Stem Cells – Canadian Perspective

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Conflict of Interest

- Tissue Regeneration Therapeutics, Toronto, Canada
- Orbsen Therapeutics Ltd, Galway, Ireland
- CommenceBio, California, USA
- Council member, Ontario Institute of Regenerative Medicine
Stem Cells – A Canadian discovery

THE GLOBE AND MAIL

ALAN BERNSTEIN

If Canada's game is hockey, its science is stem cells
What are STEM CELLS?

Resident Lung Stem Cells
Embryonic Stem Cells
Induced Pluripotent Stem Cells
Endothelial Progenitor Cells
Mesenchymal Stromal Cells

Stem cell

Differentiation

Proliferation

Mature cells

Advantages of MSCs
Stem Cell Therapies – focusing on lung Repair?
Mesenchymal stem cells enhance recovery and repair following ventilator-induced lung injury in the rat

Gerard F Curley,¹,² Mairead Hayes,¹,² Bilal Ansari,¹,² Georgina Shaw,³ Aideen Ryan,³ Frank Barry,³ Timothy O’Brien,³ Daniel O’Toole,²,³ John G Laffey¹,²,³

Anaesthetize
High Stretch Ventilation
Intubate

Assessment of Recovery from ARDS

Compliance ed 50%

Recover and extubate
MSCs enhance injury resolution following VILI

Curley et al, Thorax 2012
Hayes, Masterson et al, Anesthesiology 2014
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 Matthay²
Human mesenchymal stromal cells decrease the severity of acute lung injury induced by *E. coli* in the rat

James Devaney,¹,² Shahd Horie,¹,² Claire Masterson,¹,² Steve Elliman,³ Frank Barry,² Timothy O’Brien,² Gerard F Curley,⁴ Daniel O’ Toole,¹,² John G Laffey⁴

**Survival**

<table>
<thead>
<tr>
<th>Time (Hours)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>12</td>
<td>0.2</td>
</tr>
<tr>
<td>24</td>
<td>0.6</td>
</tr>
<tr>
<td>36</td>
<td>0.7</td>
</tr>
<tr>
<td>48</td>
<td>0.8</td>
</tr>
</tbody>
</table>

- **hMSCs (10-20 million/kg)**
- **Vehicle/Fibroblast**

Devaney et al, Thorax 2015
Human mesenchymal stromal cells decrease the severity of acute lung injury induced by E. coli in the rat

James Devaney,¹,² Shahd Horie,¹,² Claire Masterson,¹,² Steve Elliman,³ Frank Barry,² Timothy O’Brien,² Gerard F Curley,⁴ Daniel O’Toole,¹,² John G Laffey⁴

Devaney et al, Thorax 2015
Umbilical cord MSCs

- Ease of accessibility
- Absence of risk for the donor
- Absence of pain for donor
- Consistency in terms of age at collection
Sham E.Coli + Vehicle
E.Coli + UC-MSC

Cryopreserved, Xeno-Free Human Umbilical Cord Mesenchymal Stromal Cells Reduce Lung Injury Severity and Bacterial Burden in Rodent *Escherichia coli*–Induced Acute Respiratory Distress Syndrome

Gerard F. Curley, MB, PhD, FCAI;2,3; Mirjana Jerkic, MD, PhD; Steve Dixon, BSc; Grace Hogan, BSc; Claire Masterson, PhD; Daniel O’Toole, PhD; James Devaney, PhD; John G. Laffey, MD, MSc, FCAI

*Crit Care Med* 2017; 45:e202–e212
How do MSCs work?
Effects of Intratracheal Mesenchymal Stromal Cell Therapy during Recovery and Resolution after Ventilator-induced Lung Injury
Antibacterial Effect of Human Mesenchymal Stem Cells Is Mediated in Part from Secretion of the Antimicrobial Peptide LL-37

