AMYLYX

Progressive Supranuclear Palsy (PSP) Investor and Analyst Conference Call

July 26, 2023

On Today's Call

- **Welcome**
  Lindsey Allen, Head, Investor Relations and Communications, Amylyx

- **Opening Remarks**
  Josh Cohen and Justin Klee, Co-CEOs, Amylyx

- **AMX0035 Scientific Rationale in PSP**
  Dr. Jamie Timmons, Head, Global Medical Strategy and Communications, Amylyx

- **PSP Treatment Landscape**
  Prof. Dr. Günter Höglinger, Director of the Department of Neurology at LMU Hospital, Ludwig-Maximilians-University (LMU) in Munich, Germany
  Primary Investigator for Phase 3 ORION Clinical Trial of AMX0035 in PSP

- **Overview of Phase 3 PSP Trial**
  Dr. Lahar Mehta, Head, Global Clinical Development, Amylyx

- **Q&A Session**

Disclaimer

Statements contained in this presentation regarding matters that are not historical facts are “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995, as amended. Because such statements are subject to risks and uncertainties, actual results may differ materially from those expressed or implied by such forward-looking statements. Such statements include, but are not limited to, statements regarding the potential of AMX0035 as a treatment for ALS and the Company’s plans to explore the use of AMX0035 for other neurodegenerative diseases, including progressive supranuclear palsy (PSP) and expectations around the timing of initiation of a Phase 3 clinical trial in PSP and the geographic sites for enrollment; expectations about the market size for PSP; and expectations regarding our longer-term strategy. Any forward-looking statements in this presentation are based on management’s current expectations of future events and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. Risks that contribute to the uncertain nature of the forward-looking statements include: the success, cost, and timing of Amylyx’ program development activities, including ongoing and planned clinical trials, Amylyx’ ability to execute on its commercial and regulatory strategy, regulatory developments, Amylyx’ ability to fund operations, and the impact that the COVID-19 pandemic may have on Amylyx’ operations, as well as the risks and uncertainties set forth in Amylyx’ United States Securities and Exchange Commission (SEC) filings, including Amylyx’ Annual Report on Form 10-K for the year ended December 31, 2022, and subsequent filings with the SEC. All forward-looking statements contained in this presentation speak only as of the date on which they were made. Amylyx undertakes no obligation to update such statements to reflect events that occur or circumstances that exist after the date on which they were made.

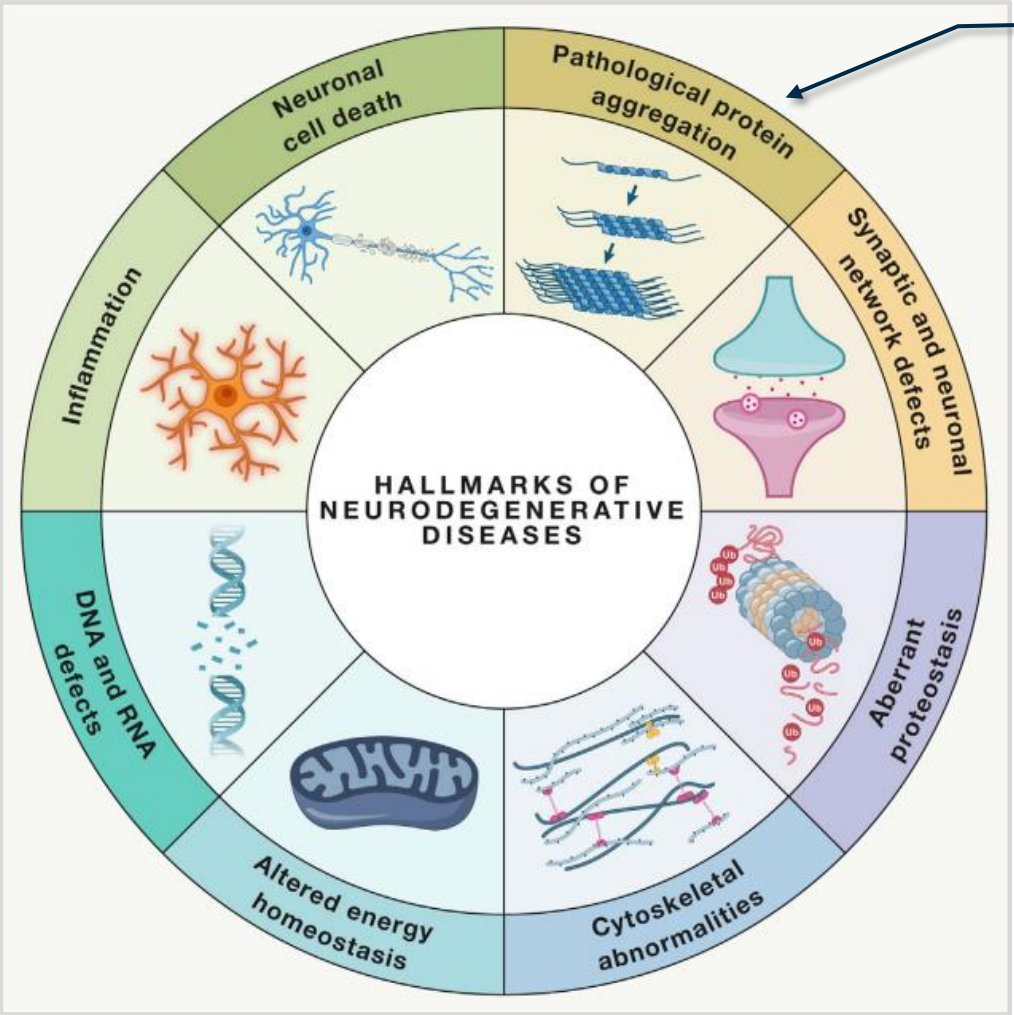
AMX0035 Scientific Rationale in PSP

Dr. Jamie Timmons

Head, Global Medical Strategy and Communications, Amylyx

Our mission is to one day end the suffering caused by neurodegenerative diseases.

Neurodegenerative Diseases Share Interconnected, Hallmark Pathological Pathways



Pathological Protein Aggregation

Amyotrophic Lateral Sclerosis (ALS)
- TDP43, tau, SOD1, FUS, DPRs

Tauopathies; e.g., Progressive Supranuclear Palsy (PSP)
- tau

Alzheimer's Disease
- tau, Aβ

The interconnectedness of these pathways highlights the need for multi-pathway therapy

Wilson DM 3rd, et al. *Cell*. 2023 Feb 16;186(4):693-714.

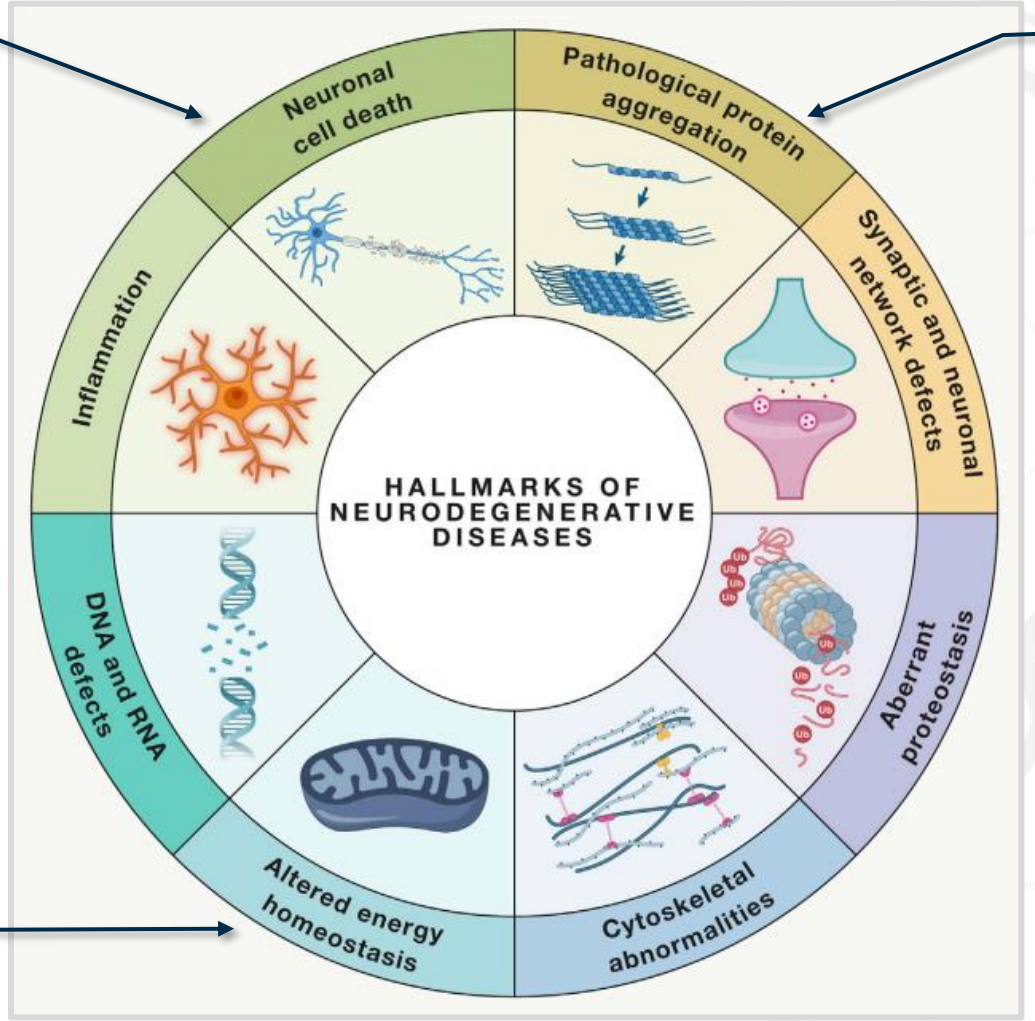
AMX0035 (Sodium Phenylbutyrate and Taurursodiol) Acts on Several Shared Hallmark Pathways to Reduce Neuronal Cell Death[1-9]

Neuronal Cell Death

- In vitro evidence of protecting neurons from death[2]
- Affects key pathways leading to cell death, including intrinsic apoptosis via the mitochondria and unfolded protein response[3-5]

Altered Energy Homeostasis

- Stabilizes mitochondrial membrane, improves mitochondrial function, increasing energy production of the cell[4,5]



Pathological Protein Aggregation

- Reduces tau in neurodegenerative disease cell and mouse models and in Alzheimer's disease clinical trial[6-9]

1. Wilson DM 3rd, et al. Cell. 2023 Feb 16;186(4):693-714. **2.** Cohen J, et al. Poster presented at: 28th International Symposium for ALS/MND; December 4-10, 2017; Boston, MA. **3.** Zhou W. J Biol Chem. 2011;286(17):14941-14951. **4.** Rodrigues CM, Steer CJ. Expert Opin Investig Drugs. 2001;10(7):1243-1253. **5.** Rodrigues CM, et al. Biochemistry. 2003;42(10):3070-3080. **6.** Ricobaraza A, et al. Neuropsychopharmacology. 2009;34(7):1721-1732. **7.** Bondulich MK, et al. Brain. 2016;139(8):2290-2306. **8.** van der Harg JM, et al. Cell Death Dis. 2014;5(8):e1393. **9.** Arnold SE, et al. Poster presented at: 15th Clinical Trials on Alzheimer's Disease; November 29-December 2, 2022; San Francisco, CA.

PSP is a Rare, Progressive and Fatal Tauopathy

- Rare neurological disorder affecting body movements, walking and balance, and eye movement.
- Lack of disease modifying therapies creates significant unmet need.
- PSP is a tauopathy associated with tau dysfunction, tau aggregation and widespread neurodegeneration.

ESTIMATED PREVALENCE:

7 in 100,000 worldwide[1,2]

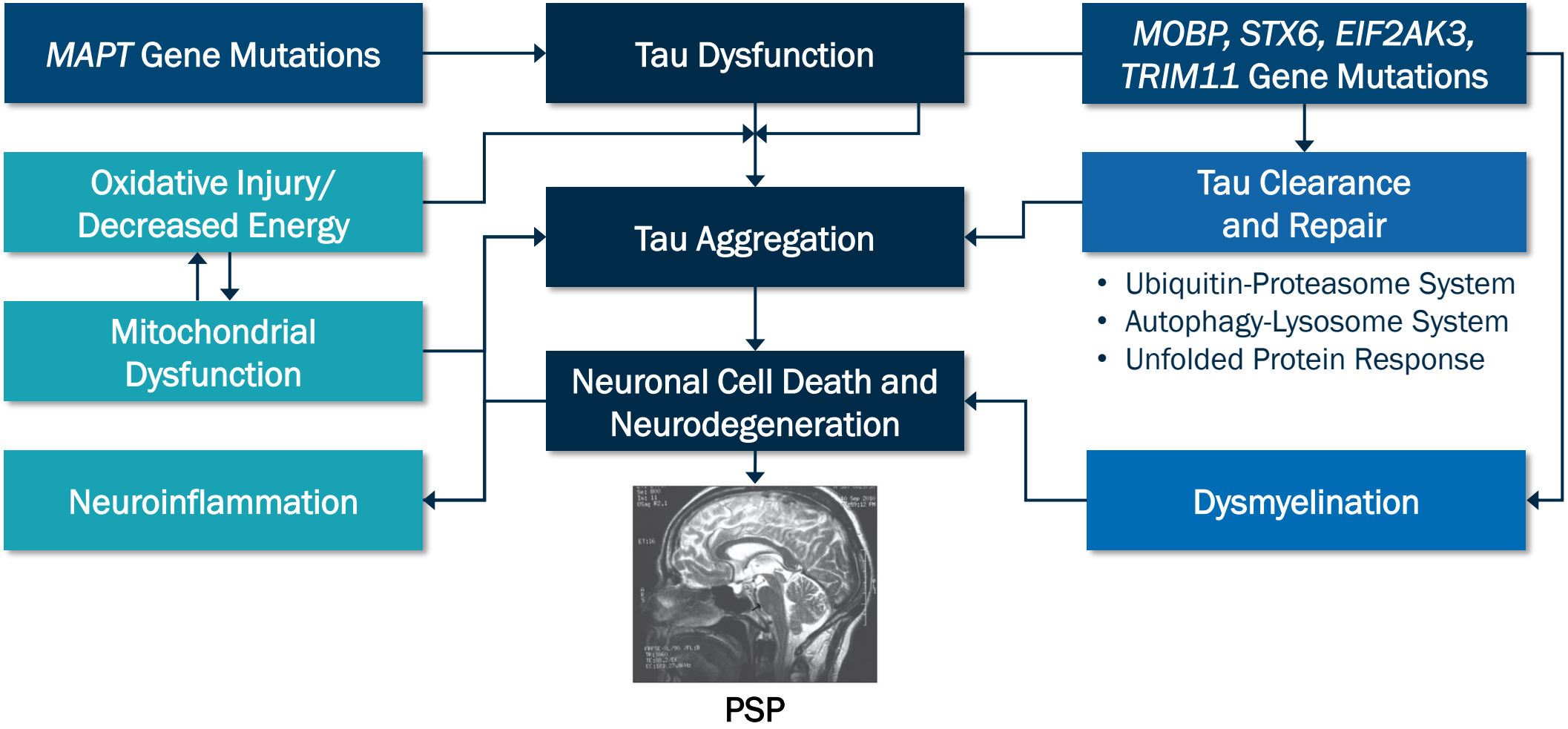
ESTIMATED INCIDENCE:

0.81 in 100,000 worldwide[2]

PSP is typically fatal within 6-8 years from symptom onset[3-6]

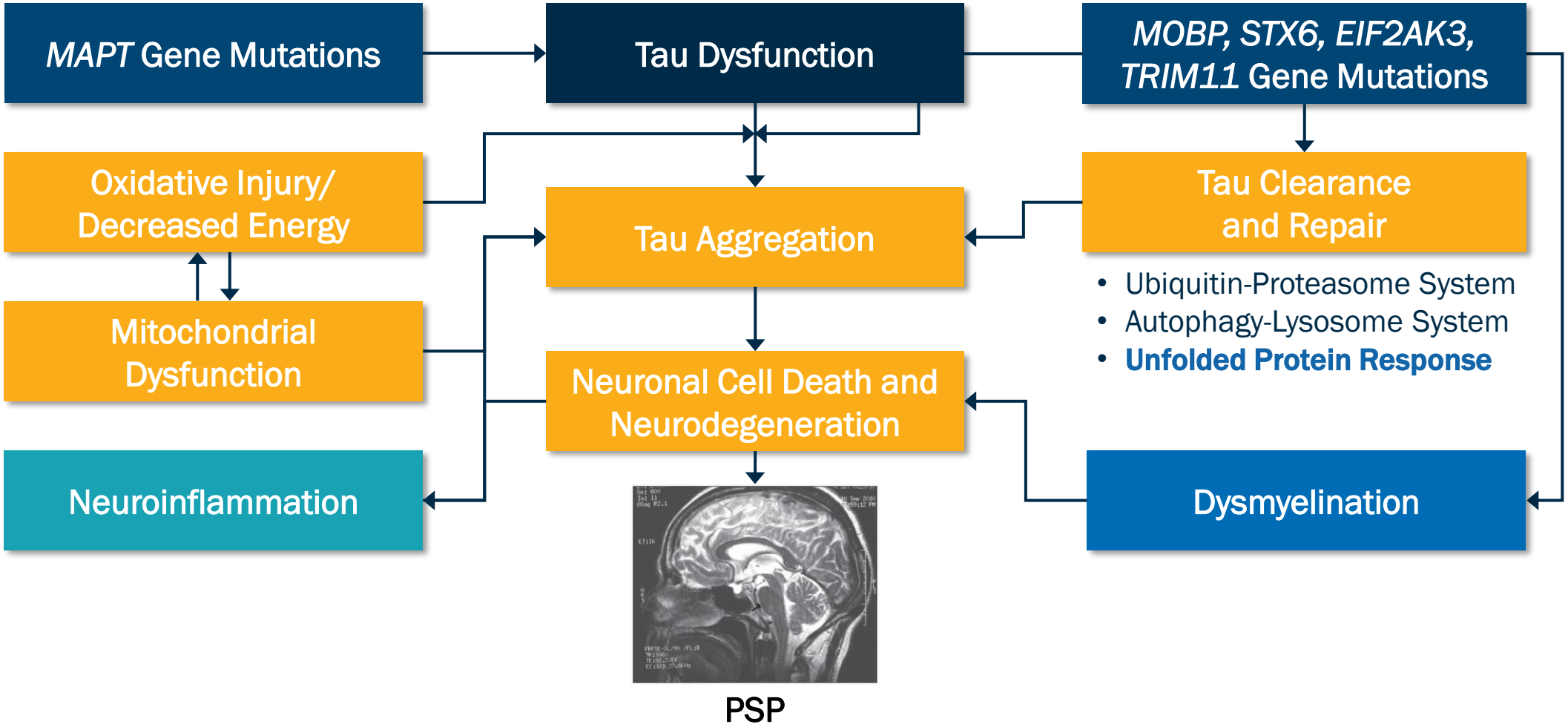
1. Swallow DMA, et al. Mov Disord Clin Pract. 2022 Jun 28;9(5):604-613. doi: 10.1002/mdc3.13489. **2.** Lyons S, et al. J Neurol.2023;June 8. epub ahead of print. **3.** Stamelou M, et al. Nat Rev Neurol. 2021;17(10):601-620. **4.** Viscidi E, et al. Front Neurol. 2021;12:571800. **5.** Golbe and Ohman-Strickland. Brain. 2007;130(6):1552-65. **6.** Swallow and Counsell. J Neurol. 2023;270(7):3464-3474

Pathophysiologic Changes Underlying PSP Provide Multiple Pathways to Target



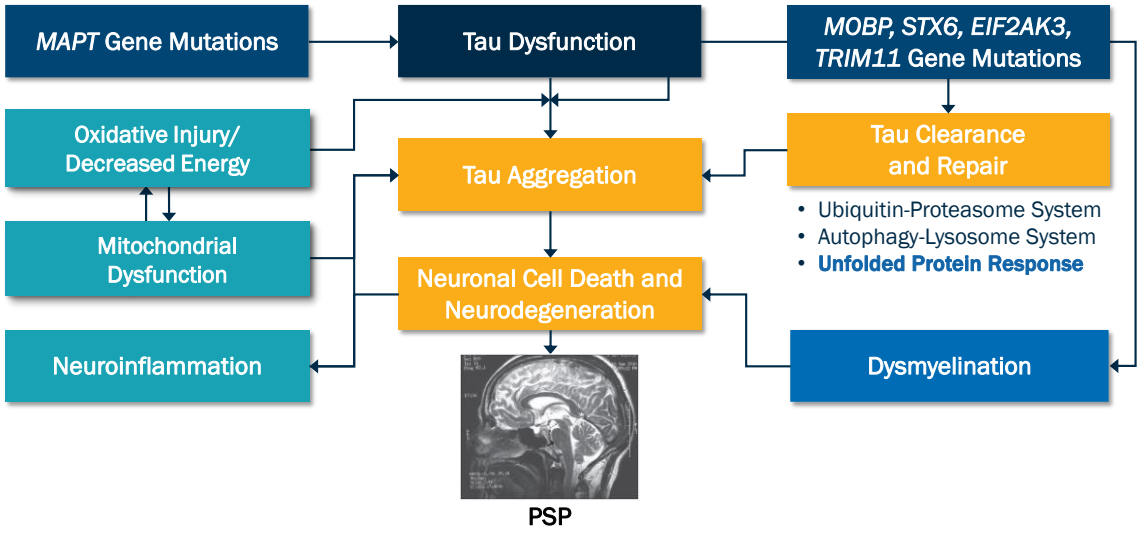
Park HK, et al. J Mov Disord. 2021; 14(2):103-113.

