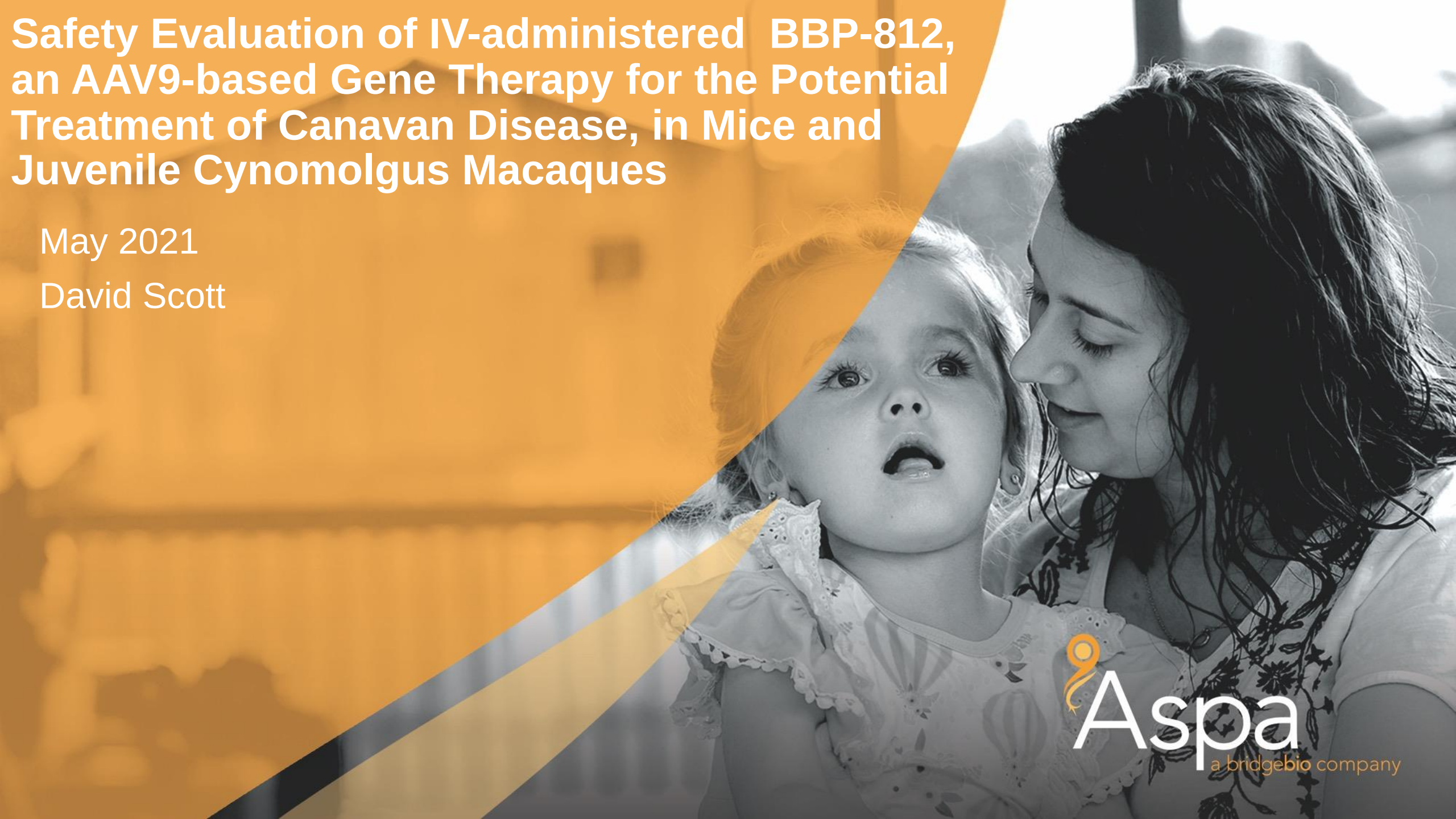
# Safety Evaluation of IV-administered BBP-812, an AAV9-based Gene Therapy for the Potential Treatment of Canavan Disease, in Mice and Juvenile Cynomolgus Macaques

