A Single, Systemic Administration of BEAM-301 Mitigated Fasting Hypoglycemia One Year after Dosing in a Transgenic Mouse Model of Glycogen Storage Disease Type-Ia

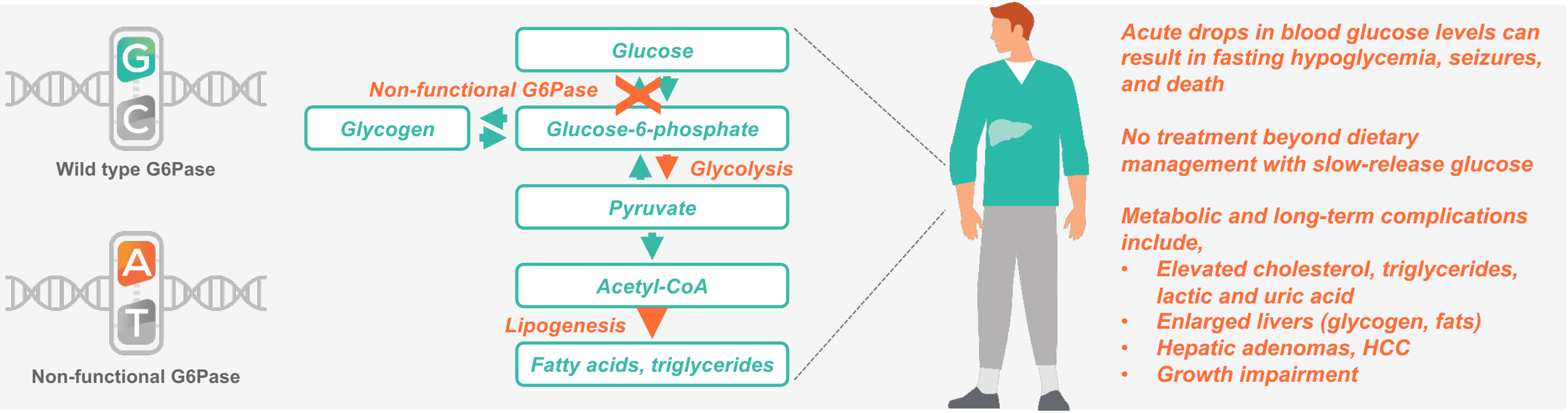
Yvonne Aratyn-Schaus

October 25, 2023

DISCLOSURE

- I am a Beam employee and shareholder

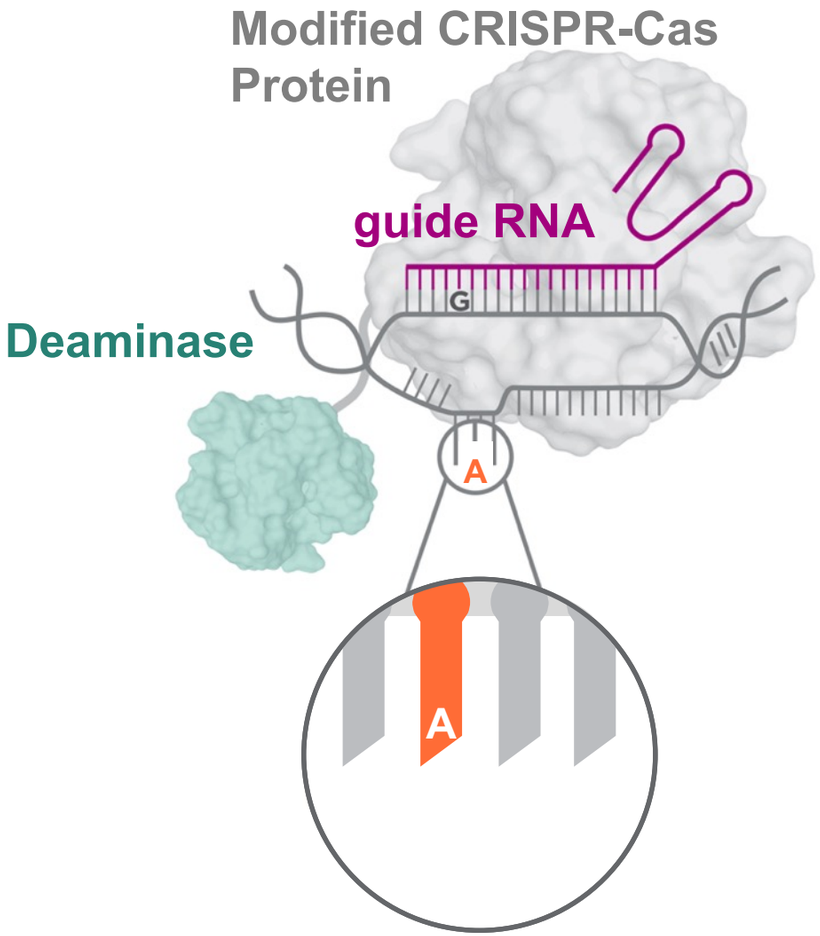
Base-editing strategy to treat a severe pathogenic variant underlying Glycogen Storage Disease Type Ia



- GSDIa is a genetic disease caused by mutations in the *G6PC* gene encoding G6Pase, a predominantly liver-expressed enzyme vital to glucose metabolism
- *G6PC-p.Arg83Cys* (R83C) is a prevalent pathogenic variant associated with severe manifestations of GSDIa
- Beam's base-editing technology has the potential to permanently correct this mutation and restore glucose metabolism

