EAS 93rd Congress

4-7 May 2025 | Glasgow, UK

A novel PCSK9 Epigenetic Editor Achieves Maximal Pharmacology with Best-in-class Potency in Non-human Primates

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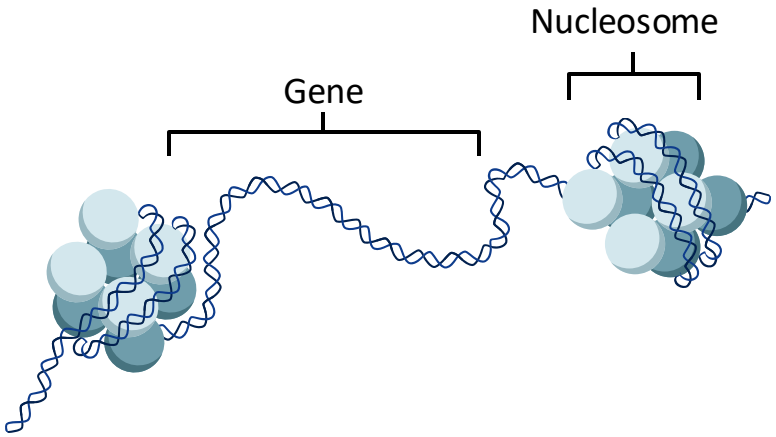
Disclosure Slide

	No, nothing to disclose
✓	Yes, please specify:

Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*	*Other (please specify)*
nChroma Bio							x	

Epigenetics: the central regulator of gene expression

Durable change in phenotype without a change in genotype



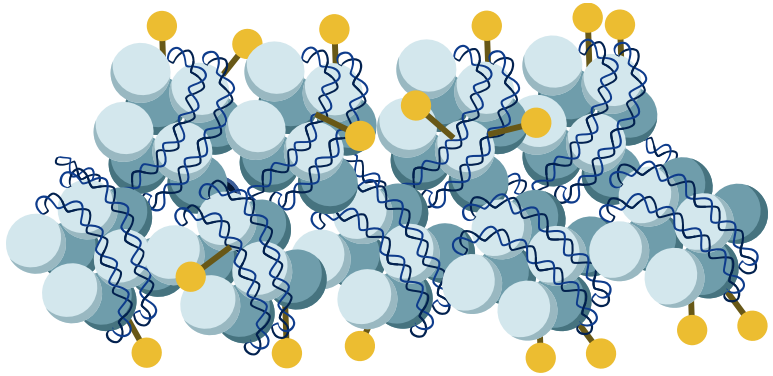
Gene is Active
DNA is Open and Accessible

