Combined CNS and Systemic Directed Gene Therapy in a Mouse Model of Pompe Disease with Advanced Disease at Treatment

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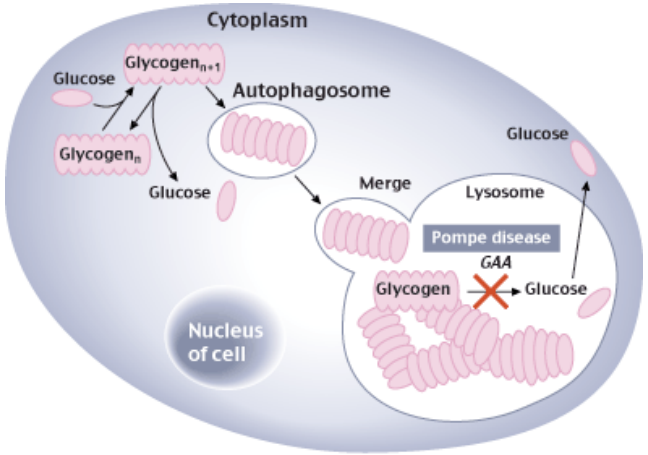
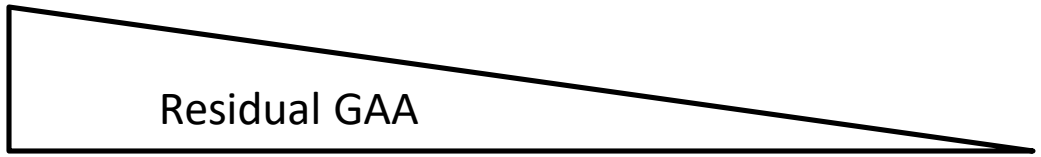
Disclosure Statement

- **J.M. Wilson** is a paid advisor to and holds equity in Scout Bio and Passage Bio; he holds equity in Surmount Bio; he also has a sponsored research agreement with Ultragenyx, Biogen, Janssen, Precision Biosciences, Moderna Inc., Scout Bio, Passage Bio, Amicus Therapeutics, and Surmount Bio which are licensees of Penn technology. **J.M. Wilson** and **J. Hordeaux** are inventors on patents that have been licensed to various biopharmaceutical companies and for which they may receive payments.
- **S. Tuske, P. Tsai** and **H. Do** are employees of Amicus Therapeutics
- **Funding**:

Background, Pompe disease



- Lysosomal storage disease due to mutations affecting the acid-alpha-glucosidase enzyme (GAA)
- Accumulation of glycogen in lysosomes muscle, heart, CNS



Late onset (LOPD)

- Higher incidence
- First symptoms median age 24 years
  - Proximal muscle weakness
  - Breathing disorders – respiratory failure
  - No cardiac disease

Glycogen storage: muscles, some motor neurons. Significant interindividual variability

Infantile onset (IOPD)

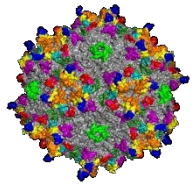
- First symptoms median age 2.8 months
  - Hypotonia
  - Failure to thrive, respiratory failure
  - Hepatomegaly
  - Hypertrophic cardiomyopathy

Glycogen storage: heart, muscles, central nervous system (CNS) especially motor neurons

Therapeutic strategy

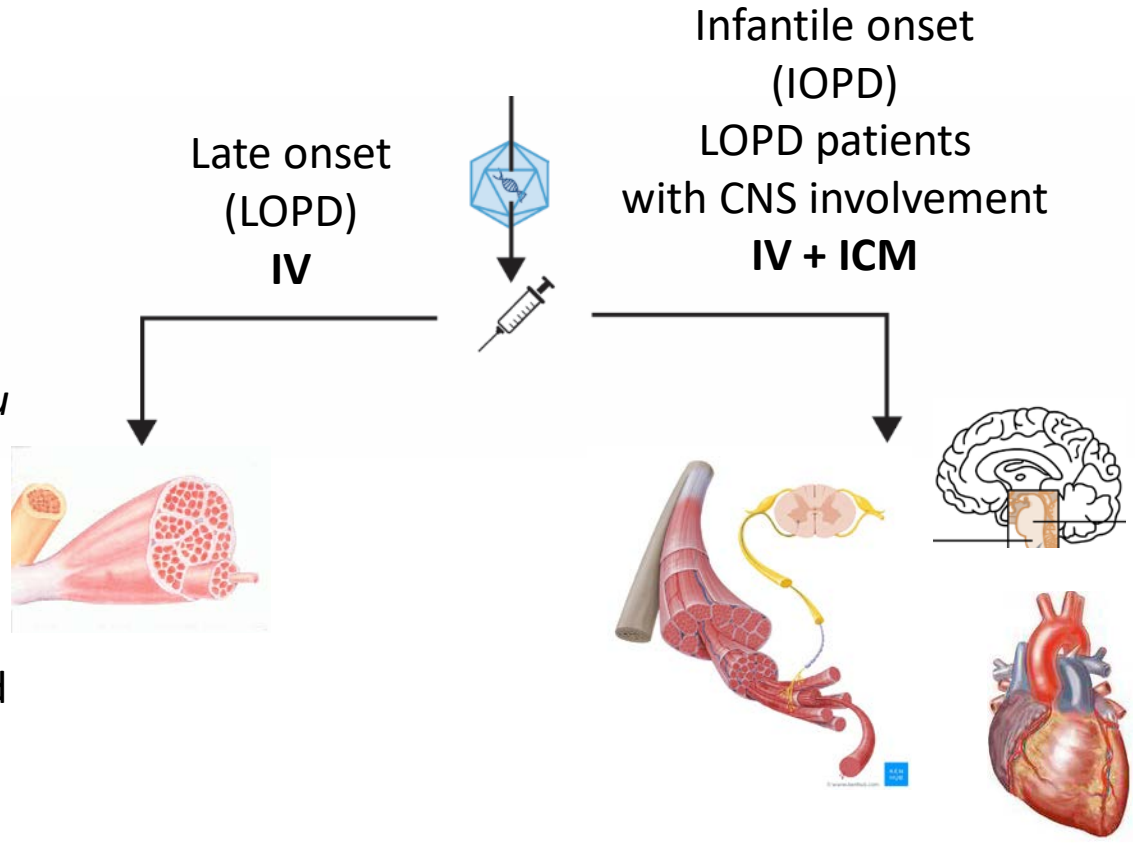
- Enzyme replacement therapy relies on cross-correction through M6P-R. Importance of manufacturing methods promoting proper glycosylation and phosphorylation

