Single, Systemic Administration of BEAM-301 Mitigates Fasting Hypoglycemia and Restores Metabolic Function in a Transgenic Mouse Model of Glycogen Storage Disease Type-Ia

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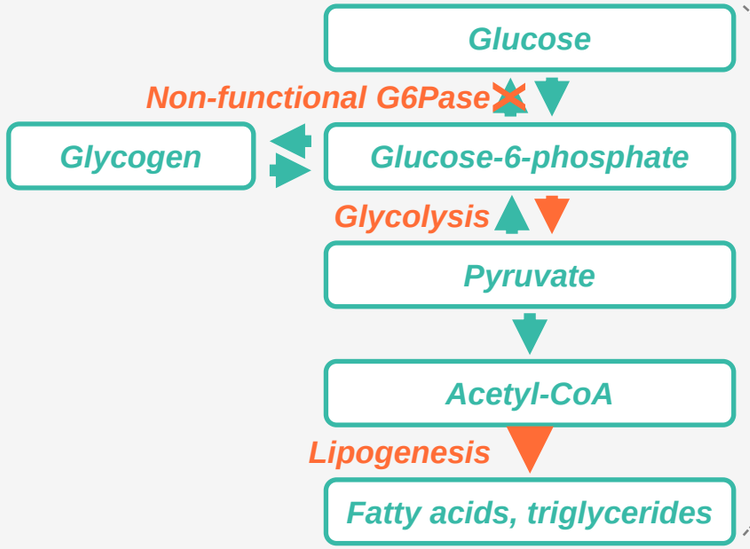
DISCLOSURE

- I am a Beam employee and shareholder

Base-editing strategy to treat Glycogen Storage Disease Type Ia

Wild type G6Pase

Non-functional G6Pase



Fasting hypoglycemia can be acutely fatal

No cure

Strict regimen of slow-release glucose required

Long-term complications include,

- ***Hyperlipidemia***
- ***Elevated lactic and uric acid***
- ***Hepatic steatosis, HCC***

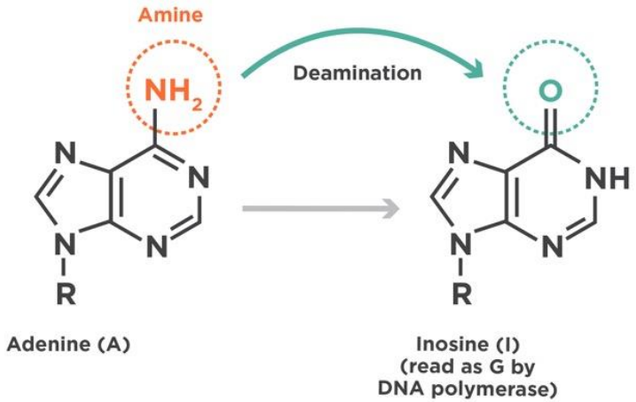
- GSDIa is a genetic disease caused by mutations in the *G6PC* gene encoding G6Pase, a predominantly liver-expressed enzyme vital to glucose metabolism
- Beam's base editing technology has the potential to permanently correct these mutations and restore regulation of glucose metabolism

Base Editors Generate Permanent and Predictable Single Nucleotide Substitutions

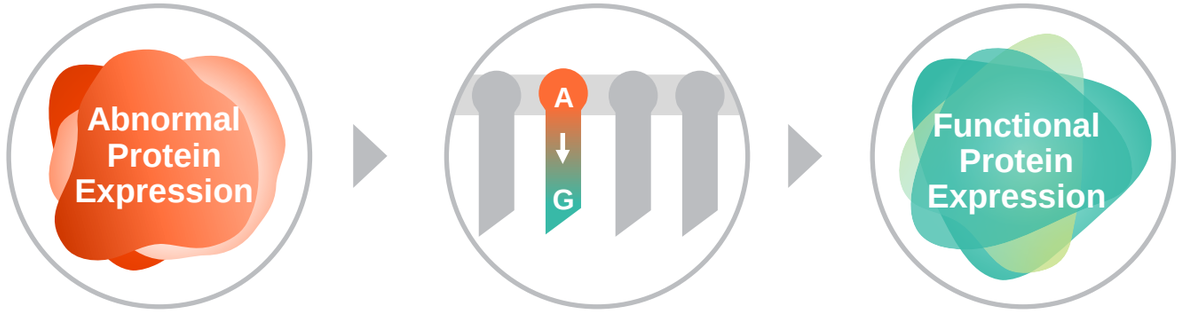
Base editor binds the target DNA and exposes a narrow editing window

