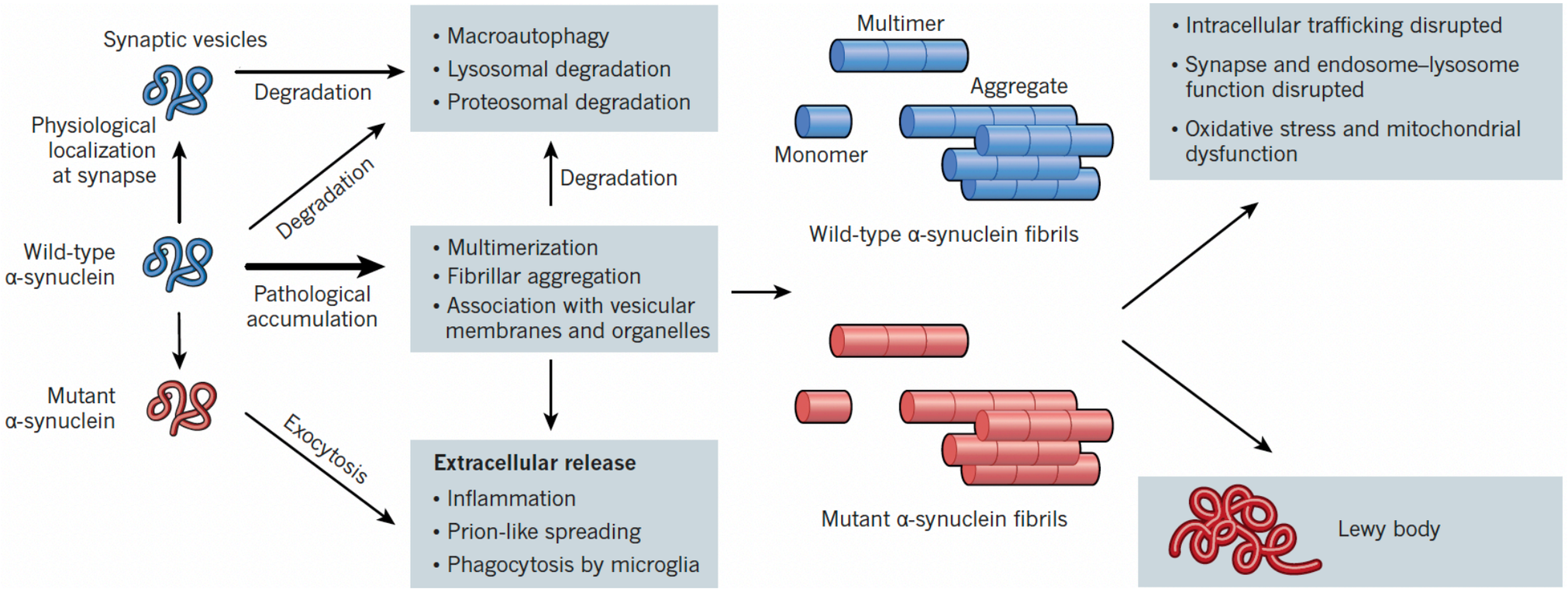
On the Relationship of α–synuclein and Parkinson's Disease

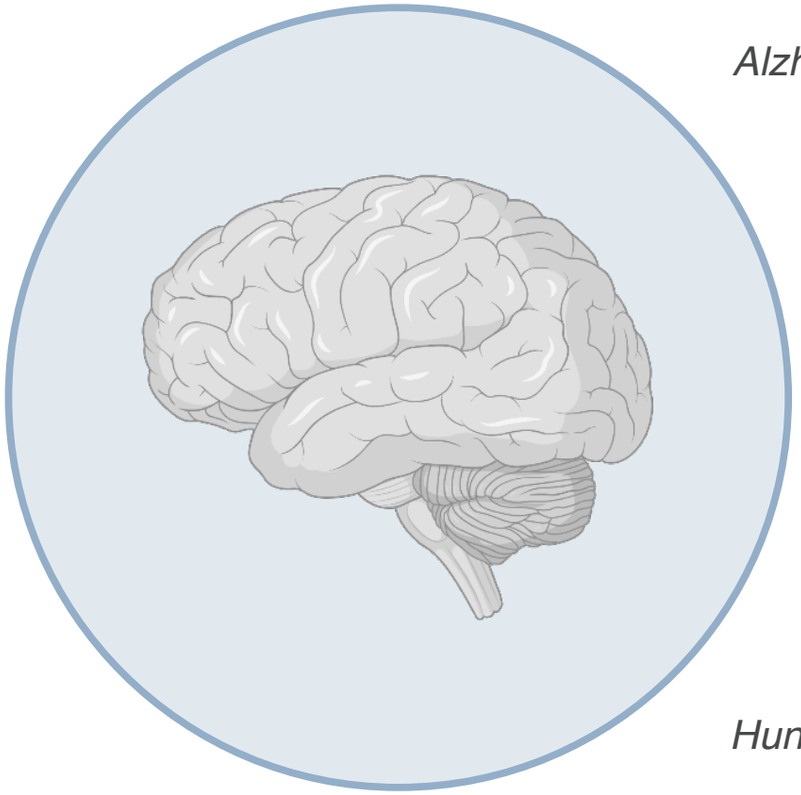


Nick Intermaggio

Group Meeting–Literature Review

Nov. 30th, 2021

Neurodegenerative Diseases



Alzheimers Disease

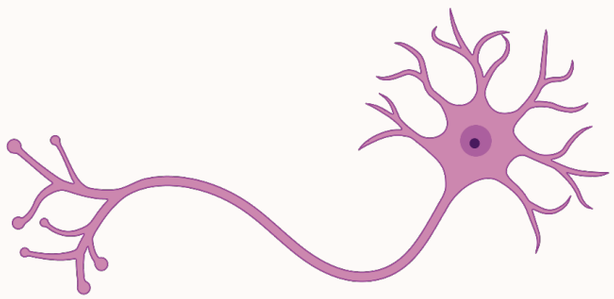
Parkinson's Disease

Multiple Sclerosis

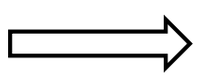
Muscular Distrophy

Amyotrophic Lateral Sclerosis

Huntington's Disease

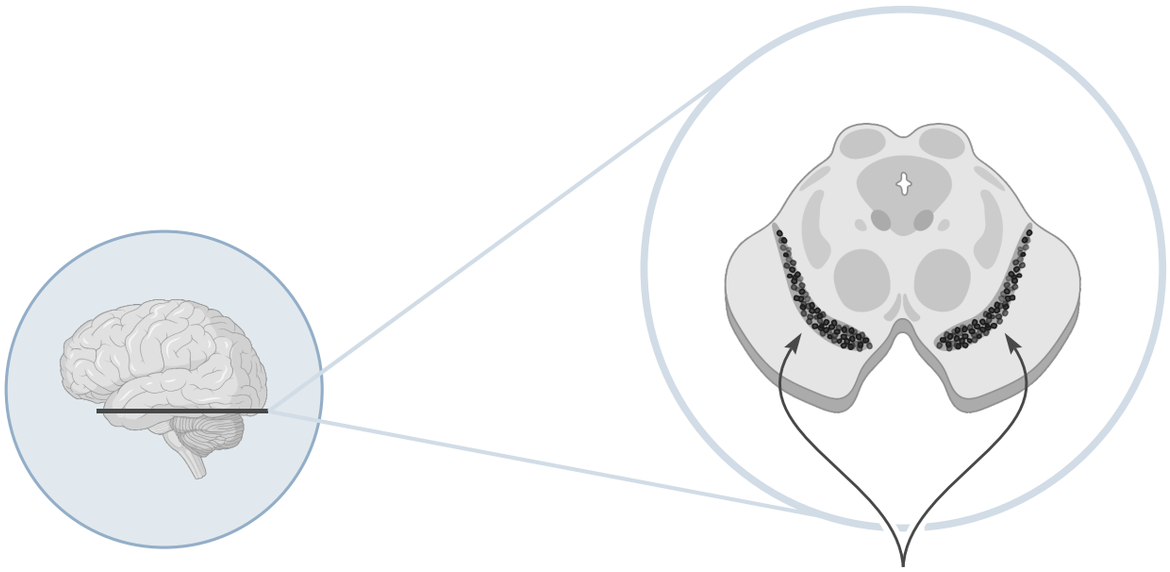


healthy neuron



degenerated neuron

Parkinson's Disease



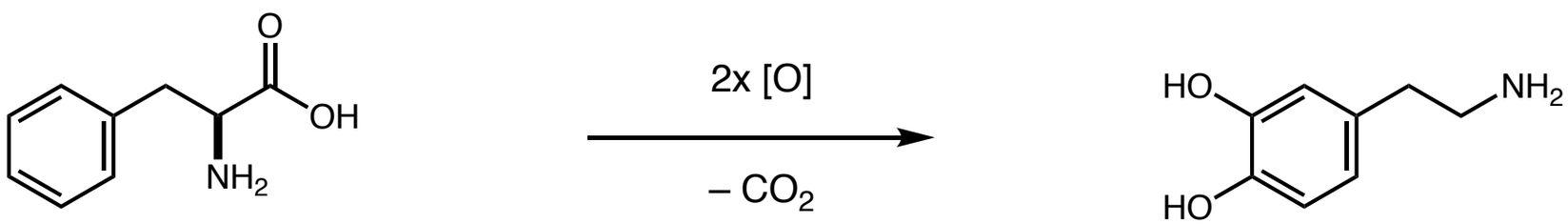
substantia nigra

death of dopaminergic neurons in substantia nigra

⇩

PD disease pathology

- Dopamine biosynthesis

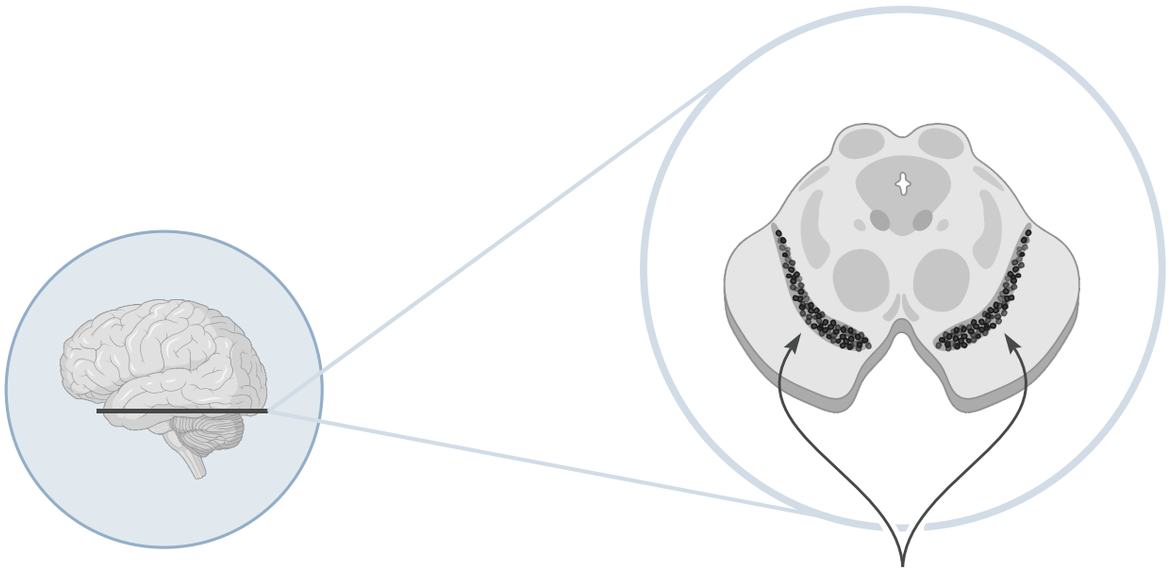


L-phenylanaline

Dopamine

Wang, X.; Li, J.; Dong, G.; Yue, J. *Eur. J. Pharmacol.* **2014**, *724*, 211

Parkinson's Disease



substantia nigra

death of dopaminergic neurons in substantia nigra

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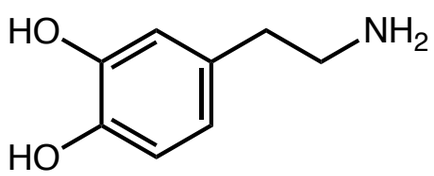
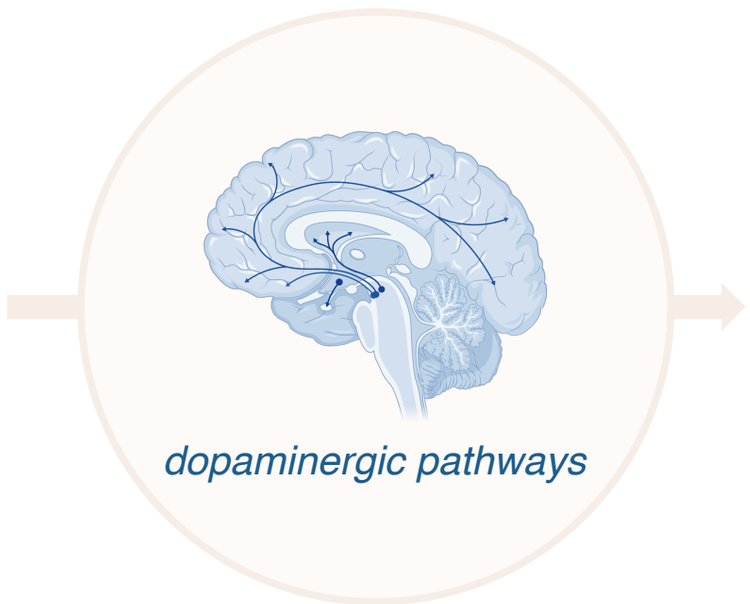
PD disease pathology



Dopamine

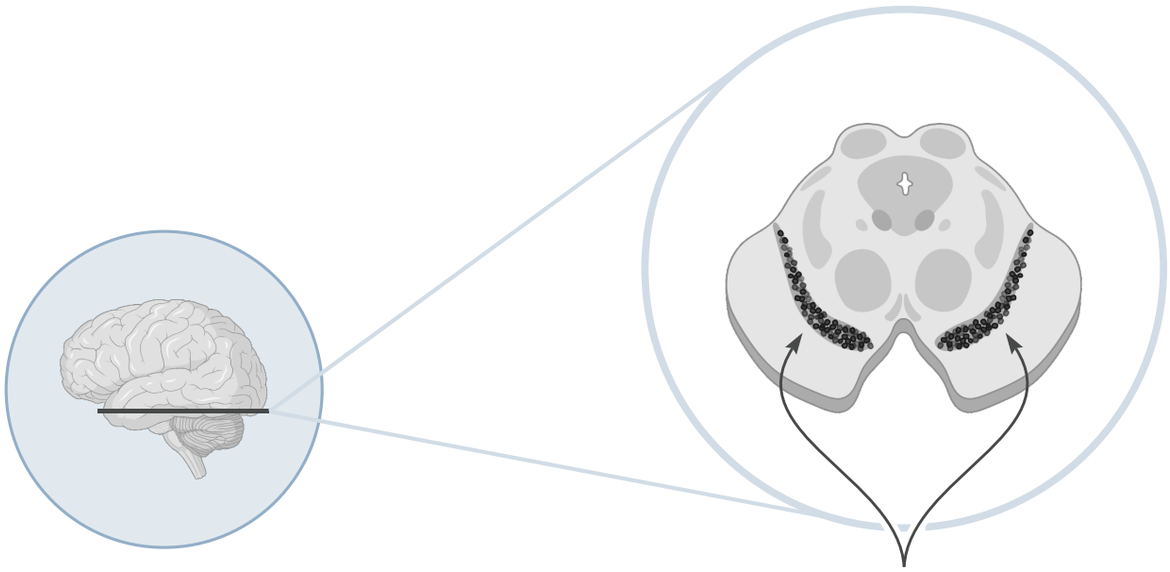


dopaminergic pathways

- *memory*
- *reward*
- *motivation*
- *motor function*

Hornykiewicz, O. *Pharmacological Reviews* **1966**, *18*, 925.