AMX0035 May Influence PSP Tau Pathology through Multiple Mechanisms[1-9]



1. Park HK, et al. J Mov Disord. 2021; 14(2):103-113. **2.** Cohen J, et al. Poster presented at: 28th International Symposium for ALS/MND; December 4-10, 2017; Boston, MA. **3.** Zhou W. J Biol Chem. 2011;286(17):14941-14951. **4.** Rodrigues CM, Steer CJ. Expert Opin Investig Drugs. 2001;10(7):1243-1253. **5.** Rodrigues CM, et al. Biochemistry. 2003;42(10):3070-3080. **6.** Ricobaraza A, et al. Neuropsychopharmacology. 2009;34(7):1721-1732. **7.** Bondulich MK, et al. Brain. 2016;139(8):2290-2306. **8.** van der Harg JM, et al. Cell Death Dis. 2014;5(8):e1393. **9.** Arnold SE, et al. Poster presented at: 15th Clinical Trials on Alzheimer's Disease; November 29-December 2, 2022; San Francisco, CA.

Preclinical Data Support Sodium Phenylbutyrate (PB) for Potential Treatment of PSP



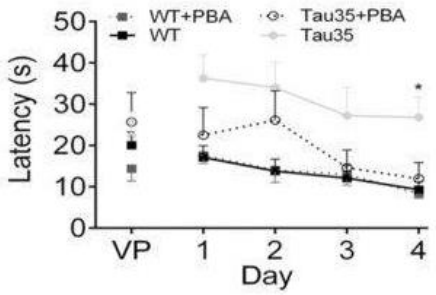
Sodium phenylbutyrate upregulates and recruits chaperone proteins, stabilizes protein folding, and reduces ER stress and the unfolded protein response (UPR) in vitro[1-4]

PB is Effective in PSP Mouse Model, Reduced Tau in AD Mouse Model

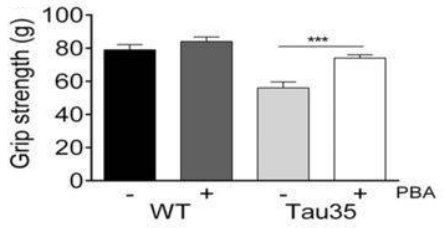
PB reduced tau pathology and improved cognitive and motor function measures in relevant mouse models[5,6]

- **Alzheimer's APP/PS1 mouse model:** reduced tau phosphorylation and improved cognition[5]
- **Tau35 PSP mouse model (shown):** reduced tau phosphorylation and improved cognition and motor function[6]

Morris Water Maze[6]

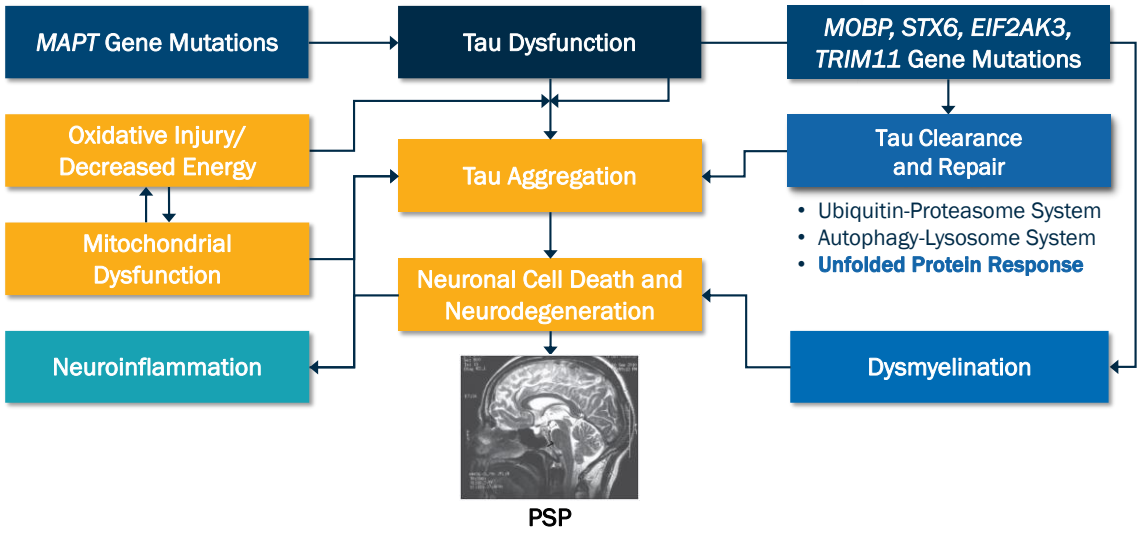


Grip Strength[6]



1. Zhou W. J Biol Chem. 2011;286(17):14941-14951. **2.** Wiley JC, et al. PLoS One. 2010;5:e9135. **3.** Mimori S, et al. Biol Pharm Bull. 2012;35:84-90. **4.** Cho JA, et al. PLoS One 2014;9:e110086. **5.** Ricobaraza A, et al. Neuropsychopharmacology. 2009;34(7):1721-1732. **6.** Bondulich MK, et al. Brain. 2016;139(8):2290-2306.

Preclinical Data Support Taurursodiol (TURSO) for Potential Treatment of PSP

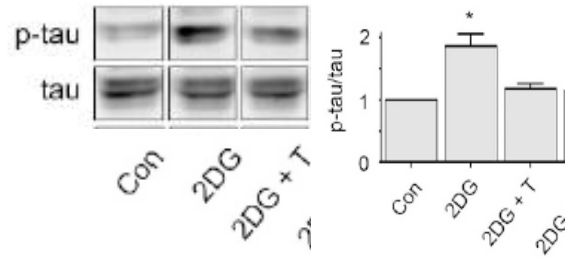


Taurursodiol stabilizes the mitochondrial membrane by reducing the translocation of cell death regulator Bax, improving mitochondrial function and energy production and increasing cell apoptotic threshold[1,2]

TURSO reduced p-tau in cellular model of metabolic stress[3]

Taurursodiol (TURSO) reduced tau phosphorylation in vitro[3]

Reduced p-tau with TURSO[3]

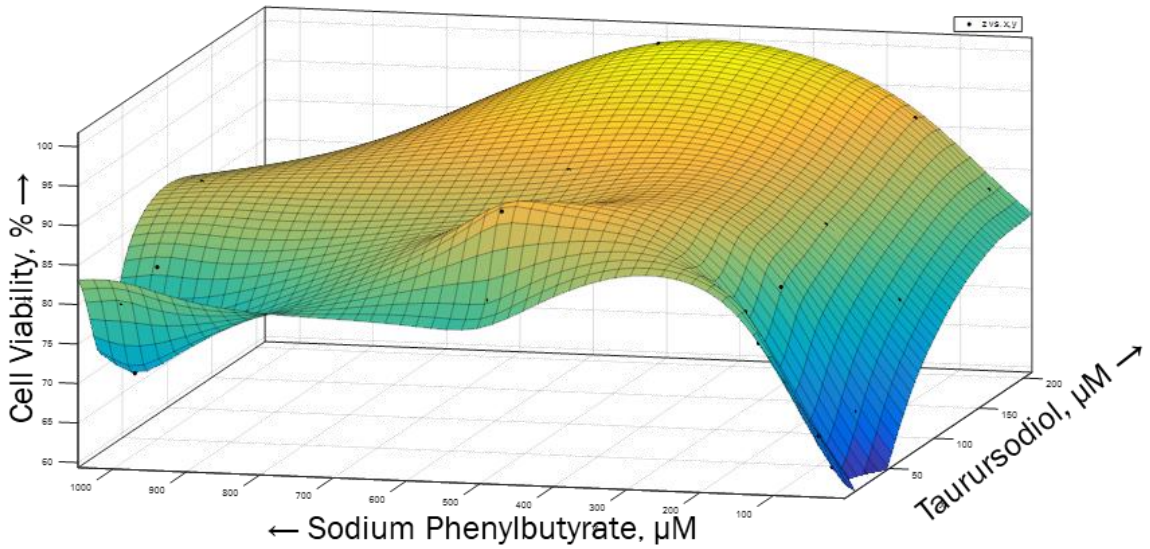


- 2 deoxy glucose (2DG) induced metabolic stress in neuronal cell model resulting in increased p-tau levels[3]
- TURSO (T) reduced increase in p-tau levels[3]

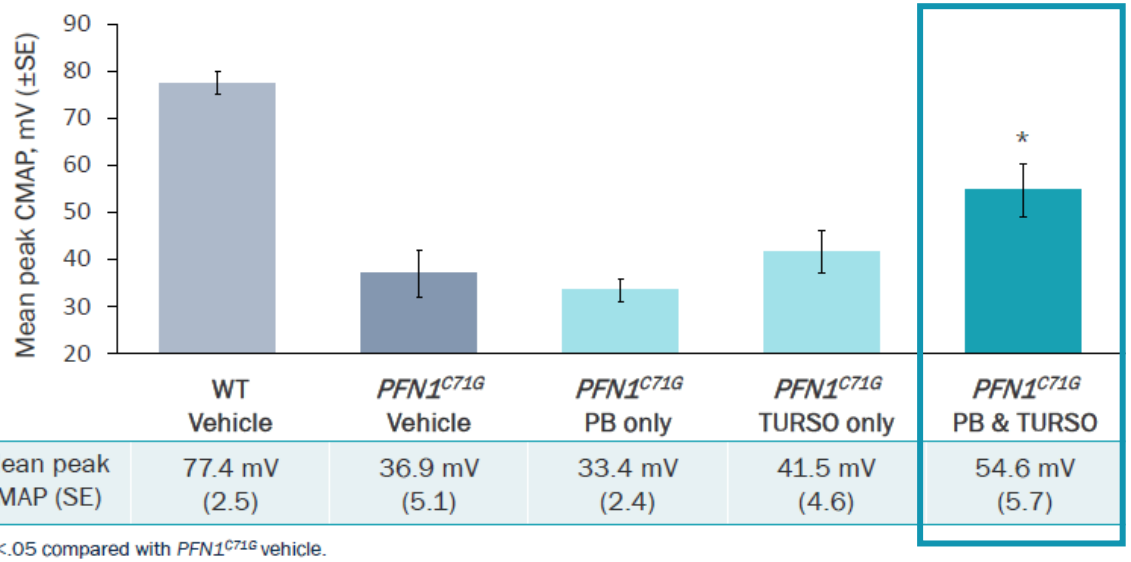
1. Rodrigues CM, Steer CJ. Expert Opin Investig Drugs. 2001;10(7):1243-1253. **2.** Rodrigues CM, et al. Biochemistry. 2003;42(10):3070-3080. **3.** van der Harg JM, et al. Cell Death Dis. 2014;5(8):e1393.

Numerous Preclinical Studies Show that AMX0035 Combination Targets Multiple Pathways Simultaneously to Prevent or Slow Cell Death

Dose-Matrix Study: Primary Cortical Neuron Damage Model[1]



Profilin Mouse Model of ALS[2]



	WT Vehicle	*PFN1*^{C71G} Vehicle	*PFN1*^{C71G} PB only	*PFN1*^{C71G} TURSO only	*PFN1*^{C71G} PB & TURSO
Mean peak CMAP (SE)	77.4 mV (2.5)	36.9 mV (5.1)	33.4 mV (2.4)	41.5 mV (4.6)	54.6 mV (5.7)

*P<.05 compared with *PFN1*^{C71G} vehicle.
CMAP, compound muscle action potential; PB, sodium phenylbutyrate; *PFN1*, profilin 1; TURSO, ursodoxicoltaurine; WT, wild type.

***In vitro*, AMX0035 combination demonstrated synergistic protection of cortical neurons against peroxide-mediated neuronal cell death**

- Either PB or TURSO administration alone prevented a moderate percentage of neuronal cell death in vitro
- AMX0035 combination prevented nearly 100% of neuronal death *in vitro*

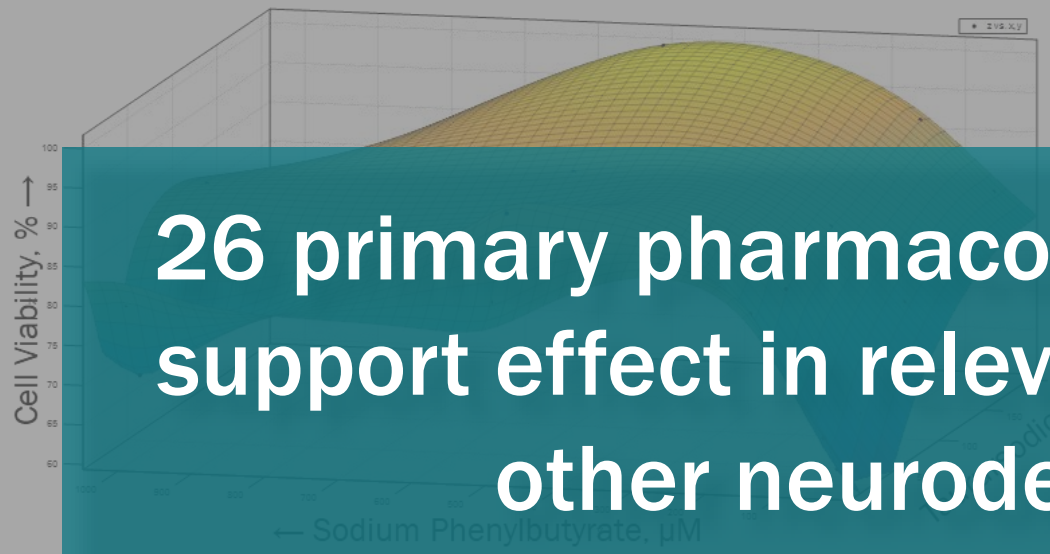
In mouse model of ALS, AMX0035 combination demonstrated synergistic decrease in motor function decline

- AMX0035 combination significantly decreased motor function decline in a mouse model of ALS
- This benefit was only seen when combining PB and TURSO and not with individual PB or TURSO treatment

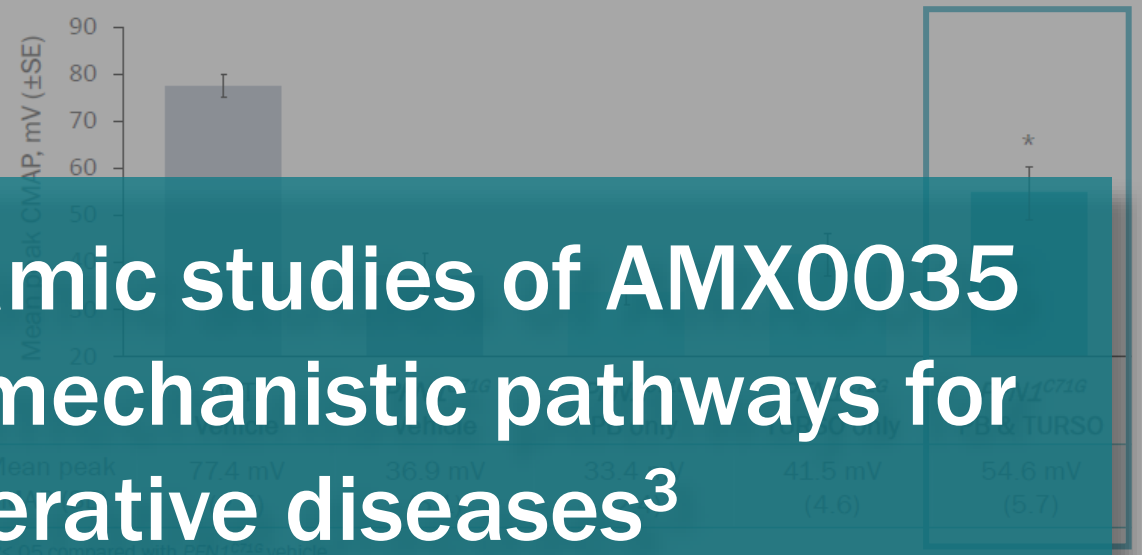
1. Cohen J, et al. Clinical trial design for a phase II, randomized, placebo-controlled trial of AMX0035 in amyotrophic lateral sclerosis (CENTAUR). Poster presented at: 28th International Symposium for ALS/MND; December 4–10, 2017; Boston, MA. **2.** Timmons J, et al. Efficacy of Sodium Phenylbutyrate and Ursodoxicoltaurine Combination in Transgenic Mice Displaying Progressive Motor Neuron Degeneration Phenotype. Poster presented at ENCALS Meeting 2023; July 12-14, 2023; Barcelona, Spain.