Epigenetic Repressor
Methylates Targets

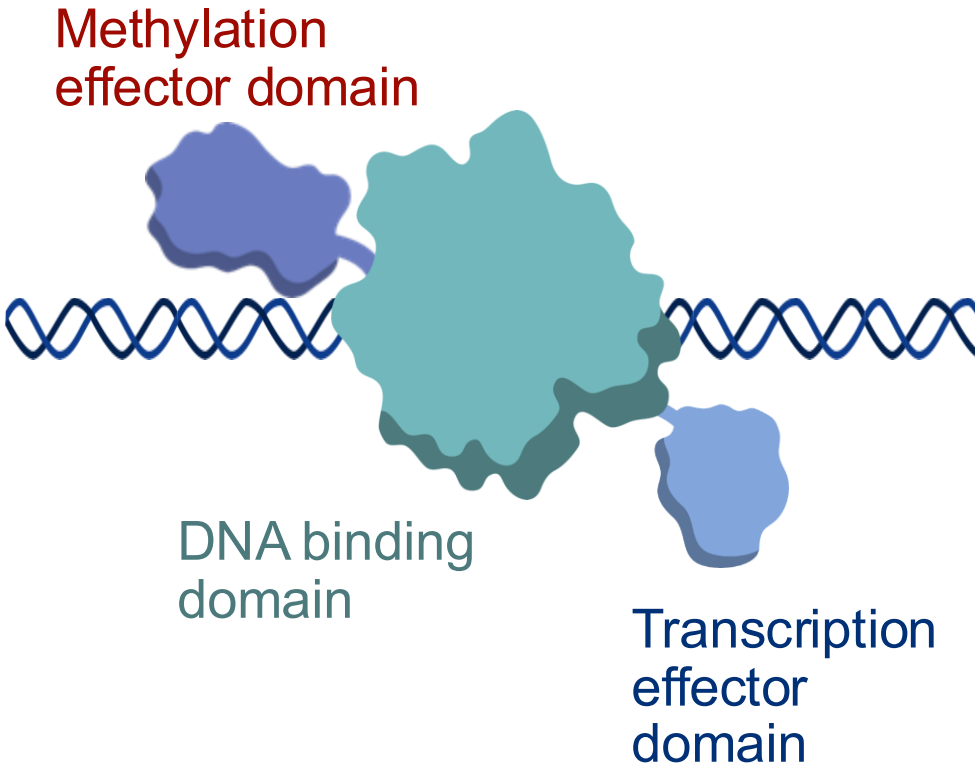
Transient Application

Epigenetic Activator
Demethylates Targets

Gene is Inactive
DNA is Closed and Inaccessible



nChroma's epigenetic editor is a modular genomic medicine

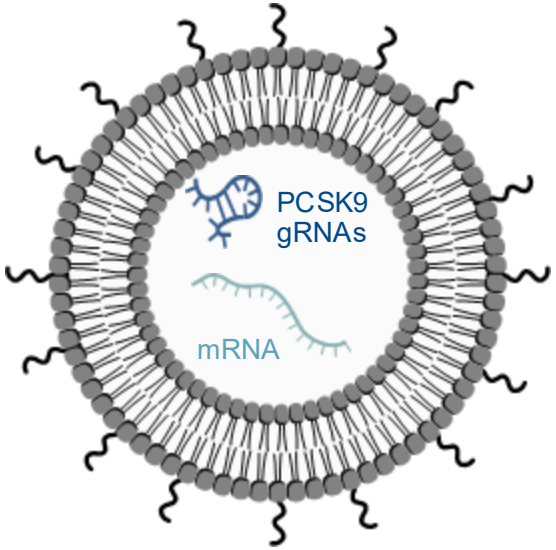


DNA binding domain precisely localizes effector domains to target sequence

Transcription effector domain transiently represses target genes

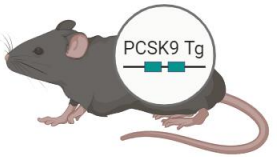
Methylation effector domain durably silences target genes

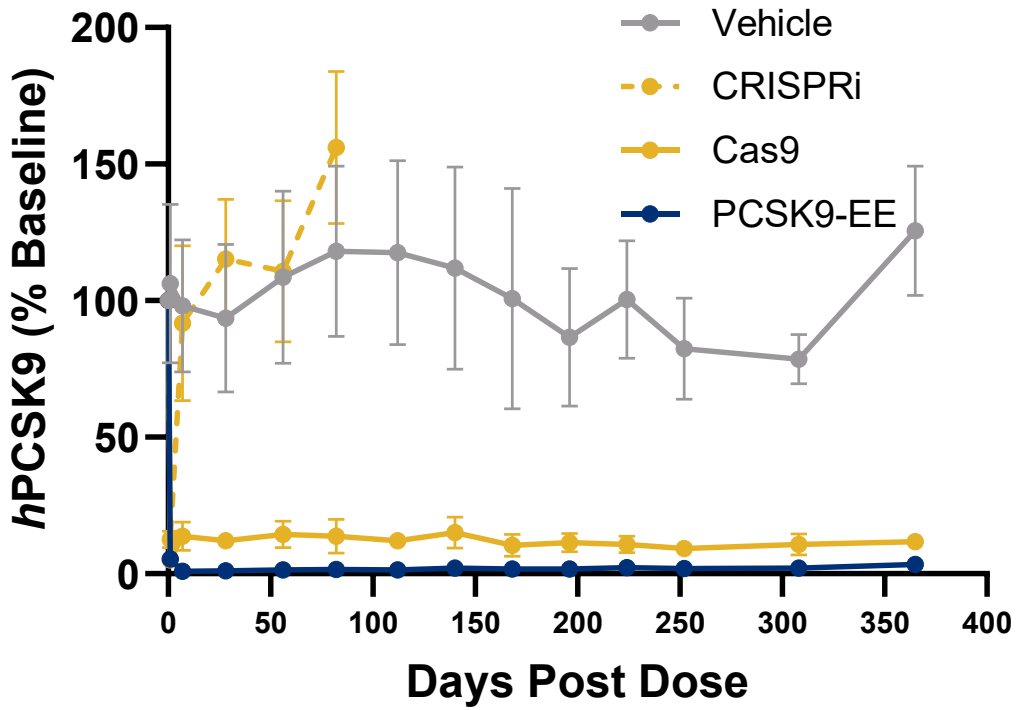
RNA / LNP

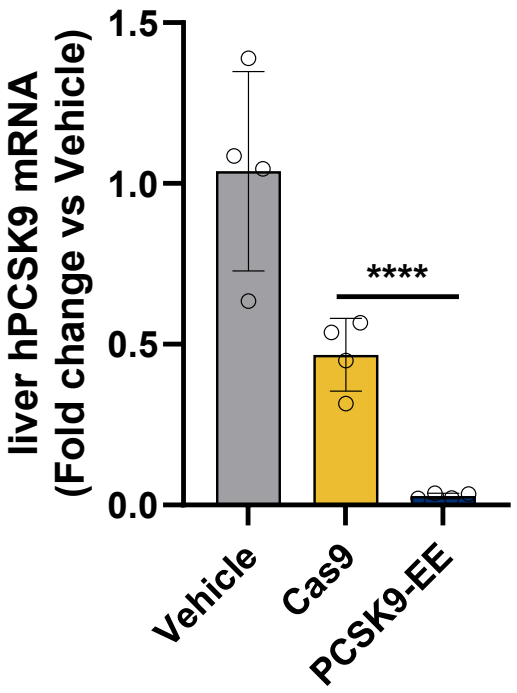


Delivered via LNP for liver-targeted indications

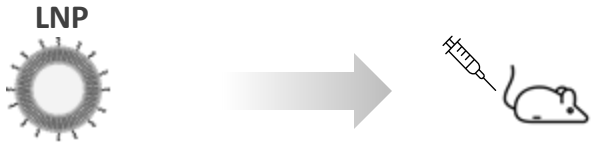
Single dose of prototype PCSK9 epigenetic editor (PCSK9-EE) drives durable, complete PCSK9 silencing in vivo