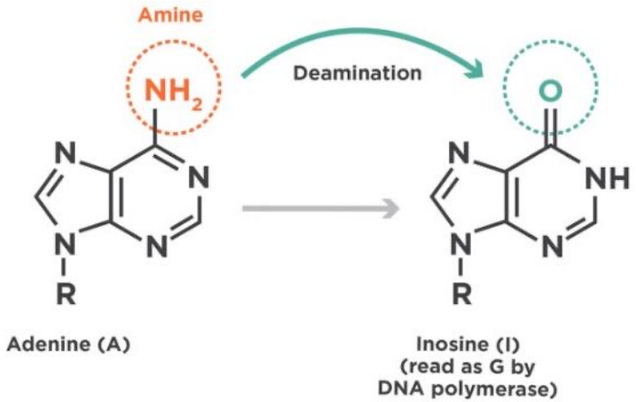
Base Editors Generate Permanent and Predictable Single Nucleotide Substitutions

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

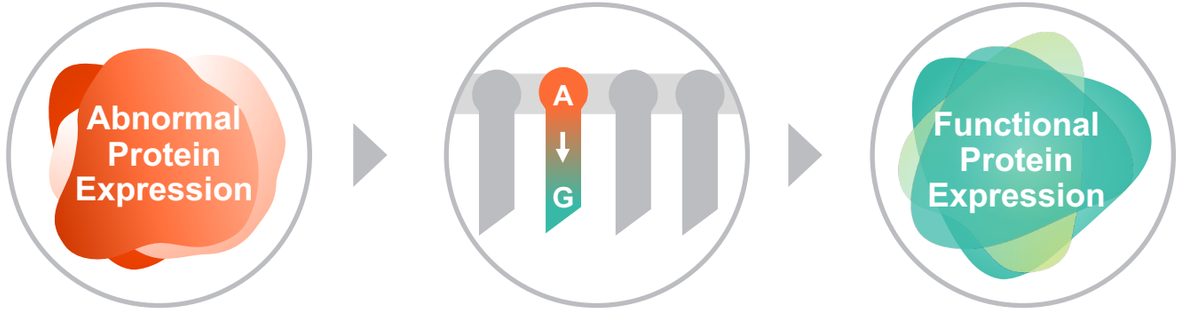


Deaminase chemically modifies target base, A>G edit made permanent by DNA repair/replication

A-to-G base editor ("ABE")

