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X Congreso Nacional de ALZHEIMER

GIJÓN. 8, 9, 10 y 11 /NOV/ 2023

“Presente y futuro del tratamiento de enfermedades neurodegenerativas basado en las células madre mesenquimales”

Dr. Francisco J. Vizoso

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ENFERMEDADES HUÉRFANAS

En torno al **40% de la población** padecerá en algún momento de su vida una **enfermedad** que va a implicar **proceso inflamatorio o autoinmune** no controlable satisfactoriamente con las terapias actuales y la **pérdida de tejido**

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Ejemplos del impacto enfermedades en el mundo en 2020

- El número de pacientes con **diabetes** se estima en 537 millones.
- La incidencia global **cáncer** se sitúa en torno a 19,3 millones con resultado de 10 millones de muertes.
- El **glaucoma**, una enfermedad que causa ceguera irreversible, afecta a más de 70 millones de personas.
- El número de pacientes con **osteo-artritis** se estima en más de 300 millones.
- **La demencia, incluyendo a la enfermedad de Alzheimer,** afecta actualmente a **50 millones de personas en el mundo**. Según la Organización Muldial de la Salud, **se espera que ese número se cuadruplique en 2050**.

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Capacidad regenerativa del Alojote mejicano

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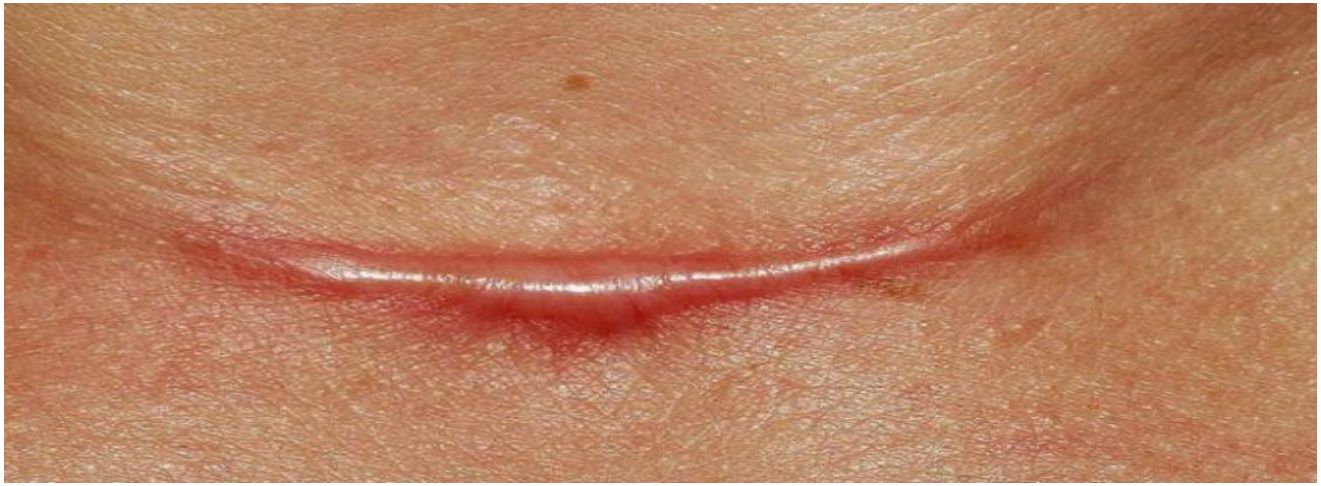
CICATRIZ



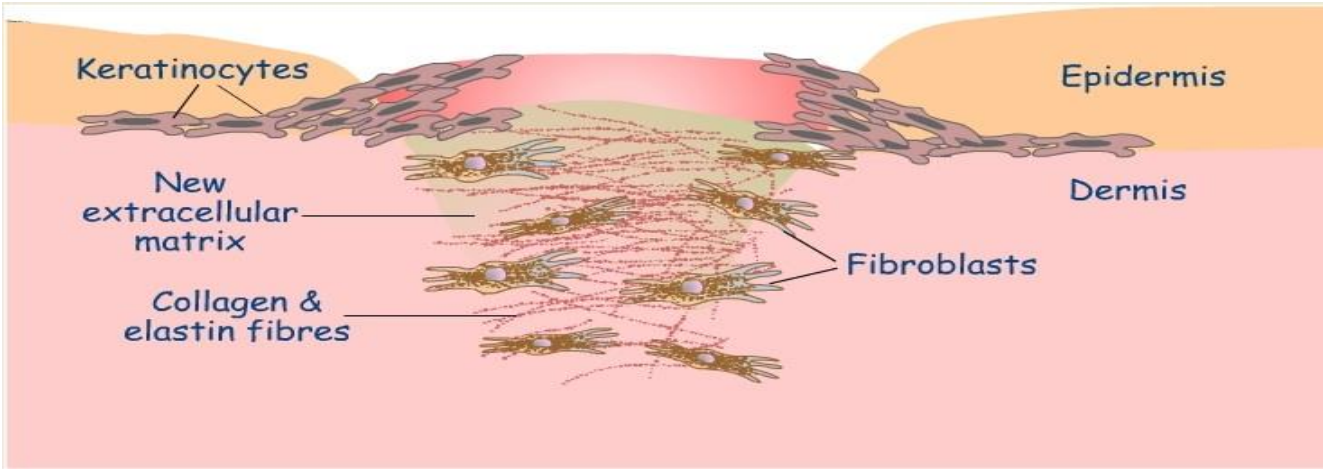
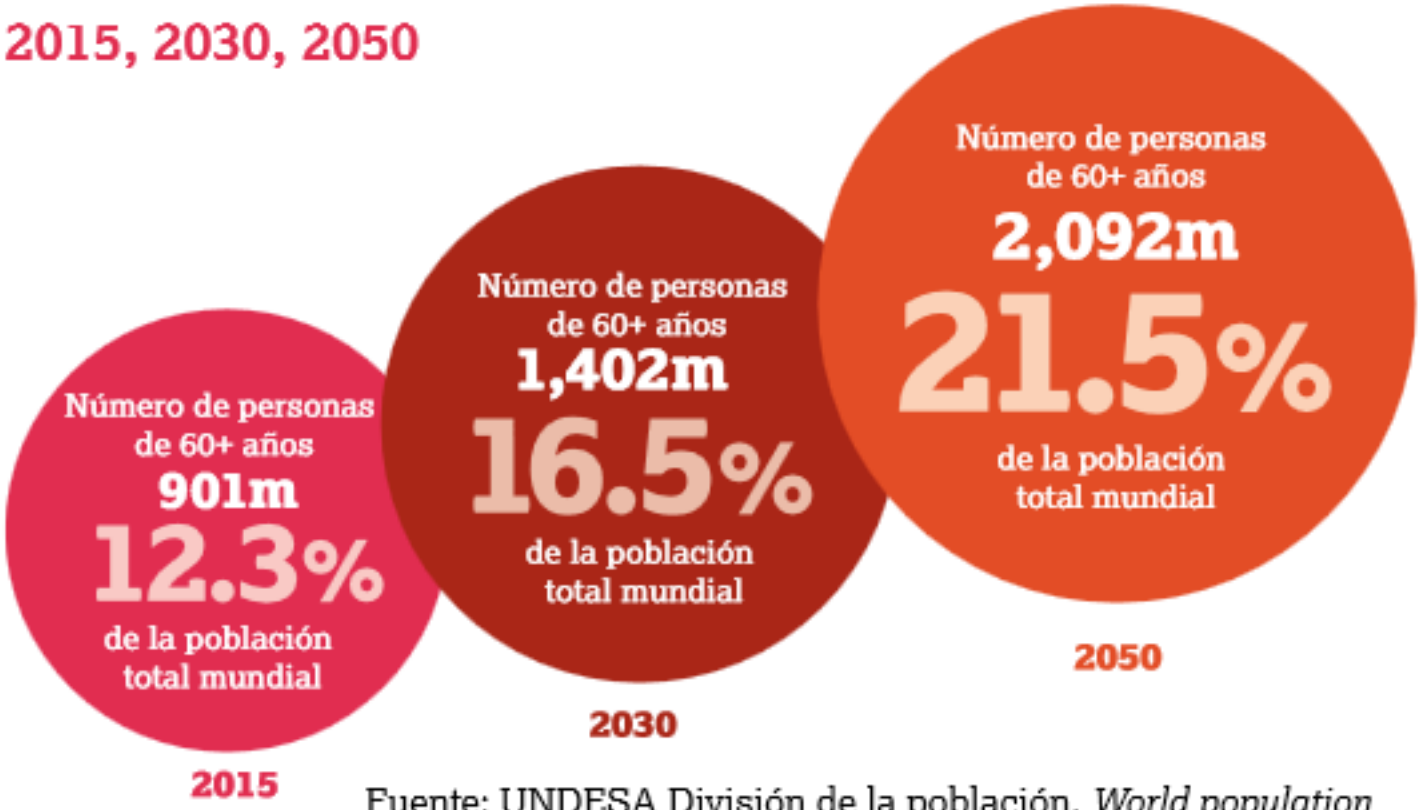


Figura 1: Número y proporción de personas adultas mayores a nivel global 2015, 2030, 2050



Fuente: UNDESA División de la población, *World population prospects: the 2015 revision ("Perspectivas de la población mundial: revision de 2015")*, edición de DVD, 2015

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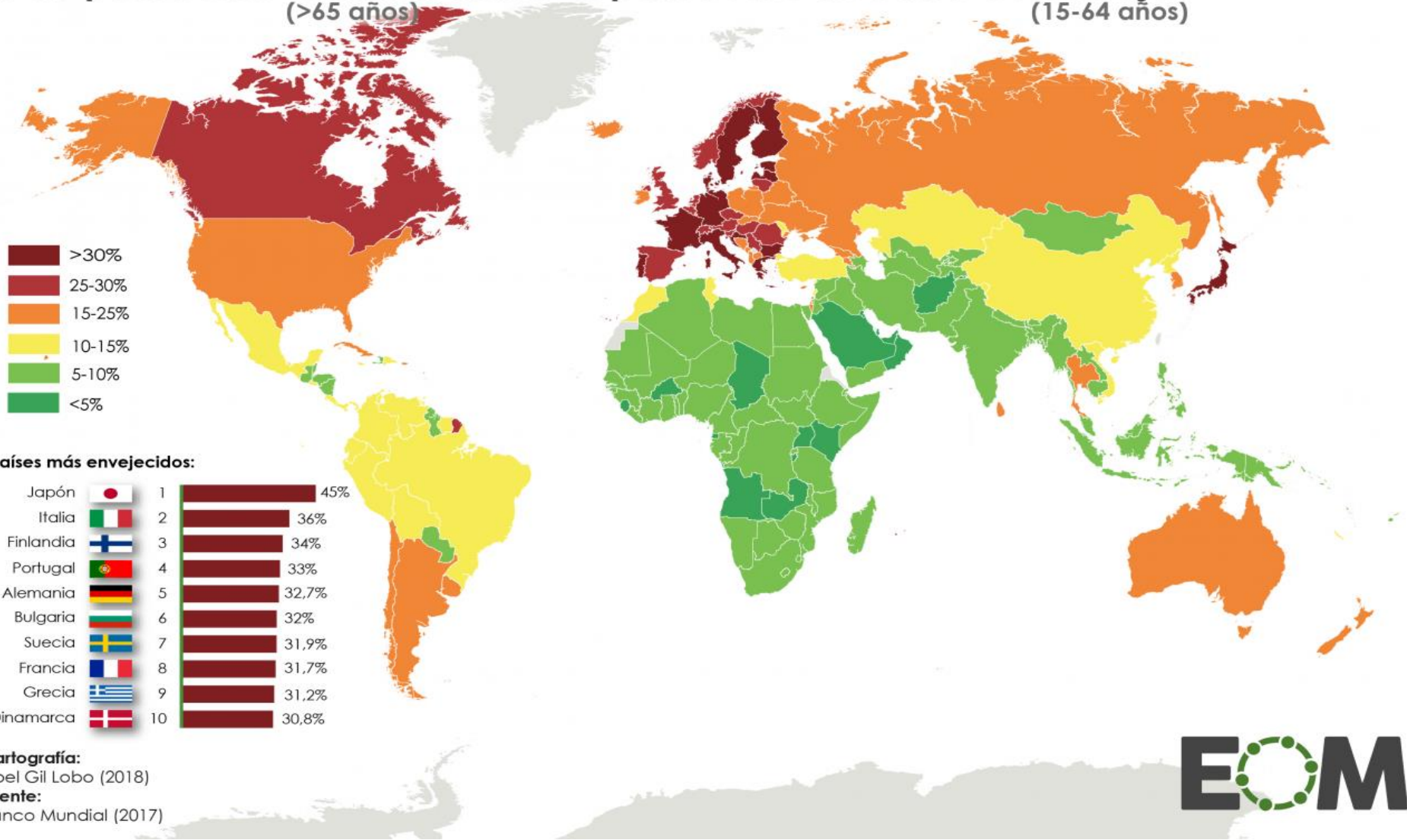
Un mundo dependiente

% de población anciana sobre la población en edad de trabajar

(>65 años) / (15-64 años)



Países más envejecidos:

Japón	1	45%
Italia	2	36%
Finlandia	3	34%
Portugal	4	33%
Alemania	5	32,7%
Bulgaria	6	32%
Suecia	7	31,9%
Francia	8	31,7%
Grecia	9	31,2%
Dinamarca	10	30,8%

Cartografía:
Abel Gil Lobo (2018)
Fuente:
Banco Mundial (2017)

EOM

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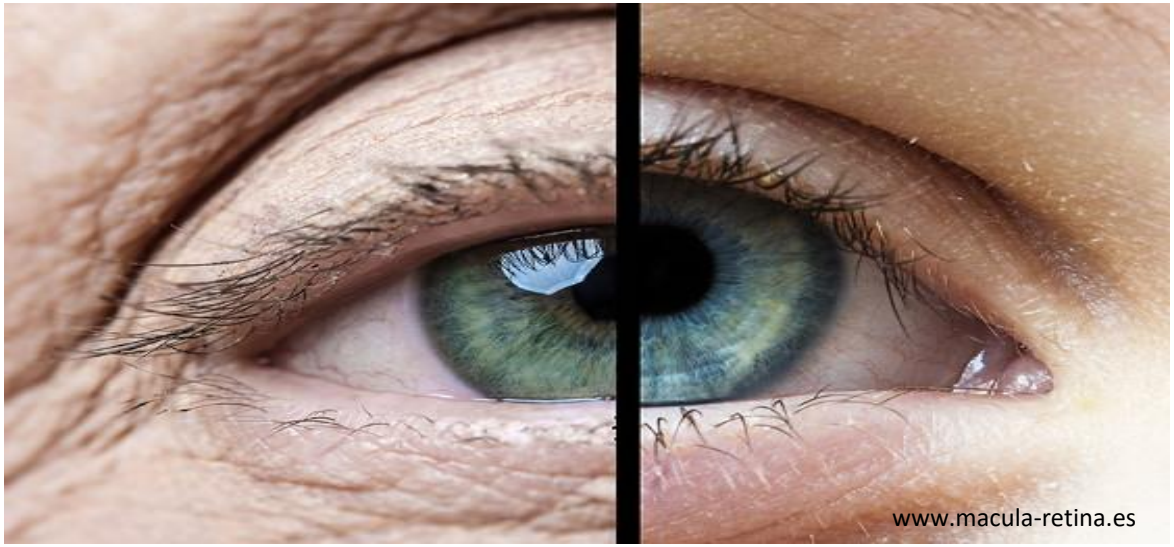
Procesos asociados al envejecimiento



- Vulnerabilidad fisiológica.
- Incremento exponencial de enfermedades degenerativas crónicas (Neurodegenerativas –Enfermedades de Alzheimer y Parkinson-, Cardiovasculares –Infarto de miocardio, hipertensión y arterioesclerosis-, Diabetes, Cáncer, Osteoporosis, Osteo-artritis).
- Mayor suceptibilidad a las infecciones graves.
- Polifarmacia (riesgo de interacciones y efectos adversos).
- Disminución e la calidad de vida.

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DIANA TERAPÉUTICA EN MEDICINA

www.diariomedico.com

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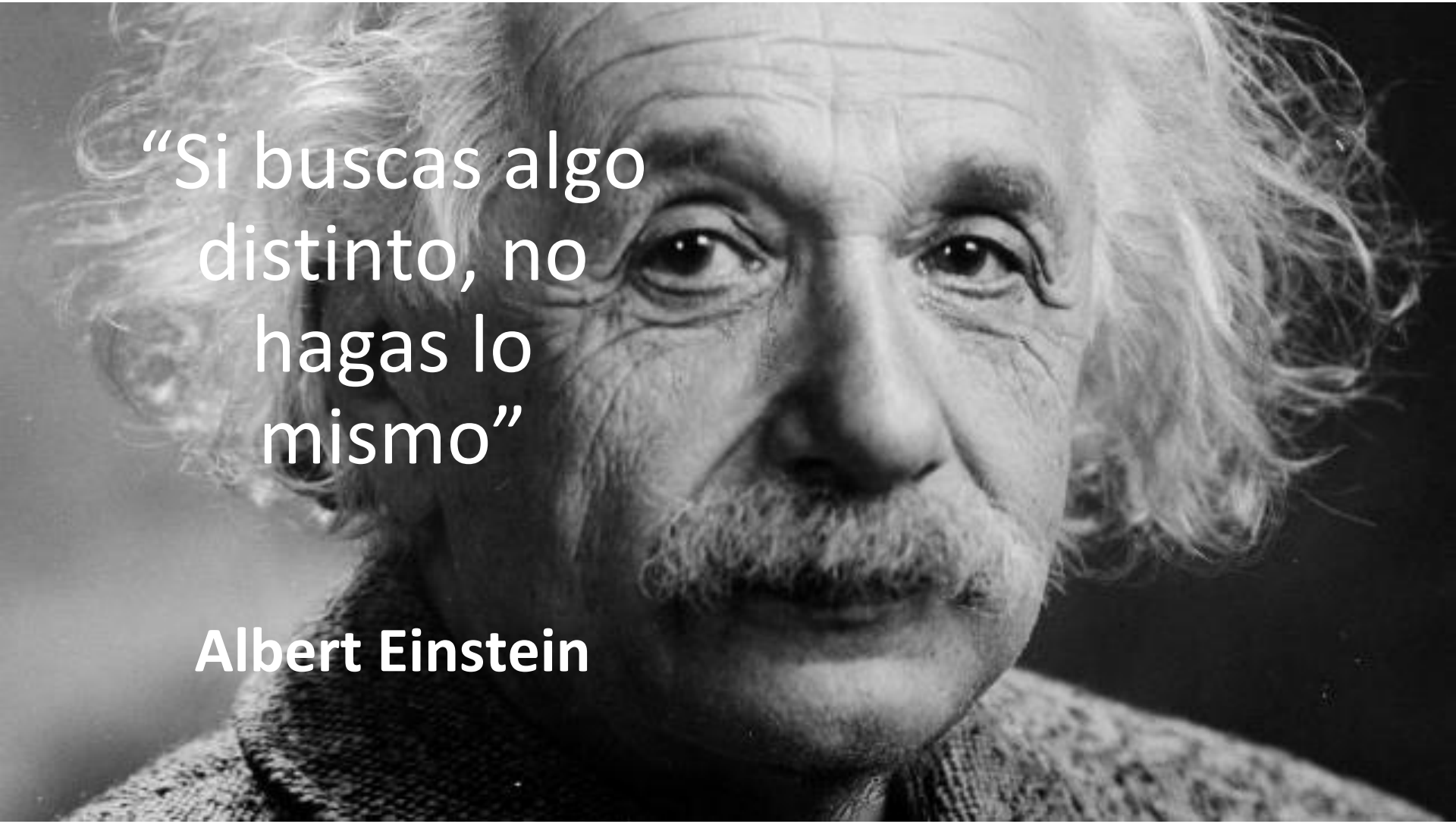
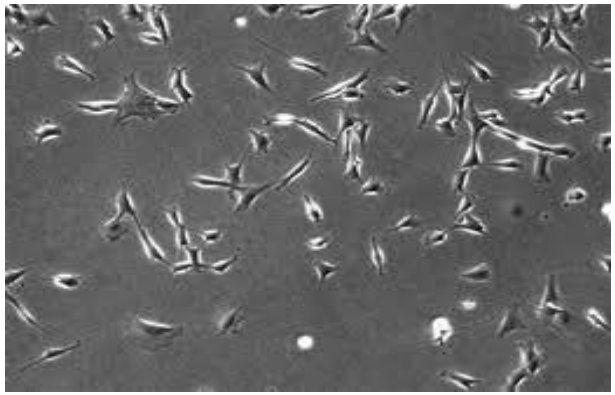
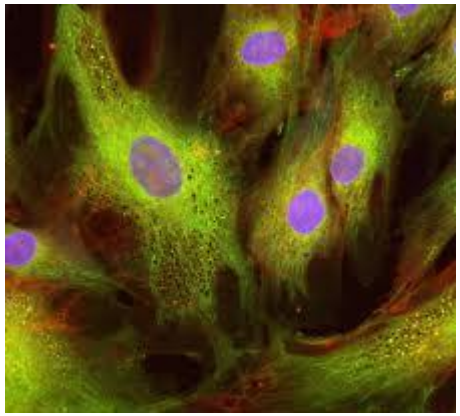
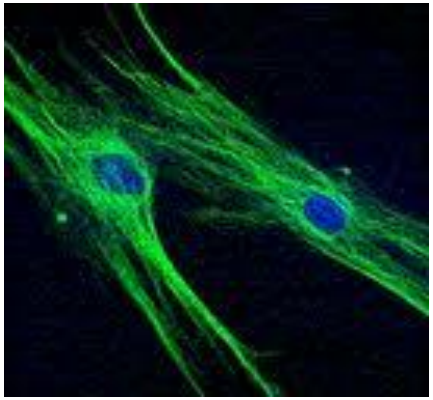


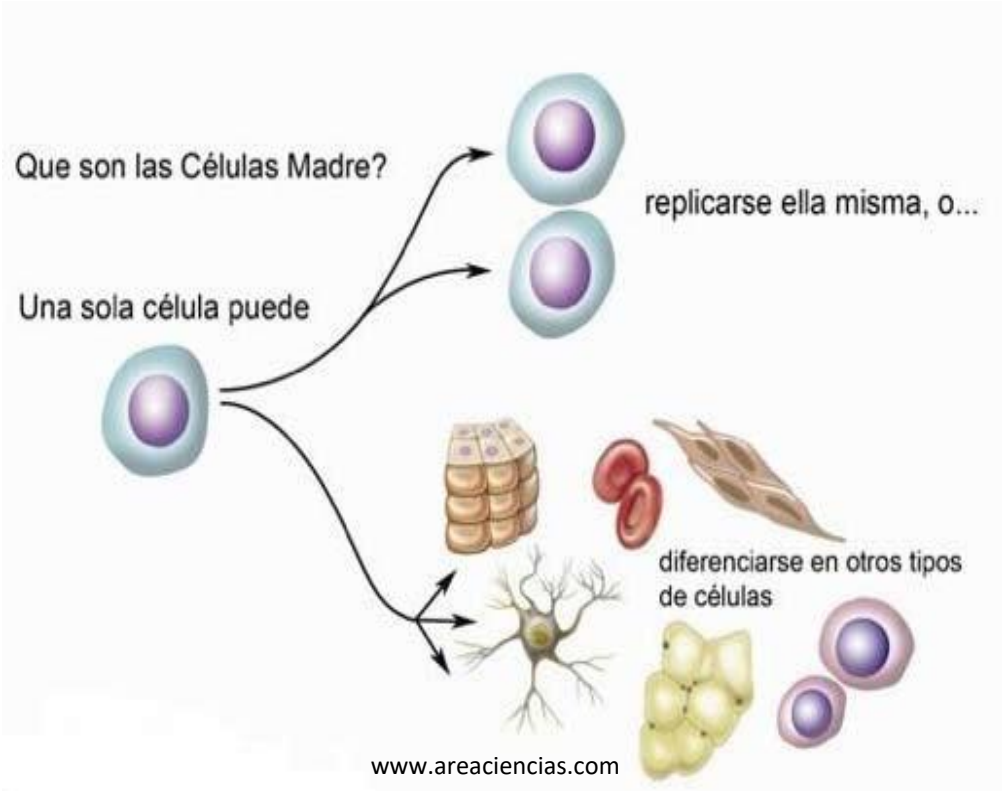






¿Qué es una célula madre?

Es una célula con:
- Capacidad de dividirse indefinidamente.
(Larga viabilidad en cultivo)
- Capacidad de renovar su población.
- Capacidad de diferenciarse a distintos tipos en lo morfológico y funcional.



TIPO DE CÉLULAS MADRE: VENTAJAS Y LIMITACIONES

-EMBRIONARIAS
-TRANSFERENCIA CELULAR
-IPS
-DEL ADULTO

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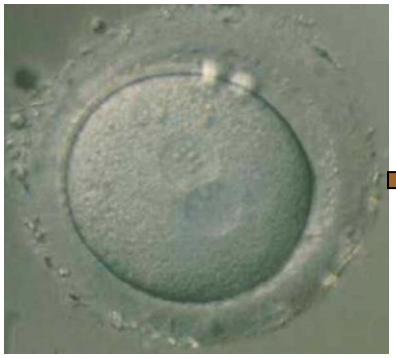
Células madre embrionarias

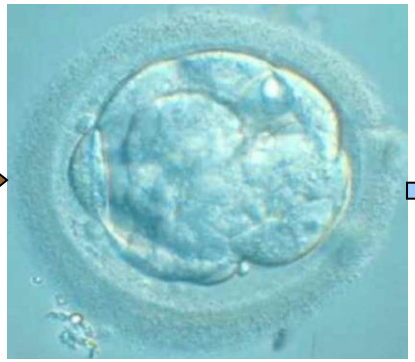
Día 0
Fecundación



Zigoto
(óvulo fecundado)

Única Célula
Totipotente

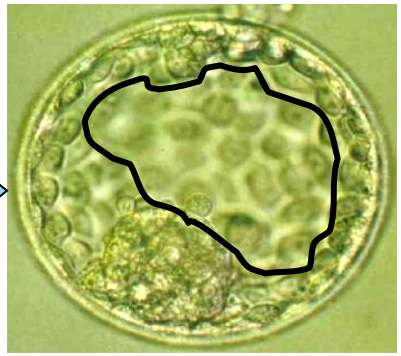
Día 3 Trompas



Mórula
(varios Blastómeros)

Masa
Celular
Totipotente

Día 7 Previo a
Implantación



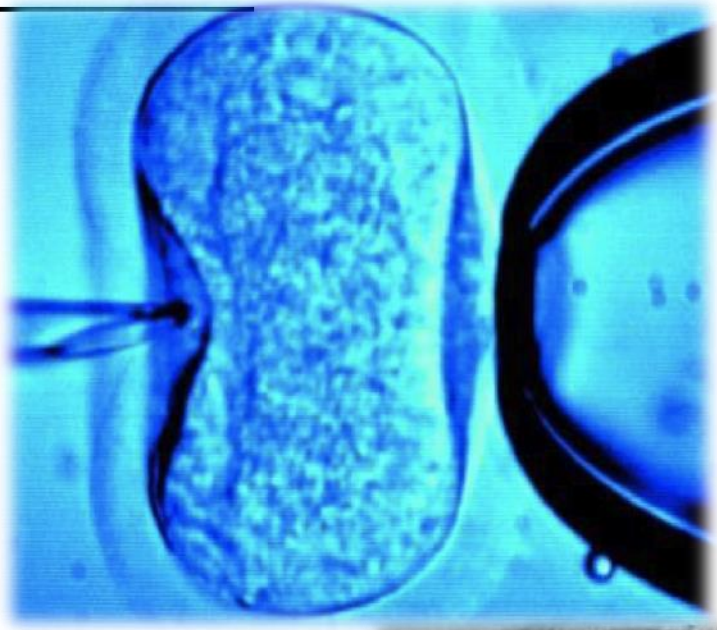
Blastocisto
(masa celular interna)

Masa Celular
Pluripotente

Células madre embrionarias

- Alta proliferación
- Pluripotentes
- No-autólogos
- Tumorigénicas
- Problemas éticos

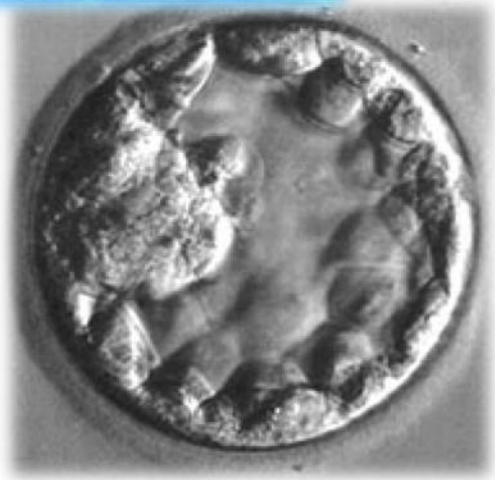
Células Madre obtenidas mediante la Técnica de Transferencia Nuclear



- A un óvulo se le retira su ADN del núcleo y se le incorpora el de una célula adulta

- Se desarrolla un embrión

- En la fase de mórula se obtienen células madre que se pueden diferenciar a diferentes tipos de células



