Hematopoietic Stem Cell Gene Therapy Corrects Neuromuscular Manifestations in Preclinical Study of Pompe Mice

Session: Musculo-skeletal Diseases II

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Niek van Til is an employee of AVROBIO.

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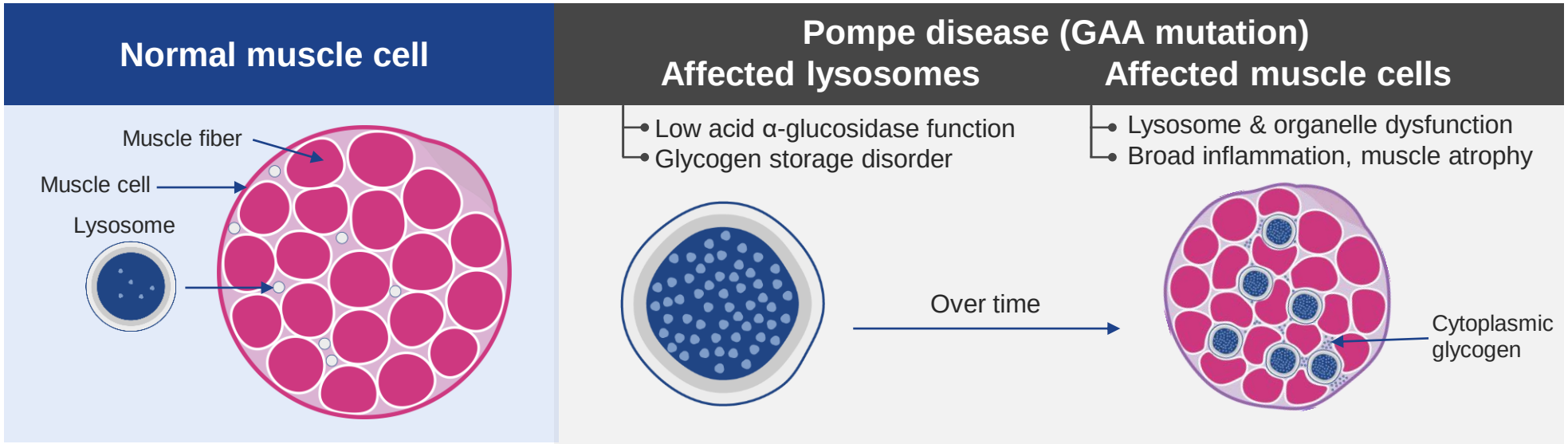
Pompe is a lysosomal and glycogen storage disease

Rare, progressive, often fatal neuromuscular disorder

POMPE DISEASE

- Mutations in the acid alpha-glucosidase (*GAA*) gene resulting in deficient enzyme activity
- Leads to accumulation of glycogen in tissues and organs, predominantly in muscles
- Manifests as a spectrum of symptoms and rates of progression across patients of different ages
  - Infantile form (<1% GAA activity)
    - Extreme muscle weakness, “floppy” appearance, enlarged heart, typically die before 1 year
  - Late / delayed onset form (2-40% GAA activity)
    - Weakness of leg and hip muscles, become wheelchair-bound and ventilator-dependent, premature death
- The standard of care is enzyme replacement therapy



Patient images courtesy of the patients/their families.

Sources: van der Ploeg, Lancet, 2008

Pompe lentiviral gene therapy program advancing

Integrated three-part approach

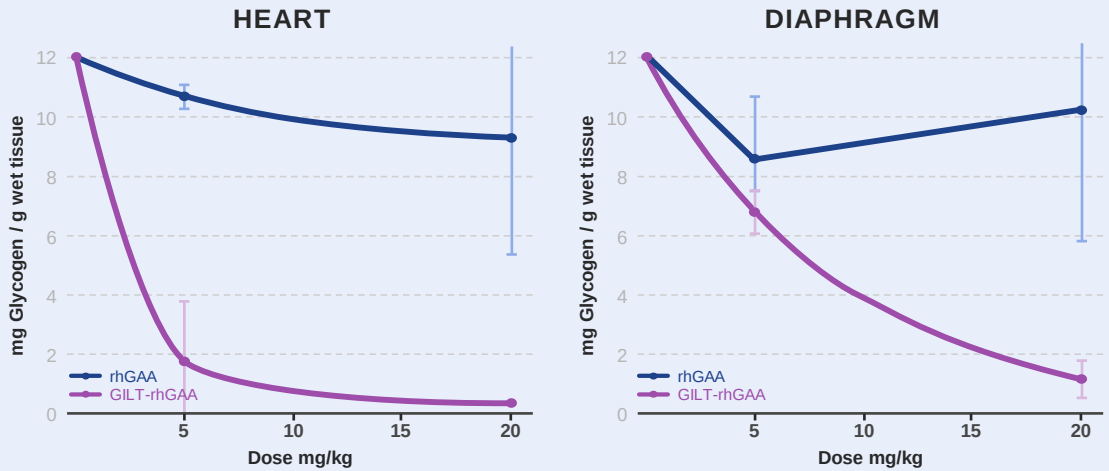
THE CHALLENGE

- Pompe requires **20x more ERT** than Fabry or Gaucher
- Requires GAA activity restored to **muscle and CNS**

