



FORCE™ Platform for the Development of Targeted Therapeutics for Rare Muscle Diseases

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New Directions in Biology and Disease of Skeletal Muscle | June 23rd, 2024

Forward-Looking Statements & Disclaimer

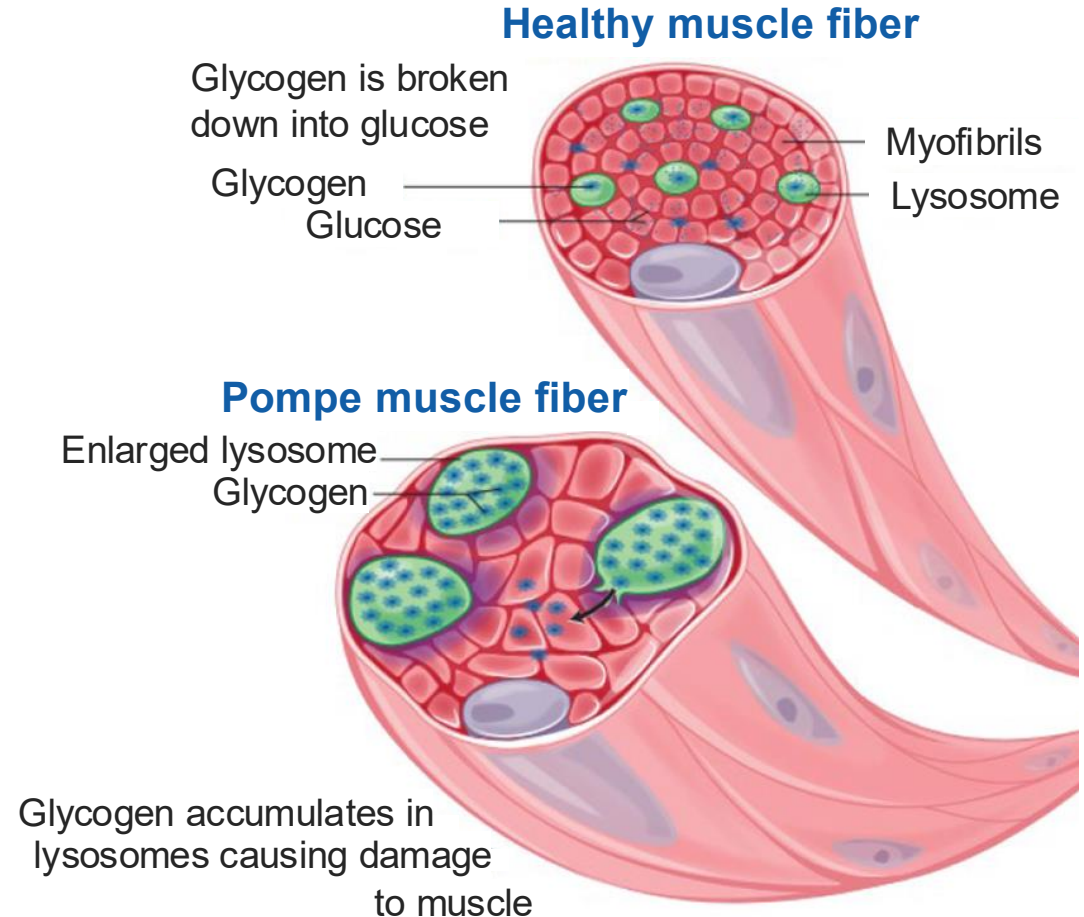
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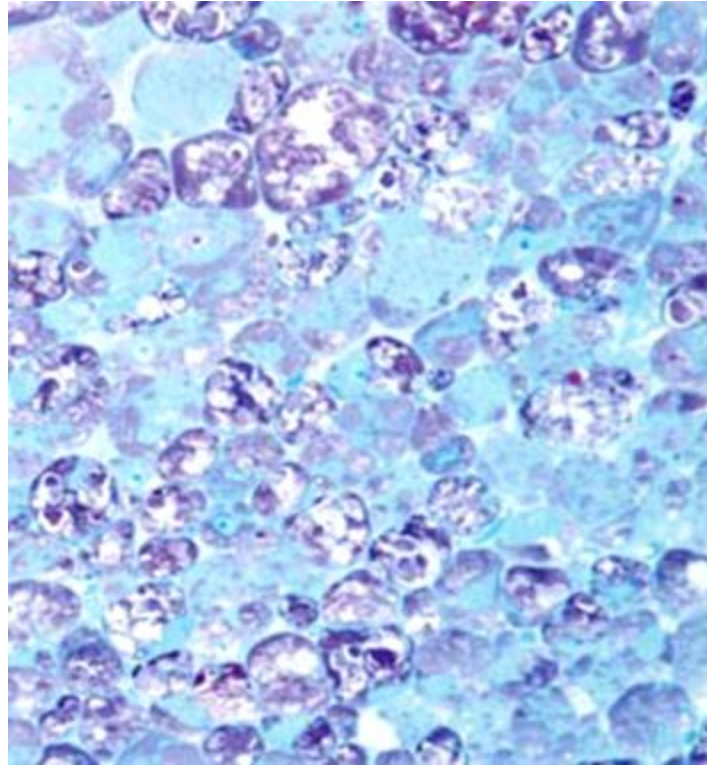
Pompe Disease is a Rare and Serious Neuromuscular Lysosomal Storage Disease (LSD)

- ~5,000-10,000 individuals affected worldwide¹
- Low alpha glucosidase (GAA) activity leads to glycogen accumulation in the lysosome²⁻⁵
- Infantile-onset (IOPD)
 - Most severe form; <1% residual GAA activity^{3,4}
 - Symptoms
 - Cardiomyopathy and cardiomegaly⁶
 - Progressive muscle weakness leading to respiratory failure^{5,6}
 - CNS manifestations⁵
- Late-onset (LOPD)
 - Less severe form; ~2-30% residual GAA activity^{3,4,6}
- **Pompe remains a high unmet medical need:** current enzyme replacement therapy (ERT) standard of care (SOC) is insufficient to address skeletal muscle and CNS manifestations^{4,7-9}

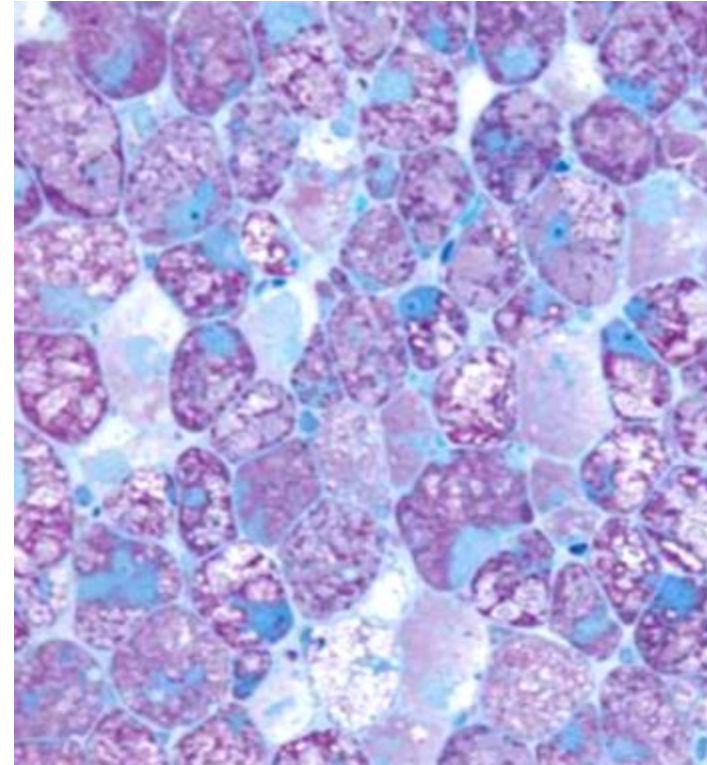


ERT SOC for Pompe Requires Frequent Dosing and has Inadequate Efficacy in Skeletal Muscle