May 2021

David Scott



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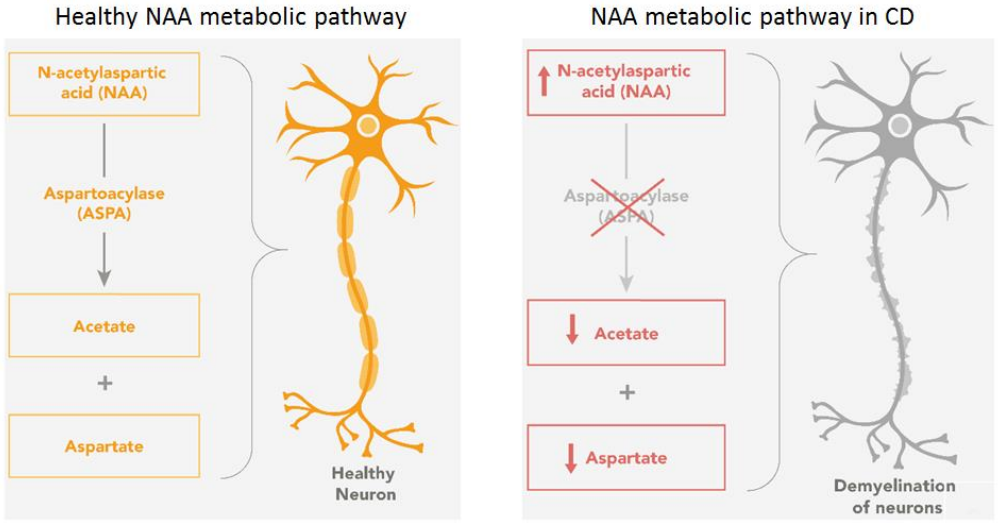
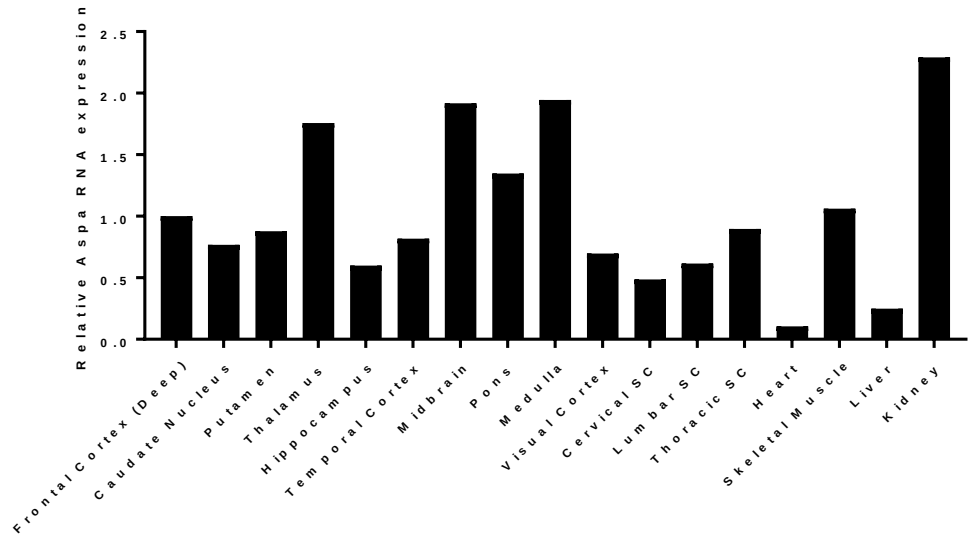
# BBP-812 is being developed as a potential therapy for Canavan disease

- Canavan disease is characterized by a loss of Aspa expression and a systemic build up of N-acetylaspariticacid (NAA).
- •In the presence of elevated NAA, neuronal demyelination occurs leading to progressive psychomotor regression.




- There are currently no approved therapies that target the underlying cause of Canavan disease.

- Aspa is expressed throughout the body and is enriched in deep, white matter regions of the brain




- BBP-812 is an AAV9-based gene therapy encoding the human Aspa gene being developed as a potential treatment for Canavan disease