Numerous Preclinical Studies Show that AMX0035 Combination Targets Multiple Pathways Simultaneously to Prevent or Slow Cell Death

Dose-Matrix Study: Primary Cortical Neuron Damage Model[1]



Profilin Mouse Model of ALS[2]



26 primary pharmacodynamic studies of AMX0035 support effect in relevant mechanistic pathways for other neurodegenerative diseases[3]

3. Data on File

***In vitro*, AMX0035 combination demonstrated synergistic protection of cortical neurons against peroxide-mediated neuronal cell death**

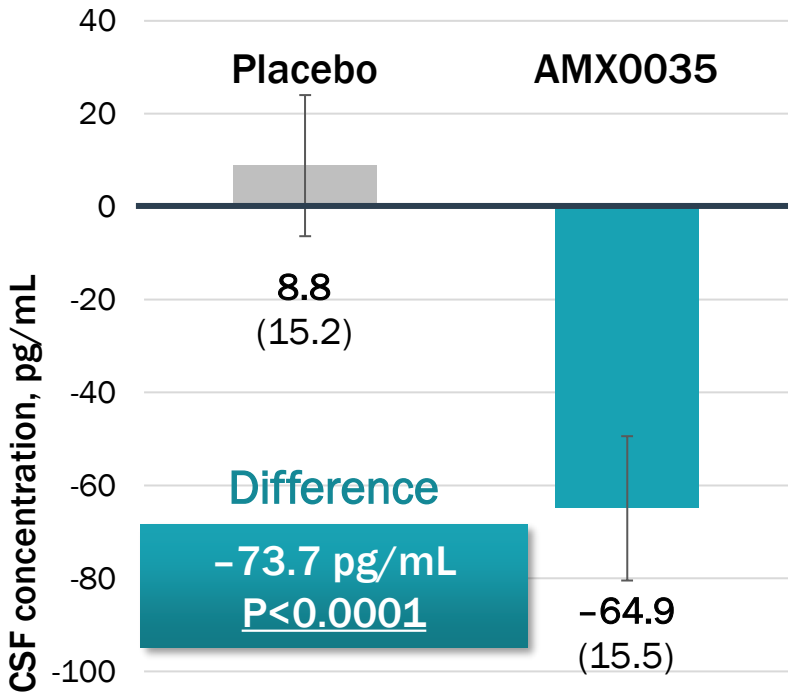
- Either PB or TURSO administration alone prevented a moderate percentage of neuronal cell death in vitro
- AMX0035 combination prevented nearly 100% of neuronal death *in vitro*

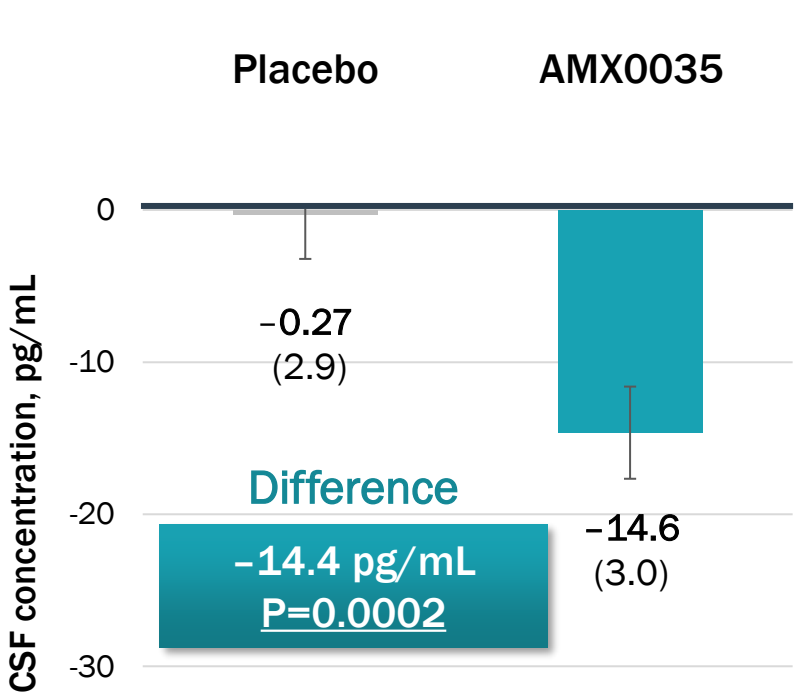
In mouse model of ALS, AMX0035 combination demonstrated synergistic decrease in motor function decline

- AMX0035 combination significantly decreased motor function decline in a mouse model of ALS
- This benefit was only seen when combining PB and TURSO and not with individual PB or TURSO treatment

1. Cohen J, et al. Clinical trial design for a phase II, randomized, placebo-controlled trial of AMX0035 in amyotrophic lateral sclerosis (CENTAUR). Poster presented at: 28th International Symposium for ALS/MND; December 4–10, 2017; Boston, MA. **2.** Timmons J, et al. Efficacy of Sodium Phenylbutyrate and Ursodoxicoltaurine Combination in Transgenic Mice Displaying Progressive Motor Neuron Degeneration Phenotype. Poster presented at ENCALS Meeting 2023; July 12-14, 2023; Barcelona, Spain.

AMX0035 Significantly Lowered CSF Tau and p-Tau in Randomized Placebo Controlled Trial in People with Alzheimer's Disease

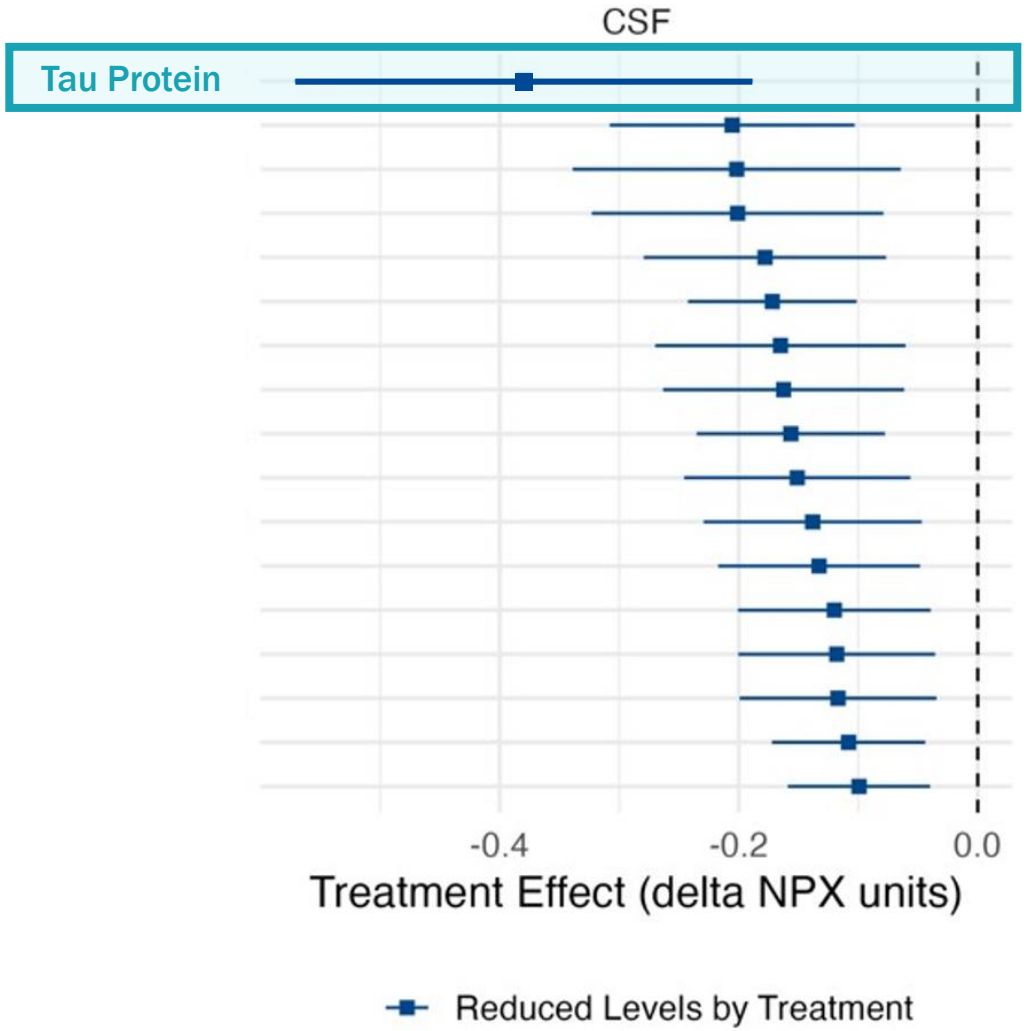




Arnold SE, et al. Cerebrospinal Fluid Biomarker Effects From a Fixed-Dose Combination of Sodium Phenylbutyrate and Taurursodiol in Alzheimer's Disease:Results From the PEGASUS Trial. Poster presented at: 15th Clinical Trials on Alzheimer's Disease CTAD, November 29-Dec2; California.

AMX0035 met the primary endpoint of safety and tolerability in the PEGASUS trial of AMX0035 for the treatment of Alzheimer's disease. The 6-month trial was not powered to evaluate differences between groups in efficacy outcomes and no differences were seen in the primary efficacy outcome, a newly developed composite outcome of cognitive, functional, and imaging measures, or secondary efficacy outcomes of cognition, function, and imaging.

AMX0035 Shown to Reduce Tau Protein in Proteomic Analysis



288

Of 288 proteins measured in CSF and plasma, Tau protein was the most significantly changed protein by AMX0035[1]

1. Data on File
The Proteomic analysis was a pre-specified, exploratory analysis in the PEGASUS trial of AMX0035 for the treatment of Alzheimer's disease.

AMX0035 Slowed Disease Progression and Prolonged Survival in ALS[1,2]

ALS and PSP Share Several Phenotypic Features and Shared Disease Mechanisms[3-5]

Suggests that a Drug Effective for ALS May be Effective for PSP[3]

Shared Disease Mechanisms[3]	Shared Phenotypic Features[4,5]
Unfolded protein response	Swallowing difficulty
Mitochondrial dysfunction	Respiratory dysfunction
Neuroinflammation	Speech disturbance
Protein misfolding and aggregation	Impaired cognition

1. Paganoni S, et al. N Engl J Med. 2020;383(10):919-930. **2.** RELYVRIO. Prescribing information. Amylyx Pharmaceuticals, Inc.; 2022. **3.** Wilson DM 3rd, et al. Cell. 2023 Feb 16;186(4):693-714. **4.** Viscidi E, et al. *Front Neurol.* 2021;12:571800. **5.** Brown RH, Al-Chalabi A. N Engl J Med. 2017;377(2):162-172.

Key Takeaways

- PSP is a tauopathy associated with tau dysfunction, tau aggregation and widespread neurodegeneration.

- Multiple pathways, are implicated in tau pathology in PSP.

- AMX0035 is proposed to mitigate tau pathology in PSP through multiple pathways.

- Pre-clinical and clinical evidence supports that AMX0035 can reduce tau pathology.

PSP Treatment Landscape

Prof. Dr. Günter Höglinger

Director of the Department of Neurology at Ludwig-Maximilians-University (LMU) Hospital
Primary Investigator for Phase 3 PSP Trial

LMU KLINIKUM
Gemeinsam. Fürsorglich. Wegweisend.

Biotech and Healthcare Analysts and Investors PSP Webinar

Progressive Supranuclear Palsy (PSP)

Dept. of Neurology, LMU Hospital, Ludwig-Maximilians-University, Munich, Germany

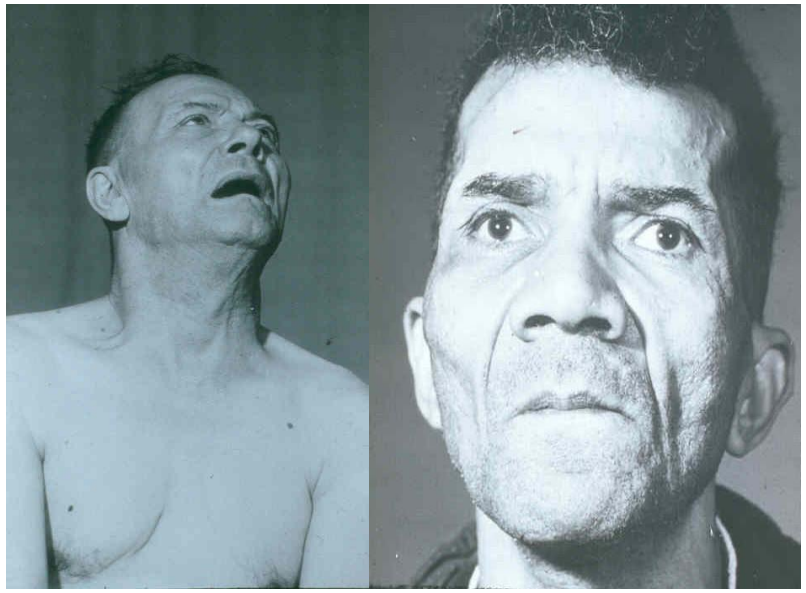
26.07.2023 | Prof. Dr. Günter Höglinger

Disclosures

Consultation for AbbVie, Alzprotect, Amylyx, Aprinoia, Asceneuron, Bayer, Bial, Biogen, Biohaven, Epidarex, Lundbeck, Novartis, Retrotope, Roche, Sanofi, Servier, Takeda, UCB.

Presentations for AbbVie, Bayer, Bial, Biogen, BMS, Roche, Teva, UCB, Zambon.

Clinical Manifestation of PSP



Progressive Supranuclear Palsy

A Heterogeneous Degeneration Involving the Brain Stem, Basal Ganglia and Cerebellum With Vertical Gaze and Pseudobulbar Palsy, Nuchal Dystonia and Dementia

JOHN C. STEELE, MD

J. CLIFFORD RICHARDSON, MD

AND

JERZY OLSZEWSKI, MD

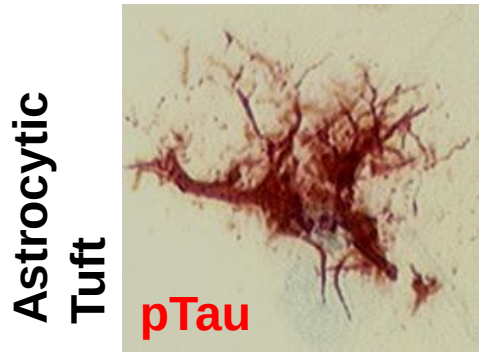
TORONTO

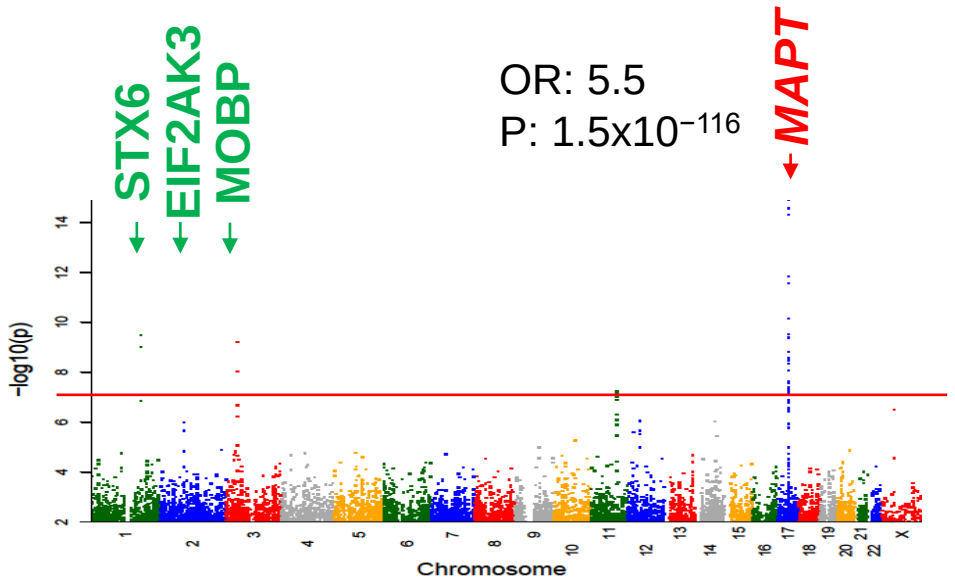
Introduction

In this report we are describing a progressive brain disease featured by supranuclear ophthalmoplegia affecting chiefly vertical gaze, pseudobulbar palsy, dysarthria, dystonic rigidity of the neck and upper trunk, and other less constant cerebellar and pyramidal symptoms. Dementia has usually remained mild. This disease would appear to be predominantly a nerve cell degeneration centered chiefly in the brain stem.

Archives of Neurology, 1964;10:333-359

Tau H1 Haplotype predisposes for PSP

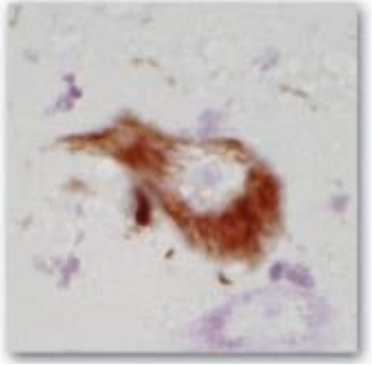


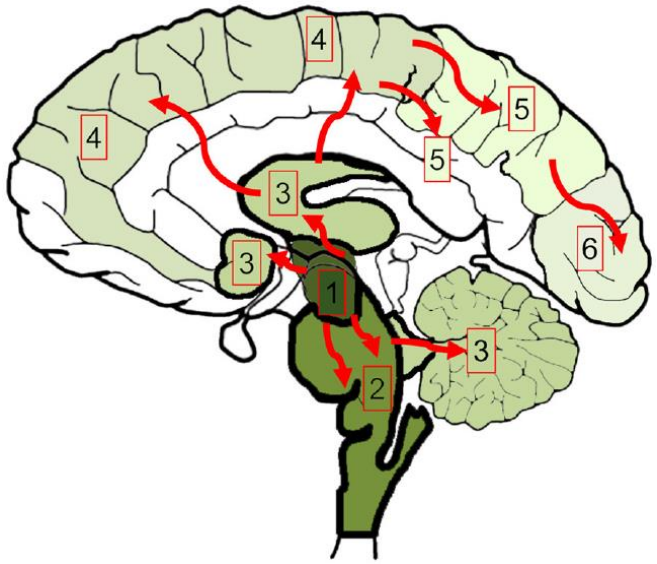


Höglinger et al., **Nature Genetics**, 2011

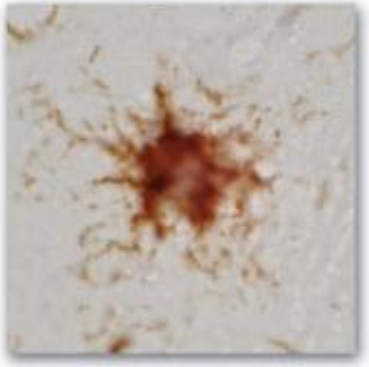
Tau Spreading in PSP

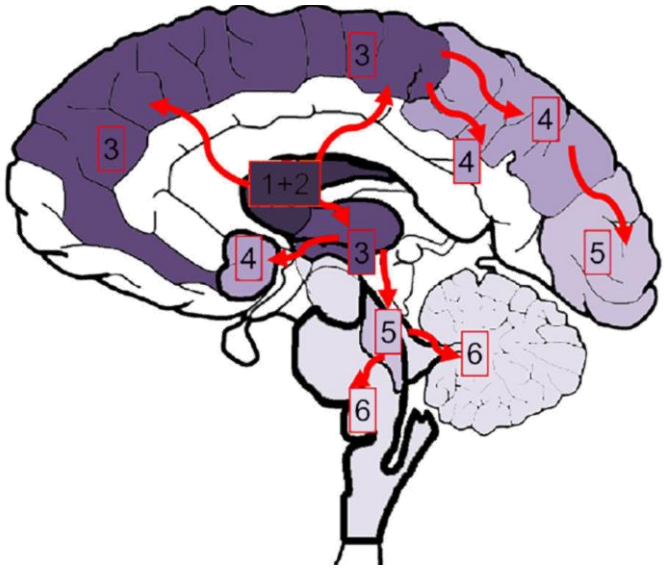
Neuronal



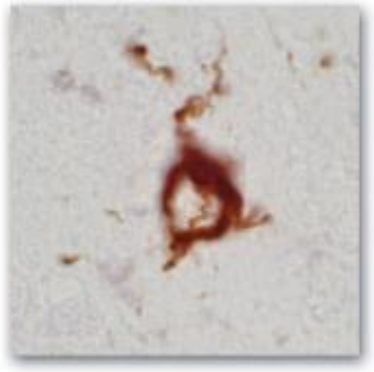


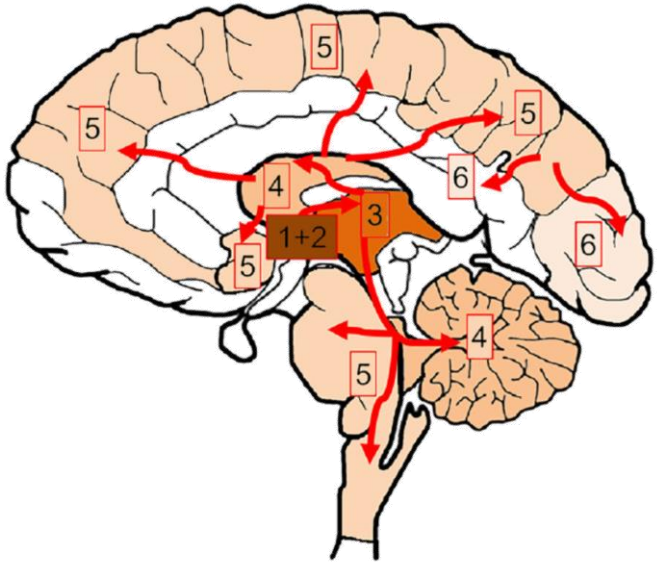
Astroglial





Oligodendroglial





Kovacs, … Höglinger, **Acta Neuropath,** 2020

CLINICAL MANIFESTATION

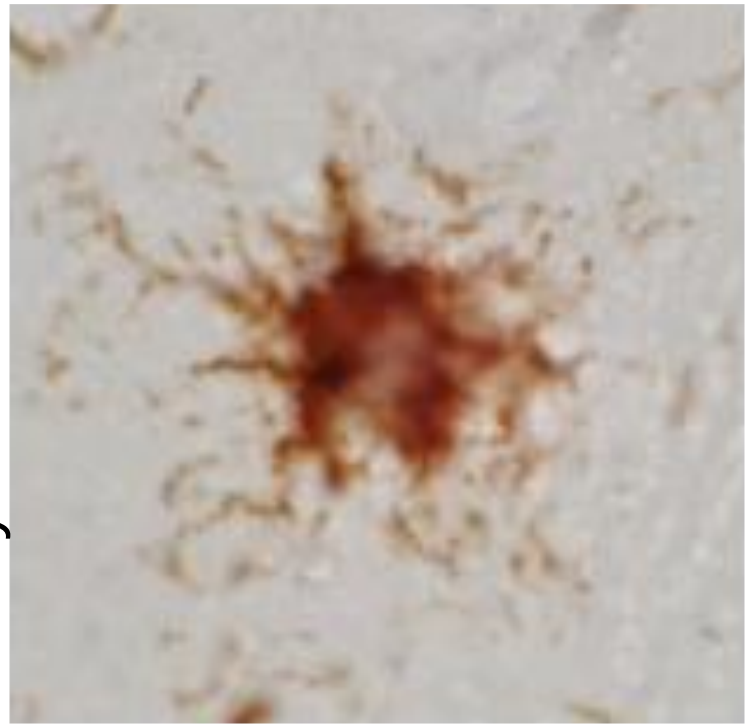
Clinical Manifestation of Definite PSP

LMU KLINIKUM

Definite PSP

(PSP, neuropathological diagnosis)

