MICROTUBULE BINDING REGION (MTBR)-SPECIFIC ANTIBODY PRX005 PREVENTS PATHOLOGICAL TAU PROGRESSION VIA BLOCKADE OF NEURONAL INTERNALIZATION

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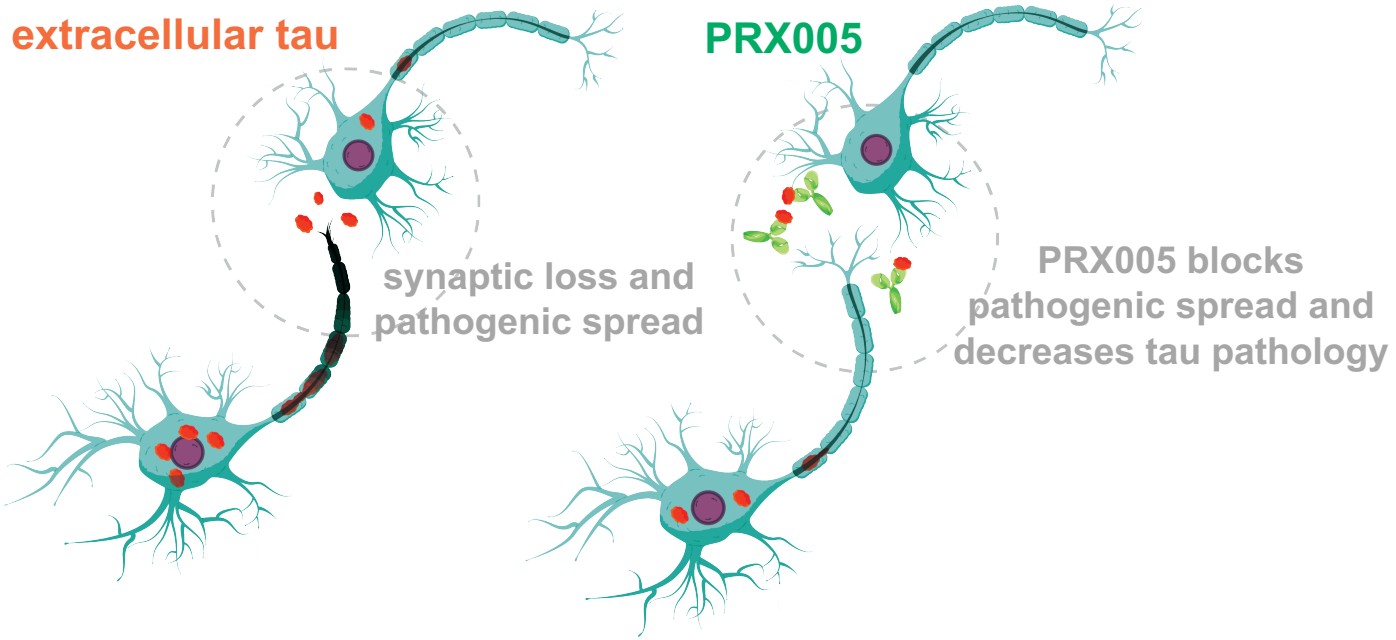
Disclosure

All authors are employees of Prothena Biosciences Inc and hold stock or stock options in Prothena Corporation plc.

Tau Immunotherapy

Reduce neurotoxicity, prevent cell-to-cell transmission, promote clearance

- Histopathological and PET studies demonstrate correlation between cognitive function and extent of tau pathology in patients with Alzheimer's disease
- Spatiotemporal staging of tau pathology suggests cell-to-cell transmission of tau pathology
- Mechanistic studies have demonstrated release and transmission of tau *in vitro* and *in vivo* to adjacent and synaptically connected neurons



PRX005 is an IgG1 humanized antibody that binds with high affinity to the MTBR of tau protein and was designed to block cell-to-cell transmission of tau pathology