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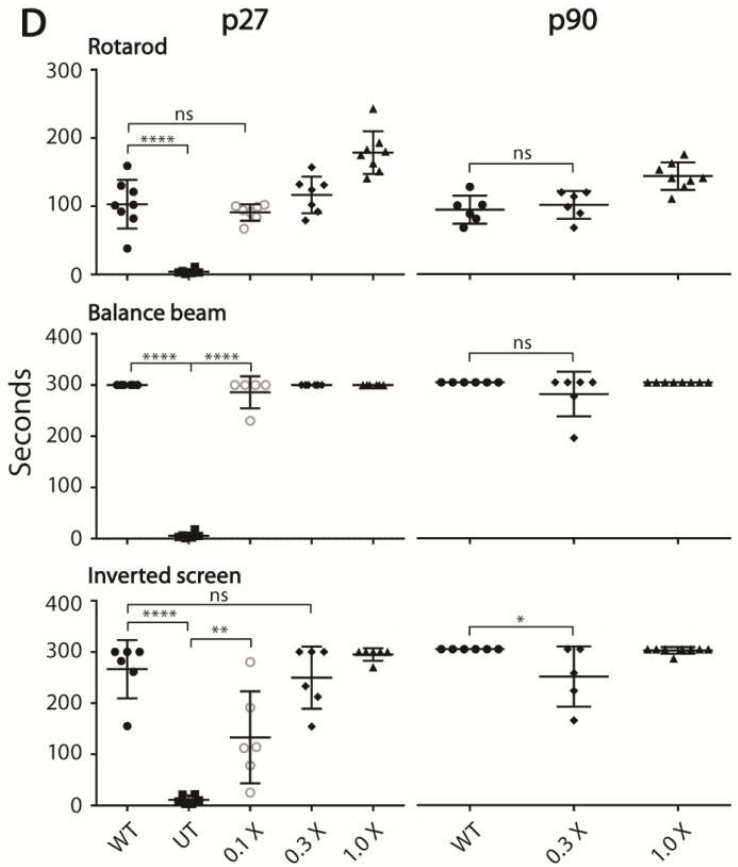
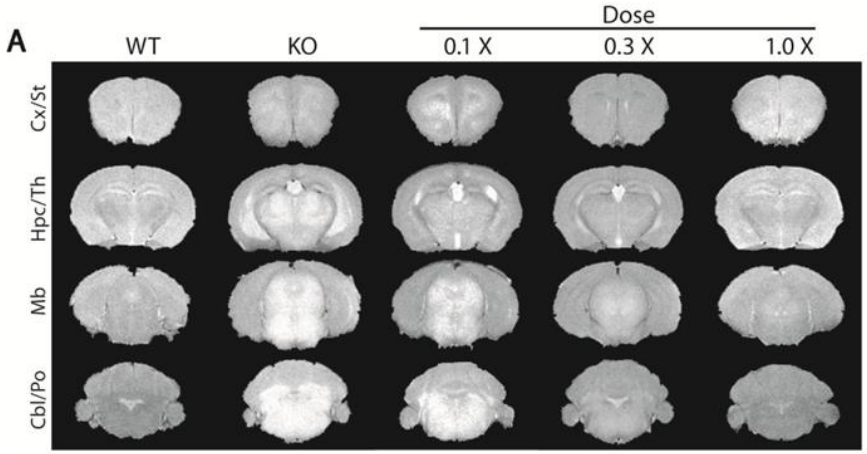
# BBP-812 provides phenotypic and biomarker normalization in a murine model of Canavan disease

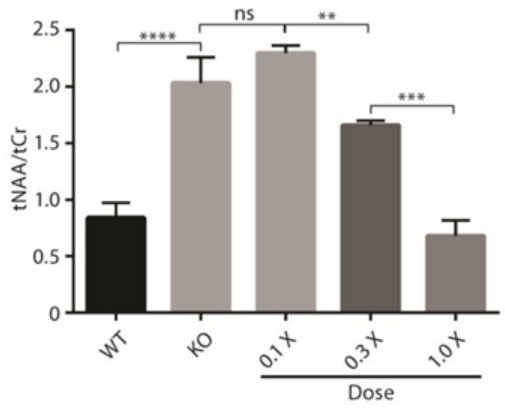
## Motor function recovery is dose-dependent




1.0X=2.66x10$^{14}$ vg/kg
0.3X=8.80x10$^{13}$ vg/kg
0.1X=2.66x10$^{13}$ vg/kg

## Dose-dependent reduction in CNS edema and NAA metabolism




*Gessler et al, 2017*



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# Evaluation of safety and biodistribution of BBP-812 in juvenile cynomolgus macaques

| Group | Vector | Group size | ROA | Dose Level | Dose/kg or brain | 3 week necropsy | 8 week necropsy |
|---|---|---|---|---|---|---|---|
| 1 | BBP-812 | N = 3 | IV | Low | $3.18x10^{13}$ vg/kg | | N = 3 |
| 2 | | N = 3 | IV | Mid | $1.15x10^{14}$ vg/kg | | N = 3 |
| 3 | | N = 6 | IV | High | $3.18x10^{14}$ vg/kg | N = 3 | N = 3 |
| 4 | | N = 6 | ICV | High | $8.98x10^{12}$ total | N = 3 | N = 3 |
| 5 | | N = 6 | IT | High | $8.98x10^{12}$ total | N = 3 | N = 3 |
| 6 | Vehicle | N = 4 | ICV/IT | - | - | N = 2 | N = 2 |

~2kg, 2-2.5yo

- **Hematology and Clinical pathology**
- **Biodistribution**
- **Immunological response to capsid and transgene**
- **Full histology panel with focus on CNS**



