Gene Therapy for the CNS Manifestations of the Pediatric Lysosomal Storage Disorders

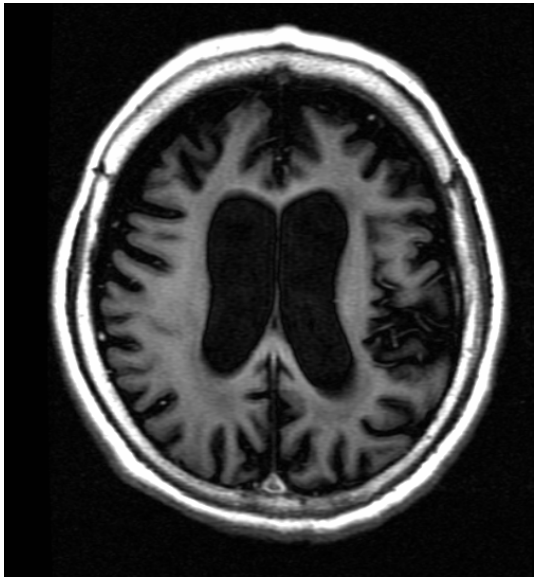
R. Crystal

Weill Cornell Medical College

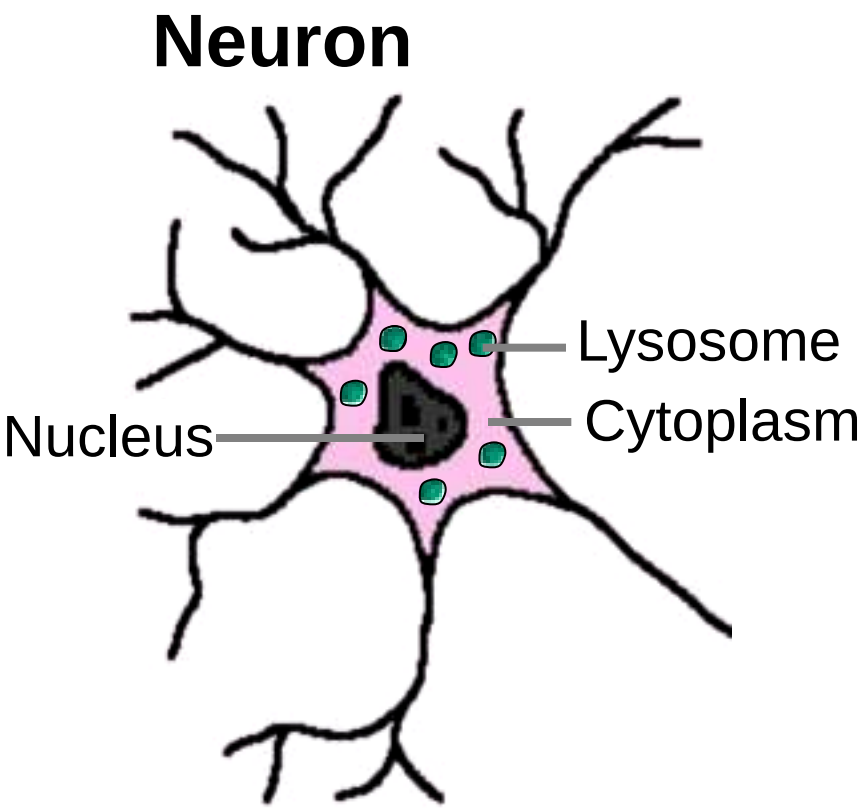
7-1-10

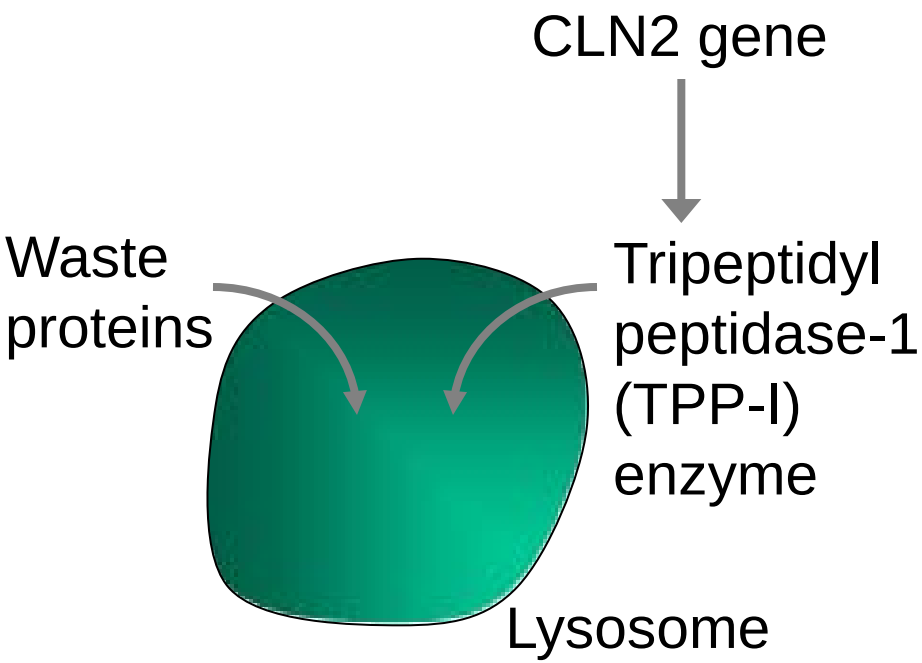
Late Infantile Neuronal Ceroid Lipofuscinoses (LINCL, Batten Disease)

- Autosomal recessive, 1 / 2 million births, ~ 200 cases worldwide
- Disease onset ages 2-4
- Cognitive impairment, visual failure, seizures, and deteriorating motor development, leading to a vegetative state and death by ages 8-12

