Prime editing precisely corrects prevalent pathogenic mutations causing Glycogen Storage Disease Type 1b (GSD1b)

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On behalf of the team at Prime Medicine

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Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make due to a number of risks and uncertainties. These and other risks, uncertainties and important factors are described in the section entitled "Risk Factors" in our most recent Annual Report on Form 10-K, as well as any subsequent filings with the Securities and Exchange Commission. Any forward-looking statements represent our views only as of the date of this presentation and we undertake no obligation to update or revise any forward-looking statements, whether as a result of new information, the occurrence of certain events or otherwise subject to any obligations under applicable law. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. No representations or warranties (expressed or implied) are made about the accuracy of any such forward-looking statements.

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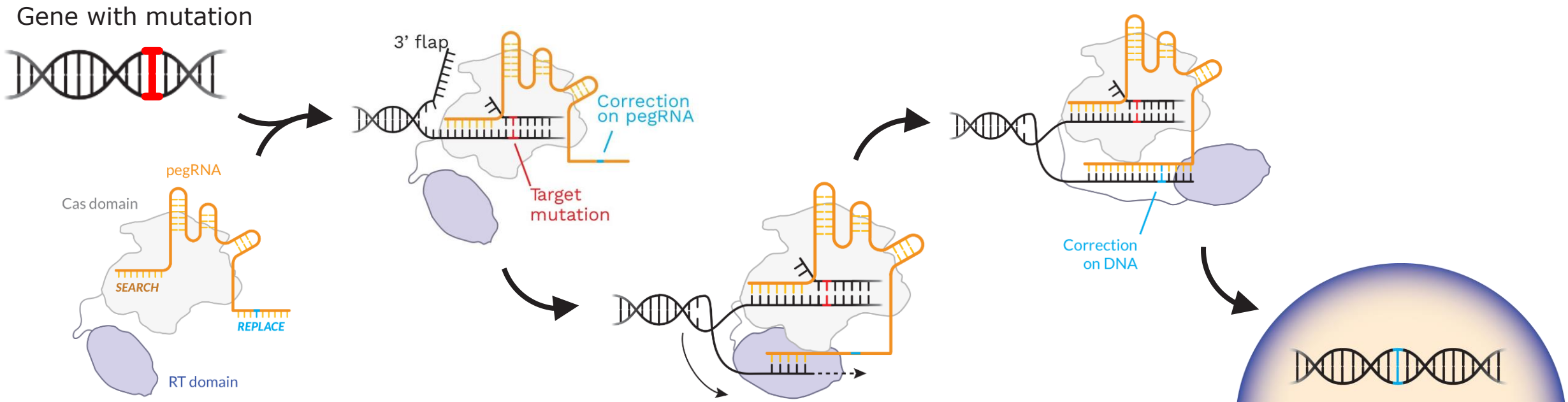
Disclosures

Jeremy Duffield declares he is a current employee of Prime Medicine, Inc. and owns equity in Prime Medicine.

Prime Editors are programmable for both *Search* and *Replace*



SEARCH

Prime editor complex initiates search for target DNA

FIND & NICK

Prime editor complex finds DNA with target mutation, nicks one strand

PRIME

Nicked DNA strand primes the RT domain for DNA synthesis

REPLACE

Prime editor complex copies in corrective DNA sequence

GENE CORRECTED

3' flap preferentially incorporated[1], excess flap repaired, gene fully corrected

[1]*Completion of an edit requires 3 'edit checks,' or places where there has to be a match between the editor and the target DNA*

Note: pegRNA = prime editing guide RNA; RT = reverse transcriptase; Cas = CRISPR associated protein

animated movie available at www.primemedicine.com

Prime Medicine is developing a universal Lipid Nanoparticle (LNP) formulation to deliver Prime Editors for all liver indications

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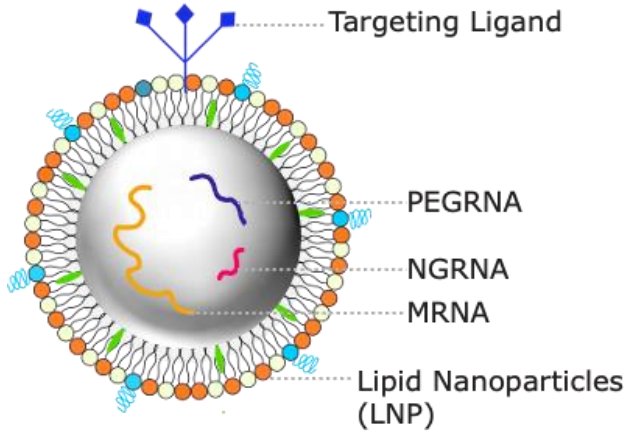
Universal liver targeted LNP for all liver indications has potential to expedite clinical development of Prime Editing for a broad spectrum of patients



Prime Medicine universal **liver** LNP contains an active targeting ligand that reduces biodistribution to secondary organs and increases Prime Editing in the liver

Universal LNP for liver indications – Potential advantages

- Addressing a new liver indication would only require swapping the guide RNAs
- Potential for:
  - Pharmacology/ADME/Safety/Toxicology packages leveraged across multiple programs
  - Faster non-clinical, clinical development and regulatory path for follow on programs
- A modular manufacturing process for universal LNP used across liver indications
- Leverage CMC packages across programs
- Significant cost of goods savings