AVROBIO's APPROACH

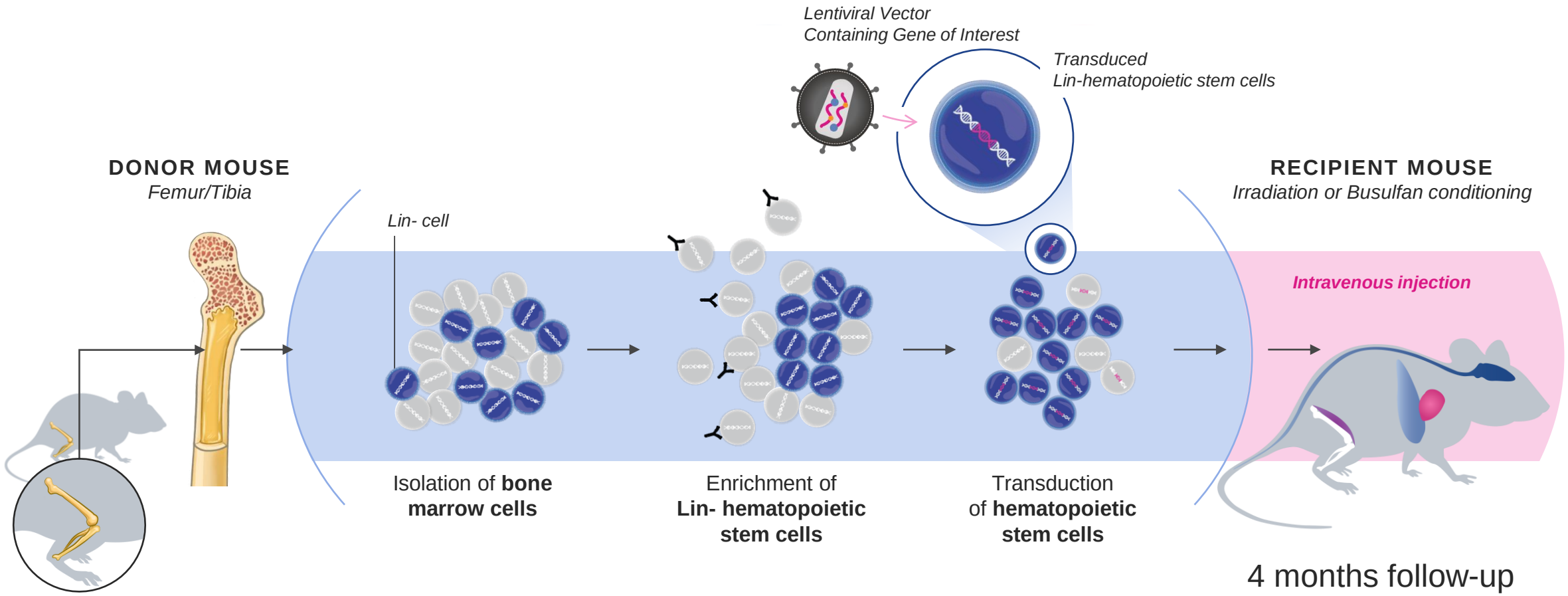
- Potent transgene promoter
- GILT uptake tag
- Bu90-TDM for CNS impact

GILT-tagged Recombinant Human (rh)GAA impacts levels of stored glycogen compared to non GILT-tagged Recombinant Human (rh)GAA in a Pompe mouse model



- ***GILT:*** *Glycosylation-Independent Lysosomal Targeting*
- ***Sources:*** *Burton B et al, J Pediatr, 2017; Ausems M et al, Eur J Hum Genet, 1999; Gungor D et al, Orphanet J Rare Dis, 2011; Maga JA et al, J of Bio Chem, 2013; Bartelink, Lancet Haematol, 2016.*

HSC gene therapy in Pompe mice



Sources: *Douillard-Guilloux G et al, J Gene Med, 2009; van Til et al, Blood, 2010; Stok M et al, Mol. Ther. Meth. Clin. Dev, 2020 in press.*

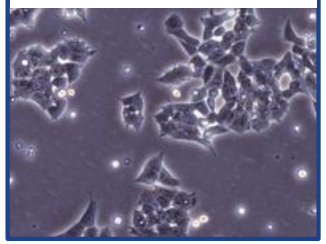
Array of lentiviral vectors tested *in vitro* and *in vivo*

		Group number:	Conditioning:		
1.	GAA		7.5Gy		
2.	GILT	2983	7.5Gy		
3.	GILT mutant v1	2984	7.5Gy	9Gy	Busulfan
4.	GILT mutant v2	2985	7.5Gy		
5.	GILT mutant v3	2986	7.5Gy		
6.	GILT + tag v1	2987	7.5Gy		
7.	GILT + tag v2	2988	7.5Gy		
8.	GILT mutant v1a	2989	7.5Gy		
9.	GILT + tag v1a	3005	7.5Gy		
10.	GILT + tag v2a	3006	7.5Gy		
11.	GILT mutant v4	3007	7.5Gy		
12.	GFP	2977R	7.5Gy		