A-to-G base editor (“ABE”)

Deaminase chemically modifies target base, A>G edit made permanent by DNA repair/replication

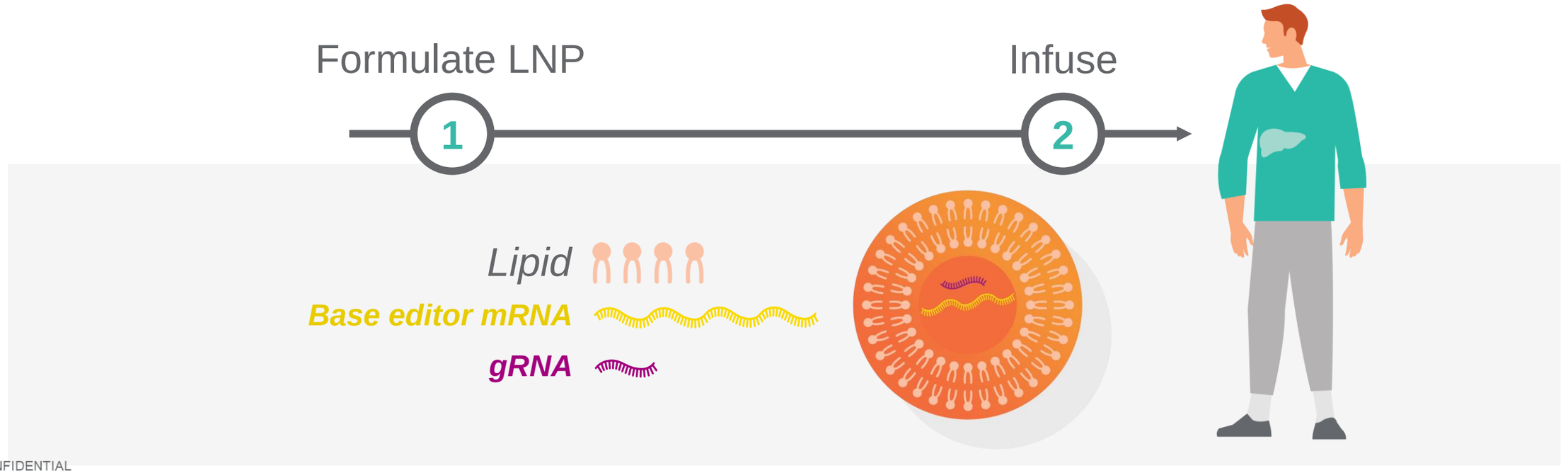


Gene Correction – Direct repair of point mutations to restore gene function

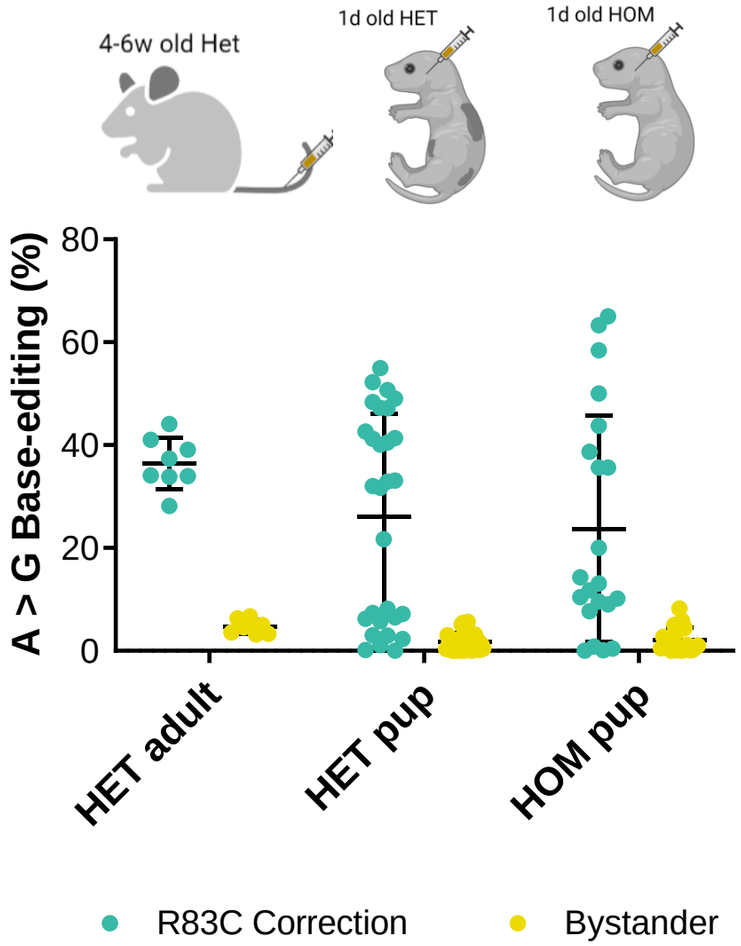


What is BEAM-301?