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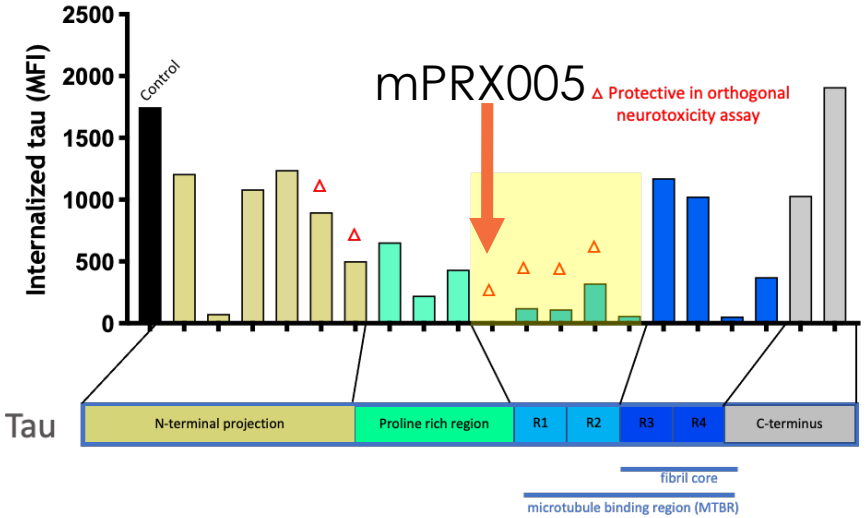
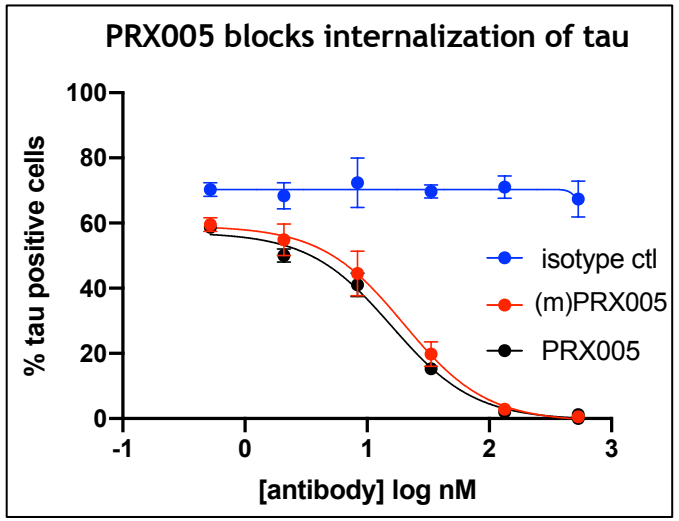
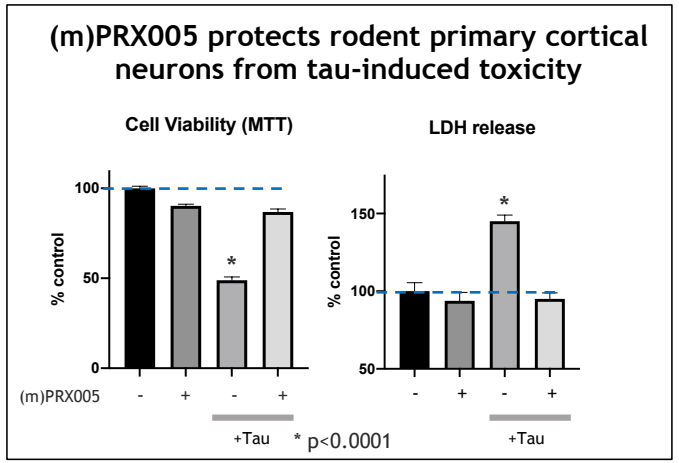
PRX005 is Superior to Other Anti-Tau Antibodies in Blocking Cellular Internalization of Tau and Downstream Neurotoxicity

Repeats 1 and 2 defined as the strongest inhibitory regions in screening with cellular internalization and neurotoxicity assays



- Panel of antibodies targeted throughout the tau molecule were screened for affinity and epitope
- These were tested *in vitro* for their ability to block internalization and toxicity





All values are mean ± SD (n=3-5)