Astrocytic Tuft



Stamelou, … Höglinger. **Brain.** 2010

Richardson‘s Syndrome

(RS, clinical diagnosis)

Supranuclear gaze palsy

DIAGNOSTIC CRITERIA

LMU KLINIKUM

RESEARCH ARTICLE

Clinical Diagnosis of Progressive Supranuclear Palsy: The Movement Disorder Society Criteria

Movement Disorders, Vol. 00, No. 00, 2017

Günter U. Höglinger, MD,[1,2*] Gesine Respondek, MD,[1,2] Maria Stamelou, MD,[3] Carolin Kurz, MD,[4] Keith A. Josephs, MD, MST, MSc,[5] Anthony E. Lang, MD,[6] Brit Mollenhauer, MD,[7] Ulrich Müller, MD,[8] Christer Nilsson, MD,[9] Jennifer L. Whitwell, PhD,[10] Thomas Arzberger, MD,[2,4,11] Elisabet Englund, MD,[12] Ellen Gelpi, MD,[13] Armin Giese, MD,[11] David J. Irwin, MD,[14] Wassilios G. Meissner, MD, PhD,[15,16,17] Alexander Pantelyat, MD,[18] Alex Rajput, MD,[19] John C. van Swieten, MD,[20] Claire Troakes, PhD, MSc,[21] Angelo Antonini, MD,[22] Kailash P. Bhatia, MD,[23] Yvette Bordelon, MD, PhD,[24] Yaroslau Compta, MD, PhD,[25] Jean-Christophe Corvol, MD, PhD,[26] Carlo Colosimo, MD, FEAN,[27] Dennis W. Dickson, MD,[28] Richard Dodel, MD,[29] Leslie Ferguson, MD,[19] Murray Grossman, MD,[14] Jan Kassubek, MD,[30] Florian Krismer, MD, PhD,[31] Johannes Levin, MD,[2,32] Stefan Lorenzl, MD,[33,34,35] Huw R. Morris, MD,[36] Peter Nestor, MD,[37] Wolfgang H. Oertel, MD,[38] Werner Poewe, MD,[31] Gil Rabinovici, MD,[39] James B. Rowe, MD,[40] Gerard D. Schellenberg, PhD,[41] Klaus Seppi, MD,[31] Thilo van Eimeren, MD,[42] Gregor K. Wenning, MD, PhD,[31] Adam L. Boxer, MD, PhD,[39] Lawrence I. Golbe, MD,[43] and Irene Litvan, MD[44]; for the Movement Disorder Society–endorsed PSP Study Group.

Tau Consortium

DZNE Deutsches Zentrum für Neurodegenerative Erkrankungen in der Helmholtz-Gemeinschaft

DFG

Heisenberg-Programm Deutsche Forschungsgemeinschaft

International Parkinson and Movement Disorder Society

Progressive Supranuclear Palsy PSPA

Deutsche PSP Gesellschaft e.V.

curePSP Society for Progressive Supranuclear Palsy

MDS diagnostic criteria of PSP

Addition of 2 Functional Domains Allows Diagnosis to Encompass Broader Range of PSP Phenotypes

	NINDS-SPSP Criteria,1996		MDS Updates to NINDS-SPSP Criteria, 2017	
Level of certainty[1]	**Ocular motor dysfunction[1,2]**	**Postural instability[1,2]**	**Akinesia[1]**	**Cognitive dysfunction[1]**
Level 1	**O1:** Vertical supranuclear gaze palsy	**P1:** Repeated unprovoked falls within 3 years	**A1:** Progressive gait freezing within 3 years	**C1:** Speech/Language disorder[a]
Level 2	**O2:** Slow velocity of vertical saccades	**P2:** Tendency to fall on the pull-test within 3 years	**A2:** Parkinsonism, akinetic-rigid, predominantly axial, and levodopa resistant	**C2:** Frontal cognitive/behavioral presentation
Level 3	**O3:** Frequent macro square wave jerks or "eyelid opening apraxia"	**P3:** >2 steps backward on the pull-test within 3 years	**A3:** Parkinsonism with tremor and/or asymmetric and/or levodopa responsive	**C3:** Corticobasal syndrome

Diagnostic certainty

MDS, International Parkinson and Movement Disorder Society; NINDS-SPSP, National Institute of Neurological Disorders and Stroke/Society for PSP; PSP, progressive supranuclear palsy.
[a]Can include nonfluent/agrammatic variant of primary progressive aphasia or progressive apraxia of speech.
1. Höglinger et al. *Mov Disord*. 2017;32:853-864. 2. Litvan et al. *Neurology*. 1996;47:1-9. Figure adapted from Höglinger et al. *Mov Disord*. 2017;32:853-864. With permission from the International Parkinson and Movement Disorder Society.

Höglinger GU et al., Mov Disord 2017 Jun;32(6):853-864.

Ocular Motor Dysfunction is a First Core Clinical Feature of PSP

Höglinger GU et al., Mov Disord 2017 Jun;32(6):853-864.
Iankova et al., Parkinsonism related disorders, 2020.

Postural Instability is a Second Core Clinical Feature of PSP

Höglinger GU et al., Mov Disord 2017 Jun;32(6):853-864.
Iankova et al., Parkinsonism related disorders, 2020.

Clinical Clues support the clinical diagnosis

Höglinger GU et al., Mov Disord 2017 Jun;32(6):853-864.
Iankova et al., Parkinsonism related disorders, 2020.

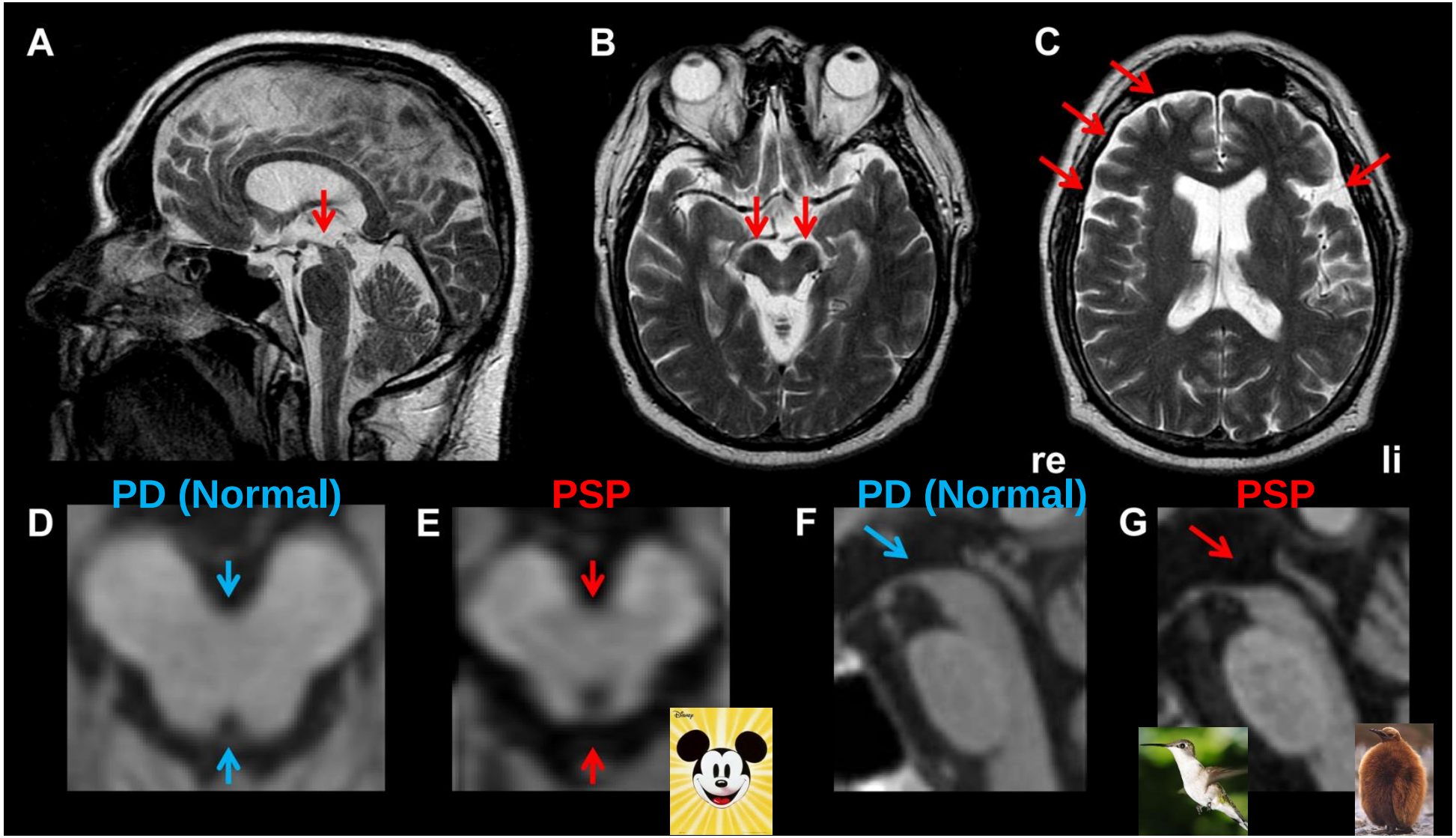
Iankova et al., Parkinsonism related disorders, 2020.

Online tool for diagnosis of PSP:
https://qxmd.com/calculate/calculator_567/

Stamelou, … Höglinger.
Nature Reviews Neurology 2021

SUPPORTIVE DIAGNOSTIC FEATURES

Progressive Supranuclear Palsy (PSP)



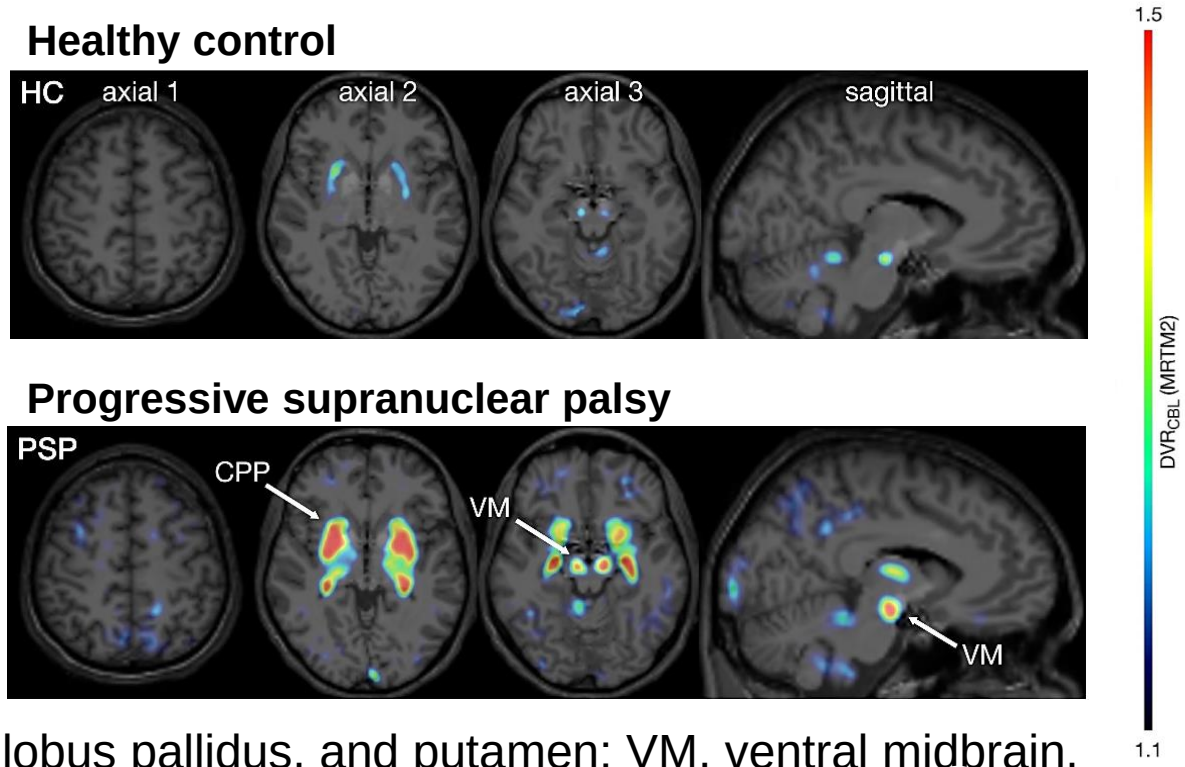
Midbrain Atrophy
a.p. < 15 mm

Mickey-Mouse Sign

Kolibri/Pinguin Sign

Höglinger et al., CBD. In: Oertel/Deuschl/Poewe (Ed.) Parkinsonsyndrome und andere Bewegungsstörungen. Thieme. 2011.

Tau Biomarker: ^{18}F-PI-2620-PET



CPP, caudate nucleus, globus pallidus, and putamen; VM. ventral midbrain.

German Imaging Initiative for Tauopathies GII4T

- Rösler et al., **Prog Neurobiol**, 2019.
- Brendl et al., **JAMA Neurology**, 2020
- Palleis et al., **Mov Disord**., 2021
- Xiang et al., **Science Translat. Med**. 2021
- Franzmeier et al., **Nature Communications**, 2022
- Messerschmidt, et al., **J Nucl Med.** 2022
- Schönecker et al., **Neuroimage Clin.** 2023
- Katzdobler et al., **Eur J Nucl Med Mol Imaging.** 2023
- …

CURRENT THERAPY

REVIEW ARTICLE

Dtsch Arztebl Int. 2016;113:61-9

The Differential Diagnosis and Treatment of Atypical Parkinsonism

Johannes Levin, Alexander Kurz, Thomas Arzberger, Armin Giese, Günter U. Höglinger

PSP

Levodopa (3–4 × 100–200 mg): mild to moderate improvement of akinetic-rigid symptoms in about 35% of cases (evidence level 2–, recommendation grade B)

Amantadine (3 × 100–200 mg): mild to moderate improvement of akinetic-rigid symptoms in about 20% of cases (evidence level 3, recommendation grade 0)

Amitriptyline (1 × 75–150 mg): mild to moderate improvement of oculomotor deficits in about 35% of cases (evidence level 3, recommendation grade 0)

Zolpidem (1 × 5–10 mg): in impaired sleep (evidence level 4, recommendation grade 0); mild improvement of motor/oculomotor deficits in about 20% and 40% of cases (evidence level 1–, recommendation grade 0)

Coenzyme Q10 (2 × daily , ≥ 2.5 µg/mL serum concentration): mild improvement of motor and neuropsychological symptoms (evidence level 1+, recommendation grade A)

Botulinum toxin A: good improvement of focal dystonia in 80% of cases (for example, apraxia of eye opening/blepharospasm in 35 % of patients) (evidence level 3, recommendation grade 0)

FUTURE THERAPIES
⇨ TRIAL DESIGN / READ-OUTS

PSP-Rating Scale (PSPRS)

LMU KLINIKUM

A clinical rating scale for progressive supranuclear palsy

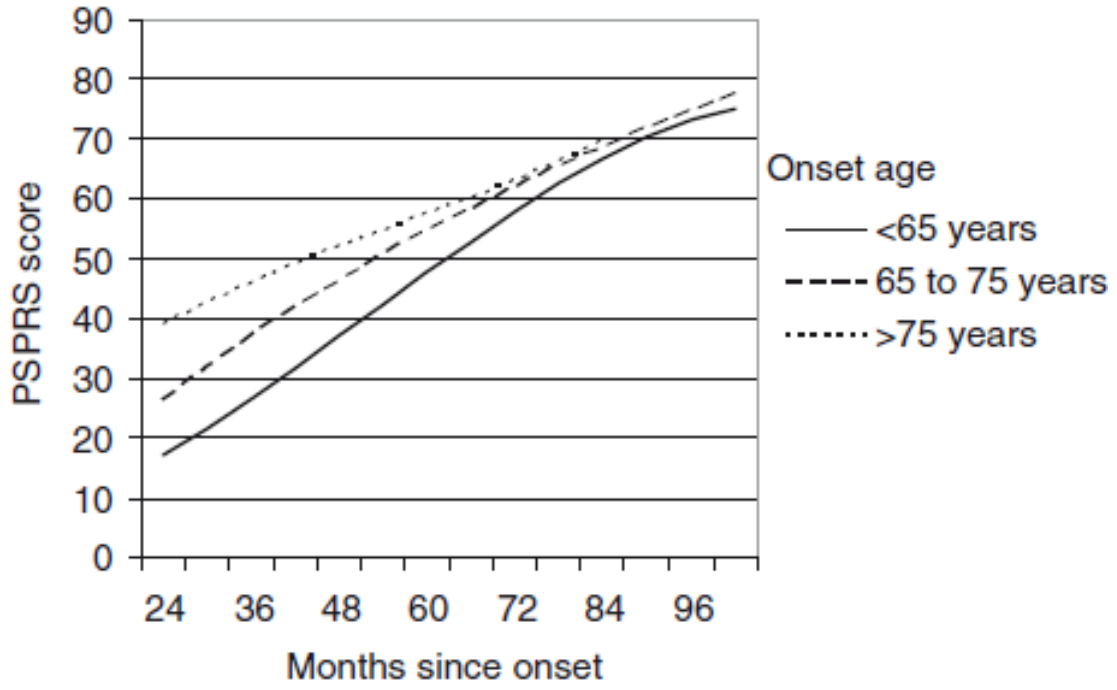
Lawrence I. Golbe[1] and Pamela A. Ohman-Strickland[2]

Brain (2007) Page 1 of 14

A **physician-rated measure** developed to quantify the **presence and progression of symptoms in PSP**.

