MG71-S1 MEDIATED *APOC3* KNOCKOUT AS A ONE-TIME TREATMENT FOR SEVERE HYPERTRIGLYCERIDEMIA

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Disclosures for Vicente Planells-Palop, PhD

Conflict	Disclosure - if conflict of interest exists
Research Support	
Director, Officer, Employee	Employee of Metagenomi Therapeutics , Inc.
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Consultant	

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From novel genome editing systems to curative therapies

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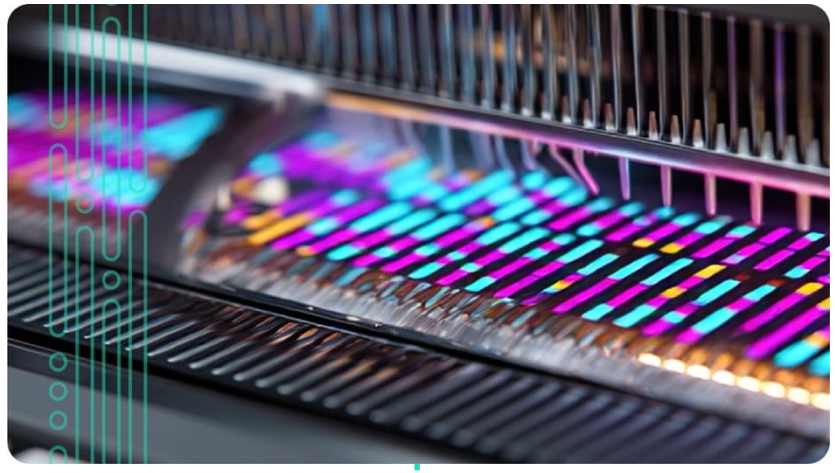
Metagenomi Therapeutics is an in vivo genome editing company capitalizing on its proprietary technologies to precisely correct a wide range of genetic mutations across the human genome. The company is focused on wholly owned programs in Hemophilia A and secreted protein disorders, and partnered assets targeting cardiometabolic indications.



2018

Discovering novel genome editing systems

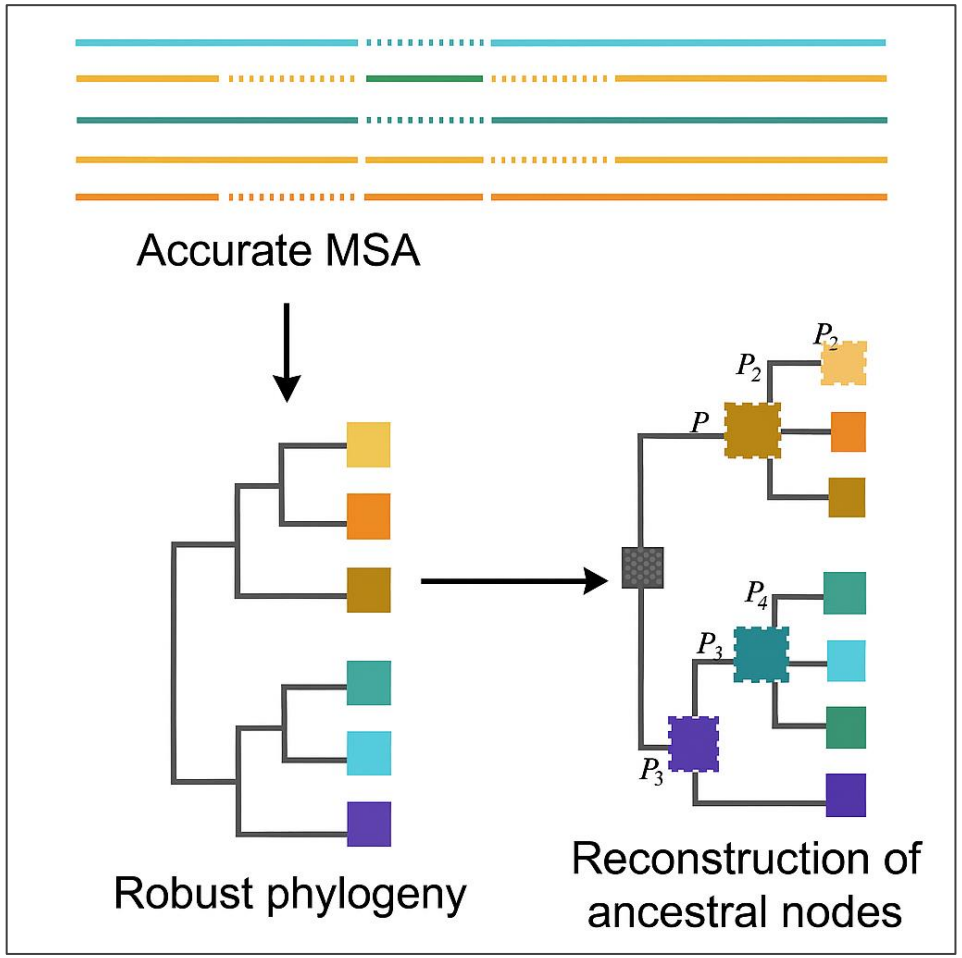
2023

NASDAQ: MGX

2025

Developing a pipeline of in vivo therapies

MGXdb was used to identify MG71-S1 through ancestral sequence reconstruction (ASR) with MG71 family members



The diversity of our proprietary database, MGXdb, allows for high-quality ancestral sequence reconstruction and the generation of novel enzymes which are otherwise inaccessible.