- Model System: Transgenic mouse containing the human PCSK9 locus
- Test Product: An early generation epigenetic editor
- **>98% silencing maintained for 1 year post single IV injection**
- **Silencing at transcriptional level (i.e., no mRNAs produced)**

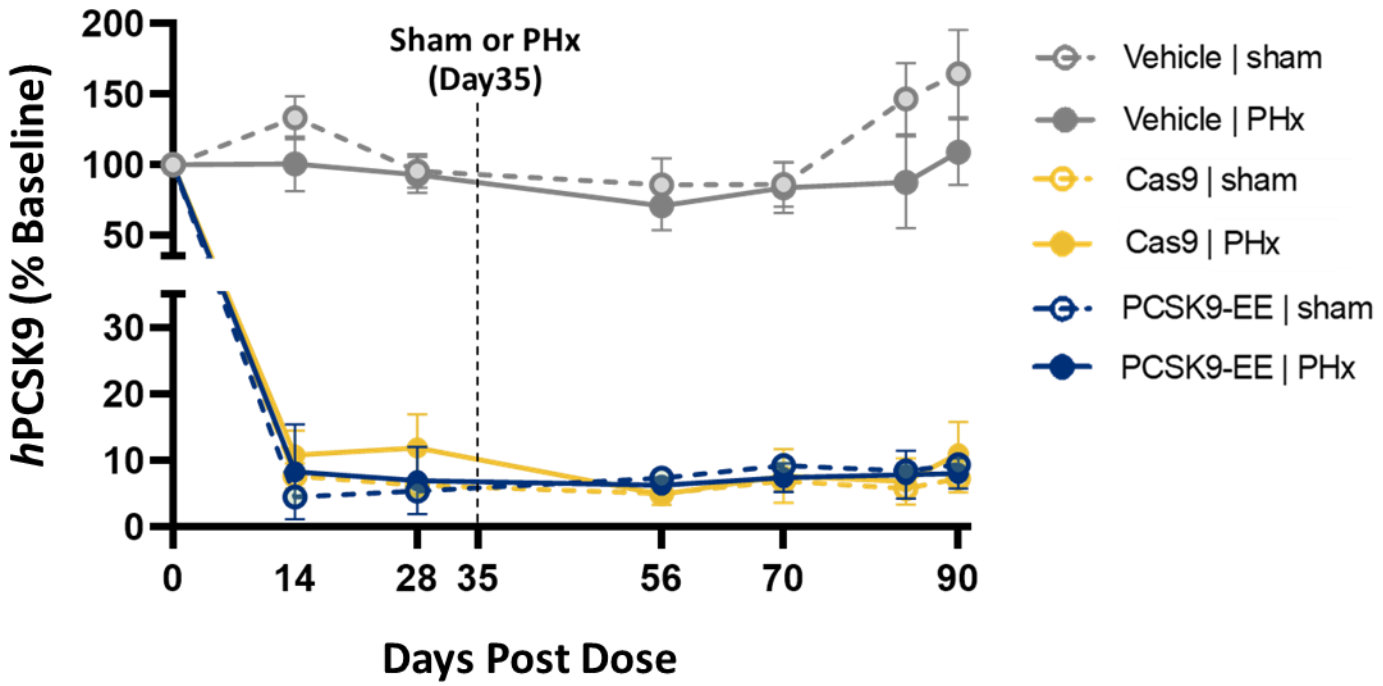


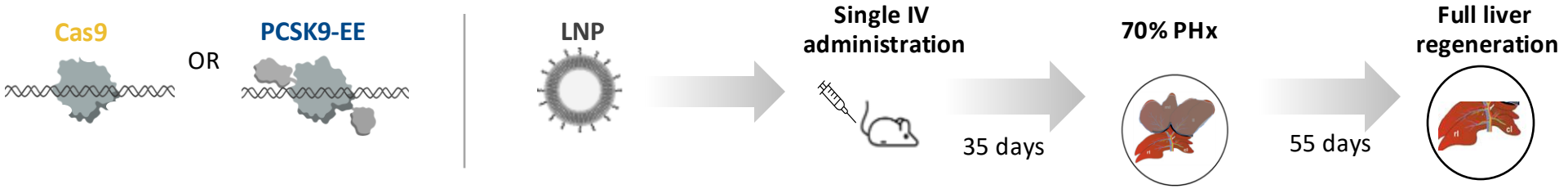
Experiment

- hPCSK9 Tg mouse
- Single IV administration
- PCSK9 analysis by ELISA

Prototype PCSK9-EE-driven silencing is fully maintained after partial hepatectomy

