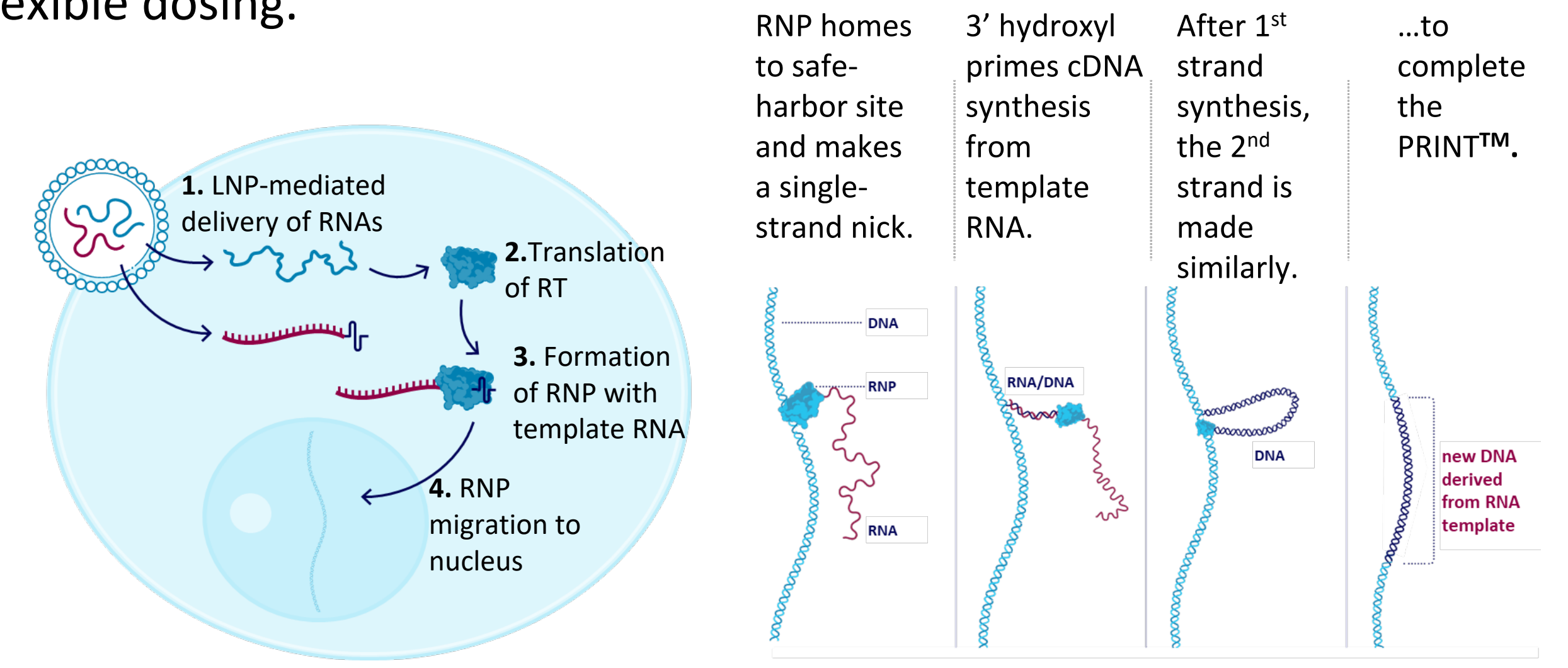


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## Background

**PRINT** (Precise RNA-mediated INsertion of Transgenes) is an all-RNA, targeted insertion platform using R2 retrotransposon-mediated reverse transcription. LNP delivery of the PRINT components enables durable protein expression and flexible dosing.

