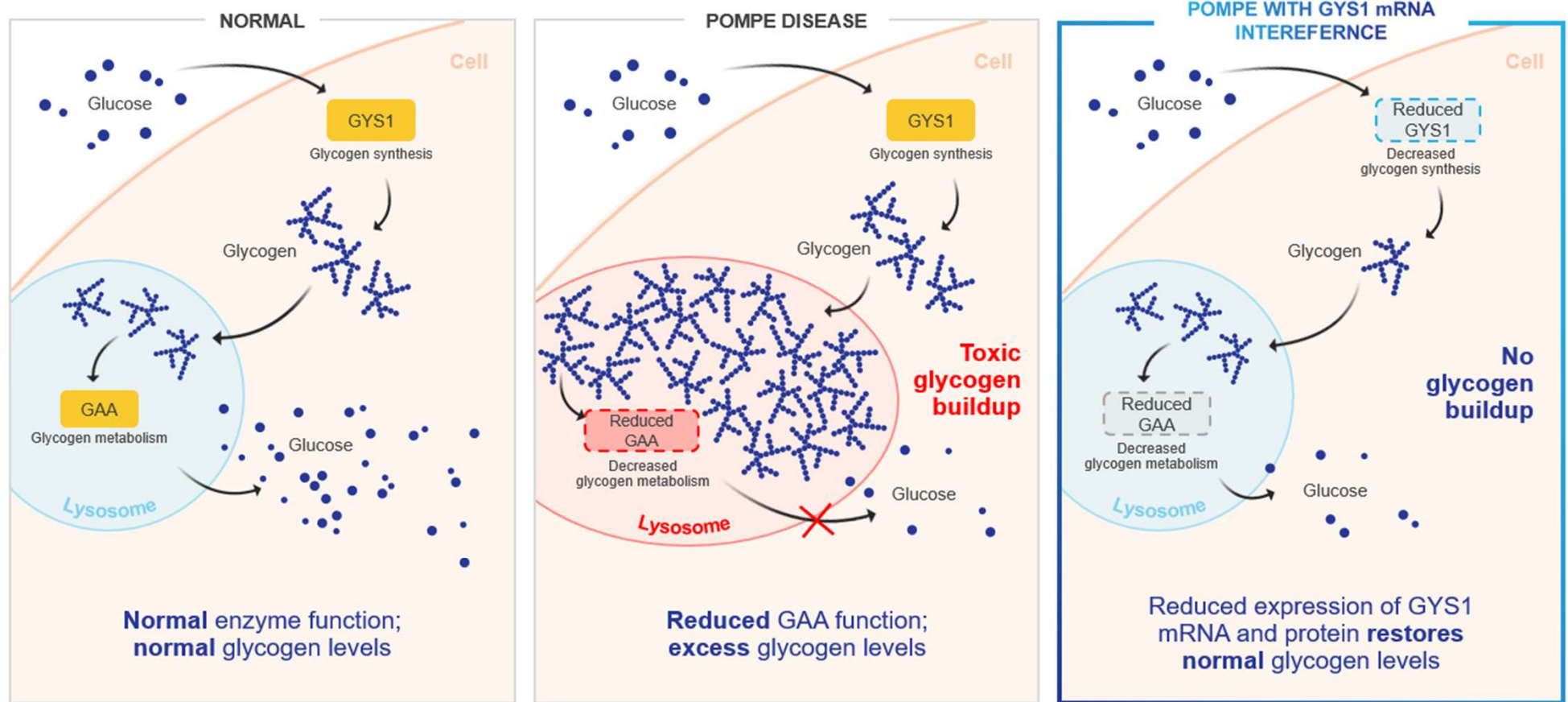


# **Centyrin-targeted glycogen synthase-1 siRNA conjugates: A novel, muscle targeted glycogen reduction therapy for the treatment of Pompe Disease**

