

Regulatory Challenges for Gene Therapy for Batten Disease

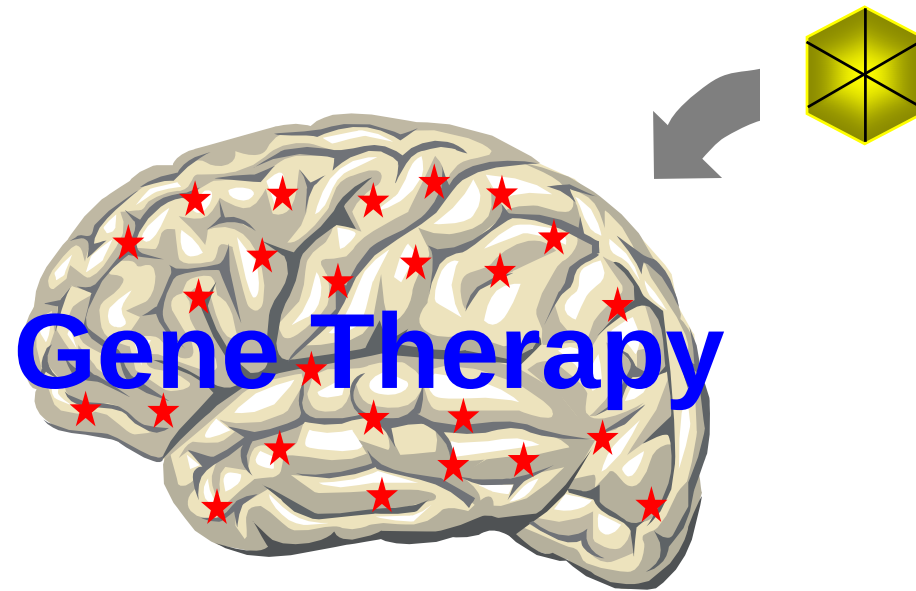
Rare Disease Scientific Workshop
Washington, DC

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Disclosure

- I have equity in and/or a consultant to the following companies with gene therapy programs: Adverum, ReGenX, BioMarin, XyloCor, Jannu and LEXEO

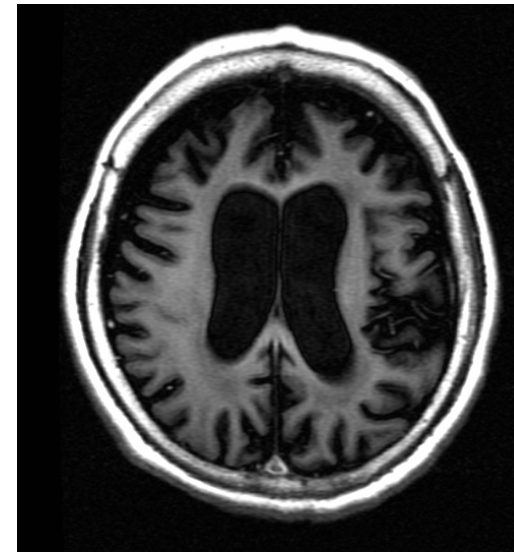
Gene Therapy for Hereditary CNS Disorders



