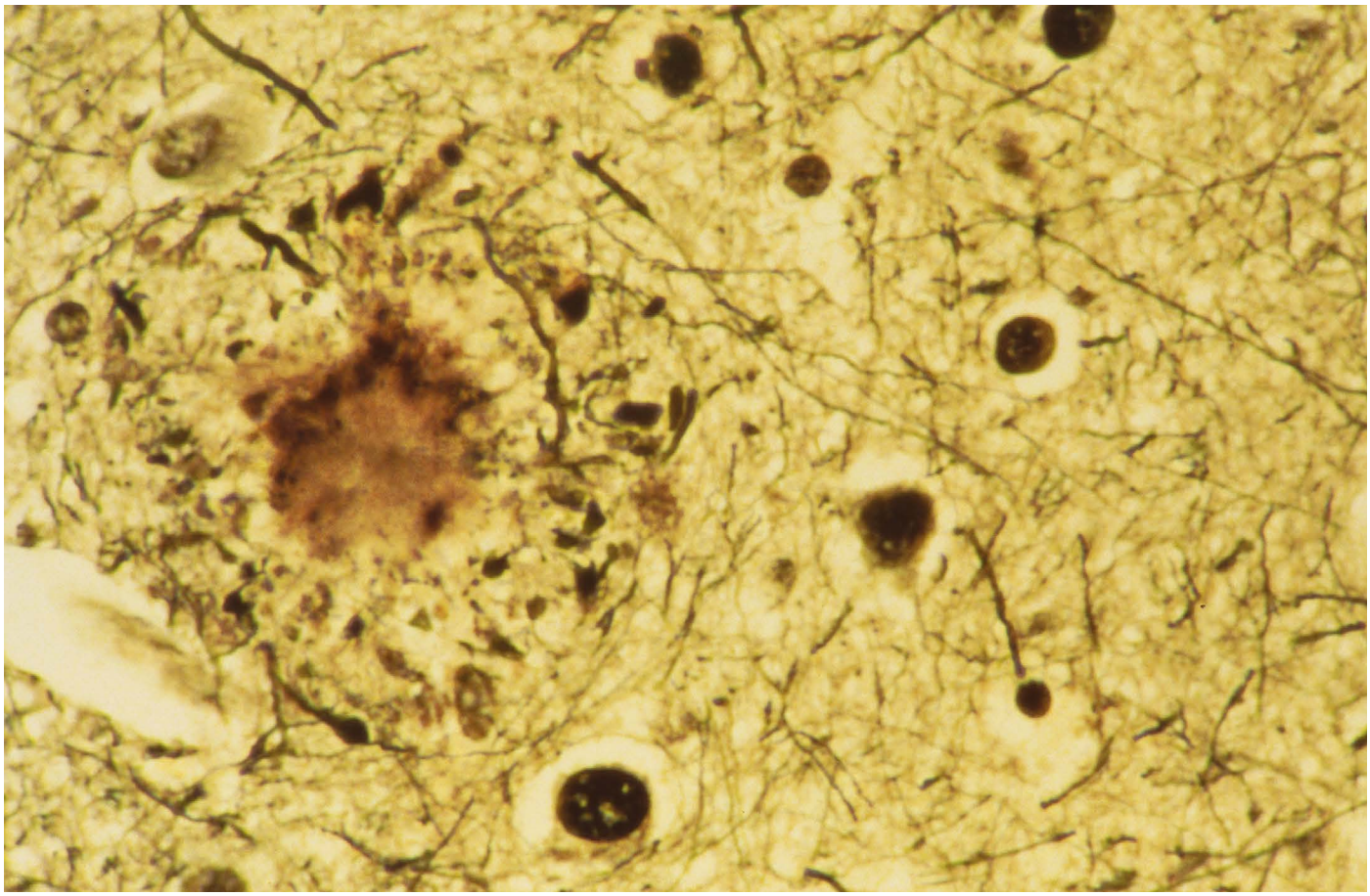
News in focus



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People with Alzheimer's disease usually develop protein plaques (circular splotch on left) in their brains.

ALZHEIMER'S DRUG SLOWS MENTAL DECLINE IN TRIAL — BUT IS IT A BREAKTHROUGH?

Researchers are cautiously optimistic after companies announce positive results for lecanemab.

By McKenzie Prillaman

Some researchers are celebrating last week's announcement that a candidate drug for Alzheimer's disease slowed the rate of cognitive decline for people in a clinical trial by 27%. Others remain hesitant, wanting to see data beyond what was disclosed in a 27 September press release. If the results stand up, the treatment — called lecanemab — will be the first of its kind to show a strong signal of cognitive benefit in a robust trial.

"It's such a win for our field," says Liana Apostolova, a neurologist at the Indiana University School of Medicine in Indianapolis.

The results are "quite promising", says Caleb Alexander, an internal-medicine specialist and epidemiologist at the Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland, and a member of an advisory committee for the US Food and Drug Administration (FDA). But, he adds, "we'll have to see what the full analysis of the trial suggests". Alexander and others also note that, although the results indicate that lecanemab does provide some clinical benefit, the degree to which it does so is small.

Developed by Eisai, a pharmaceutical company in Tokyo, and biotechnology firm Biogen in Cambridge, Massachusetts, lecanemab is a monoclonal antibody designed to clear from the brain clumps of protein that many think are a root cause of Alzheimer's disease. This theory, known as the 'amyloid hypothesis', holds that the protein amyloid-β accumulates into toxic deposits as the disease progresses, ultimately causing dementia.

Whether lecanemab confirms the amyloid

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