Therapeutic approach: LNP-mediated delivery of Prime Editor components to liver

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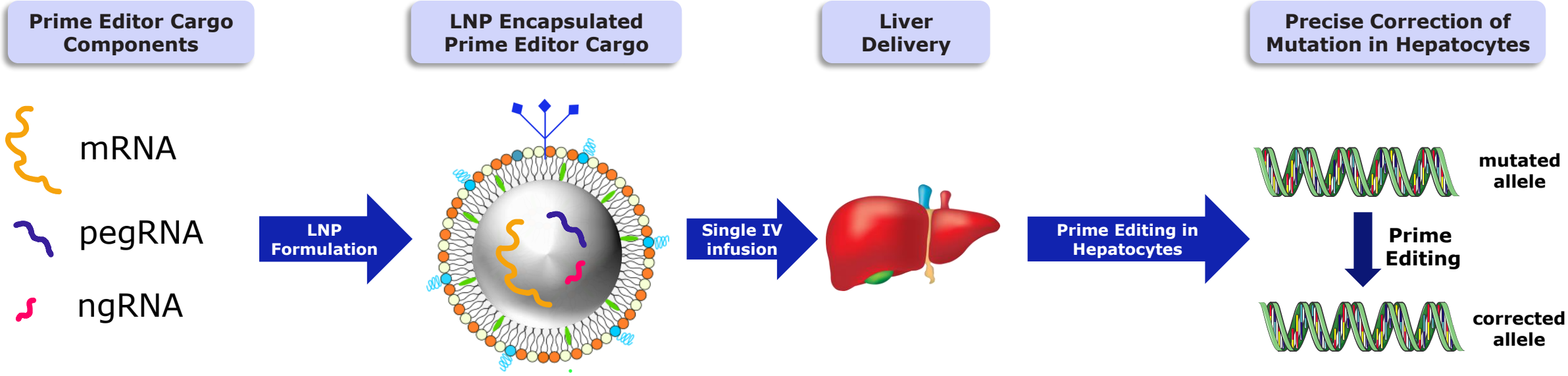
One-time delivery of LNP Prime Editor cargo to correct pathogenic mutations in the liver



Prime Medicine's approach to developing Prime Editors to treat liver and metabolic diseases

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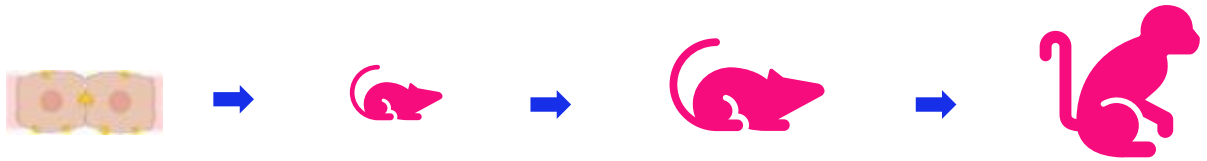
Prime Editors are specific to *human* patient DNA sequence and designed for the correction of *human* mutations

- Establish potency and activity of lead Prime Editor drug candidates
- Establish genotype to phenotype correlation and off-target profile
- Establish pharmacology, safety, tolerability
- Determine biodistribution, drug pharmacokinetics
- Determine PK/PD relationships, human dose projections



Prime Editing to correct pathogenic mutations causing von Gierke disease or Glycogen Storage Disease Type 1b

Initially correct the two most prevalent mutations that cause GSD1b, carried by ~ 50% of patients

Glycogen Storage Disease Type 1b (GSD1b)

Description:

- Rare disease preventing production of glucose during fasting state, causing hypoglycemic episodes and associated seizures

Human genetics and biology:

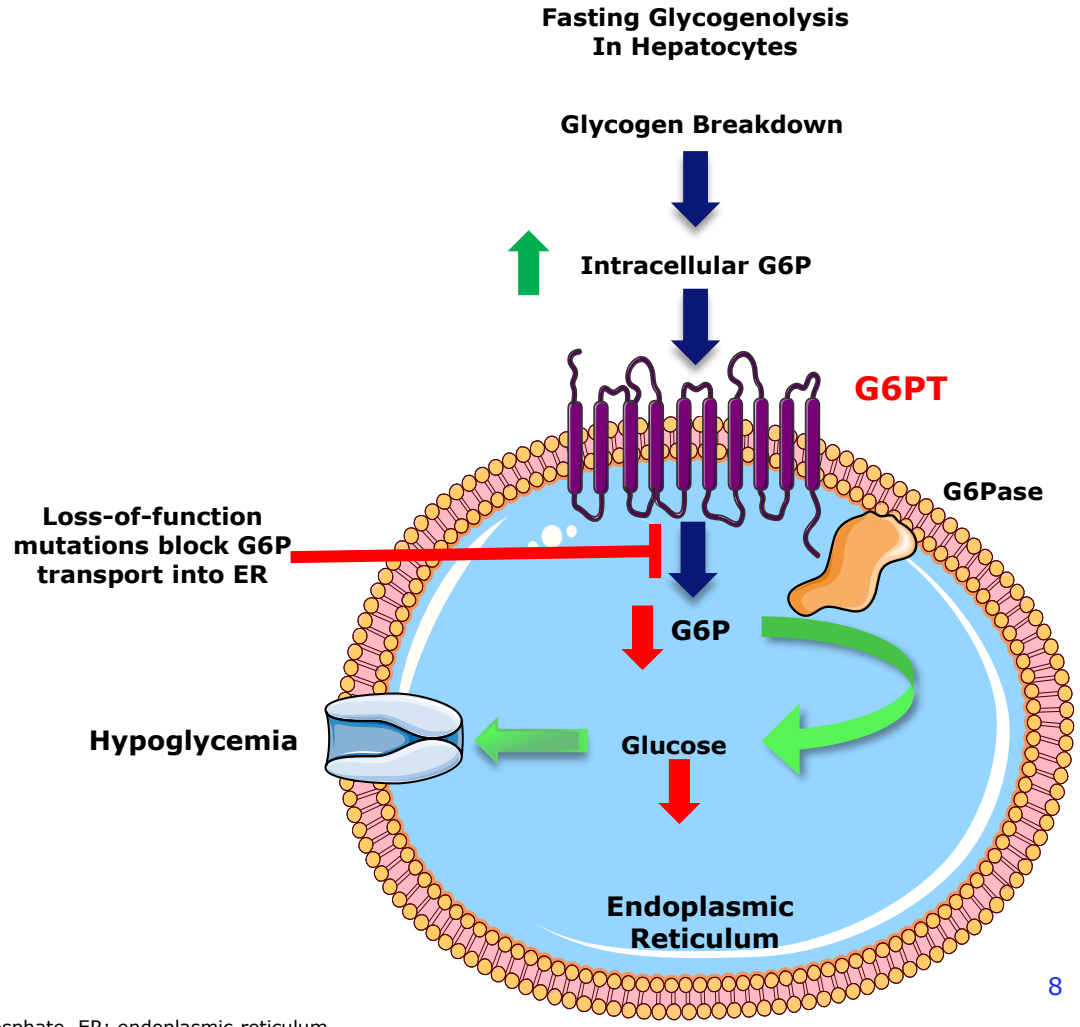
- Autosomal recessive, caused by mutations in the *SLC37A4* gene that encodes G6PT, a glucose-6-phosphate transporter
- **p.L348fs and p.G339C mutations** found in ~50% of GSD1b patient population