Anna Krasnodembskaya, a, Yuanlin Song, b Xiaohui Fang, a Naveen Gupta, c Vladimir Serikov, d Jae-Woo Lee, a, b Michael A. Matthay a, b, e
Human Mesenchymal Stem (Stromal) Cells Promote the Resolution of Acute Lung Injury in Part through Lipoxin A$_4$

Xiaohui Fang,* Jason Abbott,* Linda Cheng,* Jennifer K. Colby,† Jae Woo Lee,‡ Bruce D. Levy,† and Michael A. Matthay**§

*J Immunol* 2015; 195:875-881
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*J Immunol 2015; 195:875-881
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, Jieming Qu¹, Michael A. Matthay³,⁴,⁵, Jae W. Lee³,⁴
Human mesenchymal stromal cells decrease the severity of acute lung injury induced by *E. coli* in the rat

James Devaney,1,2 Shahd Horie,1,2 Claire Masterson,1,2 Steve Elliman,3 Frank Barry,2 Timothy O’Brien,2 Gerard F Curley,4 Daniel O’Toole,1,2 John G Laffey4

**A**

BAL Macrophages (x 10^5/ml)

- Vehicle
- 10 x 10^6 kg^-1
- 20 x 10^6 kg^-1
- Fibroblasts

**B**

Macrophage Phagocytosis (Fold)

- PBS
- hMSC

*Devaney et al, Thorax 2015*
MSCs enhance Macrophage Phagocytosis of Bacteria
MSCs – Key mechanisms of Action

Increased phagocytosis

Increased endothelial and epithelial repair

PGE2

LL-37

KGF

M2-like macrophage

Increased alveolar fluid clearance

Resolution of inflammation

\[ \text{TNF} \alpha \]

\[ \text{IL-10} \]

\[ \text{PMN} \]

\[ \text{ENaC} \]

\[ \text{ATP} \]

\[ \text{MSC} \]

St. Michael's
Inspired Care. Inspiring Science.
hMSCs for ARDS…where are we now?
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

www.thelancet.com/respiratory  Published online December 17, 2014  http://dx.doi.org/10.1016/S2213-2600(14)70291-7

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Sex</th>
<th>APACHE III</th>
<th>Primary cause of ARDS</th>
<th>Tidal volume (mL/kg PBW)</th>
<th>Plateau pressure (cm H₂O)</th>
<th>PEEP (cm H₂O)</th>
<th>PaO₂:FiO₂ (mm Hg)</th>
<th>Lung injury score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 million cells/kg PBW</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 1</td>
<td>29</td>
<td>Female</td>
<td>81</td>
<td>Pre-eclampsia</td>
<td>7.0</td>
<td>28</td>
<td>10</td>
<td>173</td>
</tr>
<tr>
<td>Patient 2</td>
<td>86</td>
<td>Female</td>
<td>121</td>
<td>Pneumonia</td>
<td>6.6</td>
<td>31</td>
<td>10</td>
<td>101</td>
</tr>
<tr>
<td>Patient 3</td>
<td>59</td>
<td>Female</td>
<td>130</td>
<td>Aspiration</td>
<td>6.0</td>
<td>25</td>
<td>10</td>
<td>168</td>
</tr>
<tr>
<td>5 million cells/kg PBW</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 4</td>
<td>67</td>
<td>Female</td>
<td>133</td>
<td>Aspiration</td>
<td>6.3</td>
<td>21</td>
<td>10</td>
<td>105</td>
</tr>
<tr>
<td>Patient 5</td>
<td>62</td>
<td>Female</td>
<td>109</td>
<td>Pneumonia</td>
<td>5.6</td>
<td>20</td>
<td>14</td>
<td>111</td>
</tr>
<tr>
<td>Patient 6</td>
<td>46</td>
<td>Female</td>
<td>83</td>
<td>Aspiration</td>
<td>6.0</td>
<td>19</td>
<td>10</td>
<td>153</td>
</tr>
<tr>
<td>10 million cells/kg PBW</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 7</td>
<td>52</td>
<td>Male</td>
<td>121</td>
<td>Pneumonia</td>
<td>7.1</td>
<td>23</td>
<td>10</td>
<td>154</td>
</tr>
<tr>
<td>Patient 8</td>
<td>55</td>
<td>Female</td>
<td>127</td>
<td>Sepsis (biliary)</td>
<td>5.9</td>
<td>34</td>
<td>10</td>
<td>194</td>
</tr>
<tr>
<td>Patient 9</td>
<td>38</td>
<td>Male</td>
<td>68</td>
<td>Pneumonia</td>
<td>6.0</td>
<td>8</td>
<td>Not measured</td>
<td>118</td>
</tr>
</tbody>
</table>

