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

<table>
<thead>
<tr>
<th>Disease</th>
<th>Lesions</th>
<th>Components</th>
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</thead>
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<tr>
<td>Alzheimer’s Disease (A multi-proteinopathy)</td>
<td>SPs (100%)</td>
<td>Aβ</td>
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<td></td>
<td>NFTs (100%)</td>
<td>Tau</td>
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<td></td>
<td>LBs (50%)</td>
<td>α-Synuclein</td>
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<td>TDP-43 (50%)</td>
<td>TDP-43</td>
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<tr>
<td>Frontotemporal Diseases</td>
<td>Inclusions</td>
<td>Tau, TDP-43, FUS</td>
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<tr>
<td>Amyotrophic Lateral Sclerosis</td>
<td>Inclusions</td>
<td>TDP-43, FUS, Tau</td>
</tr>
<tr>
<td>Parkinson’s disease +/- Dementia</td>
<td>LBs</td>
<td>α-Synuclein</td>
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<tr>
<td>Multiple System Atrophy</td>
<td>GCIs</td>
<td>α-Synuclein</td>
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<td>Prion diseases</td>
<td>SPs</td>
<td>Prions</td>
</tr>
<tr>
<td>Trinucleotide repeat diseases</td>
<td>Inclusions</td>
<td>Expanded polyglutamine repeats</td>
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</tbody>
</table>
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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PNAS | November 24, 2009 | vol. 106 | no. 47 | 20051-20056
Seeded inclusions exhibit biochemical properties of human Lewy bodies

Luk et al, PNAS, 2009
α-Syn fibril Transduction in Primary Neurons

Primary Hippocampal Neuron (5-10 DIV)

Pffs internalized by the Neuron Internalized Pffs recruit endogenous α-syn. Eventually, LB-like α-syn aggregates form in soma.

Pre-formed α-syn fibrils (Pffs)

Sonication

α-Syn fibril Transduction in Primary Neurons

Eventually, α-Syn aggregates in the Neuron and Soma (5-10 DIV).
α-Syn-hWT pre-formed fibrils (pffs) recruit endogenous α-syn to form pathologic, insoluble aggregates

Ultrastructure analysis of α-syn aggregates
Intracerebral inoculation of pathological α-synuclein initiates a rapidly progressive neurodegenerative α-synucleinopathy in mice

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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

α-Syn Filaments can be Isolated from A53T Tg Mice
Symptomatic Brain Lysate Injections Induce the Accumulation of Abnormal $\alpha$-Syn in Transgenic mice

Luk et al., JEM, online, 2012

M83 $\alpha$-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 $\alpha$-Syn Inclusions In M83 Tg Mice Resemble Authentic Human Lewy Bodies/Neurites

Luk et al., JEM, online, 2012
Transmission Induced α-Syn Inclusions Resemble Authentic α-Syn Biochemical Pathology In Human PD Brains

Luk et al., JEM, online, 2012
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
Native protein (random coil) → Misfolded proteins → Oligomers (β-pleated sheet) → Fibrils (β-pleated sheet) → Lewy neurites → Lewy bodies

Molecular chaperones

Phagosomes/lysosomes → Proteasome

Autophagy

Peptides

Oxidative Stress → Protein sequestration

Disruption of axonal transport → Synaptic dysfunction

Inhibition of UPS → Mitochondrial dysfunction

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


It Takes a Great Team!

CNDR α-SYN MODEL TEAM
The entire CNDR Team

Virginia M-Y Lee

FORMER CNDR MEMBERS AND COLLABORATORS

Supported by the NIH/NINDS Penn Udall Center, the Bellet Family, the Benaroya Family, the Keefer Family, the Picower Foundation, the Parkinson Council of Philadelphia and the Families of our Patients