Porcine Intraventricular Cannulation

Validating a Strategy for Gene Delivery to the Central Nervous System

GNS – Annual Fall Meeting - Nov, 2012
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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 …

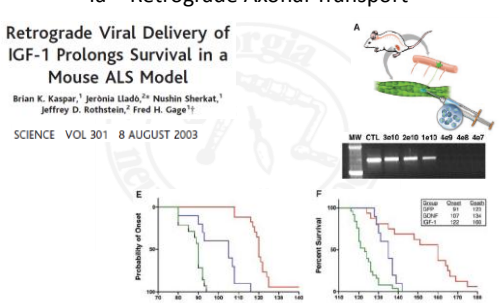
II – Porcine Anatomic Evaluation
- a – Necropy Study
- b – Survival Study
- c – Results to Date

III – Near Term Experimental Design

IV – Areas for Future Study

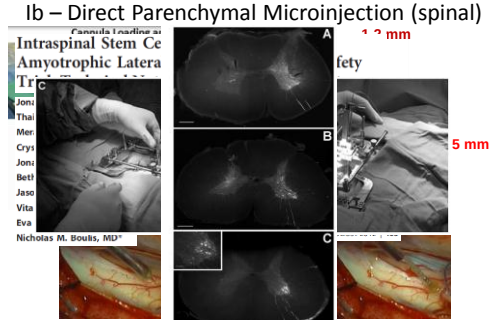
Background

Ia – Retrograde Axonal Transport



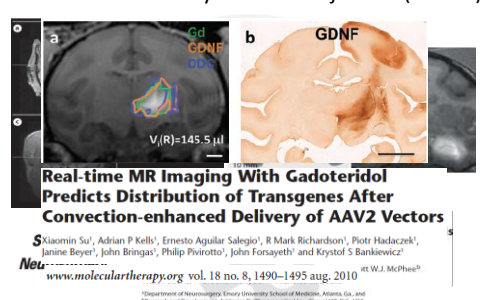
Background

Ib – Direct Parenchymal Microinjection (spinal)



Background

Ib – Direct Parenchymal Microinjection (cranial)



Background

Ic – Intrathecal Injection

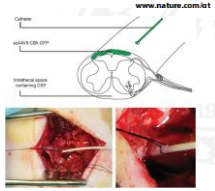
ORIGINAL ARTICLE

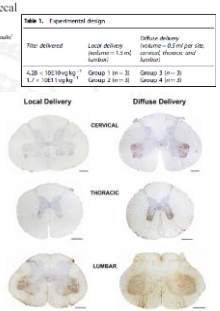
Robust spinal motor neuron transduction following intrathecal delivery of AAV9 in pigs

T Federici[1], JS Taub[1], GR Baum[1], SJ Gray[2], JC Grieger[2], KA Matthews[1], CR Handy[1], MA Passini[2], RJ Samulski[2] and NM Boulis[1]

Gene Therapy (2012) 19, 852–859

www.nature.com/gt





Diffuse Vector Delivery is Achievable through Intrathecal Delivery

Background

Id – Intraventricular Delivery

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

Lluis Samaranch,[1,*] Ernesto A. Salegio,[1,*] Waldy San Sebastian,[1] Adrian P. Kells,[1] Kevin D. Foust,[2] John R. Bringas,[1] Clementine Lamarre,[1] John Forsayeth,[1] Brian

HUMAN GENE THERAPY 23:382–389 (April 2012)
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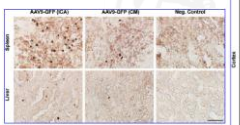
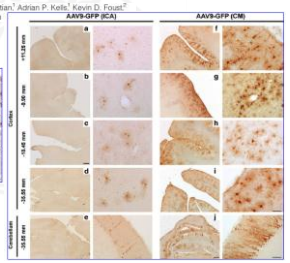
DOI: 10.1089/hum.2011.200





1) **Direct Delivery is more effective**

2) **Direct Delivery has fewer off-target effects**

Background

Id – Intraventricular Delivery (cont)

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

Rick M. Odland, MD, PhD*‡
Sandya Venugopal, MD§
John Borgos, BS*
Valerie Coppes, BS§
Alexander M. McKinney, MD¶
Gaylan Rockswold, MD, PhD‖
Jian Shi, PhD§
Scott Panter, PhD§

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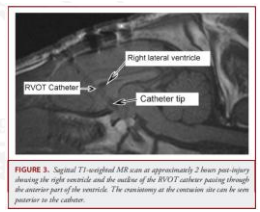


FIGURE 3. Sagittal T1-weighted MR scan at approximately 2 hours post-injury showing the right ventricle and the outline of the RVOT catheter passing through the anterior part of the ventricle. The contusion at the contusion site can be seen posterior to the catheter.

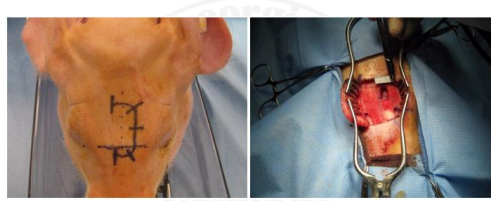
A better way to cannulate the swine ventricular system?

II – Porcine Anatomic Evaluation

Necropsy Study – Defining an Approach

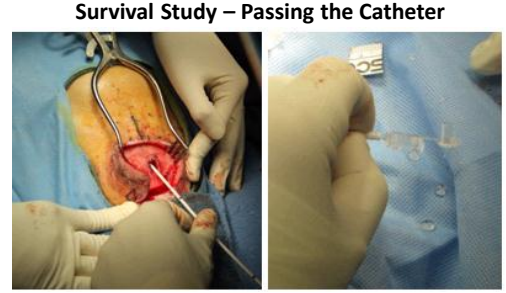
II – Porcine Anatomic Evaluation

Survival Study – Exposure and Approach



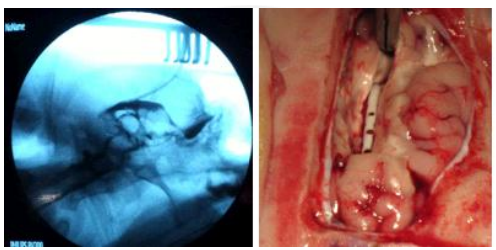
II – Porcine Anatomic Evaluation

Survival Study – Passing the Catheter



II – Porcine Anatomic Evaluation

Survival Study – Localization Confirmation



II – Porcine Anatomic Evaluation

Intraventricular Cannulation, Results to Date

TABLE 1. Procedural Outcomes

Procedure #	Flouroscopy use / findings	Cannula Passes Required	Csf Return	Tarlov Score	Post Operative Complications
1	no	1	Yes	4	one seizure
2	no	1	Yes	4	
3	yes, ventricle visible	1	Yes	4	neurologically depressed, ataxia
4	yes, inconclusive	3	Yes	4	

Lessons from Anatomic Studies:

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

What's New is Old and Old is New…

III – Near Term Experimental Design

Dose Escalation Series

- Volume Dose Escalation Series
- Constant Rate of Infusion

To Asesss

- Behavioral Outcomes –
  a) With intraventricular cannulation
  b) With dose escalation
  c) 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

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-injectable 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

Acknowledgements

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