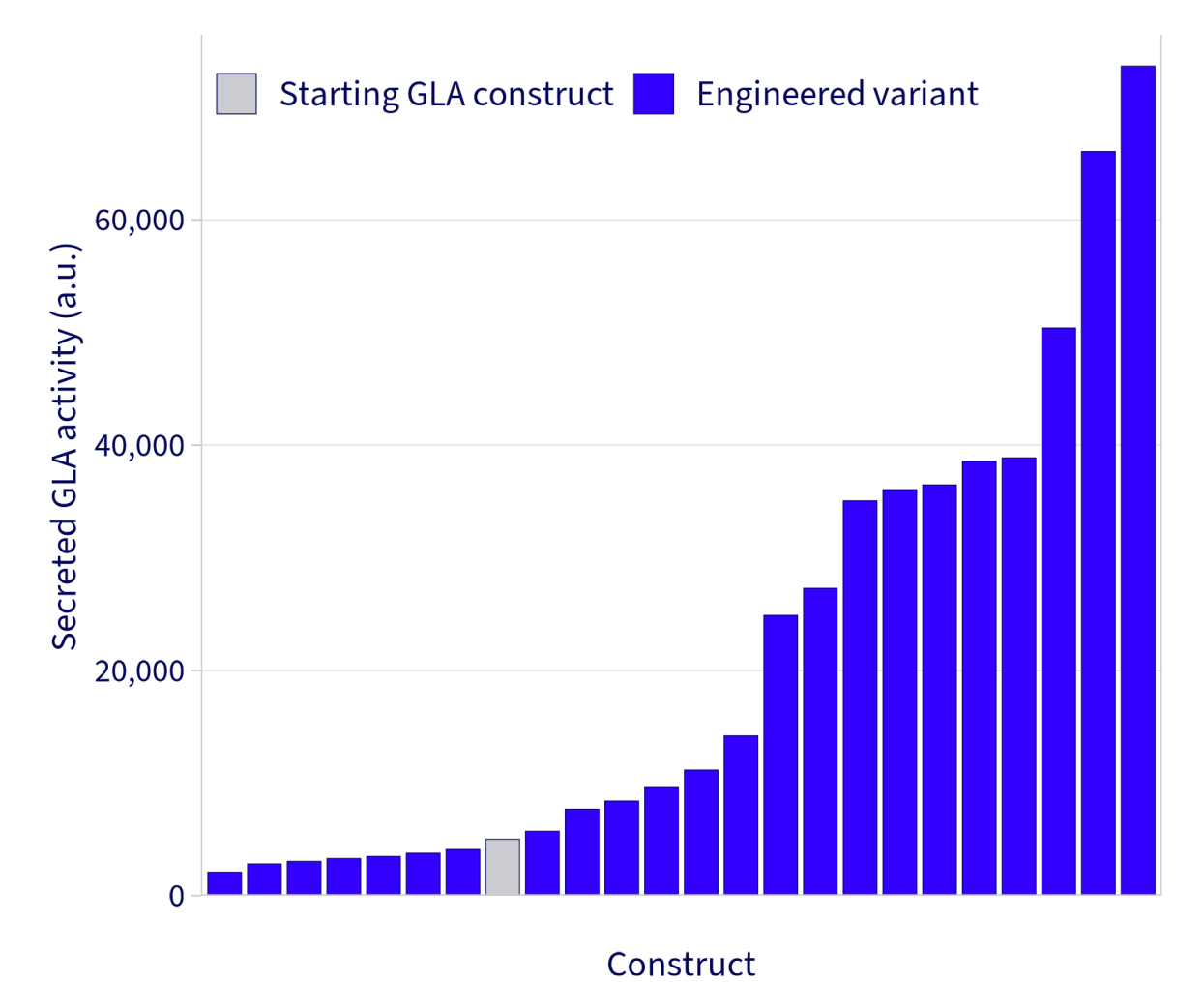


**Fabry disease:** A lysosomal storage disorder caused by *GLA* mutations, leading to deficient  $\alpha$ -Gal A activity and progressive Gb3/lyso-Gb3 accumulation in the kidney, heart, and nervous system. Enzyme replacement therapy requires life-long biweekly infusions and fails to prevent progressive renal/cardiac disease. We demonstrate therapeutic-level *GLA* PRINTing in a Fabry mouse model.