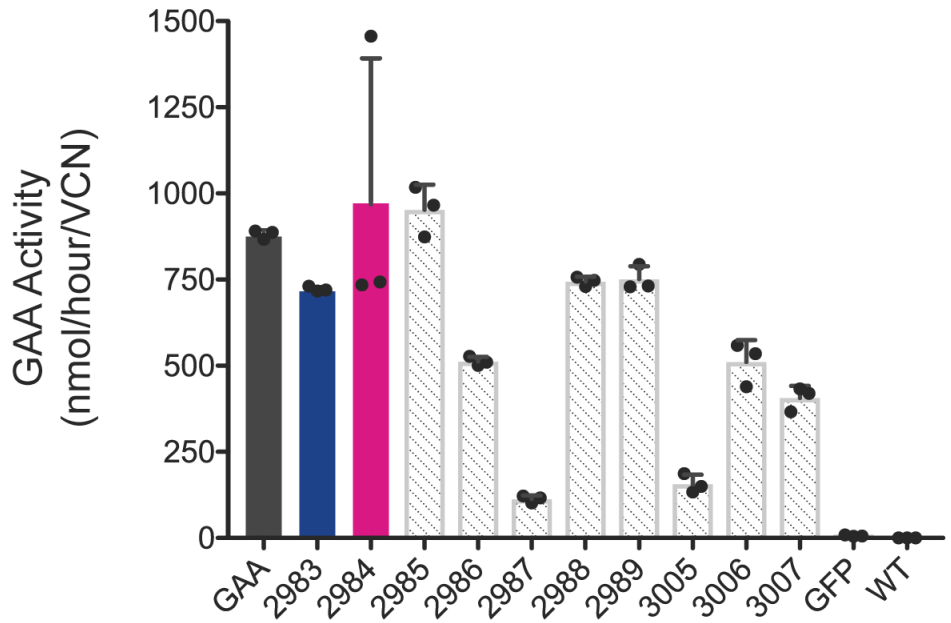
High GAA enzyme activity *in vitro*

In vitro

HAP1 GAA KO



Intracellular



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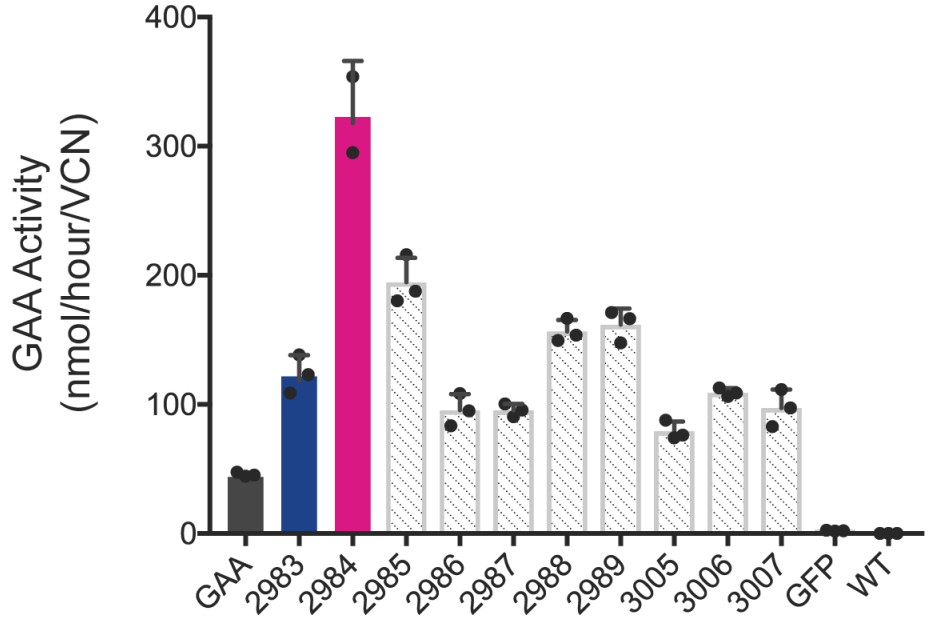
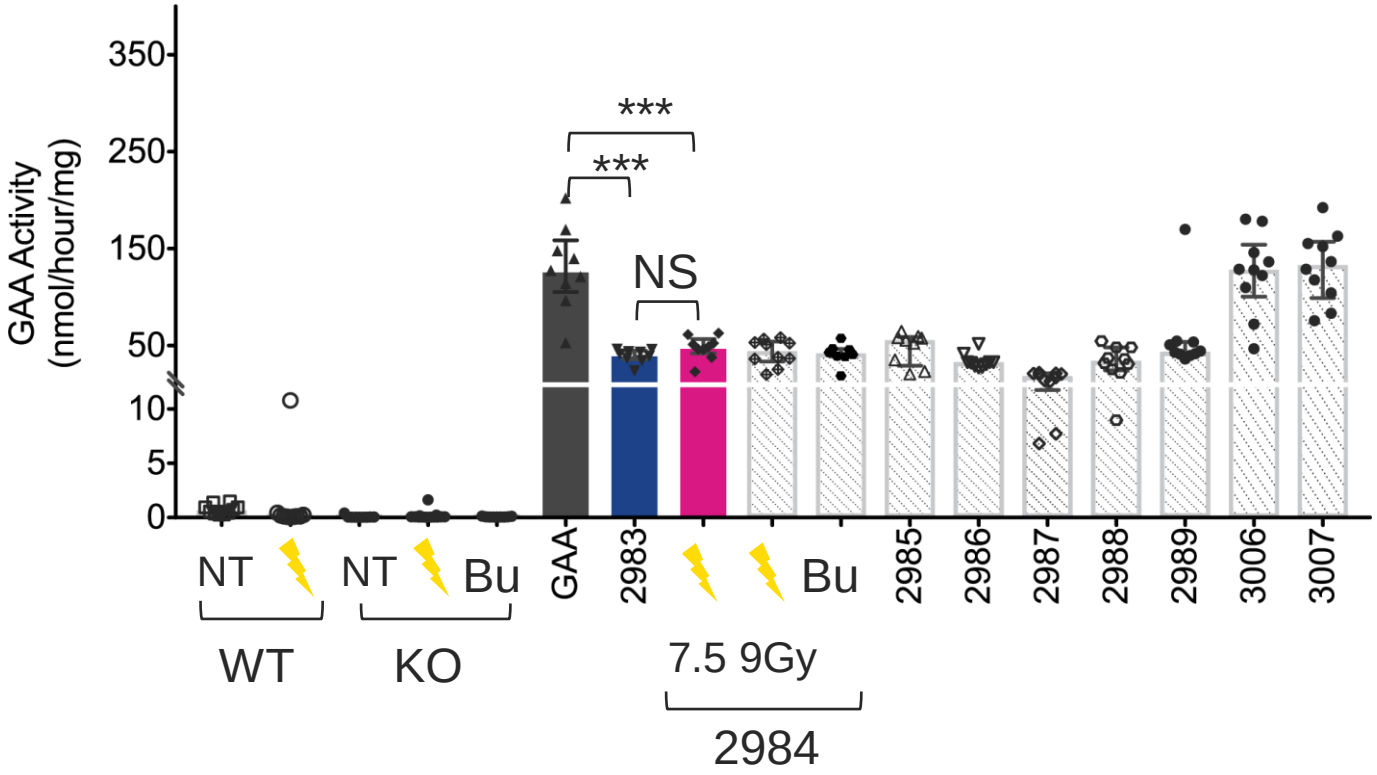


