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Harnessing a Diverse Collection of CRISPR-Associated RNA-Guided Nucleases for Precise Gene Editing

SPRING 2025

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Unlocking the Potential of Genomic Medicines Through Proprietary Editing and Delivery Capabilities

Proprietary Type II and V RNA-Guided Nucleases

- Compact (~800-1,100 aa) and efficient
- Facilitates delivery
- US Patent No. 11,162,114 (expiry June 2040)
- US Patent No. 11,859,181 (expiry May 2041)

Full-Spectrum Editing Modalities

- Knock-out
- Insertion/Repair
- A & C Base Editing
- Reverse Transcriptase Editing

Protein Discovery/ Engineering

- 20B+ proteins and counting
- Millions of candidates across diverse editing modalities
- Actively leverage AI during discovery and engineering

Broad Genome Access with PAM Diversity

- Protospacer Adjacent Motifs (PAMs) increase the number of specific sites where therapeutically meaningful edits can be made

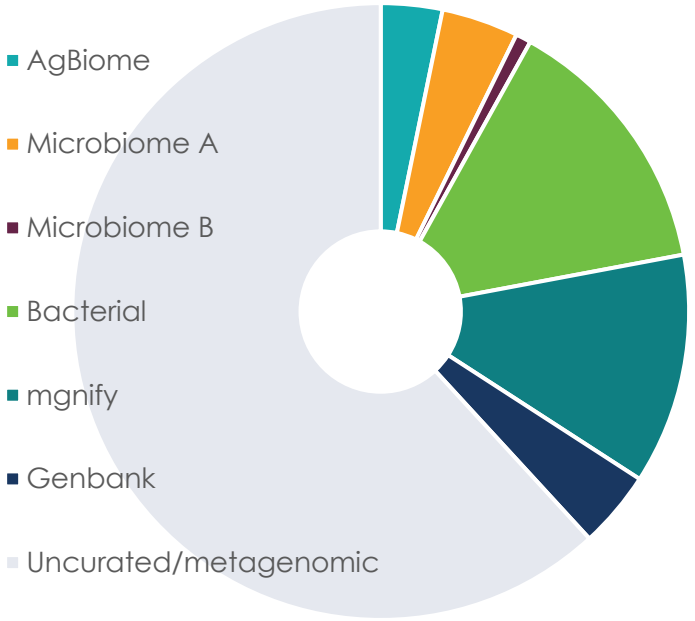
Flexible Delivery Platforms

- AAV
- Lipid nanoparticle (LNP)

In Vivo and *Ex Vivo* Therapeutics

- Multiplex base editing of up to 5 genes
- Simultaneous knock-in /knock-out in primary T-cells
- *In vivo* editing in the liver and CNS

Life Edit has a Proprietary Library of Evolutionarily Distant Nucleases with PAM Sequence Diversity



Over 2M CRISPR-Cas systems

All known Cas subtypes

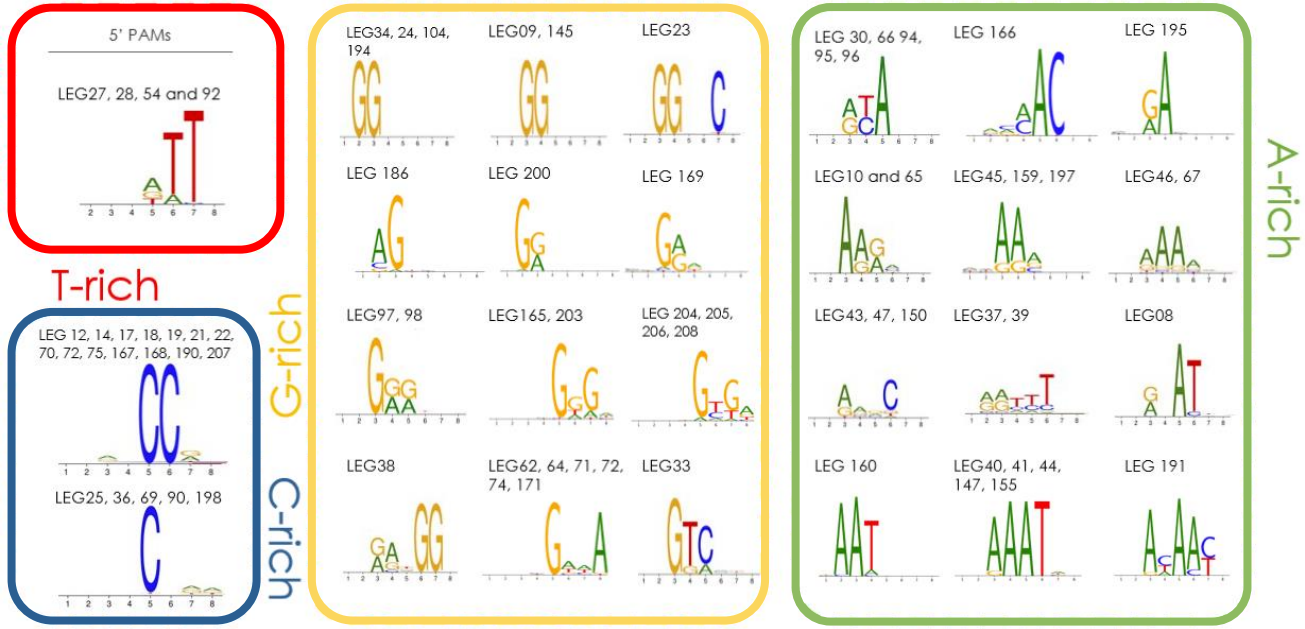
- Focus on Type II and Type V

Cataloged to capture annotations and *gene context*

10+ billion unique proteins (and counting)

Microbial database from multiple sources

Example PAM sequences



Collection of nucleases with diverse PAM sequences

Founded on exclusive access to gene editing systems identified in a proprietary microbe collection for use in human therapeutics, and **expanded** by mining additional genomic data sources

