Molecular Pathogenesis of Parkinson's Disease and Therapeutic Strategies

M. Maral Mouradian, M.D.

William Dow Lovett Professor of Neurology
Vice Chancellor for Faculty Development
Director, RWJMS Institute for Neurological Therapeutics
Chief, Division of Translational Neuroscience
Robert Wood Johnson Medical School
Rutgers Biomedical and Health Sciences

Institute for Health, Health Care Policy and Aging Research, RBHS
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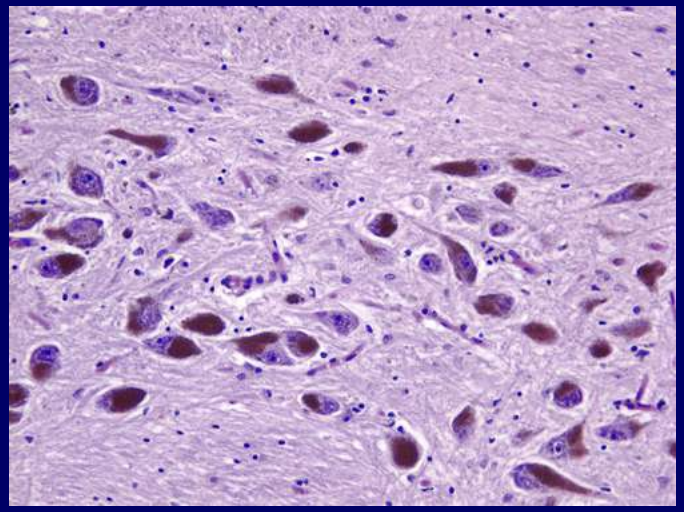
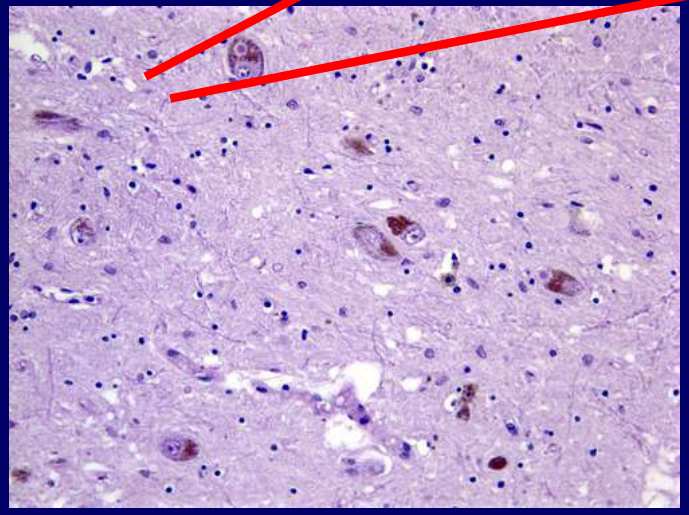
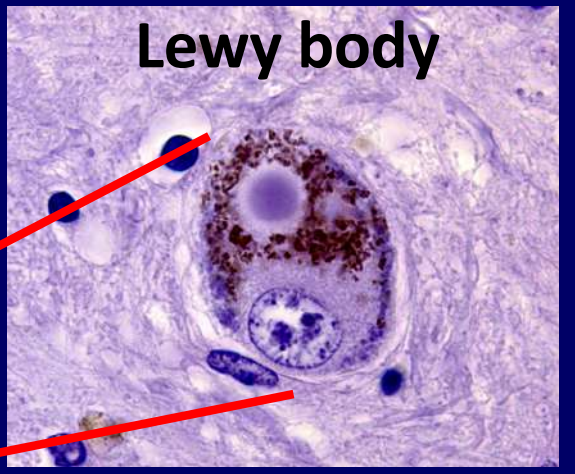
Pathology of Parkinson's Disease