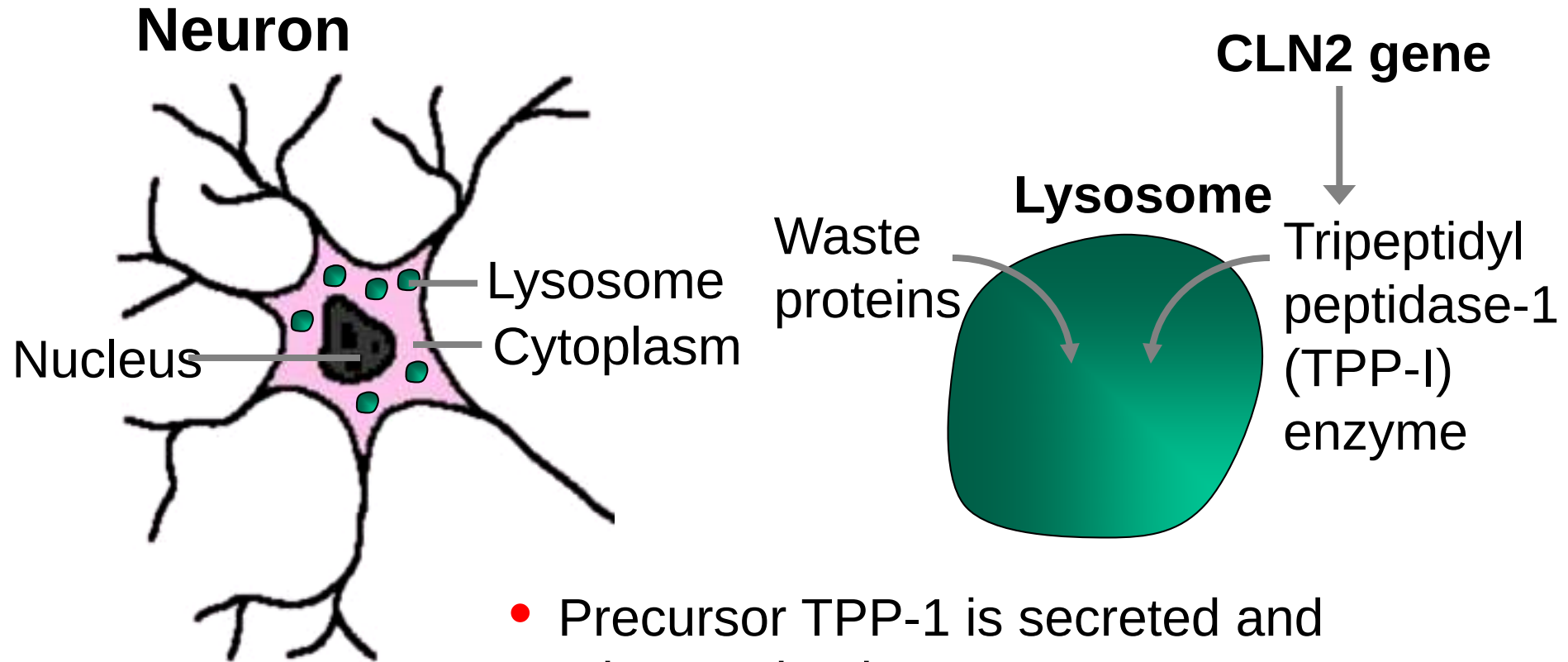
- Rationale – many of the hereditary CNS disorders affect the CNS; gene therapy directly to the brain bypasses the blood-brain barrier; if effective, a single administration will compensate for the genetic abnormality

Late Infantile Neuronal Ceroid Lipofuscinoses (LINCL, Batten Disease, CLN2 Disease)

- Autosomal recessive,
~ 400-600 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

