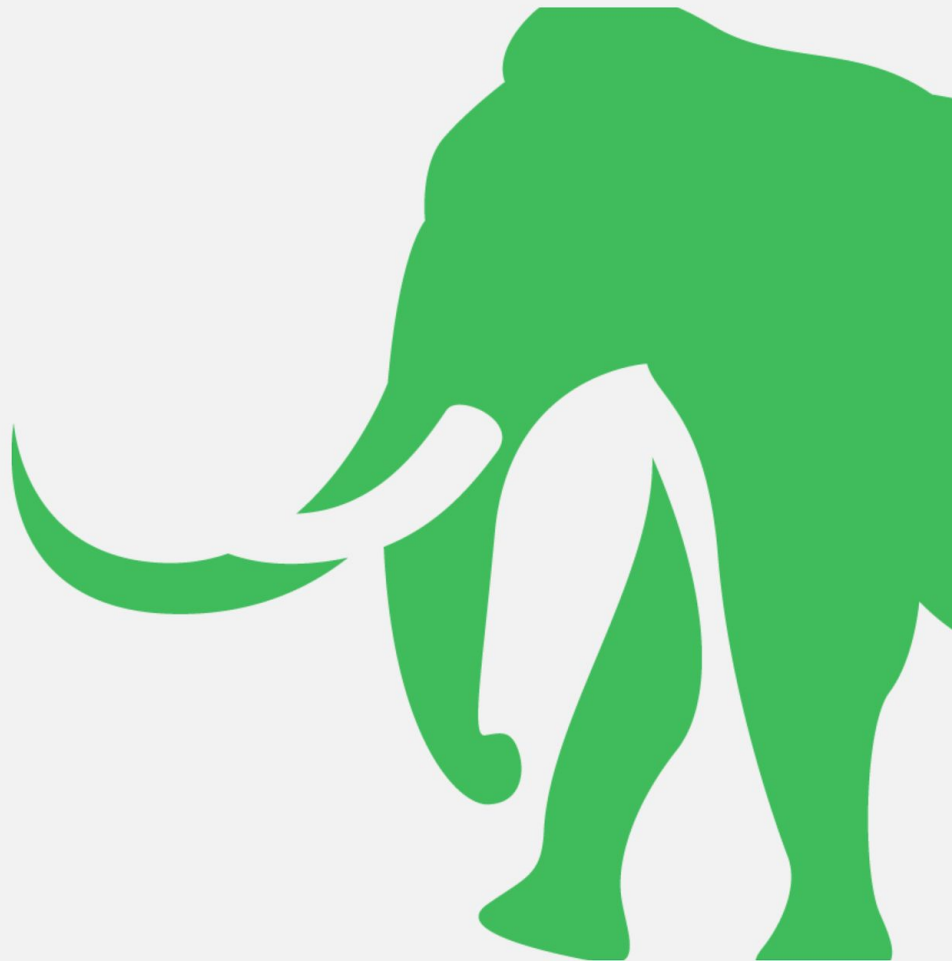


MammothBiosciences

Ultracompact CRISPR Systems for Liver Gene Editing and Beyond

ASGCT May 7th, 2024

Lucas Harrington, Cofounder & CSO

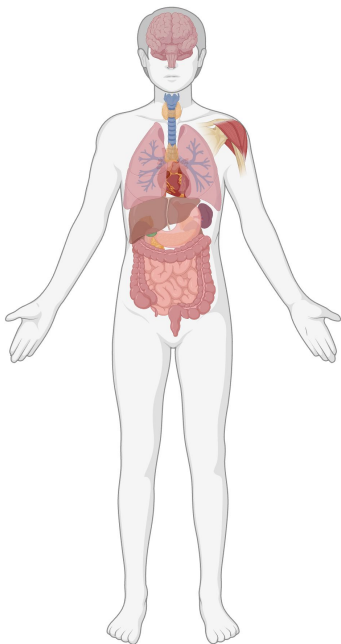


Ultracompact Systems are the Key to Expand Gene Editing

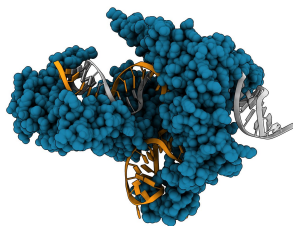
Advances in genetics and new editing technologies continue to be limited by delivery *in vivo*



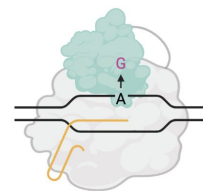
Diverse Genetic Disease
Beyond the Liver