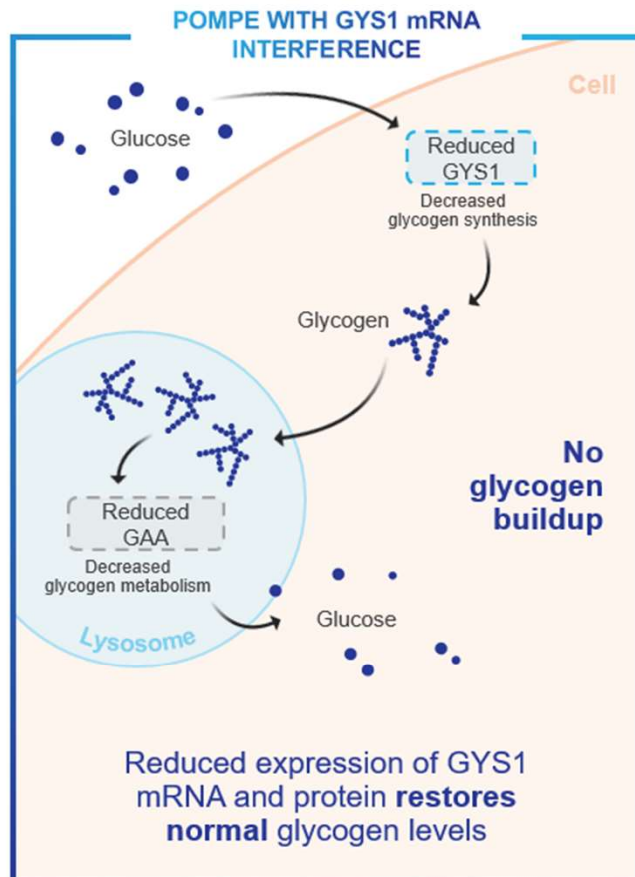
**Michael A Tortorici, PharmD, PhD  
Vice President, Nonclinical Development  
Aro Biotherapeutics  
February 2023**

# Toxic glycogen buildup in Pompe disease is **reduced by decreasing expression of glycogen synthase-1 (GYS1) mRNA and protein**

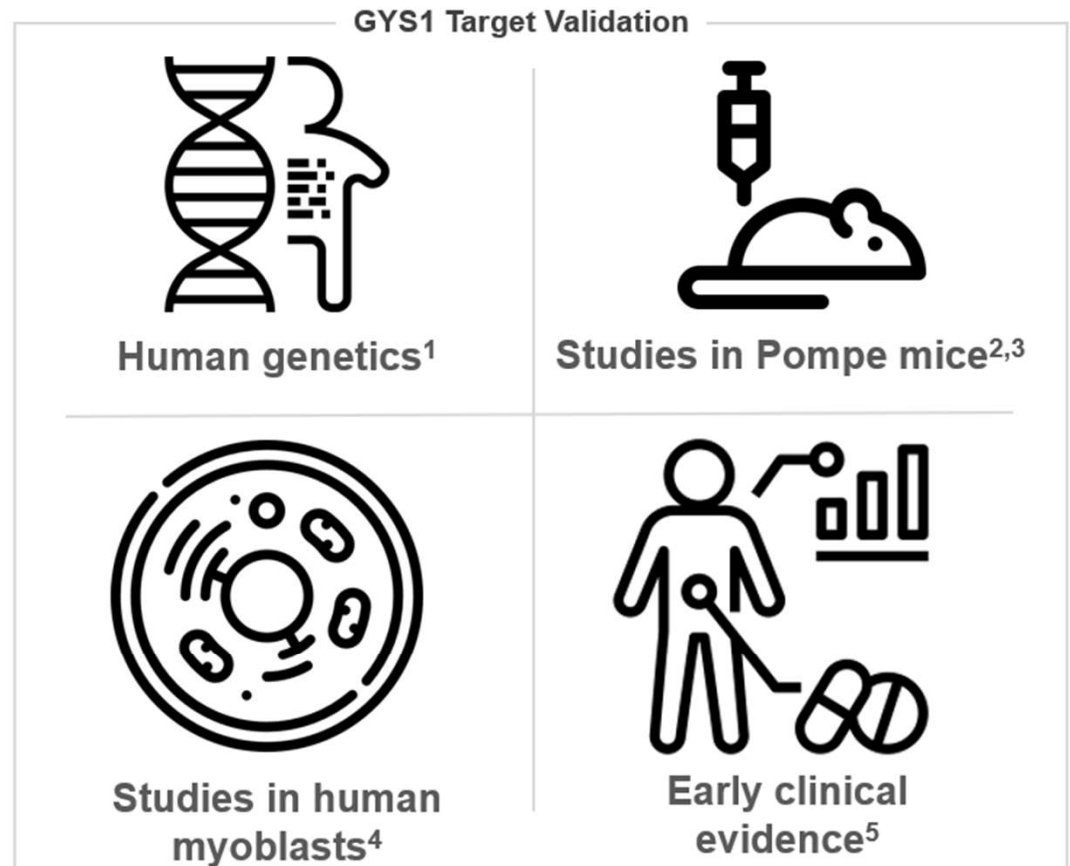


# Genetic studies confirm the critical role of Glycogen synthase 1 (Gys1) in **muscle glycogen synthesis**

Reduction in Gys1 leads to decreased muscle glycogen and is protective in Pompe mouse models