In addition to simply adding diversity, ancient proteins have been shown to have beneficial properties*

Increased stability → better in cell activity
Unique binding preferences → better targetability
On vs off-target affinity → higher specificity

MG71-S1 is an ASR from the Type II-A CRISPR-associated nuclease clade MG71 and demonstrates increased activity and targeting flexibility at the *APOC3* locus.**

*Spence MA, *et al. Curr Opin Struct Biol*. 69, 131-141 (2021); Prakinee K, *et al. JACS*. 4(12):4571-4591 (2024); Thomson RES *et al. J Biol Chem.* 298(10):102435 (2022).

**Alexander, L. M. *et al. CRISPR J*. 6, 261–277 (2023).

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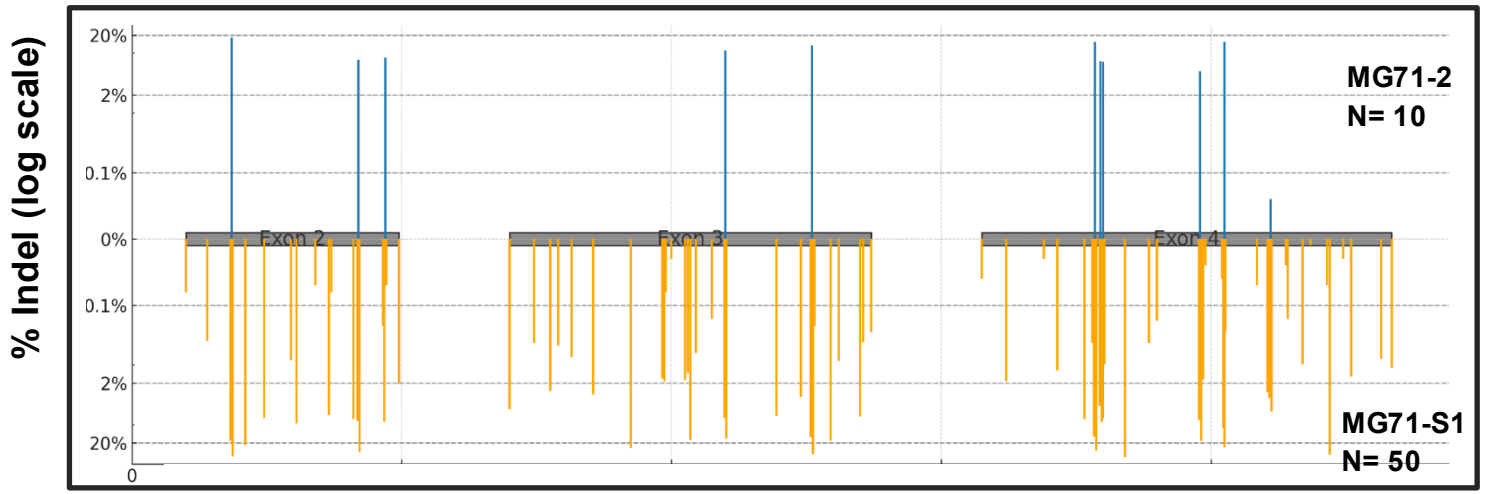
MG71-S1 has increased targeting flexibility and activity compared with natural homolog

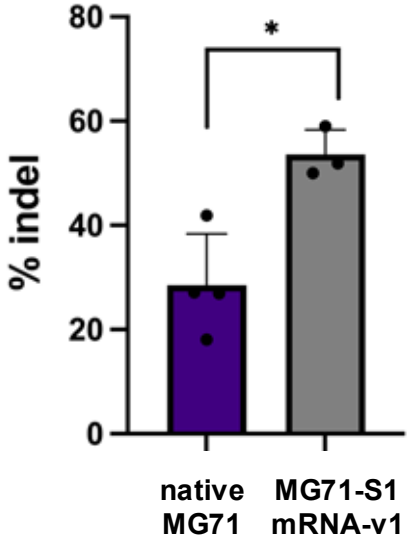
MG71-S1 flexible PAM yields more targeting opportunities at the *APOC3* locus compared to native nuclease



