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Colossal Biosciences' woolly mouse as a step towards de-extinction

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Introduction

There are currently 48,600 species on the Earth threatened with extinction (IUCN, 2025). Instead of focusing on recovery efforts such as habitat restoration or captive breeding, Colossal Laboratories & Biosciences, the world's first de-extinction company, has approached the threat of extinction differently. After founding in 2021, cofounders Harvard geneticist, Dr George Church and entrepreneur Ben Lamm have sought to engineer animals "functionally identical to extinct [keystone] species" (Bloom, 2025) which will replace an extinct species' niches, rebalancing the ecosystem (Colossal Laboratories & Biosciences, n.d.). After utilising CRISPR Cas-9 to modify the genome of grey wolf embryo, Colossal Biosciences has recreated the dire wolf and is now focused on repeating this with other extinct species, such as the woolly mammoth. However, in doing so, funding is taken away from traditional conservation practices whilst the applications of it are ambiguous. This article will consider how well Colossal Biosciences has currently measured up to its goals for the woolly mammoth project, which include de-extinction of future elephants, developing new tools and the understanding of how genetics impact traits (Colossal Laboratories & Biosciences, n.d.). To restore the woolly mammoth, Colossal Biosciences has listed a 10-step process, seen in Figure 1, aiming to produce mammoth-like Asian elephant embryos by 2028 (Markman, 2026). This process must overcome issues associated with the sequencing of woolly mammoth DNA including sample collection and identifying and inserting the genes to hybridize the cells that then undergo somatic cell nuclear transfer (SCNT), the placement of a nucleus of a somatic cell, inside of an enucleated oocyte (Ord, n.d.) (Pankammoon, et al., 2025).

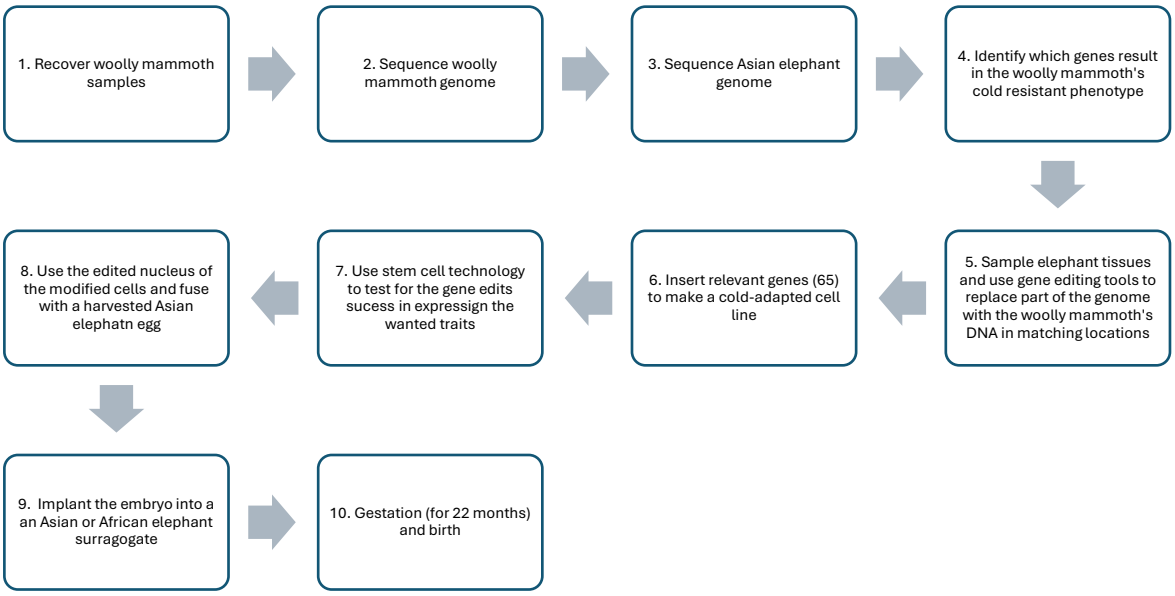

Figure 1- Colossal Bioscience's listed 10-step process for the de-extinction of the woolly mammoth (Colossal Laboratories & Biosciences, n.d.)

