# Beneficial effects of AZP2006 on neurodegenerative diseases is mediated by Progranulin

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THERAPEUTIC SOLUTIONS FOR NEURODEGENERATION
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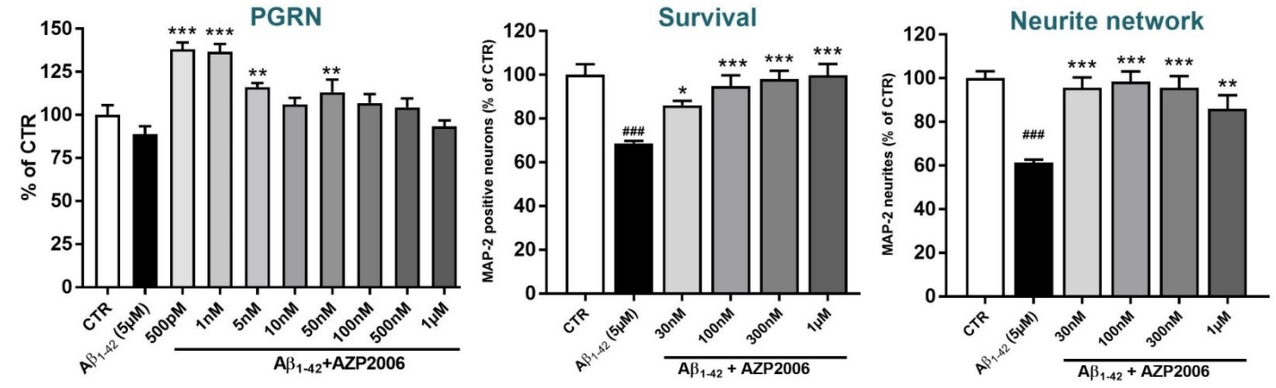
## INTRODUCTION

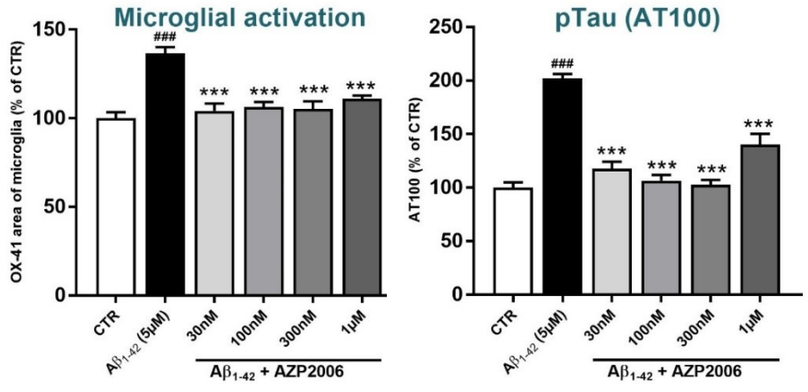
Progranulin (PGRN) is a secreted pleiotropic growth factor primarily expressed in mature neurons and microglia. It regulates neurite outgrowth, survival and neuroinflammation. The deficiency of PGRN is often correlated with neurodegenerative diseases such as FTD, AD and PD.
AZP2006 is a disease-modifying small molecule that is currently in clinical development for the treatment of Progressive Supranuclear Palsy (PSP). Orphan drug designation has been granted by the EMA and the FDA. Here we investigated its neuroprotective effects on different *in vitro* and *in vivo* models of neurodegenerative diseases. We showed that the neuroprotective action is correlated with the increase of PGRN and the reduction of neuroinflammation.

