ALTASCIENCES

CASE STUDY

Gene Therapy and Stem Cell Transplantation via MRI-Guided Intraparenchymal Delivery into Brain Regions (Cortical and Subcortical)

ABSTRACT

This stem cell transplantation therapy required midline incision, unilateral or bilateral craniotomy, implantation of cannula guides into adult rhesus and cynomolgus macaques (~2.5 to 15 kg). The animals were prepared with Isoflurane anesthesia, and MRI-compatible stereotactic frame placement. Real-time MRI imaging allowed technicians to confirm delivery of the treatment to appropriate regions of the brain, and adjust flow rate, dosage, and other parameters as needed to deliver best results.

Two procedures are described below.

Procedure 1

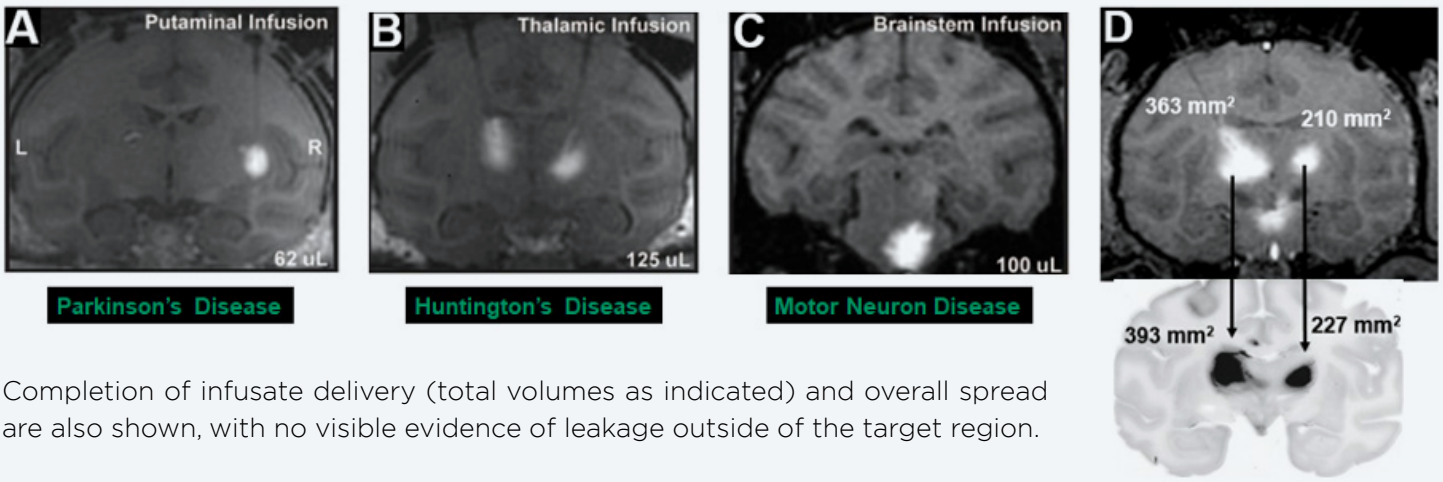
Pre-scanning was performed one week prior to scheduled dosing, to determine the volume to be distributed. An MRI clinical specialist was on-site for dosing.

An MRI-compatible cannula was advanced from the neocortical surface to both brain hemispheres, as both left and right hemispheres were deemed regions of interest. Following cannula tip placement within the cerebellar cortex, infusion was initiated. The infusate was visualized intraparenchymally using a paramagnetic contrast agent for real-time confirmation of test article delivery.

Serial MRI scans were acquired throughout administration to monitor distribution of the infusate within the targeted site (i.e., putamen, thalamus, etc.).

Volume was dependent on coverage. Coverage was monitored through serial MRI scans throughout infusion.

MRI images showing real-time monitoring of infusate into various target regions of interest:



Completion of infusate delivery (total volumes as indicated) and overall spread are also shown, with no visible evidence of leakage outside of the target region.

