Neuroregenerative Medicine: Progress in Pre-clinical Studies and Clinical Translation

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Disclosures

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  2. Intradepartmental Department of Neurology, University of Miami.
  3. Anderson Family Gift to Division of Interventional Neurology.
Outline

• Need for Neuro-regenerative medicine
• Strategies in Neuro-regeneration
• Roadmap to Clinical Translation
• Stem cell therapies in Stroke
  – Intra-arterial Stem cell Rx for acute stroke
• Stem cell therapies in AD, PD, MS and MND
Global Burden of Neurological Diseases: Disability Adjusted Life Years (DALY’s)

<table>
<thead>
<tr>
<th>Cause category</th>
<th>World (100 000 population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epilepsy</td>
<td>113.4</td>
</tr>
<tr>
<td>Alzheimer and other dementias</td>
<td>172</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>25.1</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>23.4</td>
</tr>
<tr>
<td>Migraine</td>
<td>118.9</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>788.4</td>
</tr>
<tr>
<td>Poliomyelitis</td>
<td>1.8</td>
</tr>
<tr>
<td>Tetanus</td>
<td>99.7</td>
</tr>
<tr>
<td>Meningitis</td>
<td>82.9</td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>8.7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1 434.3</strong></td>
</tr>
</tbody>
</table>

* a GBD cause categories
* b Neuropsychiatric plus other categories
Strategies in Neuroregeneration

- “Replacement of like for like”
- Stimulation of endogenous repair
- Neuroprotection: prevention of ongoing injury
- Modification of toxic microenvironment
Roadmap to Clinical Translation

- Clinically competitive; what are acceptable patient risks
- Determination of feasibility of cells to be replaced/endogenously stimulated in a given pathology
- Valid proof of efficacy in animal models
- Determination of biological mechanism of action

doi:10.1172/JCI40543
Ischemic Stroke

- Stroke is the leading cause of long term disability
- Fourth leading cause of death
- Cost of Stroke in 2010: 73 billion
- Despite advances in recanalization therapies for acute ischemic stroke (AIS) rates of good functional outcomes are around 30%

Pathophysiology of Stroke Repair

• Inflammatory reaction
  – leukocytes
  – Macrophages, microglial cells
• Pan necrosis: loss of multiple cell types: neurons, astrocytes, oligodendrocytes, endothelial cells and pericytes
• Apoptosis
• Glial scar formation
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)
- Endogenous 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