Control

Parkinson





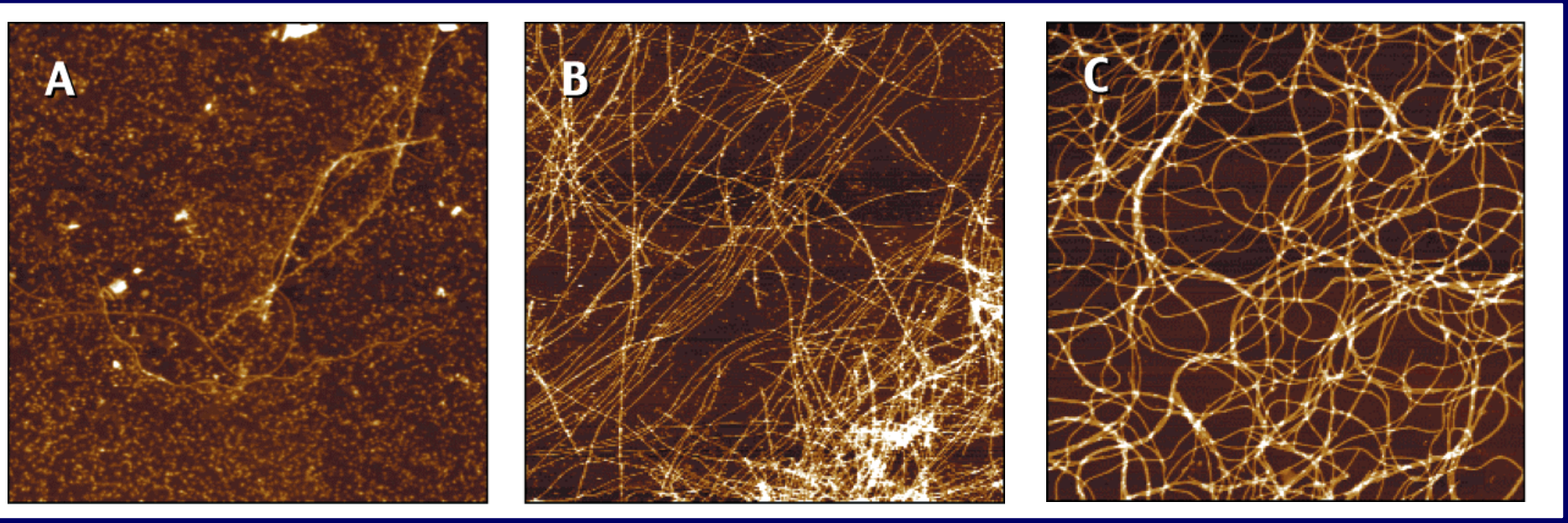


In Vitro Fibrillization of α-Synuclein

WT 300 μM
4 months

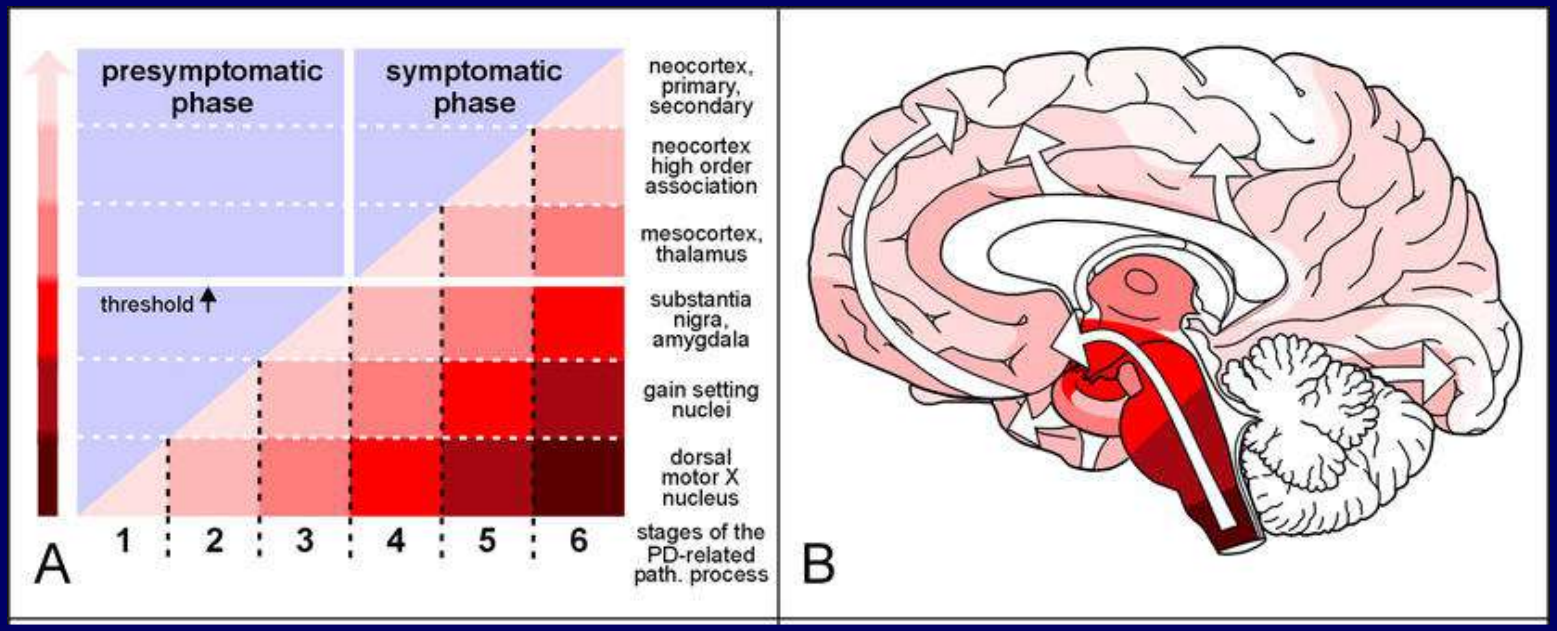
A53T 100 μM
1 month

A30P 300 μM
4 months



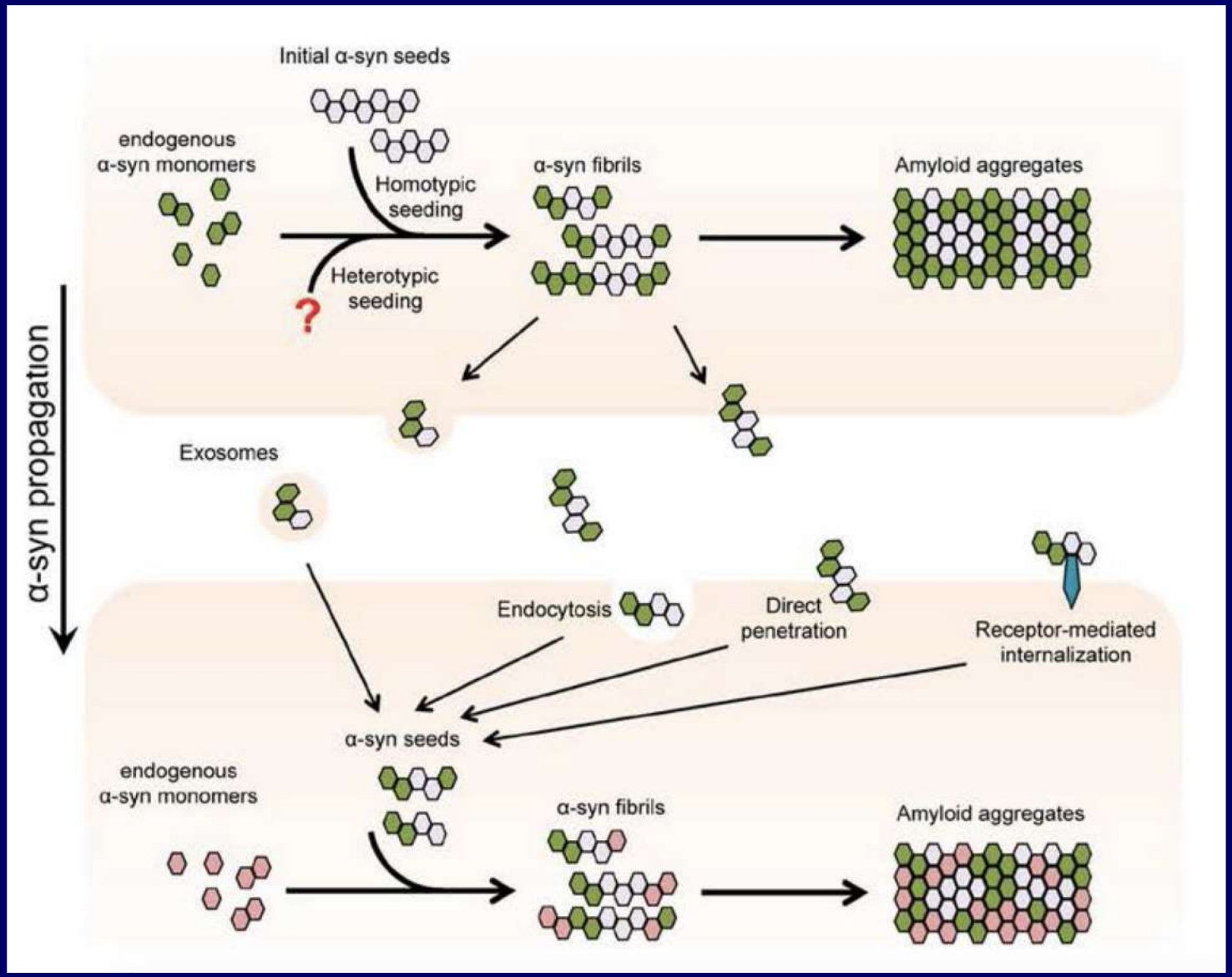
Conway, Biochemistry 39:2552, 2000

Staging PD: Pre-Symptomatic and Symptomatic Phases



Braak et al, Cell Tissue Res. 318:121, 2004

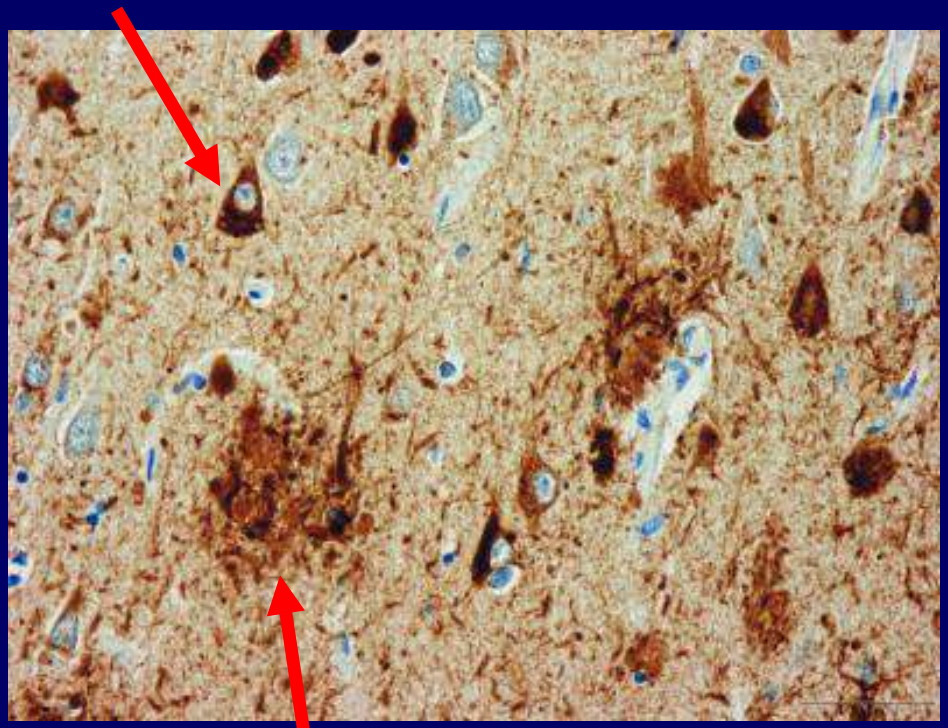
α-Synuclein Seeding and Propagation



Oueslati et al, Exp. Neurobiol. 2014

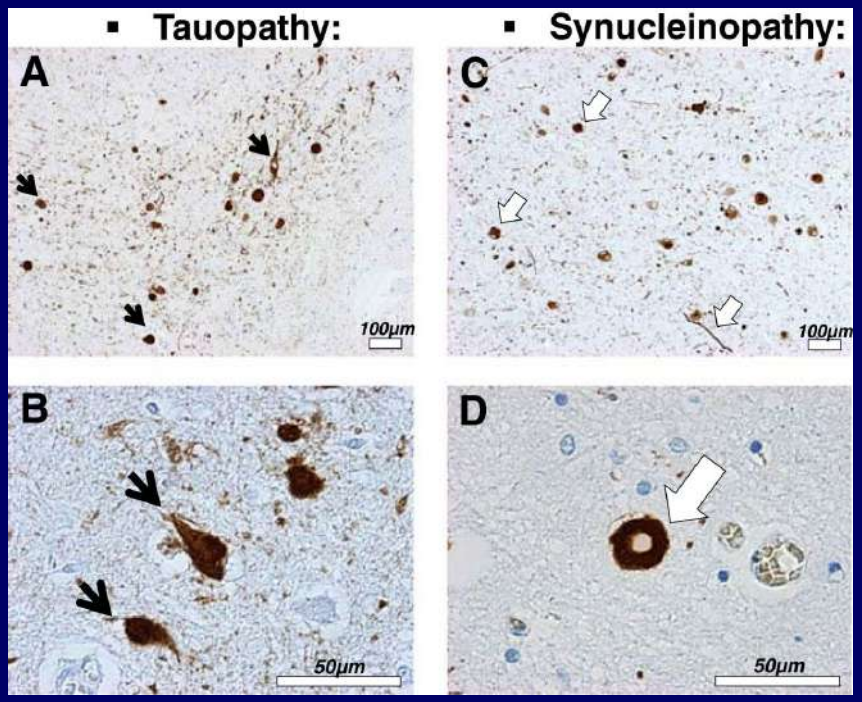