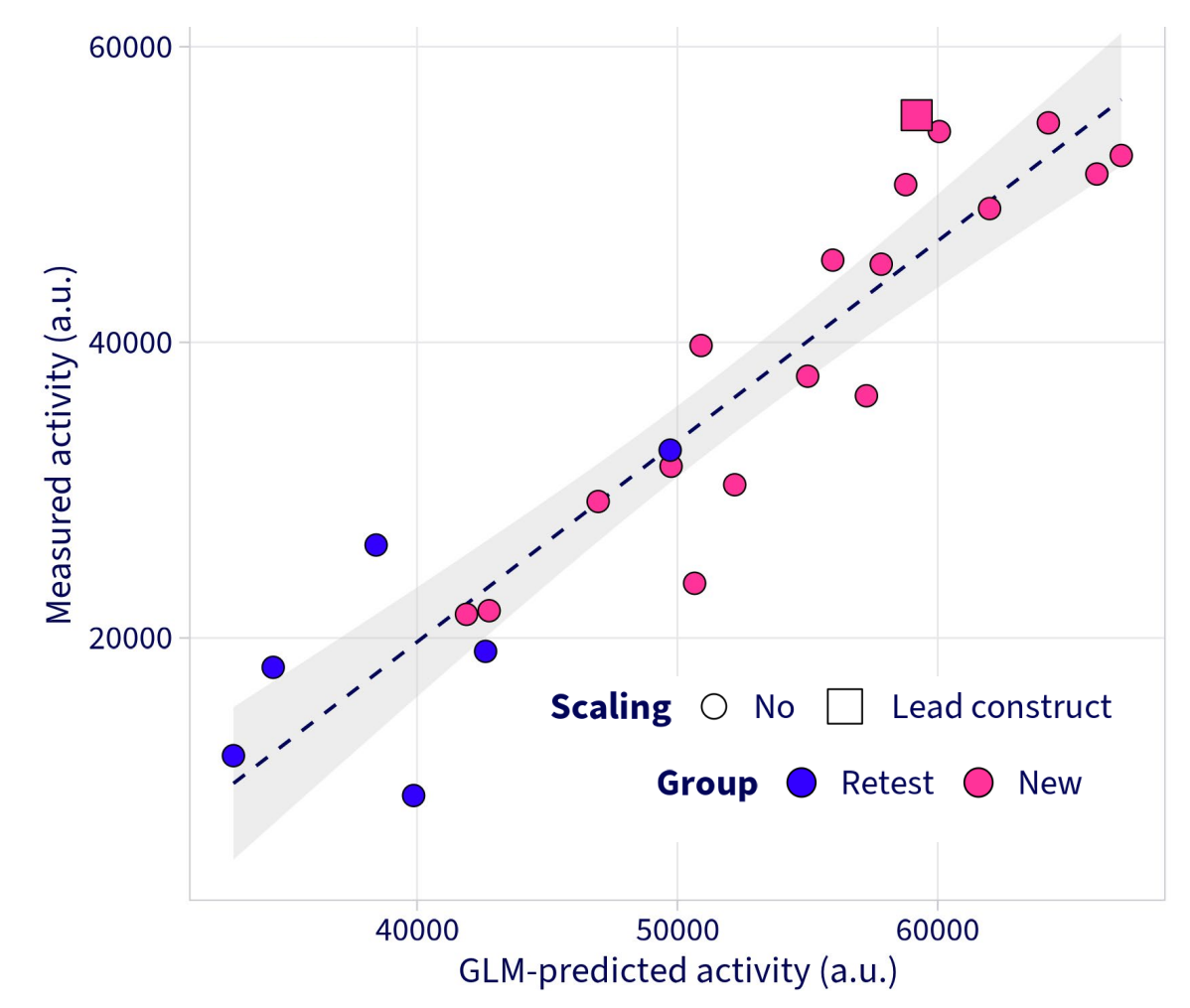
## In vitro construct optimization

*GLA* RNA template optimization was conducted in a hepatic cell line for maximal *GLA* PRINT efficiency and secretion.

### A. Round 1 secreted $\alpha$ -Gal A activity



### B. Round 2 validation



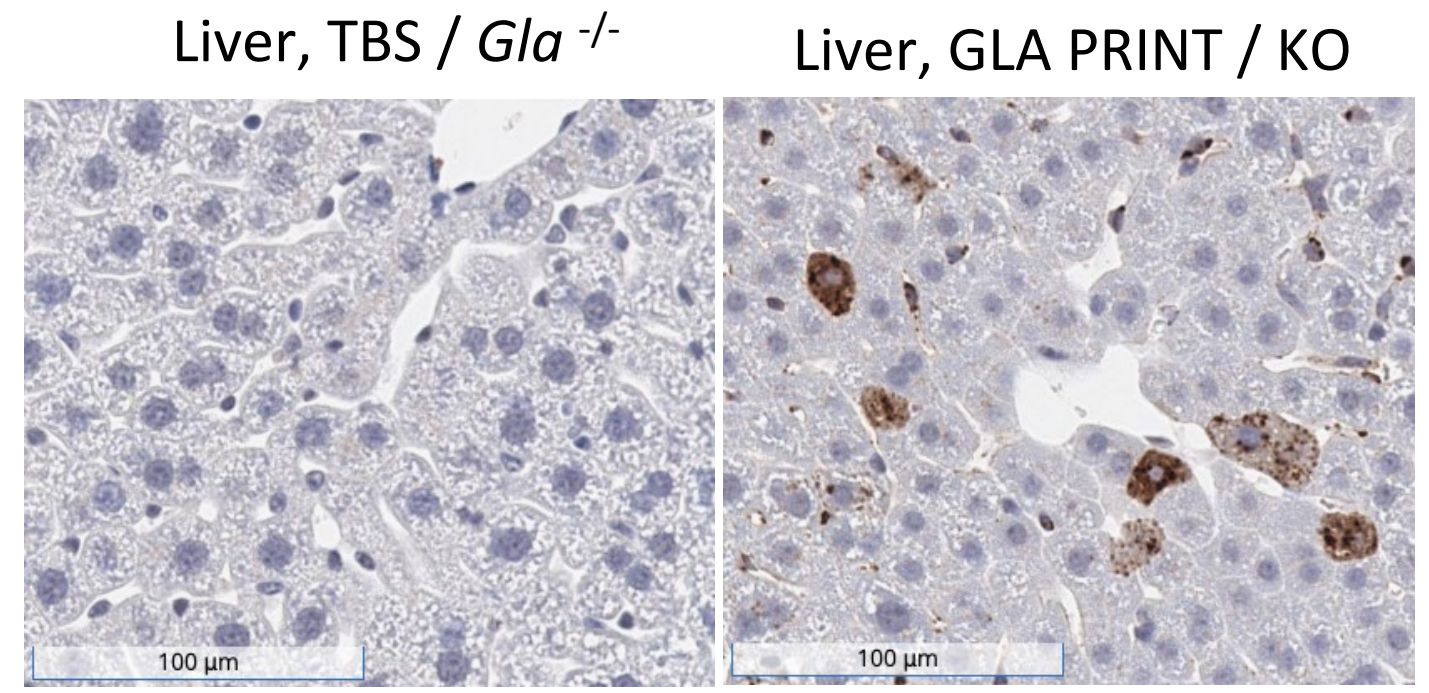
The lead construct was progressed to *in vivo* testing in *GLA* KO mice.