Quadriceps of a Pompe patient treated with ERT weekly for 52 weeks^{1,2}



Glycogen accumulation
pre-treatment

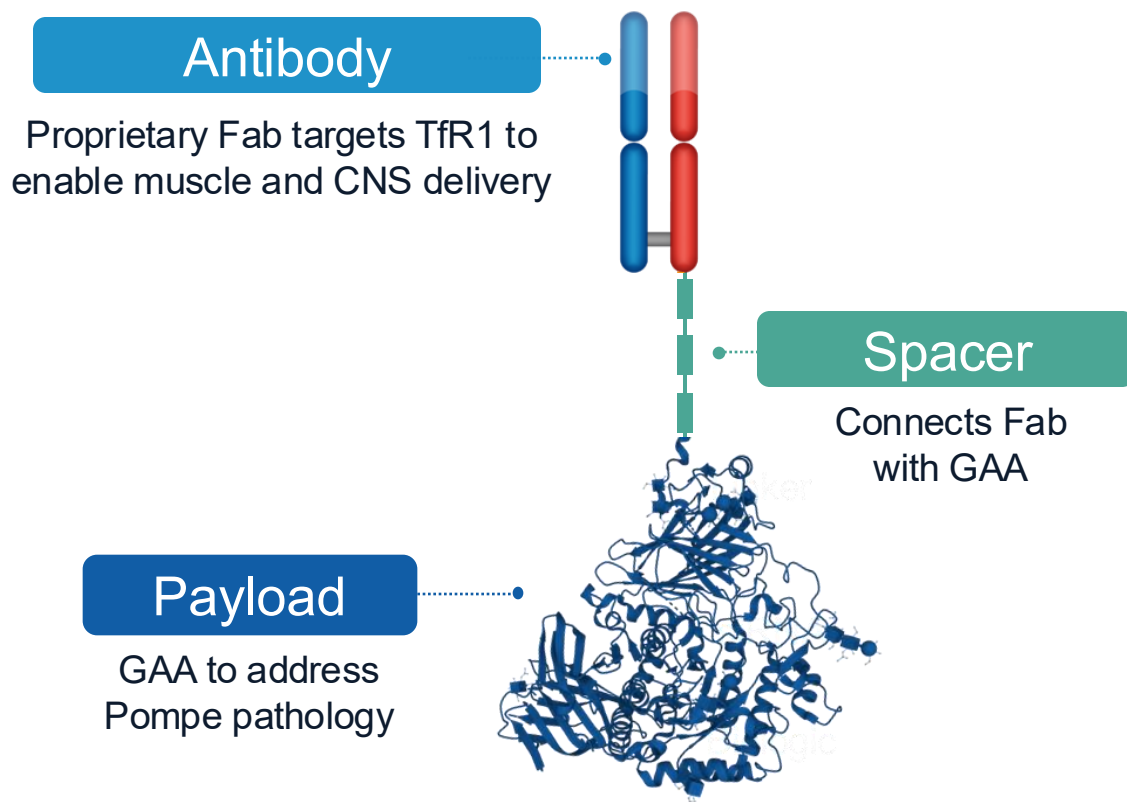


Glycogen accumulation
continues despite treatment

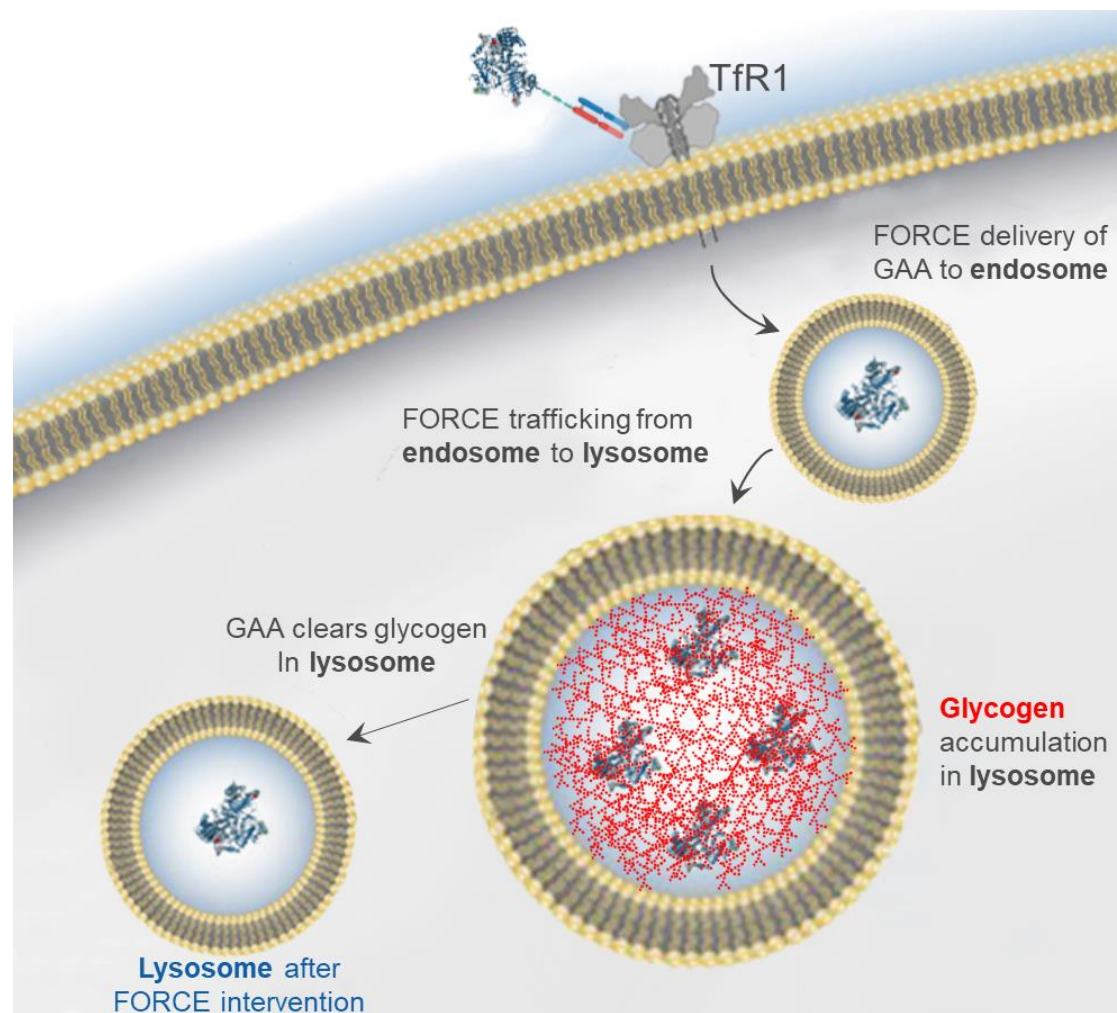
ERT does not address CNS manifestations that emerge as IOPD patients survive into adulthood^{3,4}

Leveraging FORCE to Improve Efficacy of ERT in Pompe Disease

FORCE-GAA enables TfR1-targeted ERT

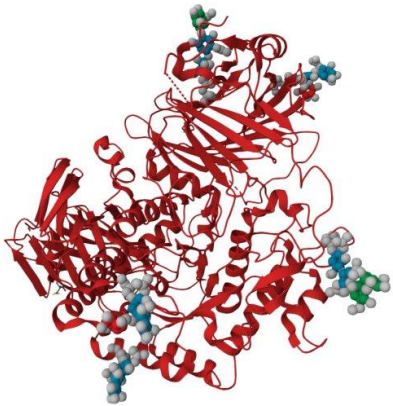


FORCE-GAA delivers to the endo-lysosomal system

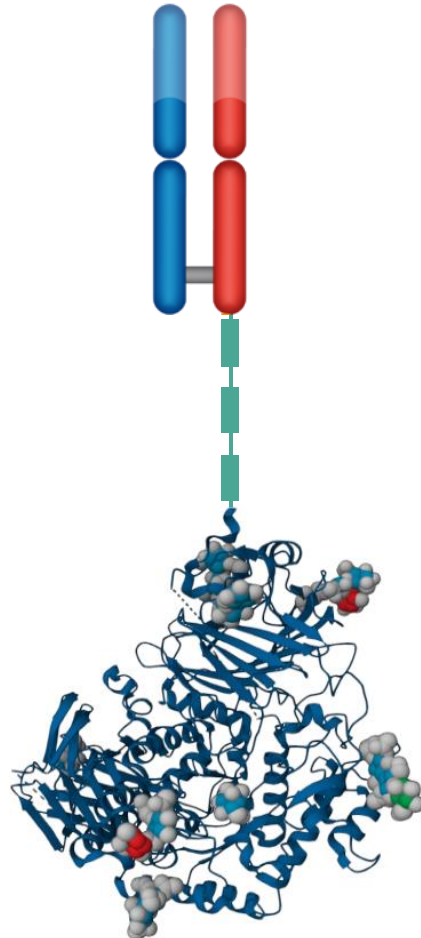


hTfR1/6^{Neo} Pompe Mouse Model Enables Evaluation of FORCE-GAA and Naked GAA *in vivo* Efficacy