Collection enables the ability to **find additional enzymatic activities** to build future editing systems (e.g., proprietary base editors, transposases, others)

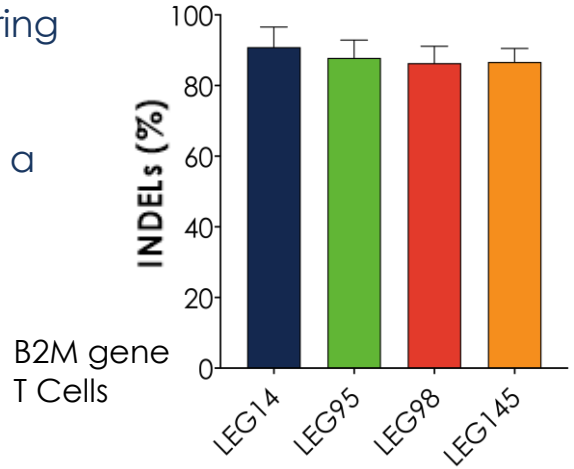
Life Edit's Nuclease Library Includes a Large Collection of Type II and Type V Nucleases

Lead Type II RNA-Guided Nucleases are Small and Allow Broad Genomic Access

Nuclease	LEG98	LEG14	LEG145	LEG95
PAM				
Protein Length	1052 aa	1071 aa	1130 aa	1150 aa

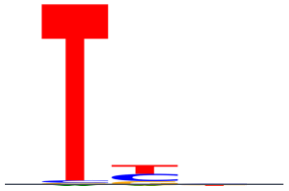
- Low homology to established systems
- Nuclease discovery and engineering further increased PAM diversity
- Smaller sizes enable packaging in a single AAV

Nuclease Editing of B2M by Lead Type II Systems



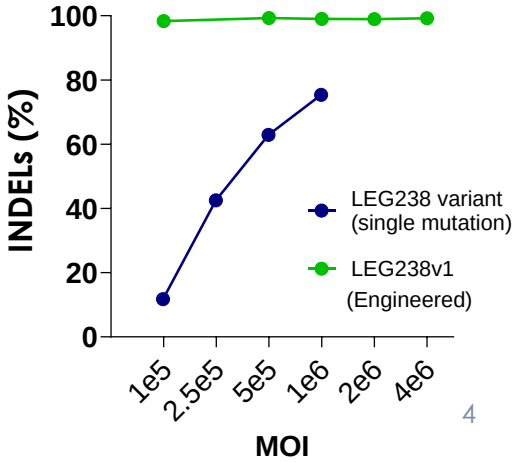
B2M gene
T Cells

Lead Type V Nucleases with A/T rich 5' PAMs are Smaller and Capable of Multiplex Editing

Nuclease	LEG238	LEG214
PAM		
Protein Length	889 aa	770 aa

- Explored 50 systems and engineered for ↑ activity
- Self processing guide RNAs enable multiplex editing
- Higher specificity (up to 17 nt of the spacer)
- Delivery by a single AAV

10X improvement of engineered nuclease (AAV6 – HEK293T cells)



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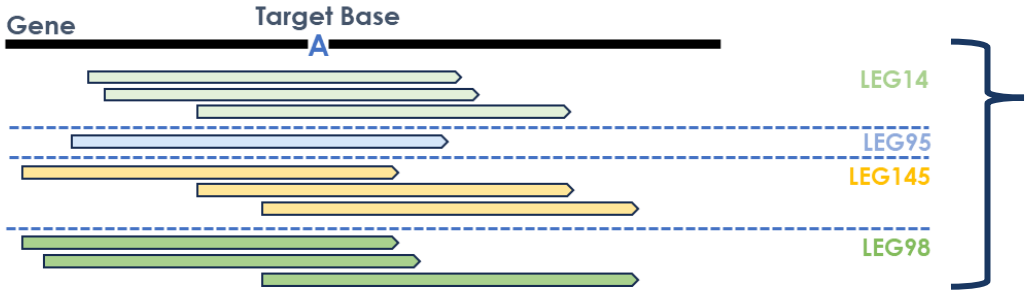
LEG = Life Edit Gene

PAM Diversity Enables Optimization of Editing Activity and Specificity



Diversity of PAM specificities enable optimal positioning of the target site

4 lead systems enabled 10 designs

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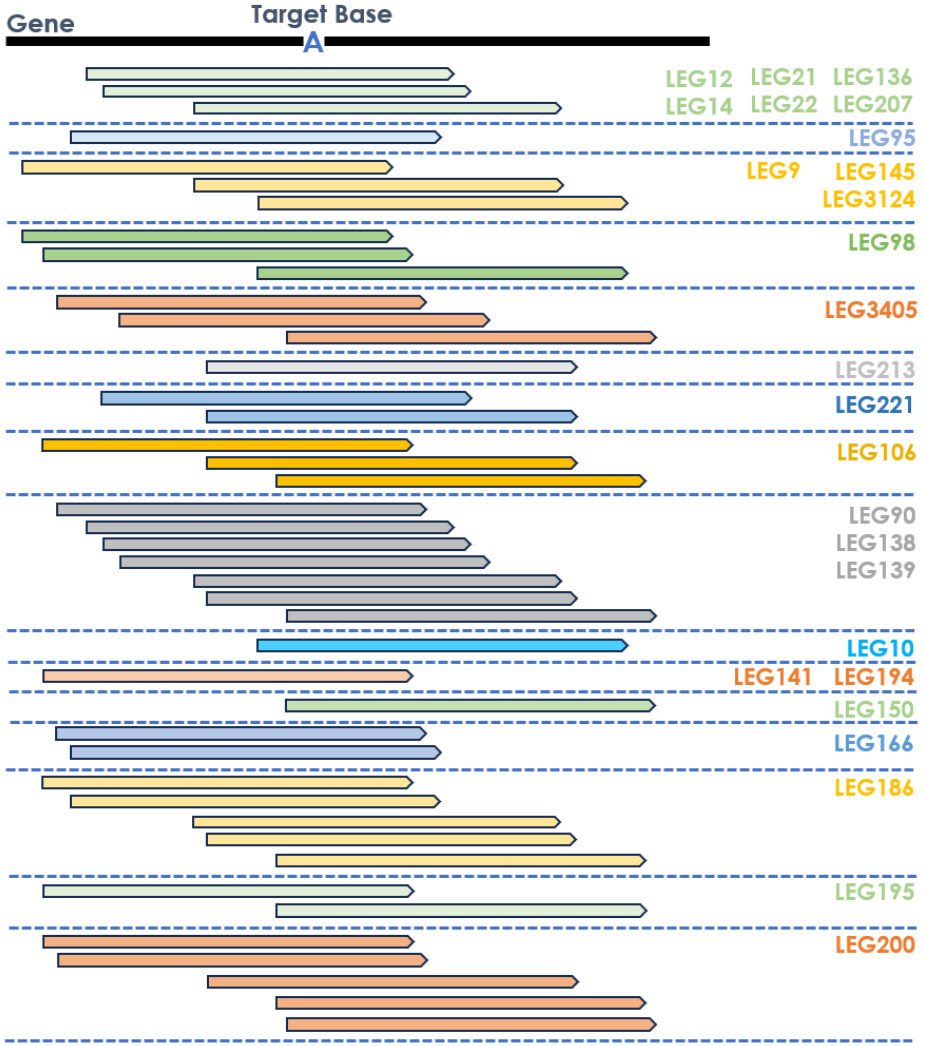
PAM Diversity Enables Optimization of Editing Activity and Specificity



