Does Transmission Of Pathological Alpha-Synuclein (A-Syn) Account For The Progression Of Parkinson's Disease (PD) Including In The 50% Of Alzheimer Patients With PD And A-Syn Pathology?

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Aging Related Neurodegenerative Diseases Are Characterized By Misfolded Disease Proteins

Disease	Lesions	Components
Alzheimer's Disease (A multi-proteinopathy)	**SPs (100%) NFTs (100%) LBs (50%) TDP-43 (50%)**	**Aβ Tau α-Synuclein TDP-43**
Frontotemporal Diseases	Inclusions	Tau, TDP-43, FUS
Amyotrophic Lateral Sclerosis	Inclusions	TDP-43, FUS, Tau
Parkinson's disease +/- Dementia	LBs	α-Synuclein
Multiple System Atrophy	GCIs	α-Synuclein
Prion diseases	SPs	Prions
Trinucleotide repeat diseases	Inclusions	Expanded polyglutamine repeats

PARKINSON'S DISEASE

Prevalence 1% >60 years of age; ~5% >85 years of age

PD is chronic, progressive

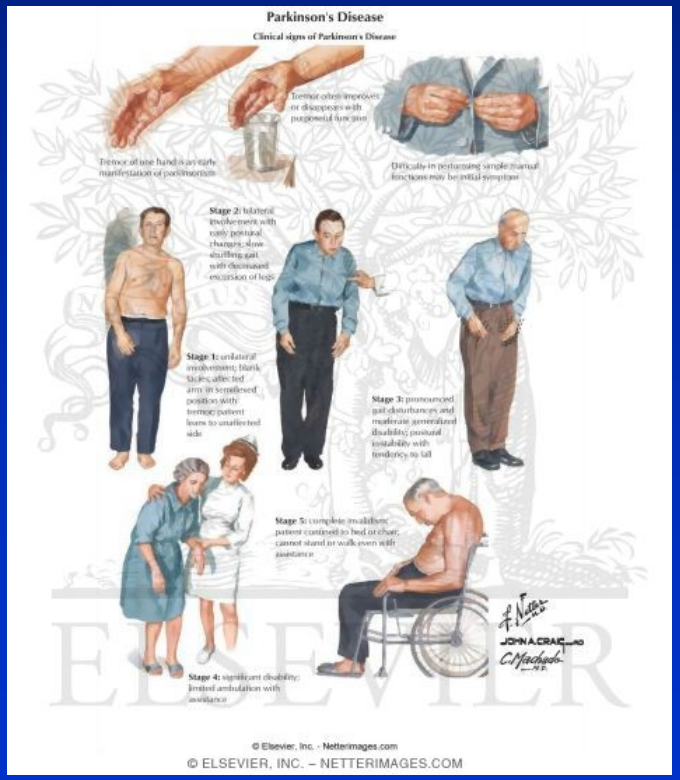
Mean disease duration 10-15 years from diagnosis until death

Motor symptoms

- Tremor, bradykinesia, rigidity, postural instability
- Degeneration of nigrostriatal pathway, loss of dopamine innervation to basal ganglia

Non-motor

- Impaired olfaction, incontinence, disrupted sleep, hallucinations
- May preseed motor symptoms
- 80% of PD patients develop dementia after living with disease for > 10 years
- Not dopamine related



Pathological Alpha-Synuclein is Closely Correlated with PD and Related Neurodegenerative Diseases

Histopathological evidence

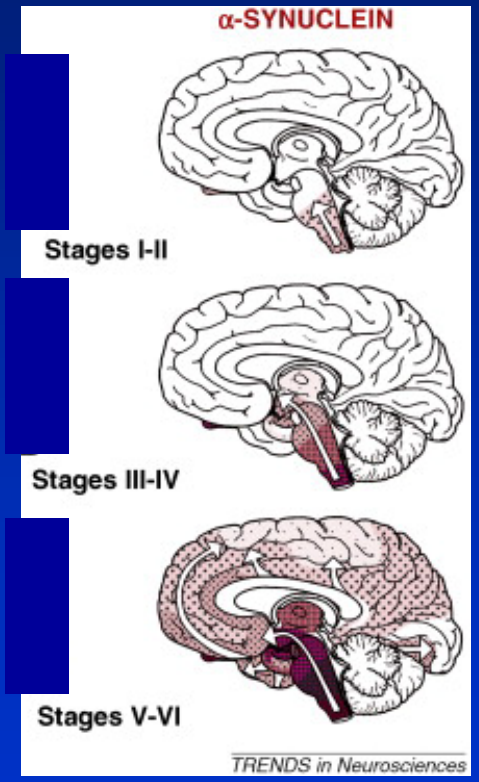
- Aggregates detected in synucleinopathies
- Parkinson's Disease (PD), Dementia with Lewy bodies
- Multiple System Atrophy (MSA)
- Distribution of aggregates correlates with symptoms (prion-like transmission?)

Genetic evidence

- Familial risk (OR 1.2 - 4)
- Point mutations (A53T, A30P and E46K)
- Gene duplication and triplication
- GWAS reproducibly link variations at α-syn related loci (*SNCA, MAPT, REP1, RAB7*) to sporadic PD populations

Experimental evidence

- Overexpression in transgenic mice, flies, C.elegans
- Adeno/Lentiviral overexpression in rats, primates
- α-synuclein aggregate formation → behavioral deficits/neurodegeneration/premature death



Braak et al, 2004

Exogenous α-synuclein fibrils seed the formation of Lewy body-like intracellular inclusions in cultured cells

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Neuron

Article

Exogenous α-Synuclein Fibrils Induce Lewy Body Pathology Leading to Synaptic Dysfunction and Neuron Death

Laura A. Volpicelli-Daley,[1] Kelvin C. Luk,[1] Tapan P. Patel,[2] Selcuk A. Tanik,[1] Dawn M. Riddle,[1] Anna Stieber,[1] David F. Meaney,[2] John Q. Trojanowski,[1] and Virginia M.-Y. Lee[1,*]

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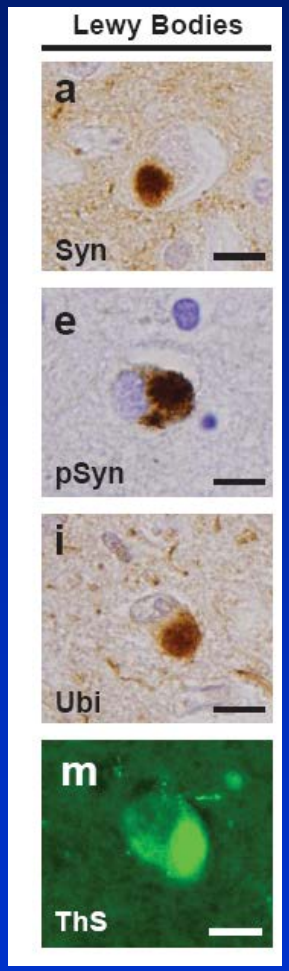
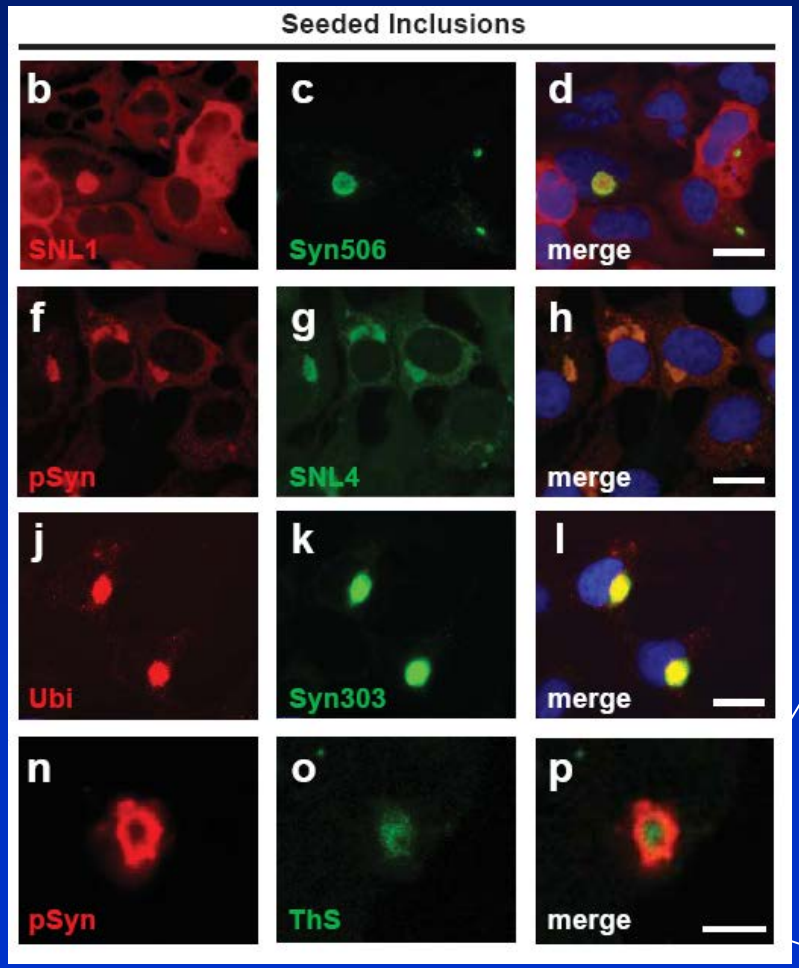
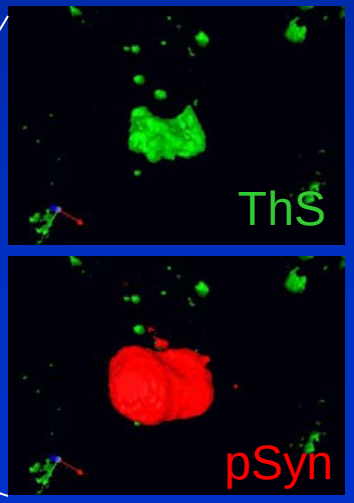
Neuron 72, 57–71, October 6, 2011

