A novel blood-brain barrier-crossing bispecific antibody targeting aggregated α-synuclein (ABL301) attenuates α-synuclein propagation and ameliorates synucleinopathy

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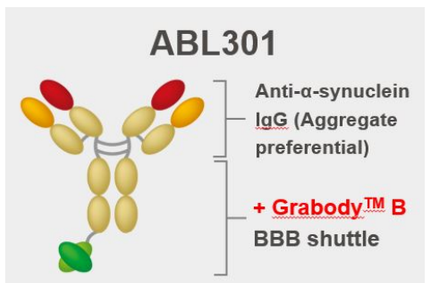
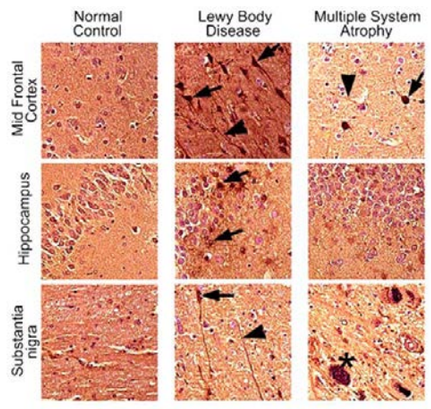
Objectives

ABL301 is a novel bispecific antibody therapeutic against synucleionopathy. Aggregated α-synuclein (α-Syn) has been known to be an important pathologic factor to Parkinson's disease (PD). ABL301 is developed for selective binding to aggregated α-Syn and better blood-brain barrier (BBB) penetration. The purpose of this study is to show improved efficacy of ABL301 by selectively targeting aggregated α-Syn with enhanced BBB penetration using in vitro and in vivo model systems.



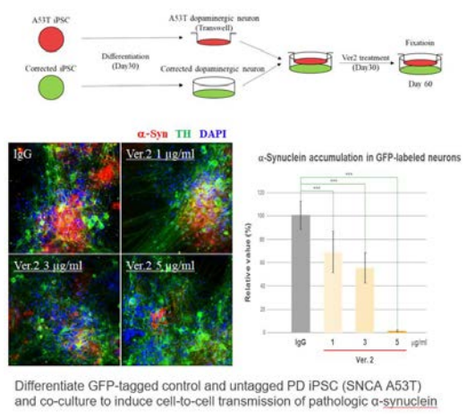
Results

Anti-α-Syn IgG of ABL301 recognized α-Syn inclusions in post-mortem human PD & MSA brains



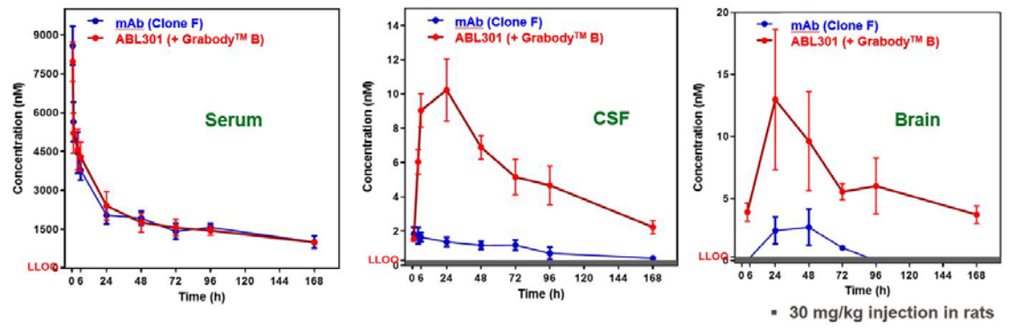
Immunohistochemistry on human PD and MSA brain tissue with mAb of ABL301. Arrows, Lewy body neurons; arrowheads, Lewy neurites; asterisk, extracellular aggregates. Done by Dr. Robert Rissman lab (UCSD)

Anti-α-Syn IgG of ABL301 reduced α-Syn transfer to GFP+ dopaminergic neurons derived from iPSC from a PD patient carrying A53T mutation



Differentiate GFP-tagged control and untagged PD iPSC (SNCA A53T) and co-culture to induce cell-to-cell transmission of pathologic α-synuclein

ABL301 showed 10-fold higher BBB penetration than mAb

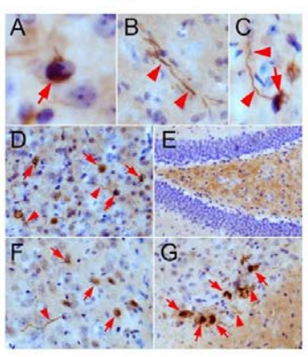


	mAb (Clone F)	ABL301
CSF AUC (hr*nmol/ml)	0.159	0.918
Brain AUC (hr*nmol/ml)	0.134	1.116

