3rd Annual International Symposium on the Fetal Brain

Molecular Imaging and Nanotechnology to Prevent Cerebral Palsy Caused by Intra-amniotic Infection

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Moriah Thomassen
Aaron White

Yoon B.H. and Romero R; Seoul National University

Yoon B.H. and Romero R; Seoul National University
Non-progressive "development disorder" of the brain
-Two years
-Manifests itself primarily with one or more motor dysfunctions:
  - Movement
  - Posture
  - Swallowing
-Although brain damage may be static, the disabilities resulting from it often change over time (worsen or improve)

“On the influence of abnormal parturition, difficult labor, premature birth and asphyxia neonatorum; on the mental health of the child, especially in relation to deformities”


Clinical Paradigm

Intrapartum Asphyxia
\[\downarrow\]
Asphyxia Neonatorum
\[\downarrow\]
Cerebral Palsy

Course

- Emergency C/section
- Complete abruptio placentae
- Birth Weight: 2,680 grams
- APGARs: 1 / 4 / 4
- pH 6.47
Pathological Basis for Cerebral Palsy

Horizontal Segment

Neurovascular Tutorial, Neuroscience Course, Loyola University Chicago, Stritch School of Medicine

Yoon B.H., Kim CJ, Chi JS and Romero R

Normal brain

Hyperechoic lesion

Cystic PVL
What is the relationship between preterm birth and cerebral palsy?

Gestational Age and Distribution and Prevalence of Cerebral Palsy

Prevalence of cerebral palsy according to gestational age among 1,764,509 live births

- National cohort study
- All deliveries in Norway 1967-2001 (n=1,764,509)
- Prevalence of cerebral palsy 1.8:1000
### Odds ratios for cerebral palsy according to gestational age at birth among 1,764,509 live births

<table>
<thead>
<tr>
<th>GA at birth (wks)</th>
<th>Absolute risk, % (No. with CP/No. in category)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted ORa (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>23–27</td>
<td>8.5 (142/1673)</td>
<td>74.0 (61.9–88.4)</td>
<td>83.4 (69.4–100.4)</td>
</tr>
<tr>
<td>28–30</td>
<td>5.6 (268/4746)</td>
<td>47.7 (41.8–54.4)</td>
<td>50.2 (43.8–57.4)</td>
</tr>
<tr>
<td>31–33</td>
<td>2.0 (309/15464)</td>
<td>16.3 (14.4–18.4)</td>
<td>16.5 (14.6–18.7)</td>
</tr>
<tr>
<td>34–36</td>
<td>0.4 (285/70437)</td>
<td>3.2 (2.6–3.7)</td>
<td>3.3 (2.6–3.7)</td>
</tr>
<tr>
<td>37–41</td>
<td>0.1 (1807/1442598)</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>42-43</td>
<td>0.3 (340/229591)</td>
<td>5.2 (1.3–1.3)</td>
<td>5.2 (1.3–1.3)</td>
</tr>
</tbody>
</table>


### What is the relationship between intra-amniotic infection/inflammation and cerebral palsy?

- What is the relationship between intra-amniotic infection/inflammation and cerebral palsy?

### Frequency of a Positive Amniotic Fluid Culture and Intraamniotic Inflammation as a Function of Gestational Age


A MINIMUM estimate of the frequency of infection in Preterm Birth

1 Of Every 3 Preterm Births are Delivered to Mothers with Intra-amniotic Infections
Is there evidence that intrauterine infection can cause brain damage?

Intrauterine Infection

Periventricular Leukomalacia

Clinical Chorioamnionitis and the Prognosis for Very Low Birth Weight Infants


<table>
<thead>
<tr>
<th>Neonatal Complications Associated with Intrauterine Infection</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 min Apgar &lt;3</td>
<td>0.5, 1.3, 2.3, 3.3, 6.9</td>
</tr>
<tr>
<td>Cord pH &lt; 7.0</td>
<td>0.5, 1.3, 2.7, 7.1</td>
</tr>
<tr>
<td>Sepsis</td>
<td>0.3, 1.5, 2.9, 5.5</td>
</tr>
<tr>
<td>RDS</td>
<td>1.5, 2.0, 4.8</td>
</tr>
<tr>
<td>IVH</td>
<td>1.6, 3.4, 4.8</td>
</tr>
<tr>
<td>PVL</td>
<td>1.2, 3.6, 6.8</td>
</tr>
<tr>
<td>Seizures</td>
<td>1.7, 3.3</td>
</tr>
<tr>
<td>Neonatal Death</td>
<td>10.5, 2, 3, 4, 5, 8, 10</td>
</tr>
</tbody>
</table>