## Results

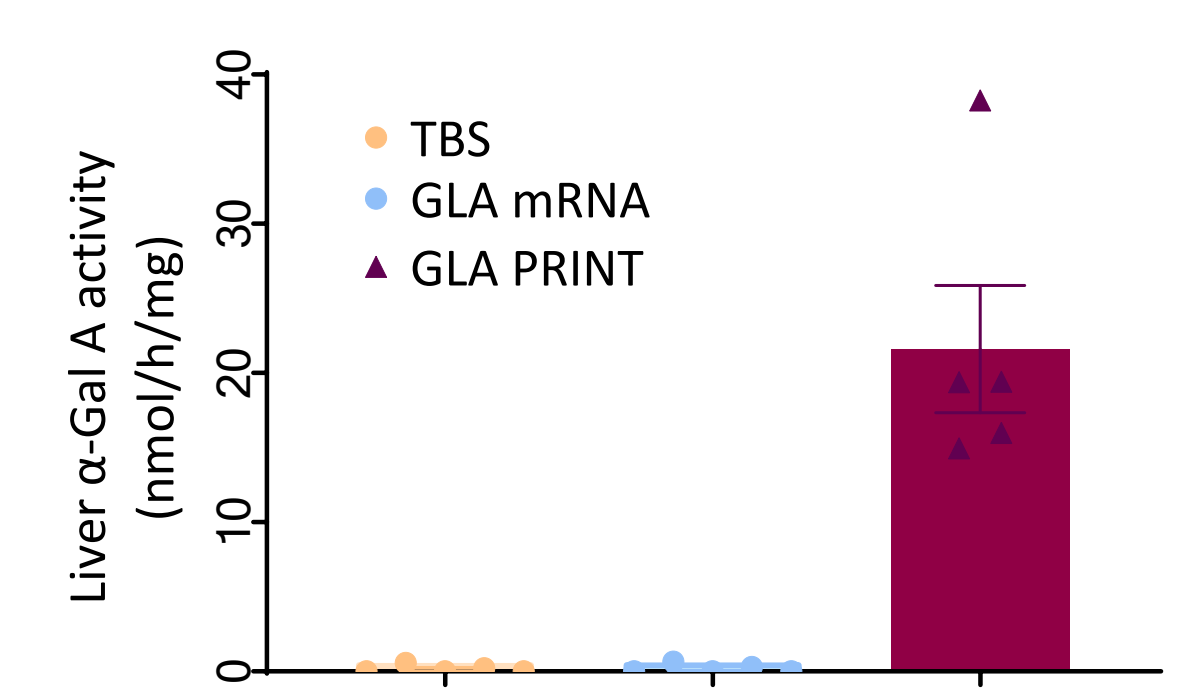
**In Vivo PoC study:** *Gla*<sup>-/-</sup> mice received a single dose of *GLA* PRINT cargo encapsulated in LNP or controls. In-life duration was 16 weeks.