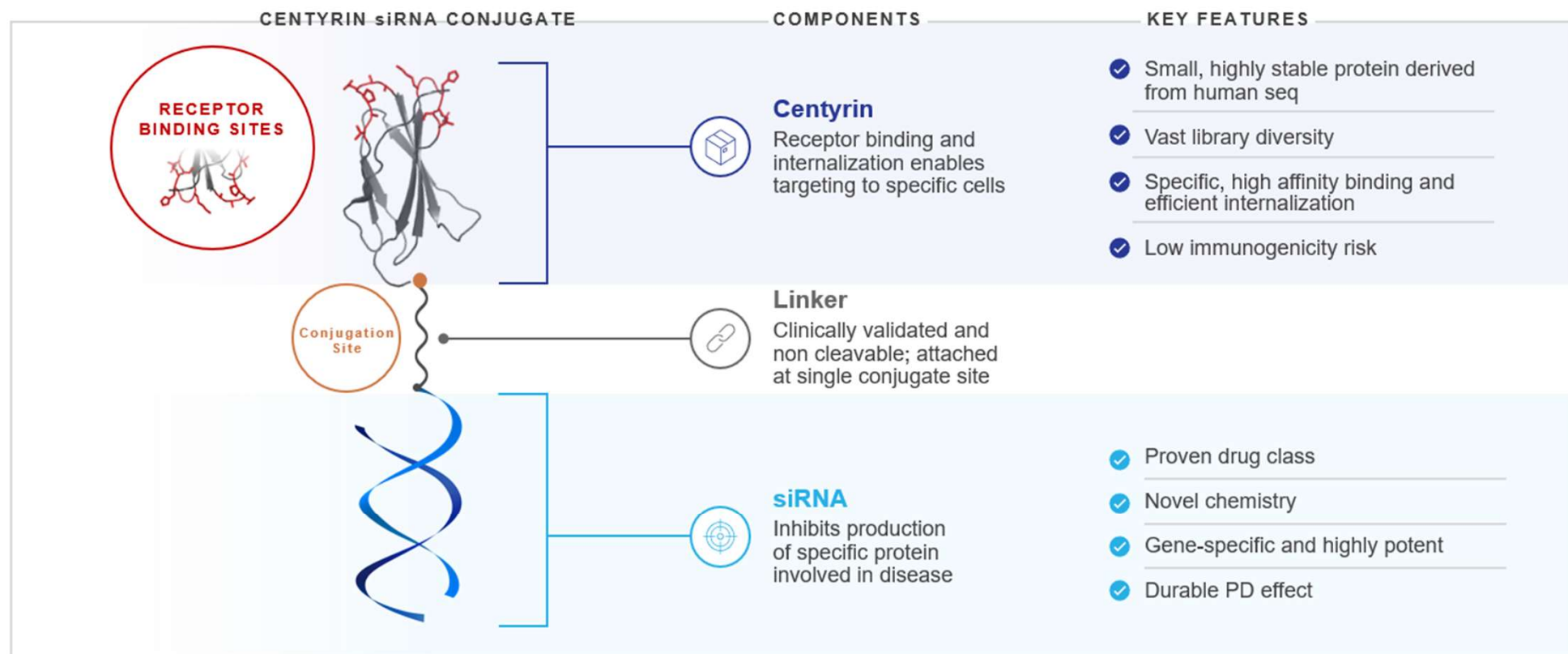


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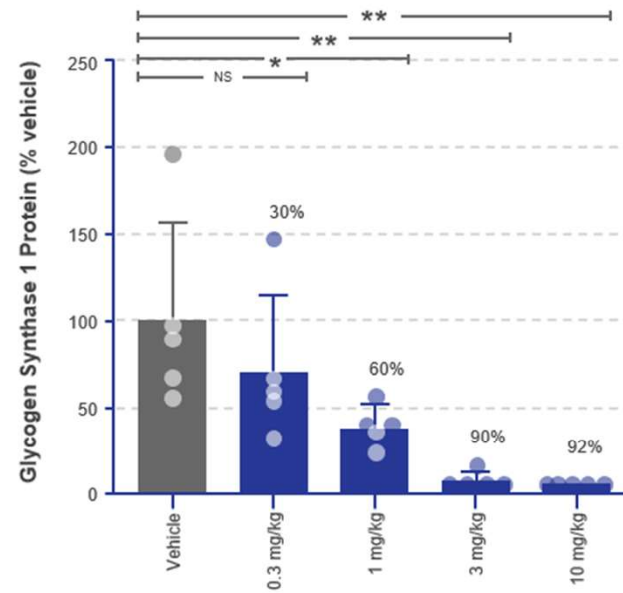
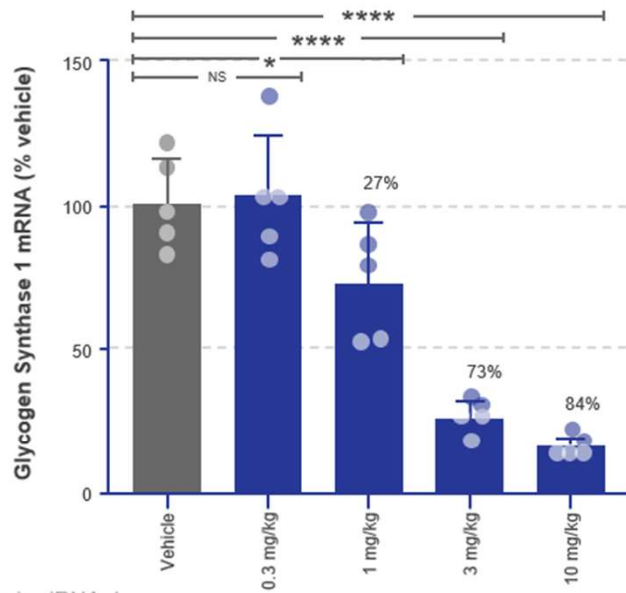
<sup>1</sup> Savage et al, 2008; <sup>2</sup> Clayton et al, 2014; <sup>3</sup> Douillard-Guilloux et al, 2008; <sup>4</sup> Douillard-Guilloux et al, 2010; <sup>5</sup> Maze Therapeutics, Inc website

## Centyrins specifically deliver siRNAs to extrahepatic tissues, overcoming the