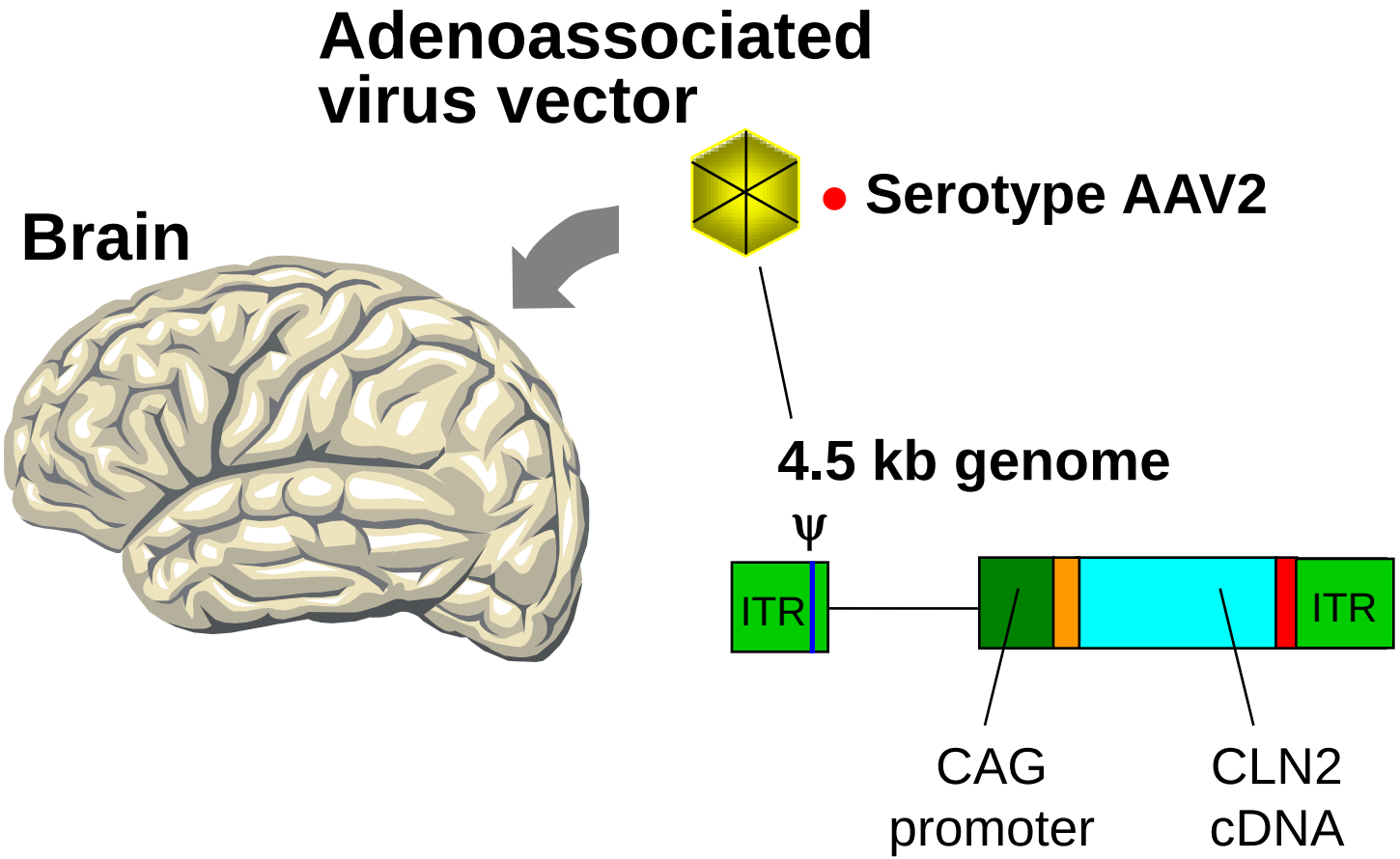


LINCL Is Caused by Mutations in the CLN2 Gene



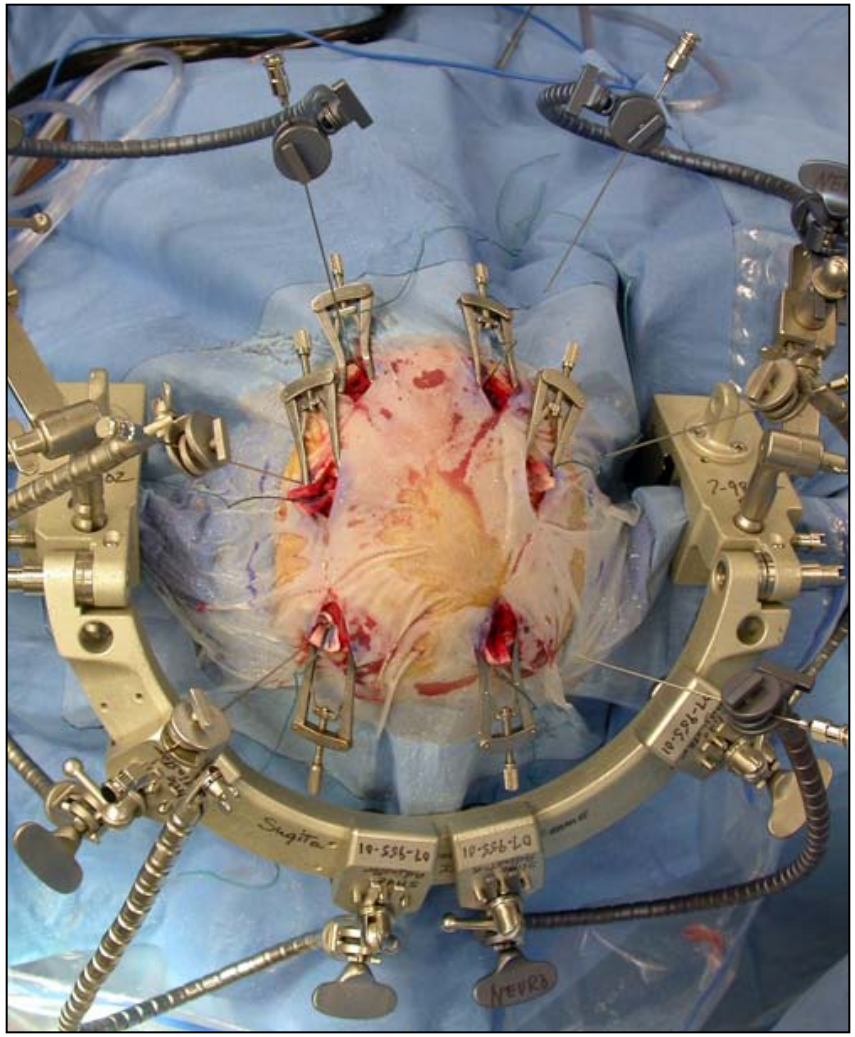


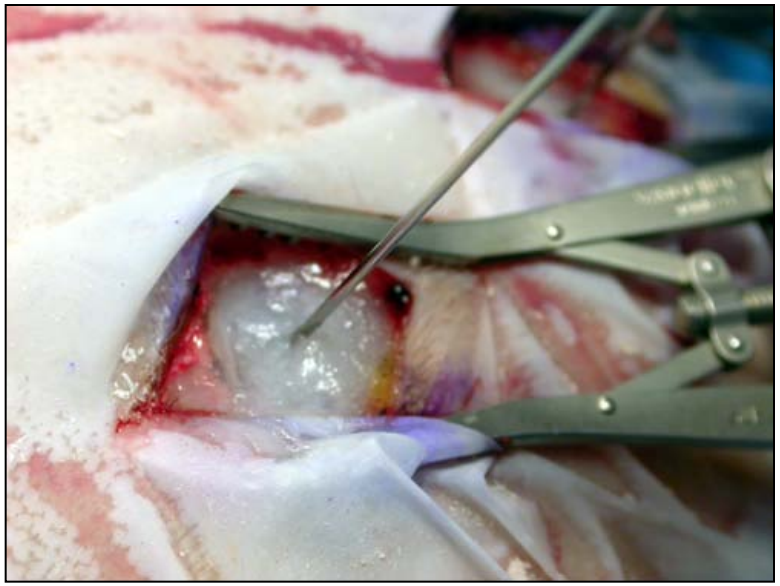
Gene Therapy for LINCL



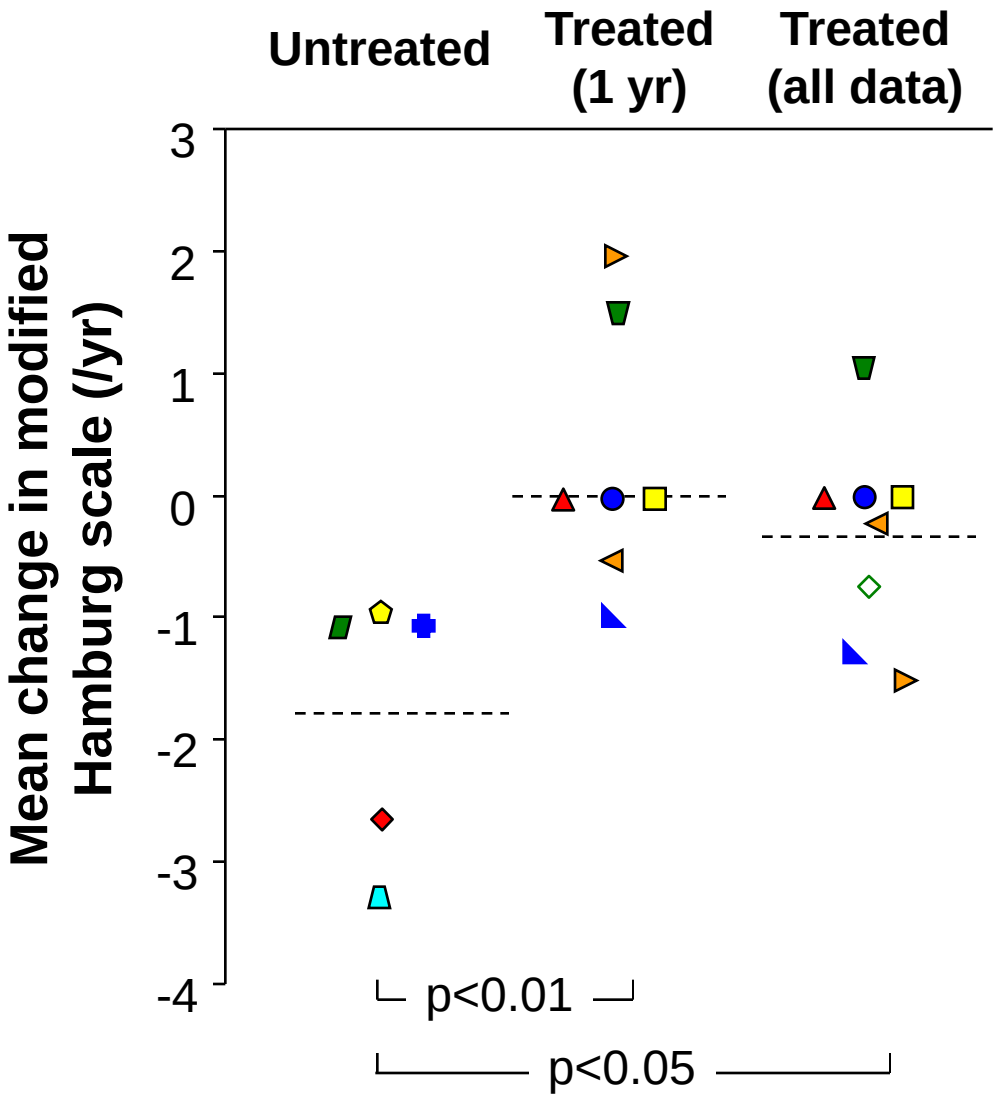
- n=10 children with LINCL, 6 male, 4 female, 3-9 yr; 5 severe and 5 moderate; assess pre-rx and post-rx at 1, 6, 12, 18 months