Seeded inclusions exhibit biochemical properties of human Lewy bodies

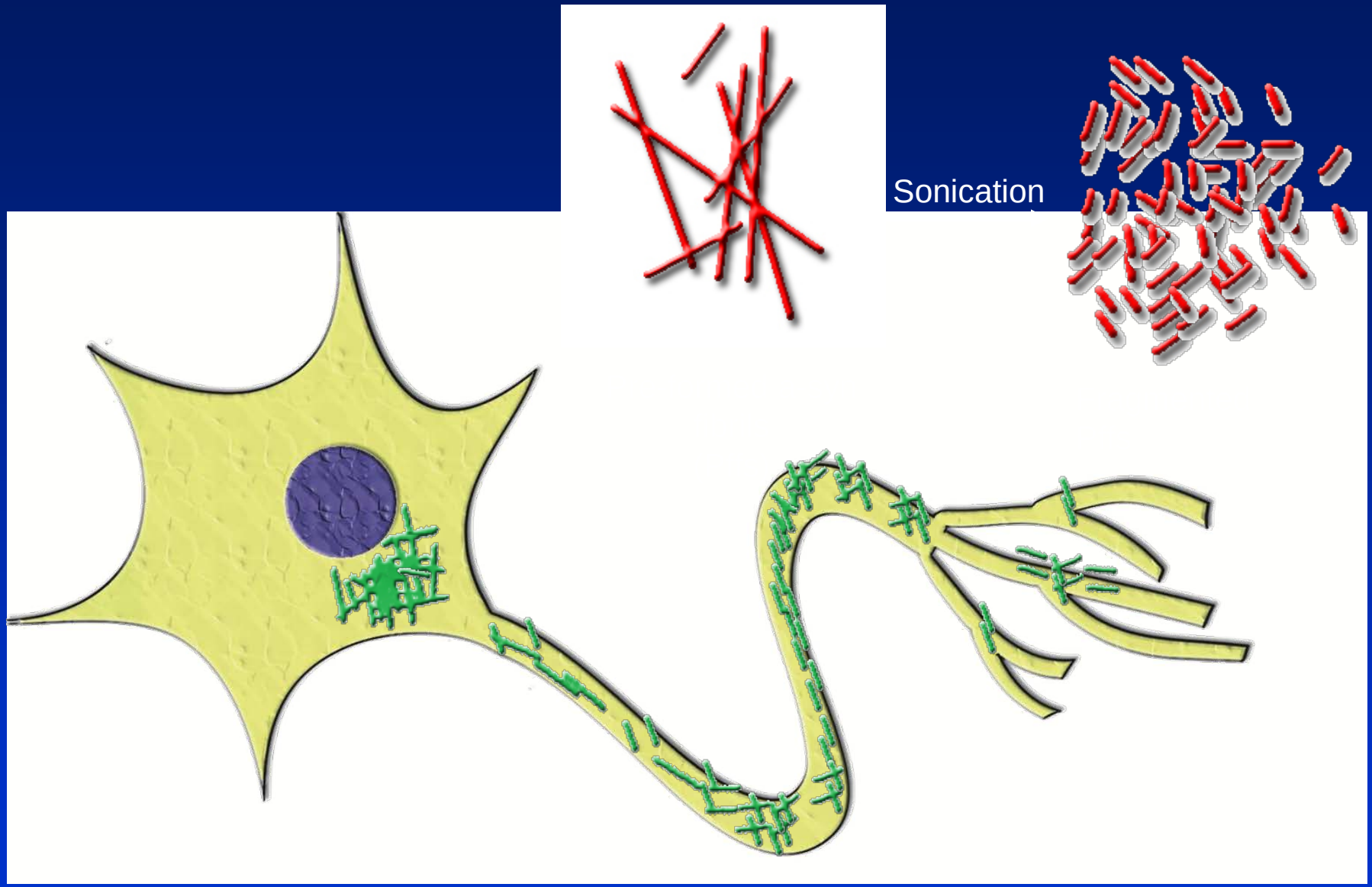




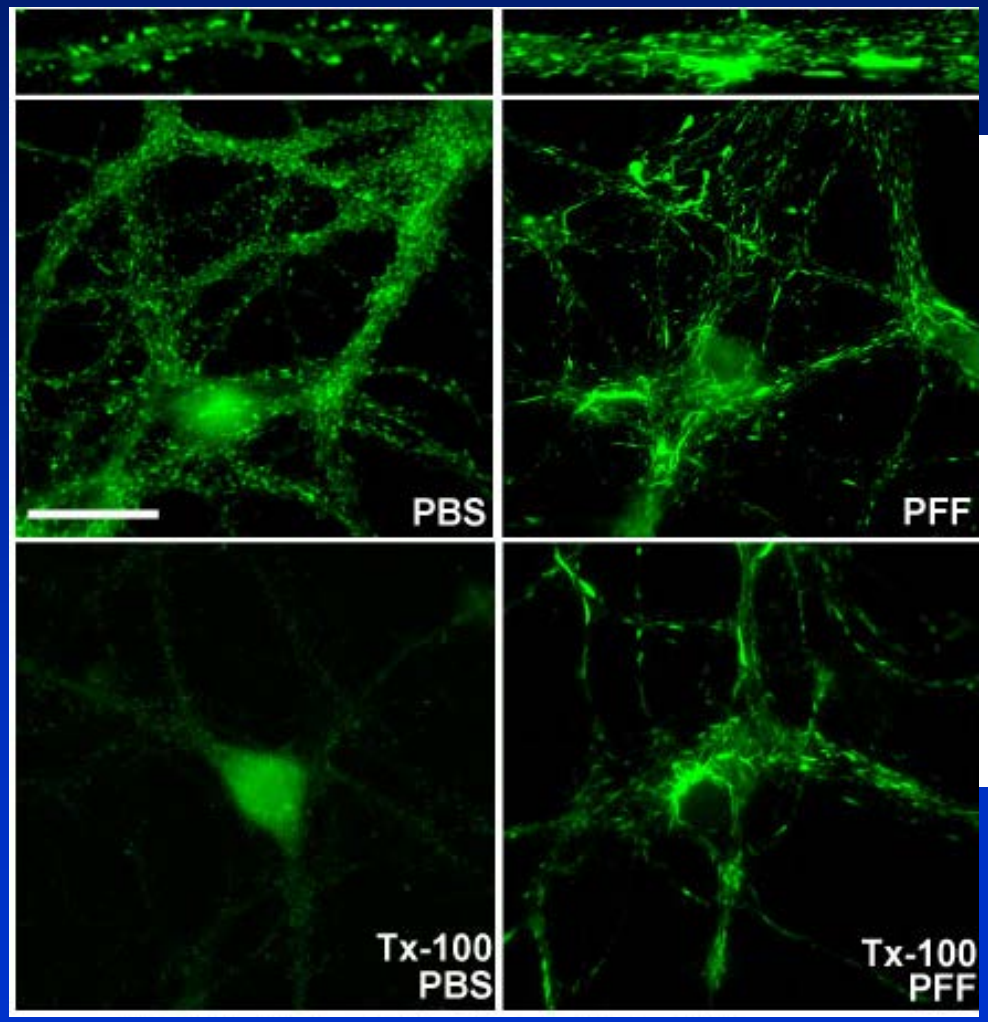


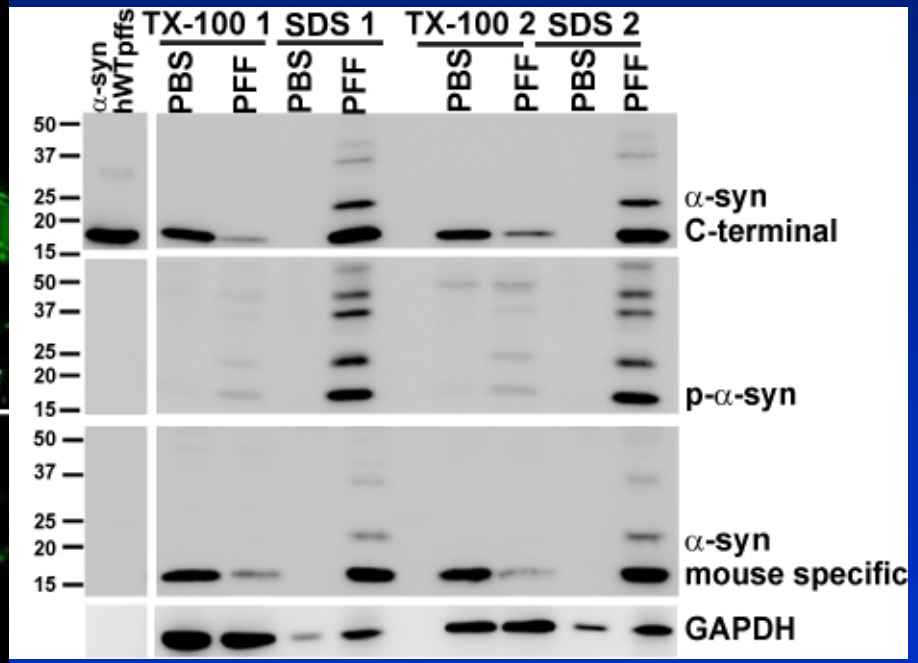
Luk et al, PNAS, 2009

α-Syn fibril Transduction in Primary Neurons



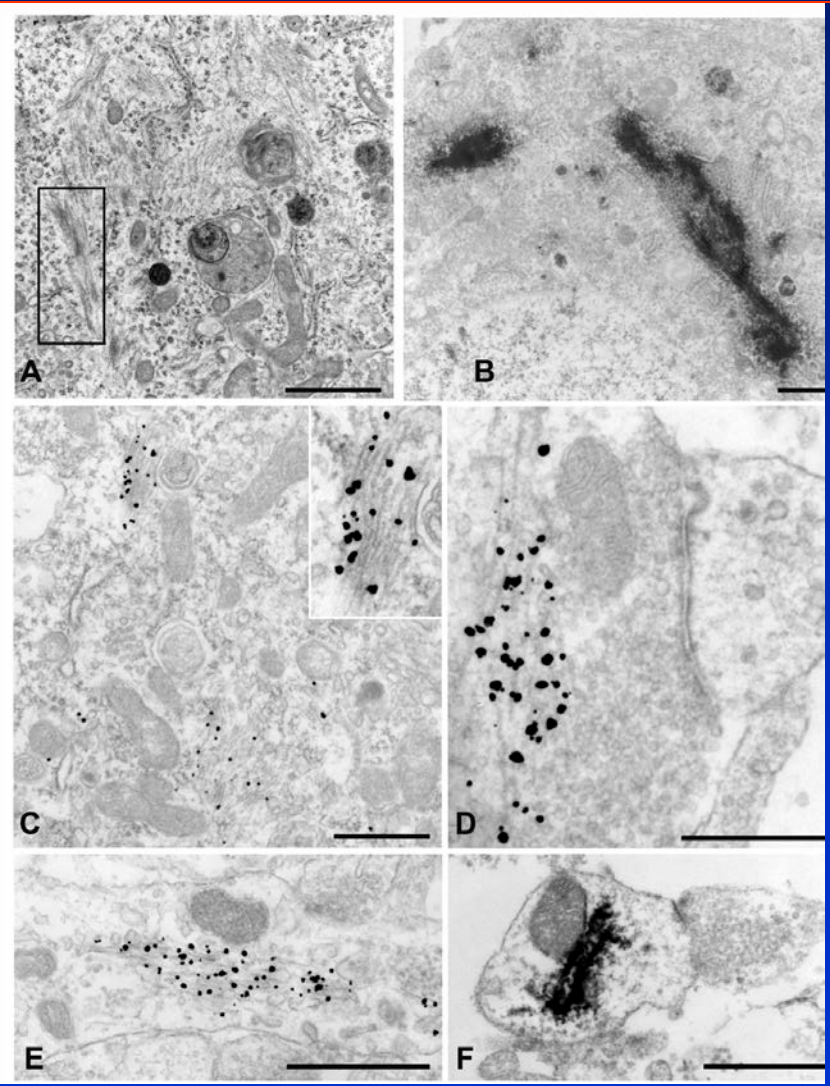
α-Syn-hWT pre-formed fibrils (pffs) recruit endogenous α-syn to form pathologic, insoluble aggregates





Vopicelli-Daley, et al., Neuron, 2011.