- 70% partial hepatectomy (PHx) is a gold standard surgical model to induce liver regeneration in rodents
- **Single administration of PCSK9-EE demonstrated durable PCSK9 silencing through full liver regeneration post-partial hepatectomy**





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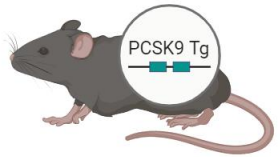
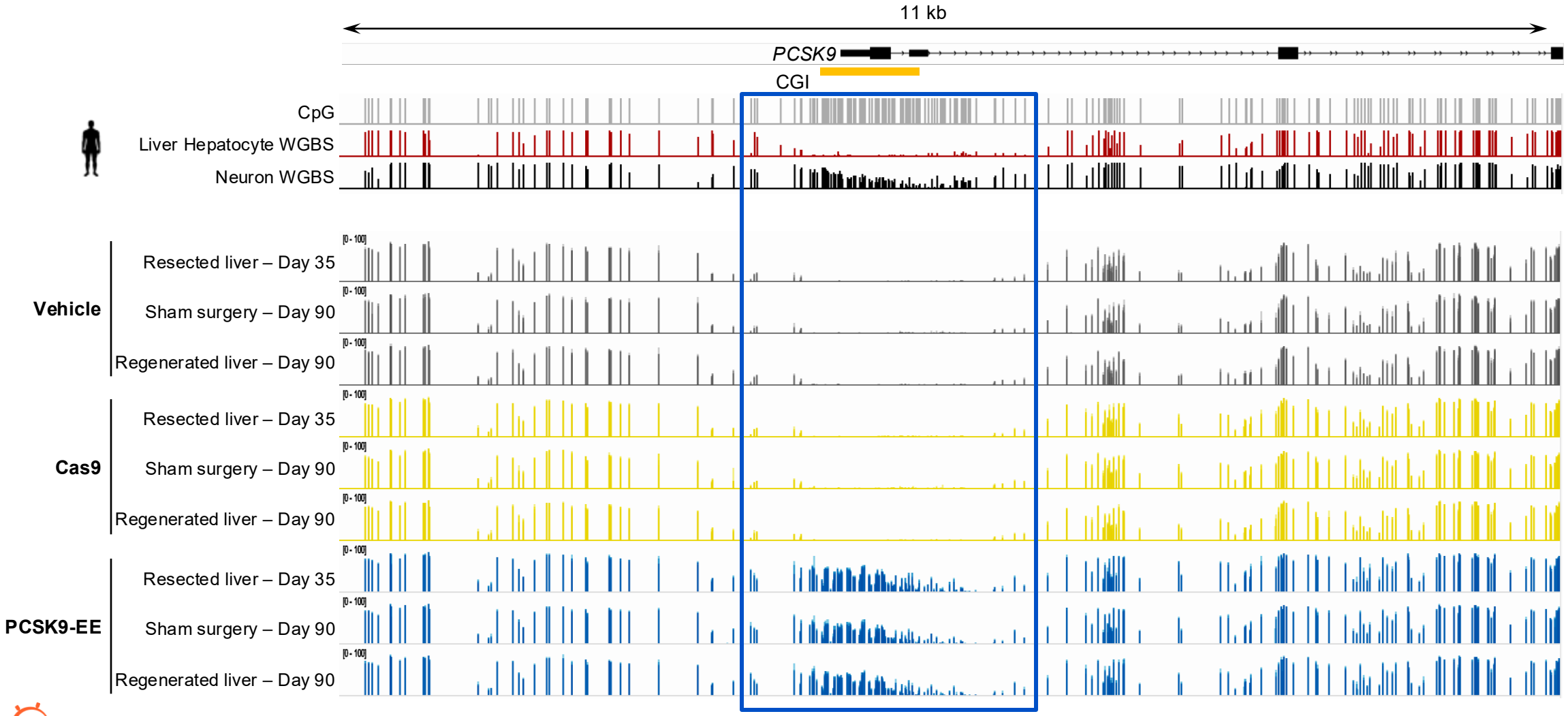
Prototype PCSK9-EE-driven methylation is fully maintained after partial hepatectomy





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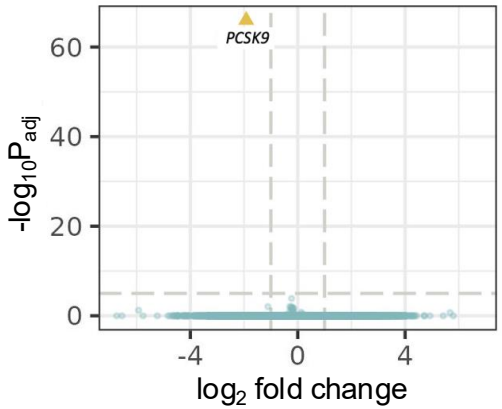
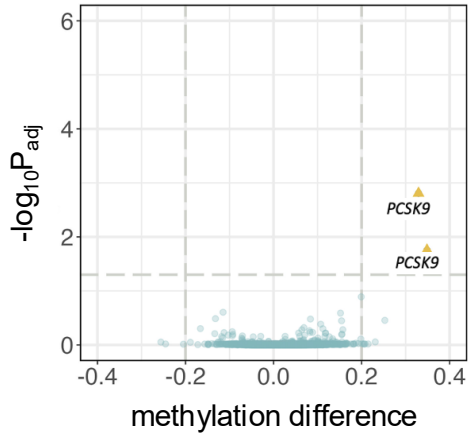
Prototype PCSK9-EE is highly specific with no detectable off-target changes

