Advancing prime editing for Wilson disease: precise and durable *in vivo* correction of *ATP7B* mutations

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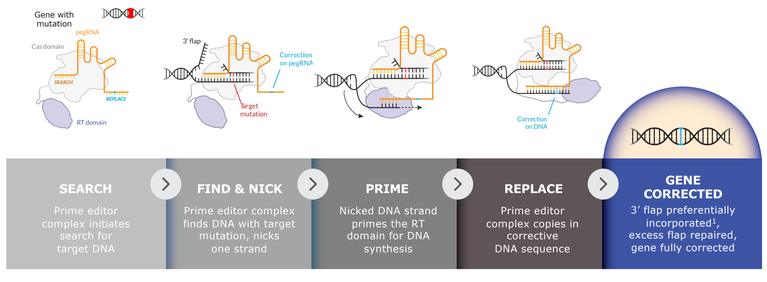
BACKGROUND

How Prime Editing works



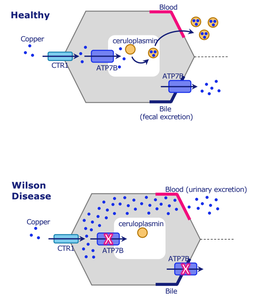
Wilson Disease Overview

Disease severity
- Common liver and systemic disease presenting in teens to 20's (prevalence approx. 1:30,000)
- Leads to liver failure, neurocognitive decline and premature death

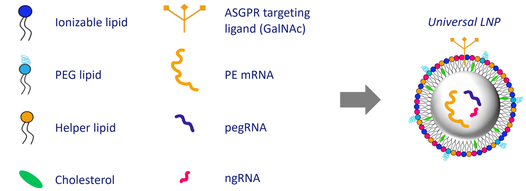
Unmet need
- Many patients die without liver transplant
- No approved disease-modifying therapies

Human biology
- Autosomal recessive due to loss of function mutations in *ATP7B*
- Affects copper homeostasis, leading to toxic accumulation of copper in liver and brain
- H1069Q and R778L are two prevalent mutations found in up to 50% of patients
- Correction of 20-30% of hepatocytes may be curative

Therapeutic approach
- Prime's universal liver-targeted LNP to deliver RNA Prime Editors to patient liver to correct mutations in *ATP7B* to restore copper metabolism



Prime Medicine's Universal Liver-Targeted LNP

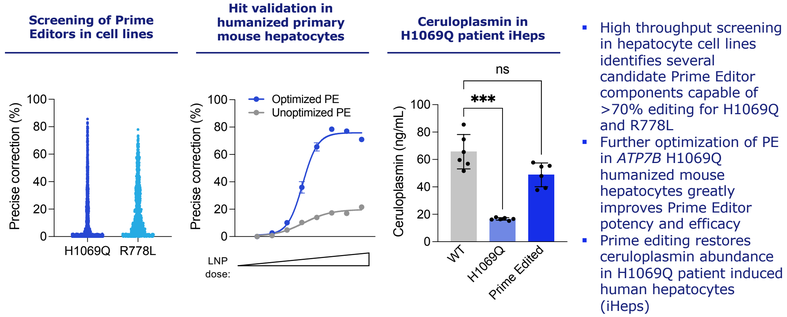


- ✓ Validated as a delivery mechanism
- ✓ Increases potency
- ✓ Improves safety profile
- ✓ Improves biodistribution profile

- Prime Medicine's universal liver-targeted LNP keeps constant 6 out of the 8 components of the LNP and PE cargo for all liver programs
- Swapping only the guide RNAs yields a new drug product with the potential for the same critical quality attributes

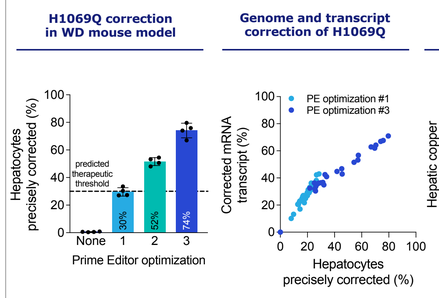
RESULTS

Hit finding and validation identify highly active Prime Editors for *ATP7B* H1069Q and R778L correction