Parkinson's Disease



substantia nigra

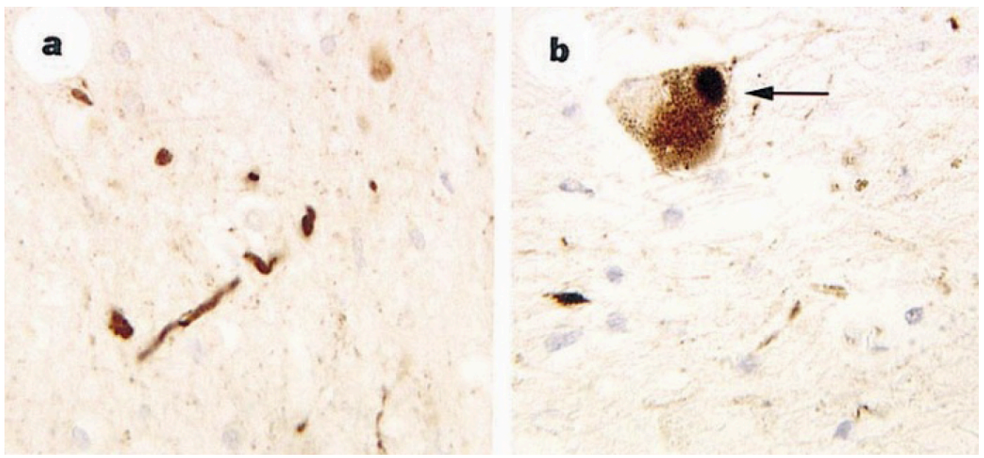
death of dopaminergic neurons in substantia nigra

PD disease pathology

Lewy Bodies

- *Insoluble protein aggregates*
- *Appearance preceeds cell death*
- *Histological Hallmark of PD*
- *Not diagnostically relevant*

Lewy Bodies in nerve cells of the substantia nigra



Spillantini, M. G.; Schmidt, M. L.; Lee, V. M.-Y.; Trojanowski, J. Q.; Jakes, R.; Goedert, M. *Science* **1997**, *388*, 839

Parkinson's Disease Pathology

- 2nd most common neurodegenerative disease
- 10 million cases worldwide, ~ 1 million cases in US
- 90% of cases currently have no validated genetic link
- **No cure or mechanism based treatment**

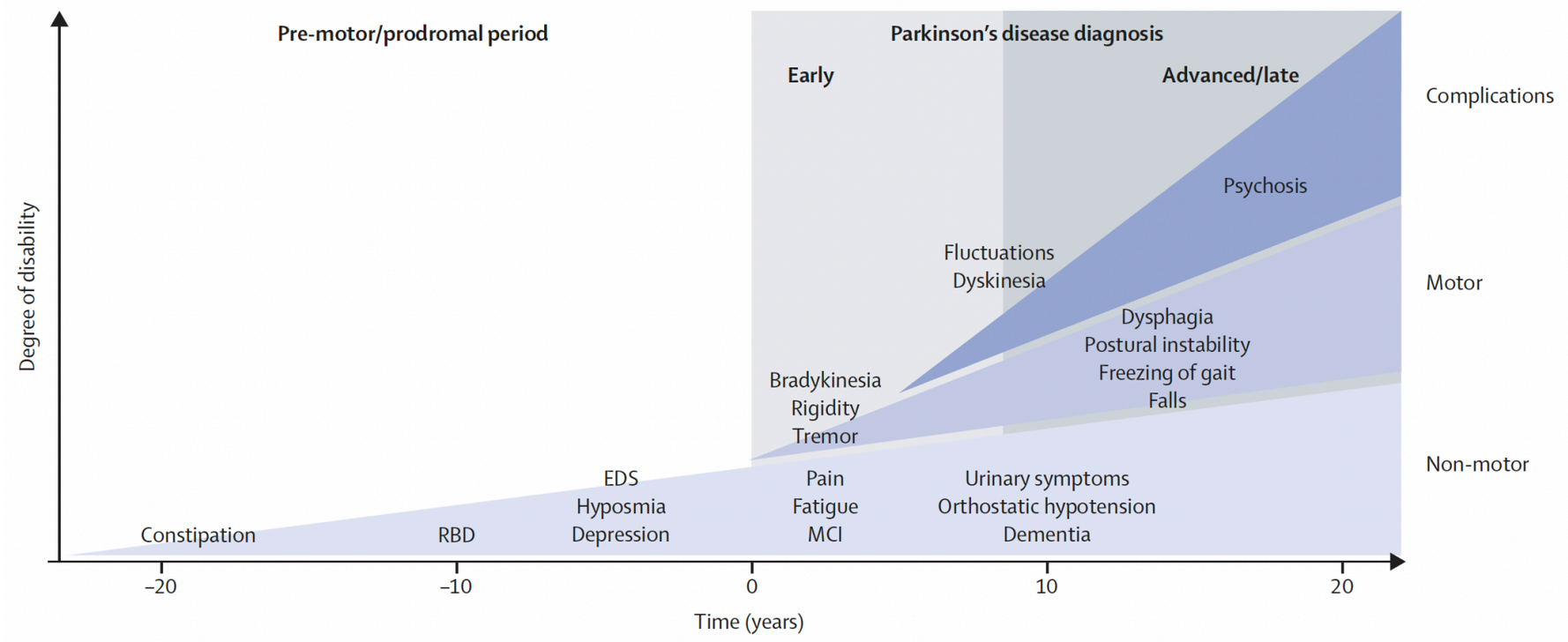
Motor Symptoms	Non-Motor Symptoms
Stiffness (rigidity)	*Cognitive problems*
Slowless (bradykinesia)	*Mood disturbances*
Resting tremor	*Psychosis*
	Difficulty sleeping

Diagnosis based on having **2 out of 3 motor symptoms**

Michael J. Fox Foundation for Parkinson's Research and *The Parkinson's Foundation*

Parkinson's Disease Pathology

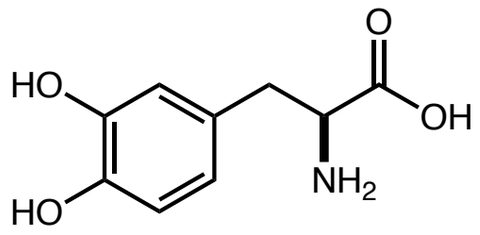
- 2nd most common neurodegenerative disease
- 10 million cases worldwide, ~ 1 million cases in US
- 90% of cases currently have no validated genetic link
- **No cure or mechanism based treatment**



Kalia, L. V.; Lang, A. E. *Lancet* **2015**, *386*, 896

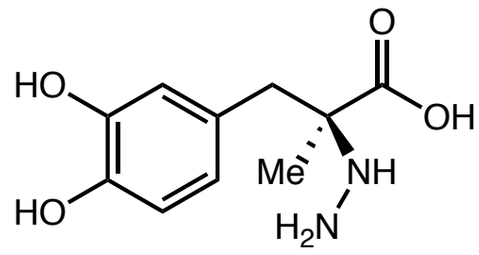
State of the Art Treatments

Sinemet®



Levadopa

biosynthetic dopamine precursor

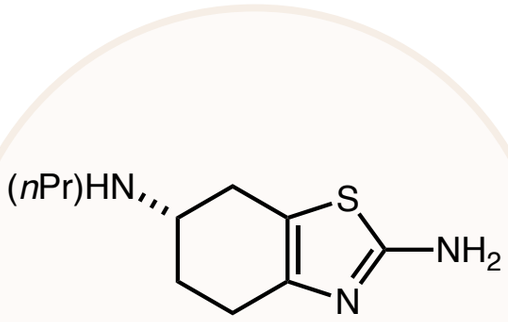


Carbidopa

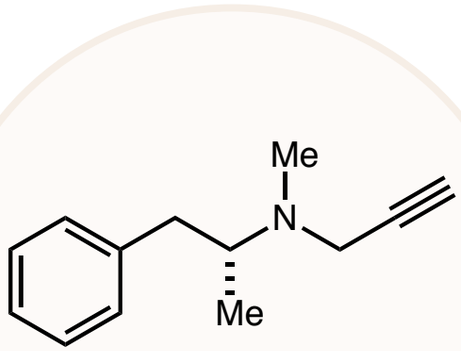
inhibitor of peripheral Levadopa metabolism

DRD3 Agonist

increases dopamine production in healthy neurons



Pramipexole



Selegiline

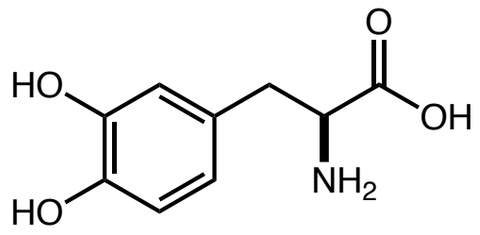
MAO-B Inhibitor

reduces dopamine metabolism in the brain

Charvin, D.; Medori, R.; Hauser, R. A.; Rascol, O. *Nat. Rev. Drug. Discov.* **2018**, *17*, 804
Marsden, C. D. *Clin. Neuropharmacol.* **1994**, *17*, S32

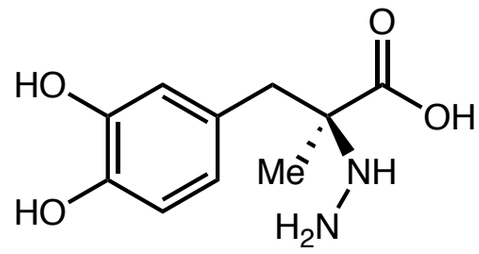
State of the Art Treatments

Sinemet®



Levadopa

biosynthetic dopamine precursor



Carbidopa

inhibitor of peripheral Levadopa metabolism

timeframe of efficacy

~ 5 years

Lack of longterm efficacy

Severe Side Effects

– dyskinesia

– motor fluctuations

– extreme behavior

Marsden, C. D. *Clin. Neuropharmacol.* **1994**, *17*, S32

State of the Art Treatments

Currently zero approved disease modifying

or neuroprotective treatments available

timeframe of

efficacy

~ 5 years

Lack of

longterm

efficacy

Severe

Side

Effects

– dyskinesia

– motor fluctuations

– extreme behavior

Marsden, C. D. *Clin. Neuropharmacol.* **1994**, *17*, S32

Limiting Factor in Novel Treatments

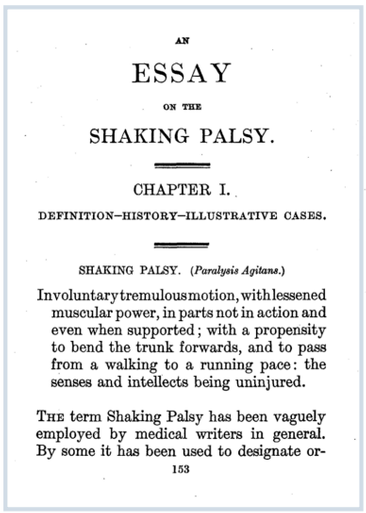
healthy neuron

degenerated neuron

What is the mechanism for selective dopaminergic cell death?

Historical Perspective

"An Essay on the Shaking Palsy" published by James Parkinson



AN

ESSAY

ON THE

SHAKING PALSY.

CHAPTER I.

DEFINITION—HISTORY—ILLUSTRATIVE CASES.

SHAKING PALSY. (*Paralysis Agitans.*)

Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured.

THE term Shaking Palsy has been vaguely employed by medical writers in general. By some it has been used to designate or-

153

James Parkinson (1755-1824)

1817

"… an important object proposed to be obtained by [this essay], is the…attention of those who humanely employ anatomical examination in ***detecting the causes and nature of diseases****… By their benevolent labors…appropriate modes of* ***relief, or even cure, can be pointed out****"*

Parkinson, J.; *An Essay on the Shaking Palsy.* London: Whittingham and Rowland for Sherwood, Neely, and Jones; **1817**

Historical Perspective

"An Essay on the Shaking Palsy" published by James Parkinson

1817

1865

Jean-Martin Charcot refers to the Shaking Palsy as "Parkinson's Disease"

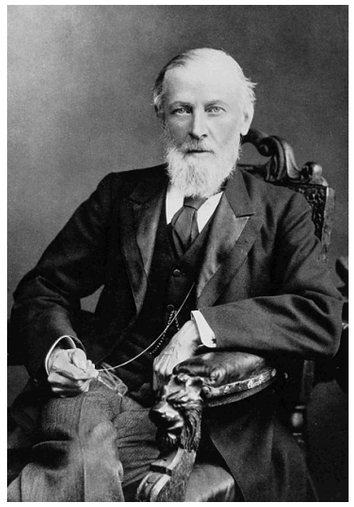
Jean-Martin Charcot
1825-1893

Przedorski, S. *Nat. Rev. Neurosci.* **2017**, *18*, 251

Historical Perspective

"An Essay on the Shaking Palsy" published by James Parkinson

William Gowers publishes "A Manual of Diseases of the Nervous System"



William Gowers (1845-1915)

1865

1817

1888

Jean-Martin Charcot refers to the Shaking Palsy as "Parkinson's Disease"

first documented visual represenation of PD phenotype

Przedorski, S. *Nat. Rev. Neurosci.* **2017**, *18*, 251

Historical Perspective

"An Essay on the Shaking Palsy" published by James Parkinson

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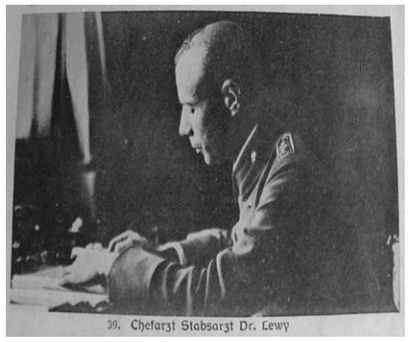
Lewy Bodies discovered and subsequently found in SN in PD

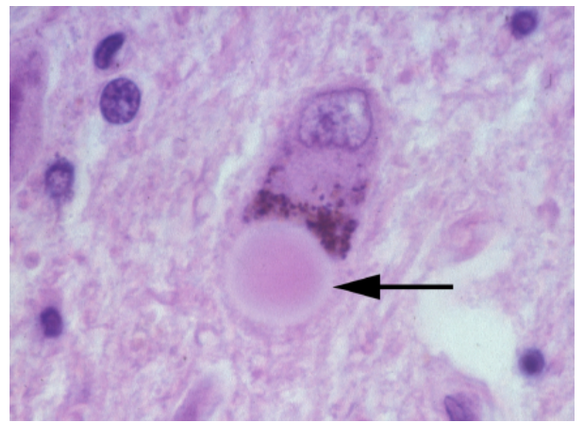
1913-1919



Fredrich Lewy (1885-1950)

Konstantin Tretiakoff (1892-1958)

Lewy bodies in substantia nigra (SN)



Donaldson, I. M. L. *J. R. Coll. Physicians Ednib* **2015**, *45*, 84
Przedorski, S. *Nat. Rev. Neurosci.* **2017**, *18*, 251

Historical Perspective

"An Essay on the Shaking Palsy" published by James Parkinson

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1865

1888

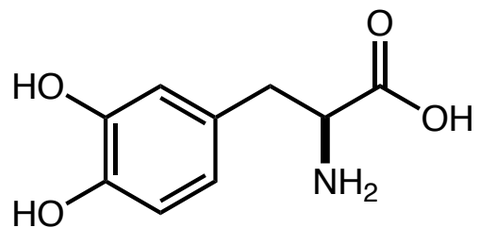
William Gowers publishes "A Manual of Diseases of the Nervous System"

Lewy Bodies discovered and subsequently found in SN in PD

1913-1919

First demonstration that L–DOPA has efficacy in treating PD symptoms

1961



levodopa (L–DOPA)

Donaldson, I. M. L. *J. R. Coll. Physicians Ednib* **2015**, *45*, 84
Przedorski, S. *Nat. Rev. Neurosci.* **2017**, *18*, 251

Historical Perspective

1817 — *"An Essay on the Shaking Palsy"* published by James Parkinson

1865 — *Jean-Martin Charcot refers to the Shaking Palsy as "Parkinson's Disease"*

1888 — *William Gowers publishes "A Manual of Diseases of the Nervous System"*

1913-1919 — *Lewy Bodies discovered and subsequently found in SN in PD*

1961 — *First demonstration that L–DOPA has efficacy in treating PD symptoms*

1990 — *2 forms of PD defined: 1) Genetic PD 2) Idiopathic PD*

Donaldson, I. M. L. *J. R. Coll. Physicians Ednib* **2015**, *45*, 84
Przedorski, S. *Nat. Rev. Neurosci.* **2017**, *18*, 251

Historical Perspective

α-synuclein linked to both genetic and sporadic forms of PD

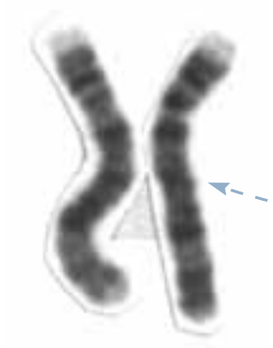
1997

Polymeropoulos, M. H. *et. al. Science* **1997**, *276*, 2045.
Spillantini, *et. al. Nature* **1997**, *388*, 839.