RNA Expression



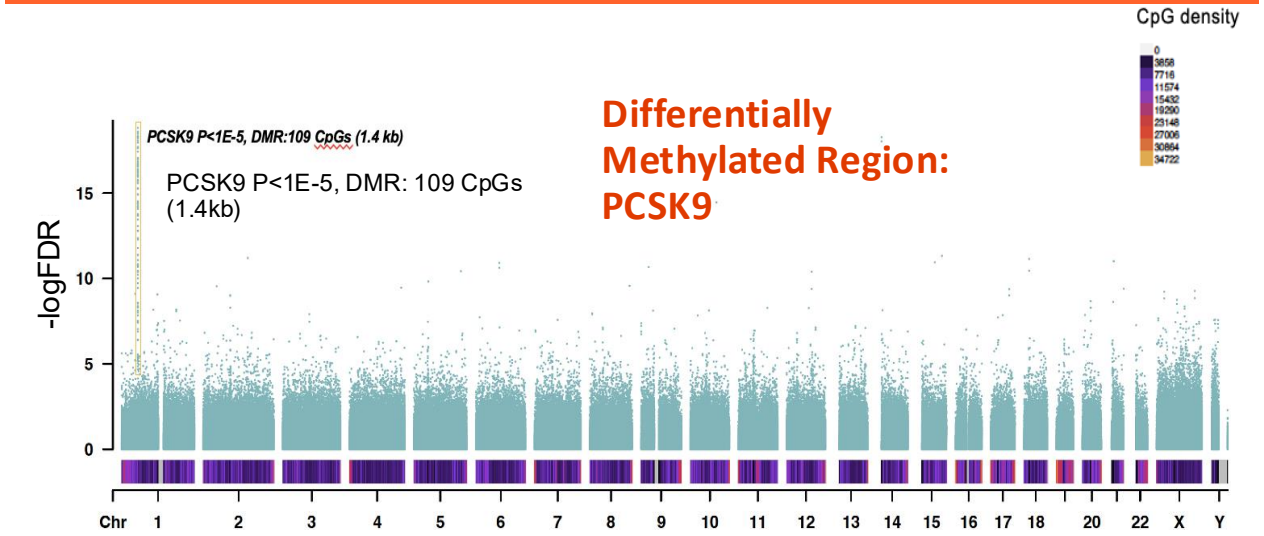
Differentially Expressed Gene: PCSK9

Methylation Profiling at CpG-Enriched Sites



Differentially Methylated Region: PCSK9

Genome-Wide Methylation Profiling



Differentially Methylated Region: PCSK9

- **PCSK9-EE is highly specific**
- **No significant off-target changes in gene expression** with PCSK9-EE in primary human hepatocytes as measured by RNA-seq
- **No significant off-target changes in methylation** with PCSK-EE in primary human hepatocytes as measured by Illumina Methylation Array and whole genome bisulfite sequencing

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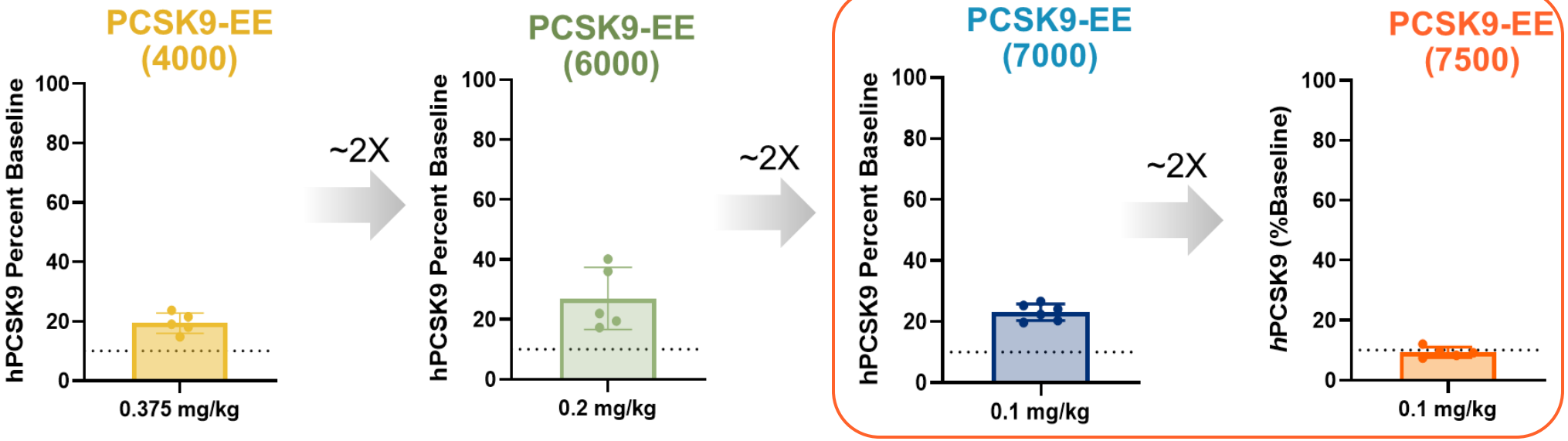
Construct optimization efforts have led to a significant increase in potency