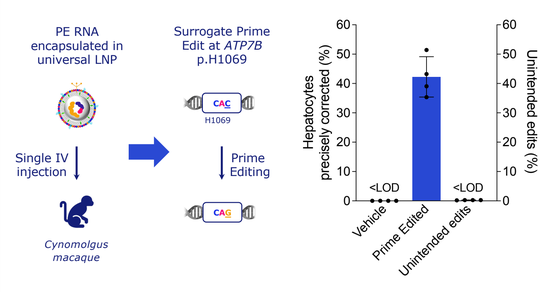
- High throughput screening in hepatocyte cell lines identifies several candidate Prime Editor components capable of >70% editing for H1069Q and R778L
- Further optimization of PE in *ATP7B* H1069Q humanized mouse hepatocytes greatly improves Prime Editor potency and efficacy
- Prime editing restores ceruloplasmin abundance in H1069Q patient induced human hepatocytes (iHeps)

2 Prime Editor optimizations enable therapeutic H1069Q correction in a fully humanized *ATP7B* H1069Q WD mouse model



- Genome correction of H1069Q by Prime Editing in the WD humanized mouse model leads to:
  - Efficient correction of *ATP7B* mRNA transcripts, which correlates with genome correction
  - Time-dependent 75% reduction in liver copper compared to saline-treated control

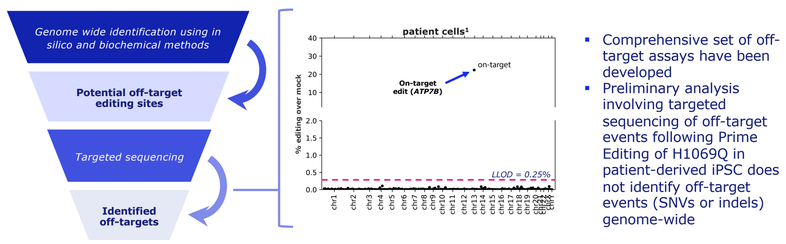
3 Universal LNP-formulated surrogate H1069 Prime Editor *in vivo* in NHP achieves up to 51% precise editing in liver hepatocytes



Prime Medicines's Universal LNP has an excellent safety profile in NHP:

- Well-tolerated with no acute reactions, clinical observations, or body weight changes
- Minimal LFT abnormalities
- No change in platelet, coagulation, or blood count
- No change in blood biochemistry
- Minimal change in IL6 production
- No other cytokine changes
- No change in liver histopathology (H&E)

No detectable off-target editing events identified in preliminary off-target analysis for H1069Q Prime Editor in patient-derived cells



- Comprehensive set of off-target assays have been developed
- Preliminary analysis involving targeted sequencing of off-target events following Prime Editing of H1069Q in patient-derived iPSC does not identify off-target events (SNVs or indels) genome-wide

CLINICAL

- Additional enabling nonclinical studies underway in anticipation of IND/ CTA filing in first half of 2026
- Planned global first-in-human, single arm, Phase I/II dose finding trial in patients with WD, will include multiple sites within Europe
- Prime Editor will be delivered as a single dose of an intravenously administered LNP encapsulating RNA
- General eligibility criteria will include:
  - Individuals currently being treated for WD, who have at least one allele bearing the H1069Q variant of *ATP7B*
  - Dose finding will initially occur in adults ≥ 18, followed by adolescents 12 - 17
- In addition to safety, key endpoints will include blood, tissue and imaging biomarkers of copper metabolism
- For additional information on the clinical trial, or if you have WD patients with the H1069Q variant who you think might be interested in an experimental gene editing study, please contact Mohammed Asmal at masmal@primemedicine.com

CONCLUSIONS

- Successfully identified several candidate Prime Editor components capable of >70% editing for *ATP7B* p.H1069Q and p.R778L
- LNP-formulated Prime Editors using Prime Medicine's Universal liver targeted LNP efficiently correct (up to 80%) the H1069Q mutation in a fully humanized *ATP7B* Wilson disease mouse model without detectable unintended edits
- Preliminary off-target analysis demonstrated H1069Q Prime Editors do not result in detectable off-target events in patient-derived iPSC
- LNP-formulated Prime Editors resolve copper accumulation in humanized mouse livers
- Using Prime Medicine's Universal LNP with a surrogate Prime Editor RNA cargo, up to 51% editing at the H1069 locus was observed in NHP *in vivo*
- Prime Medicine's Universal LNP is well-tolerated in NHP with a favorable safety profile
- These data support the advancement of a potential one-time, curative approach for Wilson's disease patients H1069Q or R778L mutations

Prime Medicine plans to recruit patients for a global Wilson Disease clinical trial using an LNP-RNA Prime Editor in the 1st half of 2026