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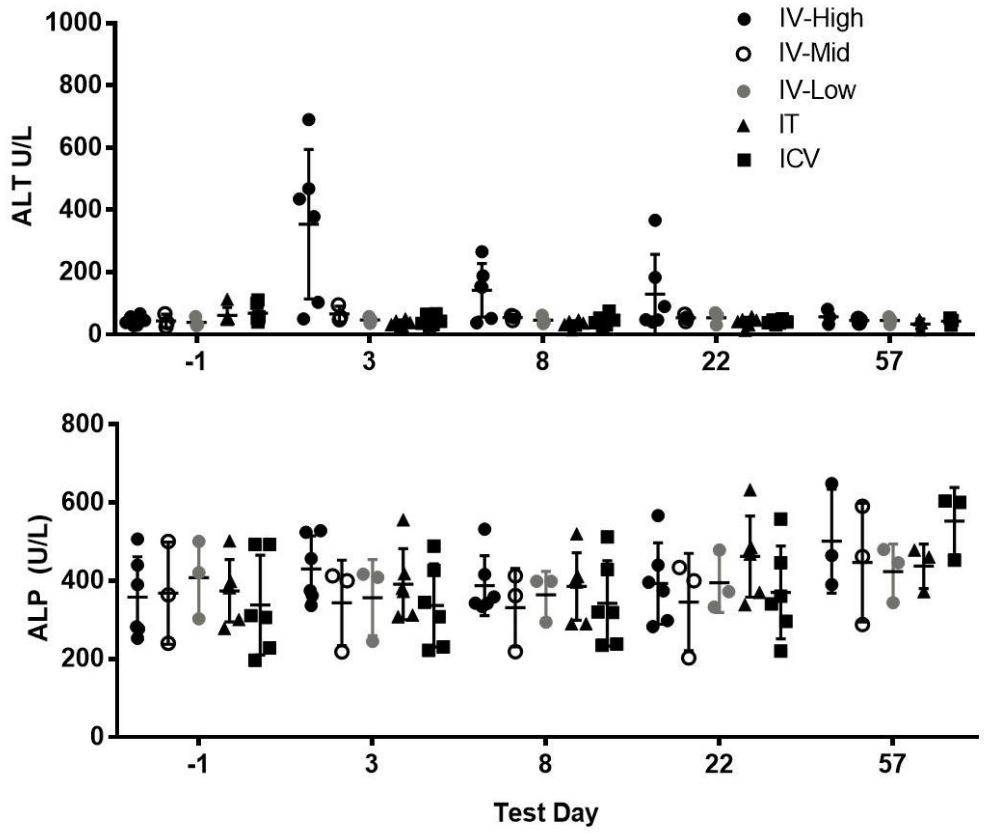
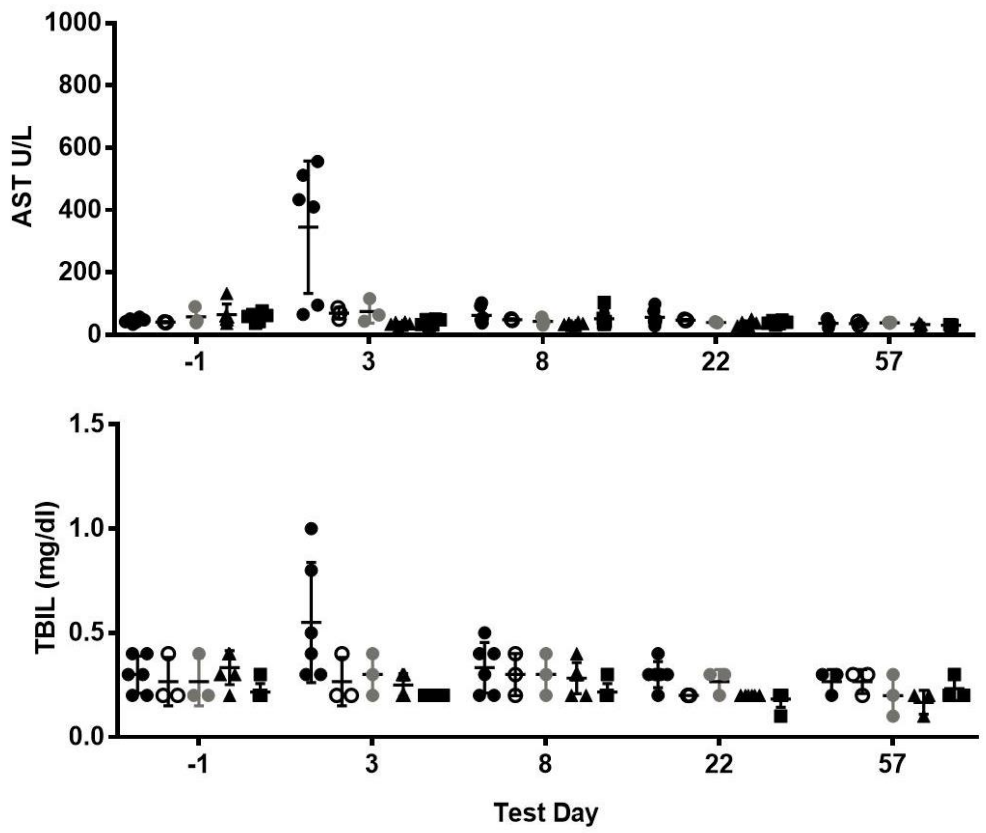
# BBP-812 induces a transient increase in transaminase levels without impacting other markers of hepatotoxicity




