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Allele-selective editing of mHTT utilizing AAV5-delivered Life Edit® CRISPR System (LETI-101) results in meaningful reduction of mHTT protein

Logan Brown Ph.D., Nancy Cheng Ph.D., Alexandra Crawley Ph.D., Helen Mao Ph.D., Jamie Moy Ph.D., Kathryn Woodburn Ph.D.

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Disclaimer & Disclosures

The information presented in this, and all sessions presented at the HSG 2023 Annual Meeting is for informational purposes only.

Relevant disclosures for this presentation, given by Logan Brown, Ph.D. include:

- An employee of Life Edit Therapeutics (an ElevateBio company)

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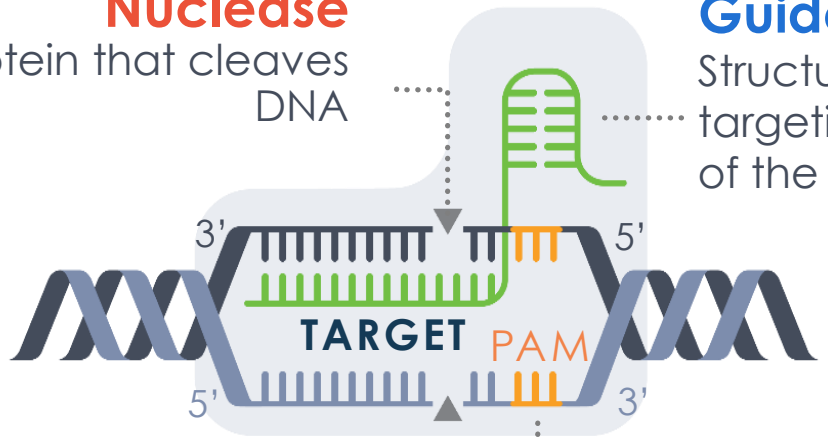
Life Edit Gene Editing Technology

Life Edit's Collections of Proprietary RNA guided Nucleases Enable Flexible Targeting of Disease-Linked Genes

CRISPR System Components

Nuclease
Protein that cleaves DNA

Guide RNA
Structure determines targeting specificity of the nuclease



PAM
Recognition sequence required for cutting

Life Edit Lead Nucleases				
Nuclease	Base Pairs	Amino Acids	MW kDa	PAM
LEG14	3213	1071	126	NNNNCC
LEG95	3450	1150	133	NNRYA
LEG98	3156	1052	124	NNGRR
LEG145	3390	1130	130	NNGG
SpCas9	4104	1368	158	NGG

- Life Edit Genes (LEGs) have diverse PAM recognition sequences enabling broad genome targeting
- Life Edit nucleases are compact, enabling efficient delivery with a single AAV vector

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LETI-101 Allele Selective Strategy for Huntington's Disease

Target Tissue	Caudate & Putamen
Delivery Vector	AAV5 (nuclease + guide all-in-one AAV)
Route of Admin.	Intrastriatal
Genetic Target	HTT Exon50 SNP 362331
Nuclease	LEG-B targeting 'T' allele

Addressable Genotype

Allele Selective Editing

PAM site generated by HTT Exon50 rs362331 SNP allows selective targeting of HTT mutant allele with Life Edit nucleases based on the presence of 'T' nucleotide

- Patient alleles must be heterozygous with T in mut allele only
- CAG repeat expansion must be in-phase with targeted allele
- **Result is selective editing of *mHTT* leading to lowered mHTT protein production while preserving WT HTT protein production**

- **LETI-101 is selective for mHTT allele based on the PAM generated by SNP rs362331 in exon 50**
- **LETI-101 is a one-time treatment that permanently modifies mHTT DNA for lasting therapeutic effect**