Ultrastructure analysis of α-syn aggregates



Published April 16, 2012

JEM

Article

Intracerebral inoculation of pathological α-synuclein initiates a rapidly progressive neurodegenerative α-synucleinopathy in mice

Kelvin C. Luk, Victoria M. Kehm, Bin Zhang, Patrick O'Brien, John Q. Trojanowski, and Virginia M.Y. Lee

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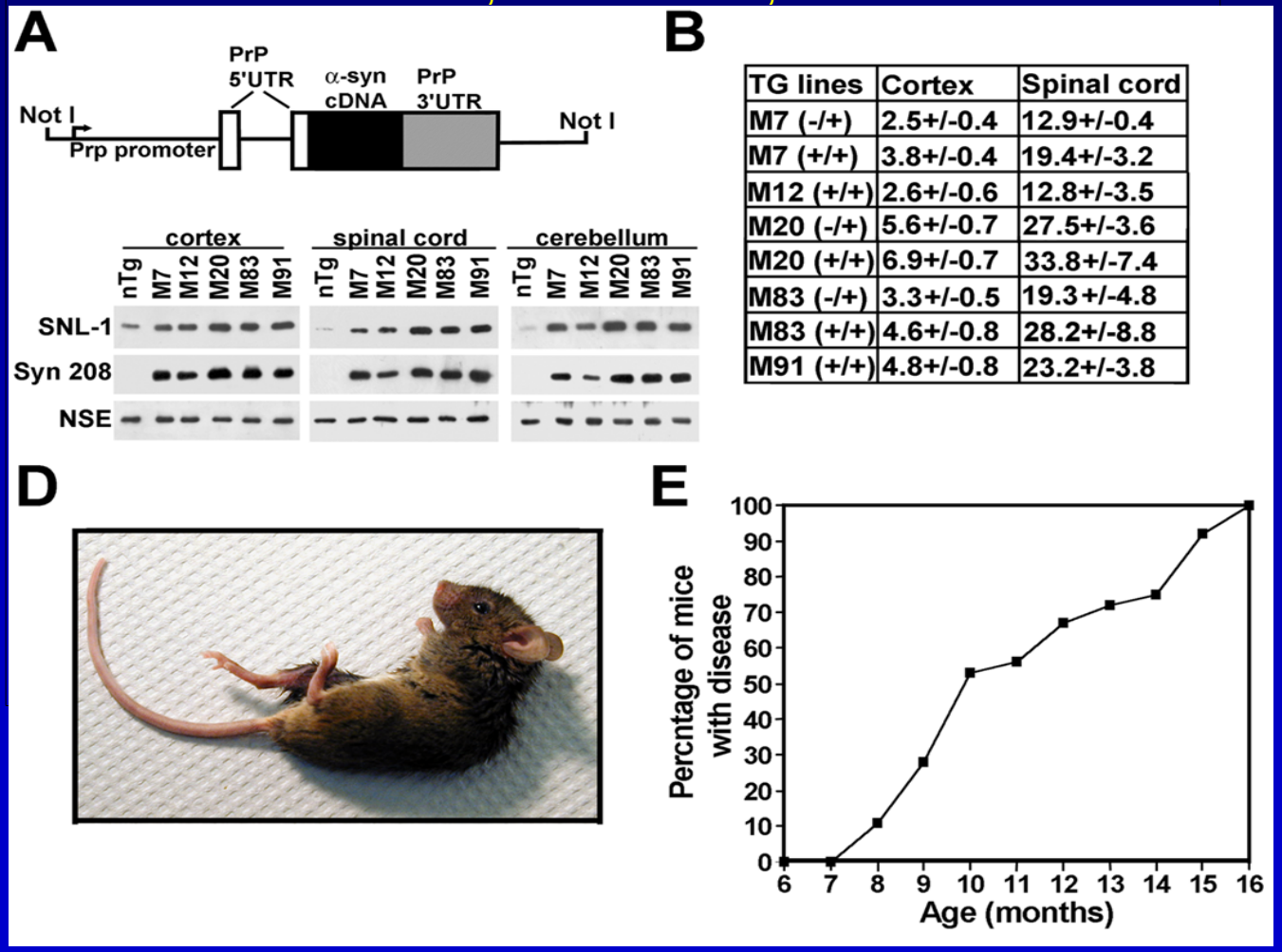
Brief Summary