- **No thrombocytopenia**
- **No coagulopathies**



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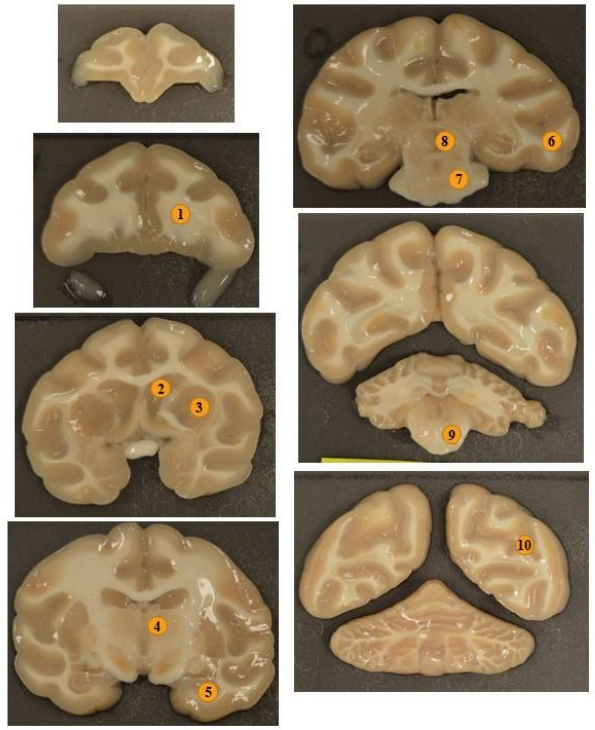
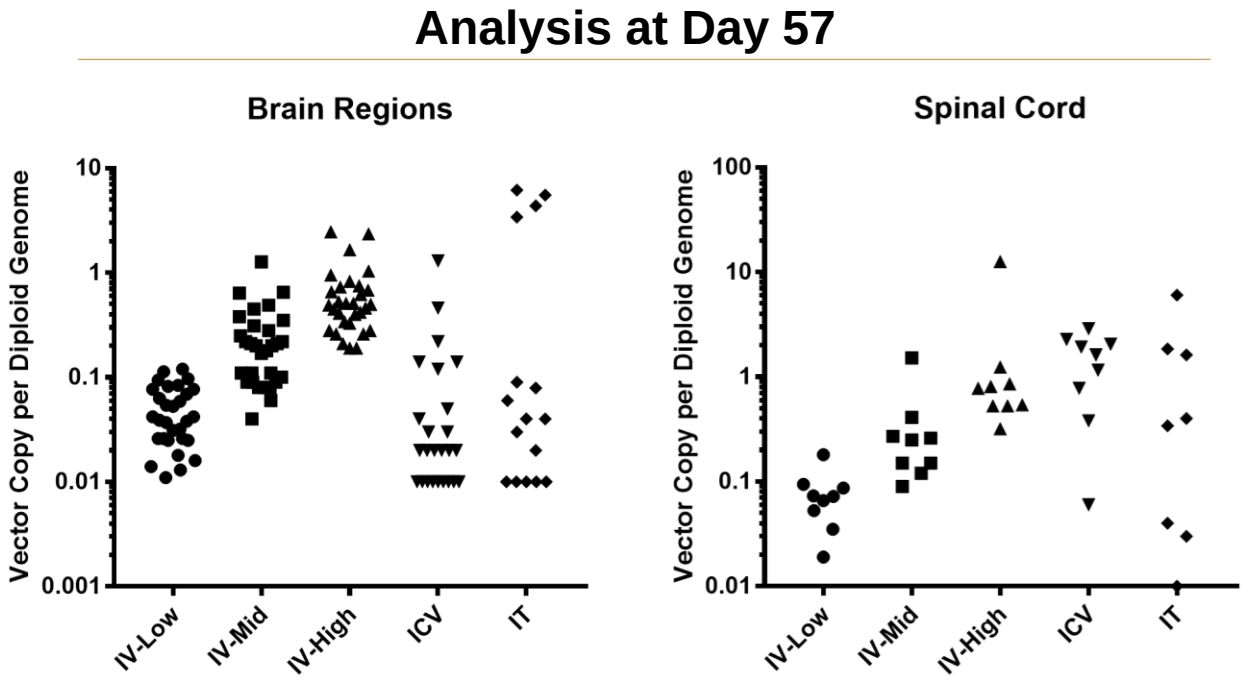
# IV-administration of BBP-812 provides superior biodistribution to brain regions when compared to ICV and IT




| Sample | Tissue |
|---|---|
| 1 | Deep frontal cortex |
| 2 | Caudate nucleus |
| 3 | Putamen |
| 4 | Thalamus |
| 5 | Hippocampus |
| 6 | Temporal cortex |
| 7 | Midbrain |
| 8 | Pons |
| 9 | Medulla |
| 10 | Visual cortex |
| 11 | Cervical Spinal Cord |
| 12 | Lumbar Spinal Cord |
| 13 | Thoracic Spinal Cord |