gRNA targeting opportunities in 3 coding exons of the human *APOC3* gene

Primary human hepatocytes

MG71-S1 has higher activity compared to native nuclease *in vivo*



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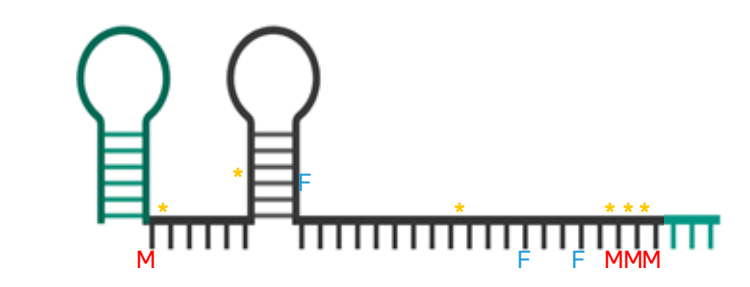
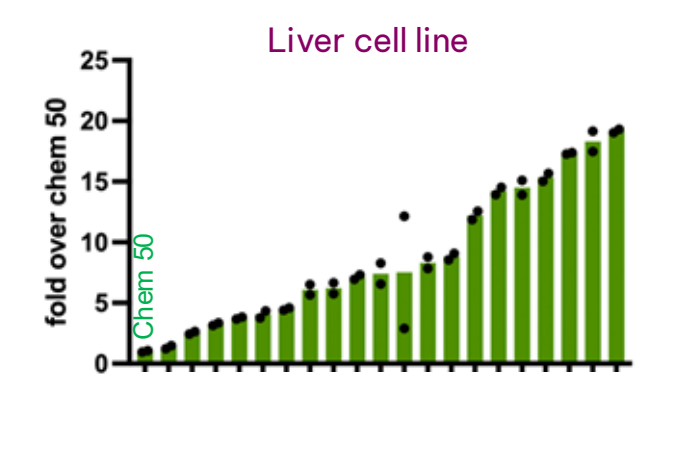
Optimization of Guide and mRNA are critical for potency

gRNA Engineering

For potent *in vivo* activity, gRNAs require significant engineering often involving chemical and sequence modification.

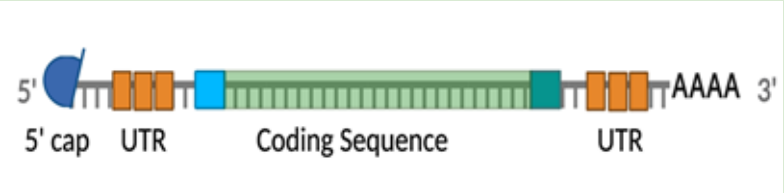


Example of guide engineering

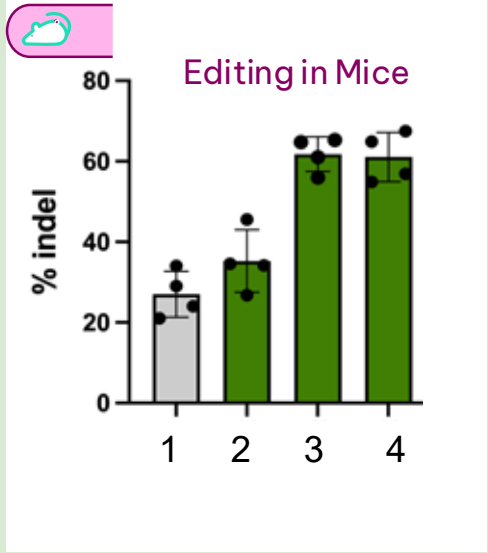


mRNA Engineering

Editor mRNAs require fusion to nuclear localization signals (NLS) and codon optimization for optimal activity.