Commonalities of Misfolded Proteins and Hyper-phosphorylated Aggregates in Synucleinopathies and Taupathies

Tau
Neurofibrillary tangles



Amyloid
plaque

p-tau p-α-synuclein



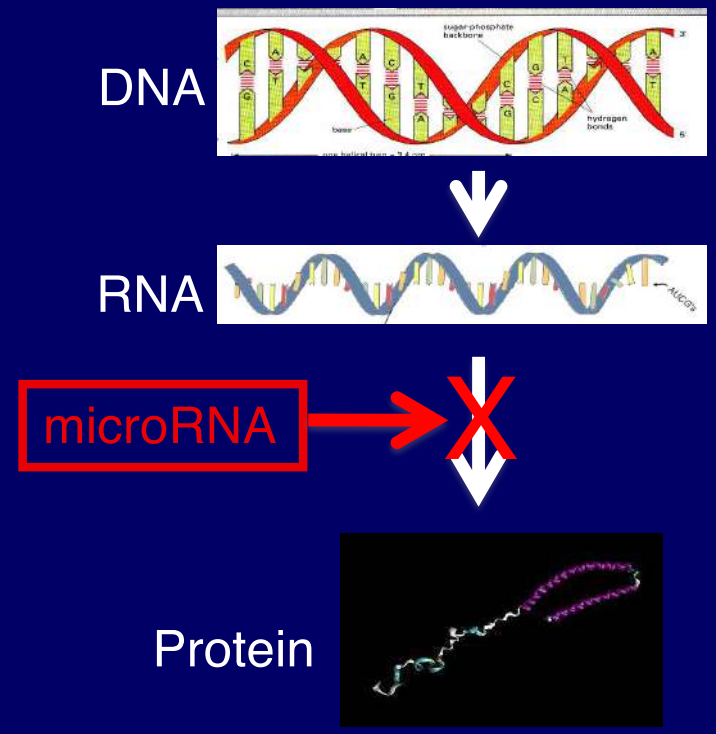
Consequences of Increased α-Synuclein Levels in Neurons

- Misfolding and aggregation
- Permeabilization of synaptic vesicles leading to dopamine leakage
- Oxidative stress
- Disruption of vesicular trafficking between the endoplasmic reticulum (ER) and the Golgi, causing ER stress
- Interference with autophagy
- Impaired proteasome function
- Interaction with other proteins