- **BEAM-301 is an *in vivo* base-editing development candidate**
- BEAM-301 is a lipid nanoparticle (LNP) formulation containing a mRNA encoding an adenine base editor and a gRNA that directs the correction of the *G6PC-p.Arg83Cys* variant
- The mRNA and gRNA are encapsulated in LNPs, which protect and transport them to hepatocytes



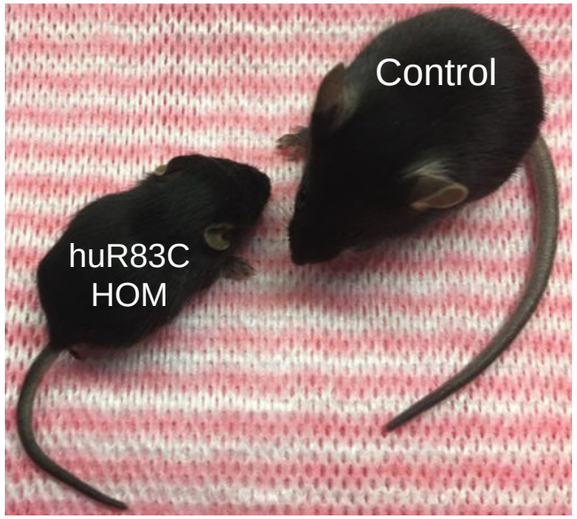
Single BEAM-301 dose yields robust rate of R83C correction in livers of transgenic huR83C mouse model

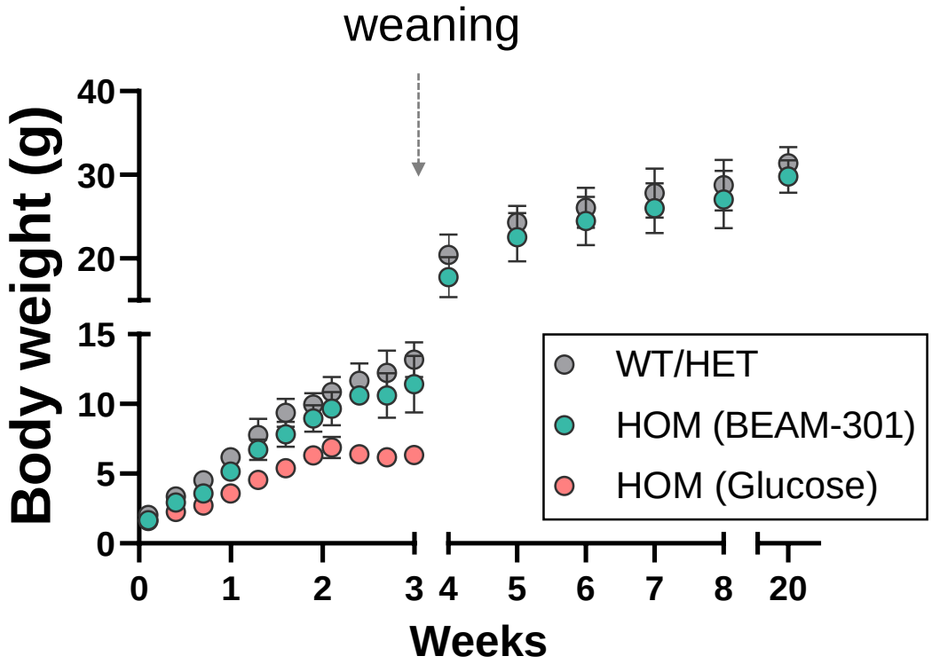


- The huR83C GSD-Ia mouse model harbors human *G6PC-p.Arg83Cys* transgene in place of mouse *G6PC*
- BEAM-301 administered via tail vein (adult) or temporal vein (newborn) in heterozygous or homozygous huR83C mice (due to pre-weaning lethality in homozygotes)
- **NGS analysis in total liver extracts yield**
  - **~40% base-editing efficiency** in adults
  - A range, **up to ~60%** in newborns
- Next step: Functional benefit via base-editing in newborn homozygotes

