hypothesis remains to be seen, researchers say.

"I don't think one study will prove a very long-standing controversial hypothesis," says Brent Forester, director of the Geriatric Psychiatry Research Program at McLean Hospital in Belmont, Massachusetts, who helped to run the clinical trial of lecanemab. "But one positive study supports the hypothesis."

Amyloid is "associated with the problem, but it isn't 'the' problem", says George Perry, a neurobiologist at the University of Texas at San Antonio and a sceptic of the amyloid hypothesis. "If you modulate it, of course you can have some small benefit."

Small, but significant

Even a modest benefit would probably be appreciated by the tens of millions of people living with Alzheimer's disease worldwide. "These are the most encouraging results in clinical trials treating the underlying causes of Alzheimer's to date," said the Alzheimer's Association, a research funder and patient-advocacy organization based in Chicago, Illinois, in a statement.

Last year, the FDA controversially approved aducanumab, another monoclonal antibody developed by Biogen, to treat Alzheimer's — without a clear signal of cognitive benefit. Two incomplete phase III trials demonstrated that the drug could clear amyloid from the brain, but only one subset of participants showed a slowing in cognitive decline.

By contrast, lecanemab's phase III trial, called Clarity AD, ran uninterrupted for 18 months and unambiguously slowed decline. The top-line results released by Eisai and Biogen describe findings from almost 1,800 people with early-stage Alzheimer's disease living in more than a dozen countries.

Participants received intravenous infusions of either lecanemab or a placebo every two weeks for the duration of the trial. Their cognition was assessed using an 18-point scale called the Clinical Dementia Rating–Sum of Boxes (CDR–SB). Clinicians calculate a person's CDR–SB score by interviewing them and their carers, and testing the person's abilities in areas such as memory and problem solving.

Not only did lecanemab decrease amyloid in people's brains, but those receiving treatment scored, on average, 0.45 points better on the CDR-SB at the 18-month mark than did those in the placebo group.

It's a "really tiny and almost unnoticeable difference from placebo", says Rob Howard, a psychiatrist at University College London. Although he and others differ on what a clinically important result would be, they give a range of 0.5 to 2 points.

Still, lecanemab could be approved as a drug on the basis of the data. The question will be whether the benefit it brings is worth the risks. During the trial, about 20% of participants who received lecanemab showed abnormalities on their brain scans that indicated swelling or bleeding, although less than 3% of those in the treatment group showed outward symptoms of these side effects. By contrast, during the phase III trials for aducanumab, 40% of participants showed signs of brain swelling on their scans.

The FDA is reviewing lecanemab for 'accelerated approval' on the basis of phase II results that showed a decrease in amyloid. The new phase III results could tip the scales in favour of approval, although they are not formally part of the review. The agency expects to announce its decision on 6 January.

"It's clear that everybody's going to be watching this one closely — as they should be," Alexander says.

Researchers say that amyloid is only one component of Alzheimer's disease, however.

"There is a very detrimental second protein called tau that needs to be addressed," says Apostolova, who has consulted for Biogen and Eisai. Tau also deposits in the brains of people who have Alzheimer's. "And tau is actually the one that really strongly correlates with cognitive decline," she adds.

A multi-drug approach targeting both amyloid and tau "would be the most successful in terms of a relentless neurodegenerative disease such as Alzheimer's", Apostolova says.

Forester widens that concept even further, suggesting that people with Alzheimer's, and their carers, need support beyond medication, including education and guidance on how to manage disease progression.

"All of this has to be a part of holistic dementia care," Forester says. "You can't intervene with a drug in a vacuum."

PIONEER OF RESEARCH ON ANCIENT DNA WINS MEDICINE NOBEL

Svante Pääbo has used genomic analysis to unmask the lives of ancient human species such as Neanderthals.

By Ewen Callaway & Heidi Ledford

This year's Nobel Prize in Physiology or Medicine has been awarded for pioneering studies of human evolution that harnessed precious snippets of ancient DNA found in fossils.

The work of Svante Pääbo, a geneticist at the Max Planck Institute for Evolutionary Anthropology (MPI-EVA) in Leipzig, Germany, led to the sequencing of the Neanderthal genome and the discovery of a new group of hominins called the Denisovans, and also spawned the fiercely competitive field of palaeogenomics.

By tracing how genes flowed between ancient hominin populations, researchers have been able to trace these groups' migrations, as well as the origins of some aspects of modern human physiology.

Pääbo's Nobel win "is an extraordinary recognition of this field maturing and of what he did in putting together everything that needed to be done to accomplish this miracle, which is getting ancient DNA from human remains", says David Reich, a population geneticist at Harvard Medical School in Boston, Massachusetts.

Chris Stringer, a palaeoanthropologist at the Natural History Museum in London, says that Pääbo's work — including recovery of the oldest ancient human DNA on record, 430,000-year-old sequences from Spain[1] — has revolutionized our understanding of the past. "It's central to human evolutionary studies now," Stringer says.