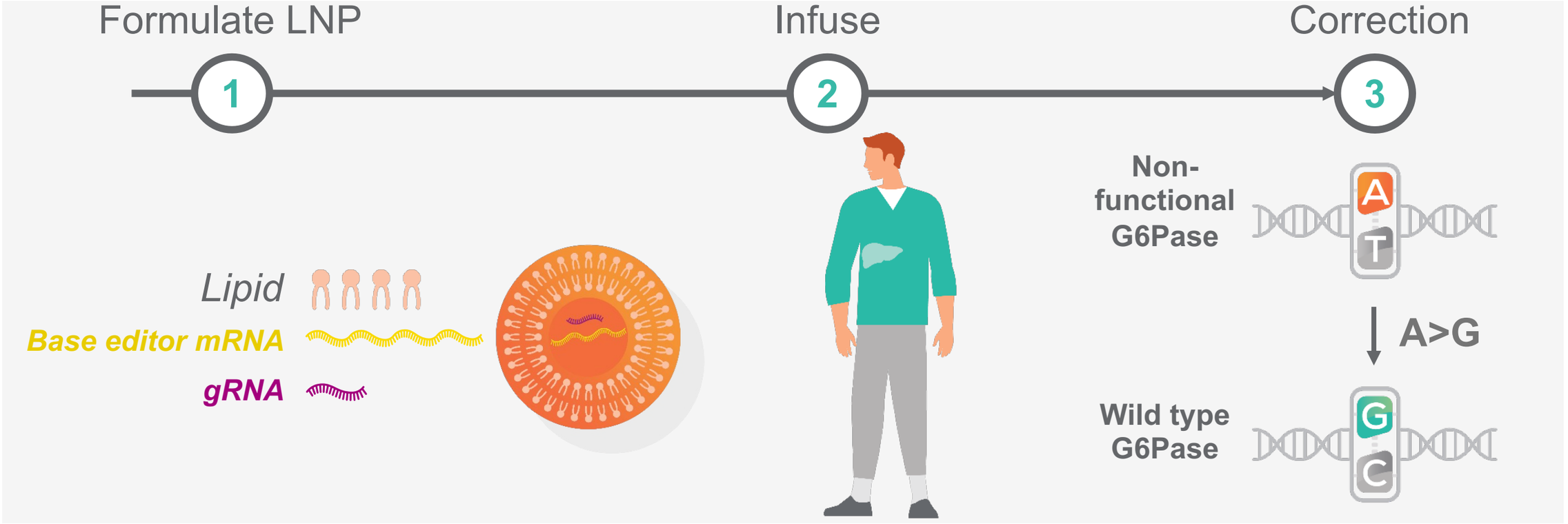


Gene Correction – Direct repair of point mutations to restore gene function

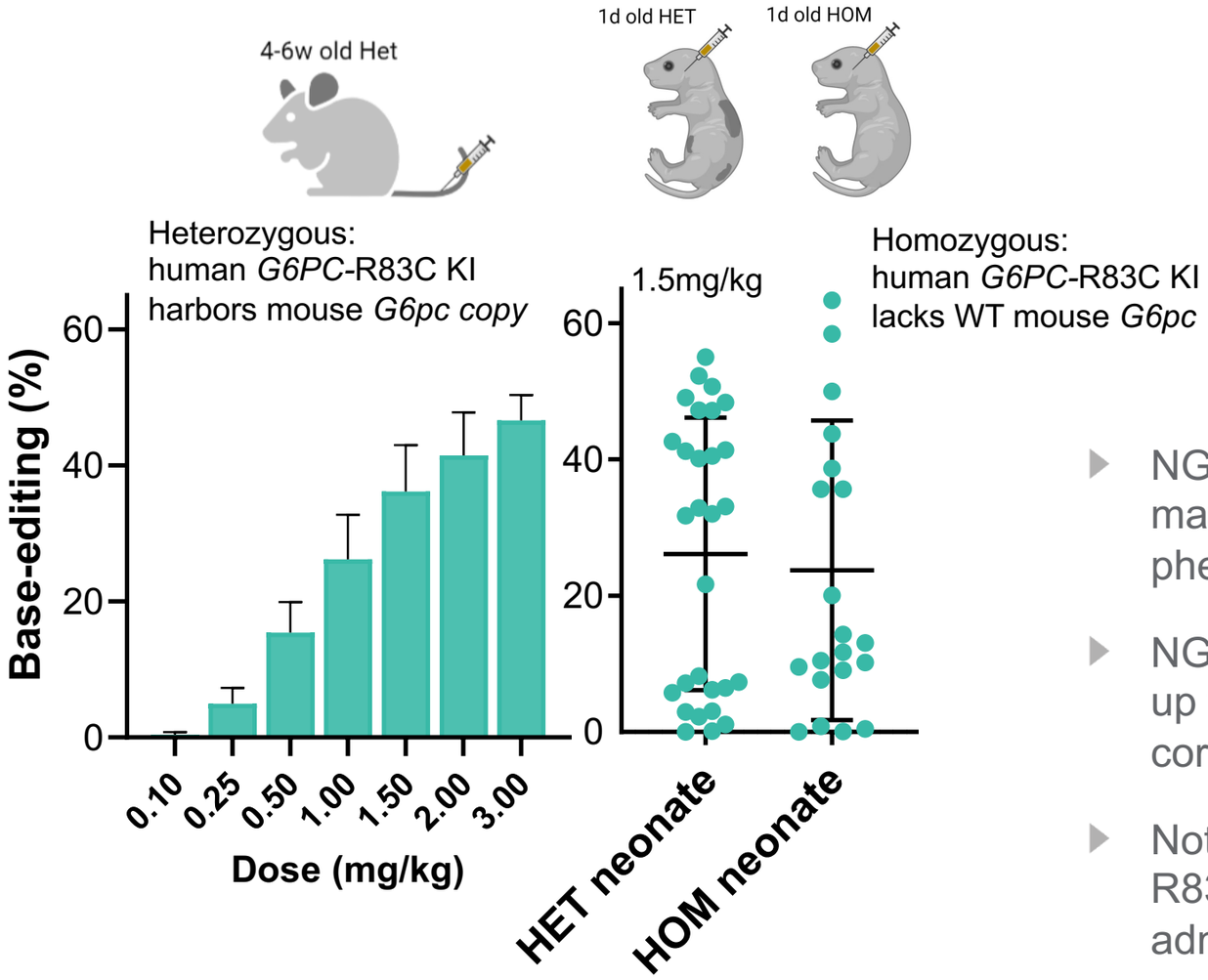


What is BEAM-301?

- **BEAM-301 is an *in vivo* base-editing development candidate** composed of an (LNP) formulation containing a mRNA encoding an adenine base editor and a gRNA that directs the correction of the *G6PC*-p.Arg83Cys (R83C) variant
- The mRNA and gRNA are encapsulated in LNPs, which protect and transport them to hepatocytes



Single BEAM-301 dose yields up to ~60% editing for R83C correction in livers of transgenic huR83C mouse model



