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ABBV-0805, a novel α-synuclein oligomer selective antibody, prolonged lifespan and prevented accumulation of α-synuclein pathology in mouse models of Parkinson's disease

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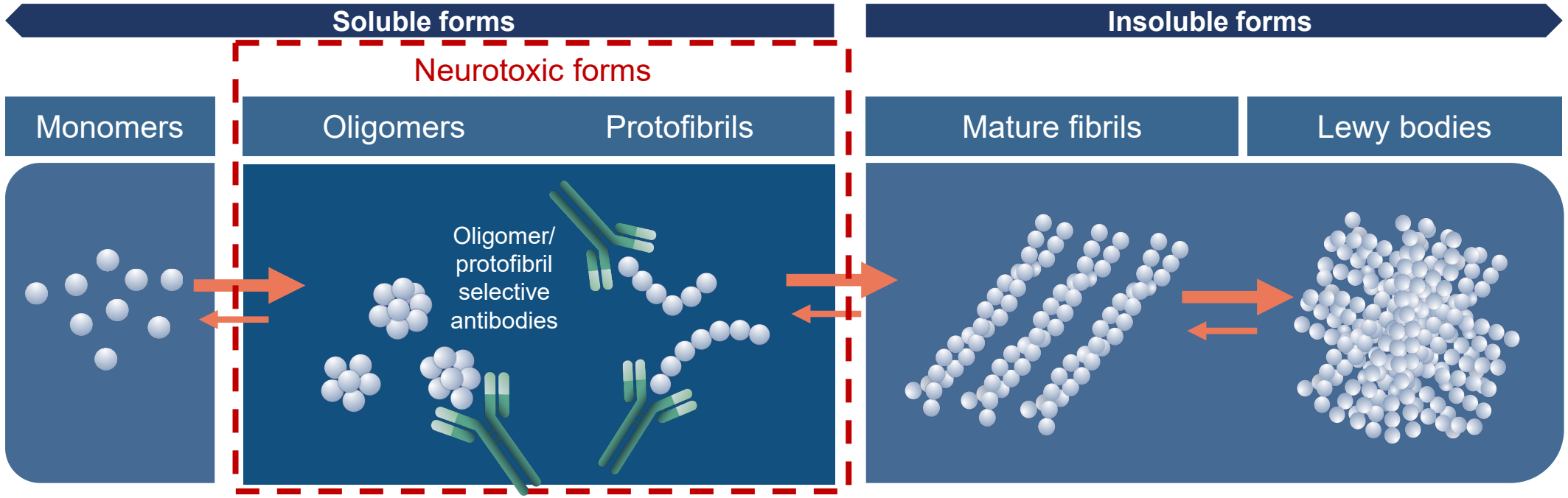
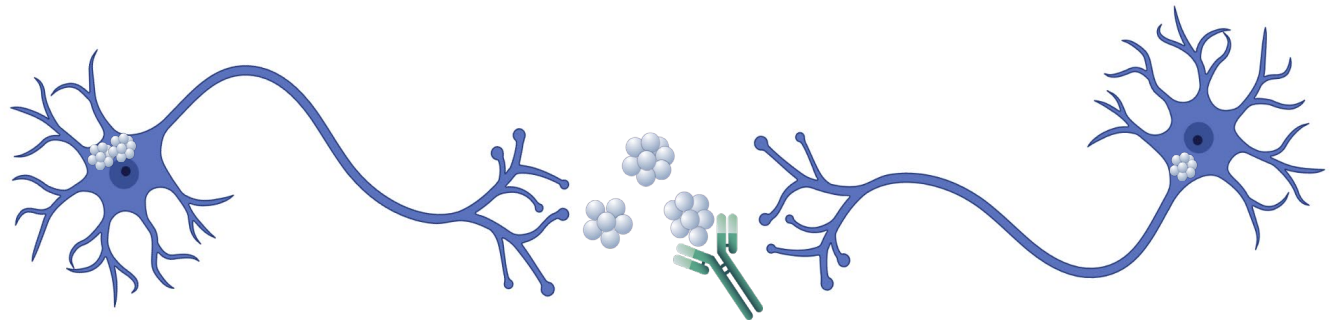
ABBV-0805: An α-synuclein antibody targeting aggregated misfolded α-synuclein targeted to reduce Neuron-to-neuron propagation of pathology