- Amicus/GTP Gene therapy strategy
  - **Pantropic capsid** and **ubiquitous promoter** for *in situ* correction of target organs
    - Less affected by anti-drug antibodies
    - Does not rely on liver secretion, no dilution



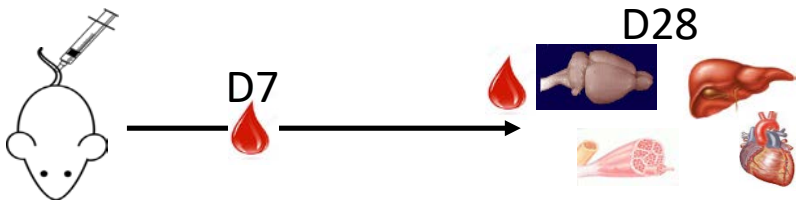
  - **Engineering of the protein** to optimize secretion and lysosomal targeting
    - Cross correction

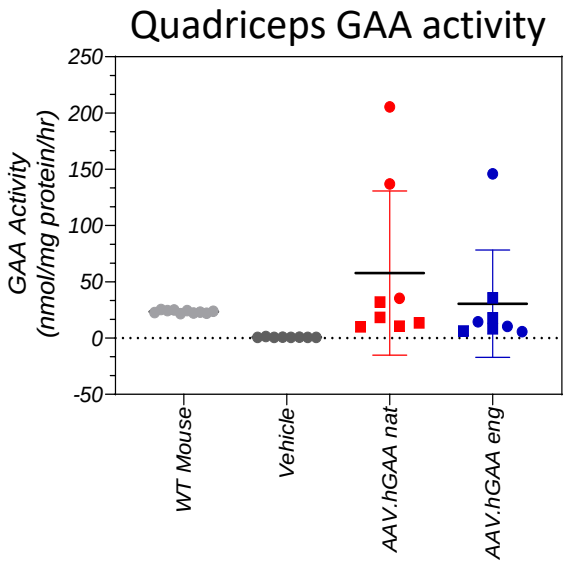
  - **Route of administration** tailored to patient needs
    - LOPD: IV
    - IOPD, some LOPD: IV + cisterna magna