Unmet need:

- Standard of care focuses on reducing symptom severity rather than treating the underlying cause of the disease
- No disease modifying therapies approved

Prime Medicine's approach:

- IV administration of liver targeted LNP Prime Editors to correct either p.L348fs mutation or the p.G339C mutation to restore glucose homeostasis in patients with GSD1b



G6P : glucose 6 phosphate, G6PT: glucose-6-phosphate transporter (SLC37A4), G6Pase: glucose-6-phosphate phosphatase, Pi: inorganic phosphate, ER: endoplasmic reticulum

Identification of pegRNAs that precisely correct the p.L348fs and p.G339C mutations *in vitro*

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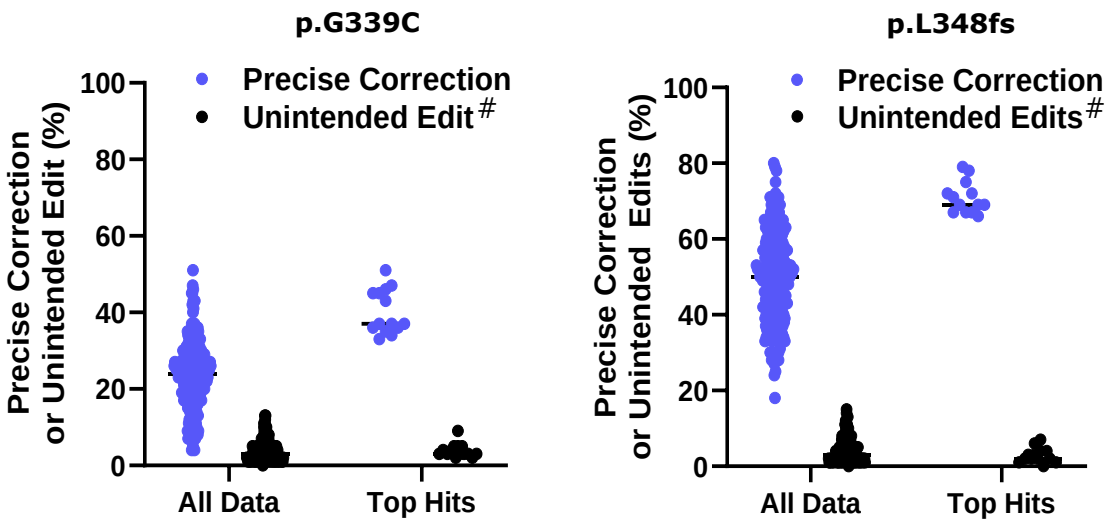
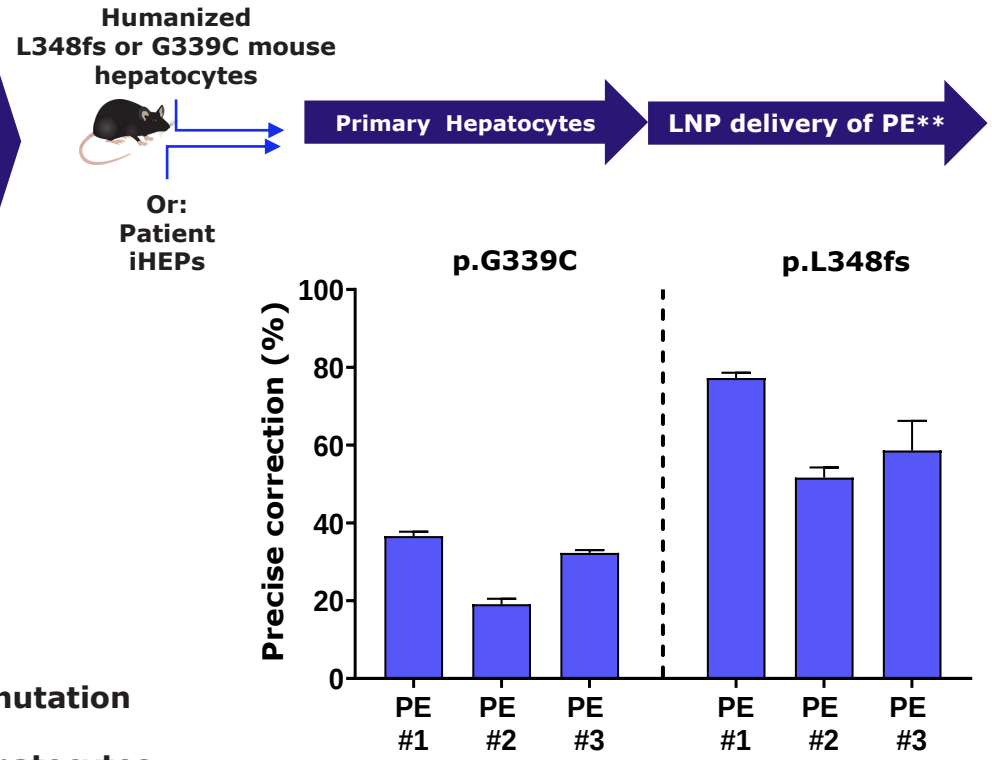
High throughput screening (HTS) identifies pegRNAs that precisely correct the p.L348fs and p.G339C mutations in hepatocytes

HTS in cells harboring the p.G339C or p.L348fs mutation



Evaluation of pegRNA potency in primary humanized hepatocytes* or patient iHEPs



Key Takeaways:

- ***In vitro* screening identified highly active candidates for each mutation**
- **77% precise correction of the p.L348fs mutation in primary hepatocytes**
- **52% precise correction of the p.G339C mutation following HTS, and 37% in primary hepatocytes – further optimizations underway**

#Unintended edits = any SNVs or indels within 300bp either side of the edit site; *Data shown using humanized primary mouse hepatocytes; **PE = Prime Editor