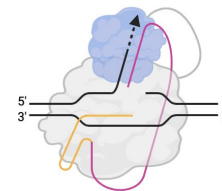
**Ultracompact
CRISPR Systems**



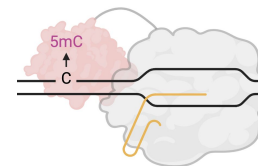
New Precise Methods for
Editing the Genome



Base Editing



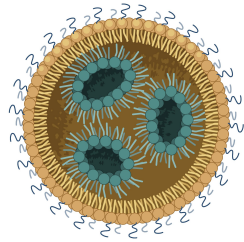
RT Editing



EpiEditing

Mammoth CRISPR Systems Enable All-In-One AAV Delivery To Unlock Targets Beyond the Liver

LNP Delivery



Smaller mRNAs allow for more efficient packaging and improved mRNA quality for delivery *in vivo*

AAV Delivery



Original CRISPR systems
exceed payload restrictions

Mammoth Cas

Leaves abundant room
for diverse payloads for precision editing applications

CRISPR+ Fusion Proteins

Integrases, Base Editing, CRISPRi/a...

Tissue Specific Promoters

Controlled Expression

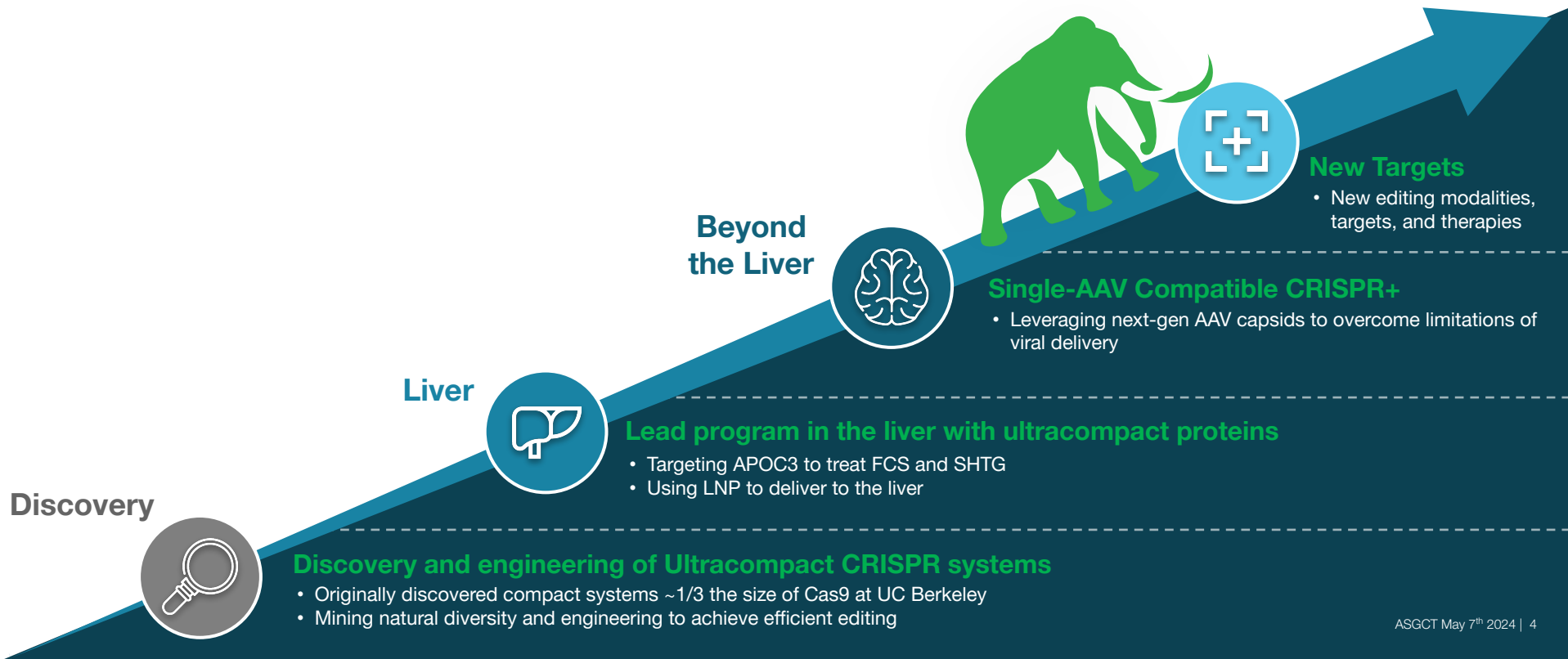
Guide RNA

Guide RNA

Multiplexing

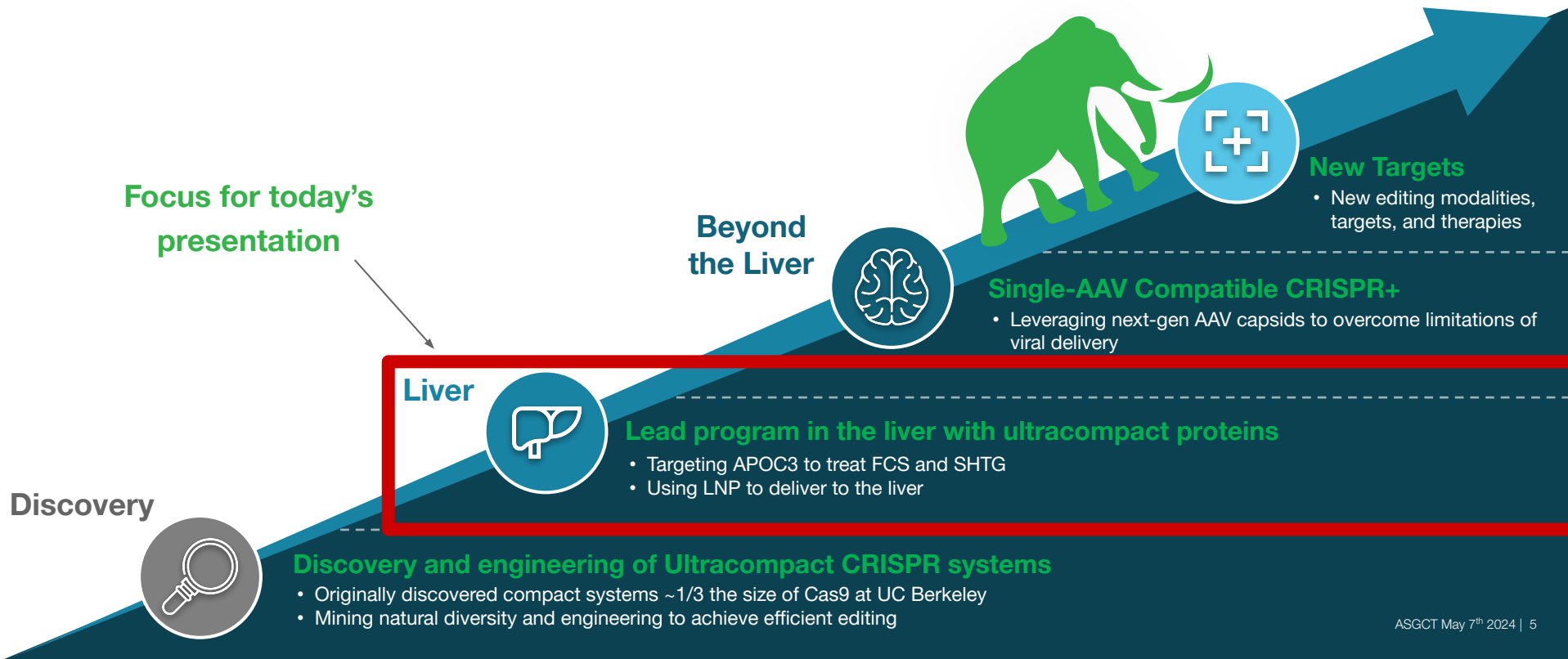
Roadmap for Developing Ultracompact Nucleases

Sequential derisking to expand gene editing applications



Roadmap for Developing Ultracompact Nucleases

Sequential derisking to expand gene editing applications

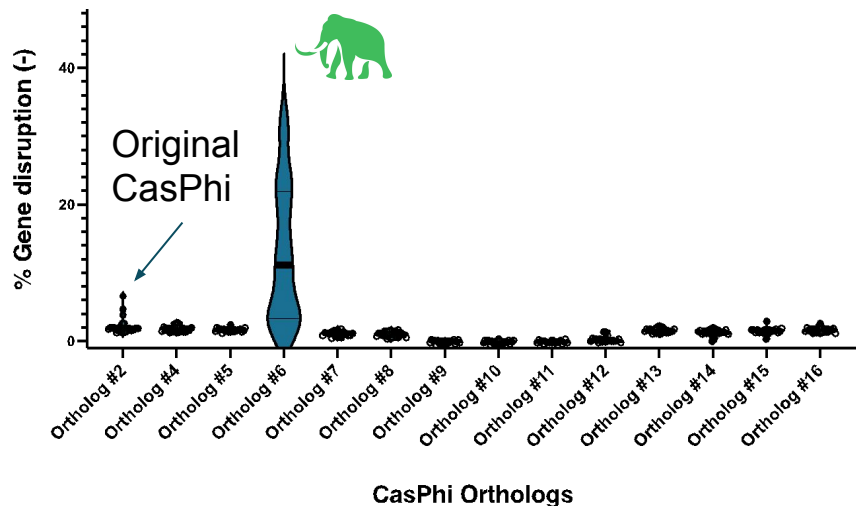
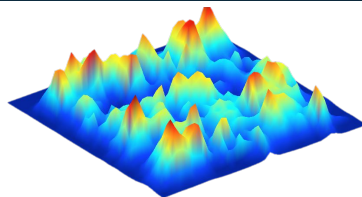


