BRN SEMINARS

Scientific workshops to foster collaborative research

Organized by: Barcelona Respiratory Network Collaborative research

Cell Therapy in ARDS

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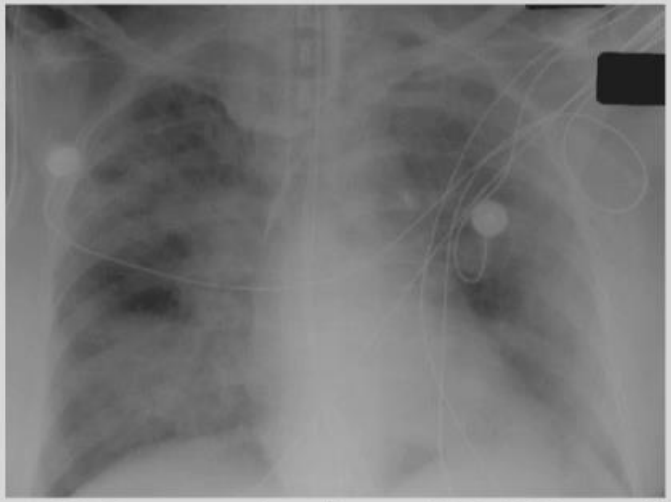
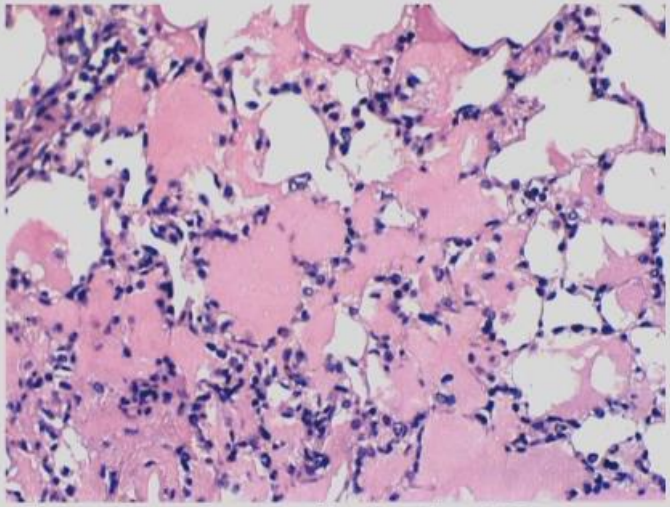
DISCLOSURES

- No relevant disclosures
- Research grants Instituto Carlos III PI12/02548, PI15/02204

The Acute Respiratory Distress Syndrome (ARDS)

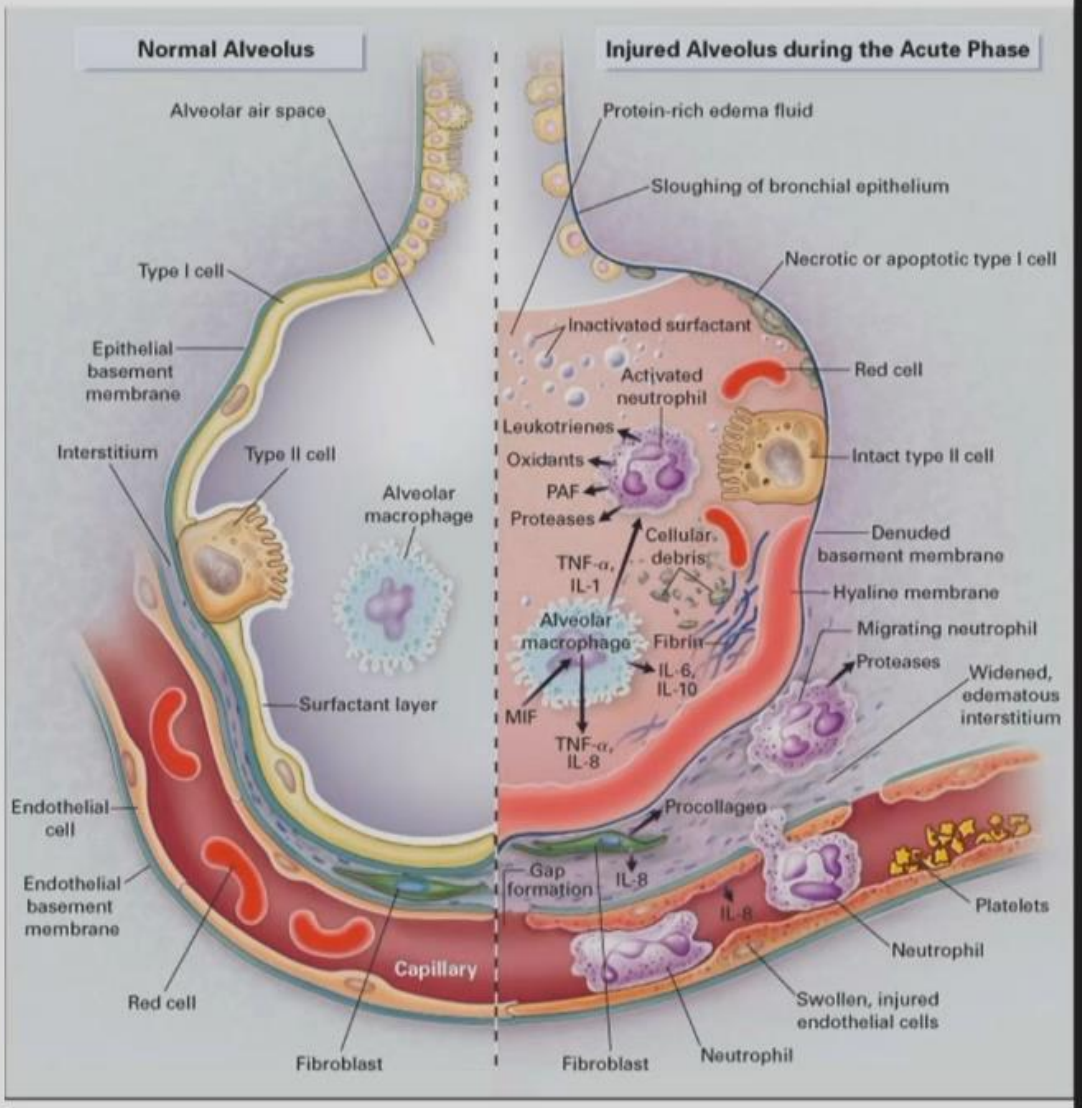




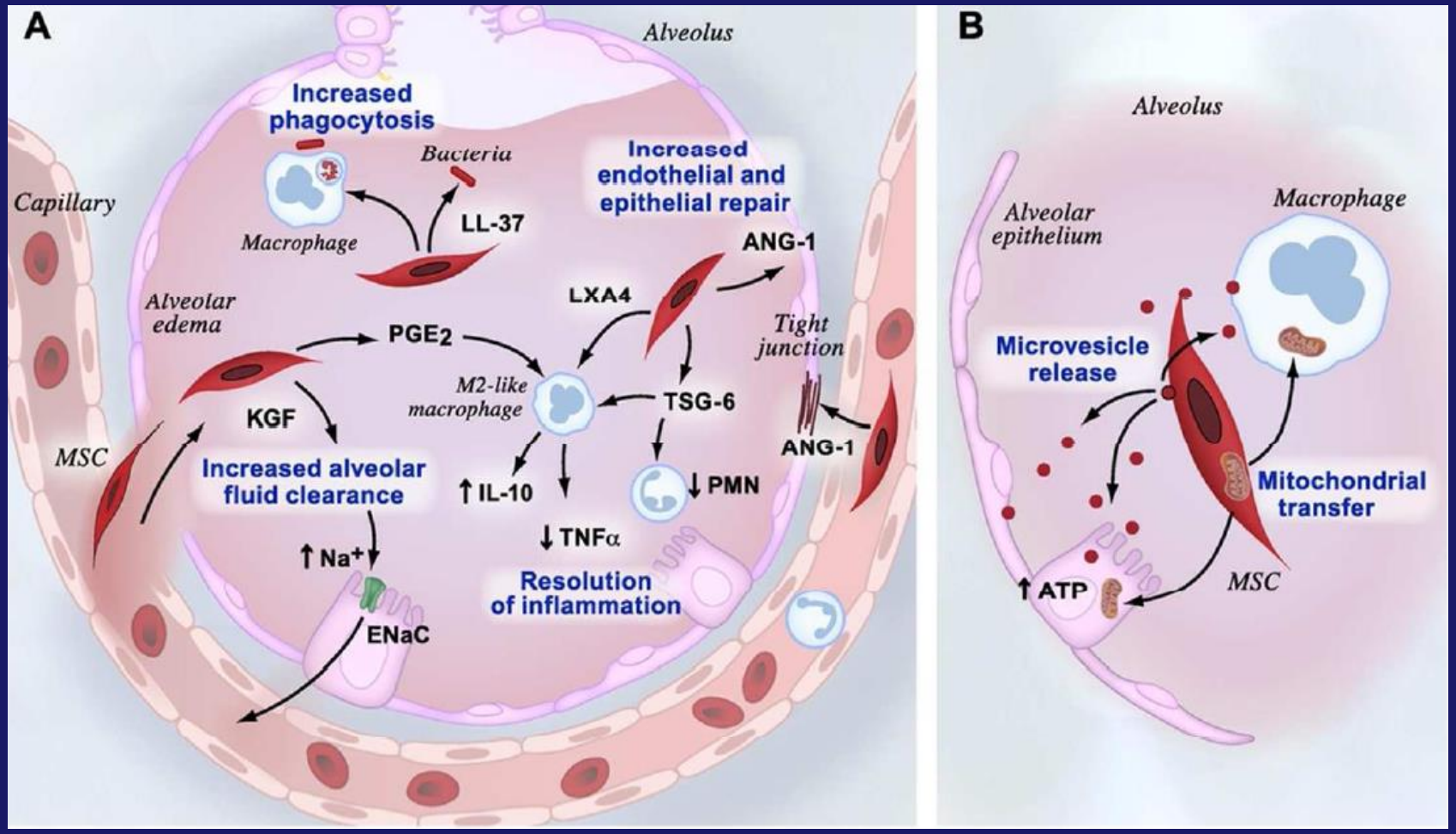
- ARDS occurs in about 200,000 ventilated patients annually in the US, bilateral infiltrates and Pa02/Fi02 < 300 mmHg
- Mortality of approximately 20-35%
- Main etiologies are bacterial & viral pneumonia, sepsis, & aspiration
- Supportive treatment with Lung Protective Ventilation and a Fluid Conservative Strategy have substantially improved clinical outcomes
  NHLBI ARDS Network Trials, NEJM 2000 & NEJM 2006