Target

PAM

5′ CCA GTA TGG ACA CTG TCC AAA GAG AAT 3′

3′ GGT CAT ACC TGT GAC AGG TTT CTC TTA 5′

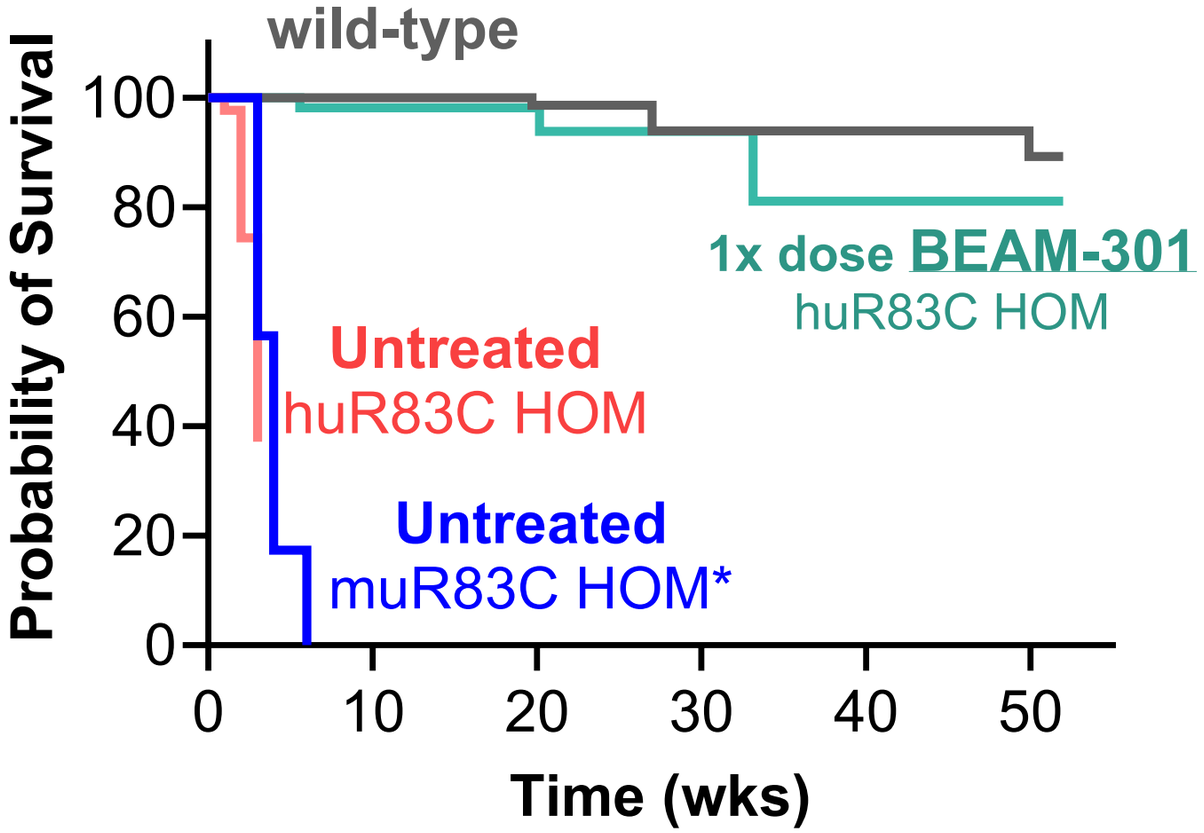
C

83

- NGS analysis in heterozygous huR83C mice (HET) yields ~45% max editing for proof-of-concept, although model lacks GSDIa phenotype
- NGS analysis in homozygous huR83C GSD-Ia mice (HOM) yields up to **~60% base-editing efficiency** in neonates; model allows for correlation of editing to pharmacology
- Note that temporal vein (vs. tail vein) administration optimized in R83C HOM neonates given post-natal lethality; Route of administration hypothesized to effect spread in editing outcomes

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

Single dose of BEAM-301 significantly improves long-term survival of huR83C homozygous mice