- Over last decade, several promising preclinical studies for stem cell therapy Tang et al. *Cell Transplant*. 2007;16(2):159-69.
<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Stroke Model*</th>
<th>Time of Delivery After Stroke</th>
<th>Route of Delivery</th>
<th>Immunosuppression Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neural cells</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPCs (7-wk gestation)</td>
<td>Unilateral 10-min CCAo, repeated 5 h later (g)</td>
<td>4 d</td>
<td>IC: ipsilateral striatum; 5 X 10^5 cells</td>
<td>Start 1 d before grafting; CSA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3• per wk</td>
</tr>
<tr>
<td>NPCs (16-to 20-wk gestation) sorted for CD133 � CD24 � lo cells</td>
<td>dMCAO</td>
<td>1 wk</td>
<td>IC: ipsilateral cortex; 3 sites; 1 x10^5 cells/site</td>
<td>Start 1 d before grafting; CSA daily</td>
</tr>
<tr>
<td>HB1.F3: immortalized NPCs (14-wk gestation)</td>
<td>2-VO � hypotension</td>
<td>24 h</td>
<td>IV or ICV: 5 x10^6 cells for both routes</td>
<td>Start 1 d before grafting; CSA daily</td>
</tr>
<tr>
<td>HB1.F32</td>
<td>90-min MCAo</td>
<td>24 h</td>
<td>IV: 5 x 10^6 cells</td>
<td>None</td>
</tr>
<tr>
<td>HB1.F34</td>
<td>Intracerebral hemorrhage</td>
<td>24 h</td>
<td>IV: 5 x;106 cells</td>
<td>None</td>
</tr>
<tr>
<td>HB1.F3 � VEGF86</td>
<td>90-min MCAo</td>
<td>24 h: cells; 48 h: VEGF</td>
<td>IV: 5 x106 cells</td>
<td>None</td>
</tr>
<tr>
<td>Immortalized NPCs (first trimester)</td>
<td>70-min MCAo</td>
<td>3–4 wk</td>
<td>IC: 2 cortex sites � striatum in each hemisphere; 2x105 cells/site</td>
<td>Start on day of transplant: medrone daily for 20 d, CSA 3• per week for entire study</td>
</tr>
<tr>
<td>hNT cells: immortalized neuronal cell line</td>
<td>60-min MCAo</td>
<td>1 mo</td>
<td>IC: ipsilateral striatum 4 x 10^5 cells</td>
<td>CSA daily starting day of grafting</td>
</tr>
<tr>
<td>hNT cells</td>
<td>60-min MCAo</td>
<td>1 mo</td>
<td>IC: ipsilateral striatum; 5, 10, 20, 40, 80, or 160 x 10^3 cells</td>
<td>CSA daily starting day of grafting</td>
</tr>
<tr>
<td>hNT cells</td>
<td>60-min MCAo</td>
<td>1 mo</td>
<td>IC: ipsilateral striatum 8 x10^4 fresh cells, or 2 x 10^4 cryopreserved cells</td>
<td>CSA daily starting day of grafting except 1 group that had no CSA given</td>
</tr>
<tr>
<td>hNT cells</td>
<td>dMCAo</td>
<td>1 wk</td>
<td>IC: ipsilateral cortex 3 sites; 1 x10^5 cells/site</td>
<td>Start 1 d before grafting; CSA daily</td>
</tr>
<tr>
<td>Bone marrow cells</td>
<td>dMCAo</td>
<td>1 wk</td>
<td>IC: ipsilateral cortex; 3 sites; 7.5 x 10^4 cells/site</td>
<td>CSA daily</td>
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<tr>
<td>--------------------------------------------------------</td>
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</tr>
<tr>
<td>MSCs79</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSCs28</td>
<td>120-min MCAo</td>
<td>24 h</td>
<td>IV: 3 x 10^6 cells</td>
<td>None</td>
</tr>
<tr>
<td>MSCs54</td>
<td>120-min MCAo</td>
<td>24 h</td>
<td>IV: 1 x 10^6 cells</td>
<td>None</td>
</tr>
<tr>
<td>CD133• fraction of bone marrow83</td>
<td>60-min MCAo</td>
<td>1 h or 3 d</td>
<td>IC: ipsilateral striatum; 1 x 10^5 cells; IV: 1 x 10^6 cells</td>
<td>CSA daily starting day of grafting</td>
</tr>
<tr>
<td>MSCs overexpressing BDNF, GDNF, CNTF, or NT330</td>
<td>90-min MCAo</td>
<td>24 h</td>
<td>IC: ipsilateral striatum; 5 x 10^5</td>
<td>CSA daily</td>
</tr>
<tr>
<td>Umbilical cord blood cells</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD34• vs CD34• population56</td>
<td>dMCAo</td>
<td>48 h</td>
<td>IV: 5 x 10^5 cells</td>
<td>None; SCID mice used</td>
</tr>
<tr>
<td>CD34• fraction46</td>
<td>60-min MCAo</td>
<td>48 h</td>
<td>IV: 1 x 10^6 cells</td>
<td>CSA daily</td>
</tr>
<tr>
<td>or</td>
<td></td>
<td>or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dMCAo (m)</td>
<td></td>
<td>1 wk</td>
<td>IC: ipsilateral cortex 7.5 x 10^4 cells</td>
<td>CSA daily</td>
</tr>
<tr>
<td>Cord blood cells82</td>
<td>Permanent MCAo</td>
<td>24 h</td>
<td>IC: ipsilateral striatum; 2.5 x 10^5 cells; IV: 1 x 10^6 cells</td>
<td>CSA daily starting day of grafting</td>
</tr>
<tr>
<td>Cord blood cells18</td>
<td>Permanent MCAo</td>
<td>24 h</td>
<td>IV: 104, 105, 106, 107, or 3–5 x 10^7 cells</td>
<td>CSA daily starting day of grafting</td>
</tr>
<tr>
<td>Cord blood cells87</td>
<td>120-min MCAo</td>
<td>24 h or 1 wk</td>
<td>IV: 3 x 10^6 cells</td>
<td>None</td>
</tr>
<tr>
<td>Cord blood cells &amp; #5; mannitol (BBB permeabilizer)29</td>
<td>60-min MCAo</td>
<td>During occlusion; mannitol coadministered</td>
<td>IV: 2 x 10^5 cells</td>
<td>None</td>
</tr>
<tr>
<td>Peripheral blood cells</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD34• cells57</td>
<td>90-min dMCAo</td>
<td>1 wk</td>
<td>IC: ipsilateral cortex 2 x 10^5 cells</td>
<td>None</td>
</tr>
<tr>
<td>Peripheral blood cells88</td>
<td>Permanent MCAo</td>
<td>24 h</td>
<td>IV: 1 x 10^6 cells</td>
<td>CSA daily starting day of grafting</td>
</tr>
<tr>
<td>Adipose tissue cells</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSCs89</td>
<td>90-min MCAo</td>
<td>24 h</td>
<td>ICV: ipsilateral lateral ventricle 1 x 10^6</td>
<td>None</td>
</tr>
</tbody>
</table>
MSCs: Mechanism of action