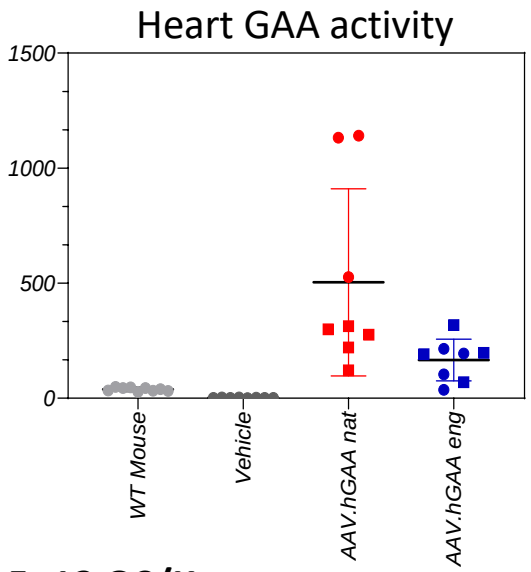


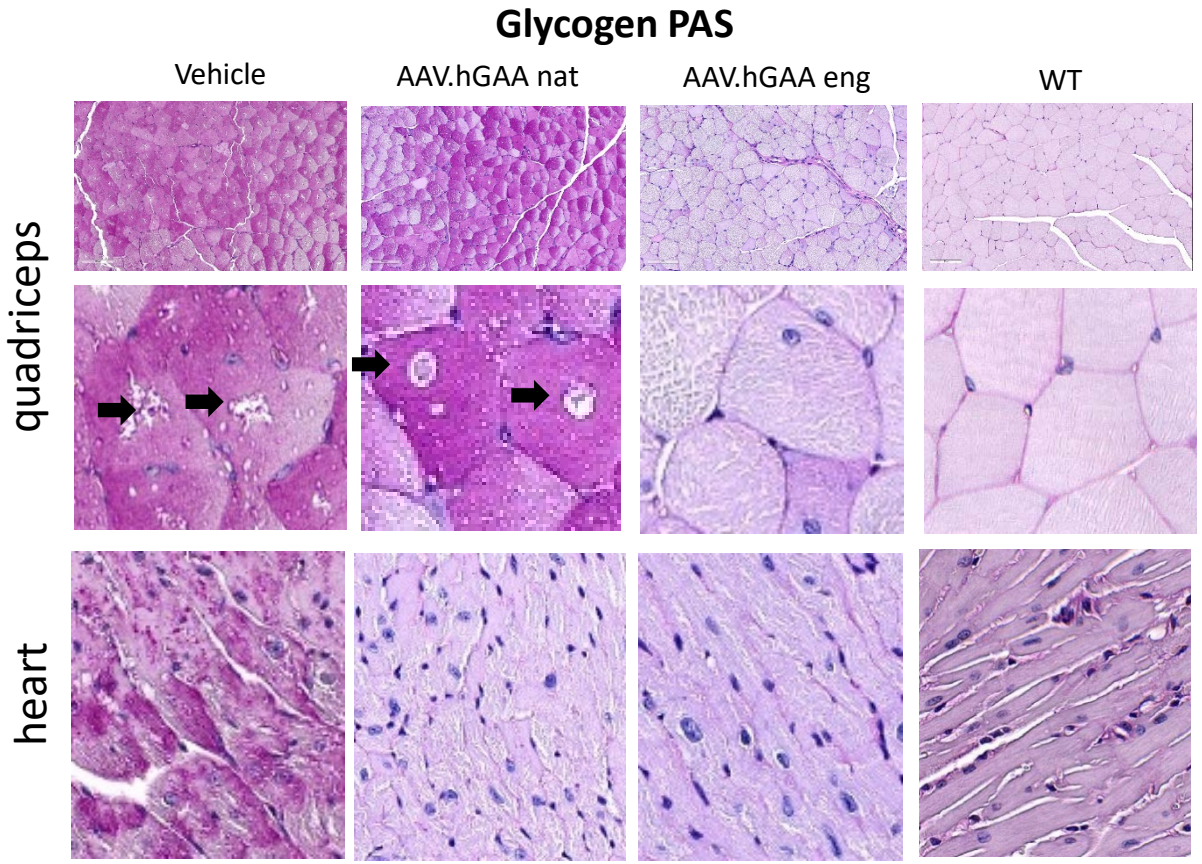
Engineered versus wild-type GAA

- AAV.hGAA nat or AAV.hGAA eng
- **IV low dose 2.5e12 GC/Kg**









LD 2.5e12 GC/Kg:

- Muscle: Storage and autophagic buildup correction with hGAA eng only
- Heart: Good correction with both hGAA constructs
- Short term study: rapid glycogen clearance

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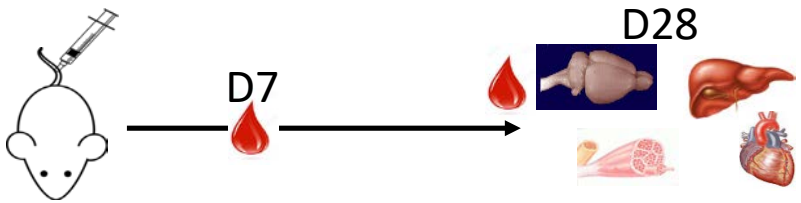
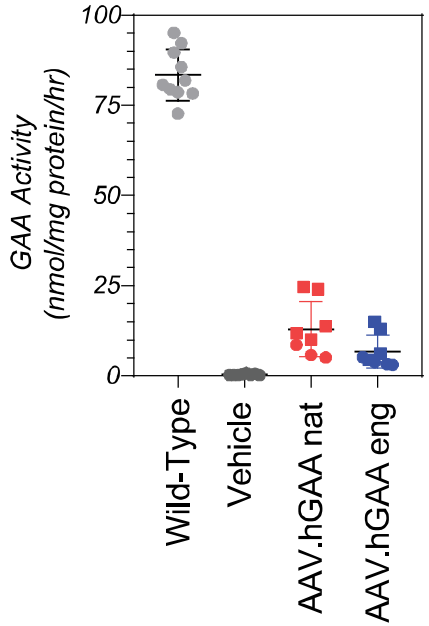
Engineered versus wild-type GAA

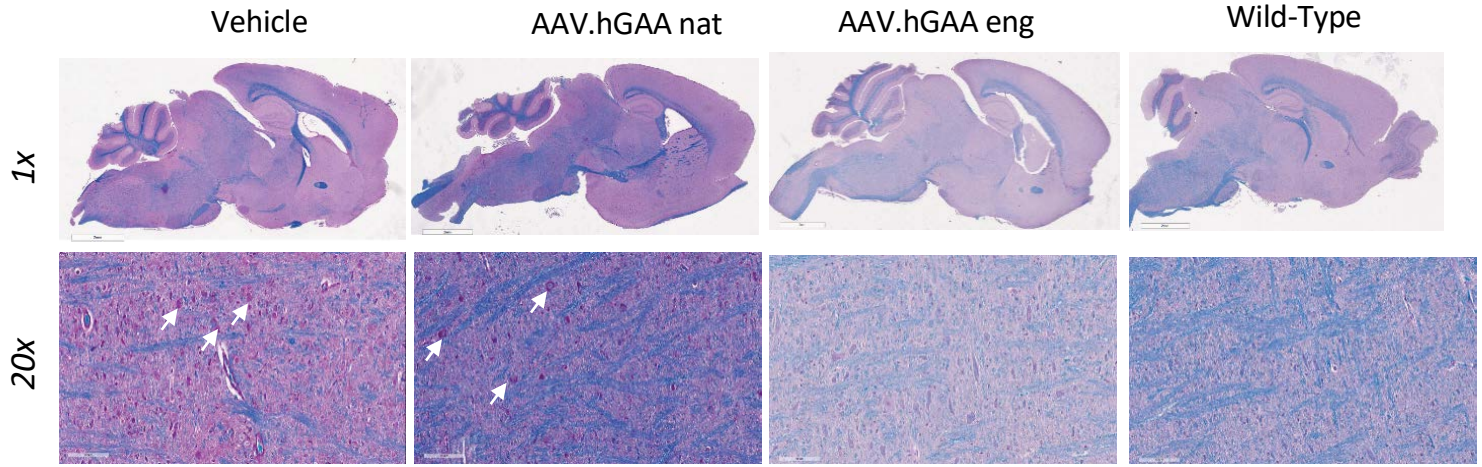
- AAV.hGAA nat or AAV.hGAA eng
- **<u>IV high dose 2.5e13 GC/Kg</u>**