**Is intra-amniotic inflammation associated with PVL?**

**Study Design**

- Amniocentesis
- Neonatal Ultrasound
- Follow-up Cerebral Palsy
Follow-up

94 Neonates

Died (<6 months) (n = 11)

Survived (>6 months) (n = 83)

No CP (n = 75)

CP (n = 8)

Cases with Cerebral Palsy

<table>
<thead>
<tr>
<th></th>
<th>GA</th>
<th>BW</th>
<th>AF culture</th>
<th>Chorio</th>
<th>PVL</th>
<th>pH</th>
<th>IL-6 (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29</td>
<td>800</td>
<td>+</td>
<td>+</td>
<td>Cystic</td>
<td>NA</td>
<td>55.4</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>1600</td>
<td>–</td>
<td>+</td>
<td>Echogenic</td>
<td>7.24</td>
<td>50.2</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>1260</td>
<td>–</td>
<td>+</td>
<td>Cystic</td>
<td>7.34</td>
<td>2.95</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>1650</td>
<td>–</td>
<td>+</td>
<td>Cystic</td>
<td>NA</td>
<td>92.5</td>
</tr>
<tr>
<td>5</td>
<td>31</td>
<td>1140</td>
<td>+</td>
<td>+</td>
<td>Cystic</td>
<td>7.35</td>
<td>7.88</td>
</tr>
<tr>
<td>6</td>
<td>31</td>
<td>1440</td>
<td>–</td>
<td>–</td>
<td>Cystic</td>
<td>7.64</td>
<td>3.00</td>
</tr>
<tr>
<td>7</td>
<td>31</td>
<td>1410</td>
<td>+</td>
<td>Cystic</td>
<td>7.33</td>
<td>34.7</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>31</td>
<td>2200</td>
<td>+</td>
<td>NA</td>
<td>Echogenic</td>
<td>7.21</td>
<td>18.9</td>
</tr>
</tbody>
</table>

Is Fetal Systemic Inflammation Associated with PVL?

172 Consecutive Preterm Births 25-36 Weeks

Umbilical Cord Birth (IL-1ß, TNF, IL-6, IL-1ra)

Neonatal Neurosonography

Periventricular Leukomalacia-Associated Lesions Analyzed by Logistic Regression

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cord IL-6 &gt; 400 pg/ml</td>
<td>6.2</td>
<td>1.1-19.1</td>
<td>P &lt; 0.002</td>
</tr>
<tr>
<td>Cord arterial pH &lt;7.15</td>
<td>5.9</td>
<td>1.4-25.4</td>
<td>P &lt; 0.02</td>
</tr>
<tr>
<td>Delivery mode</td>
<td>3.4</td>
<td>1.0-11.3</td>
<td>NS</td>
</tr>
</tbody>
</table>
Can PVL lesions be induced experimentally?

Animal Experimentation

- Pregnant rabbits
- 20-21 days of gestation
- 70% gestation

PVL lesions were induced experimentally on pregnant rabbits with 20-21 days of gestation and 70% gestation. The procedure involved the injection of 0.2 ml of E. coli, with concentrations ranging from $10^3$ to $10^4$ cfu, or saline into the uterus. The injection was performed using a Polyethylene Cannula and a Hysteroscope. This experimental approach was based on the study by Yoon BH, Kim CJ, Romero R et al. AJOG 1997; 177: 797-802.
Antibiotic treatment:
- Ampicillin
- Sulbactam
- q 8 hours
- 30 minutes after hysteroscopy

Euthanasia 5-6 days

<table>
<thead>
<tr>
<th></th>
<th>PVL</th>
<th>No PVL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>0</td>
<td>71</td>
</tr>
<tr>
<td>E. coli</td>
<td>12</td>
<td>179</td>
</tr>
</tbody>
</table>

P < 0.05; RR = 1.4

Conclusions

Experimental intrauterine infection in animals can cause neurologic injury

Summary of the Evidence

- Periventricular Leukomalacia → CP
- Intrauterine infection/inflamm. → PVL
- Amniotic fluid IL-6 → PVL
- Fetal systemic inflammation (Umbilical cord IL-6) → PVL
- Overexpression of TNF and IL-6 → PVL
- Experimental induction of PVL by intrauterine infection

Can Antibiotics Cause Harm?

