Cell Therapy in ARDS

Antonio Artigas
Critical Care Center
Sabadell Hospital
Autonomous University of Barcelona
Spain
aartigas@tauli.cat
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• No relevant disclosures

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The Acute Respiratory Distress Syndrome (ARDS)

- ARDS occurs in about 200,000 ventilated patients annually in the US, bilateral infiltrates and PaO2/FiO2 < 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

A

Increased phagocytosis
Bacteria
LL-37
Increased endothelial and epithelial repair
ANG-1
PGE2
LXA4
Tight junction
ANG-1
TSG-6
M2-like macrophage
IL-10
PMN
TNFα
Resolution of inflammation
Na+
ENaC
Increased alveolar fluid clearance
KGF
MSC

B

Alveolar epithelium
Microvesicle release
Mitochondrial transfer
MSC

AJRCC 2017. a10.1164/rccm.2017-0107CP
INTRATRACHEAL MSC IN ALI

A

48 h Survival (%)

100

75

50

25

0

PBS (n = 31)

MSC (n = 30)

Hours

0 10 20 30 40 50

B

72 h Survival (%)

100

80

60

40

20

0

PBS (n = 11)

MSC (n = 11)

Hours

0 20 40 60 80

J Immunol 2007;179:1855-
MSCs enhance injury resolution following VILI

**A**

![Bar chart showing Alveolar lung tissue (%) for Vehicle and MSCs](chart.png)

**B**

![Bar chart showing Alveolar airspace (%) for Vehicle and MSCs](chart.png)

**C**

![Micrograph of alveolar lung tissue](image_c.png)

**D**

![Micrograph of alveolar airspace](image_d.png)

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

![Images of cells with and without MSC treatment]

- E. coli
- E. coli + IB MSC
- E. coli + IV MSC
- E. coli + IB rhKGF

**Percent Phagocytosis**

- E. coli (10^9 CFU)
  - + IB MSC
  - + IV MSC

**Phagocytosis Index**

- E. coli (10^9 CFU)
  - + IB MSC
  - + IV MSC

*Significant difference
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
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 Matthay²

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**Graph**

**Survival (%)**

- PBS
- Fibroblast
- MSC

**Hours**

- 0
- 12
- 24
- 36
- 48

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**Images**

- B MSC
- B 3T3
- B PBS

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Gupta, Krasnodembskaya et al, Thorax 2012
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
Human Mesenchymal Stem Cell Microvesicles for Treatment of E. coli Endotoxin-Induced Acute Lung Injury in Mice

Ying-gang Zhu¹, Xiao-mei Feng², Jason Abbott³, Xiao-hui Fang³, Qi Hao⁴, Antoine Monsel⁴, Jie-ning Qu¹, Michael A. Matthay⁴,⁵, Jae W. Lee³,⁴
hMSCs for ARDS...where are we now?

Don’t worry. I had ARDS too and MSCs cured me!

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

<table>
<thead>
<tr>
<th>Year</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005-2006</td>
<td>Mouse Experiments</td>
</tr>
<tr>
<td>2007</td>
<td>Ex Vivo Perfused Human Lung Experiments</td>
</tr>
<tr>
<td>2008</td>
<td>Rat Studies</td>
</tr>
<tr>
<td>2009</td>
<td>Sheep Studies</td>
</tr>
<tr>
<td>2010</td>
<td>IND Preparation, Submission, and Approval</td>
</tr>
<tr>
<td>2011-2012</td>
<td>NHLBI U01</td>
</tr>
<tr>
<td>2013</td>
<td>Phase 1 Trial</td>
</tr>
<tr>
<td>2014-2015</td>
<td>Phase 2 Trial</td>
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</tbody>
</table>
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)

- Screened
  - Excluded: 
    - Exclusion present
    - Not stable for infusion
    - ARDS resolved

- Enrolled:
  - PaO2/FiO2 < 200 on PEEP ≥ 8 AND
  - Likely to achieve stable baseline for 2 hours

- Cell preparation by BMT laboratory

- Reporting to DSMB
  - After first patient in each dosing cohort
  - After each dosing cohort of 3 patients complete

- Infused

- Monitoring for AE

After 2 hours of stable baseline achieved
STem cells for ARDS Treatment (START) trial

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

Jennifer GWilson, Kathleen DLiu, Hanjing Zhuo, Lizette Cabrera, Melanie McMilan, Xiaohui Fang, Katherine Cosgrove, Rosemary Vojnik, Carolyn SCaffee, Jae-Woo Lee, Angela Rogers, Joseph Levitt, Jeanine Wiener-Kronish, Ednan K Bajwa, Andrew Leavitt, David McKenna, B Taylor Thompson, Michael A Matthay

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

Manoj M. Lalu, Lauralyn McIntyre, Christina Pugliese, Dean Fergusson, Brent W. Winston, John C. Marshall, John Granton, Duncan J. Stewart, 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

Manufacture and banking of cells
GMP cell therapy facility

Distribution of cells to sites

Receipt Into local GMP cell therapy facilities

Distribution of cell product to hospital

Receipt into the ICU at sites

 LN₂

Thaw, wash and final formulation

Quality assurance

Infusion

Study Drug
THIS IS THE STEM CELL RESEARCH LAB, THE STEM CELL ETHICS COMMITTEE IS NEXT DOOR...
Type II pneumocyte transplantation in ARDS
Why Alveolar Type II cell?

- ATII self-regeneration
- Differentiation to AT-I

Surfactant release

Antiinflammatory cytokines secretion
What mechanisms?

SURFACTANT RELEASEMENT

iNOs
IL1beta
TNFalpha
IL12p40
IL6
Advantages and disadvantages

<table>
<thead>
<tr>
<th>Alveolar Type II cells</th>
<th>Mesenchymal stem cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>More differentiated</td>
<td>Un-differentiated</td>
</tr>
<tr>
<td>Anti-inflammatory effect</td>
<td>Anti-inflammatory effect</td>
</tr>
<tr>
<td>Difficult isolation</td>
<td>Easy isolation</td>
</tr>
<tr>
<td>Do not migrate to other organs</td>
<td>Could migrate to other organs and be teratogenic</td>
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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
Antonio Artigas
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Jessica Tijero
Neus Gómez

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Raquel Herrero
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Thank you

aartigas@tauli.cat