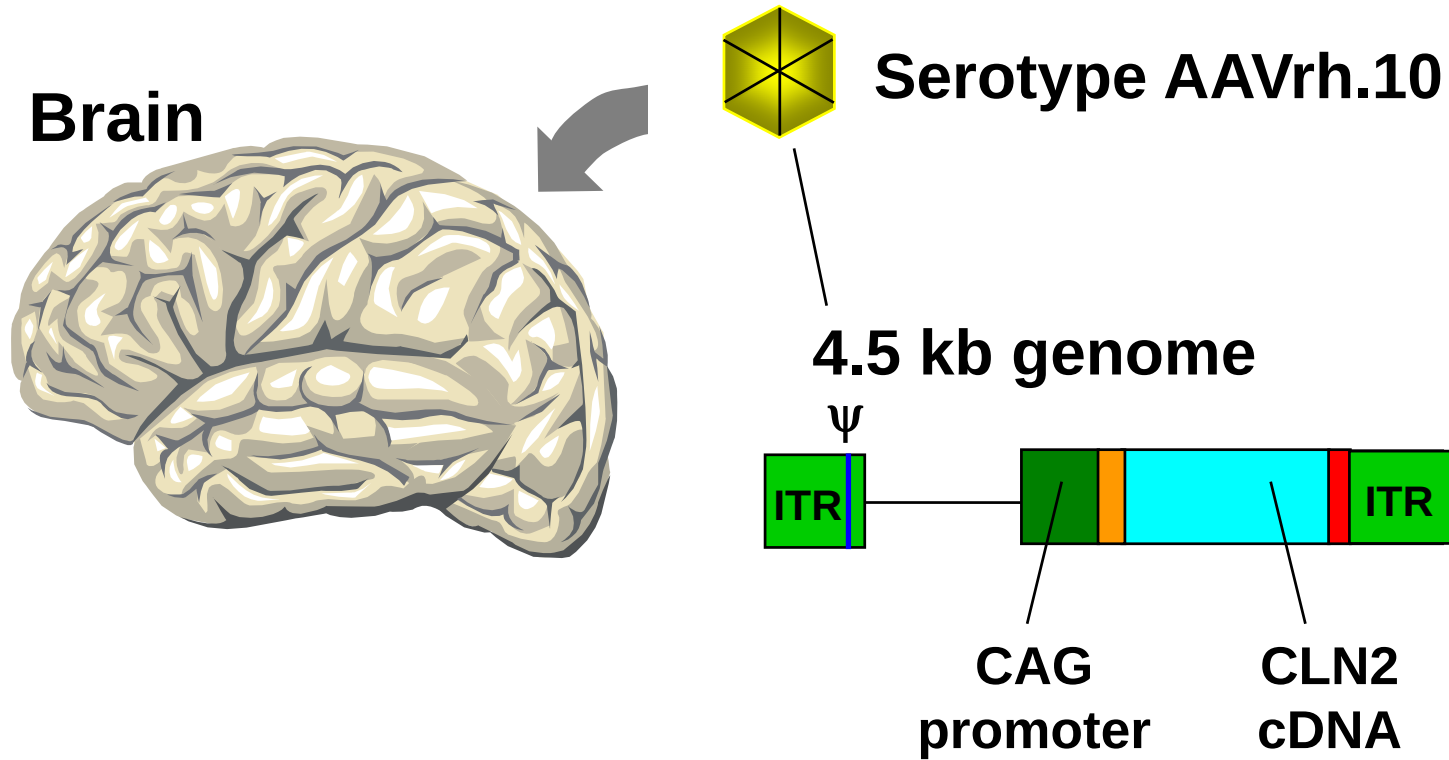


LINCL Is Caused by Mutations in the CLN2 Gene