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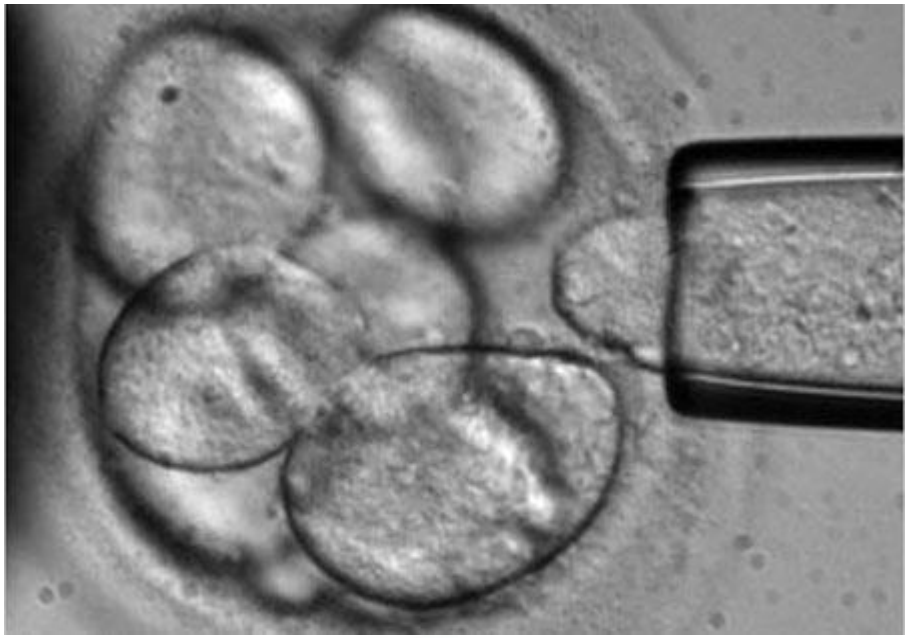

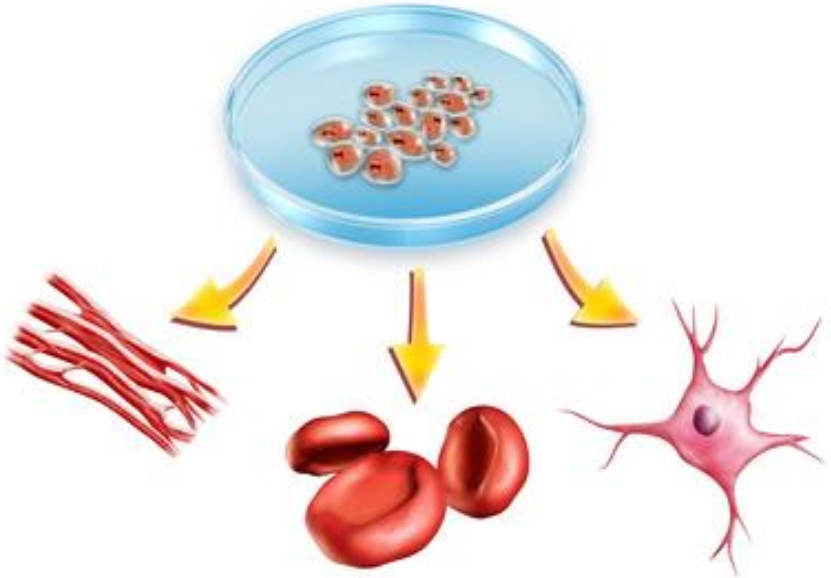

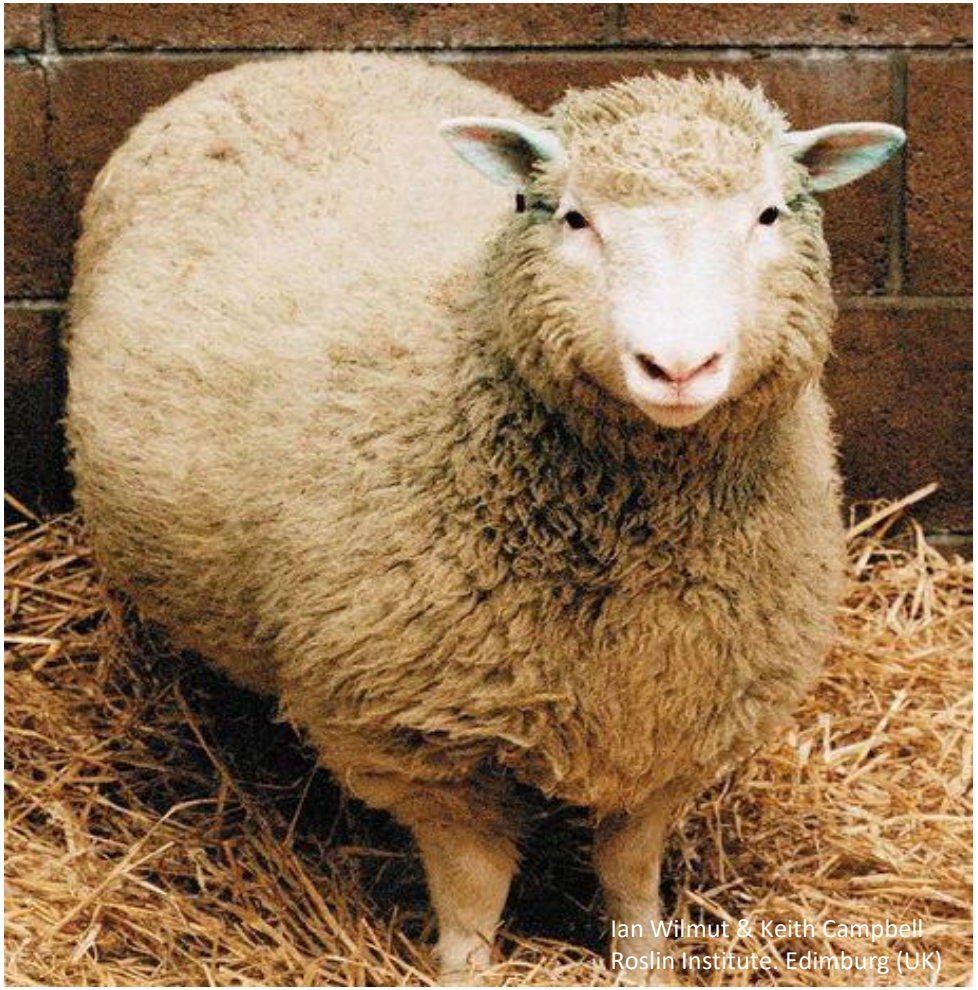

Zhong Zhong y Hua Hua
Instituto de Neurociencia de la Academia China de Ciencias en Shanghai

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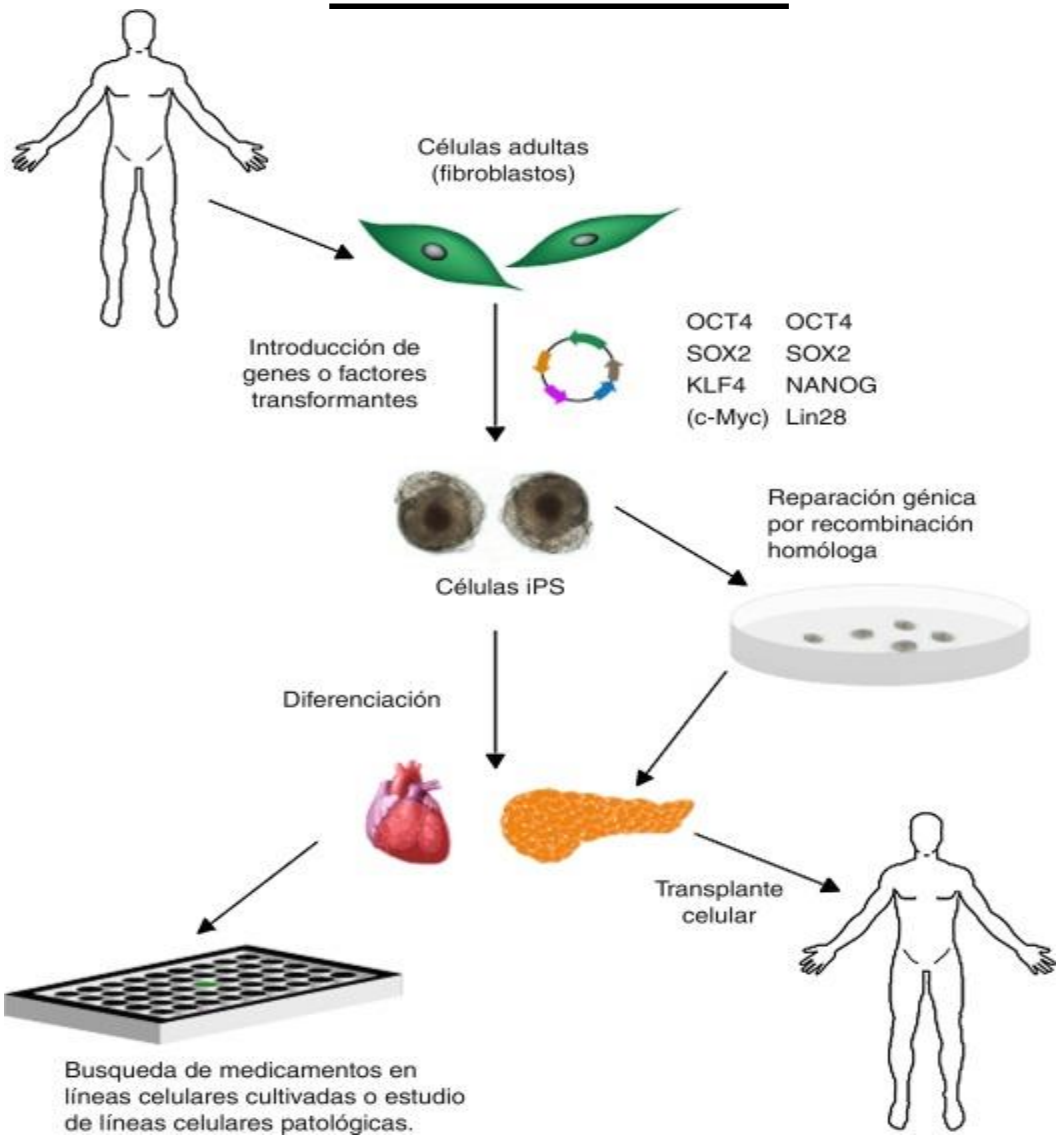
Células iPS



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Volume 217, Issue 1, January–February 2017. p30-4

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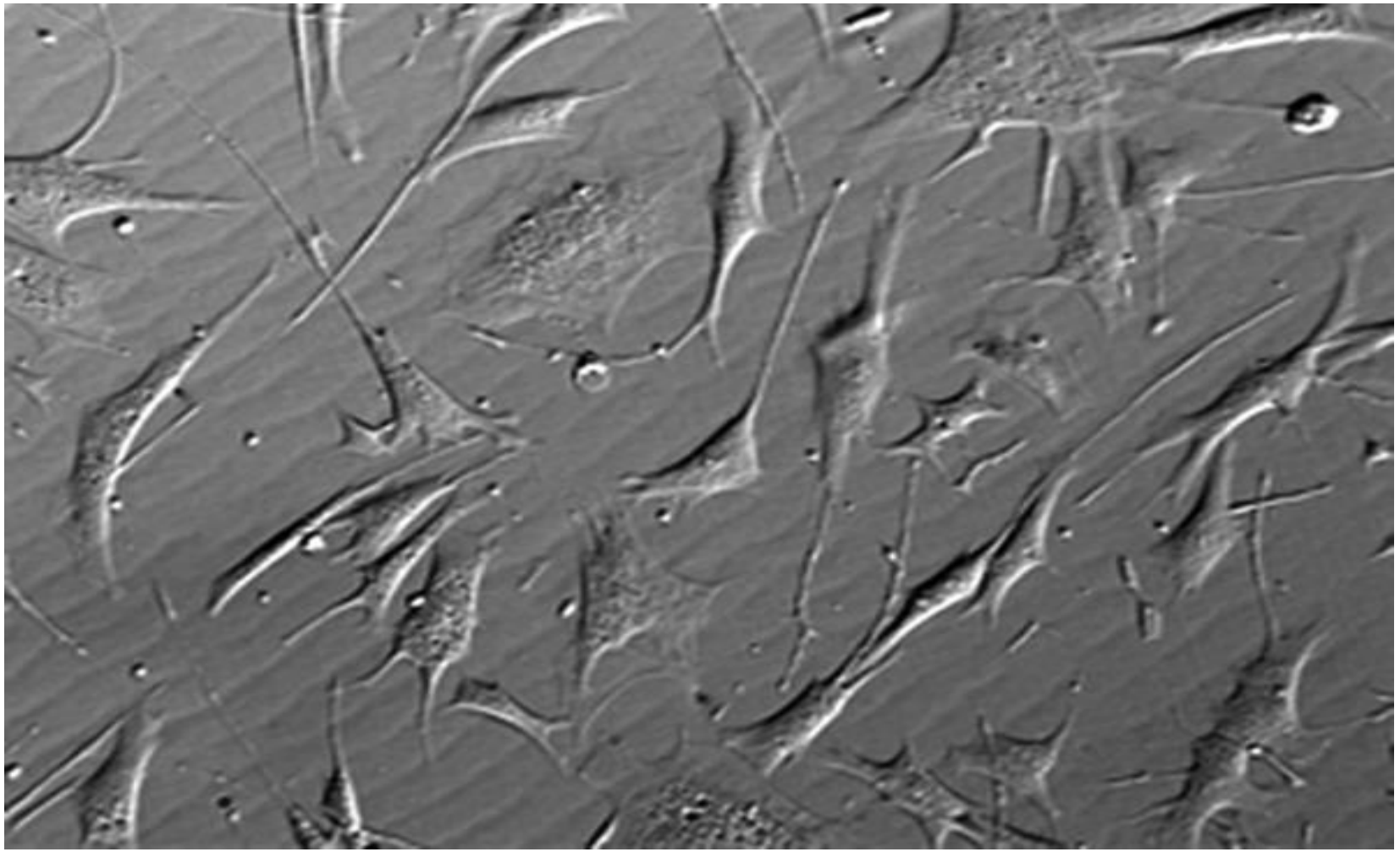
CÉLULAS MADRE MESENQUIMALES



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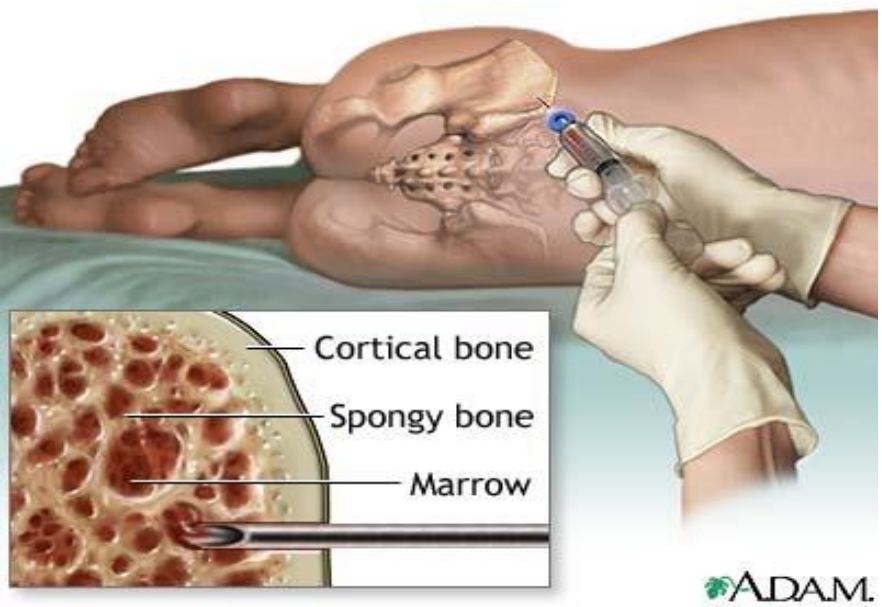
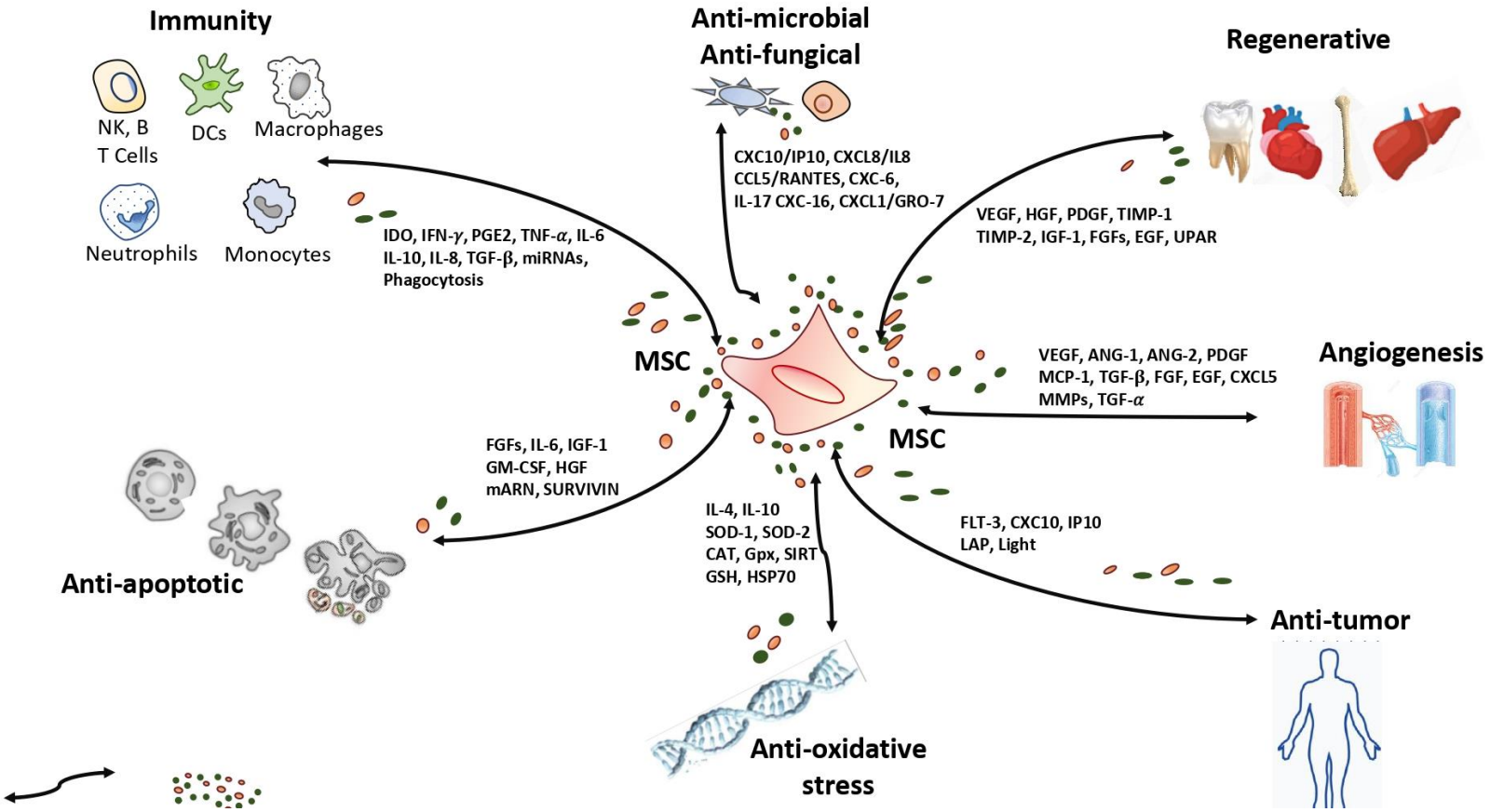
Células Mesenquimales




Immunity
NK, B
T Cells
DCs
Macrophages
Neutrophils
Monocytes
IDO, IFN-γ, PGE2, TNF-α, IL-6
IL-10, IL-8, TGF-β, miRNAs,
Phagocytosis
Anti-microbial
Anti-fungical
CXC10/IP10, CXCL8/IL8
CCL5/RANTES, CXC-6,
IL-17 CXC-16, CXCL1/GRO-7
Regenerative
VEGF, HGF, PDGF, TIMP-1
TIMP-2, IGF-1, FGFs, EGF, UPAR
MSC
MSC
VEGF, ANG-1, ANG-2, PDGF
MCP-1, TGF-β, FGF, EGF, CXCL5
MMPs, TGF-α
Angiogenesis
FGFs, IL-6, IGF-1
GM-CSF, HGF
mARN, SURVIVIN
IL-4, IL-10
SOD-1, SOD-2
CAT, Gpx, SIRT
GSH, HSP70
FLT-3, CXC10, IP10
LAP, Light
Anti-apoptotic
Anti-oxidative
stress
Anti-tumor

International Journal of *Molecular Sciences*

MDPI

Review

Mesenchymal Stem Cells in Homeostasis and Systemic Diseases: Hypothesis, Evidences, and Therapeutic Opportunities

Francisco J. Vizoso [1,*], Noemi Eiro [1], Luis Costa [1], Paloma Esparza [1], Mariana Landin [2], Patricia Diaz-Rodriguez [2], Jose Schneider [3] and Roman Perez-Fernandez [4,*]

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3 Department of Obstetrics and Gynecology, Universidad Rey Juan Carlos, Avda. de Atenas s/n, 28922 Alcorcón, Madrid, Spain
4 Department of Physiology-Center for Research in Molecular Medicine and Chronic Diseases (CIMUS), University of Santiago de Compostela, 15706 Santiago de Compostela, Spain
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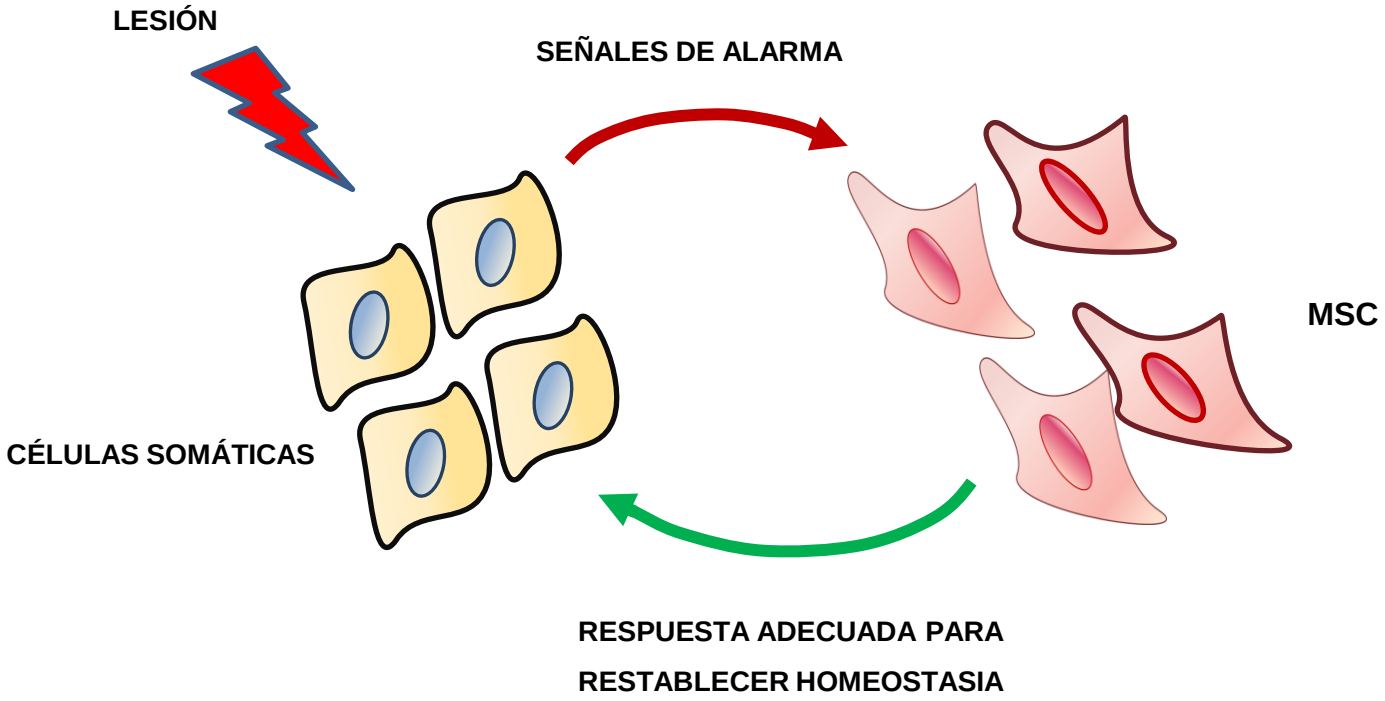
MSC totalmente funcionales



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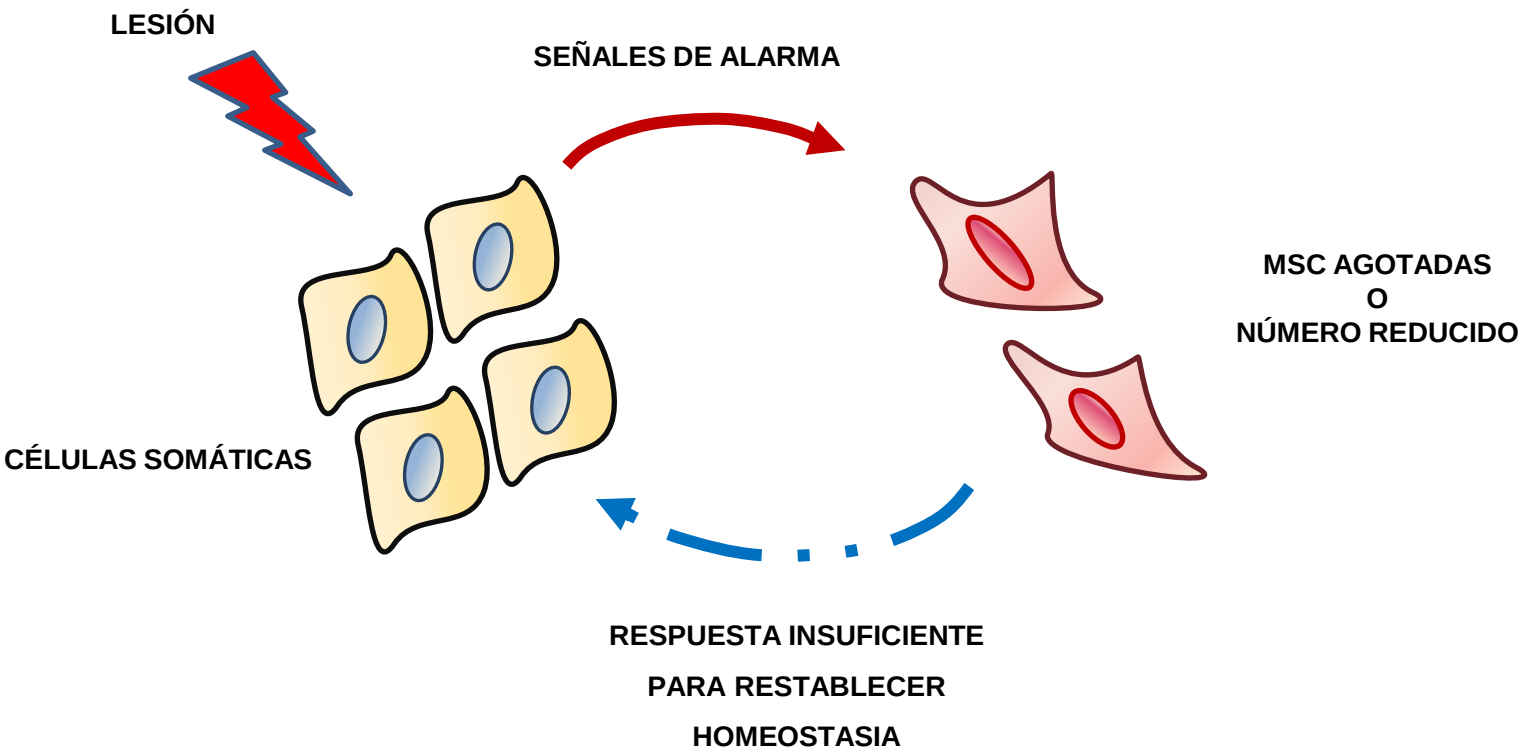
MSC Agotadas / En número reducido



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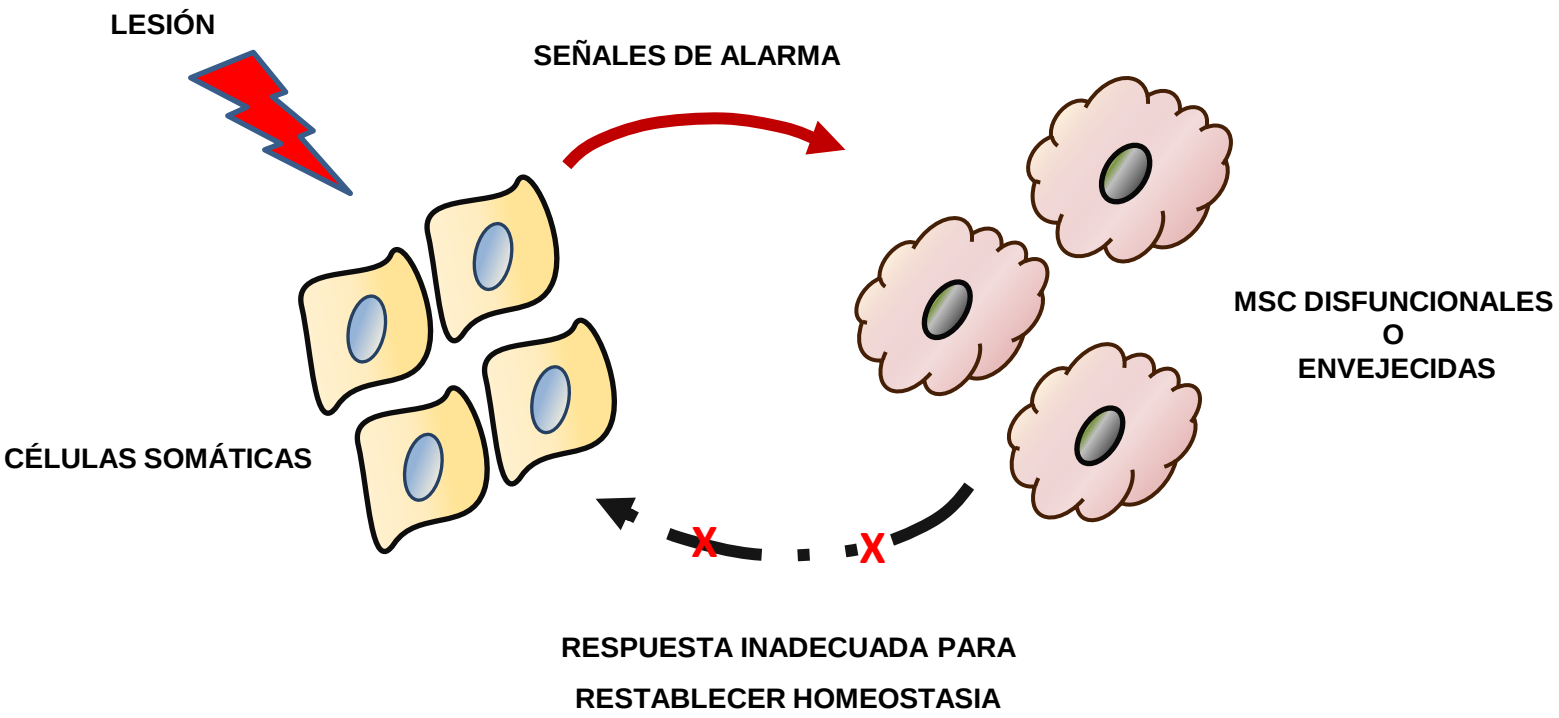
MSC Disfuncionales / Envejecidas



