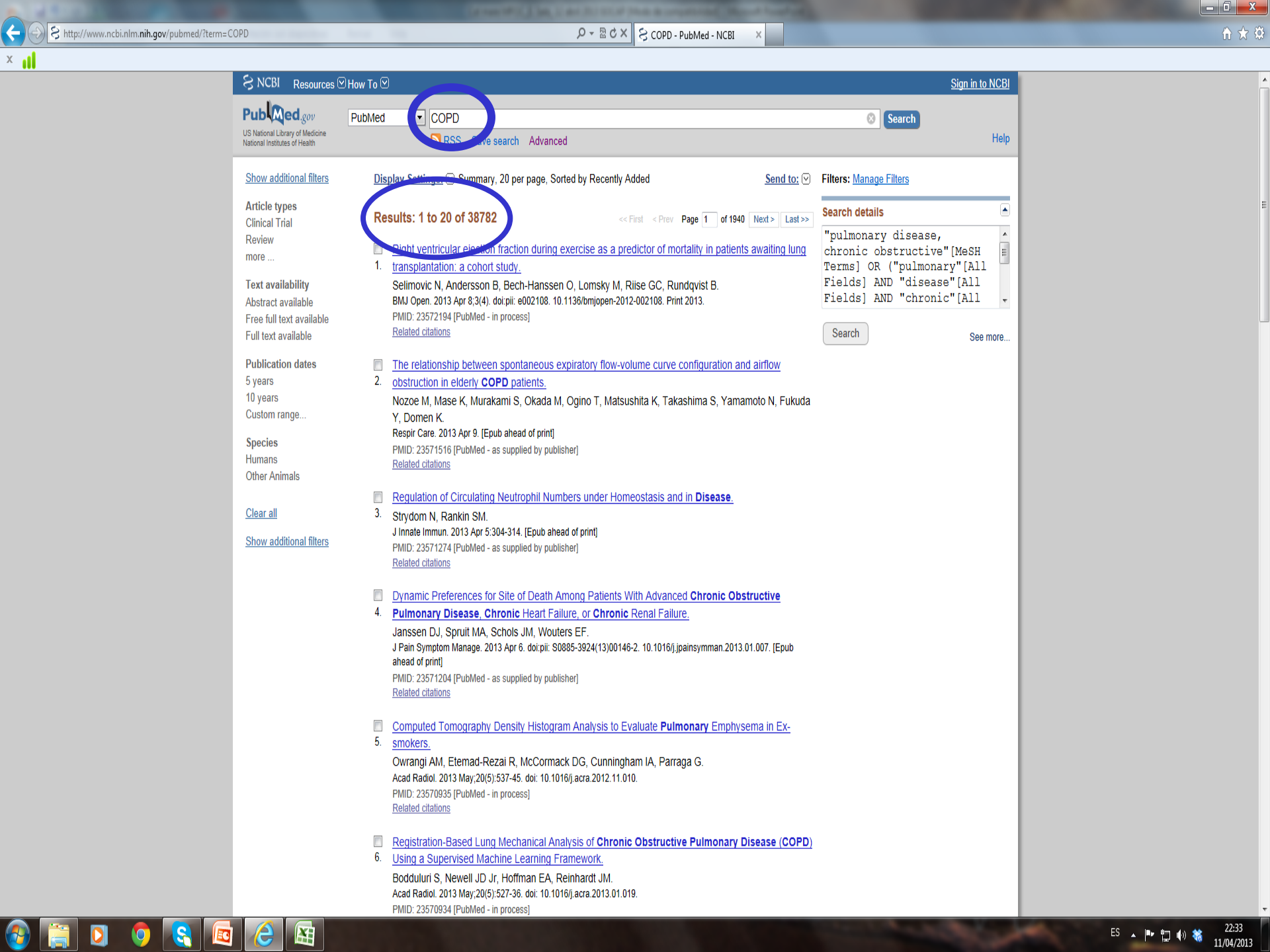
Cèl.lules mare a la Malaltia Pulmonar Obstructiva Crònica