MSC & ALI - Rationale

- Anti-inflammatory properties – lipoxin A4, IL-1ra
- Restore endothelial & epithelial barrier integrity
- Enhance alveolar & lung edema fluid clearance
- Anti-microbial properties
  - Anti-apoptotic effects
  - Role of microvesicles
  - Role of mitochondrial transfer
  - Cell contact dependent & independent effects

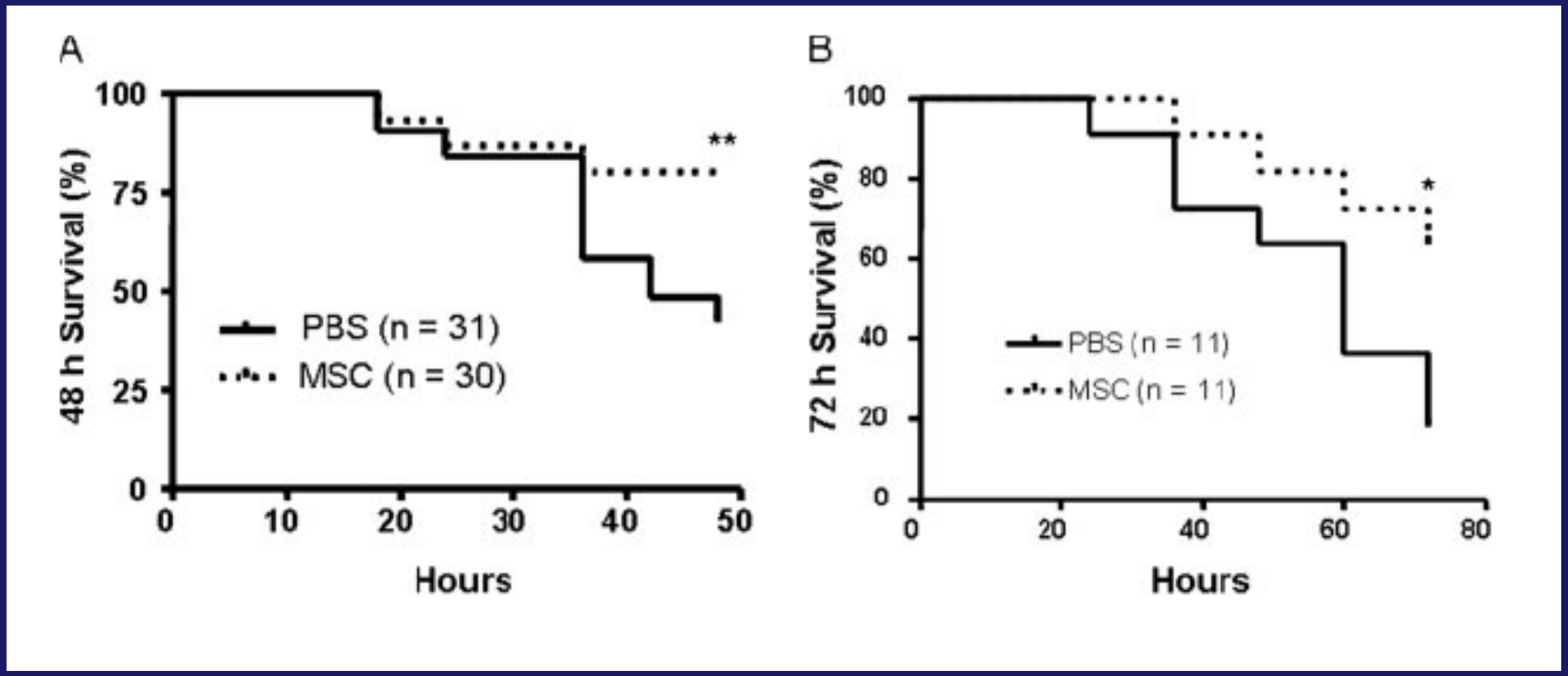


Mechanism of action of MSCs



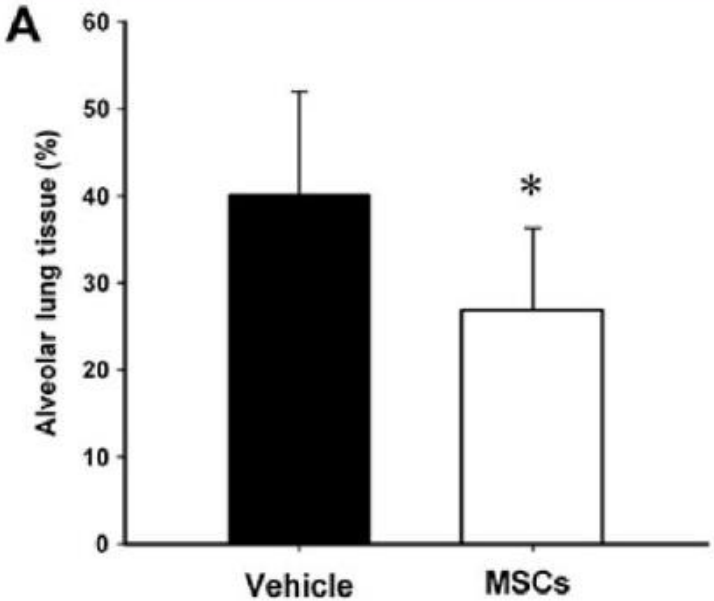
AJRCC 2017. a10.1164/rccm.2017-0107CP

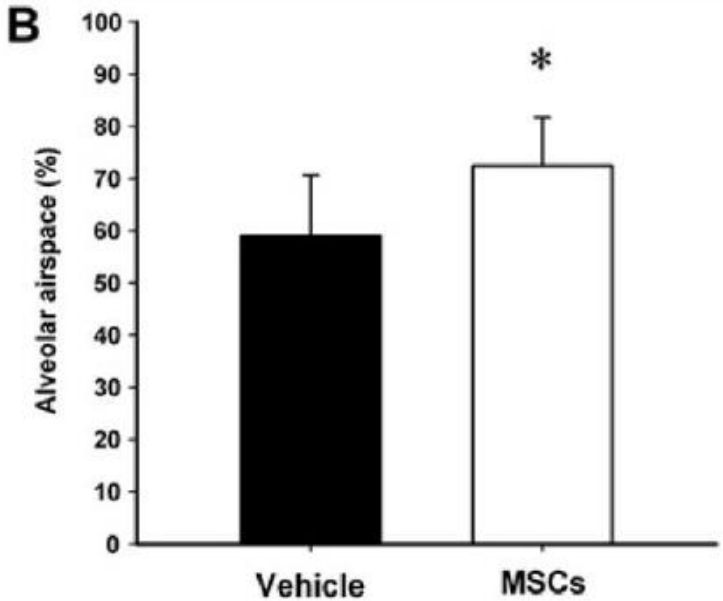
INTRATRACHEAL MSC IN ALI

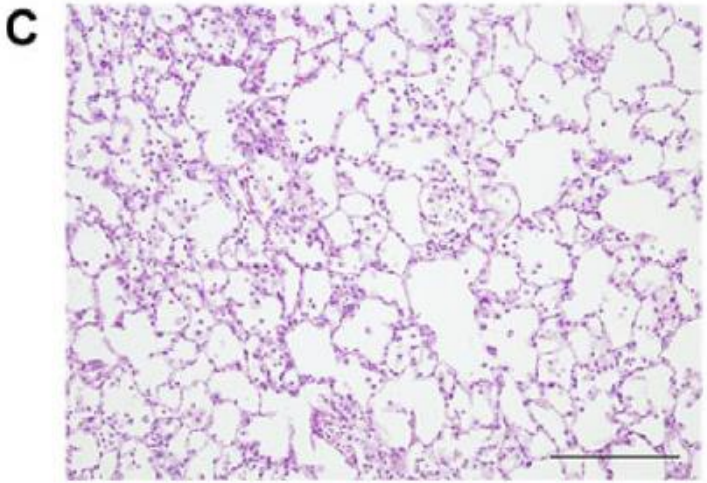


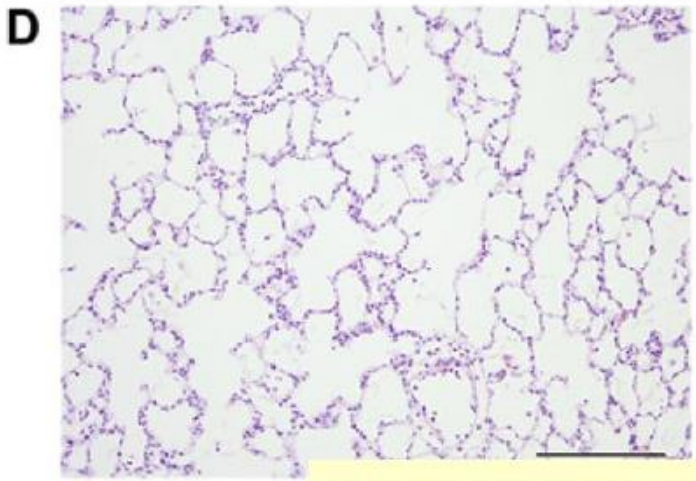