“7-day course of therapy with a combination of intravenous ampicillin and erythromycin followed by oral amoxicillin and erythromycin is recommended during expectant management of women with preterm prelabor rupture of membranes who are less than 34 0/7 weeks of gestation”
**Conclusions**

- Antibiotic administration (ceftriaxone, clindamycin, and erythromycin) rarely eradicates intra-amniotic infection in patients with preterm PROM.
- Intra-amniotic inflammation developed in one-third of patients who did not have inflammation at admission, despite antibiotic administration.
- A sub-group of patients with documented inflammation of the amniotic cavity demonstrated a decrease in the intensity of the inflammatory process after antibiotic administration.

---

Can the brain injury occur in-utero?
Can the pregnancy with sub-clinical infection be identified?

Neutrophils are a source of MMP-8 (Neutrophil Collagenase)

Amniotic Fluid MMP-8 and Preterm Parturition

MMP-8 Rapid Test

Accutest® Rapid Pregnancy Test
### Diagnostic Indices, Predictive Values and Likelihood Ratios of MMP-8 PTD Check™ for Intra-amniotic Infection and Inflammation

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>LR (+)</th>
<th>LR (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intra-amniotic Infection</td>
<td>83% (20/24)</td>
<td>95% (291/307)</td>
<td>56% (20/36)</td>
<td>94% (291/295)</td>
<td>15.9 (0.6-28.6)</td>
<td>0.2 (0.1-0.3)</td>
</tr>
<tr>
<td>Intra-amniotic Inflammation</td>
<td>81% (17/21)</td>
<td>94% (291/310)</td>
<td>47% (17/36)</td>
<td>99% (291/295)</td>
<td>13.2 (3.2-21.4)</td>
<td>0.2 (0.1-0.3)</td>
</tr>
</tbody>
</table>

Accuracy for Intra-Amniotic Infection: 94%
Accuracy for Intra-Amniotic Inflammation: 93%

Nien JK et al. AJOG 2006;195:1025-30

### Investigators

Rangaramanujan M. Kannan
Professor
Chemical Engineering and Material Science
Biomedical Engineering
Wayne State University

Sujatha Kannan, MD
Assistant Professor
Department of Pediatrics
Wayne State University

### Can the Fetus With Brain Involvement be Identified in Utero?

Animal Model
Pregnant New Zealand White rabbits (28 days) Laparotomy and intrauterine injection
- Saline
- LPS (20, 30, 40 μg/Kg) from E. Coli (Born spontaneously at term-31 days)

Control pups
Endotoxin pups
Positron Emission Tomography (PET) scan and immunohistochemistry


### Neurobehavioral Testing-Post Natal Day 1


### Microglia as a Convergence Point

Infection / Inflammation
Hypoxia / Ischemia
Microglial activation
Cytokines
ROS / RNS
Glutamate
Oligodendrocyte death

www.nku.edu
**Activated Microglial Cells**

<table>
<thead>
<tr>
<th>Saline</th>
<th>Endotoxin</th>
</tr>
</thead>
</table>

Change in morphology from ramified to more amoeboid and rounded form noted with increasing dose of endotoxin

**Can microglial activation be detected with imaging techniques?**

**Microglial Cells: Activation Process**

- **Activated Microglial cells:**
  - Expression of mitochondrial peripheral benzodiazepine binding sites (PBBS)
  - (R)-PK11195 = selective ligand for PBBS

**Neuronal Injury – Day 1**

- Impairment in dendritic branching, organization and decreased spines seen in endotoxin kits upon Golgi staining
- Associated with learning deficits and memory impairment
- Seen in brains of patients with mental disability