Optimization of Ultracompact CRISPR Nucleases

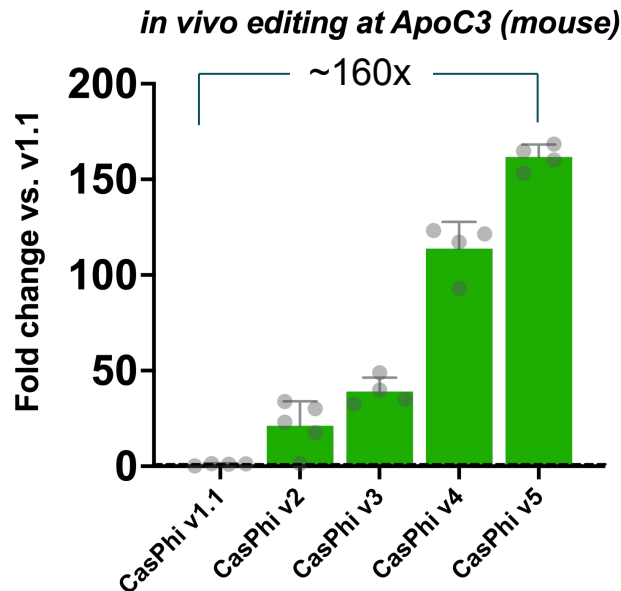
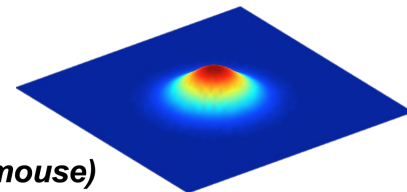


Natural diversity screening and protein engineering dramatically improve potency of CasPhi

Discovery



Engineering

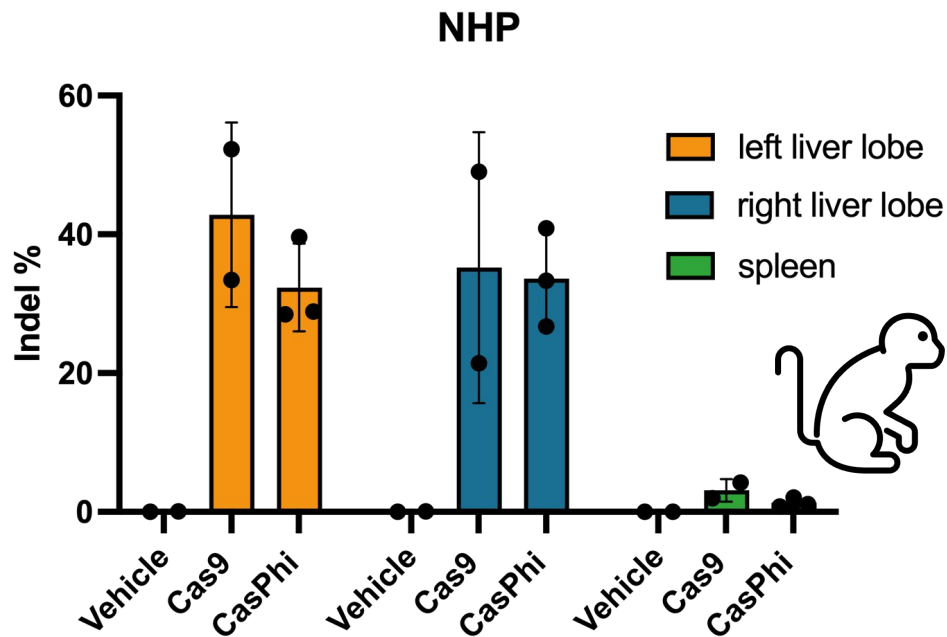


Initial Test Demonstrates Editing with Ultracompact System in NHPS

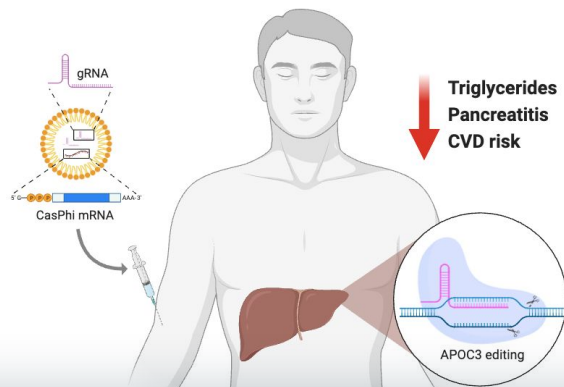


Challenging the idea that small CRISPR systems are inefficient editors

- Testing mRNA drug substance on a reference target
- Minimal editing observed outside of the liver
- Test articles were well tolerated in all animals