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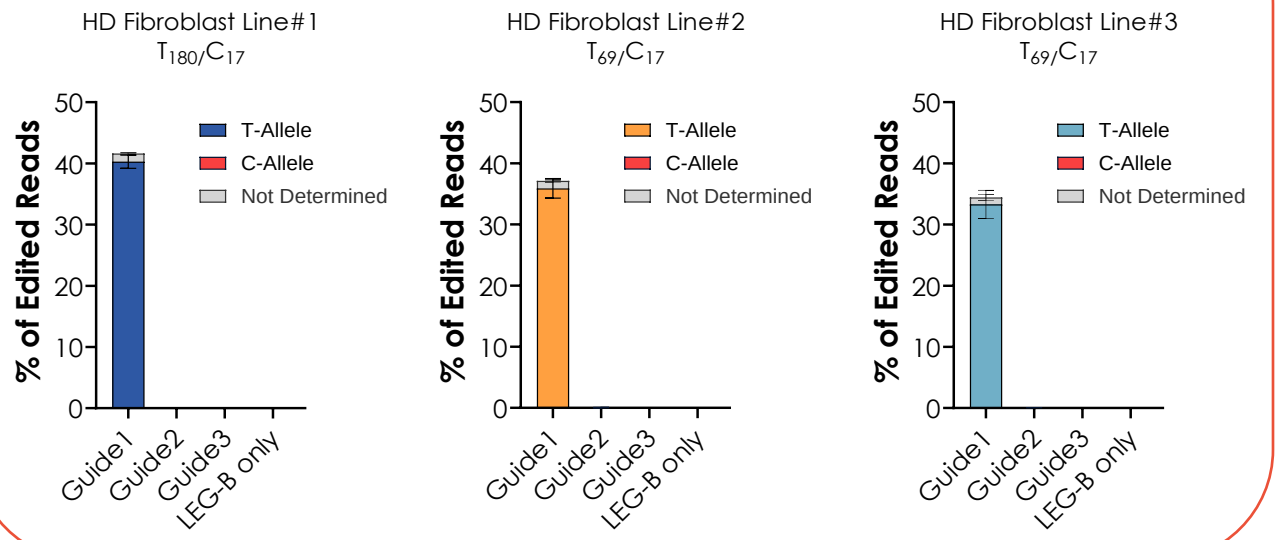
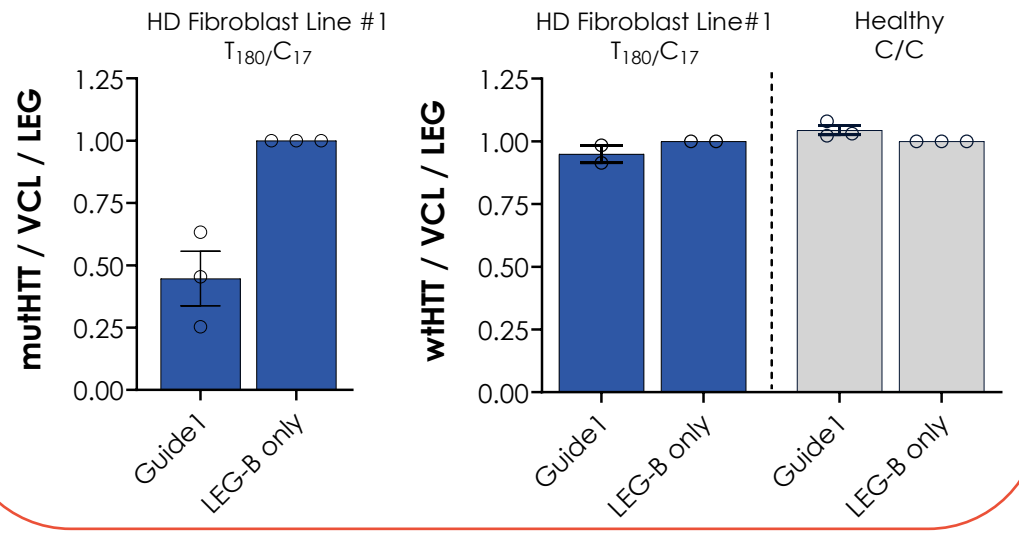
LETI-101 Allele Selective Editing in HD Patient Fibroblasts

Selective Editing of Mutant *HTT* Gene



- Guide1 – LETI-101 guide
- Guide2 – Control targeting mHTT without PAM
- Guide3 – Control targeting mouse ROSA26 gene
- LEG-B – Control; nuclease without guide

Selective Reduction of Mutant HTT Protein



Data represent mean ± SE

- mRNA/RNA transfection
- Protein quantification by capillary electrophoresis
- Subtext denotes CAG repeat length of each allele

- **LETI-101 composition 'LEG-B-Guide1' selectively edits the *mHTT* allele only in the presence of the PAM-forming 'T' SNP rs362331**
- **LETI-101 composition 'LEG-B-Guide1' selectively reduces mutant HTT protein, but does not affect wild-type HTT protein levels in either patient-derived or healthy donor cell lines**

