Intra-arterial versus Intravenous Stem Cell Therapy to Aid Ischemic Stroke Recovery: From Bench to Bedside

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Financial Disclosures

Clinical Trial Steering Committee Member:
1. Recover-Stroke (Sponsor: Cytomedix Aldagen)
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2. EV3/Covidien
3. Stryker
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UM Endovascular Stroke Translational Research Laboratory

• 1. Department of Neurology, University of Miami: 2008-2010
• 2. Interdepartmental Research Development Initiative (IRDI) grant: 2009-2010
• 4. Florida Biomedical New Investigator Grant: 2011-2014
• 5. CTSI NIH Grant: Jan 2013-May 2014
Synopsis

• Promise of Stem Cells in Stroke from the Laboratory
• Translation Data on Intra-arterial MSC’s in Stroke
• Rise in Early Clinical Trials
• RECOVER-Stroke Clinical Trial
Need for Novel Class of Stroke Therapies

- IV tPA prevents disability in only 6/1000 patients
- Over 100 clinical trials of neuroprotection agents in stroke have failed
- Endovascular Acute Stroke Therapy when standard of care may only reach 20% of ischemic stroke cases due to limited time window
- MR CLEAN results show that approx 80% pts. may not be able to return to their job
Types of Stem Cells for Rx Use
Strategies in Neuroregeneration

- “Replacement of like for like”
- Stimulation of endogenous repair
- Neuroprotection: prevention of ongoing injury
- Modification of toxic microenvironment
Endogenous Neurogenesis

• Nestin upregulated in astrocytes (Duggal et al 1997)

• **Progenitor cells from SVZ** migrate to striatum in MCA-O model in rat (Arvidsson et al 2002)

• NSC migrate up to 4 months after injury

• “Homing” due to upregulated SDF-1 in stroke lesion and CXCR4 expressed on migrating neuroblasts (Thored et al 2006)

• **Endogenous regeneration insufficient** for recovery of function
Stem Cells in Stroke

• Stem Cell studies in the laboratory are consistently promising over last 15 years


• Early clinical trials of directly delivered stem cells (Phase I/IIa) show feasibility and safety of stem cell therapy in stroke Kondziolka et al *Neurology* 2000;55:565-569

• Promising preclinical data for stem cell therapy Tang et al *Cell Transplant*. 2007;16(2):159-69.
Clinical trials in Chronic Stroke: hNT trial

- Phase II trials
- 18 patients with basal ganglia stroke
- 1-6 years from stroke with stable deficits
- Rx group: Stereotacttic transplantation (n=14) 5 or 10 x 10^6 cells
- Control group: n=4
- All pts received constraint Rx X 8 weeks

- 6 of 14 Rx patients showed non statistically significant improvement in motor ESS
- Secondary neurological measures statistically improved
Intravenous versus Intra-arterial delivery

Intravenous

- Least invasive
- Systemic and pulmonary circulation decreases number of cells homing to brain
- ~ 4% of cells entered the brain
- 74 cells/mm² in infarct lesion Guzman et al Stroke. 2008;39:1300-1306

Intra-arterial

- Relatively invasive
- Circumvents systemic circulation
- 21% of cells entered the brain (Li et al., Neurology 56:1666–1672, 2001)
- 1300 cells/mm² in infarct lesion Guzman et al Stroke. 2008;39:1300-1306
IA vs IC vs IV cell delivery: Timing of migration and distribution of Cells

Biodistribution of cells in IA vs IV delivery

Pendharkar et al. *Stroke* 2010;41;2064-2070
Dileep R. Yavagal, MD
Ultramicroscopy: IA allogenic cGFP MSCs, day 1 post injection

Control

Day 1 post IA MSCs
Acute administration of MSCs post recanalization

- If cells mediate benefit mainly through neuroprotection, acute delivery to maximize chances of tissue salvage
- Challenges: excitotoxicity, peri-infarct depolarization, reactive O2 species release
Intra-arterial delivery of Stem Cells in Stroke