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# IV-administration of BBP-812 was not associated with adverse histopathological findings including in DRG

**Summary of analysis per animal:**

- Full panel of peripheral tissues.
- Brain was analyzed at 15 levels.
- Spinal Cord was analyzed at four levels.
- At least two dorsal root ganglia and associated spinal nerve roots from each of four spinal cord levels

**Key Findings:**

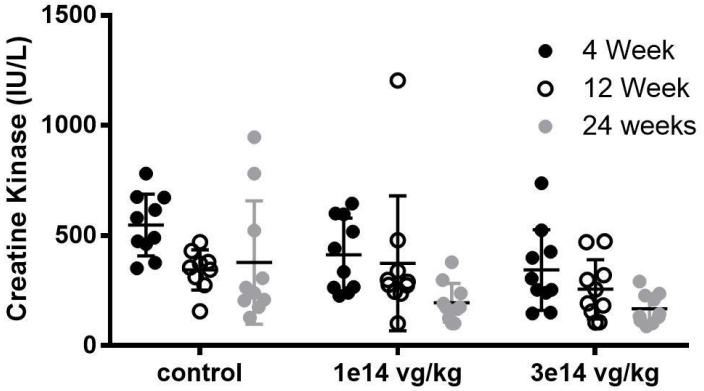
- Liver analysis demonstrated portal infiltrates and/or increased cellularity in high dose IV group which was minimal (Grade 1) and not considered adverse.
- There was a minimal (Grade 1) increase in cellularity observed in 4 of 48 DRG analyzed from highest dose IV-treated animals.
- **No evidence of axonopathy or neuronal degeneration associated with IV-administered BBP-812**

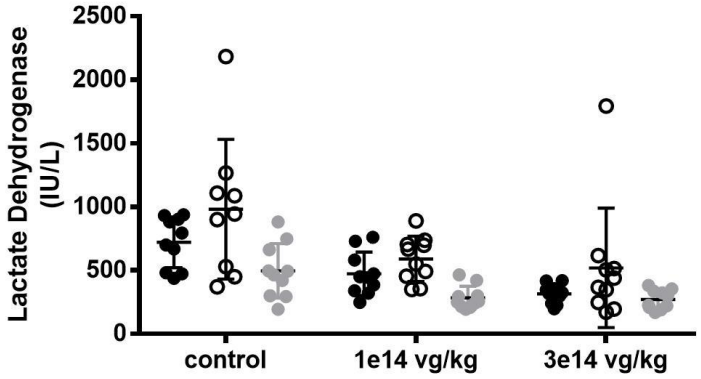
# GLP Toxicology assessment of BBP-812 in wild type C57Bl/6 mice

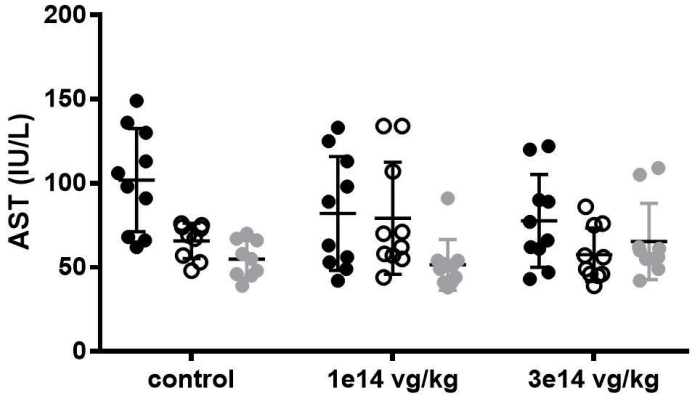
| Group | Vector | ROA | Dose Level | Dose/kg or brain | Necropsy Timepoints |
|---|---|---|---|---|---|
| 1 | BBP-812 | IV | High | $3.0x10^{14}$ vg/kg | 4, 12, and 24 weeks |
| 2 | | IV | Low | $1.0x10^{14}$ vg/kg | 4, 12, and 24 weeks |
| 3 | Vehicle | IV | - | - | 4, 12, and 24 weeks |