Example of mRNA engineering



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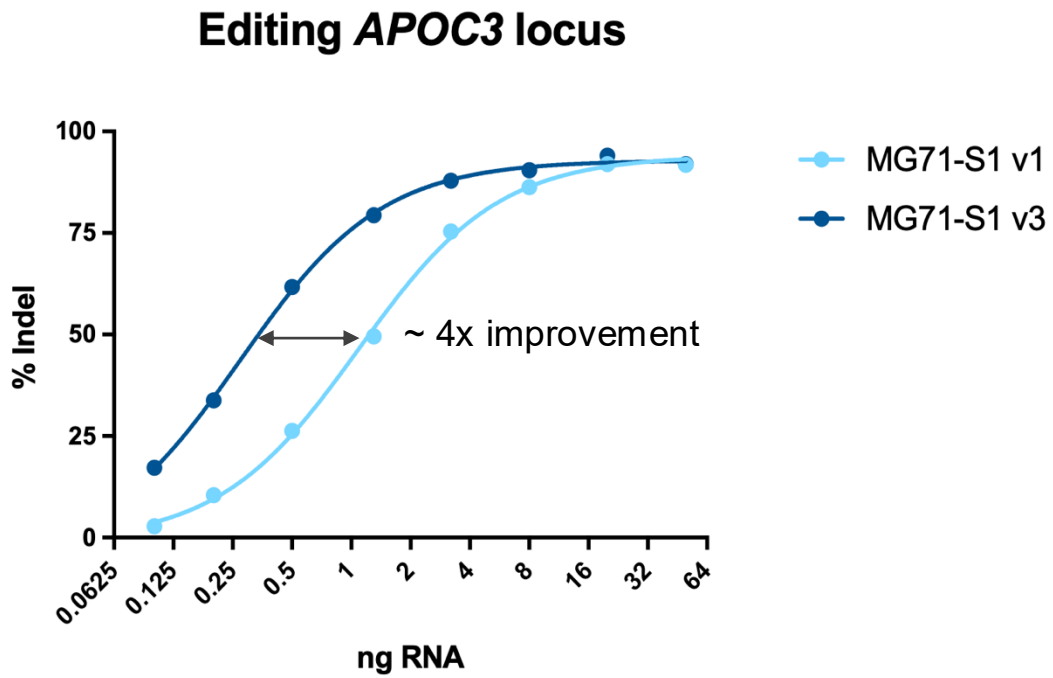
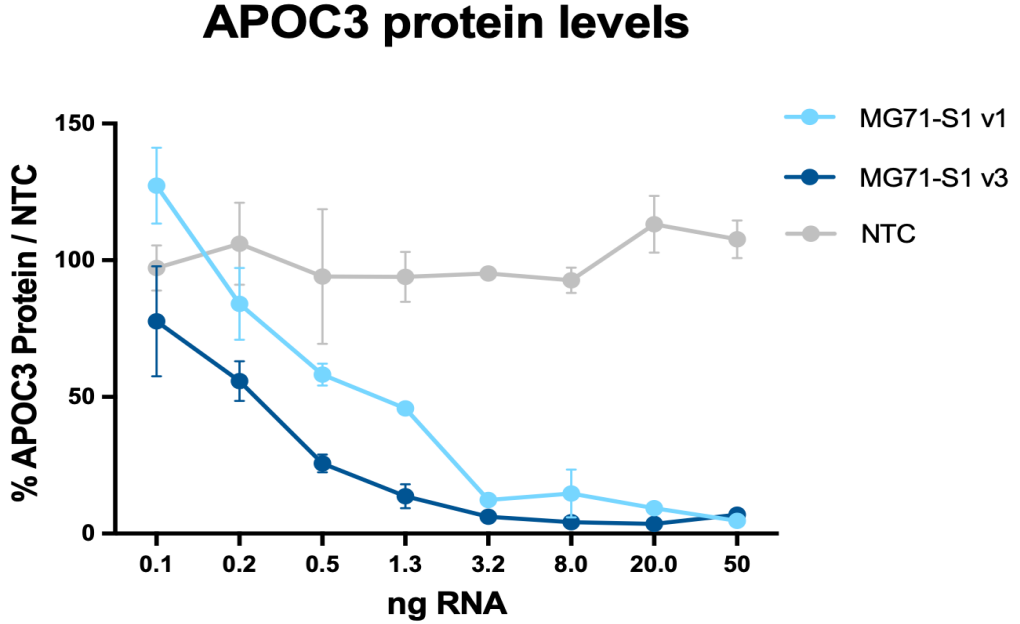
Dose dependent and potent editing at *APOC3* in Primary Human Hepatocytes (PHH) using optimized MG71-S1 mRNA and sgRNA delivered by lipid nanoparticle





>90% reduction in APOC3 protein at saturating dose; 4-fold improvement in EC50 with optimized mRNA

