Advancing the battle against Alzheimer’s Disease: a focus on targeting tau pathology by antisense oligonucleotide

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Alzheimer’s disease (AD), the most prevalent form of dementia, is an escalating public health concern that is receiving increasing attention. It is estimated that over 55 million individuals worldwide are affected by dementia, primarily due to AD, and this figure is projected to 139 million in 2050. The fundamental mechanism underlying AD remains elusive. The two primary pathological features of AD are the accumulation of Amyloid-β (Aβ) plaques and hyperphosphorylated tau (p-tau) protein, which form neurofibrillary tangles. However, current therapeutic options for AD predominantly focus on symptom management. Aducanumab and Leqembi, approved by the U.S. Food and Drug Administration (FDA) for AD, are the two disease-modifying drugs targeting aggregated forms of Aβ, following the 2003 approval of memantine. Nonetheless, ongoing debates persist regarding their efficacy and safety, such as the occurrence of amyloid-related imaging abnormalities (ARIA) subsequent to administration. Therefore, there is a pressing need for additional treatments that can modify the disease, with the aim of preventing or mitigating its progression.

In recent years, researchers have increasingly focused on tau pathology as a significant pathological alteration in the development and progression of AD. Tau related pathology is characterized by the accumulation of p-tau protein, which is believed to be responsible for the formation of neurofibrillary tangles. It has been documented that there are multiple pathways by which p-tau can accumulate, leading to synaptic dysfunction and memory deficits. In comparison to Aβ pathology, tau pathology exhibits a stronger correlation with synaptic damage, neuron death, and cognitive decline in both AD patients and animal models. PET, CSF, and plasma biomarkers of tau pathology have been widely employed to enhance the AD diagnostic process in clinical practice.

Furthermore, tau pathology is not only a consequence of Aβ, but in certain situations, it can also be a driving factor for Aβ production. Preclinical studies conducted on animal models have demonstrated that reducing tau protein levels in the brain can alleviate synaptic abnormalities and cognitive decline caused by Aβ pathology. Likewise, clinical evidence underscores the crucial role of tau pathology in the onset and progression of AD. A recent publication in Nature Medicine reported a second late-onset familial AD patient within the largest autosomal dominant inherited AD family that encompasses over 1,200 carriers of the PSEN1 E280A mutation. This patient...
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References


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Declaration of Interests

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