Fibrils were immobilized on sensor chip CM5 (GE Healthcare Life Sciences) with ~70 picomolar (pM) affinity equilibrium dissociation constant (KD) for Aβ1-42. PRX012 has previously been shown to promote phagocytic engulfment of Aβ1-42 fibrils. In addition to unmodified Aβ, pyroglutamate-modified Aβ (pE3-42) has also been described as a component of senile plaques and vascular deposits in AD brains. We hypothesized that monoclonal antibodies, such as PRX012 and anti-Aβ, can contribute to the clearance of pre-existing phagocytic engulfment of Aβ by macrophages in AD brains.

AIM

To determine whether PRX012 and unmodified Aβ promote clearance of pre-existing phagocytic engulfment in plaques of AD brains, or concentrations expended to be in the central nervous system (CNS) in therapeutic doses.

RESULTS

Generation of Antibodies

- Antibody anti-Aβ, PRX012 and 4F8 were expressed, purified and immobilized on sensor chips.

Binding Assays

- Aβ1-42, pE3-42 and Aducanumab (Adu) were immobilized on sensor chip CM5.

INSIGHTS

- The ability to directly engage fibrils has implications for the in vitro screening and clinical development of antibodies for AD.

- Binding of antibodies to Aβ1-42 fibrils was assessed by surface plasmon resonance (SPR) and mass spectrometry (MS).

- PRX012 showed strong binding to Aβ1-42 fibrils, resulting in a 15-fold greater binding affinity than Aducanumab.

- Evaluation of Aβ and Aβ1-42 confirmed increased distribution of both species in plaques and vascular deposits in the AD brain tissue sample.

- Based on the measured dissociation constant (KD) of ~70 pM, PRX012 is predicted to bind Aβ1-42 fibrils with high specificity and affinity.

- PRX012 robustly promotes clearance of Aβ1-42 in AD brain tissue sections by promoting phagocytic engulfment of Aβ1-42 in a dose-dependent manner.

CONCLUSIONS

- PRX012 promotes microglia-mediated clearance of Aβ in brain tissue from subjects with AD.

- Though PRX012 does not target the pyroglutamate modification directly, it effectively clears AβpE3-42 at concentrations predicted to be clinically relevant and with higher potency and greater biologic activity than aducanumab.

- Clearance of pyroglutamate species by PRX012 may be due to the ability of microglia to recognize pyroglutamate Aβ and deposit in a relatively short incubation period.

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