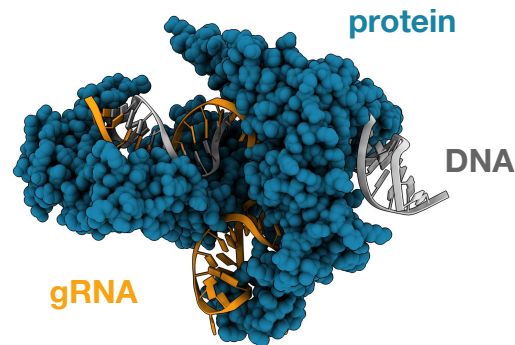


MB-111 is an *in vivo* Gene Editing Therapy to Treat Familial Chylomicronemia Syndrome (FCS) and SHTG by Targeting APOC3



We envision MB-111 as a durable cure for FCS and SHTG

- FCS and SHTG are characterized by accumulation of triglycerides in blood
- Estimated >2M patients worldwide for SHTG.
- Most severe forms of SHTG have TG >800 mg/dL and associated with acute pancreatitis.
- APOC3 encodes a small 74 aa lipoprotein that inhibits lipid catabolism, and silencing of APOC3 can speed up catabolism resulting in reduced triglycerides in serum
- MB-111 comprises of a **CasPhi nuclease mRNA and gRNA** encapsulated in a lipid nanoparticle targeting APOC3 in hepatocytes



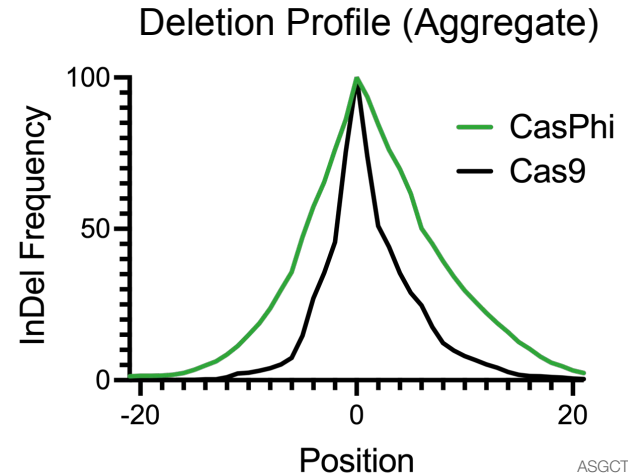
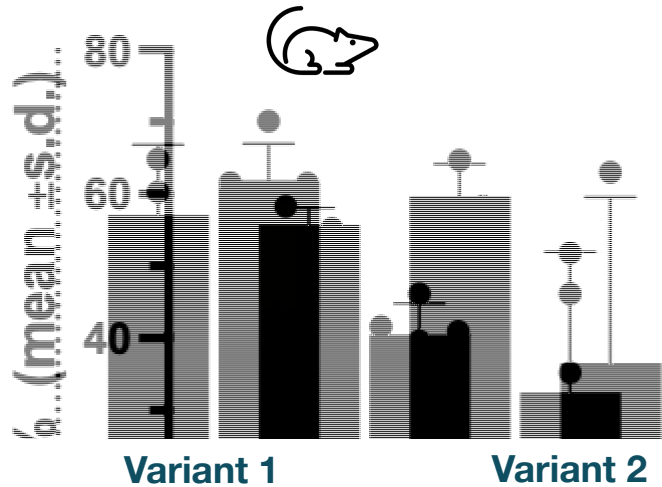
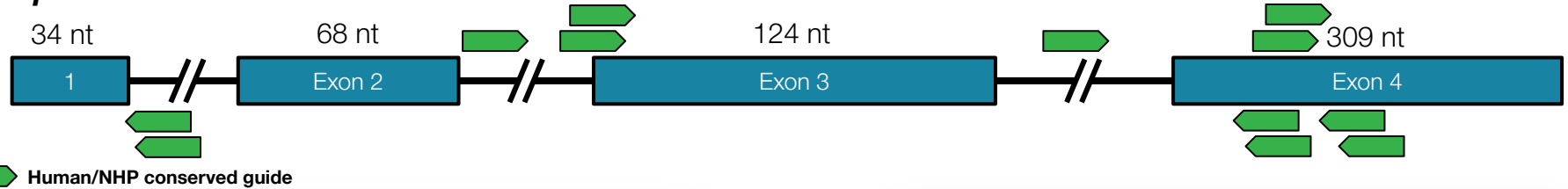
CasPhi	
Protein length	~720 aa
gRNA length	~40 nt
Single Guide?	yes
Protein structure	monomer
PAM	NTTN