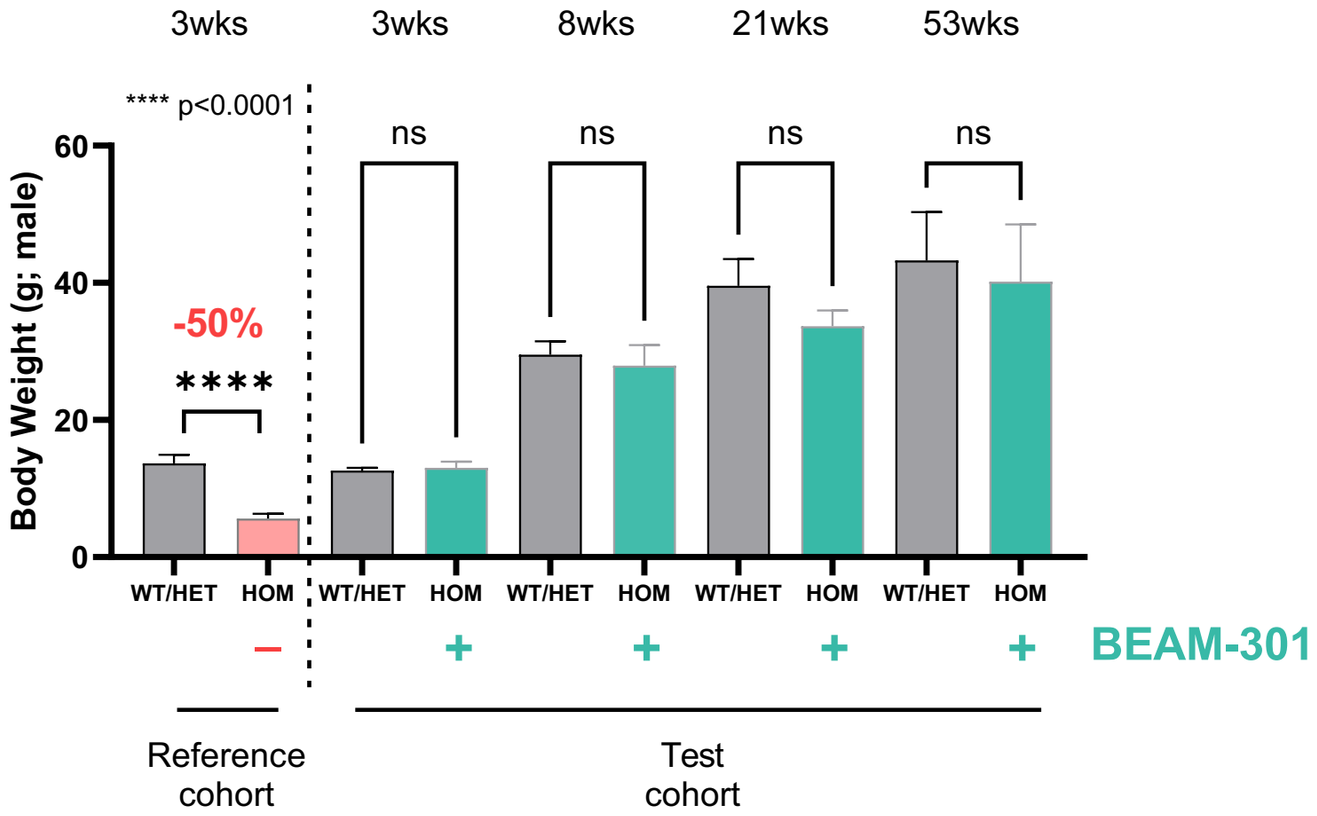


* Arnaoutova et al., Mol. Therapy, 2021

- Untreated mice that are homozygous for R83C die within several weeks of age
- Single dose of BEAM-301 **significantly improves long-term survival** of huR83C homozygous mice (>1yr!)

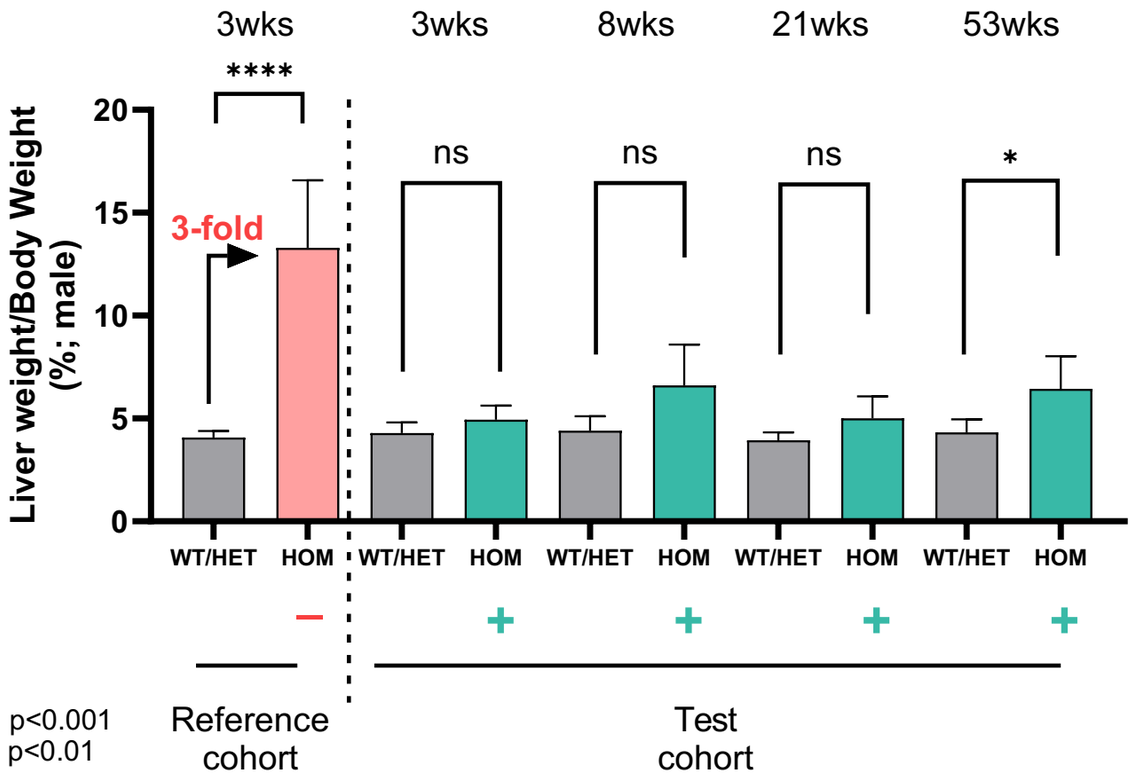
Normal body weight maintained over a year after a single dose of BEAM-301

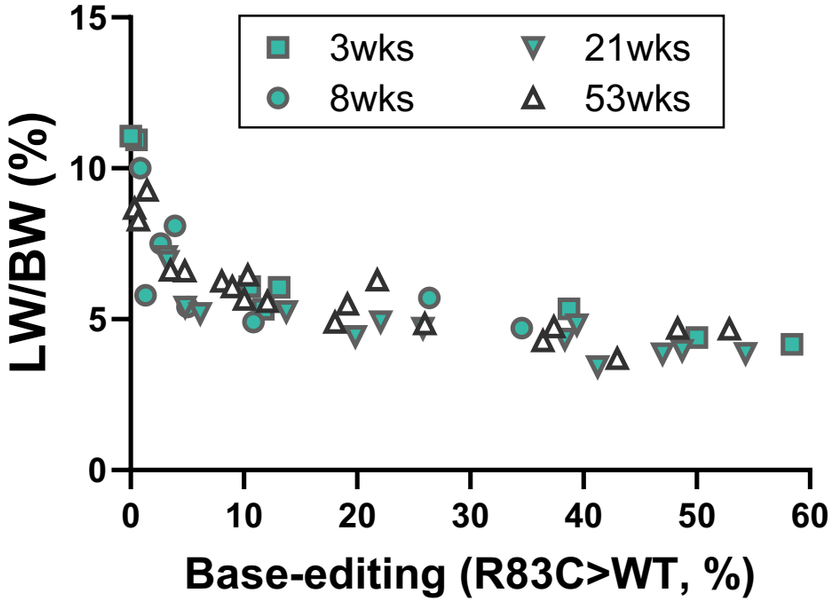
Reference cohorts: Untreated



- Untreated homozygous huR83C mice exhibit significant growth impairment relative to control littermates
- Single-dose of BEAM-301 can **recover normal gain in body weight** in the short-term and to at least one year