28 items allocated into **six categories**:
- daily activities (by history),
- mentation,
- bulbar exam,
- ocular motor exam,
- limb motor exam,
- gait/midline exam.

Raters assign **0-2 or 0-4 points** for each item, yielding a **total PSPRS score range of 0 (best) to 100 (worst).**



Reliable linear progression of PSPRS in possible and probable PSP

Reference	Study type	Population	Mean 1 year increase	N
Golbe, L.I., Ohman-Strickland, P.A., 2007. A clinical rating scale for progressive supranuclear palsy. Brain. 130**,** 1552-65.	Natural history	Possible and Probable	11.3	162
Ghosh, B.C., Carpenter, R.H., Rowe, J.B., 2013. A longitudinal study of motor, oculomotor and cognitive function in progressive supranuclear palsy. PLoS One. 8**,** e74486.	Natural history	Possible and Probable	11.3	23
Boxer, A.L., et al., 2014. Davunetide in patients with progressive supranuclear palsy: a randomised, double-blind, placebo-controlled phase 2/3 trial. Lancet Neurol. 13**,** 676-85.	Davunetide	Possible and Probable	11.8 placebo	151
Tolosa, E., et al., 2014. A phase 2 trial of the GSK-3 inhibitor tideglusib in progressive supranuclear palsy. Mov Disord. 29**,** 470-8.	Tideglusib	Possible and Probable	11.4 placebo	31
Apetauerova, D., et al., 2016. CoQ10 in progressive supranuclear palsy: A randomized, placebo-controlled, double-blind trial. Neurology - Neuroimmunology Neuroinflammation. 3.	CoQ10	Probable only	11.8 placebo	16
Leclair-Visonneau, L., et al., 2016. Randomized placebo-controlled trial of sodium valproate in progressive supranuclear palsy. Clin Neurol Neurosurg. 146**,** 35-9.	Valproate	Possible and Probable	13.6 placebo	14
Nuebling, G., et al., 2016. PROSPERA: a randomized, controlled trial evaluating rasagiline in progressive supranuclear palsy. J Neurol. 263**,** 1565-74.	Rasagiline	Possible only	10.8 placebo	22

Solid natural history data for power calculation based on PSPRS in PSP Richardson's syndrome

LMU KLINIKUM

Power Calculations and Placebo Effect for Future Clinical Trials in Progressive Supranuclear Palsy

Maria Stamelou, MD, PhD,[1,2,3]* Jakob Schöpe, MSc,[4] Stefan Wagenpfeil, MSc PhD,[4] Teodoro Del Ser, MD,[5,6] Jee Bang, MD,[7] Iryna Y. Lobach, MD, PhD,[7] Phi Luong, MD,[7] Gesine Respondek, MD,[7] Wolfgang H. Oertel, MD,[1] Adam L. Boxer, MD, PhD,[7] and Günter U. Höglinger, MD,[1,8,9] for the AL-108-231 Investigators, Tauros Investigators, and MDS-Endorsed PSP Study Group

TABLE 2. Sample sizes required for a 2-arm, 1-year follow-up therapeutic trial to detect 20%, 25%, 30%, 40%, and 50% change

		20% change (c = 0.20)		25% change (c = 0.25)		30% change (c = 0.30)		40% change (c = 0.40)		50% change (c = 0.50)	
Rating scales	Difference mean (SD)	Effect Size	Sample Size[a]	Effect Size	Sample Size[a]	Effect Size	Sample Size[a]	Effect Size	Sample Size[a]	Effect Size	Sample Size[a]
SEADL	−0.177 (0.185)	0.191	430 (498)	0.239	276 (320)	0.287	192 (223)	0.383	109 (127)	0.478	70 (82)
CGIDS	0.84 (0.95)	0.178	498 (577)	0.222	319 (370)	0.267	222 (257)	0.356	126 (146)	0.445	81 (94)
PSPRS											
Total score	11.24 (9.95)	0.226	309 (358)	0.282	198 (230)	0.339	138 (160)	0.452	78 (91)	0.565	51 (60)
Bulbar score	1.00 (1.32)	0.152	682 (790)	0.190	437 (506)	0.228	304 (352)	0.304	172 (200)	0.380	110 (128)
Gait score	3.33 (3.29)	0.202	384 (445)	0.253	246 (285)	0.304	172 (200)	0.405	97 (113)	0.506	63 (73)
History score	2.44 (3.30)	0.148	718 (832)	0.185	460 (533)	0.222	320 (371)	0.296	181 (210)	0.370	116 (135)
Limb score	1.42 (2.25)	0.126	990 (1146)	0.158	634 (734)	0.189	441 (511)	0.252	249 (289)	0.315	160 (186)
Mentation score	1.21 (2.88)	0.084	2226 (2577)	0.105	1425 (1650)	0.126	990 (1146)	0.168	558 (646)	0.210	357 (414)
Ocular score	1.83 (2.39)	0.153	671 (777)	0.191	430 (498)	0.230	299 (347)	0.306	169 (196)	0.383	109 (127)
VF	−2.23 (4.56)	0.098	1642 (1901)	0.122	1051 (1217)	0.147	730 (845)	0.196	412 (477)	0.245	264 (306)
FAB	0.56 (2.50)	0.045	7769 (8992)	0.056	4973 (5756)	0.067	3454 (3998)	0.090	1943 (2249)	0.112	1244 (1440)
SAS	1.56 (6.64)	0.047	7095 (8212)	0.059	4541 (5256)	0.071	3154 (3651)	0.094	1775 (2055)	0.118	1136 (1315)
UPDRSII	7.43 (5.94)	0.250	252 (292)	0.313	162 (188)	0.375	113 (131)	0.500	64 (75)	0.626	42 (49)
LVF	2.26 (5.67)	0.080	2460 (2848)	0.100	1575 (1823)	0.120	1094 (1267)	0.160	616 (713)	0.200	395 (458)
CVF	−3.84 (9.05)	0.085	2179 (2522)	0.106	1395 (1615)	0.127	969 (1122)	0.170	546 (632)	0.212	350 (406)
GDS	0.82 (4.89)	0.033	13989 (16191)	0.042	8954 (10364)	0.050	6218 (7197)	0.067	3498 (4049)	0.084	2240 (2593)

Sample sizes are before adjusting for drop-out rate. To adjust for a dropout rate of 26% (eg, the combined dropout rate from both trials), the following formula should be used: sample size/0.74 (eg, 51/0.74 = 69). SD, standard deviation; SEADL, Schwab and England Activities of Daily Living Scale; CGIDS, Clinical Global Impression of Disease Severity; PSPRS, Progressive Supranuclear Palsy Rating Scale; VF, verbal fluency (F, A, or S words per minute); FAB, Frontal Assessment Battery; SAS, Starkstein Apathy Scale; UPDRSII, Unified Parkinson's Disease Rating Scale II; LVF, two letter verbal fluency; CVF, Category Verbal Fluency; GDS, Geriatric Depression Scale.

[a]Per group, based on a significance level of 5% and a power of 80%; approximations of the sample size for the Mann–Whitney *U* test in parentheses.

Longitudinal Magnetic Resonance Imaging in Progressive Supranuclear Palsy: A New Combined Score for Clinical Trials

Movement Disorders, Vol. 00, No. 00, 2017

Günter U. Höglinger, MD,[1,2,3*] Jakob Schöpe, MSc,[4] Maria Stamelou, MD,[3,5] Jan Kassubek, MD,[6] Teodoro del Ser, MD,[7] Adam L. Boxer, MD, PhD,[8] Stefan Wagenpfeil, PhD,[4] and Hans-Jürgen Huppertz, MD,[9] for the AL-108-231 Investigators, the Tauros MRI Investigators, and the Movement Disorder Society-Endorsed PSP Study Group

Power calculation on N=99 longitudinal volumetric MRIs for clinical trials in PSP

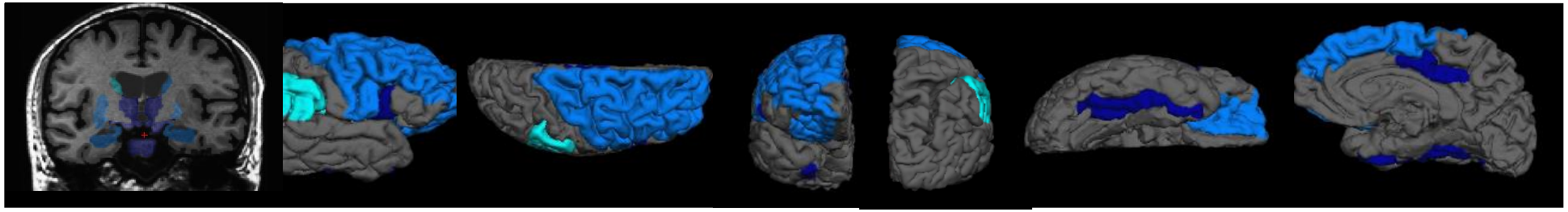


TABLE 3. Correlation between 1-year changes in clinical rating scales and annualized brain volume changes

	SEADL	CGIDS	PSPRS total
Third ventricle	$r = -0.35$ ***/*	$r = 0.25$ */n.s.	$r = 0.24$ */n.s.
Frontal lobe	$r = 0.23$ */n.s.	$r = 0.09$ n.s./n.s.	$r = -0.21$ */n.s.
Midbrain	$r = 0.26$ */n.s.	$r = 0.22$ */n.s.	$r = -0.31$ **/*
Combined: Midbrain + Frontal Lobe − Third Ventricle	$r = 0.42$ ***/*	$r = -0.28$ **/*	$r = -0.34$ **/*

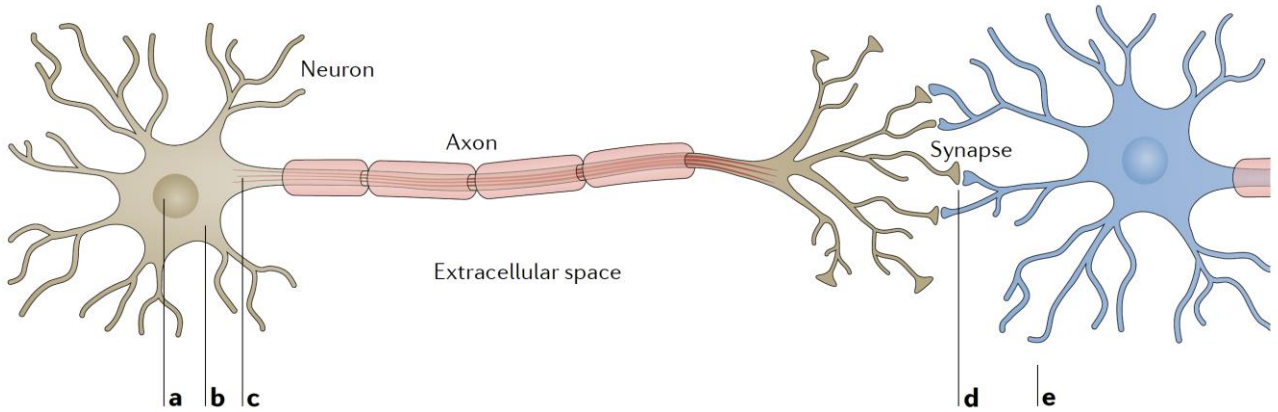
Pearson's *r* was calculated on the basis of 95 cases with complete availability of all clinical and MRI data (in 4 of the total 99 cases, individual clinical data points were missing). *P* values are shown uncorrected/corrected for multiple testing based on Holm's method. SEADL, Schwab and England Activities of Daily Living Scale; CGIDS, Clinical Global Impression of Disease Severity; PSPRS, Progressive Supranuclear Palsy Rating Scale; n.s., nonsignificant.
*$P < .05$, **$P < .01$, ***$P < .001$.

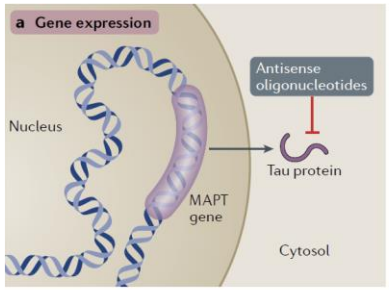
MRI volumetry:
a valid surrogate endpoint

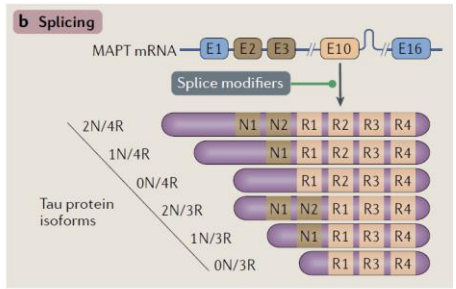
MOLECULAR MECHANISMS
⇨ THERAPIES

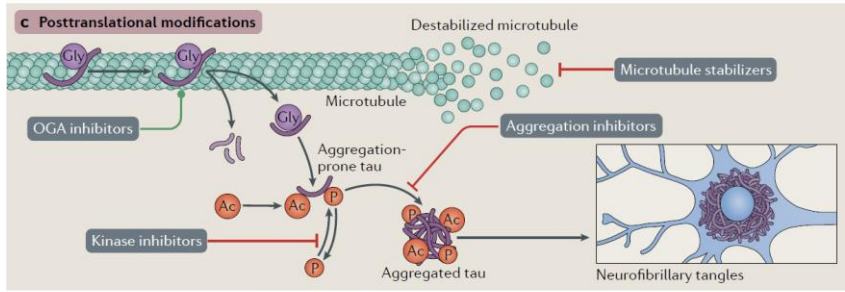
PSP – Therapeutic Pipeline

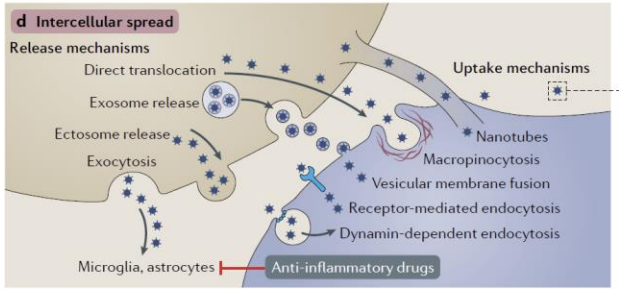
Opportunities for Intervention

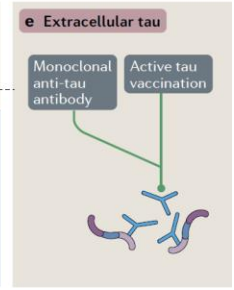






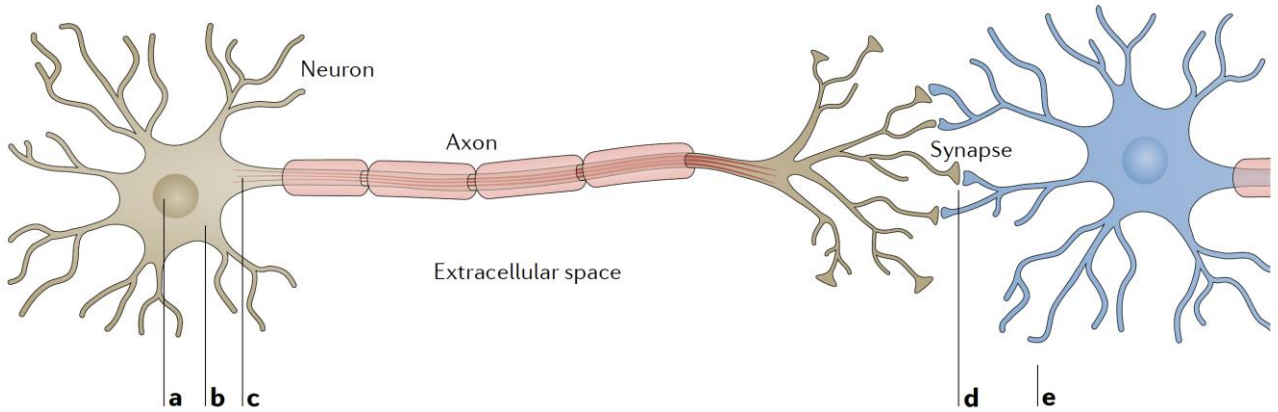


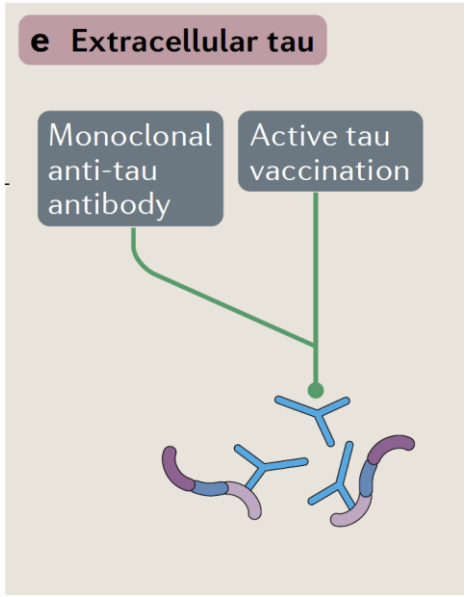




Stamelou, … Höglinger, **Nature Reviews Neurology** 2021

Interventions: Antibodies





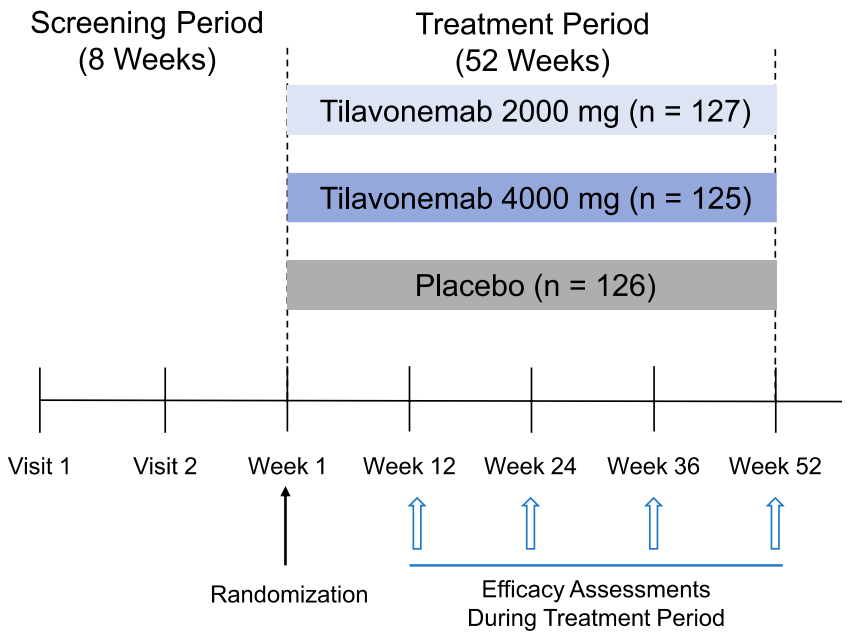
Stamelou, … Höglinger, **Nature Reviews Neurology** 2021

PSP – Therapeutic Pipeline

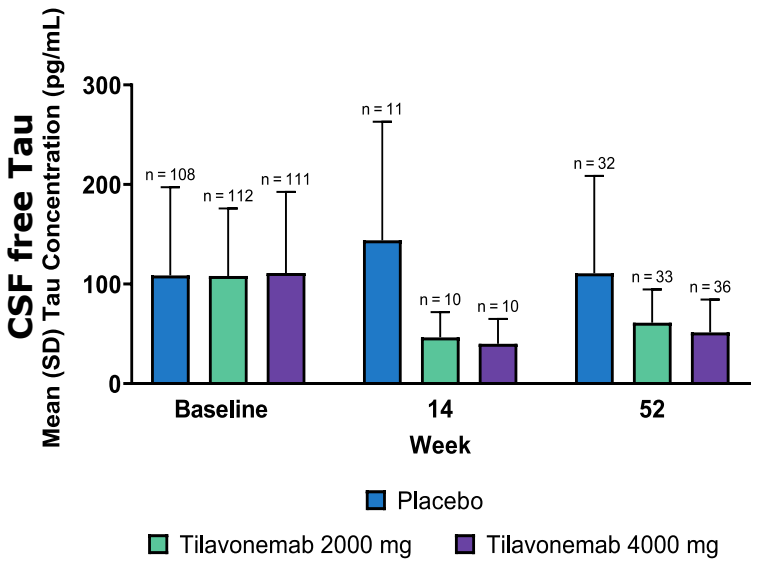
N-terminal Tau Antibodies

Safety and efficacy of the anti-tau monoclonal antibody tilavonemab in PSP: A randomized, placebo-controlled phase 2 study.