Reducing α-synuclein levels can be beneficial

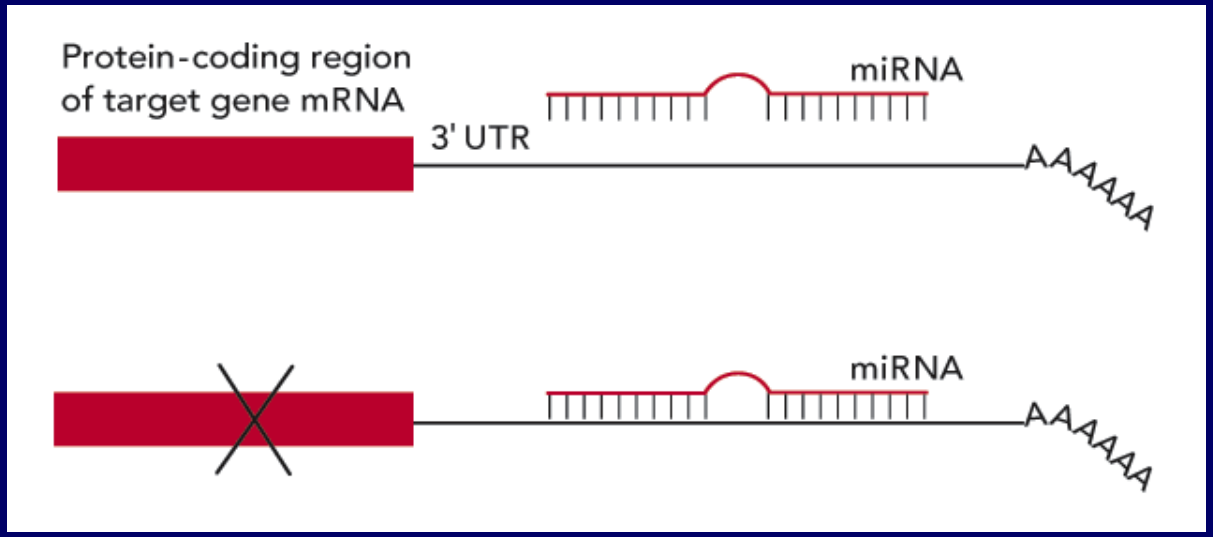
Reducing α-Synuclein Levels as a Therapeutic Strategy

- **Reduce production**
  - Inhibit transcription
  - Inhibit translation
- **Enhance clearance**
  - Autophagy
  - Proteasome

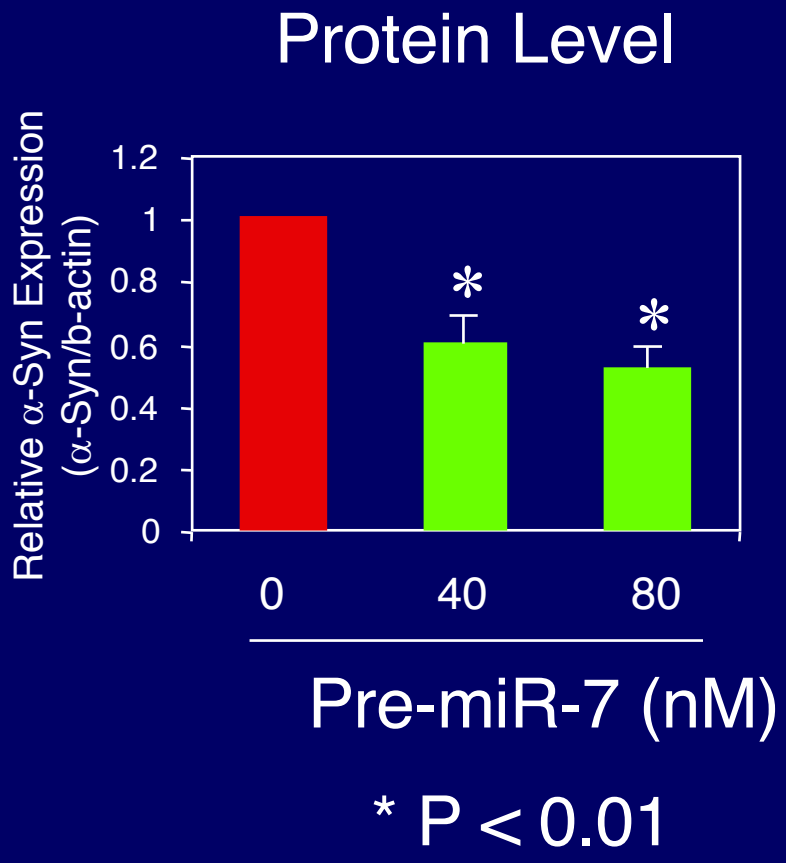


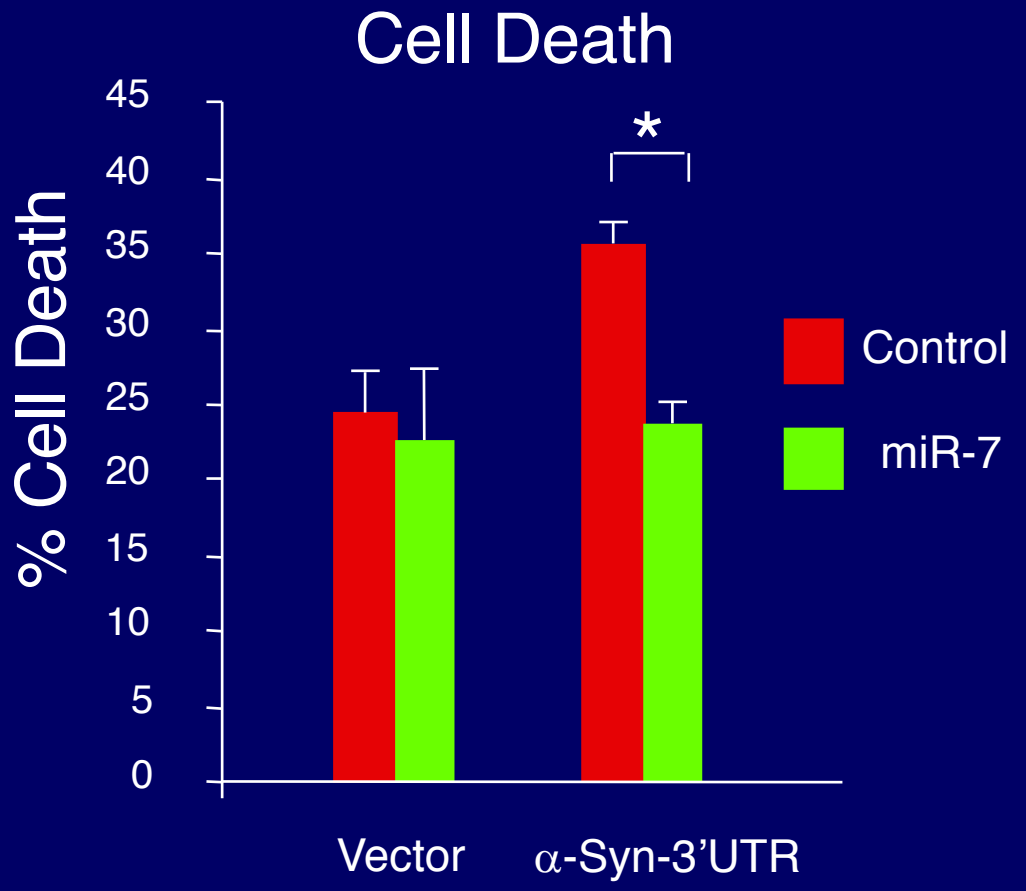
MicroRNA

- Small noncoding RNA molecules
- Regulate gene expression post-transcriptionally



