the three main genetic ancestries found today in Europe (the western hunter-gatherers) was fully formed, when the Villabruna and Goyet Q2 mixed. This group — which Posth *et al.* now rename Oberkassel — seems to be genetically homogeneous from present-day Poland to the United Kingdom, indicating an expansion that was possibly related to the abrupt warming during the Bølling–Allerød period (14.8 to 12.9 ka).

Farther east, another population (in which individuals with lighter skin and darker eye colours were more frequent at the time than was the case in Oberkassel populations) eventually developed the Sidelkino culture of western Russia. Posth *et al.* detected Sidelkino-related genetic ancestry in individuals from northern Iberia,and its frequency increased in the Baltics shortly after the time of the thermal maximum approximately 8 ka — a period when the Oberkassel genetic influence also extended as far east as the Don–Volga region in Russia. Whether such population movements were the sole product of the warming climate, or a response to groups of farmers expanding outwards from Anatolia, remains unknown. Although the spread of Anatolian farmers into Europe changed the genetic make-up of local populations, Posth and co-workers found that individuals of mainly Oberkassel ancestry persisted in Germany until roughly 5.2 ka, in line with a previous study of northern France[10]. This could reflect local communities limiting admixture with incoming farmers but adopting a farming lifestyle.

Posth and colleagues have revealed population turnovers that shaped the European genetic landscape in the face of climate change. Their findings caution against simple narratives equating lithic industries and ethnicity. More genetic analyses are, however, needed to gain finer-grained resolution of the formation and expansion timing of several groups (such as the Villabruna) and their possible links to lithic industries currently omitted from genetic analyses (such as the Badegoulian). In the future, sequencing of DNA molecules preserved in cave sediments might help to overcome the limitations of sequencing only available skeletal samples[11], and could even reveal the social structure of the underlying human communities[12], including those that first entered Europe.

The European continent has a long tradition of archaeology, where excavation methods were developed in the early nineteenth century. It is therefore not surprising that this continent is also the best characterized archaeogenetically, with extensive genomic time series now extending from the present day to the Upper Palaeolithic period (50–12 ka). The resulting resources and increased understanding of the human past should be commended, but are also an invitation to redouble efforts outside Europe, to avoid developing a Eurocentric vision of human prehistory. For now, the fluidity of ancestries in the deep genetic history of Europe provides an important lesson: no modern population can claim a single origin from the human groups that first became established on the continent.

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Neurodegeneration

Drug trial for Alzheimer's disease is a game changer

Eric M. Reiman

An antibody treatment reduces measurements of brain abnormalities called amyloid plaques in people with Alzheimer's disease, and lessens clinical decline. This result will help in developing therapies to treat and prevent the disease.

Researchers have long sought a treatment for Alzheimer's disease that could target the biological underpinnings of the condition and slow cognitive decline and its disabling consequences in definitive clinical trials. Writing in the *New England Journal of Medicine*, van Dyck *et al.*[1] provide compelling evidence that an antibody treatment called lecanemab can drastically reduce measurements of a characteristic Alzheimer's brain abnormality called amyloid plaques, alter other biomarkers of the disease and reduce the clinical decline in people with the condition. Although lecanemab did not stop clinical decline completely, the trial results promise to have a profound effect on Alzheimer's research, patient care and the successful development of therapies that could modify or even prevent the disease.

"This treatment offers hope for many patients and family caregivers."

For more than 30 years, proponents of the 'amyloid hypothesis' have contended that the amyloid-β (Aβ) protein triggers a cascade of neurobiological changes that contribute to the development of Alzheimer's disease. The postulated cascade includes: aggregation of Aβ into soluble clumps and insoluble fibrils, the main component of plaques; phosphorylation, aggregation and spread of another protein called tau, the main component of tangles (a microscopic brain abnormality that, along with Aβ plaques, defines the disease); neuroinflammation; and neurodegeneration[2]. A growing number of drugs have been and continue to be developed to target Aβ and other elements of this cascade[3].

In 2016, the antibody aducanumab became the first drug shown to cause a notable reduction in Aβ plaques[4]. At the time, I suggested that it would be a game changer if the treatment's plaque-reducing effects were found to be linked with a clear clinical benefit in its phase III trials[5]. Unfortunately, those trials were discontinued early, after an interim analysis mistakenly concluded that aducanumab was unlikely to demonstrate sufficient clinical benefit. When remaining data from the two discontinued trials became available, one trial showed improvements, one did not. Post-hoc analyses suggested a clinical benefit in people who received the highest dose for at least one year[6].

In a review of aducanumab, the US Food and Drug Administration (FDA) conducted a meta-analysis of available findings from various anti-Aβ antibody therapy trials[7] and found a relationship between greater Aβ-plaque reduction and slower clinical decline. The meta-analysis included the aducanumab trials; phase II trials of lecanemab[8] and another antibody called donanemab[9,10] (both of which showed significant Aβ plaque reductions and suggested a clinical benefit); and trials of four other antibody therapies with more