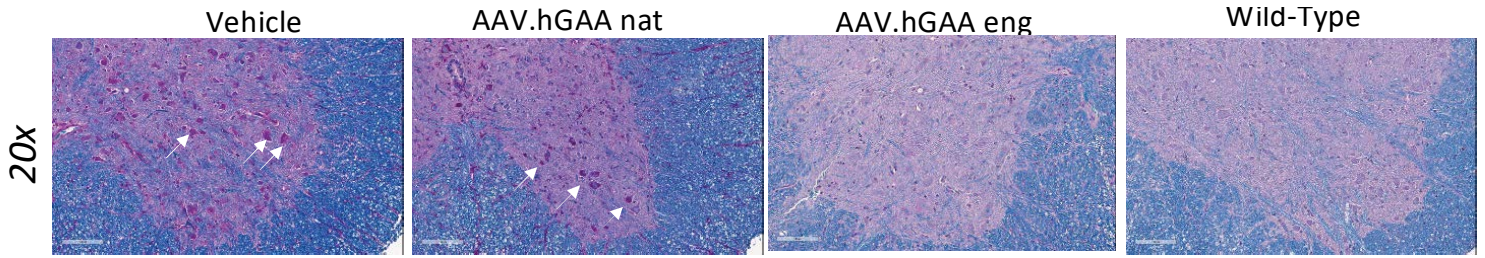
Brain GAA activity



Glycogen luxol/PAS - brain



Glycogen luxol/PAS – cervical spinal cord

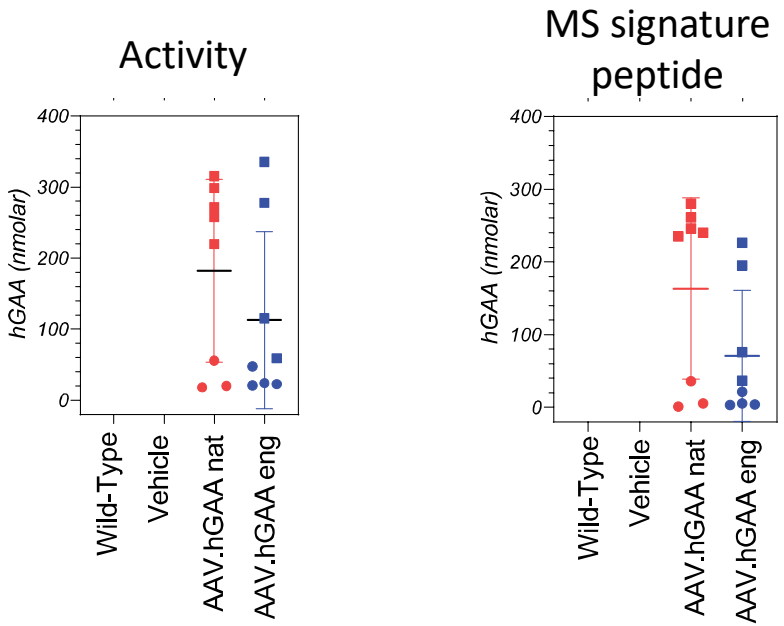


HD 2.5e13 GC/Kg:

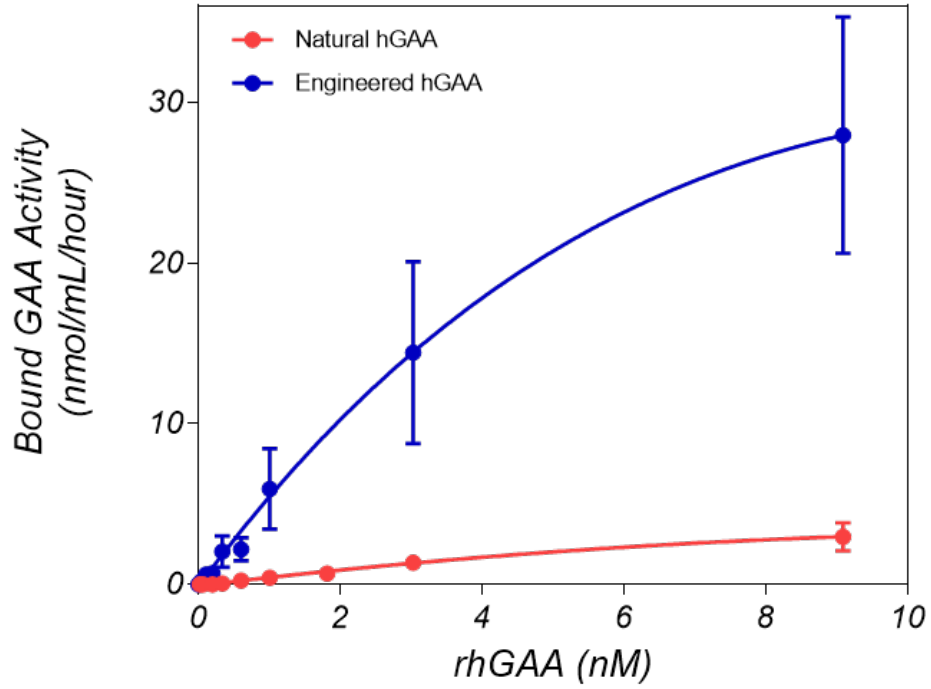
- Brain and spinal cord storage correction with hGAA eng only

Engineered versus wild-type GAA

- Plasma isolated 28 days post AAV.hGAA nat or AAV.hGAA eng IV administration to Pompe mice