Ernest Sala
Servei de Pneumologia
Hospital Son Espases
Mallorca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Results: 1 to 20 of 38782
<< First < Prev Page 1 of 1940 Next > Last >>
1. Right ventricular ejection fraction during exercise as a predictor of mortality in patients awaiting lung transplantation: a cohort study.
Selimovic N, Andersson B, Bech-Hanssen O, Lomsky M, Riise GC, Rundqvist B.
BMJ Open. 2013 Apr 8;3(4). doi:pii: e002108. 10.1136/bmjopen-2012-002108. Print 2013.
PMID: 23572194 [PubMed - in process]
Related citations
2. The relationship between spontaneous expiratory flow-volume curve configuration and airflow obstruction in elderly COPD patients.
Nozoe M, Mase K, Murakami S, Okada M, Ogino T, Matsushita K, Takashima S, Yamamoto N, Fukuda Y, Domen K.
Respir Care. 2013 Apr 9. [Epub ahead of print]
PMID: 23571516 [PubMed - as supplied by publisher]
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3. Regulation of Circulating Neutrophil Numbers under Homeostasis and in Disease.
Strydom N, Rankin SM.
J Innate Immun. 2013 Apr 5:304-314. [Epub ahead of print]
PMID: 23571274 [PubMed - as supplied by publisher]
Related citations
4. Dynamic Preferences for Site of Death Among Patients With Advanced Chronic Obstructive Pulmonary Disease, Chronic Heart Failure, or Chronic Renal Failure.
Janssen DJ, Spruit MA, Schols JM, Wouters EF.
J Pain Symptom Manage. 2013 Apr 6. doi:pii: S0885-3924(13)00146-2. 10.1016/j.jpainsymman.2013.01.007. [Epub ahead of print]
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Related citations
5. Computed Tomography Density Histogram Analysis to Evaluate Pulmonary Emphysema in Ex-smokers.
Owrangi AM, Etemad-Rezai R, McCormack DG, Cunningham IA, Parraga G.
Acad Radiol. 2013 May;20(5):537-45. doi: 10.1016/j.acra.2012.11.010.
PMID: 23570935 [PubMed - in process]
Related citations
6. Registration-Based Lung Mechanical Analysis of Chronic Obstructive Pulmonary Disease (COPD) Using a Supervised Machine Learning Framework.
Bodduluri S, Newell JD Jr, Hoffman EA, Reinhardt JM.
Acad Radiol. 2013 May;20(5):527-36. doi: 10.1016/j.acra.2013.01.019.
PMID: 23570934 [PubMed - in process]
Search details
"pulmonary disease, chronic obstructive"[MeSH Terms] OR ("pulmonary"[All Fields] AND "disease"[All Fields] AND "chronic"[All
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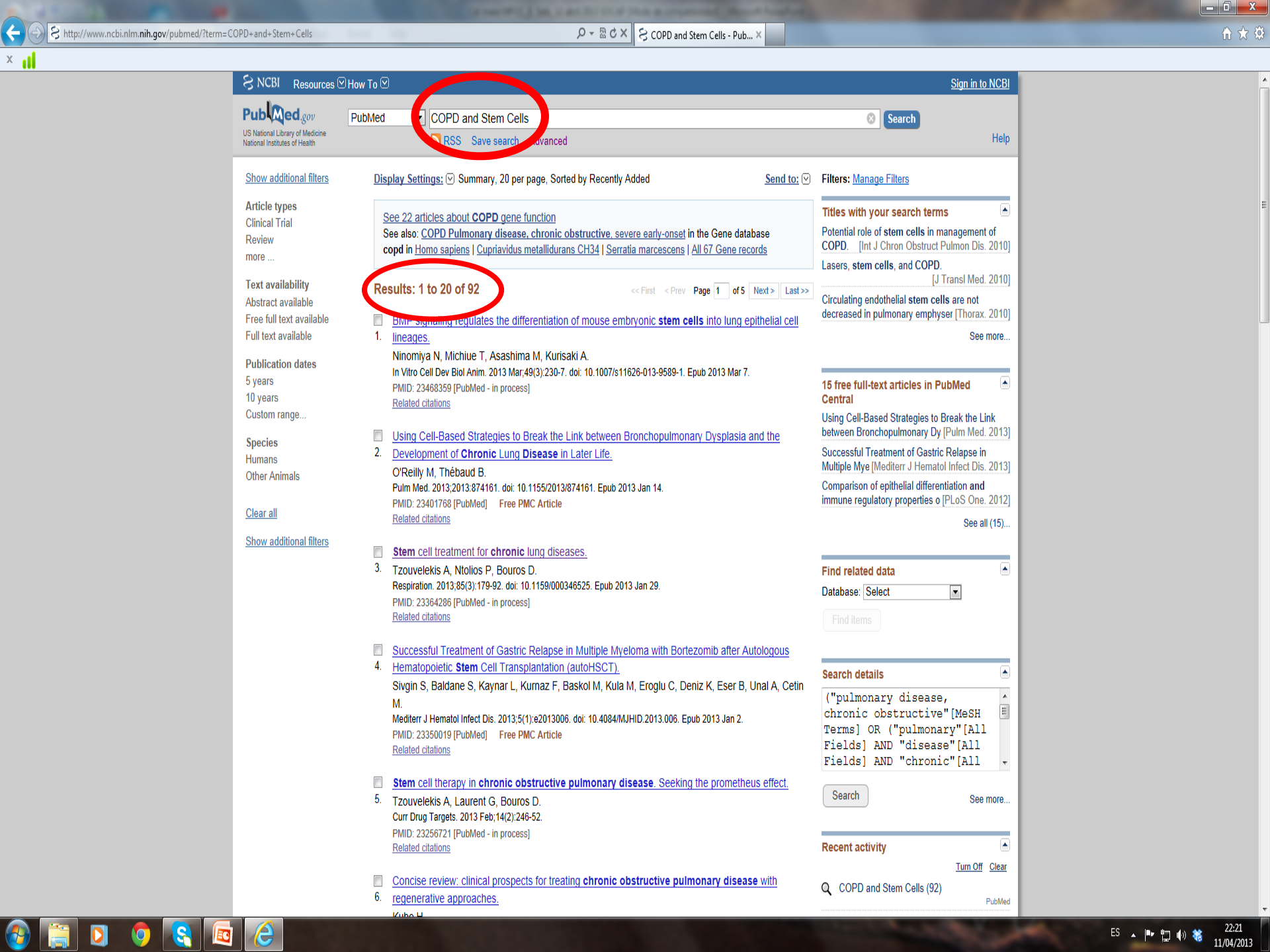
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See also: COPD Pulmonary disease, chronic obstructive, severe early-onset in the Gene database
copd in Homo sapiens | Cupriavidus metallidurans CH34 | Serratia marcescens | All 67 Gene records
Results: 1 to 20 of 92
<< First < Prev Page 1 of 5 Next > Last >>
1. BMP signaling regulates the differentiation of mouse embryonic stem cells into lung epithelial cell lineages.
Ninomiya N, Michiue T, Asashima M, Kurisaki A.
In Vitro Cell Dev Biol Anim. 2013 Mar;49(3):230-7. doi: 10.1007/s11626-013-9589-1. Epub 2013 Mar 7.
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Related citations
2. Using Cell-Based Strategies to Break the Link between Bronchopulmonary Dysplasia and the Development of Chronic Lung Disease in Later Life.
O'Reilly M, Thébaud B.
Pulm Med. 2013;2013:874161. doi: 10.1155/2013/874161. Epub 2013 Jan 14.
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Related citations
3. Stem cell treatment for chronic lung diseases.
Tzouvelekis A, Ntolios P, Bouros D.
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PMID: 23364286 [PubMed - in process]
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4. Successful Treatment of Gastric Relapse in Multiple Myeloma with Bortezomib after Autologous Hematopoietic Stem Cell Transplantation (autoHSCT).
Sivgin S, Baldane S, Kaynar L, Kurnaz F, Baskol M, Kula M, Eroglu C, Deniz K, Eser B, Unal A, Cetin M.
Mediterr J Hematol Infect Dis. 2013;5(1):e2013006. doi: 10.4084/MJHID.2013.006. Epub 2013 Jan 2.
PMID: 23350019 [PubMed] Free PMC Article
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5. Stem cell therapy in chronic obstructive pulmonary disease. Seeking the prometheus effect.
Tzouvelekis A, Laurent G, Bouros D.
Curr Drug Targets. 2013 Feb;14(2):246-52.
PMID: 23256721 [PubMed - in process]
Related citations
6. Concise review: clinical prospects for treating chronic obstructive pulmonary disease with regenerative approaches.
Titles with your search terms
Potential role of stem cells in management of COPD. [Int J Chron Obstruct Pulmon Dis. 2010]
Lasers, stem cells, and COPD. [J Transl Med. 2010]
Circulating endothelial stem cells are not decreased in pulmonary emphyser [Thorax. 2010]
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Desenvolupament de la xerrada

- **<u>Necessitat</u>:** Fan falta nous tractaments a la MPOC?
- **<u>Expectativa</u>:** Les cèl.lules mare pel tractament de les malalties respiratòries:
  - Cèl. Mare Exògenes
  - Cèl. Mare endògenes (pulmonars)
- **<u>Realitat a la MPOC</u>:** Evidència del tractament de la MPOC amb cèl.lules mare
- **<u>Més futur</u>:** Factors paracrins de les MSCs
- **Sumari / Conclusions**

Necessitat de nous tractaments a la MPOC

- Mortalitat de la MPOC en augment (3ª causa 2030)
- No hi ha tractaments que redueixin la mortalitat (teràpia amb O2, abandonament tabac)
- Prevalença 10.2% en població adulta