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Disfunción de Células Madre Mesenquimales en Enfermedades Sistémicas

- Lupus
- Diabetes
- Esclerosis Múltiple
- Fibrosis Pulmonar Idiopática
- Artritis Reumatoide
- Enfermedad de Parkinson
- Esclerosis Lateral Amiotrófica
- Psoriasis
- Síndromes Mielodisplásicos

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Ensayos clínicos fase III con células madre mesenquimales con resultados positivos

- Enfermedad del injerto contra el huésped
- Lupus
- Infarto de miocardio
- Cirrosis hepática
- Enfermedad de Crohn
- Diabetes
- Esclerosis múltiple

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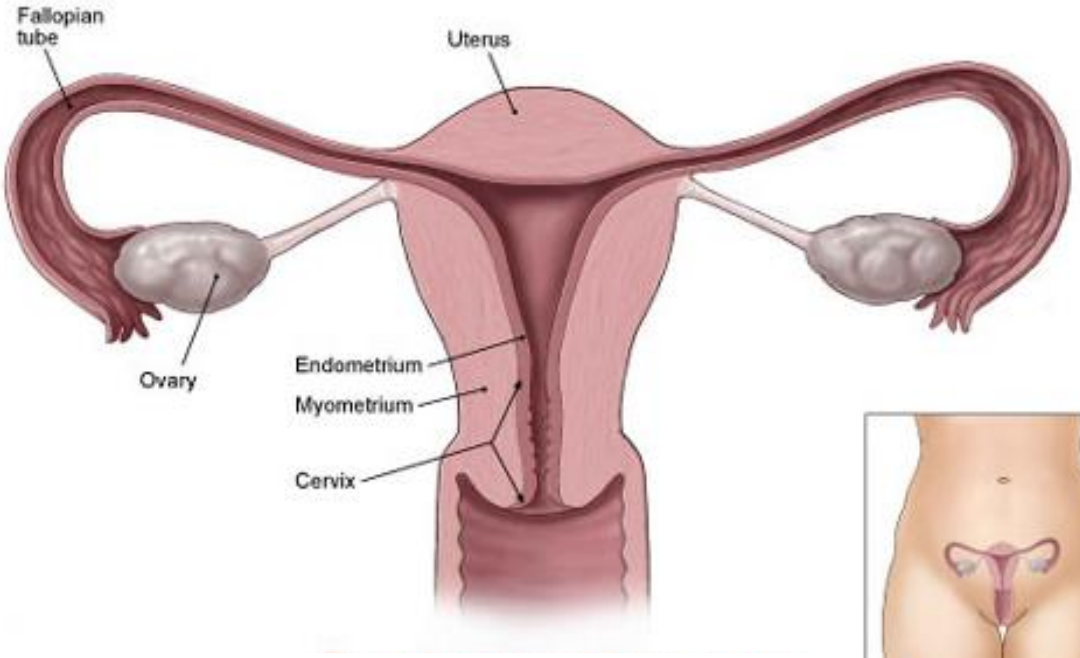
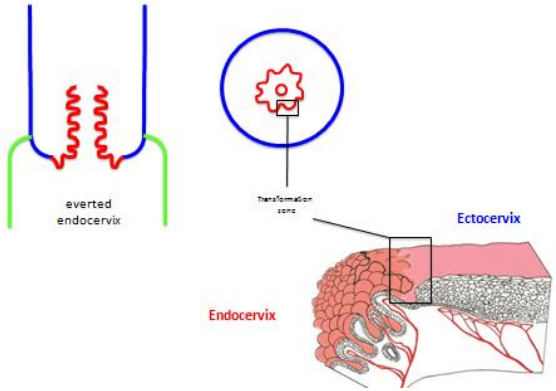
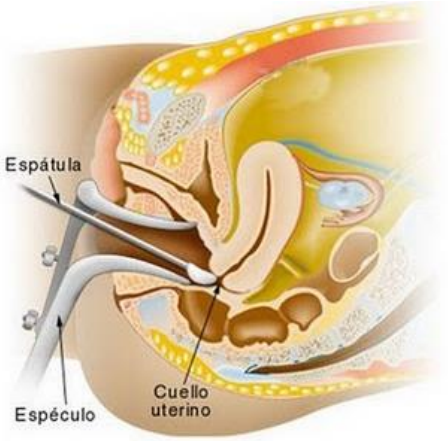
Células madre mesenquimales del cérvix uterino







hUCESC: human Uterine Cervical Stem Cells

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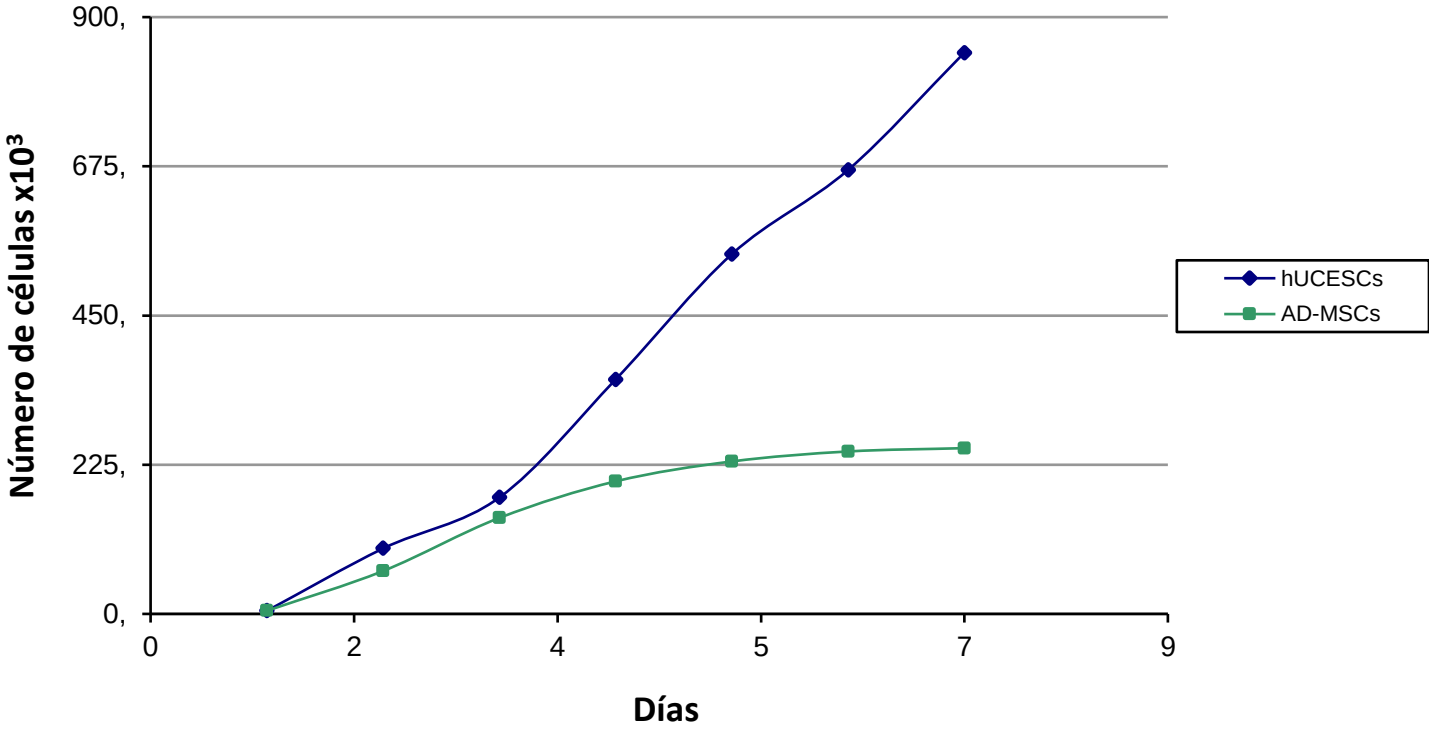
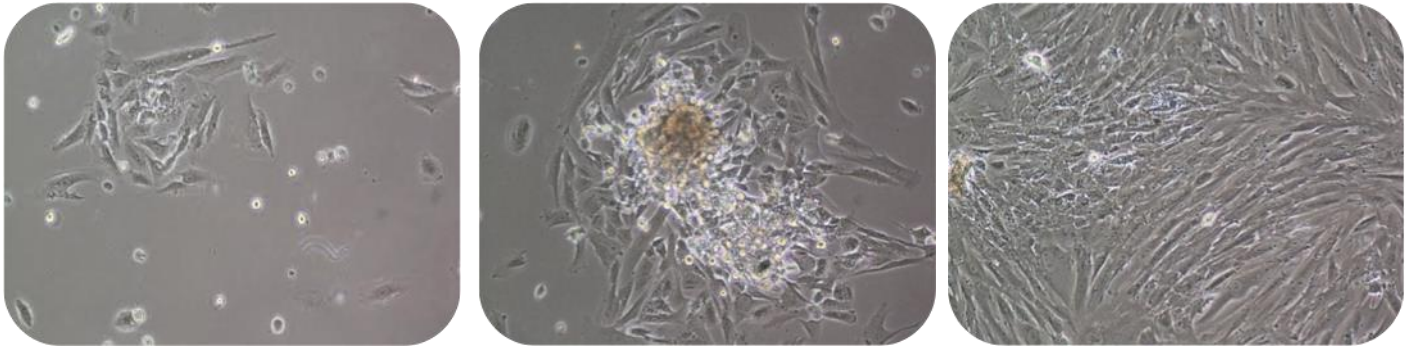
TASA DE CRECIMIENTO





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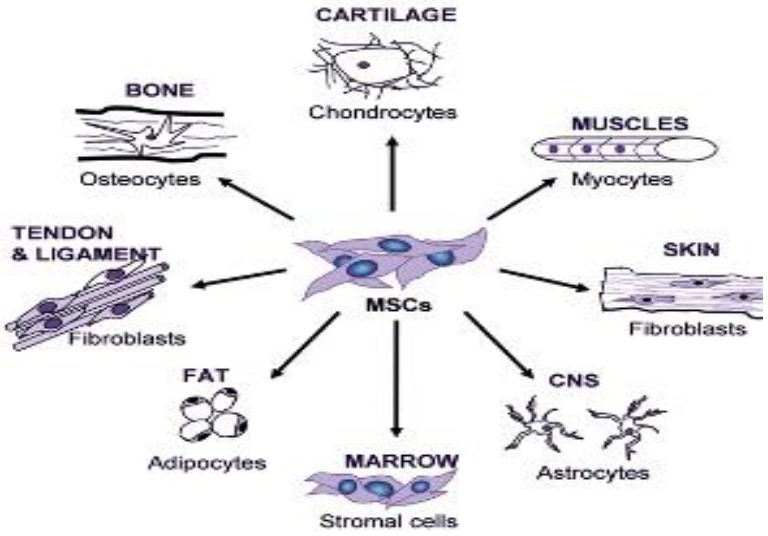
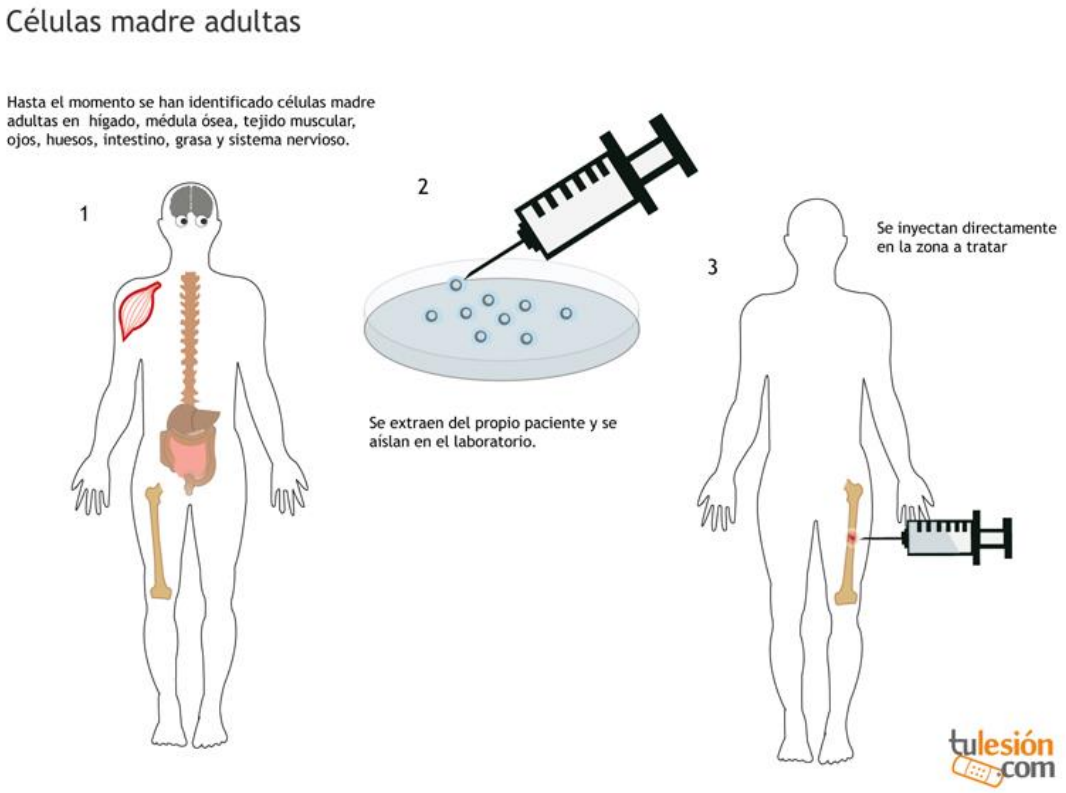
TERAPIA CELULAR CON CÉLULAS MADRE MESENQUIMALES





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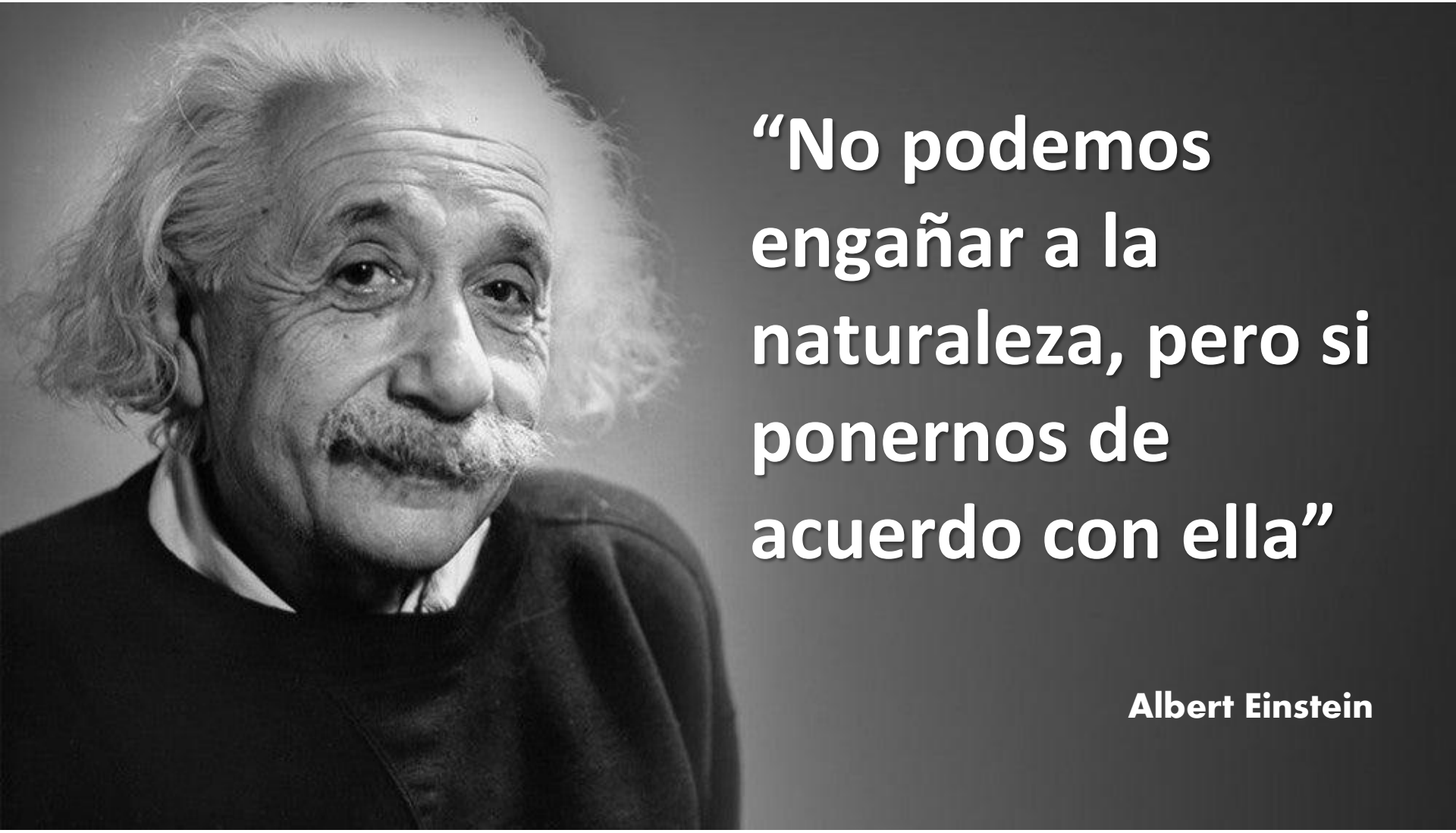
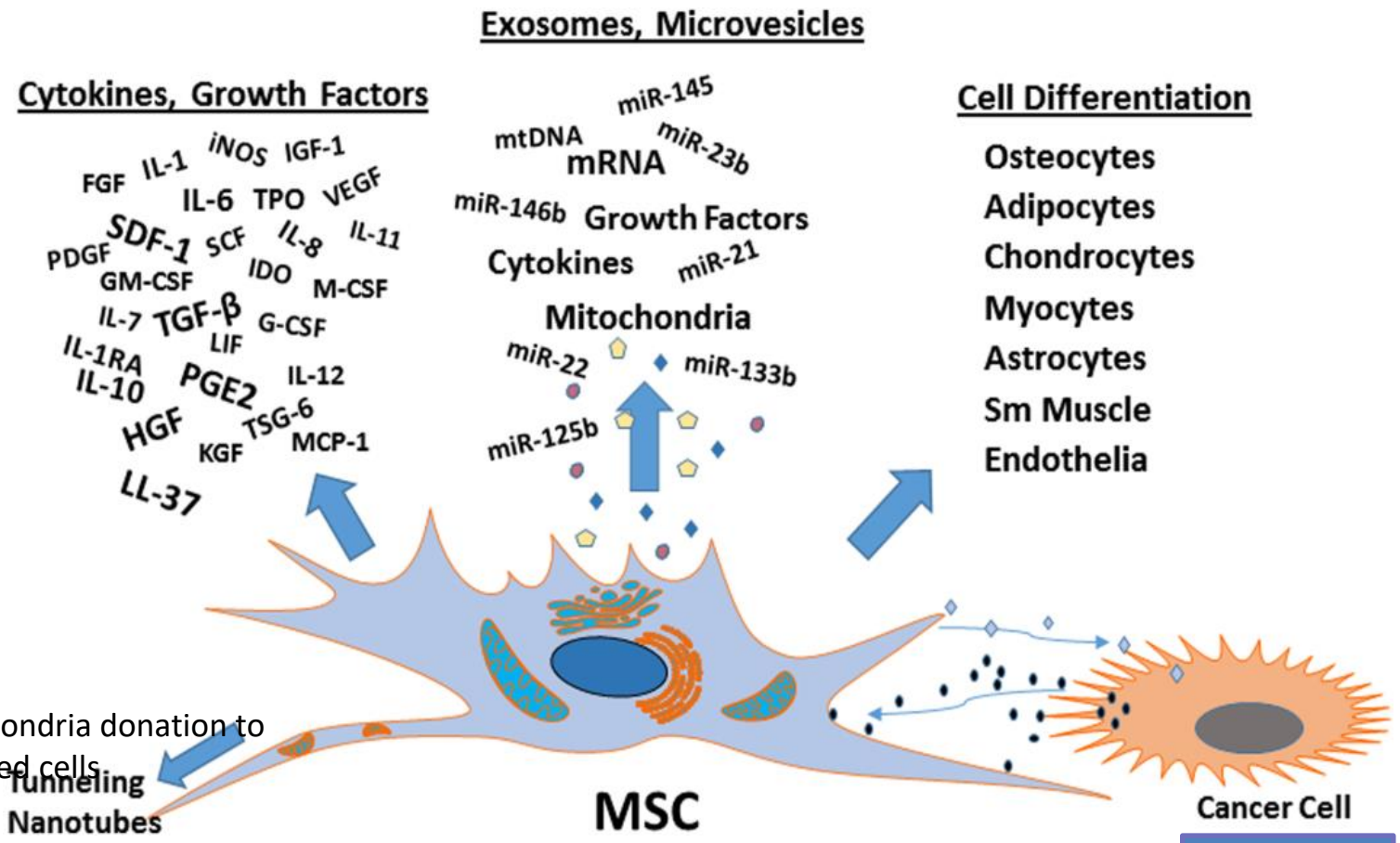
Dificultades de la terapia celular

- **Método de aislamiento invasivo.**
- Dificultad de cultivar y de **crecer en cantidades suficientes.**
- **Incompatibilidad inmunológica.**
- Formación de tumores.
- Formación de émbolos.
- Posible transmisión de infecciones.
- Entrada de las células senescencia durante los cultivos.
- **Evaluación de seguridad, dosis y potencia?**
- Dificultad de lograr condiciones adecuadas de almacenamiento.
- **Elevado coste económico.**
- **Uso clínico poco práctico.**
- Difícil disponibilidad de grandes cantidades para uso inmediato.
- Heteregoneidad de las células en relación con el donante y origen tisular.

(Vizoso y cols, Int J Mol Sci 2017; Vizoso y cols., Int J Mol Sci 2019)


“No podemos engañar a la naturaleza, pero si ponernos de acuerdo con ella”
Albert Einstein



Mitochondria donation to damaged cells

Regulatory, protective activities

Bionin Nanobiotech, Inc.

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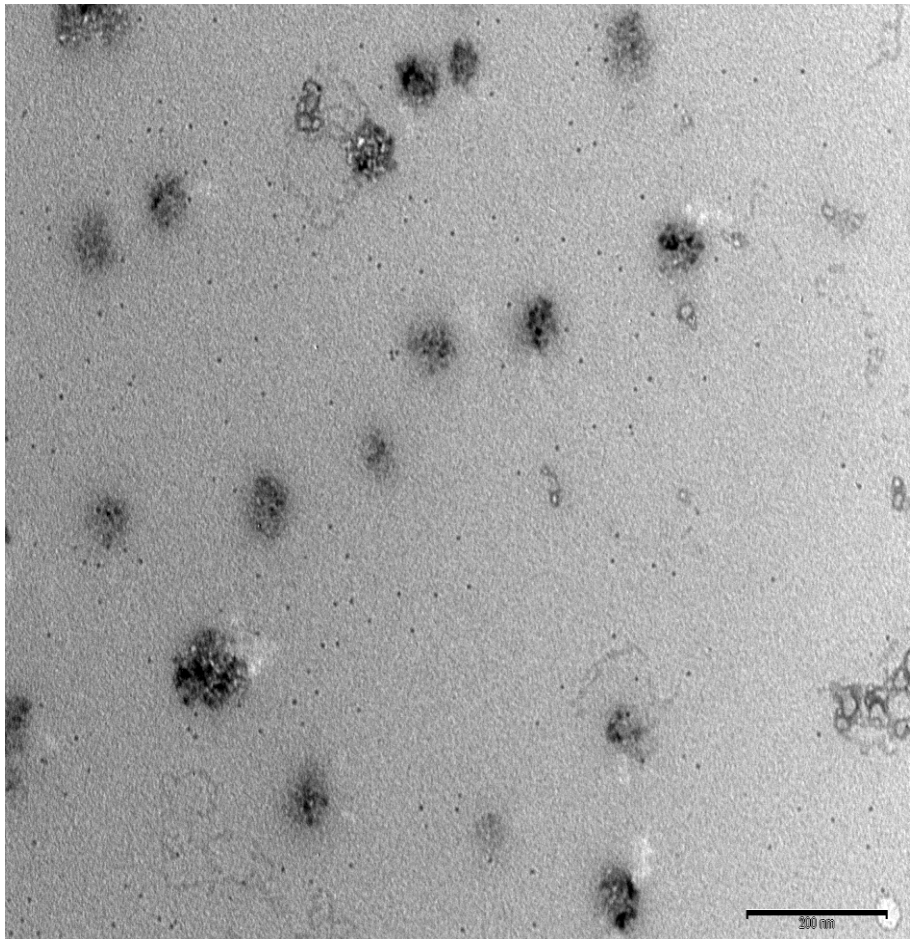
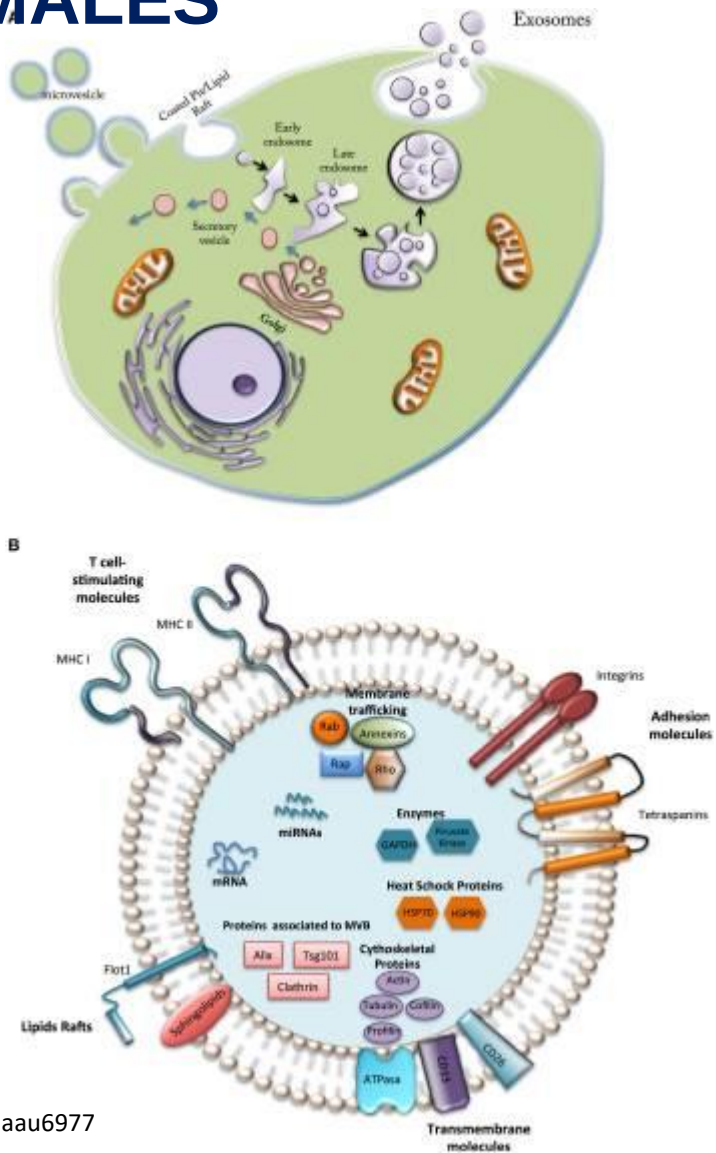
EXOSOMAS DE CÉLULAS MADRE MESENQUIMALES



La barra de la escala es de 200 nm



Kalluri R & LeBleu V.
Science367,eaau6977(2020).DOI:10.1126/science.aau6977

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Producción del medio condicionado de las hUCESCs

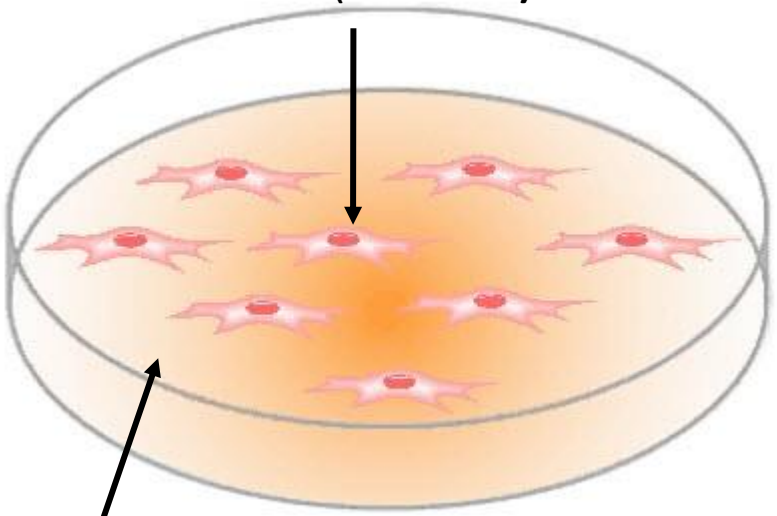
Medio de cultivo

+

hUCESCs

=

Células (**hUCESCs)**



“Medio condicionado”
(medio + productos secretados por las hUCESCs)

Recogida del medio

Liofilización

International Journal of *Molecular Sciences*

MDPI

Review

Mesenchymal Stem Cell Secretome: Toward Cell-Free Therapeutic Strategies in Regenerative Medicine

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2 Department of Obstetrics & Gynecology, C/Ramon y Cajal 7, University of Valladolid, 47005 Valladolid, Spain; jose.schneider@urjc.es
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* Correspondence: franvizoso@gmail.com (F.J.V.); roman.perez.fernandez@usc.es (R.P.-F.); Tel.: +34-985-320-050 (F.J.V.); +34-881-815-421 (R.P.-F.); Fax: +34-985-315-710 (F.J.V.)