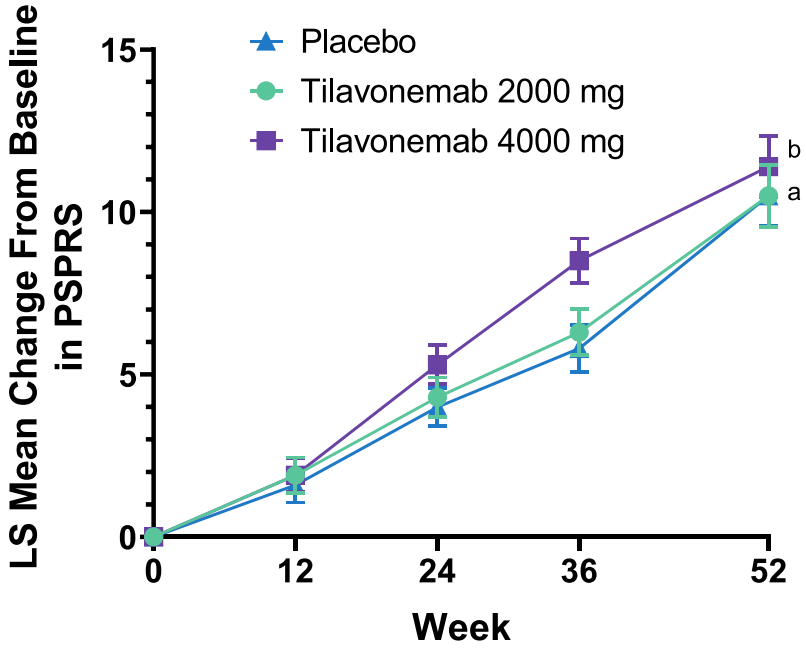
Study Design



Target Engagement



Clinical Efficacy



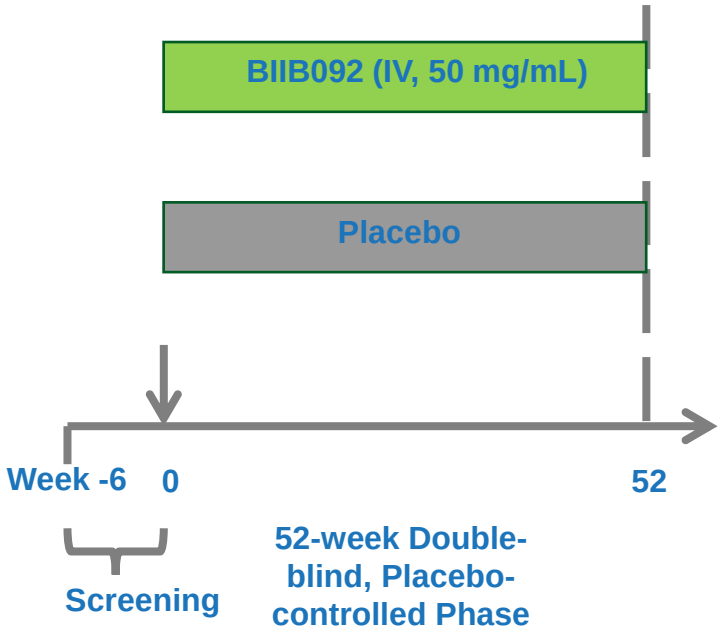
Höglinger et al. **Lancet Neurology** 2021

PSP – Therapeutic Pipeline

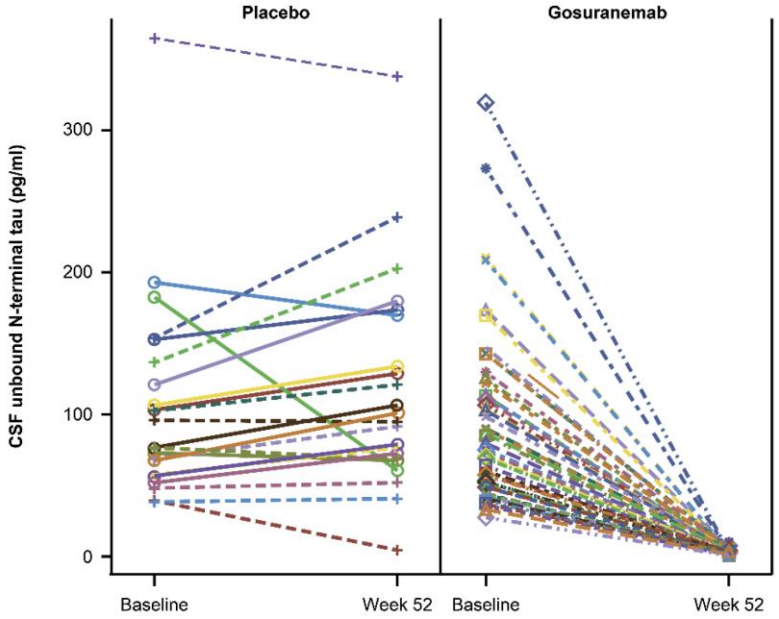
N-terminal Tau Antibodies

Safety and efficacy of the anti-tau monoclonal antibody gosuranemab in PSP: A randomized, placebo-controlled phase 2 study.

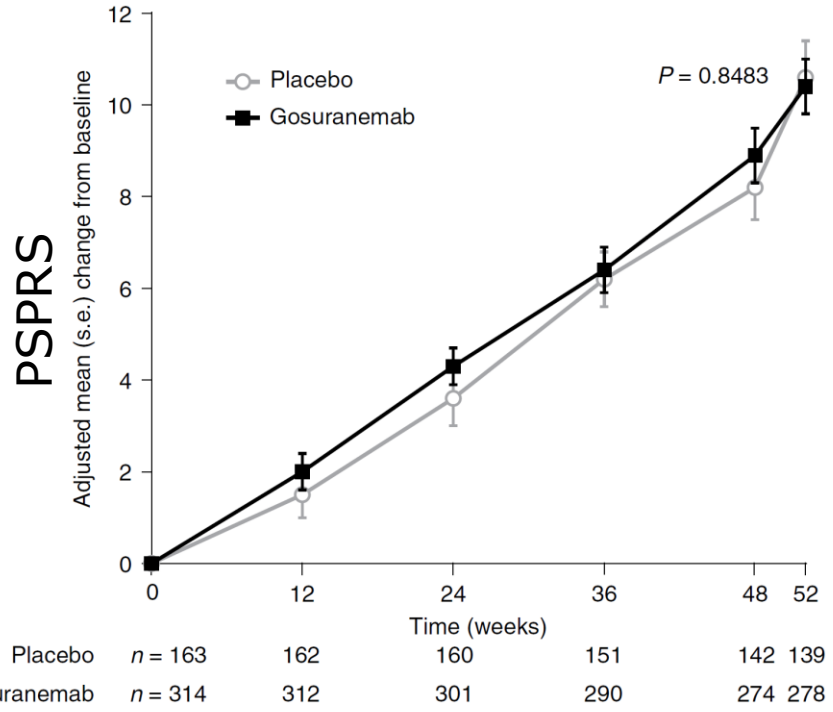
Study Design



Target Engagement



Clinical Efficacy

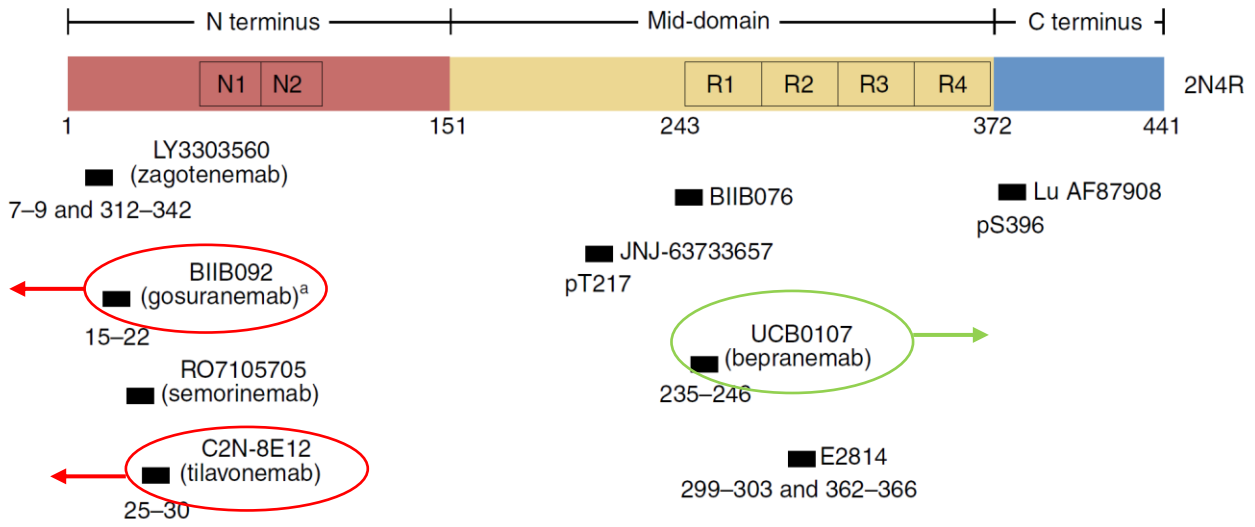


Dam, … Höglinger, …, PASSPORT Study Group, **Nature Medicine** 2021

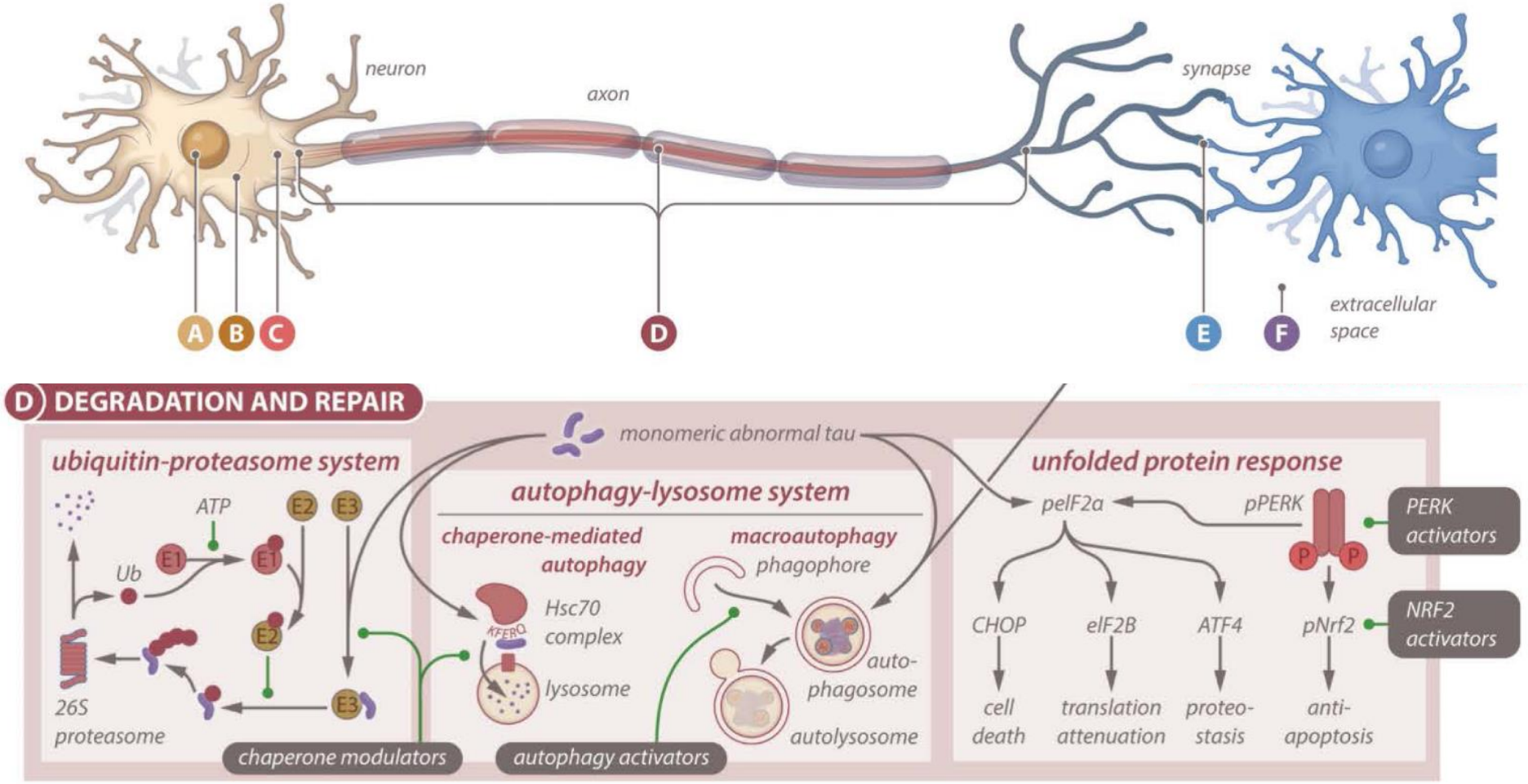
PSP – Therapeutic Pipeline

N-terminal Tau Antibodies

Tau-Antibodies: wrong Epitope?
Jabbari E, Duff KE, **Nature Medicine** 2021



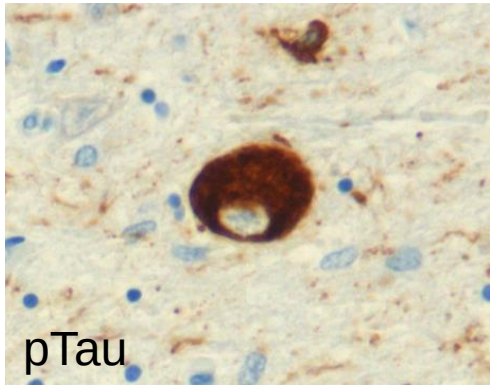
Interventions: Degradation/Unfolded Protein Response

