**Disclosure**

I have nothing to disclose
Life-Long Consequences of Extreme Prematurity
Emphysema in Young Adult Survivors of Moderate-to-Severe BPD

Thin section CT of a 20 year old non-smoking male born 1355g at 28 weeks gestation, dependent upon supplementary oxygen to 321 days postpartum. There is severe emphysema and almost complete replacement of the right upper lobe with a large bulla.

Wong PM et al. Eur Respir J 2008

Slide courtesy Steven Abman

Putative Repair Mechanisms in the Lung

Alveolar Type 2 cell dedifferentiation

Griffiths MJD et al. Lancet 2005

Hematopoietic Stem Cells:
The best described Adult Stem Cell

stemcells.nih.gov (© 2008 Terese Winslow)
Bone Marrow-derived MSCs: ...

to potent repair cell

Experimental O₂-induced “BPD” in Newborn Rodents

Airway and i.v. delivery of BM-derived MSC Prevents O₂-induced Lung Injury and Inflammation in Rodents

Harnessing the Healing Potential of Human Umbilical Cord/Cord Blood-derived Stem Cells

- 100 Million births world-wide
- Used to be Discarded
- Clinically relevant
- Painless and Safe Collection
- No ethical dilemma
- Potent stem cells
- Superior repair potential
Parabiosis Experiments Demonstrate the Effects of Young vs Old Stem Cells and the Influence of a Young vs Old Environment

Young–young (Isochronic)  Young–old (Heterochronic)  Old–old (Isochronic)

“Best”  “Better”  “Not so good”

Conboy I et al. Nature 2005

Cell Manufacturing
“The Process is the Product”

1. Sample Collection
2. Wash
3. Select & Cult
4. Digest & Cell Harvesting
5. Culture
6. Final Storage

Maria Pierro, MD

Airway Delivery of UCB-derived MSC Rescues Arrested Alveolarization in O₂-induced BPD

Mean Linear Intercept (µm)

Pierro et al. Thorax 2013
Long term (6 months) Safety and Efficacy

Long term (8 mo) Efficacy on Lung Vascular Density

Systematic Review of Preclinical MSC Studies in Experimental Neonatal Lung Injury

Favors MSC
Systematic Review of Preclinical MSC Studies in Experimental Neonatal Lung Injury

Risk of Bias

<table>
<thead>
<tr>
<th>Risk of Bias Item</th>
<th>Low</th>
<th>Unclear</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomization (BPD or Treatment)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Random Sequence Generation (BPD or Treatment)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allocation Concealment (BPD or Treatment)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding of Personnel (Treatment)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding (i.e. histology)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete Outcome Data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective Outcome Reporting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample Size Calculation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Source of Funding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conflict of Interest</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Augustine et al. Unpublished


- To assess the safety and feasibility of allogeneic human umbilical cord blood-derived MSC transplantation in preterm infants
- Low dose (1 × 10^7 cells/kg); High dose (2 × 10^7 cells/kg)
- Intratracheal MSC transplantation in 9 preterm infants
  Mean GA 25.3 ± 0.9 weeks, Mean BW 793 ± 127 g
  Timing: Mean age of 10.4 ± 2.6 days after birth
- Safe, feasible, and warrants a phase II study

Unprecedented Access to a Unique Large Animal Model closely mimicking the Human Scenario to provide Critical Pre-clinical Safety and Efficacy data

Marius Möbius

Discrepancy between Cell Engraftment and Therapeutic Benefit

CFSE  SP-C  Merge

Engrafted cells: 3.7% ± 2.9%
Conversion: 75.3%± 24.5%
MSC act via “Paracrine” Effects: 
*In vitro* Evidence with MSC-derived CdM

1. Protects from O\(_2\)-Induced Injury of Type II Alveolar Epithelial Cells
   - 85% O\(_2\)
   - 36 hours
   - Apoptosis & Proliferation