Walczak et al. Stroke 2008;39;1569-1574
Methods

- Female Sprague-Dawley rats 250-300 g
- 90 min suture induced reversible MCA occlusion (rMCAO)
- At 60 min post recanalization: Intra-carotid (IC) injection of vehicle or allogenic male rat MSCs in escalating dose groups
- Continuous Laser doppler flow signal (LDFS) monitoring over ipsilateral cortex

Longa et al. Stroke 1989;20:84-91
Efficacy and Dose-Dependent Safety of Intra-Arterial Delivery of Mesenchymal Stem Cells in a Rodent Stroke Model

Dileep R. Yavagal¹ ² ³ *, Baowan Lin¹, Ami P. Raval¹ ², Philip S. Garza¹, Chuanhui Dong², Weizhao Zhao², Erika B. Rangel³, Ian McNiece³, Tatjana Rundek², Ralph L. Sacco², Miguel Perez-Pinzon¹ ², Joshua M. Hare³ ⁴

May 7th, 2014
CBF worsening is normalized on dose-de-escalation to $1 \times 10^5$ MSCs
Cerebro-Microvascular MSC Transport: Diapedesis
Pre-Clinical Efficacy Study

A

- 90’
- 60’ or 24h

rMCAo
Reperfusion
Post-injection

Injection

Neurodeficit assessment
At 1, 7, 14, 21 and 28 days

Real time laser-Doppler flowmetry (LDF)
Significant Functional Benefit with 24h_IC MSC
Infarction frequency map and Statistical comparison

PBS-control (n=5)  MSCc-treated (n=9)  Fisher’s Exact Test
The Trouble with Animal Models

The Trouble With Animal Models Why did human trials fail By Andrea Gawrylewski

Related Articles Why sex matters in mouse models Trials and error On October 26, 2006, at the opening day of the Joint World Congress for Stroke in Cape Town, South Africa, disappointing news spread quickly among the attendees: The second Phase III clinical trial for NXY-059 had failed. The drug, a free-radical spin trap agent for ischemic stroke, had been eagerly anticipat

By Andrea Gawrylewski | July 1, 2007

The Trouble With Animal Models

Why did human trials fail

By Andrea Gawrylewski
Unique Advantages of Large Animal Studies

- Route of Cell Administration
- Cell dose finding
- Cell Tracking in a larger brain
- DTI in larger brain?
Canine Neurovascular Anatomy
Dog CCA bifurcation
Superselective catheterization of ICA
Canine Endovascular MCA occlusion Model

Yavagal et al, SVIN 4th Annual Meeting
MRA COW
D10-009; subacute IA 10 x 10^6 MSCs

48 hrs post stroke FLAIR

29 days post stroke FLAIR
D10-011; subacute IA $10^6$ MSCs

48 hrs post stroke FLAIR

21 days post stroke FLAIR
D10-002; treatment with IV
5 x 10^6 MSCs

3 day post stroke T2

58 day post stroke T2
Safety of IA cell delivery in canine stroke model

- Subacute IA (n=4)
- Subacute IV (n=2)
- Placebo (n=2)
- Acute IA (n=2)

Base
Post stroke/ Pre injection
Post Injection
Last Recorded
Intraarterially Delivered Human Umbilical Cord Blood-Derived Mesenchymal Stem Cells in Canine Cerebral Ischemia


Dai-Jung Chung,¹ Chi-Bong Choi,² Sung-Ho Lee,¹ Eun-Hee Kang,¹
Jae-Hoon Lee,¹ Soo-Han Hwang,³ Hoon Han,³ Jong-Hwan Lee,⁴
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Seoul, Republic of Korea
Proposed IA MSC Acute Stroke Trial: STEM-STROKE