Naked GAA



FORCE-GAA



hTfR1/6^{Neo} Pompe Mouse Model

Uptakes human TfR1
targeting Fabs



hTfR1

Established Pompe model
to evaluate GAA ERT¹



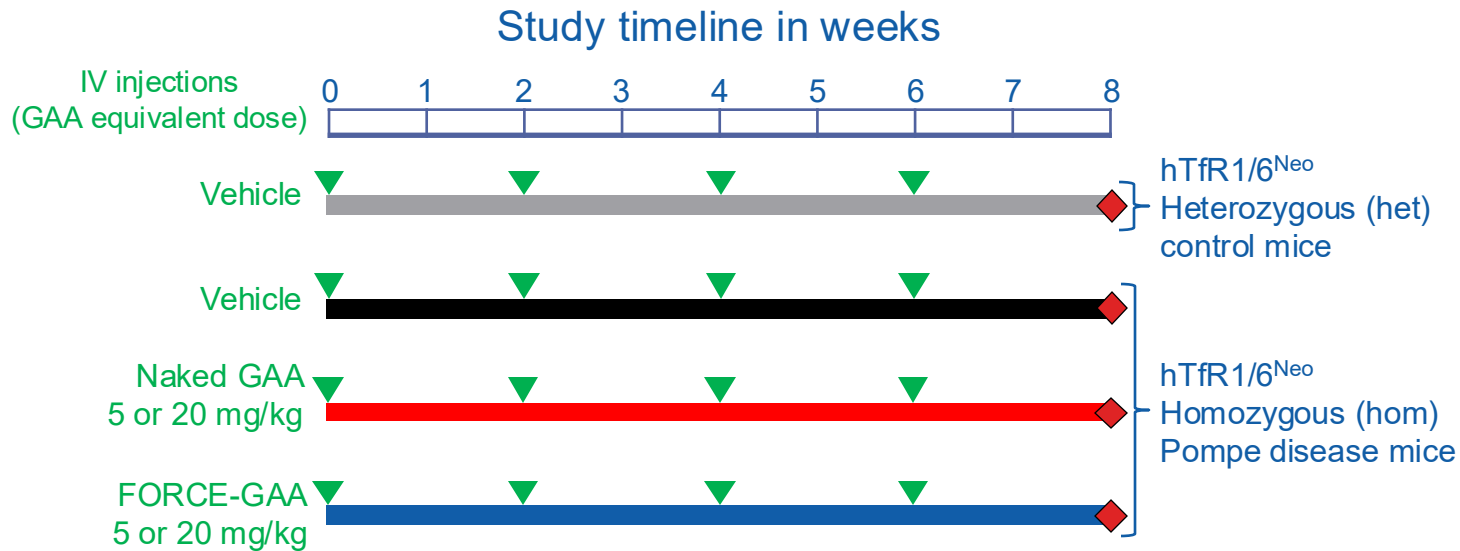
6^{Neo}



hTfR1/6^{Neo}

- Enables assessment of fully human FORCE-GAA in Pompe disease model
- Allows comparison to naked GAA

FORCE-GAA was Compared to Naked GAA in a Study Mimicking SOC Q2W Dosing Regimen



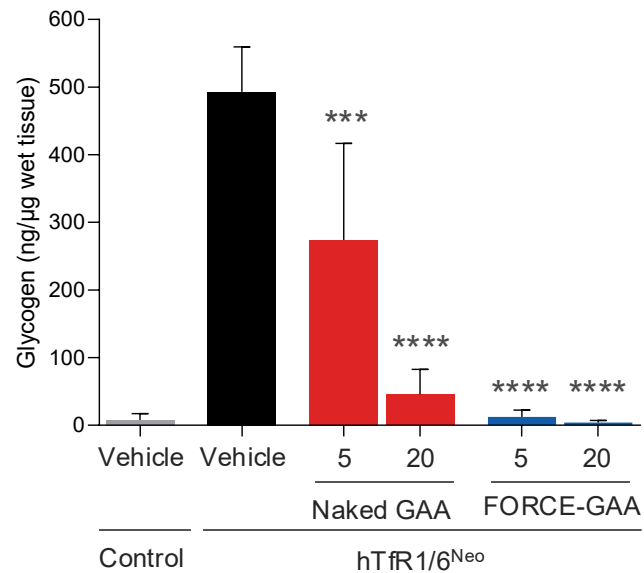
Readouts:

- Muscle and CNS datasets
 - Total tissue glycogen levels
 - Muscle and CNS histology with PAS
 - Muscle and CNS lysosome staining with LAMP1
 - CNS GFAP and IBA1 staining
- Serum neurofilament light chain (NF-L) levels

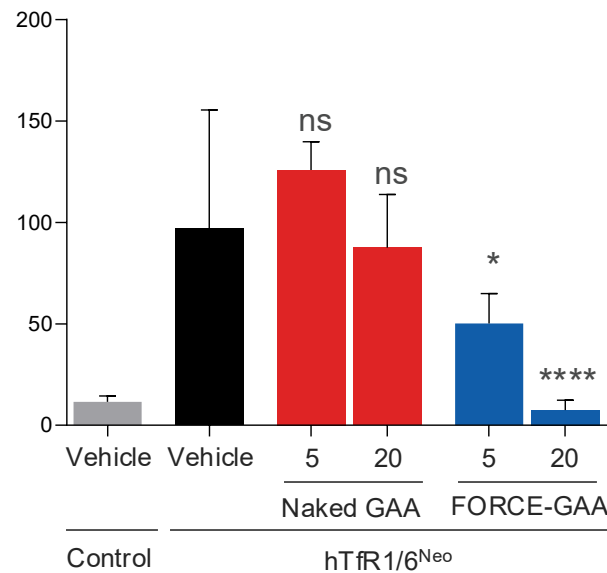
FORCE-GAA Achieves Superior Glycogen Clearance in Muscle Compared to Naked GAA Using the SOC Dosing Regimen