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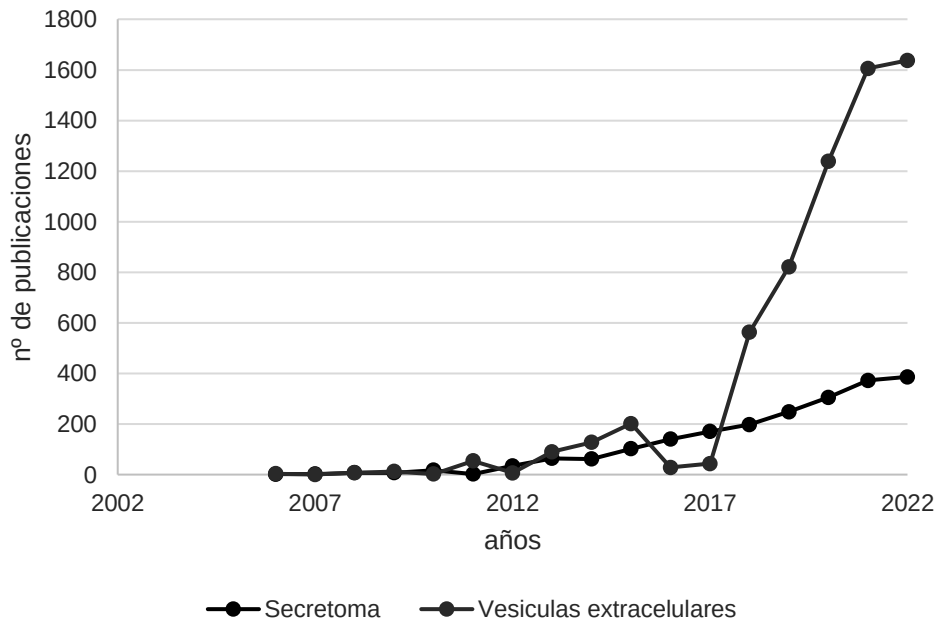
Abstract: Earlier research primarily attributed the effects of mesenchymal stem cell (MSC) therapies to their capacity for local engrafting and differentiating into multiple tissue types. However, recent studies have revealed that implanted cells do not survive for long, and that the benefits of MSC therapy could be due to the vast array of bioactive factors they produce, which play an important role in the regulation of key biologic processes. Secretome derivatives, such as conditioned media or exosomes, may present considerable advantages over cells for manufacturing, storage, handling, product shelf life and their potential as a ready-to-go biologic product. Nevertheless, regulatory requirements for manufacturing and quality control will be necessary to establish the safety and efficacy profile of these products. Among MSCs, human uterine cervical stem cells (hUCESCs) may be a good candidate for obtaining secretome-derived products. hUCESCs are obtained by Pap cervical smear, which is a less invasive and painful method than those used for obtaining other MSCs (for example, from bone marrow or adipose tissue). Moreover, due to easy isolation and a high proliferative rate, it is possible to obtain large amounts of hUCESCs or secretome-derived products for research and clinical use.

integrando la innovación

Evolución del número de estudios sobre el secretoma de las células madre mesenquimales



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Patente

Europäisches Patentamt
European Patent Office
Office européen des brevets

URKUNDE | **CERTIFICATE** | **CERTIFICAT**

Es wird hiermit bescheinigt, dass für die in der Patentschrift beschriebene Erfindung ein europäisches Patent für die in der Patentschrift bezeichneten Vertragsstaaten erteilt worden ist.

It is hereby certified that a European patent has been granted in respect of the invention described in the patent specification for the Contracting States designated in the specification.

Il est certifié qu'un brevet européen a été délivré pour l'invention décrite dans le fascicule de brevet, pour les Etats contractants désignés dans le fascicule de brevet.

Europäisches Patent Nr. / European patent No. / Brevet européen n°
2770050

Patentinhaber / Proprietor of the patent / Titulaire du brevet

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A61K 35/48 *(2006.01)* ***C12N 5/074*** *(2010.01)*

(21) Application number: **13156348.8**

(22) Date of filing: **22.02.2013**

(54) **Human uterine cervical stem cell population and uses thereof**
Menschliche Gebärmutterhalsstammzellenpopulation und Verwendungen davon
Population de cellules souches de col utérin humain et leurs utilisations

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(56) References cited:
WO-A1-2011/042547 CN-A- 102 229 911

- **BAEGE ASTRID C ET AL: "Cervical stem cells: Isolation, characterization, and potential role in human papillomavirus (HPV)-induced cervical carcinogencsis.", PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL MEETING, vol. 47, April 2006 (2006-04), page 938, XP9169094, & 97TH ANNUAL MEETING OF THE AMERICAN-ASSOCIATION-FOR-CANCER-RESEARCH (AACR); WASHINGTON, DC, USA; APRIL 01 -05, 2006 ISSN: 0197-016X**
- **T. MARUYAMA ET AL: "Human uterine stem/progenitor cells: their possible role in uterine physiology and pathology", REPRODUCTION, vol. 140, no. 1, 1 July 2010 (2010-07-01), pages 11-22, XP055031068, ISSN: 1470-1626, DOI: 10.1530/REP-09-0438**
- **LÓPEZ JACQUELINE ET AL: "Human papillomavirus infections and cancer stem cells of tumors from the uterine cervix.", THE OPEN VIROLOGY JOURNAL 2012, vol. 6, 2012, pages 232-240, XP002695938, ISSN: 1874-3579**
- **SUN XIAOCHUN ET AL: "Mesenchymal stem cells isolated from human uterine cervix cancer**

integrando la Innovación

Líneas estratégicas en Salud Humana

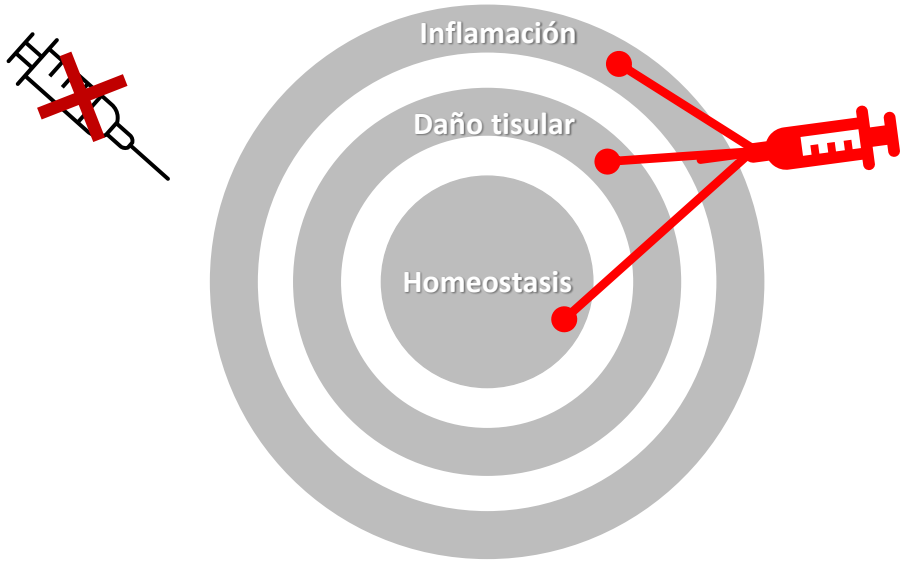
Med-Tech Innovation

integrando la Innovación

SOS: Necesidad de nuevos tratamientos

- Existe la necesidad de una alternativa terapéutica que cubra toda la etiopatogenia.

- CM-hUCESC aporta al tratamiento del SOS:
  - Efecto regenerativo.
  - Efecto antiinflamatorio.
  - Actividad antimicrobiana.



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Cornea

Corneal Epithelial Wound Healing and Bactericidal Effect of Conditioned Medium From Human Uterine Cervical Stem Cells

Maria A. Bermudez,[1] Juan Sendon-Lago,[2] Noemi Eiro,[3,4] Mercedes Treviño,[5] Francisco Gonzalez,[1,6] Eva Yebra-Pimentel,[7] Maria Jesus Giraldez,[7] Manuel Macia,[8] Maria Luz Lamelas,[3] Jorge Saa,[3,9] Francisco Vizoso,[3,4] and Roman Perez-Fernandez[2]

[1]Department of Surgery, Center for Research in Molecular Medicine and Chronic Diseases (CIMUS), University of Santiago de Compostela, Santiago de Compostela, Spain
[2]Department of Physiology, Center for Research in Molecular Medicine and Chronic Diseases (CIMUS), University of Santiago de Compostela, Santiago de Compostela, Spain
[3]Unidad de Investigación, Fundación Hospital de Jove, Gijón, Spain
[4]Fundación para la Investigación con Células Madre Uterinas (FICEMU), Gijón, Spain
[5]Servicio de Microbiología, Complejo Hospitalario Universitario de Santiago de Compostela, Santiago de Compostela, Spain
[6]Service of Ophthalmology, Complejo Hospitalario Universitario de Santiago de Compostela, Santiago de Compostela, Spain
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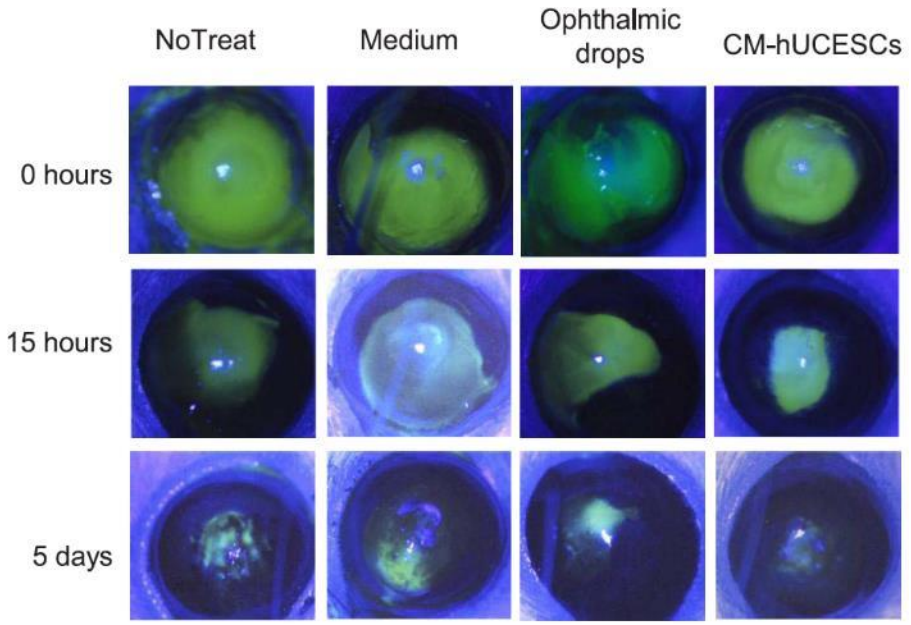
[8]Department of Obstetrics and Gynecology, University of Santiago de Compostela, Santiago de Compostela, Spain
[9]Service of Ophthalmology, Fundación Hospital de Jove, Gijón, Spain



Experimental Eye Research 180 (2019) 110–121

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/yexer

Corneal regeneration by conditioned medium of human uterine cervical stem cells is mediated by TIMP-1 and TIMP-2

Juan Sendon-Lago[a], Samuel Seoane[a], Anxo Martinez-Ordoñez[a], Noemi Eiro[b], Jorge Saa[b,c], Francisco J. Vizoso[b], Francisco Gonzalez[d,e], Roman Perez-Fernandez[a,**], Maria A. Bermudez[f,*]

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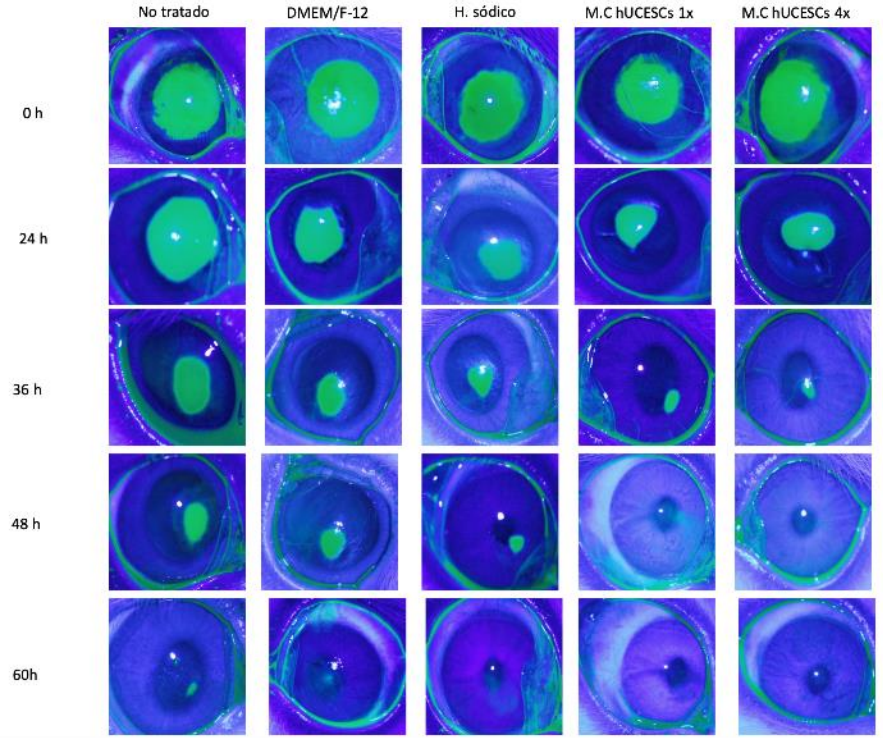
[b] Research Unit, Hospital Fundacion de Jove, Gijón, Spain
[c] Service of Ophthalmology, Fundación Hospital de Jove, Gijón, Spain
[d] Department of Surgery and CIMUS, University of Santiago de Compostela, Spain
[e] Service of Ophthalmology and IDIS, Complejo Hospitalario Universitario de Santiago de Compostela, Spain
[f] Department of Biology, Faculty of Science, University of A Coruña, Spain



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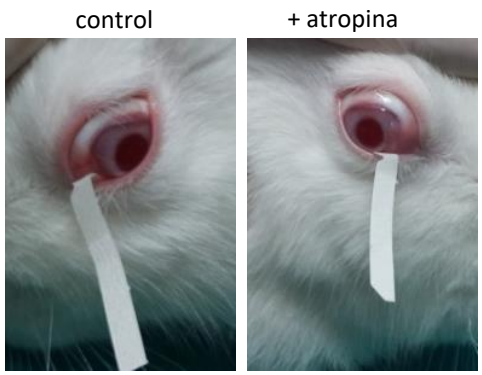
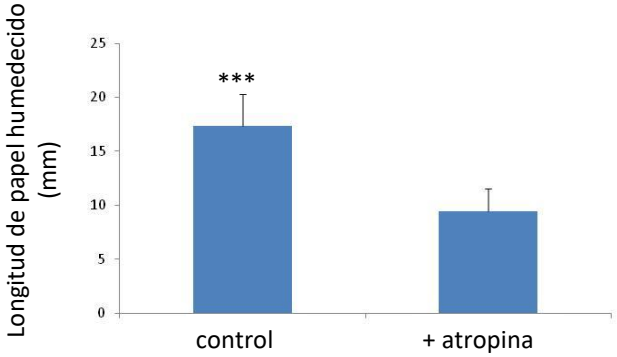
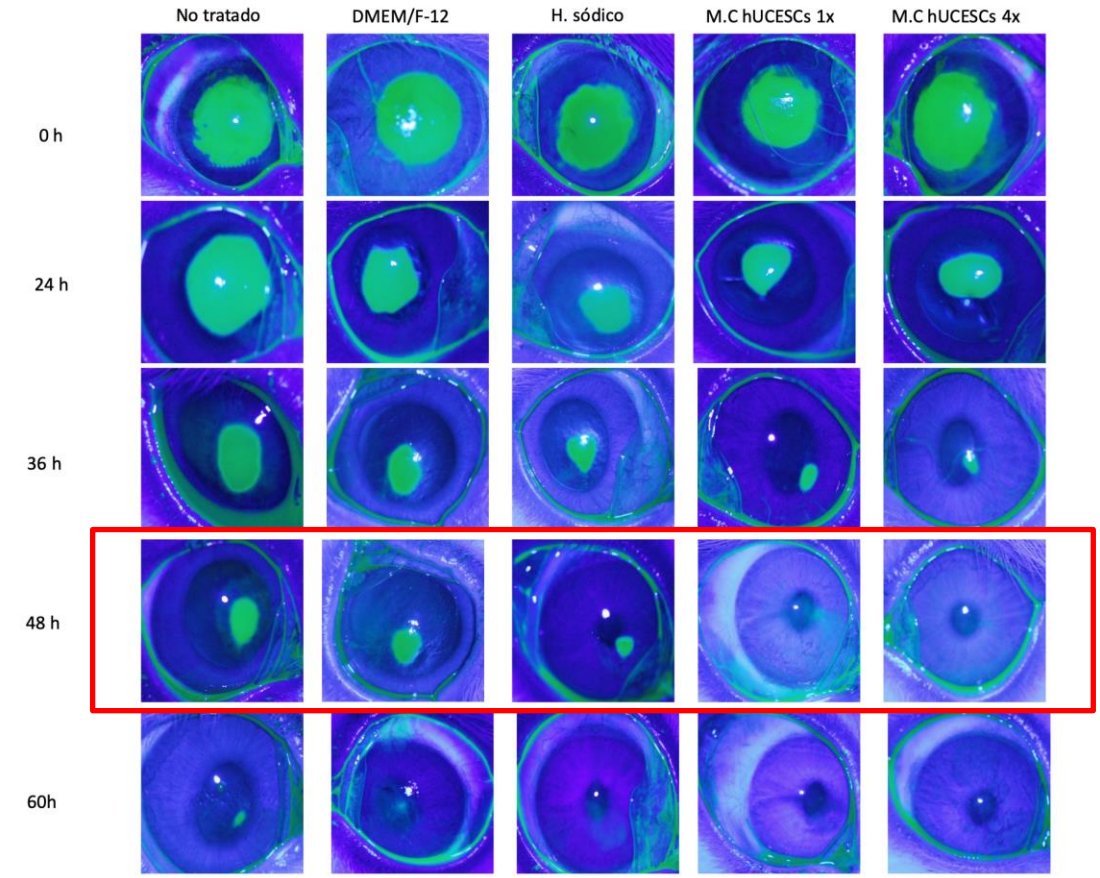
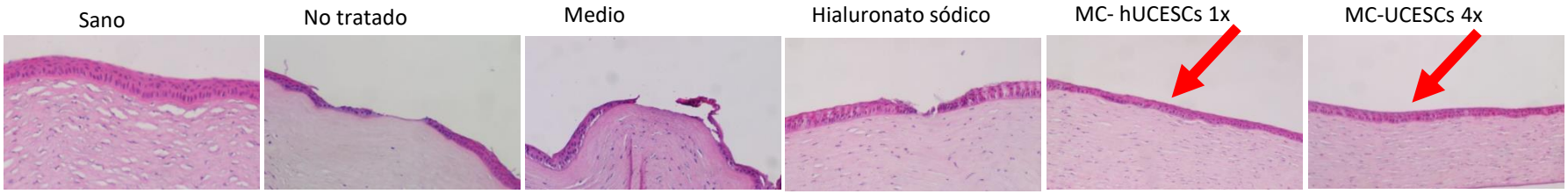
Agencia Española del Medicamento



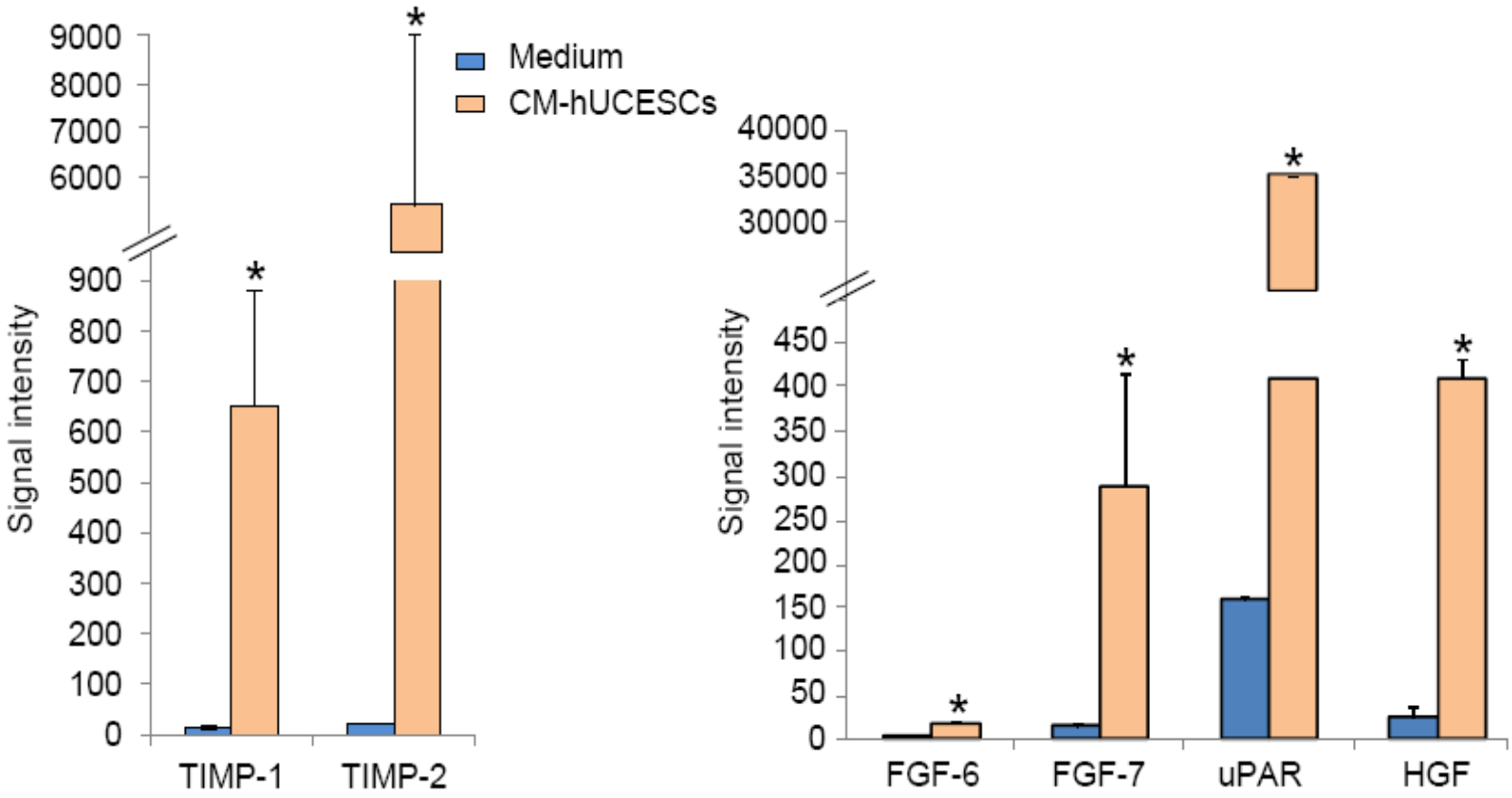






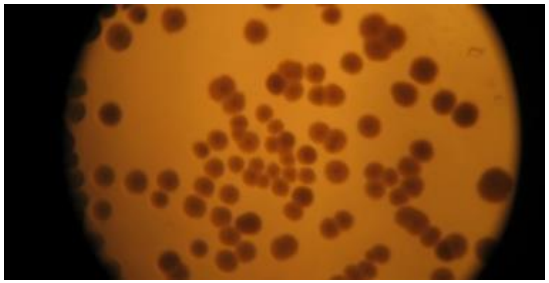
Sendon-Lago y cols, no publicado 2016

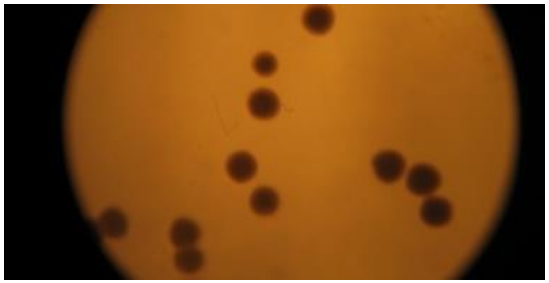
Identificación de proteínas con actividad regenerativa presentes en el medio condicionado de las hUCESCs

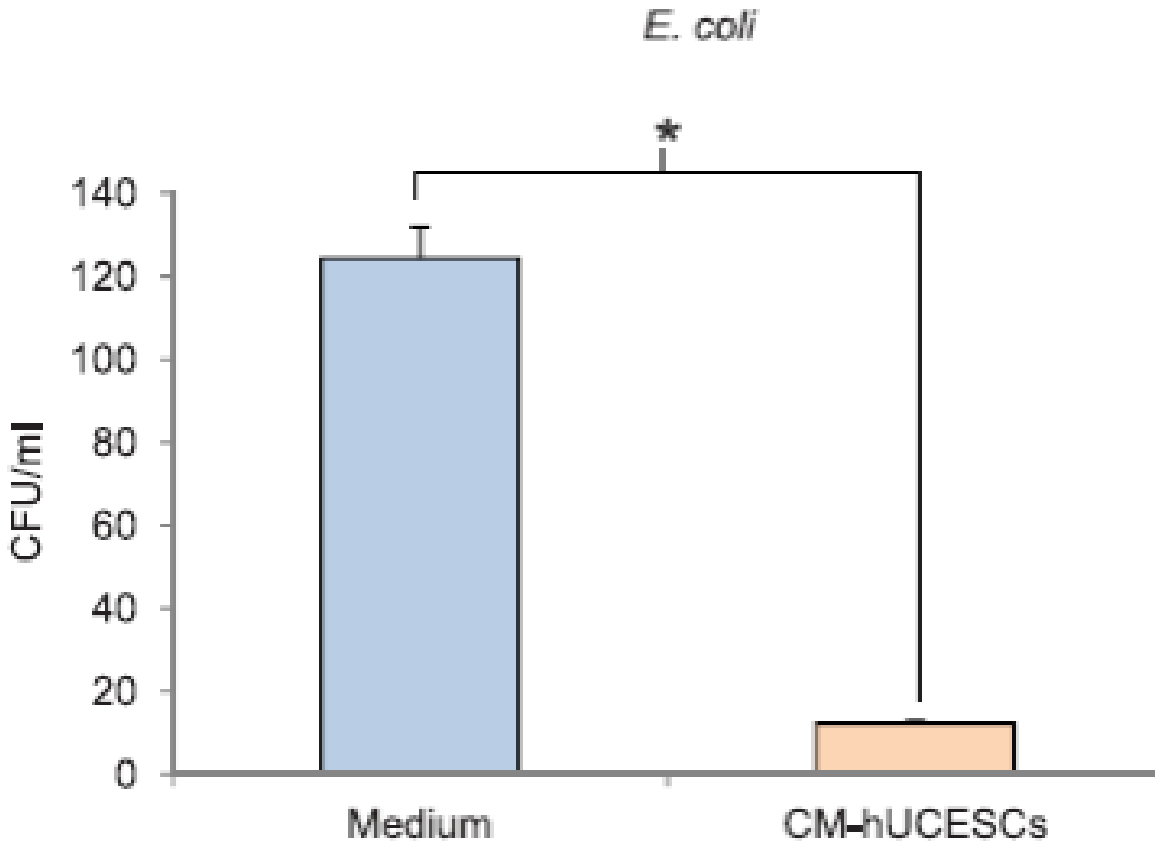


Bermúdez MA. et al., IOVS, 2015


Technology Networks






E. coli
*
140
120
100
80
60
40
20
0
CFU/ml
Medium
CM-hUCESCs

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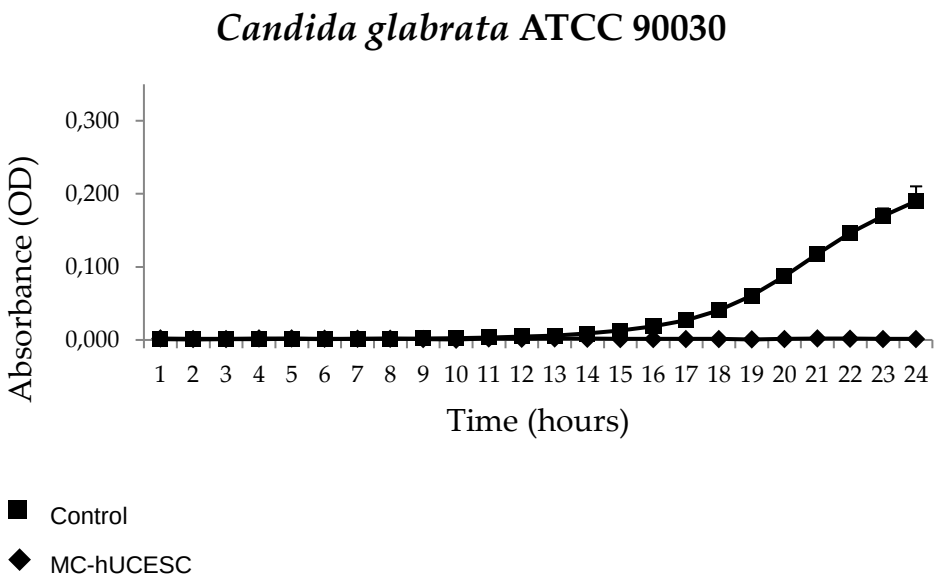