MicroRNA-7 Reduces α-Synuclein Protein Levels and Protects against its Toxicity



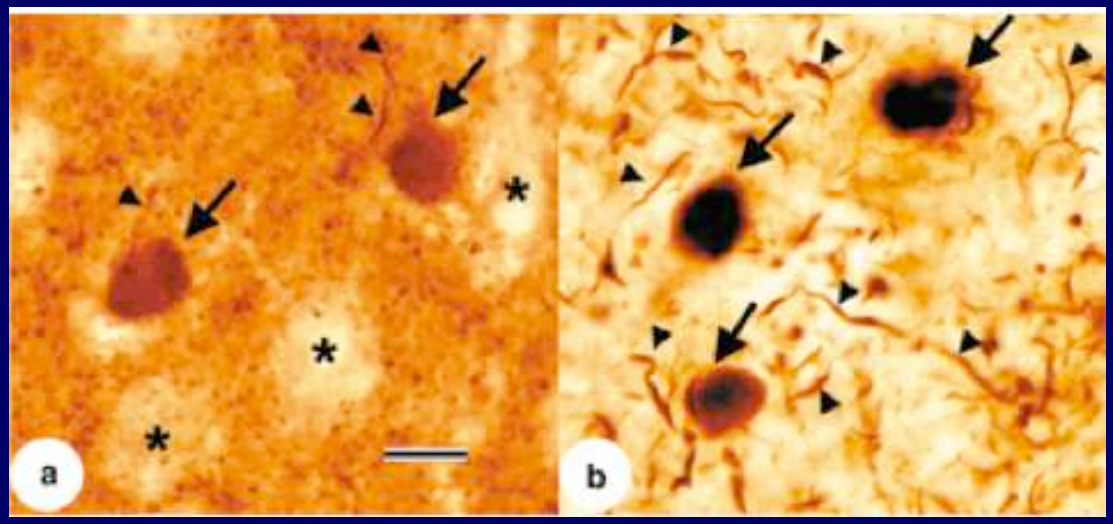


Junn et al, PNAS,106(31): 13052, 2009

α-Synuclein Phosphorylation as a Therapeutic Target in PD and DLB

Misfolded α-Synuclein is Phosphorylated in α-Synucleinopathies

Human DLB

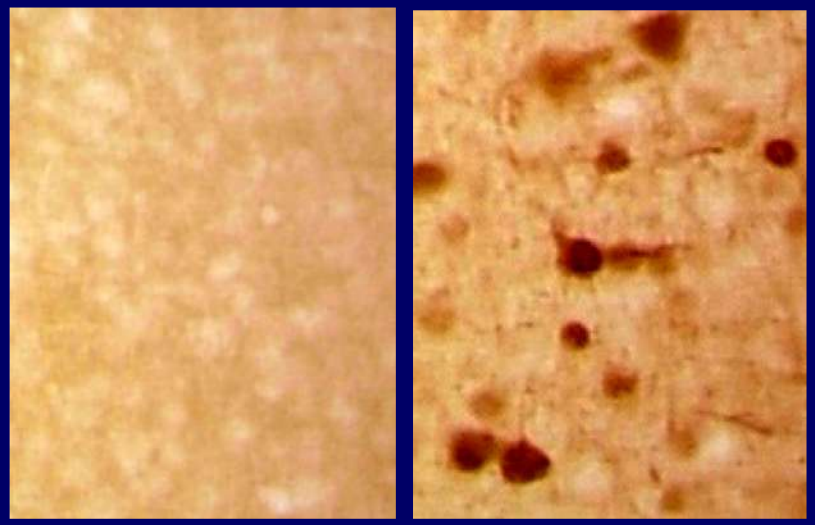


LB509 Anti-p-Ser129

Fujiwara et al NCB 4:160, 2002

Mice

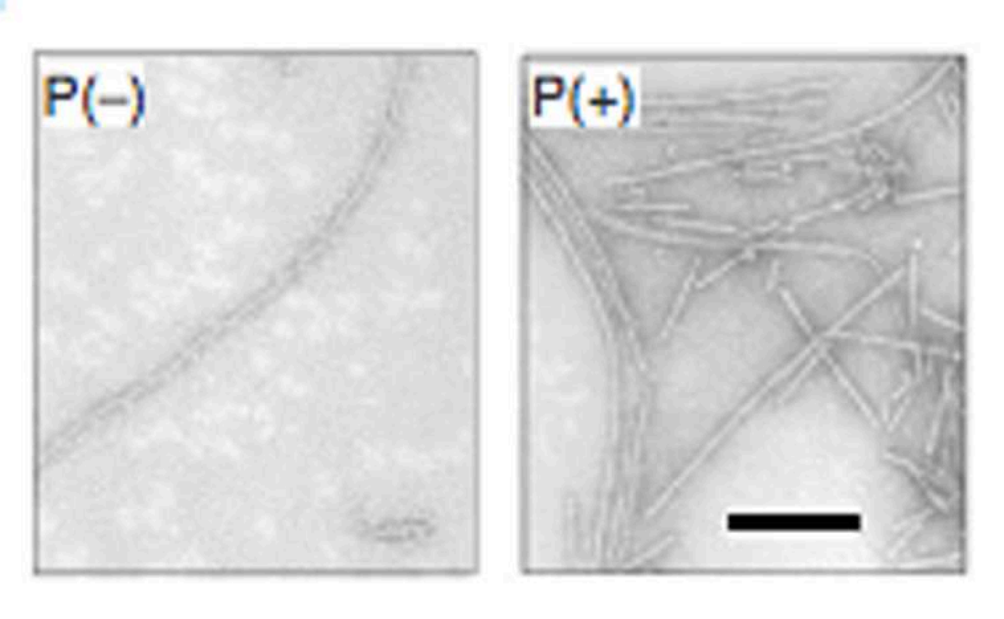
WT α-Synuclein^{Tg}



Anti-p-Ser129

Lee…Mouradian, J. Neurosci. 31: 6963, 2011

α-Synuclein Phosphorylation Promotes its Fibrillization in vitro



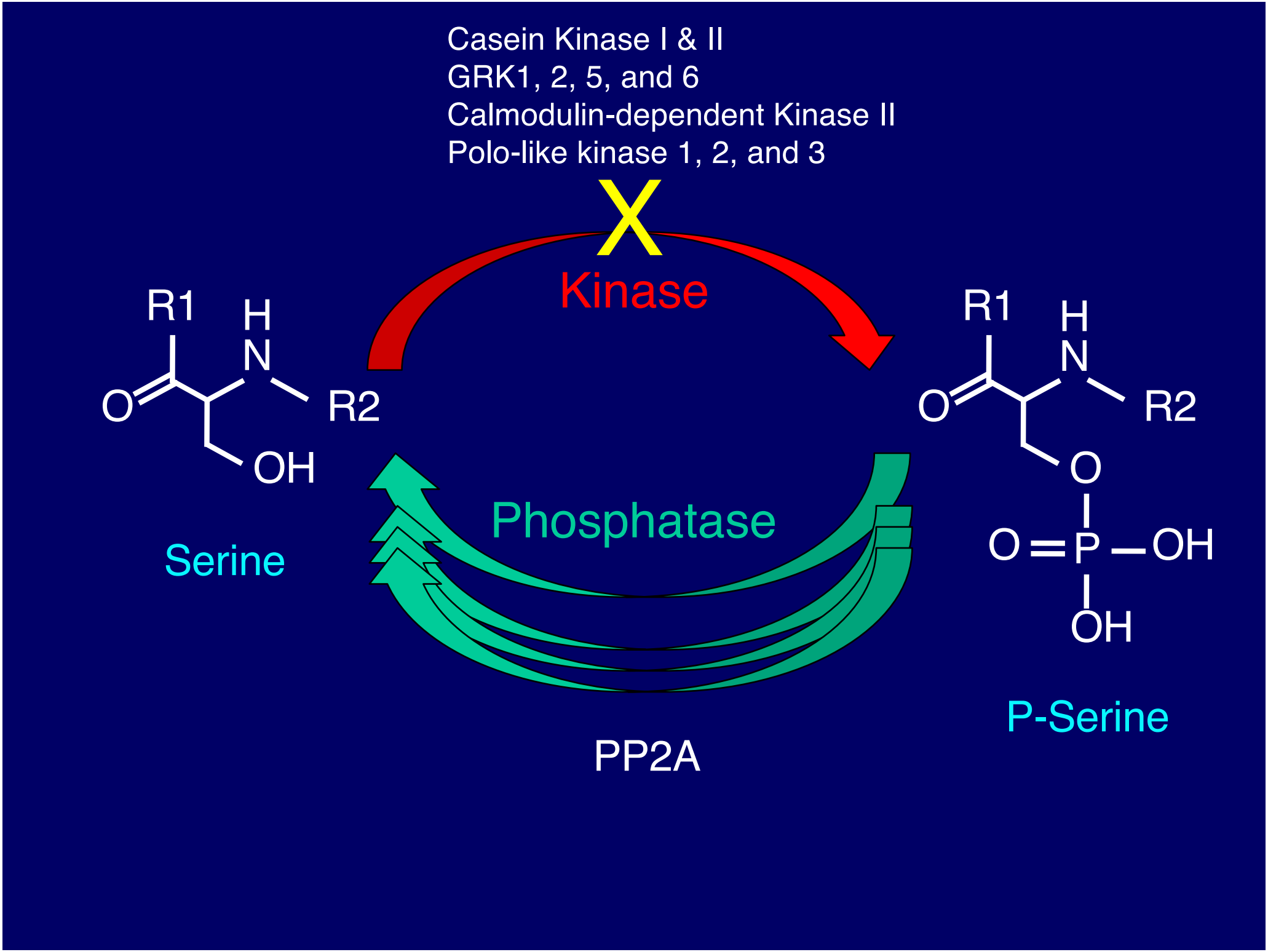
Fujiwara et al NCB 4:160, 2002

Therefore,

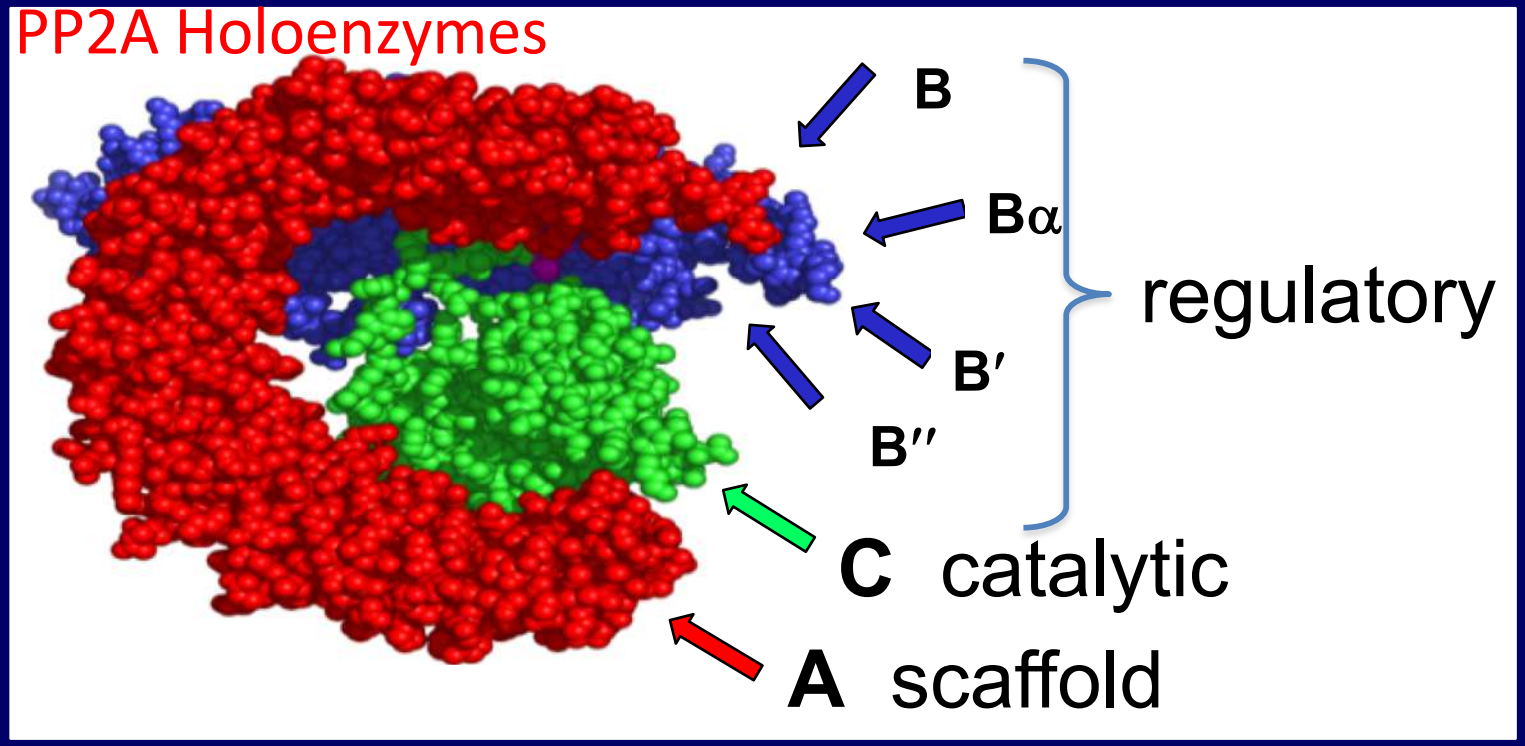
Decreasing the Phosphorylation State of

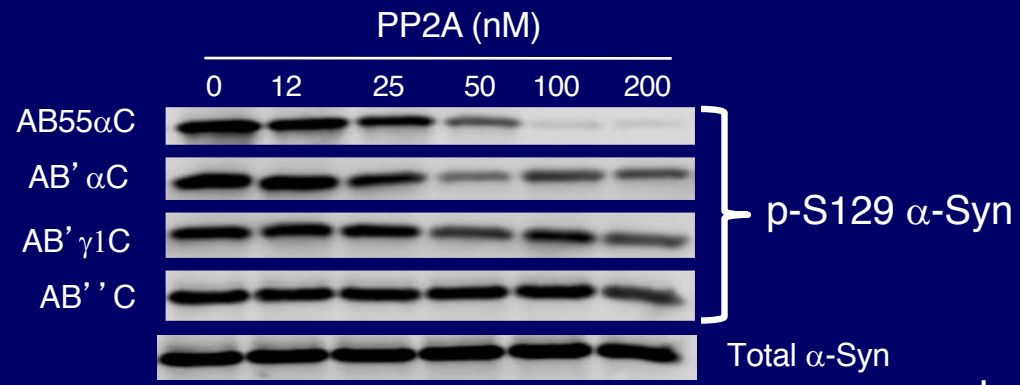
α-Synuclein is a Plausible

Therapeutic Strategy


Casein Kinase I & II
GRK1, 2, 5, and 6
Calmodulin-dependent Kinase II
Polo-like kinase 1, 2, and 3
X
Kinase
R1
H
N
O
R2
OH
Serine
Phosphatase
R1
H
N
O
R2
O
O
P
OH
OH
P-Serine
PP2A

