failures," says geneticist Michael Stebbins, a consultant and former White House science office official. The new agency would help promising ideas cross the so-called valley of death that prevents many discoveries from reaching patients. He thinks ARPA-H's proposed $6.5 billion budget is warranted "because of the scale of the challenge."

Breaking the existing NIH mold is important, agrees Robert Cook-Deegan, a research policy professor at Arizona State University, Tempe, and longtime proponent of a DARPA-like agency at NIH. "I'm totally in favor of giving senior NIH people a lot of money and the flexibility to push the boundaries and work outside the existing system of peer review," he says. But he wonders about the premise that new technologies are the key to improving health outcomes in the United States. "I'm not sure that curing cancer is an engineering problem," he says.

As vice president, Biden became a champion of cancer research after his son Beau Biden died from brain cancer in 2015, and he led the Obama administration's Cancer Moonshot that aimed to accelerate cures. He floated the idea of ARPA-H during his presidential campaign and more recently during a visit to a plant making a COVID-19 vaccine.

But Biden's plan to place ARPA-H within the notoriously cautious NIH surprised some of the idea's staunchest advocates. "If it's just another fund within the NIH, we're not optimistic that it's going to succeed," says Liz Feld, president of the Suzanne Wright Foundation, a pancreatic cancer research advocacy group. Instead, Feld and allies want ARPA-H to stand alone within NIH's parent agency, the Department of Health and Human Services.

Other research advocates worry ARPA-H would divert money from NIH's existing 27 institutes and centers and say it should start smaller. "We do not believe it is in the nation's interest to channel funding away from other research priorities," says Mary Woolley, president of Research!America, which is seeking a 10% boost for NIH's core programs.

The fate and final form of ARPA-H and the other proposed ARPA-like entities will not be clear for months. Biden's proposal is the opening move in a budget process for the fiscal year that begins on 1 October and will involve extensive negotiations with Congress. Separately, legislators have already started to debate Biden's $2 trillion infrastructure plan, which includes a one-time injection of $200 billion for a host of research initiatives, including the new tech directorate at NSF. ■

With reporting by Jocelyn Kaiser.

Researchers excavating Estatuas cave in Spain found a long record of Neanderthal DNA in the sediments.

PALEOANTHROPOLOGY

DNA from cave dirt traces Neanderthal upheaval

First nuclear DNA from sediment shows turnover, migration among ancient cave dwellers in Spain

By **Ann Gibbons**

Estatuas cave in northern Spain was a hive of activity 105,000 years ago. Artifacts show its Neanderthal inhabitants hafted stone tools, butchered red deer, and may have made fires. They also shed, bled, and excreted subtler clues onto the cave floor: their own DNA. "You can imagine them sitting in the cave making tools, butchering animals. Maybe they cut themselves or their babies pooped," says population geneticist Benjamin Vernot, a postdoc at the Max Planck Institute for Evolutionary Anthropology (MPI-EVA), whose perspective may have been colored by his own baby's cries during a Zoom call. "All that DNA accumulates in the dirt floors."

He and MPI-EVA geneticist Matthias Meyer report this week in *Science* that dirt from Estatuas has yielded molecular treasure: the first nuclear DNA from an ancient human to be gleaned from sediments. Earlier studies reported shorter, more abundant human mitochondrial DNA (mtDNA) from cave floors, but nuclear DNA, previously available only from bones and teeth, can be far more informative. "Now, it seems that it is possible to extract nuclear DNA from dirt, and we have a lot of dirt in archaeological sites," says archaeologist Marie Soressi of Leiden University.

"This is a beautiful paper," agrees population geneticist Pontus Skoglund of the Francis Crick Institute. The sequences reveal the genetic identity and sex of ancient cave dwellers and show that one group of Neanderthals replaced another in the Spanish cave about 100,000 years ago, perhaps after a climate cooling. "They can see a shift in Neanderthal populations at the very same site, which is quite nice," Skoglund says.

To date, paleogeneticists have managed to extract ancient DNA from the bones or teeth of just 23 archaic humans, including 18 Neanderthals from 14 sites across Eurasia. In search of more, Vernot and Meyer's team sampled sediment from well-dated layers in three caves where ancient humans are known to have lived: the Denisova and Chagyrskaya caves in Siberia and Estatuas cave in Atapuerca, Spain.

In what Skoglund calls "an amazing technical demonstration," they developed new genetic probes to fish out hominin DNA, allowing them to ignore the abundant sequences from plants, animals, and bacteria. Then, they used statistical methods to home in on DNA unique to Neanderthals and compare it with reference genomes from Neanderthals in a phylogenetic tree.

All three sites yielded Neanderthal nuclear and mtDNA, with the biggest surprise coming from the small amount of nuclear

PHOTO: © JAVIER TRUEBA/MADRID SCIENTIFIC FILMS

DNA from multiple Neanderthals in Estatuas cave. Nuclear DNA from a Neanderthal male in the deepest layer, dating to about 113,000 years ago, linked him to early Neanderthals who lived about 120,000 years ago in Denisova cave and in caves in Belgium and Germany.

But two female Neanderthals who lived in Estatuas cave later, about 100,000 years ago, had nuclear DNA more closely matching that of later, "classic" Neanderthals, including those who lived less than 70,000 years ago at Vindija cave in Croatia and 60,000 to 80,000 years ago at Chagyrskaya cave, says co-author and paleoanthropologist Juan Luis Arsuaga of the Complutense University of Madrid.