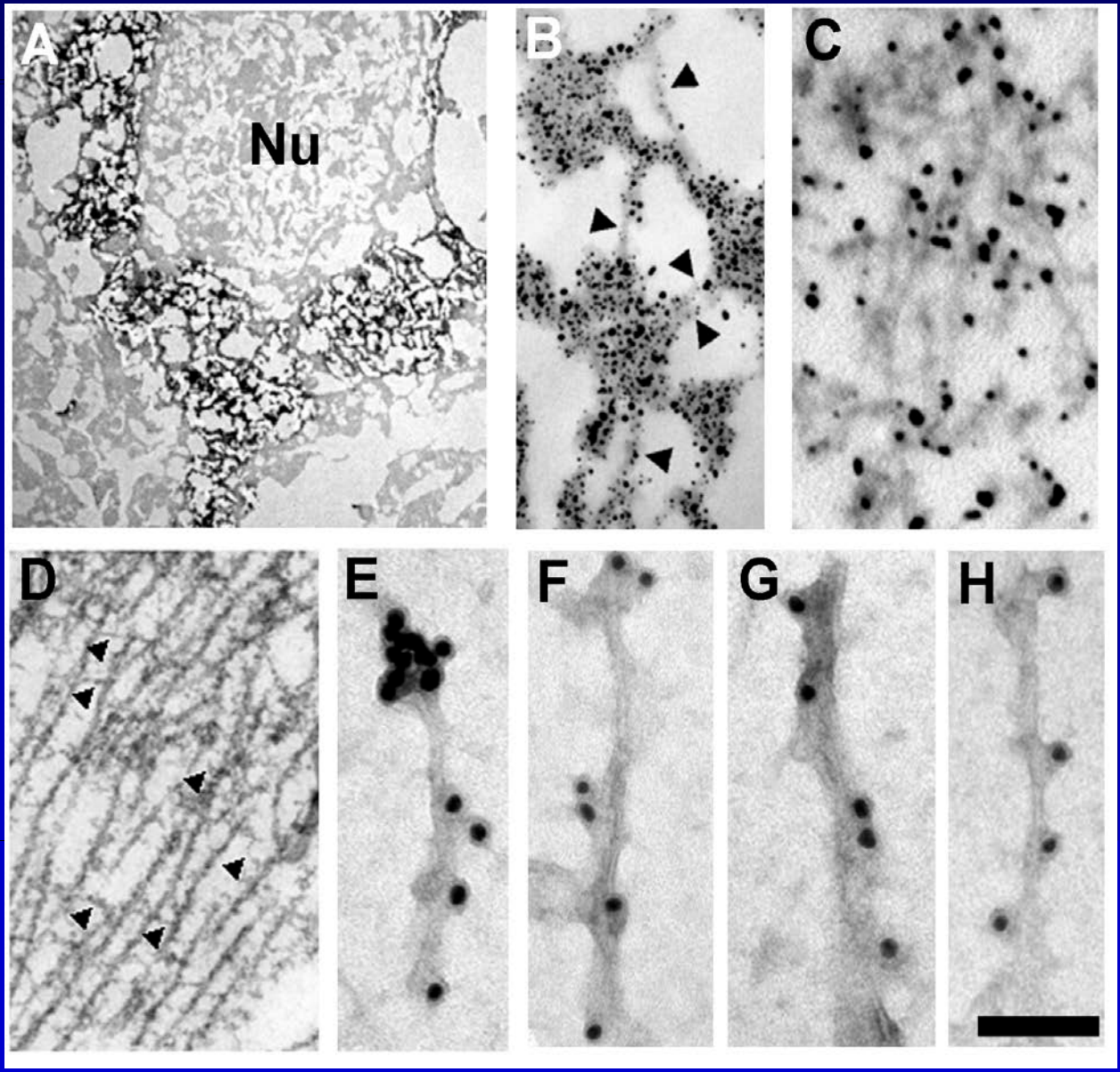
1) Intracerebral injections of brain homogenates from symptomatic A53T α-syn Tg mice with α-Syn pathology or synthetic α-syn fibrils accelerate formation of α-syn inclusions and clinical disease
2) Pathologic α-syn propagates along CNS pathways far beyond injection sites and reduces survival in inoculated Tg mice
3) Synthetic α-syn fibrils are sufficient to initiate PD-like α-syn pathology and transmit disease *in vivo*
4) These findings open up new avenues for understanding the progression of PD and developing novel therapies for PD

Neuronal alpha-synucleinopathy with severe movement disorder disorder in mice expressing A53T human alpha-synuclein. Giasson BI, Duda JE, Quinn SM, Zhang B, Trojanowski JQ, Lee VM-Y. Neuron, 34:521-533, 2002

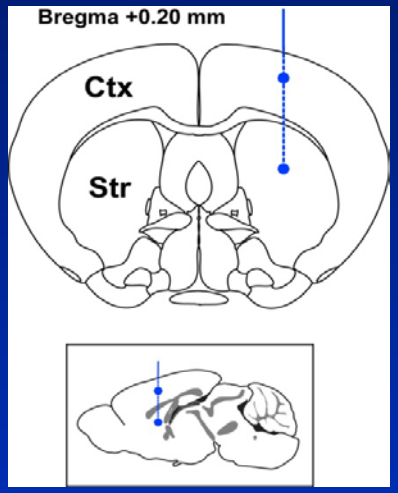
Initiation and synergistic fibrillization of tau and alpha-synuclein Giasson BI, Forman MS, Higuchi M, Golbe LI, Graves CI, Kotzbauer PT, Trojanowski JQ, Lee VM-Y. Science, 300:636-640, 2003.