Diversity of PAM specificities enable optimal positioning of the target site

4 lead systems enabled 10 designs

vs.

Expansion to 16 PAMs enables 43 designs

Optimal positioning accelerates lead development by mitigating risks –

- **Potency at target** - all editing modalities
- **Off-target reduction** – all editing modalities
- **Bystander reduction** – Base Editors
- **Distance to edit** – RT Editors

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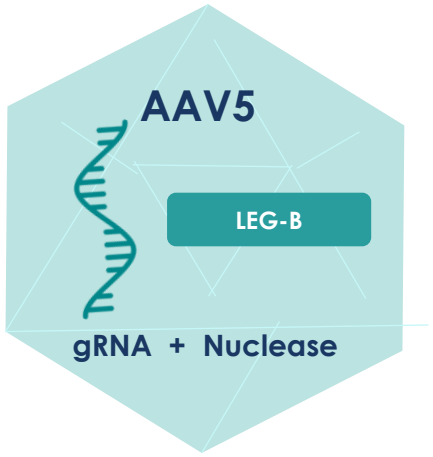
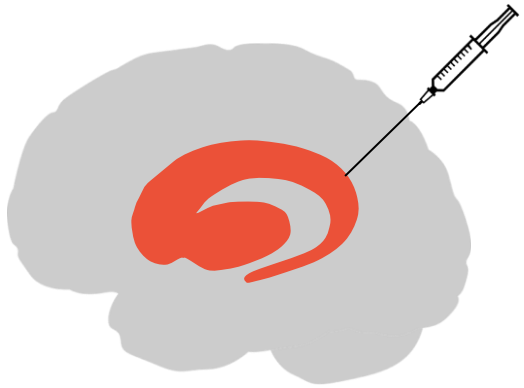
LETI-101: A Novel Precision Editing Approach as Potential One-Time Treatment for Huntington's Disease

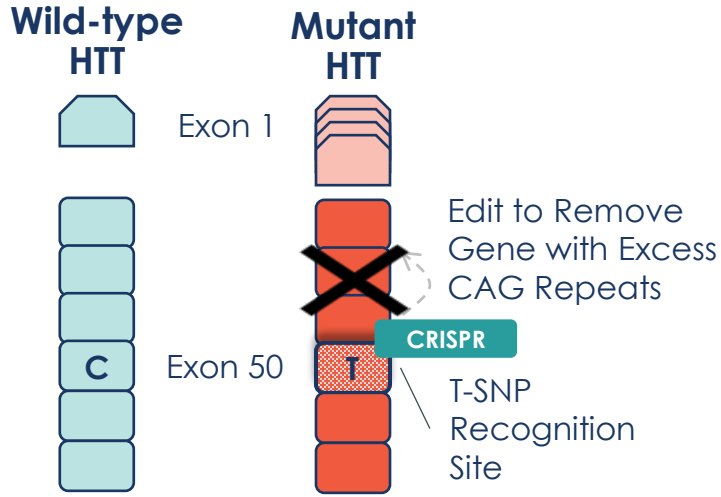
NOVEL CRISPR SYSTEM	TARGETED CNS DELIVERY	ALLELE-SELECTIVE EDITING



Proprietary, compact CRISPR system, packaged in AAV5 vector



One-time, bilateral intrastriatal administration



Potent and selective reduction in mutant while preserving wild-type; selective approach made possible by diverse genomic recognition sites

LETI-101 OFFERS POTENTIAL FOR A DURABLE, **ONE-TIME TREATMENT** WITH AN IMPROVED SAFETY PROFILE THROUGH SELECTIVE TARGETING