At the same time, the more plentiful mtDNA from Estatuas cave shows declining diversity. Neanderthals in the cave 113,000 years ago had at least three types of mtDNA. But the cave's Neanderthals 80,000 and 107,000 years ago had only one type. Existing ancient DNA from Neanderthal bones and teeth had also pointed to a falloff in genetic diversity over the same period.

Arsuaga suggests Neanderthals thrived and diversified during the warm, moist interglacial period that started 130,000 years ago. But about 110,000 years ago, temperatures in Europe dipped suddenly as a new glacial period set in. Soon after, all but one lineage of Neanderthals disappeared. Members of the surviving lineage repopulated Europe during later, relatively warm spells, with some taking shelter in Estatuas cave.

Those survivors and their descendants include what Arsuaga calls the "famous" classic Neanderthals, such as skulls from Vindija and La Ferrassie in France. He notes they had bigger brains—up to 1750 cubic centimeters (cm^3)—than earlier Neanderthals, whose cranial capacities were no larger than 1400 cm^3. Arsuaga says this mirrors a similar pattern in modern humans in Africa, who also underwent a surge in brain size and multiple population replacements with the onset of the ice age.

"This pattern—dispersal over perhaps long distances and population replacement or admixture—is one that we find almost everywhere we look," in humans or other mammals, says Beth Shapiro, a molecular biologist at the University of California, Santa Cruz.

Cave dirt DNA is likely to yield more clues. Paleogeneticist Viviane Slon, a co-author of the *Science* paper now at Tel Aviv University, says she and the MPI-EVA team are analyzing ancient DNA from sediments at dozens of sites worldwide. "Hopefully soon, we'll start to get a very high-resolution, fine-scale view of ancient humans and who was where at what time," she says. ■

BIOMEDICINE

Lab-grown embryos mix human and monkey cells

Insights from these chimeras could boost efforts to grow replacement human organs in livestock

By **Mitch Leslie**

By slipping human stem cells into the embryos of other animals, we might someday grow new organs for people with faltering hearts or kidneys. In a step toward that goal, researchers have created the first embryos with a mixture of human and monkey cells. These chimeras could help scientists hone techniques for growing human tissue in species better suited for transplants, such as pigs.

"The paper is a landmark in the stem cell and interspecies chimera fields," says stem cell biologist Alejandro De Los Angeles of Yale University. The findings hint at mechanisms by which cells of one species can adjust to survive in the embryo of another, adds Daniel Garry, a stem cell biologist at the University of Minnesota (UM), Twin Cities.

In 2017, researchers reported growing pancreases from mouse stem cells inserted into rat embryos. Transplanting the organs into mice with diabetes eliminated the disease. But cells from more distantly related species, such as pigs and humans, haven't gotten along as well. That same year, developmental biologist Juan Carlos Izpisúa Belmonte of the Salk Institute for Biological Studies and colleagues reported injecting human stem cells into pig embryos. After the embryos had developed in surrogate mother pigs for 3 to 4 weeks, only about one in 100,000 of their cells were human.

> **The chimeras "can't experience pain and aren't conscious."**
>
> **Katrien Devolder**, University of Oxford

The pig study used human skin cells that had been reprogrammed into stem cells. But so-called extended pluripotent stem (EPS) cells, made by exposing stem cells to a certain molecular cocktail, can spawn a greater variety of tissues. In the new study, Izpisúa Belmonte, reproductive biologist Weizhi Ji of Kunming University of Science and Technology, and colleagues tested those more capable cells in a closer human relative—cynomolgus monkeys. They inserted 25 human EPS cells into each of 132 monkey embryos and reared the chimeras in culture dishes for up to 20 days.

The team reports this week in *Cell* that the human cells showed staying power: After 13 days, they were still present in about one-third of the chimeras. The human cells seemed to integrate with the monkey cells and had begun to specialize into cell types that would develop into different organs.

By analyzing gene activity, the researchers identified molecular pathways that were switched on or turned up in the chimeras, possibly promoting integration between human and monkey cells. Izpisúa Belmonte says manipulating some of those pathways may help human cells survive in embryos of species "more appropriate for regenerative medicine."

Still, the human and monkey cells didn't quite mesh, notes UM stem cell biologist Andrew Crane. The human cells often stuck together, making him wonder whether there's "another barrier that we aren't seeing" that could prevent human cells from thriving if the embryos were to develop further.

In the United States, federal funding cannot be used to create certain types of chimeras, including early nonhuman primate embryos containing human stem cells. The new study was performed in China and funded by Chinese government sources, a Spanish university, and a U.S. foundation. Bioethicist Karen Maschke of the Hastings Center in New York says she is satisfied that the work, which passed layers of institutional review and drew on advice from two independent bioethicists, was performed responsibly.

Human-monkey chimeras do raise a worry, addressed in a report released last week by the National Academies of Sciences, Engineering, and Medicine (p. 218): that human nerve cells might enter animals' brains and alter their mental capabilities. But that concern is moot for the chimeras in this study because they don't have a nervous system. They "can't experience pain and aren't conscious," says bioethicist Katrien Devolder of the University of Oxford. "If the human-monkey chimeras were allowed to develop further," she says, "that would be a very different story." ■

DNA from cave dirt traces Neanderthal upheaval

Ann Gibbons

Science **372** (6539), 222-223.
DOI: 10.1126/science.372.6539.222