**Journal of Nuclear Medicine, published on May 15, 2007 as doi:10.2967/jnumed.106.306329**

Microglial Activation in Perinatal Rabbit Brain Induced by Intraventricular Inflammation: Detection with 11C-(R)-PK11195 and Small-Animal PET


**Resting state**

- Activated state

Expression of PK 11195 binding site

Banati, 1999; Cagnin 2002

**Resting state**

- Activated state

Expression of PK 11195 binding site

Banati, 1999; Cagnin 2002
Molecular Imaging of Activated Microglia
PET Scan

11C-PK11195 uptake in the neonatal rabbit brain indicates presence of activated microglia in the endotoxin kits

S.Kannan et al., J. Nuclear Medicine, 2007

Fetuses who will be Born Preterm have
Diminished Neuroconnectivity


Can Injury Be Prevented?

A new anti-microbial combination prolongs the latency period, reduces acute histologic choioamnionitis as well as funisitis, and improves neonatal outcomes in preterm PROM

Jin Young Lee, Eun Sook Bae, Gye Mi Jang, Hye Sun Moon, Hyoung Hee Kang, Byung Heung Lee, Hyo Seok Lee, Jeong Ki Park, Young Seok Joo, and Do Hoock Yoon.

**N-acetylcysteine**

\[
\text{HS} - \text{CH}_2 - \text{CH} - \text{COOH} \\
\downarrow \\
\text{HN} - \text{CO} - \text{CH}_3
\]

**NAC: Study Design: pre + post**

- **Insults**
  - LPS i.p. (0.1 mg/kg)
  - H2O 48 hr

- **Treatment**
  - NAC, i.p. (25mg, 200mg/kg)

**Results: Pre+post Treatment (200 mg/kg) with NAC**

NAC reduces tissue loss (%) at multiple levels of the brain

**Could Treatment Work if Delivered after the Insult?**

**Nanotechnology in Perinatal Medicine**

**Ronald Reagan National Airport**

Dendrimers: ‘Tree-like polymers’

Tree-like architecture in widely prevalent in the human body. Dendrimers are well-defined, tree-like polymers made synthetically, with a size of ~ 4 – 20 nm.

Liposomes/Nanoparticles
- Size varies from 200-2000 nm
- Particle volume 10^5 times larger than dendrimers

Dendrimers
- Size varies from 2 - 20 nm
- Single molecular micelles - stable
- Can target, deliver and signal
- < 30kDa (~5-10 nm), cleared intact

Dendrimers
- Large surface area/volume ratio (for the same mass)
- Size density and molecular density advantages-pay load
- Flexible, open structure, where each component of the tree can be manipulated
- Biocompatible, can be made biodegradable
- Multifunctionality (therapy, imaging, targeting)

Can this be used to Deliver Therapeutics to Target Cells?

Investigators

Rangaramanujan M. Kannan
Professor
Chemical Engineering and Material Science
Biomedical Engineering
Wayne State University

Sujatha Kannan, MD
Assistant Professor
Department of Pediatrics
Wayne State University

Nano Platforms: Why Dendrimers?

Liposomes/Nanoparticles
- Nanoparticles (~200 nm)
- Liposomes (~200 nm)
- Dendrimers (~ 5 nm)

Dendrimers
- Size varies from 2 - 20 nm
- Can target, deliver and signal
- < 30kDa (~5-10 nm), cleared intact

PAMAM-G5-NAC
- NAC linked by disulfide bond

Cell

Internalization

Cell


Delivery of the Drug

Cell


Where do Dendrimers Go?

Dendrimers are seen in activated microglia and astrocytes in endotoxin kits and not in controls following IV administration.

Control
Endotoxin

Biodistribution of Dendrimers in the Brain

Control
Endotoxin

Biodistribution of Dendrimers-IV

Microglia Labeling (Tomato Lectin)

Astrocyte Labeling (GFAP)

Unpublished data, provisional patent filed; Rangaramanujam M. Kannan, Sujatha Kannan, Romero R et al PRB Nanotechnology Lab, NICHD
Dendrimers Preferentially Localize in Activated Microglia and Astrocytes, even upon Intravenous Administration


Does Treatment have Any Effect on Function?