APACHE=Acute Physiology and Chronic Health Evaluation. ARDS=acute respiratory distress syndrome. PBW=predicted bodyweight. PEEP=positive end-expiratory pressure.

Table 1: Baseline characteristics
### Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Observational (n = 21)</th>
<th>Intervventional (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, Median (range)</strong></td>
<td>61 (23-95)</td>
<td>71 (38-91)</td>
</tr>
<tr>
<td><strong>Sex, (female), No (%)</strong></td>
<td>12 (57)</td>
<td>5 (56)</td>
</tr>
<tr>
<td><strong>APACHE II Score, Median (range)</strong></td>
<td>26 (17-32)</td>
<td>25 (11-28)</td>
</tr>
<tr>
<td><strong>MODS, Median (range)</strong></td>
<td>5 (1 – 15)</td>
<td>5 (3 – 10)</td>
</tr>
<tr>
<td><strong>Weight, Median (range)</strong></td>
<td>85 (48-148)</td>
<td>81 (42-110)</td>
</tr>
<tr>
<td><strong>Qualifying Organ Failure, No(%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory Failure</td>
<td>15 (71)</td>
<td>5 (56)</td>
</tr>
<tr>
<td>Coagulation Failure</td>
<td>4 (19)</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>8 (38)</td>
<td>5 (56)</td>
</tr>
<tr>
<td>Organ Hypoperfusion</td>
<td>15 (71)</td>
<td>4 (44)</td>
</tr>
</tbody>
</table>
## Cellular Immunotherapy for Septic Shock (CISS): A Phase I Clinical Trial

Lauralyn A. McIntyre, MD, FRCPC, MHSc\textsuperscript{1,2,3*}, Duncan J. Stewart, MD, FRCPC\textsuperscript{2,4}, Shirley H. J. Mei, PhD\textsuperscript{2,5}, David Courtman, PhD\textsuperscript{2,5}, Irene Watpool, RN, BScN\textsuperscript{2}, John Granton\textsuperscript{6}, John Marshall, MD, FRCSC, FACS\textsuperscript{7}, Claudia dos Santos, MD, MSc, FRCPC\textsuperscript{7}, Keith R. Walley, MD\textsuperscript{8}, Brent W. Winston, MD, FRCPC\textsuperscript{9}, Kenny Schlosser, PhD\textsuperscript{2,5}, Dean A. Fergusson, PhD\textsuperscript{2,3}, For the Canadian Critical Care Trials Group and the Canadian Critical Care Translational Biology Group