The Small Size of the APOC3 Gene Reduces Pool of Potential Guide RNAs



NTTN PAM, deletion profile and protein engineering expand guide options

H. sapiens APOC3



No Off-Target Sites Confirmed for Potential MB-111 Guide RNA



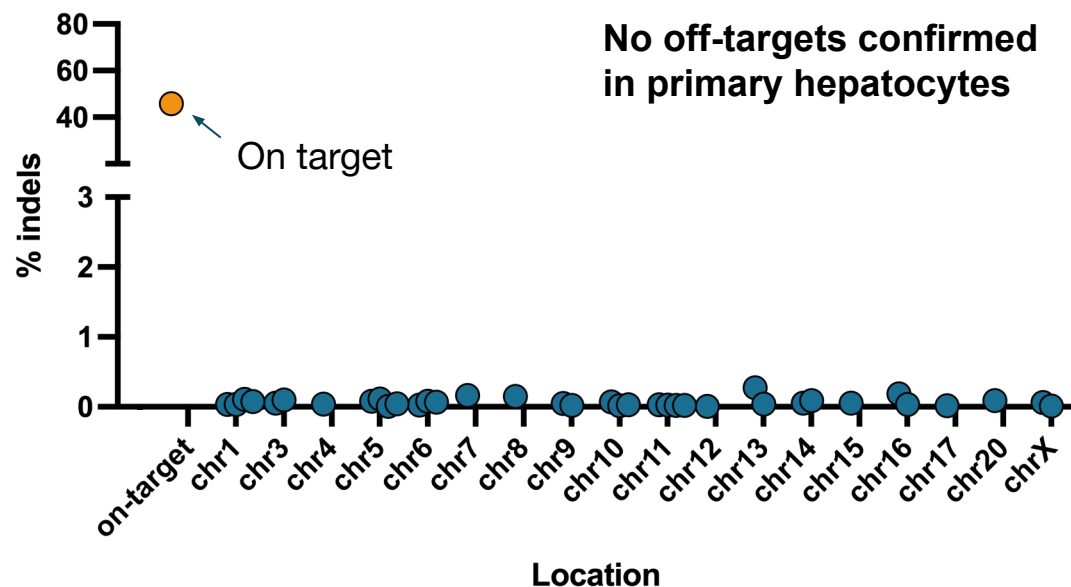
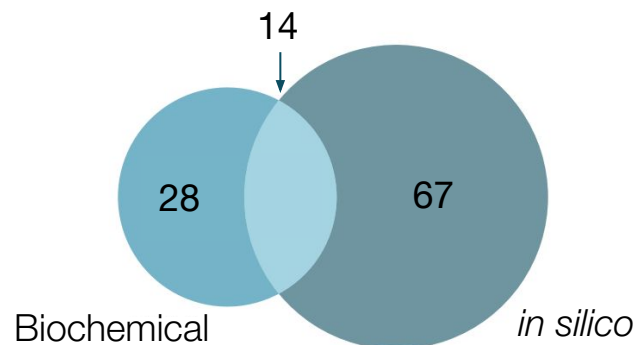
Discovery