ABBV-0805

ABBV-0805 selectively binds and eliminates aggregated α-synuclein hypothesized to mediated neuron-to-neuron propagation of pathology

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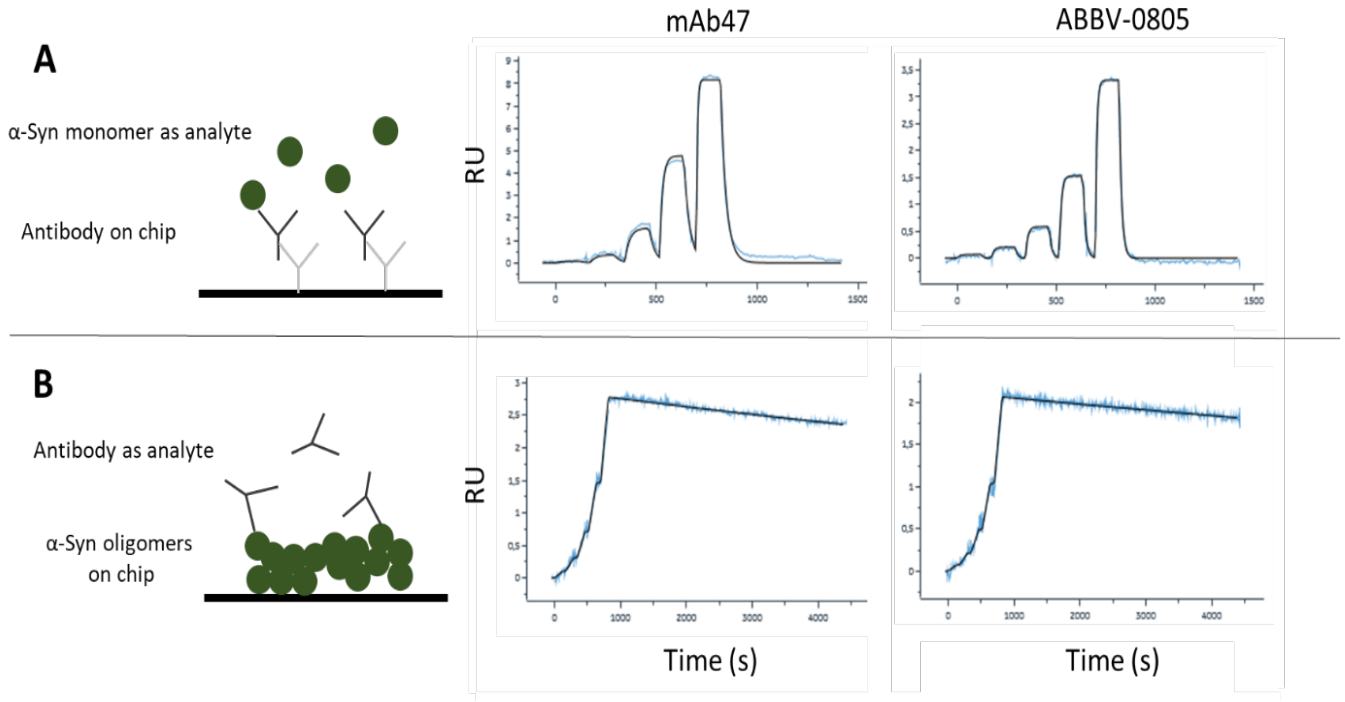
In vitro binding and selectivity of mAb47 and ABBV-0805