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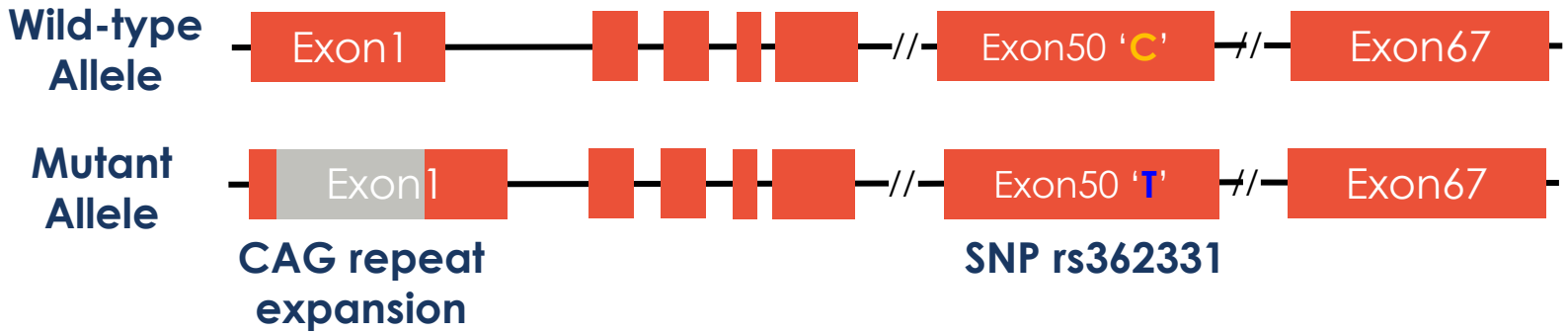
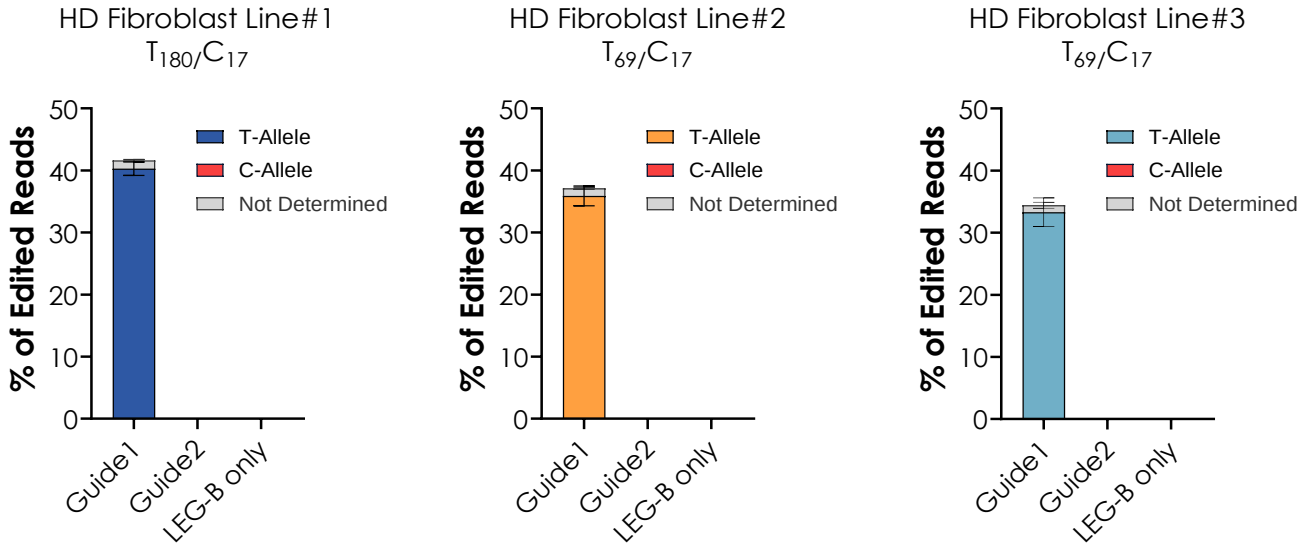
PAM Diversity Enables LETI-101 Allele Selective Strategy for Huntington's Disease



LETI-101 is selective for mutant *HTT* allele based on the PAM generated by exon 50 SNP

- Patient alleles must be heterozygous for target SNP
- Disease causing CAG repeat expansion in exon 1 must be on the allele containing targeted T SNP
- Estimated to capture ~35% of total HD patient population

Selective Editing of Mutant *HTT* Gene



Guide1: LETI-101 mHTT guide

Guide2: Control targeting ROSA26 gene

LEG-B only: nuclease without guide

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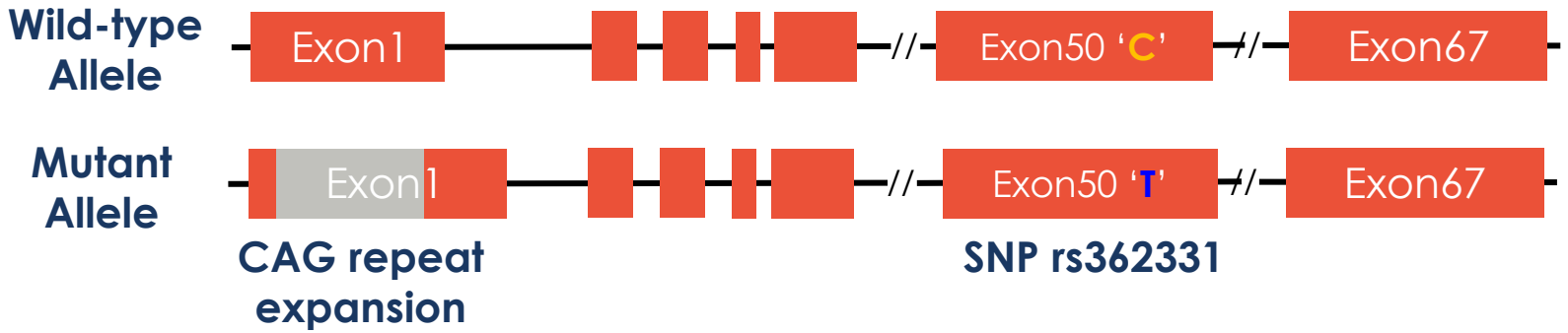
LETI-101 Dose-Dependent Activity in Striatum of BACHD Transgenic Rodent Model



Delivery Vector
AAV5 (nuclease + guide all-in-one AAV)