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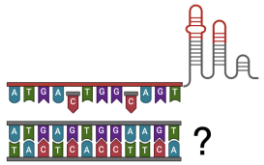
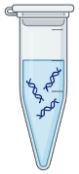
Off-Target Analysis Reveals Specificity of LETI-101

Off-Target Identification Strategy





Bioinformatic Prediction

Predicts off-targets based on homology to guide

Population Variation Analysis

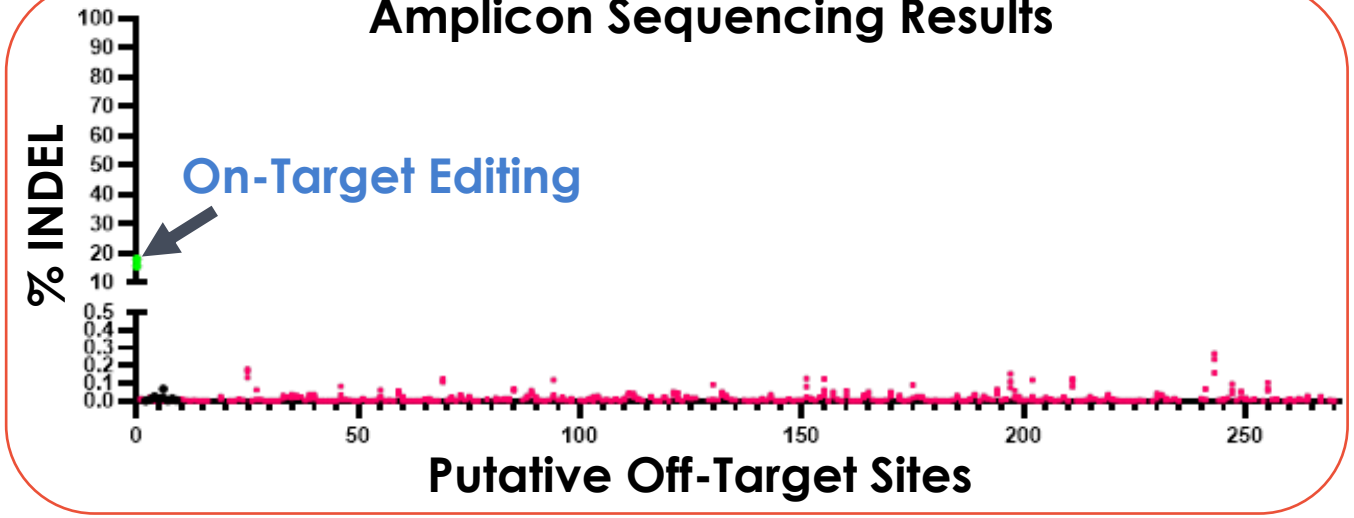
Identifies SNPs that could pose off-target risks

Digenome-Seq

Unbiased biochemical method to identify putative off-targets

~300 putative off-target sites identified and profiled via amplicon sequencing using genomic material from HD patients edited with mRNA/RNA delivery

Amplicon Sequencing Results



No off-target editing observed at sequenced sites & no off-target liabilities identified

