Porcine Intraventricular Cannulation
Validating a Strategy for Gene Delivery to the Central Nervous System

Disclosures and Conflicts

- Nicholas Boulis, MD
  - Medtronic,
  - Ceregene,
  - Genzyme,
  - Neuralstem

Introduction

I – Background - Gene Therapy Delivery Routes
a – Retrograde Axonal Transport
b – Direct Parenchymal Microinjection
   Intraspinal
   Intracranial
c – Intrathecal Injection
d – Intraventricular Injection...

II – Porcine Anatomic Evaluation
a – Necropy Study
b – Survival Study
c – Results to Date

III – Near Term Experimental Design

IV – Areas for Future Study

Background

Ia – Retrograde Axonal Transport

Retrograde Viral Delivery of IGF-1 Prolongs Survival in a Mouse ALS Model

Science Vol. 301 8 August 2003

Background

Ib – Direct Parenchymal Microinjection (spinal)

Background

Ib – Direct Parenchymal Microinjection (cranial)

Real-time MR Imaging With Gadoteridol Predicts Distribution of Transgenes After Convection-enhanced Delivery of AAV2 Vectors

Nature Vol. 11, 1499-1507 Aug 2011

Jonathan Riley, MD
Emory University Department of Neurological Surgery

GNS – Annual Fall Meeting - Nov, 2012
**Background**

**Ic – Intrathecal Injection**

Diffuse Vector Delivery is Achievable through Intrathecal Delivery

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**Background**

**Id – Intraventricular Delivery**

Adeno-Associated Virus Serotype 9 Transduction in the Central Nervous System of Nonhuman Primates

1) Direct Delivery is more effective

2) Direct Delivery has fewer off-target effects

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**Background**

**Id – Intraventricular Delivery (cont)**

Efficacy of Reductive Ventricular Osmotherapy in a Swine Model of Traumatic Brain Injury

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**II – Porcine Anatomic Evaluation**

**Necropsy Study – Defining an Approach**

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**II – Porcine Anatomic Evaluation**

**Survival Study – Exposure and Approach**

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**II – Porcine Anatomic Evaluation**

**Survival Study – Passing the Catheter**

A better way to cannulate the swine ventricular system?
**II – Porcine Anatomic Evaluation**

**Survival Study – Localization Confirmation**

**TABLE 1. Procedural Outcomes**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Fluoroscopy use / findings</th>
<th>Cannula Passes Required</th>
<th>CSF Return</th>
<th>Tarlov Score</th>
<th>Post Operative Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>no</td>
<td>1</td>
<td>Yes</td>
<td>4</td>
<td>one seizure</td>
</tr>
<tr>
<td>2</td>
<td>no</td>
<td>1</td>
<td>Yes</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>yes, ventricle visible</td>
<td>1</td>
<td>Yes</td>
<td>4</td>
<td>neurologically depressed, ataxia</td>
</tr>
<tr>
<td>4</td>
<td>yes, inconclusive</td>
<td>3</td>
<td>Yes</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

**Lessons from Anatomic Studies:**

Optimal Trajectory - 5mm lateral to midline, posterior to frontal sinus, shallow trajectory, no to minimal mediolateral angulation

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**III – Near Term Experimental Design**

**Dose Escalation Series**

- Volume Dose Escalation Series
- Constant Rate of Infusion

**To Assess**

- Behavioral Outcomes –
  - With intraventricular cannulation
  - With dose escalation
  - Define a maximum tolerated dose
- Biodistribution with dose escalation

**Considerations**

- Will drain equivalent amount of CSF to added volume prior to infusion
- Leave catheter for 10 minutes prior to removal at infusion completion
- Role for fluoroscopy:
  - a) Identification of Superoposterior border of frontal sinus
  - b) Small bolus of contrast to confirm intraventricular localization

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**IV – Areas for Future Consideration**

- Delineation of Maximum Tolerated Dose
- Assessment of Alternate Infusion Parameters
  - Rate of Infusion
  - Vector Concentration
- Evaluation of Agents to increase ependymal permeability
- Imaging Co-injectables
  - MR or CT-compatible co-injectates to evaluate intraventricular spread
  - Validation of co-injectate spread with vector expression
- Possible Need for bilateral cannulation
- Alteration in rate of delivery or volume of delivery
- Validation of co-injectate biodistribution for translational purposes

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**What’s New is Old and Old is New...**

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