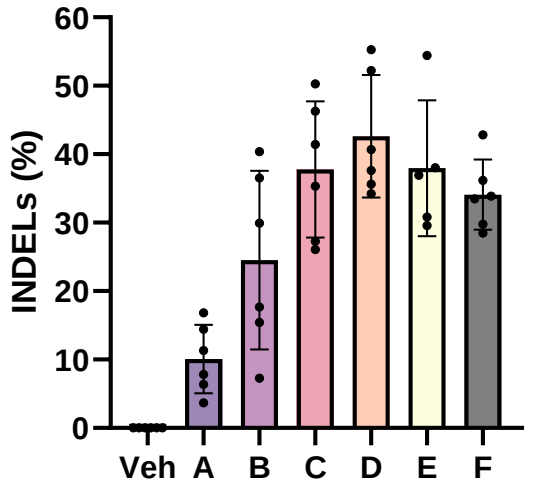
Target Tissue
Caudate & Putamen

- Intrastriatal injections of **LETI-101** in BACHD mice at **six ascending doses** (cohorts A-F)
- **3-month post injection** → bulk striatal tissue harvested and analyzed

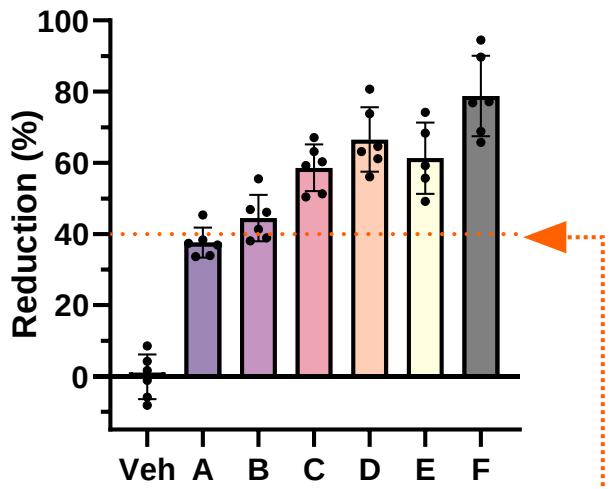
Bilateral intrastriatal delivery of LETI-101 resulted in:

- Dose-dependent AAV vector copy, guide RNA expression, & LEG expression
- Dose-dependent, on-target editing of mHTT allele and up to **80% reduction of mHTT protein**

Editing of Mutant *HTT* DNA



Reduction of Mutant HTT Protein



Clinically relevant threshold of 40% reduction

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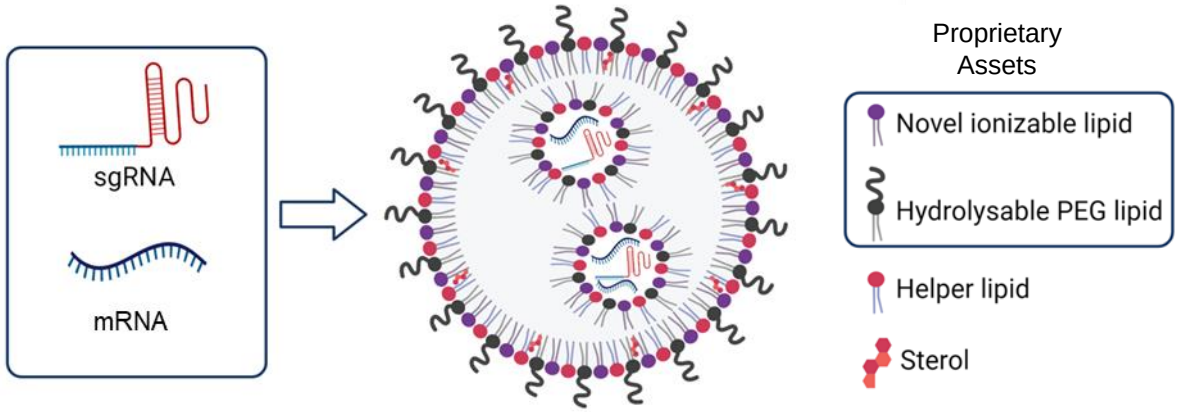
Life Edit's Proprietary LNP Platform

Unique Components

- Ionizable lipids with favorable chemical properties for clinical therapeutic application
- Hydrolysable PEG-lipid with advantageous properties:
  - Tunable pharmacokinetics
  - Low immunogenicity –**opportunity for repeat dosing**
  - Strong physicochemical profile – stable at -20°C



Platform Highlights

- Demonstrated efficient delivery to the liver
- Process developed for scale-up and manufacturing
- Enables *in vivo* delivery of nucleases, base editors, and RT editors

Have validated PK/PD and safety of lead life edit formulation, LNP1, following repeated IV administration, without immunosuppression, in mouse, rat, and NHPs

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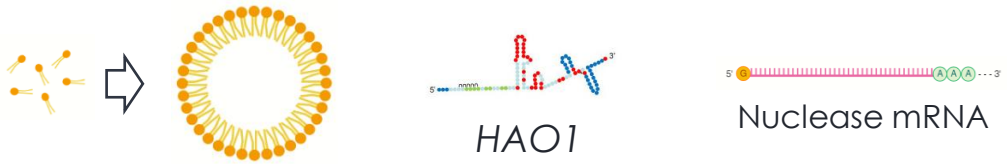
Nuclease Delivered by LNP1 to the Mouse Liver Results in Dose Dependent Gene Knock-Out of HAO1

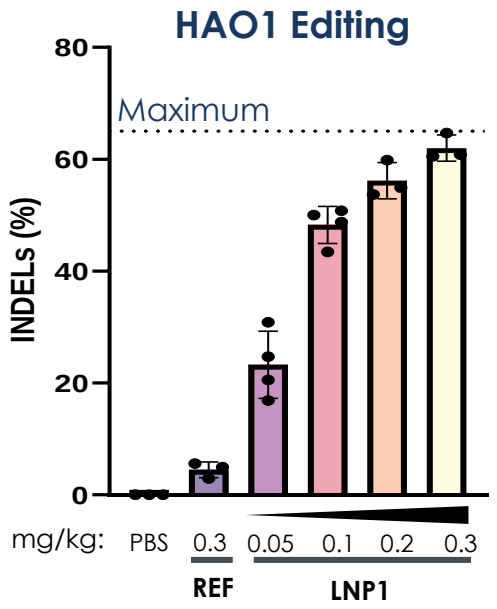
- **HAO1** is a convenient target for LNP development with an easily assayed serum biomarker
  - Primary hyperoxaluria type 1 (PH1) → loss-of-function mutations in the AGXT gene
  - Knocking-out upstream enzyme HAO1 alleviates symptoms
- HAO1 knock-out → increase in serum glycolate