• Neuronal differentiation unlikely
• Likely biological mechanism of benefit:
  – angiogenesis and
  – neurogenesis
  – Immunomodulation
  – Anti-apoptosis
Pathotropism of MSC’s in stroke

- Stromal cell derived factor-1 (SDF-1) and CXCR4 essential for stem cell migration
- SDF-1 significantly upregulated in ischemic hemisphere in rats
- Most upregulated in the infarct border zone (IBZ) and remains for 30 days
- CXCR4 expressed by MSC’s
- Interaction b/w CXCR4 and SDF-1 serves to guide migration of MSC’s to brain ischemic areas

Wang et al. _Brain Research_ Vol 1195, 21 February 2008, Pages 104-112
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
IA vs IC vs IV cell delivery: Timing of migration and distribution of Cells

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
Biodistribution of cells in IA vs IV delivery

Pendharkar et al

Stroke 2010; 41; 2064-2070
Dileep R. Yavagal, MD
Intra-arterial delivery of Stem Cells in Stroke

Walczak et al. Stroke 2008;39;1569-1574
Maximum tolerated IA dose study

A

90' 60' 60'
MCAO Reperfusion Post-injection
Injection
Real time laser-Doppler flowmetry
Neurodeficit assessment at 4, 24, 48, 72 and 96 hours

B

CBF change (folds)
MCAO (90') Reperfusion (60')
Base line

C

p < 0.05
Pre-sacrifice mortality

1 mL PBS (n = 6) 0.5 mL PBS (n = 11)
LDFS% change post intra-carotid MSC injection
Neurological outcomes at escalating IA doses

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Number of Subjects (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>11</td>
</tr>
<tr>
<td>$5 \times 10^4$</td>
<td>7</td>
</tr>
<tr>
<td>$1 \times 10^5$</td>
<td>7</td>
</tr>
<tr>
<td>$2 \times 10^5$</td>
<td>5</td>
</tr>
<tr>
<td>$5 \times 10^5$</td>
<td>6</td>
</tr>
<tr>
<td>$1 \times 10^6$</td>
<td>7</td>
</tr>
</tbody>
</table>

$p < 0.05$

Median final neurodeficit
Treatment with IA MSCs improves scores in a neurodeficit battery
Rat MCAo Infarct volume post IA MSC

Infarct Volume mm$^3$

- Placebo
- IA MSCs

p < 0.05
Rat MCAo Infarct volume post IA MSCs

Placebo

MSCs
Infarction frequency map and Statistical comparison

PBS-control (n=5)  MSCc-treated (n=9)  Fisher’s Exact Test
Subacute Intra-carotid MSCs

Intra-carotid NSCs at 48 hours post mouse hypoxia-ischemic model

- Guzman et al. Stroke 2008;39;1300-1306
Intra-arterial delivery of MSC’s in Endovascular canine stroke model

- Test intra-arterial delivery in larger arterial system
- Confirm beneficial effect found in small animals
- White matter ischemic injury in large animals similar to humans
- Correlate in vivo imaging with good spatial resolution with functional recovery
Superselective catheterization of ICA
TCD Velocities over Canine MCA’s

During IA delivery of $10 \times 10^6$ MSCs

Post IA MSCs
D10-009; subacute IA 10 x 10^6 MSCs

48 hrs post stroke FLAIR

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

48 hrs post stroke FLAIR

21 days post stroke FLAIR
D10-002; treatment with IV
$5 \times 10^6$ 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)
54 Y African American woman 4 days post LMCA stroke with NIHSS 17, mRS 4