2. Accelerates Wound Healing of Type II Alveolar Epithelial Cells

3. Preserves Lung Microvascular Endothelial Cell Cord Formation in O\(_2\)
   - MATRIGEL

---

**“Cell Therapy without the Cell”**

**Exosomes: Therapeutic Membrane-Derived Nano-Particles**

- **Lungs harvested** 8 hours ventilation, 10% O\(_2\)
- **Mean Linear Intercept (µm)**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Mean Linear Intercept (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>75</td>
</tr>
<tr>
<td>VILI</td>
<td>80</td>
</tr>
<tr>
<td>VILI+CdM</td>
<td>82</td>
</tr>
<tr>
<td>VILI+Placebo</td>
<td>85</td>
</tr>
</tbody>
</table>

- Data from Dylan Burger, uOttawa

---

**MSC-CdM attenuates Structural Lung Injury in Mechanically Ventilated Newborn Mice**

- **VILI+Placebo** vs. **VILI+CdM** vs. **Control**
- **Mean Linear Intercept (µm)**

---

**Intratracheal Exosomes attenuate Structural Lung Injury in Mechanically Ventilated Newborn Mice**

- **Data from Dylan Burger, uOttawa**

---

**Exosomes**

- **Mean size:** 86 nm
- **% in size range (40-100 nm):** 94.0%

- **Microparticles**

- **Mean size:** 223 nm
- **% in size range (100-1000 nm):** 96.6%

---

**TSG101** (42 kDa)

**Caveolin-1** (21 kDa)

---

**Kourembanas S. Ann Rev Physiol 2015**

---

**Streueby et al. unpublished**
MSCs Act via a Paracrine Mechanism

Stem/Progenitor cell replacement

Stem/Progenitor cell
Release of repair modulating factors

Paracrine activity

The “Medicinal MSC”

Paracrine Mechanism may explain the Pleiotropic Effects of MSCs...

Support of growth and differentiation of stem and progenitor cells

Antiscarring (anti-fibrosis)

Immunomodulation

Antiproliferation

Angiogenesis

Chemotraction


Arnold I. Caplan and Diego Correa. Cell Stem Cells 2011
Anti-inflammatory

Anti-Fibrotic

Anti-oxidant
Summary

- Perinatal tissues are a rich source of stem/progenitor cells with potentially high repair capacity
  - Mesenchymal Stromal Cells
  - Endothelial Progenitor Cells
  - Amnion Epithelial Cells
  - Macrophages
  - Mononuclear cells
- Pre-clinical studies of cord/blood-derived MSCs show feasibility, safety and structural and functional short- and long-term benefit in neonatal rodents exclusively
- MSCs act via a paracrine effect
- Early Phase Clinical Trials underway

Perspectives

- Improve understanding of the biology of repair cells
  - Determine their mechanism of action
  - Identify the best repair cell
- Identify reliable and reproducible potency assays
- Optimize manufacturing process: impacts cell quality (e.g. clinical trial results)
- Perform methodologically robust pre-clinical studies in relevant animal models to best inform clinical trials
- Streamlining the process (“Incubator”) may ensure accelerated and successful bench-bed side translation
INCuBATOR Roadmap for the Safe and Timely Translation of Human UC-MSC into the Clinic

<table>
<thead>
<tr>
<th>2016</th>
<th>2017</th>
<th>2018</th>
<th>2019</th>
<th>2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td>Q2</td>
<td>Q3</td>
<td>Q4</td>
<td>Q1</td>
</tr>
<tr>
<td>Q2</td>
<td>Q3</td>
<td>Q4</td>
<td>Q1</td>
<td>Q2</td>
</tr>
<tr>
<td>Q3</td>
<td>Q4</td>
<td>Q1</td>
<td>Q2</td>
<td>Q3</td>
</tr>
<tr>
<td>Q4</td>
<td>Q1</td>
<td>Q2</td>
<td>Q3</td>
<td>Q4</td>
</tr>
</tbody>
</table>