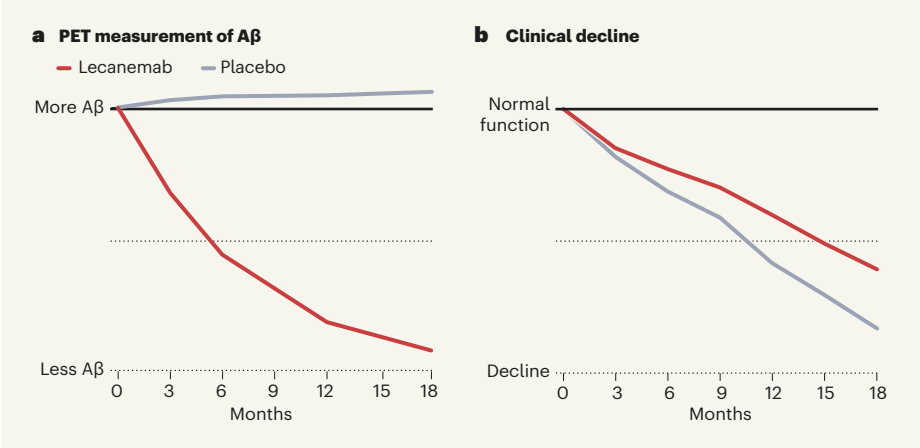

Figure 1 | An antibody that can slow the progression of Alzheimer's disease. a, In a clinical trial[1], the antibody treatment lecanemab reduced levels of Alzheimer's-associated abnormalities called amyloid-β (Aβ) plaques in the brain (as measured by positron emission tomography; PET) compared with a placebo, along with other biomarker measurements of disease progression (not shown). **b**, The treatment also lessened a measure of clinical decline known as the CDR sum of boxes, along with other measures of cognitive and functional decline (not shown). (Adapted from Fig. 2a,b of ref. 1.)

modest Aβ-plaque-reducing effects.

On the basis of the apparent relationship between the antibody therapies' plaque-reducing effects and a clinical benefit, the FDA designated measurements of Aβ plaques taken by positron emission tomography (PET) as a 'surrogate endpoint' for clinical trials of this type. A surrogate endpoint is a biomarker measurement that is thought to reflect part of the disease pathway and is at least "reasonably likely" to predict an anti-Aβ antibody therapy's clinical benefit. On the basis of its surrogate-endpoint effects, aducanumab was considered reasonably likely to have a clinical benefit and granted conditional marketing approval — because of its notable Aβ-plaque-reducing effects — under the FDA's accelerated approval mechanism for serious conditions with an unmet medical need[7,11] (see go.nature.com/3jtei3e).

The decision was controversial[11], with lingering questions about Aβ's role in the development and treatment of Alzheimer's disease, aducanumab's benefits, risks and proposed cost, and the criteria that would be used to support the approval and financial coverage of treatments for modifying Alzheimer's disease. Aducanumab has not yet been approved for use in other countries.

Van Dyck and colleagues' lecanemab trial now provides a major boost to anti-Aβ treatments, and it is hoped that the phase III trial of donanemab will show a similar benefit when findings are reported in mid-2023. The 18-month lecanemab trial evaluated the drug's ability to reduce Aβ plaques, modify other disease biomarkers and lessen clinical decline in nearly 1,800 people who had clinical and biomarker evidence of mild cognitive impairment or mild dementia owing to Alzheimer's disease. Lecanemab markedly reduced PET measurements of Aβ plaques, along with cerebrospinal fluid- and blood-based biomarker measurements of Aβ plaques and Aβ-mediated tau phosphorylation. The treatment slowed increases in the accumulation of tau tangles, altered neuroinflammatory and neurodegenerative biomarker measurements, and reduced key measures of cognitive decline and disability by 24–37%. Differences between the treatment group and people taking a placebo were highly significant and grew over time (Fig. 1).

Aβ-plaque-reducing antibodies can cause amyloid-related imaging abnormalities (ARIAs) — side effects that include localized brain swelling (known as ARIA-E) or haemorrhages (ARIA-H), and that require magnetic resonance imaging to detect and manage. ARIAs occur more frequently in people who carry the *APOE4* gene — a variant that confers a high risk of developing Alzheimer's disease. Among lecanemab-treated participants, 12.6% had ARIA-E, although only 2.8% of them had associated symptoms (such as headaches) and these symptoms were usually reversible. Symptoms of ARIA-H were seen in 0.7% of participants. One person treated with lecanemab died from brain haemorrhage during the trial, as did one person receiving the placebo. Three more lecanemab-treated participants died of brain haemorrhage after the trial was over (see go.nature.com/4tvsvcq), emphasizing the need to further clarify the magnitude and risk factors for this rare catastrophic side effect following the drug's probable approval.

There are several reasons why van Dyck and colleagues' trial marks a turning point in the fight against Alzheimer's disease. First, it makes lecanemab the first Alzheimer's-disease-modifying treatment for which there is compelling evidence of a clinical benefit. The treatment clears Aβ plaques, alters other disease biomarkers and lessens clinical decline in people who have mild cognitive impairment or mild dementia. It offers hope for many patients and family caregivers, who will value the chance to learn about the treatment's potential benefits, risks, costs and requirements, and to determine whether the treatment is right for them.

Second, it confirms the hypothesis that certain Aβ aggregates are involved in the development, treatment and potential prevention of Alzheimer's disease. It provides a foundation for the development of combination therapies that simultaneously target Aβ and downstream elements (tau, neuroinflammatory or neurodegenerative) of the disease. It hugely increases the chance that these, and other anti-Aβ therapies, could have a profound impact on the prevention of this increasingly common, costly and devastating disease.

Third, it will help researchers and clinicians to identify those Aβ, tau, neuroinflammatory or neurodegenerative biomarker outcome measurements that are reasonably likely to be associated with a treatment's clinical benefit. These biomarkers could be used to inform the successful development of disease-modifying treatments in smaller, shorter, early-phase trials. Furthermore, they could be used to help find and support the accelerated approval of effective prevention therapies within the next few years.

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