


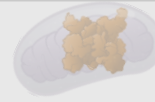






# Glycogen storage disease type 1a (GSD1a) (mRNA-3745)

Last updated: May 8, 2019

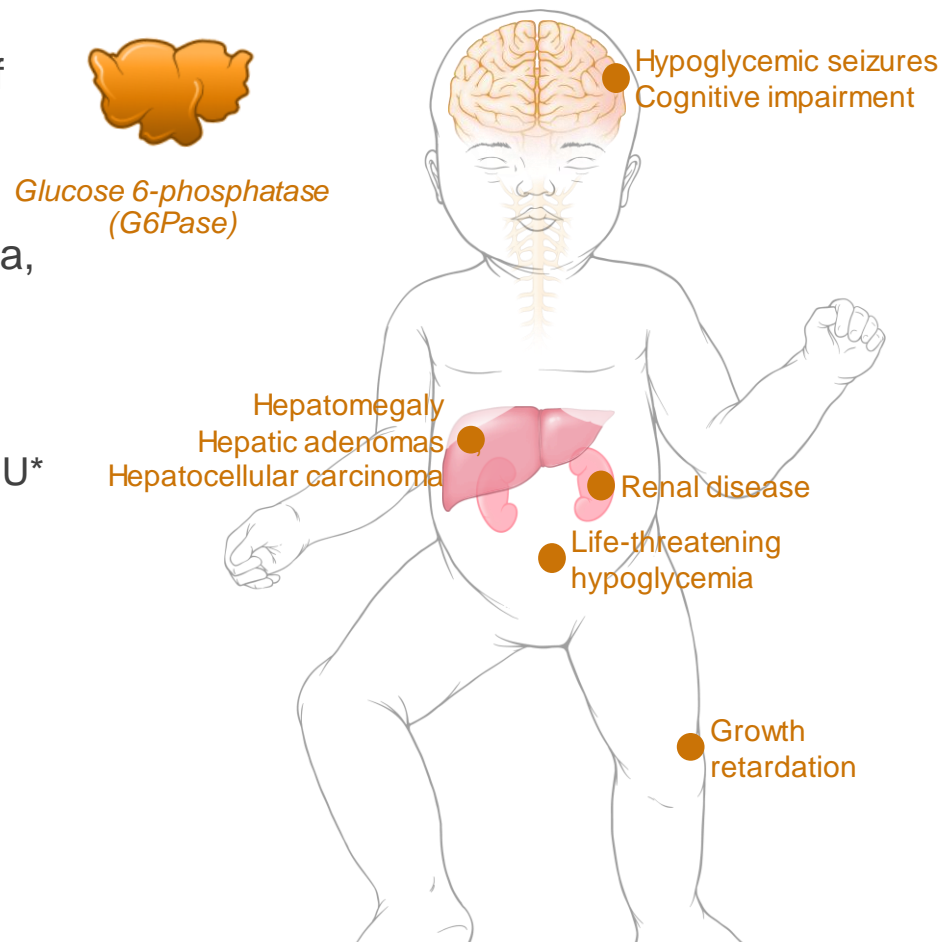
Modality	Program #	Program Indication		Preclinical development	Phase 1	Phase 2	Phase 3 and commercial	Moderna rights
 Systemic intracellular therapeutics	mRNA-3704	MUT <i>Methylmalonic acidemia, MMA</i>						Worldwide
	mRNA-3927	PCCA+PCCB <i>Propionic acidemia, PA</i>						Worldwide
	mRNA-3283	PAH <i>Phenylketonuria, PKU</i>						Worldwide
	<b>mRNA-3745</b>	G6Pase <i>Glycogen storage disease type 1a, GSD1a</i>						Worldwide

**mRNA-3745 nominated as fourth systemic intracellular therapeutics DC**

# Glycogen storage disease type 1a (GSD1a) overview

## New intracellular therapeutics DC – mRNA-3745

- GSD1a is a rare inherited metabolic disease resulting from a deficiency in the metabolism of glucose, due to mutations within the enzyme glucose 6-phosphatase, G6Pase
- **Disease burden:** Life-threatening hypoglycemia, long-term liver & kidney damage
- **Target population:** Incidence of ~1:100k live births
  - 2,500 patients in US\*, and >4,000 patients in the EU\*
- Standard of care:
  - Strict diet control
  - Frequent consumption of uncooked cornstarch to improve hypoglycemia



**Moderna concept: IV-administered mRNA encoding G6Pase enzyme to restore deficient or defective intracellular enzyme activity**

