Tau Targeted Immunotherapy in Alzheimer's Disease

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ABSTRACT

Alzheimer's Disease (AD) is a prevalent neurodegenerative disease that affects an estimated 6.2 million Americans over the age of 65. This number is only projected to go higher, with an estimate that by 2050, there will be 12.7 million people with AD. The classic hallmarks of AD are amyloid plaques and neurofibrillary tangles that are made up of aggregated, hyperphosphorylated tau. Careful analysis must be done in order to look for valuable venues of research and treatment for AD. The objective of this study is to look more into tau as a target for immunotherapy in AD while comparing it to amyloid-beta immunotherapy. When conducting immunotherapies, it is important to determine which protein to target, which includes its conformations, post-translational modifications and aggregated forms, and how to target them with antibodies. There are challenges which include the blood brain barrier (BBB), extracellular versus intracellular targeting, and risks of inflammation or worse side effects. The discussed amyloid-beta immunotherapies include bapineuzumab, solanezumab, aducanumab, and AN1792 and the discussed tau immunotherapies include AADvac1, ACI-35, BIIB076, BIIB092, and UCB0107. The results show that lowering amyloid-beta levels or tau levels doesn't mean that cognitive decline will improve, as shown with BIIB092 and bapineuzumab, suggesting that measuring amyloid-beta and tau levels may not be a strong measure of a treatment's success. Similarly, while AADvac1's second trial did result in lower neurofilament light chain levels in its patients, it is unknown whether this will translate to a reduction in cognitive decline. In conclusion, tau immunotherapies show promise but there is still more to learn when it comes to targeting the various forms of diseased tau and how preventing its aggregation can treat AD effectively.

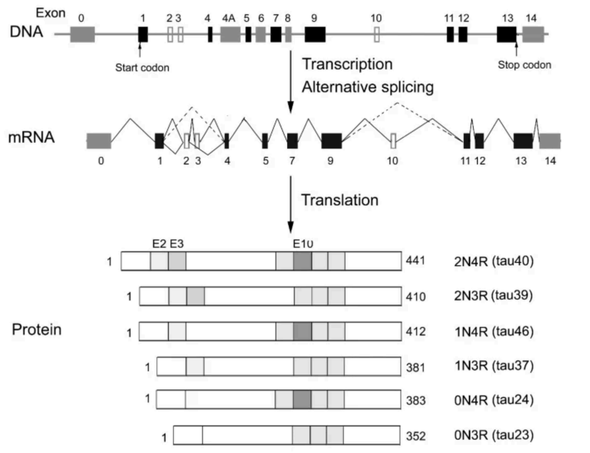
METHODS

Topics of Research:

- Tau background, such as its role, isoforms, and neurofibrillary tangles
- Recent tau immunotherapy trials
- Amyloid-Beta trials for comparison

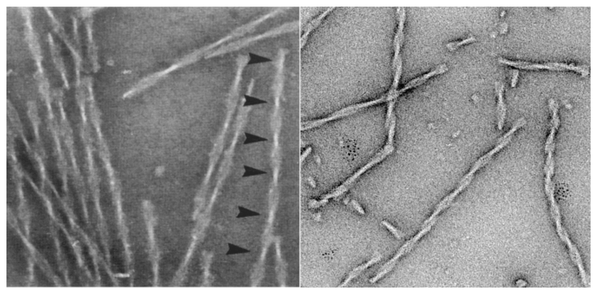
BACKGROUND ON TAU

MAPT gene and splicing

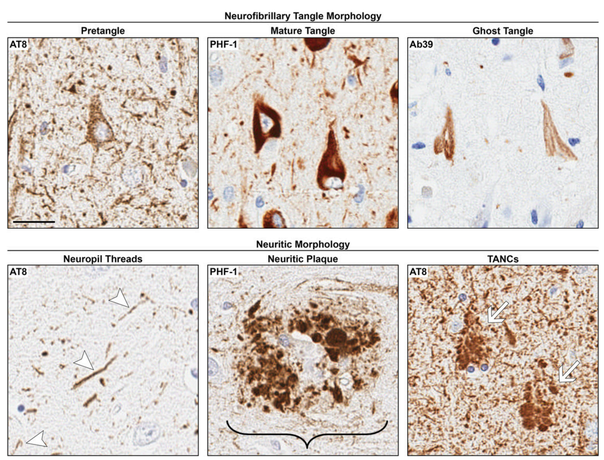


(Liu and Gong 2008)

Paired helical filaments



(Bergen et al. 2007)



(Lowe et al. 2021)

BETA-AMYLOID AND TAU IMMUNOTHERAPY TRIALS

Beta-Amyloid:

Bapineuzumab
- N-terminus of amyloid-beta

Solanezumab
- Amyloid-beta peptides, "peripheral sink hypothesis"

Aducanumab
- Amyloid-beta amino acids 3-7

AN1792
- Amyloid-beta peptides on QS21 to stimulate immune response

Tau:

AADvac1
- Microtubule-binding domain

ACI-35
- Immune response against phosphorylated tau

BIIB076
- Monomeric and pre-formed fibrillar tau

BIIB092
- N-terminally truncated tau

UCB0107
- Amino acids 235-250, near microtubule-binding domain

TREATMENT CONSIDERATIONS

- Improvement in cognition
- Antibody specificity and targets (ex. oligomers and isoforms)
- In the brain, inside neurons, or outside
- Maintain effective titer of antibodies
- Specific Alzheimer's stages

PRELIMINARY CONCLUSIONS

So far, there isn't a treatment that improves cognitive decline. However, in both types of trials, some of them do successfully reduce the levels of the proteins they're targeting without adverse side effects. This suggests that we can effectively target these proteins in the brain, the only issue is translating these lowered levels into improvement in cognition or slowing the rate of cognitive decline. A possible direction could be combining the targeting of amyloid-beta and tau or long-term trials. Pathology of AD still needs further research that can directly be applied to treatments