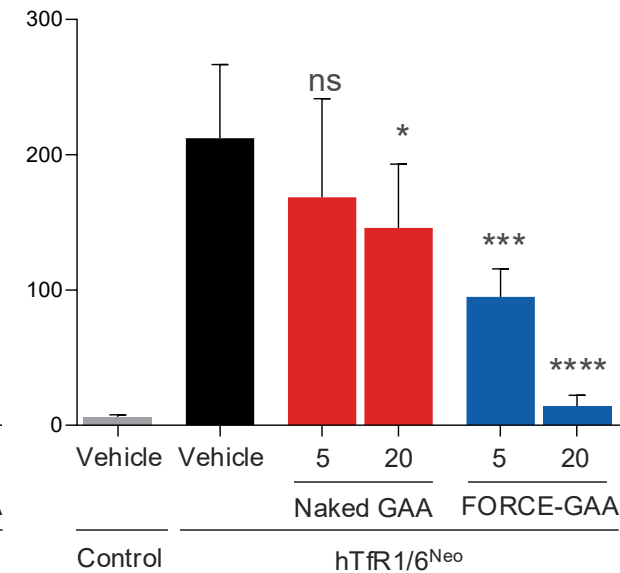
Heart



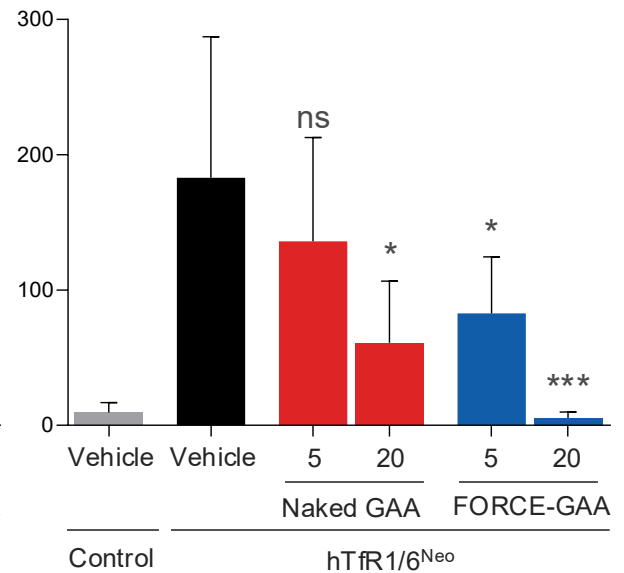
Diaphragm



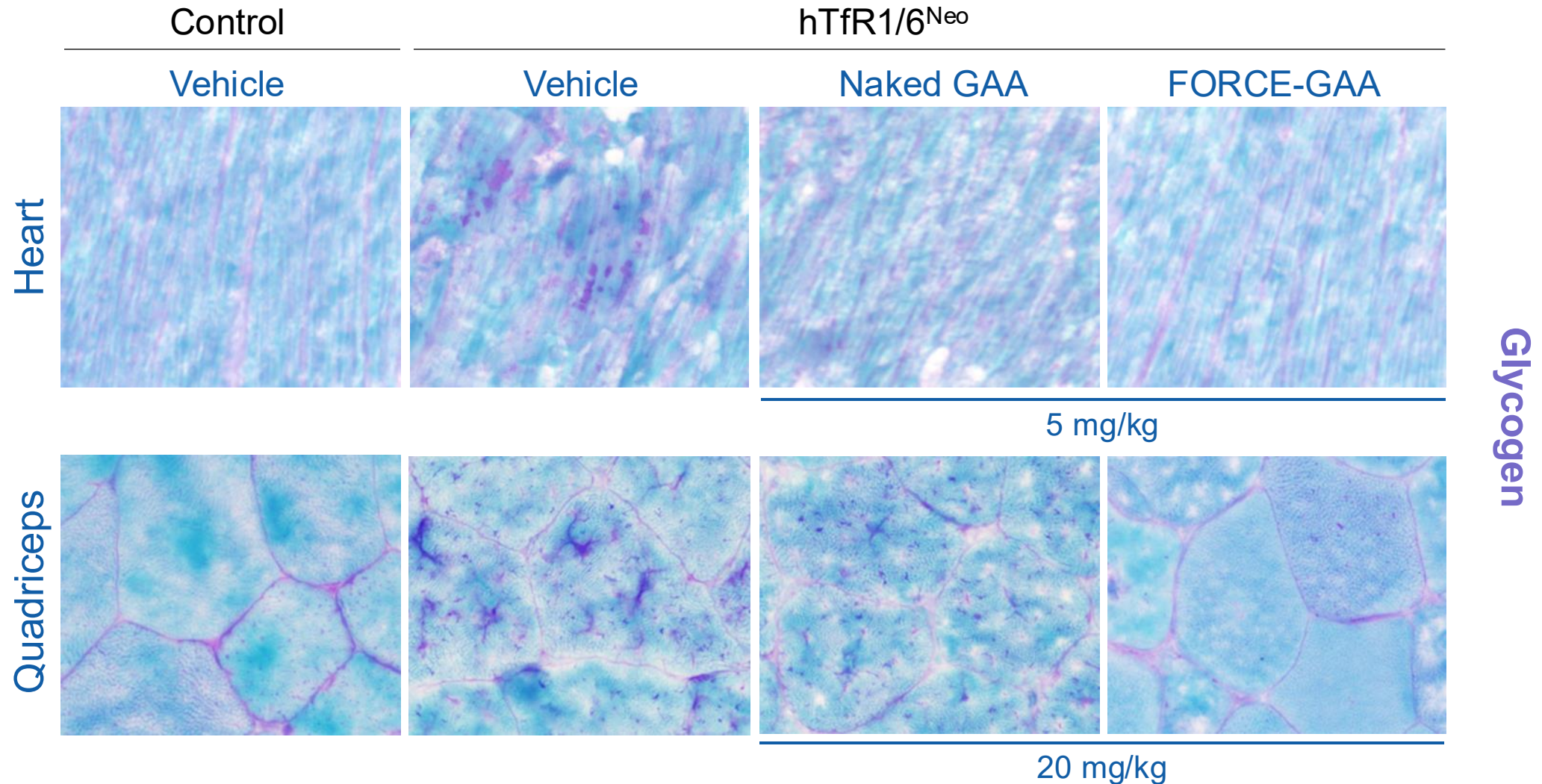
Quadriceps



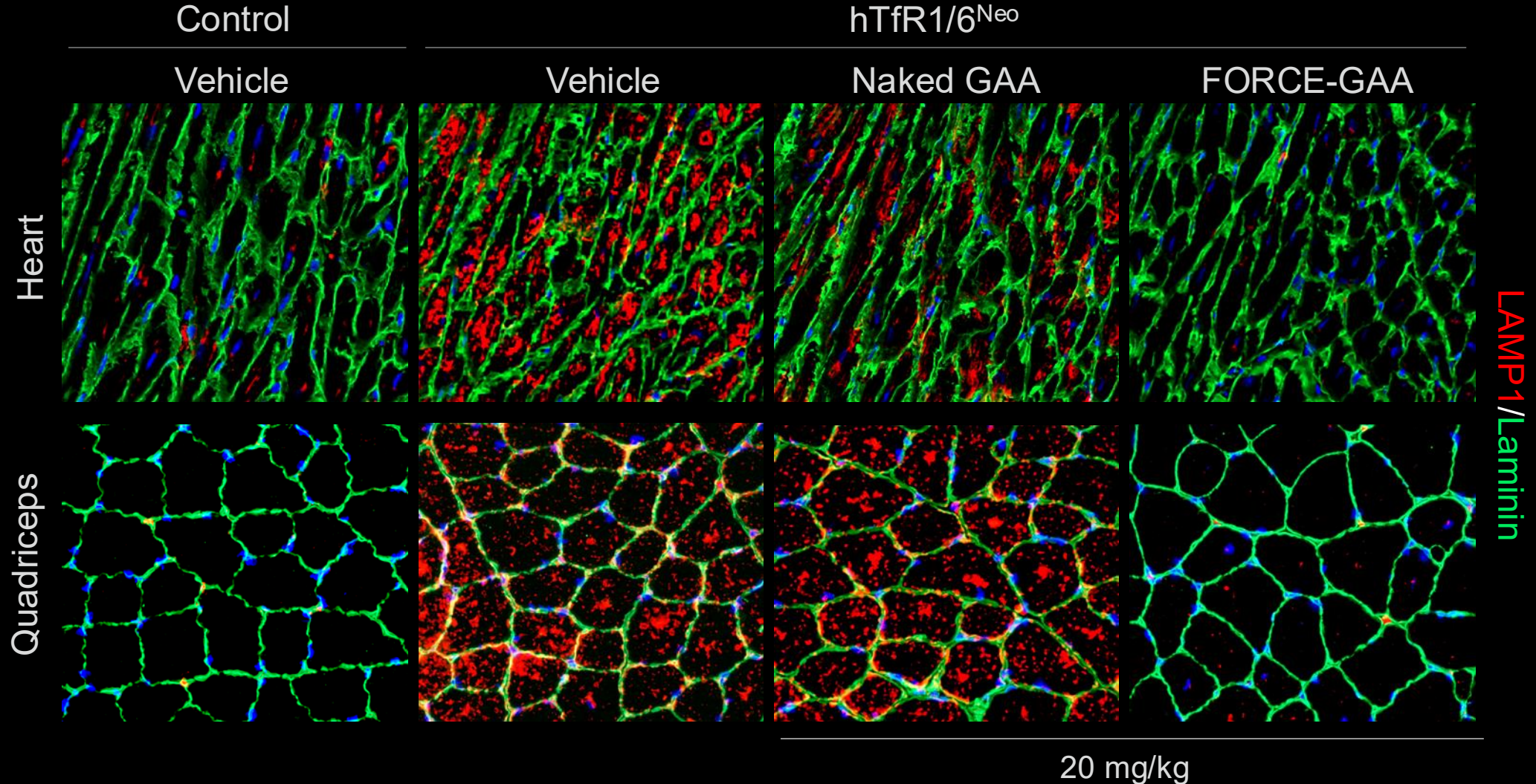
Soleus



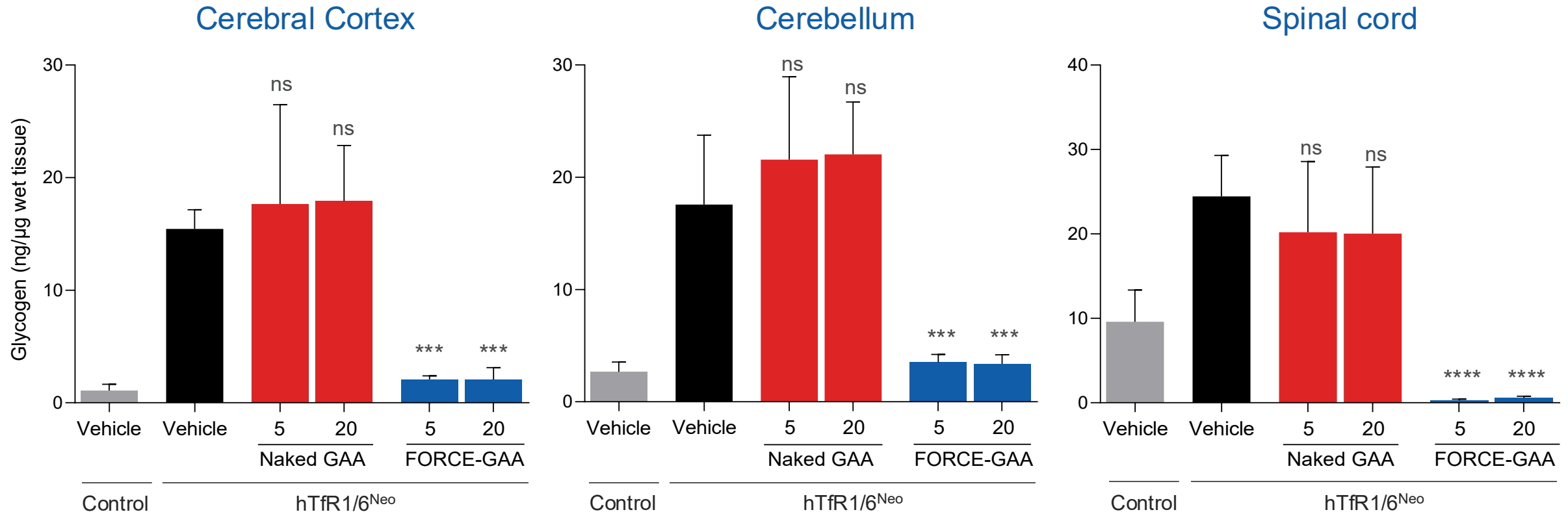