RNA/LNP Drug product → Epigenetic editor protein complex with gRNA (RNP) → RNP localize to nucleus → Methylating CpG in the target region

Improve protein expression

Improve nucleus transportation

Improve methylation activity



Tested in NHPs

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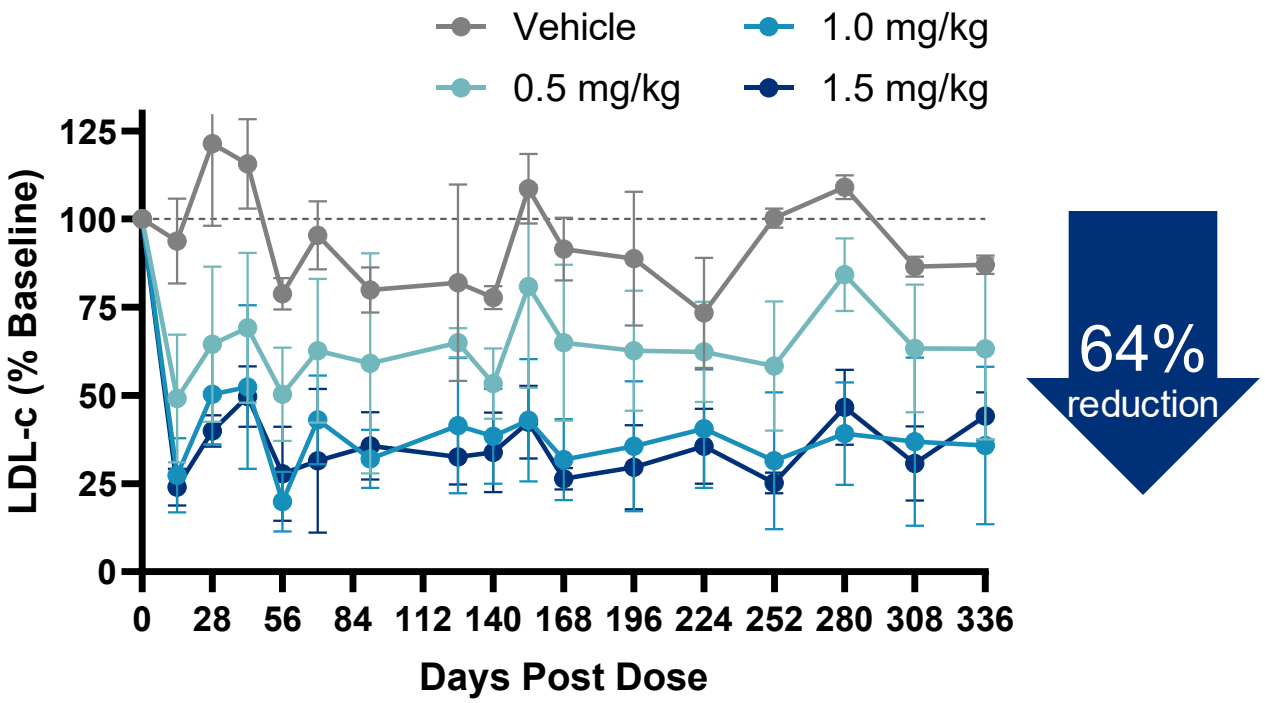
PCSK9-EE(7000) achieved durable, saturating LDL-c lowering efficacy at therapeutically relevant dose in NHPs

LDL-C Reduction



LDL-c reduction % calculated as time-averaged LDL-c reduction following PCSK9-EE treatment

Safety

- PCSK9-EE(7000) was well-tolerated without any clinical signs in all animals
- Transient, non-adverse elevations in liver transaminases that normalized within 2 weeks post-dose at highest dose tested