INCuBATOR concept to accelerate the successful translation of cell therapies for BPD

- Pre-clinical Baboon studies
- Systematic Review: Pre-clinical and Clinical
- Patient/Physician Engagement
- Economic Evaluation
- Health Canada/REB
- Phase I clinical trial UC-MSC for BPD

Further maturation of the INCuBATOR concept as a "one-stop shop" to propel cell therapies from discovery to clinic/market

Collaborators
- Bill Stanford, Michael Rudnicki, Duncan Stewart, Marjorie Brand, David Moher, Dean Fergusson, Shawn Aaron, OHRI, Ottawa
- Sherri Katz, CHEO, Ottawa
- Anne Monique Nuyt, Mai Luu Hôpital Sainte-Justine, Montréal, QC
- Mario Rüdiger, University Hospital C. G. Carus, Dresden, Germany
- Fabio Mosca, Milano, Italy
- Steven Seidner, Cynthia Blanco, University of Texas Health Center, San Antonio, Texas
- Roger Soll, University of Vermont College of Medicine, Burlington, VT
- Mery Yoder, Indiana University, Indianapolis
- Robin Ohls, Suzanne McConaghy, University of New Mexico, Albuquerque, NM
- Larry Nogee, Johns Hopkins, Baltimore, MD
- Jeffrey Whitsett, Cincinnati, OH
- Alice Tarantal, UC Davis, CA
- Katharina Staub, former president, CPBF, Edmonton, AB

Funding Agencies
- Canadian Institutes of Health Research
- Kiwanis Club of Ottawa
- CWANS Club of Ottawa
- CHEO
- OIRM
- CCIRM
- Canadian Foundation for Innovation
- Heart & Stroke Foundation of Canada
- Lung Association
- OHRI

The Discovery of Stem Cells by Canadian Researchers in 1961

"At the time, you don’t think you are going to do something historic"

Dr. Ernest Armstrong McCulloch

Dr. James Edgar Till

"It Takes a Village to Cure a Lung"
Patterns of Pulmonary Disease Among Infants < 28 weeks Gestation: ELGAN Study Cohort

Laughon M et al. Pediatrics 2009

MSC exist in all organs and contribute to tissue repair.
Exogenous umbilical cord-derived MSCs prevent lung injury in BPD models. Why do endogenous lung MSCs not prevent/repair lung injury?

Hyperoxia Impairs Human Fetal Lung MSCs (hfLMSC)

Decreased colony forming efficacy of hfLMSCs in hyperoxia

Moebius M, unpublished
### Clinical Cell Therapy Trials for BPD

**clinicaltrials.gov accessed January, 2017**

**Phase I:**
- ucMSCs (3.10^6/kg) i.t.; n=10; registered in 2010; Status: unknown
- MSCs (3 doses of 5.10^6); Still on of mechanical ventilation FiO2>30% at day 14; n=10; registered in 2015; Status: not yet recruiting

**Phase II:**
- Open-Label Dose Escalation Trial to Evaluate the Safety and Efficacy of Two Dose Levels of PNEUMOSTEM® in Premature Infants at High Risk for BPD
  Umbilical cord blood-derived MSC; Dose A: 10^7/kg  Dose B: 2.10^7/kg at postnatal age 3 to 14 days; Status: recruiting
- Randomized, Double-blind, Multi-center to Evaluate the Efficacy and Safety of Pneumostem® Versus a Control Group for Treatment BPD; Single intratracheal administration of Pneumostem® (10^7/kg), n=70; Status: Active, not recruiting

**Follow-up:**
- Phase I Pneumostem®; ages=4 Months to 2 Years; Status: Active, not recruiting
- Long-term Follow-up of Phase I of Pneumostem® Phase-I; ages=45-63 months; Status: Active, not recruiting
- Follow-up Safety and Efficacy Phase-II Clinical Trial Status: Recruiting