1. Perinatology Research Branch, NICHD/NIH
2. Wayne State University Department of Pediatrics and Children’s Hospital of Michigan, Detroit Medical Center
3. Wayne State University Department of Chemical Engineering
4. Wayne State University School of Medicine - Department of Family Medicine


In Vivo Therapy with NAC and D-NAC Experimental Design

Pregnant New Zealand White rabbits 28 days gestation

Controls- No intervention

Laparotomy and endotoxin injection

Litter mates treated at birth with a single dose of:

1. Saline
2. NAC 100 mg/kg
3. Dendrimer (control)
4. Dendrimer-NAC 1 mg/kg
5. Dendrimer-NAC 10 mg/kg (N=8-10 kits per group)

Neurobehavioral Assessment Post-Natal Evaluation – Day 1

Control

Endotoxin Exposed: PBS

Endotoxin Exposed: Dendrimer-NAC
Neurobehavioral Assessment
Post-Natal Evaluation – Day 5

Control
Endotoxin Exposed: PBS
Endotoxin Exposed: Dendrimer-NAC

Day 3  Day 5


Cerebral Palsy Develops in utero

Ongoing inflammation
TNF-α, IL-1β, Microglial activation; Neuron damage
G28: Laparotomy
G31/PND1: Day of birth
Endotoxin
D-NAC treatment (6x)

Can the fetus be treated by intra-amniotic administration?

Dendrimer-Cy5 Solution Spread Quickly in the Amniotic Fluid within 1 to 3 Seconds


Dendrimers were Absorbed through Intestinal Villi


No Accumulation of D-OH and D-COOH (PAMAM Dendrimer) in the Brain Parenchyma of Normal Fetus


D-OH Uptake in Activated Microglia in the Cerebral Palsy Model

N-Acetylcysteine in Humans

Study Design

22 Mothers
>24 weeks with clinical chorioamnionitis

Saline

Postnatal Treatment

N-acetyl cysteine <100mg/kg/dose

Postnatal 5 days

Serum Cytokine Concentrations Before and After Treatment with N-acetylcysteine

Conclusions

N-acetylcysteine treatment of fetuses/neonates exposed to chorioamnionitis was safe, preserved cerebrovascular regulation, and increased an anti-inflammatory neuroprotective protein.
Antibiotics……?

Study Design

- Retrospective study
- PROM <34 weeks
  - 1993-2003 - Ampicillin or Cephalosporins (n=195)
  - 2003-2012 - Ceftriaxone, Clarithromycin and Metronidazole (n=119)

Results

Antibiotic to Delivery Interval

Results

Pregnancy Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Ampicillin and/or Cephalosporins (n=195)</th>
<th>Ceftriaxone + Clarithromycin + Metronidazole (n=119)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age at delivery (weeks)</td>
<td>33.0 (29.0–34.6)</td>
<td>31.4 (27.0–33.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Birthweight (g)</td>
<td>1970 (1380–2410)</td>
<td>1640 (980–2110)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Spontaneous preterm delivery (%)&lt;37 weeks</td>
<td>82.1 (128/156)</td>
<td>95.8 (69/72)</td>
<td>0.005</td>
</tr>
<tr>
<td>&lt;34 weeks</td>
<td>60.1 (101/168)</td>
<td>66.7 (58/87)</td>
<td>NS</td>
</tr>
<tr>
<td>&lt;32 weeks</td>
<td>57.0 (65/114)</td>
<td>56.9 (37/65)</td>
<td>NS</td>
</tr>
<tr>
<td>Acute histologic chorioamnionitis (%)</td>
<td>66.7 (102/153)</td>
<td>50.5 (49/97)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Funisitis (%)</td>
<td>42.9 (66/154)</td>
<td>13.9 (14/101)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Results