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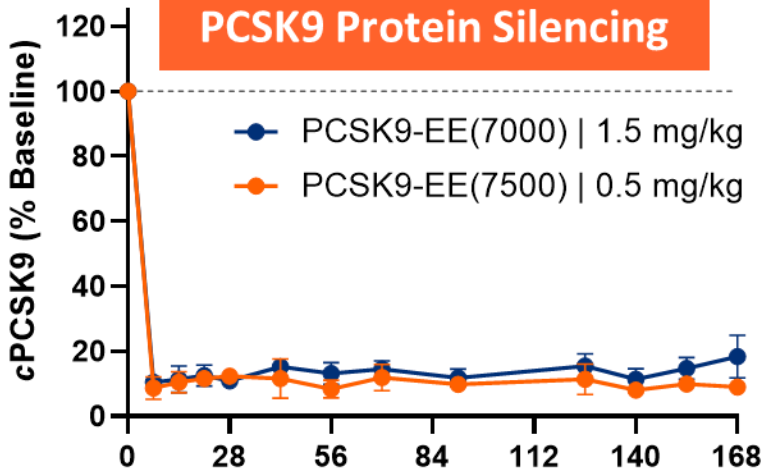
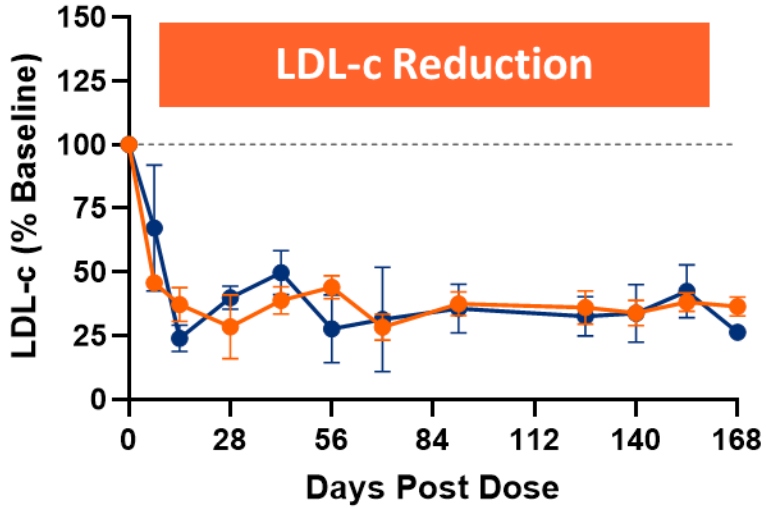
PCSK9-EE(7500) achieved >3X improved potency over 7000 series editor in NHPs