J Immunol 2007;179:1855-

MSCs enhance injury resolution following VILI



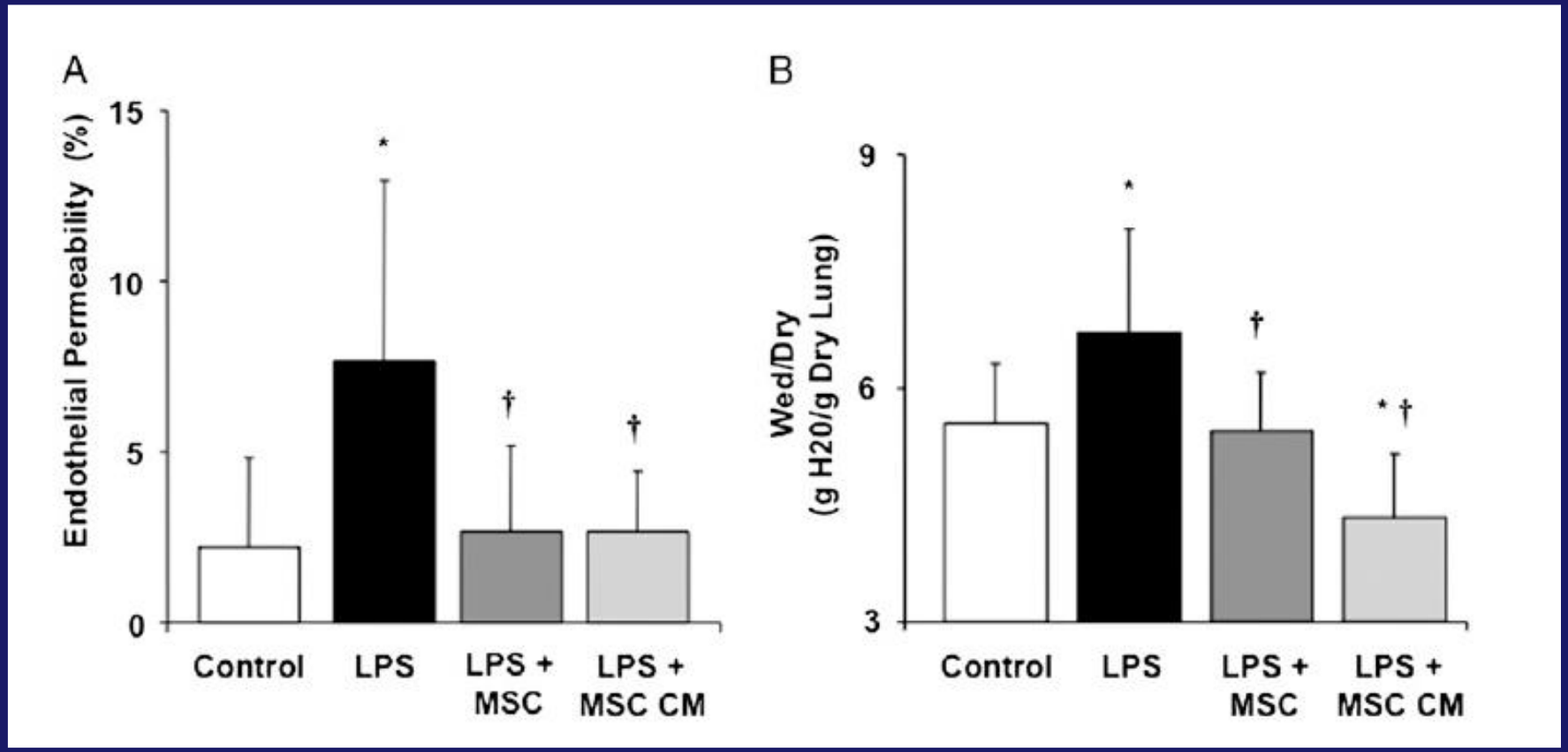






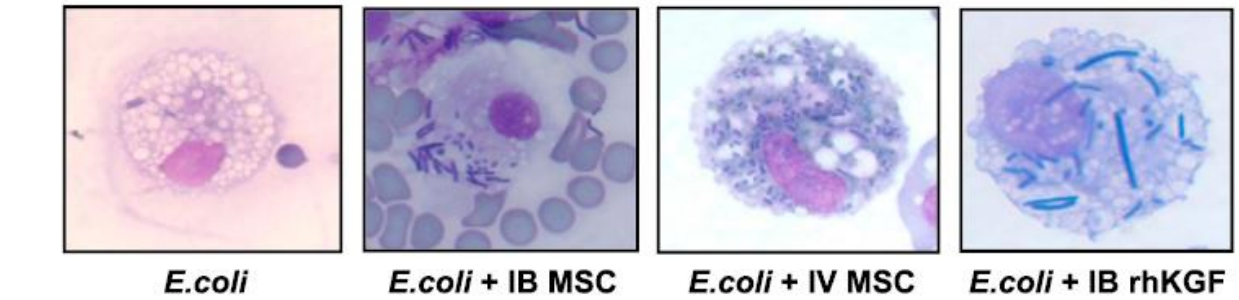
Curley et al, Thorax 2012

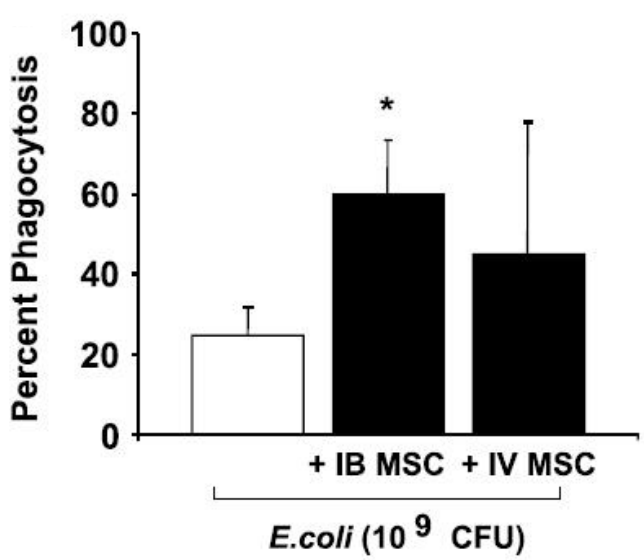
MSC RESTORED LUNG ENDOTHELIAL PERMEABILITY IN ENDOTOXIN ALI

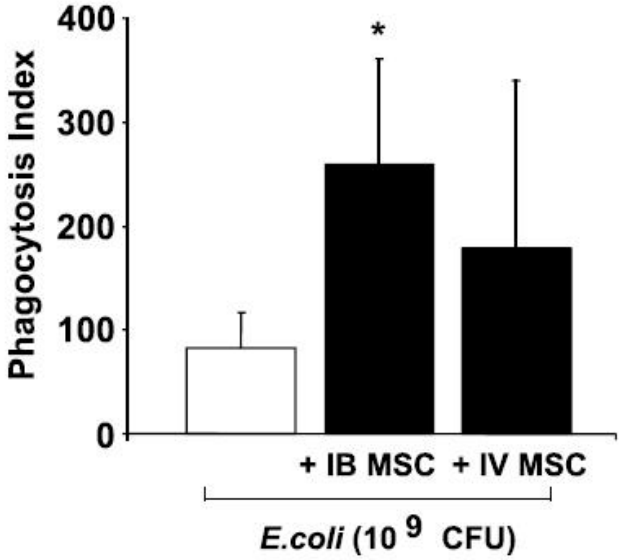


Proc Nat Acad Sci USA 2009;106:16357-62

MSC INCREASED MCF PHAGOCYTOSIS

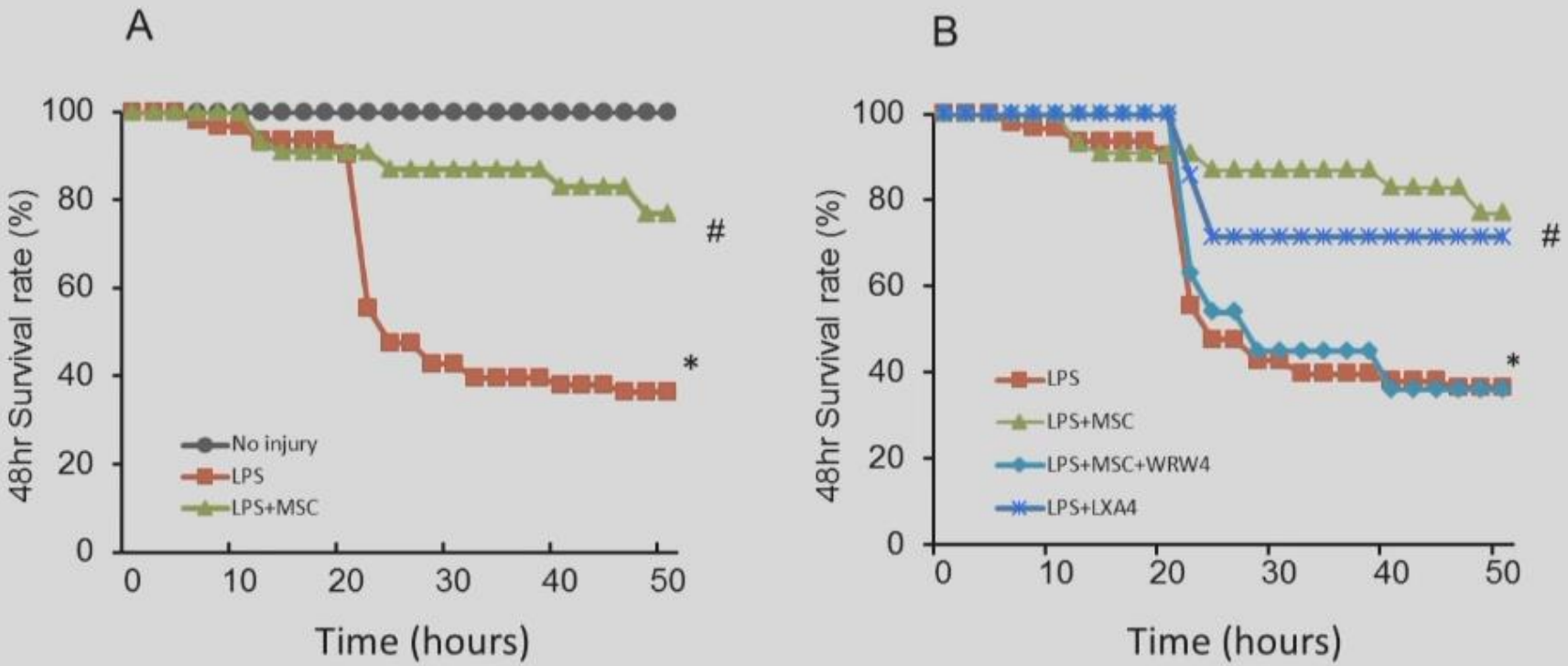






Am J Respir Crit Care Med 187;751-760

Lipoxin A4 receptor antagonist WRW4 decreases the effect of MSC on improving survival and lipoxin A4 itself enhances survival in endotoxin-injured mice