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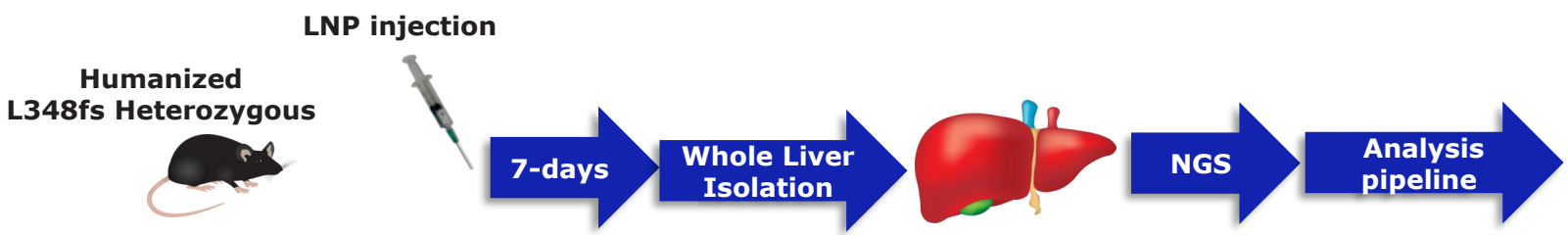
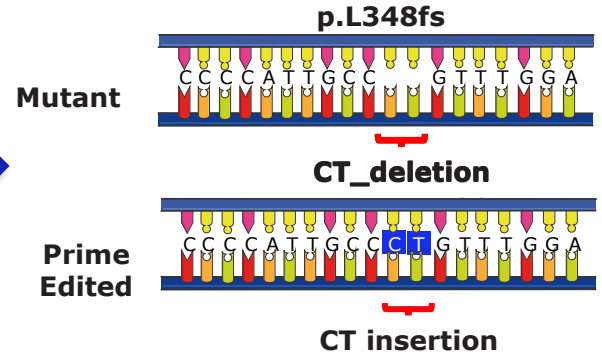
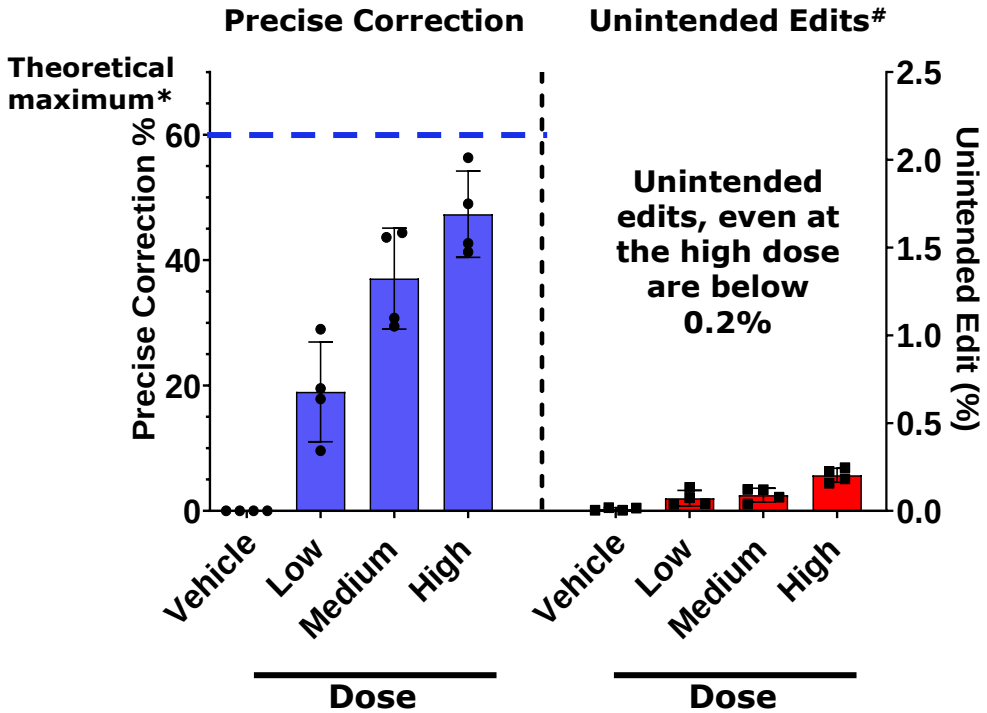
LNP delivery of Prime Editor components to the liver precisely corrects the p.L348fs mutation in humanized mice

Up to 56% whole liver precise correction in GSD1b humanized mouse





Determine Precise Edit & Unintended Edit Frequency



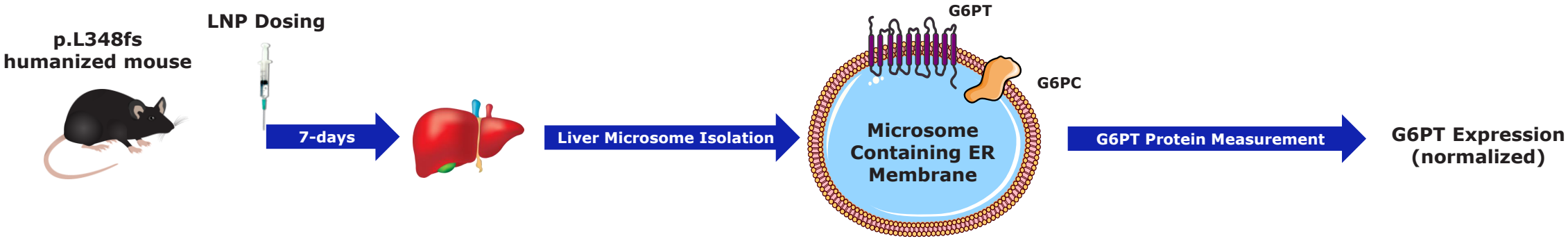
Key Takeaways:

- **A dose-dependent increase in precise correction of the p.L348fs mutation is observed following LNP-mediated delivery of Prime Editor components to the liver**
- **Unintended edit rates are below 0.2% at every dose tested**

