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Editorial

Beyond amyloid: New approaches to Alzheimer's disease treatment

In March, 2019, Biogen announced its decision to halt further research on its amyloid-targeting antibody, aducanumab, on the basis of interim futility analyses from two identically designed, phase 3 randomised controlled trials—EMERGE and ENGAGE. In a stunning subsequent announcement in October, the company reversed course, indicating they would be now be seeking US Food and Drug Administration approval of aducanumab on the basis of analyses of a larger dataset from the trials. On Dec 5, 2019, results from both randomised controlled trials were presented at the 12th Clinical Trials on Alzheimer's Disease conference in San Diego (CA, USA). Both EMERGE and ENGAGE aimed to evaluate efficacy of aducanumab in slowing cognitive decline in patients with early Alzheimer's disease. The primary endpoint of improvement in the Clinical Dementia Rating scale Sum of Boxes score, as well as two out of three secondary endpoints related to cognitive function, appear to have been met—albeit only in the high-dose group of just one of the two studies (EMERGE). The low-dose group of EMERGE, and both high-dose and low-dose group of ENGAGE, did not reach any of the primary or secondary endpoints. Biogen claims the differences seen between the two trials are probably due to the greater number of individual high-dose treatments received by EMERGE participants within the trial duration. Despite renewed enthusiasm for aducanumab, it should be noted that the effects seen on cognitive decline were modest and not without serious potential side effects, including cerebral oedema. Critics argue that the risks might not be worth the benefits, and that more studies are needed to confirm whether targeting this pathway remains a worthwhile therapeutic endeavour.

Considering that several previous trials targeting amyloid have failed, the field is anxious to move forward and explore other treatment options. Although targeting tau and associated neurofibrillary tangles has been another major direction of potential therapeutic investigation, 2019 has been an exciting year for translational Alzheimer's disease research outside the major focus areas of amyloid and tau targeting.

Alzheimer's disease is known to have a heritable component, and two major genome-wide analyses published in *Nature Genetics* in March, 2019, have expanded and refined the list of potential causative genes and functional pathways associated with the disease. In addition to well known pathways related to amyloid processing and degradation, it is becoming clear from these and other studies that microglia and other components of the innate immune system are likely to play key regulatory roles in the pathology of Alzheimer's disease. Of particular interest, loss-of-function variants of the microglial TREM2 receptor are known to increase risk of late-onset Alzheimer's disease. A study in the Aug 28, 2019, issue of *Science Translational Medicine* followed a small cohort of 385 older individuals over a period of 4 years to show that increased concentrations of soluble TREM2 in cerebrospinal fluid (CSF) are associated with reduced proportions of patients with cognitive decline and clinical manifestations of Alzheimer's disease. However, a definitive explanation for how TREM2-mediated signalling in microglia might modulate disease pathology has yet to be revealed. Whether microglial activation is protective or detrimental in Alzheimer's disease is also an incompletely resolved question. Several studies have suggested that microglia-associated TREM2 might bind to amyloid β and mediate its phagocytosis and clearance, and thus could be protective. However, some evidence has suggested that activated microglia might exacerbate disease— both by increasing amyloid plaque deposition and by favouring tauopathy in some models. Therefore, targeting microglia as a therapeutic approach for Alzheimer's disease treatment might partly depend on disease stage-specific contexts of pathology.

The microbiome might also play a role in Alzheimer's disease by modulating the activation status of microglia. A work published in May, 2019, in the *Journal of Experimental Biology* suggests that, in a mouse model of amyloid β amyloidosis, alteration of the microbiome by treatment with antibiotics results in so-called resting state (M0) of microglia, inflammation reduction, and slowing of cerebral amyloidosis in the brains of male mice. Faecal transfer from untreated mice to antibiotic-treated mice restored the microbiome and turned microglial activation back on, which resulted in an increase in amyloid plaque formation. Interestingly, the same course of antibiotic treatment in female mice had no effect on reducing plaque formation. Whether these results translate similarly to humans and whether they could provide some insight into why women have a higher incidence of Alzheimer's disease than men, remains to be seen. This work adds to a body of data suggesting that manipulation of the microbiome might be worth considering as a treatment approach for Alzheimer's disease.

The sleep-wake cycle is another area of intense Alzheimer's disease research, given that sleep deprivation has been shown to lead to an increase in both amyloid β and tau levels. A paper published by David Holtzman (Washington University, St. Louis, Missouri, USA) and colleagues in the Feb 22, 2019, issue of *Science* showed that chronic sleep deprivation not only increases tau in human CSF but also resulted in increased tau seeding and spreading in a mouse model of tauopathy. Interestingly, an Oct 31,2019, study in *Science* found that during sleep, there is a decrease in blood flow, with a concurrent increase in the flow of CSF through the brain. It is tempting to speculate that CSF flow during sleep serves as a deep-cleaning cycle to remove toxic proteins from the brain that have accumulated during wakefulness. It might be worth considering whether a way to switch on this wash cycle can be found to help remove Alzheimer's disease-related toxins from the brain. In the meantime, aiming for improved sleep hygiene might be a reasonable, albeit simplistic, approach to reducing Alzheimer's disease-related toxic effects.

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Given that there are currently no approved disease-modifying treatments for Alzheimer's disease, we need to look beyond amyloid for therapeutic targets, and it seems evident that the community is ready for a shift toward a more comprehensive approach. One example of this readiness to shift was a one-day symposium held at the New York Academy of Sciences (New York, NY, USA) entitled Alzheimer's Disease Therapeutics: Alternatives to Amyloid 2019. The symposium was dedicated to discussing new therapeutic avenues, such as manipulating the innate immune system, and the need for new biomarkers to help clinicians treat the disease at an earlier stage—well before amyloid deposition and onset of symptoms.

Beyond the recent excitement surrounding aducanumab, at *EBioMedicine* we feel optimistic about the increasing recognition of the need for a broader approach to solving this devastating disease.

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