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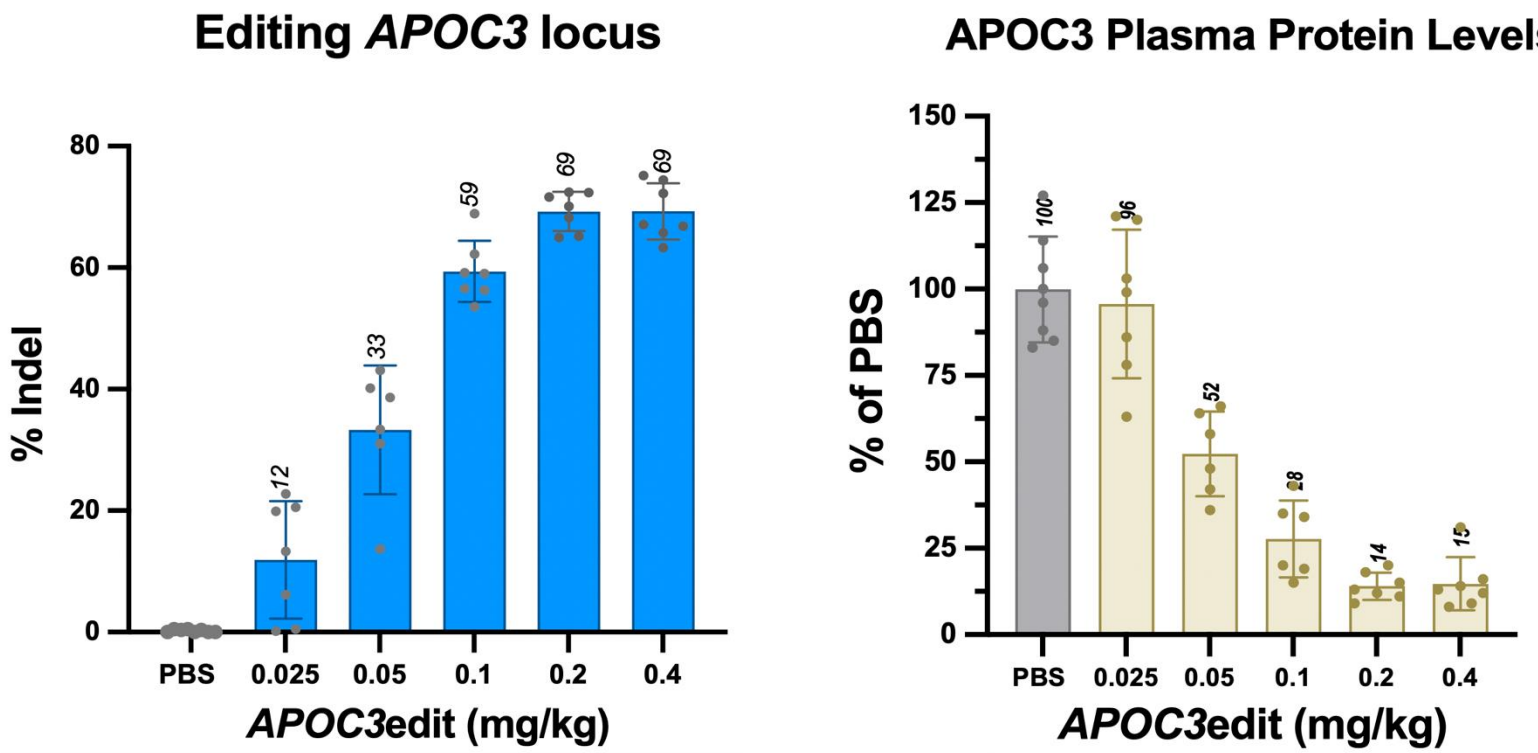
Potent gene editing and APOC3 protein reduction in single copy human apoCIII transgenic mice



Saturating levels of editing achieved at low dose of LNP in single copy transgenic mouse model

Concomitant APOC3 protein reduction observed (up to 85%)

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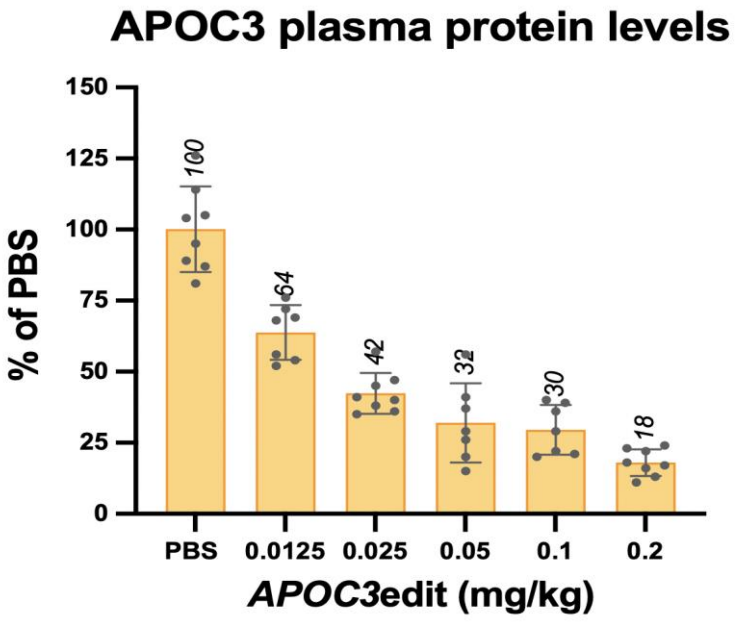
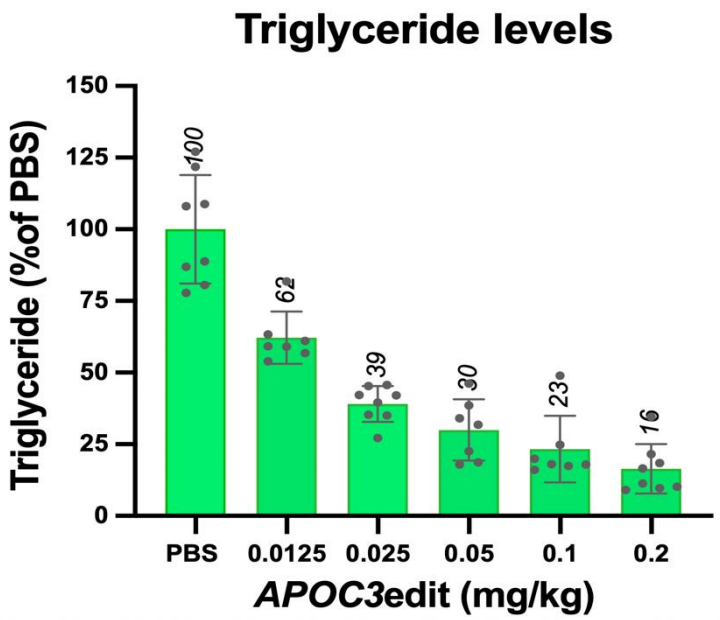
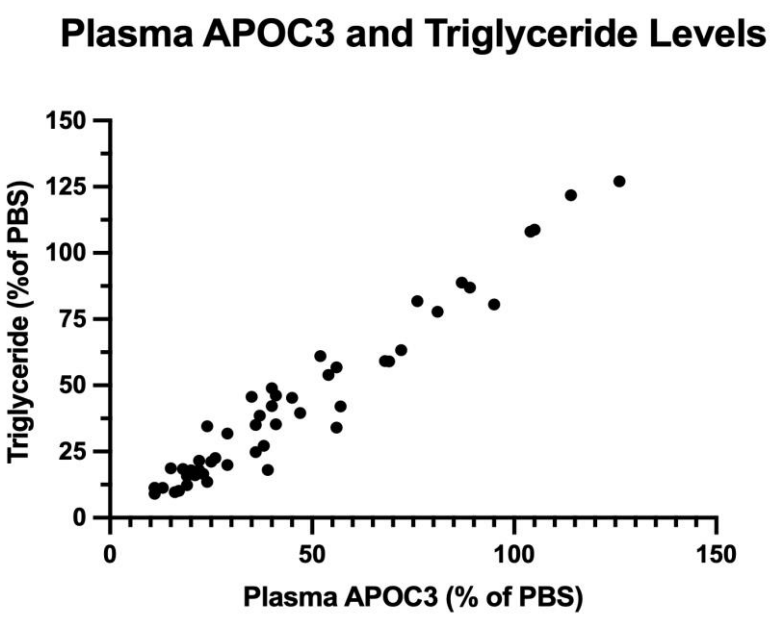
Potent APOC3 protein and triglyceride reduction in multicopy human apoC3 transgenic mice