- Proposed Trial:
  - STEM-STROKE: A Safety Trial of Intra-Arterial Mesenchymal Stem Cells in Ischemic Stroke
  - Safety study of intra-carotid allogeneic MSC delivery post AIS at
  - Dose ranging using Continual Reassessment Method (CRM)
<table>
<thead>
<tr>
<th>Study/Country</th>
<th>Type of stroke</th>
<th>Design</th>
<th>No. of patients</th>
<th>Cell type</th>
<th>Timing of IA delivery</th>
<th>Dose</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mendonca 2006; Correa 2007/Brazil</td>
<td>MCA ischemic stroke</td>
<td>Case reports on phase I, nonrandomized, open label</td>
<td>2 (no controls)</td>
<td>Auto BM-MNCs</td>
<td>5d &amp; 9d</td>
<td>1 x 10^8 (1 pt.) and 3 x 10^7 (1 pt.)</td>
<td>2-4 mo</td>
</tr>
<tr>
<td>Battistella 2011; Rosadode-Castro, 2013/Brazil</td>
<td>MCA ischemic stroke</td>
<td>Phase I, nonrandomized, open label</td>
<td>12 (no controls)</td>
<td>Auto BM-MNCs</td>
<td>19-89 d (mean 64.5d)</td>
<td>1 x 10^8 to 5 x 10^8 (mean 3.1 x 10^8)</td>
<td>6 mo</td>
</tr>
<tr>
<td>Friedrich, 2012/Brazil</td>
<td>MCA ischemic stroke</td>
<td>Phase I/II, nonrandomized, single-blind (CT)</td>
<td>20 (no controls)</td>
<td>Auto BM-MNCs</td>
<td>3-10 days (mean 6 d)</td>
<td>5.1 x 10^7 to 6 x 10^8 (mean 2.2 x 10^8)</td>
<td>6 mo</td>
</tr>
<tr>
<td>Moniche et al., 2012/Spain</td>
<td>MCA ischemic stroke</td>
<td>Phase I/II, nonrandomized, single-blind</td>
<td>10 (10 controls)</td>
<td>Auto BM-MNCs</td>
<td>5-9d (mean 6.4 d)</td>
<td>mean 1.6 x 10^8</td>
<td>6mo</td>
</tr>
<tr>
<td>Jiang et al., 2012/China</td>
<td>MCA ischemic (3) hemorrhagic (1) stroke</td>
<td>Phase I, nonrandomized, open label</td>
<td>4 (no controls)</td>
<td>Allogeneic UC-MSCs</td>
<td>11 to 50 days (mean 25.5)</td>
<td>2 · 10^7</td>
<td>6 mo</td>
</tr>
</tbody>
</table>
RECOVER-Stroke:

Clinical Trial of Autologous Marrow Cell in Stroke

- Phase 1 / 2 Study of ALD-401 Via Intracarotid Infusion in Ischemic Stroke

- Randomized trial of Autologous stem cells
- 2 weeks (13-19 days) post stroke
- 100 patients
- IA delivery within 48 hours of bone marrow harvest
- Safety endpoints: Clinical AE’s and SAE’s
- Efficacy endpoints: Clinical functional recovery scales at 90 days, 6 mo and 12 months
SYNOPSIS

• Sponsor – Aldagen, Inc.
• ALD-401 Cells from autologous bone marrow
• Phase 2
• Steering Committee:
  • Sean Savitz, MD., UT Houston
  • Dileep R. Yavagal, MD, University of Miami
  • David Huang, MD, University of North Carolina
  • Jim Hinson, MD, Aldagenic
ALDH\textsuperscript{br} Cells Mediate Brain Tissue Volume Loss

Cerebral hemispheres with infarction showed a volume decrease (encephalomalacia) of 9.3% in control animals compared with 2.9% in animals receiving ALDH\textsuperscript{br} cells.