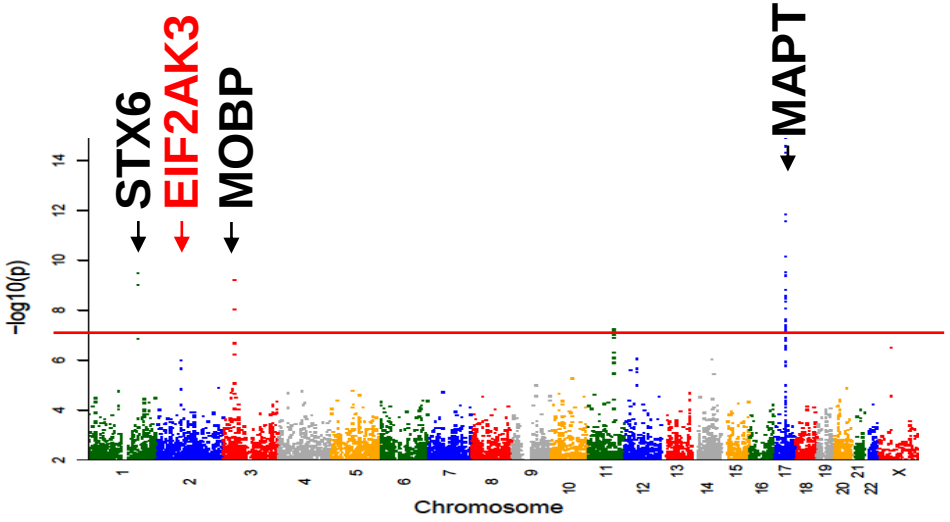


Rösler, … Höglinger, **Progress in Neurobiology** 2019

Interventions: Degradation/Unfolded Protein Response

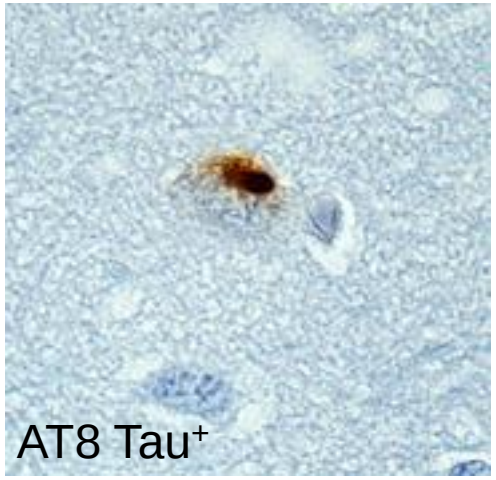
PSP



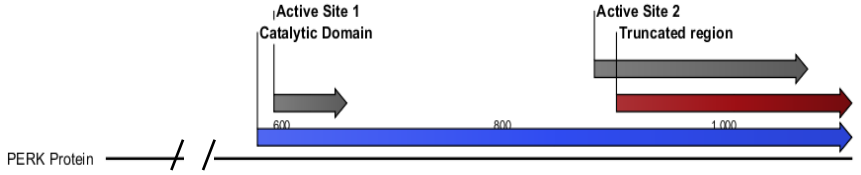


Höglinger, ..., ***Nature Genetics,*** 2011

WRS



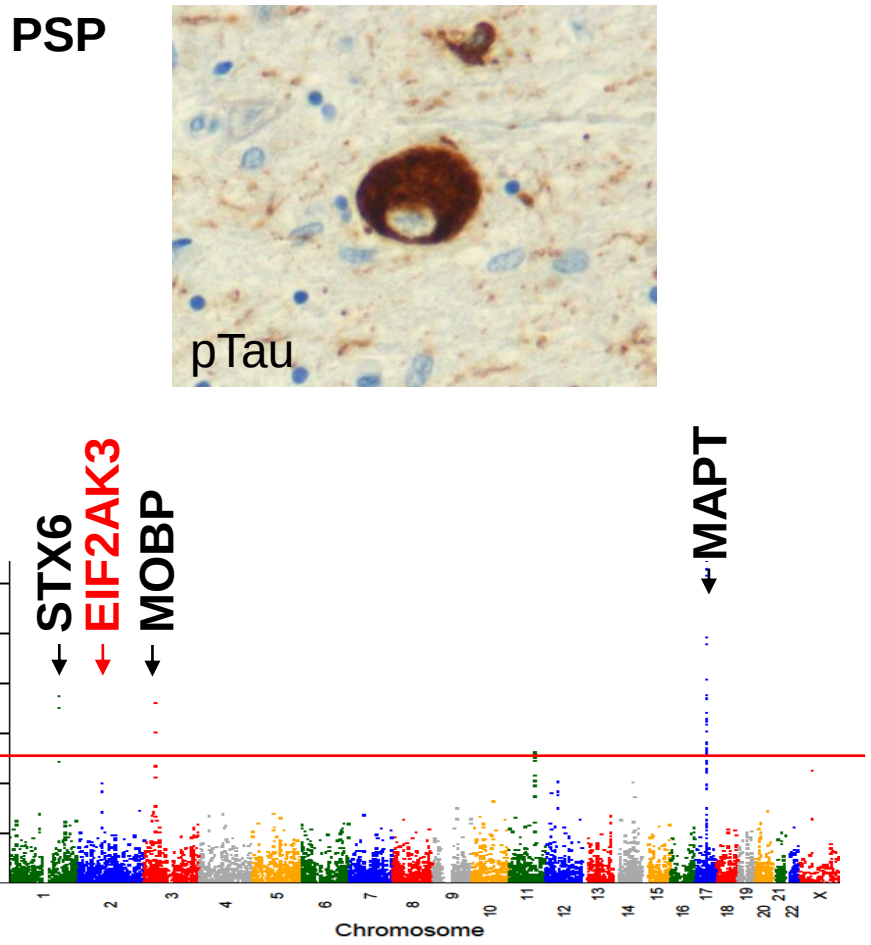
Globose neurofibrilläre Tangles



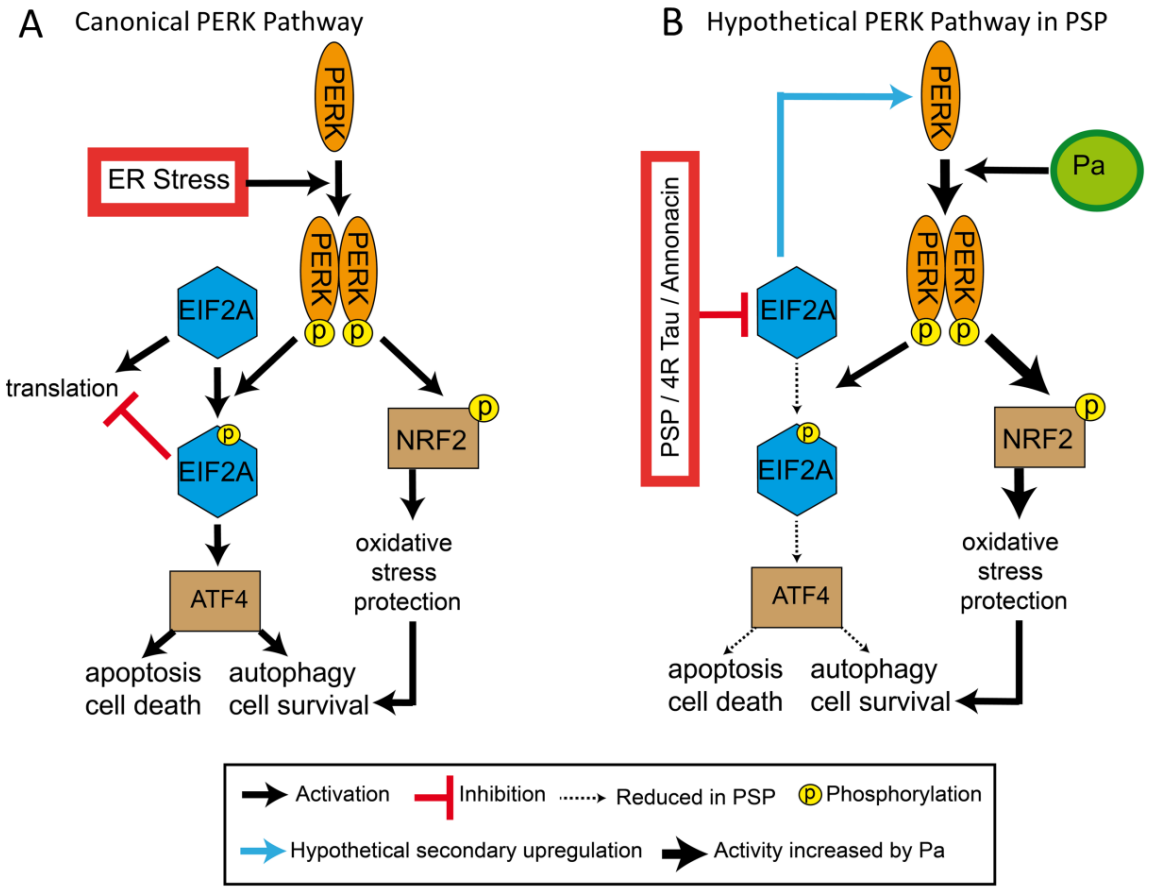
Homozygote EIF2AK3R902stop Mutation

Bruch, … Höglinger, ***JNEN***, 2016

Interventions: Degradation/Unfolded Protein Response



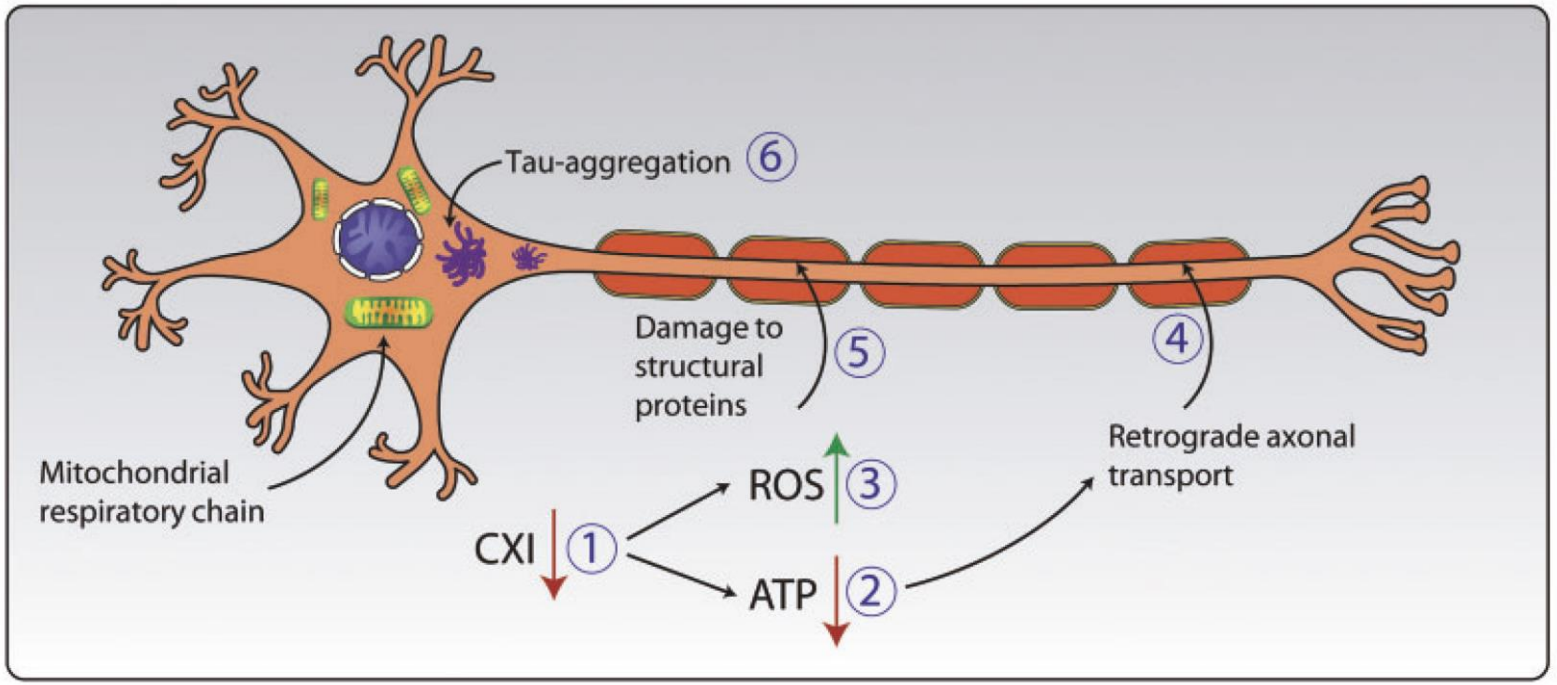
Höglinger, ..., ***Nature Genetics,*** 2011



Bruch, ... Höglinger, ***EMBO Mol. Med.,*** 2017

PSP – Therapeutic Pipeline

Mitochondria



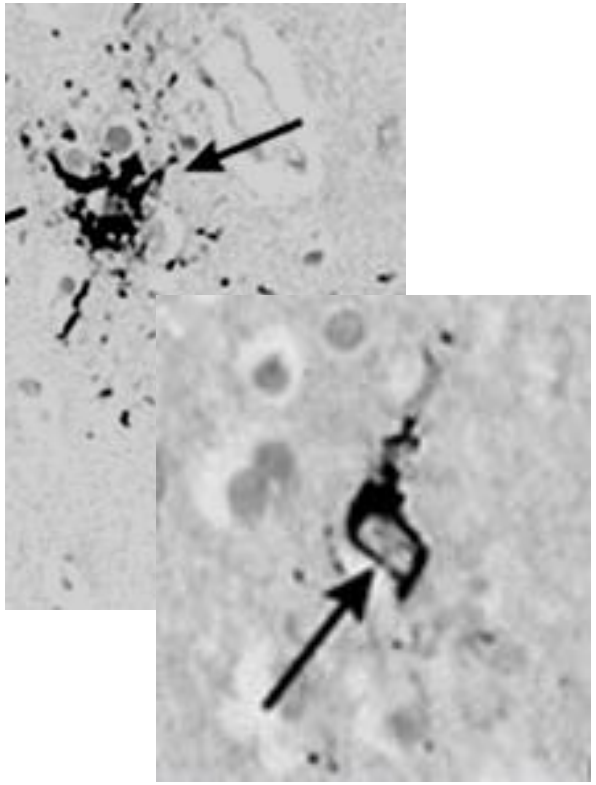
Stamelou, … Höglinger. **Brain** 2010

doi:10.1093/brain/awl347

LMU KLINIKUM

Atypical parkinsonism in Guadeloupe: a common risk factor for two closely related phenotypes?

Annie Lannuzel,[1,3] G. U. Höglinger,[5] S. Verhaeghe,[1] L. Gire,[2] S. Belson,[1] M. Escobar-Khondiker,[3] P. Poullain,[2] W. H. Oertel,[5] E. C. Hirsch,[3] B. Dubois[4] and M. Ruberg[3]

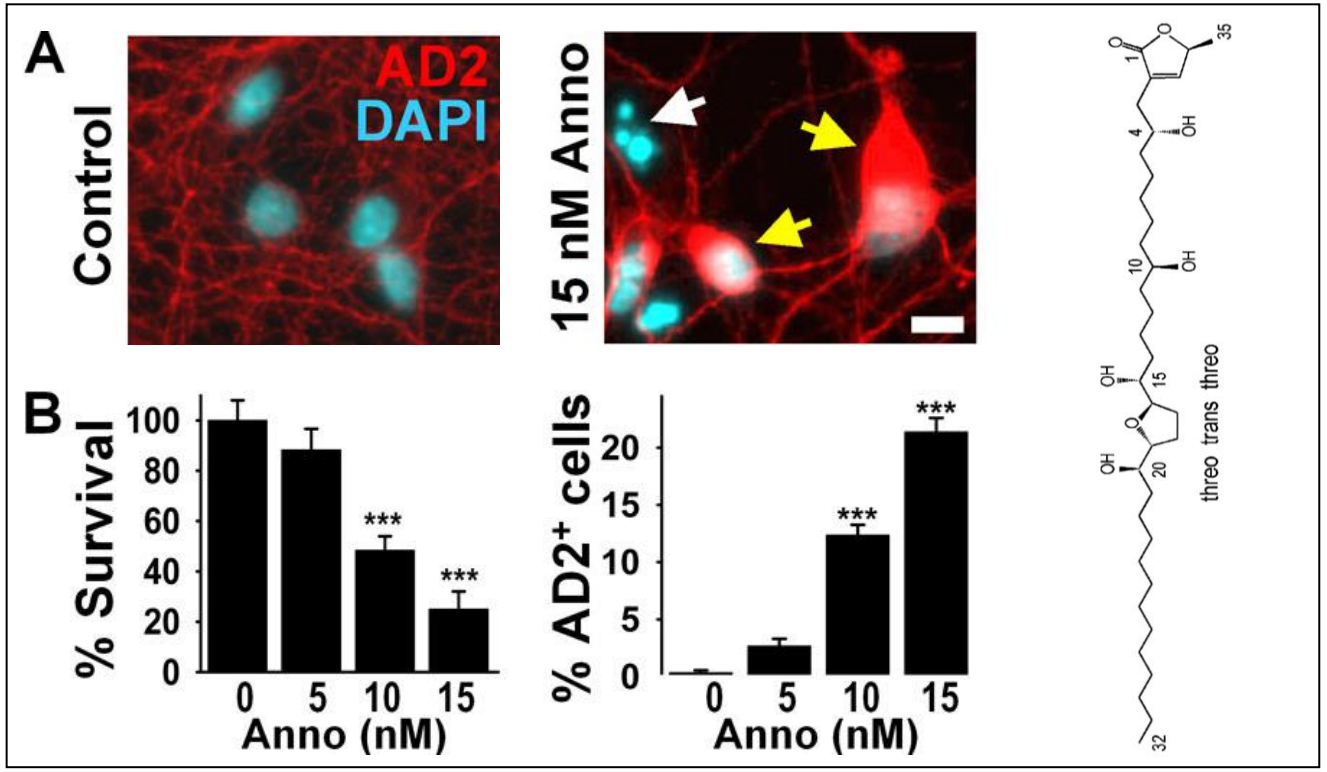


Patient group	PD	Gd-PSP
N	14	16
Fruits / year	3	23

The Journal of Neuroscience, July 18, 2007 • 27(29):7827–7837 • 7827

Annonacin, a Natural Mitochondrial Complex I Inhibitor, Causes Tau Pathology in Cultured Neurons

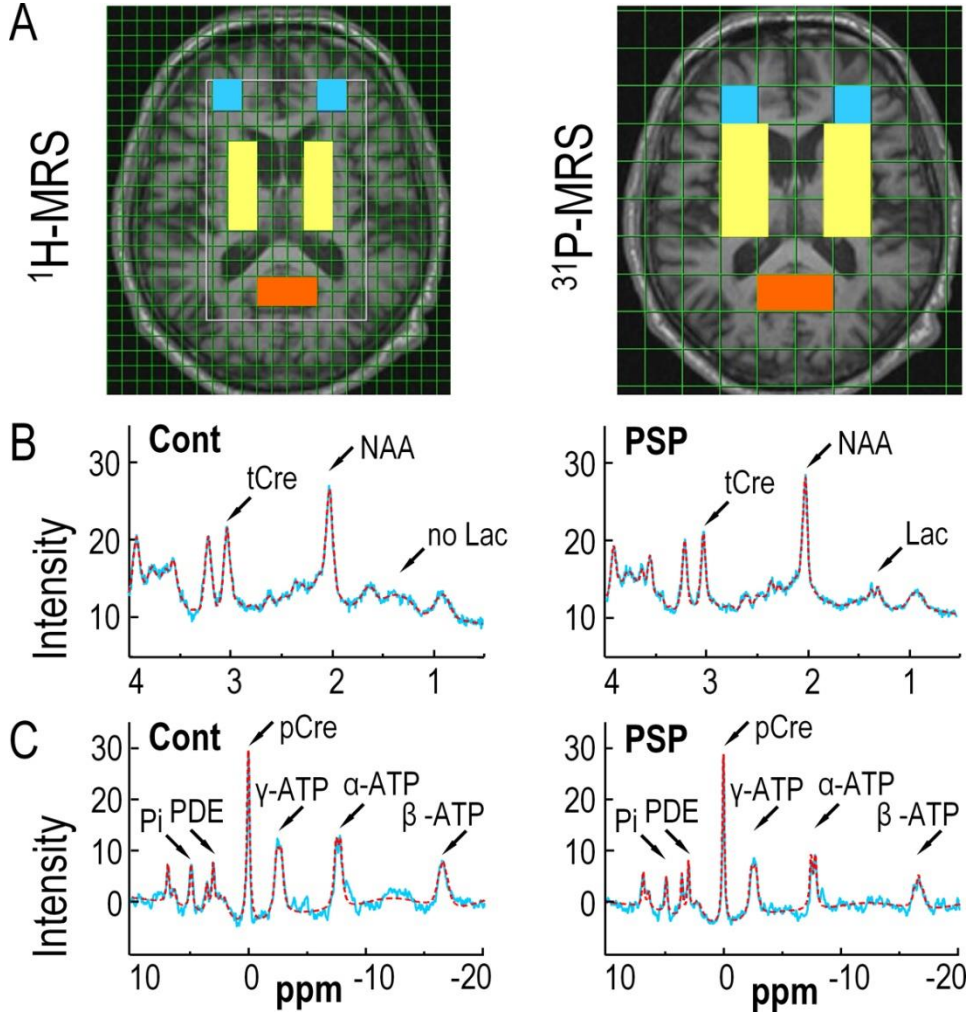
Myriam Escobar-Khondiker,[1,2,3] Matthias Höllerhage,[1] Marie-Paule Muriel,[2,3] Pierre Champy,[4] Antoine Bach,[2,3] Christel Depienne,[2,3] Gesine Respondek,[1] Elizabeth S. Yamada,[1] Annie Lannuzel,[2,3,6] Takao Yagi,[5] Etienne C. Hirsch,[2,3] Wolfgang H. Oertel,[1] Ralf Jacob,[7] Patrick P. Michel,[2,3] Merle Ruberg,[2,3] and Günter U. Höglinger[1]

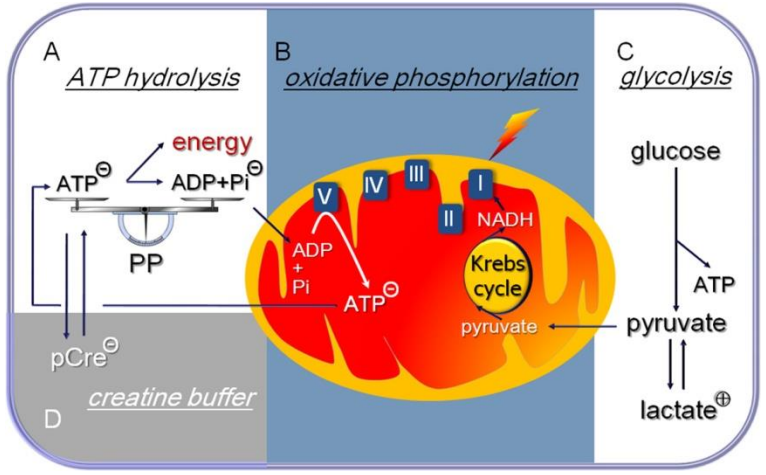


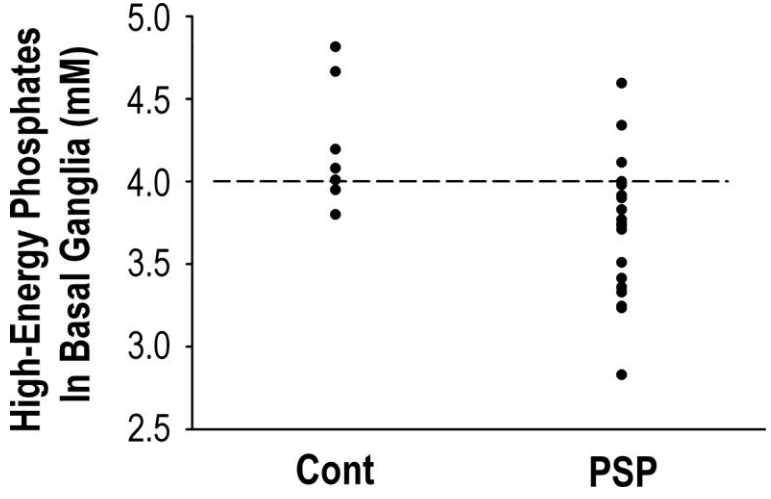
In vivo evidence for cerebral depletion in high-energy phosphates in progressive supranuclear palsy

Journal of Cerebral Blood Flow & Metabolism (2009), 1–10

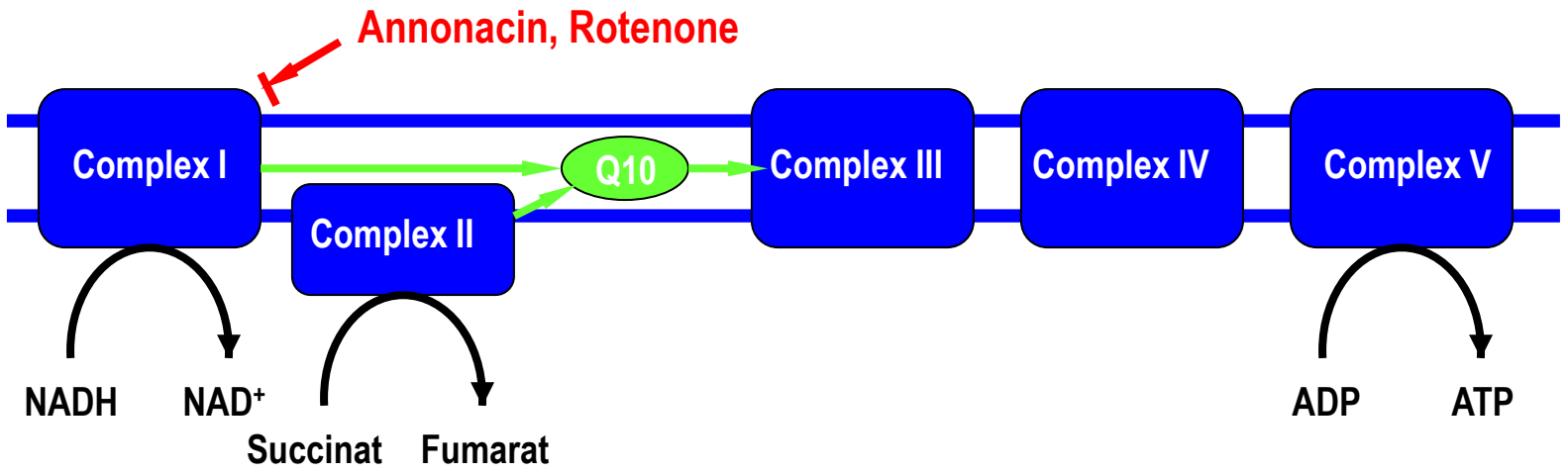
Maria Stamelou[1,5], Ulrich Pilatus[2,5], Alexander Reuss[3], Jörg Magerkurth[2], Karla M Eggert[1], Susanne Knake[1], Merle Ruberg[4], Carmen Schade-Brittinger[3], Wolfgang H Oertel[1] and Günter U Höglinger[1]







A rationale for a causal therapy?