Sequencing the woolly mammoth genome

Permafrost preservation within Siberia and Alaska has allowed many woolly mammoth samples to be recovered, including full tusks, cheek teeth and rib fragments as well as soft tissues allowing for DNA and RNA mapping (Rowe, et al., 2024). DNA can be extracted then amplified through PCR by using a hammer and chisel, or Dremel tool to prepare bone and teeth samples (Debruyne, et al., 2008). DNA is generally recoverable due to its stability, sometimes lasting millions of years, but RNA rarely remains after death due to RNAses, enzymes that rapidly break down RNA. This makes it difficult to study insights RNA can provide about how cells function, develop and respond to their environments (Mármol-Sánchez, et al., 2026) (National Human Genome Research Institute, 2024). Genome mapping tools are software used align raw genetic data to their gene loci based on a standard reference's allowing for comparisons to be made. When comparing the mismatch rate of aligning aRNA sequences to Asian elephant transcriptome, Bowtie2 had a lower mismatch rate compared to other software such as Bowtie and BWA, especially for ultrashort sequences (Mármol-Sánchez, et al., 2026). This was advantageous for minimising misalignments and increasing accuracy when aligning the even more fragile and degraded woolly mammoth samples. However, genome mapping tools depend on a standard reference to filter and assemble the sequence, so references that themselves are incorrectly sequenced can result in accumulating mismatches. This is relevant because there are limited sequences of woolly mammoth aRNA that new sequences can be compared to, increasing potential for false positives.

Bowtie2 allowed researchers to identify “300 protein-coding mRNAs and around 60 different microRNAs in woolly mammoth skeletal muscle” (Mármol-Sánchez, et al., 2026). However, similar species such as the Asian elephants have approximately 23 thousand protein coding genes (Tollis, et al., 2020) which then can undergo alternative splicing allowing for a single gene to produce multiple distinct mRNA transcripts, demonstrating how many more protein-coding mRNAs there are. To identify more, multi-tissue studies, greater optimisations within RNA isolation and sequencing methods are needed. This would provide greater insights into the expression of a desirable phenotype within a genetically modified organism (Mármol-Sánchez, et al., 2026).

SCNT

As part of step 6, Colossal Biosciences intends to insert CRISPR libraries containing woolly mammoth DNA into the genome of an Asian elephant, making changes to its phenotype. This is due to Asian elephants being the woolly mammoth’s closest living ancestor, sharing 99.4% of its DNA (Ord, n.d.). After the 65 relevant genes have been inserted into induced pluripotent stem cells, these stem cells can then develop into multiple tissues which can be checked to see if they display the traits of the woolly mammoth, through stem cell embryogenesis (Chen, 2024). Thus, SCNT can be used for the recreation of a woolly mammoth embryo.

However, SCNT has varying success, especially in this case where hybridized stem cells are to be used. Within interspecies SCNT (iSCNT), when the nucleus and somatic cell are of different species, developmental failure can arise from disruptions in nucleocytoplasmic interactions, mitonuclear incompatibilities and epigentic programming (Pankammoon, et al., 2025). Firstly, issues can occur within nucleocytoplasmic transport, the movement of molecules between the nucleus and the cytoplasm. This is because within the iSCNT process, the nuclear envelope breaks down and reforms is constructed of mix of nucleoporins, proteins that control the movement of molecules between the nucleus and cytoplasm, from the donor and recipient(Pankammoon, et al., 2025). Due to species-species differences, this can lead to incomplete maturation which can then impair transport during mitotic division, preventing cell division for growth. Secondly, following iSCNT, mitonuclear communication occurs between donor nuclear DNA, donor mitochondrial DNA and recipient mitochondrial DNA which can lead to dysfunction due to the heteroplasmy, presence of nuclei from different origins. This is because both the nuclear and mitochondrial DNA code for proteins needed to build oxidative phosphorylation

(OXPHOS), as they build the electron transport chain together, various membrane proteins that act as enzymes to couple redox reactions, gradually releasing energy from aerobic respiration (Liu, 2026). If proteins are incompatible, the electron transport chain will be disrupted, impairing mitochondrial function. Additionally, heteroplasmy can lead to dysfunction due to the alteration of cellular metabolism, where gene expression and oxidative stress is altered (Pankammoon, et al., 2025).

Thirdly, iSCNT technology aims to reprogram the somatic donor nuclei into a totipotent state, so that the hybrid cell can then mimic the developmental processes of a fertilized embryo by being able to specialise into all cell types. However, some somatic nuclei retain epigenetic marks of an adult cell that need to be erased for proper reprogramming and hence allowing for correct nucleus, mitochondrion and cytoplasm crosstalk (Pankammoon, et al., 2025). If not achieved before genome activation, failed patterns will be copied and expressed, resulting in foetal abnormalities due to incorrect genes being transcribed (Malin, et al., 2022).

Woolly mice

Despite these possible failure mechanisms, Colossal Biosciences were nevertheless able to achieve iSCNT. In 2025, as a proof of concept, they created “woolly mice”, mice with up to seven genes altered, to have a phenotype consisting of curly, golden-brown, textured coats (Chen, et al., 2025), as seen in Figure 2. To make these genetic changes, Colossal Biosciences combined “RNP-mediated knockout, multiplex precision genome editing, and precision homology directed repair (HDR)”. These advanced genetic engineering techniques were able to edit multiple specific genes simultaneously to achieve high editing efficiencies (CRISPR Medicine News, 2025).This showcases Colossal Biosciences’ ability to drive predictable phenotypes validating the viability of recreating the woolly mammoth.