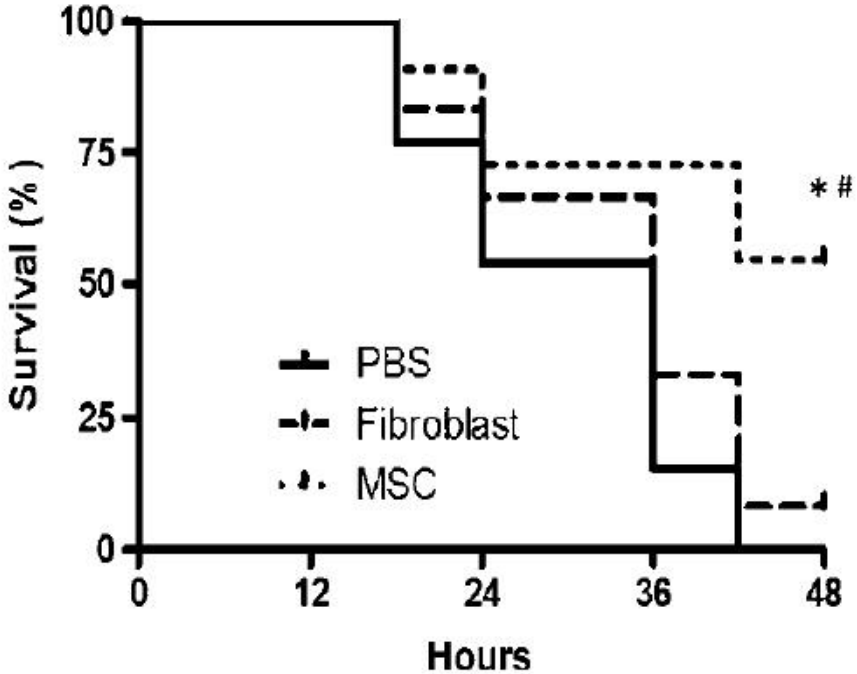


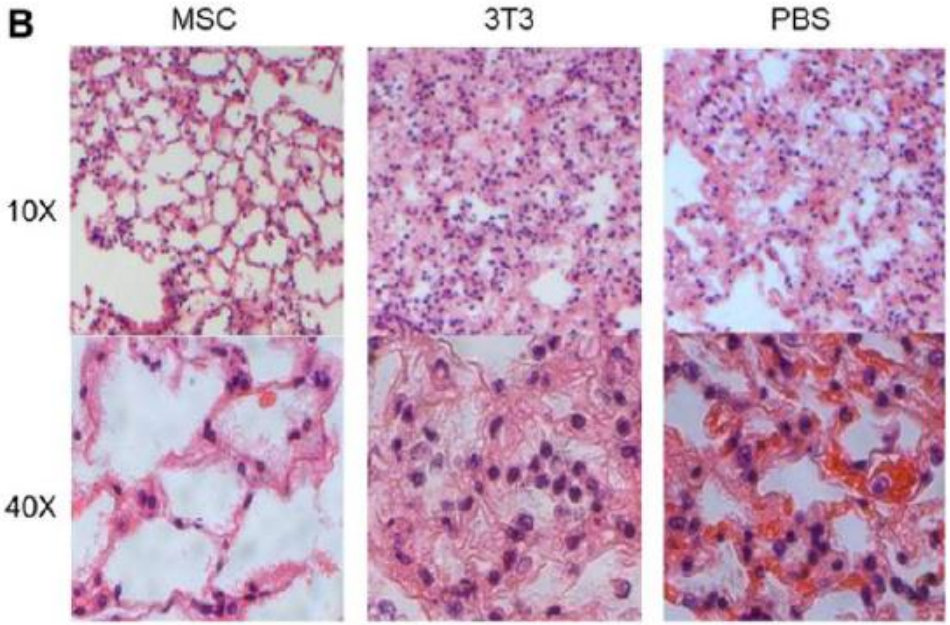
Fang et al, J Immunology, 2015

ORIGINAL ARTICLE

Mesenchymal stem cells enhance survival and bacterial clearance in murine *Escherichia coli* pneumonia

Naveen Gupta,[1,*] Anna Krasnodembskaya,[2,*] Maria Kapetanaki,[1] Majd Mouded,[1] Xinping Tan,[1] Vladimir Serikov,[3] Michael A Matthay[2]





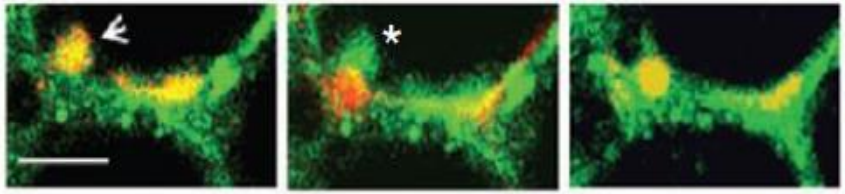
Gupta, Krasnodembskaya et al, Thorax 2012

nature medicine

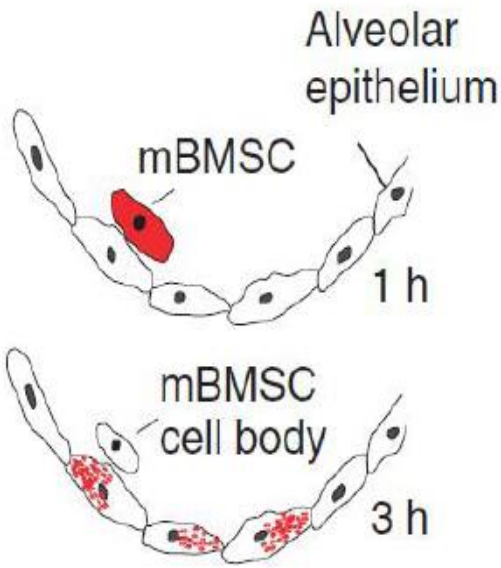
ARTICLES

Mitochondrial transfer from bone-marrow–derived stromal cells to pulmonary alveoli protects against acute lung injury