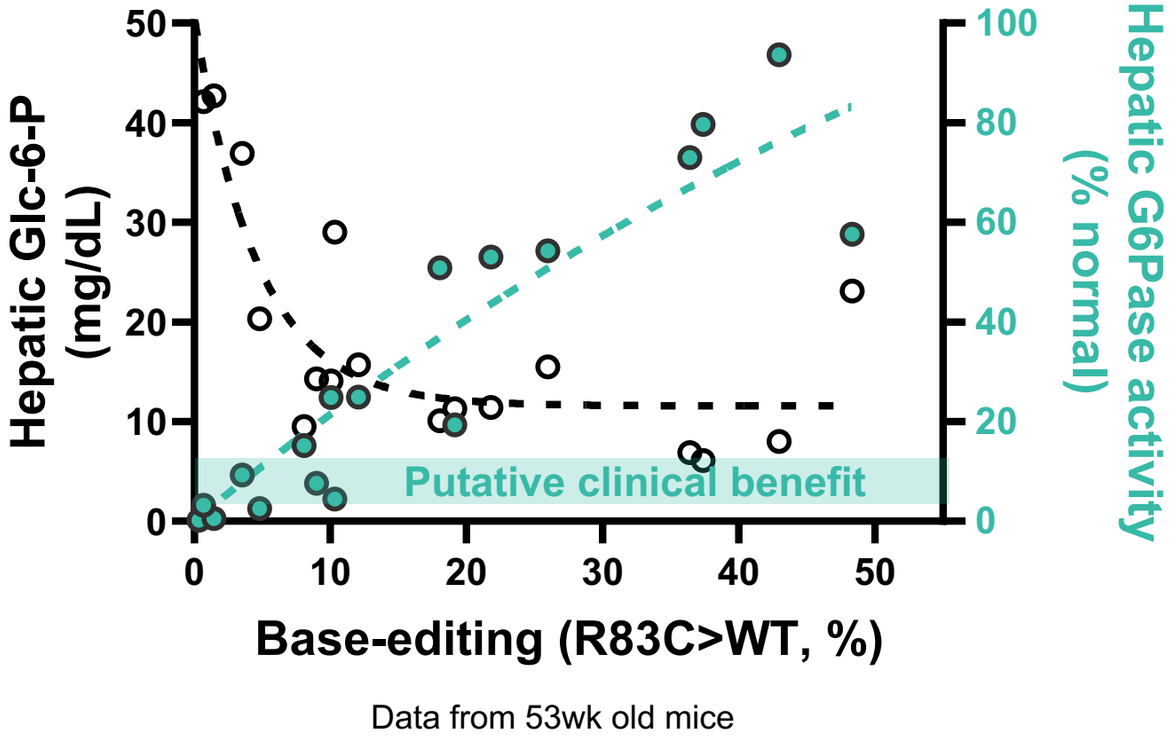
Normal liver size maintained over a year after a single dose of BEAM-301



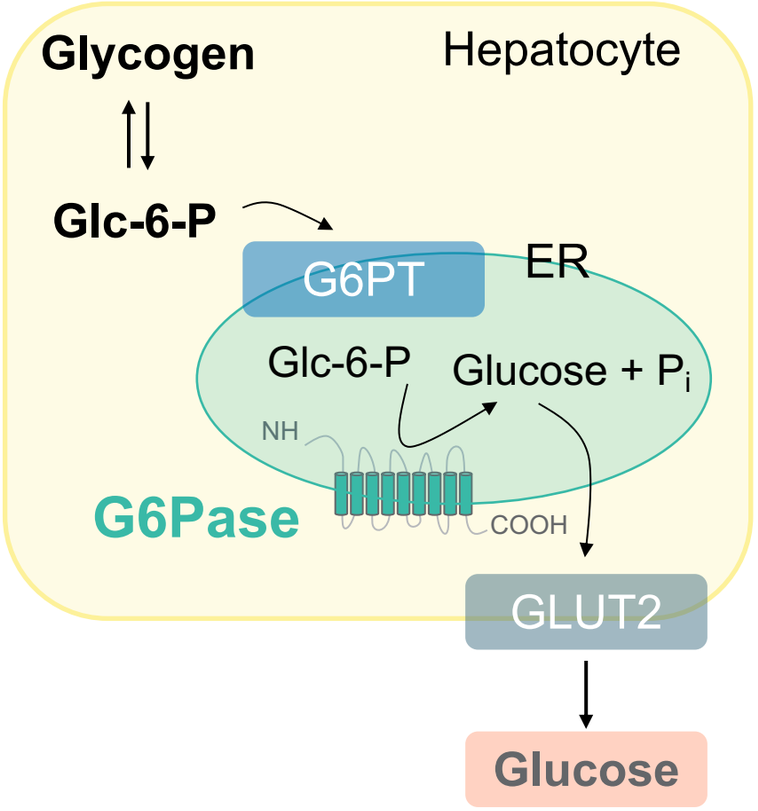


- Liver size is 3-fold larger than normal in untreated huR83C homozygous mice (elevated glycogen, fats)
- BEAM-301 dosing resulting in ≥5% hepatic base-editing efficiency yields **normal liver size** that is apparent by 3wks and maintained to at least 1year post BEAM-301 dosing

