

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 – Necropsy Study
- b – Survival Study
- c – Results to Date

III – Near Term Experimental Design

IV – Areas for Future Study

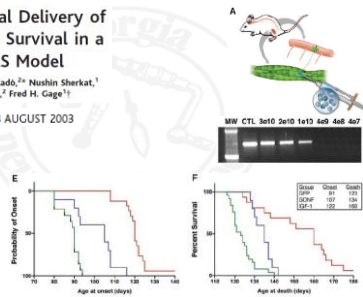
Background

Ia – Retrograde Axonal Transport

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

Brian K. Kaspar,¹ Jeronía Llado,^{2*} Nushin Sherkat,¹ Jeffrey D. Rothstein,² Fred H. Gage^{1†}

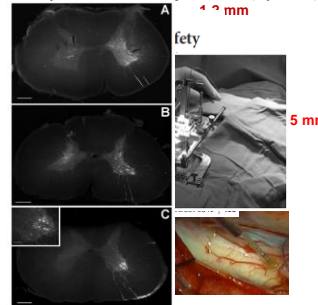
SCIENCE VOL 301 8 AUGUST 2003



Background

Ib – Direct Parenchymal Microinjection (spinal)

Intraspinal Stem Cell Amyotrophic Lateral Sclerosis
 Jonathan Riley, MD
 Nicholas M. Boulis, MD*



Background

Ib – Direct Parenchymal Microinjection (cranial)

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

S Xiaomin Su¹, Adrian P Kelli¹, Ernesto Aguilar Salegio², R Mark Richardson¹, Piotr Hadaczek¹, Janine Beyer¹, John Bringas¹, Philip Pivrotto¹, John Forsayeth¹ and Krystof S Bankiewicz¹

www.moleculartherapy.org vol. 18 no. 8, 1490–1495 aug. 2010

¹Department of Neurosurgery, Emory University School of Medicine, Atlanta, GA, and ²Research and Development, Amgen Biopharmaceutical Inc., Denver, CO, USA

Background Ic – Intrathecal Injection

ORIGINAL ARTICLE

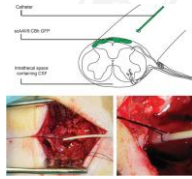
Robust spinal motor neuron transduction following intrathecal delivery of AAV9 in pigs

T. Fehon^{1,2}, B. Tsai¹, G.R. Breen¹, S.J. Gray¹, J.C. Granger¹, K.A. Matthews¹, G.R. Haskins¹, M.K. Patten¹, G. Samulski¹ and M.R. Booth¹

Gene Therapy (2012) 19, 852–859

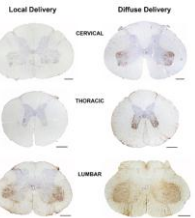
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www.nature.com/gt



Diffuse Vector Delivery is Achievable through Intrathecal Delivery

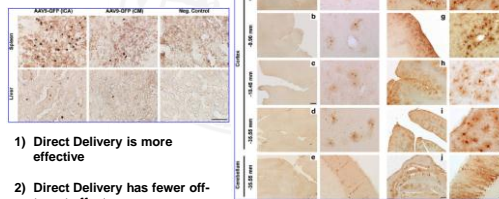
Year delivered	Local delivery (volume = 1.5 ml, carrier)	Diffuse delivery (volume = 0.5 ml, carrier, rhBMP-2 and carrier)
4, 28, 100 (10 µg/kg)	Group 1 (n = 3) Group 2 (n = 2)	Group 3 (n = 3) Group 4 (n = 2)



Background Id – Intraventricular Delivery Adeno-Associated Virus Serotype 9 Transduction in the Central Nervous System of Nonhuman Primates

Luis Samarano¹, Ernesto A. Gallego¹, Wally San Sebastian¹, Adrian P. Kellis¹, Kevin D. Foust¹, John R. Bangari¹, Chennellian Laramie¹, John Fougeat¹, Brian

HUMAN GENE THERAPY 23:982–989 (April 2012)
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DOI: 10.1089/hgtb.2011.1200



- 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, PhD¹;
Sandy Venugopal, MD²
John Borgos, BS³
Valerie Coppes, BS⁴
Alexander M. McKinney, MD¹
Gaylan Rockswold, MD, PhD¹
Jian Shi, PhD⁵
Scott Panter, PhD⁵

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A better way to cannulate the swine ventricular system?

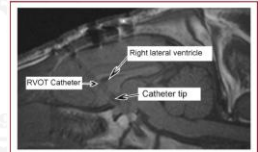


FIGURE 3. Sagittal T1-weighted MR scan at approximately 2 hours post-injury showing the right ventricle and the outline of the RVOT catheter passing through the anterior part of the ventricle. The consistency of the contrast dye can be seen posterior to the catheter.

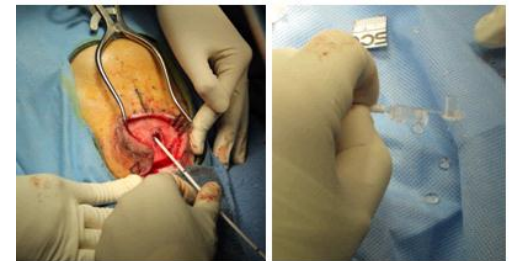
II – Porcine Anatomic Evaluation Necropsy Study – Defining an Approach



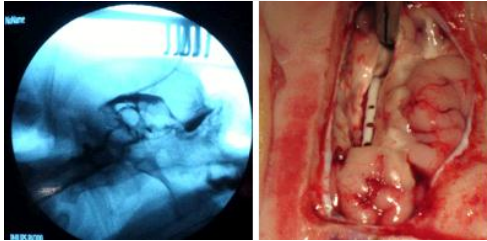
II – Porcine Anatomic Evaluation Survival Study – Exposure and Approach



II – Porcine Anatomic Evaluation Survival Study – Passing the Catheter



II – Porcine Anatomic Evaluation Survival Study – Localization Confirmation



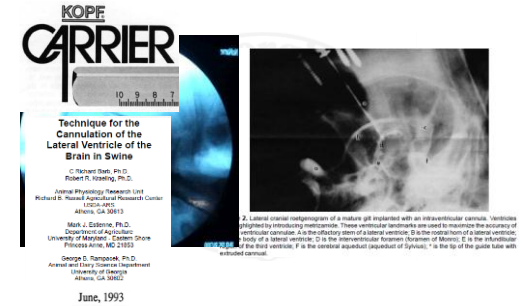
II – Porcine Anatomic Evaluation Intraventricular Cannulation, Results to Date

TABLE 1. Procedural Outcomes					
Procedure #	Fluoroscopy 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 Assess

- 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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