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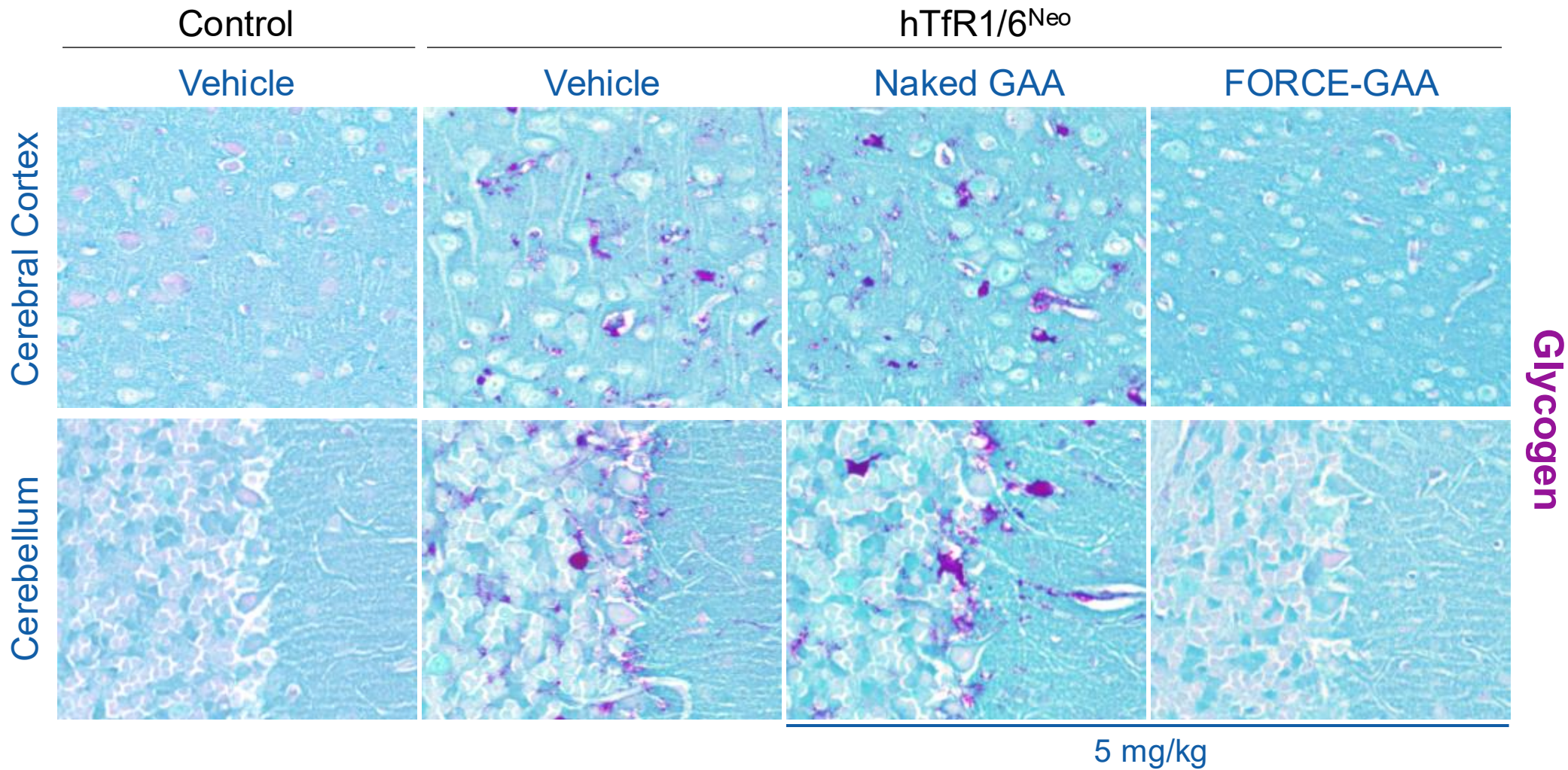
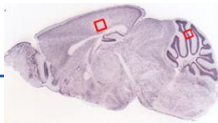
FORCE-GAA Outperforms Naked GAA and Demonstrates Superior Reduction of Lysosomal Enlargement in Muscle Using SOC Dosing