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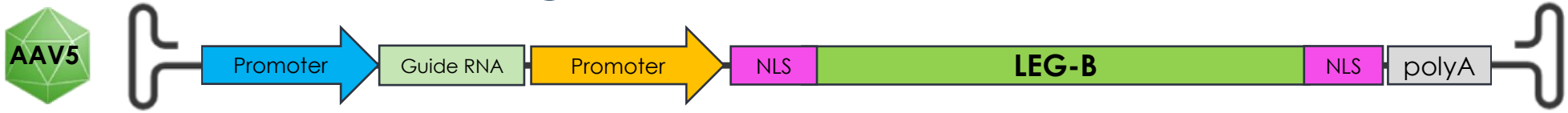
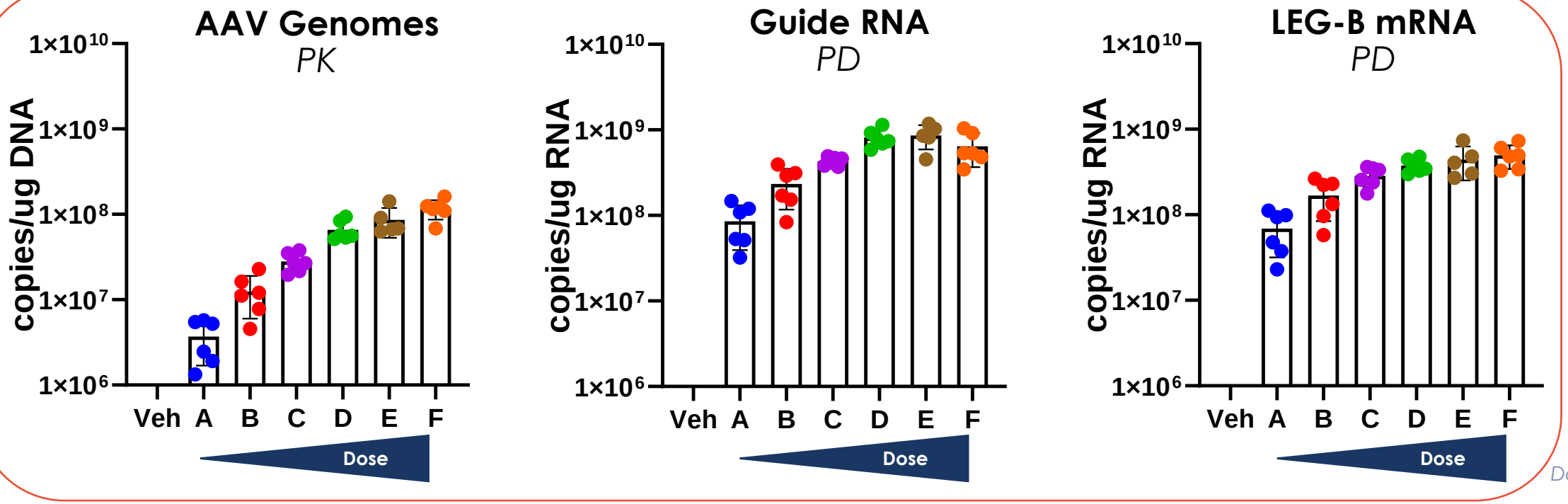
LETI-101 Dose-Dependent Expression & Activity in Striatum of BACHD Transgenic Rodent Model





Data represent mean ± SD

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

