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Scientists Have Bred Woolly Mice on Their Journey to Bring Back the Mammoth

SCIENCE CLIMATE CHANGE

Scientists Genetically Engineer Mice with Woolly Mammoth …

by Jeffrey Kluger
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Extinction is typically for good. Once a species winks out, it survives only in memory and the fossil record. When it comes to the woolly mammoth, however, that rule has now been bent. It's been 4,000 years since the eight-ton, 12-foot, elephant-like beast walked the Earth, but part of its DNA now operates inside several litters of four-inch, half-ounce mice created by scientists at the Dallas-based Colossal Laboratories and Biosciences. The mice don't have their characteristic short, gray-brown coat, but rather the long, wavy, woolly hair of the mammoth reappearance of the mammoth itself as early as 2028.

“The Colossal woolly mouse marks a watershed moment in our de-extinction mission,” said company CEO Ben Lamm in a statement. "By engineering multiple cold-tolerant traits from mammoth evolutionary pathways into a living model species, we've proven our ability to recreate complex genetic combinations that took nature millions of years to create."

Woolly mice at Colossal Biosciences lab. *Courtesy of Colossal Biosciences*

Colossal has been working on restoring the mammoth ever since the company’s founding in 2021. The animal’s relatively recent extinction—just a few thousand years ago as opposed to the tens of millions that mark the end of the reign of the dinosaurs—and the fact that it roamed the far north, including the Arctic, means that its DNA has been preserved in multiple remains embedded in permafrost. For its de-extinction project, Colossal collected the genomes of nearly 60 of those recovered mammoths.

traits that separate the mammoth from the Asian elephant—its close evolutionary relation—editing an elephant stem cell to express those traits, and introducing the stem cell into an elephant embryo. In the alternative, scientists could edit a newly conceived Asian elephant zygote directly. Either way, the next step would be to implant the resulting embryo into the womb of a modern-day female elephant. After 22 months—the typical elephant gestation period—an ice age mammoth should, at least theoretically, be born into the computer-age world.

But speedbumps abound. The business of rewriting the genome takes extensive experimentation with hundreds of embryos to ensure that the key genes are properly edited. The only way to test if they indeed are is to follow the embryos through gestation and see if a viable mammoth pops out; the nearly two years it would take for even a single experimental animal to be born, however, would make that process impractical. What's more, Asian elephants are highly social, highly intelligent, and endangered, raising intractable ethical obstacles to experimenting on them. Enter the mouse, an animal whose genome lends itself to easy manipulation with CRISPR—a gene-editing tool developed in 2012, based on a natural process bacteria use to defend themselves in the wild. What's more, mice need only 20 days to gestate, making for a quick turnaround from embryo to mouse pup.

In the current experiment, researchers identified seven genes that code for the mammoth's shaggy coat—identifying distinct ones that make it coarse, curly, and long. They also pinpointed one gene that guides the production of melanin—which gives the coat its distinctive gold color—and another that governs the animal's prodigious lipid metabolism. Relying on CRISPR, they then took both the stem cell and zygote approach to rewriting the mouse's stem cell to express those traits. The next steps involved more than a little hit and miss.

Over the course of five rounds of experiments, the Colossal scientists produced nearly 250 embryos. Fewer than half of them developed to larger, more-viable 200- to 300-cell embryos, which were then implanted in the womb of around a dozen surrogate females. Of these, 38 mouse pups were born. All of them successfully expressed the gold, woolly hair of the mammoth as well as its accelerated lipid metabolism. The Colossal scientists see the creature they've produced as a critical development.

"The woolly mouse project doesn't bring us any closer to a mammoth, but it does validate the work we are doing on the path to a mammoth," Lamm tells TIME. "[It] proves our end-to-end pipeline for de-extinction. We started this project in September and we had our first mice in October so that shows this works—and it works efficiently."

There's plenty still to accomplish. A mammoth is much more than its fur and its fat, and before one can lumber into the twenty-first century, the scientists will have to engineer dozens of other genes, models, and only if they succeed there try the same technique on an elephant.

"The list of genes will continue to evolve," says Lamm. "We initially had about 65 gene targets and expanded up to 85. That number could go up or down with further analysis, but that's the general ballpark for the number of genes we think we will edit for our initial mammoths."

Woolly mice at Colossal Biosciences lab. *Courtesy of Colossal Biosciences*

Colossal scientists see all of this work as just a first step in developing a more widely applicable de-extinction technology. In addition to the mammoth, they would also like to bring back the dodo and the thylacine—or Tasmanian tiger.

"Our three flagship species for de-extinction—mammoth, thylacine, and dodo—capture much of the diversity of the animal tree of life," says Beth Shapiro, Colossal's chief science officer. "Success with each requires solving a different suite of technical, ethical, and ecological challenges."

The work can't start soon enough. The company points to studies suggesting that by 2050 up to 50% of the Earth's species could have been wiped out, most of them lost to the planet's rapidly changing climate. The Center for Biological Diversity puts the figure at a somewhat less alarming 35%, but in either case, the widespread dying could lead to land degradation, loss of diversity, the rise of invasive species, and food insecurity for humanity. Arresting climate change and the loss of species that will result is a critical step away from that brink, but one that policymakers and the insurance policy against environmental decline.

“We do not argue that gene editing should be used instead of traditional approaches to conservation, but that this is a ‘both and’ situation,” says Shapiro. “We should be increasing the tools at our disposal to help species survive.”

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