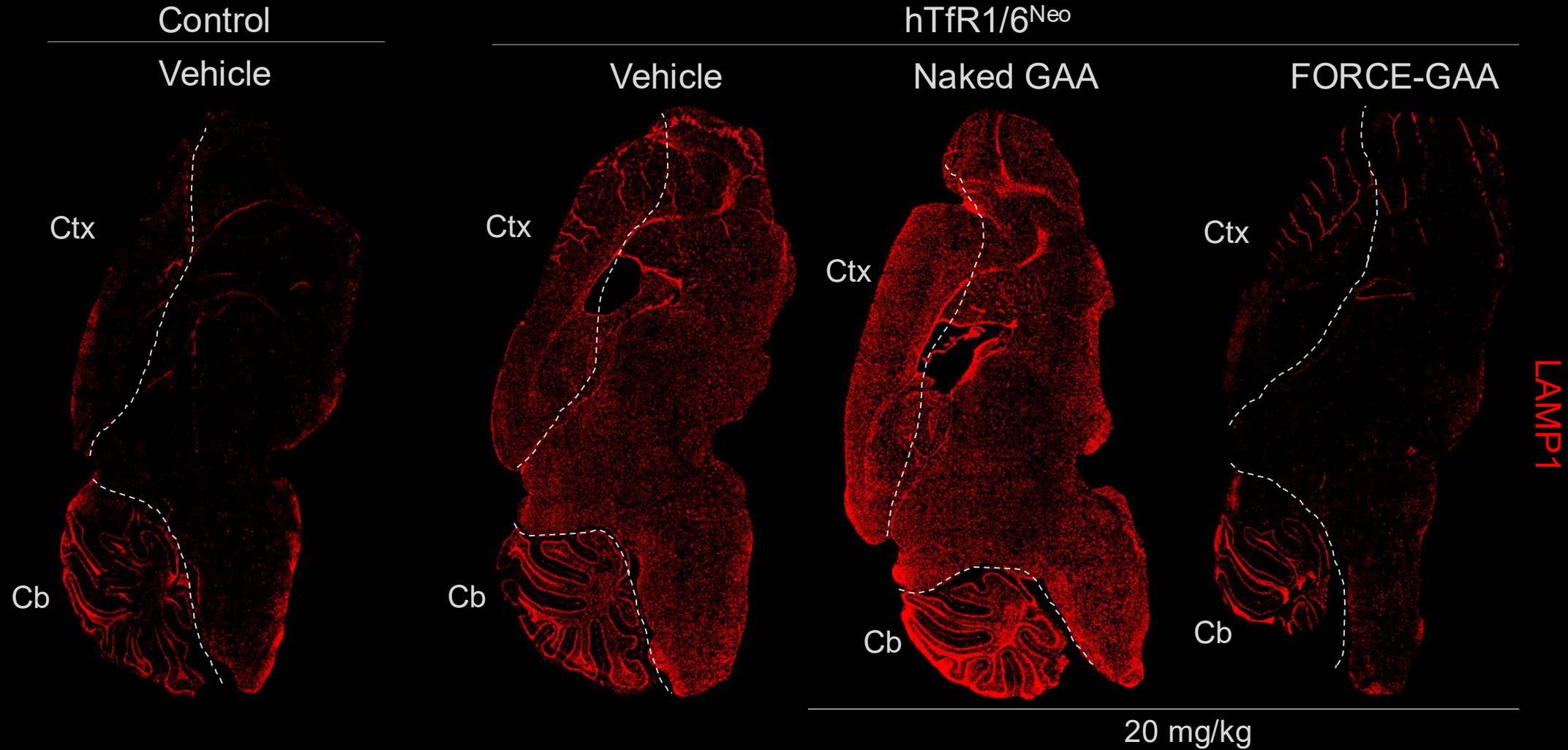
FORCE-GAA Clears Glycogen in CNS with SOC Dosing Regimen



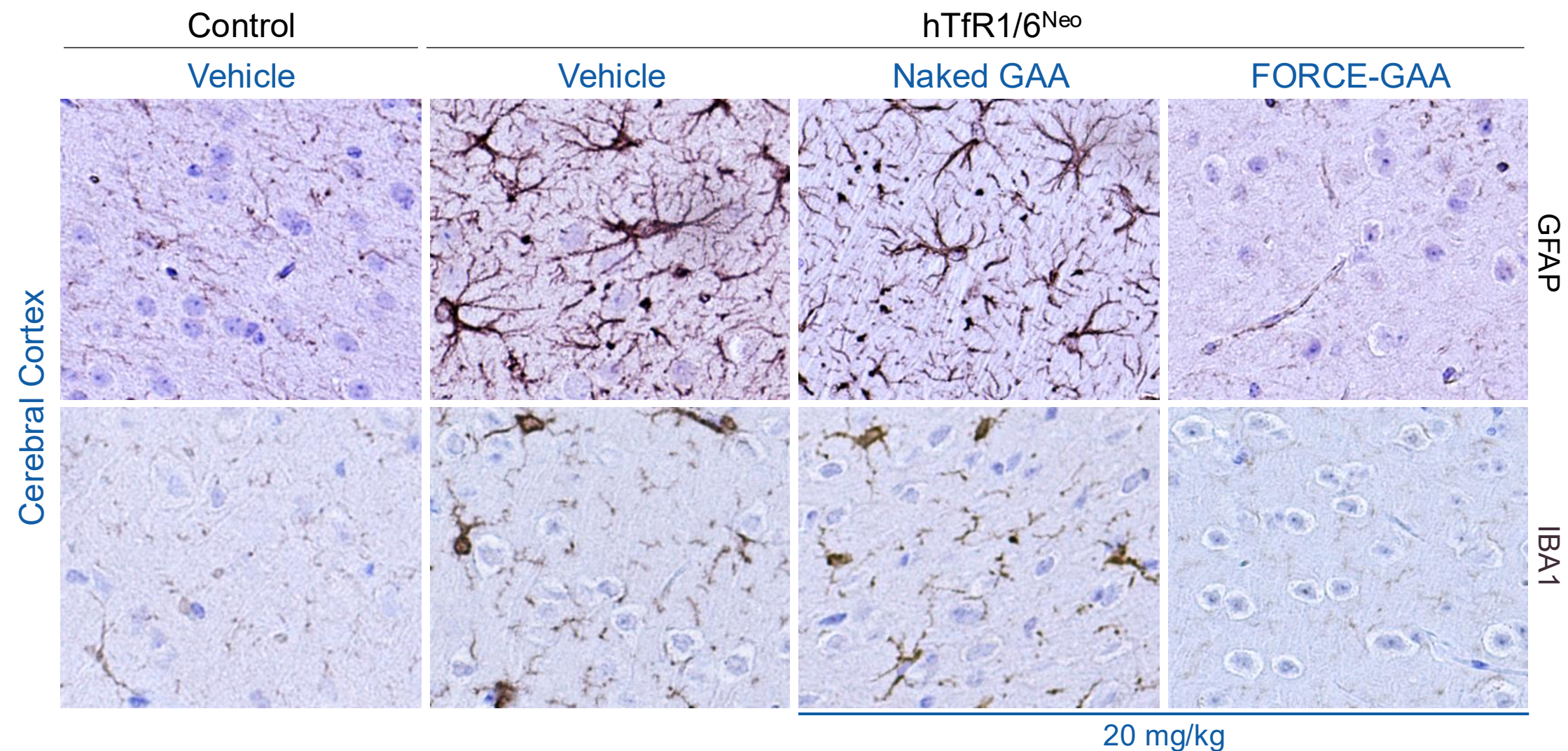
FORCE-GAA Clears Glycogen in CNS with SOC Dosing Regimen



FORCE-GAA Achieves Widespread Lysosomal Size Normalization in CNS Using SOC Dosing



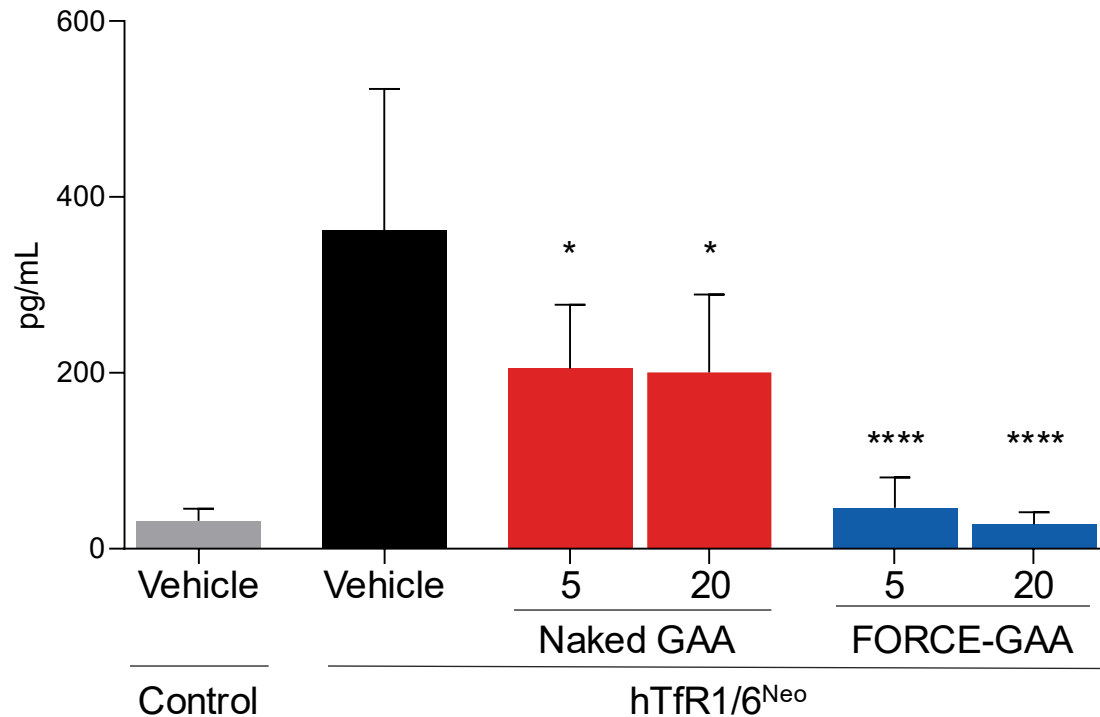
FORCE-GAA Substantially Reduces Neuroinflammation in the CNS