Internalized pHrodo-tau (pH-sensitive dye) measured by FACS

IC_{50}=9 nM
[tau] = 167nM

(m)PRX005 = murine form of PRX005

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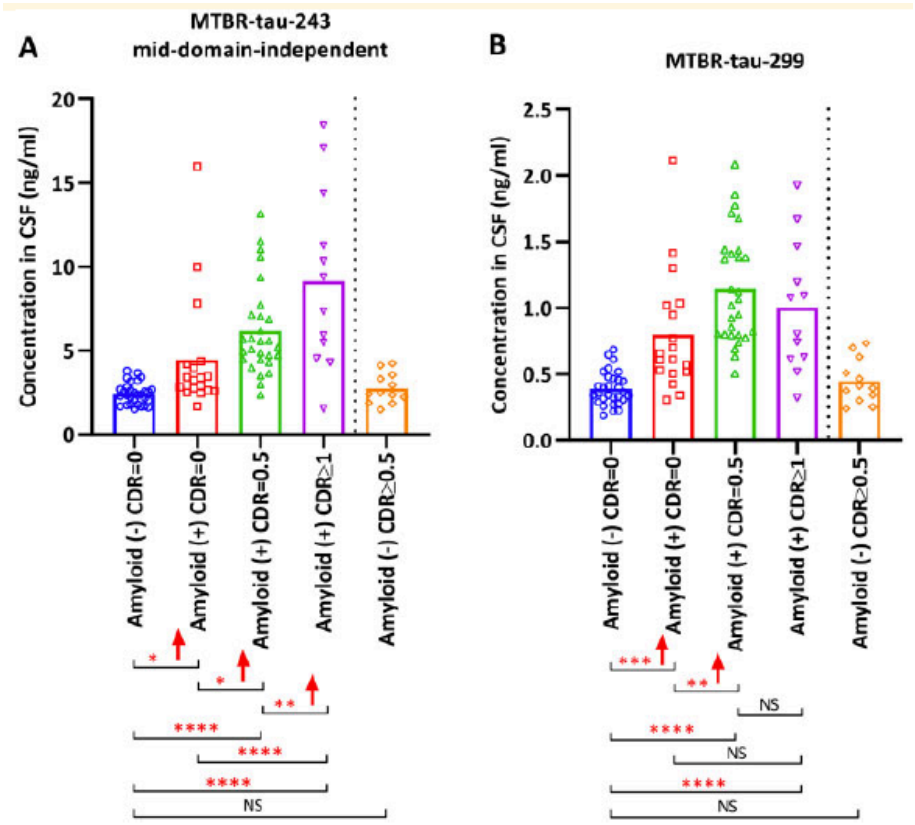
Tau Pathogenesis and the Microtubule Binding Region (MTBR)

- A recent study (right) confirmed the presence of MTBR tau in extracellular fluid (CSF), and correlated MTBR-tau with AD clinical progression[1]
- Correlation of MTBR peptides with dementia stages in AD is superior to other tau markers measured (N-terminal, mid-domain)
- MTBR mediates tau aggregation via nucleation-dependent mechanism[2]
- Another C-terminal tau fragment detected in CSF, tau368, was also correlated with PET tau pathology[3,4], lending further support to the disease relevance of extracellular MTBR