Two Key Breakthroughs in 1997

Polymeropoulos et. al.

June 1997



human chromosome 4

α-synuclein gene

(SNCA) 4q21–q22

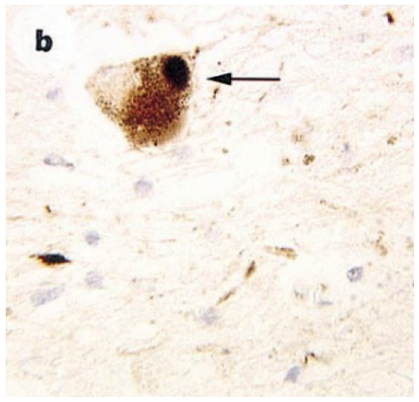
mutated in familial PD

Spillantini et. al.

August 1997

α-synuclein aggregates

are the main component of Lewy Bodies in Parkinson's Disease



Polymeropoulos, M. H. *et. al. Science* **1997**, *276*, 2045.
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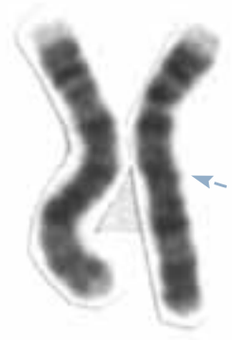


human chromosome 4

α-synuclein gene

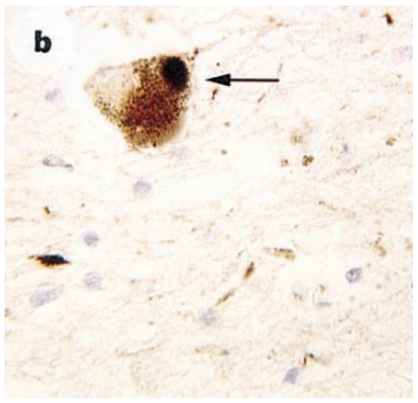
(SNCA) 4q21–q22

mutated in familial PD

Spillantini et. al.

August 1997

*"… a presynaptic protein with **no known function**"*



Polymeropoulos, M. H. *et. al. Science* **1997**, *276*, 2045.
Spillantini, *et. al. Nature* **1997**, *388*, 839.

Two Key Questions

what is the native function of α-synuclein?

is α-synuclein neurotoxic?

On the Link Between α-synuclein and Parkinson's Disease

I. Evidence for aSyn neurotoxicity

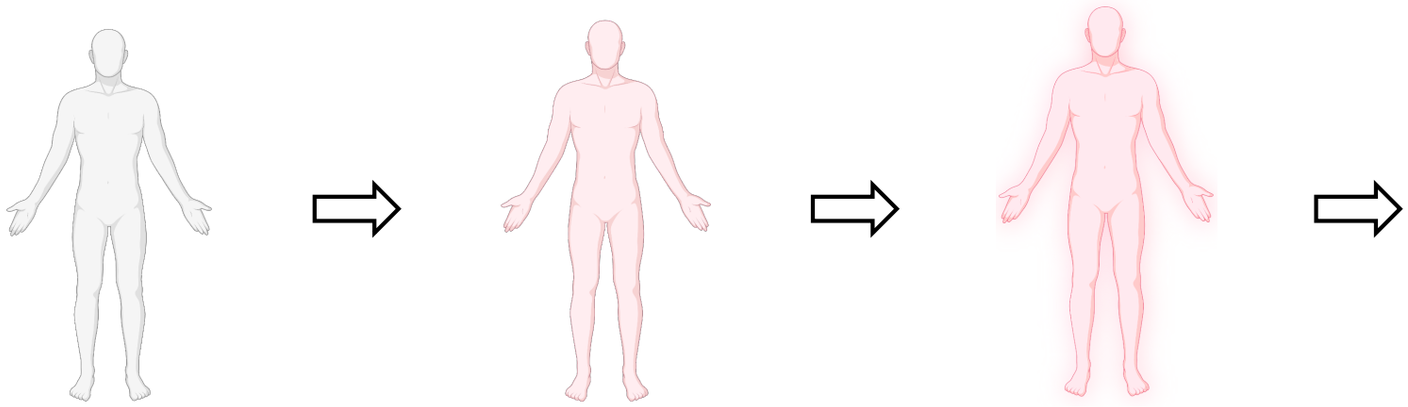
- *Evidence for aSyn toxicity*
- *aSyn structural polymorphism*

II. Link between aSyn function and neurodegeneration

- *Synaptic vesicle trafficking*
- *Autophagy/lysosomal disfunction*
- *Prion hypothesis*

III. Outlook

Genetic Evidence for α-synuclein Neurotoxicity



normal SNCA → *2x SNCA* → *3x SNCA*

- *early onset*
- *rapid cognitive decline*

expression of endogenous α-synuclein

↓

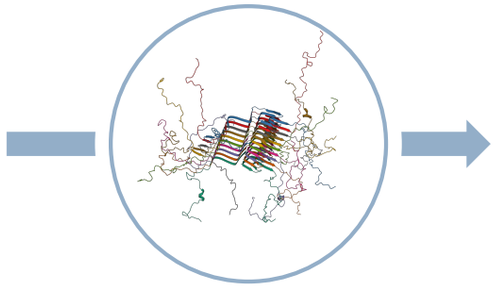
severity of disease phenotype

"allelic" **dose response relationship** links **expression and pathology**

Oliveira, L. M. A., *et. al. npj Parkinsons Dis.* **2021**, *7*, 65

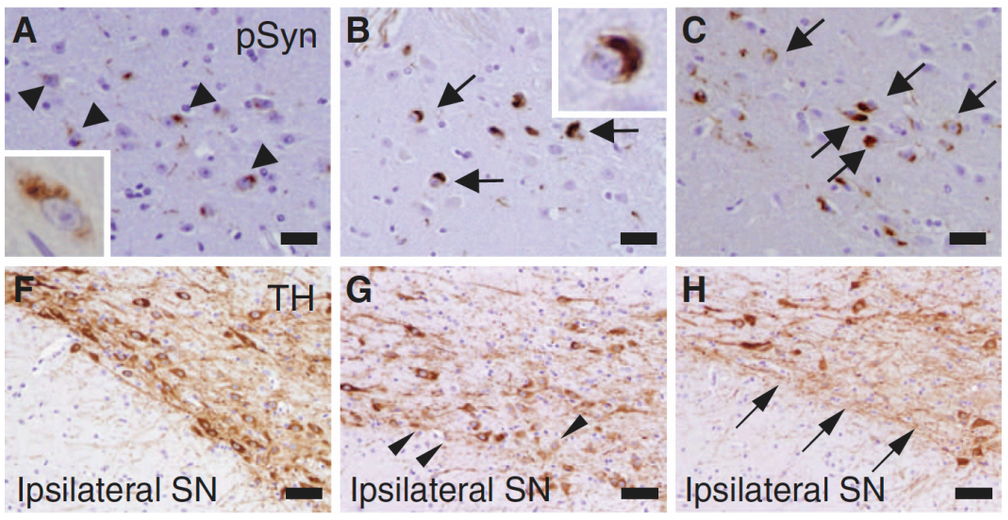
Evidence for Insoluble α-synuclein Aggregates as Neurotoxic Entities

wild type mouse

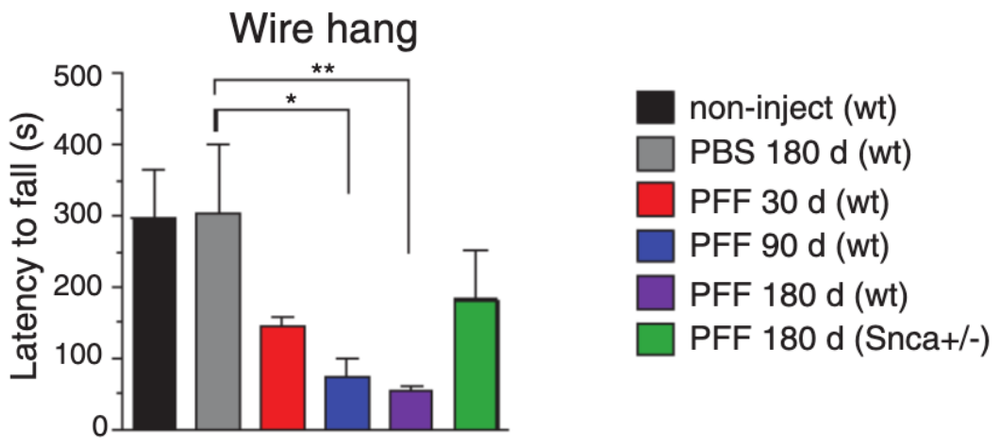


α-synuclein aggregate

PD phenotype



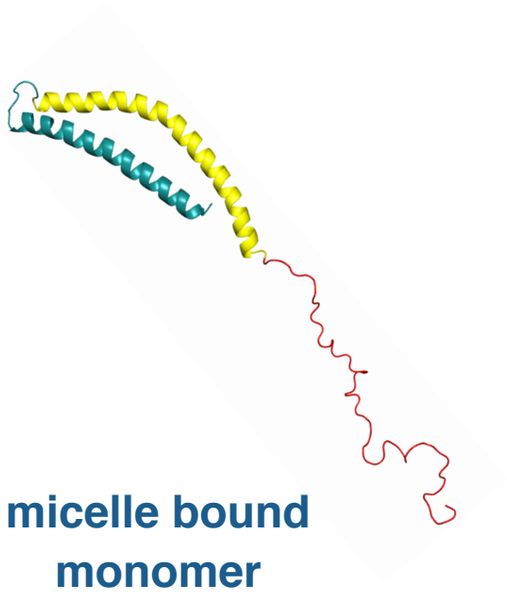
30 dpi 90 dpi 180 dpi



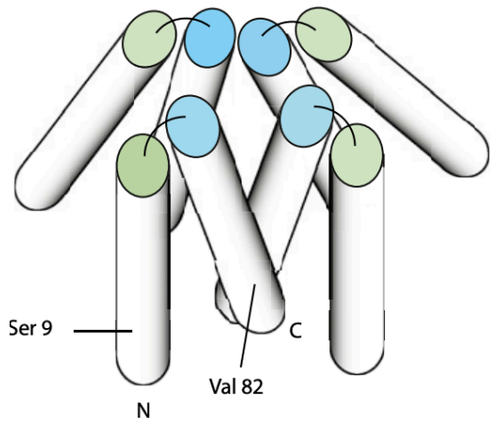
α-synuclein aggregates are neurotoxic ⇨ mechanism?

Luk, K. C. *et. al. Science* **2012**, *338*, 949

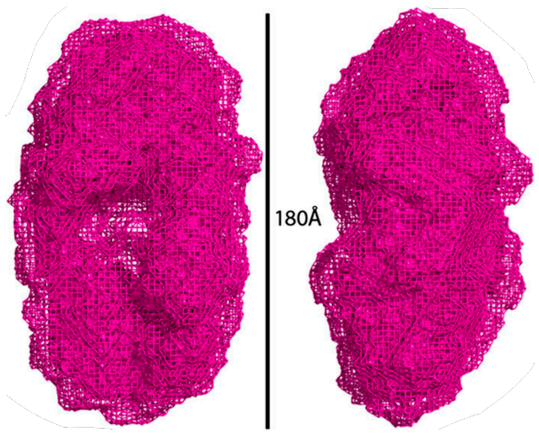
α-synuclein: Structure and Polymorphism



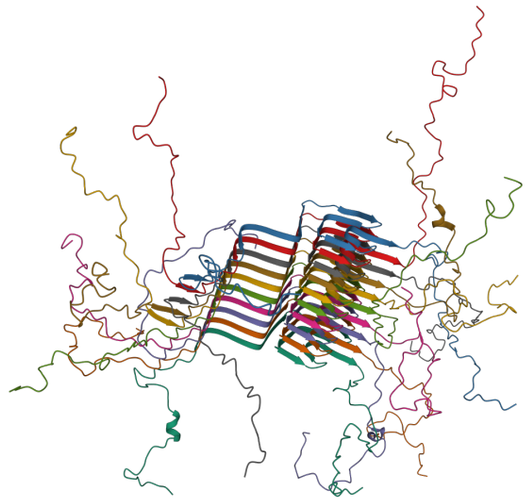
micelle bound monomer



tetramer



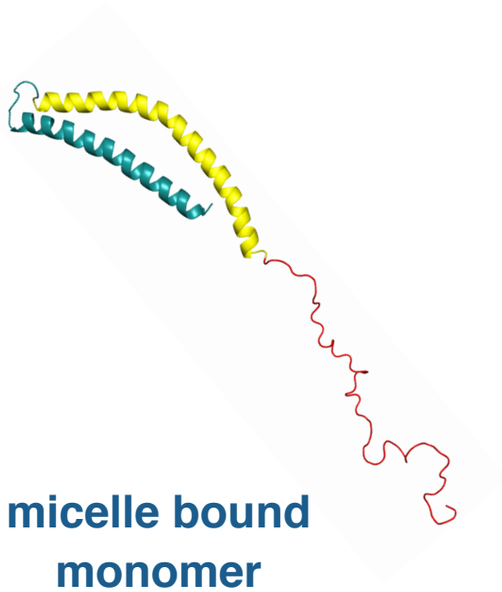
pre-amyloid fibrils



aggregated fibrils

Wang, W. *et. al. PNAS* **2011**, *108*, 17797,
Abeliovich, A. *et. al. Nature* **2016**, *539*, 207, Giehm, L. *et. al. PNAS*, **2011**, *108*, 3246

α-synuclein: Structure and Polymorphism



micelle bound monomer

*generally considered to be **non-toxic** but **non-innocent** in neurodegeneration*