- High levels of engineered and natural hGAA are measured in plasma at day 28

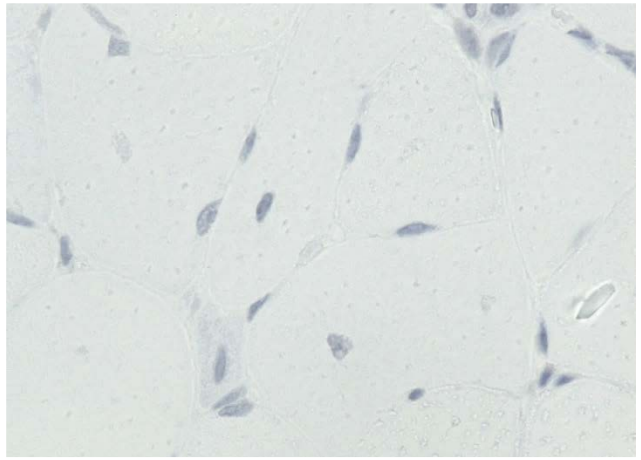
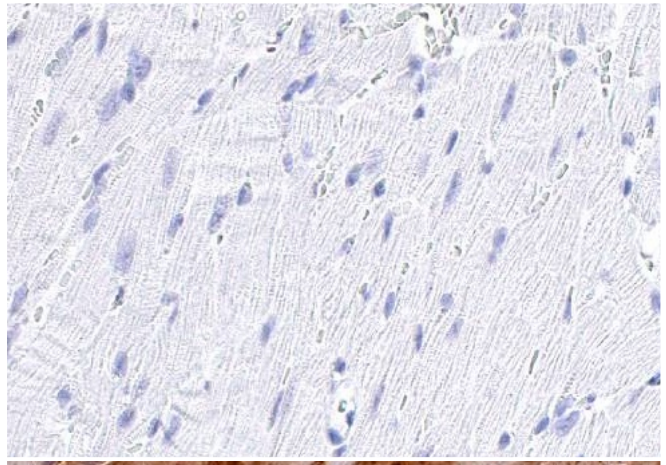
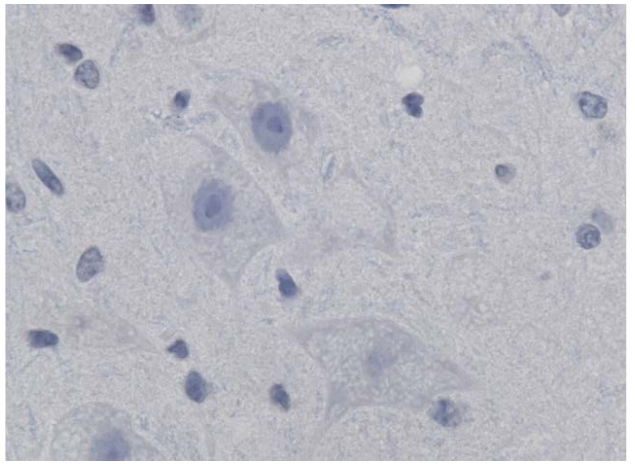
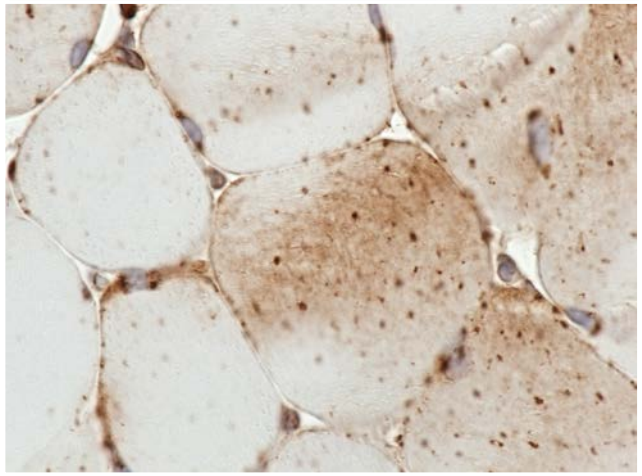
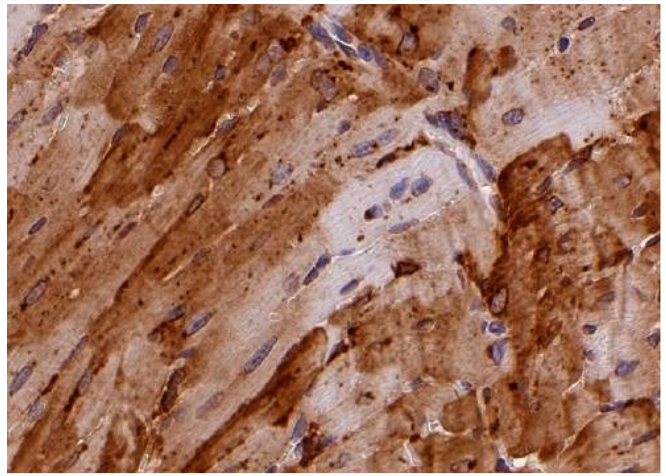
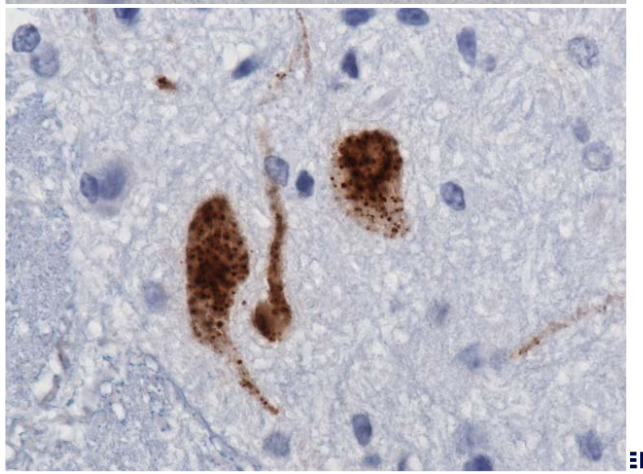


- Engineered hGAA efficiently binds the intended receptor to enable cellular uptake