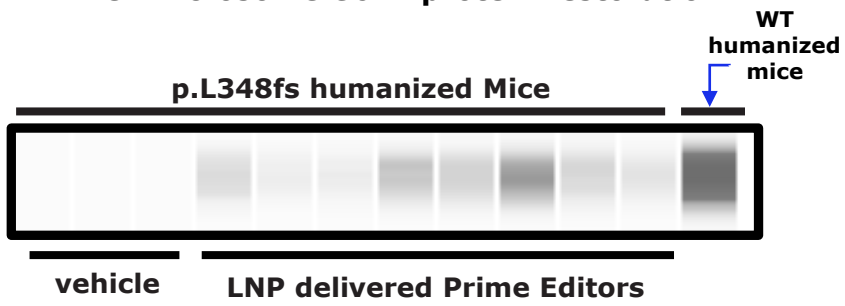
*Based on PK/PD relationships and quantification of cell types in liver:
Wang et al Sci. Rep. (2021) 11:19396; MacParland et al Nat Commun (2018) 9:4383; Hansel et al, Curr Protoc Toxicol (2014) 62:14.12.1; Kmiec, Adv Anat Embryol Cell Biol. (2001) 161:III–XIII. 1–151
Unintended edits = any SNVs or indels within 300bp either side of the edit site

G6PT transcripts and protein are restored in humanized p.L348fs mouse liver following delivery of Prime Editors

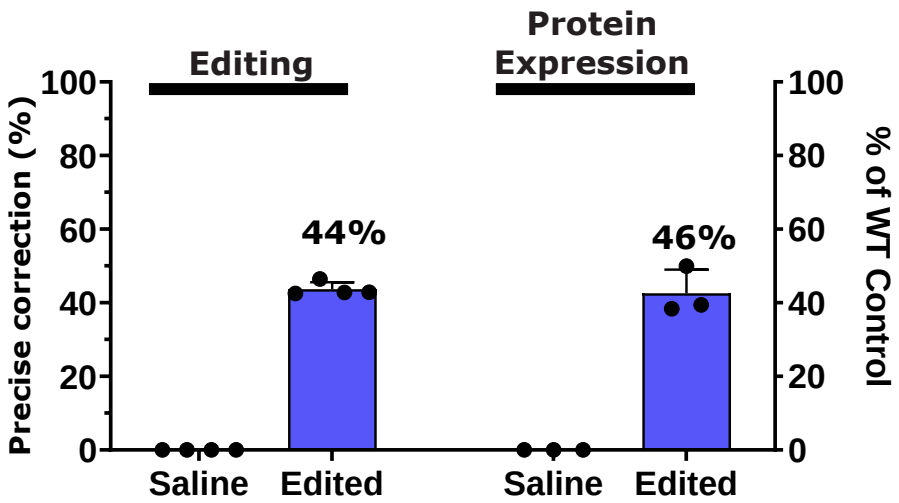
Precise editing of the G6PT gene restores G6PT protein expression