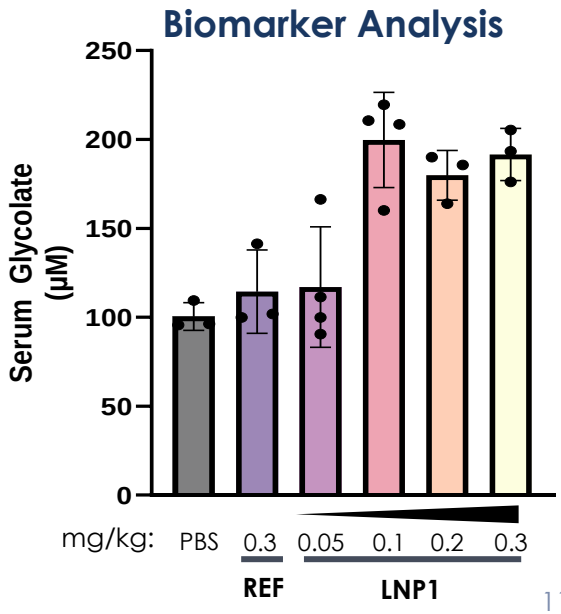


Key Takeaway

Achieved high editing in the mouse liver with our nuclease and lead LNP1 formulation at a low dose of 0.3 mg/kg

- LEG-A nuclease - single IV administration, WT C57BL/6 mice
- REF = comparator LNP included at 0.3 mg/kg





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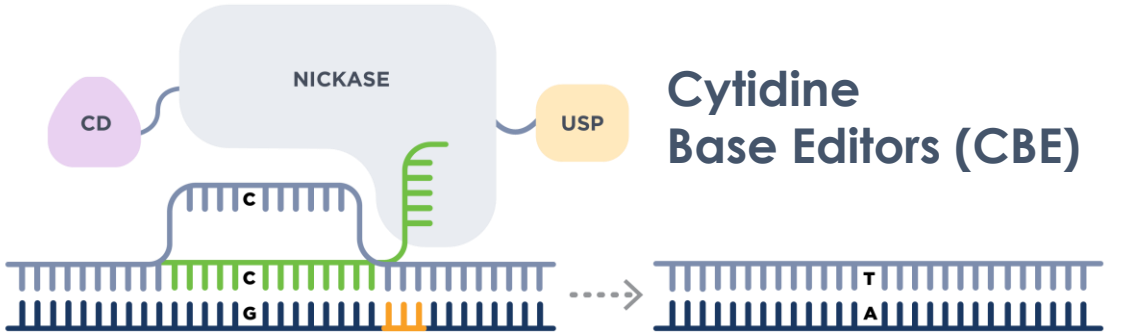
Life Edit's Proprietary Base Editing Systems

- Modular and proprietary nucleases & deaminases
- Efficient and specific C>T and A>G editing
- No double-stranded breaks
- Low indel formation



Cytidine Base Editors (CBE)

- Introduction of stop codons & disruption of splice sites
- Can correct disease-causing SNPs
- Planned utilization in cell therapy as an enabling technology

Adenosine Base Editors (ABE)

- Disruption of splice sites
- Can correct disease-causing SNPs
- Planned utilization primarily for *in vivo* editing

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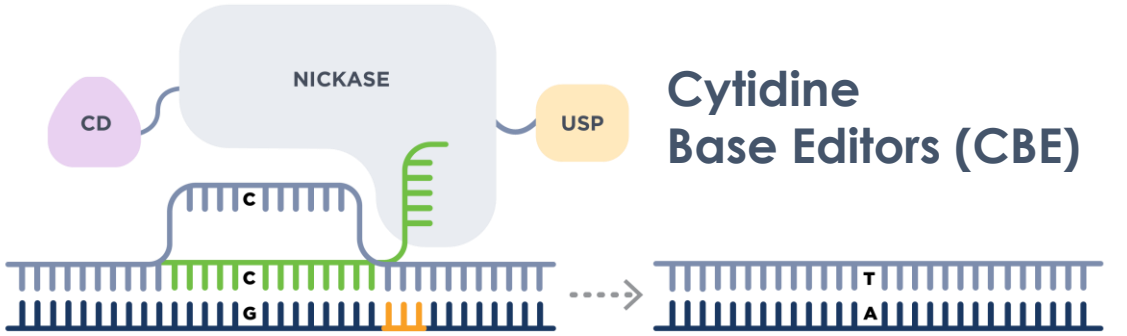

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Adenine Base Editing System Delivered with LNP1 Results in Efficient Editing of PCSK9 in the Mouse Liver

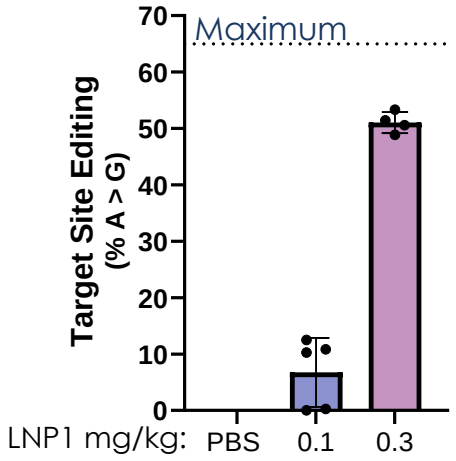
- **Proprotein convertase subtilisin/kexin type 9 (PCSK9)** is a key regulator of LDL-R expression - made in the liver
- PCSK9 inactivation / knock-out reduces serum LDL-C
- Potential therapeutic target to treat familial hypercholesterolemia and severe ASCVD