Global Initiative for Chronic Obstructive Lung Disease

GesEPOC guía española de la EPOC

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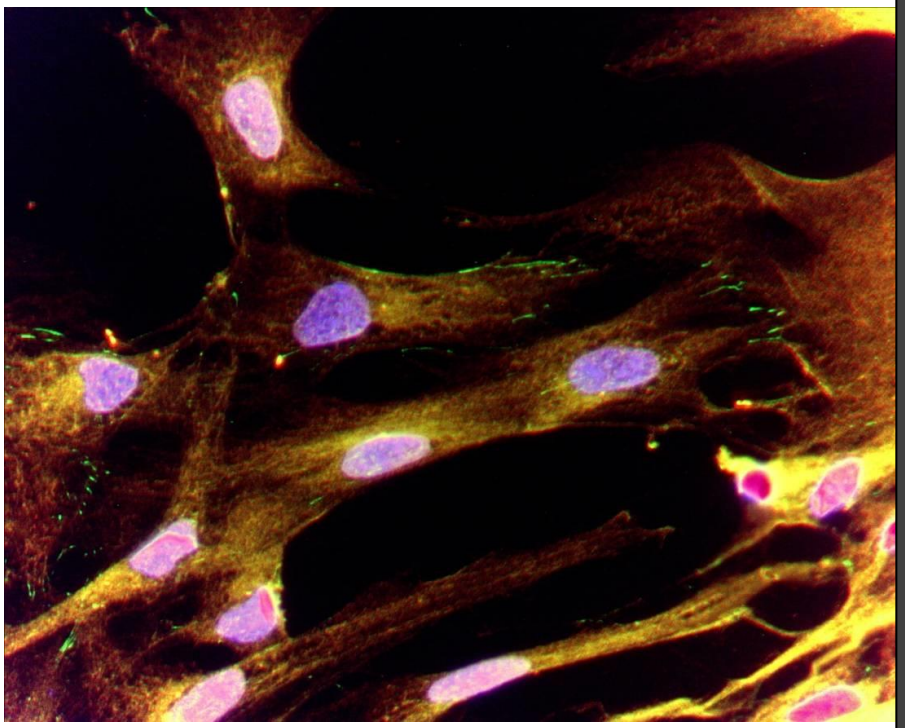
- **Sumari / Conclusions**

Definició de (*adult*) *Stem Cells*



Cèl.lules mare mesenquimals (MSCs)

Cèl.lules mare residents (pulmó)

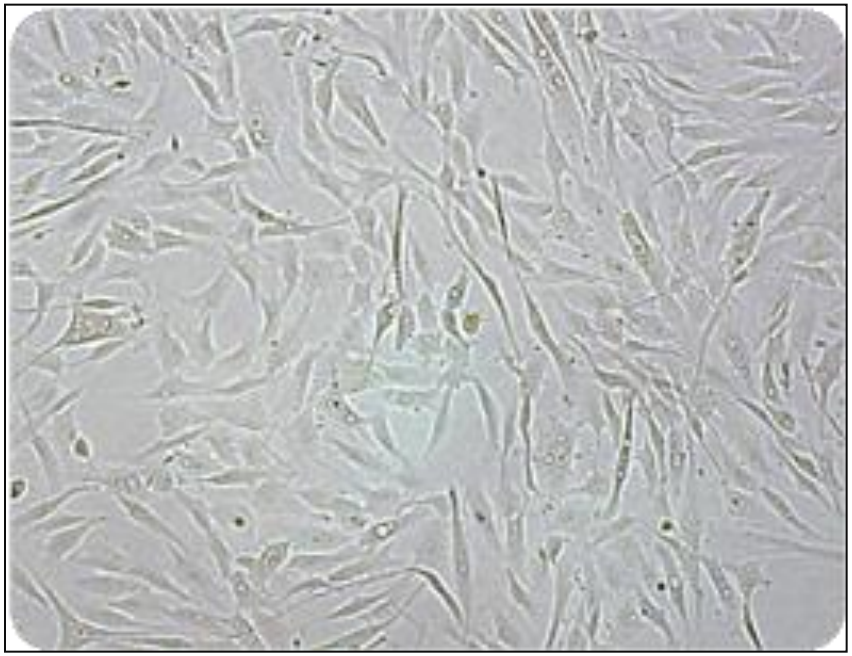
Weiss DJ et al. Proc Am Thorac Soc 2011; 8, 223-272

Minimal criteria for defining multipotent mesenchymal stromal cells (MSCs): the International Society for Cellular Therapy position statement

Dominici M et al. *Cytotherapy* 2006; 8:315–317

- MSCs term first coined in 1991
- The concept of a nonhematopoietic SC in BM did not resonate worldwide until 1999 (work of Pittenger et al.)

- Plastic adherence in standard tissue culture conditions
- Expression of CD73, CD90, and CD105
- No expression of CD11b, CD14, CD19, CD34, CD45, CD79, HLA-DR
- Differentiation *in vitro* to osteoblasts, adipocytes, and chondroblasts



Fonts de MSCs

Multiple tissues including adipose tissue, skeletal muscle, synovium, spleen, thymus, blood, lung, fetal blood and amniotic fluid. By far the best characterized source of MSC is the bone marrow.

PARAMETRO	Médula ósea	Tejido adiposo
Éxito de aislamiento	100%	100%
Formación de monocapa adherente	4 - 5 días	4 - 5 días
UFC-F obtenidas en la monocapa adherente (número)	83 ± 61	557± 673
Capacidad de diferenciación osteogénica	71.4%	78.8%
Capacidad de diferenciación adipogénica	100%	94%
Capacidad de diferenciación condrogénica	100%	100%
Expresión antígenos (%)		
CD44	97.5 ± 5.1	99.8 ± 0.2
CD73	90.0 ± 20.0	99.6 ± 0.5
CD90	99.1 ± 2.5	99.6 ± 0.2
CD105	88.1 ± 7.4	90.4 ± 5.9
HLA I	95.2 ± 6.0	98.8 ± 2.8

Adaptado de Kern S et al. 2006 / Wagner W et al. 2005

Avantatges de les MSCs per a la teràpia cel.lular

- Ability to home areas of injury, with low percentage of engraftment (paracrine effects)
- "in vitro" immunomodulatory, anti-inflammatory and non-immunogenic properties:
  - ✓ Secrete anti-inflammatory cytokines, growth factors, PGE2
  - ✓ Inhibit the proliferation and function of a broad range of immune cells, including T cells, B cells, natural killer (NK) cells and dendritic cells (DCs) in in vitro models systems
  - ✓ Used as allogeneic graft as they lack various major histocompatibility complex and costimulatory cell-surface antigens
- Vehicles for delivering therapeutic agents

Hare MJ et al. J Am Coll Cardiol 2009
Weiss DJ et al. Proc Am Thorac Soc 2011

- Reduce cell apoptosis and have anti-protease activity

Guan XJ et al. J Cell Biochem 2013

Potencial de les MSCs en la MPOC

Inflamació pulmonar (i sistèmica): macròfags, neutròfils, cèl. epitelials…

Estrés oxidatiu, proteasses

DANY PARÈNQUIMA PULMONAR

(HIPERSECRECIÓ)

