

Jan 31, 2025 8:00 AM Eastern Standard Time

Mammoth Biosciences Announces New Results on NanoCas – the First Efficient Ultracompact Extrahepatic Gene Editor

Share      ...

New research shows potent in vivo gene editing in skeletal muscle of non-human primates by a novel, ultracompact CRISPR system delivered via a single AAV vector

BRISBANE, Calif.--(BUSINESS WIRE)--Mammoth Biosciences, Inc., a biotechnology company harnessing its proprietary next-generation CRISPR gene editing platform to create potential one-time curative therapies, today announced new preclinical research, published on the preprint server [bioRxiv](#), that establishes proof-of-concept of NanoCas™, the first ultracompact CRISPR system capable of efficient extrahepatic editing when delivered systemically using a single adeno-associated viral (AAV) vector.

Gene editing holds promise for curing genetic diseases, but faces delivery challenges that limit its therapeutic applications. Current methods are restricted to *ex vivo* approaches or *in vivo* liver editing. First-generation CRISPR systems, such as Cas9 and Cas12a, are too large for efficient *in vivo* delivery via a single AAV vector.

This study describes the discovery, engineering and benchmarking of NanoCas – a novel Cas enzyme approximately one third the size of Cas9 – which can be easily accommodated within a single AAV vector, while leaving ample room for additional payload such as regulatory elements, guide RNAs, or non double strand break editing machinery for techniques such as reverse transcriptase editing, base editing, and epigenetic editing. Discovering the NanoCas system required comprehensive screening of naturally occurring CRISPR variants, leading to the

functional evaluation of more than 150 candidates, followed by targeted protein engineering to enhance its editing efficiency.

"We have been focused on discovering and engineering novel ultracompact CRISPR systems at Mammoth and are excited to share the first demonstration of robust *in vivo* extrahepatic editing in a muscle target with NanoCas with the scientific community," said Lucas Harrington, Ph.D., CSO and co-founder of Mammoth Biosciences. "At Mammoth, we have always believed in the therapeutic potential of CRISPR, and this study demonstrates that ultracompact systems can be potent and delivered in a single AAV vector to tissues outside the liver."

Key takeaways from the study include:

- **Editing efficiency matches that of first-generation CRISPR systems:** When targeting the PCSK9 gene in mouse liver *in vivo*, NanoCas showed saturating editing efficiencies of approximately 60%, on par with that of SaCas9, which is about three-fold larger in size. Both CRISPR systems reduced serum PCSK9 protein to undetectable levels.
- **Robust single AAV editing across multiple muscle tissues:** NanoCas demonstrated 10% to 40% editing of the dystrophin gene across the quadricep, calf and heart muscle in a humanized mouse model of Duchenne Muscular Dystrophy (DMD), when delivered via a single AAV vector.
- **First demonstration of single AAV muscle editing in non-human primates:** NanoCas achieved *in vivo* editing efficiencies of up to 30% when targeting dystrophin in the skeletal muscle of *cynomolgus macaques*. NanoCas also showed 15% editing across the heart, compared to 10% with SaCas9. Analysis of liver tissue showed minimal off-target editing.

"Potent editing of extrahepatic tissues *in vivo* has been a roadblock for the gene editing field," said Trevor Martin, Ph.D., co-founder and chief executive officer of Mammoth Biosciences. "NanoCas' compact size makes it compatible with a wide range of gene editing modalities – including base editing, reverse transcriptase editing, and epigenetic modification – while still allowing for delivery using a single AAV vector. This study is a major step toward enabling any edit to be made in any cell *in vivo*, thereby dramatically increasing the number of patients who could benefit from genetic medicines and delivering on the full promise of CRISPR."

About Mammoth Biosciences

Mammoth Biosciences is a biotechnology company focused on leveraging its proprietary ultracompact CRISPR systems to develop potential long-term curative therapies for patients with life-threatening and debilitating diseases. Founded by CRISPR pioneer and Nobel laureate Jennifer Doudna and Trevor Martin, Janice Chen, and Lucas Harrington, the company's ultracompact systems are designed to be more specific and enable *in vivo* gene editing in difficult to reach tissues utilizing both nuclease applications and new editing modalities beyond double stranded breaks, including base editing, reverse transcriptase editing, and epigenetic editing. The company is building out its wholly owned pipeline of potential *in vivo* gene editing therapeutics and capabilities and has partnerships with leading pharmaceutical and biotechnology companies to broaden the reach of its innovative and proprietary technology platform. Mammoth's deep science and industry experience, along with a robust and differentiated intellectual property portfolio, have enabled the company to further its mission to transform the lives of patients and deliver on the promise of CRISPR technologies.

Contacts

Media Contact:

Mohana Ray

Email: Mammoth.PR@hdmz.com

Phone: 312-506-5210

Industry: [Biotechnology](#) [Pharmaceutical](#) [Genetics](#) [Health](#)



MAMMOTH BIOSCIENCES, INC.

RELEASE SUMMARY

NanoCas, an ultracompact nuclease, enables efficient muscle editing in NHPs using a single AAV - advancing gene editing for hard-to-target tissues.