- First *in vivo* study utilizing proprietary lipid and ABE to target PCSK9
- LEG-A ABE - single IV administration, WT C57BL/6 mice

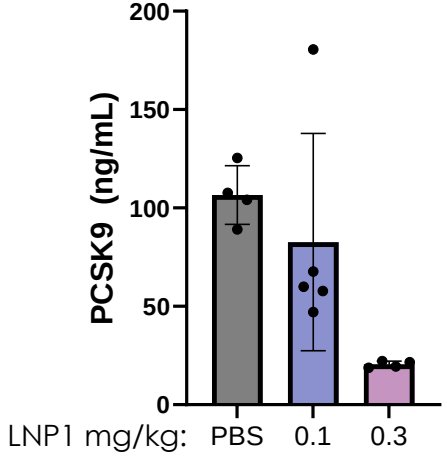
Key Takeaways

- Treatment was well-tolerated
- High potency base editing at 0.3 mg/kg with robust reduction in serum PCSK9 and lower total cholesterol

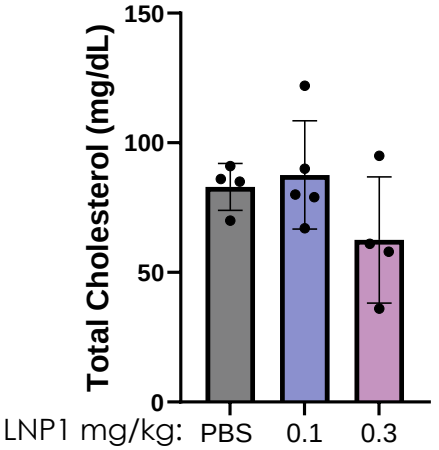
Pcsk9 Liver Editing



Serum PCSK9



Serum Total Cholesterol



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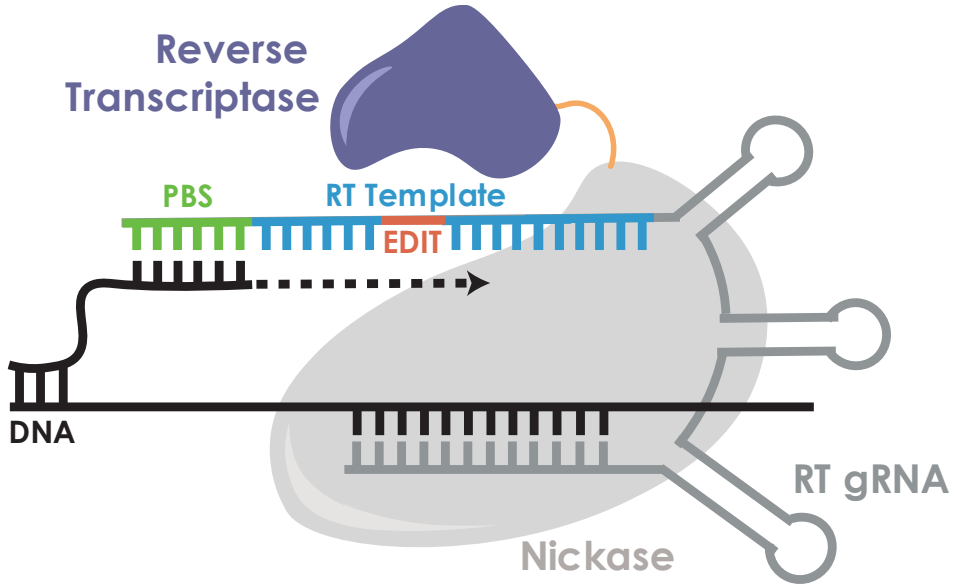
Reverse-Transcriptase Editors

Utilizes proprietary nucleases and reverse transcriptases

Precise insertions, deletions, and substitutions

No double-stranded breaks



Life Edit Platform

- PAM diversity enables increased optionality for gene targeting
- Pooled lentiviral library RT guide screening platform
- Novel RT discovery and engineering
- Dual RT editing approach

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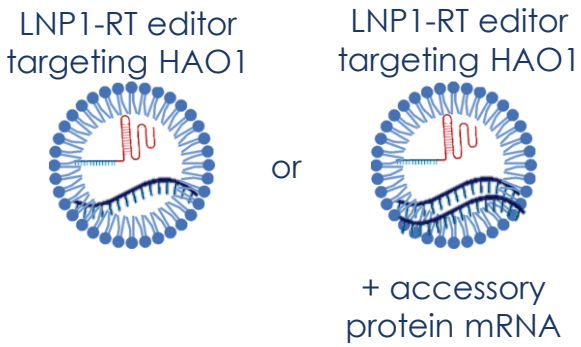
Reverse Transcriptase Editing *In vivo* Assessment in the Mouse Liver Using Proprietary LNP1 Formulation