* Base-editing evaluated at 7d post dose in adults, 3wks post dose in newborns

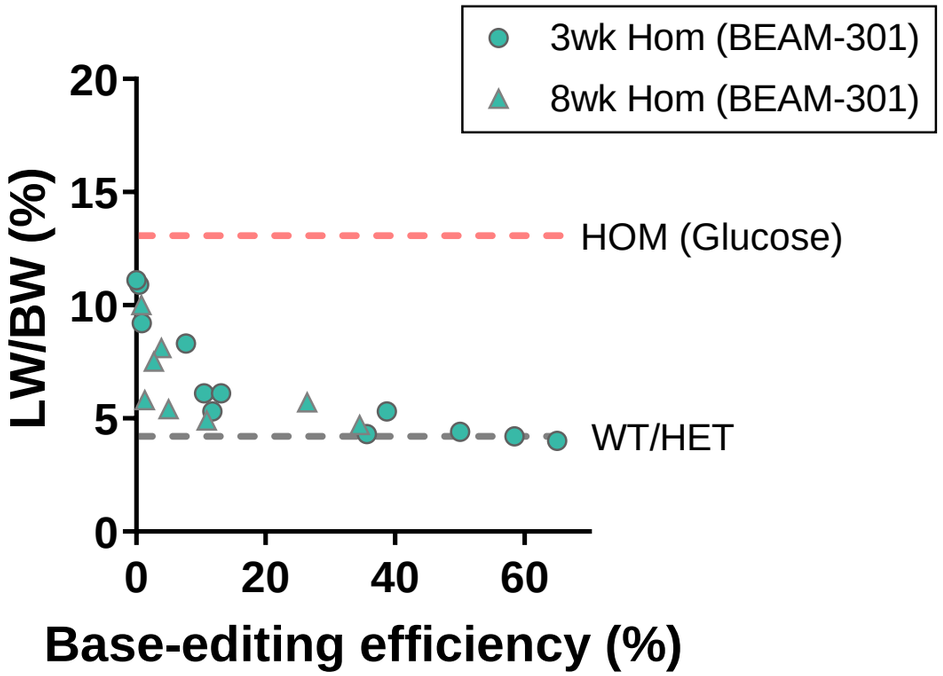
BEAM-301 improves long-term survival and restores normal growth in homozygous huR83C mice

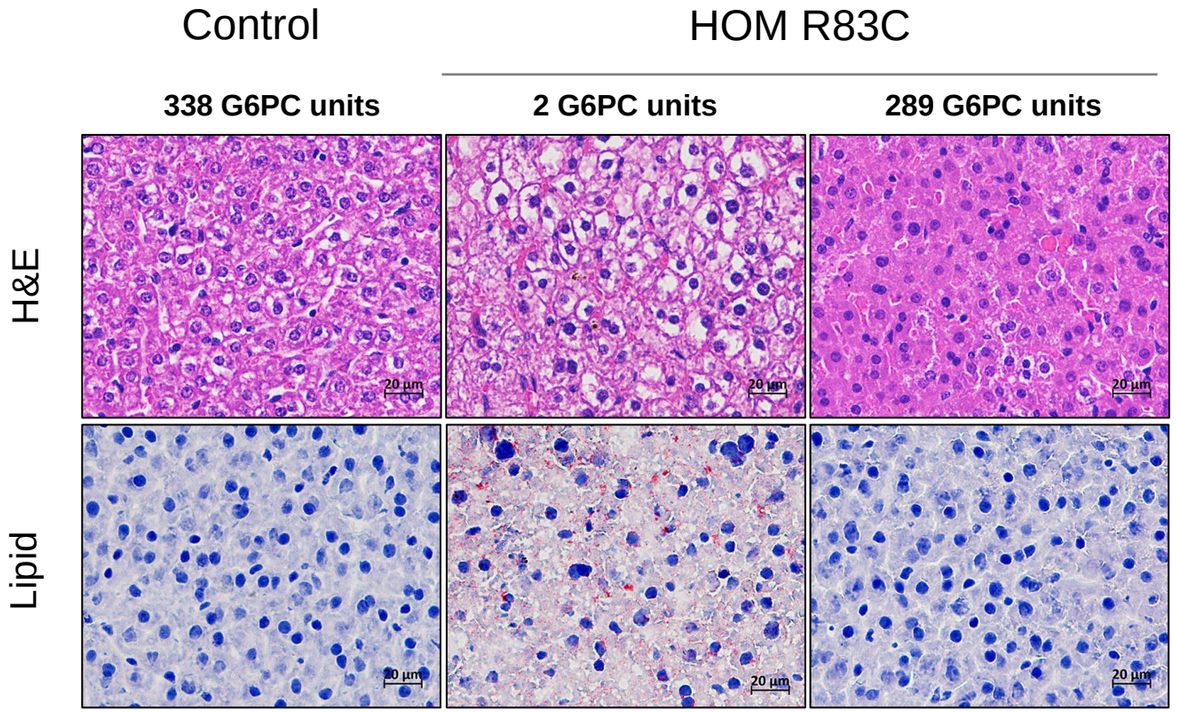




- Homozygous huR83C mice on glucose-supplementation exhibit growth impairment relative to wild-type and heterozygous littermates
- Single-dose of BEAM-301 yields **improved survival and normal growth trend**