- Multicopy mouse model has elevated triglycerides (TG), unlike single copy model
- Enables evaluation of impact of gene editing on TG levels







Triglyceride reduction up to 84%, proportional to APOC3 protein reduction

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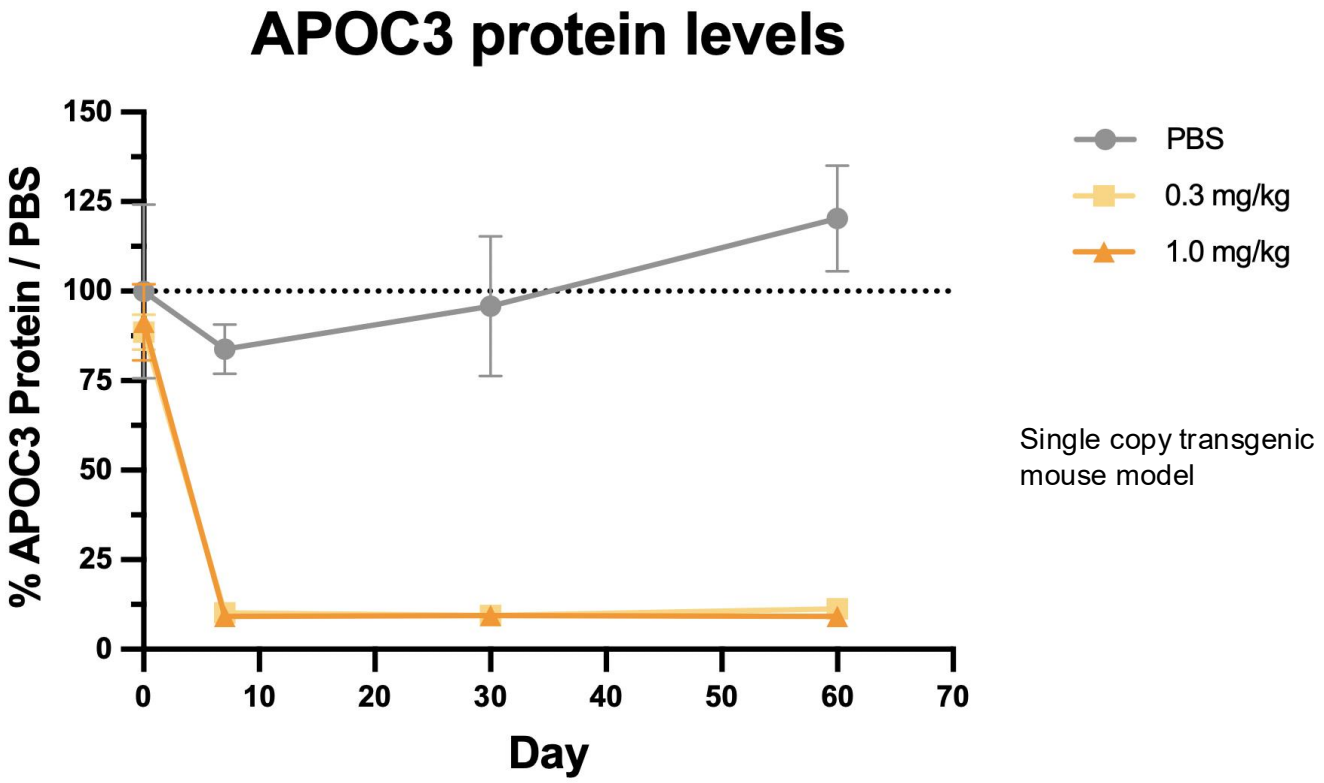
APOC3 protein reduction is durable in mice



