DIFFERENTIAL IN VITRO AND IN VIVO BINDING PROFILES OF BIIB037 AND OTHER ANTI-ABETA CLINICAL ANTIBODY CANDIDATES

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Objectives: Compare in vitro and in vivo binding of BIIB037 to other anti-Aβ antibodies that have undergone clinical evaluation.

Methods: Selectivity of murine analogs of BIIB037 (^{ch}BIIB037), bapineuzumab (3D6), solanezumab (m266), and gantenerumab (mGt) was determined in vitro using biochemical assays with monomeric or aggregated Aβ peptides. In vivo selectivity was determined by dosing old Tg2576 mice with Cy3-labeled antibodies, and quantifying antibody colocalization with either parenchymal or vascular amyloid deposits. Clearance of amyloid deposits was determined following chronic dosing of Tg2576 mice with ^{ch}BIIB037. Incidence of microhemorrhage was assessed in old Tg2576 treated with a high dose of BIIB037.

Results: ^{ch}BIIB037 and mGt bound to fibrillar Abeta with high selectivity and subnanomolar affinities. 3D6 displayed similar affinities for soluble and fibrillar Aβ, and m266 showed exclusive binding to soluble Aβ.

Following peripheral administration, ^{ch}BIIB037 preferentially bound to parenchymal amyloid deposits and 3D6 preferentially bound to vascular amyloid deposits. mGt binding was equally distributed between parenchymal and vascular deposits. No binding of m266 to parenchymal or vascular amyloid was detected.

Chronic dosing of Tg2576 mice with ^{ch}BIIB037 significantly reduced amyloid load in both cortex and hippocampus. Differential quantification of parenchymal and vascular amyloid deposits demonstrated that ^{ch}BIIB037 only reduced parenchymal amyloid. Microhemorrhage was not increased compared to controls.

Conclusions: In vitro and in vivo binding characteristics of four Aβ-targeting passive immunotherapeutics were compared directly. The target selectivity, high affinity, brain uptake, biological clearance activity and favorable safety profile of BIIB037 support its development for the treatment of AD.