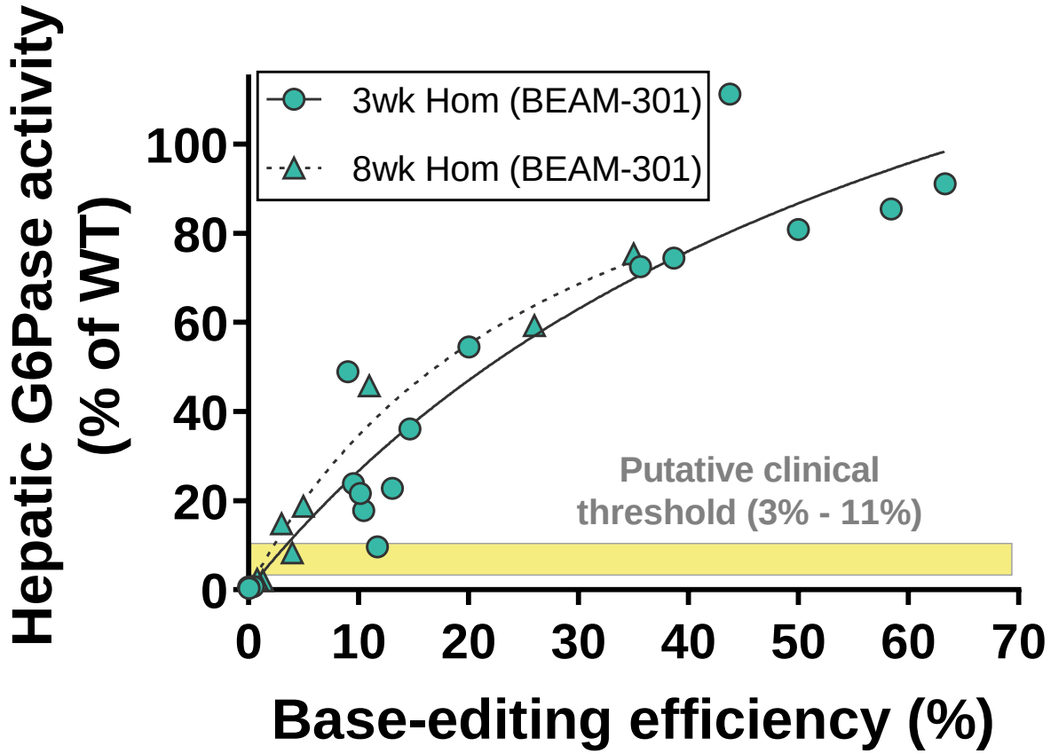
Reduction in liver size in BEAM-301-dosed homozygous huR83C mice