[1]Horie et al., BRAIN 2020

[2]von Bergen et al., 2005
[3]Leuzy et al., 2019
[4]Blennow et al., 2020

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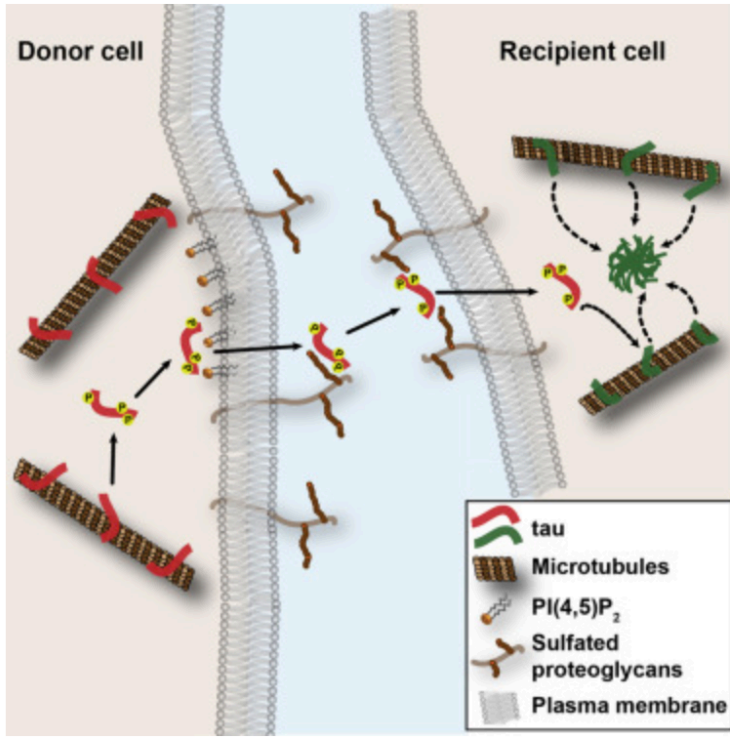
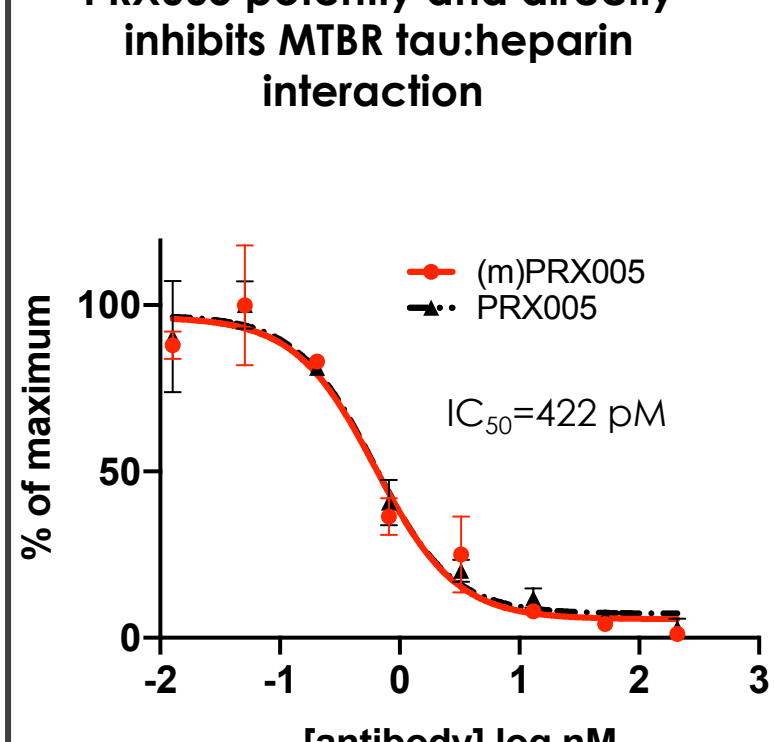
PRX005 Potently Blocks Interaction of a Repeat Region in the MTBR with HSPG Analog

- Tau-HSPG interactions occur across a broad interface, largely within the MTBR
- Tau-HSPG interactions are critical for tau secretion and uptake
- Block of tau-HSPG by PRX005 might prevent tau pathogenesis by blocking tau secretion and cell uptake

Sibille et al., 2006; Holmes et al., 2013; Zhao et al., 2017; Katsinelos et al., 2018; Merezhko et al., 2018; Stopschinski et al., 2020)



Katsinelos et al., 2018



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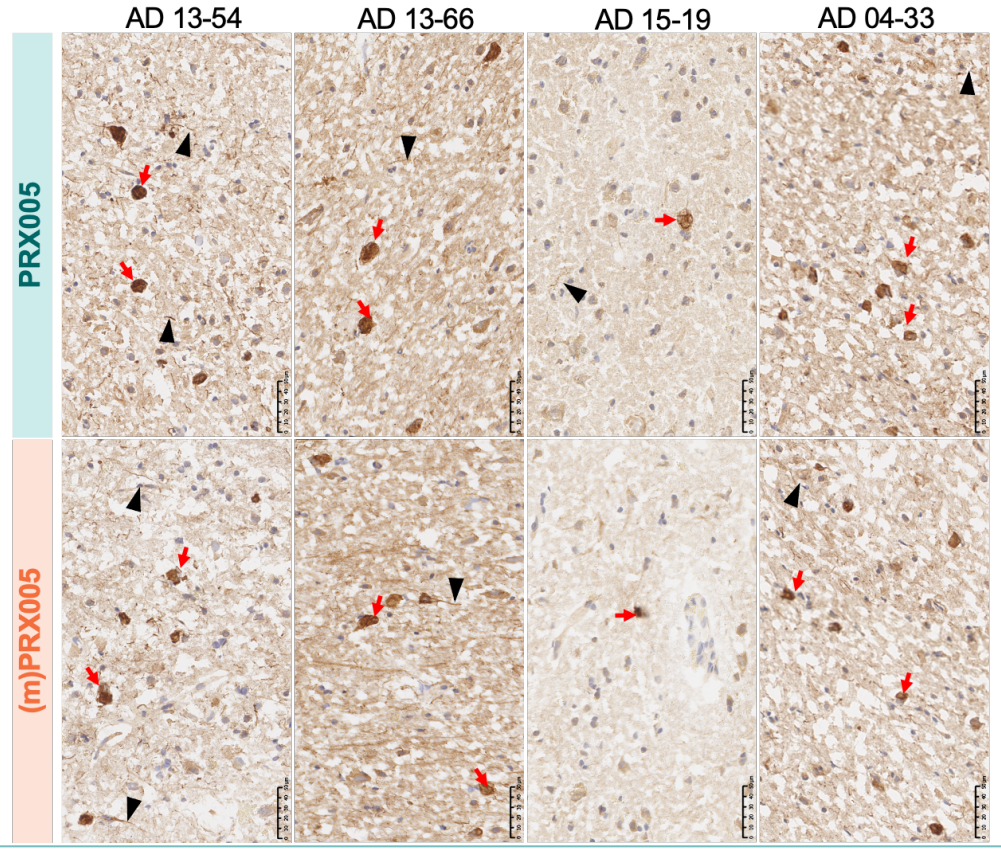
PRX005 Binds Phospho and 3R/4R Isoforms of Tau with High Affinity