A decreased complex I activity results in reduced ATP production and increased free radical generation.

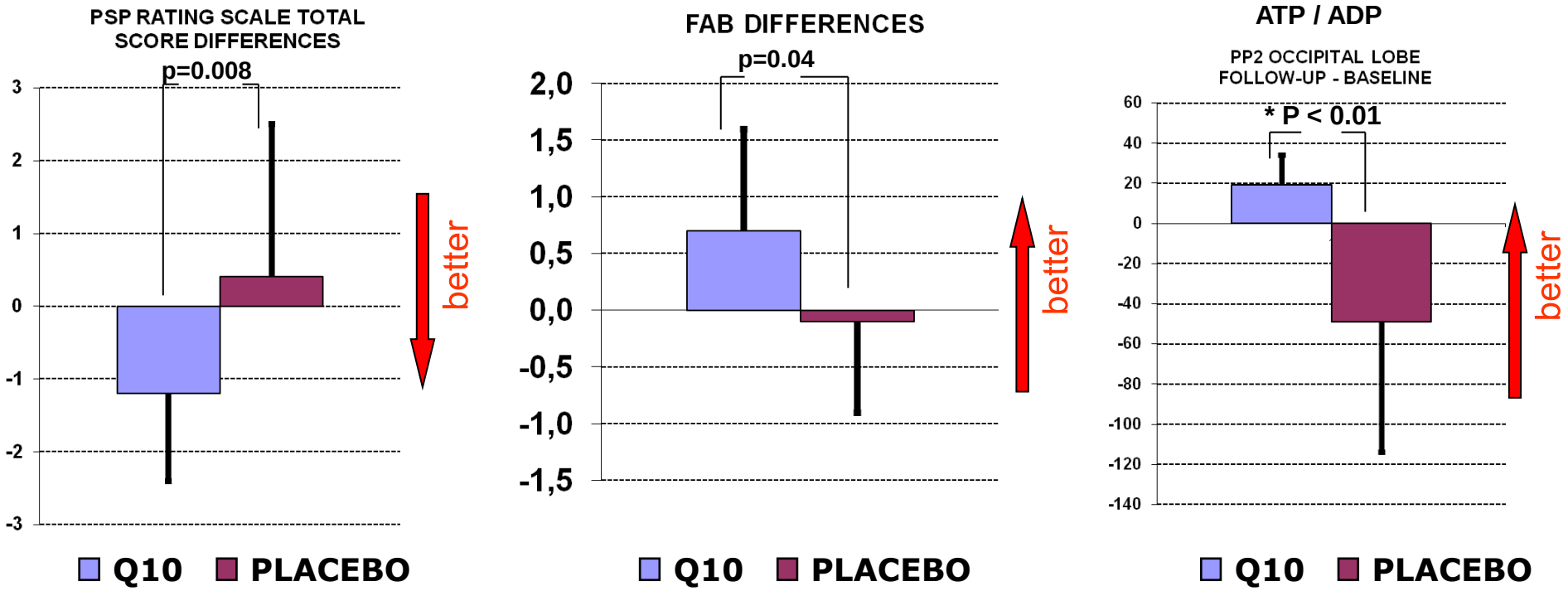
- **CoQ10** is the physiological electron recipient of complex I.
- **CoQ10** enhances the electron transport by complex I.
- **CoQ10** powerfully scavenges free radicals.
- **CoQ10** reduces the toxicity of MPTP and Rotenone.

(Schulz et al., 1995; Menke et al. 2003)

Short-Term Effects of Coenzyme Q_{10} in Progressive Supranuclear Palsy: A Randomized, Placebo-Controlled Trial

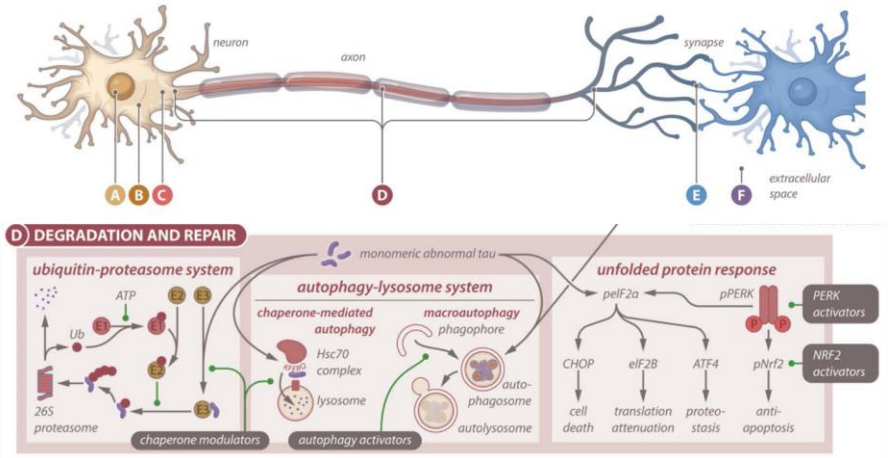
Movement Disorders
Vol. 23, No. 7, 2008, pp. 942–949

Maria Stamelou, MD,[1] Alexander Reuss, MSc,[2] Ulrich Pilatus, PhD,[3] Jörg Magerkurth, MSc,[3] Petra Niklowitz, PhD,[4] Karla M. Eggert, MD,[1] Andrea Krisp, PhD,[1] Thomas Menke, MD,[4] Carmen Schade-Brittinger, MSc,[2] Wolfgang H. Oertel, MD,[1] and Günter U. Höglinger, MD[1]*



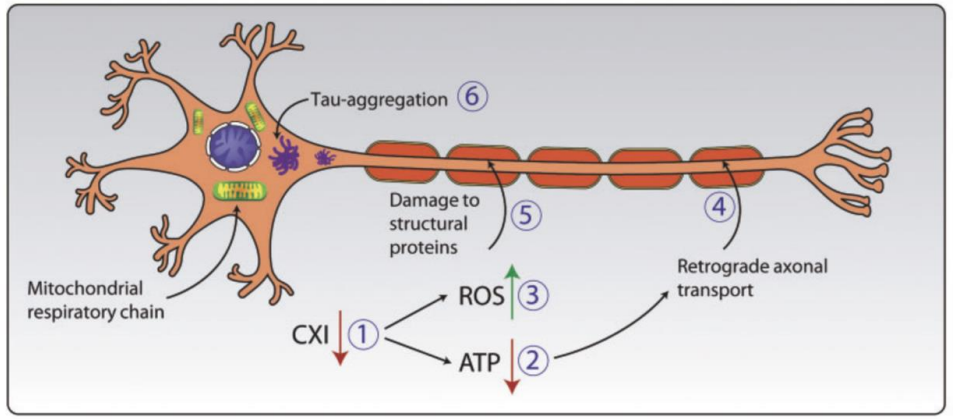
Interventions: Multiple Pathways

Degradation/Unfolded Protein Response



+

Mitochondria



AMX0035 targets multiple pathways upstream of tau aggregation

Stamelou, … Höglinger, **Nature Reviews Neurology** 2021

Stamelou, … Höglinger. **Brain** 2010

PSP - an ideal disease to study

Tau-targeting, disease-modifying therapies

- Primary Tauopathy (no A-Syn, no A-beta)
- Frequent enough (10/100.000)
- Specific diagnostic criteria (MDS-PSP)
- Validated scales ((m)PSPRS, SEADL, CGI, PSP-QoL)
- Natural history (Power calculation)
- Surrogate markers on MRI (volumetry)
- No gold-standard therapy (Placebo-comparator)

LMU KLINIKUM
Gemeinsam. Fürsorglich. Wegweisend.

We are not there yet, but we will be!

Many thanks for your attention!

Contact:

Univ.-Prof. Dr. med. Günter Höglinger, FEAN
Neurologische Klinik und Poliklinik mit Friedrich-Baur-Institut
Klinikum der Universität München

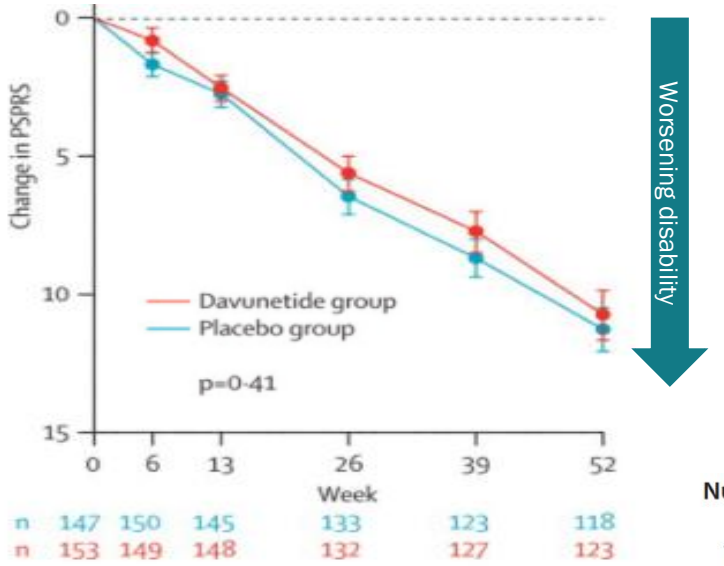
E-Mail: Guenter.Hoeglinger@med.uni-muenchen.de

ORION Phase 3 PSP Trial Design

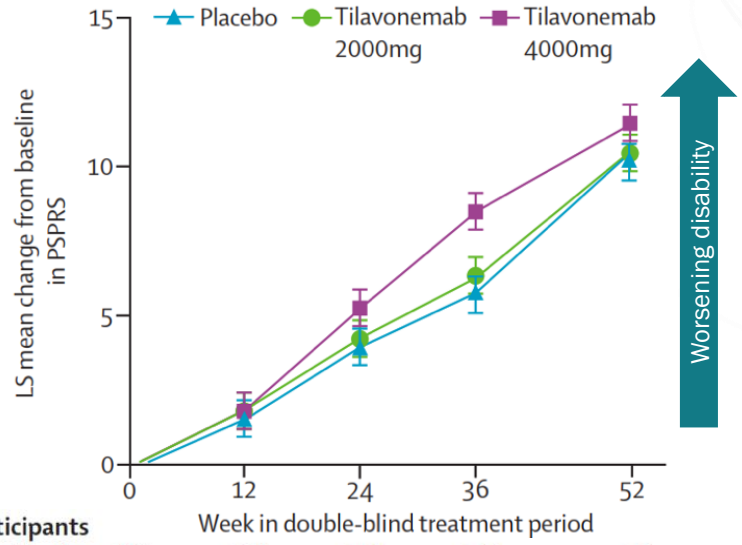
Dr. Lahar Mehta

Head, Global Clinical Development, Amylyx

Completed PSP Clinical Studies Exhibit Consistent and Measurable Progression on Validated Endpoint

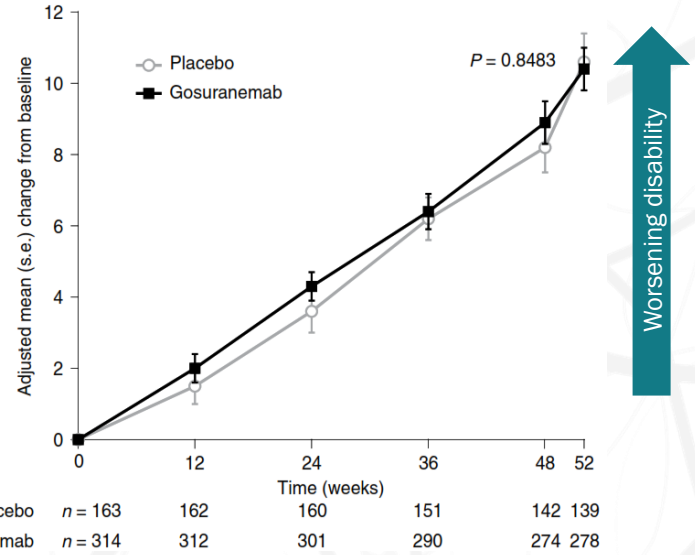


Boxer et al 2014.



Number of participants					
Placebo	126	120	116	102	59
Tilavonemab 2000 mg	126	119	116	105	56
Tilavonemab 4000 mg	125	123	118	109	59

Höglinger et al 2021.



Placebo	*n* = 163	162	160	151	142	139
Gosuranemab	*n* = 314	312	301	290	274	278

Dam et al 2021.

Three large, global clinical trials conducted to date show consistent progression of ~10 points/year on Progressive Supranuclear Palsy Rating Scale (PSPRS) with relative low noise

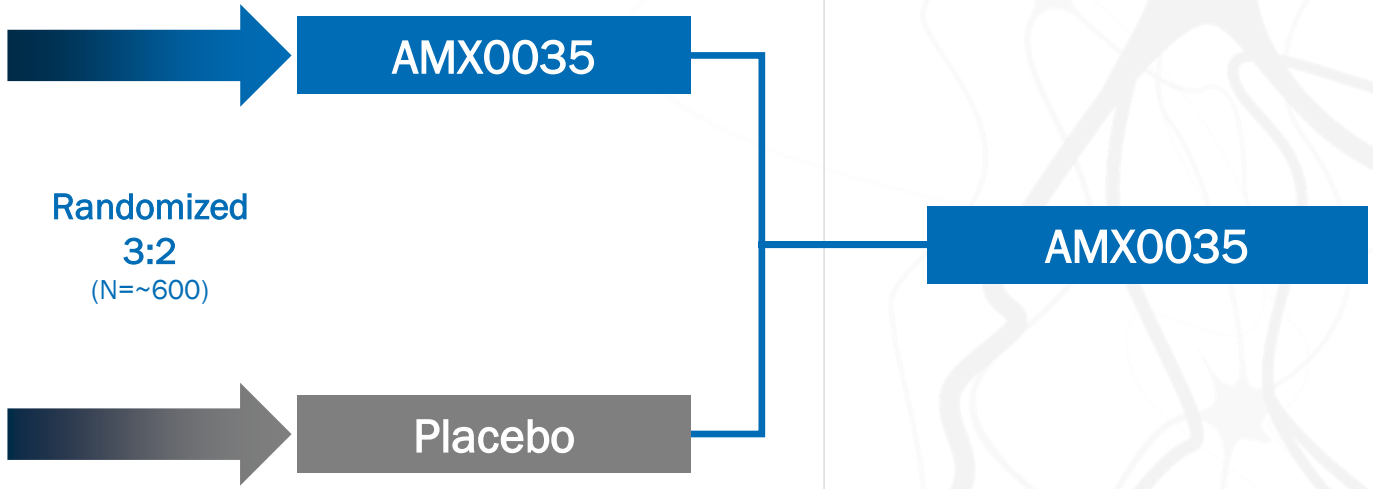
ORION: Phase 3 Clinical Trial of AMX0035 in PSP

Key Eligibility Criteria

- Adults 40-80 years old
- Possible or Probable PSP (Steele-Richardson-Olszewski Syndrome) according to MDS 2017 criteria [1,2]
- Presence of PSP symptoms < 5 years
- Able to walk independently or with minimal assistance[3]
- PSPRS total score < 40
- MMSE score ≥ 24
- Study partner required
- No feeding tube use

ORION

Primary Objective: To assess the impact of AMX0035 compared to placebo on disease progression rate as measured by PSPRS



Screening	Double-Blind Treatment	Open Label Extension
≤ 6 weeks	52 weeks	52 weeks

MDS, Movement Disorders Society; MMSE, mini-mental status exam; PSPRS, Progressive Supranuclear Palsy Rating Scale

1. Gradually progressive disorder, with age at disease onset ≥ 40 years 2. Either or both of the following two items are met: i. Vertical supranuclear gaze palsy OR slow velocity of vertical saccades AND postural instability with repeated unprovoked falls within 3 years OR tendency to fall on the pull-test within 3 years ii. Slow velocity of vertical saccades AND postural instability with more than two steps backward on the pull-test within 3 years. 1,2. Höglinger et al. Movement Disorders 2017. **3.** Ability to walk 5 steps with minimal assistance (stabilization of one arm).

ORION Clinical Trial Endpoints

Primary Endpoint	**Disease Progression** • Total PSPRS[1] score (28-item)	
Secondary Endpoints	**Disease Progression** • Modified 10-item PSPRS[1] score	**Motor Aspects of Activities of Daily Living** • MDS-UPDRS[2] Part II score
Additional Endpoints	**Brain Atrophy** • Brain volume (MRI)[3] **Burden and Quality of Life** • Participant QoL[4] and caregiver burden	**Biomarkers** • CSF[5] and plasma biomarkers of neuronal injury and neuro-inflammation **Overall Survival**

Plan to initiate trial by year-end 2023

Plan to enroll sites in U.S., Canada, Europe, and Japan

1. PSPRS, Progressive Supranuclear Palsy Rating Scale **2.** MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale **3.** MRI, magnetic resonance imaging **4.** QoL, quality of life
5. CSF, cerebrospinal fluid

PSP Meets Rigorous Criteria for Our Next Potential Indication for AMX0035

- ☑ Clear unmet need
- ☑ Strong scientific rationale
- ☑ Biomarker evidence
- ☑ Adjacencies and synergies with ALS
- ☑ Existing and robust understanding of the natural history of the disease
- ☑ Interest and support from KOLs and advocacy groups

AMYLYX

Q&A Session