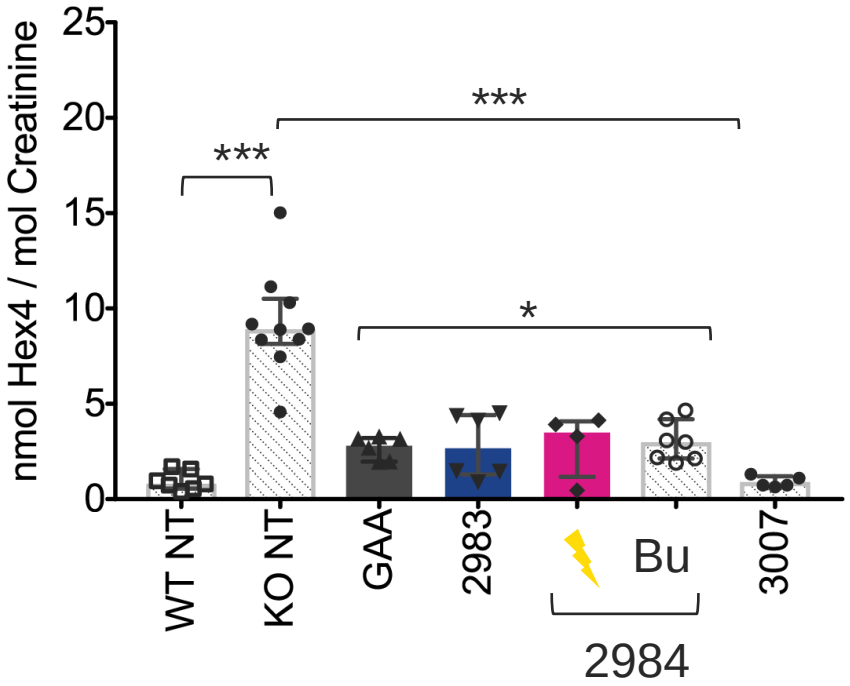
High GAA enzyme activity and therapeutic response *in vivo*