Mohammad Naimul Islam, Shonit R Das, Memet T Emin, Michelle Wei, Li Sun, Kristin Westphalen, David J Rowlands, Sadiqa K Quadri, Sunita Bhattacharya & Jahar Bhattacharya



Subpleural depth (μm):	6	6	10
Time after mBMSC instillation (h):	1	3	3

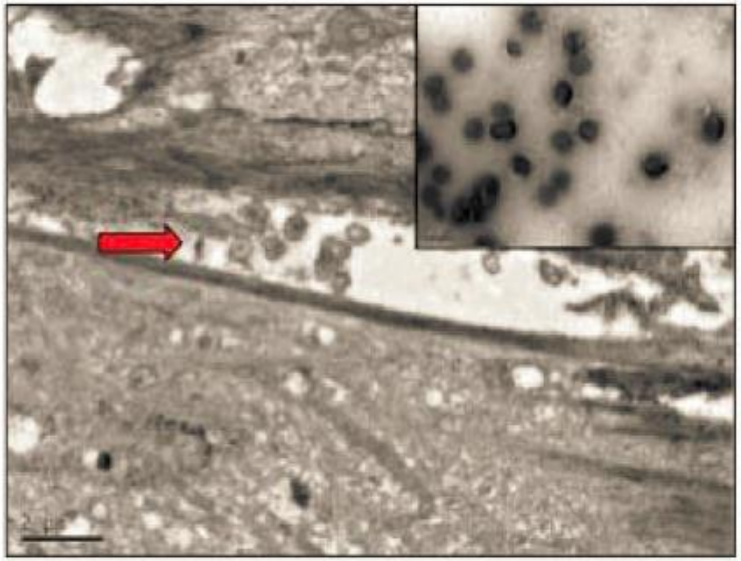


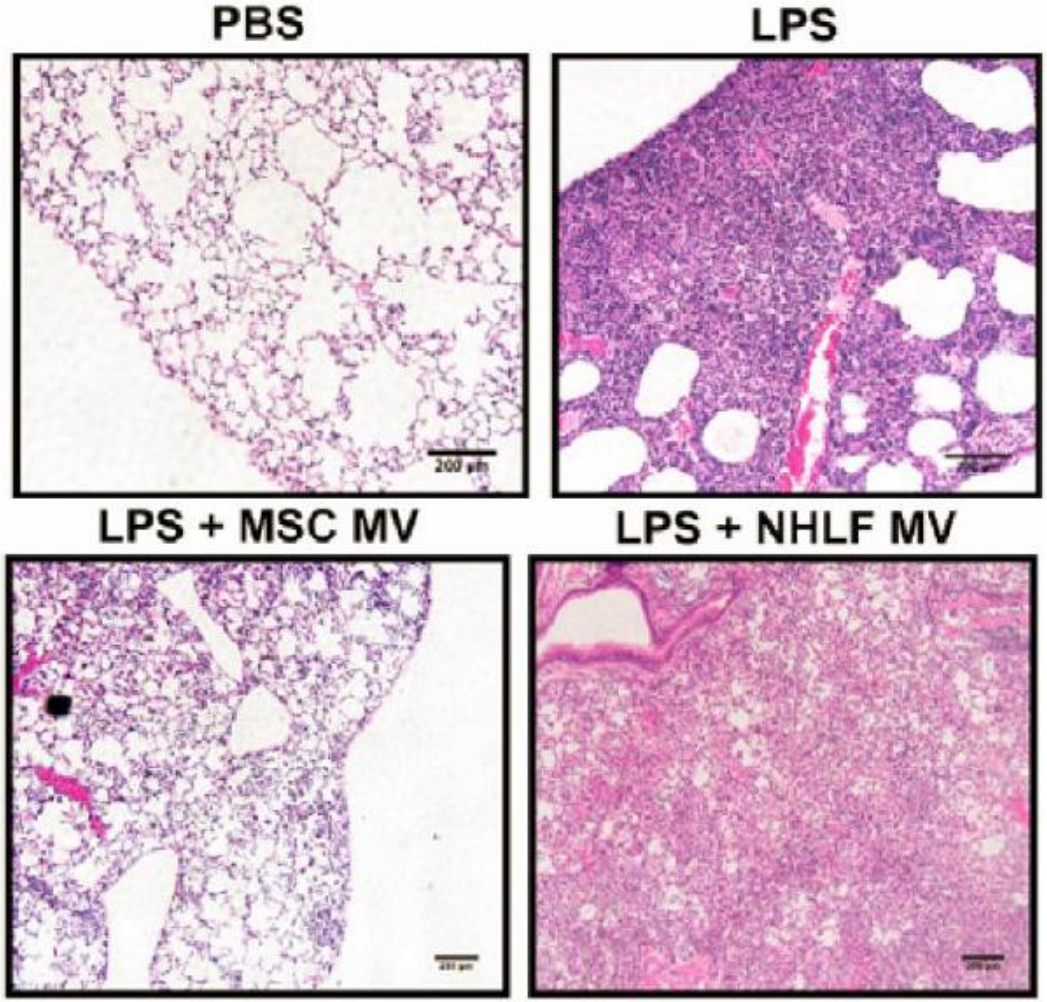
STEM CELLS®

TRANSLATIONAL AND CLINICAL RESEARCH

Human Mesenchymal Stem Cell Microvesicles for Treatment of *E.coli* Endotoxin-Induced Acute Lung Injury in Mice

Ying-gang Zhu[1], Xiao-mei Feng[2], Jason Abbott[3], Xiao-hui Fang[3], Qi Hao[4], Antoine Monsel[4], Jie-ming Qu[1], Michael A. Matthay[3,4,5], Jae W. Lee[3,4]

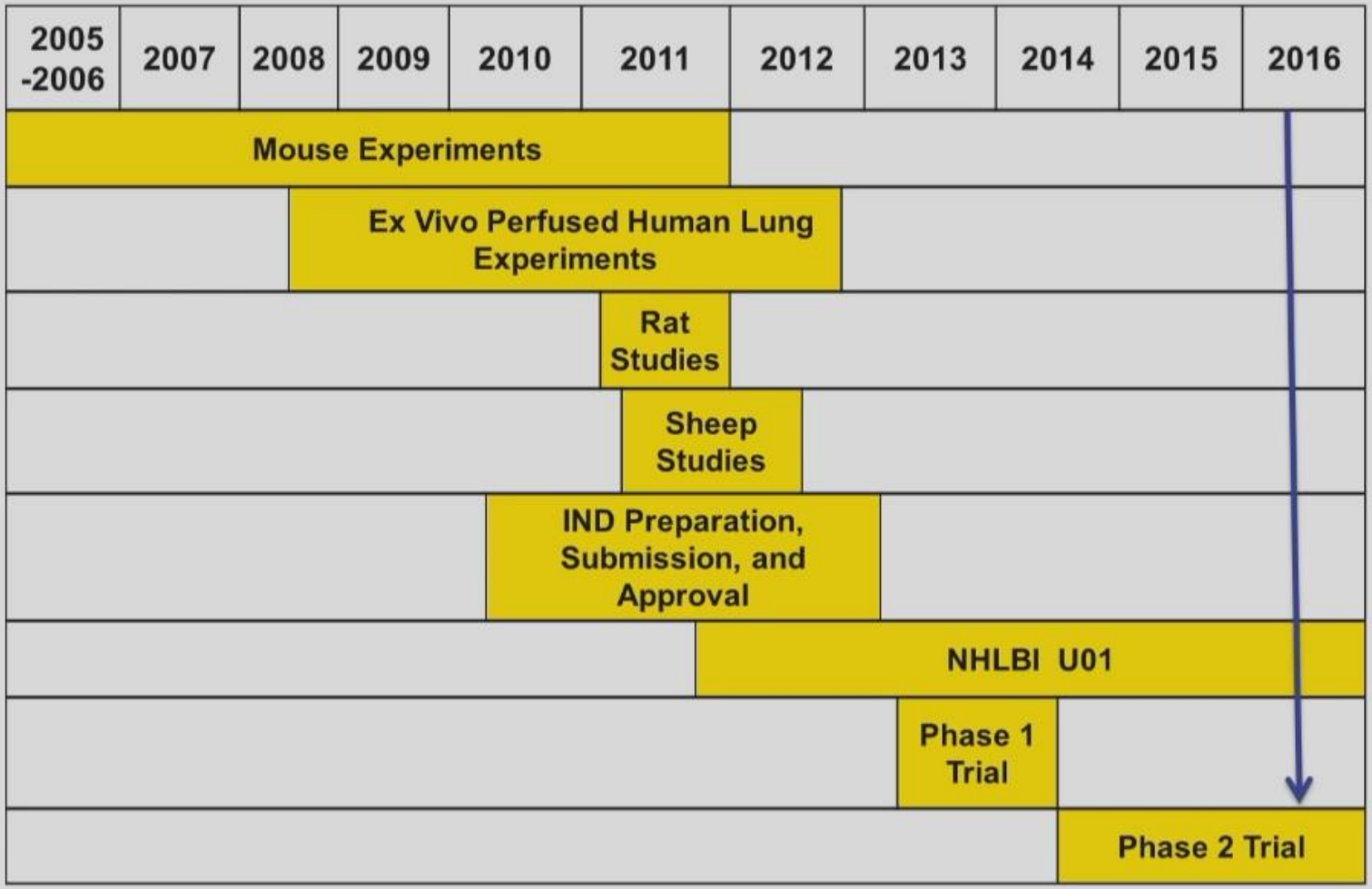




hMSCs for ARDS…where are we now?