## RESULTS

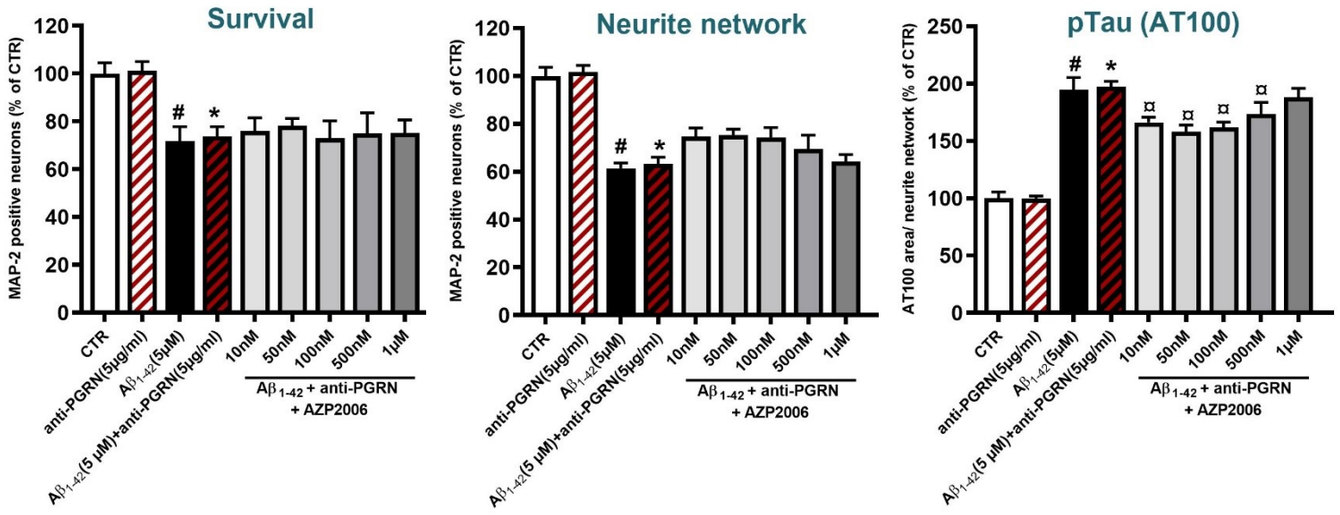
1 In **primary rat cortical neurons cultured with microglia injured with $A\beta_{1\text{-}42}$ oligomers** for 72h, AZP2006 increased secreted PGRN, neuron survival and neurite network.