challenge associated with delivery



# Single dose CD71 Centyrin-Gys1 siRNA **efficiently targets muscle** in **Pompe Mouse** Potent *Gys1* dose-dependent mRNA and protein reduction in the Gastrocnemius

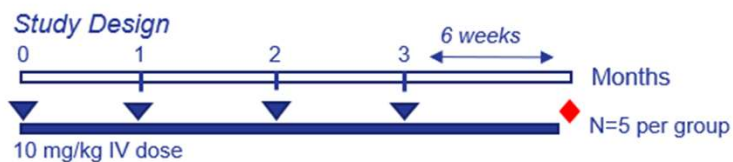
## Study Design



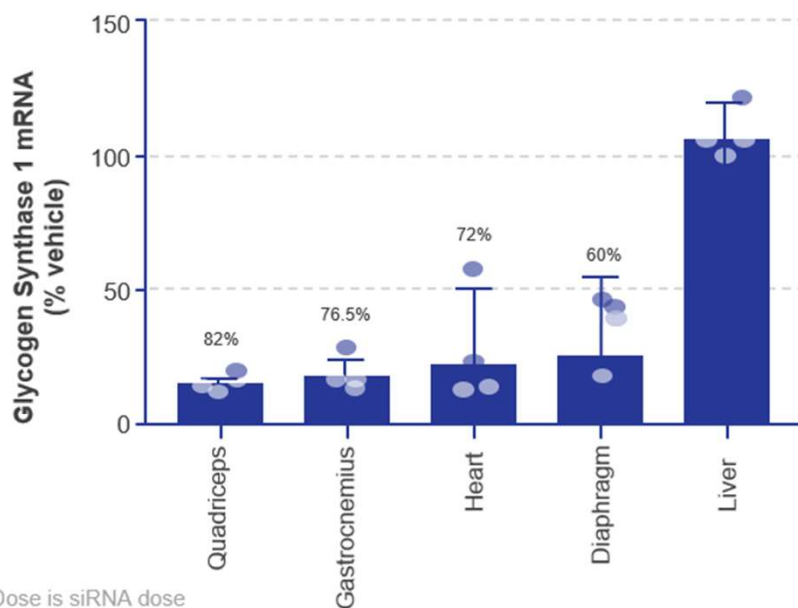
Dose is siRNA dose  
 Mean (± S.D.) one-way ANOVA, Bonferroni's post-hoc  
 \*p<0.05, \*\*p<0.01, \*\*\*p<0.001, \*\*\*\*p<0.00001, ns = not significant

