MSC IN THE TREATMENT OF EXPERIMENTAL SEPSIS

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Disclosures......

I wished!!!
Improving clinical trials in the critically ill

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Google Scholar Search (www.scholar.google.com)

Over 104 Phase III RCTs

…..waiting for novel approaches

Table 1. Key areas for improvement in clinical trials

Better translation from bench to trial
- Improve in vivo models of critical illness
- Greater use of new mathematical tools to model complex disease processes
- Better-match patients to interventions using theragnostics

Better design and conduct
- Expand the arena for clinical trials outside of the intensive care unit
- Use outcome measures other than just short-term mortality
- Better use of pilot studies
- Increased co-enrollment of patients in multiple trials when feasible
- Use new study designs in addition to the established randomized control trial

Better infrastructure
- More national and international clinical trials groups and collaborations
- Improved industry–academia partnerships
- More transparent data collection and availability
Novel discoveries are ‘hampered’ by the intrinsic bias in the literature
- Importance of unbiased discovery
- Incorporating ‘heterogeneity’

**Animal Models**
- Mimic reality of critical care
- Not just ‘more’.....more ‘complex’

**Mathematical modeling of complexity**
- Perturbations of the system
- Capitalizing on the Pilots
Figure 3. MSC interactions with immune cells. MSCs are immunoprivileged cells that inhibit both innate (neutrophils, dendritic cells, natural killer cells) and adaptive (T cells and B cells) immune cells. Illustration credit: Cosmocyte/Ben Smith. INF-γ indicates interferon-γ; TNF, tumor necrosis factor. (Illustration credit: Cosmocyte/Ben Smith.)
Mesenchymal Stem Cells Reduce Inflammation while Enhancing Bacterial Clearance and Improving Survival in Sepsis

Shirley H. J. Mei¹,², Jack J. Haitsma², Claudia C. Dos Santos², Yupu Deng¹, Patrick F. H. Lai⁴, Arthur S. Slutsky²,⁴, W. Conrad Liles³,⁴,⁵, and Duncan J. Stewart¹,⁴

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**Caecum Ligation and Puncture**

Sham or CLP

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**Organ collection for microarray studies**

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**Time 0**

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**6 hrs**

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**Fluid resuscitation and pain management**

1. Saline
2. MSC (2 x 10⁵ cells)

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28 hrs

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**Sacrifice**
MSC DECREASES MORTALITY IN EXPERIMENTAL MODEL OF SEPSIS

![Survival Curve](Image)

- **CLP / Saline**
- **CLP / MSCs**

% Survival

Time (hours)

\[ p < 0.05 \]
MSC ATTENUATE LEVELS OF SYSTEMIC PRO-INFLAMMATORY MEDIATORS

Mei et al. AJRCCM, 2010
MSCS RESULT IN INCREASED BACTERIAL CLEARANCE
ENHANCED PHAGOCYTIC ABILITY

Isolated CD11b positive cells

Peritoneal Cells

S. aureus

E. coli

Fluorescence Intensity

Time (min)

Clp / Saline
Clp / MSCs

Fluorescence Intensity

Time (min)

Clp / Saline
Clp / MSCs

Clp / Saline
Clp / MSCs

Clp / Saline
Clp / MSCs

Clp / Saline
Clp / MSCs

Mei et al. AJRCCM, 2010
Antibacterial Effect of Human Mesenchymal Stem Cells Is Mediated in Part from Secretion of the Antimicrobial Peptide LL-37

Anna Krasnodebskaya, Yuanlin Song, Xiaohui Fang, Naveen Gupta, Vladimir Serikov, Jae-Woo Lee, Michael A. Matthay
Network Analysis of Transcriptional Responses Induced by Mesenchymal Stem Cell Treatment of Experimental Sepsis


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Lung Heart Liver Kidney Spleen

(5 x 4 x 3) + (4 x 3)

N = 72 samples

A

B

C

Tissues
Spleen Heart Lung Kidney Liver

Treatment
CLP MSC Sham
Network Analysis of Common Transcriptional Responses Induced by MSCs in Sepsis
Changes in Toll-Like Receptor signaling pathways after treatment with MSCs

i. Response to LPS

ii. Toll-like Receptor signaling (GSEA)

FDR q-value 0.016
MSC TREATMENT FOR LPS INDUCED LUNG INJURY

Mesenchymal Stem/Stromal Cells

[Images of cell cultures and flow cytometry graphs are shown]

Manuscript under revision
Intrapulmonary

Intravenous

Day 2

MMP-8
MMP-2
MMP-9
Gapdh

C ALI Day 1 ALI-SAL Day 2 ALI-CELL Day 2

Day 2

MMP-8
MMP-2
MMP-9
Gapdh

C ALI Day 1 ALI-SAL Day 2 ALI-CELL Day 2

Manuscript under revision
The chemokine system in diverse forms of macrophage activation and polarization

Alberto Mantovani\textsuperscript{1,2,*}, Antonio Sica\textsuperscript{2}, Silvano Sozzani\textsuperscript{2,3}, Paola Allavena\textsuperscript{2}, Annunciata Vecchi\textsuperscript{2} and Massimo Locati\textsuperscript{1}

\textbf{M1}

- IFN-\gamma + LPS or TNF
- iNOS
- CD86
- MHC II
- RNI
- ROI
- IL-12 high
- IL-23
- IL-10 low

\textbf{M2}

- IL-4 and IL-13
- MHC II
- Arg
- Polyamine
- MR
- SRs
- IL-10 high
- IL-10 Decoy IL-1RI
- IL-1ra

\textbf{M1}

- Classical

\textbf{M2a}

- Alternative

\textbf{M2b}

- Type II

\textbf{M2c}

- Deactivated

\textbf{Th1 RESPONSES:}
- TYPE I INFLAMMATION
- DTH
- KILLING OF INTRACELLULAR PATHOGENS
- TUMOR RESISTANCE

\textbf{Th2 RESPONSES:}
- TYPE II INFLAMMATION
- ALLERGY
- KILLING AND ENCAPSULATION OF PARASITES

\textbf{Th1 ACTIVATION:}
- IMMUNOREGREULATION

\textbf{Th2 RESPONSES:}
- ALLERGY
- IMMUNOREGREULATION
- KILLING AND ENCAPSULATION OF PARASITES
- MATRIX DEPOSITION AND REMODELING
- TUMOR PROMOTION

\textbf{IMMUNOREGREULATION:}
- MATRIX DEPOSITION AND REMODELING
Mesenchymal Stromal Cells: New Directions

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DOI 10.1016/j.stem.2012.05.015

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**proinflammatory**

- TLR-4 + lipopolysaccharide

**polarization**

- MSC
- MSC 1
- MSC 2

**inflammation, injury, allosresponse**
- INFγ, TNFα, IL-1α, IL-1β

* levels / activity not affected by receptor activation

**proinflammatory**

- prevents suppression of T-cells

**immunosuppressive**

- increases MSC migration

**M1**

**M2**

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MSC TREATMENT HAS DIFFERENT EFFECTS ON PRIMARY VERSUS SECONDARY ALI
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