Neonatal Outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Ampicillin and/or Cephalosporins (n=195)</th>
<th>Ceftriaxone + Clarithromycin + Metronidazole (n=119)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory distress syndrome (%)</td>
<td>11.0 (19/173)</td>
<td>15.2 (15/98)</td>
<td>NS</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia (%)</td>
<td>12.7 (23/186)</td>
<td>28.1 (27/96)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Intraventricular hemorrhage (%)</td>
<td>19.0 (32/165)</td>
<td>2.1 (2/97)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Periventricular leukomalacia (%)</td>
<td>6.1 (10/165)</td>
<td>1.0 (1/98)</td>
<td>0.058</td>
</tr>
<tr>
<td>Necrotizing enterocolitis (%)</td>
<td>3.5 (6/171)</td>
<td>9.2 (9/98)</td>
<td>0.051</td>
</tr>
<tr>
<td>Cerebral palsy (%)</td>
<td>5.7 (9/157)</td>
<td>0.0 (0/96)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Conclusion

- Combination of Ceftriaxone, Clarithromycin, and Metronidazole treatment in patients with preterm PROM
  - Prolonged the latency period
  - Reduced acute histologic chorioamnionitis/funisitis
  - Improved neonatal outcomes


Is There a Role for Stem Cells?

Stem Cells

- Pluripotent stem cell
  - Hematopoietic stem cell
  - Neural stem cell
  - Mesenchymal stem cell

- Committed stem cell
  - Lymphocyte
  - Erythrocyte
  - Granulocyte
  - Platelets
  - Macrophage
  - Osteocyte
  - Adipocyte

- Differentiated cell
  - Neuron
  - Astrocyte
  - Oligodendrocyte
  - Cardiomyocyte
  - Fibroblast
  - Chondrocyte

Mezey E et al. Science 2000; 290: 1779

The Henry Ford Hospital

www.henryford.com

Turning Blood into Brain: Cells Bearing Neuronal Antigens Generated in Vivo from Bone Marrow

Éva Mezey,1* Karen J. Chandross,2 Gyöngyi Harta,1 Richard A. Maki,3,4 Scott R. McKeicher3

Mezey E et al. Science 2000; 290: 1779

Intravenous Bone Marrow Stromal Cell Therapy Reduces Apoptosis and Promotes Endogenous Cell Proliferation After Stroke in Female Rat

Effect of Adipose-derived Mesenchymal Stem Cells on Size of Acute Ischemic Stroke Induced by Middle Cerebral Artery Occlusion in Adult Sprague-Dawley rats

Leu S et al. J Transl Med 2010; 8: 63

Hypoxic Ischemic Encephalopathy Model of Perinatal Ischemia

Hidetsugu T, Andresson K, Stanford University School of Medicine

Regeneration of the ischemic brain by engineered stem cells: Fuelling endogenous repair processes

Cindy T.J. van Velthoven**, Annaemiek Kavelaars**, Frank van Bal, Cobi J. Heijnen***

van Velthoven TJ et al. Stem Cell Rev 2010; 6: 1

Repeated Mesenchymal Stem Cell Treatment after Neonatal Hypoxia–Ischemia Has Distinct Effects on Formation and Maturation of New Neurons and Oligodendrocytes Leading to Restoration of Damage, Corticospinal Motor Tract Activity, and Sensorimotor Function

Cindy T.J. van Velthoven**, Annaemiek Kavelaars**, Frank van Bal, Cobi J. Heijnen***

van Velthoven TJ et al. J Neurosci 2010; 30: 9603

Effect of treatment with Mesenchymal Stem Cells on lesion size

van Velthoven et al J. Neurosci 2010;30:9603–9611

Unilateral Frontal Lobe Contusion and Forelimb Function: Chronic Quantitative and Qualitative Impairments in Reflexive and Skilled Forelimb Movements in Rats

Home Cage Test

van Q. Whishaw, J. Donmez, M. Pechacek, J. Fiona Zeffiro, and Donald C. Steen


Rota-rod Test

tmc.amica.edu.tw/rotarod.html
Performance on the rotarod at 21 and 28 days after Perinatal cerebral hypoxia–ischemia

Mesenchymal Stem Cells: Proposed Function

The Future

Stem/progenitor cells from bone marrow decrease neuronal death in global ischemia by modulation of inflammatory/immune responses

A Goal for the 21st Century...

To Remodel and Rebuild the Damaged Fetal/Neonatal Brain

Thank You