- ✓ Single dose highly effective in muscle
- ✓ No effect in liver or kidney
- ✓ Return to baseline mRNA levels 12 weeks post-dose

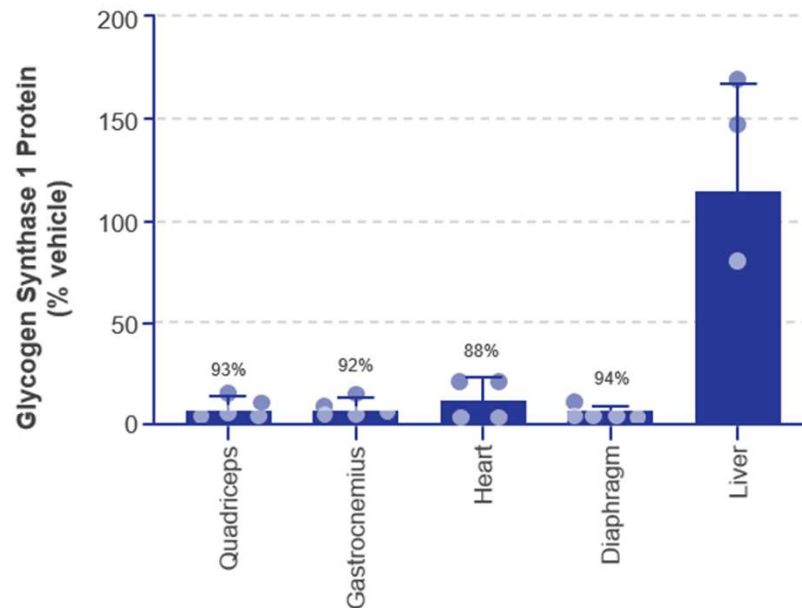
## Monthly dosing of CD71 Centyrin-Gys1 siRNA conjugate demonstrates efficient **Gys1 mRNA and protein reduction in Pompe mouse muscle tissue**



**Gys1 mRNA**

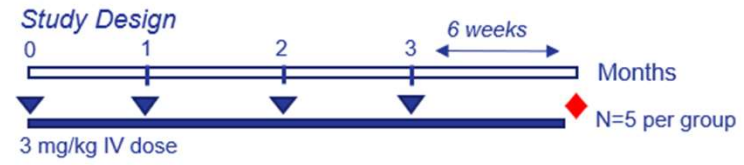
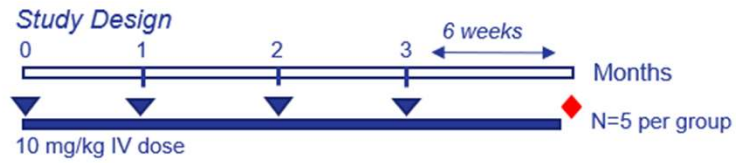


