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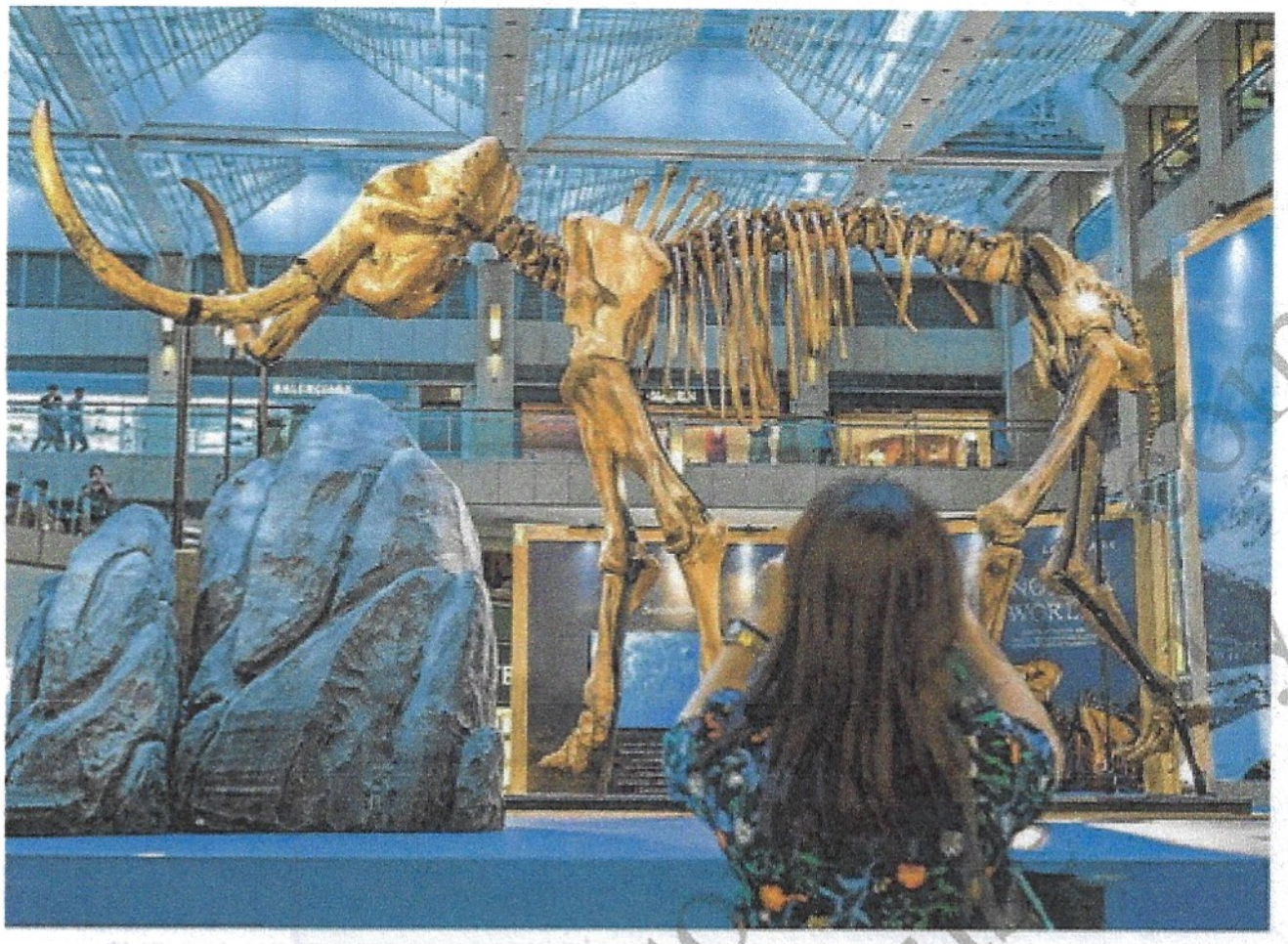

Scientists identified a compound called mammuthusin in the genetic code of a species of mammoth from 4,000 years ago. HOU YU/ CHINA NEWS SERVICE/ VCG/ GETTY IMAGES

Search for New Antibiotics Turns Back Time

BY DOMINIQUE MOSBERGEN

Buried in the DNA of the long extinct woolly mammoth is a compound that scientists hope will one day yield a lifesaving antibiotic.