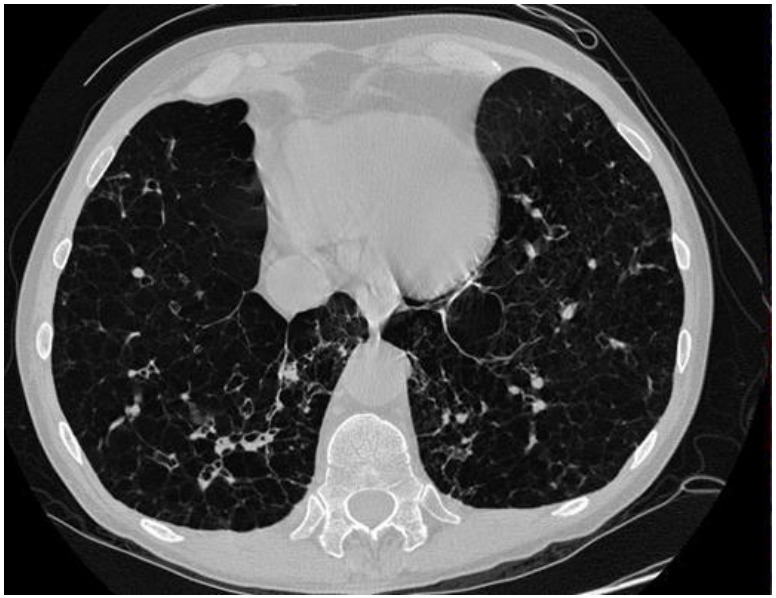
Apoptosi: cèl. epitelials, cèl. endotelials…

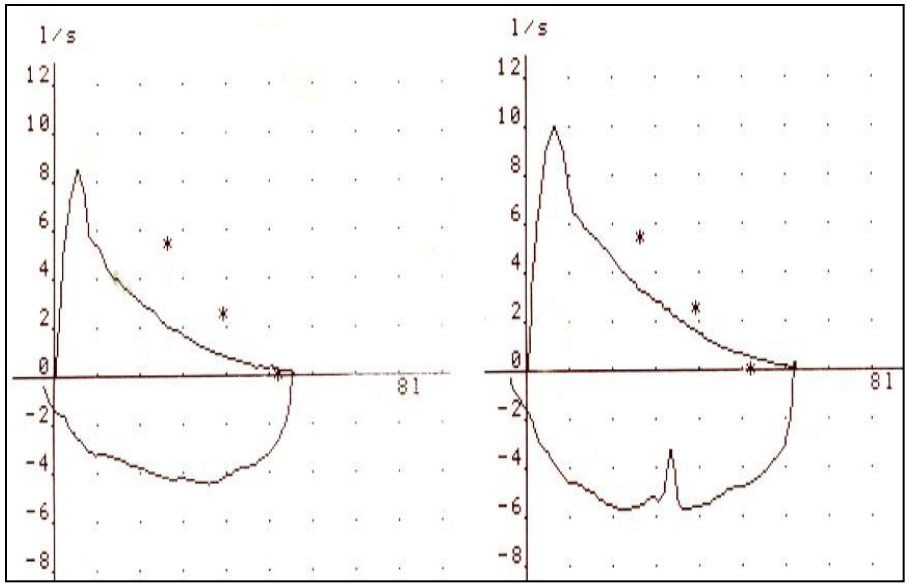
EMFISEMA

Cèl. epitelials, fibroblasts

Fibrosi, inflamació

MALALTIA DE LA PETITA VIA AÈRIA





Evidència de Cèl.lules mare residents (pulmó)

Lab Invest. 2011 Mar;91(3):363-78.

Isolation of alveolar epithelial type II progenitor cells from adult human lungs.
Fujino N, Kubo H, Suzuki T, Ota C, Hegab AE, He M, Suzuki S, Suzuki T, Yamada M, Kondo T, Kato H, Yamaya M.

Source
Department of Advanced Preventive Medicine for Infectious Disease, Tohoku University Graduate School of Medicine, Aobaku, Sendai, Japan.

Plos One 2012;7(5):e35639. Epub 2012 May 2.

Comparison of epithelial differentiation and immune regulatory properties of mesenchymal stromal cells derived from human lung and bone marrow.
Ricciardi M, Malpeli G, Bifari F, Bassi G, Pacelli L, Nwabo Kamdje AH, Chilosi M, Krampera M.

Source
Stem Cell Research Laboratory, Section of Hematology, Department of Medicine, University of Verona, Verona, Italy.

Evidència de Cèl.lules mare residents (pulmó)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 12, 2011 VOL. 364 NO. 19

Evidence for Human Lung Stem Cells

Jan Kajstura, Ph.D., Marcello Rota, Ph.D., Sean R. Hall, Ph.D., Toru Hosoda, M.D., Ph.D., Domenico D'Amario, M.D., Fumihiro Sanada, M.D., Hanqiao Zheng, M.D., Barbara Ogórek, Ph.D., Carlos Rondon-Clavo, M.D., João Ferreira-Martins, M.D., Alex Matsuda, M.D., Christian Arranto, M.D., Polina Goichberg, Ph.D., Giovanna Giordano, M.D., Kathleen J. Haley, M.D., Silvana Bardelli, Ph.D., Hussein Rayatzadeh, M.D., Xiaoli Liu, M.D., Ph.D., Federico Quaini, M.D., Ronglih Liao, Ph.D., Annarosa Leri, M.D., Mark A. Perrella, M.D., Joseph Loscalzo, M.D., Ph.D., and Piero Anversa, M.D.

Barry Stripp, *Nature Medicine 2011*:

My bottom line: until this work independently replicated, clinicians, biotech companies and funding agencies should proceed with utmost caution.

Desenvolupament de la xerrada

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- **Més futur:** Factors paracrins de les MSCs
- **Sumari / Conclusions**

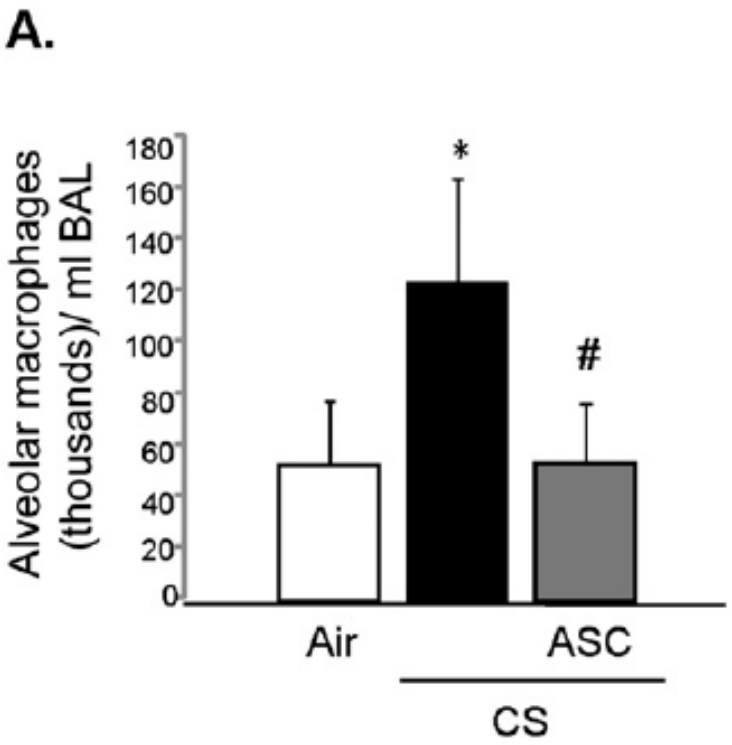
Any de l'estudi	Tipus de Cèl.lules	Model animal	Via adminis.	Resultats	Mecanisme
Shigemura et al. 2006	ADSCs rata	Rata / Elastassa	Tòpica	Millora la reparació (histologia)	Secreció HGF
Shigemura et al. 2006	ADSCs rata	Rata / Elastassa	IV	Disminueix l'apoptosi, reparació de la histologia, millora I.Gasos i tolerància a l'exercici.	Secreció HGF
Zehn et al. 2008	BM-MSCs rata	Rata / papaveína	IV	Disminueix el dany histològic i l'apoptosi de les AEC	No específic Mediadors solubles (?)
Zehn et al. 2010	BM-MSCs rata	Rata / papaveína	IT	Disminueix el dany histològic i es recupera l'expressió de VEGF pulmonar	No específic Mediadors solubles (?)
Katsha et al. 2011	BM-MSCs ratolí	Ratolí / Elastassa	IT	Reducció de: colagen, inflamació i citokines profibròtiques (TNF-a, TGF-b, IL-10)	No específic Mediadors solubles (?)
Huh et al. 2011	BMCs i BM-MSCs rata	Rata / Tabac	IV	Disminueix el dany histològic	
Schweitzer et al. 2011	ADSCs ratolí i humanes	Ratolí / Tabac	IV	Reducció de: colagen, fibrosi, metaloprot., pèrdua de pes i supressió MO	No específic Mediadors solubles (?)