CNS Administration

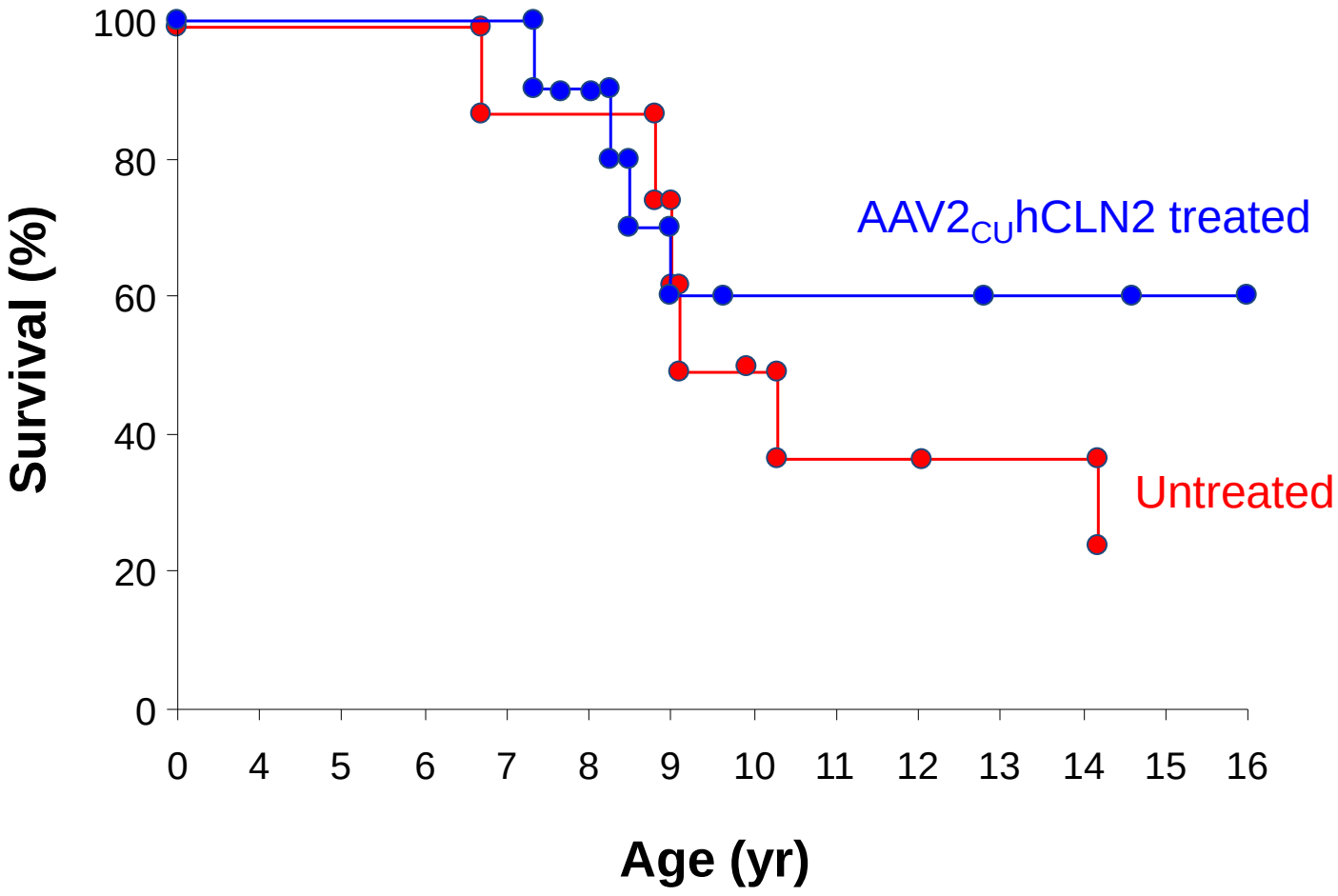




1° Variable – Modified Hamburg LINCL Scale

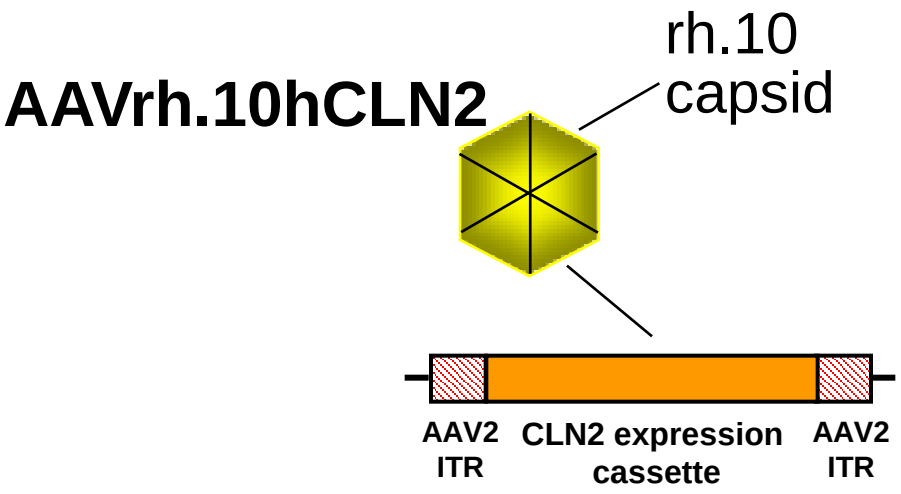


AAV2 Trial Post-therapy Survival Compared to Untreated Controls



AAVrh.10hCLN2

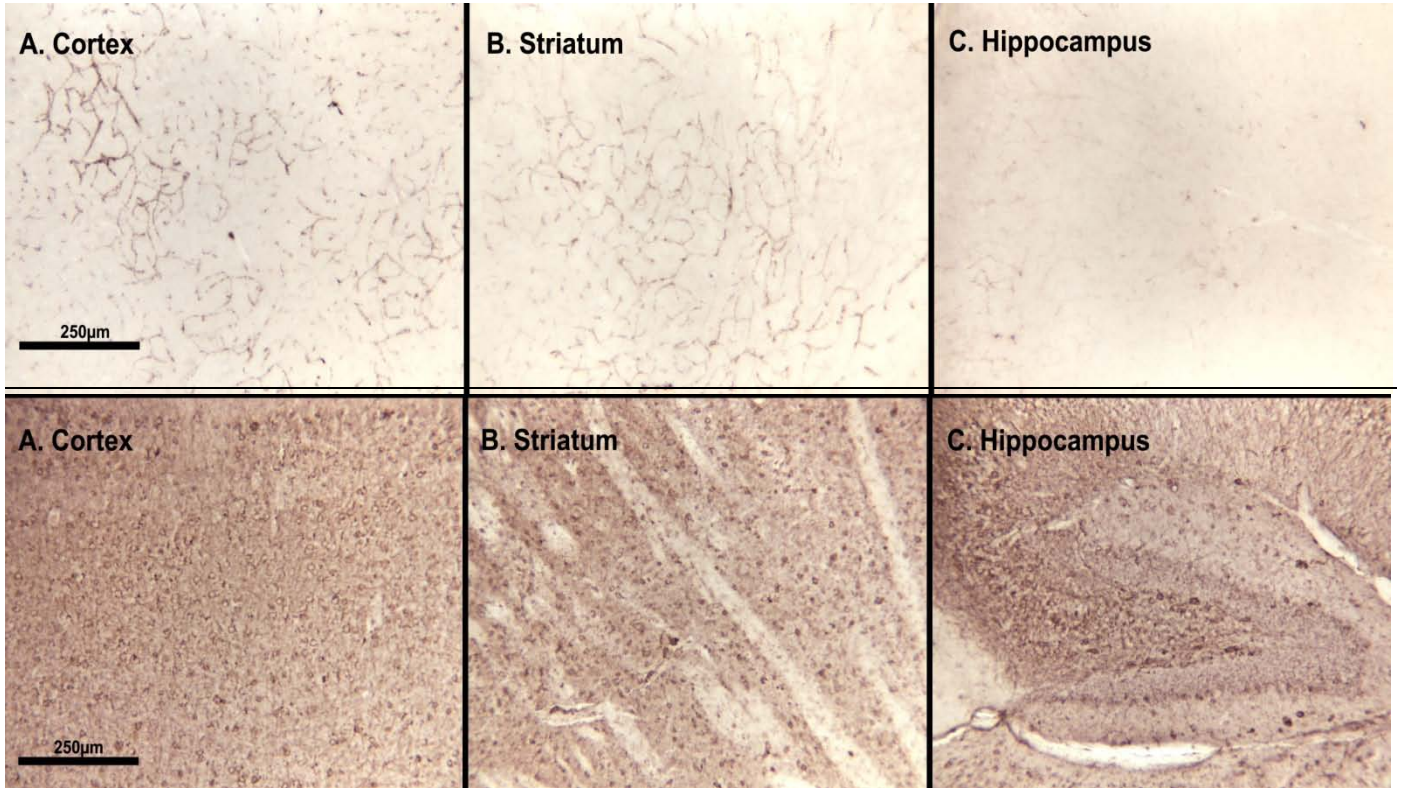
- Clade E AAV, derived from Rhesus macaque
- Mediates high levels of protein expression in multiple organs
- AAV2 ITRs with expression cassette, pseudotyped with rh.10 capsid



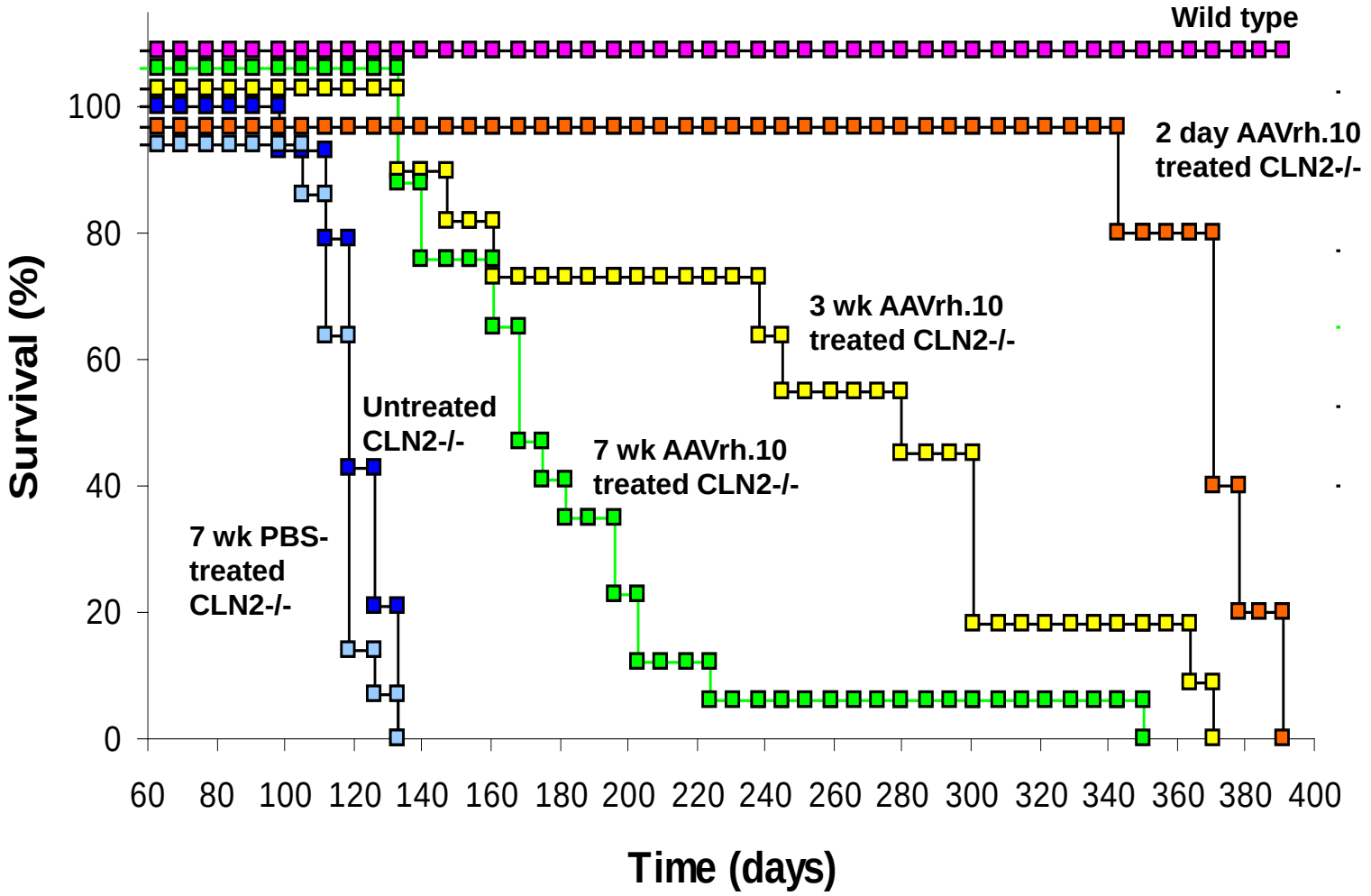
CNS TPP-I Expression Following AAVrh.10hCLN2 Gene Transfer to Day 2 CLN2 -/- Mice and Assessment at 1 yr