<table>
<thead>
<tr>
<th>*Expected Adverse Events No (%: 95%CI)</th>
<th>Observational (n = 21)</th>
<th>Intervventional (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nosocomial bacterial infection</td>
<td>10 (48: 24-71)</td>
<td>2 (22: 0-56)</td>
</tr>
<tr>
<td>Nosocomial fungal infection</td>
<td>5 (24: 4-44)</td>
<td>3 (33: 0-72)</td>
</tr>
<tr>
<td>Clinically important bleeding</td>
<td>3 (14: 0-31)</td>
<td>2 (22: 0-56)</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>2 (10: 0-23)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Tachyarrhythmia/bradyarrhythmia</td>
<td>3 (14: 0-31)</td>
<td>4 (44: 4-85)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Outcomes</th>
<th>Observational (n = 21)</th>
<th>Intervventional (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality No (%: 95%CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU</td>
<td>4 (19: 1-37)</td>
<td>2 (22: 0-56)</td>
</tr>
<tr>
<td>90 days</td>
<td>4 (19: 1-37)</td>
<td>2 (22: 0-56)</td>
</tr>
<tr>
<td>ICU length of stay (survivors), Median (range)</td>
<td>13 (4-50)</td>
<td>12 (7-30)</td>
</tr>
</tbody>
</table>
The Results of the Russian Clinical Trial of Mesenchymal Stromal Cells (MSCs) in Severe Neutropenic Patients (pts) with Septic Shock (SS) (RUMCESS trial)

Gennadii M. Galstian, Elena N. Parovichnikova, Polina M. Makarova, Larisa A. Kuzmina, Vera V. Troitskaya, Eduard Gemdzhian, Nina I. Drize and Valeri G. Savchenko
Stem Cells for ARDS – Challenges

- Understanding mechanisms of action

Laffey and Matthay, AJRCCM 2017
• Canadian contributions to health research and medicine. Two stand out as landmarks: the discovery of insulin in the 1920s and the discovery of stem cells in the 1960s.

• Canada founded the entire field of stem-cell science...discovering neural stem cells, skin stem cells and cancer stem cells.

• Canada does this for a dime...The “all in” investment in stem-cell research in Canada is about $75-million [2012 Figures].

• Funding still seriously lags behind California, which, with roughly the same population as Canada, has committed $3-billion over 10 years for stem-cell research.
Cell therapy trials in Ontario 2015-16

**Brain and/or nerves**
- **Phase II** using MSCs for Multiple Sclerosis: Toronto*
- **Phase III** using diabetes drug to stimulate brain repair for malignant brain tumours: Toronto*

**Blood**
- **Phase I** using immune cells for blood cancer relapse after bone marrow transplantation: Toronto*

**Joints**
- **Phase I-II** using stem cells mid- to late-stage knee osteoarthritis: Toronto*

**Heart**
- **Phase II** using genetically modified stem cells following heart attack: Ottawa and Toronto*
- **Phase II** using MSCs for advanced heart failure with left ventricular assist device: Toronto*

**Spine**
- **Phase I/II** using neural stem cells for spinal cord trauma: Toronto*

**Digestive system**
- **Phase III** using MSCs to induce remission of Crohn’s disease: London and Toronto

**Critical care**
- **Phase I** using MSCs for septic shock: Ottawa*

- **2015-16**
  - 9 trials
  - 11 partners
  - 3 Ontario cities
  - 655+ patients
  - Billions of stem cells

* OIRM researchers leading trial
Hematopoietic stem cell transplantation

Timeline: History of stem cell transplantation

- **1954**: First Animal studies
- **1954**: Human Allogenic BM Transplant
- **1957**: First Human studies
- **1977**: First Proof of efficacy (in AML)
- **1982/6**: Proof of efficacy in CML
- **2001-16**: Ongoing Discoveries e.g. MSCs for GVHD

Proof of efficacy in CML

Start of an exciting journey....

**First Animal studies**

**Human Allogenic BM Transplant**
Stem Cells - A Canadian Perspective

- Stem cells offer considerable potential for Critical Illnesses
  - Pre-clinical studies highly encouraging
  - MSCs now in early phase Clinical Studies for ARDS

- Clinical Translational pathway likely to be lengthy and there will be setbacks...

- Twin-track strategy of pre-clinical research and early phase clinical translational studies in progress

- Canada’s role in realizing clinical potential of stem cells
  - World leading Preclinical/Discovery science
  - CISS-1 Study a major step forward in Sepsis

Laffey and Matthay, AJRCCM 2017
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Sergio Grinstein
Timothy O’Brien