Intra-LMCA injection of autologous BMMNC10 x 107/ml x 3 ml over 10 min

TCD, EEG monitoring

60 day NIHSS 9, mRS 3
• 37 Y M, D9, LMCA stroke, NIHSS 5
• Intra-LMCA delivery of 3 x 10^7 Tc-99 labelled ABM-MNC
• Posterior LMCA occluded
• Accumulation of SPECT signal in L anterior MCA territory, liver and spleen
Intra-coronary stem cell delivery clinical trials


• Ongoing:
  – COMPARE AMI trial; 14 patients treated
  – SWISS AMI
Early Phase Clinical Trials of Intra-arterial Cell Therapy for Stroke in the US

• None

• Planning stages:
  – STEM-STROKE: A Safety Trial of Intra-Arterial Mesenchymal Stem Cells in Ischemic Stroke
  – Safety and preliminary efficacy study of subacute intra-carotid allogeneic MSC delivery post AIS
  – Dose ranging
  – Historical control
Clinical trials in Chronic Stroke: hNT trials

• Phase 1 trial
  – 12 pts with basal ganglia stroke
  – 44-74 years
  – 6 months to 4.5 years out with stable motor deficits
  – Stereotactic transplantation of hNT2 cells into infarct cavity
  – Immunosuppression for 8 wks after sx
  – No cell related adverse events even 5 years out

• Cell tracking:
  – Some hNT cells detectable at 27 months after transplantation on autopsy in one patient
  – PET scans at 6 mo showed high metabolic activity in graft area

• 6 of 12 patients improved on European Stroke Scale correlating with PET fgd activity
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: Stereotactic 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
## 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</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>
<tr>
<td>Autologous Bone Marrow Stem Cells in Middle Cerebral Artery Acute Stroke Treatment.</td>
<td>5-9 days</td>
<td>I/II</td>
<td>N</td>
<td>Spain</td>
</tr>
<tr>
<td>Study of ALD-401 Via Intra-carotid Infusion in Ischemic Stroke Subjects</td>
<td>2 wks</td>
<td>I &amp; II</td>
<td>Y</td>
<td>USA</td>
</tr>
</tbody>
</table>
Alzheimer’s Disease

- 5.3 million Americans affected; 9.5 million by 2050,
- 18 million affected worldwide
- Loss of cholinergic neurons in hippocampus, entorhinal cortex, basal forebrain
- Progressive memory and learning dysfunction
Neural stem cells improve cognition via BDNF in a transgenic model of Alzheimer disease


Department of Neurobiology and Behavior and Institute for Memory Impairments and Neurological Disorders, University of California, Irvine, CA 92697;
Center for Regenerative Medicine, The Scripps Research Institute, La Jolla, CA 92037; and Zentrum für Integrative Psychiatrie, 24118 Kiel, Germany

www.pnas.org/cgi/doi/10.1073/pnas.0901402106

Graphs showing the effects of NSC injection and behavioral testing on latency and platform crosses in a transgenic model of Alzheimer disease.
Neural stem cells increase synaptic density and produce BDNF
MSC transplantation decreases A-beta deposition in the brain. Lee et al. STEM CELLS 2010;28:329–343
Improvement in spatial and memory impairments in MSC group

A

B

C

Escape latency (sec)

Days

WT

PBS

BM-MSCs

Crossing platform

WT

PBS

BM-MSCs

* \*
Clinical Trials

• The Safety and The Efficacy Evaluation of NEUROSTEM®-AD (Human Umbilical Cord Blood Derived Mesenchymal Stem Cells) in Patients With Alzheimer's Disease

• This study is currently recruiting participants.

• South Korea

• Direct injection
Parkinson’s Disease

- 2nd leading neurodegenerative disease in US
- 1.5 million Americans affected
- Lifetime risk: 2% for men, 1.3% for women

Mesenchymal stem cells therapy exerts neuroprotection in a progressive animal model of Parkinson's disease

Hyun Jung Park,*† Phil Hyu Lee,‡ Oh Young Bang,§ Gwang Lee* and Young Hwan Ahn*

(a) Control
After MG-132 inject
13 weeks
After first hMSC inject
8 weeks

(b) The number of TH-labeled cells

(c) Dopamine level (ng/mg tissue)

(d) Ubiquitinated proteins

(e) Control
After MG-132 inject
13 weeks
After first hMSC inject
8 weeks

(f) Procaspase-3
Cleaved caspase-3
Actin

(g) Density (Arbitrary unit)
Intraarterial Autologous Implantation of Adult Stem Cells for Patients with Parkinson Disease