Figure 2 - Woolly mice created by Colossal Biosciences (CRISPR Medicine News, 2025)

Future steps

While the woolly mouse is a significant milestone, Colossal Bioscience's still has significant progress to make to de-extinct the woolly mammoth, including the increased complexities of going from a model species, mice, to Asian elephants. George Church, a cofounder of Colossal Biosciences claimed that to accomplish their goal, 65 genes in an Asian elephant would need to be altered (Tapon & Mendoza, 2025), which increases chances of mistakenly modifying DNA regions similar to the target sequences. Additionally, the understanding of the relationship between editing polygenetic traits and the resulting phenotypes needs further development, especially due to the differences in biological processes within mice and elephants such as metabolism. Also altering the Fabp2 gene, associated with lipid metabolism and fatty acid formation (CRISPR Medicine News, 2025), led to no observable differences within the woolly mice (Tapon & Mendoza, 2025). Furthermore, mice have a 20-day gestation period, much shorter than the 22 months of an Asian elephant which leads to a lengthier and costlier process for evaluating success (Colossal Laboratories & Biosciences, n.d.).

Limitations

However, even if Colossal Biosciences were able to bring back the woolly mammoth, it is ambiguous if it will have its intended effects. Firstly, the woolly mammoths once inhabited Pleistocene steppe-tundra, a vast, cold and dry treeless biome. The biome was maintained by megafauna through processes such as trampling, uprooting and seed dispersal (Poquérusse, et al., 2024). Church claims that mammoths scraping away layers of snow allowed cold air to reach soil, maintaining the permafrost but after the mass extinction of megafauna ~12-15 ka ago, the lack of trampling led to its melting, which also released greenhouse gases. Therefore, the revival of the woolly mammoth would reverse this process (Neuman, 2021). However, some are sceptical of this. Professor in evolutionary genetics at the Stockholm-based centre for Paleogenetics, Love Dalèn, believes that woolly mammoth de-extinction will not have "any measurable impact" on the permafrost (Neuman, 2021). Also, today the ecosystem has paludified, turning from a dry, vegetated land into a peatland. And so having the phenotype of a woolly mammoth within the current ecosystem is unlikely help it to survive and bring back the plants and animals the co-inhabited the ecological niche (Mann, et al., 2013) (Neuman, 2021). Additionally, Colossal Bioscience's research requires the use of Asian elephants, an endangered species (WWF, n.d.), which diverts funding that could be otherwise used for other conservation projects such as the International IFAW Asian Elephant Protection (AEP). Colossal Biosciences have received over $558 million dollars of funding (TexAU, n.d.), despite uncertainty of its ability to conserve natural

habitats, compared to traditional conservation practices. Furthermore, CRISPR-Cas9 still faces limitations due to the chances of off-targeting, which can induce undesirable and unpredictable mutations (Chen, 2024). When these malfunctioning genes are spread across the population's gene pool, it reduces the chances of organisms acquiring biological fitness (Lavazza, 2019).

Applications

However, the need to prevent CRISPR-Cas9 leading to undesirable outcomes has helped develop and refine existing techniques which can be applied in other areas. The woolly mouse serves as a pivotal organism due to the ability to customise the genome, allowing for more accurate models of diseases and observation of relationships between genotypes and phenotypes, having cross-disciplinary applications including neurological research and metabolism (Khanra, et al., 2025). Within cancer research, the woolly mouse has helped scientists to understand the gene-environment conditions that drive tumorigenesis, the process by which normal cells transform into cancerous ones and proliferate to become a tumour. By introducing mutations similar to those in human tumours, it has enabled researchers to observe antitumour immune responses that more closely mirror those of human cancer physiology (Connolly, et al., 2022). Ethical concerns also stem from this, centring on ensuring humane treatment of the mice and minimising harm during genetic modification (Khanra, et al., 2025). Furthermore, Colossal Bioscience's has also used technology developed during their research to develop four of their own commercial ventures, including 'Breaking' which developed Microbe X-32 which is able to breakdown various plastics (Bloom, 2025) (Breaking, n.d.).

Conclusion

Colossal Biosciences have made significant progress towards the de-extinction of the woolly mammoth, as marked by the woolly mouse. The woolly mouse overcame challenges associated with woolly mammoth DNA collection and failure mechanisms of iSCNT. But to repeat this with the Asian elephant, there are further associated challenges with iSCNT that Colossal Biosciences such as greater regulations as an endangered species and its lengthier gestation period. Currently, the woolly mouse has applications within other fields such as oncology, where genetically modified mice have better mimicked the human physiological responses to tumours. These applications are also seen within Colossal Bioscience's own commercial ventures such as Breaking. However, it is currently ambiguous whether the woolly mammoth will be able to have

the intended effects on an ecological niche that no longer exists and raises ethical concerns on how the funding for this project instead have been funded traditional conservation efforts.

Word Count: 1648

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