\*Based on estimated incidence of 1:100,000

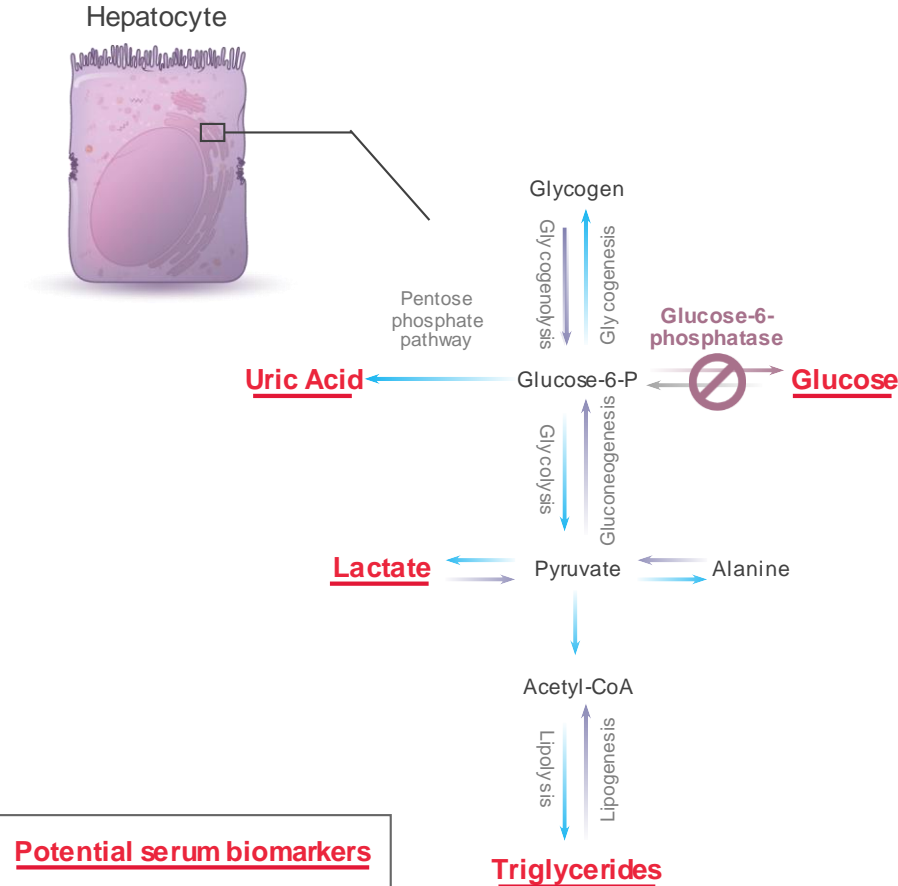
Slide 2

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# Glycogen storage disease type 1a (GSD1a) etiology

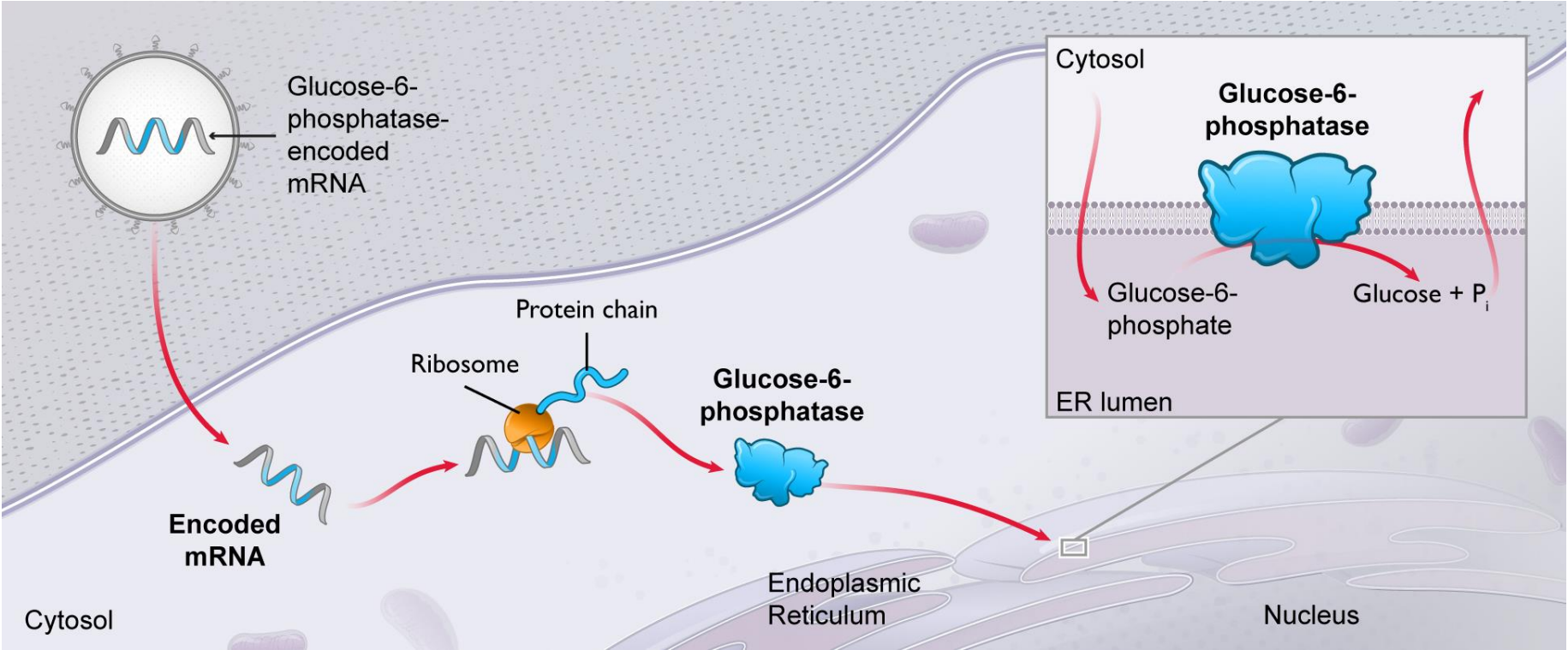
## Defect in G6PC gene disrupts glucose metabolism pathways