Dose-dependent AAV vector copy, guide RNA expression, & LEG-B expression

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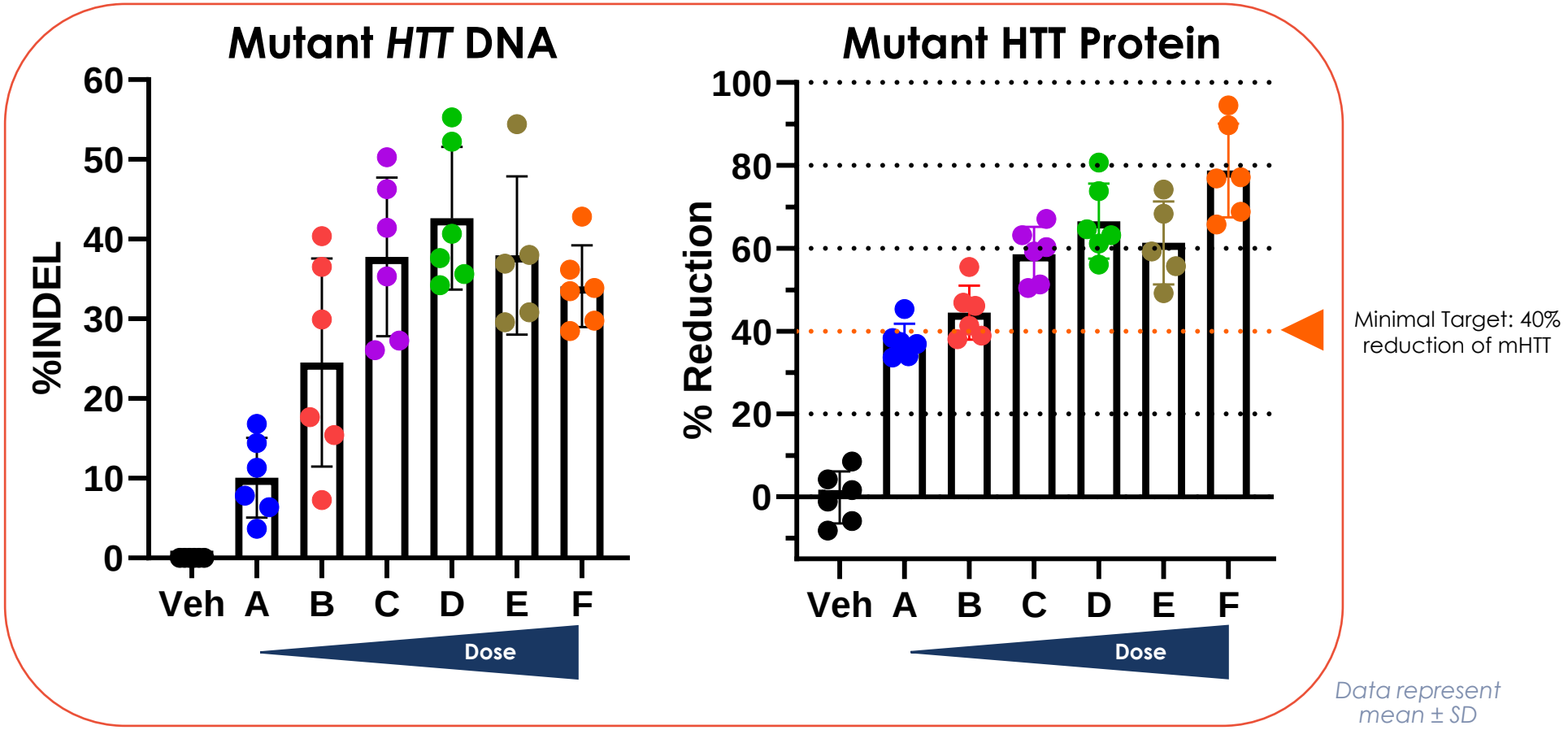
LETI-101 Dose-Dependent Expression & Activity in Striatum of BACHD Transgenic Rodent Model