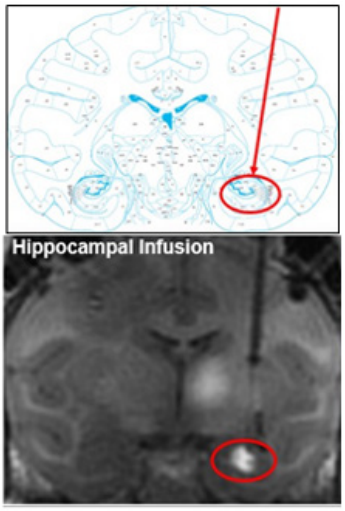
Procedure 2

In this procedure, we infused regions of interest deeper in the brain. Four adult cynomolgus macaques were involved. Three were infused with a vehicle containing gadolinium (Gd) as a contrast agent. One was infused with AAV5 vector encoding enhanced green fluorescent protein (eGFP) and mixed with Gd.

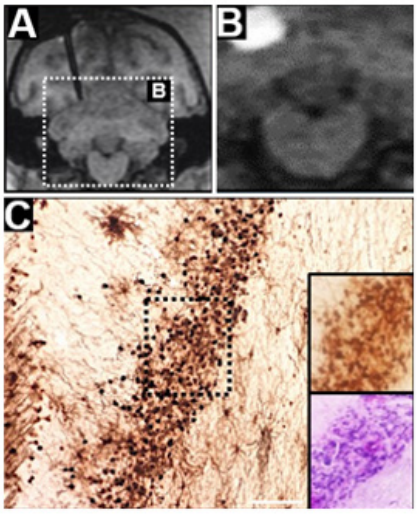
Hematoxylin and eosin staining and immunostaining against green fluorescent protein staining was performed six weeks post infusion.

Hippocampal and cerebellum delivery: images demonstrate looking at an atlas and confirming the delivery into the hippocampus without real-time MRI delivery.

Hippocampal Delivery



Cerebellum Delivery



Altasciences has robust experience and demonstrated expertise in MRI analysis of brain activity following infusion of gene and stem cell therapies.

These published articles detail the described procedures; preclinical work was conducted at Altasciences' Sacramento facility[2,3,4,5]:

Salegio EA, Kells AP, Richardson RM et al. Magnetic Resonance Imaging-Guided Delivery of Adeno-Associated Virus Type 2 to the Primate Brain for the Treatment of Lysosomal Storage Disorders. Hum Gene Ther. 2010 Sep; 21(9):1093-1103. http://doi.org/10.1089/hum.2010.040

Salegio EA, Samaranch L, Jenkins R et al. Safety Study of Adeno-Associated Virus Serotype 2-Mediated Human Acid Sphingomyelinase Expression in the Nonhuman Primate Brain. Hum Gene Ther. 2012 Aug; 23(8): 891–902. https://doi.org/10.1089/hum.2012.052

Salegio EA, Cmpagna V, Allan P et al. Targeted Delivery and Tolerability of MRI-Guided CED Infusion into the Cerebellum of Nonhuman Primates. Hum Gene Ther Methods. 2018 Aug; 29(4):169-176. http://doi.org/10.1089/hgtb.2018.049

Salegio EA, Cukrov M, Lortz R et al. Feasibility of Targeted Delivery of AAV5-GFP into the Cerebellum of Nonhuman Primates Following a Single Convection-Enhanced Delivery Infusion. Hum Gene Ther. 2022 Jan; 33(1).86-93. http://doi.org/10.1089/hum.2021.163

ABOUT ALTASCIENCES

Altasciences is an integrated drug development solution company offering pharmaceutical and biotechnology companies a proven, flexible approach to preclinical and clinical pharmacology studies, including formulation, manufacturing, and analytical services. For over 25 years, Altasciences has been partnering with sponsors to help support educated, faster, and more complete early drug development decisions. Altasciences' integrated, full-service solutions include preclinical safety testing, clinical pharmacology and proof of concept, bioanalysis, program management, medical writing, biostatistics, clinical monitoring, and data management, all customizable to specific sponsor requirements. Altasciences helps sponsors get better drugs to the people who need them, faster.