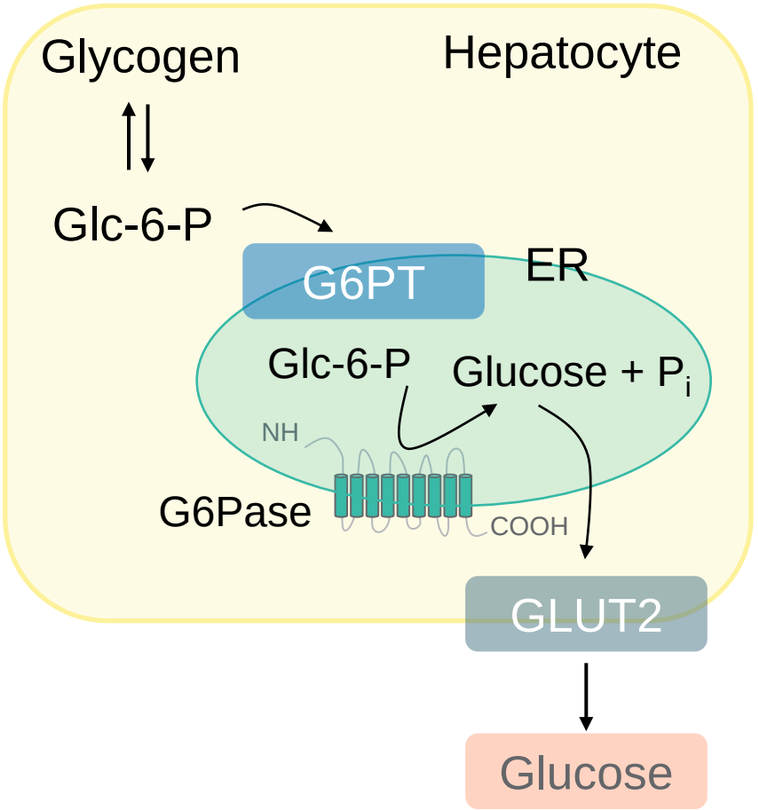




- Glucose-supplemented huR83C homozygotes exhibit enlarged livers, hepatocyte size, and elevated lipids
- BEAM-301-induced base editing is associated with **reduction in liver size and lipid deposition**

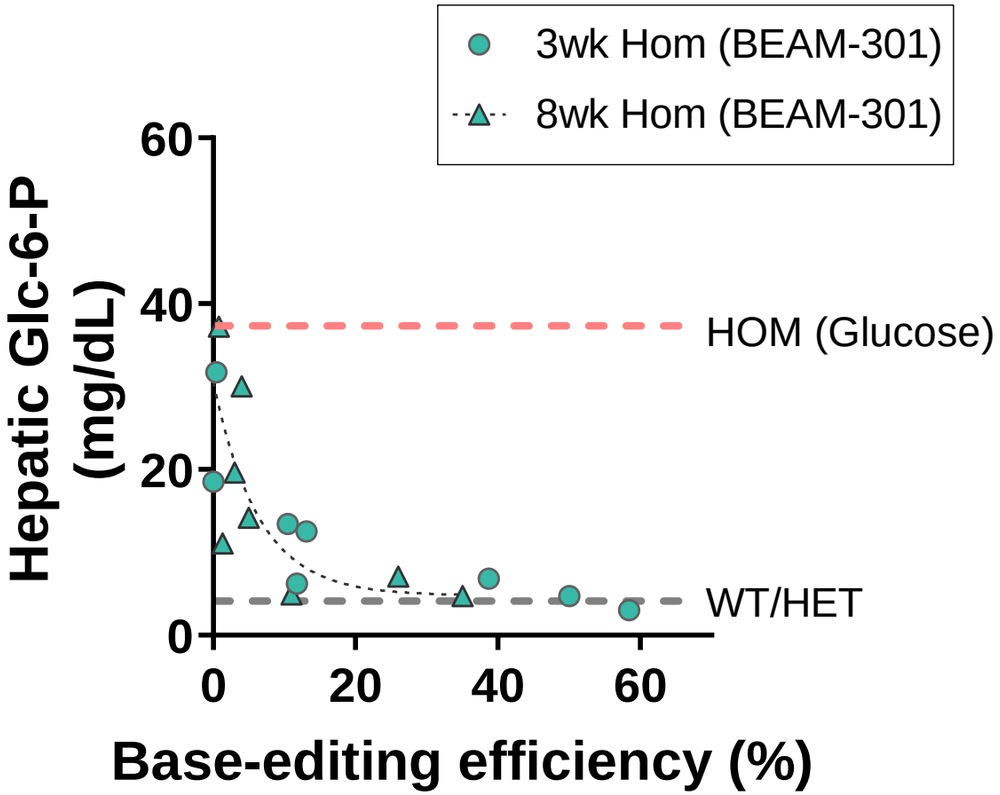
Restoration of hepatic G6Pase activity at single-digit base-editing rates for R83C correction