- Second *in vivo* study utilizing LNP1 and RT Editor to target HAO1

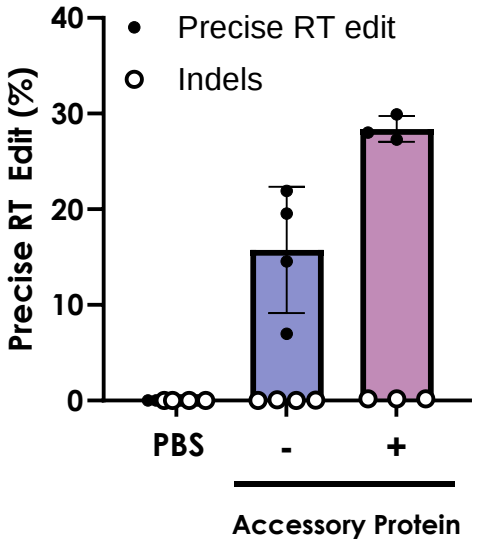


Key Takeaways

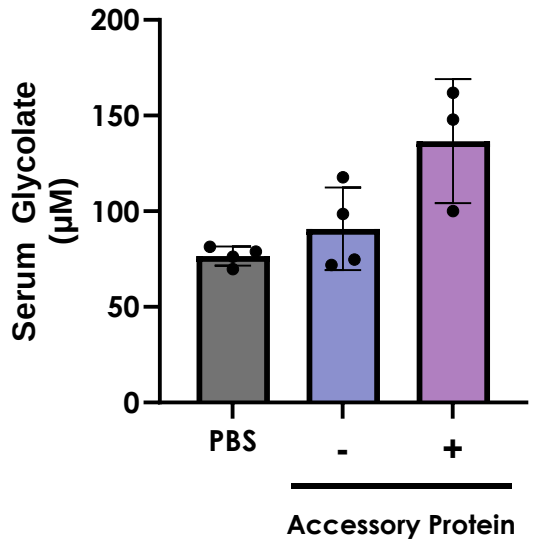
- LNP1 delivered RT editor was well tolerated
- Up to 28.4% RT editing at 2 mg/kg
- Presence of accessory protein improved editing by 1.8x (~12%)

- LEG-B RT - single IV administration, WT C57BL/6 mice

HAO1 RT Editing



Biomarker Analysis



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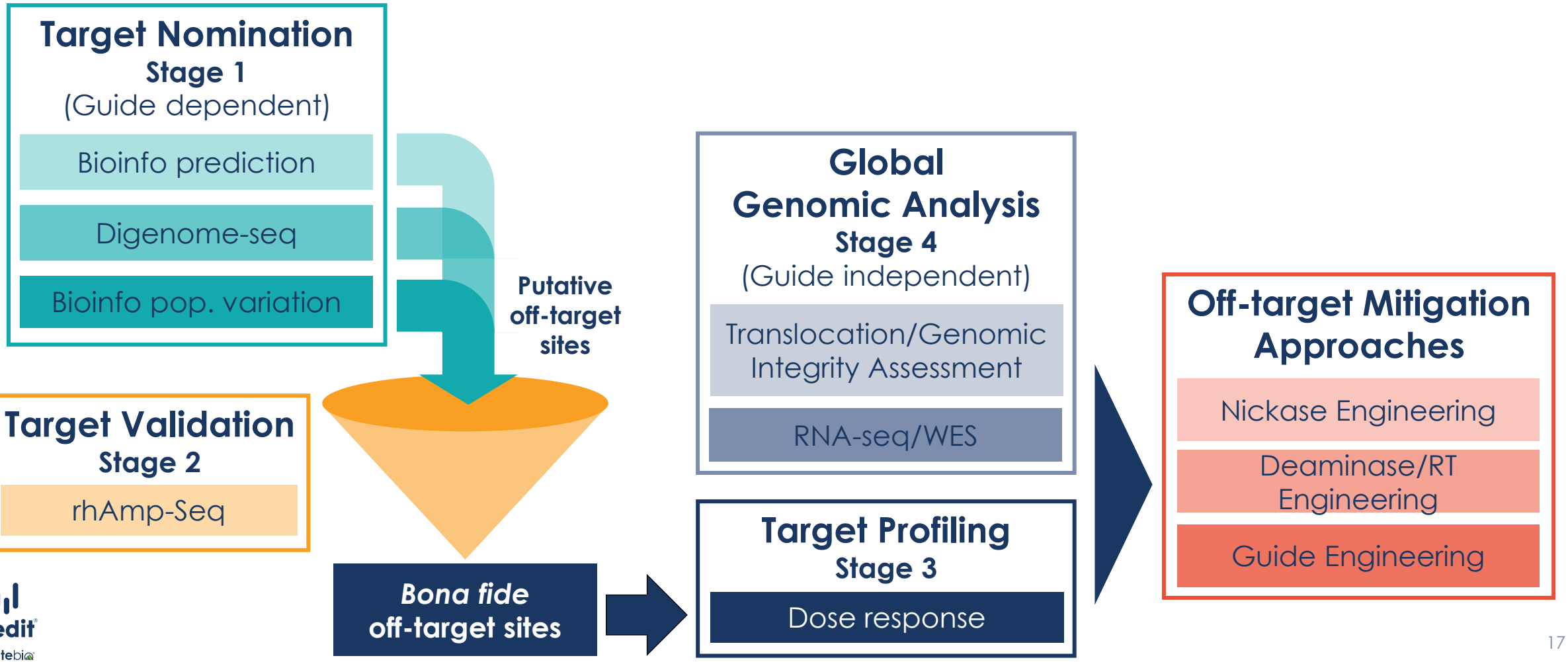
Off-Target Strategy to Assess Editing Modalities

Life Edit has an established workflow to characterize off-target profile of editors and boost specificity with directed evolution engineering approaches



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Unlocking the Potential of Genomic Medicines Through Editing and Delivery Capabilities

POTENT DISEASE-SPECIFIC GENE EDITING

Clinically-relevant reduction of mutant HTT protein in Huntington's disease

- On-target editing resulted in **up to 80% reduction of mHTT protein** in HD transgenic rodent model
- **Small size of Life Edit nucleases** enable packaging in single AAV for efficient delivery to the brain
- Exquisite allele-specific editing of mutant HD gene enabled by **diverse PAM recognition sites**

PROPRIETARY EDITING & DELIVERY SOLUTIONS

Lipid nanoparticle (LNP) technology for effective delivery of genomic medicines to the liver (and beyond)

- **LNP delivery of LEG nuclease** achieved high editing in the mouse liver at a low LNP dose
- **LNP delivery of A-base editor** elicited therapeutically relevant editing of PCSK9 in vivo at low LNP doses resulting in robust reduction of total cholesterol
- **mRNA-LNP delivery of RT editor** resulted in ~30% precise editing of a liver target in vivo in mice

NEXT-GENERATION GENOMIC MEDICINES

Unlocking the future of genetic medicines

Leveraging AI and our deep expertise in computational biology to:

- Improve existing gene editing functionalities and expand into additional ones
- Improve success rates of therapeutic development by customizing proteins to the disease

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