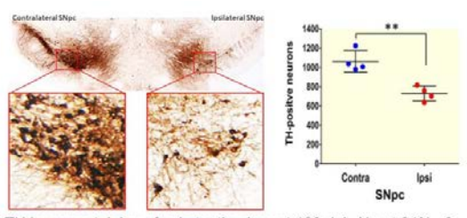
Serum half life: mAb: 124 h and bsAb (ABL301): 118 h
Peak at 24h and CNS retention up to 168 hrs post-treatment
Brain and CSF AUC of bsAb is 8-9 fold higher than mAb

α-Syn PFF injection model was established

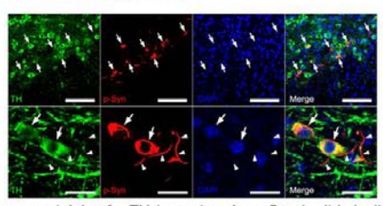
Stereotaxic α-Syn PFF injection into the striatum & confirm of injection site



α-Syn PFF-induced propagation and generation of inclusions in neuron cell bodies (arrows) and neurites (arrowheads) at 90 days post injection (dpi) (A, B, C, cerebral cortex; D, striatum; E, hippocampus; F, amygdala; F, substantia nigra pars compacta). Arrow, Lewy body-like pathology; arrowheads Lewy neurite-like pathology



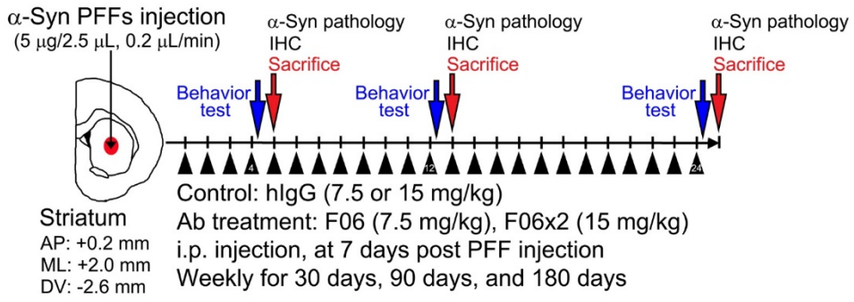
TH immunostaining of substantia nigra at 180 dpi. About 31% of TH-positive neurons were lost in the ipsilateral to the injection side compared to the contralateral side.



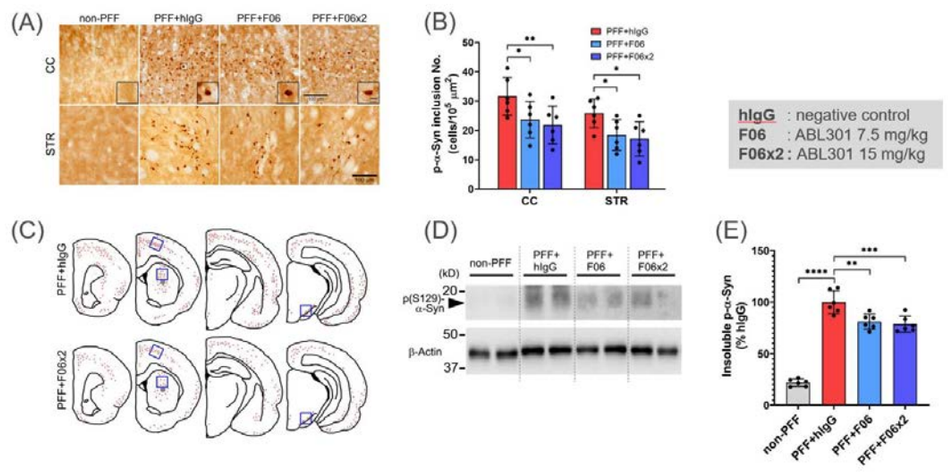
Double immunostaining for TH (green) and p-α-Syn (red) in ipsilateral SNpc. Images are representing colocalization of p-α-Syn inclusions to DA neurons (white arrows). Scale bars, 100 μm in upper panel and 20 μm in lower panel.