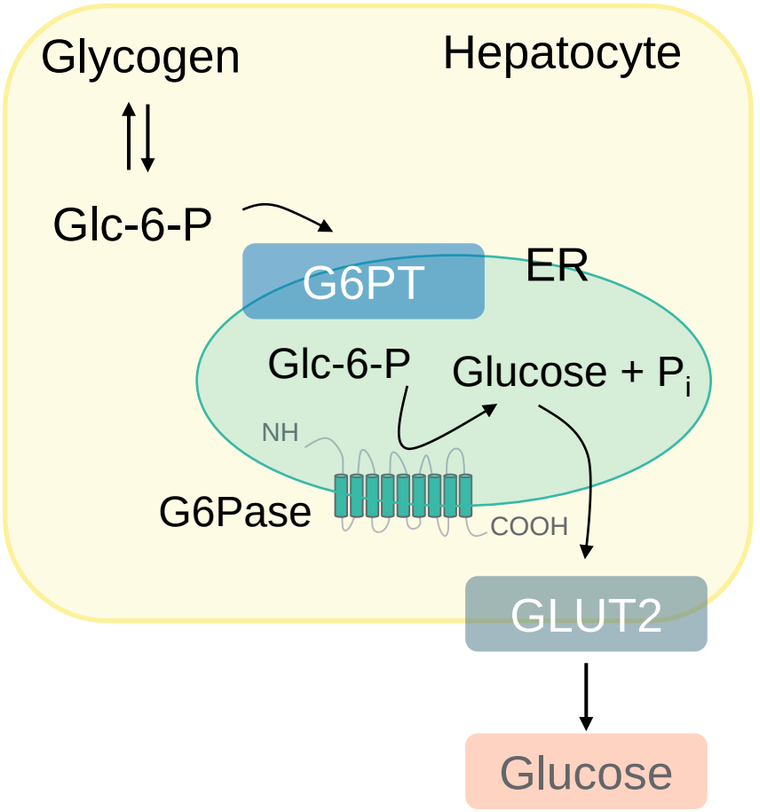




- **Restoration of G6Pase activity at clinically-relevant levels** achieved at single-digit base-editing efficiencies for R83C correction
- Durable effect; correlation maintained to early adulthood

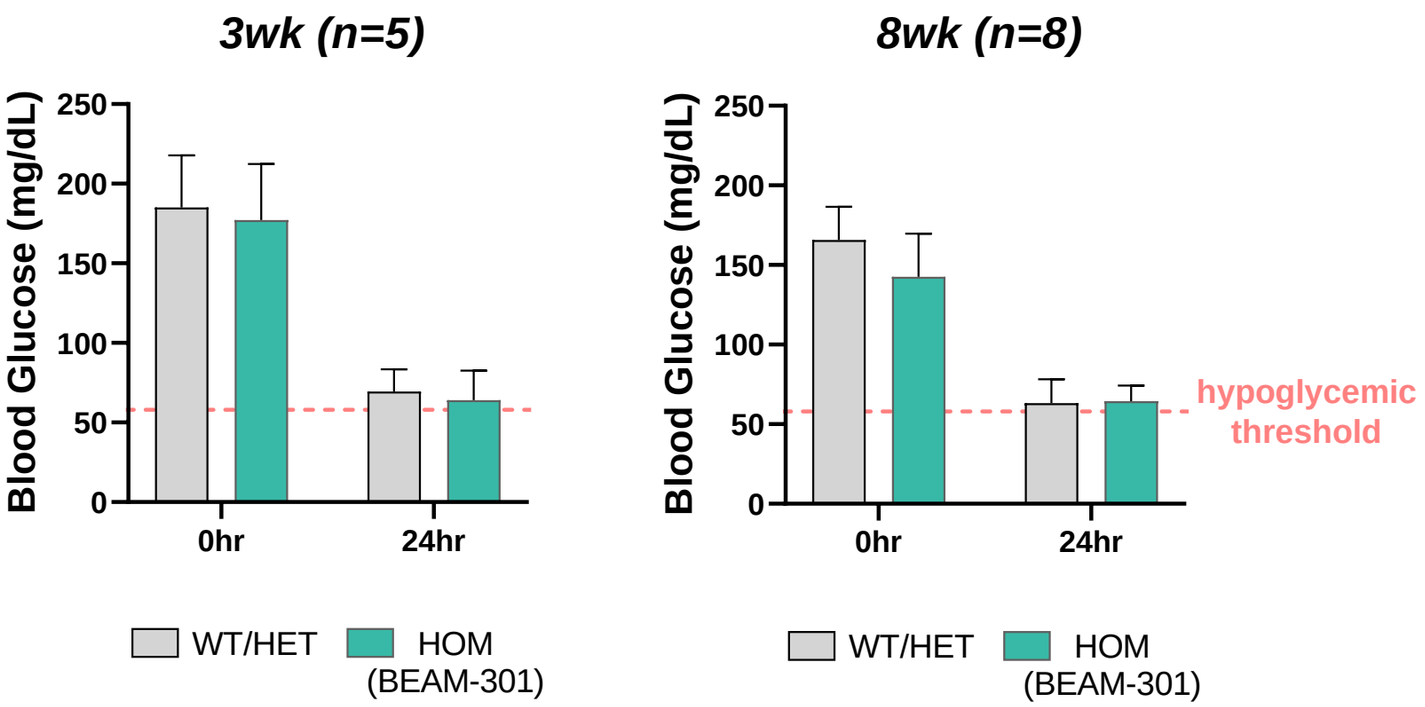
Decline in hepatic Glucose-6-Phosphate (Glc-6-P) levels at ≤10% base-editing rates for R83C correction