Wang, W. *et. al. PNAS* **2011**, *108*, 17797,
Abeliovich, A. *et. al. Nature* **2016**, *539*, 207, Giehm, L. *et. al. PNAS*, **2011**, *108*, 3246

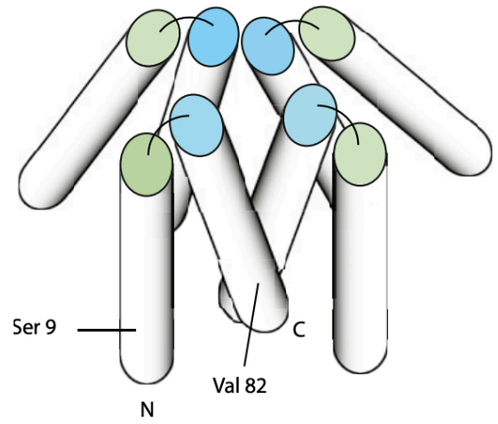
α-synuclein: Structure and Polymorphism

resists aggregation

and proposed to be a

non toxic aSyn

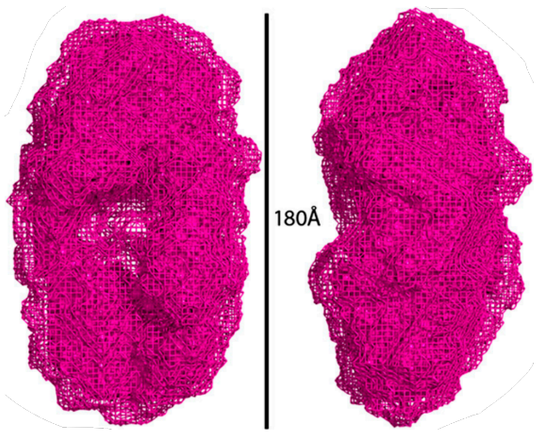
“resting state”



tetramer

Wang, W. *et. al. PNAS* **2011**, *108*, 17797, Bartels, T. *et. al. Nature* **2011**, *477*, 107
Abeliovich, A. *et. al. Nature* **2016**, *539*, 207, Giehm, L. *et. al. PNAS*, **2011**, *108*, 3246

α-synuclein: Structure and Polymorphism



pre-amyloid fibrils

proposed to be

*a t**oxic form of aSyn**.*

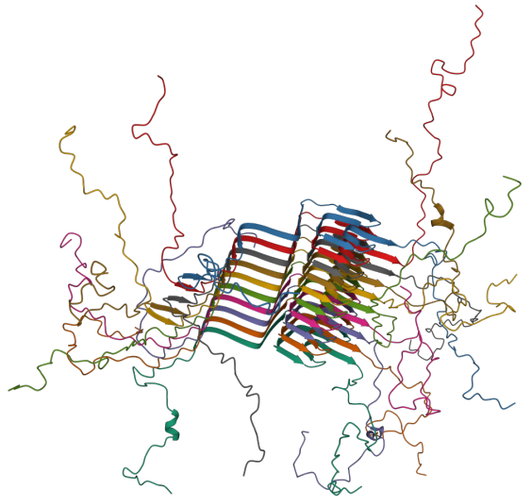
in vivo evidence for

“prion like” behavior

Wang, W. *et. al. PNAS* **2011**, *108*, 17797, Bartels, T. *et. al. Nature* **2011**, *477*, 107
Abeliovich, A. *et. al. Nature* **2016**, *539*, 207, Giehm, L. *et. al. PNAS*, **2011**, *108*, 3246

α-synuclein: Structure and Polymorphism

main component of ***Lewy Bodies****. Less neurotoxic than pre-amyloid fibril*



aggregated fibrils

Wang, W. *et. al. PNAS* **2011**, *108*, 17797,
Abeliovich, A. *et. al. Nature* **2016**, *539*, 207, Giehm, L. *et. al. PNAS*, **2011**, *108*, 3246

On the Link Between α-synuclein and Parkinson's Disease

I. Evidence for aSyn neurotoxicity

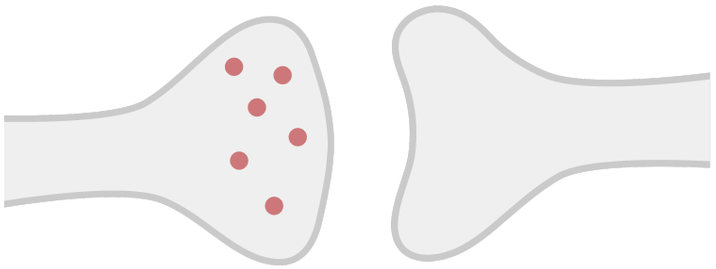
- *Evidence for aSyn toxicity*
- *aSyn structural polymorphism*

II. Link between aSyn function and neurodegeneration

- *Synaptic vesicle trafficking*
- *Autophagy/lysosomal disfunction*
- *Prion hypothesis*

III. Outlook

α-synuclein: Native Function



native disordered
aSyn in equilibrium

- native function not fully understood
- monomers/tetramers localize to presynaptic terminal
- involved in synaptic vesicle trafficking

aSyn KO mice

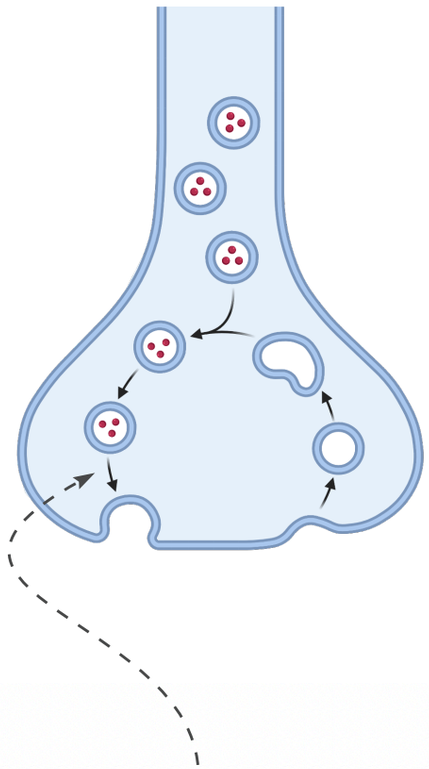
- **no functional defects**
- **increased** dopamine release
- no increase in cytosolic [dopamine]

overexpressed aSyn

- **neurodegeneration**
- **decreased** dopamine release
- altered **vesicle distribution**

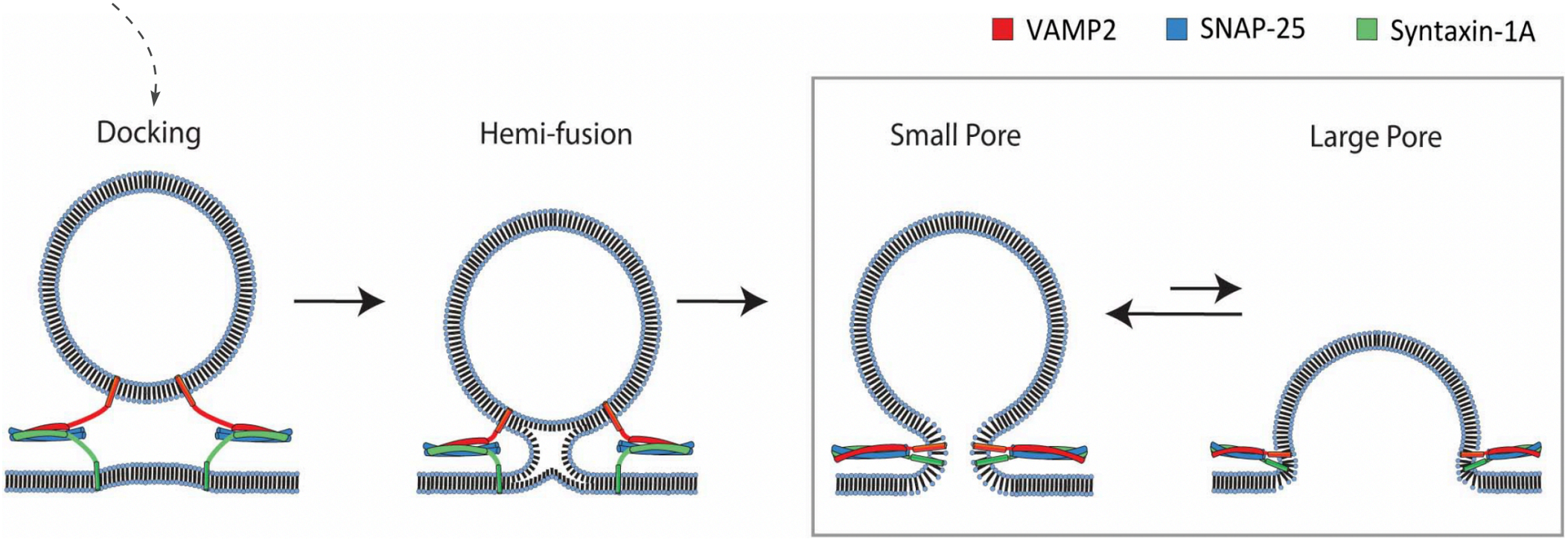
Wong, Y. C.; Krainc, D. *Nat. Med.* **2017**, *23*, 1

α-synuclein: SNARE Complex Formation



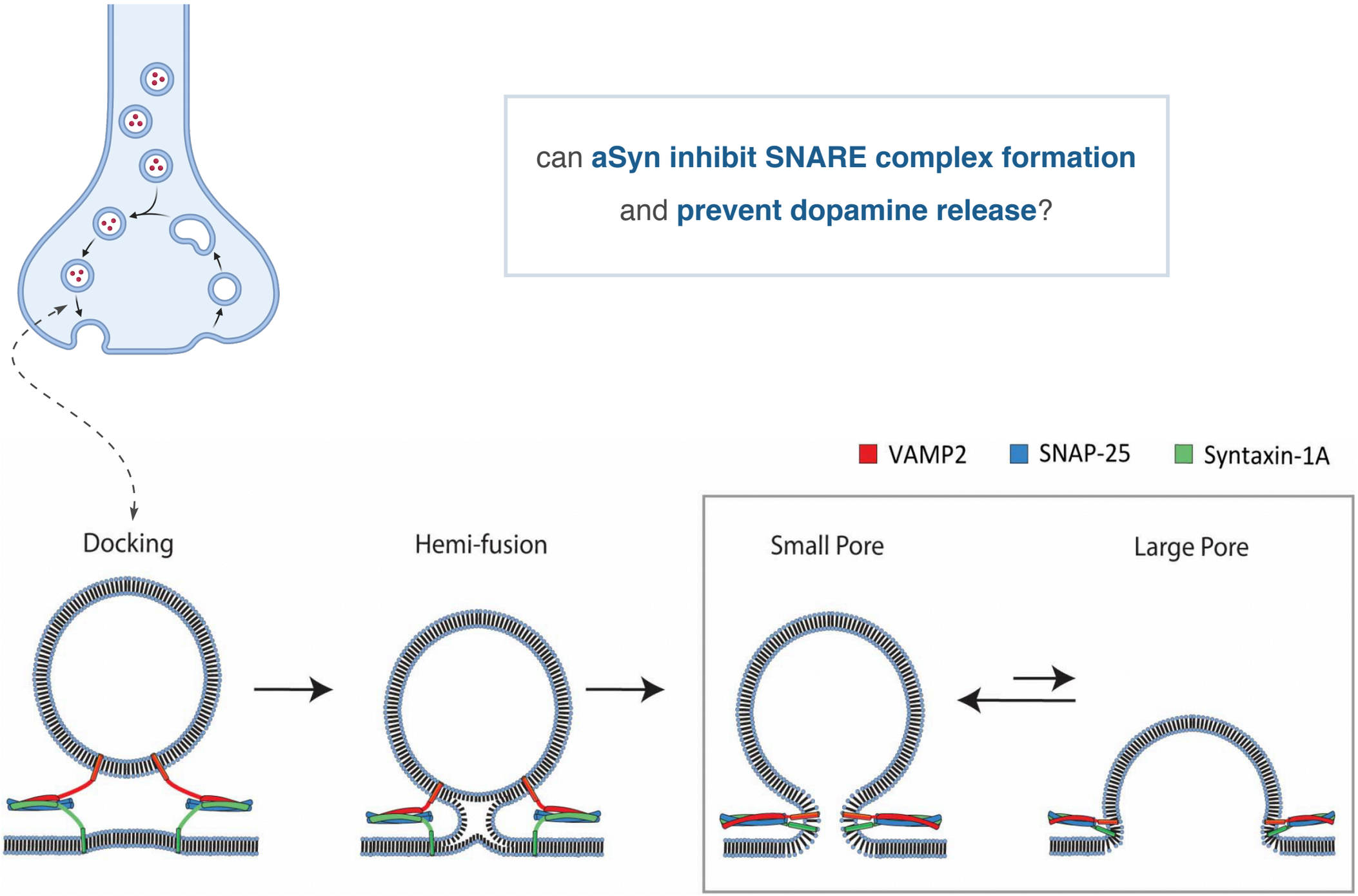
SNARE Complex

- *formation mediates exocytosis*
- *responsible for release of neurotransmitters*
- *aSyn alters synaptic vesicle trafficking*



Wong, Y. C.; Krainc, D. *Nat. Med.* **2017**, *23*, 1

α-synuclein: SNARE Complex Formation

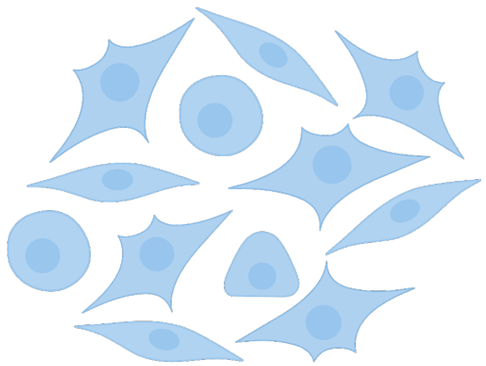


can **aSyn inhibit SNARE complex formation**

and **prevent dopamine release**?