First clue that the latest medical breakthrough isn't quite there yet.

Roadmap for Translation of Human Mesenchymal Stem (Stromal) Cells to a Clinical Trial for ARDS



MSCs CLINICAL TRIALS

Phase 1. January 2014 (NCT02097641)

Single iv dose:

- $1x10^6$ MSCs/Kg (n=3)
- $5x10^6$ MSCs/Kg (n=3)
- $10x10^6$ MSCs/Kg (n=3)

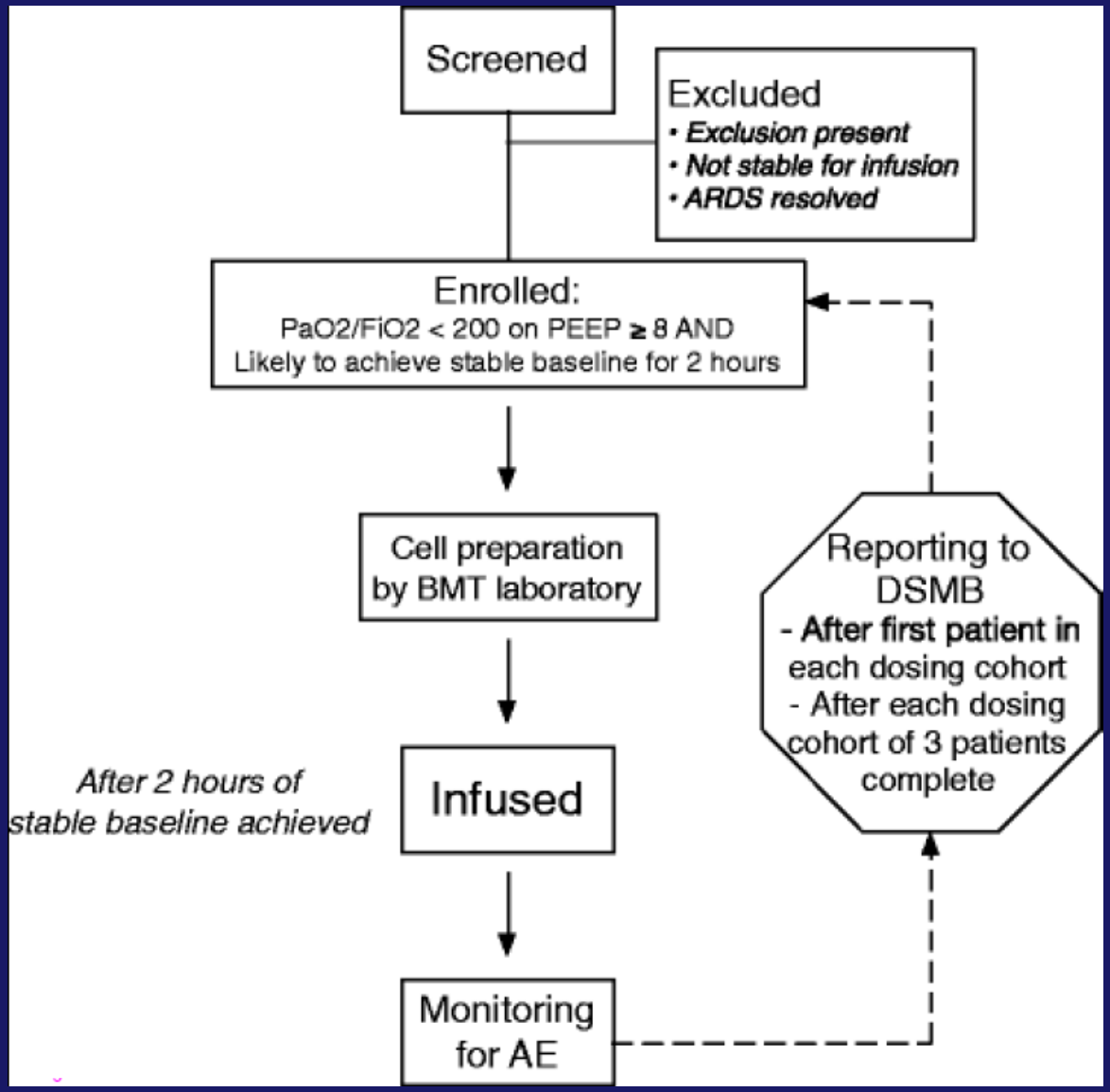
Lancet Respir Med 2015;3:24-32

Phase 2. April 2014 (NCT01775774)

- 60 patients
- RCT (2:1): Placebo (Plasmalyte) vs MSCs 1 hour
- Stable baseline (2 hours) + Observation (4 hours)

Ann Intensive Care 2014;4:22

START Study: Flow Diagram (Phase 1)

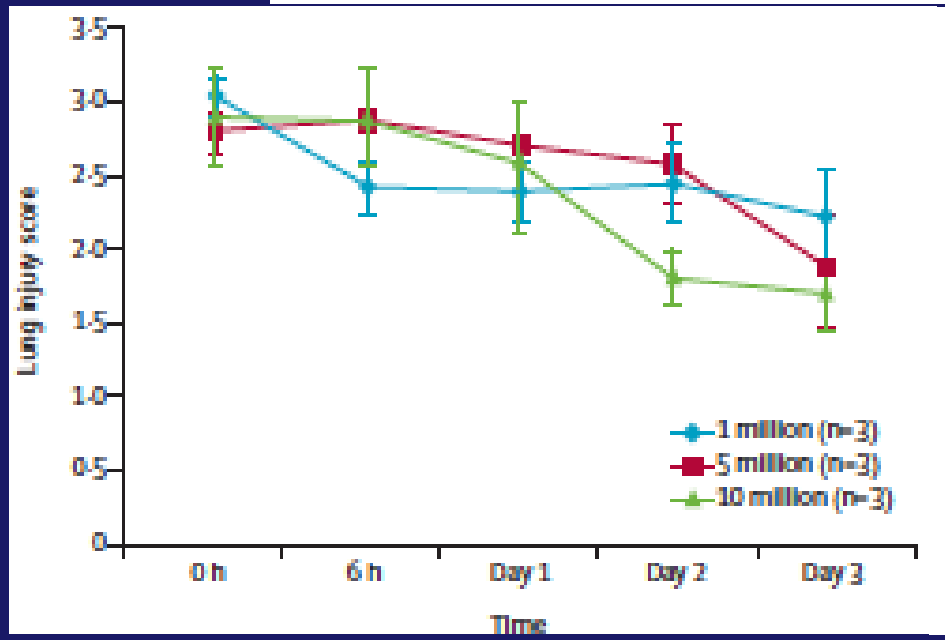


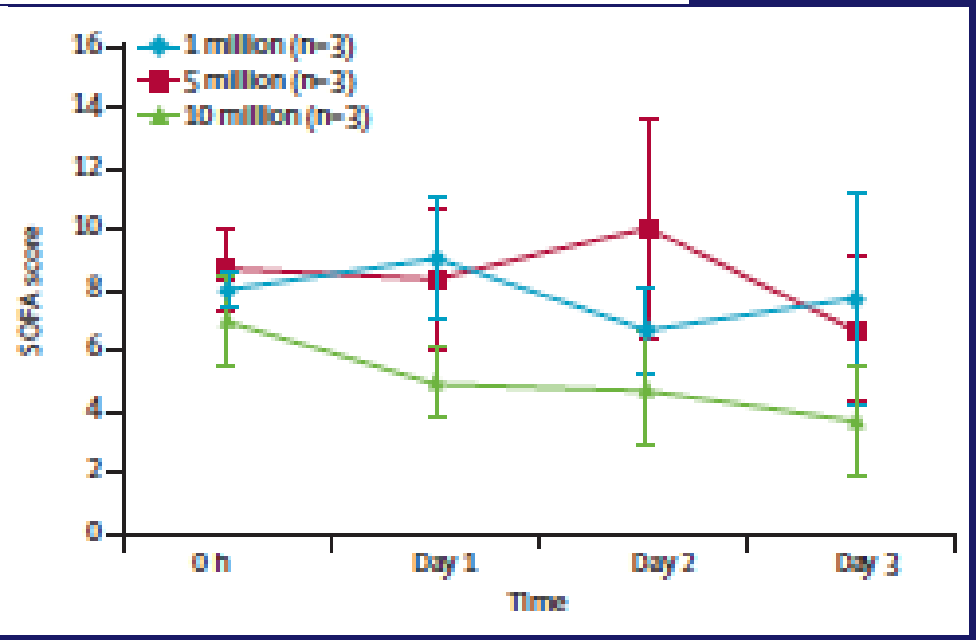
Annals Intensive Care Med 2014

STem cells for ARDS Treatment (START) trial

Mesenchymal stem (stromal) cells for treatment of ARDS: a phase 1 clinical trial

Jennifer G Wilson, Kathleen D Liu, Hanjing Zhuo, Lizette Caballero, Melanie McMillan, Xiaohui Fang, Katherine Cosgrove, Rosemary Vojnik, Carolyn S Calfee, Jae-Woo Lee, Angela J Rogers, Joseph Levitt, Jeanine Wiener-Kronish, Ednan K Bajwa, Andrew Leavitt, David McKenna, B Taylor Thompson, Michael A Matthay





Lancet Respir Med 2015;3:24–32

What Are the Barriers to Clinical Translation for ARDS?