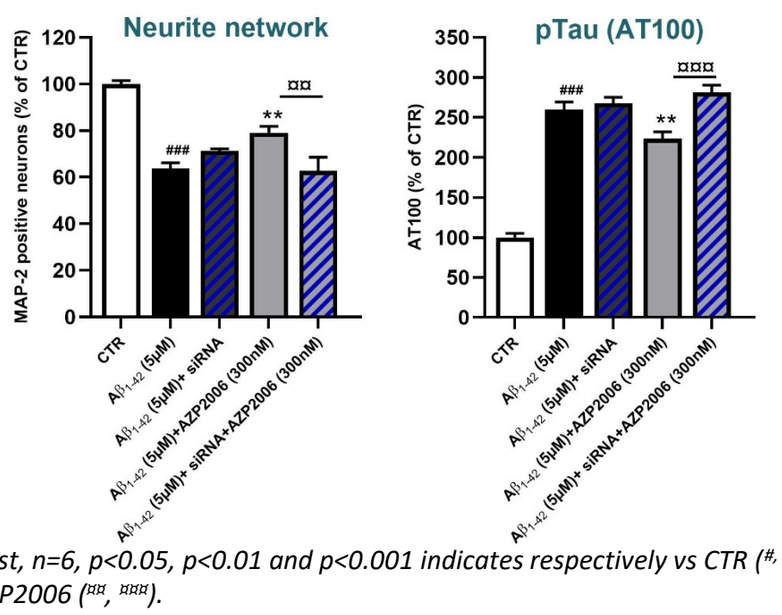

2 AZP2006 abolished microglia activation and Tau phosphorylation (AT100).




3 Anti-PGRN antibody abolished AZP2006 effect on cell survival and neurite network, but only partially on pTau (AT100).

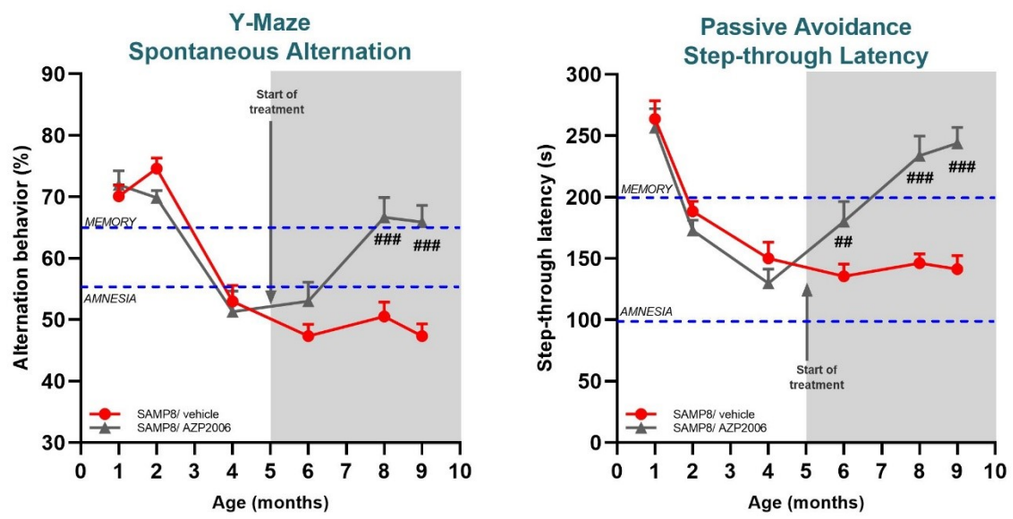



4 PGRN + Prosaposin (a PGRN regulator) siRNA abolished AZP2006 effect on neurite network and pTau (AT100).



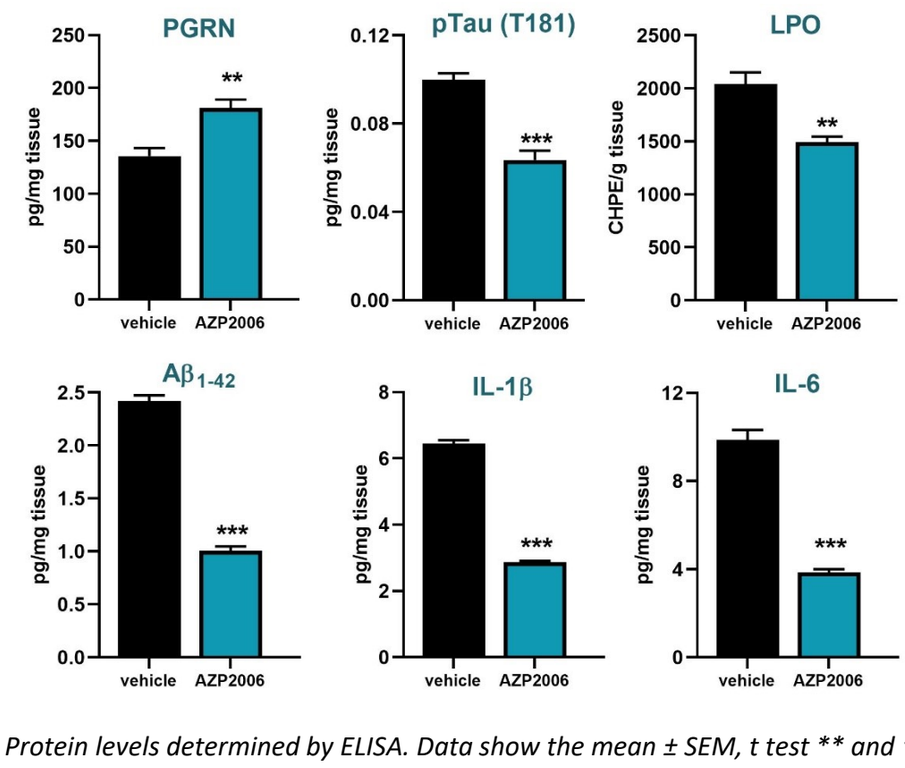

*Protein levels determined by ELISA. Data show mean ± SEM (100% = no $A\beta_{1\text{-}42}$, no compound). One-way ANOVA followed by Fisher's LSD test, n=6, p<0.05, p<0.01 and p<0.001 indicates respectively vs CTR (#, ##, ###) , vs $A\beta_{1\text{-}42}$ condition (*, **, ***), vs $A\beta_{1\text{-}42}$+ anti-PGRN (¤) or vs $A\beta_{1\text{-}42}$+siRNA+AZP2006 (¤¤, ¤¤¤).*

5 AZP2006 neuroprotective effects were studied in the **Senescence-Accelerated Mouse-Prone 8 (SAMP-8) mice model**, which displays Tau hyperphosphorylation, abnormal Aβ accumulation, increased oxidative stress, gliosis, impaired immune response and deficits of learning and memory from the age of 2 months.
Mice were daily treated p.o. (drinking water) with vehicle or 3mg/kg/day AZP2006 from the age of 5 to 10 months.
AZP2006 significantly reversed cognitive dysfunctions determined by the Y-Maze and Step-Through Passive Avoidance tests.