Wong, Y. C.; Krainc, D. *Nat. Med.* **2017**, *23*, 1

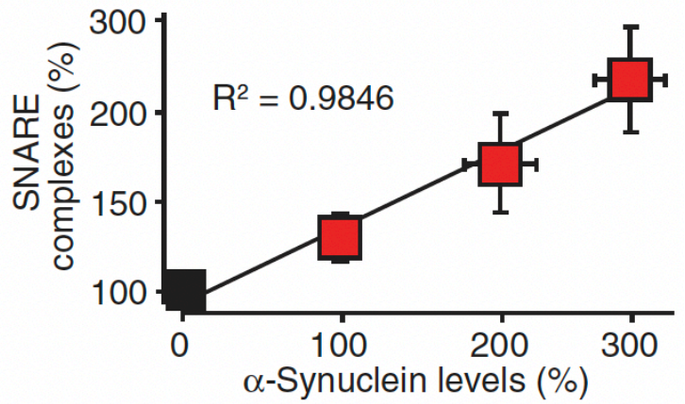
α-synuclein Promotes SNARE Complex Formation

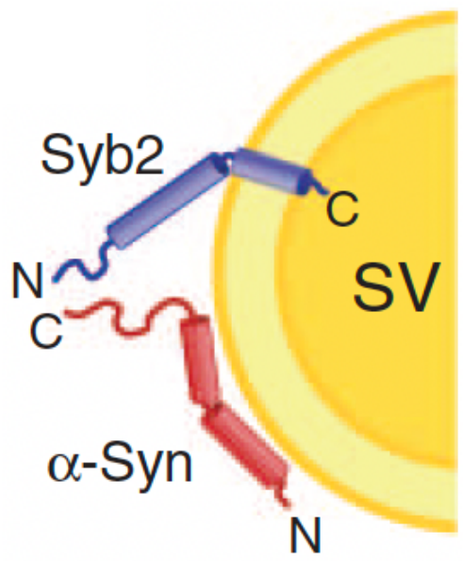


HEK293 T Cells

transfect with

aSyn



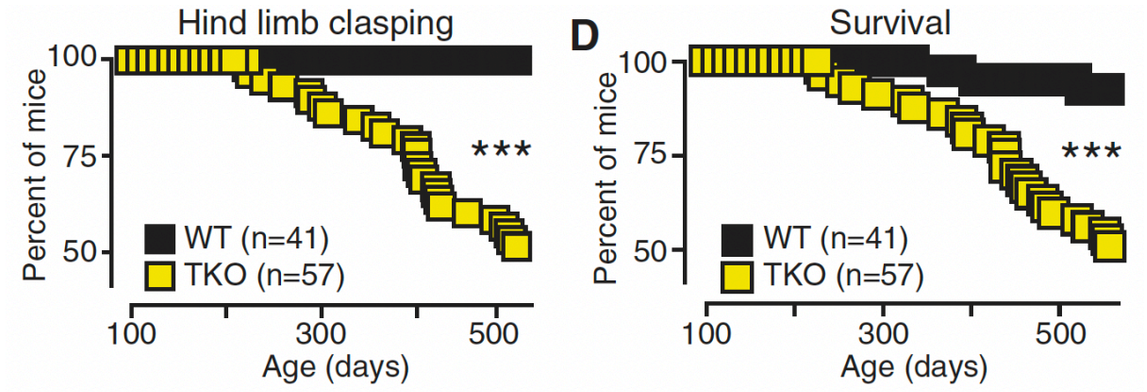


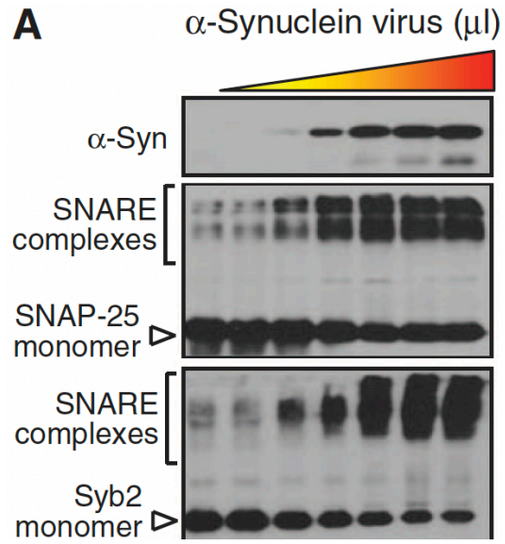
*aSyn binds **simultaneously***
*to **synaptic vesicles** and*
*surface protein **Syb2***
*to **facilitate SNARE formation***

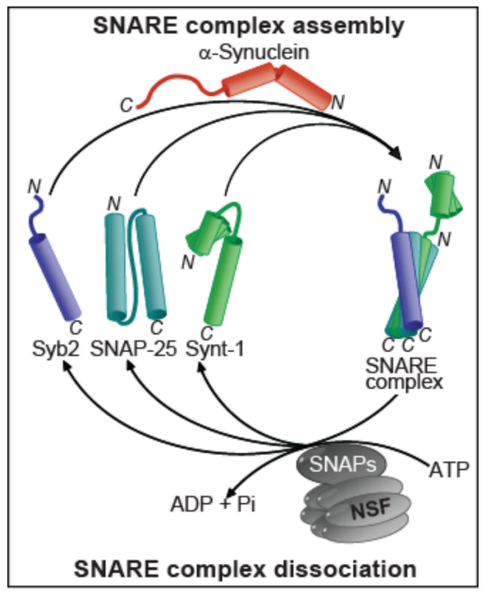
Burre, J. *et. al. Science* **2010**, *329*, 1663

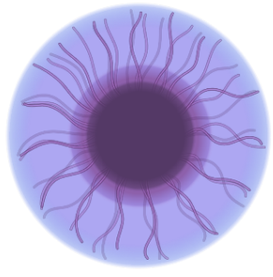
α-synuclein Promotes SNARE Complex Formation

TKO mice (α,β,γ-synuclein)









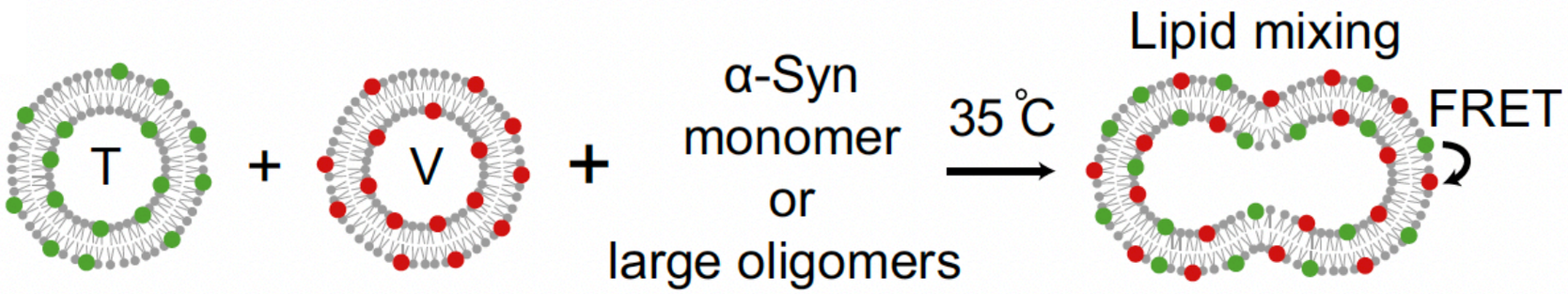
Lewy Body

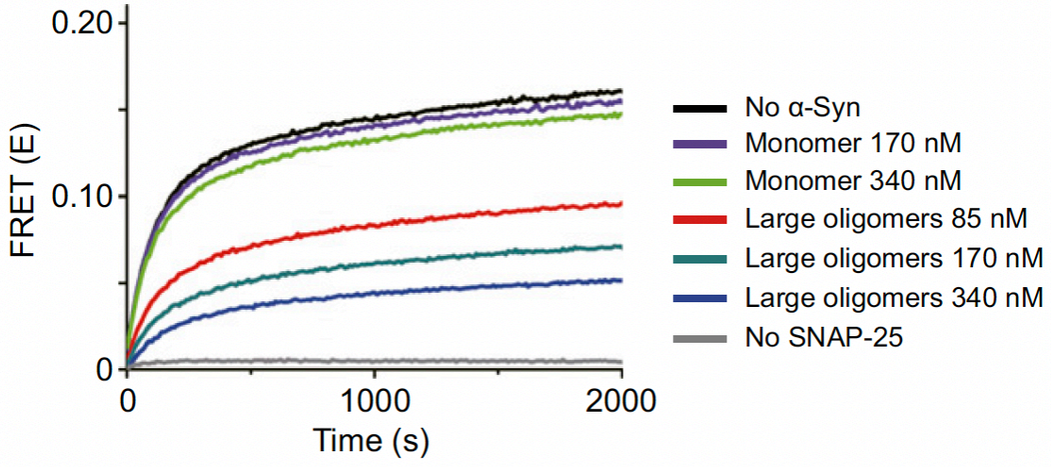
Hypothesis

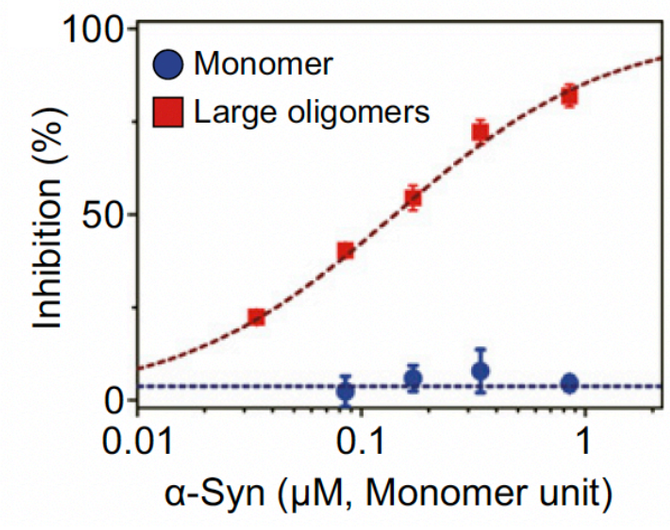
Age dependent ***sequestration of aSyn*** *by Lewy Bodies drives* ***neurodegeneration***

Burre, J. *et. al.* **2010**, *329*, 1663

α-synuclein Oligomers Inhibit Vessicle Fusion



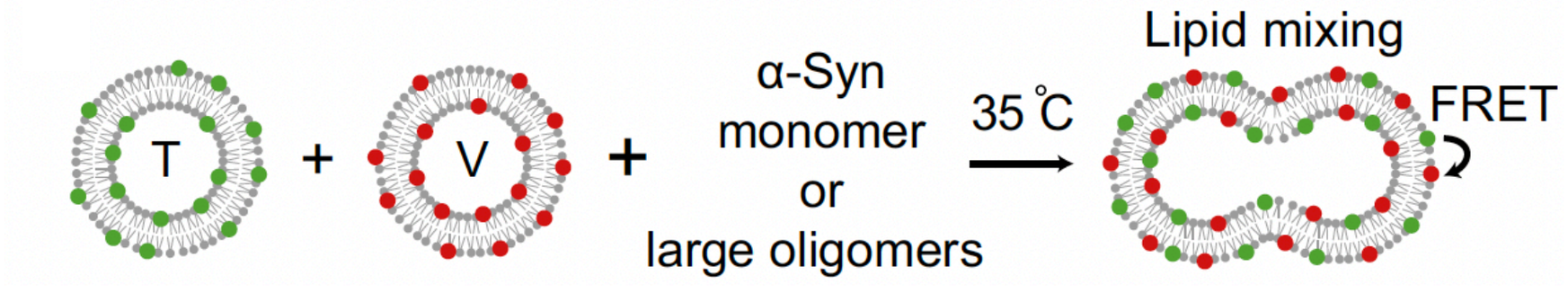


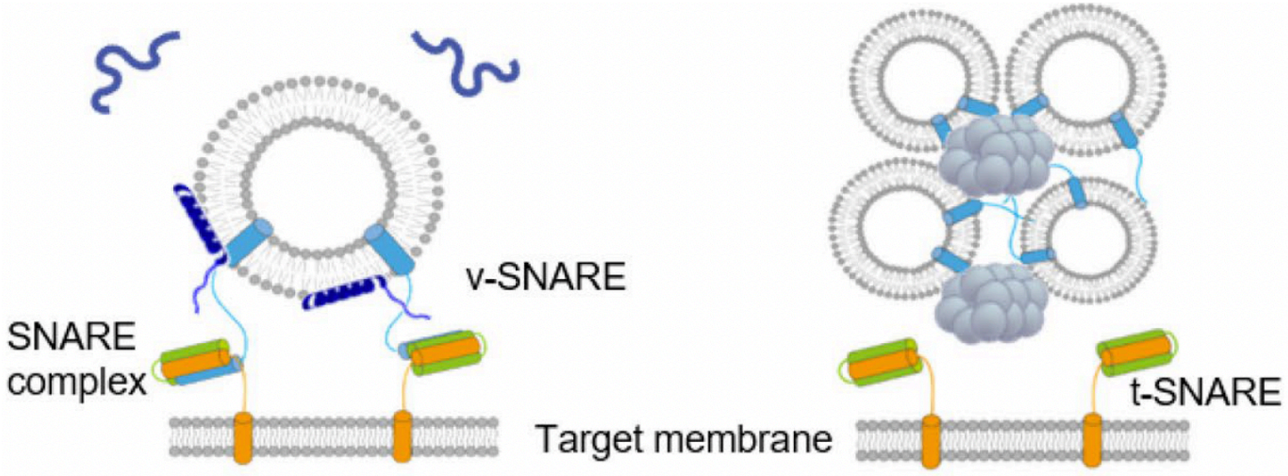


aSyn–SNARE interaction is **dependent on aSyn morphology**

Choi, B. K. *PNAS* **2013**, *110, 4087*

α-synuclein Oligomers Inhibit Vessicle Fusion





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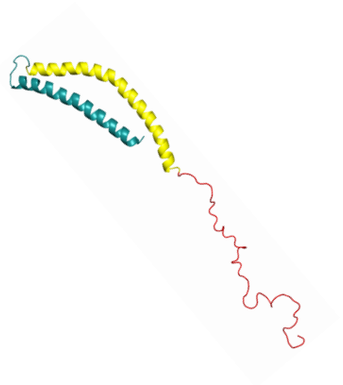
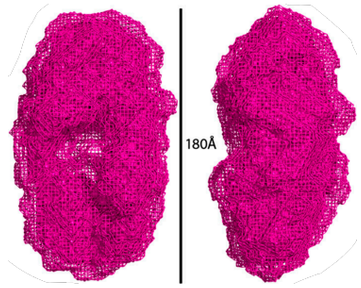
α-synuclein Monomers Potentiate Oligomer Toxicity

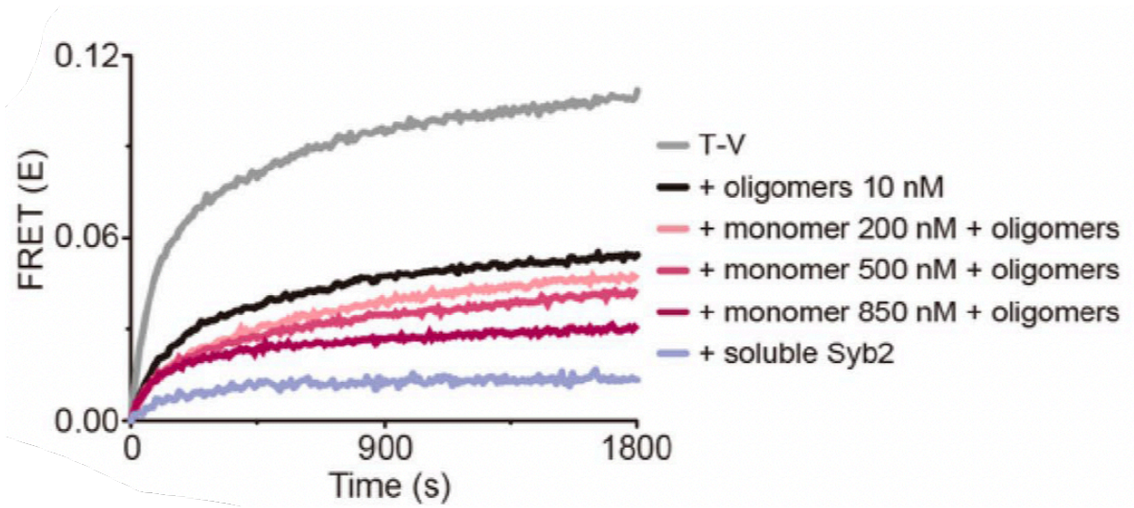


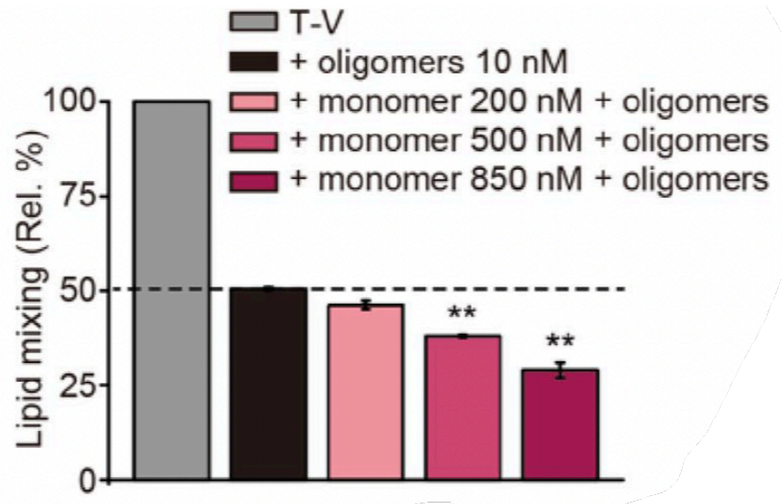
soluble monomer

cooperative inhibition



prefibril oligomers

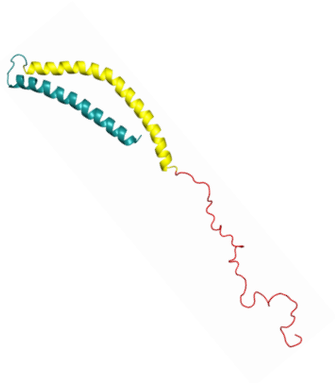




aSyn **monomers potentiate oligomer** driven **inhibition** of lipid mixing

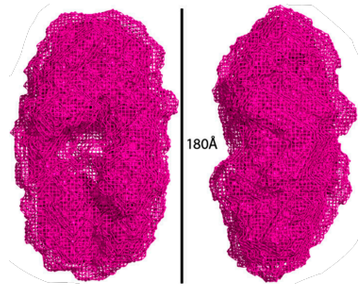
Yoo, G. *Sci. Rep.* **2021** *11*, 10955