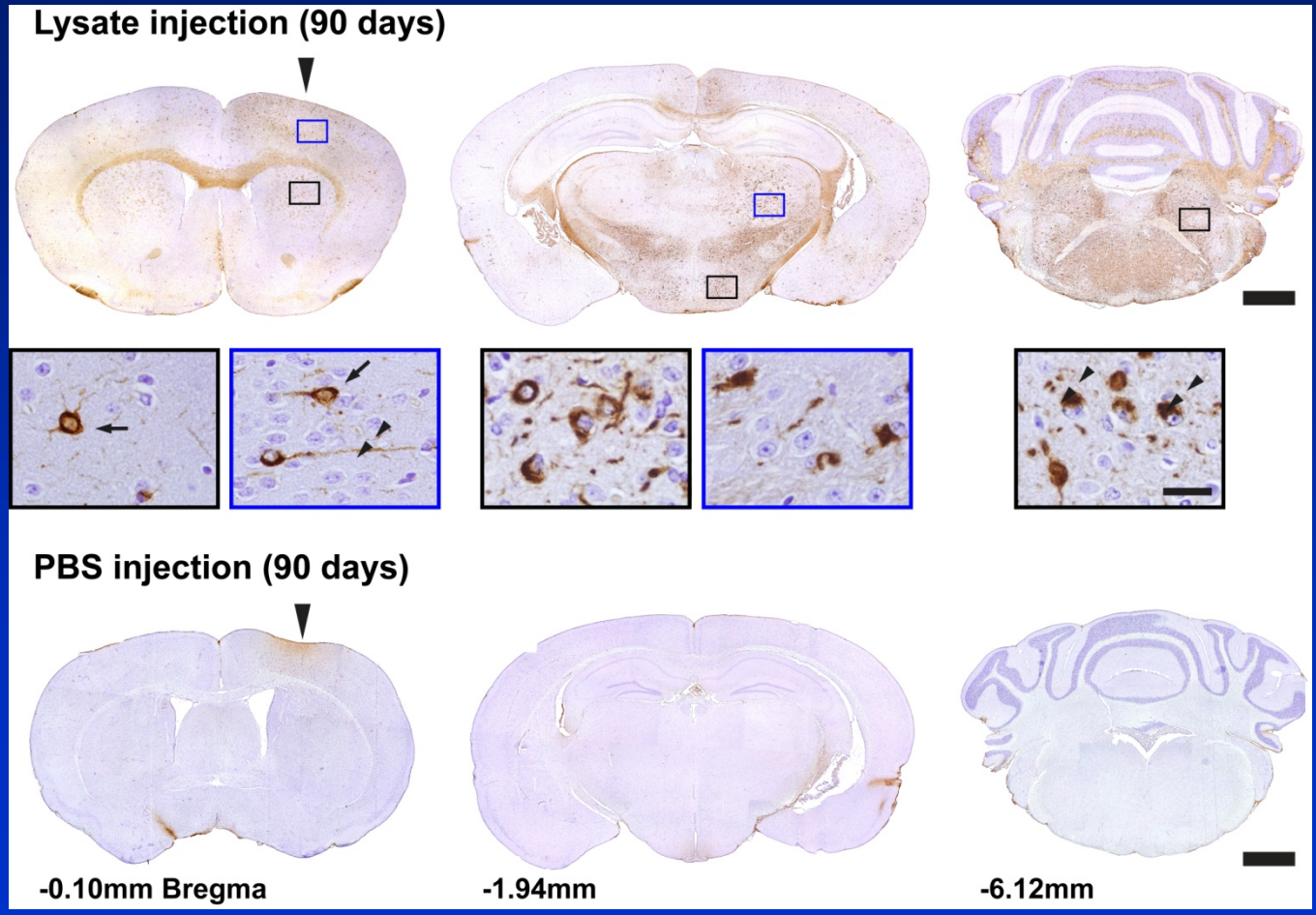


α-Syn Filaments can be Isolated from A53T Tg Mice



Symptomatic Brain Lysate Injections Induce the Accumulation of Abnormal α-Syn in Transgenic mice

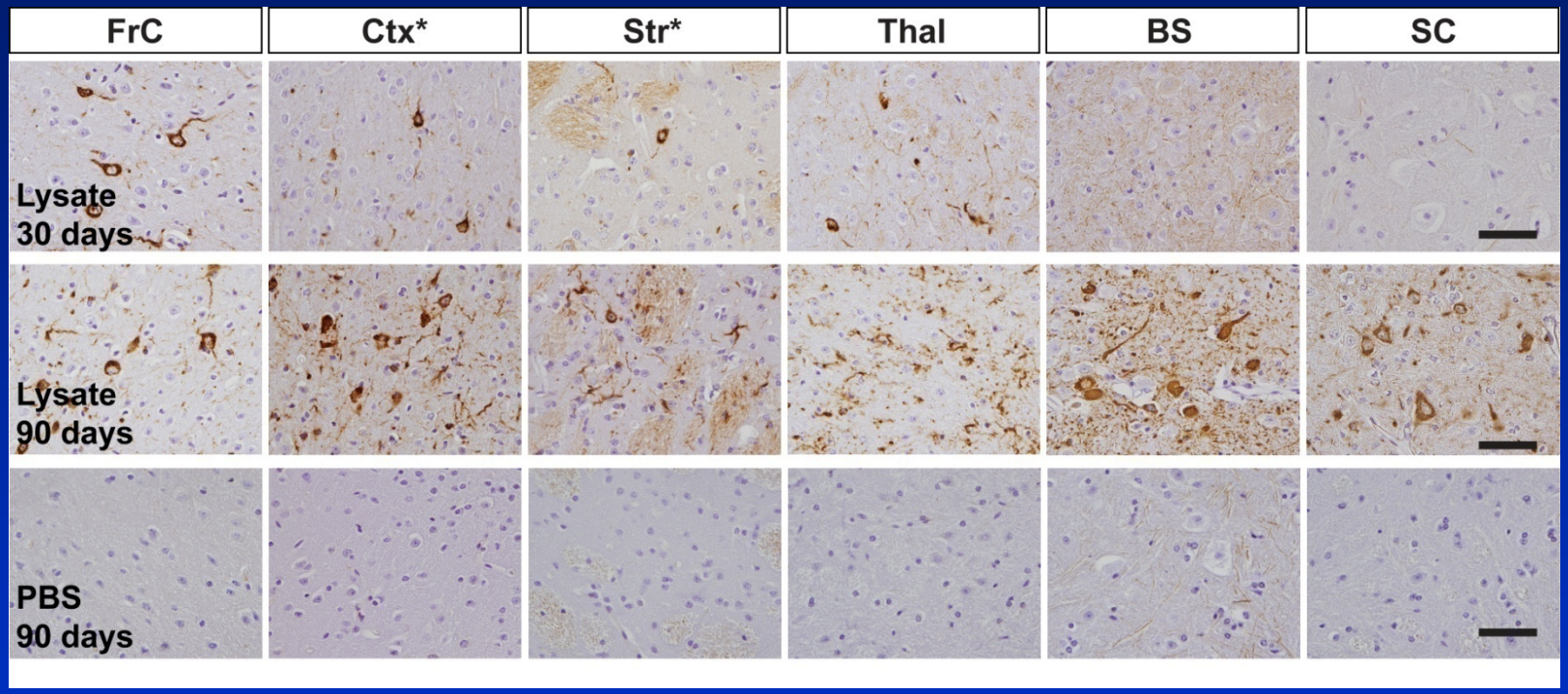


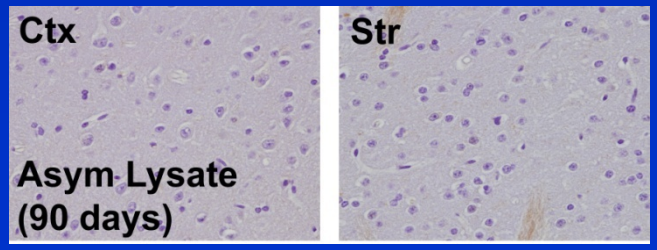


Luk et al., JEM, online, 2012

M83 α-syn Tg mice do not develop motoric phenotype until >10 months of age

Seeded α-Syn Pathology Develops in a Time Dependent Manner

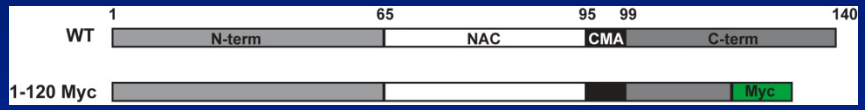




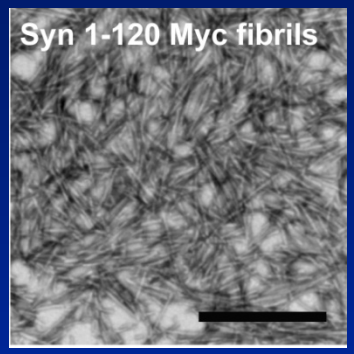
Symptomatic lysate contains pathologic agent