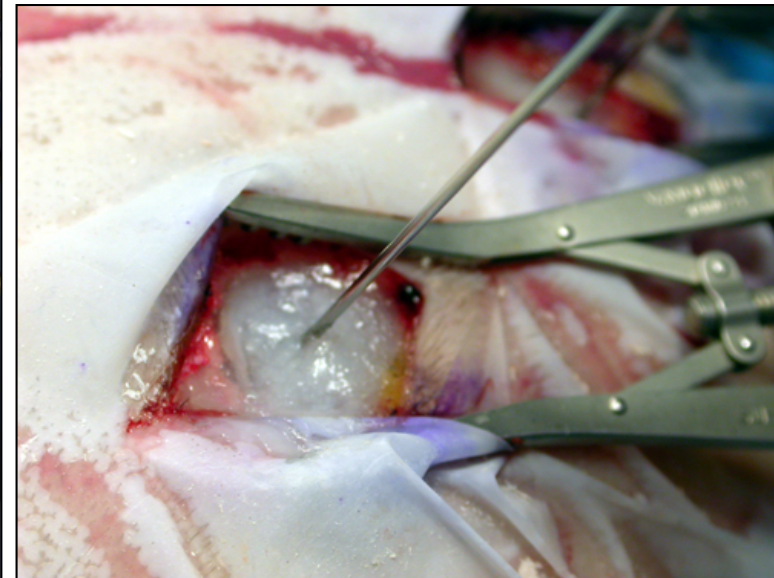
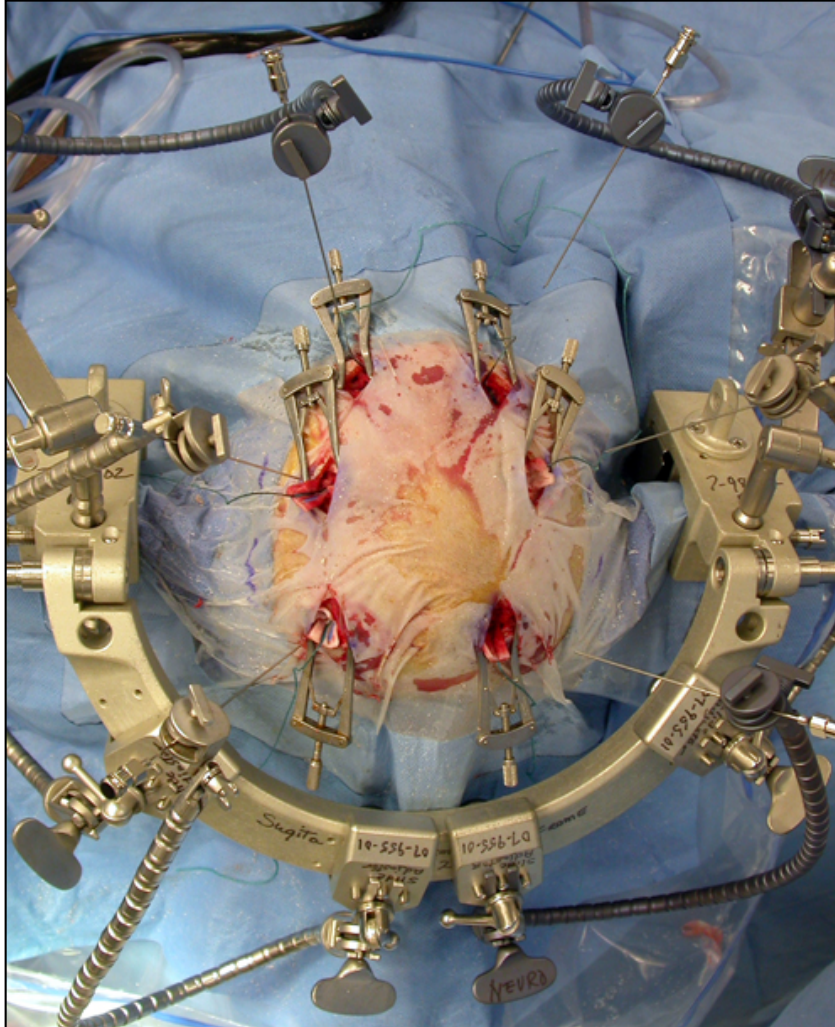