in silico

Biochemical

Confirmation

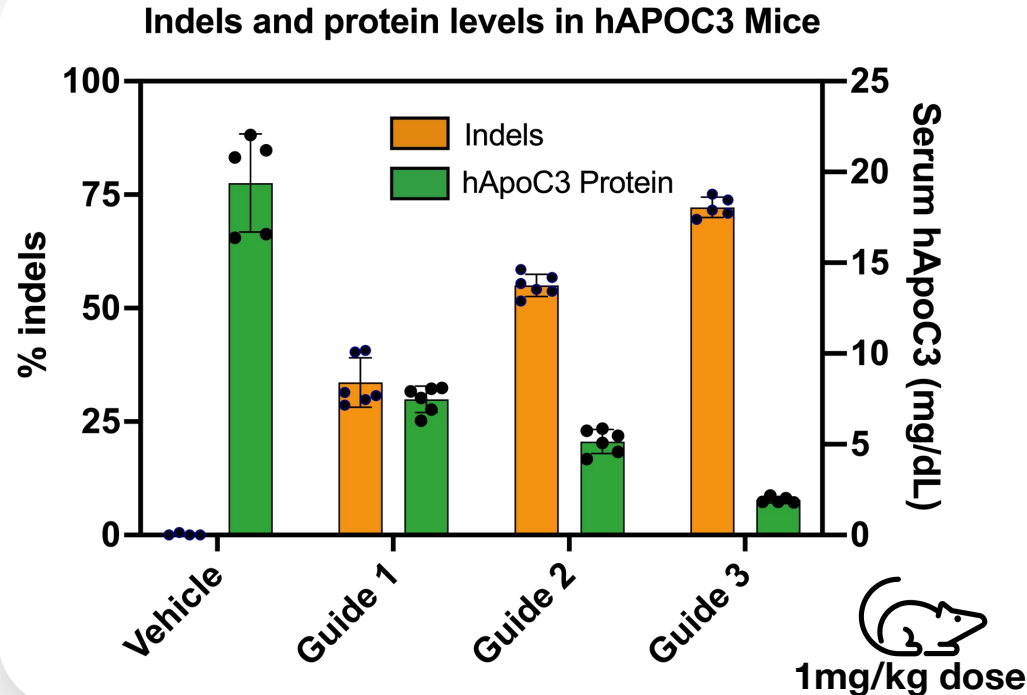
rhAmpSeq



in vivo Editing of Humanized Mouse Model Shows Saturating Indels and ~90% Reduction in Protein Level



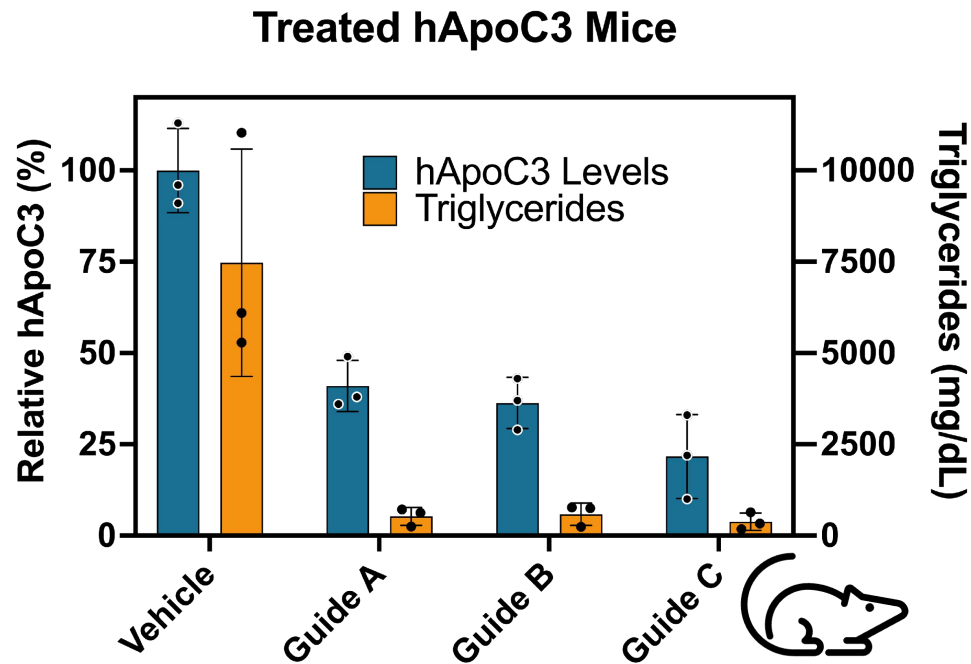
- Homozygous hAPOC3 knock-in mouse
- Saturating indels at >70% with 1mg/kg dose
- Reduction in APOC3 protein by up to 90%