Liver microsome G6PT protein restoration



Anti-human G6PT specific antibody

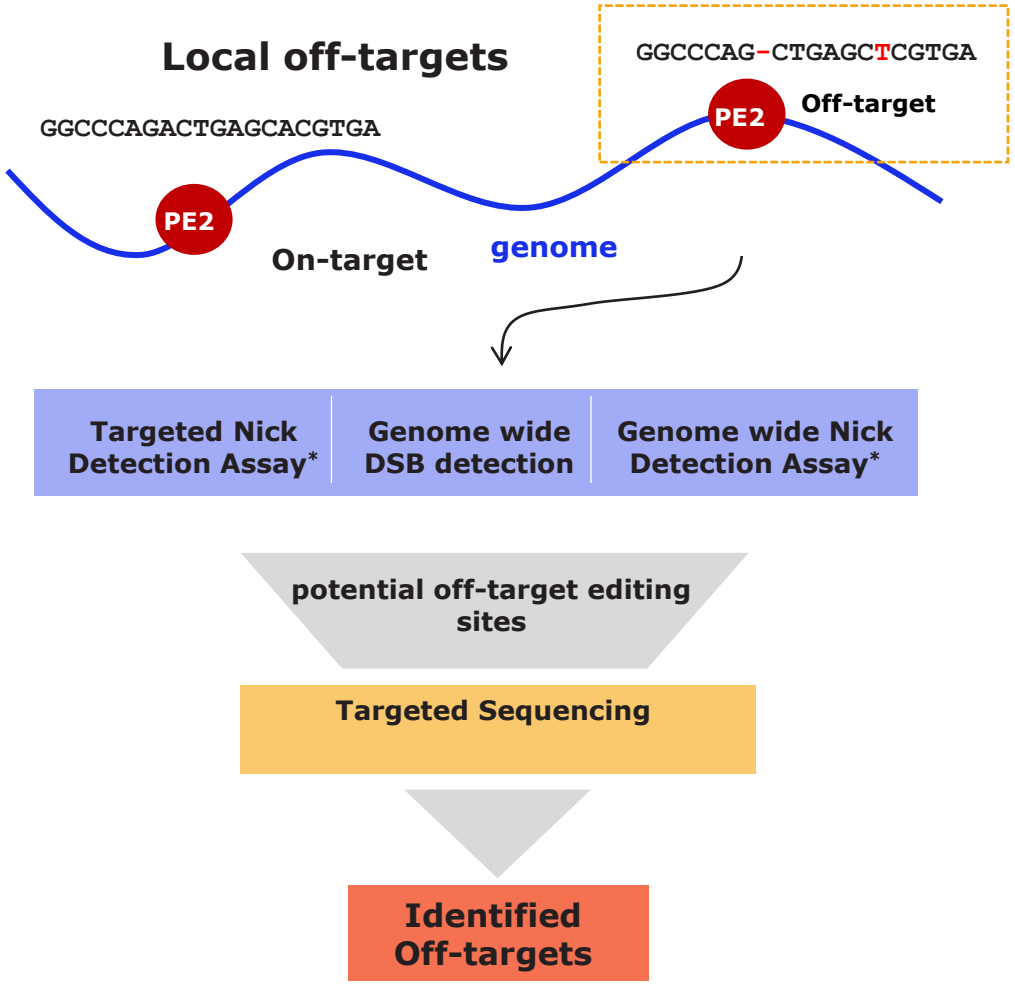


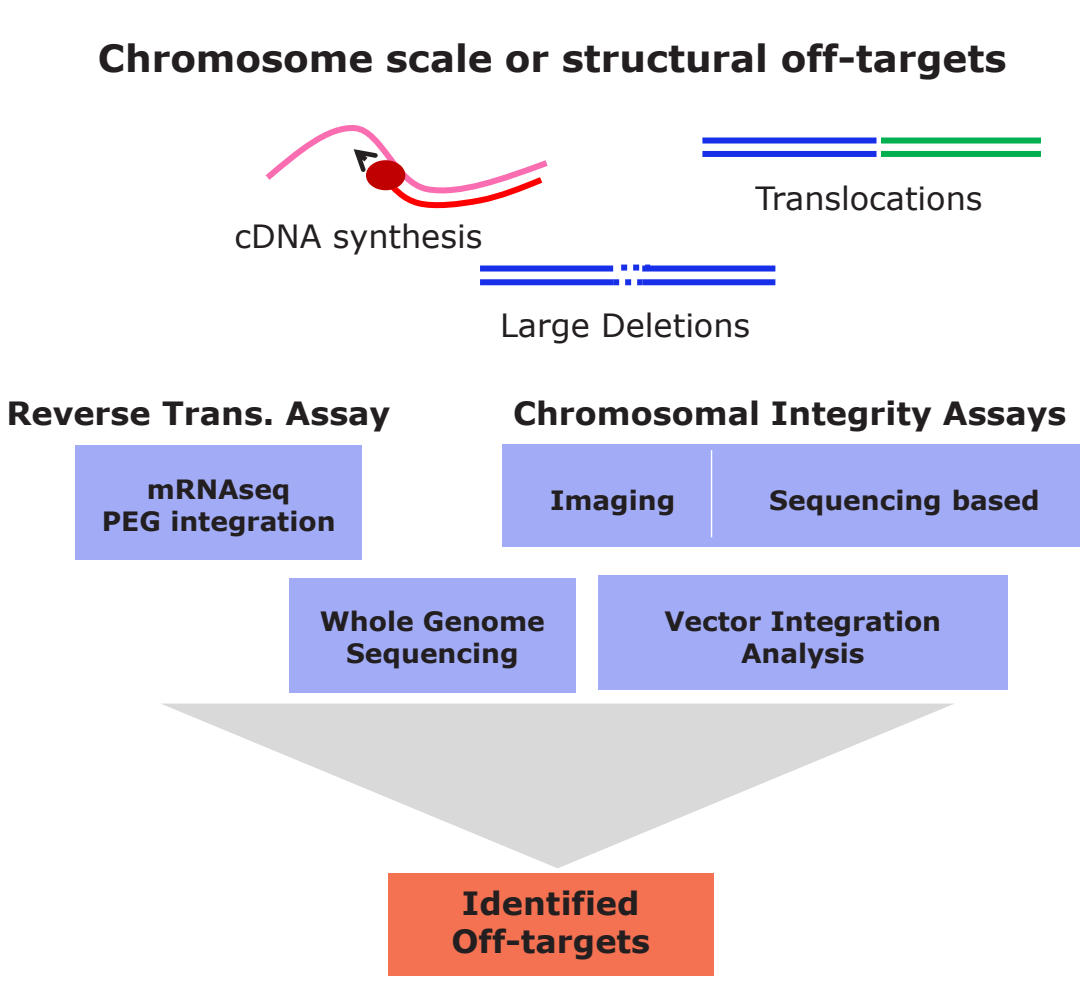
Key Takeaways:

- **Prime Editing restores expression of G6PT protein**
- **Extent of G6PT mutation correction correlates with extent of G6PT protein restoration**

G6PT: glucose-6-phosphate translocase, het: heterozygous, WT: wild-type, ER: endoplasmic reticulum