Data represent mean ± SD

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

Dose-dependent, on-target editing of mHTT allele and up to 80% reduction of mHTT protein

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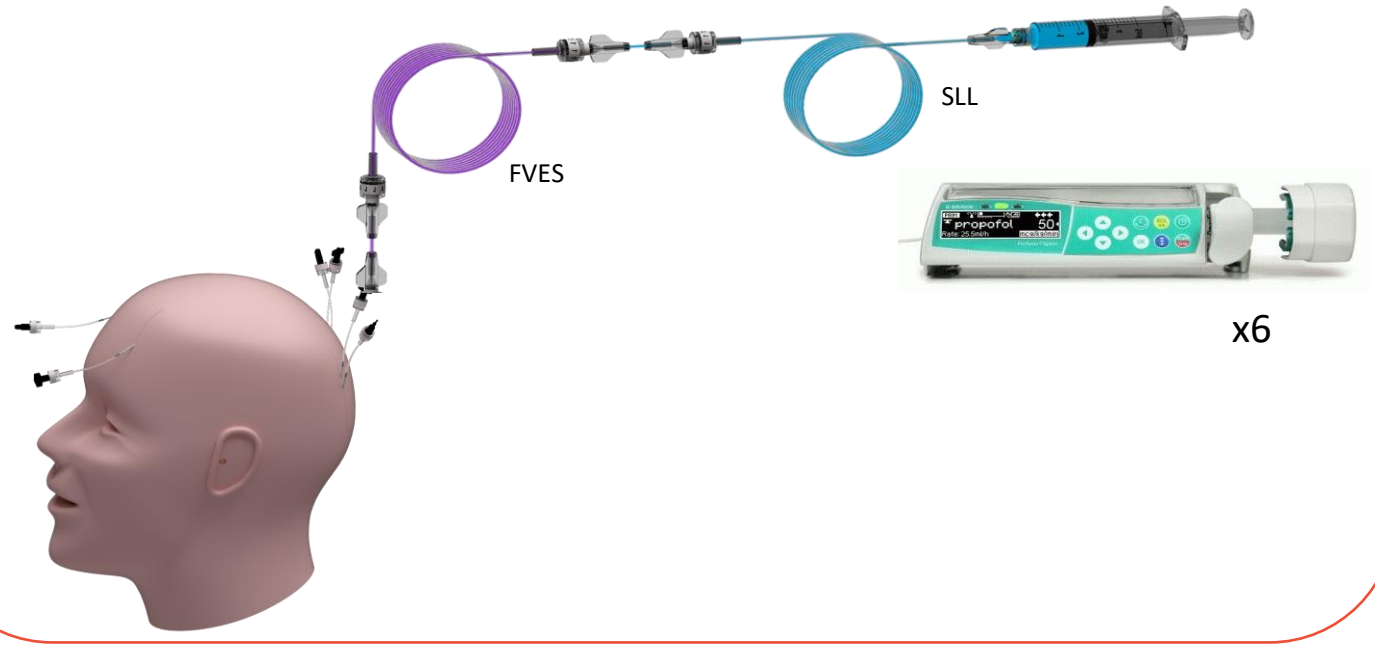
Overview of Combination Product LETI-101+neuroinfuse™ intraparenchymal drug delivery system (Renishaw)