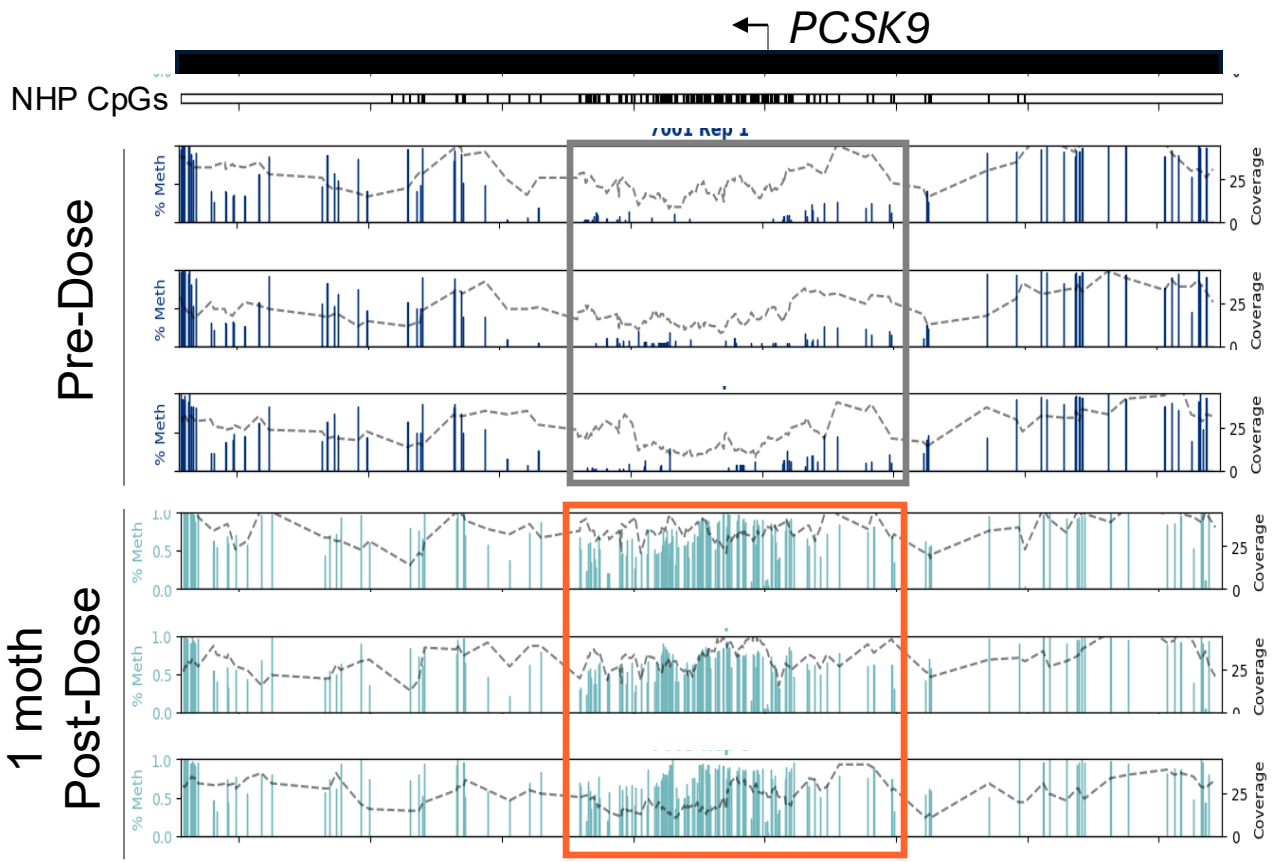
PCSK9 Protein Silencing



LDL-c Reduction



Methylation in *PCSK9* locus



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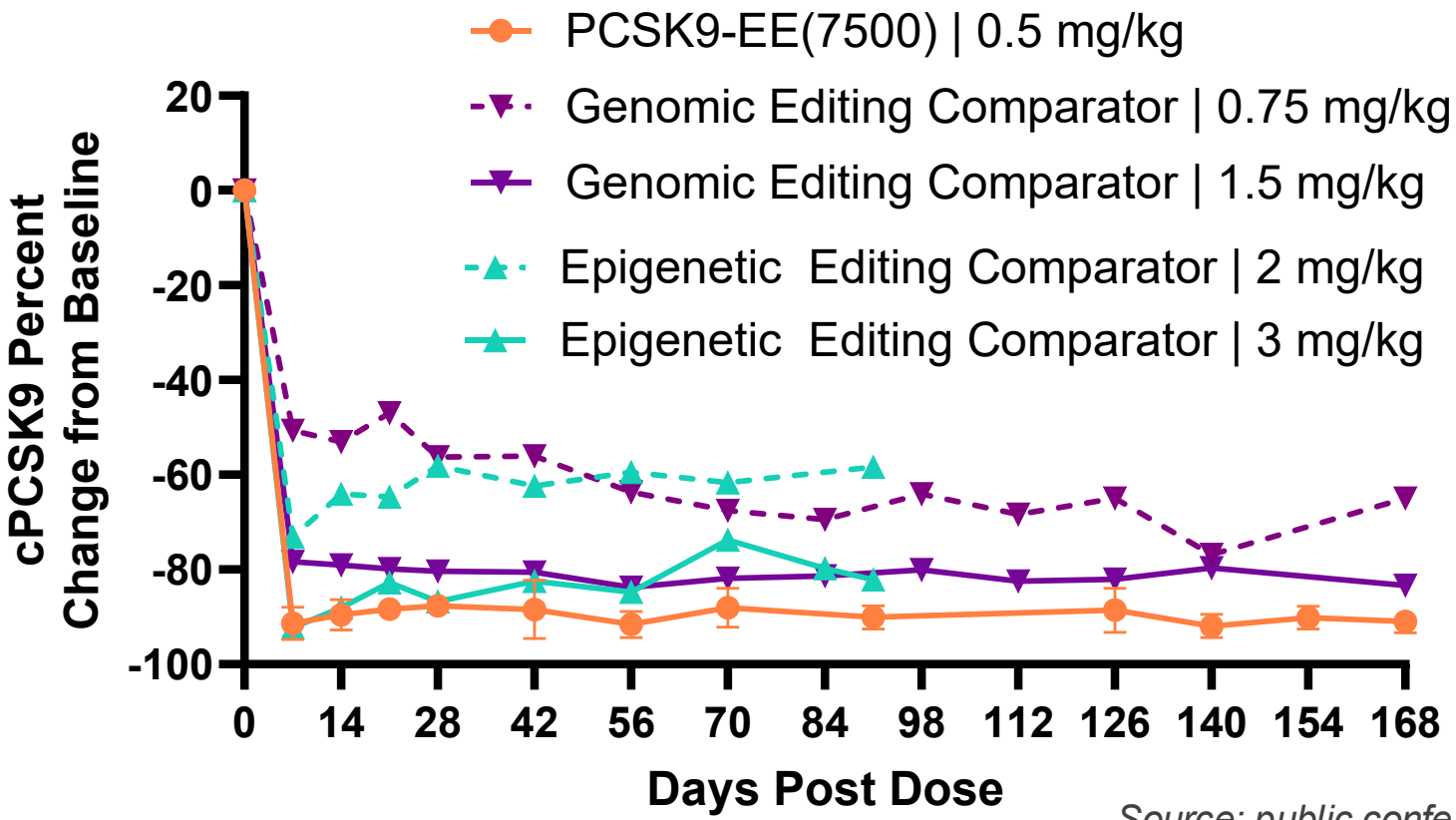
PCSK9-EE(7500) editor achieved **best-in-class** potency in NHPs



Source: public conference presentations

- nChromaBio is using the epigenetic editing technology to develop a therapy for chronic HBV (CTA in 2025) and has prioritized PCSK9 program for partnering

Acknowledgements

Thank you to the entire nChroma Bio team, our collaborators, and partners!

LNP Technology provided by Acuitas Therapeutics, Inc.