- Missing or defective G6Pase leads to:
  - Hypoglycemia
  - Lactic acidemia
  - Hyperlipidemia
- Metabolite buildup associated with hepatomegaly, hepatocellular adenomas, and higher risk of liver cancer
- Restoring G6Pase activity should increase blood glucose levels, decrease uric acid, lactic acid, triglyceride levels

# Glycogen storage disease type 1a (GSD1a) (mRNA-3745)

*mRNA-encoded enzyme localized to endoplasmic reticulum*



# Glycogen storage disease type 1a (GSD1a) (mRNA-3745)

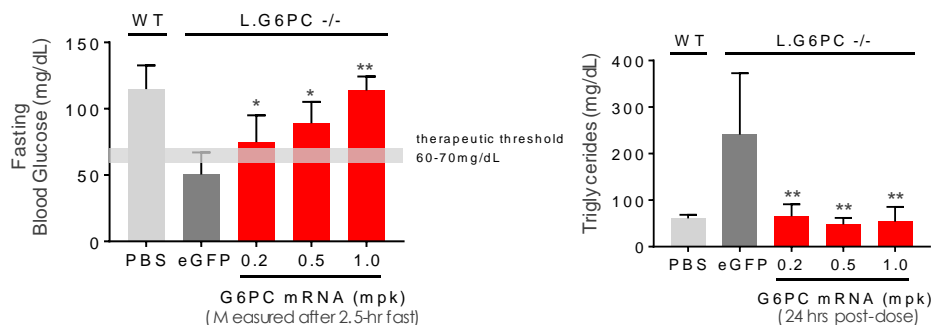
## Pre-clinical data – restoration of enzymatic activity

**Study Design:** • Animals: Liver-Specific G6PC Knockout (L.G6PC -/-)

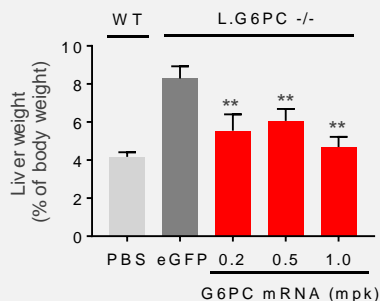
**Species:**  
**Mouse**

- Dose: 0.2, 0.5, 1.0 mpk
- Dosing Schedule: single dose
- Injection Route: IV
- Sample Size: 5-8

### Serum biomarkers after single dose of G6Pase mRNA



### Reduction in liver weight 24 hours after IV administration of G6Pase mRNA



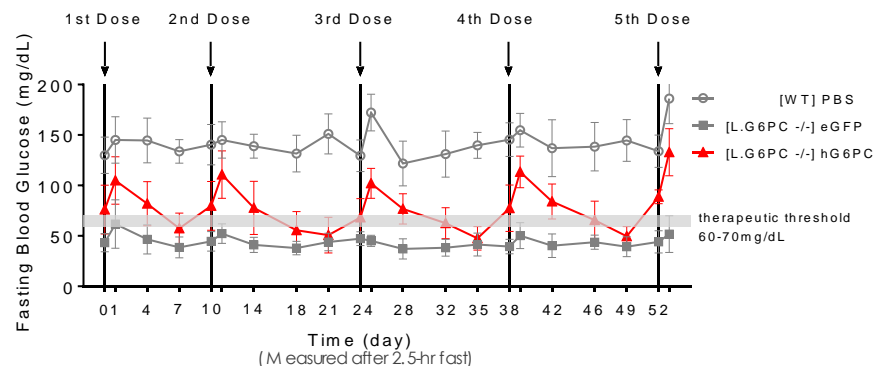
Notes: eGFP is a negative control. Asterisks based on one-way ANOVA of post-treatment vs. eGFP levels:  
\*p<0.05  
\*\*p<0.0001

**Study Design:** • Animals: Liver-Specific G6PC Knockout (L.G6PC -/-)

**Species:**  
**Mouse**

- Dose: 0.25 mpk
- Dosing Schedule: approx. every other week
- Injection Route: IV
- Sample Size: 7-9

### Restoration of blood glucose above therapeutic threshold with repeat dosing of G6Pase mRNA



*We have demonstrated preclinical proof-of-concept for G6Pase mRNA therapy in vivo studies*

# Special note regarding forward-looking statements

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