**GLY1 protein**

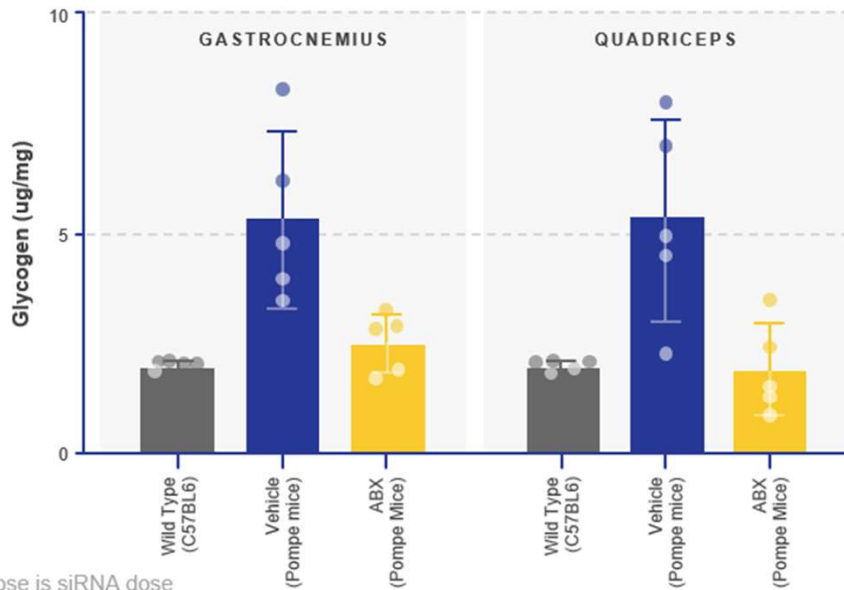




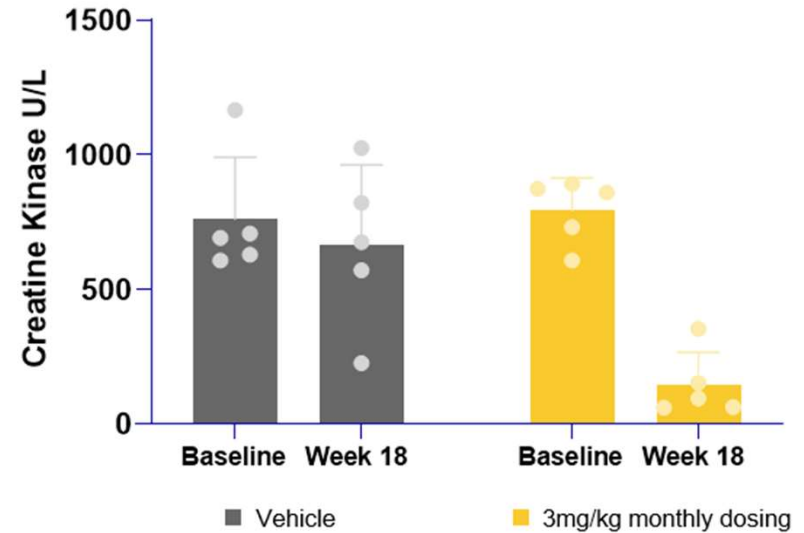
## Monthly dosing CD71 Centyrin-Gys1 siRNA reduces skeletal muscle glycogen in muscle tissue and reduces creatinine kinase in Pompe mice



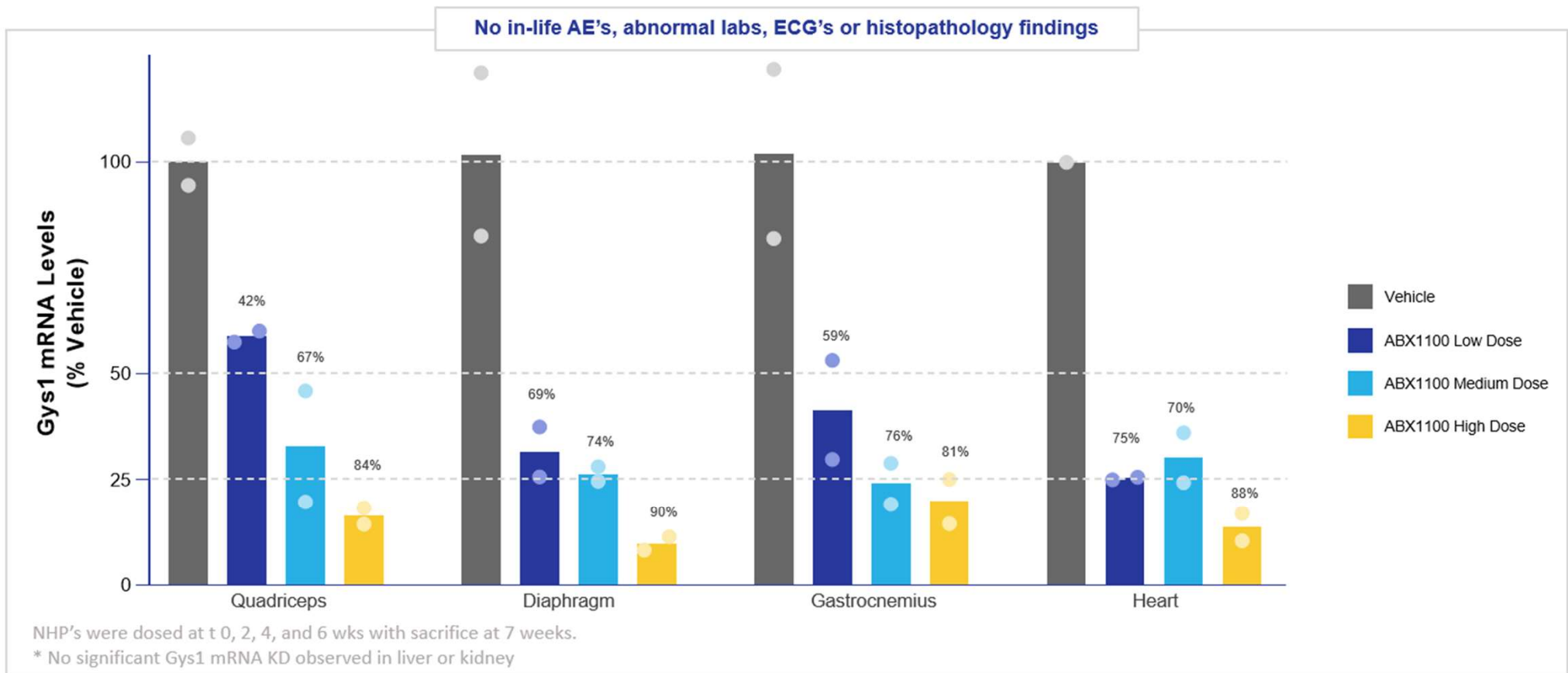
**Pompe vs Normal Mice Glycogen Levels**