Schematic Representation of Delivery System



- Reflux inhibiting feature facilitating convection enhanced delivery forms a pressure gradient at tip of infusion catheter to deliver drug product directly through the interstitial space
- Implantation of catheters and infusion can be performed outside MRI; all infusions can be performed simultaneously reducing procedure time
- LETI-101 can be safely administered quickly while patient is awake, reducing exposure to anesthesia

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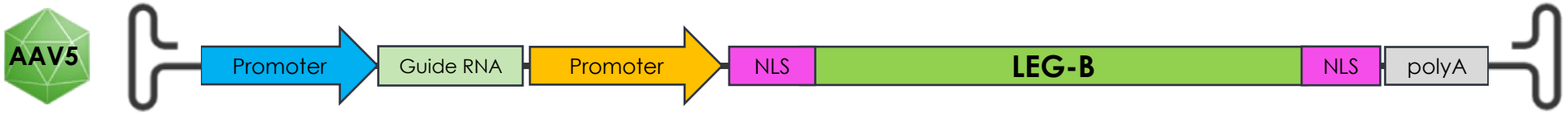
One Month Tolerability and Biodistribution of LETI-101 in Adult Cynomolgus Monkeys



Group	Subjects	Treatment	Dose (vg/brain)	Volume per Hemisphere (µL)
Vehicle	1M	Vehicle	0	Caudate: 75, Putamen: 150
Low Dose	1M / 1F	LETI-101	Low Dose	Caudate: 75, Putamen: 150
High Dose	1M / 2F	LETI-101	High Dose	Caudate: 75, Putamen: 150

- Administration performed using the Renishaw Acute Drug Delivery system with Neuroinfuse™ catheters
- No LEG-B PAM in NHP *HTT* exon 50 homologous region

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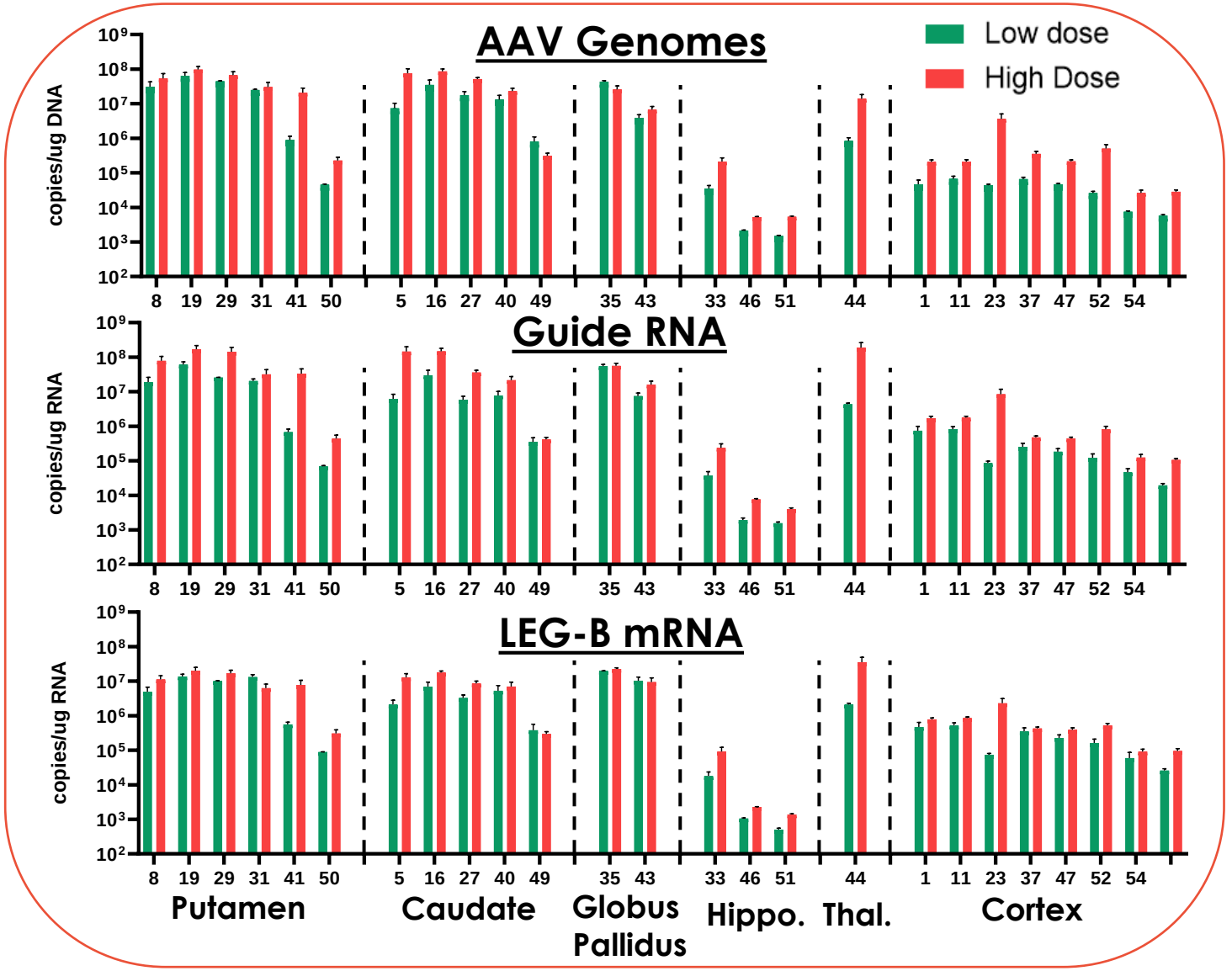
LETI-101 Dose-Dependent Biodistribution in HD Critical Brain Regions of Cynomolgus Macaque