Ubiquitous AAV gene therapy strategy

- AAV.hGAA eng 2.5e13 GC/Kg IV
- hGAA IHC 28 days post-injection

hGAA IHC

	Muscle	Heart	Spinal cord
PBS control			
AAV treated			

Treatment of post-symptomatic aged Pompe mice

Study design

- Pompe mice **6-7 months old**
- **AAV.hGAA eng**

IV
HD 5e13 GC/Kg
LD 1e13 GC/Kg

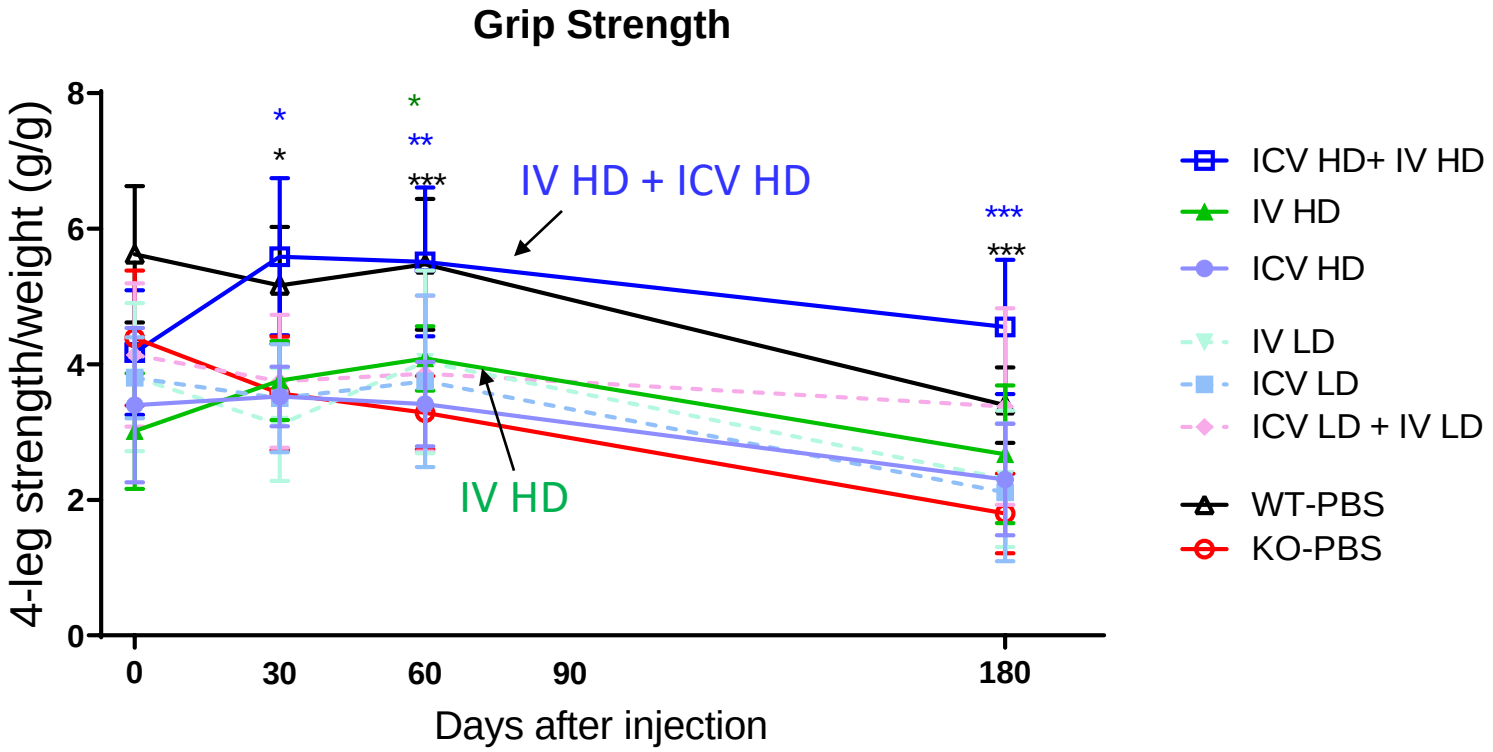
ICV
HD 1e11 GC
LD 5e10 GC

IV + ICV
HD + HD 5e13 GC/Kg + 1e11 GC
LD + LD 1e13 GC/Kg + 5e10 GC

D0-D180
Neurobehavior testing

D210
Euthanasia
13-14 months old

Treatment of post-symptomatic aged Pompe mice

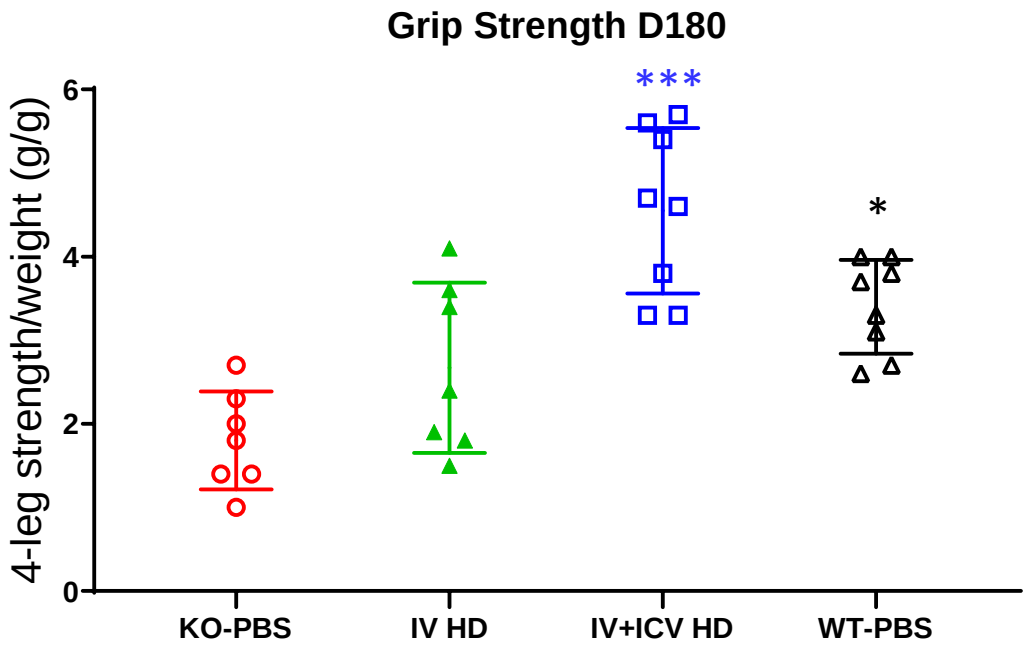


N= 4M and 4F per group
2-way ANOVA, post-hoc multiple comparison test, compared to KO-PBS
* p<0.05, ** p<0.01, ***p<0.001

- Grip strength already impaired at baseline
- **HD IV** significantly improves strength compared to baseline and compared to PBS controls
- **HD IV+ HD ICV** rescues strength to WT levels

- Low dose single or dual ROA no significant benefit
- Other tests did not show rescue (rotarod, plethysmography)