ALDH\textsuperscript{br} cells may provide both neuroprotective and neuroregenerative signals.
Treatment Schedule

**Days Post Primary Stroke Event**

- Formal Screening should begin 7 day post primary stroke
- Randomization about 48 hours prior to bone marrow harvest
- Bone Marrow Harvest 2-4 days prior to dosing
- Dosing 13-19 post the primary stroke
Intra-Arterial Delivery
Initial Results Press Release: May 2nd, 2014

• All patients in treatment arm underwent successful harvest (160±20 ml) and received the target dose of 1 to 3 million ALDHbr cells

• 90 days results :
  – **Efficacy**: Mean mRS NO different between the ALD-401 and sham treatment groups.
  – Secondary endpoints were not different between groups.
  – **Safety**: At 90 days NO serious adverse events attributable to the use of ALD-401, demonstrating good tolerability and safety.

• 1 year results: All patients will be followed for 1 year,
  – plan for final results at in 2015
Next Steps

• In light of the foregoing, Cytomedix does not plan to go forward with next phase
• Safety of approach should encourage other funding groups for new trials
Intra-arterial Delivery Is Not Superior to Intravenous Delivery of Autologous Bone Marrow Mononuclear Cells in Acute Ischemic Stroke

Bing Yang, MD; Elton Migliati, PhD; Kaushik Parsha, MD; Krystal Schaar, MS; XiaoPei Xi, BS; Jaroslaw Aronowski, PhD; Sean I. Savitz, MD

Stroke. published online October 10, 2013;

Intra-Arterial Bone Marrow Mononuclear Cells in Ischemic Stroke: A Pilot Clinical Trial
Francisco Moniche, Alejandro Gonzalez, Jose-Ramon Gonzalez-Marcos, Magdalena Carmona, Pilar Piñero, Ildefonso Espigado, David Garcia-Solis, Aurelio Cayuela, Joan Montaner, Cristina Boada, Anna Rosell, Maria-Dolores Jimenez, Antonio Mayol and Alberto Gil-Peralta

- 10 patients and 10 controls
- Mean NIHSS 15
- Intra- MCA, M1 injection of $1.5 \times 10^8$ BMMCs
- No stroke recurrence, death or tumor formation at 6 months
- Two patients with partial seizures
Multistem: Stroke Stem Cell Trial

- Double-Blind, Randomized, Placebo-Controlled Phase 2 Safety and Efficacy Trial of MultiStem® in Adults With Ischemic Stroke
- Intravenous Bone marrow stem cells from healthy donors
- Given within 48 hours of stroke symptom onset
Patient Eligibility: Key Criteria

1. 18-83 years of age
2. Cortical MCA cerebral ischemic stroke
3. NIHSS 8-20
4. Onset of Stroke must have occurred within 24-48 hours
5. Acute cortical lesion measuring $\geq 5\text{mL}$ and $\leq 100\text{mL}$
6. Subjects who received tPA or mechanical thrombectomy are allowed

• If they do, we are happy to transfer the patient preferably before the 24 hour mark to allow us time for enrollment procedures and infusion of the stem cells (off the shelf from healthy donors bone marrow) before 48 hours from stroke symptom onset.
Ongoing/Starting Stem Cell Clinical Trials in Stroke

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Rx Timing</th>
<th>Phase</th>
<th>Randomized</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety/Feasibility of Autologous Mononuclear Bone Marrow Cells in Stroke Patients (IV)</td>
<td>24-72h</td>
<td>I</td>
<td>N</td>
<td>USA</td>
</tr>
<tr>
<td>Intravenous Stem Cells After Ischemic Stroke (ISIS)</td>
<td>&lt;6 Wks</td>
<td>II</td>
<td>Y</td>
<td>France</td>
</tr>
<tr>
<td>Efficacy Study of CD34 Stem Cell in Chronic Stroke Patients</td>
<td>6-60 mo</td>
<td>II</td>
<td>Y</td>
<td>China</td>
</tr>
</tbody>
</table>
Conclusions

1. Intra-arterial Stem Cell Delivery for AIS has stroke biologic and pre-clinical basis
2. 6 Early Clinical Trials show feasibility and good safety
3. Optimal Cell Type and Timing of delivery not well established in pre-clinical studies:
   - Earlier is better
4. Phase 2b studies will be critical to define the role of this promising therapy
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  ISCI, University of Miami
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