Single copy transgenic mouse model

85% reduction in APOC3 protein sustained over two months

(Study ongoing)

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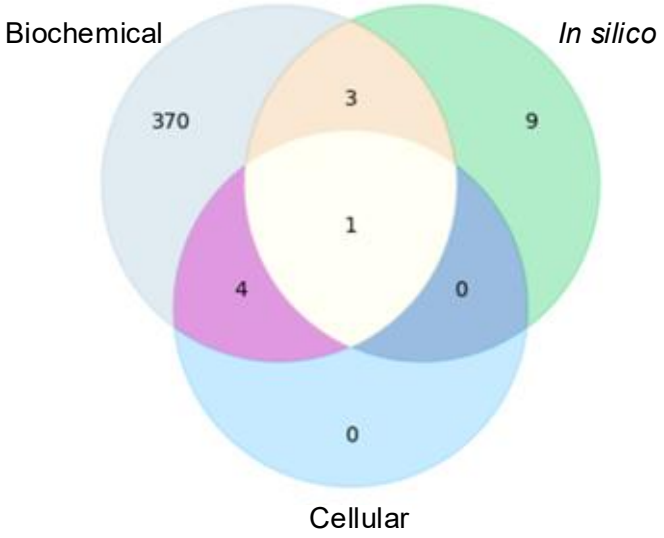
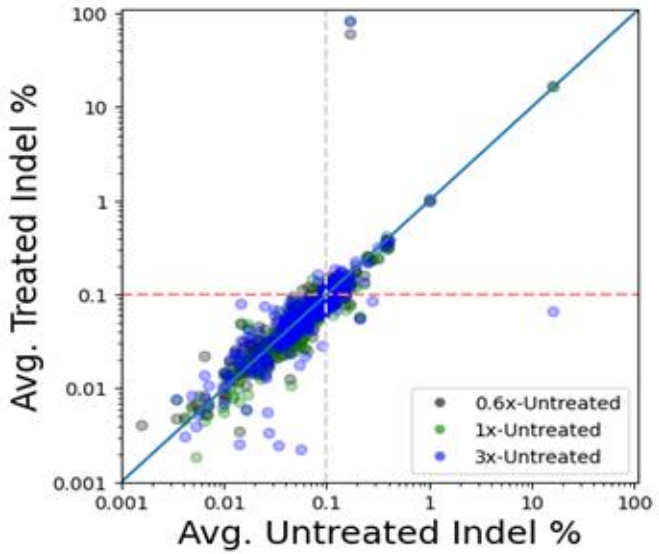
*APOC3*edit demonstrates exquisite specificity

*APOC3*edit off target discovery



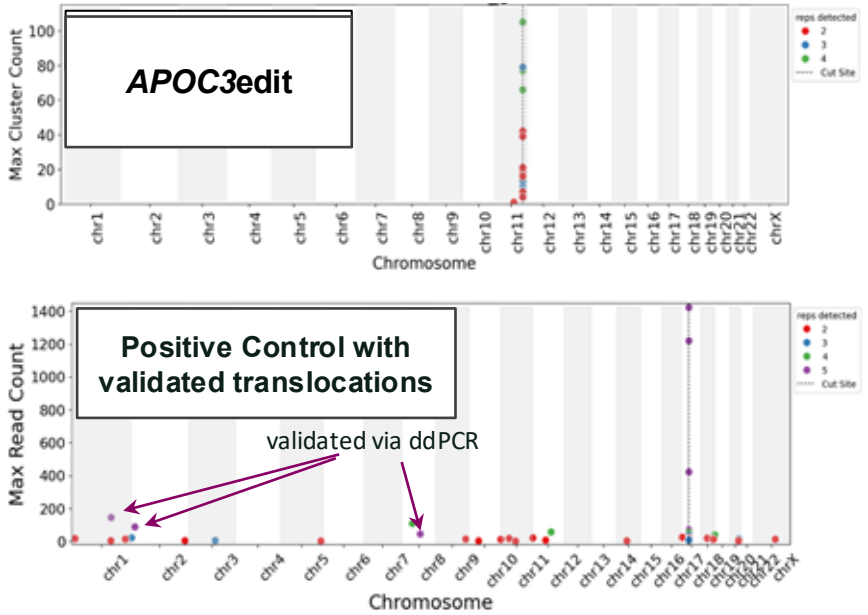
386 potential OT sites nominated via three orthogonal assays