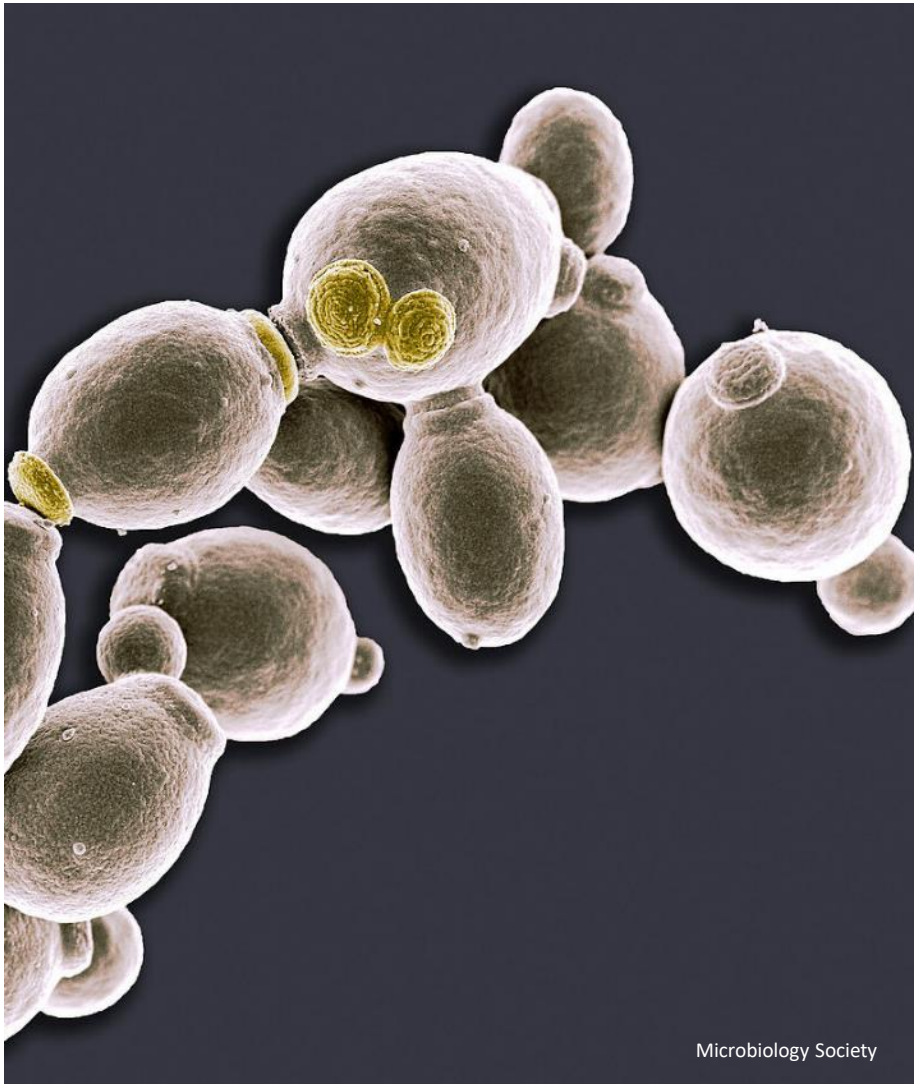

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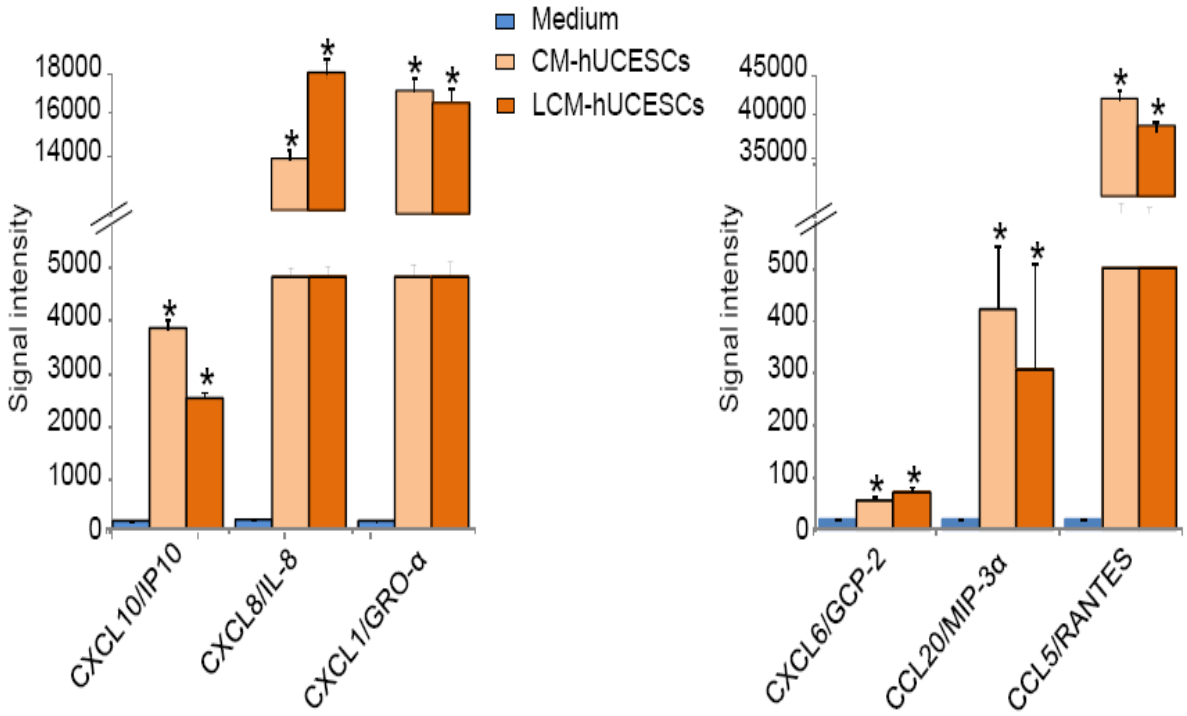
Identificación de moléculas de efecto antimicrobiano en el medio condicionado de las hUCESCs



De la ciencia básica al uso clinico

ENFERMEDAD

- Idea

- Investigación científica
  - Articulos científicos
  - patentes
- Pre-clinicos Ensayos

- Ensayos Clinicos

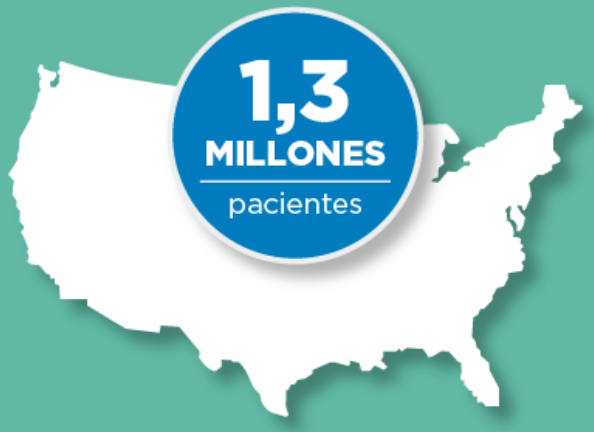
TRATAMIENTO & CURACIÓN

integrando la innovación

Enfermedad inflamatoria intestinal

¿CUÁNTAS PERSONAS TIENEN EII?

EUROPA



ESTADOS UNIDOS

ESPAÑA

CARACTERÍSTICAS GENERALES

CURSO CRÓNICO	LESIONES INTESTINALES	NO CURACIÓN ESPONTÁNEA	EVOLUCIÓN DIFÍCIL DE PREDECIR	TRATAMIENTO NO ESPECÍFICO
	De profundidad y extensión variable		Alternan periodos de mayor y menor intensidad sintomática	

MANIFESTACIONES EXTRAINTESTINALES (MEI)

ARTICULACIONES 30-35%

Artropatía periférica (20-25%)

***Localización**: Articulaciones: Rodillas, tobillos, codos, muñecas, dedos*

***Síntomas**: Dolor (artralgias) e inflamación (artritis)*

Espondilitis anquilosante (2-7%)

***Localización**: Columna vertebral*

***Síntomas**: Dolor lumbar y rigidez matutina*

Mayor frecuencia en hombres

Sacroileitis (14%)

***Localización**: articulación sacroiliaca (pelvis)*

***Síntomas**: dolor en parte baja espalda que irradia a muslo.*

Mayor frecuencia en hombres

Osteoporosis (30-50%)

Disminución masa osea

***Factores de riesgo**: edad, tabaco, alcohol, corticoides, antecedentes familiares*

PIEL: 13-14%

Pioderma gangrenoso (1%): Lesión dolorosa en piel con punto central de pus, de crecimiento y ulceración rápida.

***Localización:** Extremidades, abdomen, pecho, periostomía.*

Mayor incidencia en Colitis ulcerosa

Eritema nodoso (4%): Nodulos inflamatorios rojo-violaceos.

***Localización:** Piernas, tobillos y muslos*

Mayor incidencia en mujeres jovenes

Aftas bucales (10%)

Psoriasis. Mayor incidencia en EII especialmente E.Crohn **(7-11%)**

OJOS <5%

Uveítis, epiescleritis

Inflamación de capas del ojo: Uveitis, epiescleritis

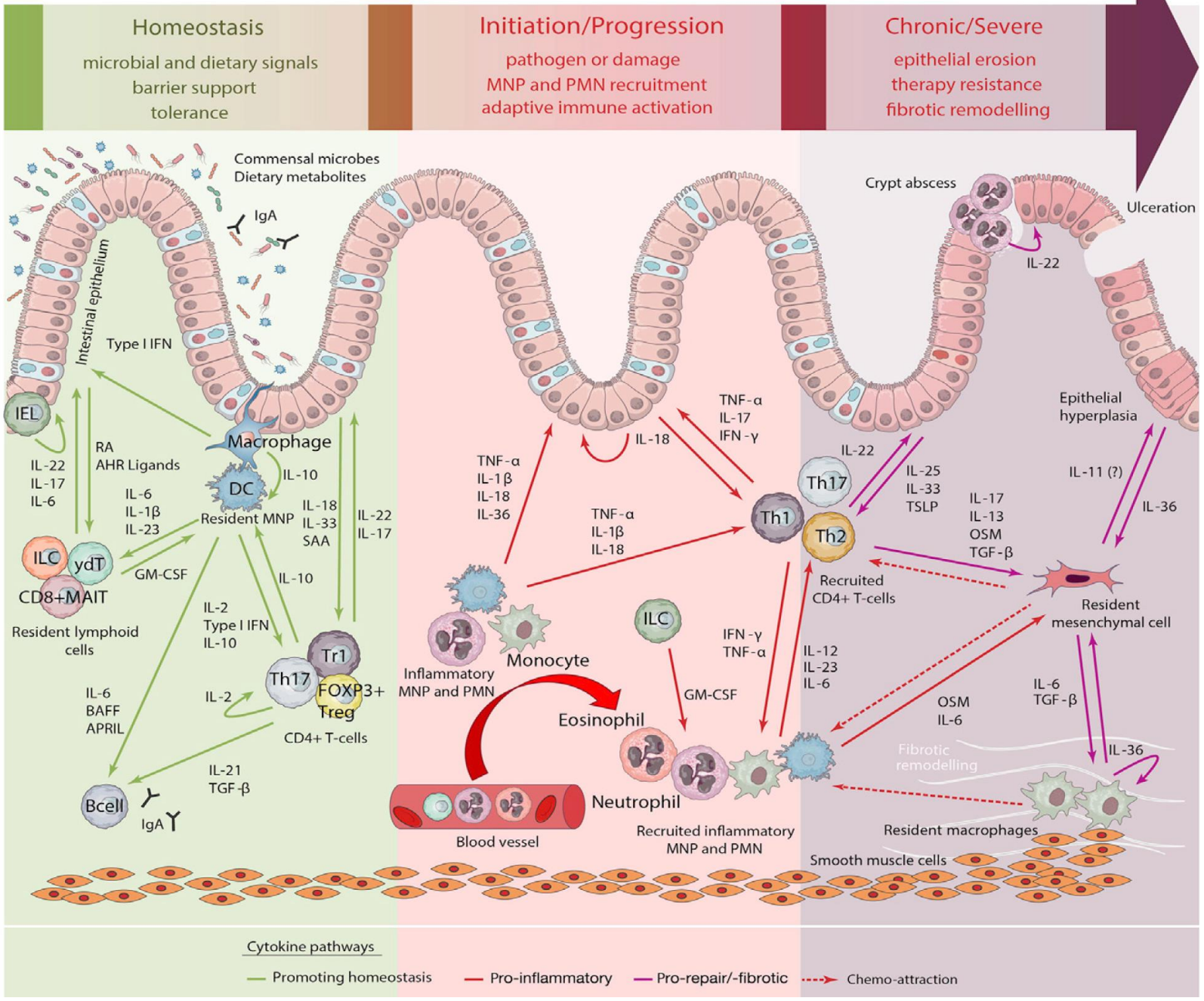
***Síntomas**: dolor, enrojecimiento,*

HIGADO <5%

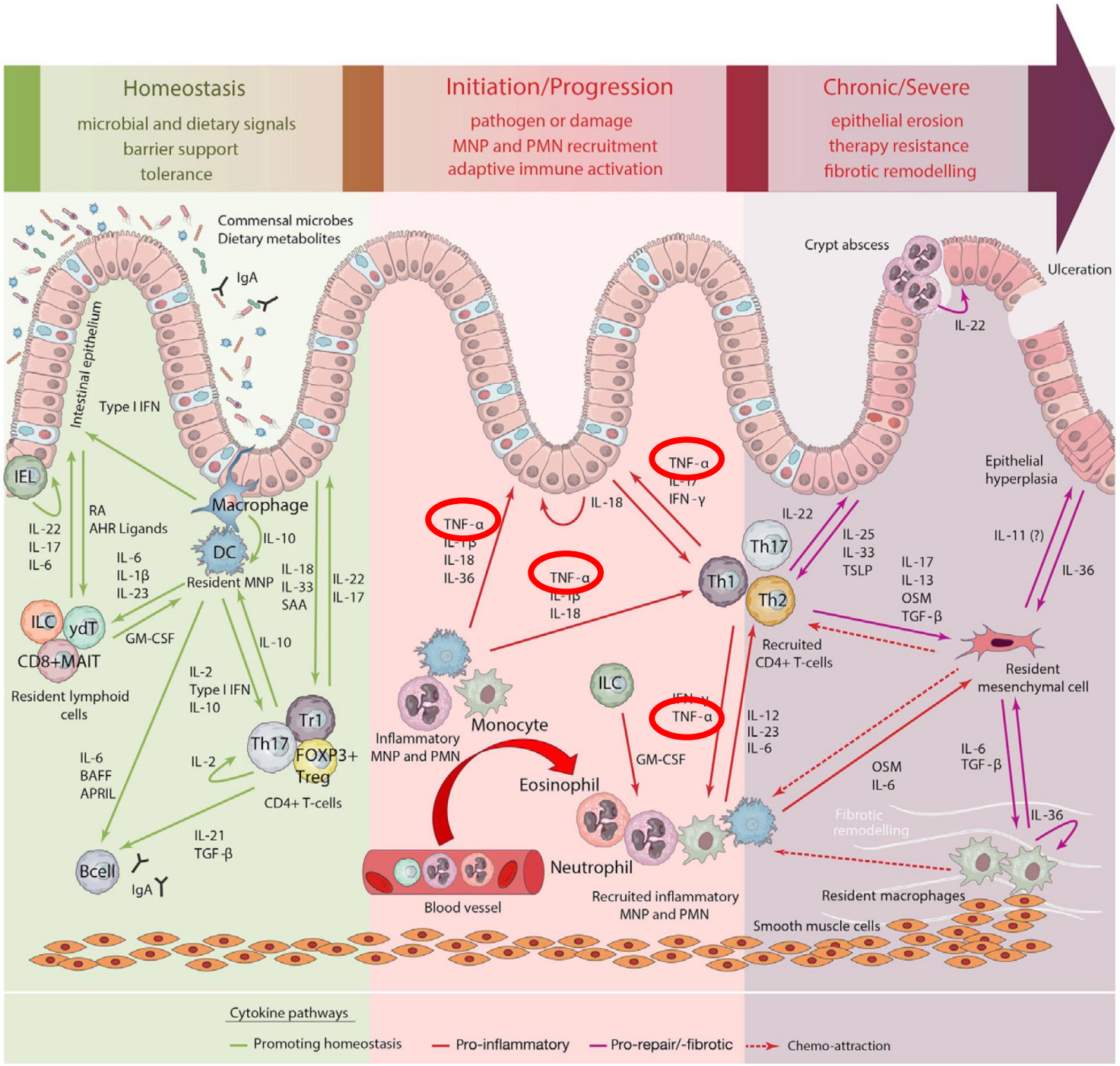
Colangitis esclerosante primaria CEP (<2%)

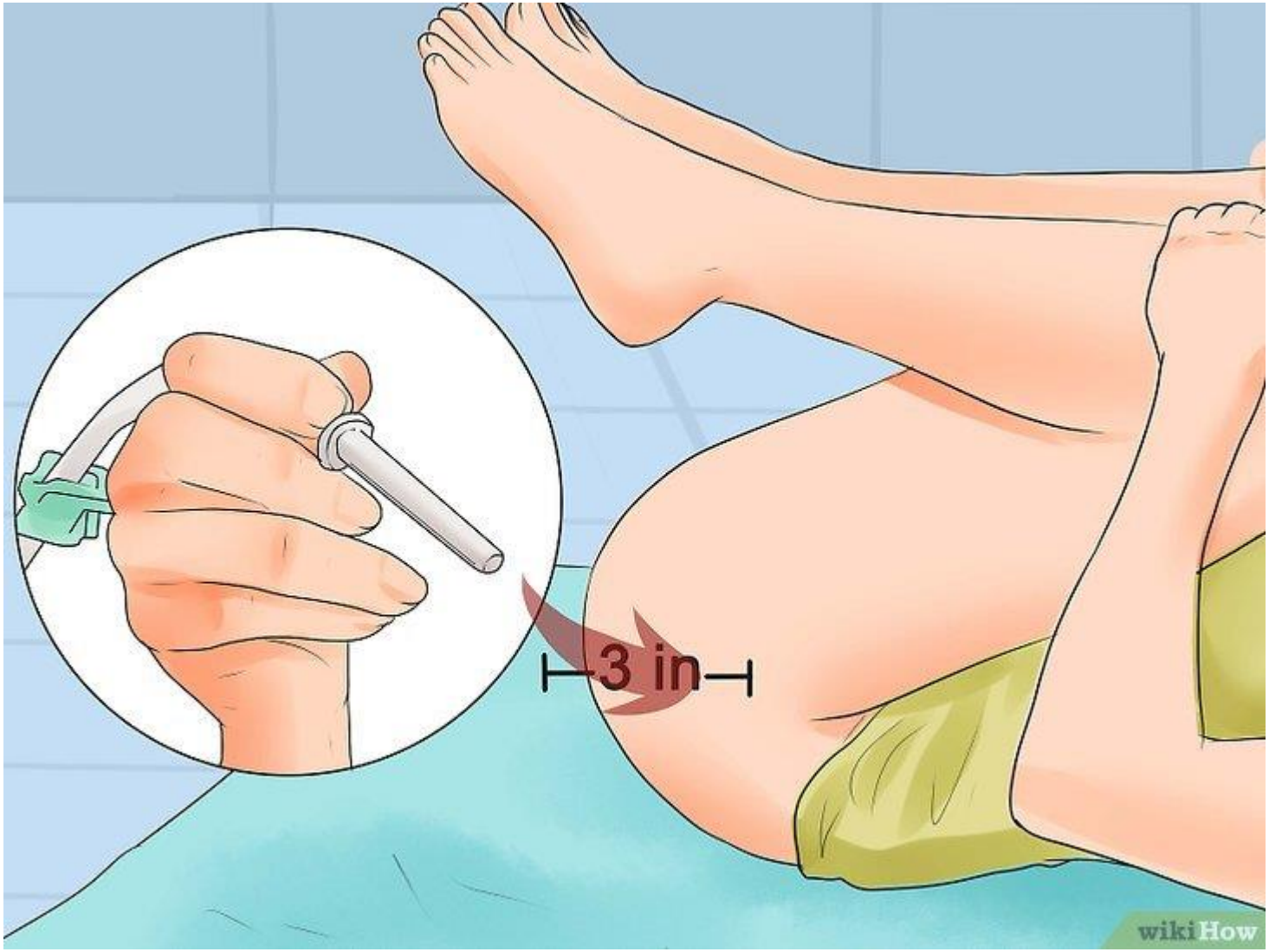
Inflamación conductos hepáticos

***Síntomas:** Picor, fatiga, alteración pruebas hepáticas*



Gareb, B.; et al.
Pharmaceutics 2020, 12, 539. https://doi.org/10.3390/pharmaceutics12060539


Homeostasis
microbial and dietary signals
barrier support
tolerance
Initiation/Progression
pathogen or damage
MNP and PMN recruitment
adaptive immune activation
Chronic/Severe
epithelial erosion
therapy resistance
fibrotic remodelling
Commensal microbes
Dietary metabolites
IgA
Intestinal epithelium
Type I IFN
IEL
IL-22
IL-17
IL-6
RA
AHR Ligands
Macrophage
DC
Resident MNP
IL-10
IL-6
IL-1β
IL-23
IL-18
IL-33
SAA
IL-22
IL-17
ILC
ydT
CD8+MAIT
Resident lymphoid cells
GM-CSF
IL-10
IL-2
Type I IFN
IL-10
Tr1
Th17
FOXP3+ Treg
CD4+ T-cells
IL-2
IL-6
BAFF
APRIL
IL-21
TGF-β
Bcell
IgA
Crypt abscess
Ulceration
IL-22
Epithelial hyperplasia
IL-11 (?)
IL-36
TNF-α
IL-1β
IL-18
IL-36
IL-18
TNF-α
IL-17
IFN-γ
Th1
Th17
Th2
IL-22
IL-25
IL-33
TSLP
IL-17
IL-13
OSM
TGF-β
Recruited CD4+ T-cells
Resident mesenchymal cell
Inflammatory MNP and PMN
Monocyte
ILC
GM-CSF
TNF-α
IL-12
IL-23
IL-6
Eosinophil
OSM
IL-6
IL-6
TGF-β
Fibrotic remodelling
IL-36
Neutrophil
Blood vessel
Recruited inflammatory MNP and PMN
Resident macrophages
Smooth muscle cells
Cytokine pathways
Promoting homeostasis
Pro-inflammatory
Pro-repair/-fibrotic
Chemo-attraction


3 in
wikiHow

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HIDROGEL COMO VEHICULO INTELIGENTE PARA EL SECRETOMA DE LAS hUCESCs

pharmaceutics

MDPI

Article

Tailored Hydrogels as Delivery Platforms for Conditioned Medium from Mesenchymal Stem Cells in a Model of Acute Colitis in Mice

Juan Sendon-Lago [1,†], Lorena Garcia-del Rio [2,†], Noemi Eiro [3,†], Patricia Diaz-Rodriguez [2], Leandro Avila [1], Luis O. Gonzalez [3], Francisco J. Vizoso [3,*], Roman Perez-Fernandez [1,*] and Mariana Landin [2,*]

1 Center for Research in Molecular Medicine and Chronic Diseases (CIMUS), Department of Physiology, Universidade de Santiago de Compostela, Avda. de Barcelona 22, 15706 Santiago de Compostela, Spain; bautistax@hotmail.com (J.S.-L.); leandro.avila@usc.es (L.A.)
2 Department of Pharmacology, Pharmacy and Pharmaceutical Technology, Universidade de Santiago de Compostela, 15782 Santiago de Compostela, Spain; lorena.garcia.delrio@rai.usc.es (L.G.-d.R.); patricia.diaz.rodriguez@usc.es (P.D.-R.)
3 Research Unit, Hospital Fundación de Jove, Avda. Eduardo de Castro 161, 33290 Gijón, Spain; noemi.eiro@gmail.com (N.E.); investigacion@hospitaldejove.com (L.O.G.)
* Correspondence: franvizoso@gmail.com (F.J.V.); roman.perez.fernandez@usc.es (R.P.-F.); m.landin@usc.es (M.L.)
† These authors contributed equally to this work.

Citation: Sendon-Lago, J.; Rio, L.G.-d.; Eiro, N.; Diaz-Rodriguez, P.; Avila, L.; Gonzalez, L.O.; Vizoso, F.J.; Perez-Fernandez, R.; Landin, M. Tailored Hydrogels as Delivery Platforms for Conditioned Medium from Mesenchymal Stem Cells in a Model of Acute Colitis in Mice. *Pharmaceutics* **2021**, *13*, 1127. https://doi.org/10.3390/pharmaceutics13081127

Abstract: Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is increasingly prevalent and current therapies are not completely effective. Mesenchymal stem cells are emerging as a promising therapeutic option. Here, the effect of local hydrogel application loaded with conditioned medium (CM) from human uterine cervical stem cells (hUCESC-CM) in an experimental acute colitis mice model has been evaluated. Colitis induction was carried out in C57BL/6 mice by dissolving dextran sulfate sodium (DSS) in drinking water for nine days. Ulcers were treated by rectal administration of either mesalazine (as positive control) or a mucoadhesive and thermosensitive hydrogel loaded with hUCESC-CM (H-hUCESC-CM). Body weight changes, colon length, and histopathological analysis were evaluated. In addition, pro-inflammatory TNF-α, IL-6, and IFN-γ mRNA levels were measured by qPCR. Treatment with H-hUCESC-CM inhibited body weight loss and colon shortening and induced a significant decrease in colon mucosa degeneration, as well as TNF-α, IFN-γ, and IL-6 mRNA levels. Results indicate that H-hUCESC-CM effectively alleviated DSS-induced colitis in mice, suggesting that H-hUCESC-CM may represent an attractive

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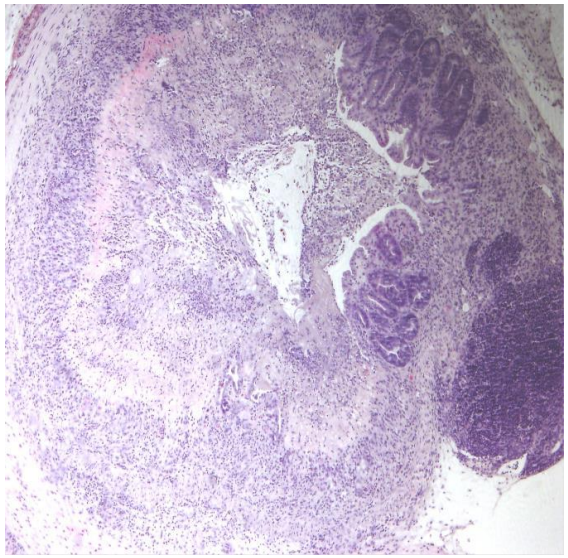
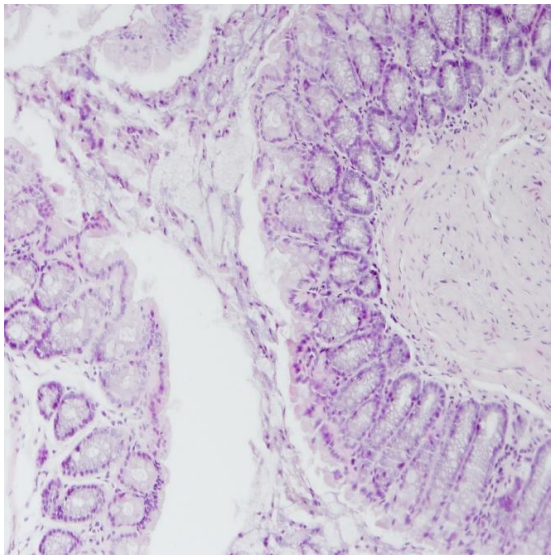
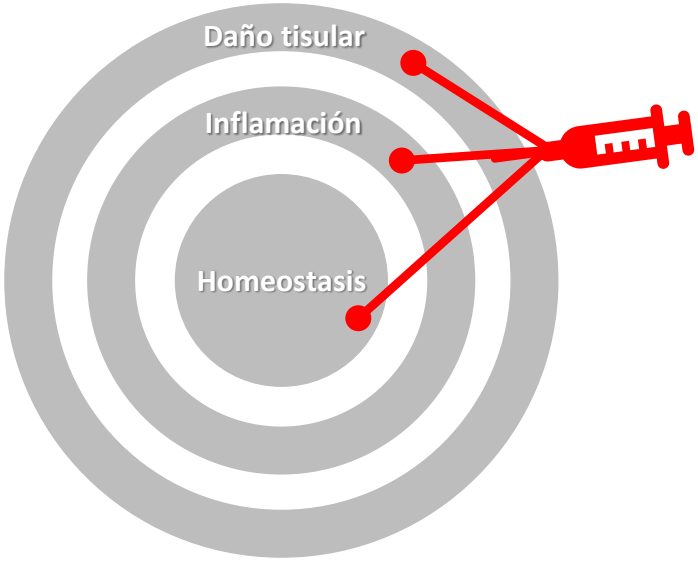
Efecto del MC-hUCESC