- Intrastriatal injections of LETI-101 in Cynomolgus monkeys at 2 dose levels
- X-axis denotes tissue punch #
- 1-month in-life duration
- Data represent mean ± SD

- **Intrastriatal delivery of LETI-101 in cynomolgus macaques was well-tolerated; all animals survived to scheduled necropsy with no noted untoward clinical observations**
- **Dose-dependent vector biodistribution, guide RNA expression, & LEG-B expression in the striatum was observed 1-month following bilateral intrastriatal CED administration**
- **NOAEL obtained for highest dose level evaluated**

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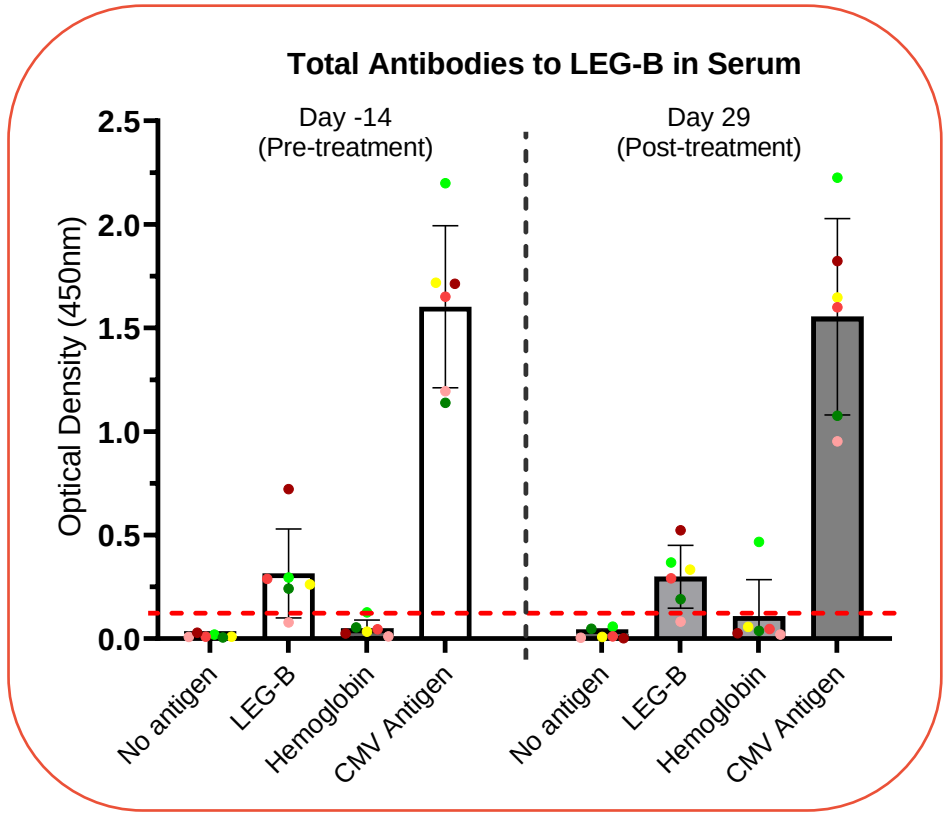
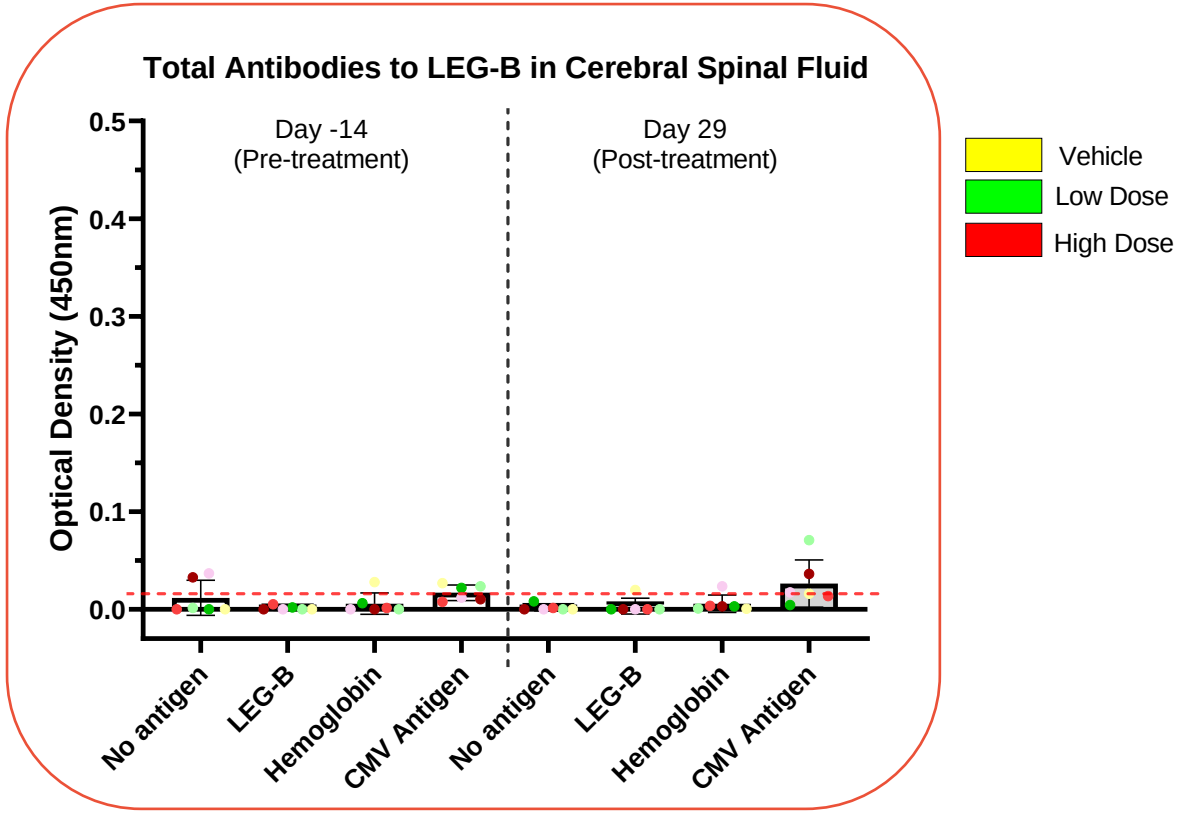
One Month Tolerability and Biodistribution of LETI-101 in Adult Cynomolgus Monkeys





No change in immune response to LEG-B nuclease observed in serum or CSF following bilateral intrastriatal administration of LETI-101

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LETI-101 Summary

1. Delivery with a single AAV vector
2. Allele specific targeting of *mHTT*
3. Efficient delivery to CNS when delivered via AAV5
4. Clinically relevant reduction of mHTT protein in BACHD transgenic mice
5. Dose-dependent biodistribution and transgene expression across brain regions that are critically vulnerable in HD in NHPs

Life Edit Therapeutics met with MHRA in September 2024 to review LETI-101 program

- Preclinical data package well received; deemed "sufficient and comprehensive" including off-target characterization strategy
- Concurrence with overall clinical trial design and CMC strategy

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End