**CK Levels vs. Baseline**



ABX1100 activity in NHP muscle after biweekly dosing (x4)  
**80-90% Gys1 mRNA knockdown in muscles with no adverse safety findings\***



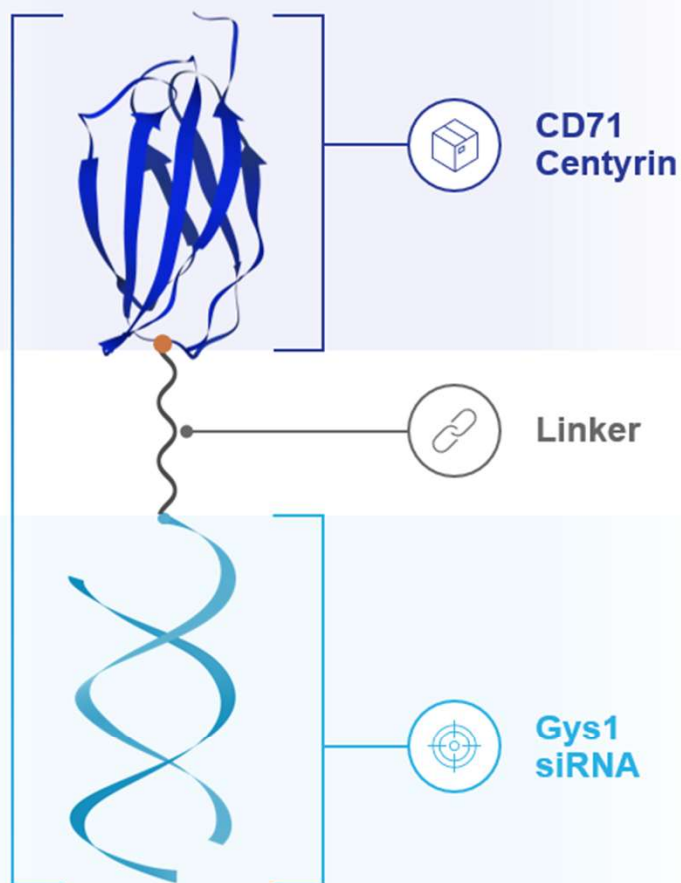


**ABX1100, a muscle targeted Gys1 siRNA therapeutic** offers new hope for patients with Pompe Disease

CENTYRIN siRNA CONJUGATE

COMPONENTS

KEY FEATURES



- ✓ POC in murine Pompe model and in NHP's
- ✓ Gys1 specific reduction in muscle and durable mechanism of action
- ✓ Convenient monthly or Qly dosing, wide therapeutic window, no toxicities in initial NHP study
- ✓ Orphan Drug and Rare Pediatric Disease Designation received from FDA

**First muscle targeted SRT for Pompe disease**

**FIH in 2023**

# **Acknowledgements**

## **Co-Authors**

**Steve Nadler**

**Chase Archer**

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**Karyn O'Neil**

## **Materials**

**Alex Meltzer**