- Optimization of dosage regimens
- Incomplete mechanistic knowledge
- Concerns regarding in vitro culture
- Immunogenecity of MSCs
- Safety concerns: pulmonary fibrosis, malignant tranformation

Safety

OPEN ACCESS Freely available online

PLOS | ONE

Safety of Cell Therapy with Mesenchymal Stromal Cells (SafeCell): A Systematic Review and Meta-Analysis of Clinical Trials

Manoj M. Lalu[1,5], Lauralyn McIntyre[2,5*], Christina Pugliese[5], Dean Fergusson[5], Brent W. Winston[6], John C. Marshall[7], John Granton[8], Duncan J. Stewart[3,4], for the Canadian Critical Care Trials Group

1 Department of Anesthesiology, University of Ottawa, Ottawa, Canada, 2 Department of Medicine (Division of Critical Care), University of Ottawa, Ottawa, Canada, 3 Regenerative Medicine Program, The Ottawa Hospital Research Institute, Ottawa, Canada, 4 Department of Cell and Molecular Medicine, University of Ottawa, Ottawa, Canada, 5 The Ottawa Hospital Research Institute, Clinical Epidemiology Program, Ottawa, Canada, 6 Department of Critical Care Medicine, University of Calgary, Calgary, Canada, 7 Department of Surgery (Critical Care), University of Toronto, Toronto, Canada, 8 Department of Medicine (Critical Care), University of Toronto, Toronto, Canada

PLOS one 2012 7:e47559.