Recovery of hepatic G6Pase activity and decline in Glucose-6-Phosphate levels is correlated with base-editing

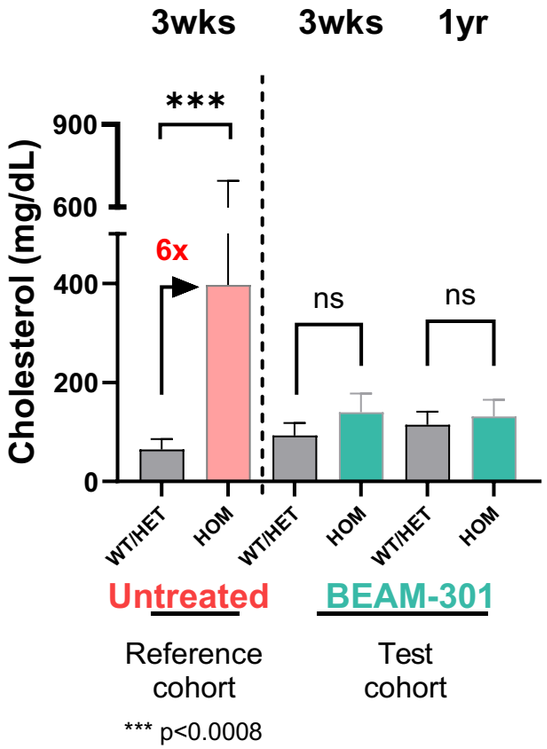


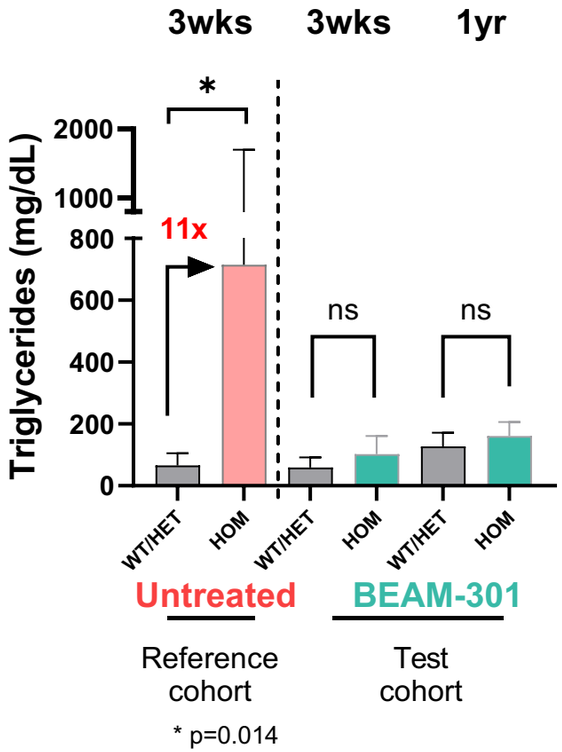
Data from 53wk old mice

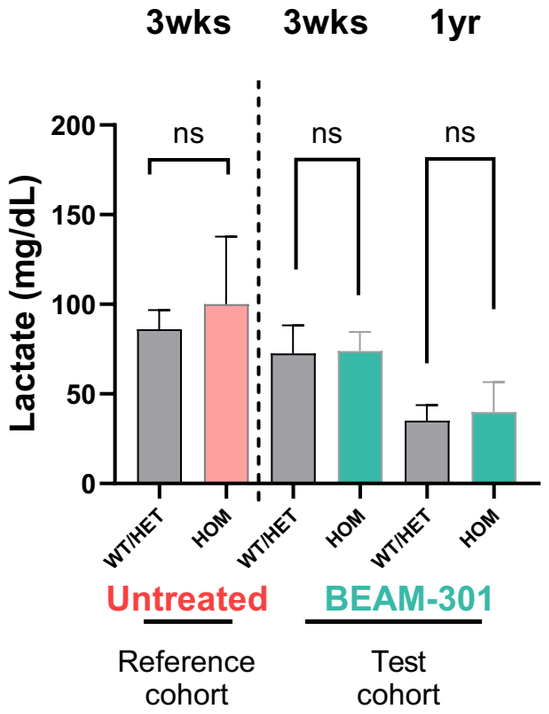


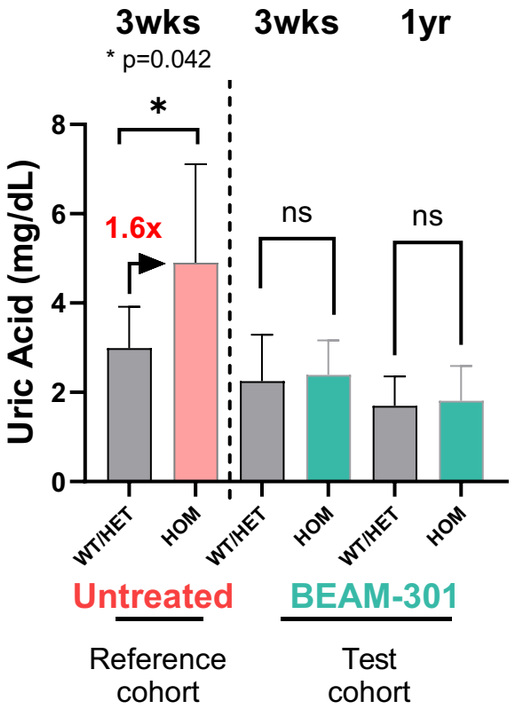
- **Restoration of G6Pase activity at clinically-relevant levels** (3% - 11% normal G6Pase activity) achieved at single-digit base-editing efficiencies for R83C correction
- **Decline in hepatic Glc-6-P levels**, approaching healthy (WT) levels by 10% base-editing rate