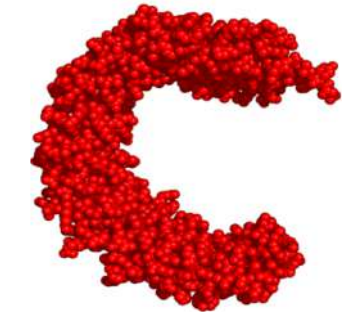
PP2A B55α is the Major Ser/Thr Phosphatase for α-Synuclein



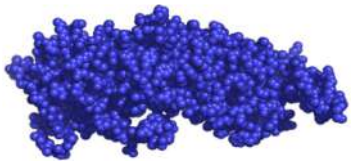


Lee et al, J. Neurosci. 31(19): 6963, 2011

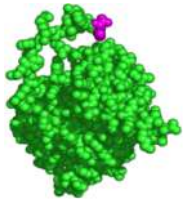
Methylation Affects PP2A-B55α Holoenzyme Assembly



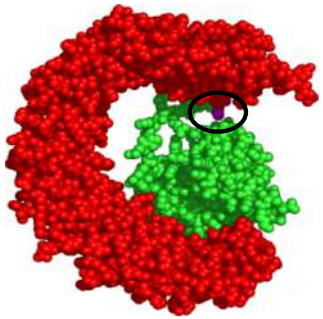
scaffold (A) subunit



regulatory (B) subunit

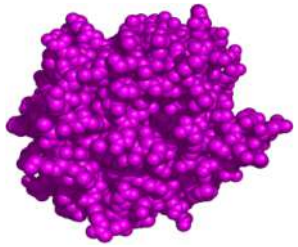


Catalytic (C) subunit



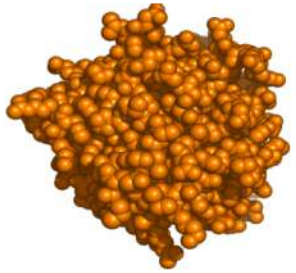
AC core dimer

LCMT-1

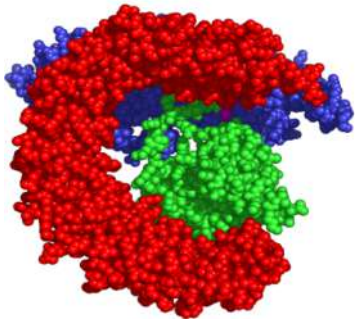


(+) CH_3

(–) CH_3



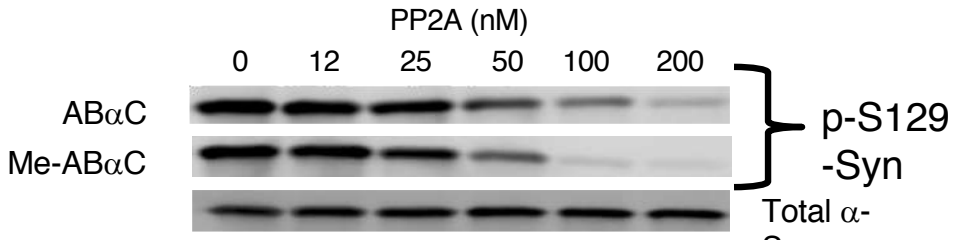
PME-1



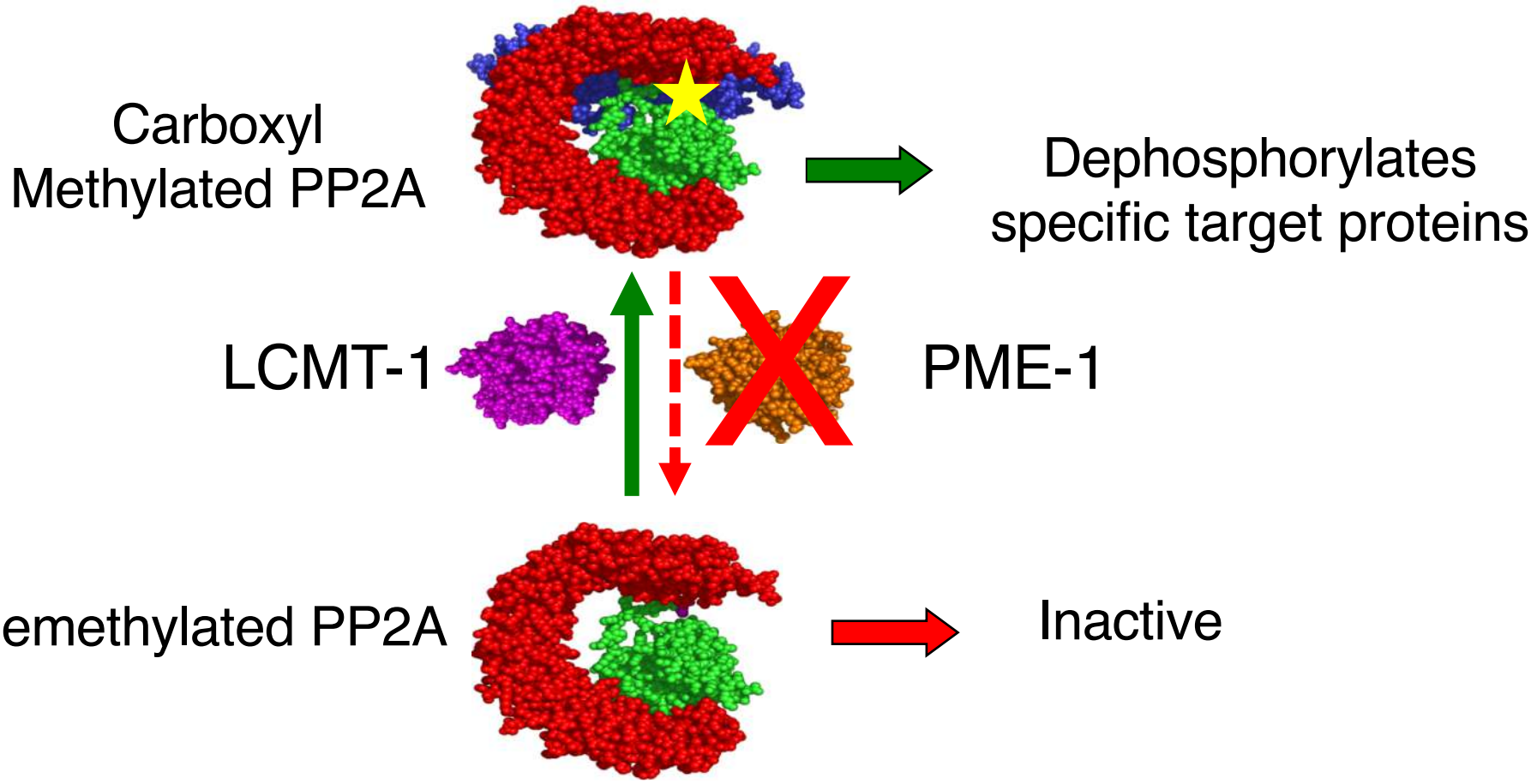
PP2A holoenzyme

Dephosphorylate specific Phospho-proteins

Methylated PP2A is more effective in de-phosphorylating α-Synuclein

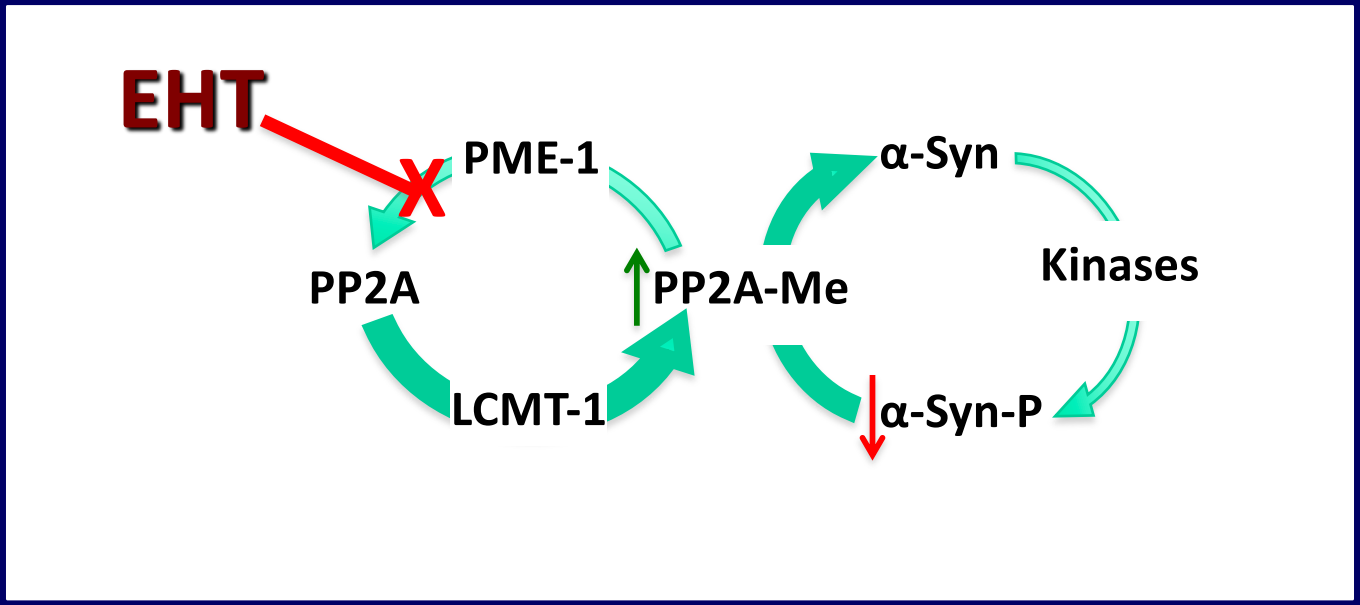


An Approach to Promote PP2A Activity



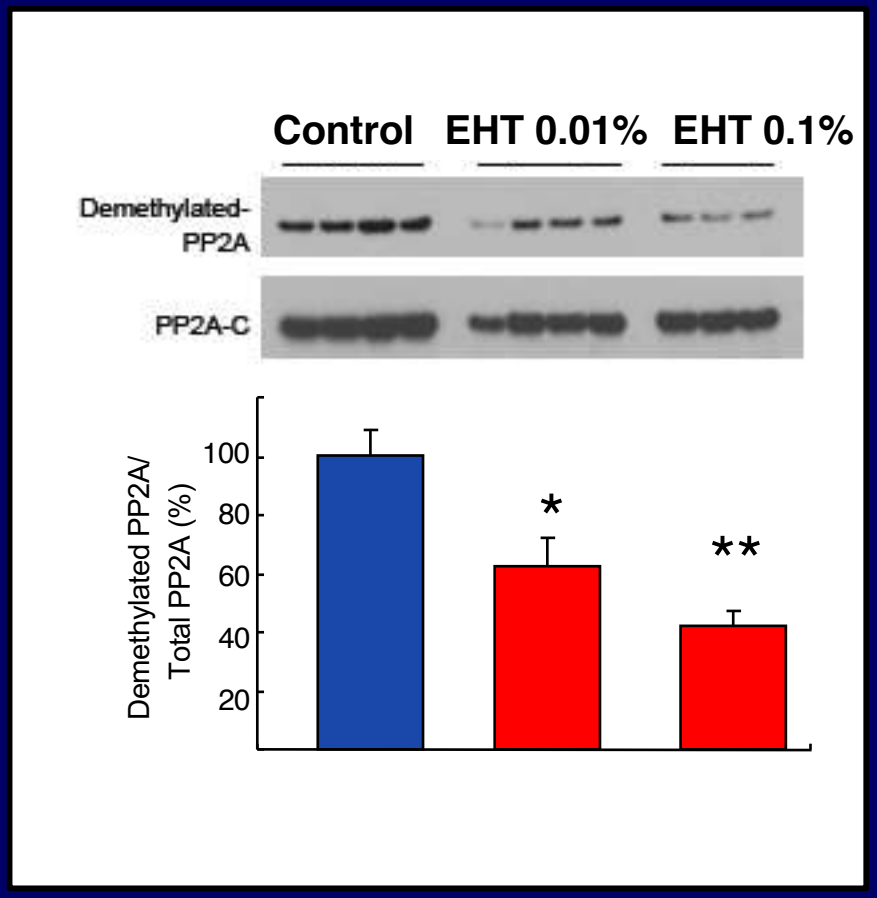
EHT Keeps PP2A Methylated leading to De-Phosphorylation of α-Synuclein

PP2A Demethylation Inhibitor

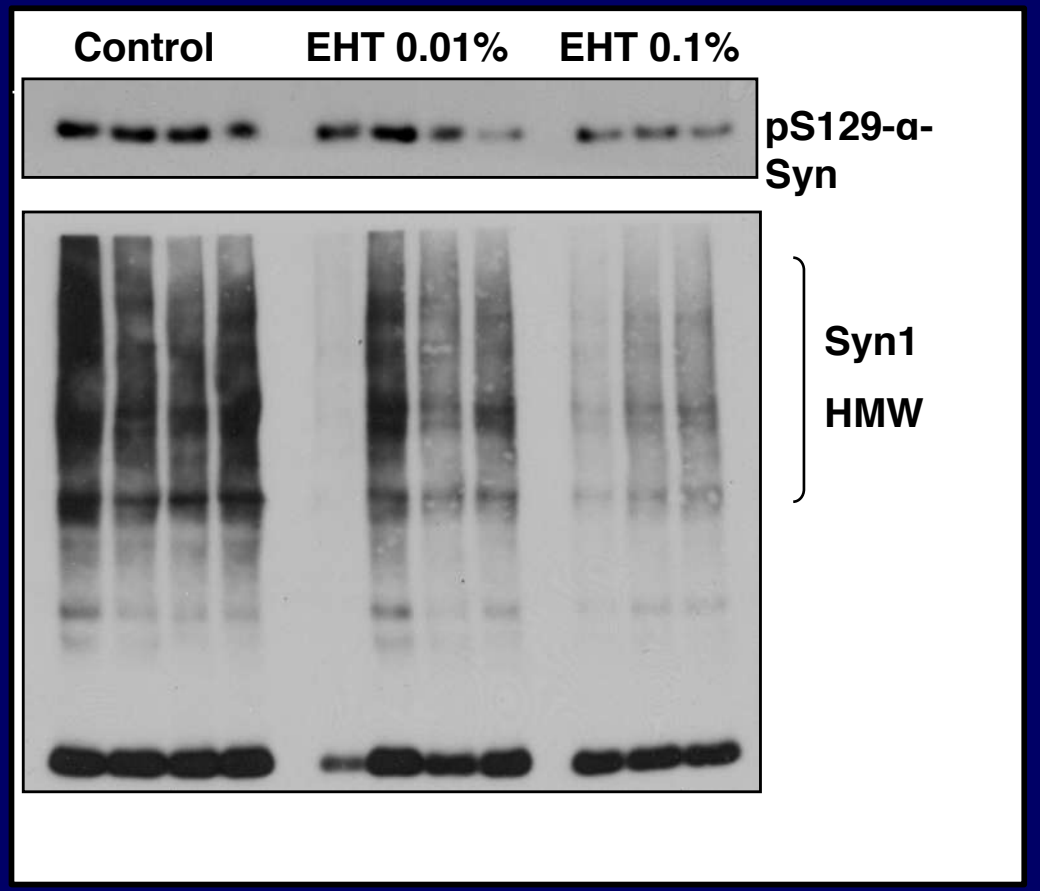


EHT Modulates PP2A Methylation and Reduces α-Synuclein Aggregation in α-Syn Transgenic Mice