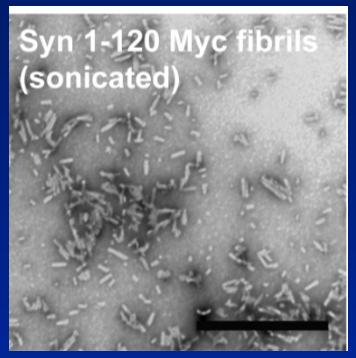
Luk et al., JEM, online, 2012

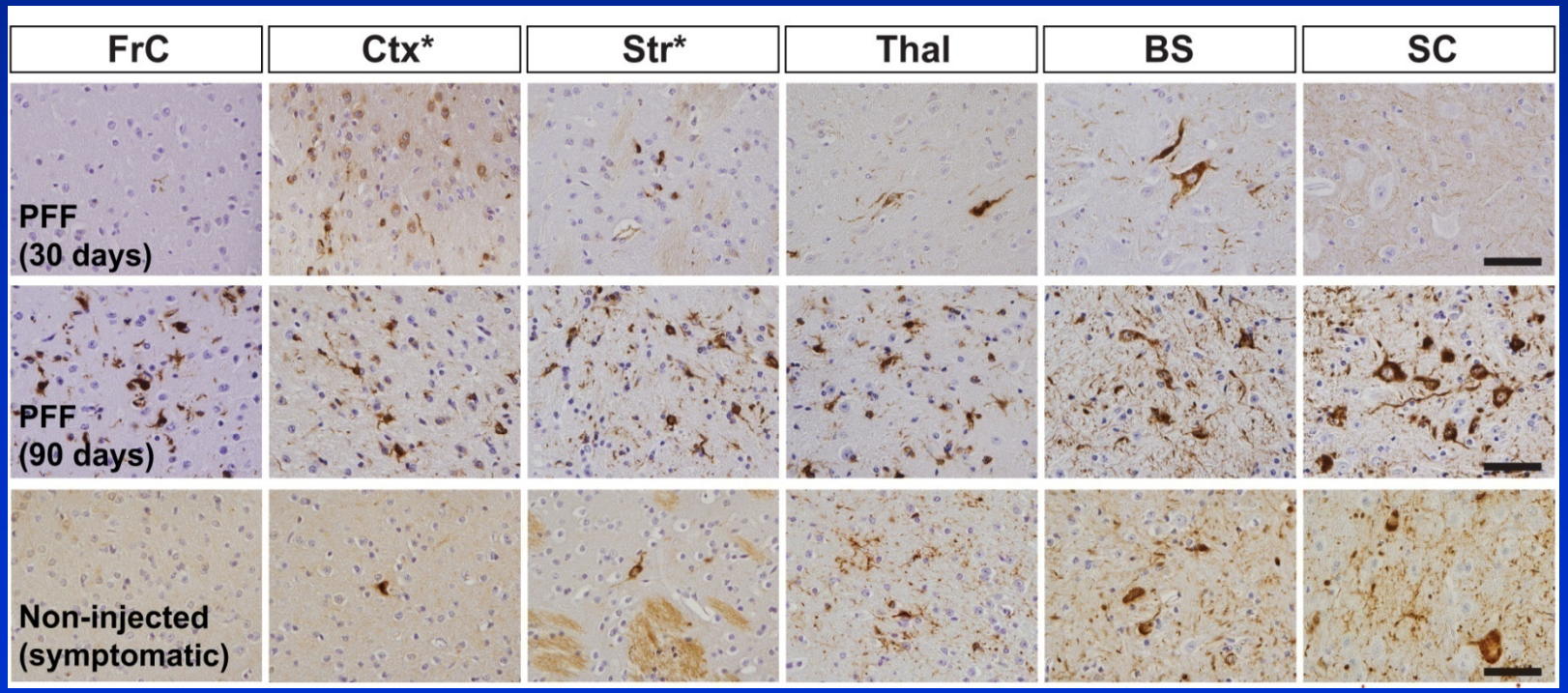
Recombinant α-Syn Preformed Fibrils (PFFs) Accelerate α-Syn Pathology *in vivo*



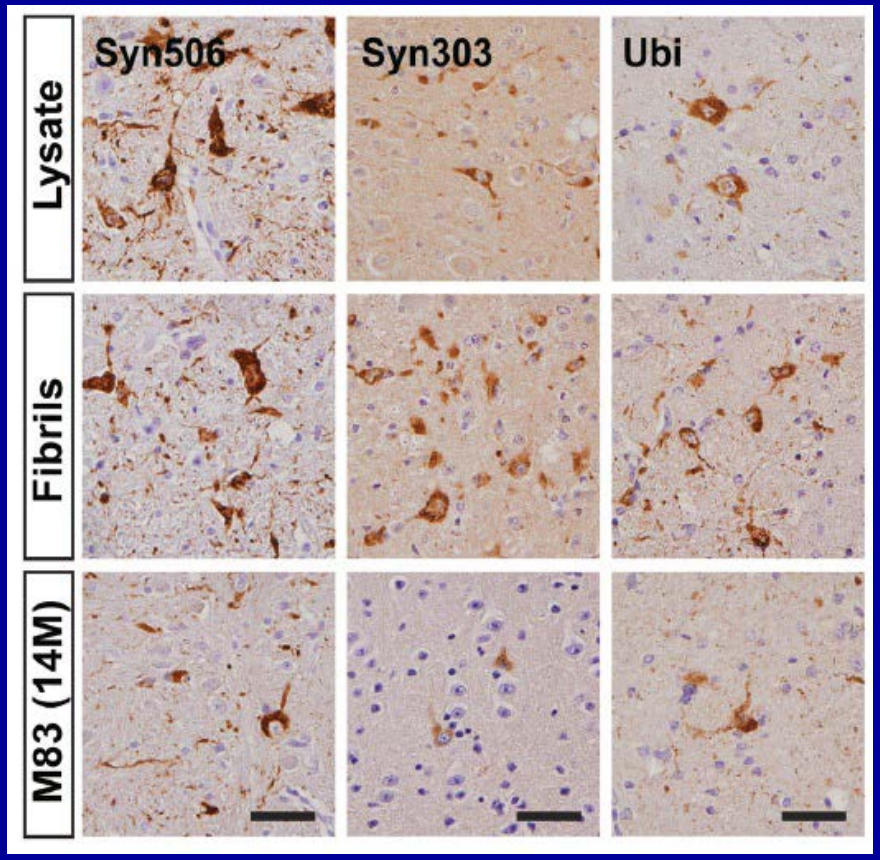
Luk et al., JEM, online, 2012

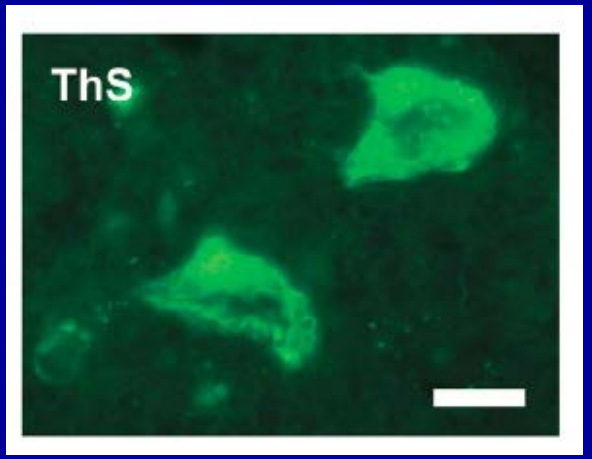


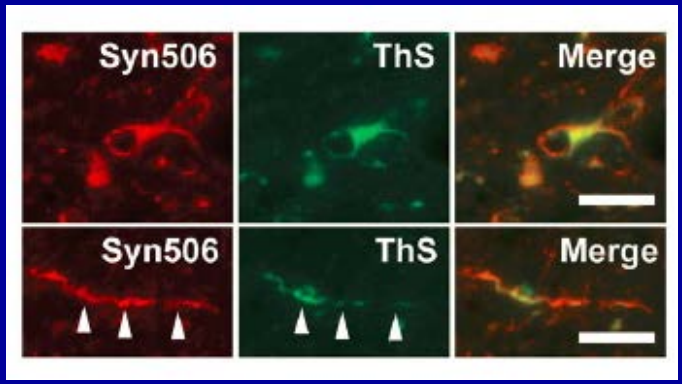




Transmission Induced α-Syn Inclusions In M83 Tg Mice Resemble Authentic Human Lewy Bodies/Neurites