Maintenance of normal serum metabolites at 1 year post BEAM-301 dosing in homozygous huR83C mice



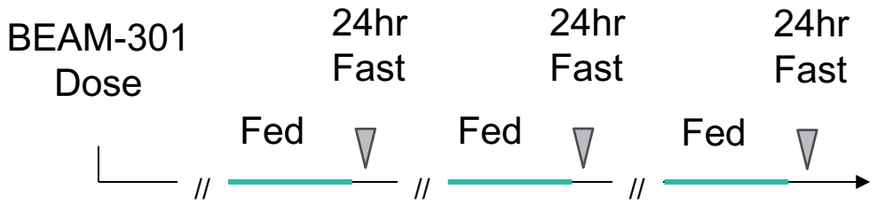


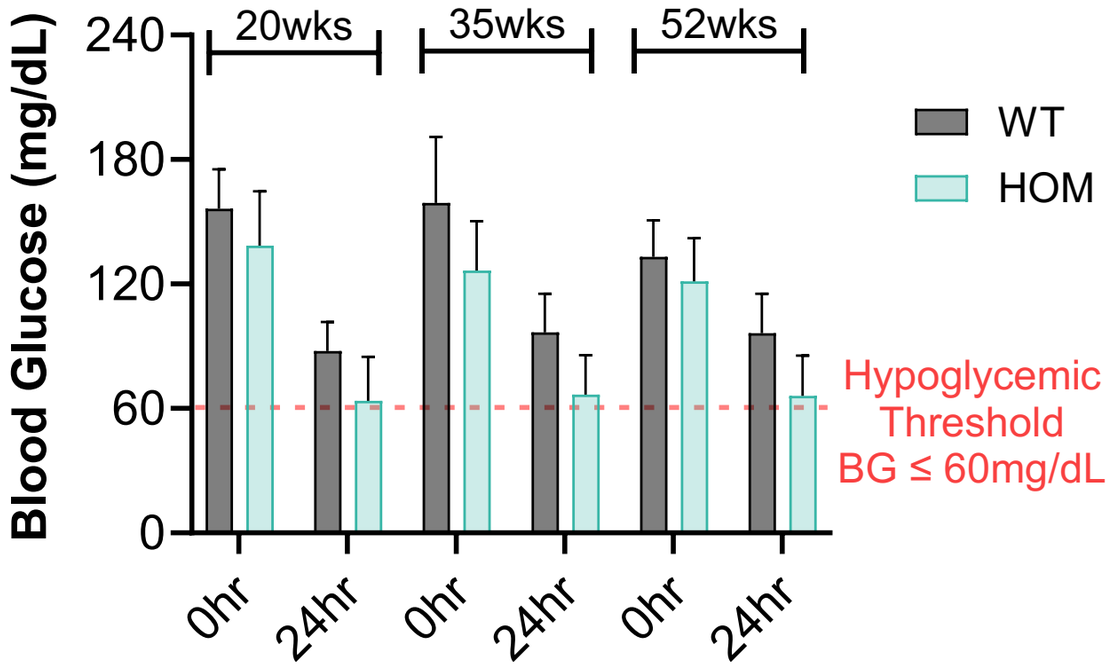




- Untreated huR83C homozygotes exhibit predominantly elevated serum metabolites at 3wks of age
- huR83C homozygotes administered BEAM-301 exhibit **normal secondary serum metabolites, maintained through at least 1yr** (including subjects with single-digit base-editing rates)

Homozygous huR83C mice survive multiple 24hr fasting challenges through 1yr post BEAM-301 dose





- **100% of BEAM-301 dosed homozygous huR83C adult mice survived** a 24-hr fasting challenge
- Blood glucose levels maintained above the hypoglycemic threshold during the 24hr fast, for multiple fasting challenges
- Untreated homozygous R83C mice do not survive beyond 6wks and exhibit hypoglycemic seizures. Therefore, they are not able to survive a fasting challenge

Summary

Single BEAM-301-dose restores clinically meaningful endpoints

- **Long-term survival** to at least 1yr; normal growth and reduction in liver size and lipid content
- **Restoration of enzymatic G6Pase** activity to clinically meaningful levels with ability to maintain normal glucose levels and survive multiple fasting challenges
- **Normal serum metabolites**, including cholesterol, triglyceride, lactate, and uric acid levels

Next Steps

- Complete **IND-enabling studies in pharmacology** (including durability, dose response)
- Complete **IND-enabling safety and toxicology** studies to support regulatory filing for FIH Phase I/II clinical trial

Thank You

NIH

- Irina Arnaoutova
- Lisa Zhang
- Janice Chou

Beam Therapeutics, Inc.

- Dominique Leboeuf
- Steven Boulé
- Tom Fernandez
- Thomas Leete
- Victoria Huang
- Sneha Gampa
- Lo-I Cheng
- Faith Musenge
- Jeremy Decker
- Sarah Smith
- Regina Raz
- Arthur Lo
- Martina Schinke
- Rodrigo Laureano
- Sunita Goyal
- Bahru Habtemarian
- Michael Packer
- Francine Gregoire
- Giuseppe Ciaramella

Beam THERAPEUTICS