- PRX005 equivalently binds phosphorylated and non-phosphorylated tau
- PRX005 binds all splice isoforms of tau

Kinetic binding parameters of PRX005 to 3R- and 4R-tau determined by SPR

	K_D
3R2N-tau	**154** pM
4R2N-tau	**206** pM

PRX005 Binds Alzheimer's disease brain tissue from multiple donors[1]



[1]Subset of tissue panel displayed here
Red arrows: neurofibrillary tangles
Black arrowheads: dystrophic neurites

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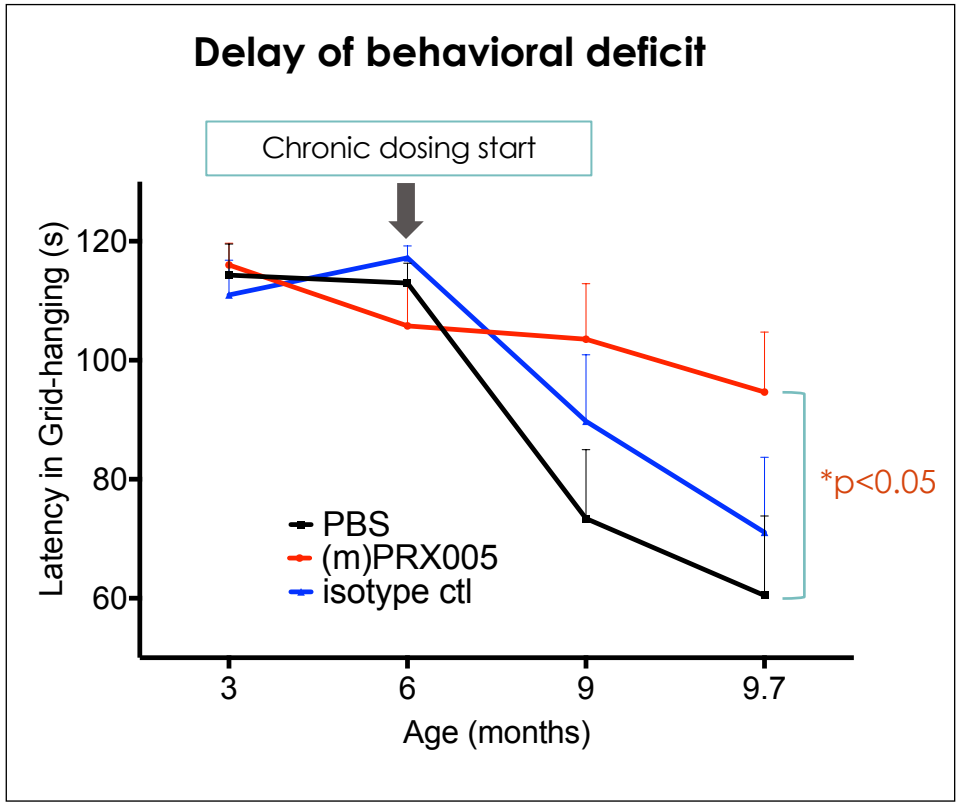
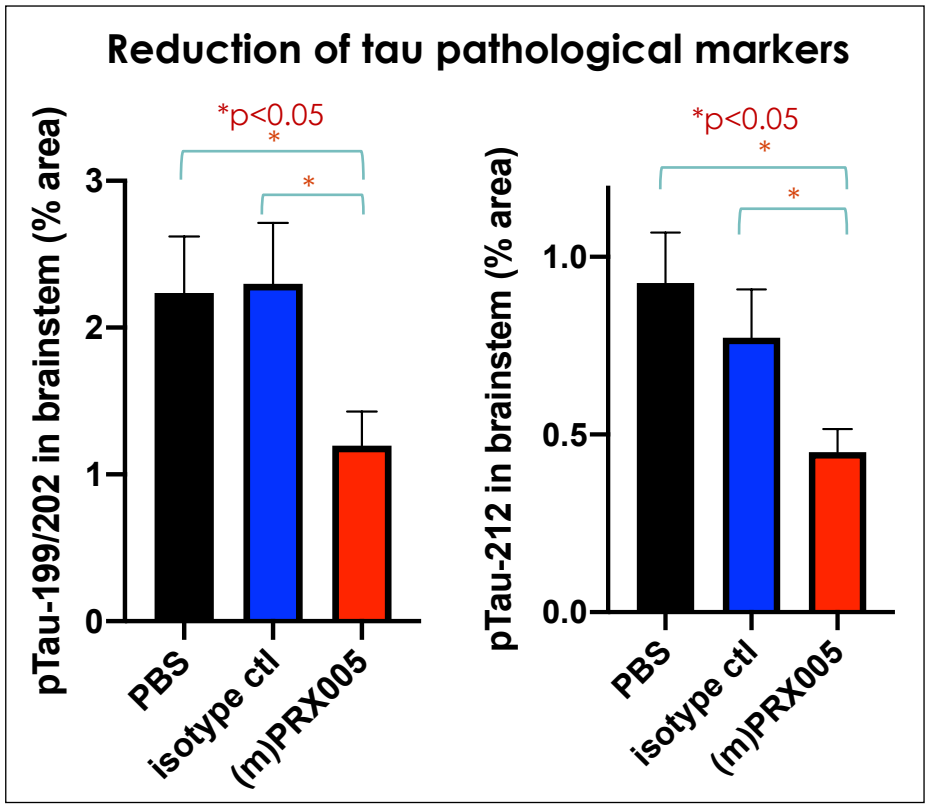
(m)PRX005 Treatment Reduces Pathological Tau and Ameliorates Behavior Deficit in a Transgenic Tau Mouse Model