- Precursor TPP-1 is secreted and taken up by the mannose-6-phosphate pathway of neighboring cells

2nd Generation Gene Therapy for LINCL

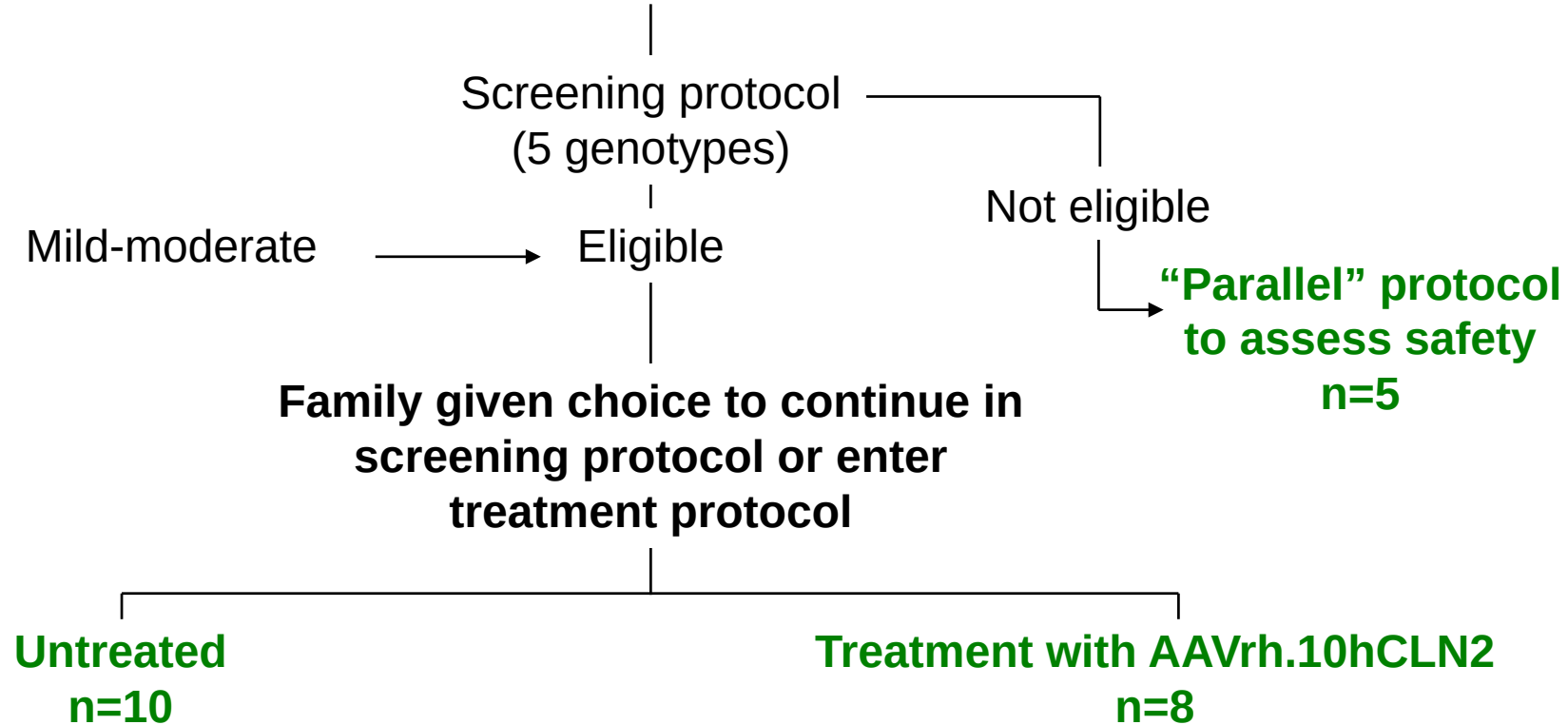


AAV Vector CNS Administration



Trial Design

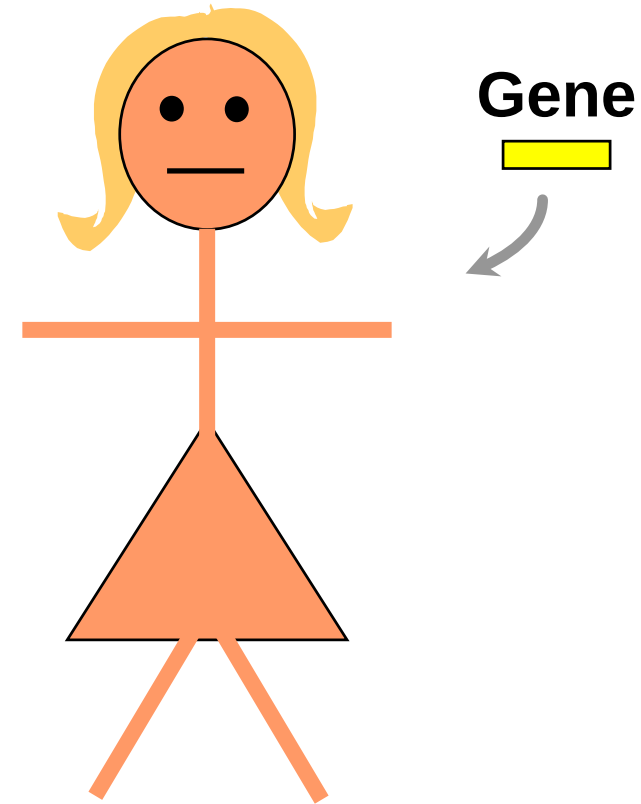
Child with LINCL



- ▣ Phenotypes assessed over 18 months
 - Clinical score
 - Quantitative MRI

Risks to *In Vivo* Gene Therapy with DNA Vectors

- Germ line gene transfer
- Recombination
- Contamination of the environment
- Persistent and/or overexpression
- Systemic or organ-specific anti-vector and/or transgene product immunity
- Off-target effects



Regulatory Challenges

- Toxicology
- Communication
- Reporting
- Control groups

Vector Toxicology Guidelines

Issue

- There is extensive experimental animal and human safety data relating to *in vivo* administration of DNA vectors
- Toxicology-related studies are often repetitive, and provide little additional information than what is already known

Recommendation

- Significant effort and cost could be eliminated by having periodic guidance documents that state common concepts/guidelines that could eliminate some of the repetitive toxicology work

Communication

Issue

- The FDA knows what all companies and academics are doing and the data they have generated, while the individual investigator groups know only their own data, what is public and gossip
- This is particularly relevant in issues relating to vectors, including manufacturing, e.g., acceptable cell lines, quality of plasmids, quality of final products

Recommendation

- When serious issues arise that the agency is aware of that may alter protocol design and manufacturing practices, it would be of significant help to provide information to the community of the FDA's concerns that can have major implications to programs based on long term commitments
- For consideration – a symposium at the annual ASGCT meeting organized jointly by the ASGCT and the FDA to discuss these issues

Reporting

Issue

- There is now a 25 year experience with *in vivo* administration of DNA vectors, and the 15 year reporting requirement for many gene therapy applications is no longer relevant to many *in vivo* DNA vector applications

Recommendation

- As articulated in the July 2018 Draft guidance document, it is rational to have reporting requirements that are vector and disease-specific, with some requiring long-term observation and others short-term or no observation at the end of the clinical protocol
- It would be very useful for the FDA to publish a data-driven document of the 15 year monitoring data generated over the past 25 years

Control Groups

Issue

- For many of the rare diseases, placebo studies are not feasible
- This is not specific to *in vivo* use of DNA vectors

Recommendation

- For many rare, fatal disorders, natural history studies are the only way to demonstrate efficacy
- An FDA guidance document focused on control groups would be useful, and might also be a topic for an ASGCT joint symposium

Regulatory Challenges for *In Vivo* Gene Therapy with DNA Vectors