### 1. Hepatic *GLA* insertion enables functional $\alpha$ -Gal A expression and lyso-Gb3 reduction in liver

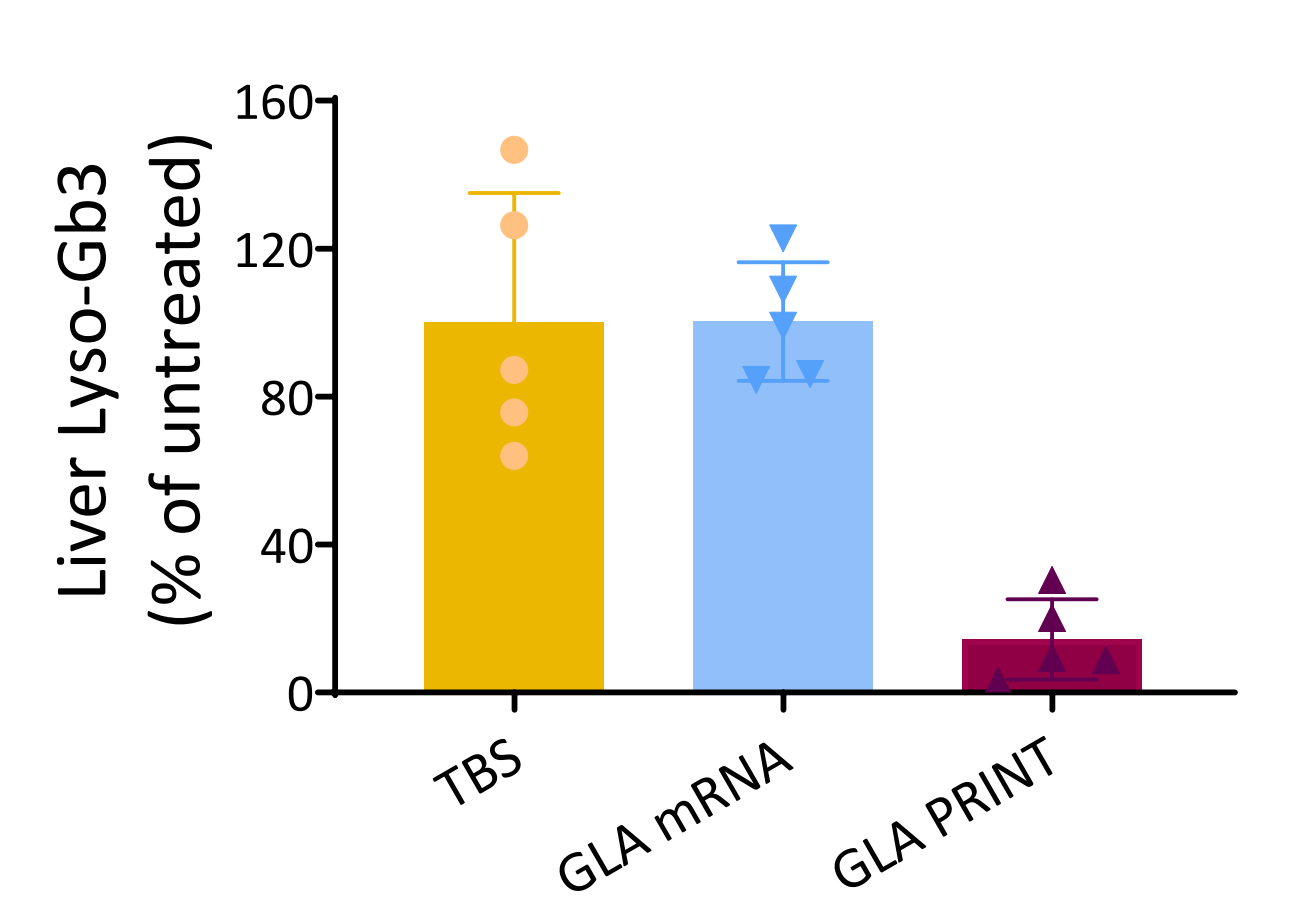
#### A. Hepatic $\alpha$ -Gal A expression by IHC