All values are mean ± SE (n=15-20)

- PS19 transgenic mice overexpressing tau mutation (P301S) cause high levels of neuronal tau pathology and resultant behavioral deficits
- Initiation of treatment (weekly i.p.) at the onset of pathological development (treatment mode) with (m)PRX005 delays brainstem tau pathology and consequent behavioral deficits

(m)PRX005 = murine form of PRX005

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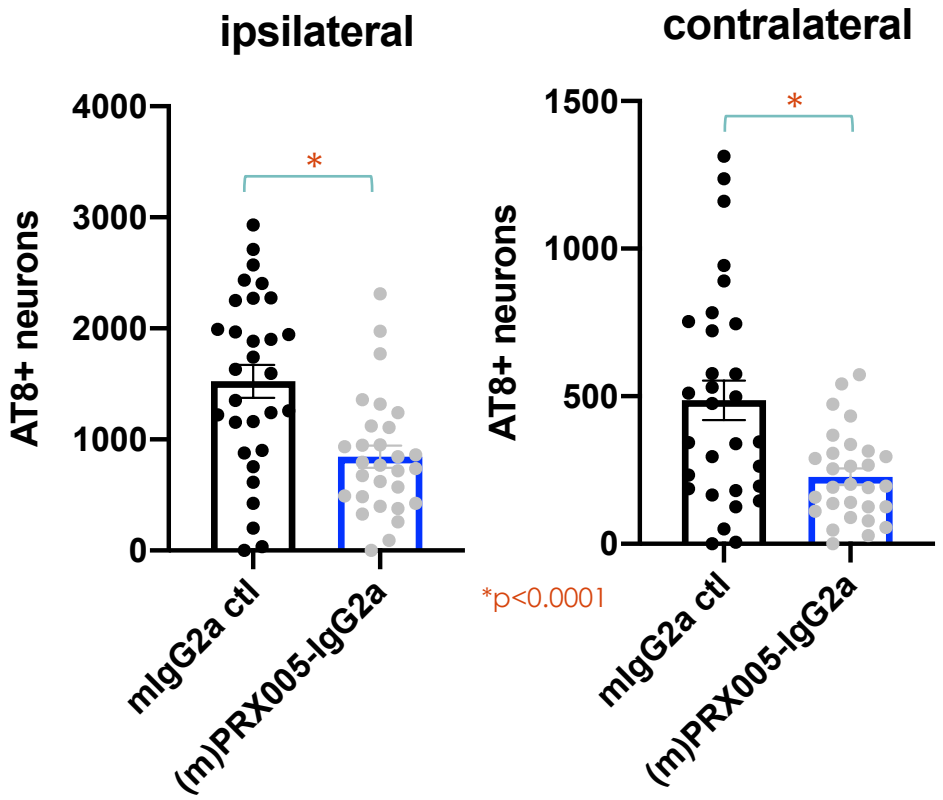
(m)PRX005 Treatment Reduces Pathological Tau Development in an Induced Tau Seeding Model with AD Extracts