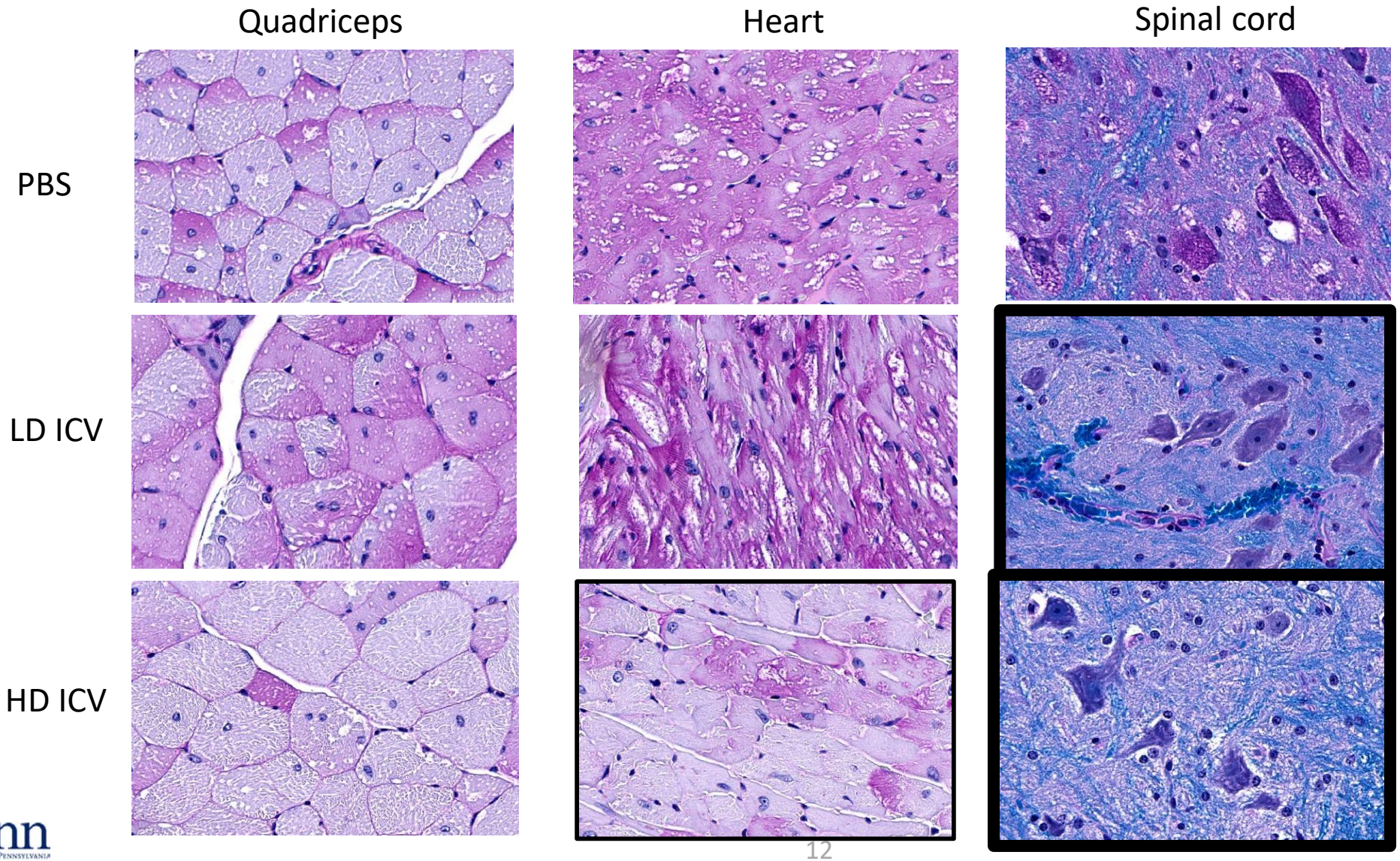
Treatment of post-symptomatic aged Pompe mice



- Incremental benefit of HD ICV and HD IV

N= 4M and 4F per group
1-way ANOVA, post-hoc multiple comparison test compared to KO-PBS
* p<0.05, ***p<0.001