Safety: Prime's comprehensive suite of IND-ready assays for off-target discovery





*Proprietary assay developed by Prime Medicine

Preliminary analysis showed no detectable off-target editing in patient cells

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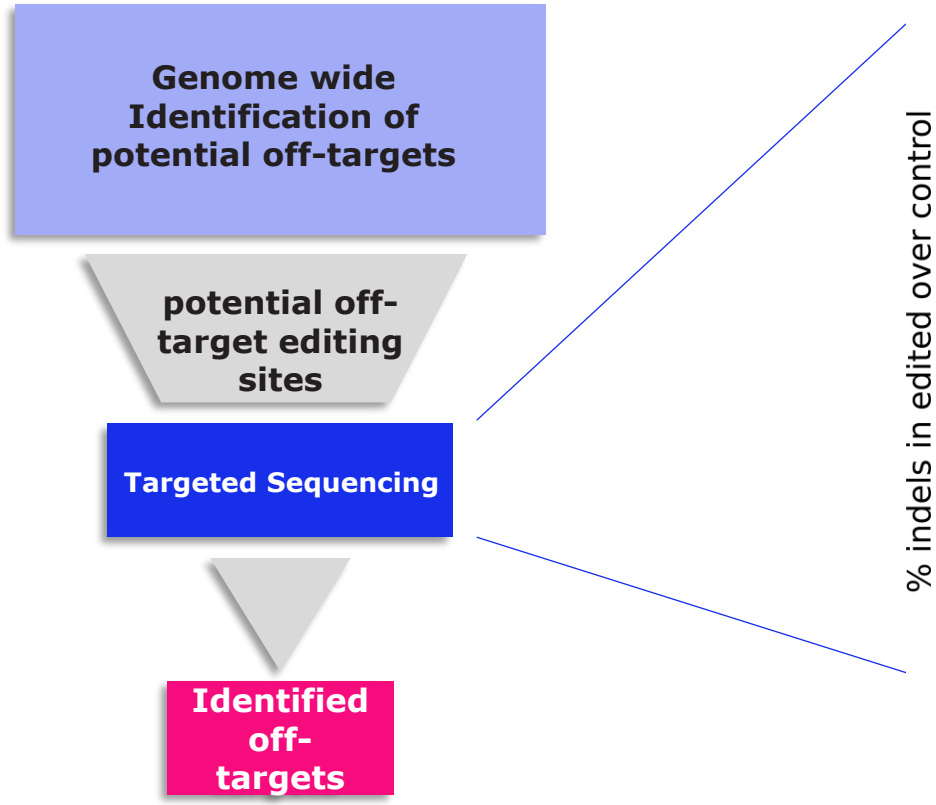
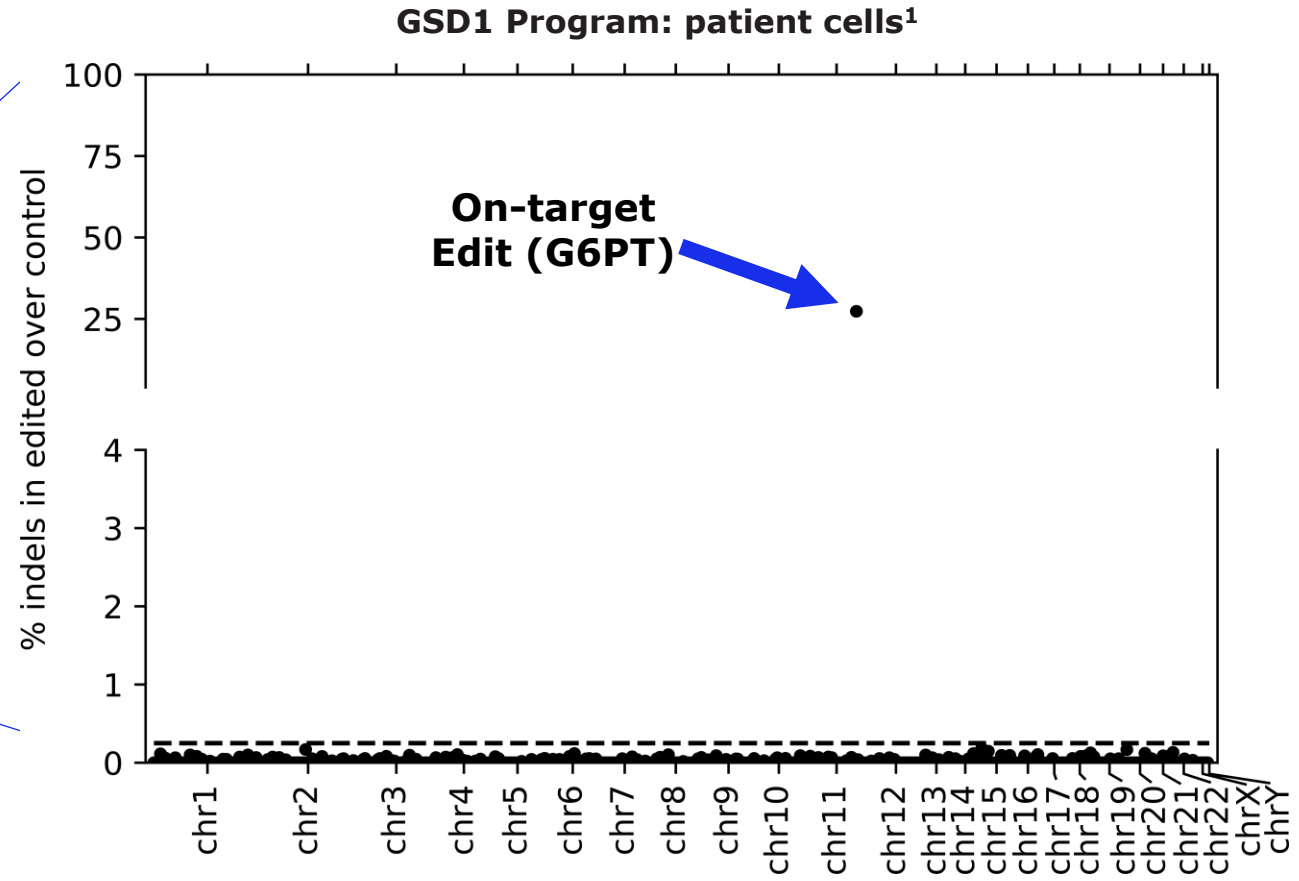
Performed using a lead p.L348fs pegRNA and lead LNP delivery system





[1]Targeted Analysis of potential off-target sites using deep sequencing in Prime Edited human iPSC cells carrying the p.L348fs

Approach to cynomolgus monkey liver Prime Editing to support safety and pharmacology for the GSD1 program

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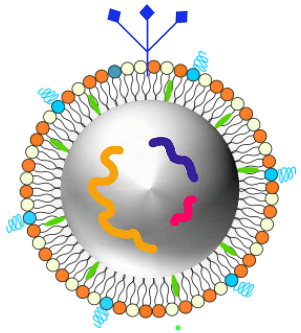
Precisely edit the p.L348 codon in *SLC37A4* (G6PT) gene with single base substitution in healthy Cynomolgus adult monkeys

- Prime Editing guide RNAs (pegRNAs) for Cynomolgus monkey are surrogates for the human pegRNAs
- As close to the lead human pegRNA sequence as possible with similar potency and activity
- All other Prime Editing components are held constant
- Wherever possible non-terminal studies are performed

mRNA, pegRNA & ngRNA
Formulated in:
Prime Universal liver LNP



Liver Bx = liver biopsy; GSD1 = glycogen storage disease type I; SLC47A4 = gene name for the glucose 6 phosphate transporter or G6PT

Surrogate Prime Editor efficiently and precisely edits p.L348 in *SLC37A4* (G6PT) gene in healthy cynomolgus monkey liver

