilatados, cicatrices de acné, etc.)</li> <li>Regeneración fundamental de la piel y efectos antiinflamatorios</li> </ul>

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# ASCE<sup>plus</sup><sup>TM</sup>

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