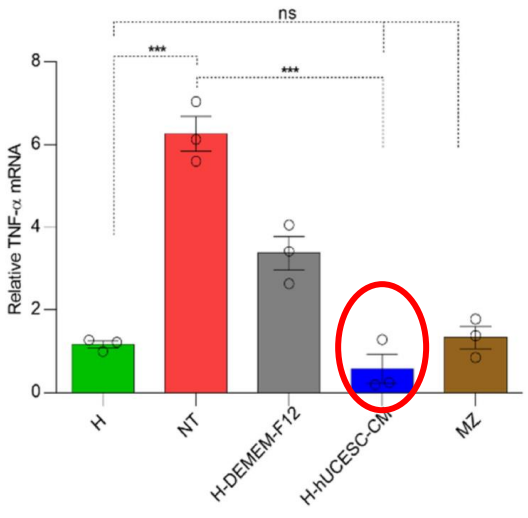
No tratados

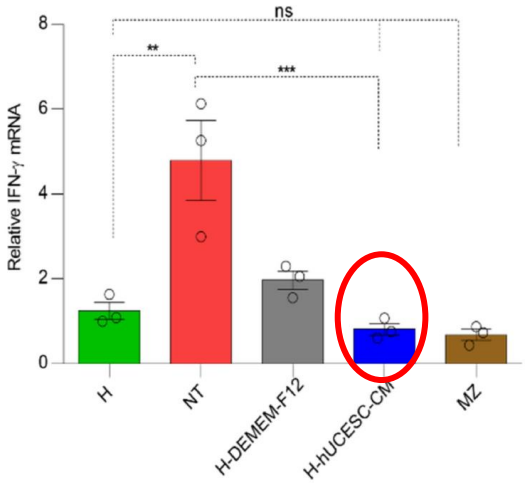


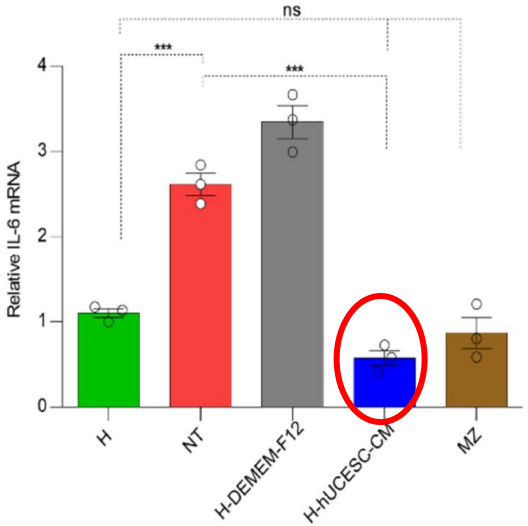
Tratados con MC-hUCESC











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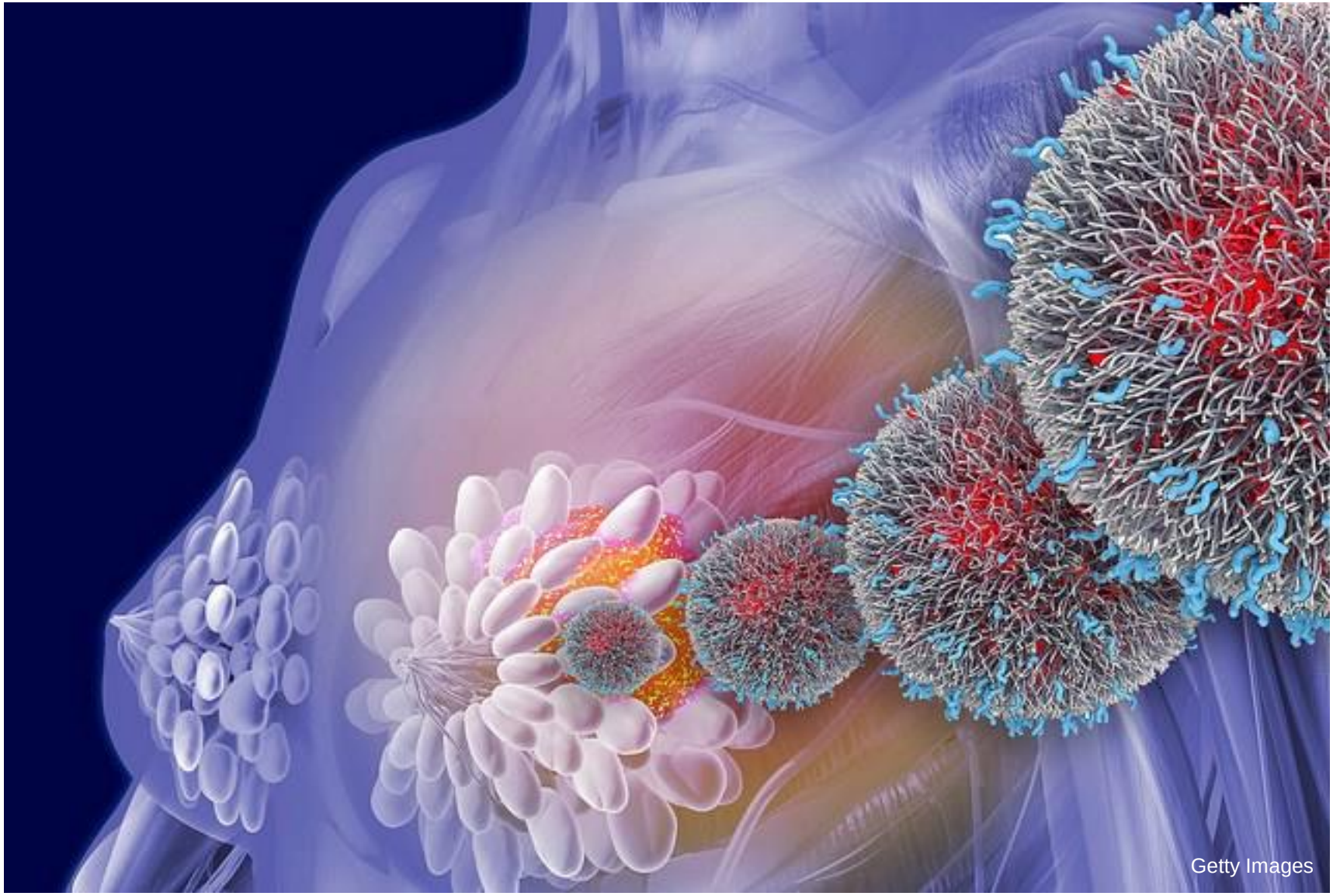

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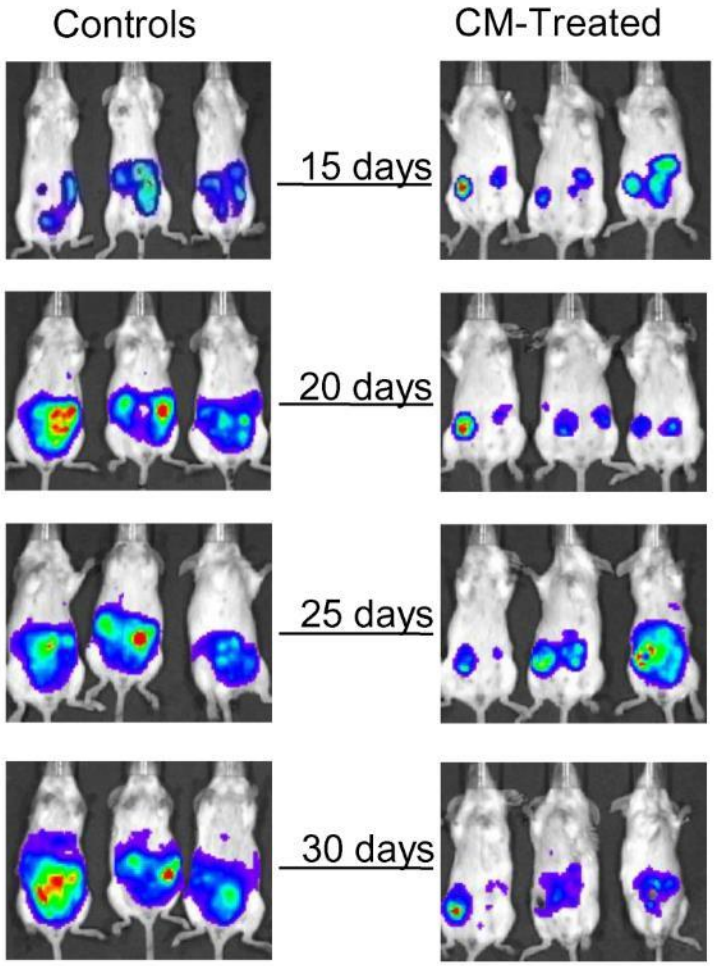

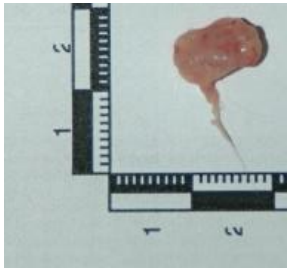

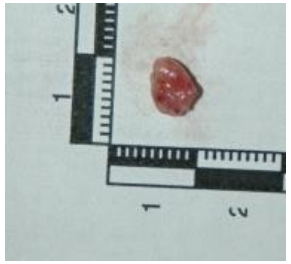

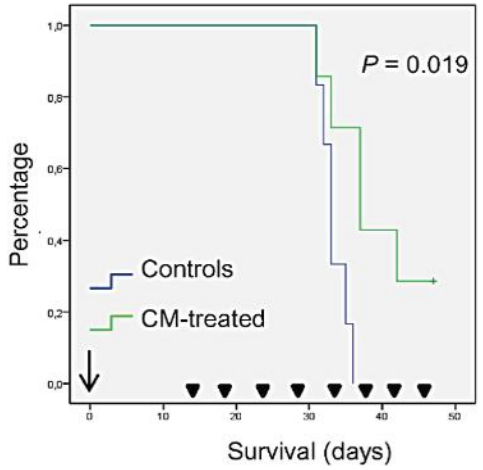

www.impactjournals.com/oncotarget/ Oncotarget, Vol. 5, No. 21

Potential therapeutic effect of the secretome from human uterine cervical stem cells against both cancer and stromal cells compared with adipose tissue stem cells

Noemí Eiró[1,5,*], Juan Sendon-Lago[2,*], Samuel Seoane[2], María A. Bermúdez[2], Maria Luz Lamelas[1], Tomás Garcia-Caballero[3], José Schneider[4,5], Roman Perez-Fernandez[2,5] and Francisco J. Vizoso[1,5]

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[*] These authors contributed equally to this work

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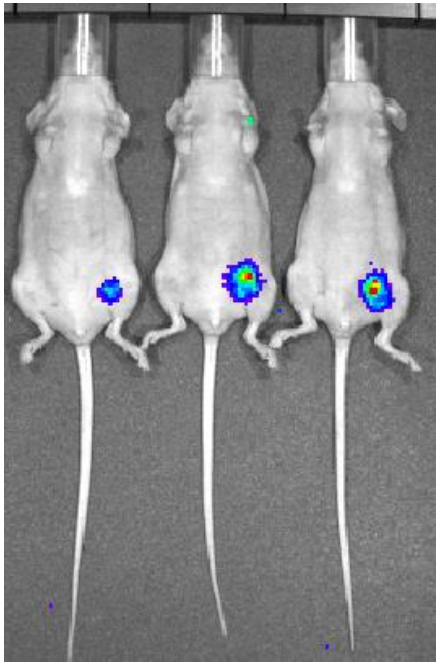
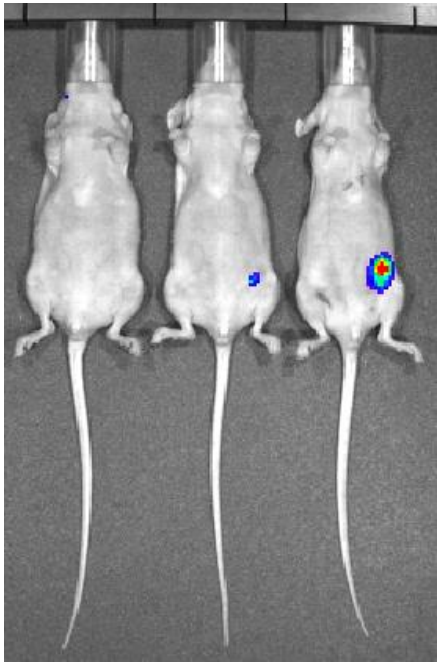
Combinación del MC-hUCESC con quimioterapia

Quimioterapia



MC-hUCESC + Quimioterapia



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Cérvix uterino: ¿ la puerta de la casa de la vida?

https://enfamilia.aeped.es

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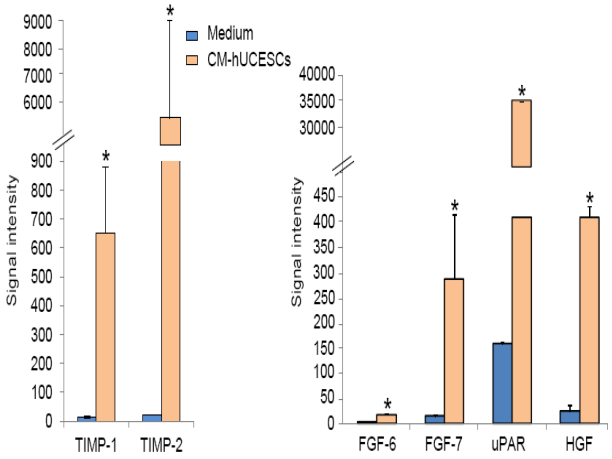
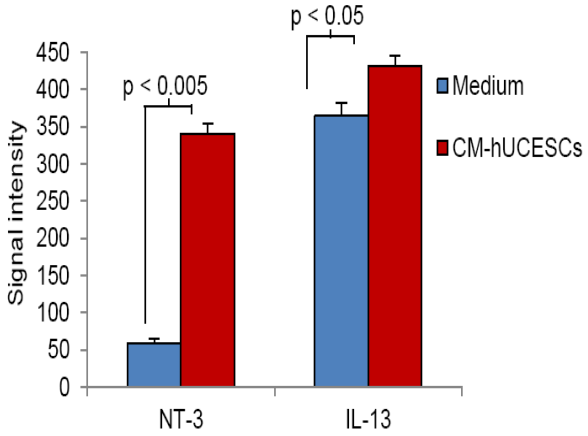
Propiedades del secretoma de las hUCESCs

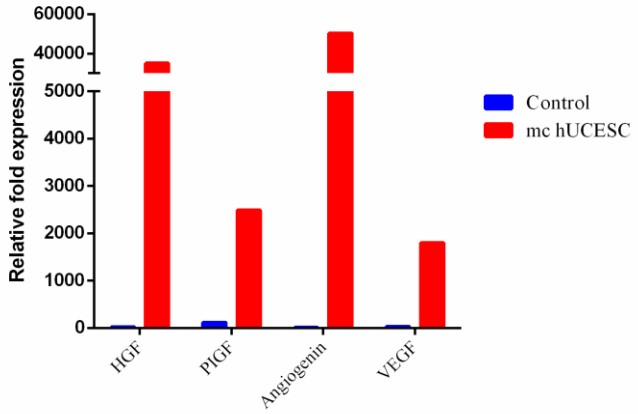
Actividad regenerativa



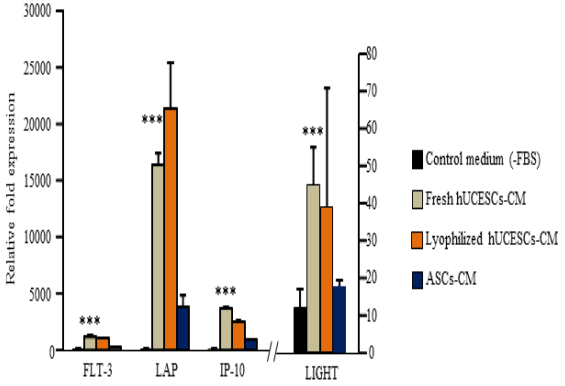
Actividad anti-inflamatoria



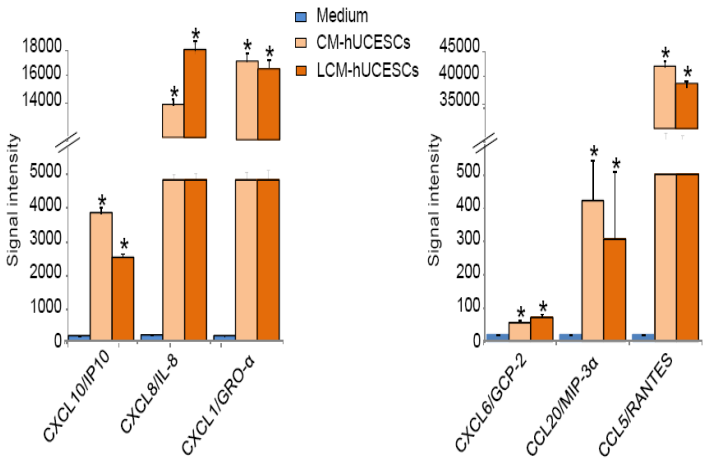
Actividad angiogenica



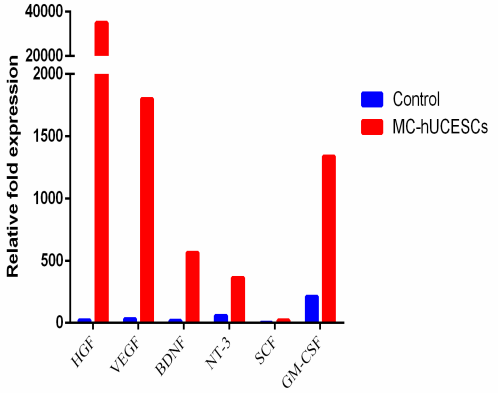
Actividad antitumoral



Actividad anti-bacteriana



Actividad neurotrofica



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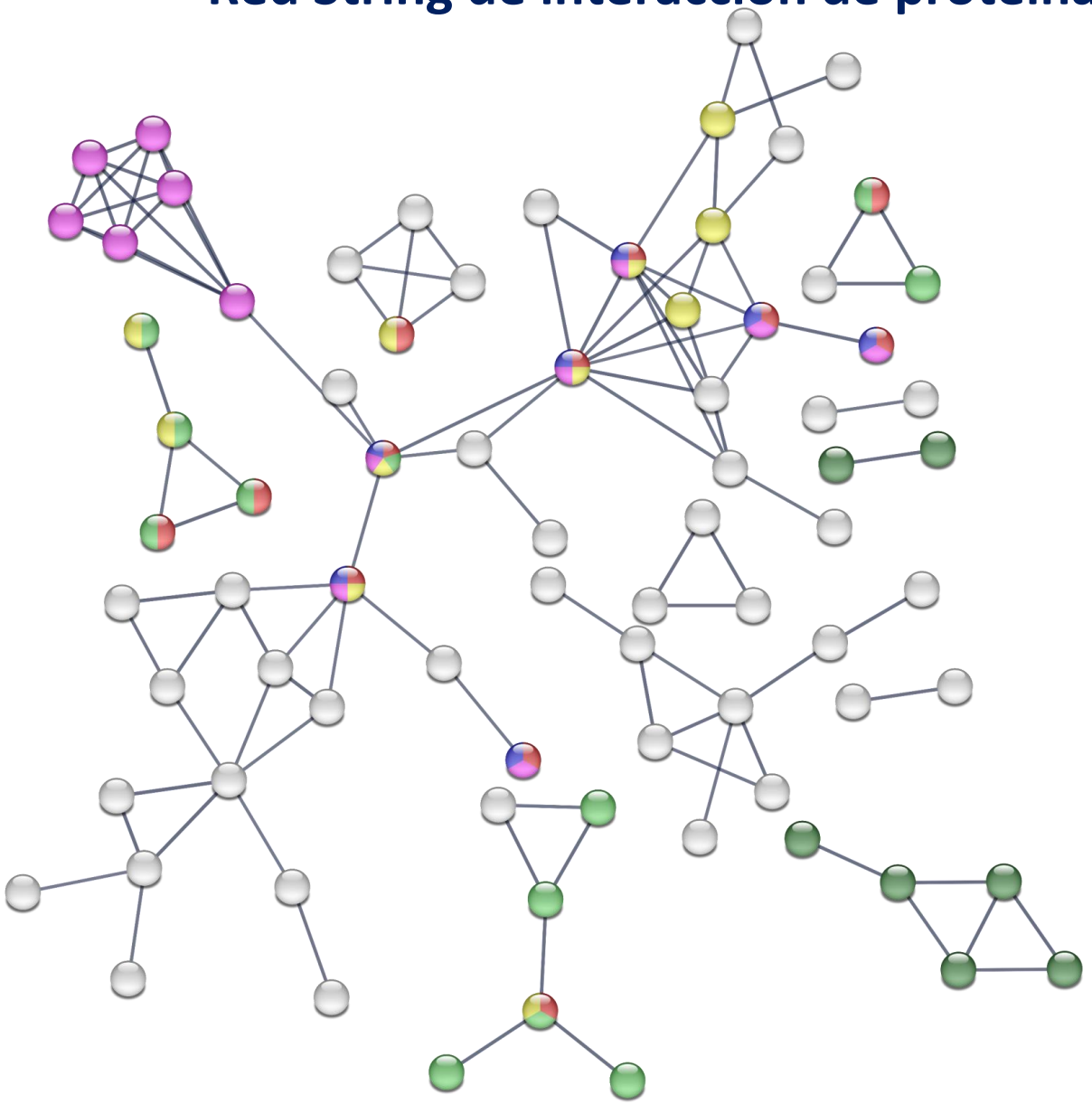
Red String de interacción de proteínas mayoritarias



Rutas metabólicas más significativas

- Adhesión Focal
- Interacción receptor ECM
- Regulación citoesqueleto actina
- Proteoglicanos en cáncer
- Ruta PI3K-Akt de señalización
- Glicólisis

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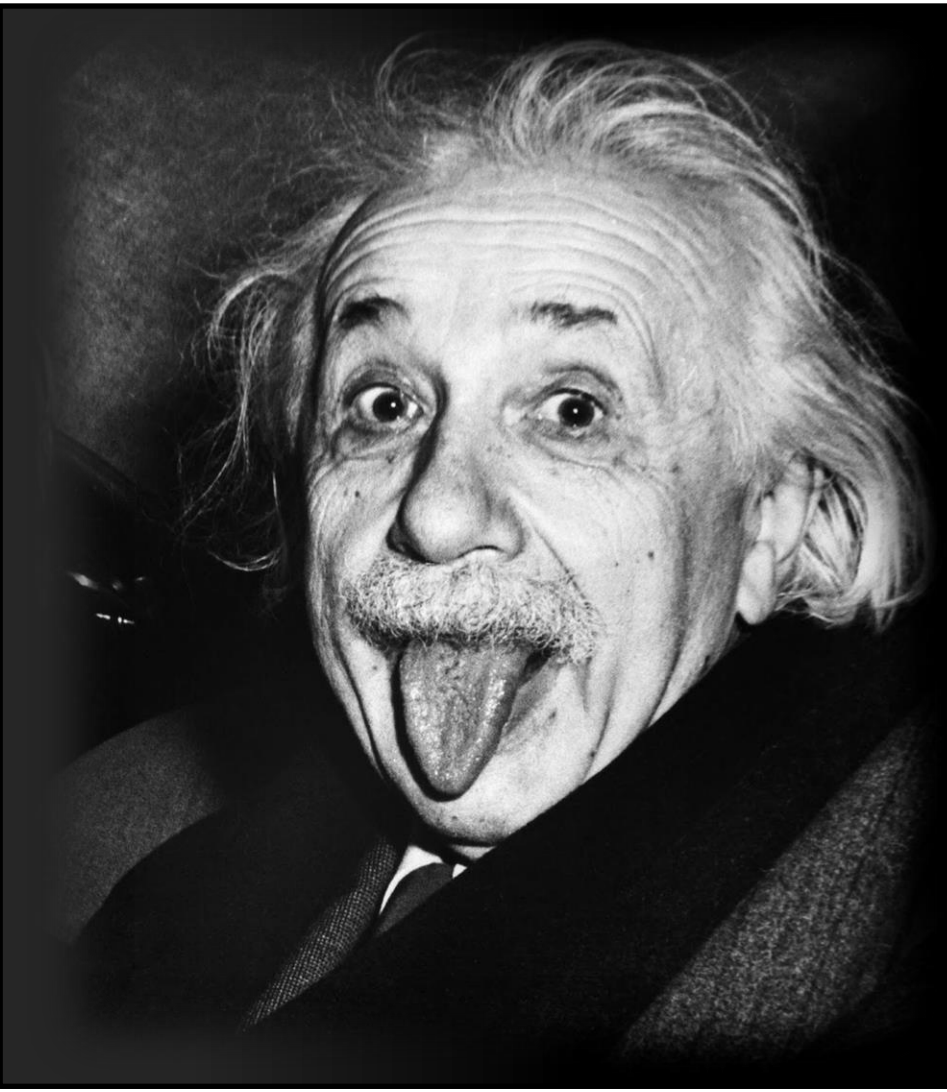
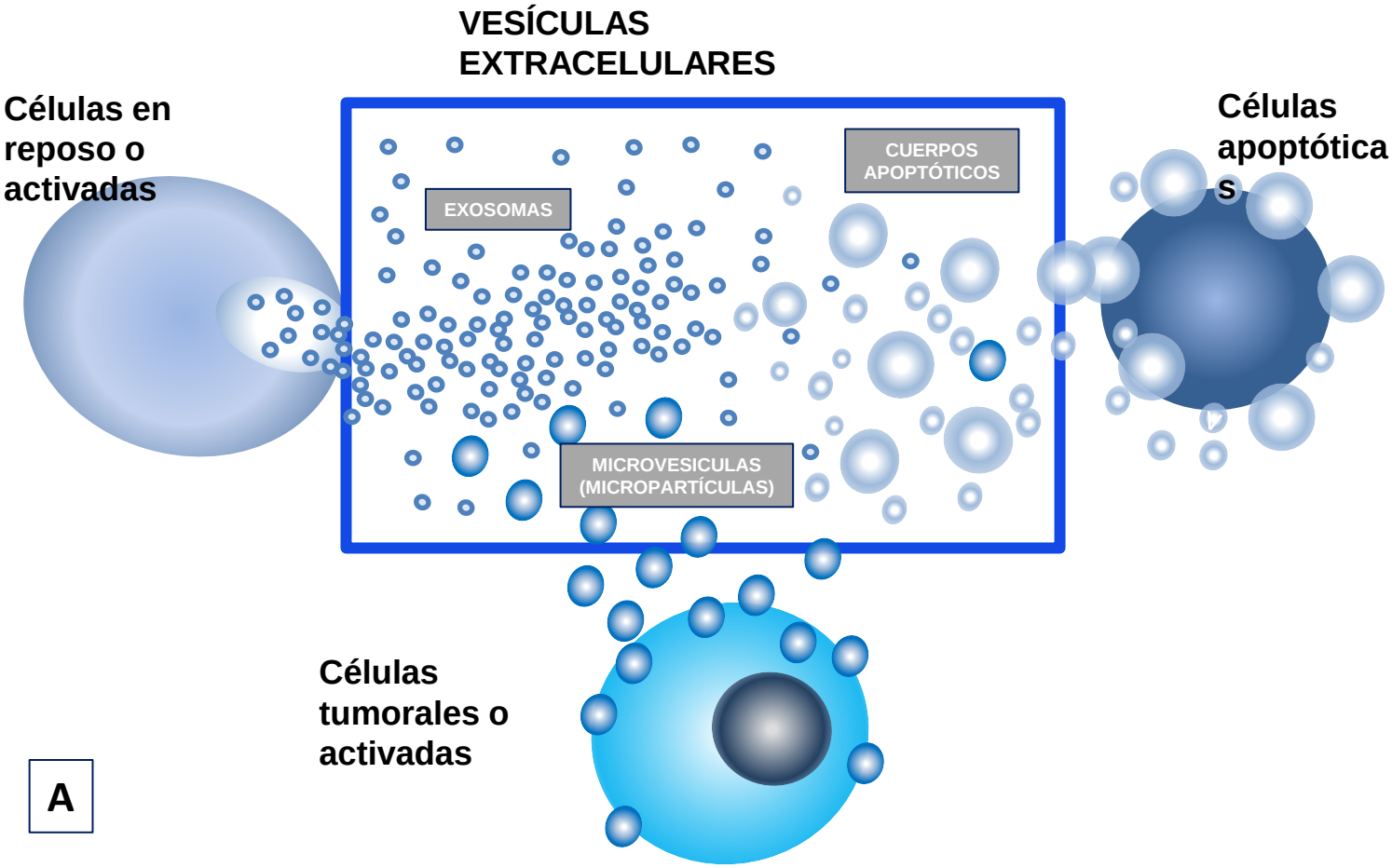


“Todo lo que puedes imaginar, la naturaleza lo ha creado ya”

Albert Einstein


VESÍCULAS EXTRACELULARES
Células en reposo o activadas
EXOSOMAS
CUERPOS APOPTÓTICOS
Células apoptóticas
MICROVESICULAS (MICROPARTÍCULAS)
Células tumorales o activadas
A

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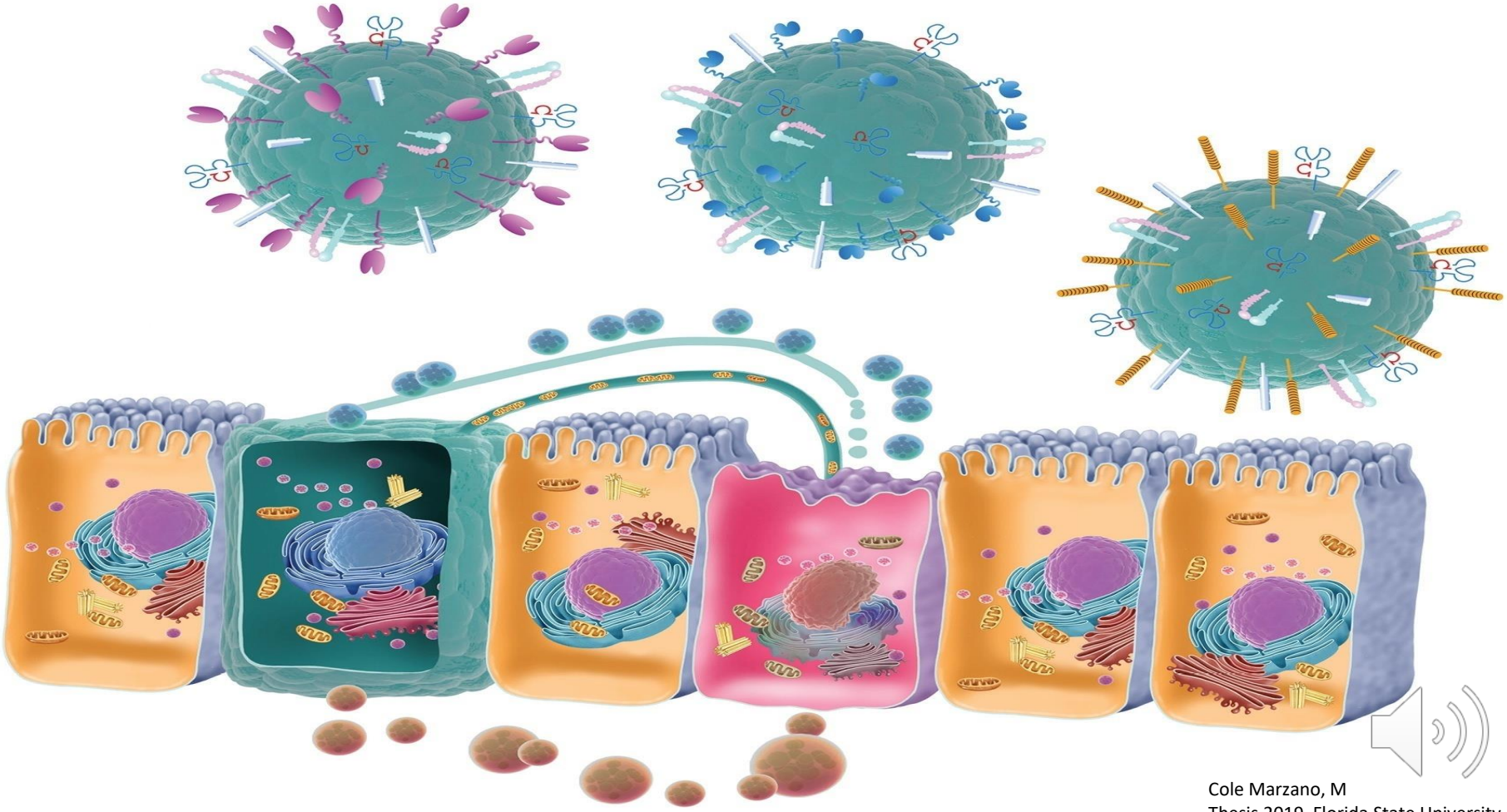
VESÍCULAS EXTRACELULARES (MICROVESÍCULAS, EXOSOMAS Y CUERPOS APOPTÓPSICOS)

Efectos paracrinos mediados por VE entre células madre y células del parénquima.