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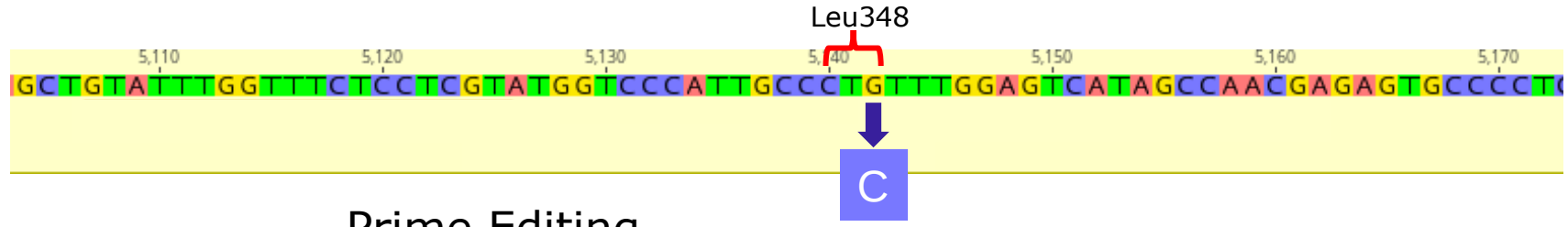
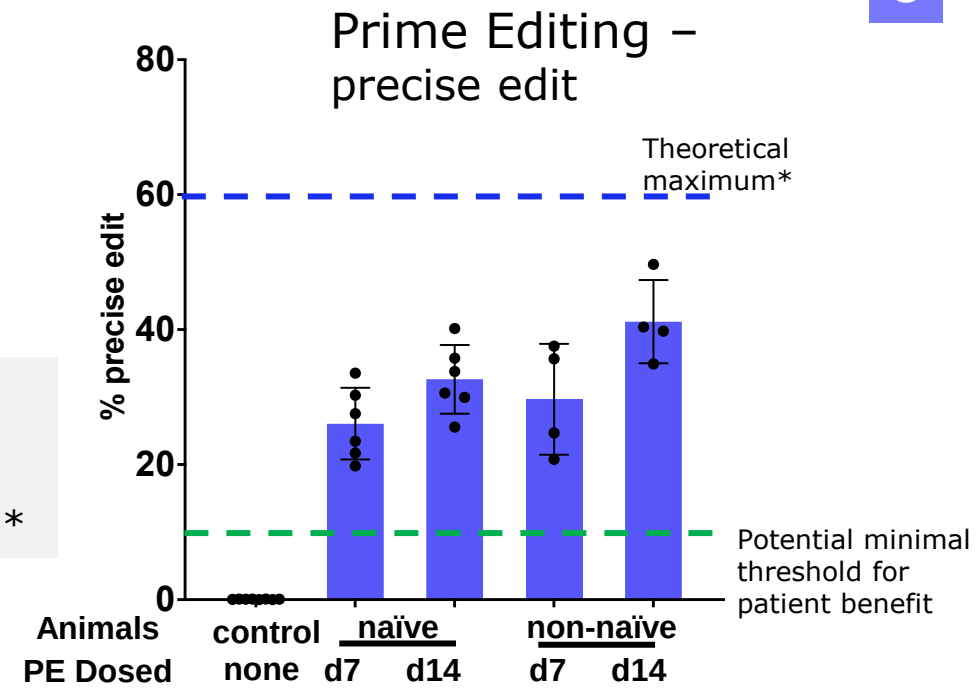
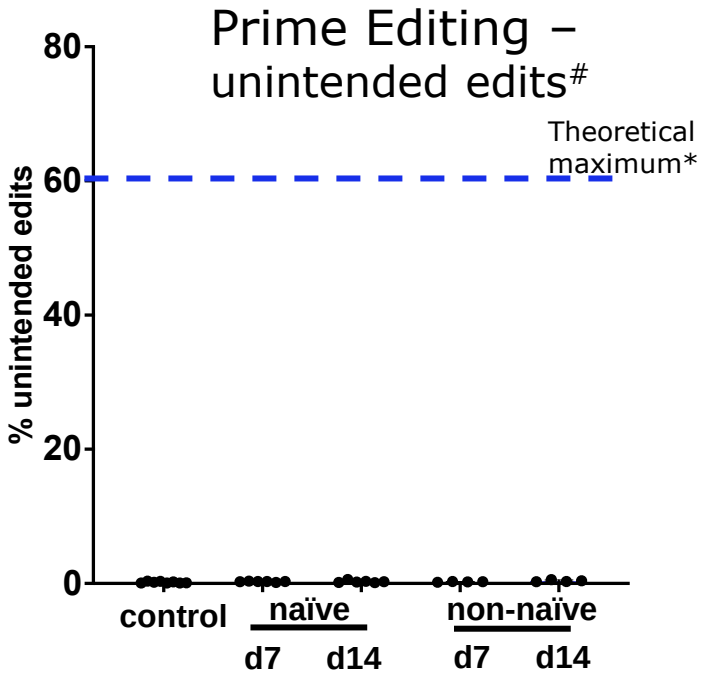
Up to 50% whole liver precise editing in Cynomolgus monkey



Estimated up to 83% of hepatocytes Prime Edited (both alleles) from single dose of Prime Editor LNP**





Non-naïve cynomolgus monkeys had previously received Prime's Universal LNP to target a different gene

*Based on PK/PD relationships and quantification of cell types in liver: Wang et al Sci. Rep. (2021) 11:19396; MacParland et al Nat Commun. (2018) 9:4383; Hansel et al, Curr Protoc Toxicol (2014) 62:14.12.1; Kmiec, Adv Anat Embryol Cell Biol. (2001) 161:III–XIII. 1–151. ** Calculation based on 60% of cells in whole liver are hepatocytes; # Unintended edits = any SNVs or indels within 300bp either side of the edit site

Prime Medicine's liver-targeted LNP-RNA Prime Editor drug was well tolerated by cynomolgus monkeys

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- No infusion reactions
- No body weight changes
- Transient, modest liver function test changes and minimal transient cytokine abnormalities
- Redosing of LNP-RNA drug (non-naïve) was tolerated similarly to naïve animals

Summary

- Prime is developing a universal LNP-RNA platform to deliver Prime Editors to treat liver and metabolic diseases
- Potent Prime Editors correcting the two most prevalent GSD1b mutations identified and engineered resulting in high levels of allele correction up to 56% correction of the p.L348fs mutation in humanized mouse whole liver
- GSD1b LNP-RNA Prime Editors restore G6PT protein expression consistent with allele correction
- Initial studies from Prime's off target pipeline have not detected any off-target editing genome-wide
- Large animal cynomolgus monkey studies using the universal LNP-RNA platform with a surrogate pegRNA show high levels of up to 50% of precise editing of G6PT at p.L348 in whole liver equivalent to ~83% of hepatocytes at a dose that was well tolerated

THANK YOU!

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