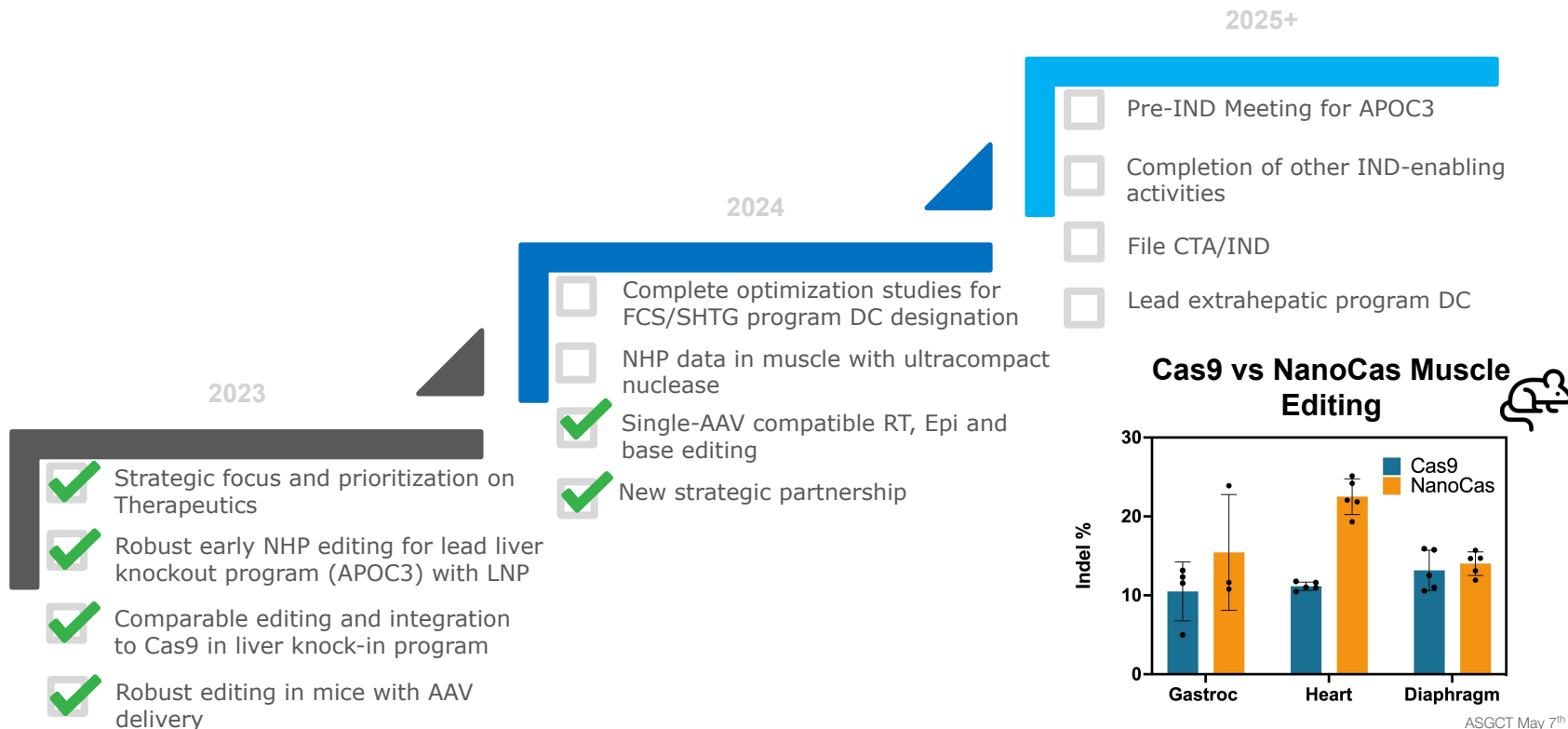
in vivo Editing of Hypertriglyceridemic hAPOC3 Mouse Reduces Triglycerides by up to 95%



- Contains ~10 copies of human APOC3
- Hypertriglyceridemic mouse model
- Reduction in APOC3 protein by up to 80%
- Reduction in triglycerides by up to 95%
- LNP functions in hypertriglyceridemic conditions



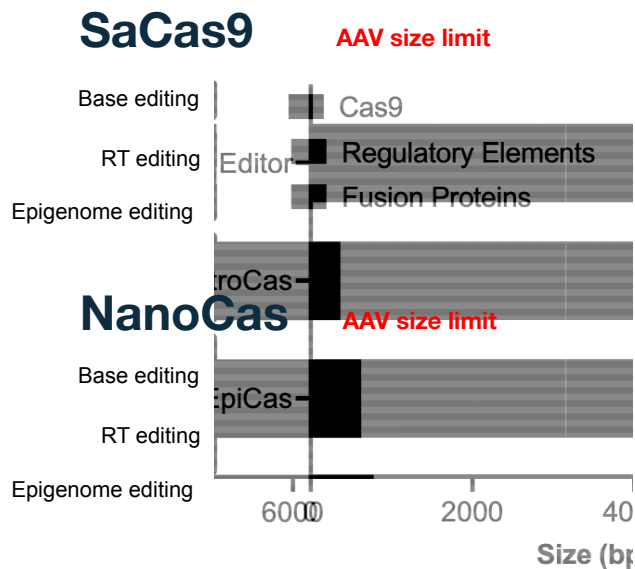
Next Steps for APOC3 Program and Expansion Into Non-Liver Targets



New Collaboration to Combine our Ultracompact Nucleases with Regeneron's Next-Gen Delivery



In addition to our existing collaborations with Bayer and Vertex



REGENERON®

April 25, 2024 at 7:00 AM EDT



« Back

REGENERON AND MAMMOTH BIOSCIENCES COLLABORATE TO PURSUE NEXT-GENERATION CRISPR-BASED GENE EDITING FOR MULTIPLE DISEASES

Mammoth's proprietary ultracompact CRISPR-based gene editing platform and Regeneron's proprietary delivery technologies set to advance *in vivo* programs in multiple tissue and cell types

Mammoth to receive \$100 million total upfront payment and equity investment from Regeneron at signing

Thanks to the Amazing Team at Mammoth!