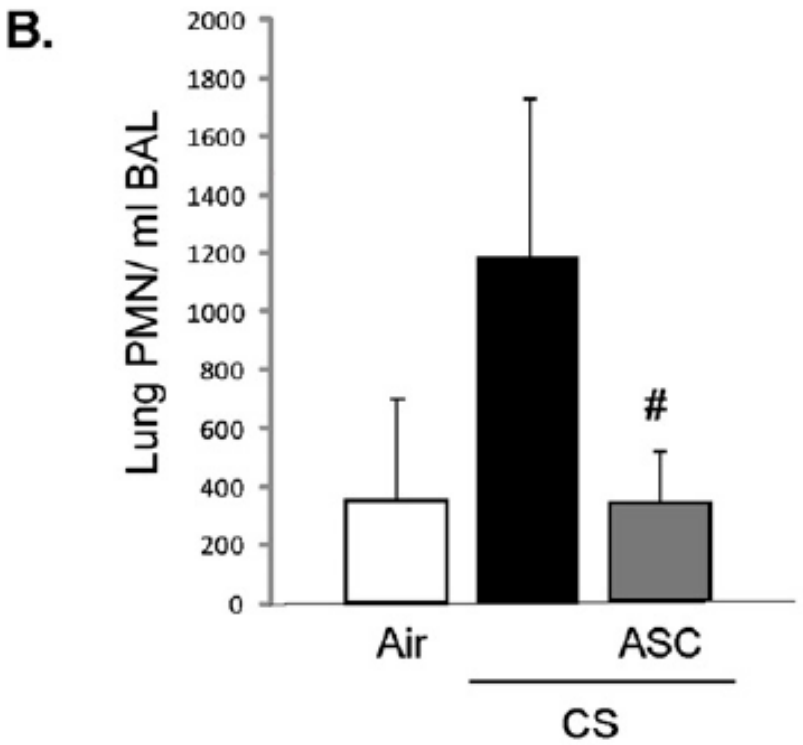
Tzouvelekis A et al. Respiration 2013

Adipose stem cell treatment in mice attenuates lung and systemic injury induced by cigarette smoking

Schweitzer KS et al; Am J Respir Crit Care Med 2011

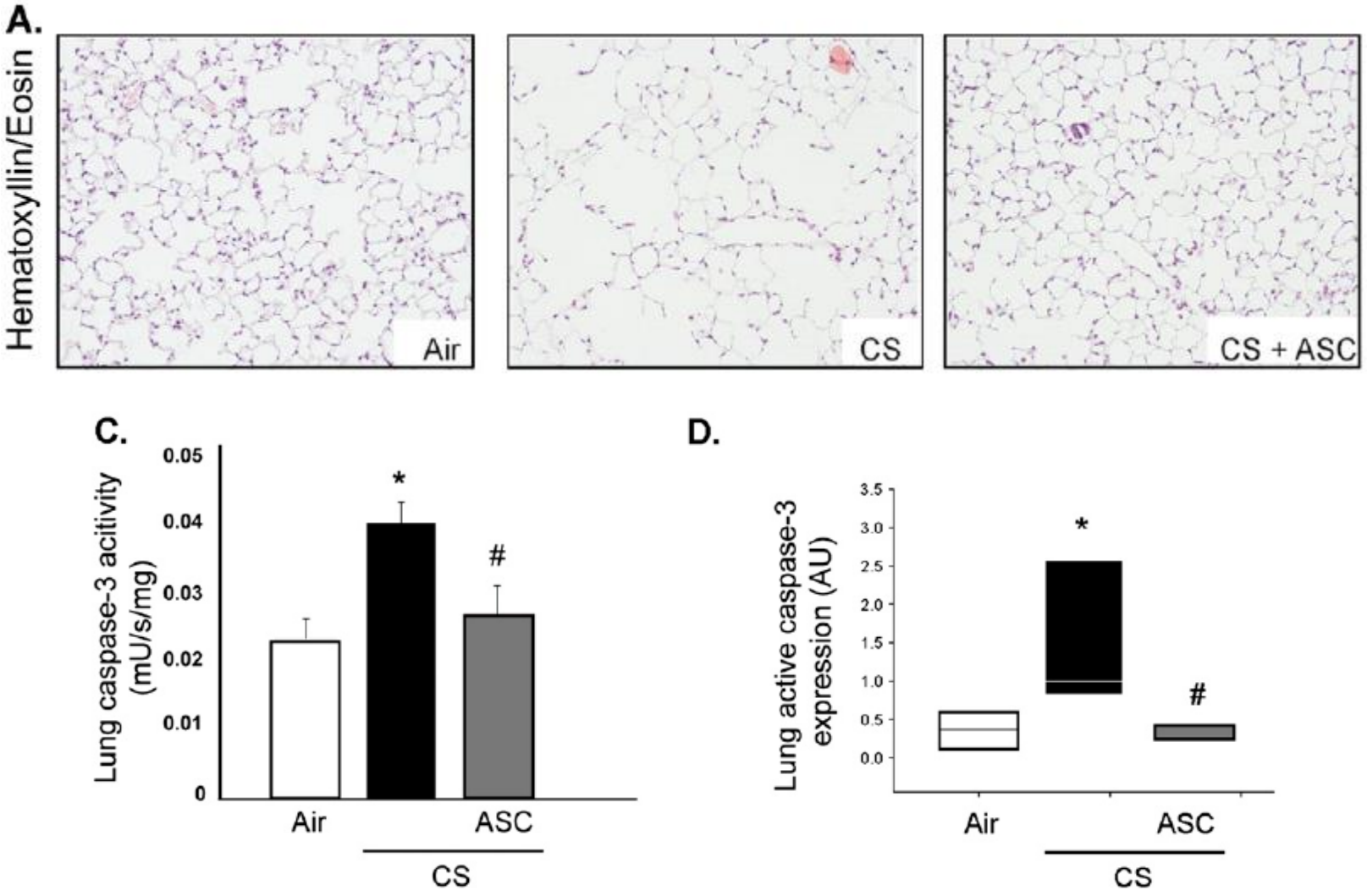
- Male DBA/2J mice were exposed to C. Smoke for 4 months
- Mice and human adipose stem cells (ASC, $3x10^5$ cells, i.v.)
- ASC every 2 weeks last 2 months