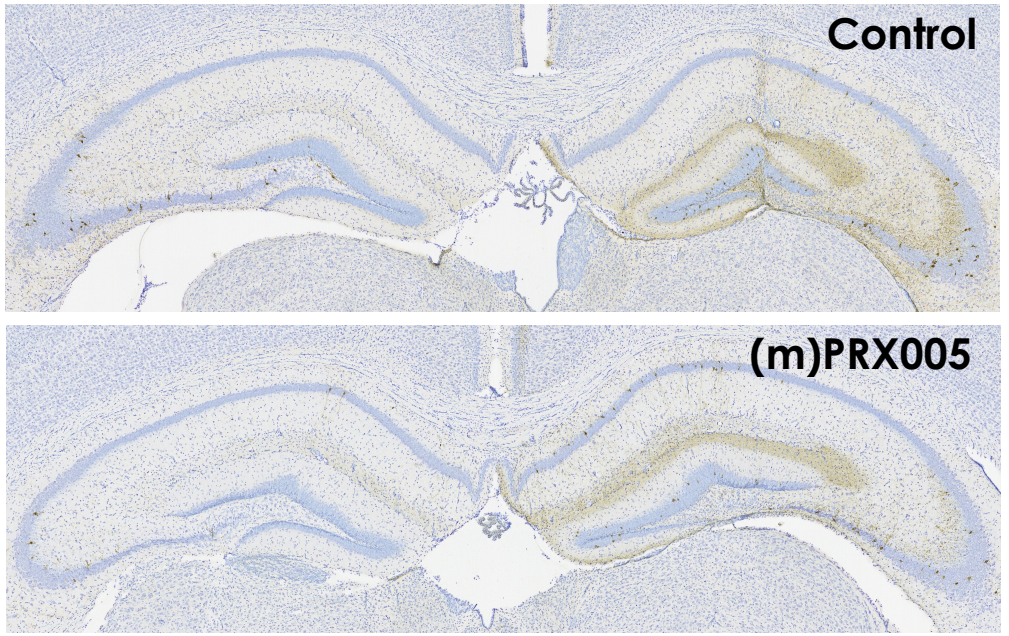


All values are mean ± SE (n=30)

- PS19 mice
- 3m: Unilateral injection of AD material
- 5m: Pathology measurements in ipsilateral and contralateral Hpc
- Tx: i.p. weekly

- Murine IgG2a promotes faster tau clearance by phagocytes *in vitro,* compared to IgG1
- Mouse IgG2a is the closest in function/biology to human IgG1

Representative images



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Summary of Findings

- *In vitro* screening of antibodies spanning the whole length of the tau protein indicated R1/R2 of MTBR displayed superior activity against tau uptake and neurotoxicity

- The murine precursor of PRX005 has a high affinity for MTBR tau epitope and superior profile versus other antibodies
  - Direct inhibition of the tau-HSPG interaction may contribute to blockade of tau internalization, toxicity, and development of intracellular tau pathology

- *In vivo* treatment with (m)PRX005 in transgenic tau mice and a seeding model reduces intraneuronal tau pathology and downstream behavioral deficits

The consistent, superior profile of PRX005 across a broad range of *in vitro* and *in vivo* systems supports advancing PRX005 as a clinical candidate for the potential treatment of Alzheimer's disease

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