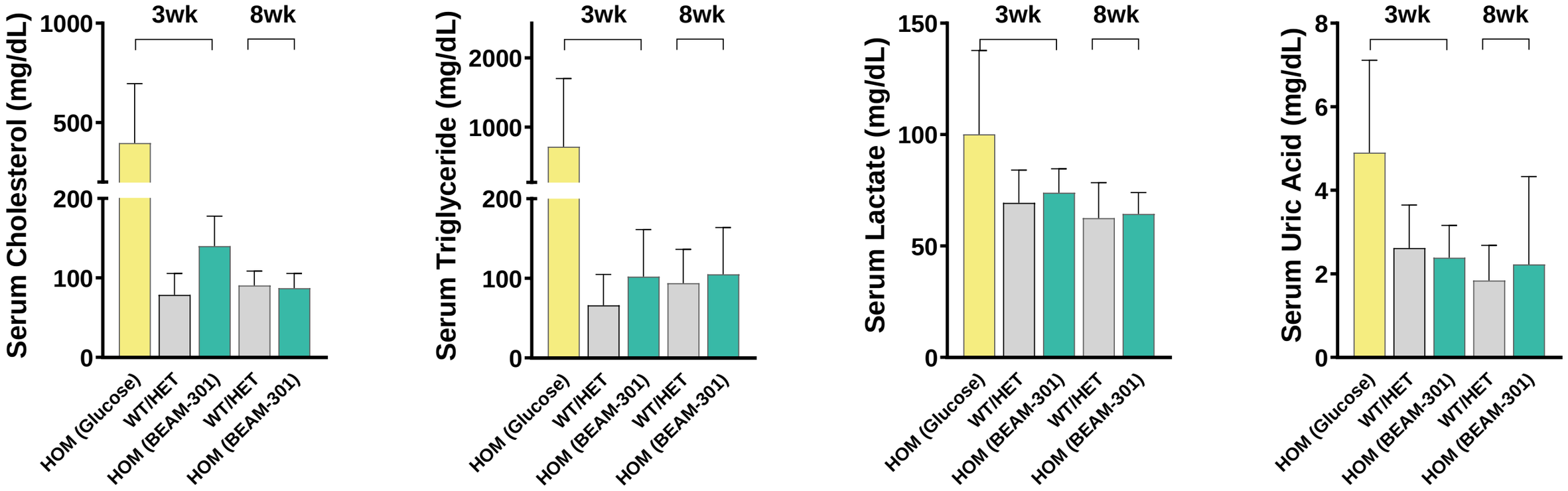
- **Decline in hepatic Glc-6-P levels**, approaching average healthy (WT) levels
- Will restoration of glucose homeostasis mitigate fasting hypoglycemia? Restore serum metabolites?

Homozygous huR83C mice survive a 24h fasting challenge more than 8 weeks after BEAM-301 dose



- **100% of homozygous mice survive a 24-hr fasting challenge, some with as little as 1% base-editing**
- Blood glucose levels maintained above hypoglycemic threshold, at levels of healthy control animals
- Ongoing long-term studies include **successful fasting challenge at 20wk and 35wk** (data not shown)

Durable maintenance of near-normal serum metabolites in BEAM-301 treated homozygous huR83C mice



- Glucose-supplemented huR83C homozygotes exhibit elevated serum metabolites
- Through early adulthood, huR83C homozygotes administered BEAM-301 exhibit **near-normal secondary serum metabolites** (including subjects with single-digit base-editing rates)

Summary and Next Steps

BEAM-301 Preclinical Pharmacology

- Up to **~60% base-editing efficiency**
- **Long-term survival**, with normal body weight and liver weight
- Restoration of **clinically-relevant hepatic G6Pase activity**
- **Survival through a 24hr fast with single-digit base-editing rates**
- **Normal secondary serum metabolites** in adult mice

Preliminary low-risk off-target profile (ongoing)

- Guide-dependent off-target base editing detected at 3 intergenic sites in primary human hepatocytes (<0.9% editing at a saturated dose)
- No evidence of upregulated guide-independent A>G mutagenesis in WGS of clonally expanded immortalized cells

Next steps

- Ongoing durability studies in BEAM-301-dosed huR83C mice
- Continued off-target evaluation
- IND-enabling studies

Thank You

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