Luk et al., JEM, online, 2012

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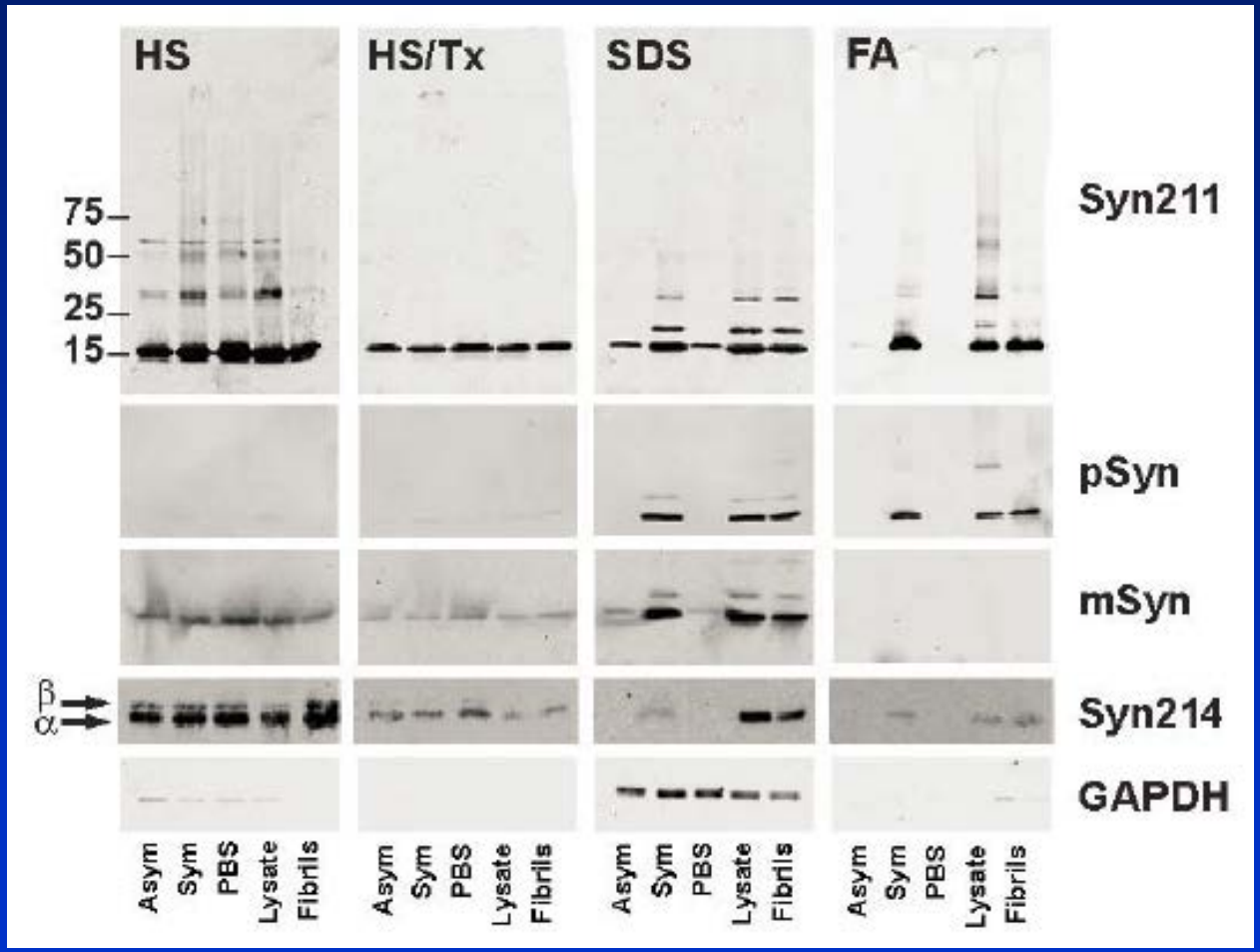
Transmission Induced α-Syn Inclusions Resemble Authentic α-Syn Biochemical Pathology In Human PD Brains



Luk et al., JEM, online, 2012

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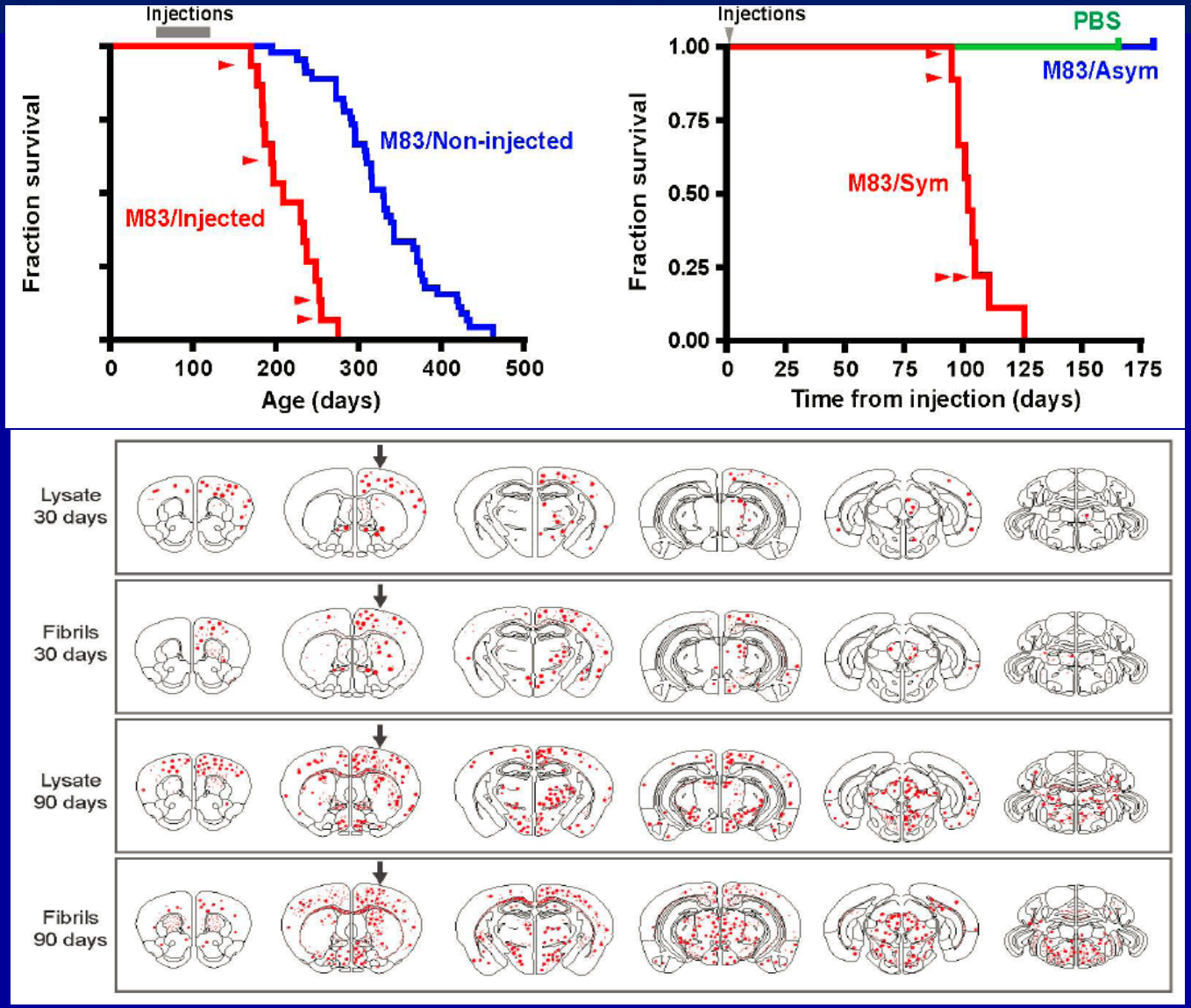
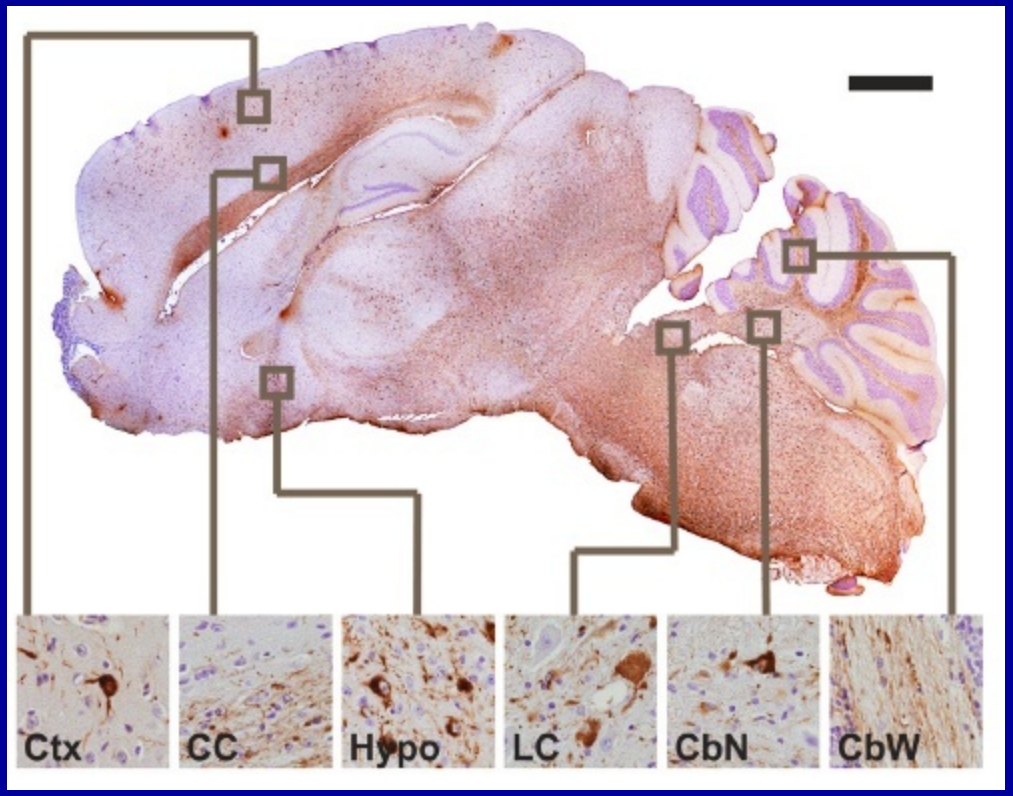
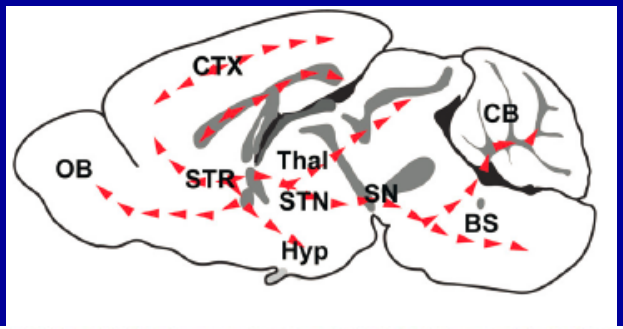
Transmission Induced α-Syn Pathology Accelerates Disease Onset And Correlates With Earlier Death Compared To Non-Injected M83 Tg Mice