PBS control

AAVrh.10hCLN2



Survival of CLN2-/- Mice Treated at Different Times with AAVrh.10hCLN2



Clinical Trial

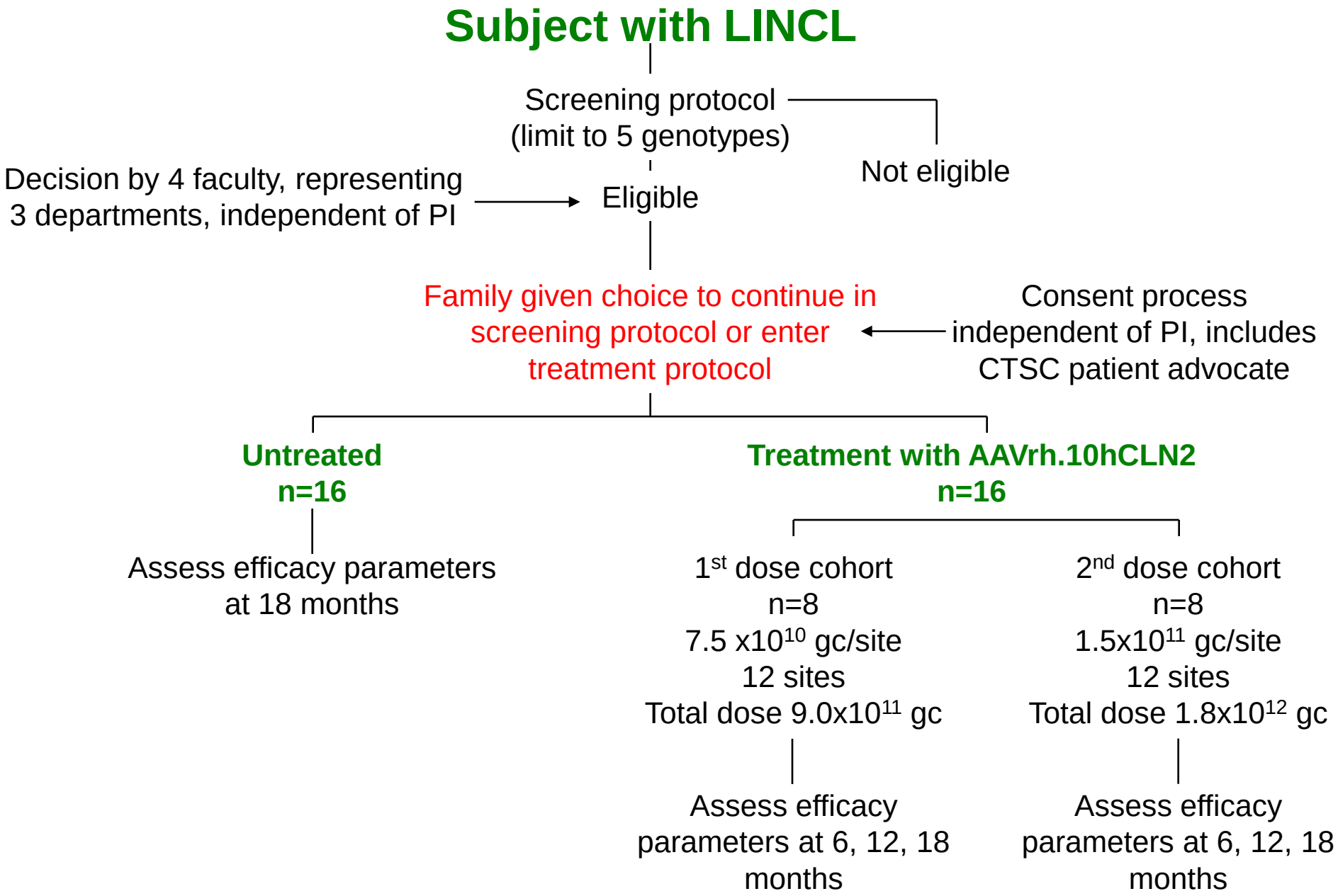
Design

- AAVrh.10hCLN2 *vs* no therapy
- 16 children each group
- Mild-moderate disease

Primary outcome parameters

- Weill Cornell LINCL scale
- MRI
  - Cortical apparent diffusion coefficient
  - % ventricular volume
  - % grey matter volume

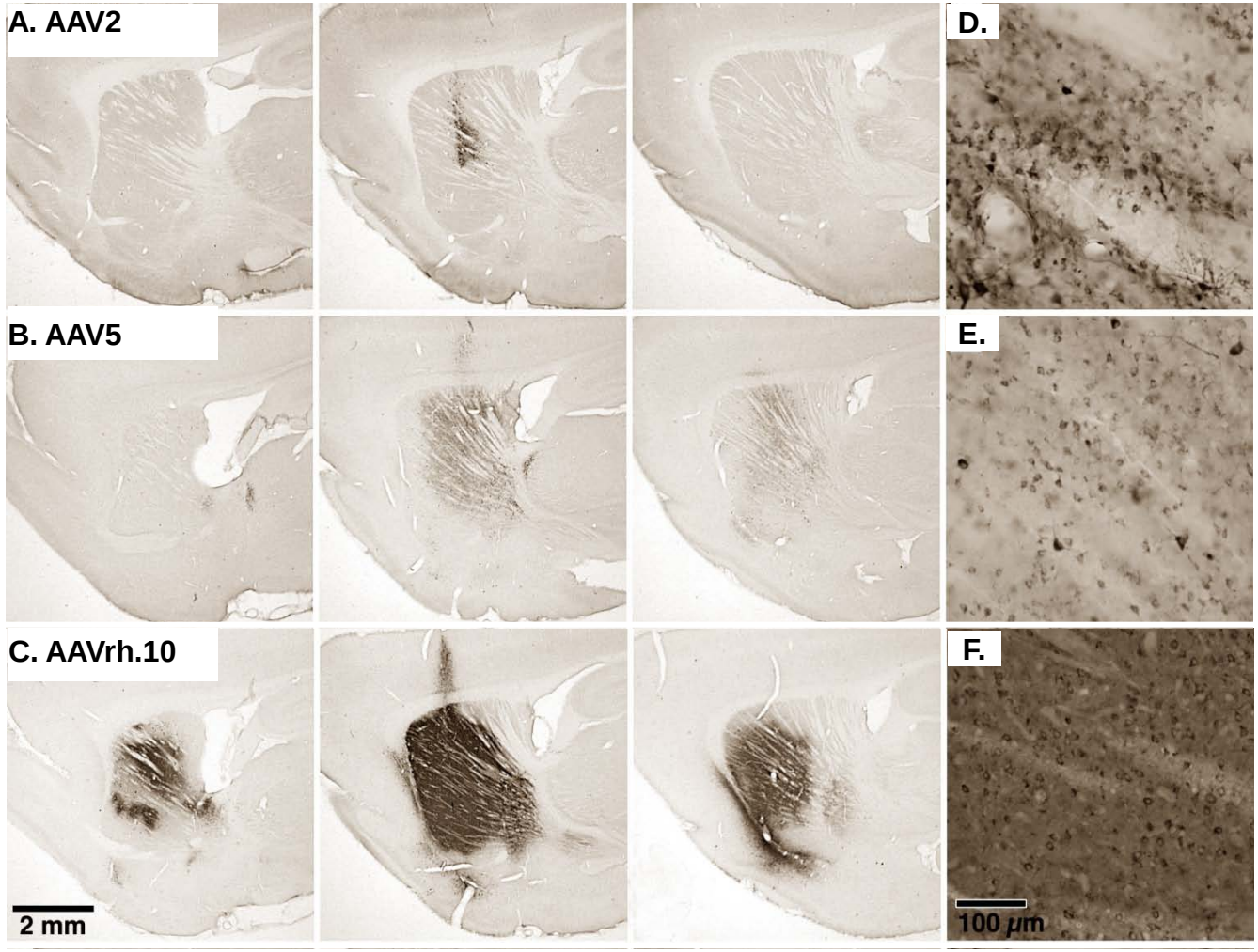
Overall Design of the Trial



Controls and Ethical Issues

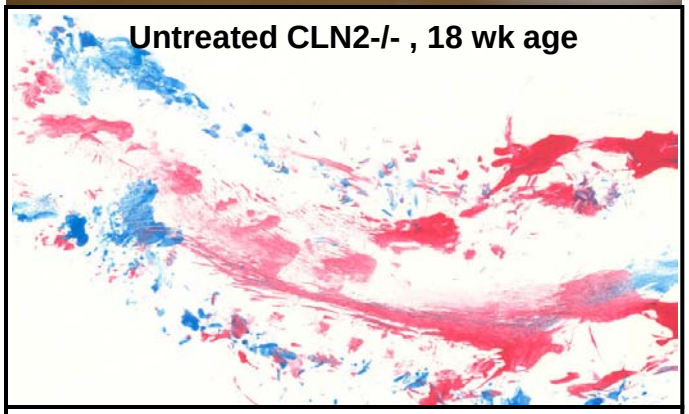
- Fatal, childhood disease for which there is no therapy
- No pre-natal or newborn screening
- Therapy requires invasive, neurosurgical procedure
- Therapeutic misconception
- Challenge – what do we use as controls?
- Regulatory approval is a giant hurdle