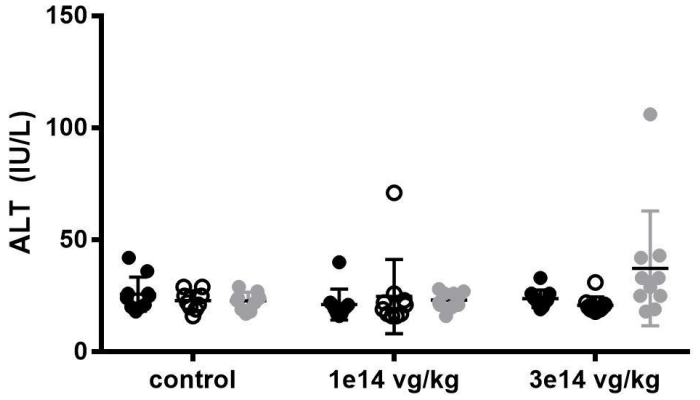
- **Hematology and Clinical pathology**
- **Biodistribution**
- **Immunological response to capsid and transgene**
- **Full histology panel**

# IV-administration of BBP-812 was not associated with any adverse changes in hematology or clinical chemistry



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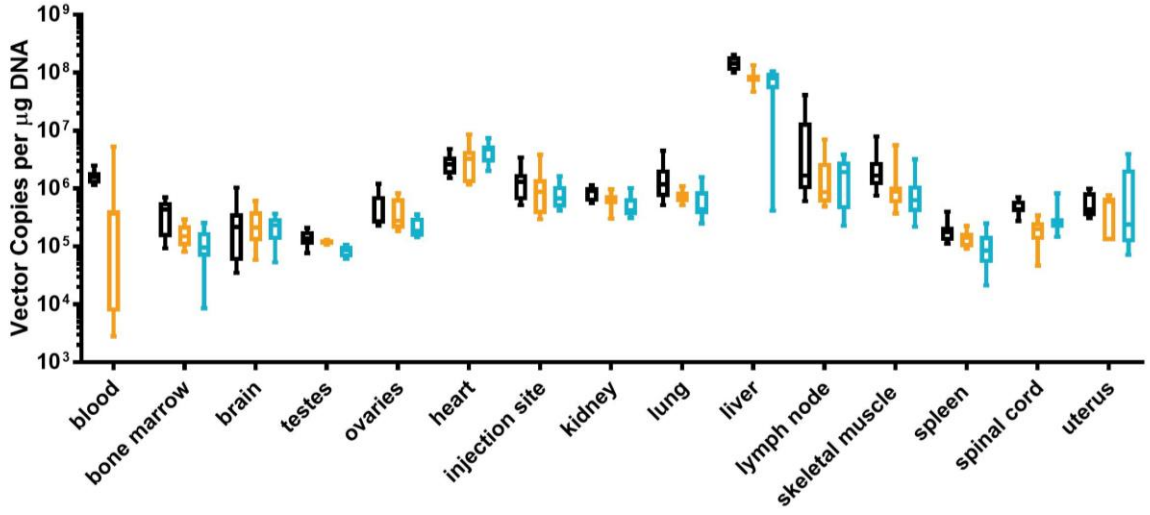
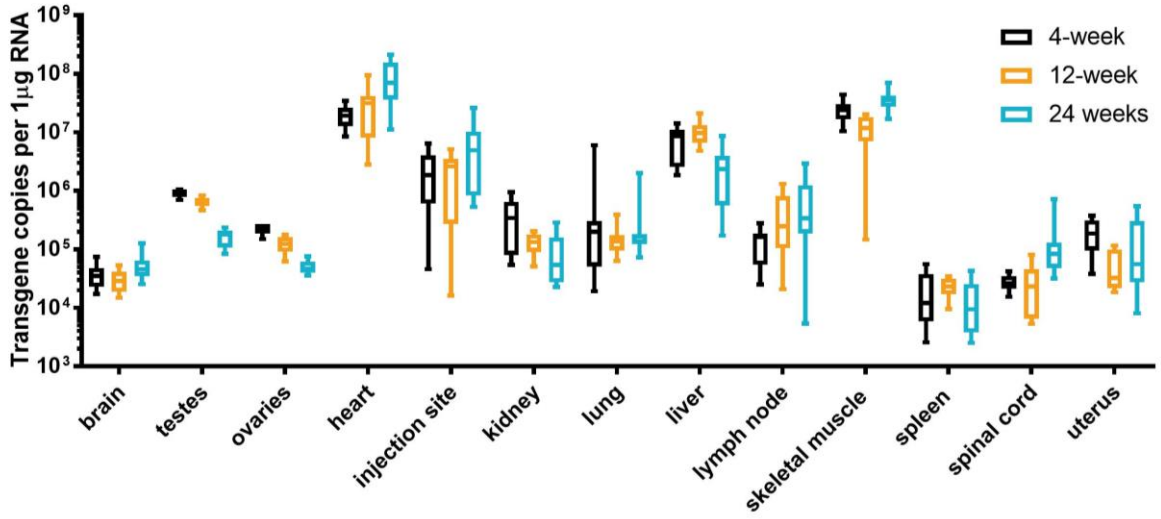
# IV-administration of BBP-812 provided broad and persistent biodistribution




