Failure of Aβ Removal to Improve Alzheimer’s Dementia Opens the Door to New Thinking

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For the past century, Alzheimer (AD) and Parkinson disease (PD) research has focused on the abnormal filaments as hallmarks and later, on etiology of disease. This appealing path, removal of the abnormality, has been the therapeutic gateway for drug development for the past two decades. The most advanced approaches along the lines are the amyloid/tau vaccine and protease modulations to block fiber build up. Success in filament removal has been met, but patients have continued to suffer in a continuous slide of cognition. Numerous trials have confirmed that Aβ removal does not benefit sporadic AD patients whether applied early or late in the course of the disease. These findings clearly show Aβ removal has no benefits, yet instead of reassessing the hypothesis of pathology as causative, more trials are being initiated to remove Aβ prior to disease onset or in those where Aβ metabolism led to altered Aβ. While these new efforts could provide therapeutic benefit, failure of extensive testing to determine if Aβ is, in fact a critical protective response to aging could lead to increased dementia. Failure of Aβ removal to benefit patients is not being too early or too late, but rather working against the processes essential to maintaining normal function as we age, and who’s failure in AD lead to even greater Aβ deposition. Whether removal of tau or synuclein will meet similar fates remain to be tested. This is an exciting time in AD and PD research, a time when new opportunities will arise to understand how the brain maintains normal function as we age.