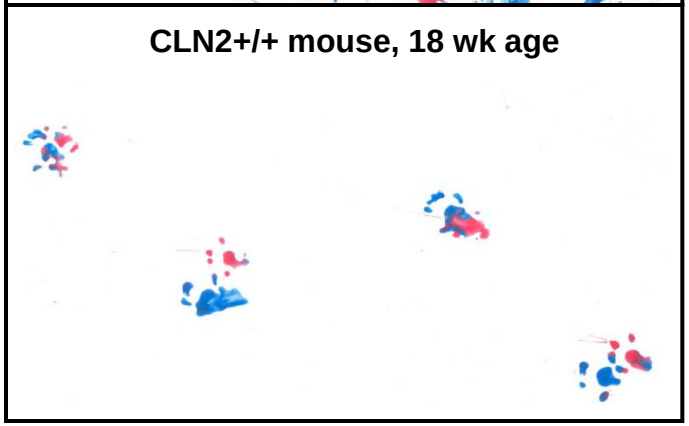
Comparison of TPP-I Gene Expression Among AAV Serotypes

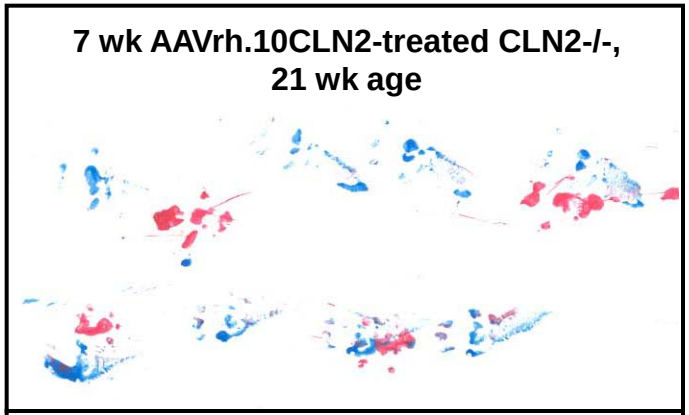


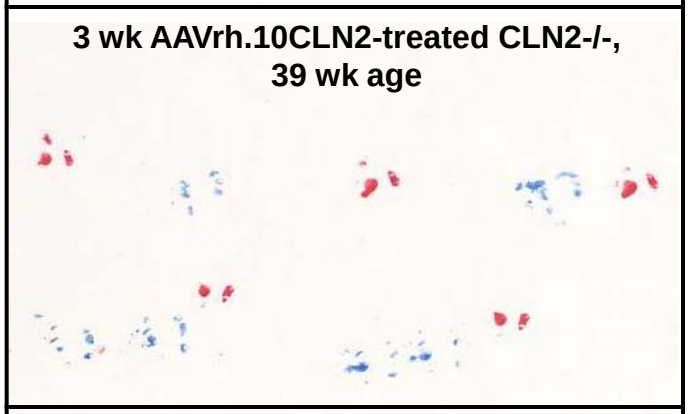
Medial → Lateral

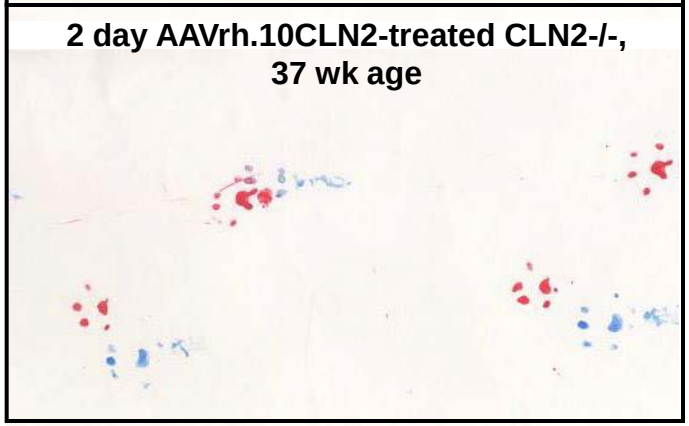
Gait Analysis of CLN2-/- Mice Treated at Different Times with AAVrh.10hCLN2