FORCE-GAA Normalizes Serum Neurofilament Light Chain (NF-L), a Potential Biomarker of CNS Involvement in Pompe



Serum NF-L normalization

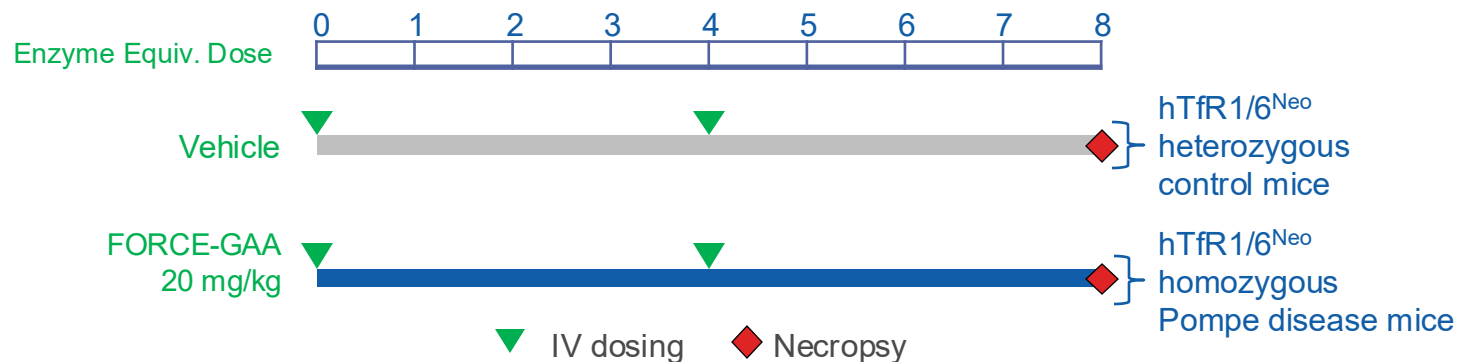


- In humans, NF-L elevation in serum correlates with neurological manifestations in multiple disorders^{1,2}
- In infantile Pompe patients, serum NF-L increases as IQ decreases³
- Data in hTfR1/6^{Neo} mice suggest potential use of a validated clinical biomarker to monitor CNS benefit

FORCE-GAA was Assessed Using a Monthly Dosing Regimen



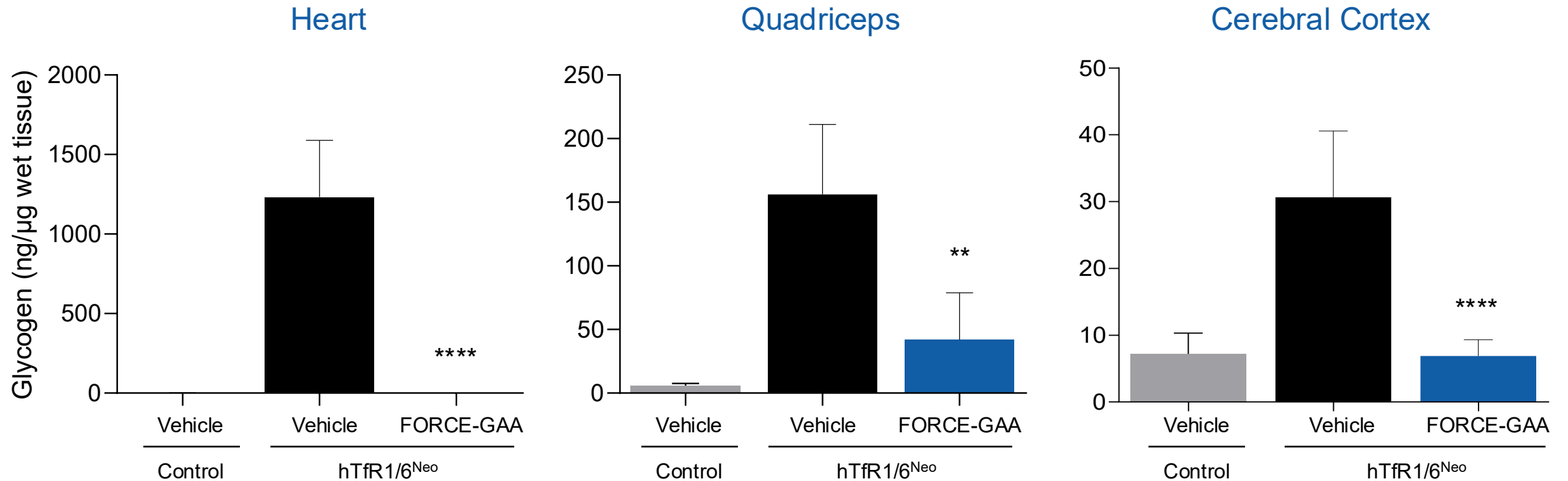
Study timeline in weeks



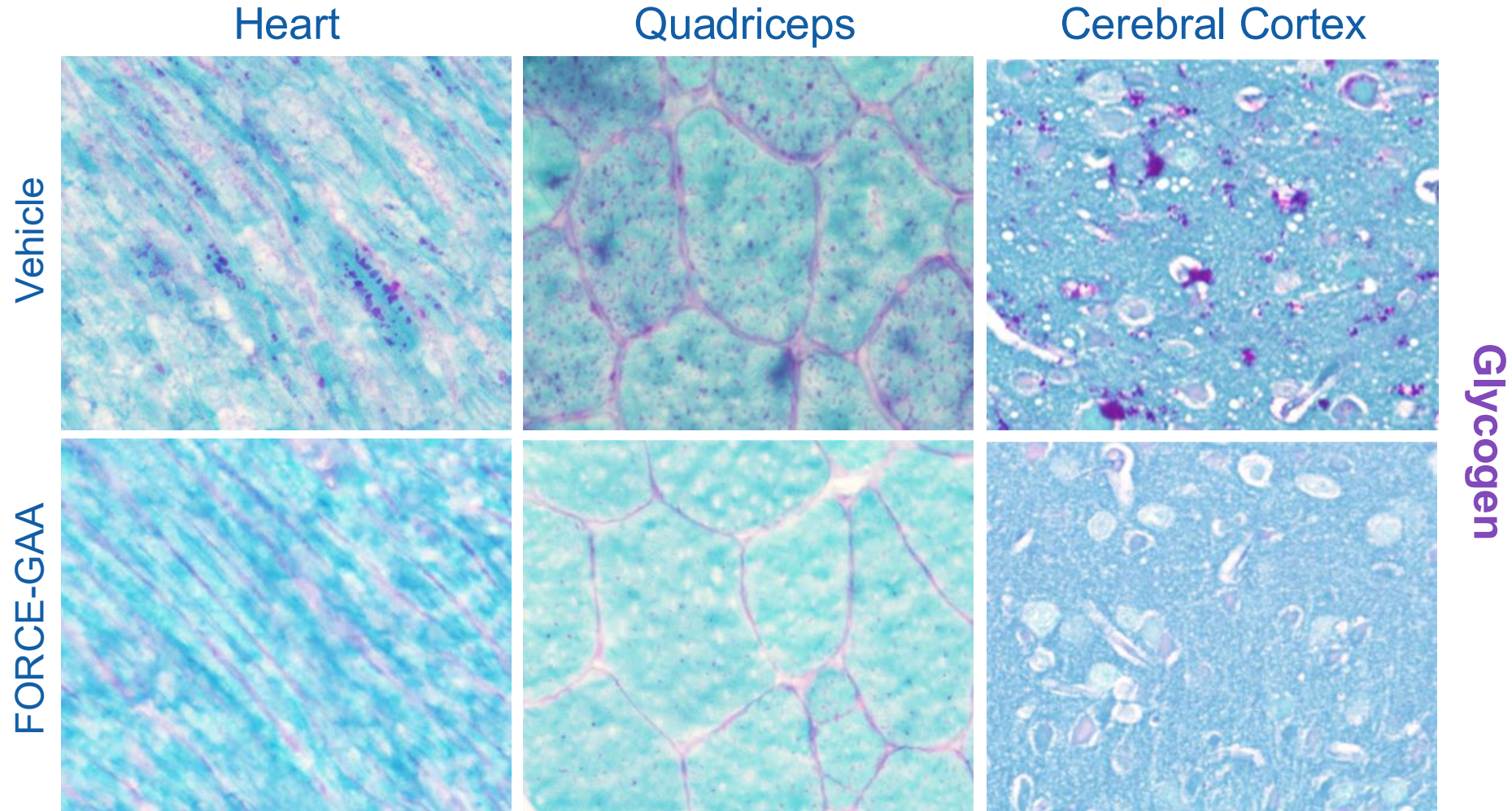
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- Serum NF-L levels