Scalability – platform for delivery

Distribution of cells to sites

Receipt Into local GMP cell therapy facilities

Distribution of cell product to hospital

Receipt into the ICU at sites

Manufacture and banking of cells

GMP cell therapy facility

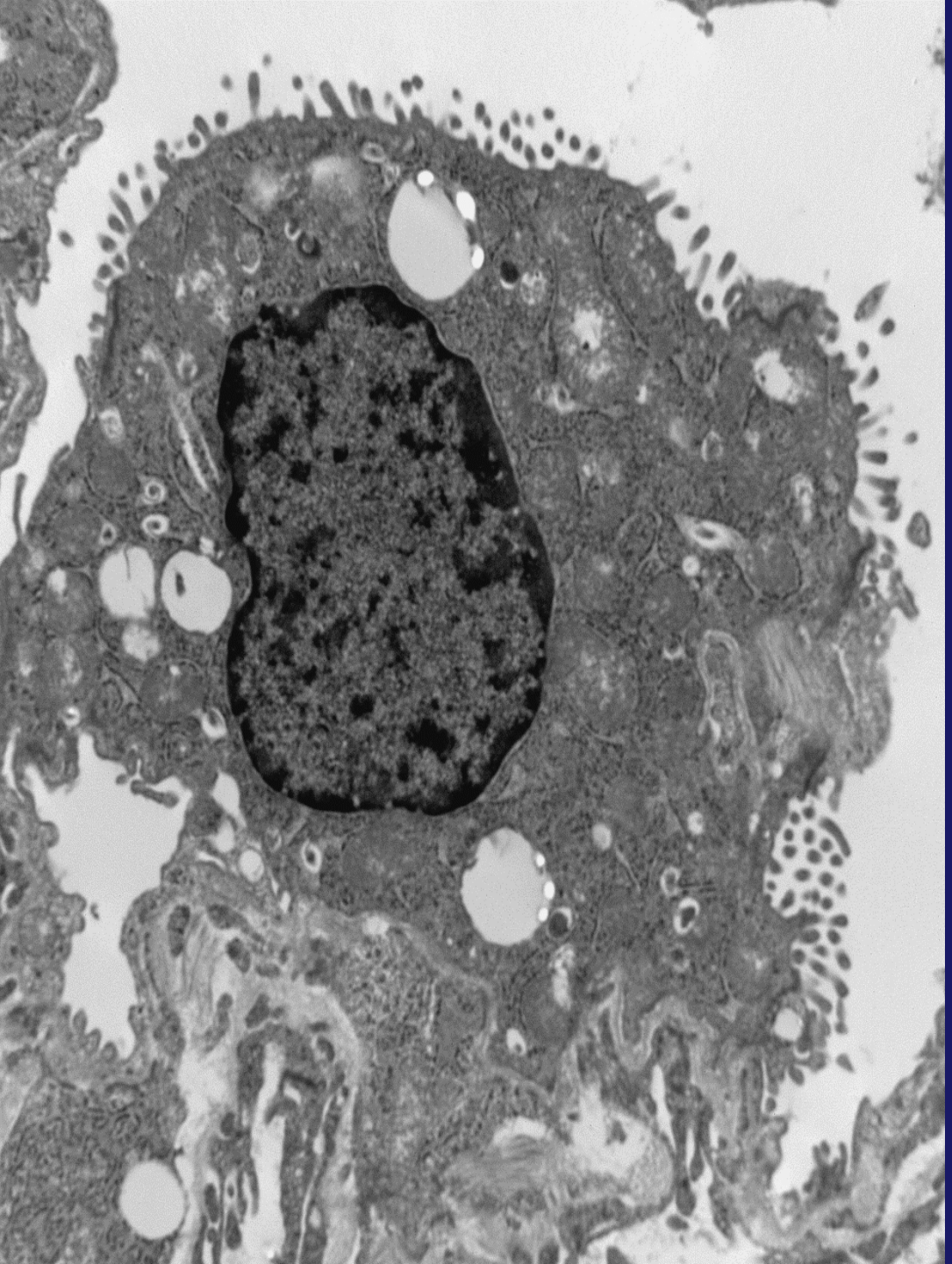
LN_2

Thaw, wash and final formulation

Quality assurance

Infusion

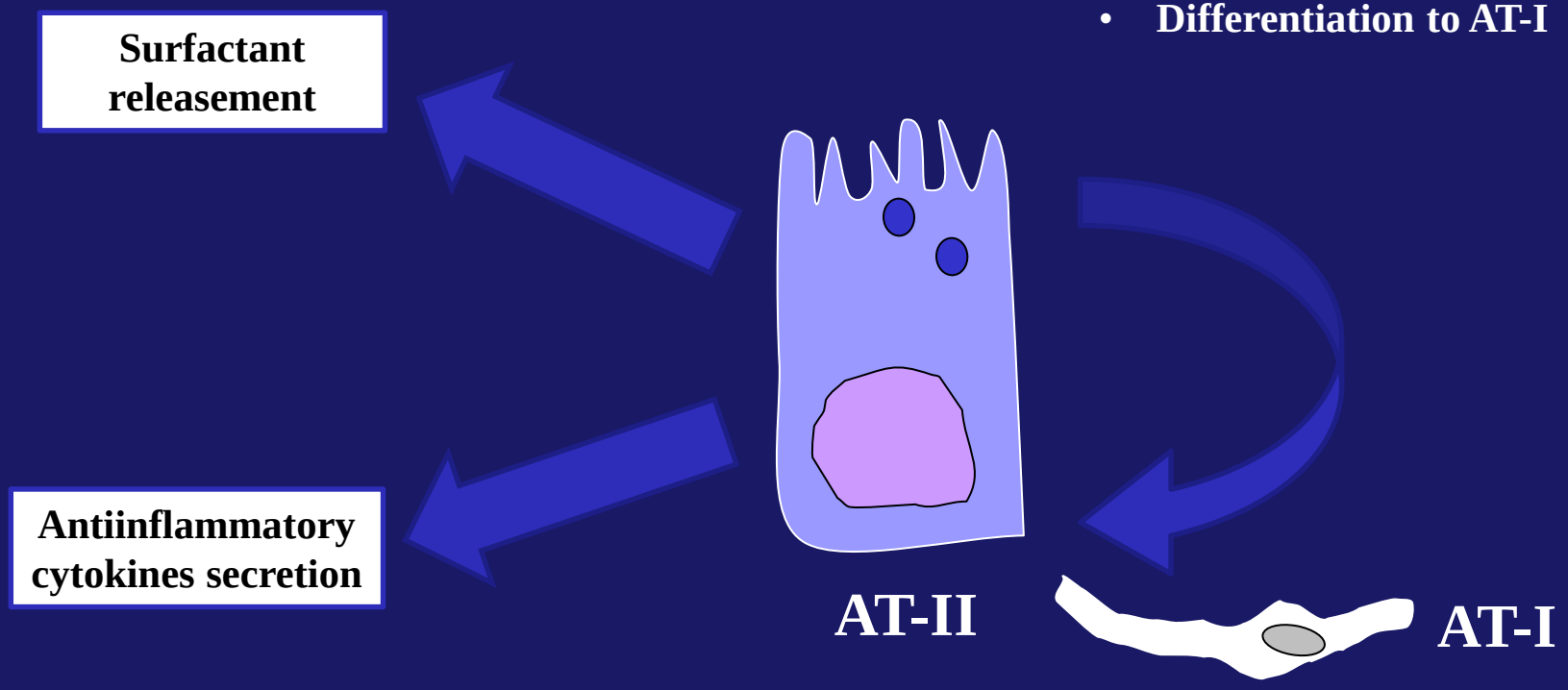

THIS IS THE STEM CELL RESEARCH LAB, THE STEM CELL ETHICS COMMITTEE IS NEXT DOOR...
KUDELKA

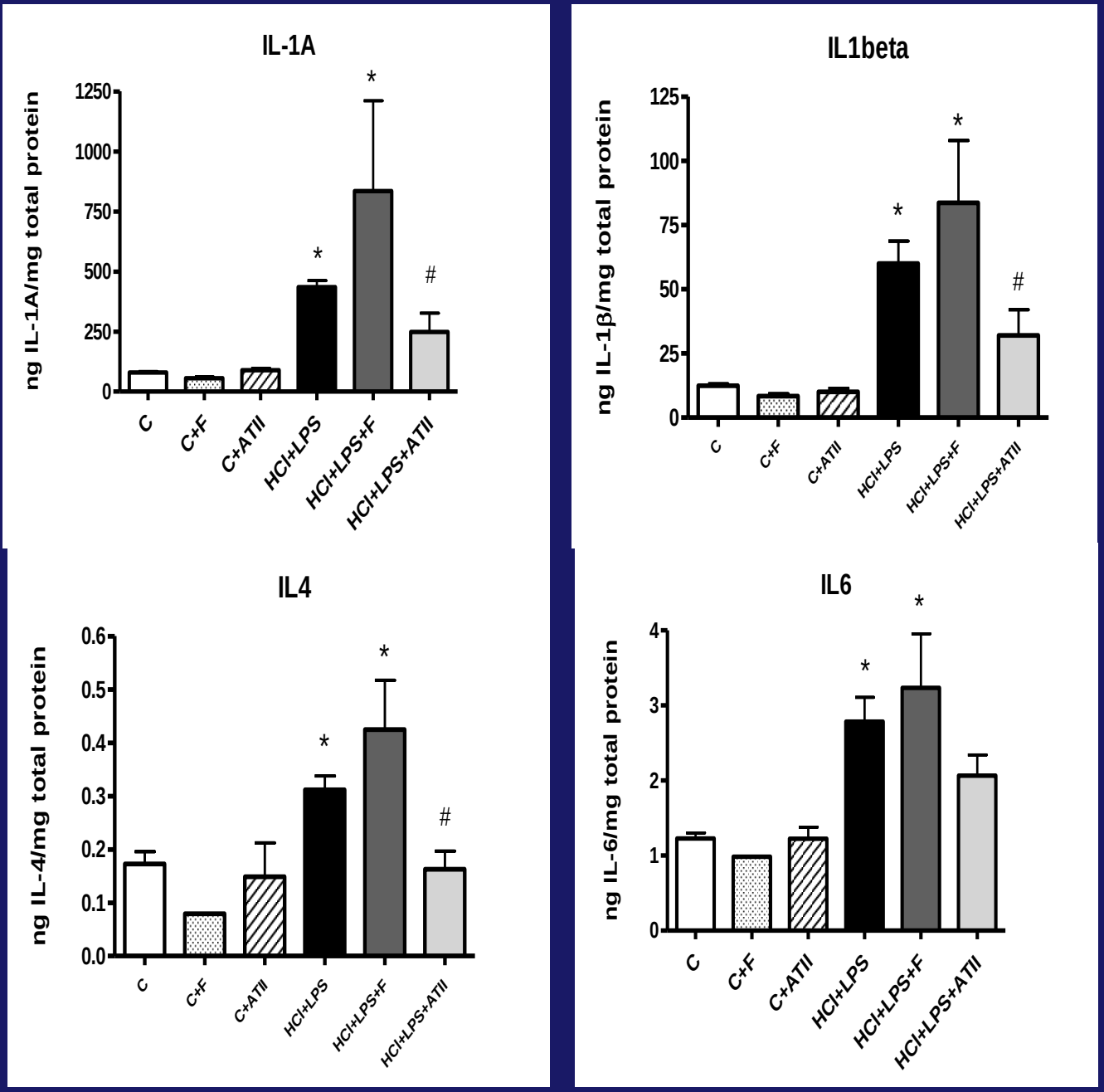


Type II pneumocyte transplantation in ARDS

Why Alveolar Type II cell?

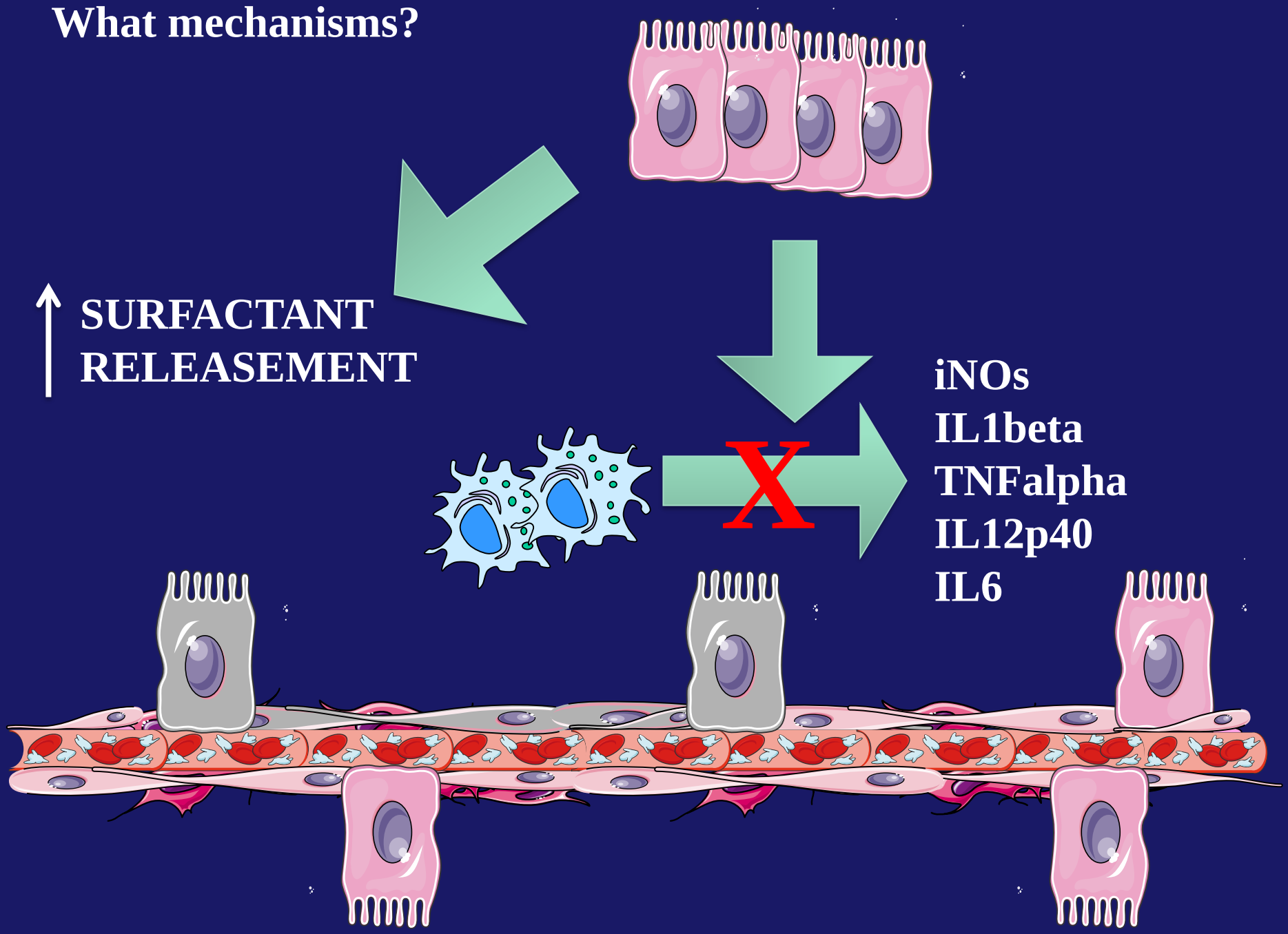
- ATII self-regeneration
- Differentiation to AT-I





J Heart Lung Transplant. 2018; 37(6):782-791

What mechanisms?



Advantages and disadvantages

Alveolar Type II cells	Mesenchymal stem cells
More differentiated	Un-differentiated
Anti-inflammatory effect	Anti-inflammatory effect
Difficult isolation	Easy isolation
Do not migrate to other organs	Could migrate to other organs and be teratogenic

Conclusions and Questions

- Preclinical studies have supported the rationale for testing MSCs-AT-II in moderate to severe ARDS
- What are the contributions of the paracrine mechanisms and mitochondrial transfer, including microvesicles?
- How do preparation regimens influence activity of MSCs?
- Will MSCs be safe & effective in moderate severe ARDS?
- Feasibility to scale up delivery needs to be confirmed

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4titude

Thank you

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