α-synuclein Monomers Potentiate Oligomer Toxicity

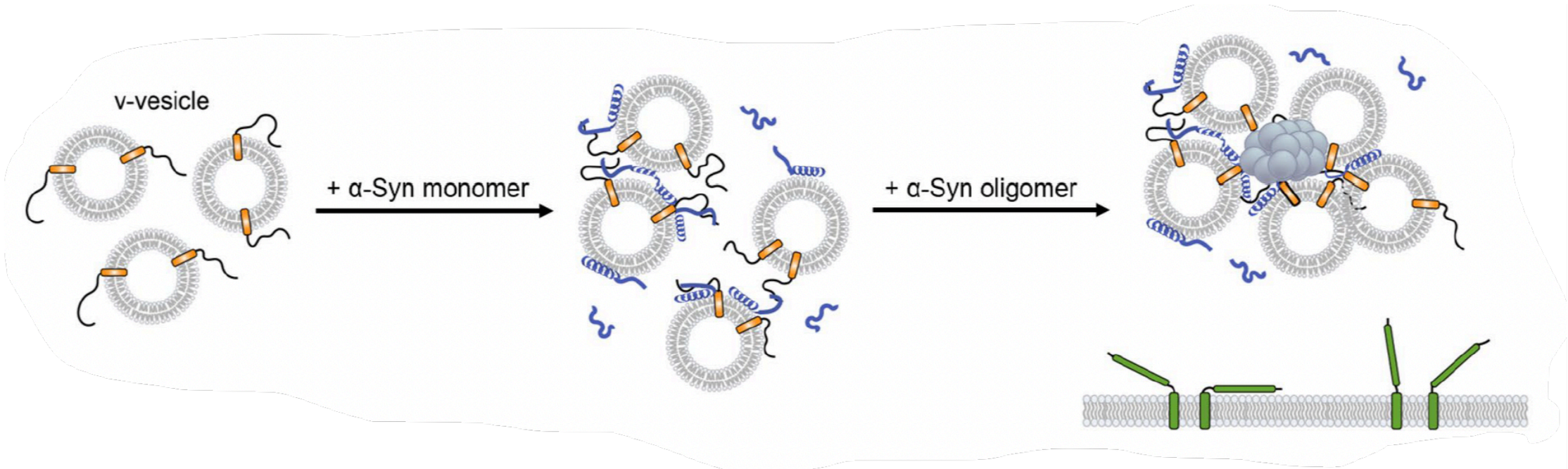


soluble monomer

cooperative inhibition



prefibril oligomers



Yoo, G. *Sci. Rep.* **2021** *11*, 10955

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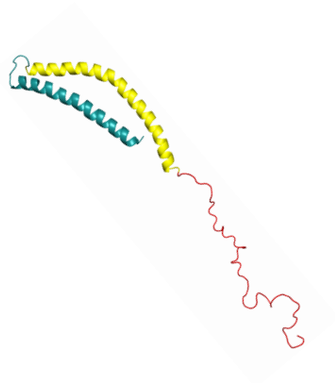
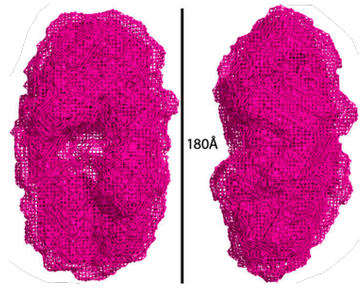


soluble monomer

cooperative inhibition



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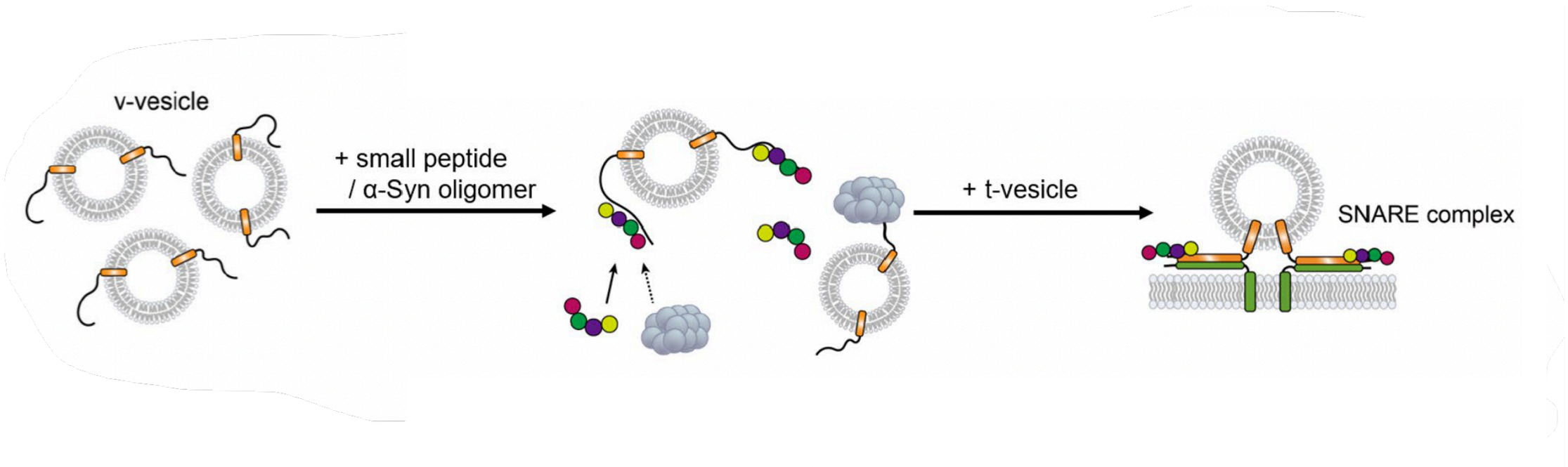


competitive binders to vesicle receptors prevent initial binding by aSyn monomers and inhibit deleterious vessicle clustering

Yoo, G. *Sci. Rep.* **2021** *11*, 10955

Synaptic Vessicle Trafficking

Vessicle Trafficking Hypothesis

aSyn monomers potentiate aSyn oligomer **inhibition of SNARE complex formation and exocytosis**

⇩

inhibited exocytosis prevents **dopamine and other neurotransmitters from reaching their destinations**, inhibiting motor function and ultimately leading to **neuron death**

On the Link Between α-synuclein and Parkinson's Disease

I. Evidence for aSyn neurotoxicity

- *Evidence for aSyn toxicity*
- *aSyn structural polymorphism*

II. Link between aSyn function and neurodegeneration

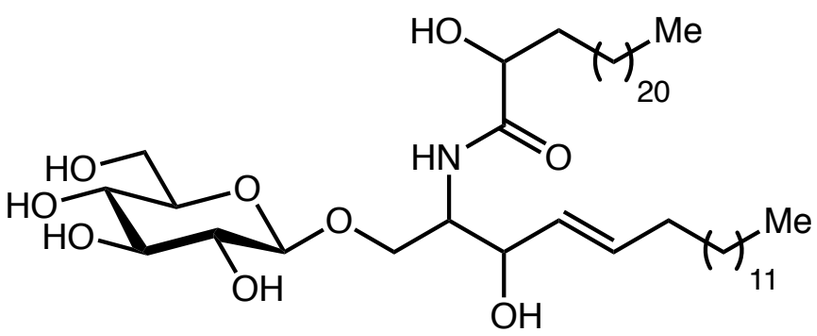
- *Synaptic vesicle trafficking*
- *Autophagy/lysosomal disfunction*
- *Prion hypothesis*

III. Outlook

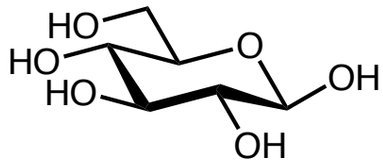
Additional Genetic Risk Factors – GBA and GCase

glucocerebrosidase (GCase)

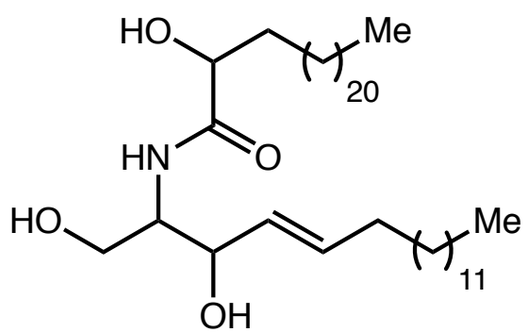
- *GBA mutation is the highest genetic risk factor for sporadic PD*
- *GBA codes for lysosomal protein* ***GCase***
- *Autosomal recessive GCase mutations cause Gaucher's Disease (GD)*
- *All mutations leading to* ***GCase disfunction increase PD risk***



glucosylceramide (GlcCer)



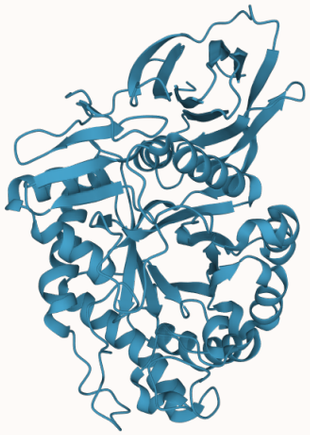
glucose



ceramide

Sidransky, E. *et. al. N. Eng. J. Med.* **2009**, *361*, 1651
Stirnemann, J. *et. al. Int. J. Mol. Sci.* **2017**, *18*, 441

Additional Genetic Risk Factors – GBA and GCase



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- *GBA codes for lysosomal protein **GCase***
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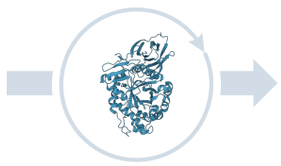
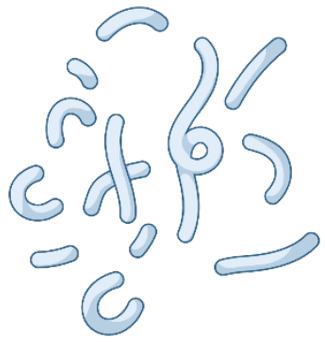
- *All mutations leading to **GCase disfunction increase PD risk***

aSyn monomer

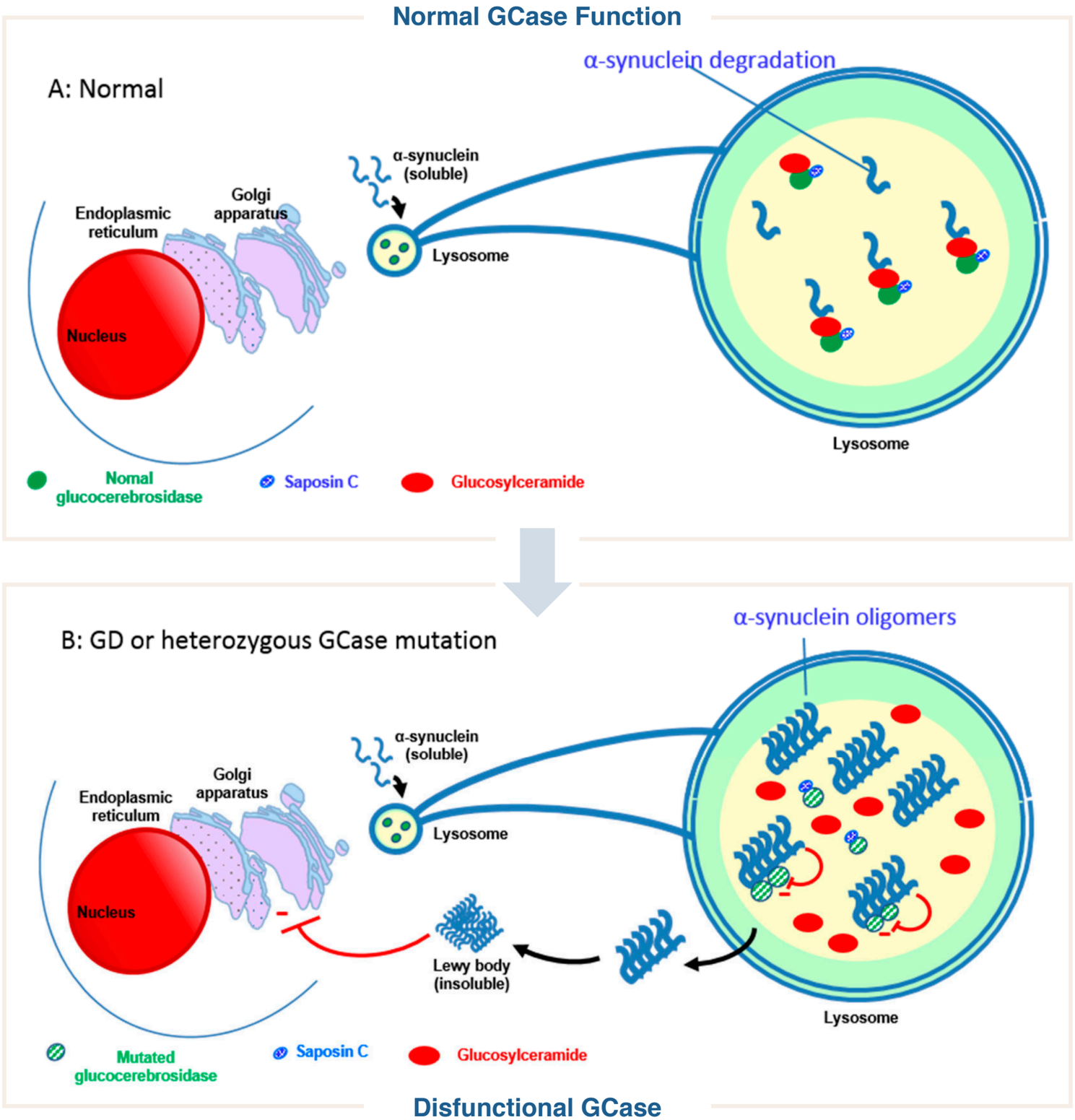




aSyn degredation

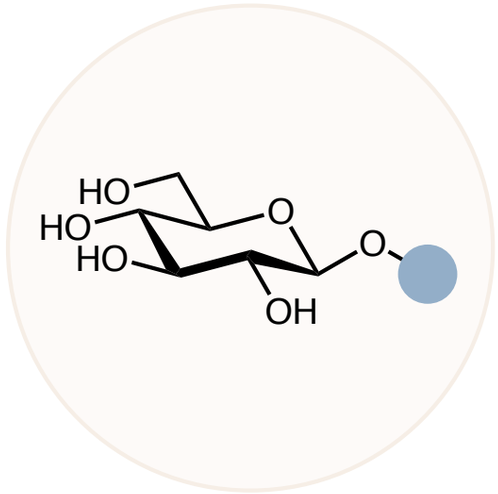
Sidransky, E. *et. al. N. Eng. J. Med.* **2009**, *361*, 1651
Stirnemann, J. *et. al. Int. J. Mol. Sci.* **2017**, *18*, 441