Antibody	α-synuclein oligomers/PF K_D (pM)	α-synuclein monomer K_D (nM)
ABBV-0805	18.5±7.3	2190±540
mAb47	16.8±8.0	307±35

ABBV-0805 and its murine counterpart mAb47, a monoclonal antibody that exhibits a high selectivity for toxic α-synuclein oligomers/protofibrils and very low affinity for monomers

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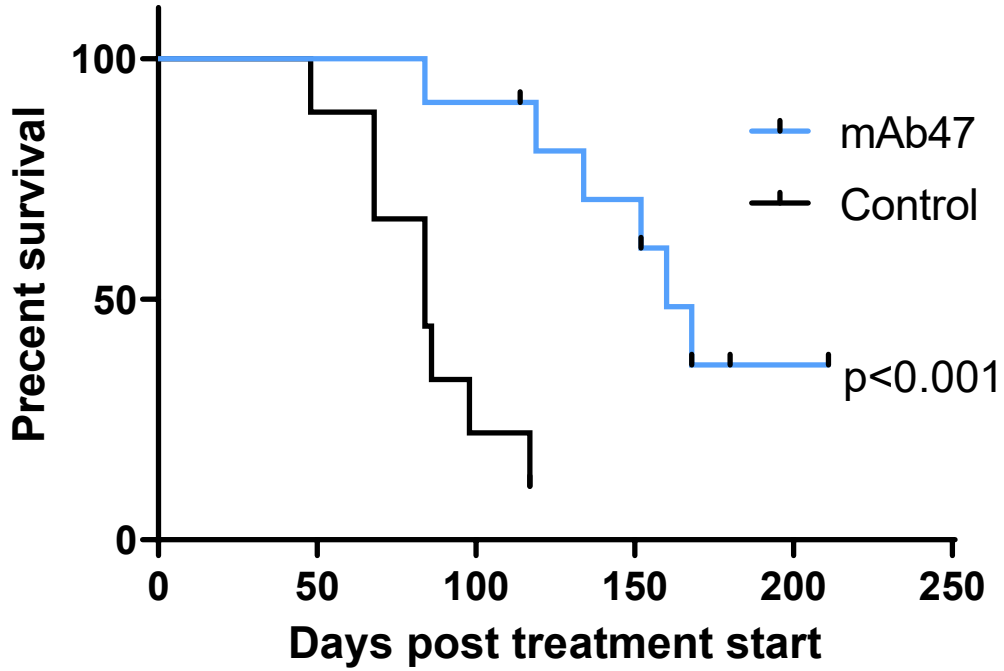
Prolonged survival of α-synuclein transgenic mice after mAb47 treatment



- hA30P tg mice
- 10 mg/kg mAb47, bi-weekly
- Treatment starting at 12 mo

In α-synuclein (Thy1)-hA30P transgenic mice mAb47 prolonged survival with a doubling of lifespan after onset of treatment