In experiments, mammuthusin, as the compound is called, has eradicated superbugs— bacteria that are resistant to today's antibiotics and cause infections that are hard to treat—says César de la Fuente, the bioengineer who helped discover the molecule.

De la Fuente, a professor at the University of Pennsylvania, is among the scientists probing ancient and unlikely places— from genetic remnants of Neanderthals and extinct animals to unassuming backyard dirt— to find new antibiotics. He says the search is desperate: "Antibiotic resistance is one of the greatest challenges we face as a society."

Infections caused by superbugs contribute to the deaths of more than five million people globally each year. Antibiotics are increasingly losing potency against even common infections. Without new drugs, antibiotic resistance could kill 39 million people by 2050, a study last year predicted.

Now, fresh approaches to research are coming to an industry that has been slow to make new drugs and has been stymied by bacteria's ability to rapidly evolve defenses against those that exist. Most of the antibiotics we use today, and that have saved hundreds of millions of lives, were found in nature—many of them decades ago and several by accident. Alexander Fleming discovered penicillin in 1928 after returning from vacation and finding that mold on a petri dish had prevented harmful bacteria from growing.

To help combat superbugs, doctors say we need new antibiotics with novel chemical structures or mechanisms of action. But only a handful of such drugs has entered the market over recent decades.

De la Fuente is banking on artificial intelligence to help end this dry spell. He and his collaborators have built deeplearning algorithms to comb through enormous genetic databases to find peptides, or protein fragments, that have antibacterial properties. They have used this method to analyze animal venoms, the human microbiome and archaea, an underexplored group of microorganisms.

They have also mined the genetic codes from fossils of long-extinct animals and humans, including Neanderthals and Denisovans. "This deeplearning model has opened a window into the past," de la Fuente says.

Most antibiotics used today are small-molecule drugs, mostly derived from bacteria and fungi. Small molecules can usually penetrate cell membranes with ease and are commonly administered as pills. Peptides, made up of short chains of amino acids, are larger and more complex. They tend to be more unstable in the body and can't easily be made into pills.

But advances have been made in recent years to improve the ability of peptide drugs—which include some IV antibiotics, GLP-1s and insulin— to be absorbed and used by the body. Antibacterial peptides are also plentiful in nature, as they are a part of the immune system in most organisms.

"Peptides are the next big thing in medicine," says de la Fuente, who launched a startup in January to further explore the antibiotic potential of mammuthusin and other peptides.

When the algorithms identify a new peptide with antibiotic potential, de la Fuente and his team use robots to make the compound in their lab and then test it in mice infected with bacteria. So far, a few hundred peptides made in de la Fuente's lab have safely and effectively cured sick mice.

One of them was mammuthusin, identified in the genetic code of *Mammuthus primigenius* , a species of mammoth that last roamed the Earth about 4,000 years ago. The researchers discovered the peptide after mining a National Center for Biotechnology Information database of DNA se quencing data obtained from the fossils of extinct animals.

In experiments, mammuthusin was as potent as polymyxin B, an antibiotic often used as a last resort for serious infections, according to a paper published in Nature. The mammoth peptide effectively eradicated a type of bacterium that the World Health Organization has designated a critical pathogen because of its resistance to many common antibiotics.

The work with extinct species is "expanding the chemical space that we could explore," says James Collins, a bioengineer at the Massachusetts Institute of Technology. "These are molecules that evolved in a different time and a different setting."