Selection of an Anti-tau Antibody Candidate Targeting Pathological Tau for the Treatment of Alzheimer’s Disease

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INTRODUCTION
The current hypothesis for the propagation of tau pathology in Alzheimer’s disease (AD) is that monomer-to-tau transition of pathological tau, including especially trans-neuronal propagation, plays a major role. Our goal is to identify a selective, potent and efficacious anti-tau antibody clinical candidate that blocks pathological tau spreading in vivo for the treatment of AD.

In vivo studies with AD patient-derived PHF-tau (paired helical filament tau) as the immune target yielded 113 anti-tau antibodies with significant binding to PHF-tau and an absence of detectable binding to wild-type recombinant tau. These antibodies were characterized and prioritized based on affinity, biochemical characteristics, efficacy in animal models of tau spreading and differentiation from clinically ineffective anti-tau antibodies.

Four anti-tau antibodies were selected (Ab01, Ab02, Ab04 and Human Ab5) with novel sequences and epitopes that fit our target profile based on selectivity, functional inhibition in vitro and in vivo, and developability. Ab01, Ab02 and Ab04 are marine antibodies that target the same C-terminal epitope, whereas Human Ab5 targets the mid-domain of tau. Among these four antibodies, Ab01 demonstrated superior efficacy in the mouse seeding model and has been humanized.

We plan to leverage the Ab01 antibody for a passive immunotherapy for AD. The clinical candidate has been chosen on selectivity for pathological tau, potency, functional inhibition in vitro and developability.

OVERVIEW
Figure 1. Voyager Anti-Tau Antibody Discovery

GOAL: Identify anti-tau antibodies that block tau-seed mediated propagation of pathology

APPROACH: Generate a diverse starting pool of anti-tau Abs

- Starting pool
- 113
- 27
- 11

Generate a diverse starting pool of anti-tau Abs

- Grow a diverse starting pool of anti-tau Abs
- Eliminate cross-reactive Abs
- Select Abs based on desired characteristics

Screen and prioritize anti-tau Abs based on:

- Biological selectivity for pathological tau
- IC50 selectivity for AD/HTP in WT human brain
- Functional inhibition of PHF seeding in vitro and in vivo

- Developability based on two properties and lack of segregation

Characterize additional antibodies

- Sequence
- Epitope
- TauWnt binding to KCNQ2, PS2, or WT human brain

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