- Inhibits PP2A demethylation

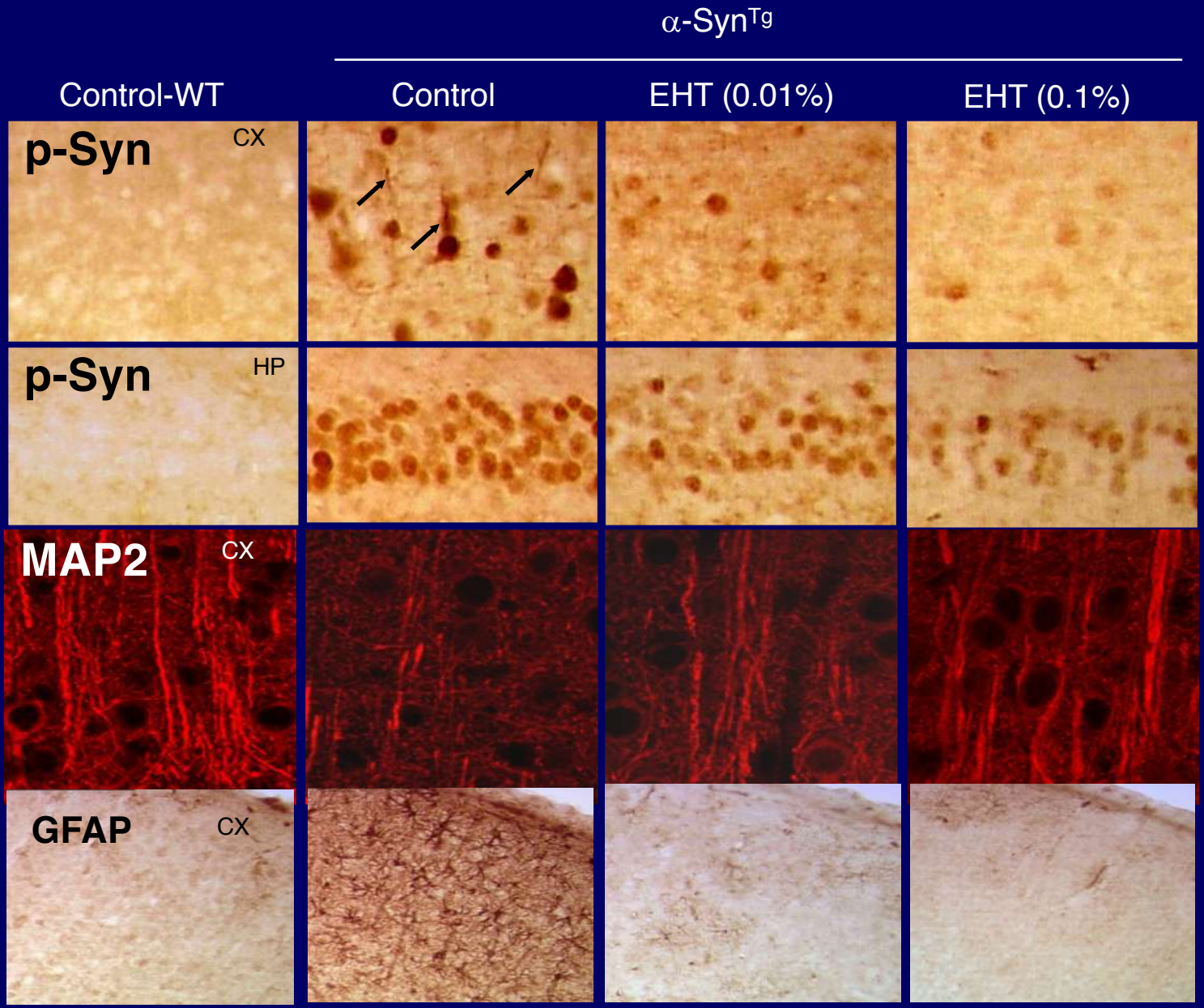


- Reduces α-synuclein S129 phosphorylation
- Reduces α-synuclein oligomers



Lee et al, J. Neurosci. 31(19): 6963, 2011

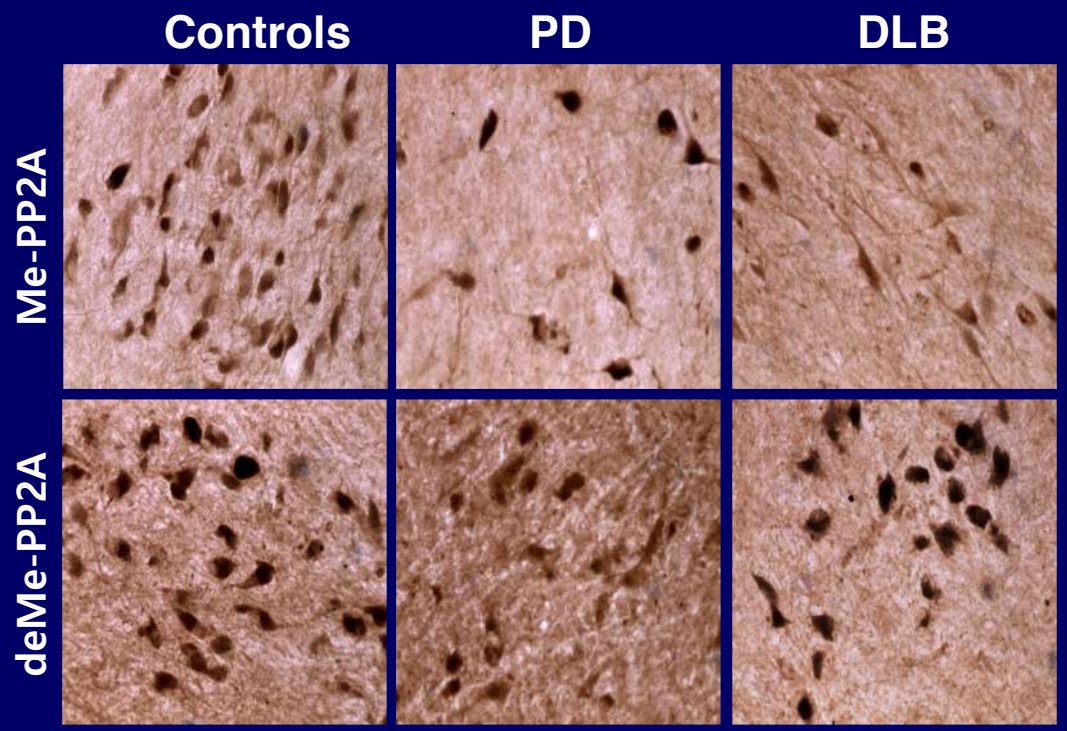
EHT Treatment Improves the Neuropathology of α-Synuclein Transgenic Mice

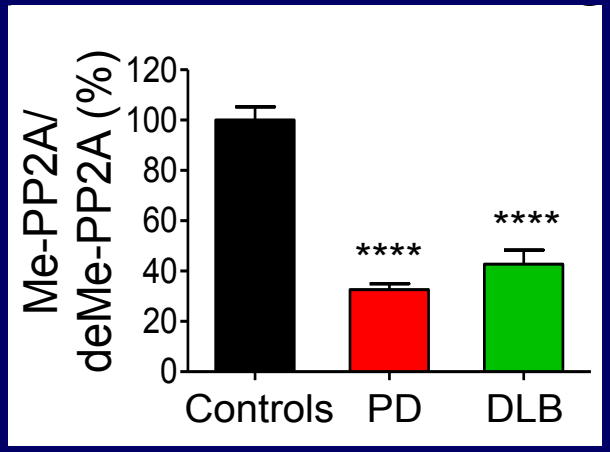


Lee et al, J. Neurosci. 31(19): 6963, 2011

What drives hyper-phosphorylation of pathogenic proteins in α-synucleinopathies and tauopathies?

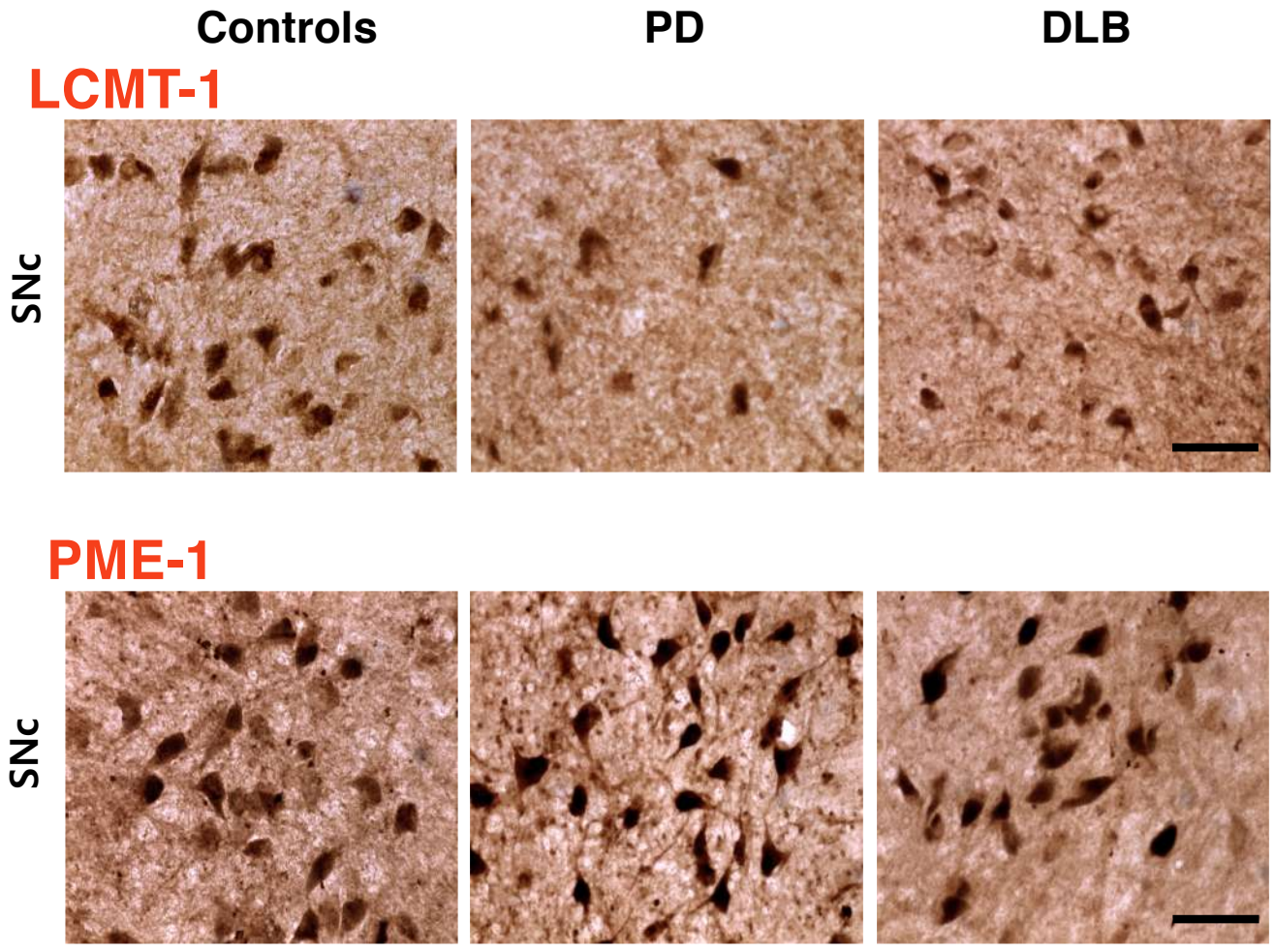
PP2A is De-Methylated in α-Synucleinopathies