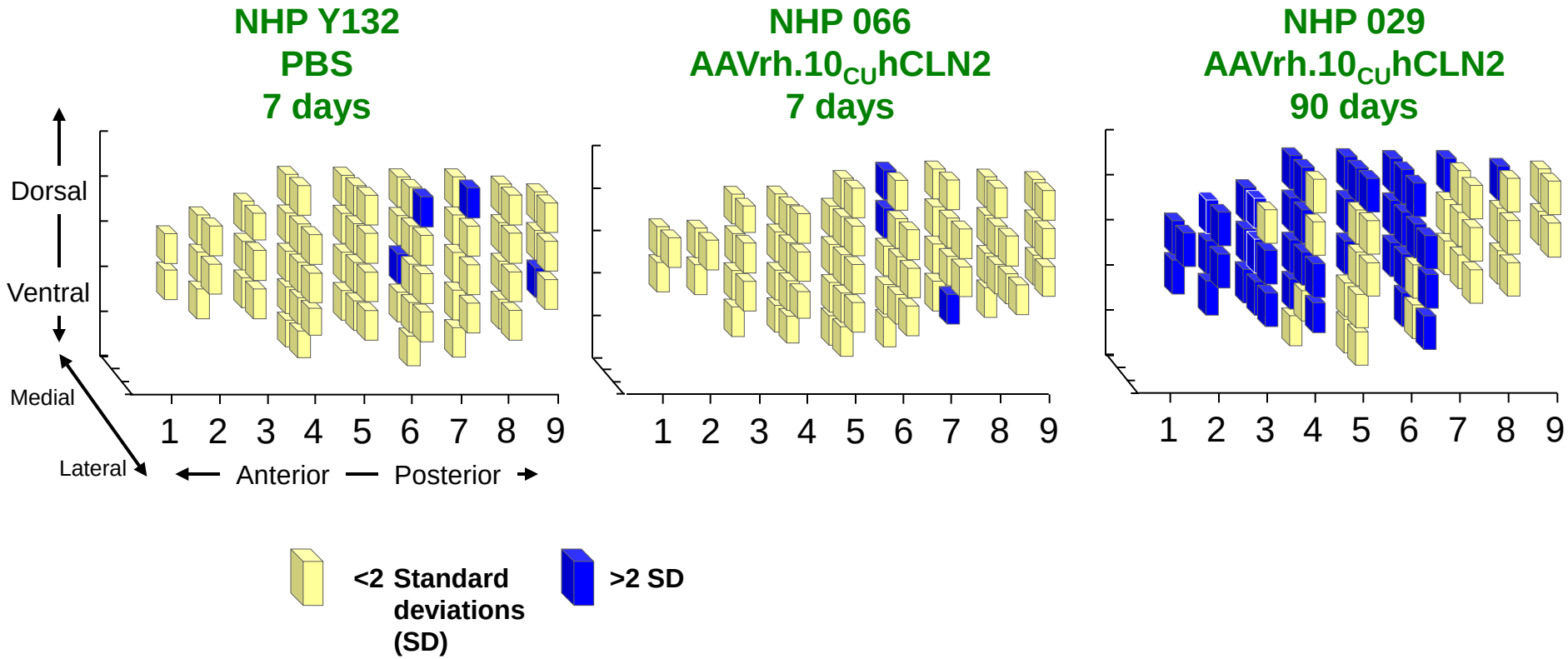




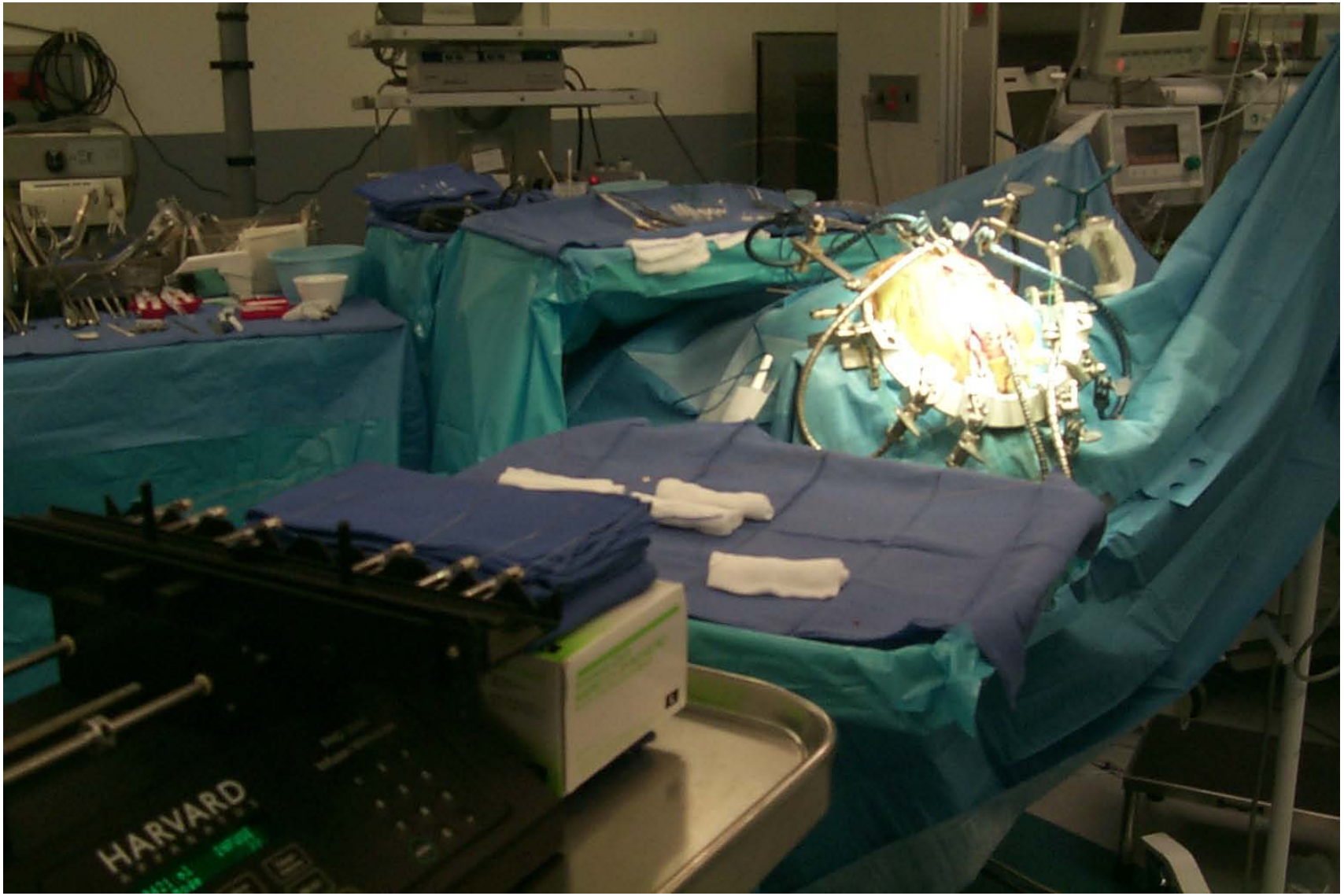




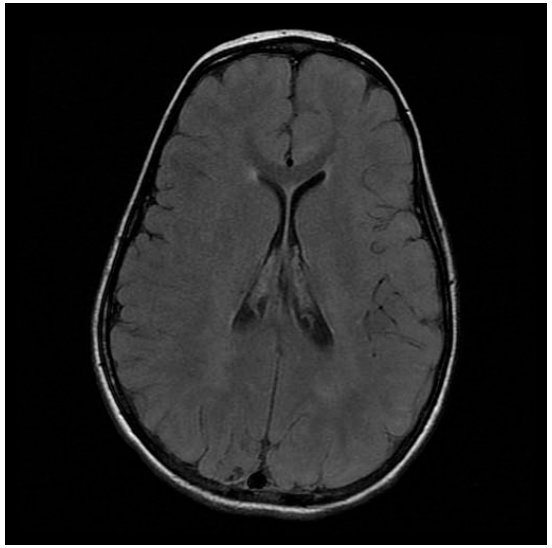
Distribution of TPP-I Activity in the CNS of Non-human Primates Following CNS Administration of AAVrh.10$_{CU}$hCLN2