No detectable OT editing at supersaturating levels of editing



3 PHH donors were treated with LNP and probed at the nominated OT sites by multiplexed PCR (0.1% sensitivity)

No detectable translocations at supersaturating levels of editing



NGS assay that detects split reads between the on-target and other genomic sites

No validated off target sites identified

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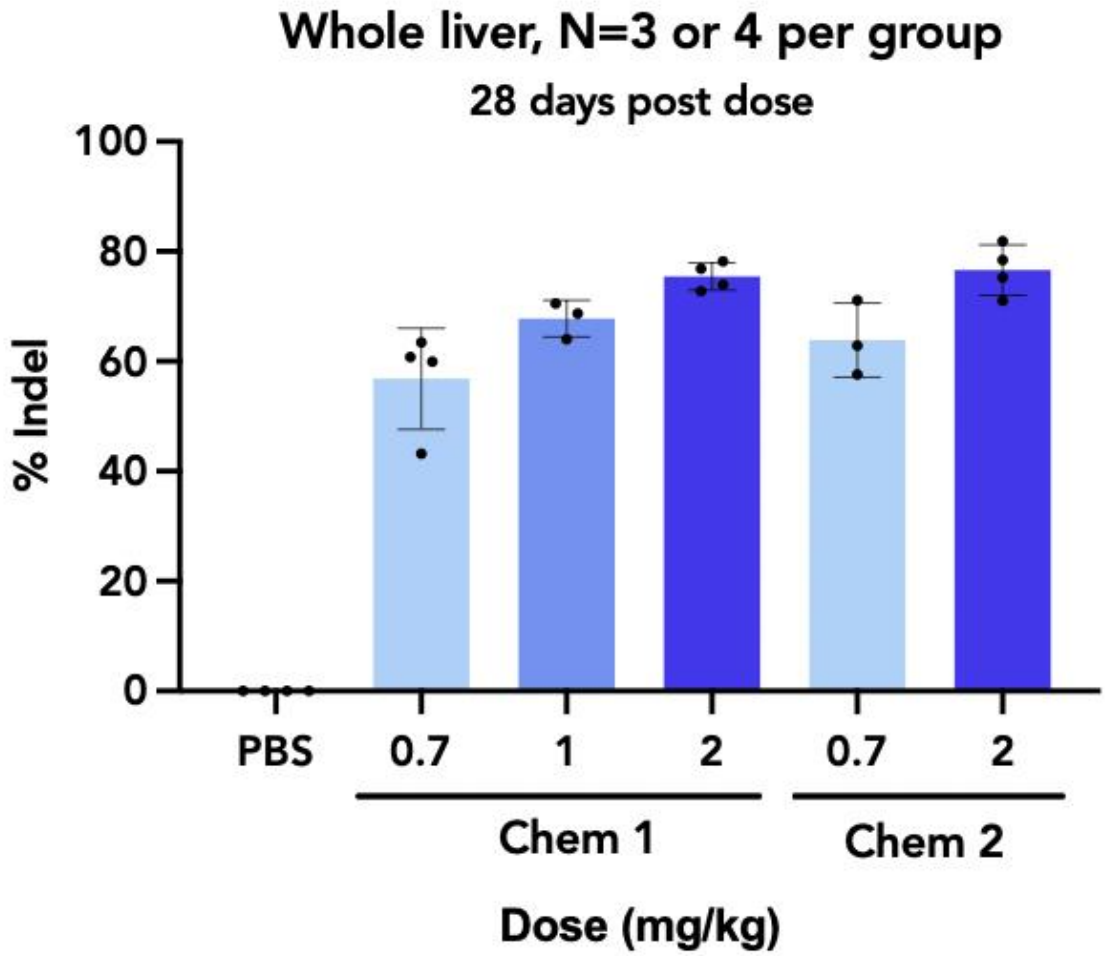
Potent editing at *APOC3* locus in NHP



Saturating and near saturating levels of editing observed in NHP with different gRNA chemistries*

Well tolerated at all dose levels

*Lipid nanoparticle provided by Acuitas Therapeutics, Inc.

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MG71-S1 MEDIATED *APOC3* KNOCKOUT AS A ONE-TIME TREATMENT FOR SEVERE HYPERTRIGLYCERIDEMIA

- MG71-S1, a novel Type II CRISPR-associated nuclease derived from ancestral sequence reconstruction, enabled increased potency and targeting flexibility at the *APOC3* locus
- Enabled the selection of a potent and highly specific guide RNA
- Optimization of the guide RNA sequence and chemistry combined with optimization of the mRNA resulted in multi-fold improvements in editing
- No off-target editing detected in PHH with the lead guide
- Dose dependent editing at the human *APOC3* gene and concomitant reduction of APOC3 protein was achieved in primary human hepatocytes (PHH) and in humanized mouse models at low doses
- Reduction in APOC3 protein resulted in the expected reduction in triglycerides
- Preliminary results in non-human primates demonstrated saturating editing

Acknowledgements

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Thank You