- **Vector detected in all tissues assessed with a gradual decline over time**
- **Transgene RNA detected in all tissues assessed and remained steady throughout study**



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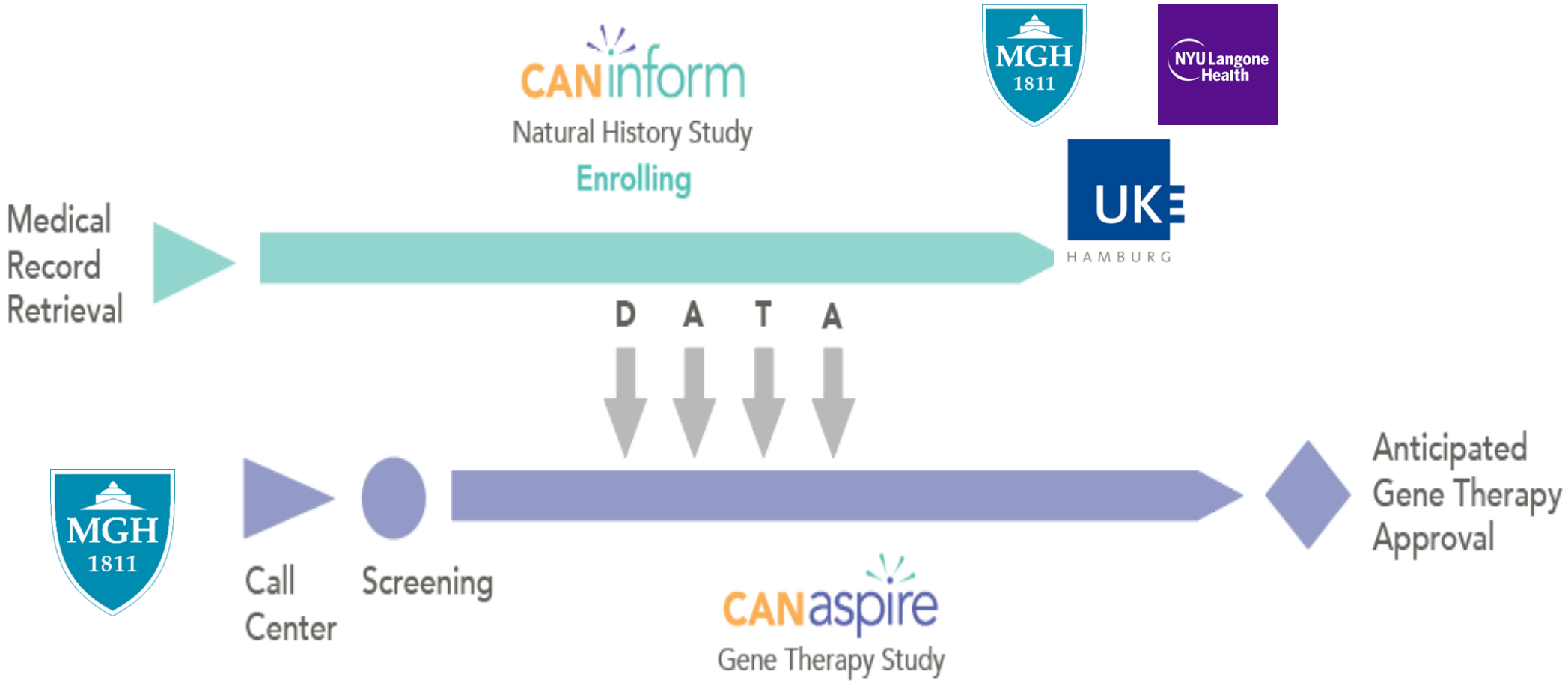
# Conclusions

- Transient elevation in AST/ALT in NHPs returned to baseline without intervention and a similar increase was not observed in mice.
- IV-administration resulted in broad CNS biodistribution to deep brain regions that was superior to IT or ICV administration.
- No adverse histopathological findings were observed in either NHPs or mice at any dose.
- NOAELs were determined to be $3.18x10^{14}$vg/kg in NHP and $3.0x10^{14}$ vg/kg in mice.
- Results support the continued clinical development of BBP-812 for the treatment of Canavan disease.

# ASPA CLINICAL PROGRAM OVERVIEW

**treatcanavan.com**

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# Acknowledgements

**Bridge Bio Gene Therapy Team**

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