Therapeutically relevant urine Hex4 biomarker response in treated Pompe mice

Peripheral blood WBCs: Week 16



Urine Hex4: Week 16



* P<0.05
*** P<0.0001

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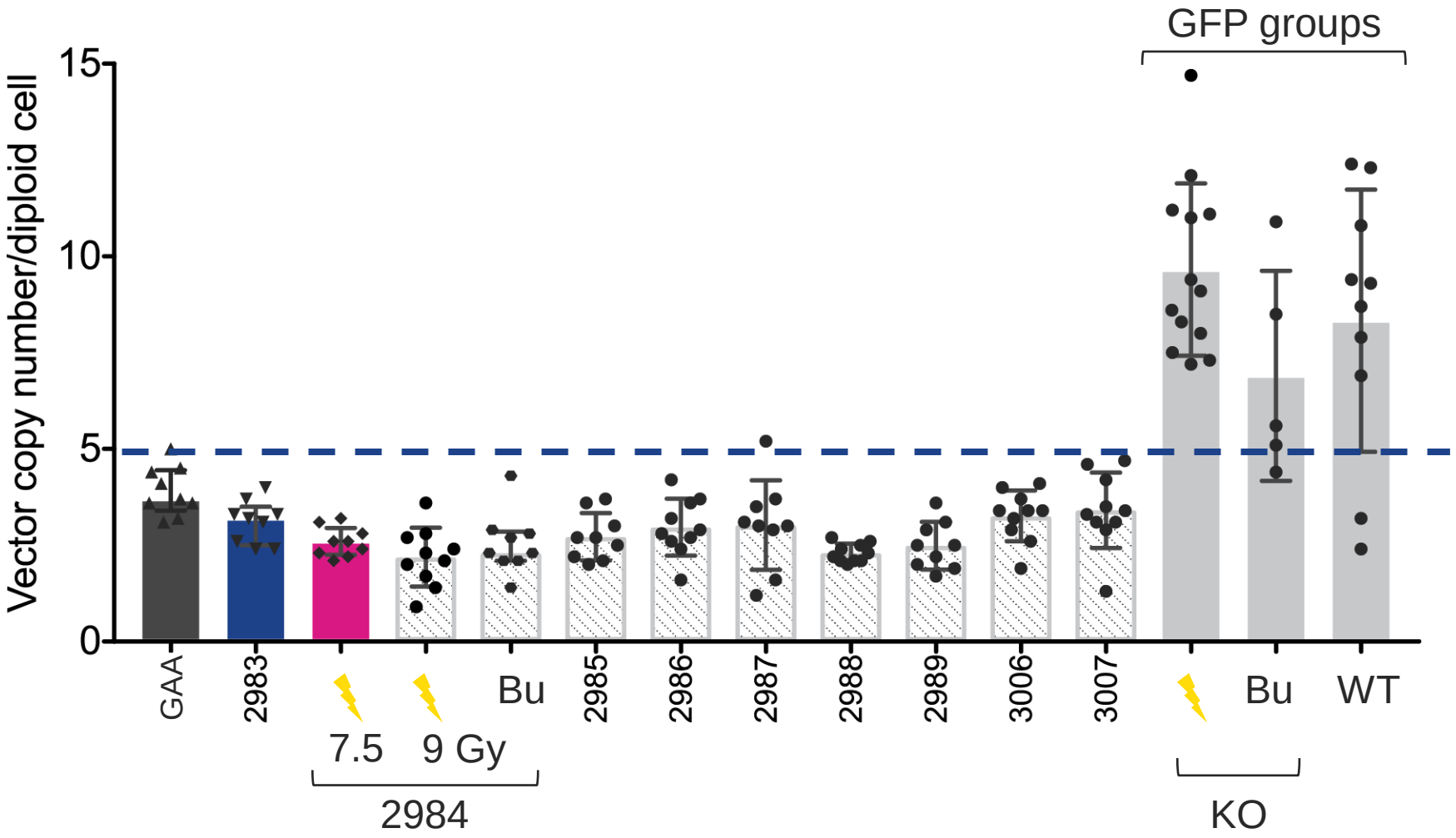
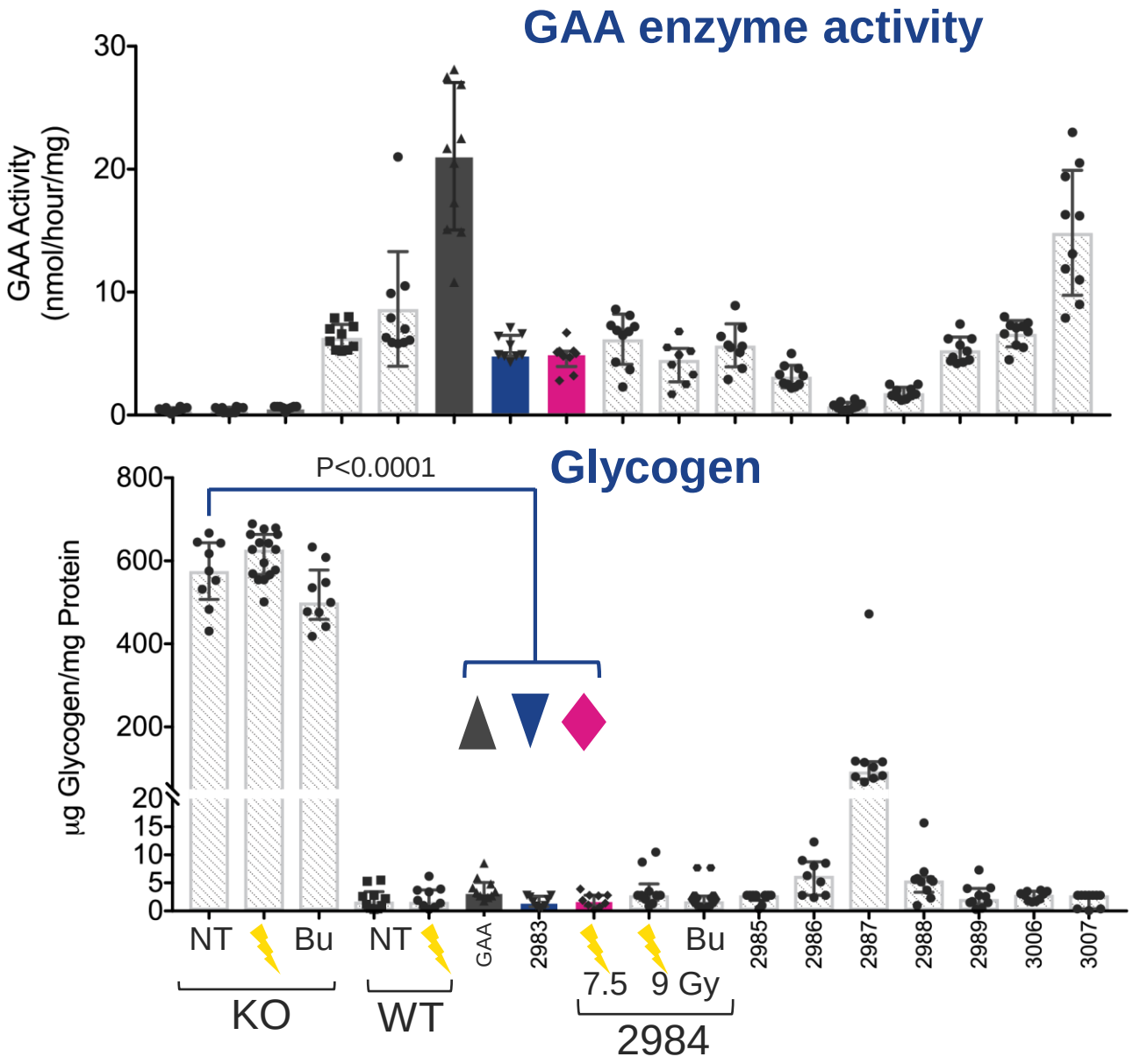
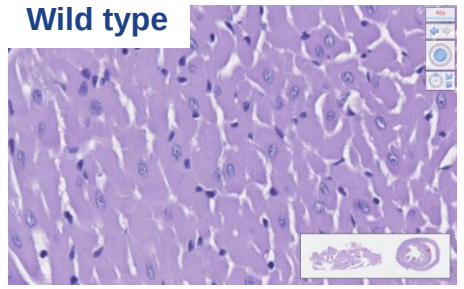
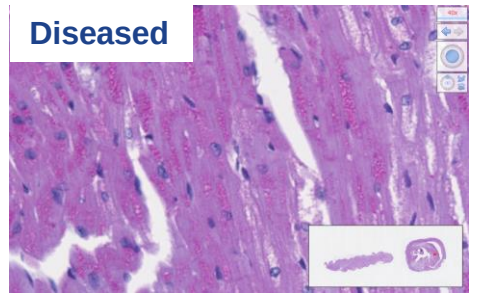
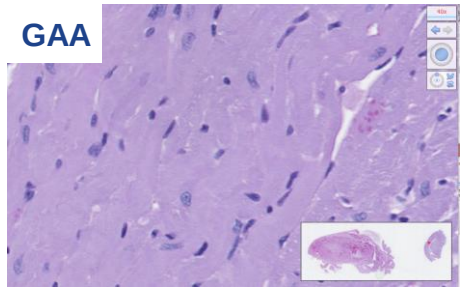


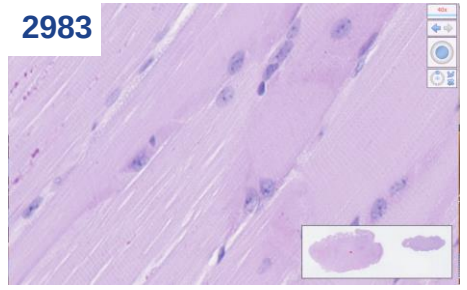
GILT and GILT mutant v1 reduce glycogen by >99% in heart