Augusto Brazzini, MD, Raúl Cantella, MD, Antonio De la Cruz, MD, Jorge Yupanqui, MD, Carlos León, MD, Tamara Jorquera, MD, Mariana Brazzini, MD, Melitón Ortega, MD, and Luis N. Saenz, MD

Autologous Mesenchymal Stem Cell Transplant for Parkinson's Disease

- Single arm, uncontrolled
- Direct stereotactic injection of MSC’s into striatum
- Improvement in UPDRS scale over 18 months
- India
Amyotrophic Lateral Sclerosis

- 30,000 individuals in the U.S.
- Relatively rapid degeneration of upper and lower motor neurons
- Death normally occurring 2–5 years following diagnosis due to respiratory failure

Focal transplantation–based astrocyte replacement is neuroprotective in a model of motor neuron disease

Angelo C Lepore¹, Britta Rauck¹, Christine Dejea¹, Andrea C Pardo¹, Mahendra S Rao², Jeffrey D Rothstein¹,³ & Nicholas J Maragakis¹

- Extended survival and disease duration
- Slowed declines in forelimb motor and respiratory functions
- Neuroprotection mediated in part by astrocyte glutamate transporter GLT1
Safety and Immunological Effects of Mesenchymal Stem Cell Transplantation in Patients With Multiple Sclerosis and Amyotrophic Lateral Sclerosis

Dimitrios Karussis, MD, PhD; Clementine Karageorgiou, MD; Adi Vaknin-Dembinsky, MD, PhD; Basan Gowda-Kurkalli, PhD; John M. Gomori, MD; Ibrahim Kassis, MSc; Jeff W. M. Bulte, PhD; Panayiota Petrou, MD; Tamir Ben-Hur, MD, PhD; Oded Abramsky, MD, PhD; Shimon Slavin, MD

ARCH NEUROL/VOL 67 (NO. 10), OCT 2010
Induced Pluripotent Stem Cells Generated from Patients with ALS Can Be Differentiated into Motor Neurons

Clinical Trial on The Use of Autologous Bone Marrow Stem Cells in Amyotrophic Lateral Sclerosis

- Spain
- Phase I/II, recruiting
- Randomized, uncontrolled intrathecal, intra-spinal vs. intrathecal saline infusion
Multiple Sclerosis (MS)

- 2.5 million people affected worldwide
- 400,000 in the US
- Commonest progressive disabling condition of the young
  - Average age of diagnosis is 37 yrs
- Chronic autoimmune disease affecting brain and spinal cord
- Progressive axonal loss
- Failure to regenerate myelin by adult oligodendrocyte precursor cells (OPCs)
Migration of hESC derived NPs to host white matter

Minimal differentiation to mature oligodendrocytes and remyelination

Attenuation of inflammatory process

Immunosuppressive neuroprotective mechanism
• 21 patients with relapsing remitting MS, failed interferon beta Rx
• Mobilized peripheral blood hemopoietic stem cells
• 81% showed at least one point improvement in neurological disability scale
• All pts free of disease progression at mean of 37 months and 16/21 free of relapses
Stem Cell Therapy for Patients With Multiple Sclerosis Failing Interferon A Randomized Study (MIST)

- Efficacy of autologous peripheral blood stem cell transplantation (PBSCT) versus FDA approved standard of care
- Northwestern University, Chicago, IL
- NCT00273364
Summary

- No proven stem cell therapy for neurological illness yet
- Potential for radical new therapies for neurological illnesses without effective treatments
- Continuous development of different cell production technology; iPS
- Effect of pathological environment on grafted and endogenous stem cells
- Mechanism of action, behavior of progeny: areas of active research, effective control of transplanted cells
- Solid scientific understanding foundation for clinically competitive and successful therapies
- Burden on scientists, regulators and clinicians and ethicists to act together for responsible clinical translation
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Front Row: Tienlong Pham, Philip Garza, BS, Baowan Lin, MD,
Back Row: Dalia Milan, Ami Raval PhD, Pedro Cifuentes, MD,
Steven Amatangelo, MS.

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  Joshua Hare, MD
  Ian McNiece, PhD
  Miguel Pérez-Pinzón, PhD
  Tanja Rundek, MD, PhD
Thank you!
MSC Infusion Angiogram

Before IA MSC infusion
MSC Infusion Angiogram

After IA MSC infusion