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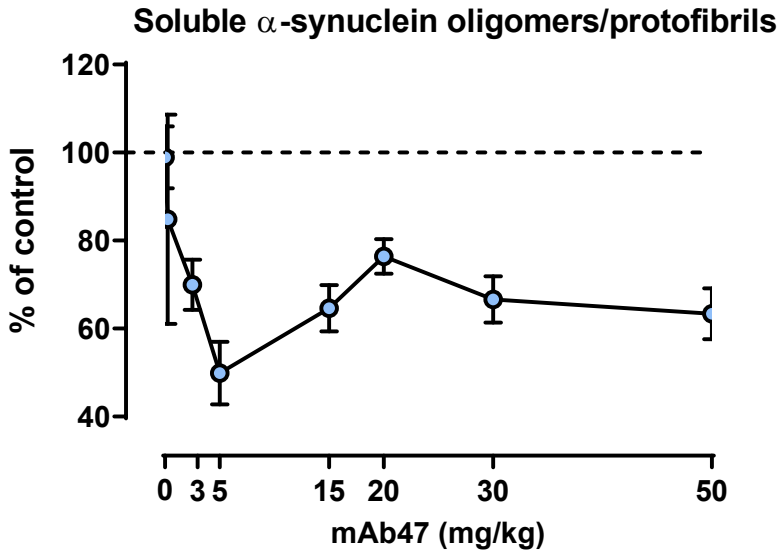
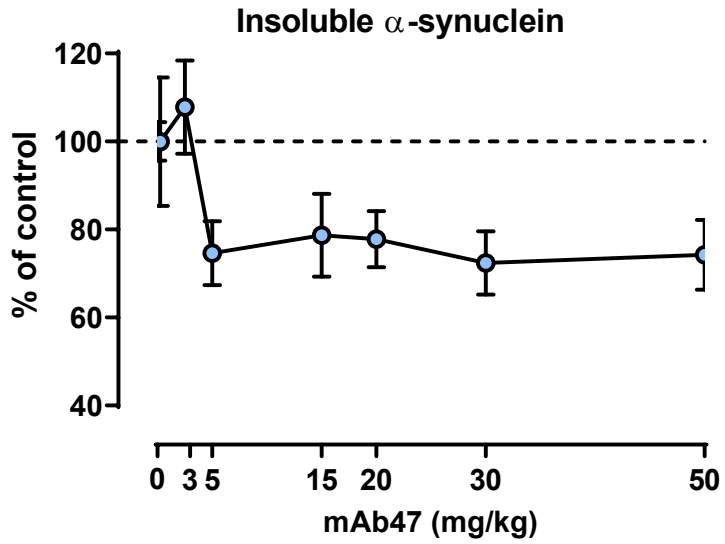
Dose-dependent reduction of α-synuclein oligomers/protofibrils and insoluble α-synuclein in brain following therapeutic mAb47 treatment of PFF-hA30P tg mice





- hA30P tg mice
- I.m PFF injection (1µg)
- mAb47, weekly (IP), 1 week post PFF injection

In α-synuclein PFF- hA30P transgenic mice mAb47 displayed dose-dependent reduction of both soluble and insoluble α-synuclein aggregates in brain

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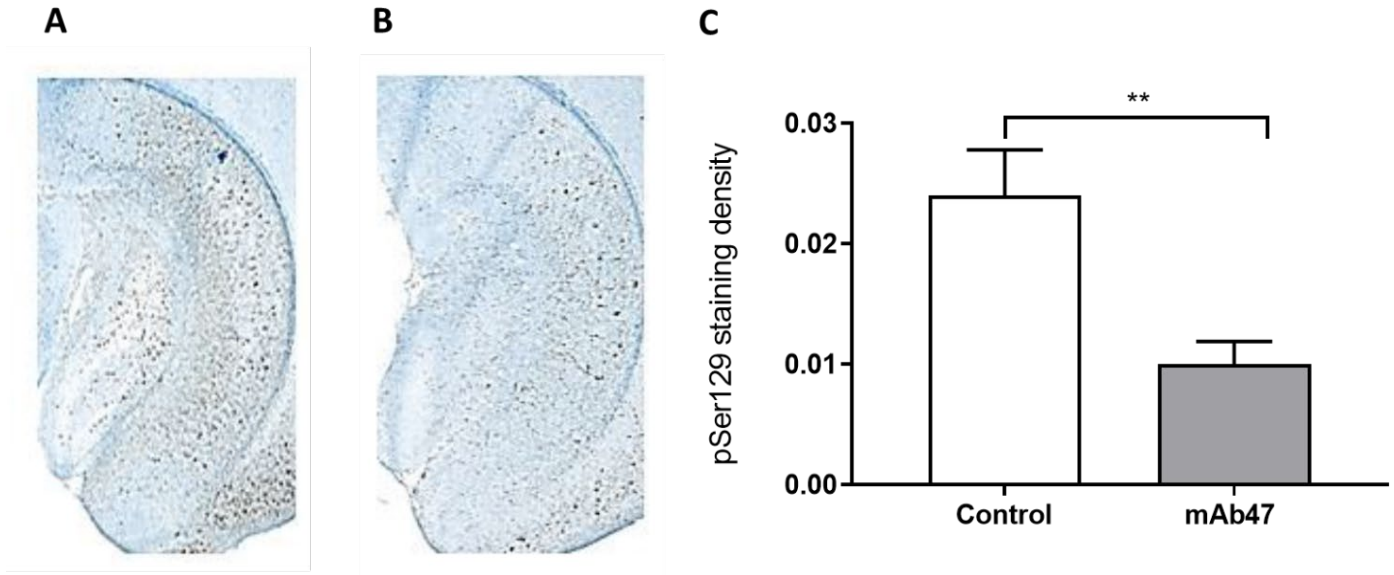
mAb47 treatment inhibits pSer129 α-synuclein propagation to the contralateral hippocampus in A53T +/- (M83) tg mice