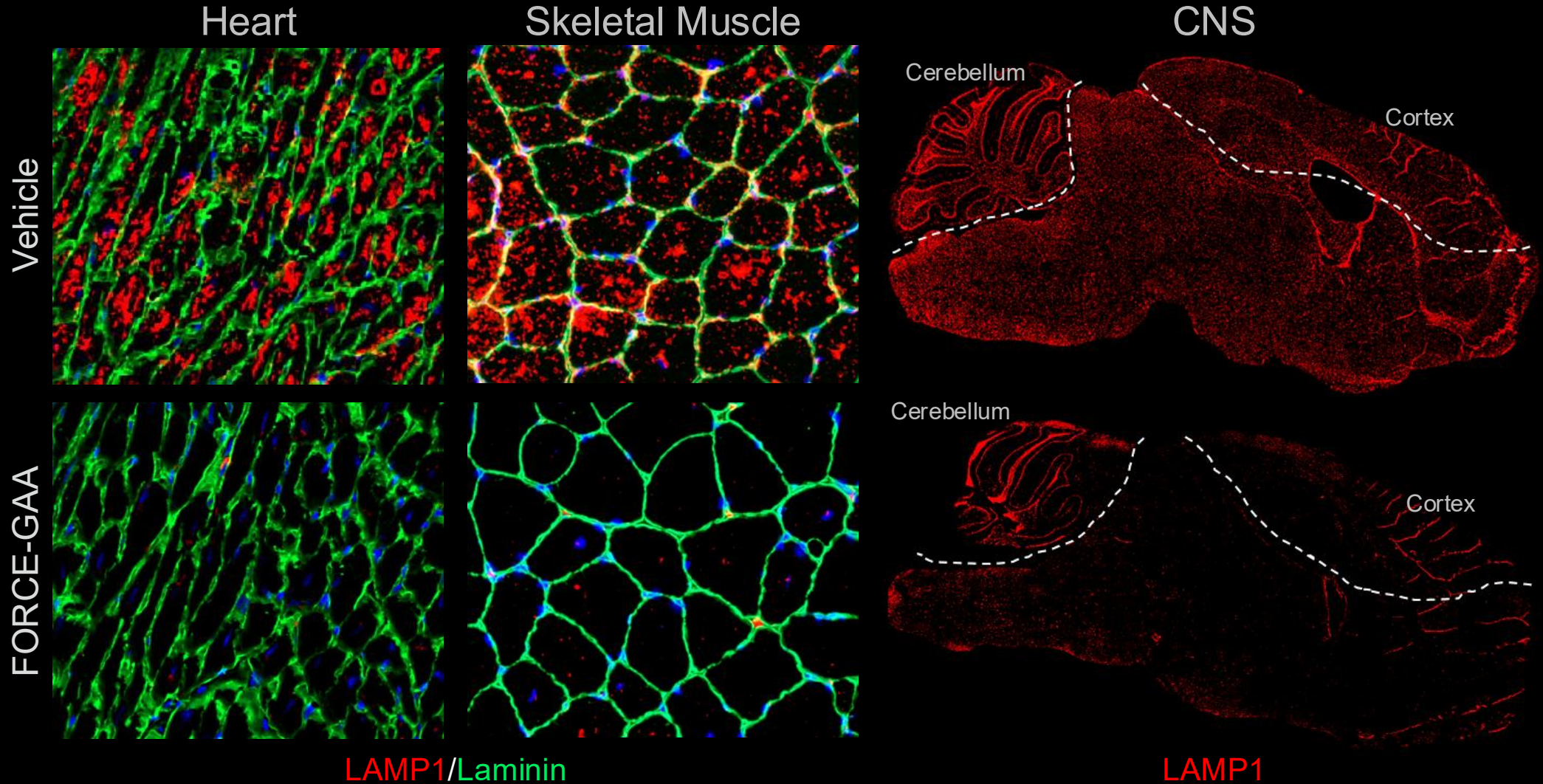
FORCE-GAA Monthly Dosing Clears Glycogen in Muscle and CNS



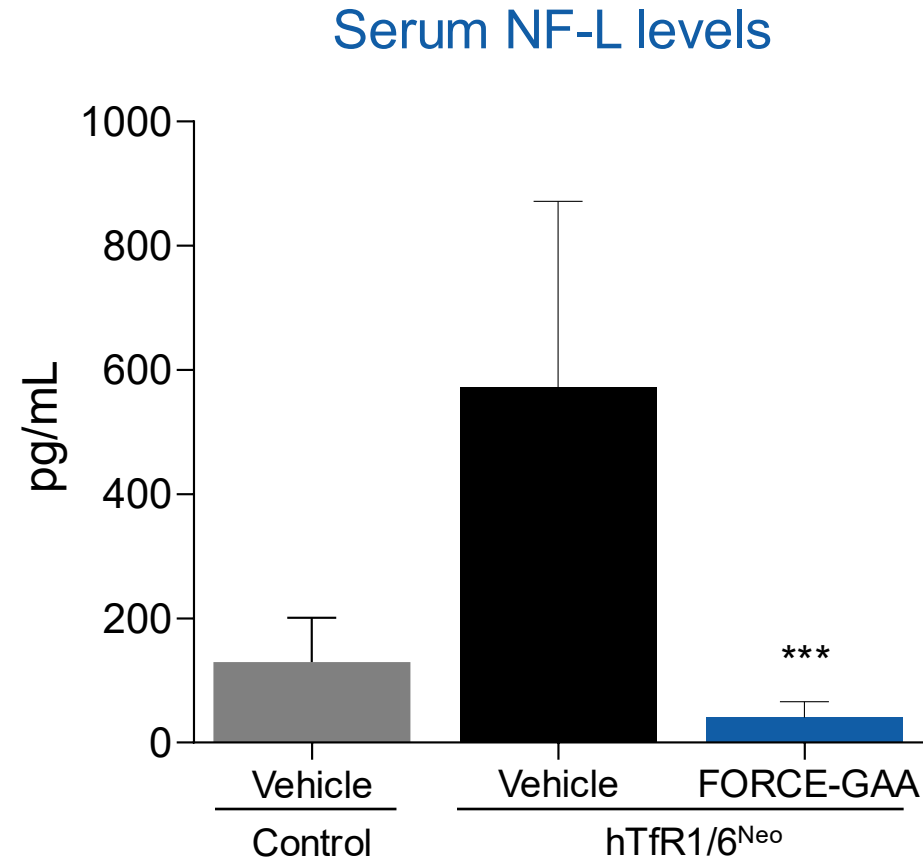
FORCE-GAA Monthly Dosing Demonstrates Profound Glycogen Clearance in Cardiac and Skeletal Muscle as well as CNS



Monthly Dosing with FORCE-GAA Leads to Broad Reversal of Lysosomal Pathology in Muscle and CNS



FORCE-GAA Monthly Dosing Normalizes Serum NF-L Levels



Conclusions

- FORCE displayed superior efficacy in cardiac and skeletal muscle compared to naked GAA in a well-established mouse model of Pompe disease
- FORCE enables effective ERT delivery throughout the CNS that translates into normalization of serum NF-L levels in a mouse model of Pompe disease
- Durability of pharmacodynamics in muscle and CNS indicates potential for monthly or less frequent dosing
- Modularity of FORCE as delivery platform for muscle and CNS is demonstrated with a biologic payload

Data support applicability of the FORCE platform for the treatment of Pompe

Acknowledgements

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