Damaged DNA

Pääbo had to develop ways of analysing DNA that had been damaged by thousands of years of exposure to the elements, and contaminated with sequences from microorganisms and modern humans. He and his collaborators then put these techniques to work sequencing the Neanderthal genome, which was published in 2010 (ref. 2). This genetic analysis led to the finding that Neanderthals and *Homo sapiens* interbred, and that 1–4% of the genome of modern humans of European or Asian descent can be traced back to the Neanderthals.

> **"We've never come so close to understanding what makes humans humans."**

Pääbo's techniques were also used to identify the origins of a 40,000-year-old finger bone found in a southern Siberian cave in 2008. DNA isolated from the bone indicated that it was from neither Neanderthals nor *H. sapiens*, but came from an individual

ALAMY

Svante Pääbo's work helped to spawn the competitive field of palaeogenomics.

belonging to a new group of hominins[3]. The group was named the Denisovans, after the cave in which the bone was found. Ancient humans living in Asia interbred with this group, too, and Denisovan DNA can be found in the genomes of billions of people alive today.

During the early years of ancient DNA research — led by Pääbo and other scientists in the 1980s and 1990s — the field was plagued by concerns over contamination from modern human DNA. But, thanks to methods developed in Pääbo's laboratory, as well as the advent of new sequencing technologies, contamination is no longer the 'bogeyman' it once was.

"When I started, we weren't even sure you could work with ancient human DNA," says Pontus Skoglund, a palaeogeneticist at the Francis Crick Institute in London. "But now, and I think led by Svante's department, we have an approach where contamination is really not a major issue anymore."

Health implications

Pääbo's work teasing out DNA from Neanderthals, Denisovans and other hominins also has important implications for modern medicine. Although the share of the human genome comprised of archaic DNA is small, this material seems to punch above its weight, making an important contribution to the risks of diseases ranging from schizophrenia[4] to severe COVID-19 (ref. 5). And people living on the Tibetan Plateau can thank Denisovans for gene variants linked to high-altitude adaptation[6].

"The fact that a good fraction of the people running around in the world today have DNA from archaic humans like Neanderthals is of important consequence to who we are," says Reich. "Knowing that and trying to understand the implications of that for health is something that will be with us for the rest of our time as a species."

With genomes from multiple Neanderthals and Denisovans available, it is now possible to identify uniquely human genes, says Johannes Krause, a palaeogeneticist at MPI-EVA. In September, researchers showed that a gene variant found in humans but not in Neanderthals or Denisovans is linked to greater neuronal growth in lab-grown brain organoids[7]. "We've never come so close to understanding what makes humans humans," Krause says.

Researchers describe Pääbo as intense and driven, but also collegial and generous. His department at MPI-EVA has produced a generation of palaeogeneticists who are pushing the field ever further.

Viviane Slon, a palaeogeneticist at Tel Aviv University in Israel who did her PhD under Pääbo's supervision, says her former mentor has an "uncanny" ability to see the larger picture while remaining laser-focused on details. When Slon was working on remains that turned out to be a first-generation Denisovan–Neanderthal hybrid[8], the sequence of maternally inherited mitochondrial DNA matched that of a Neanderthal. But, when publishing those results, Pääbo urged Slon to reserve judgement until they had sequenced nuclear DNA inherited from both parents. "He wouldn't let me write that it's a Neanderthal because we didn't know that, and in fact it turned out to be a mixed offspring," Slon says.

Pääbo's influence on ancient DNA work has been such that it's hard to imagine where the field would be without him. "He's the godfather of the field," says Skoglund.

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WHAT A NEW PRESIDENT IN BRAZIL COULD MEAN FOR SCIENCE

Science-friendly candidate Luiz Inácio Lula da Silva is leading the election polls.

By Jeff Tollefson

In June, the Brazilian Academy of Sciences issued a report to the various candidates competing to be Brazil's next president, calling for investments in science, education and sustainable development. Only one responded. Representatives from the campaign of Luiz Inácio Lula da Silva, who is the front runner heading into the 30 October run-off election, visited scientists at the academy in Rio de Janeiro a few weeks later.

For Luiz Davidovich, a physicist at the Federal University of Rio de Janeiro who presided over the meeting, it was a singular moment that underscores the hope that many scientists have for Lula, who is running for re-election after 12 years out of office. "Lula's team talked about the things they were thinking of, but they also listened to us," Davidovich says.

During Lula's first stint as president, from 2003 to 2010, his administration invested heavily in science and innovation while promoting social and environmental policies that drastically reduced deforestation in the Amazon and lifted millions of people out of poverty. Today, Brazil's science funding is lower than it has been in around 15 years, and the country is enduring an economic crisis that has left 33 million people without food.