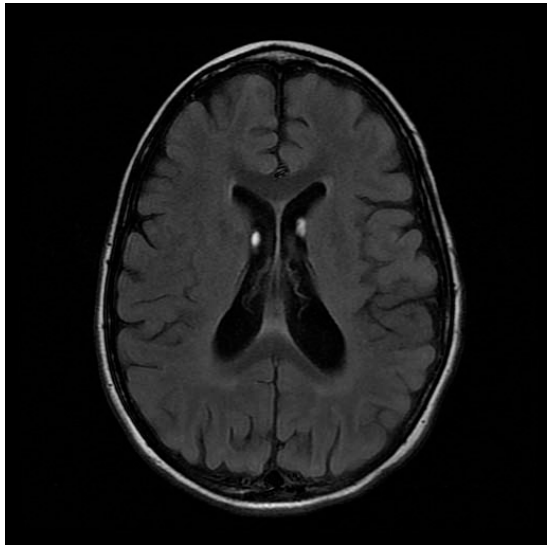
Vector Administration



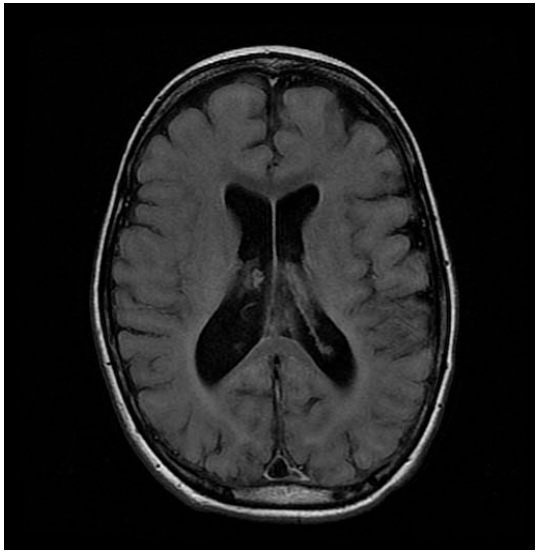
Magnetic Resonance Imaging



LINCL 9

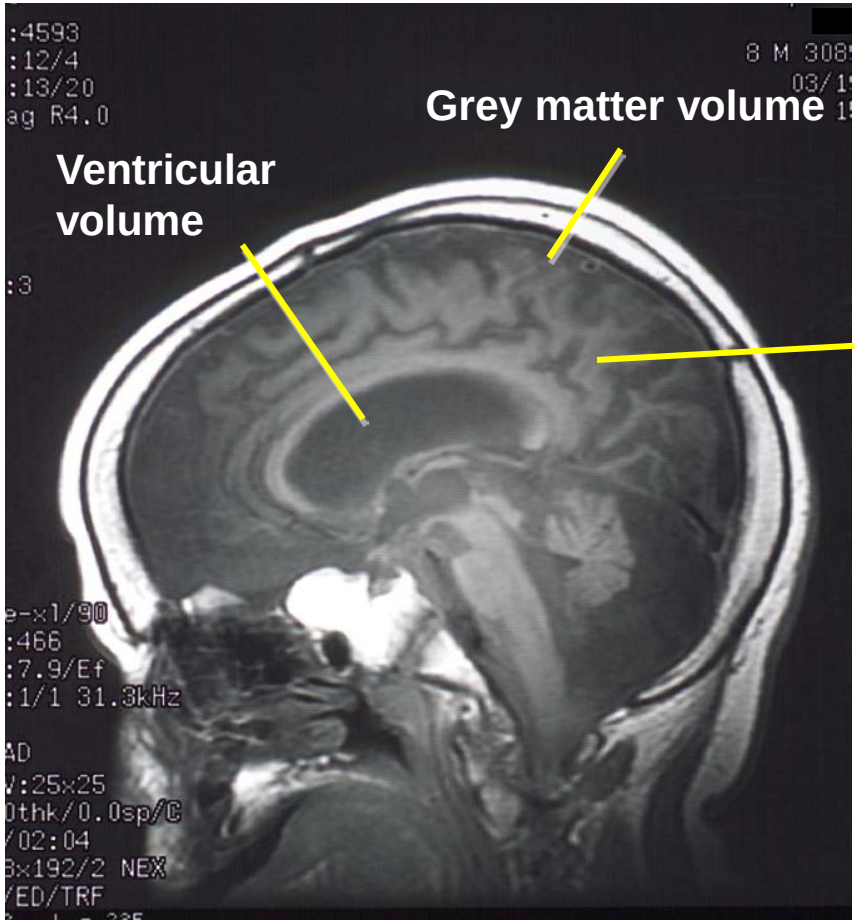


LINCL 6

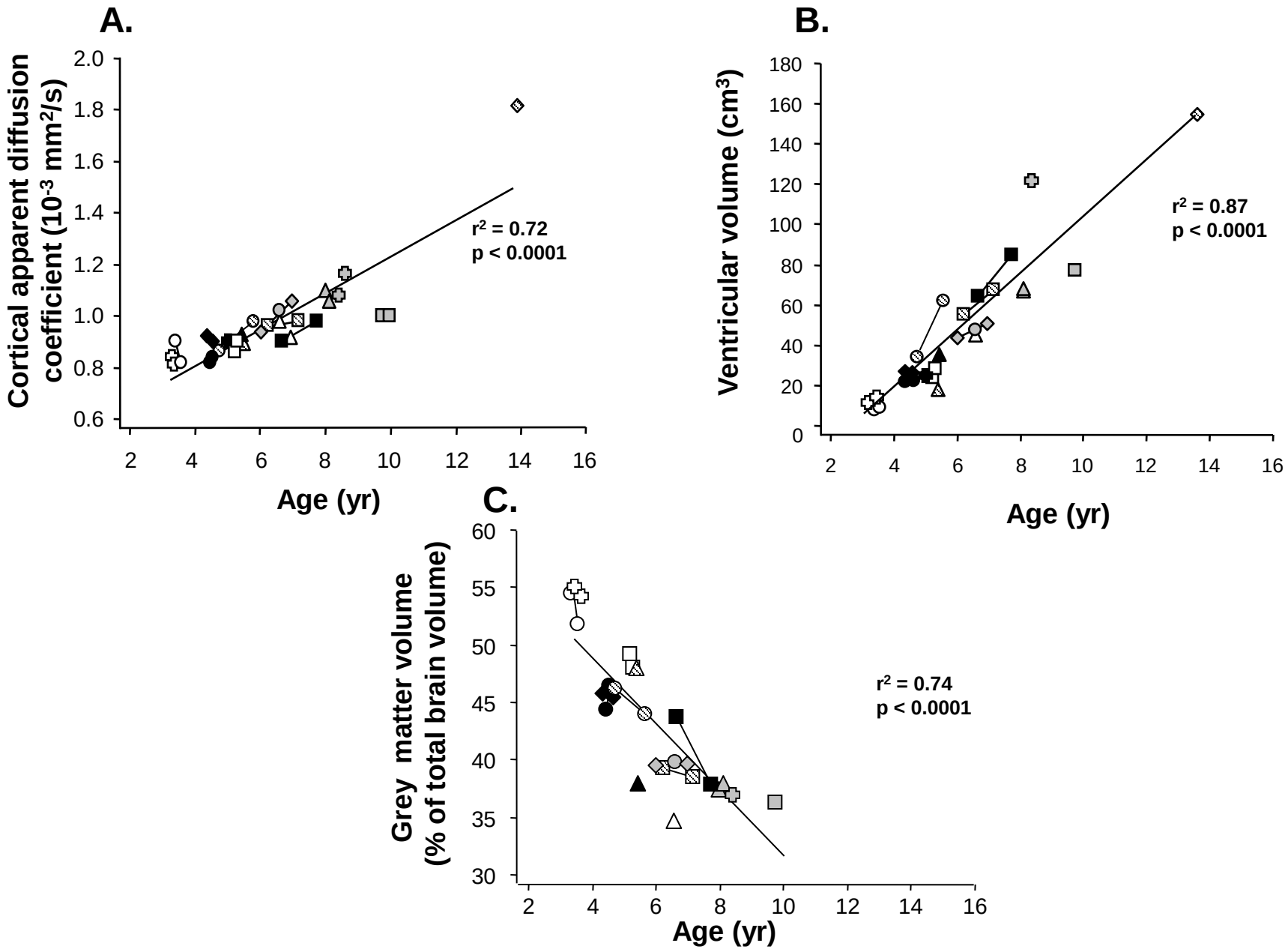


LINCL 3

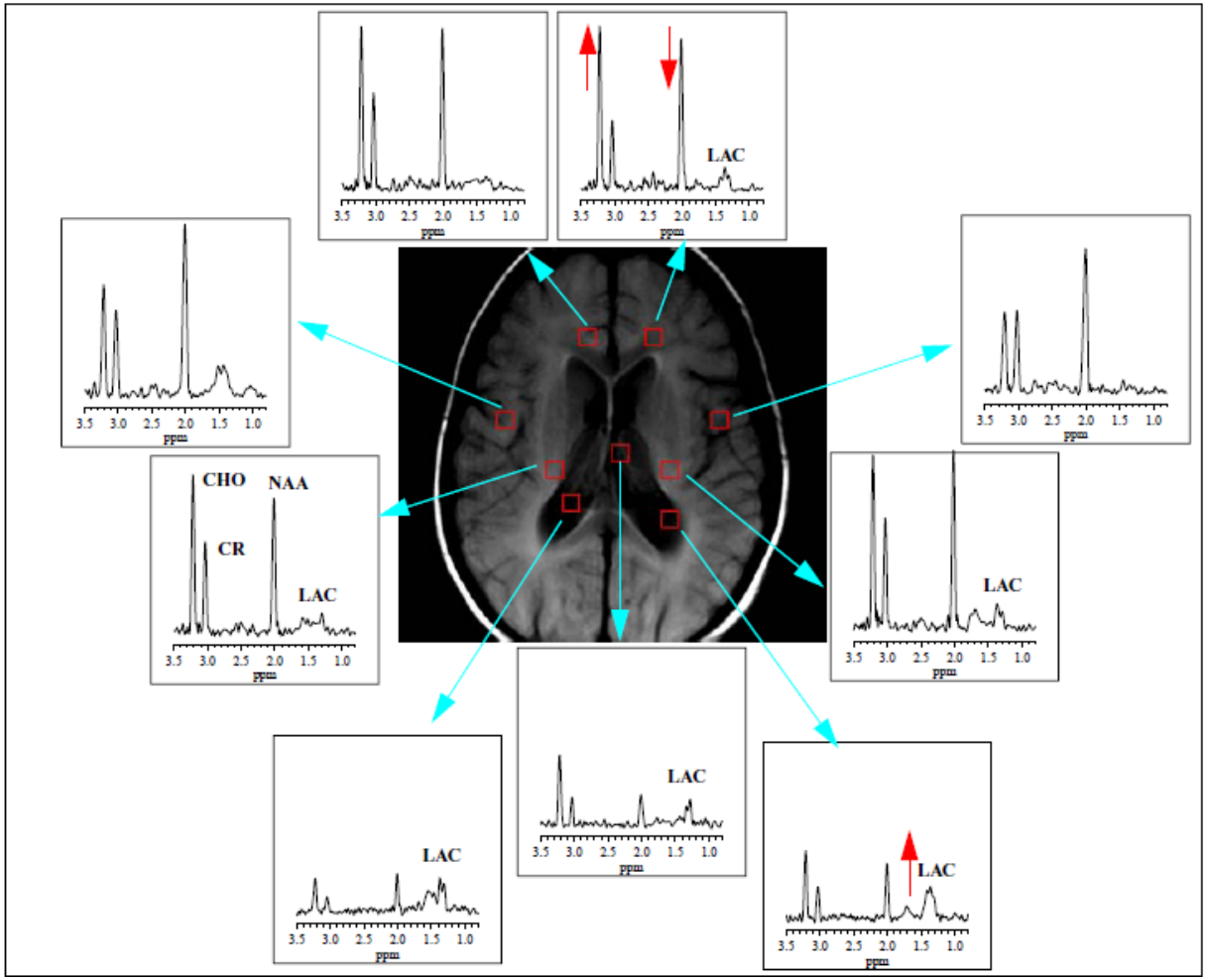
Quantitative MRI



Primary Variable: MRI Parameters

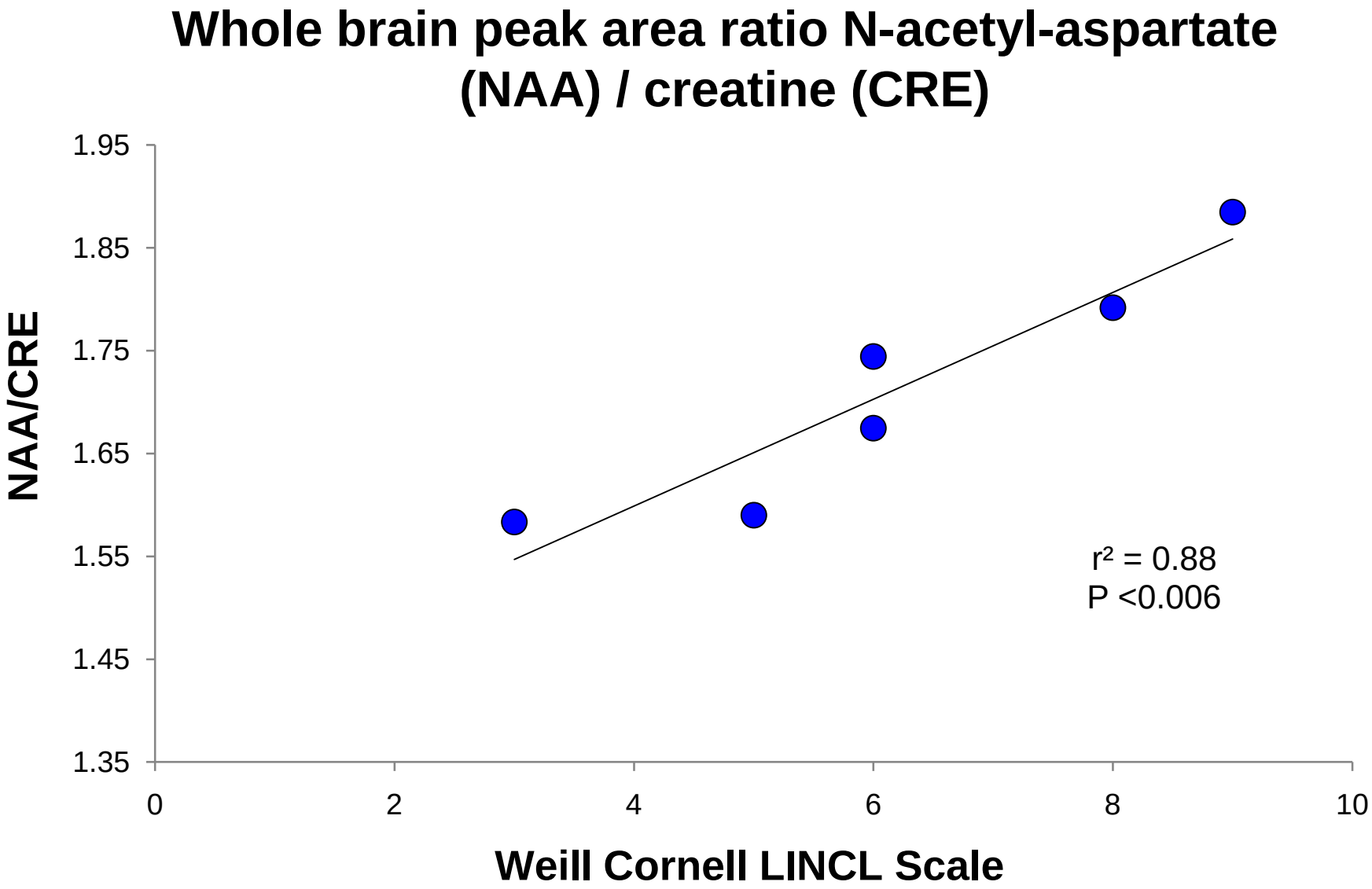


Magnetic Resonance Spectroscopy

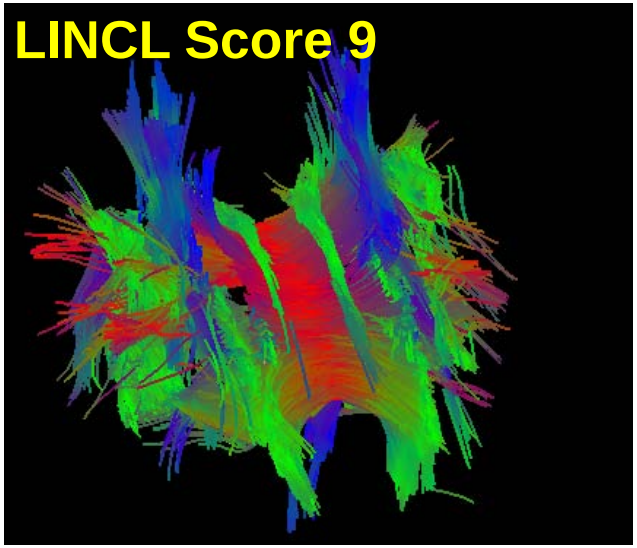


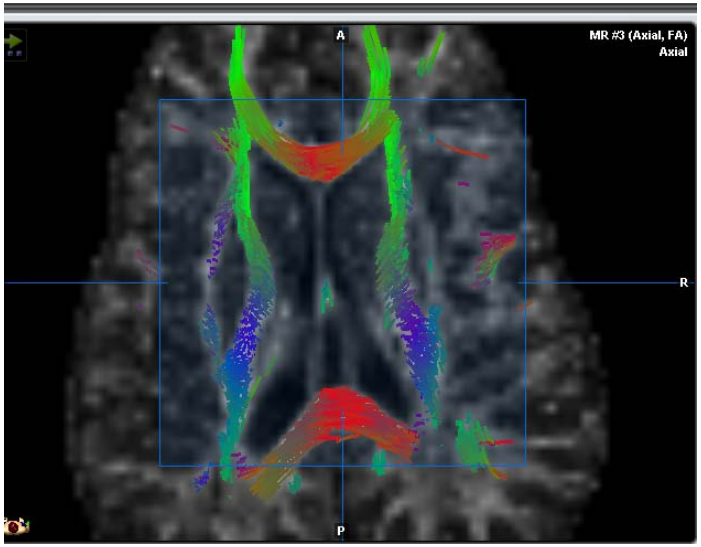
LAC=lactate; CHO=choline; CR=creatine; NAA=N-acetyl aspartate