Cole Marzano, M
Thesis 2019, Florida State University

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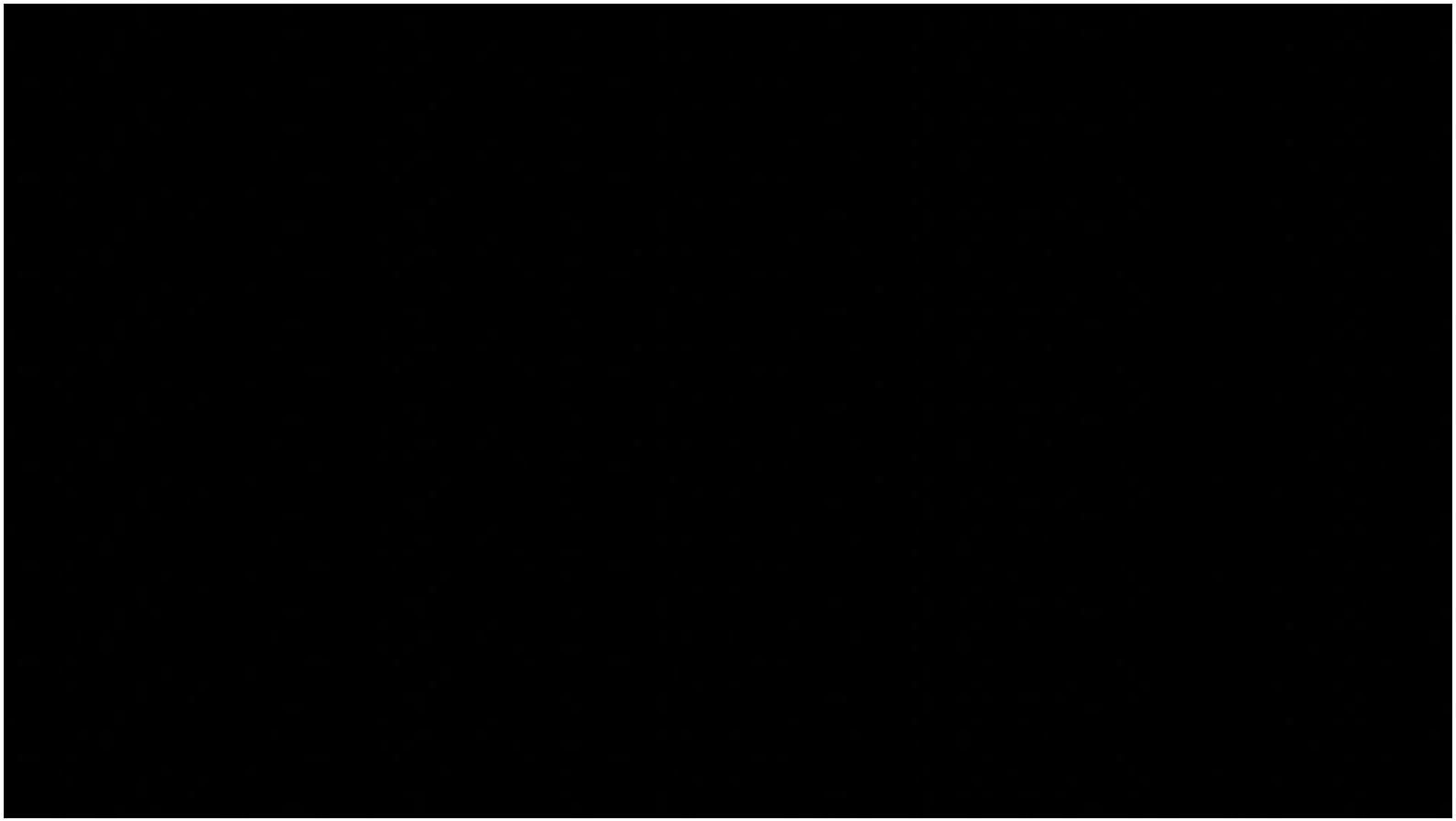
EXOSOMAS DE LAS CÉLULAS MADRE MESENQUIMALES COMO NUEVA ESTRATEGIA TERAPÉUTICA



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Artículos publicados por nuestro Grupo

1. Potential therapeutic effect of the secretome from human uterine cervical stem cells against both cancer and stromal cells compared with adipose tissue stem cells, Eiro et al. ***Oncotarget*** 2014
2. Corneal Epithelial Wound Healing and Bactericidal Effect of Conditioned Medium From Human Uterine Cervical Stem Cells. Bermudez et al. **Investigation Ophtalmology and Visual Sciences** 2015
3. Anti-inflammatory effect of conditioned medium from human uterine cervical stem cells in uveitis. Bermudez et al. ***Experimental Eye Research*** 2016
4. Human Uterine Cervical Stromal Stem Cells (hUCESCs): Why and How they Exert their Antitumor Activity. Schneider et al. **Cancer Genomics & Proteomics** 2016
5. Mesenchymal Stem Cell Secretome: Toward Cell-Free Therapeutic Strategies in Regenerative Medicine. Vizoso et al. **International Journal Molecular Sciences** 2017
6. Antifungal Activity of the Human Uterine Cervical Stem Cells Conditioned Medium (hUCESC-CM) Against Candida albicans and Other Medically Relevant Species of Candida. Schneider et al. ***Frontiers in Microbiology*** 2018
7. Non Pregnant Human Uterus as Source of Mesenchymal Stem Cells. Eiro et al. **Current Stem Cell Research & Therapy** 2018
8. Mesenchymal Stem Cells in Homeostasis and Systemic Diseases: Hypothesis, Evidences, and Therapeutic Opportunities. Vizoso et al. **International Journal Molecular Sciences** 2019
9. Corneal regeneration by conditioned medium of human uterine cervical stem cells is mediated by TIMP-1 and TIMP-2. Sendon-Lago et al. ***Experimental Eye Research*** 2019
10. Functional heterogeneity of mesenchymal stem cells from natural niches to culture conditions: implications for further clinical uses. Costa et al. **Cellular and Molecular Life Sciences** 2020
11. The Coronavirus Pandemic (SARS-CoV-2): New Problems Demand New Solutions, the Alternative of Mesenchymal (Stem) Stromal Cells. Eiro et al. **Frontiers in Cell and Developmental Biology** 2020
12. Mesenchymal Stem Cells as a Cornerstone in a Galaxy of Intercellular Signals: Basis for a New Era of Medicine. **Int J Mol Sci.** 2021
13. Importance of the origin of mesenchymal (stem) stromal cells in cancer biology: "alliance" or "war" in intercellular signals. **Cell Bioscience** 2021
14. Mesenchymal Stem Cell-Based Therapy as an Alternative to the Treatment of Acute Respiratory Distress Syndrome: Current Evidence and Future Perspectives. **International Journal Molecular Sciences** 2021
15. Tailored Hydrogels as Delivery Platforms for Conditioned Medium from Mesenchymal Stem Cells in a Model of Acute Colitis in Mice. **Pharmaceutics.** 2021
16. Conditioned medium from human uterine cervical stem cells regulates oxidative stress and angiogenesis of retinal pigment epithelial cells. **Ophthalmic Research .** 2022
17. *In Vivo* Effects of Conditioned Medium from Human Uterine Cervical Stem Cells in an Ovarian Cancer Xenograft Mouse Model. **Cancer Genomics Proteomics**. 2022.
18. Mesenchymal (Stem) Stromal Cells Based as New Therapeutic Alternative in Inflammatory Bowel Disease: Basic Mechanisms, Experimental and Clinical Evidence, and Challenges. Int J Mol Sci. 2022.
19. Aging and Mesenchymal Stem Cells: Basic Concepts, Challenges and Strategies. **Biology** (Basel). 2022.
20. Towards a new concept of regenerative endodontics based on mesenchymal stem cell-derived secretomes products. Bioengineering. 2023.

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ENFERMEDAD DE ALZHEIMER

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Enfermedades neurodegenerativas en las que las células madre mesenquimales han demostrado cierto grado de efectividad

- Enfermedad de Alzheimer
- Enfermedd de Parkinson
- Esclerosis lateral amiotrófica
- Esclerosis múltiple
- Ictus
- Daño cerebral traumático
- Status epiléptico

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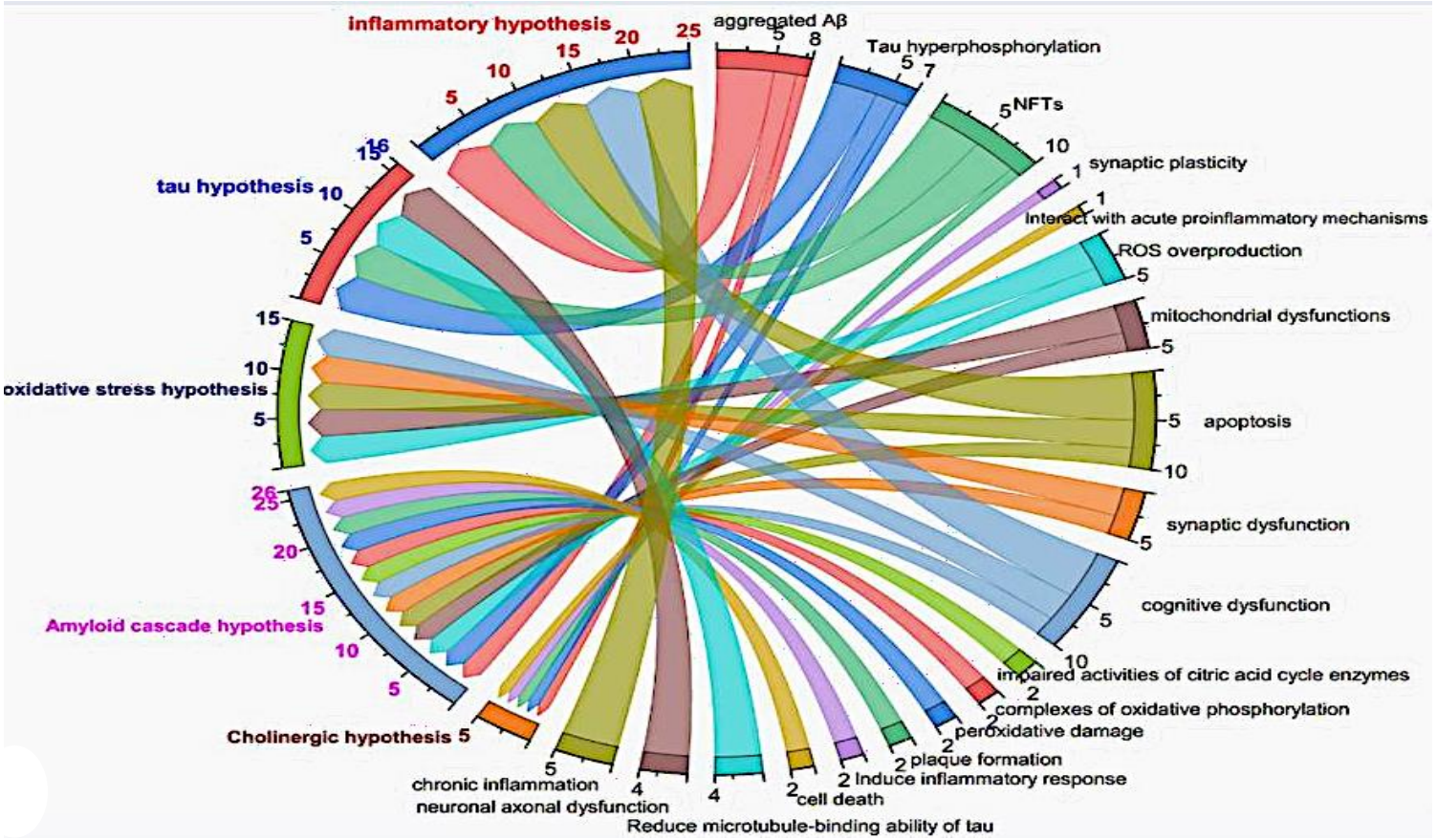
Mecanismos fisiopatológicos asociados a la enfermedad de Alzheimer

(Xie D, Deng T, Zhai Z, Sun T, Xu Y. The cellular model for Alzheimer's disease research: PC12 cells. Front Mol Neurosci. 2023 Jan 4;15:1016559. doi: 10.3389/fnmol.2022.1016559. PMID: 36683856; PMCID: PMC9846650)



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Modelo animal

Características de Alzheimer (antes del trasplante de MSC)

M1- Microglía pro-inflamatoria

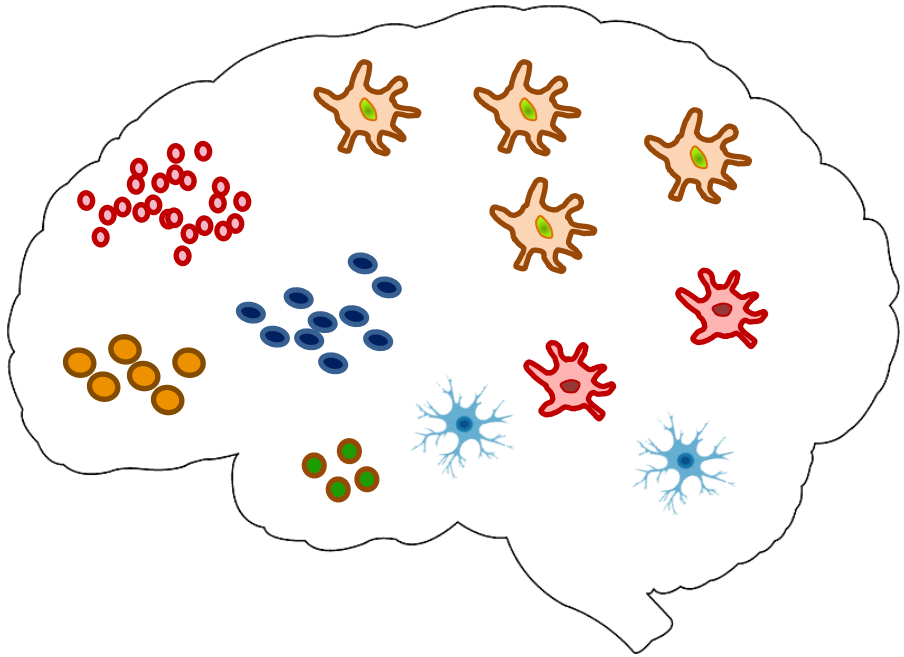
Proteína β amiloide (placas)

ROS (Factores oxidativos)

Factores pro-inflamatorios

M2- Microglía anti-inflamatoria

Factores anti-inflamatorios



Neuronas

Zhang K, et al
Journal of Alzheimer's Disease (2023)
DOI 10.3233/JAD-221253

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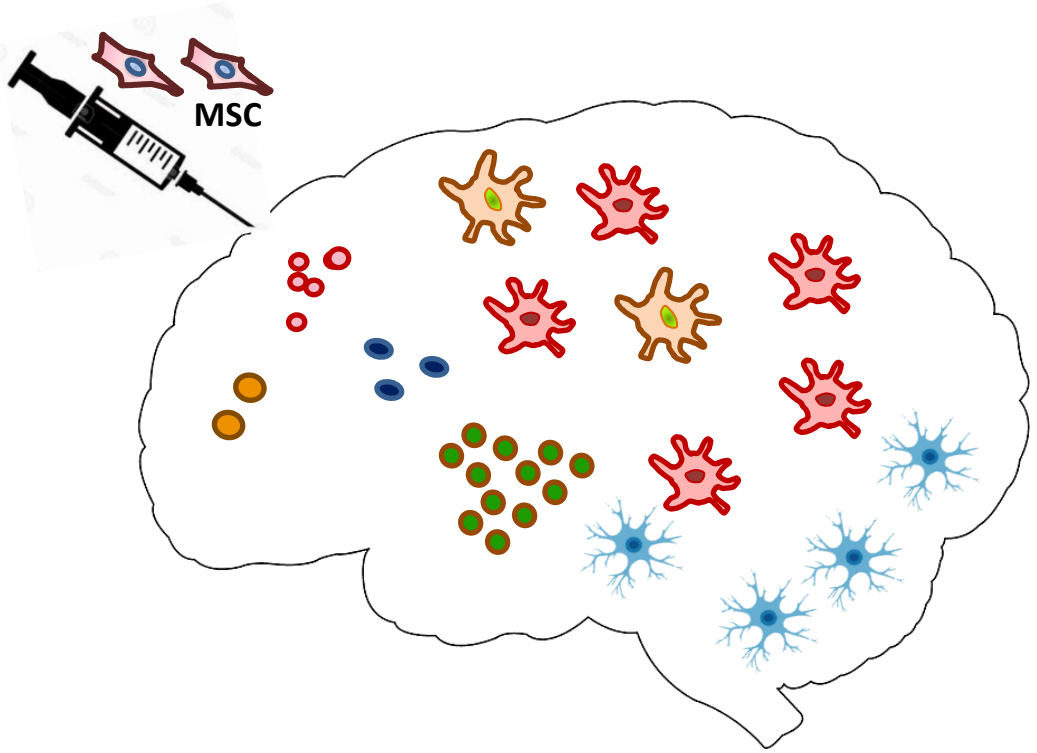
Post transplante de MSC

Modelo animal

MSC



M1
Microglía

M2
Microglía

Factores anti-inflamatorios

Neuronas (neurogénesis endógena)

Factores pro-inflamatorios

Proteína β amiloide (placas)

ROS (Factores oxidativos)

Zhang K, et al
Journal of Alzheimer's Disease (2023)
DOI 10.3233/JAD-221253

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Ensayos clínicos actuales de Células madre y exosomas (Jeyaraman y cols. Heliyon 2023)

Sl. No	NCT Number	Title	Status	Interventions	Locations
1	NCT02833792	Allogeneic Human Mesenchymal Stem Cells for Alzheimer's Disease	Recruiting	BM-MSCs	USA
2	NCT04855955	Autologous Human Adipose-Derived Mesenchymal Stem Cells in Alzheimer's Disease	Available	AD-MSCs	USA
3	NCT02600130	Allogeneic Human Mesenchymal Stem Cell Infusion Versus Placebo in Patients With Alzheimer's Disease	Active, not recruiting	BM-MSCs	USA
4	NCT04040348	Alzheimer's Disease Stem Cells Multiple Infusions	Recruiting	BM-MSCs	USA
5	NCT02672306	Safety and Exploratory Efficacy Study of UCMSCs in Patients With Alzheimer's Disease	Unknown status	UC-MSCs	China
6	NCT03724136	Alzheimer's Autism and Cognitive Impairment Stem Cell Treatment Study	Recruiting	BM-MSCs	UAE
7	NCT01547689	Safety and Efficiency of Umbilical cord-derived Mesenchymal Stem Cells(UC-MSC) in Patients With Alzheimer's Disease	Unknown status	UC-MSCs	China
8	NCT01297218	The Safety and The Efficacy Evaluation of NEUROSTEM®-AD in Patients With Alzheimer's Disease	Completed	UC-MSCs	Korea
9	NCT02054208	Safety and Exploratory Efficacy Study of NEUROSTEM® Versus Placebo in Patients With Alzheimer's Disease	Completed	UC-MSCs	Korea
10	NCT04388982	the Safety and the Efficacy Evaluation of Allogenic Adipose MSC-Exos in Patients With Alzheimer's Disease	Recruiting	MSC Exos	China
11	NCT04482413	Study to Evaluate the Safety and Efficacy of AstroStem in the Treatment of Alzheimer's Disease	Not yet recruiting	AD-MSCs	USA
12	NCT03117738	A Study to Evaluate the Safety and Efficacy of AstroStem in the Treatment of Alzheimer's Disease	Completed	AD-MSCs	USA
13	NCT04954534	Exploratory Efficacy Study of NEUROSTEM® in Subjects Who Control Group of NEUROSTEM®	Not yet recruiting	UC-MSCs	Korea
14	NCT03172117	Follow-up Study of Safety and Efficacy in Subjects Who Completed NEUROSTEM® Phase-I/IIa Clinical Trial.	Recruiting	UC-MSCs	Korea
15	NCT01696591	The Long-Term Safety and Efficacy Follow-Up Study of Subjects Who Completed the Phase I Clinical Trial of NEUROSTEM®-AD	Unknown status	AD-MSCs	KOREA
16	NCT03297177	Autologous Stem/Stromal Cells in Neurological Disorders and Disease	Not yet recruiting	ADMSCs	USA
17	NCT04684602	Mesenchymal Stem Cells for the Treatment of Various Chronic and Acute Conditions	Recruiting	ADMSCs	USA
18	NCT00874783	Development of iPS From Donated Somatic Cells of Patients With Neurological Diseases	Recruiting	iPSCs	Israel
19	NCT04388982	The Safety and the Efficacy Evaluation of Allogenic Adipose MSC-Exos in Patients With Alzheimer's Disease	Recruiting	ADSC-Exos	China

Limitaciones del tratamiento de la Enfermedad de Alzheimer con células madre mesenquimales (CMM)

- Las CMM *in vitro* muestran una capacidad proliferativa reducida y una disminución de su vida media.
- Un limitado número de CMM alcanzan las lesiones cerebrales tras su inyección.
- La exposición de las CMM trasplantadas al ambiente tóxico tisular (estrés oxidativo e inflamatorio) de la enfermedad degenerativa inhibe su reclutamiento e induce su apoptosis.

Ophthalmic Research

Research Article

Ophthalmic Res
DOI: 10.1159/000524484

Received: October 26, 2021
Accepted: March 27, 2022
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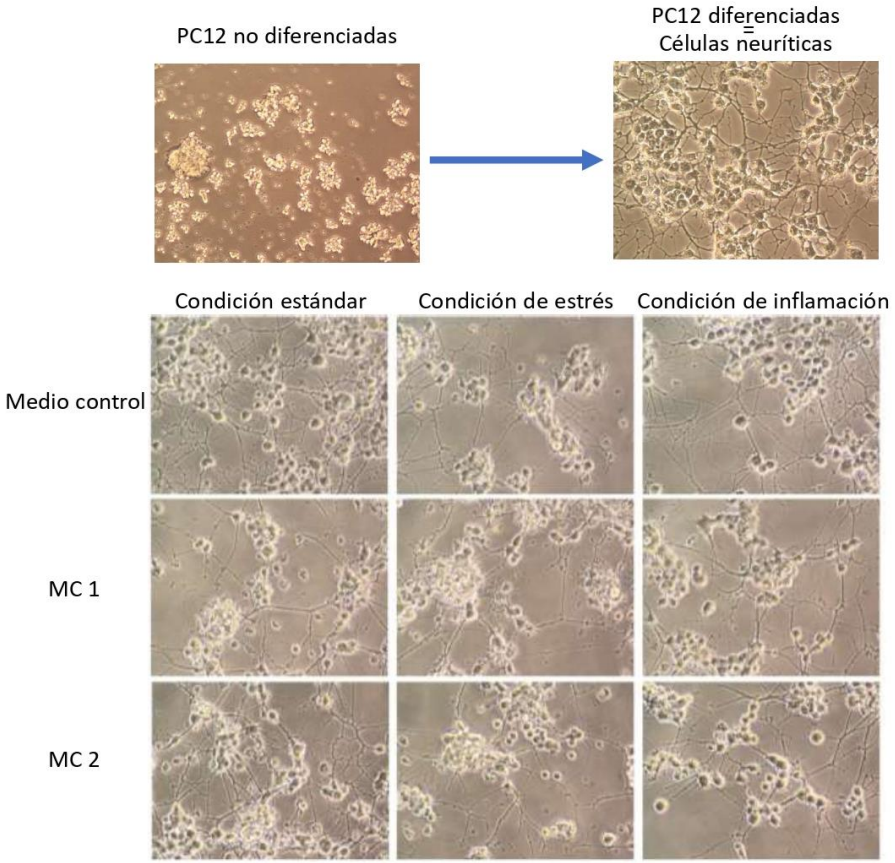
Conditioned Medium from Human Uterine Cervical Stem Cells Regulates Oxidative Stress and Angiogenesis of Retinal Pigment Epithelial Cells

Noemi Eiro[a] Juan Sendon-Lago[b] Sandra Cid[a] Jorge Saa[a, c]
Nagore de Pablo[a] Belen Vega[a] Maria A. Bermudez[d]
Roman Perez-Fernandez[b] Francisco J. Vizoso[a]

[a]Unit Research, Fundación Hospital de Jove, Gijón, Spain; [b]Department of Physiology-CIMUS, University of Santiago de Compostela, Santiago, Spain; [c]Ophthalmology Service, Fundación Hospital de Jove, Gijón, Spain; [d]Department of Biology, Faculty of Science, University of A Coruña, A Coruña, Spain

Efecto del **secretoma** de **hUCESC** sobre las **PC12 diferenciadas a células neuríticas**