LB/LN-like pathology begins about 90 days post injection (dpi) in this PFF-injection model (wt human α-Syn PFFs)
Degeneration of DA neurons in SNpc was evident at 180 dpi

Experiment scheme of ABL301 efficacy study

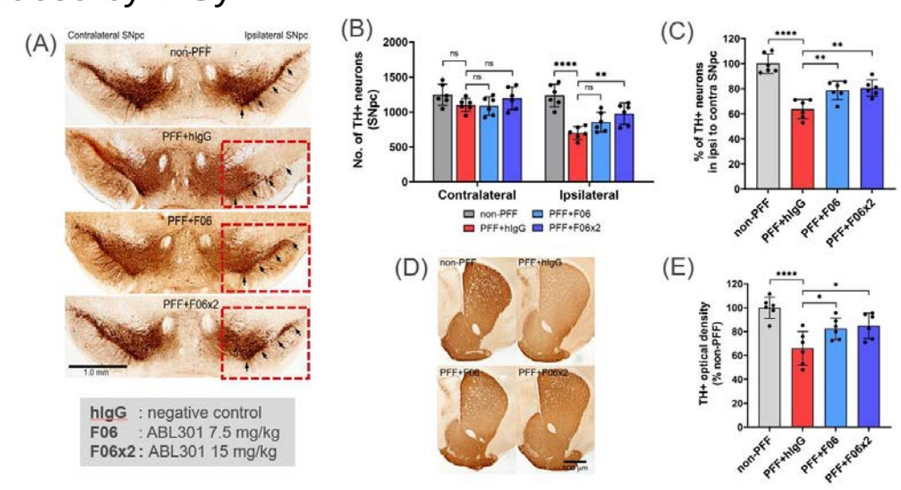


ABL301 reduced Lowy body-like inclusions after 90 days post injection



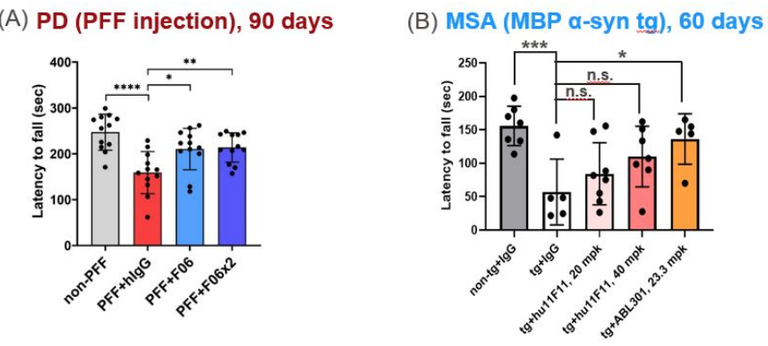
(A) Representative p-α-Syn immunohistochemistry images in the cerebral cortex (CC) and striatum (STR). (B) Quantifications of the number of p-α-Syn inclusions. (C) Distribution of LB/LN-like pathology in the CNS of α-syn PFF-injected hemisphere. (D) Representative western blots illustrating the differences in band intensities of p-α-Syn in the cerebral cortex of α-syn PFF-injected hemisphere. (E) Quantifications of p-α-Syn expressions. Mean ± SD; n = 6; One-way ANOVA with Dunnett's test; * p <0.05, ** p < 0.01, *** p < 0.001, **** p < 0.0001.

ABL301 protected dopaminergic tracts/cells from degeneration induced by α-Syn PFF



(A) Representative TH immunohistochemistry images of SNpc. Arrows indicate TH-positive neurons in SNpc. (B) Quantifications of the number of TH-positive neurons in SNpc. (C) Percentages of the number of TH-positive neurons in ipsilateral SNpc compared to contralateral SNpc. (D) Representative TH immunostaining images of the striatum of α-Syn PFF-injected hemisphere. (E) Quantifications of TH-immunopositive fiber densities in ipsilateral striatum. Mean ± SD; n = 6; One-way ANOVA with Dunnett's test; * p <0.05, ** p < 0.01, *** p < 0.001; **** p < 0.0001; ns, not significant.

ABL301 improved behavioral deficits of mouse models with synucleinopathies



Effect of ABL301 on behavioral deficits of α-Syn PFF-injected mice (A) and MBP human α-Syn tg mice (B). Assessments of movement (balance and motor coordination) deficits measured by the rotarod test. Mean ± SD; n = 12; One-way ANOVA with Dunnett's test; * p <0.05, ** p < 0.01, **** p < 0.0001.

Conclusion

- ABL301 induces a significant reduction in p-α-Syn burden in α-Syn PFF-injected mice.
- ABL301 shows apparent protection against degeneration of dopaminergic system in α-Syn PFF-injected mice.
- ABL301 improves motor impairmnt in α-Syn PFF-injected mice and MBP-α-syn tg mice.
- ABL301 is developed as a best-in-class antibody therapeutics for the treatment of α-synucleinopathy by aggregate-selective targeting and improved BBB penetration.