GCase and aSyn



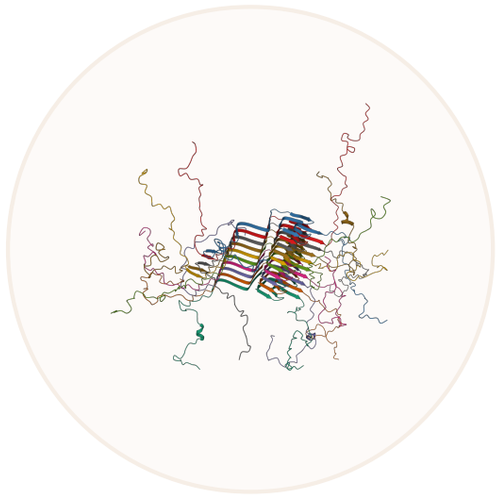
GCase and aSyn

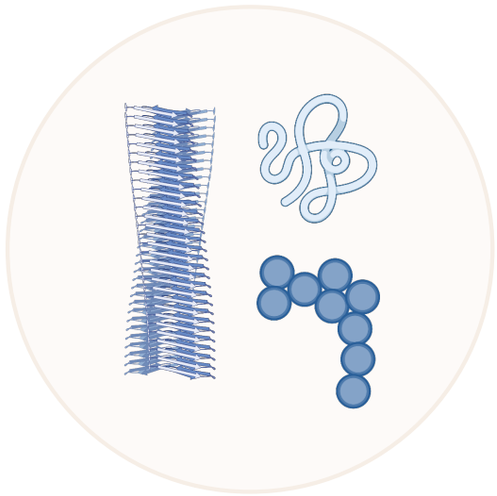
inhibition or deficient GCase enzyme activity



increase in lysosomal GlcCer concentration

GlcCer stabilizes aSyn oligomers





increased concentration of aSyn polymorphs

Sidransky, E. *et. al. N. Eng. J. Med.* **2009**, *361*, 1651
Stirnemann, J. *et. al. Int. J. Mol. Sci.* **2017**, *18*, 441

GCase and aSyn

can defective GCase activity be connected to **neurodegeneration?**

Sidransky, E. *et. al. N. Eng. J. Med.* **2009**, *361*, 1651
Stirnemann, J. *et. al. Int. J. Mol. Sci.* **2017**, *18*, 441

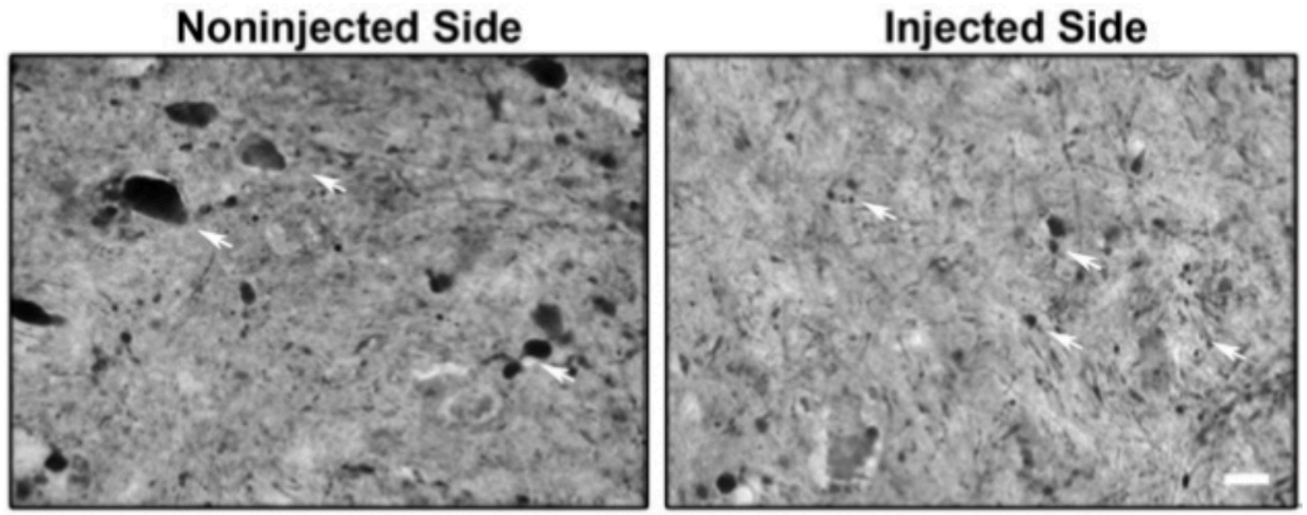
GCase and aSyn

intra-nigral injection of
AAV-aSyn

upregulation of

aSyn in SN

death of dopaminergic neurons (> 6 months)



co-injection of
AAV-aSyn and *AAV-GCase*

overexpression of **GCase prevents**
aggregation and **increases clearance of aSyn**

Rocha, E. M. *et. al. Neurobiology of Disease* **2015**, *82*, 495

GCase and aSyn

intra-nigral injection of
AAV-aSyn

upregulation of

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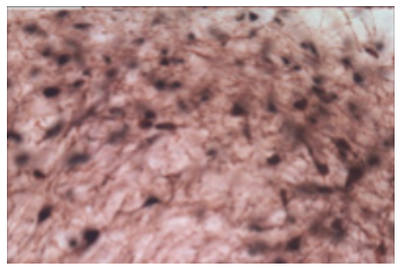
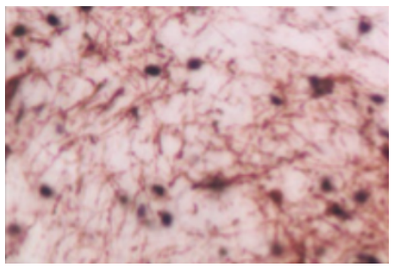
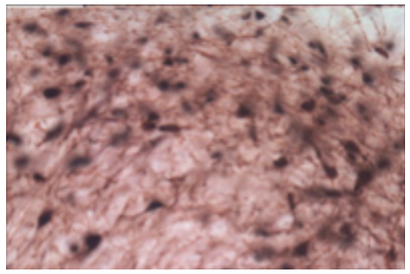


control
(healthy neurons)

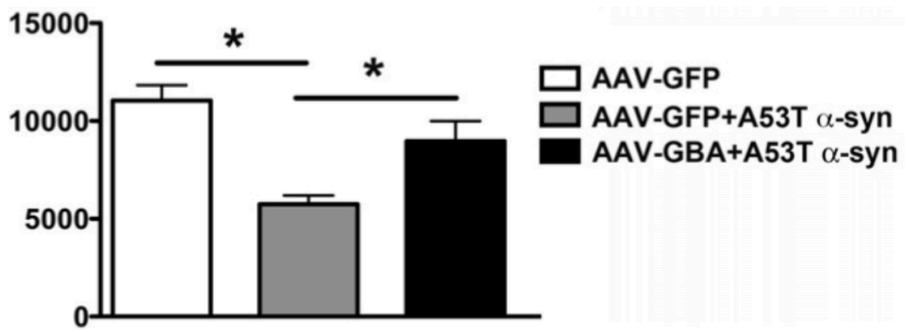


AAV-aSyn



AAV-aSyn + AAV-GCase

co-injection of
AAV-aSyn and AAV-GCase



Rocha, E. M. *et. al. Neurobiology of Disease* **2015**, *82*, 495

GCase and aSyn

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AAV-aSyn

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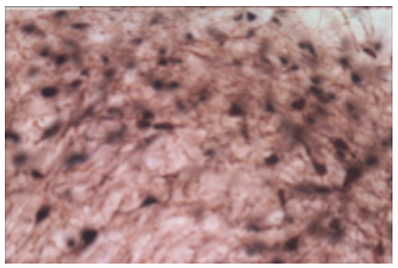

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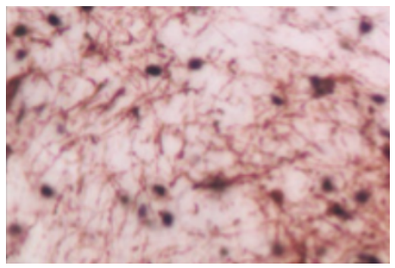
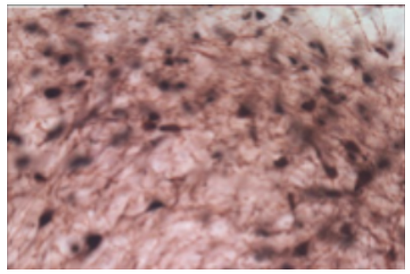


AAV-aSyn



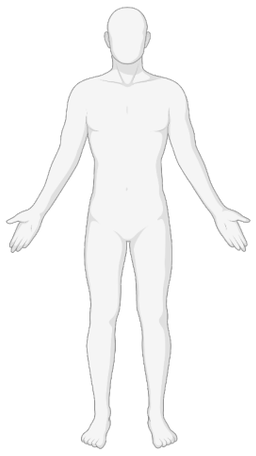
AAV-aSyn + *AAV-GCase*

co-injection of
AAV-aSyn and *AAV-GCase*

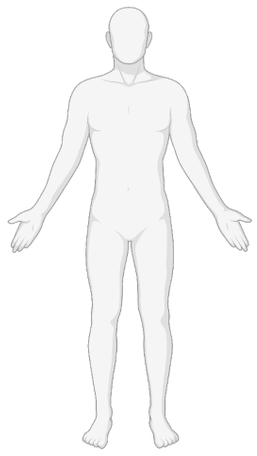
overexpression of **GCase is neuroprotective**
in a rodent model of PD

Rocha, E. M. *et. al. Neurobiology of Disease* **2015**, *82*, 495

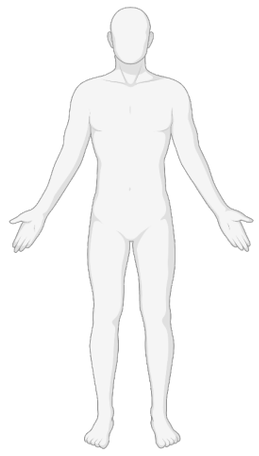
Clues from In Human Gauche's Disease Therapy



control

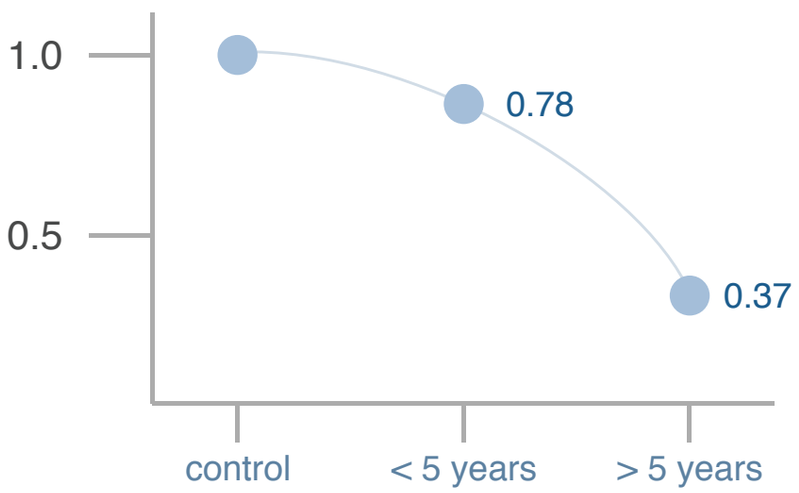


ERT < 5 years



ERT > 5 years

aSyn levels in plasma



increased levels of **GCase** can **reduce**

endogenous, human aSyn oligomers

Pchelina, S. N. *et. al. Neuroscience Letters* **2014**, *583*, 188

Lysosomal/Autosomal Function

Lysosomal Disfunction

Defficient GCase activity is responsible for build up of **aSyn oligomers**

⇩

aSyn oligomers initiate a **positive feedback loop** leading to **increased aSyn levels** that can interfere with several cellular functions

On the Link Between α-synuclein and Parkinson's Disease

I. Evidence for aSyn neurotoxicity

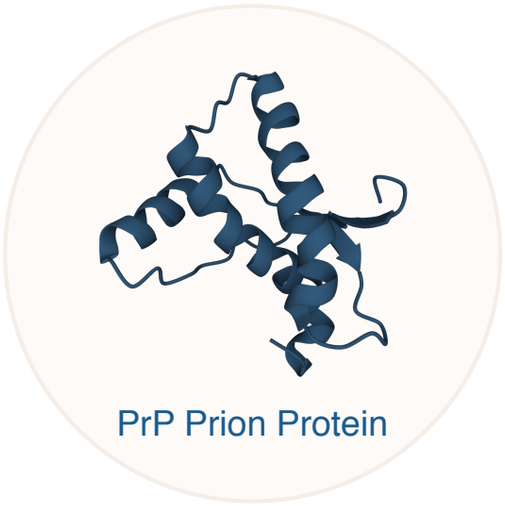
- *Evidence for aSyn toxicity*
- *aSyn structural polymorphism*

II. Link between aSyn function and neurodegeneration

- *Synaptic vesicle trafficking*
- *Autophagy/lysosomal disfunction*
- *Prion hypothesis*

III. Outlook

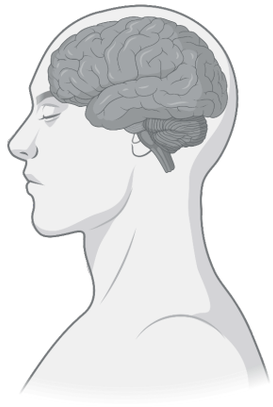
Prions and Misfolded Proteins



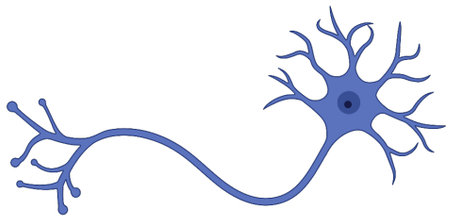
misfolded proteins capable of **transmitting their misfolded shape** on to normal variants of the same protein

Riek, R. *et. al. Nature* **1996**, *382*, 180
Balchin, D. *et. al. Science* **2016**, *353*, 42

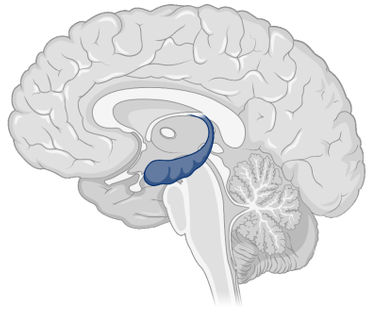
Prion Hypothesis in PD - Initial Evidence