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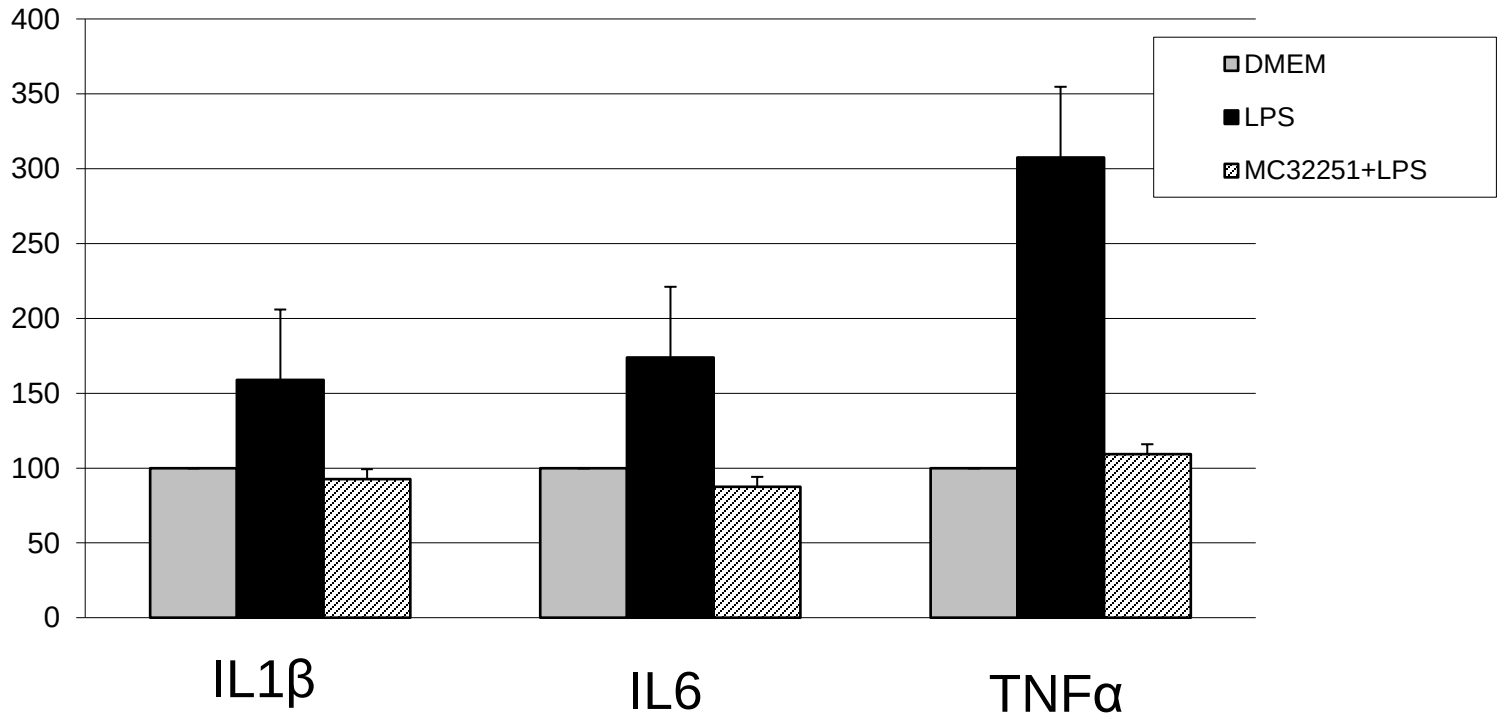
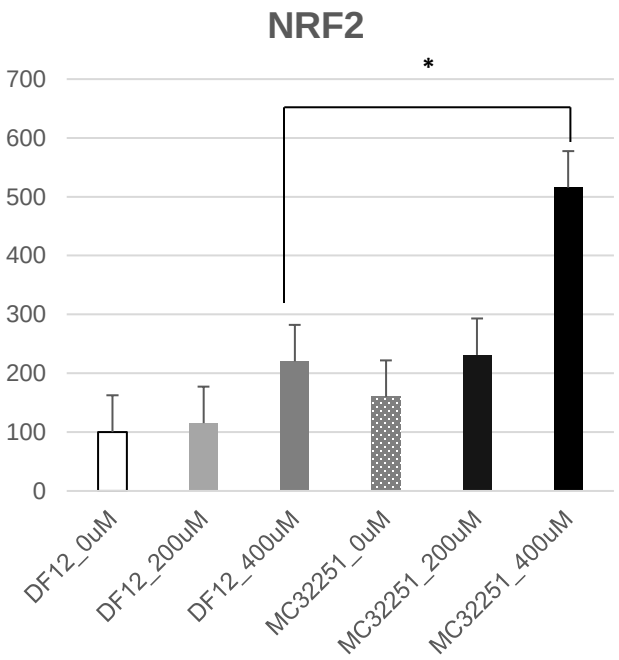
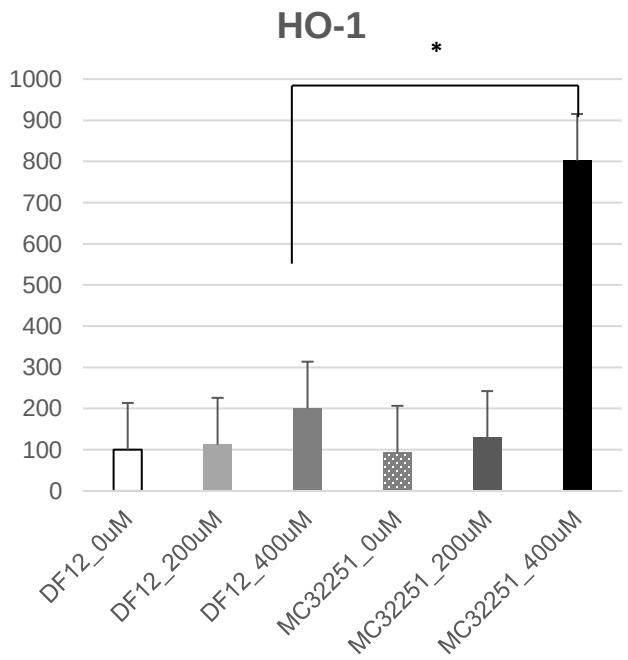
Efecto anti-inflamatorio del medio condicionado de **hUCESC** sobre las **PC12 diferenciadas a células neuríticas**



Efecto **anti-estrés oxidativo** del medio condicionado de **hUCESC** sobre las **PC12 diferenciadas a células neuríticas** sometidas a H2O2





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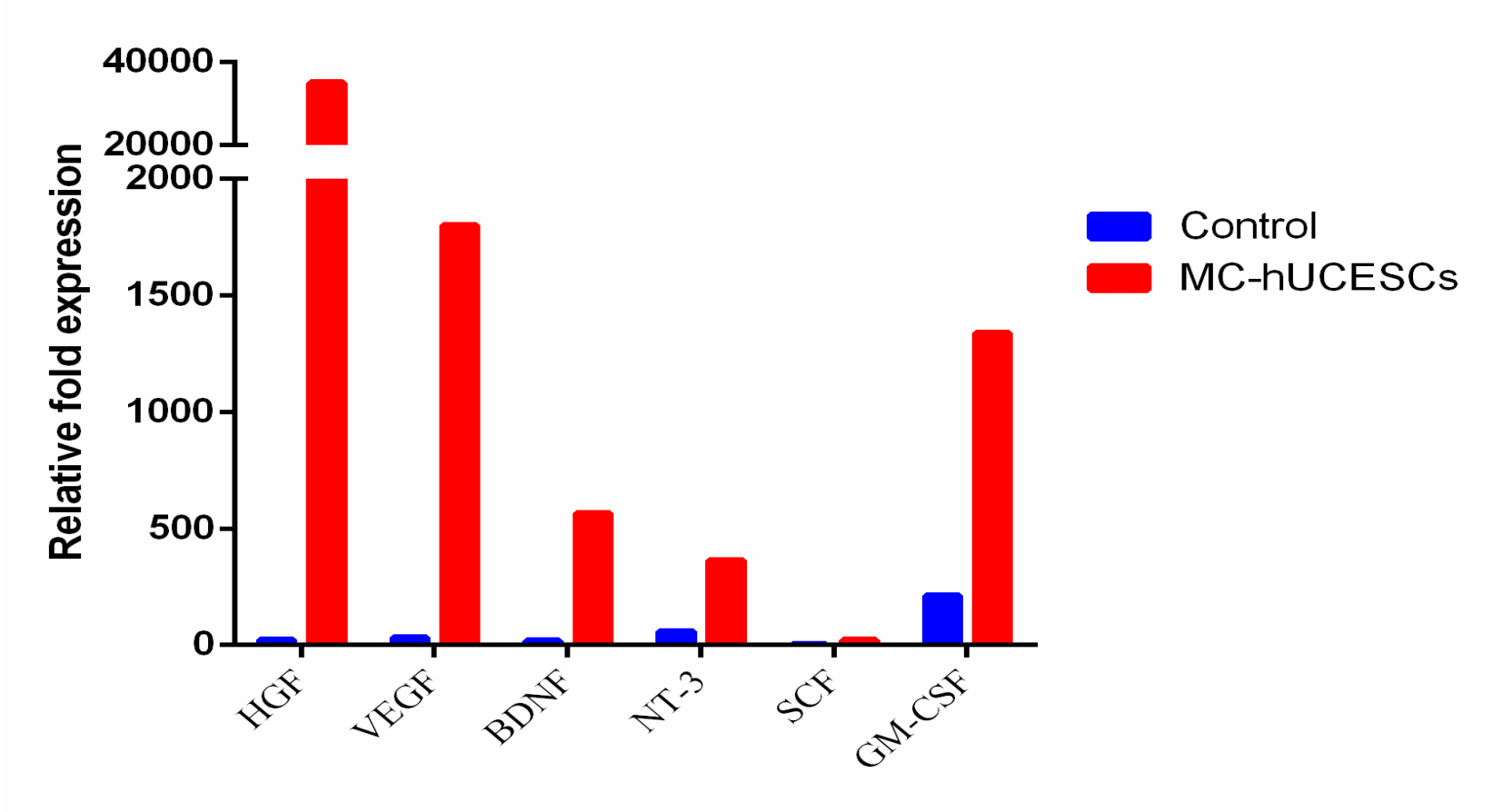
Identificación de moléculas neurotróficas en el medio condicionado de las hUCESCs



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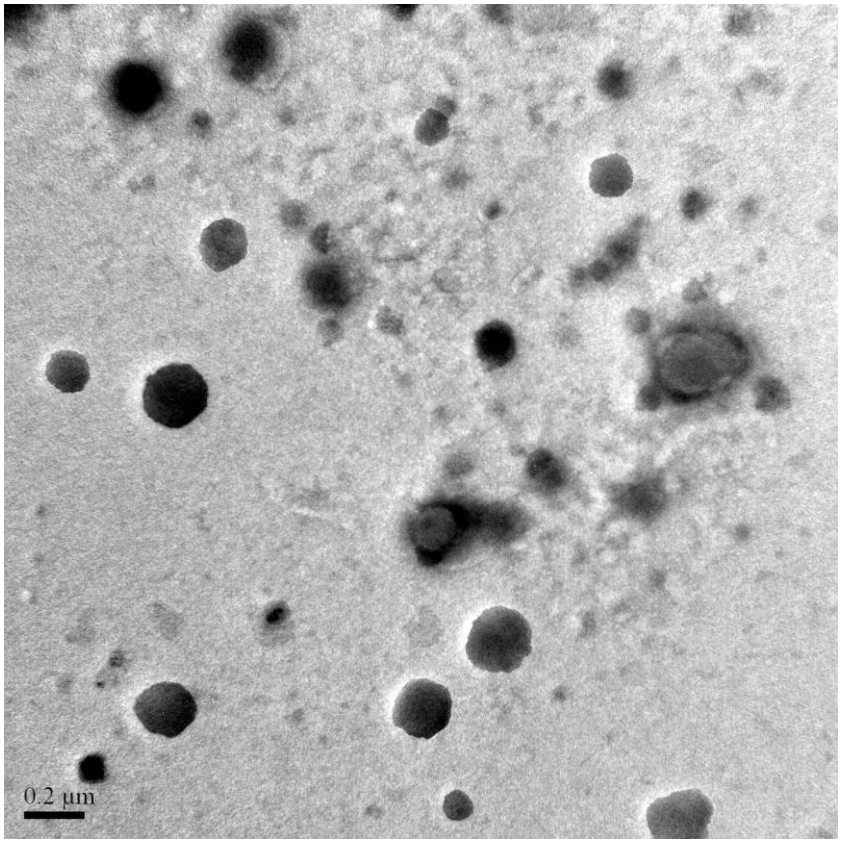
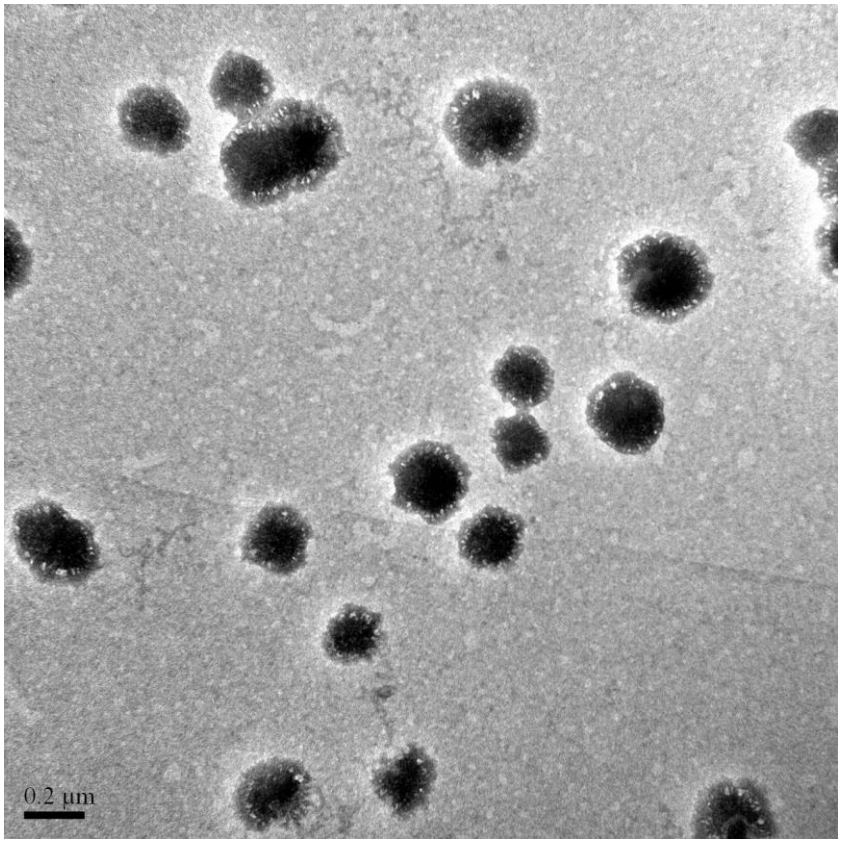
Exosomas de hUCESCs





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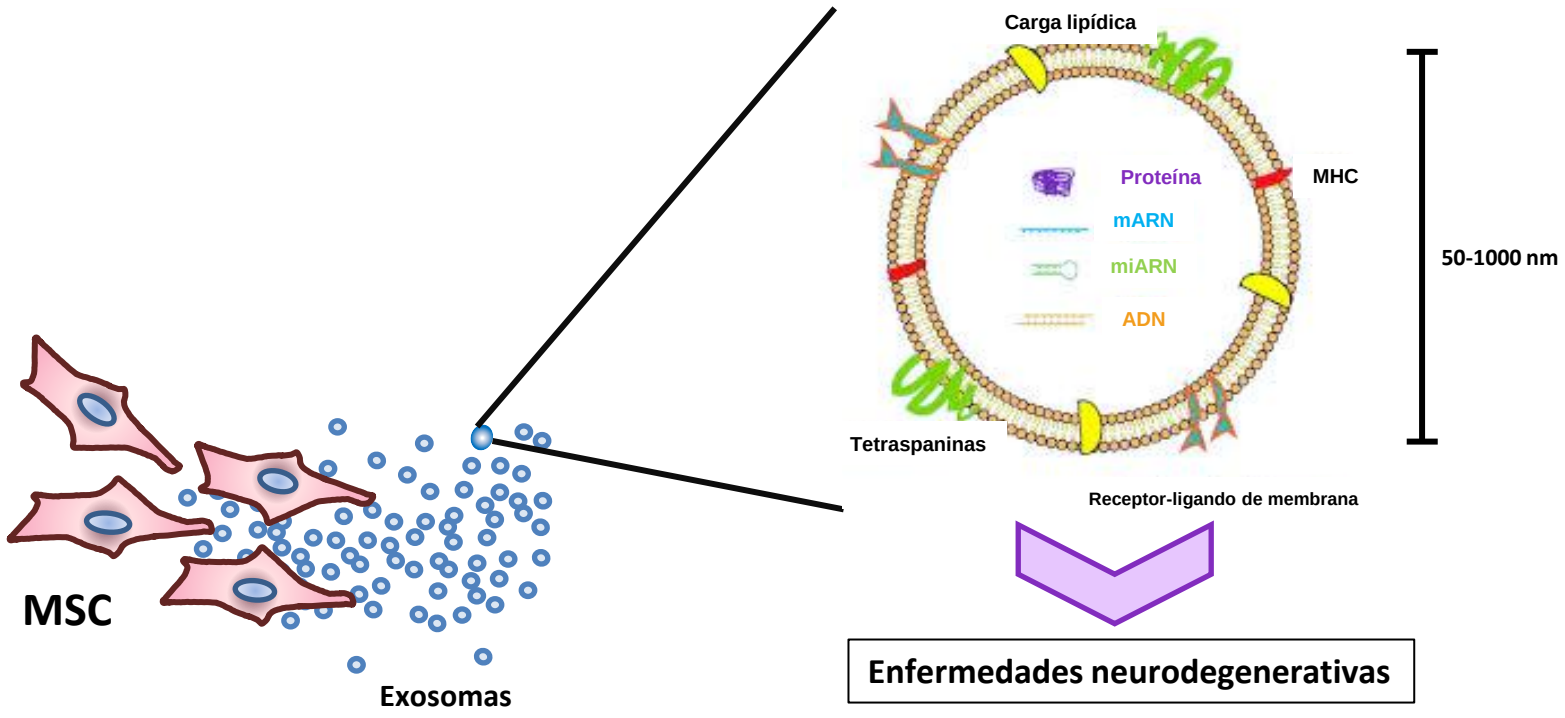

Enfermedades neurodegenerativas

- Alzheimer
- Parkinson
- ELA
- Neuroinflamación
- ACV
- Epilepsia
- Esclerosis múltiple
- Hipoxia - Isquemia
- Lesiones traumáticas

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Cell Death & Differentiation (2021) 28:203–218
https://doi.org/10.1038/s41418-020-0592-2

Cell Death & Differentiation

ARTICLE

Intranasal delivery of mesenchymal stem cell secretome repairs the brain of Alzheimer's mice

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www.jove.com/es/v/10215/compound-administration-rodents-intranasal

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Ensayos clínicos actuales de Células madre y exosomas (Jeyaraman y cols. Heliyon 2023)

Sl. No	NCT Number	Title	Status	Interventions	Locations
1	NCT02833792	Allogeneic Human Mesenchymal Stem Cells for Alzheimer's Disease	Recruiting	BM-MSCs	USA
2	NCT04855955	Autologous Human Adipose-Derived Mesenchymal Stem Cells in Alzheimer's Disease	Available	AD-MSCs	USA
3	NCT02600130	Allogeneic Human Mesenchymal Stem Cell Infusion Versus Placebo in Patients With Alzheimer's Disease	Active, not recruiting	BM-MSCs	USA
4	NCT04040348	Alzheimer's Disease Stem Cells Multiple Infusions	Recruiting	BM-MSCs	USA
5	NCT02672306	Safety and Exploratory Efficacy Study of UCMSCs in Patients With Alzheimer's Disease	Unknown status	UC-MSCs	China
6	NCT03724136	Alzheimer's Autism and Cognitive Impairment Stem Cell Treatment Study	Recruiting	BM-MSCs	UAE
7	NCT01547689	Safety and Efficiency of Umbilical cord-derived Mesenchymal Stem Cells(UC-MSC) in Patients With Alzheimer's Disease	Unknown status	UC-MSCs	China
8	NCT01297218	The Safety and The Efficacy Evaluation of NEUROSTEM®-AD in Patients With Alzheimer's Disease	Completed	UC-MSCs	Korea
9	NCT02054208	Safety and Exploratory Efficacy Study of NEUROSTEM® Versus Placebo in Patients With Alzheimer's Disease	Completed	UC-MSCs	Korea
10	NCT04388982	the Safety and the Efficacy Evaluation of Allogenic Adipose MSC-Exos in Patients With Alzheimer's Disease	Recruiting	MSC Exos	China
11	NCT04482413	Study to Evaluate the Safety and Efficacy of AstroStem in the Treatment of Alzheimer's Disease	Not yet recruiting	AD-MSCs	USA
12	NCT03117738	A Study to Evaluate the Safety and Efficacy of AstroStem in the Treatment of Alzheimer's Disease	Completed	AD-MSCs	USA
13	NCT04954534	Exploratory Efficacy Study of NEUROSTEM® in Subjects Who Control Group of NEUROSTEM®	Not yet recruiting	UC-MSCs	Korea
14	NCT03172117	Follow-up Study of Safety and Efficacy in Subjects Who Completed NEUROSTEM® Phase-I/IIa Clinical Trial.	Recruiting	UC-MSCs	Korea
15	NCT01696591	The Long-Term Safety and Efficacy Follow-Up Study of Subjects Who Completed the Phase I Clinical Trial of NEUROSTEM®-AD	Unknown status	AD-MSCs	KOREA
16	NCT03297177	Autologous Stem/Stromal Cells in Neurological Disorders and Disease	Not yet recruiting	ADMSCs	USA
17	NCT04684602	Mesenchymal Stem Cells for the Treatment of Various Chronic and Acute Conditions	Recruiting	ADMSCs	USA
18	NCT00874783	Development of iPS From Donated Somatic Cells of Patients With Neurological Diseases	Recruiting	iPSCs	Israel
19	NCT04388982	The Safety and the Efficacy Evaluation of Allogenic Adipose MSC-Exos in Patients With Alzheimer's Disease	Recruiting	ADSC-Exos	China

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Aplicación vía nasal Secretoma / EV

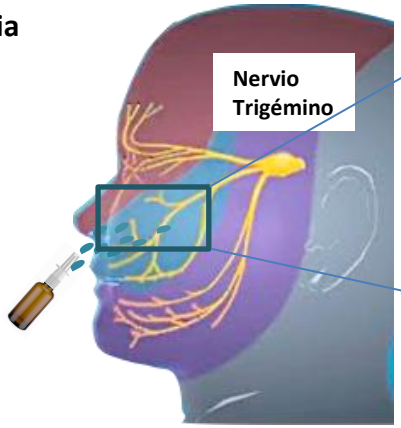
Potenciadores de absorción

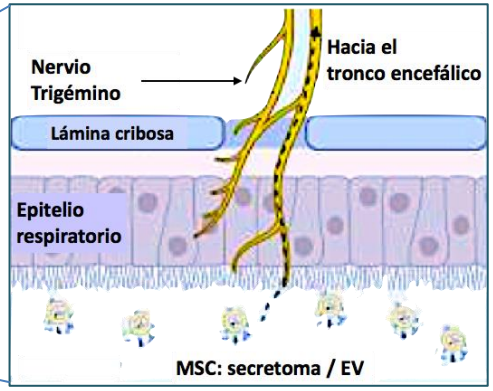
Polímeros mucoadhesivos

Formas de dosificación aplicación nasal

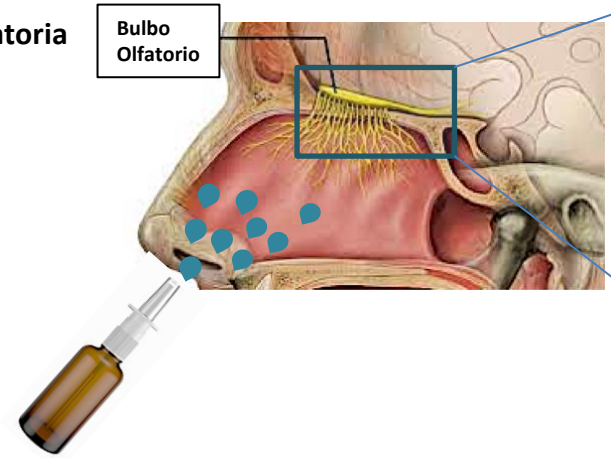
- Líquido
- Semisólido
- Particulado

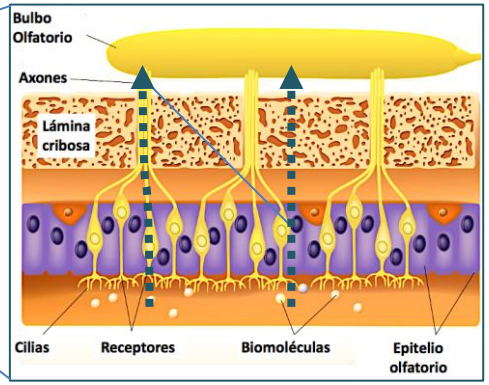
Vía Respiratoria





Vía Olfatoria





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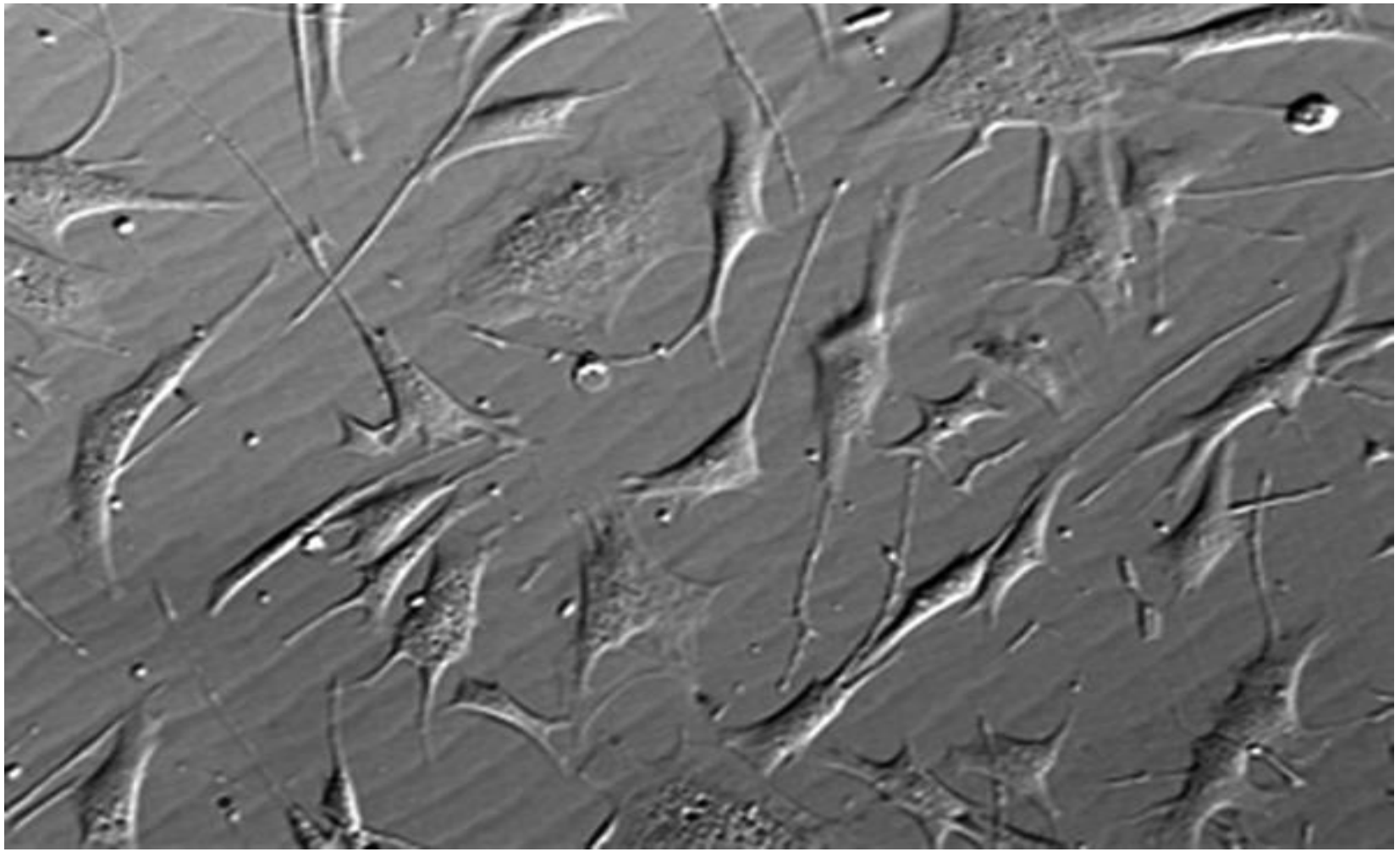
CÉLULAS MADRE MESENQUIMALES



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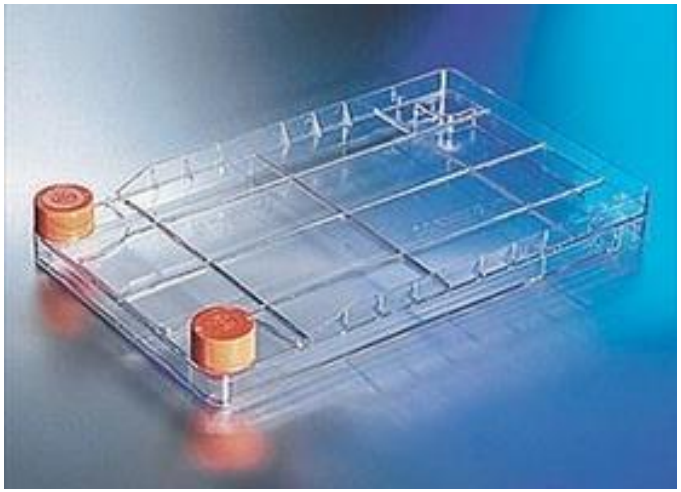
Sala blanca – estandarización de la producción

30 ml

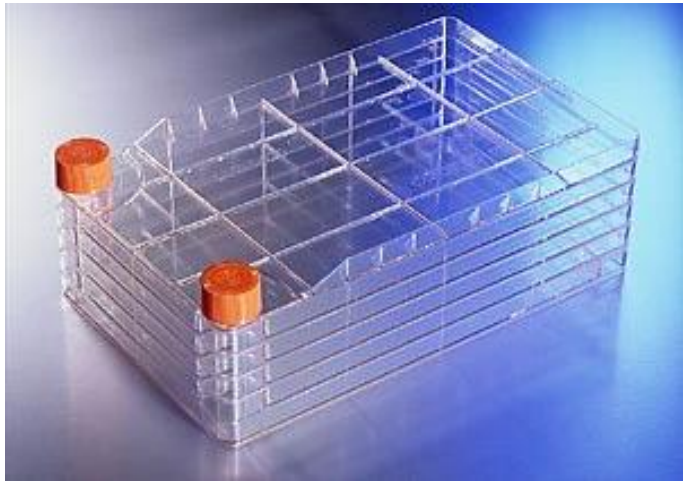
18 ml

636 cm^2



58 ml

3.180 cm^2



288 ml

Validación de las condiciones de producción

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Industrialización


RETHINK
REIMAGINE
REINVENT
DISRUPT

Secretoma de las hUCESC:

- Un cambio de paradigma terapéutico.
- Una propuesta disruptiva para una nueva medicina.


Fundación
Hospital de Jove
Científicos Españoles Regeneran Córneas Ulceradas, con Células Madre Uterinas.
Gijón
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