Adipose stem cell treatment in mice attenuates lung and systemic injury induced by cigarette smoking

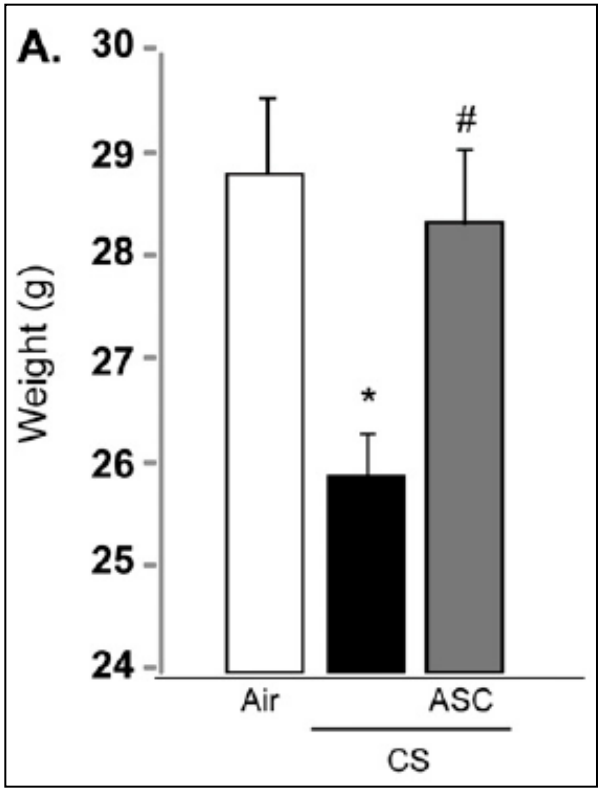
Schweitzer KS et al; Am J Respir Crit Care Med 2011

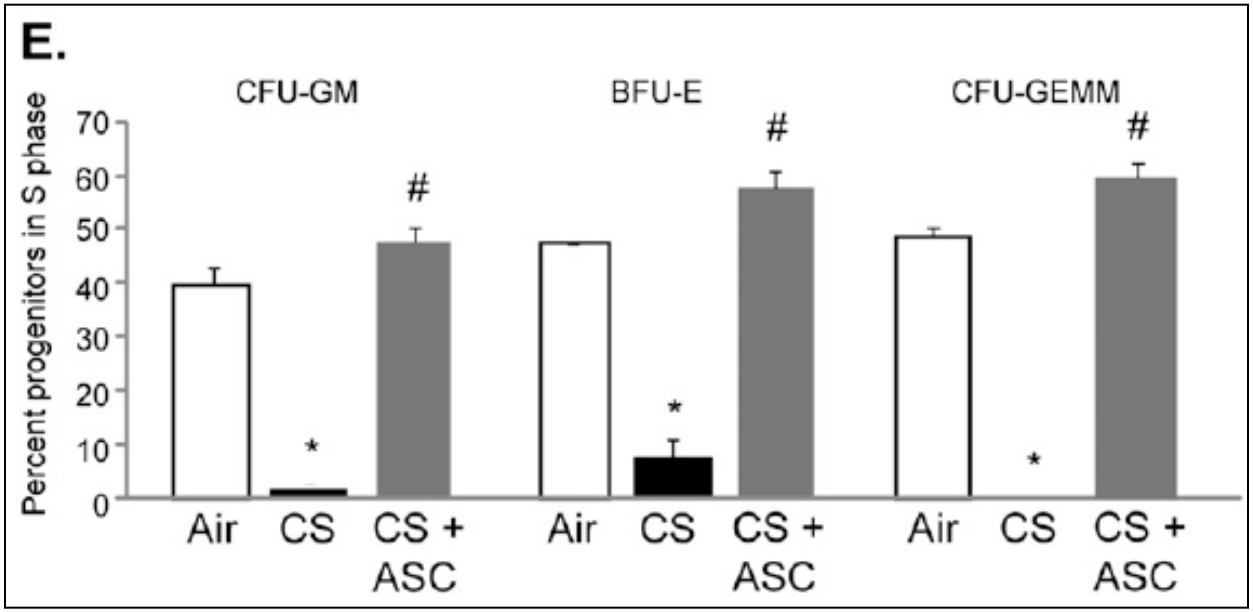


Adipose stem cell treatment in mice attenuates lung and systemic injury induced by cigarrette smoking