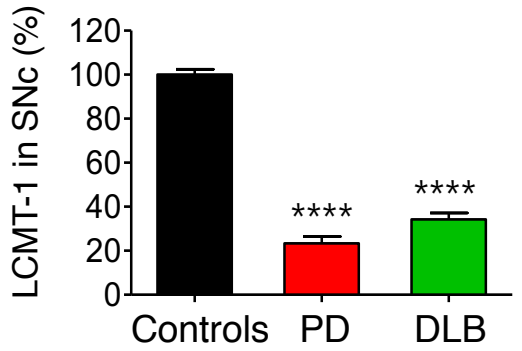


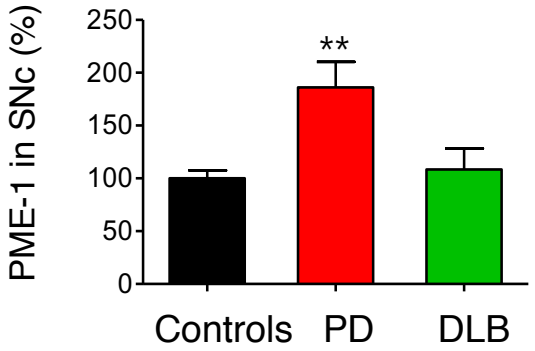


Park H.-J. et al, Ann. Clin. Transl. Neurol., 3(10):769, 2016

Dysregulation of PP2A Methylating Enzymes in α-Synucleinopathies

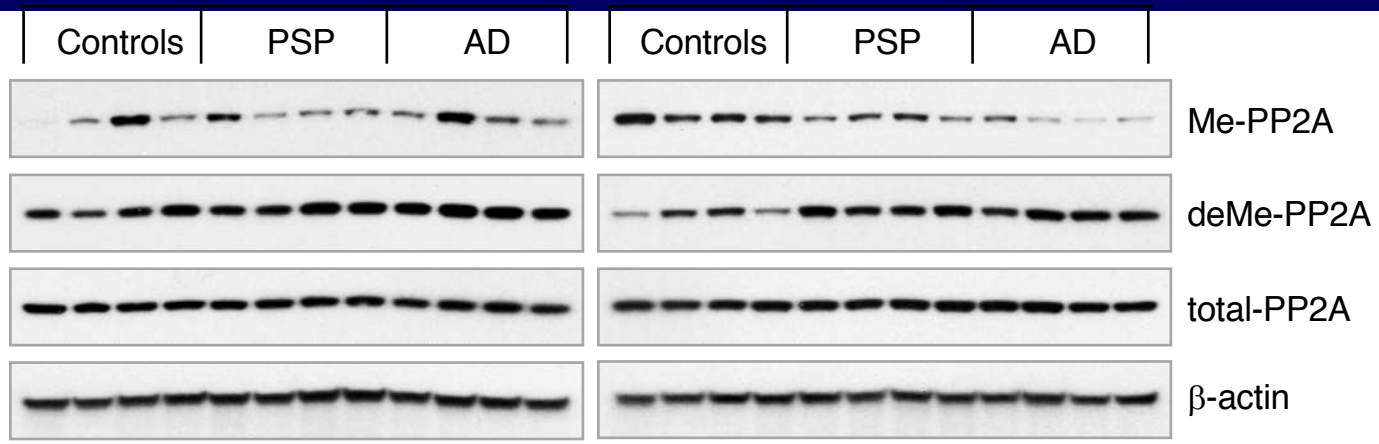


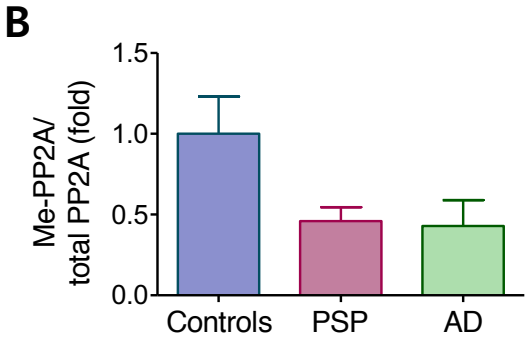


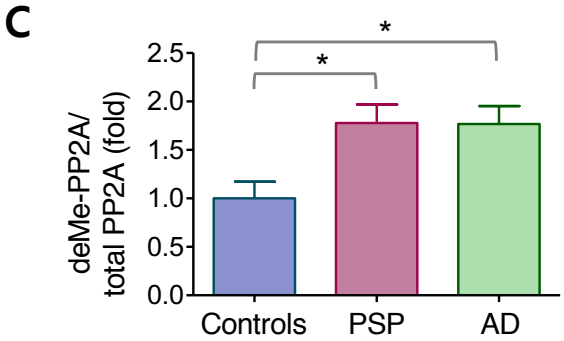


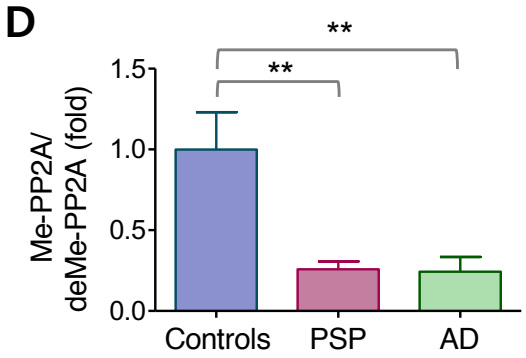
Park H.-J. et al, Ann. Clin. Transl. Neurol., 3(10):769, 2016

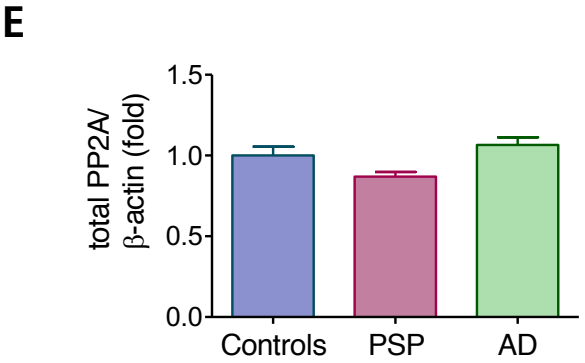
PP2A is DeMethylated in Tauopathies





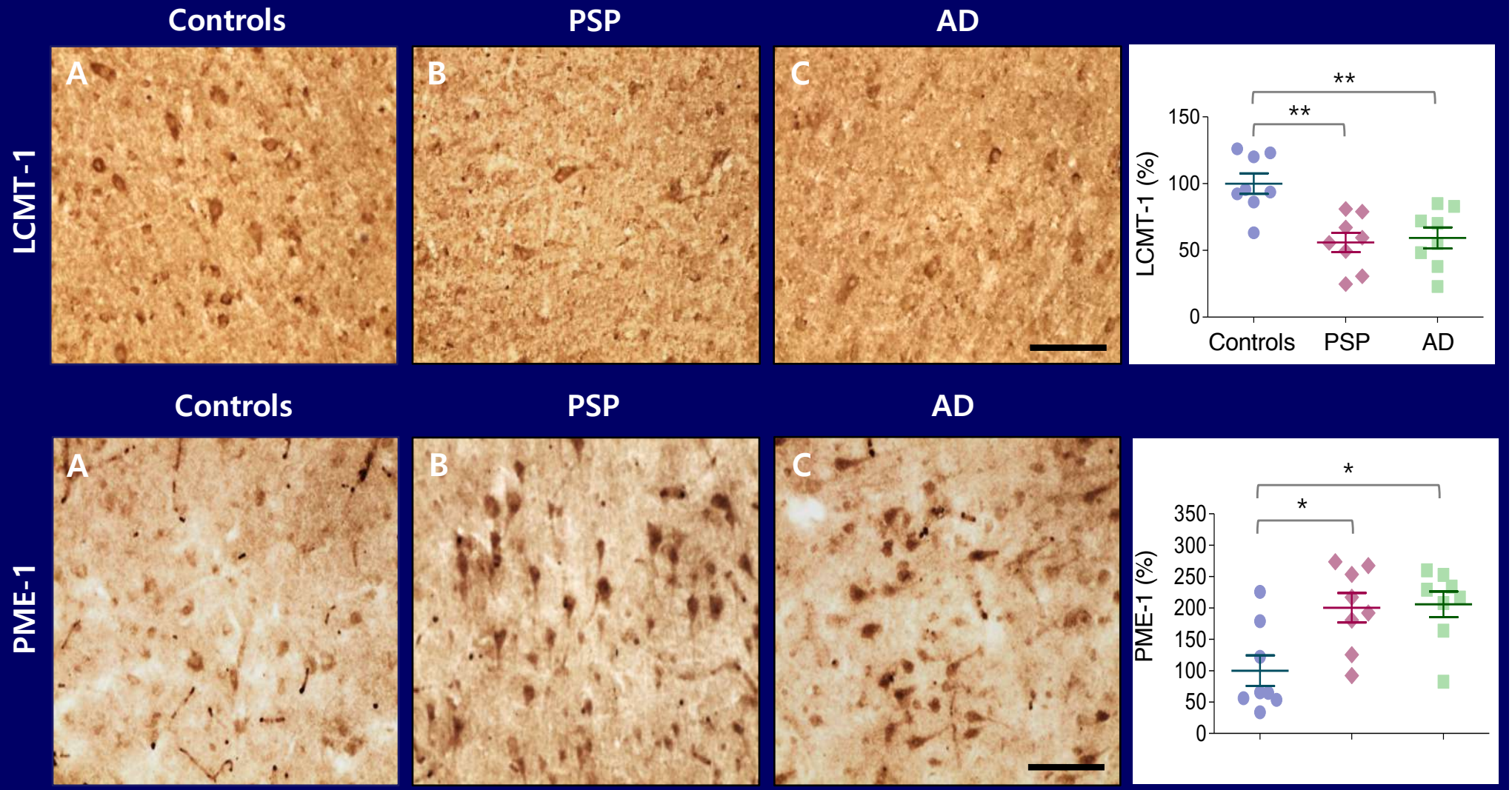






Park H.-J. et al, J. Neuropathol. Exp. Neurol, 77(2):139, 2018

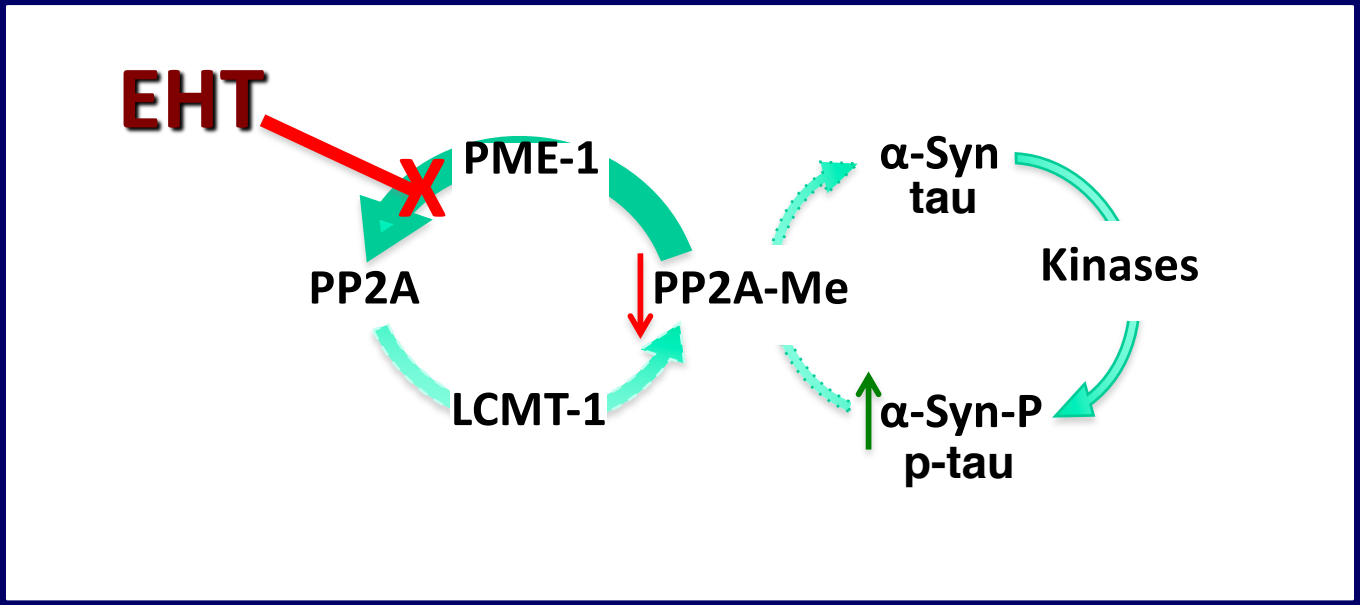
PP2A Methylating Enzymes are Dysregulated in Alzheimer and PSP



Park H.-J. et al, J. Neuropathol. Exp. Neurol, 77(2):139, 2018

Dysregulation of PP2A Methylation Leads to Hyper-Phosphorylation of α-Synuclein & tau

α-Synucleinopathy / Tauopathy



Summary

- Considerable molecular similarities exist among neurodegenerative diseases of aging
- Protein misfolding and fibrillization are considered pathogenic
- Increased levels of these proteins and their hyper-phosphorylation accelerate their misfolding
- Both these factors are tractable therapeutic targets for disease prevention and disease modification