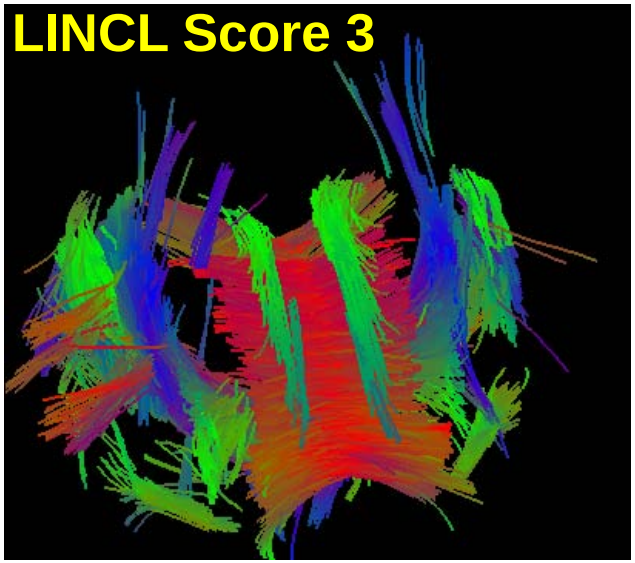
Magnetic Resonance Spectroscopy

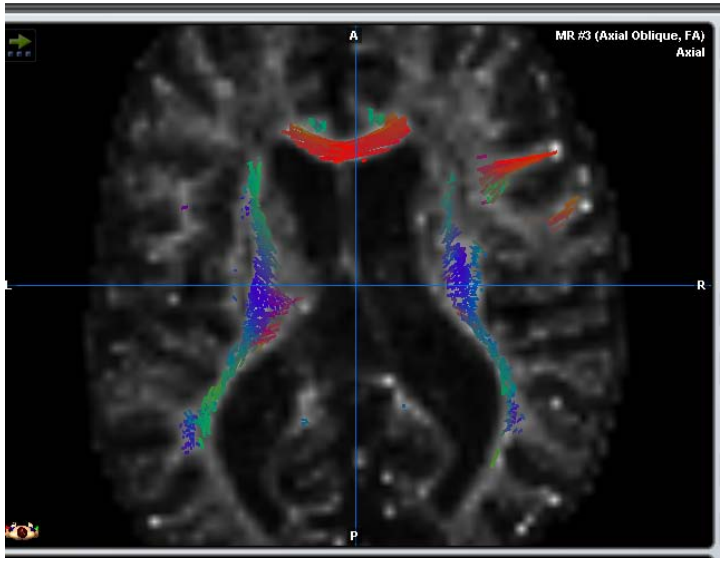


Diffusion Tensor Imaging – White Matter Tractography





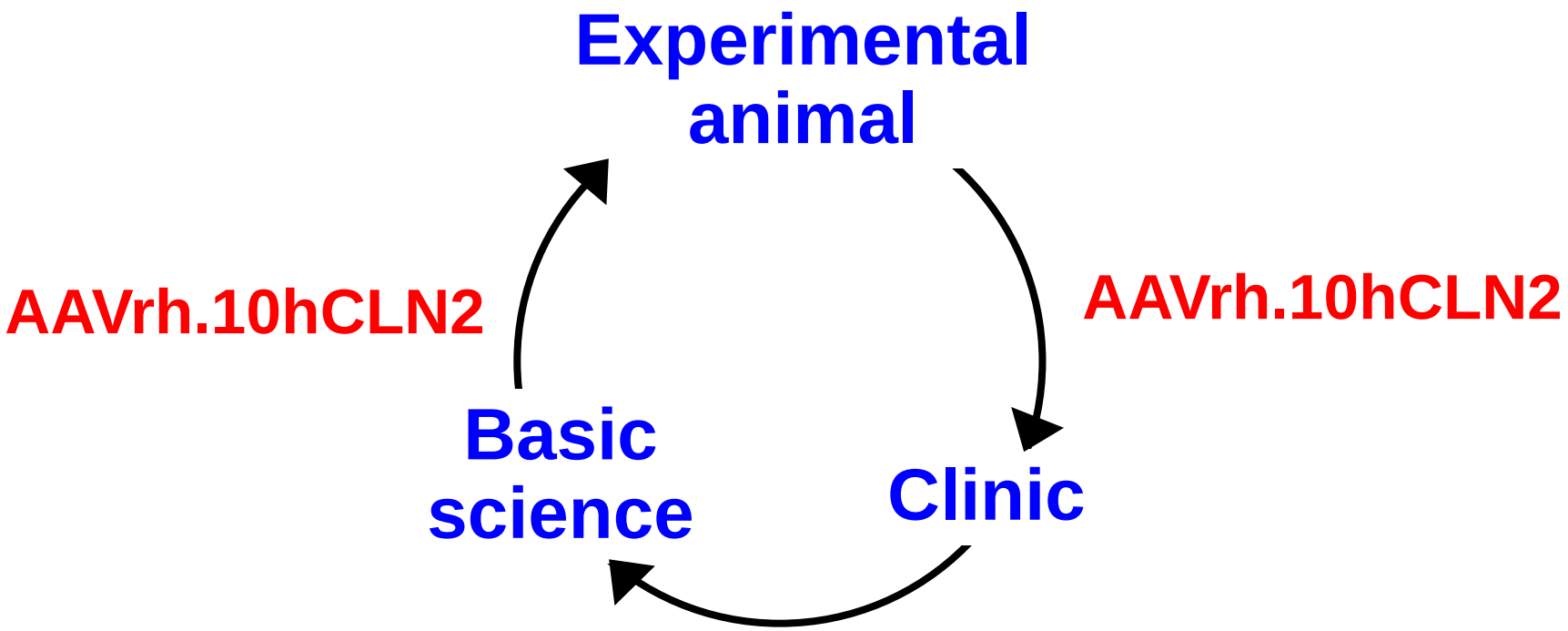




Resources – Who Supports Translational Research for Rare Diseases?

- From gene to clinical study with the AAV2 vector total cost ~ $10 million
- Resources
  - Nathan's Battle Foundation
  - NINDS, NIH
  - Departments of Genetic Medicine, Pediatrics, Radiology, Neurosurgery, Anesthesiology, Neurology + multiple collaborators
  - New York Presbyterian Hospital

How Do We Achieve Success with Genetic Medicines?



Balance Beam Test

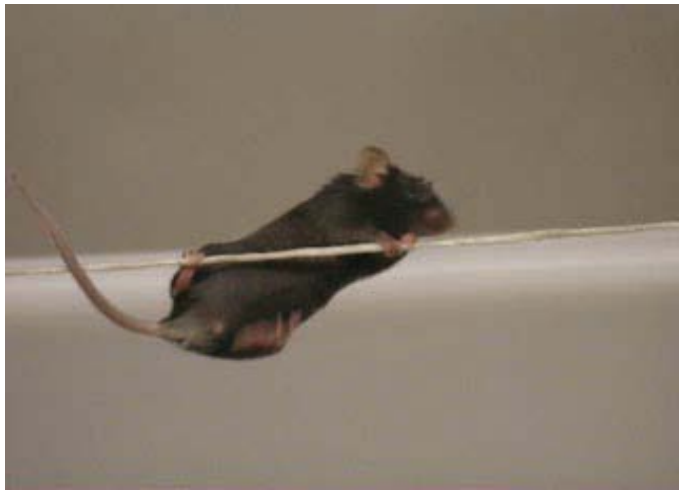
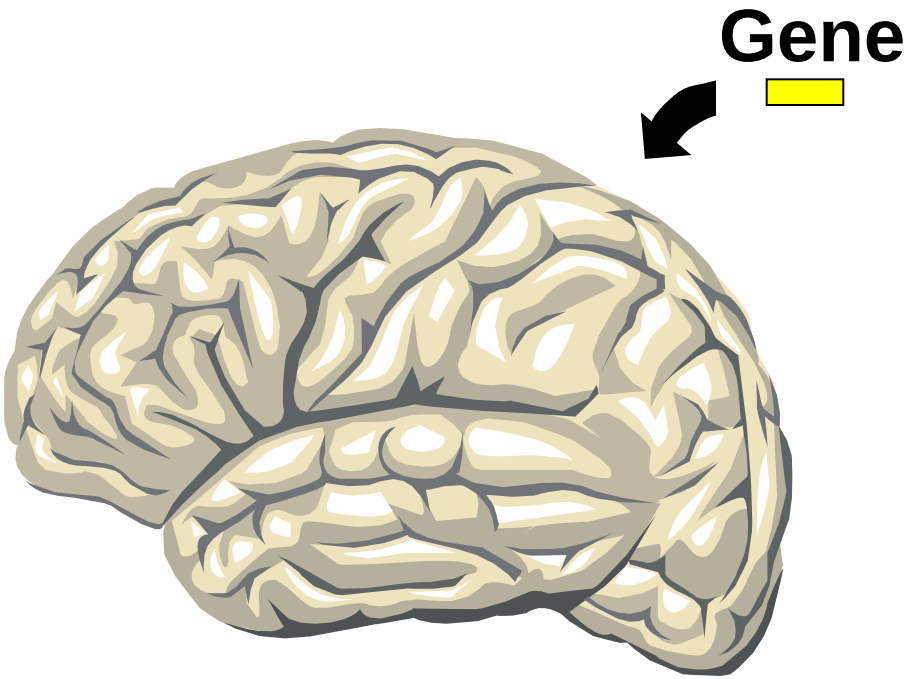
Naive CLN2-/-

AAVrh.10CLN2-treated CLN2-/-

Grip Strength Test

Naive CLN2-/-

AAVrh.10CLN2-treated CLN2-/-



Genetic Modification of the CNS