pSer129 α-synuclein staining in the contralateral side of hippocampus in vehicle treated (A) and mAb47 treated (B)

- A53T +/- (M83) tg mice
- AON PFF injection
- 20 mg/kg mAb47 (IP) weekly, 1 week post PFF injection

In α-synuclein A53T +/- (M83) transgenic mice mAb47 prevents α-synuclein spreading

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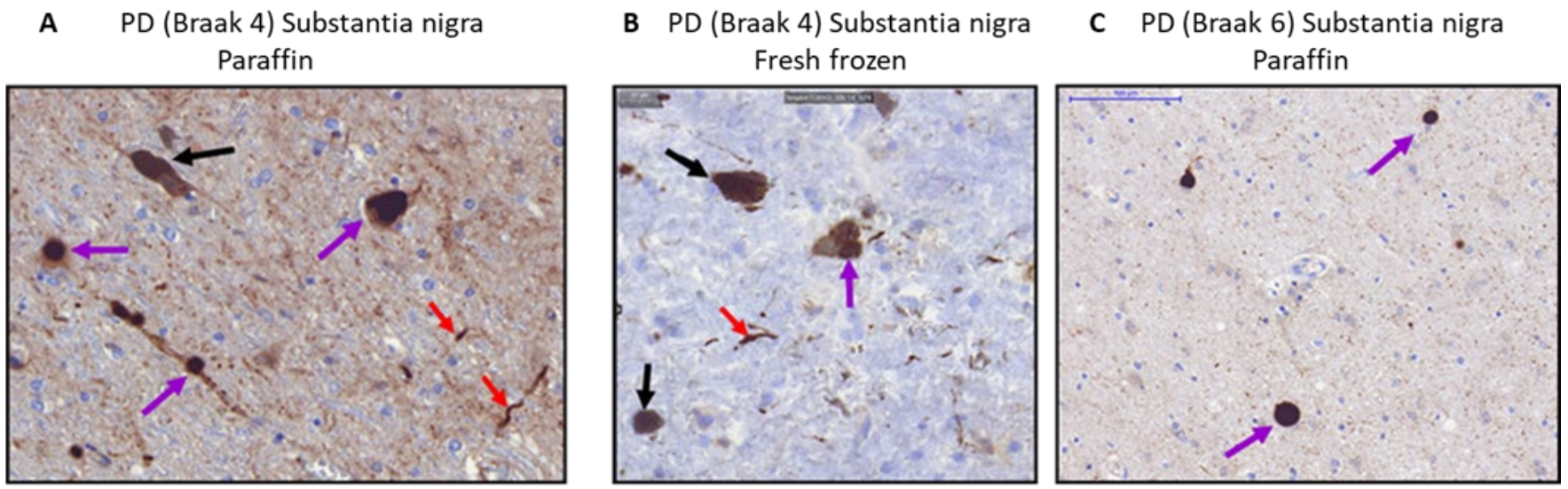
Human target binding of ABBV-0805 in Parkinson disease brain