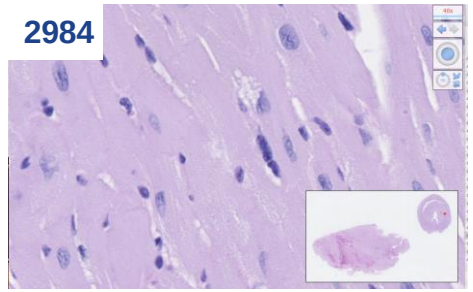


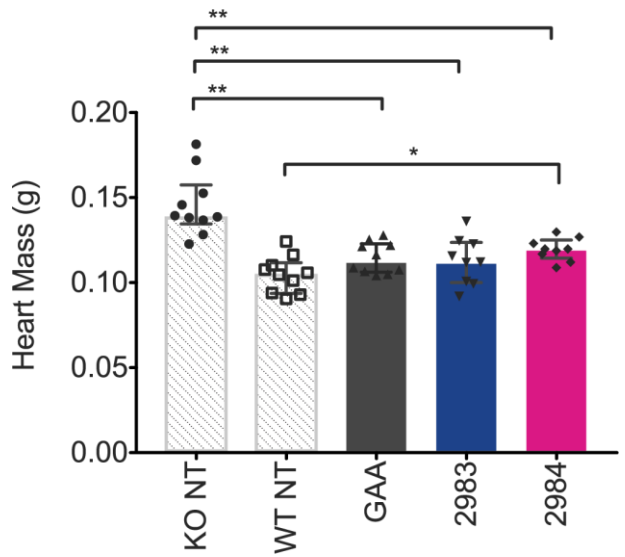








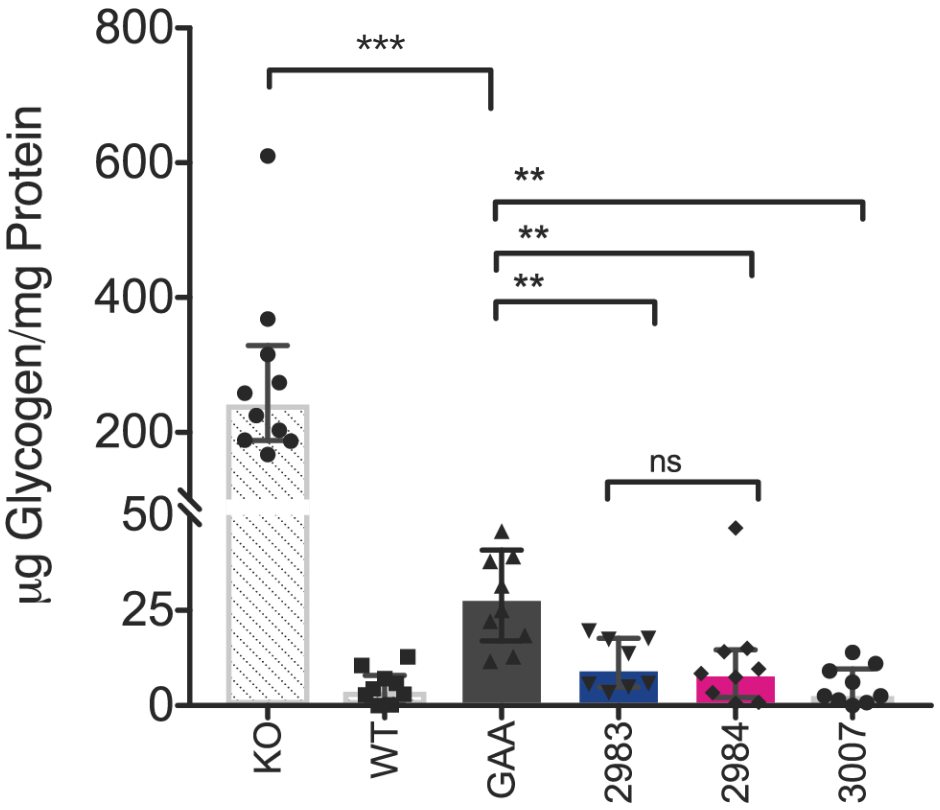




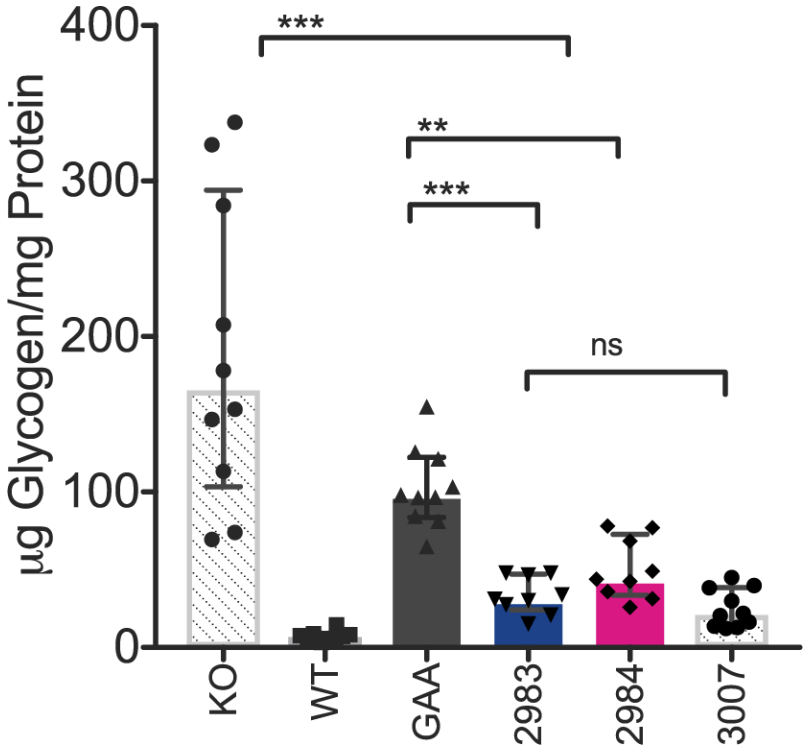
* P<0.01
** P<0.001

GILT and GILT mutant v1 significantly reduce glycogen in clinically relevant skeletal muscles