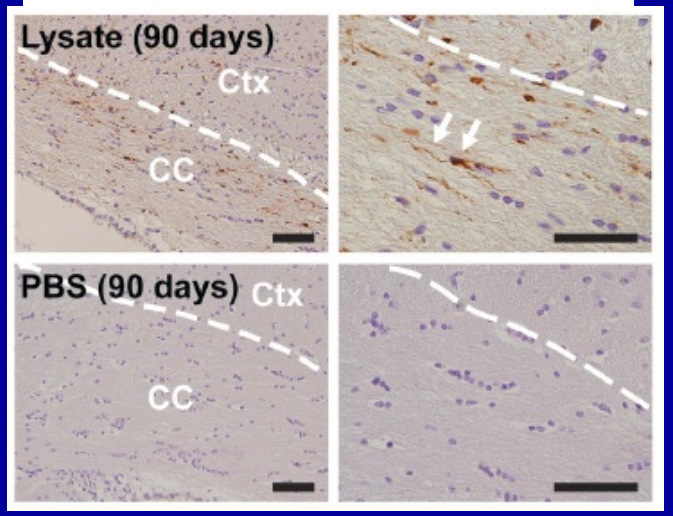


Luk et al., JEM, online, 2012

Pathways & Destinations Of Propagation & Transmission Of Injected Pathological α-Syn







Luk et al., JEM, online, 2012

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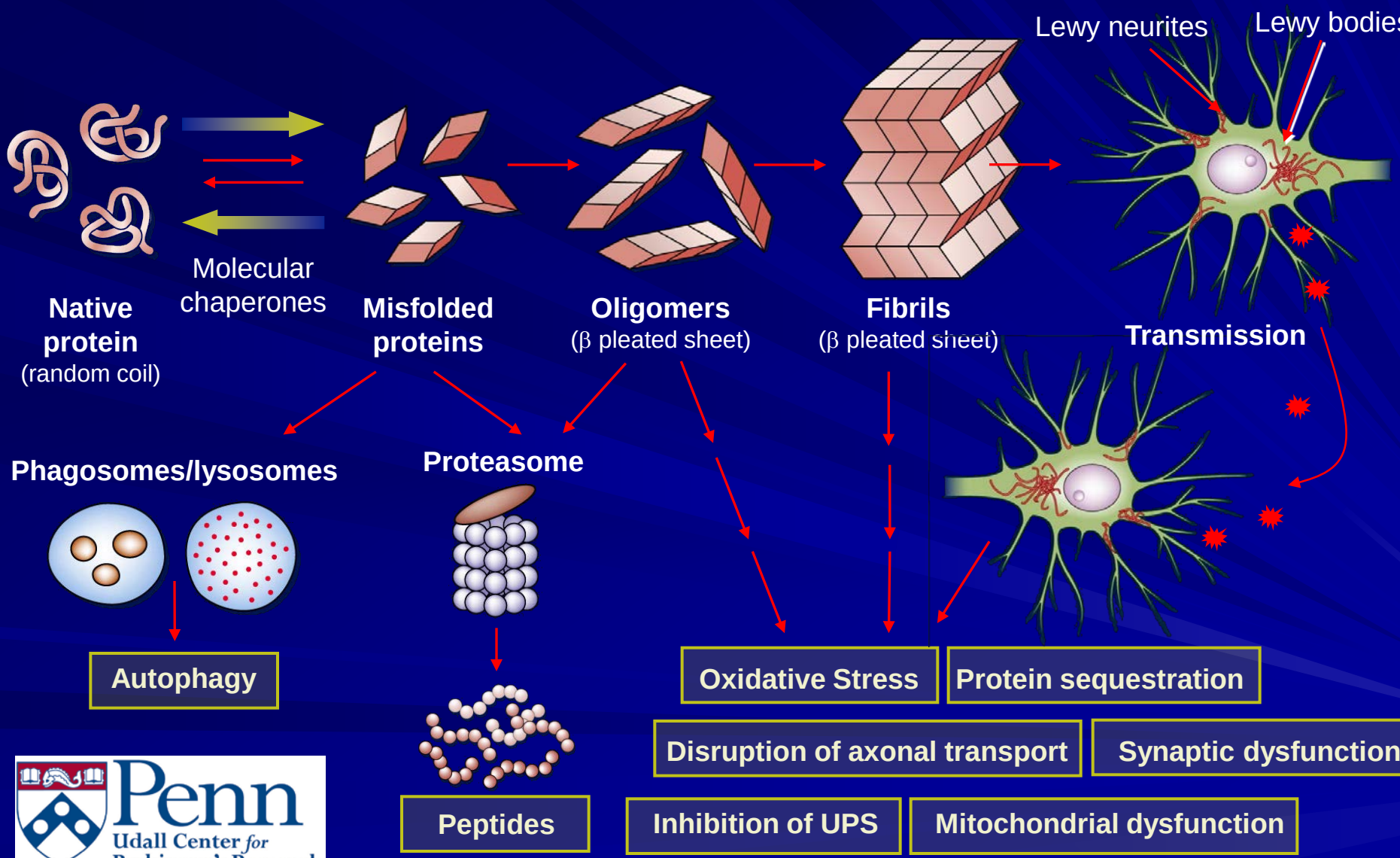
New Model of PD Progression by Transmission of α-Syn Pathology



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Does Transmission = Infectious Capability?

For CJD, the answer is yes, but for PD as well as AD, ALS, FTLD, published studies argue against this based on the data from the use of postmortem human pituitary extracts to treat thousands of children with GH deficiency from 1958 to 1985 when this treatment was stopped after the appearance of the papers below. In our collaborative studies with the CDC, we find that there have been no similar reports of the transmission of PD, AD, ALS or FTLD to this cohort, a small number of whom developed CJD ~20 years after treatment.

Brown P, Gajdusek DC, Gibbs CJ Jr., Asher DM. Potential epidemic of Creutzfeldt-Jakob disease from human growth hormone therapy. N Engl J Med 1985; 313: 728–731.

Powell-Jackson J, Weller RO, Kennedy P, Preece MA, Whitcombe EM, Newsom-Davis J. Creutzfeldt-Jakob disease after administration of human growth hormone. Lancet 1985; ii: 244–246.

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It Takes a Great Team!

CNDR α-SYN MODEL TEAM

V. Kehm, C. Li, K.C. Luk, P. O'Brien, D.M. Riddle, A. Stieber, S.A. Tanik, L.A. Volpicelli-Daley, B. Zhang
The entire CNDR Team

Virginia M-Y Lee

FORMER CNDR MEMBERS AND COLLABORATORS

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