Brain material from NBB



Lewy neurites and inclusion bodies were identified in and around dopaminergic neurons (neuromelanin positive). Black arrows= neuromelanin, Purple arrows= Lewy bodies, Red arrows= Lewy neurites

Binding of ABBV-0805 to pathological α-synuclein was demonstrated in brains of Parkinson's disease patients at different Braak stages (4 & 6)

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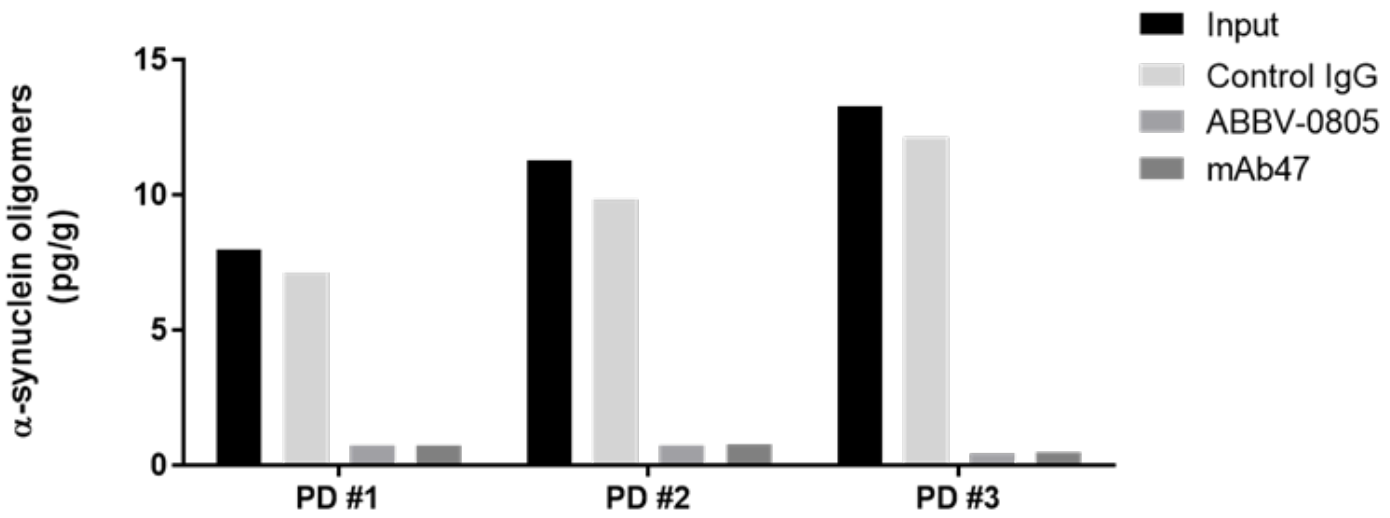
Human target binding of ABBV-0805 in Parkinson disease brain

Brain material from NBB



Binding of ABBV-0805 to pathological α-synuclein was demonstrated in brains of Parkinson's disease patients by Immunodepletion

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Summary and Conclusion

- ABBV-0805 selectively targets soluble toxic α-synuclein oligomers/protofibrils with a picomolar affinity and low affinity for monomers
- In α-synuclein transgenic mice, the murine version of ABBV-0805, mAb47, displayed dose-dependent reduction of both soluble and insoluble α-synuclein aggregates in brain, prevents α-synuclein spreading and prolonged lifespan
- Binding of ABBV-0805 to pathological α-synuclein was demonstrated in brains of Parkinson's disease patients both by IHC and immunodepletion
- Based on the strong preclinical findings, ABBV-0805 has been out licensed to AbbVie and progressed into clinical development as a potential disease-modifying treatment for Parkinson's disease
- Overall, the human exposure and safety data being gathered in Phase I FIH-SAD study supports Phase II development of ABBV-0805 (T1/2: 30 days supporting Q28 days dosing)

  Ref: MDS 2021 poster 403 & 404 H Kalluri et al AbbVie Inc.

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