Schweitzer KS et al; Am J Respir Crit Care Med 2011

ASC on systemic effects of tobacco smoke





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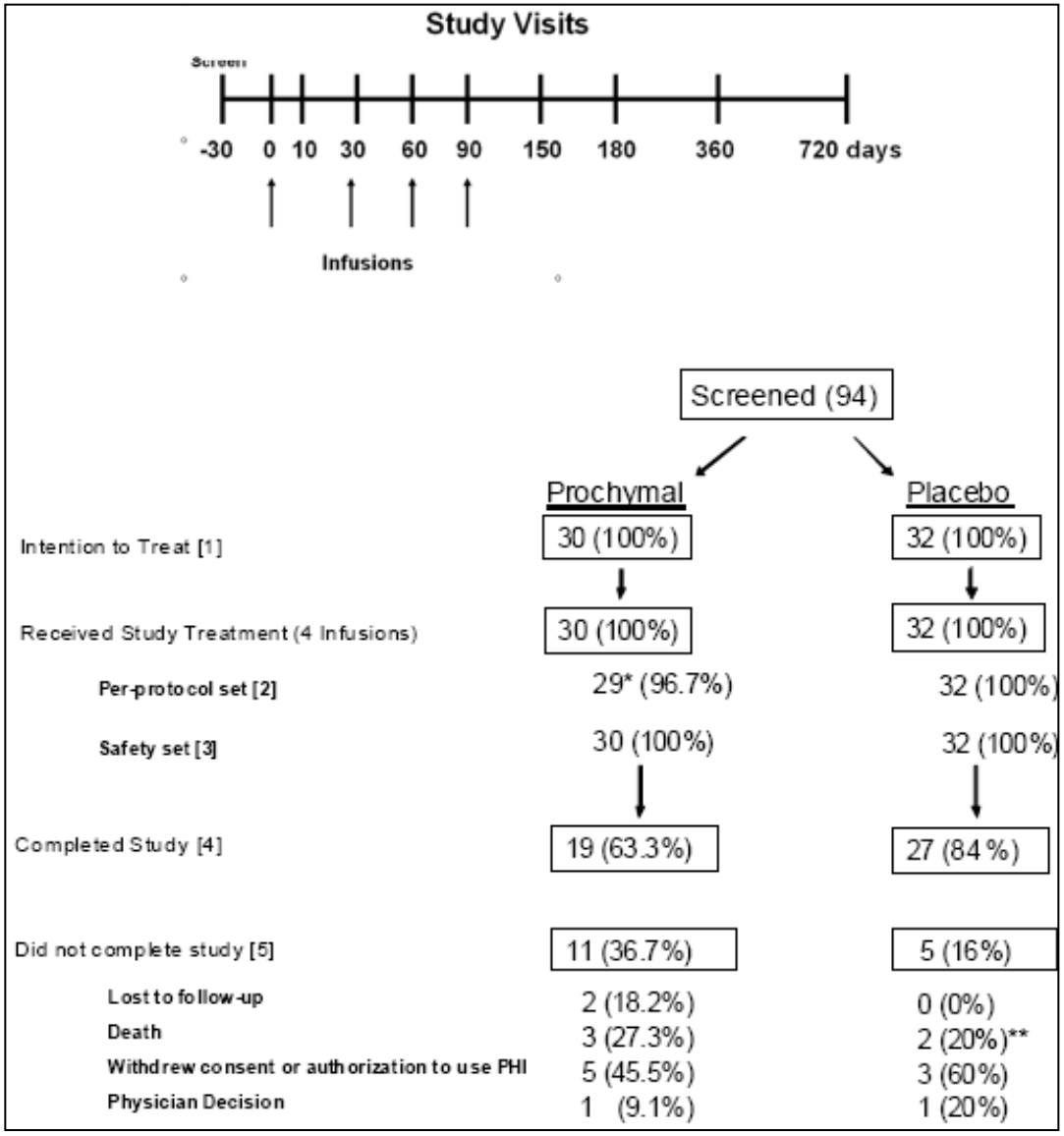
Rank	Status	Study
1	Completed	PROCHYMAL™ (Human Adult Stem Cells) for the Treatment of Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD) **Conditions:** Pulmonary Disease, Chronic Obstructive; Pulmonary Emphysema; Chronic Bronchitis **Interventions:** Drug: PROCHYMAL™; Drug: Placebo
2	Completed Has Results	Safety Study of Cell Therapy to Treat Chronic Obstructive Pulmonary Disease **Conditions:** Chronic Obstructive Pulmonary Disease; Pulmonary Emphysema **Interventions:** Drug: Stem cells stimulation; Procedure: stem cells collection; Genetic: stem cells infusion
3	Unknown †	Detection of Circulating Endothelial Progenitors Cells (EPCs) in Non-small Cell Lung Cancer (NSCLC) **Conditions:** Non-small Cell Lung Cancer; Chronic Obstructive Pulmonary Disease **Intervention:** Biological: Enumeration of endothelial cell progenitor in peripheral blood by flow cytometry, Endothelial cell progenitor characterization by primary cell cultures
4	Recruiting	Safety and Efficacy of Adipose Derived Stem Cells for Chronic Obstructive Pulmonary Disease **Condition:** Chronic Obstructive Pulmonary Disease **Intervention:** Procedure: Adipose-Derived Stem Cell (ADSC) Therapy
5	Completed	Endothelial Dysfunction in Chronic Obstructive Pulmonary Disease **Conditions:** Chronic Obstructive Pulmonary Disease; Endothelial Dysfunction **Intervention:**
6	Recruiting	Study on Systemic and Airway Biomarkers in Haemopoietic Stem Cell Transplantation **Condition:** Hematological Diseases

A Placebo-Controlled Randomized Trial of Mesenchymal Stem Cells in Chronic Obstructive Pulmonary Disease

Weiss DJ, et al. Chest. 2012 Nov 22. [Epub ahead of print]

Criteris d'inclusió

Pacients entre 40-80a. ; > 10 p/a
FEV1 / FVC < 0.7 ; FEV1 30-70 %
Permesos tots els ttments habituals



A Placebo-Controlled Randomized Trial of Mesenchymal Stem Cells in Chronic Obstructive Pulmonary Disease

Weiss DJ, et al. Chest. 2012 Nov 22. [Epub ahead of print]

Bon perfil de seguretat

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Factores paracrins de les MSCs

Studies reported striking protective effects of MSC therapy despite low engraftment rates, supporting the concept that those protective effects may be largely mediated through production of paracrine mediators (Lee RH, 2009; Ortiz LA, 2007; van Haaften T, 2009; Aslam M, 2009). The identification of those paracrine mediators would allow to overcome technical and practical limitations related to the invasive methods of harvest and low abundance of either stem or progenitor cells that may delay the adoption of them in clinical applications.

- Medio condicionado: proteínas, miRNA, micropartículas, microvesículas, exosomas…