Diaphragm



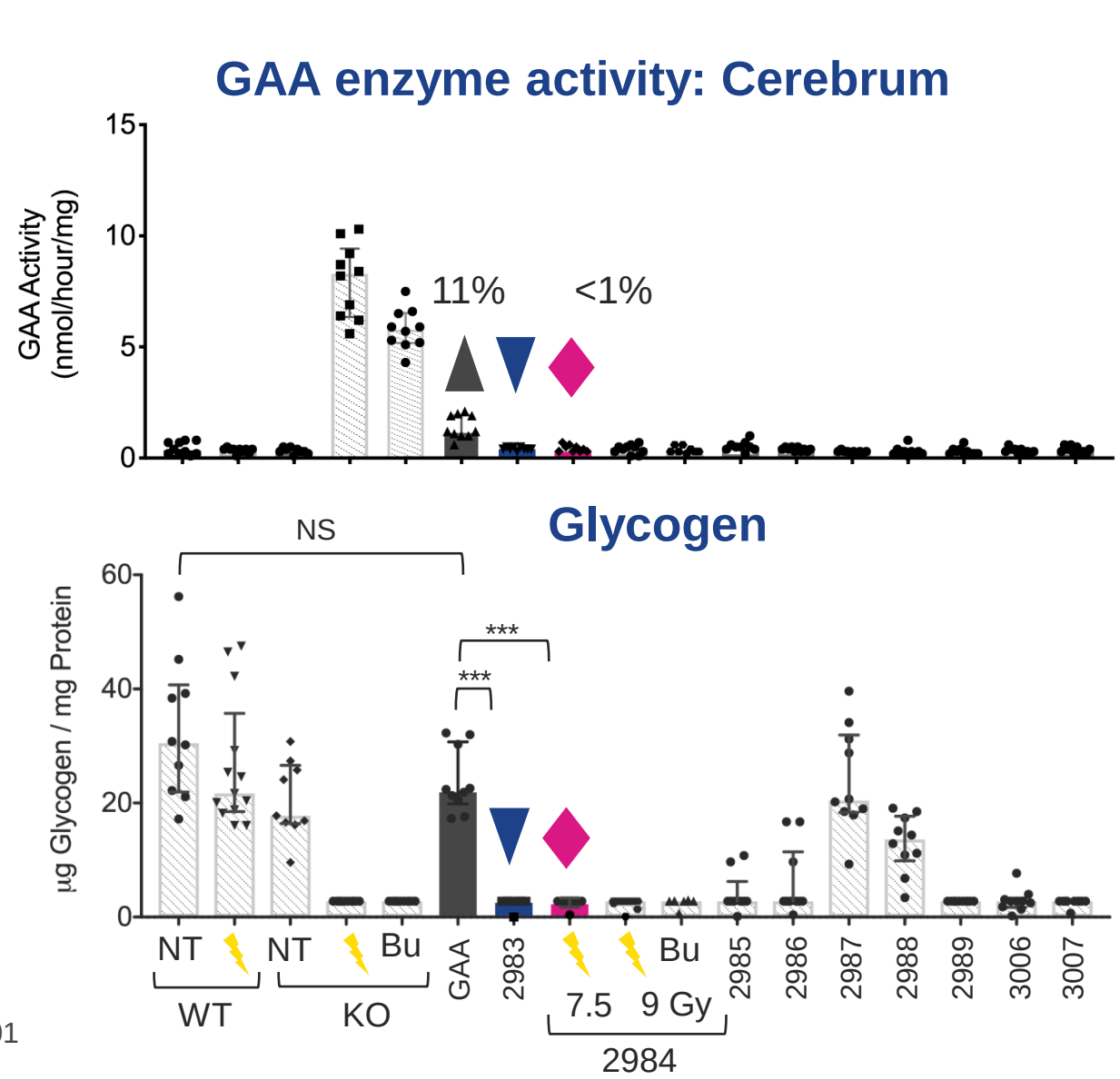
Gastrocnemius



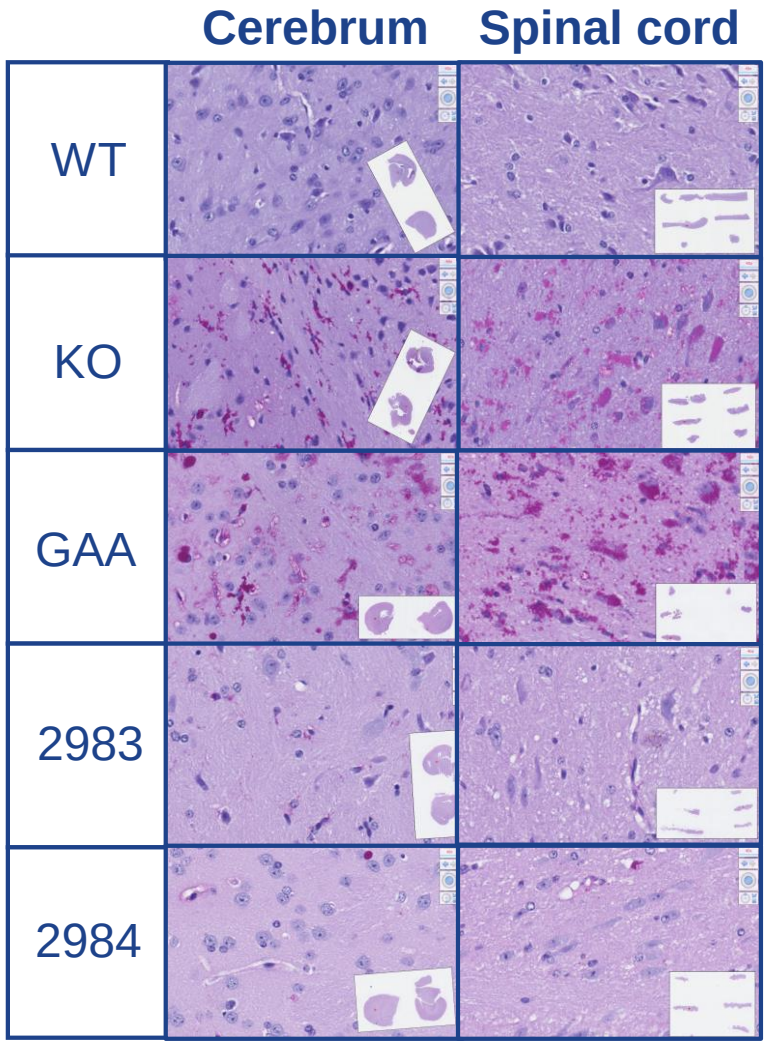
** P<0.01
*** P<0.001

Glycogen and GILT and GILT mutant v1 similar to wildtype mice

GILT tag is essential for glycogen clearance in CNS and PNS

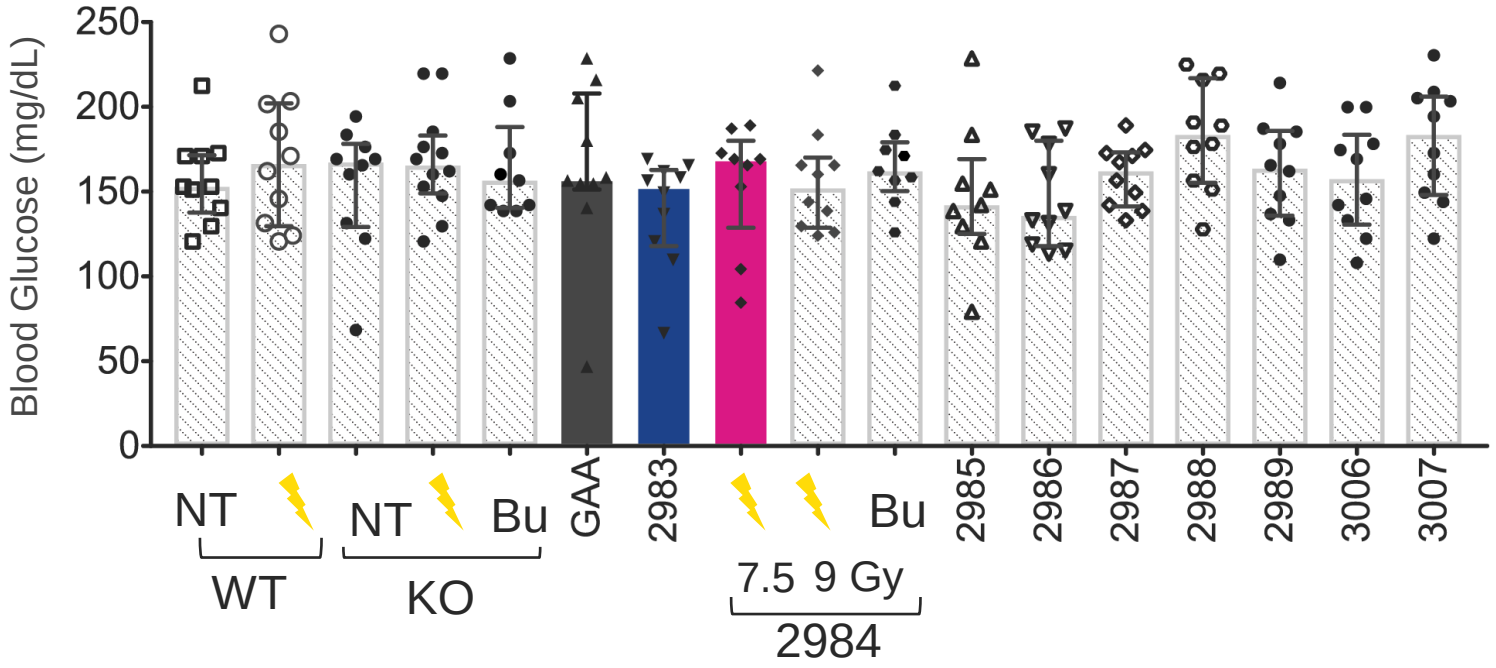


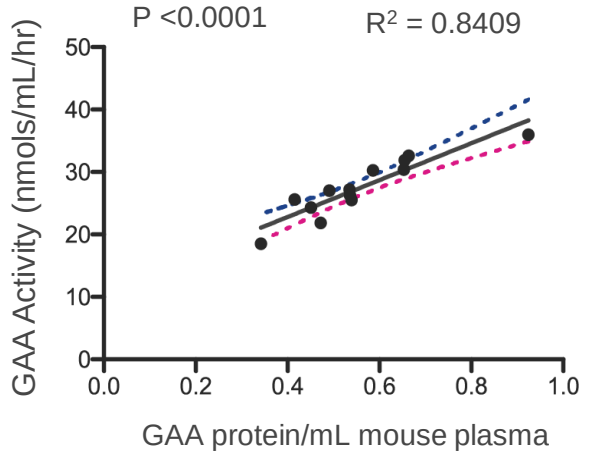
*** P<0.001

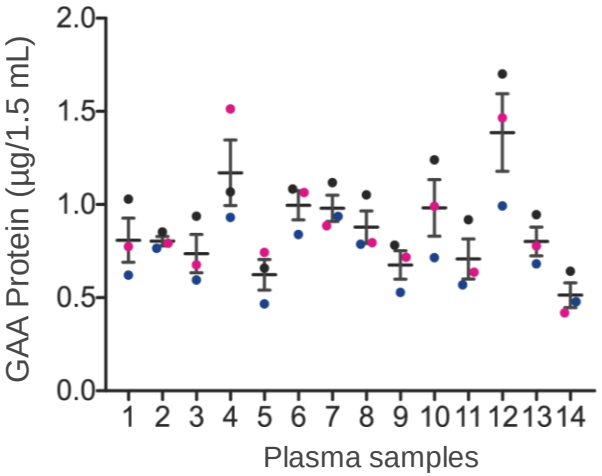


GILT and GILT mutant v1 do not impact plasma glucose levels

GAA protein concentration approximately 300-fold lower than ERT







Conclusions

1. Glycogen was significantly cleared in clinically relevant tissues including heart, CNS and skeletal muscles of Pompe mice
2. GILT tag is essential for efficient clearance of glycogen in CNS
3. IND-enabling studies are advancing
4. Clinical development plan is underway

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AVROBIO Pompe Team

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charles river

KOAS

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