*Data show mean ± SEM ,Two-way ANOVA and Dunnett's test ## p < 0.01 ### p < 0.001 vs. SAMP8 / Veh group at same month; n=10-12.*

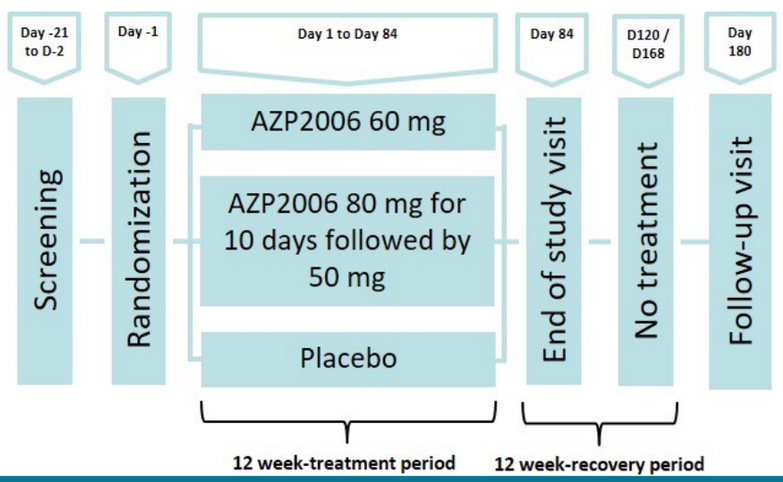
6 The 5-month AZP2006 treatment increased the levels of PGRN, reduced pTau (T181) and the lipid peroxidation (LPO) in the hippocampus. The levels of $A\beta_{1\text{-}42}$ , IL-1β and IL-6 were reduced in the cortex.




*Protein levels determined by ELISA. Data show the mean ± SEM, t test ** and *** indicate p<0.01 and p<0.001 respectively, n=6-7.*

7 **AZP2006 Clinical Trial:**

AZP2006C04 is a Phase 2a multi-center, randomized, double-blind, placebo-controlled study to assess tolerability, safety, PK and effect of AZP2006 in 36 patients with PSP. The effect of AZP2006 will be determined on CSF biomarkers.




**CSF biomarkers**

- Tau
- pTau (T181)
- $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$
- PGRN
- 8-oxo-dG
- 4-HNE
- Ferritin
- IL-6, TNFα, IFNγ, IL-1β, IL-8, MIP-1β, MCP-1, IP-10, IL-10
- NfL, pNfH

## CONCLUSIONS

We showed that AZP2006 protected neurons, decreased Tau hyperphosphorylation and reduced the neuroinflammation via Progranulin.
AZP2006 is currently in clinical phase 2a in PSP patients for a 3 month-treatment and similar biomarkers will be investigated in CSF and plasma.

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