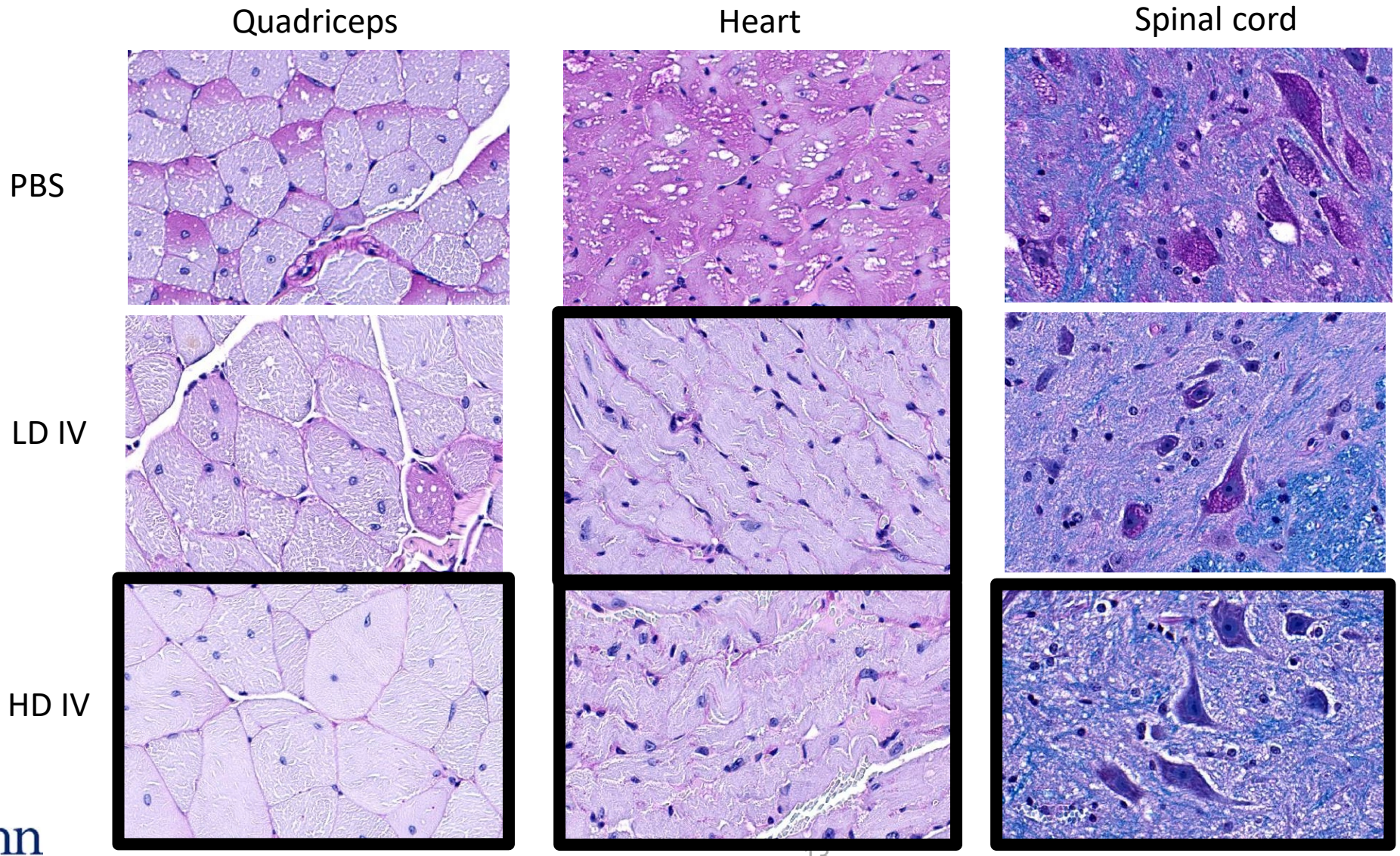
Treatment of post-symptomatic aged Pompe mice – ICV route



Glycogen storage is corrected at both doses

Partial correction in heart after HD ICV

Treatment of post-symptomatic aged Pompe mice – IV route



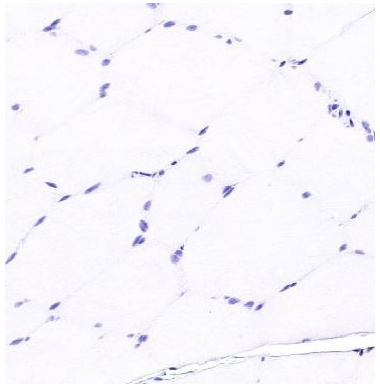
Glycogen storage is corrected

Dual ROA pending processing

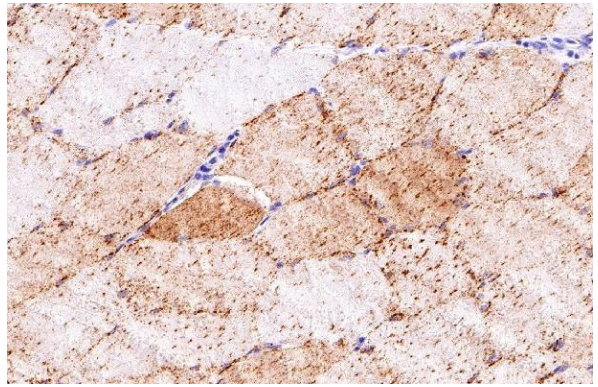
Translation to nonhuman primates

- Similar doses are being evaluated in rhesus macaques: IV only 1 to 5e13 GC/Kg, ICM only 1 to 3e13 GC, dual
- In-life still ongoing for part of the animals. Preliminary data suggest good expression levels in key target organs at the lowest dose tested

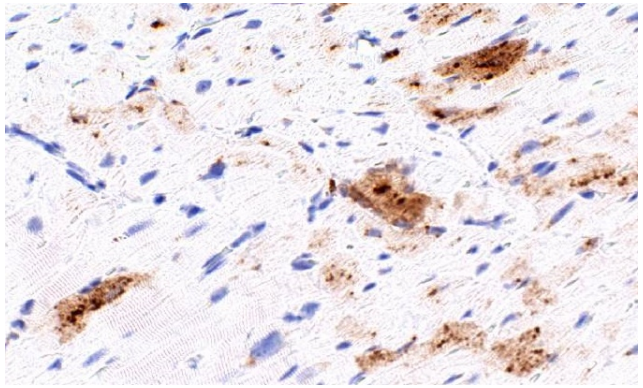
Quadriceps
Non injected NHP



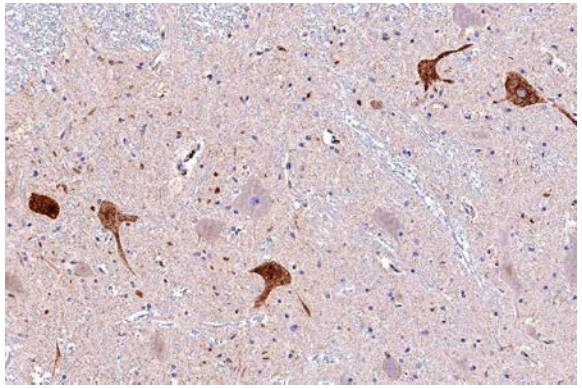
Quadriceps
AAV-hGAA eng
IV 1e13 GC/Kg



Heart
AAV-hGAA eng
IV 1e13 GC/Kg



Spinal cord
AAV-hGAA eng
ICM 1e13 GC



Conclusion

- Gene therapy with pantropic capsid and ubiquitous promoter allows global correction of all target organs in Pompe disease
- Engineered hGAA shows better targeting and clearance of glycogen storage at low doses in Pompe mice
- High dose IV therapy shows strength rescue in a mouse model with advanced disease at treatment. Addition of high dose ICV therapy provides incremental benefit
- Preliminary data in NHP suggest therapeutically relevant expression levels in target organs: muscles, heart, motor neurons