Medio de cultivo

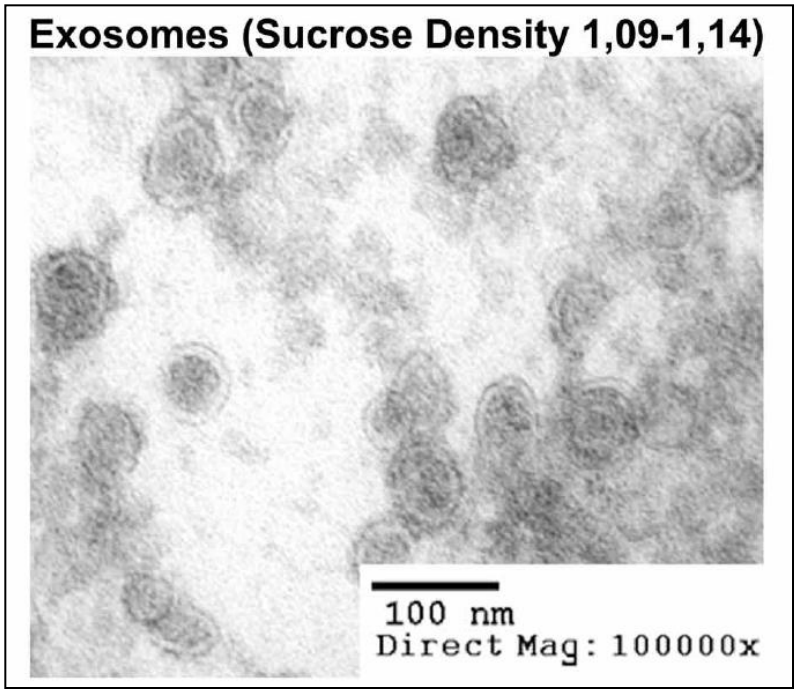
Característiques dels Exosomes

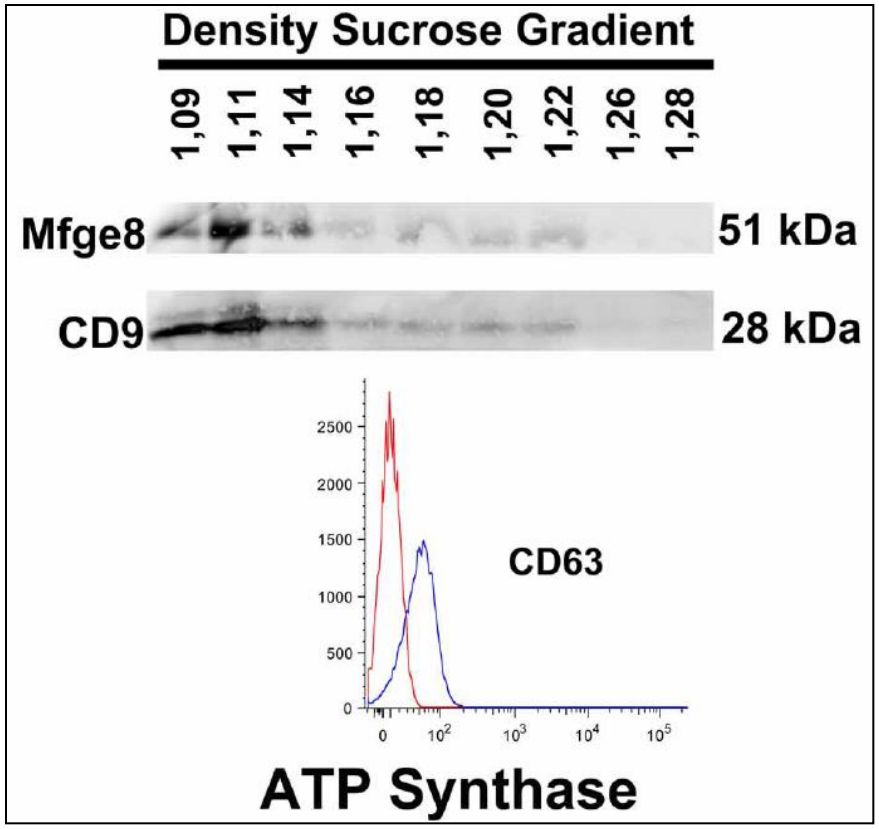
- Tamaño 40-100 nm
- Sedimentan a 100,000 g
- Contienen miRNA y proteínas. Base de datos con información referente al contenido de los exosomas: http://www.exocarta.org/
- Membrana lipídica (Colesterol, Esfingomielina, Ceramida)
- Tetraspaninas (CD 81, CD 63, CD9), Alix, Tsg 101)
- Comunicación célula-célula con múltiples funciones potenciales

Chai Lai R et al. Regen. Med. 2011

Exosomes obtinguts de hMSCs

Differential Expression Of MicroRNA In Mesenchymal Stem Cell Derived Exosomes.
G. DeLuliis, M. Di Giuseppe, D. Phinney, E. Sala, N. Kaminski, L.A. Ortiz



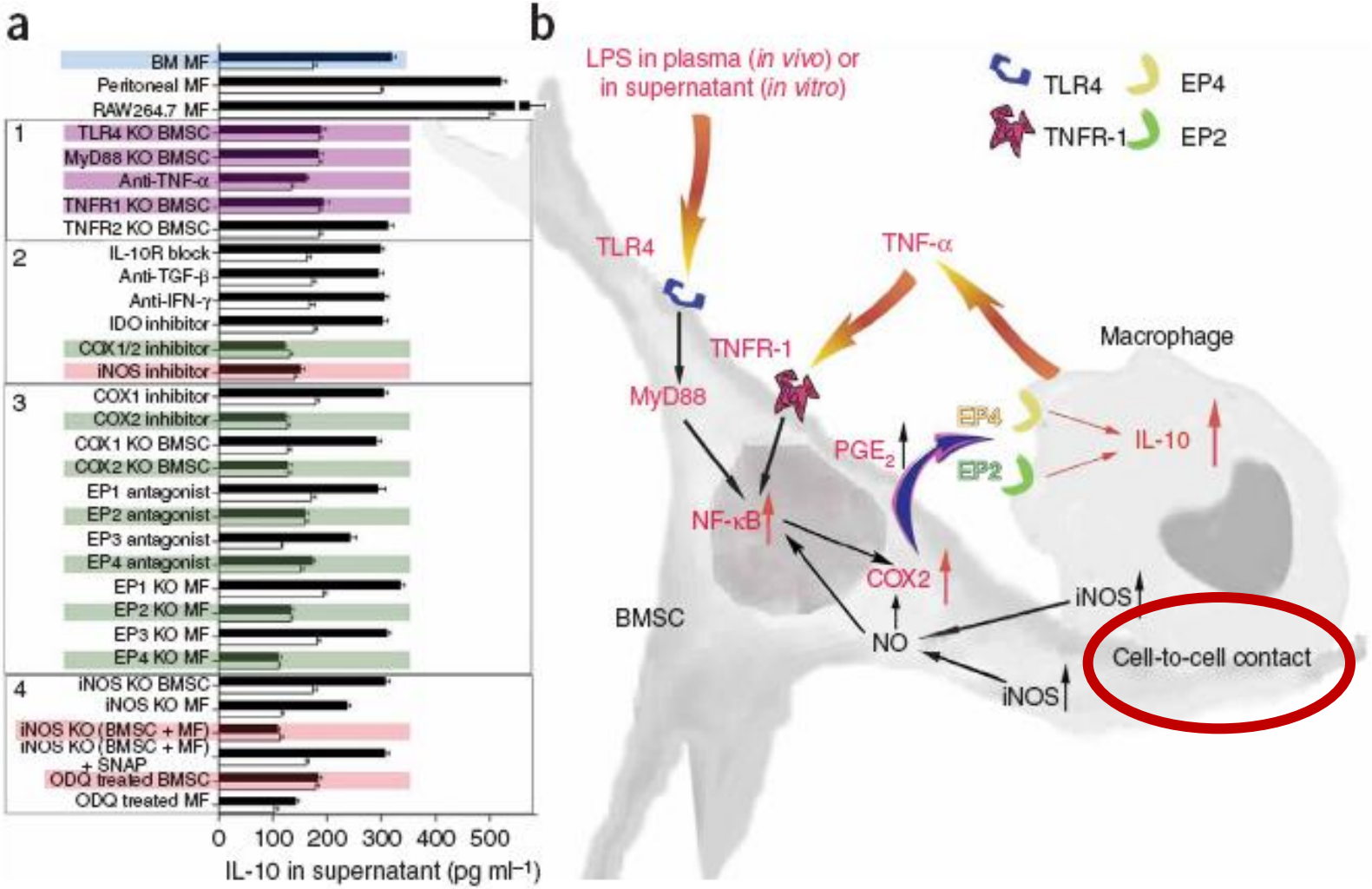


Exosomes vs *Stem cells*

- Reducen el potencial efecto de las células si éstas persisten
- Disminuyen el riesgo de oclusión vascular (pequeño tamaño)
- Protegen el contenido (seleccionable ?) de la degradación
- Se pueden mantener a -20ºC 6 meses
- Pueden ser específicos

Chai Lai R et al. Regen. Med. 2011

Bone marrow stromal cells attenuate sepsis via prostaglandin E_2–dependent reprogramming of host macrophages to increase their interleukin-10 production



Krisztián Németh et al.

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Conclusions

- La teràpia amb Stem Cells (MSCs) podria ser una potencial alternativa (de futur) als tractaments actuals
- Hi ha més preguntes que respostes:
  - Característiques de les MSCs i de les CM residents a la MPOC (patogènia): Tx allogenic / autòleg
  - Com, quan i quant (ttments clínics)
  - Quins són els pacients diana d'aquestes teràpies
- Els exosomes podrien substituir a la cèl.lula en els tractaments, amb certes avantatges