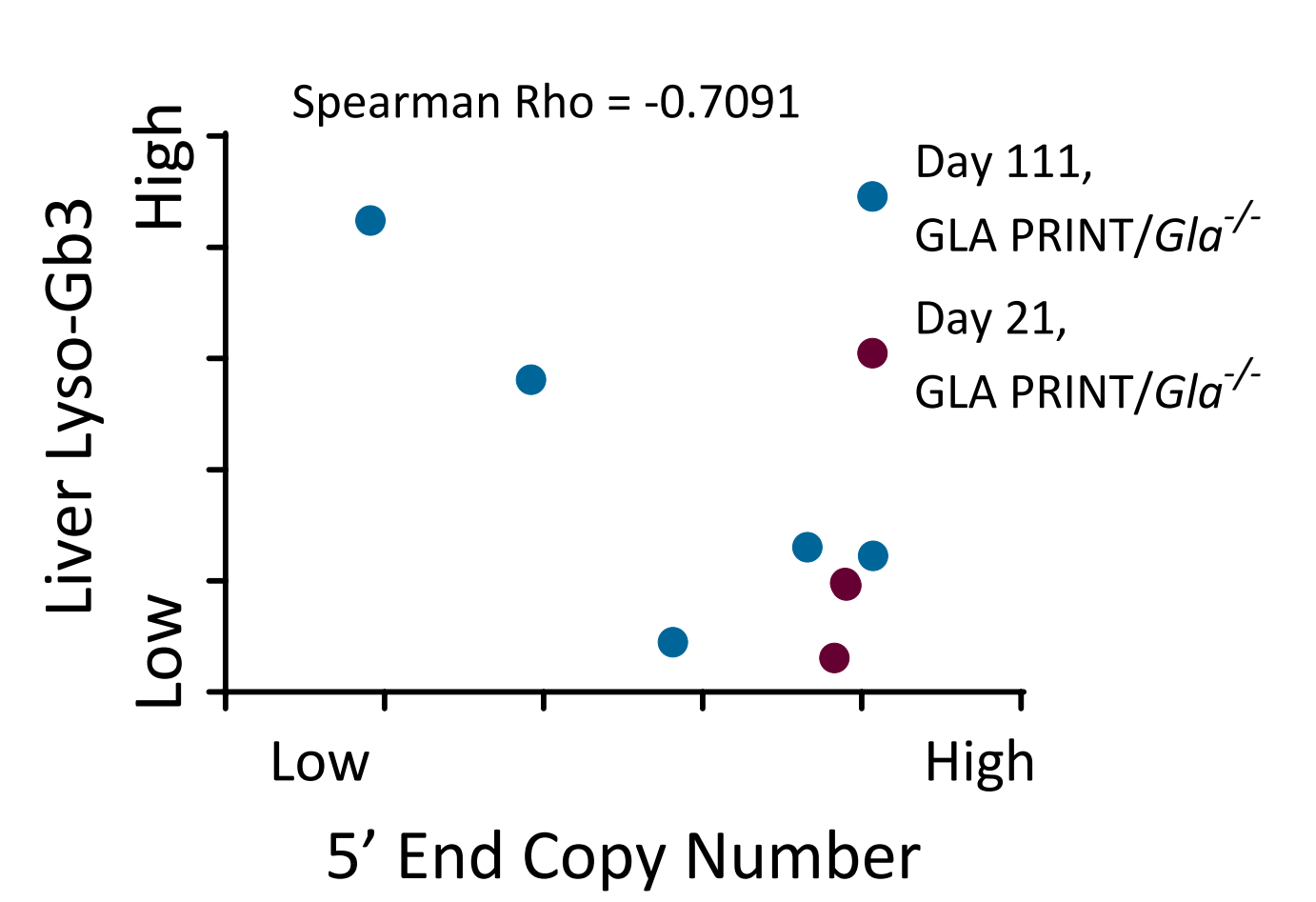
#### C. Liver $\alpha$ -Gal A activity



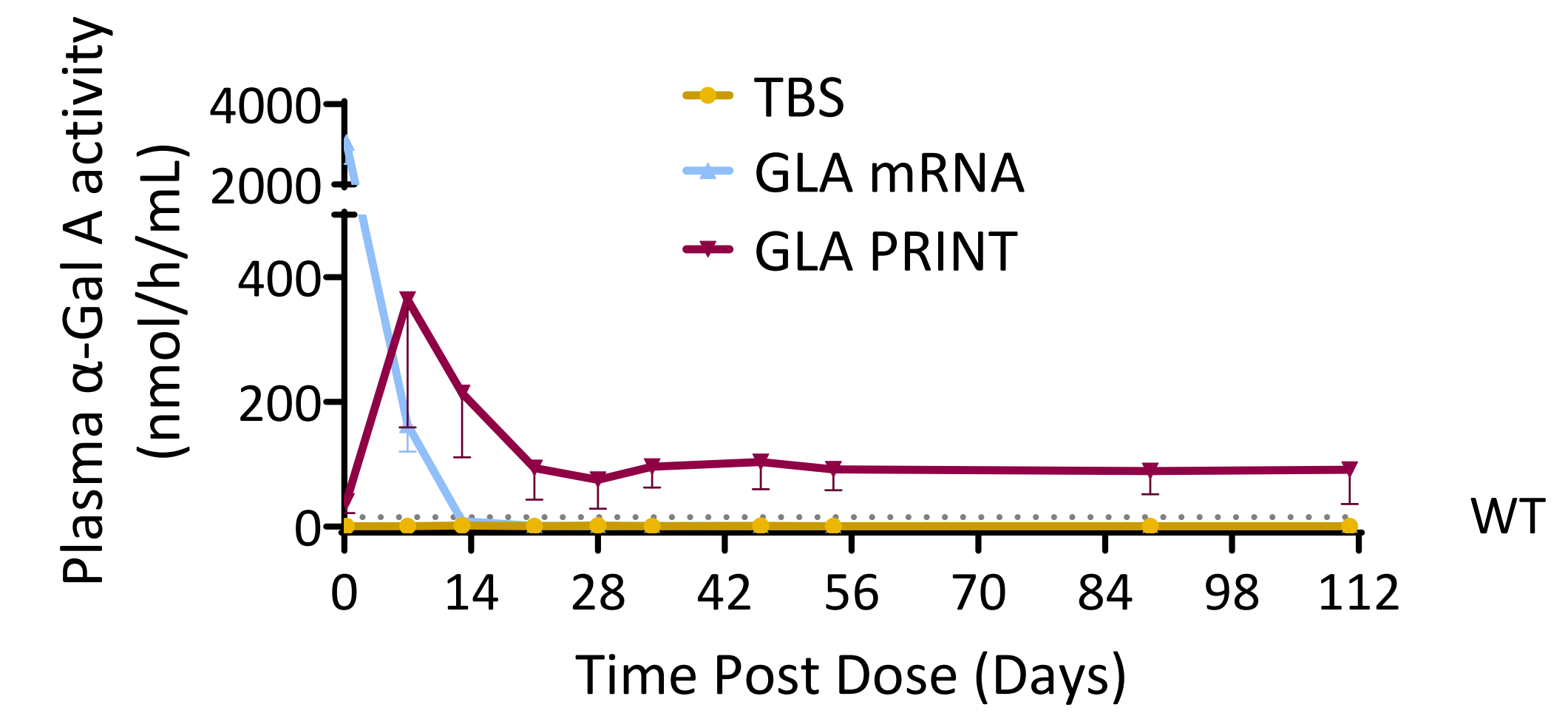
#### B. Liver Lyso-Gb3 levels



#### D. Correlation: ddPCR & Lyso-Gb3

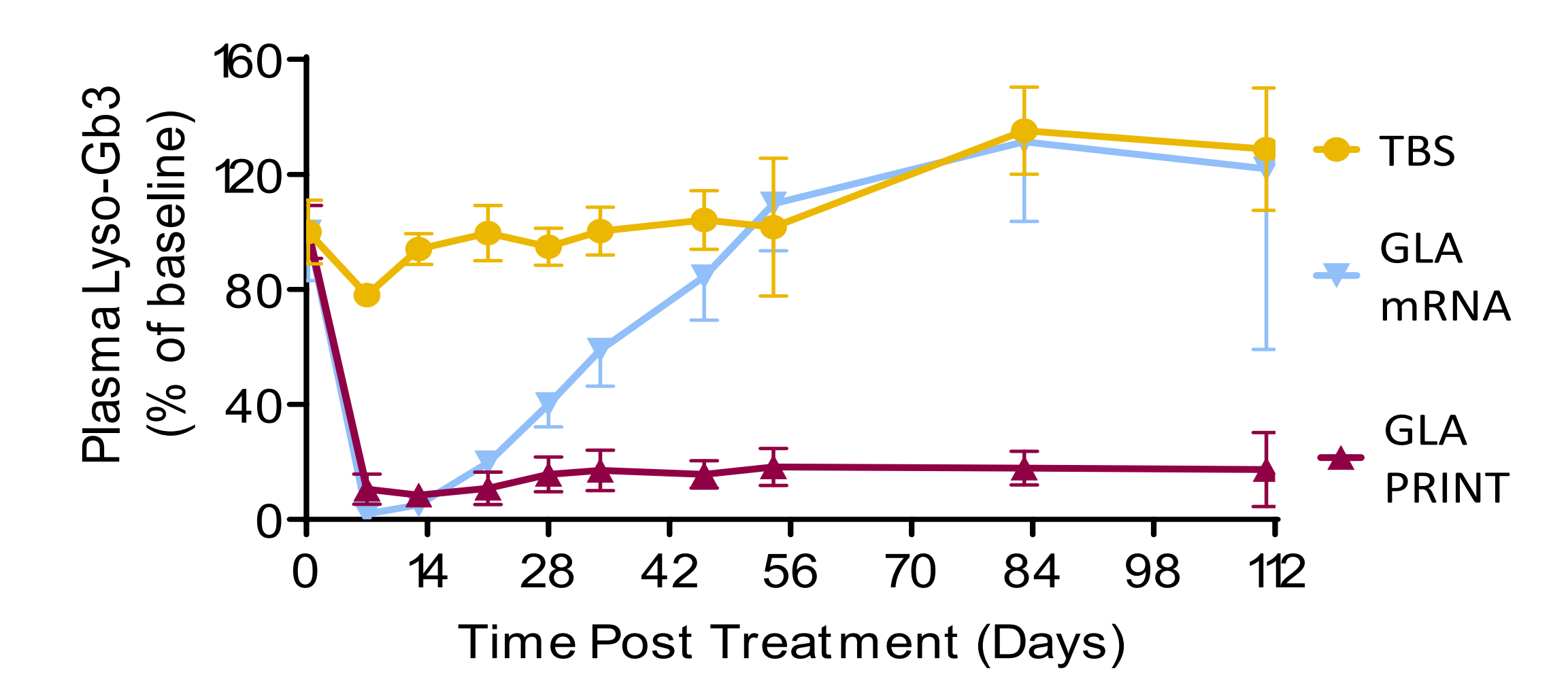


### 2. Hepatic *GLA* insertion provides sustained, supra-physiological levels of $\alpha$ -Gal A activity in plasma

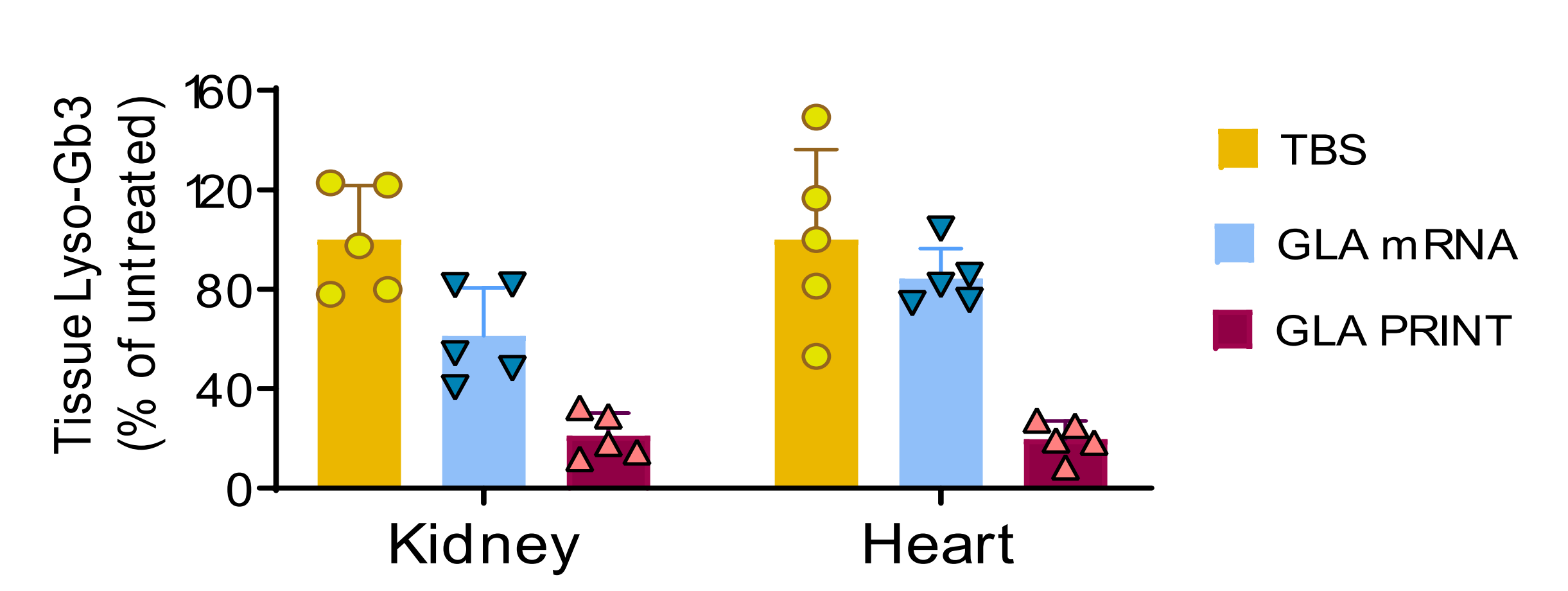


### 3. Durable systemic and significant key tissue lyso-Gb3 reduction

#### A. Plasma Lyso-Gb3 levels



#### B. Tissue Lyso-Gb3 levels



- Significantly reduced kidney and heart lyso-Gb3 is consistent with cross-correction from liver-produced  $\alpha$ -Gal A

## Conclusions

- Administration of a single dose of PRINT *GLA* reagents in a Fabry mouse model drove durable, supraphysiologic plasma  $\alpha$ -Gal A activity and robust plasma and tissue lyso-Gb3 reduction. This demonstrates the positive therapeutic impact of liver-derived PRINTed  $\alpha$ -Gal A. This suggests PRINT can generate a durable, RNA-based gene-insertion therapy for Fabry disease.