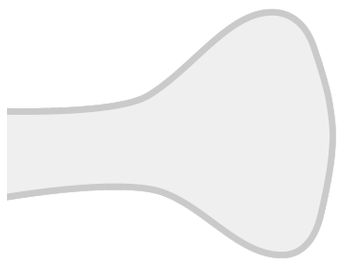
Patient with Parkinson's Disease



grafting of healthy dopaminergic neurons in to PD patients

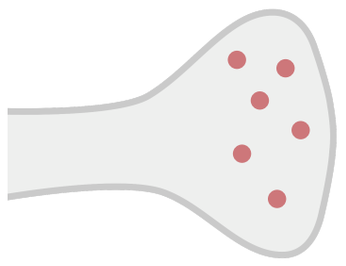


Patient with grafted healthy dopaminergic neurons



grafted neurons before transplant

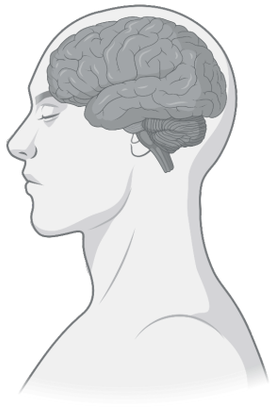
16 years



autopsy:
Lewy Body Pathology

Li, J.-Y *et. al. Nat. Med.* **2008**, *14*, 501

Prion Hypothesis in PD - Initial Evidence



Patient with Parkinson's Disease

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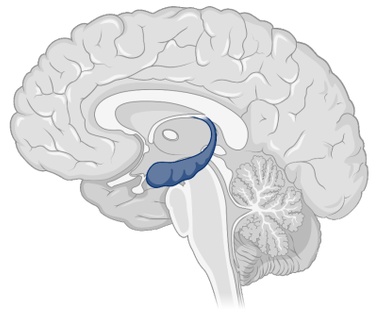
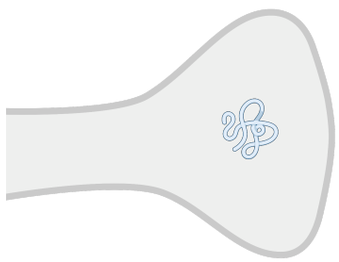
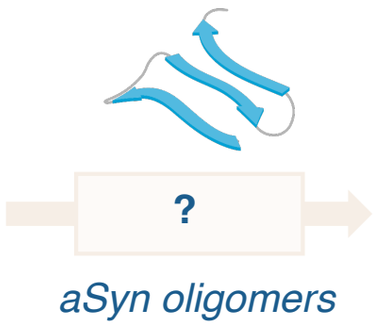


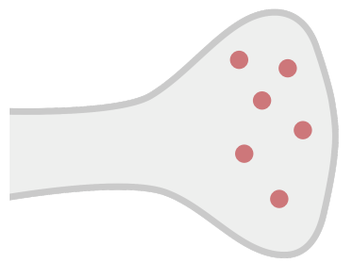
Patient with grafted healthy dopaminergic neurons



native, monomeric, soluble aSyn



aSyn oligomers



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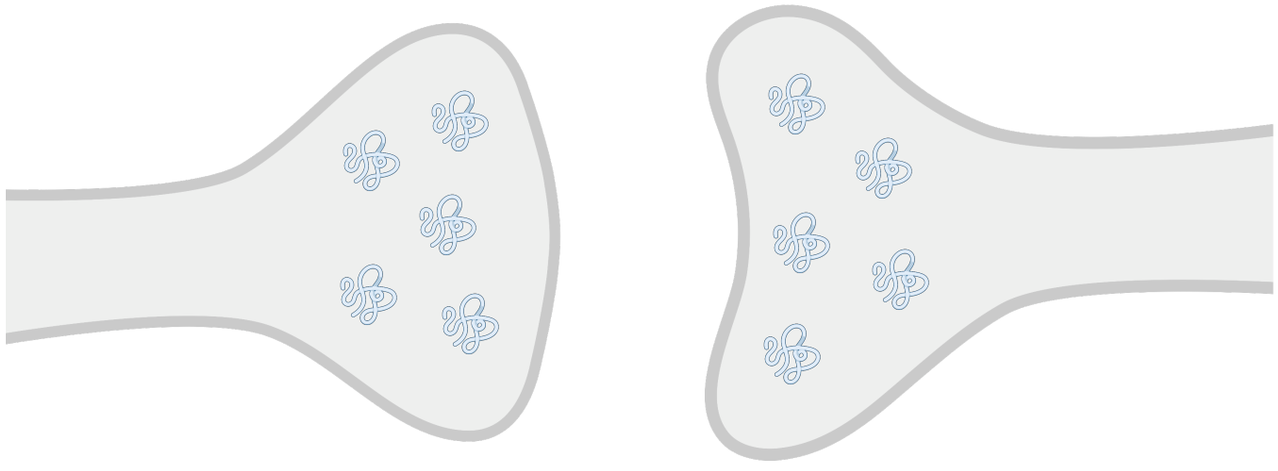
Preformed Fibrils Can Initiate Aggregation

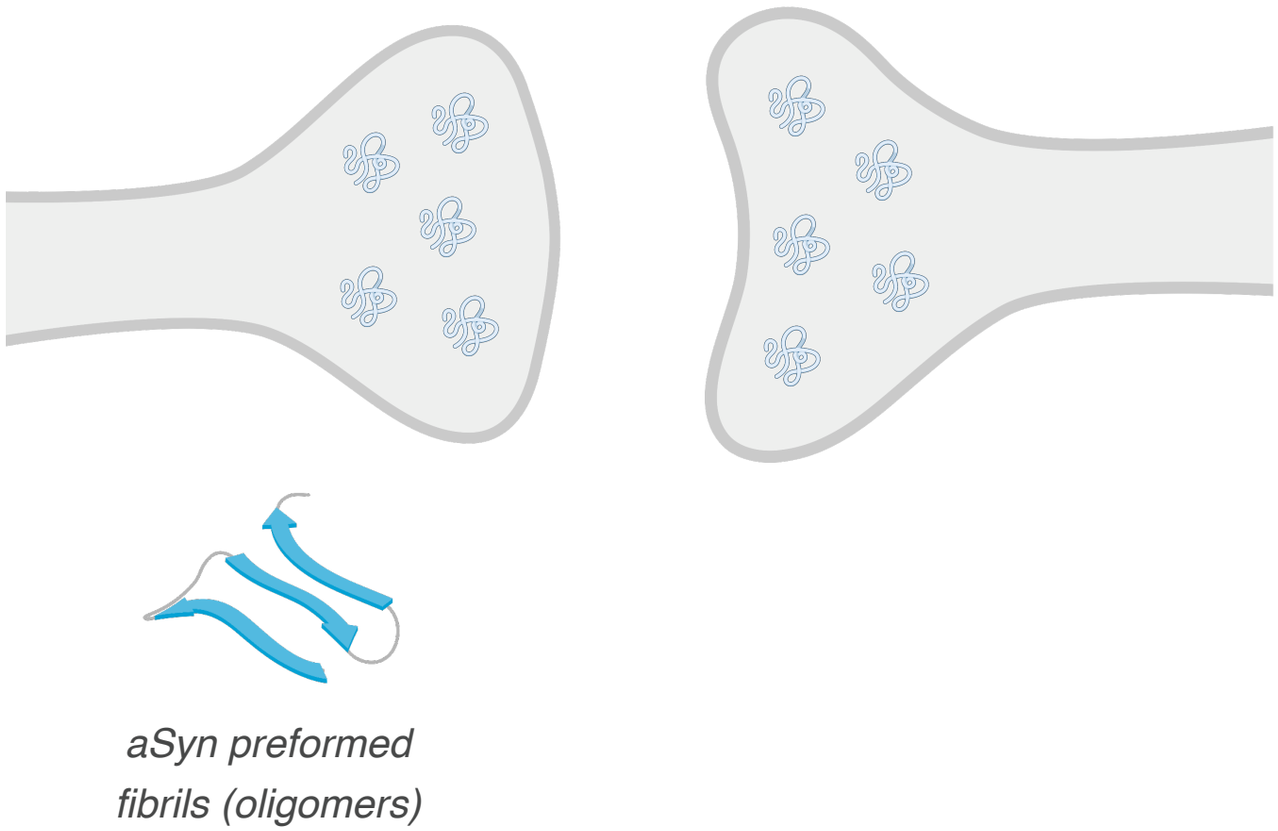


wild type mouse

hippocampal neurons

Volpicelli-Daley, L. A. *et. al. Neuron* **2011**, *72*, 57

Preformed Fibrils Can Initiate Aggregation



wild type mouse

hippocampal neurons

aSyn preformed

fibrils (oligomers)

Volpicelli-Daley, L. A. *et. al. Neuron* **2011**, *72*, 57

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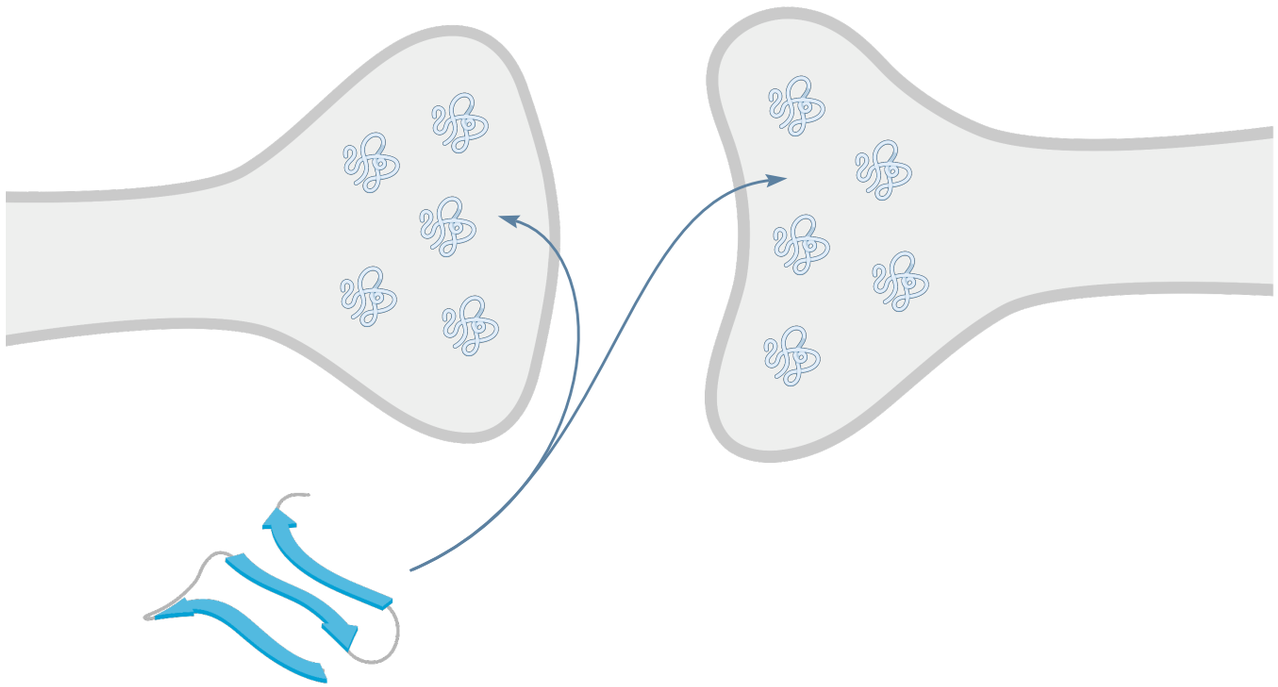

aSyn preformed fibrils (oligomers)

wild type mouse hippocampal neurons

Volpicelli-Daley, L. A. *et. al. Neuron* **2011**, *72*, 57

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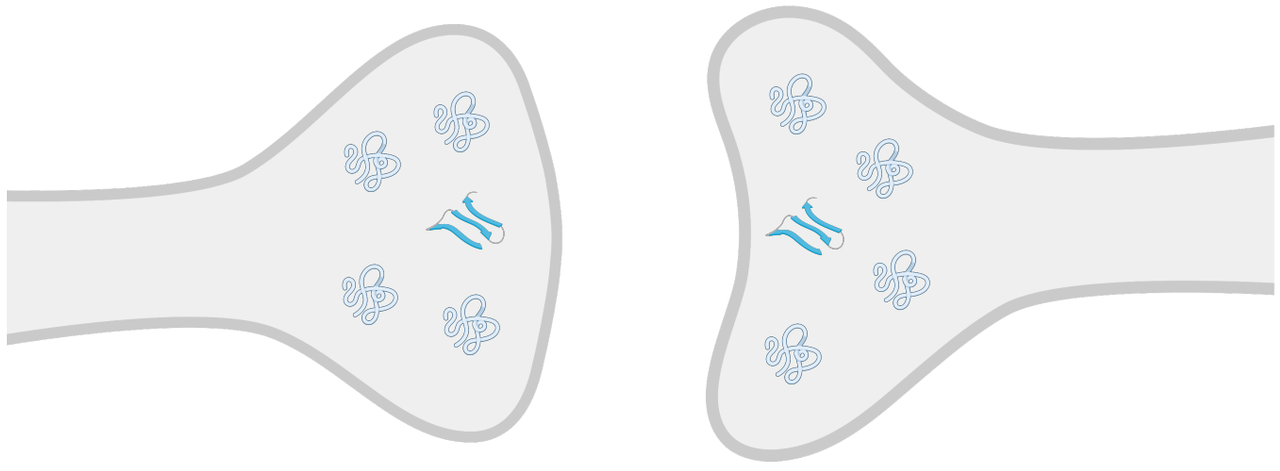

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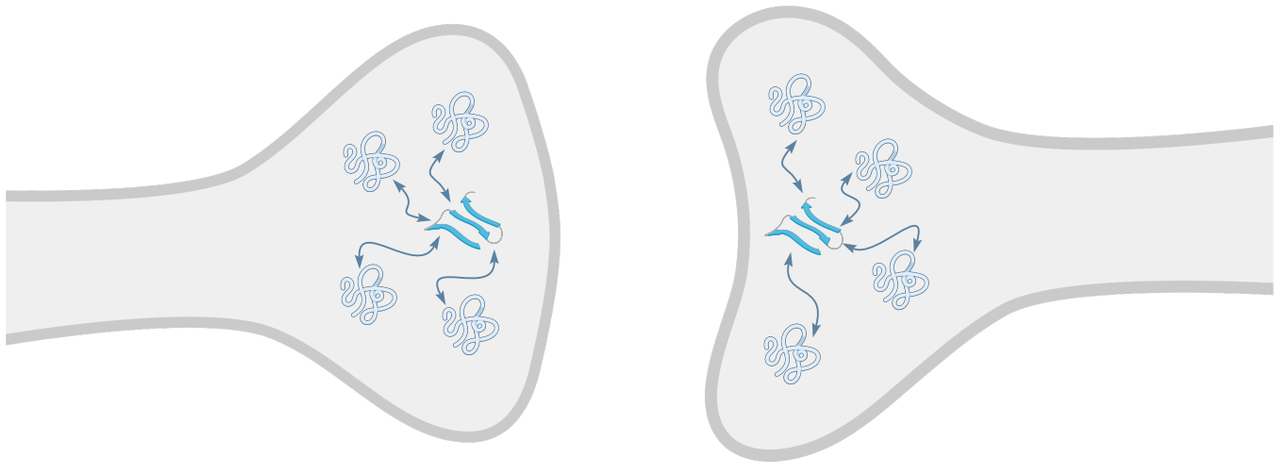

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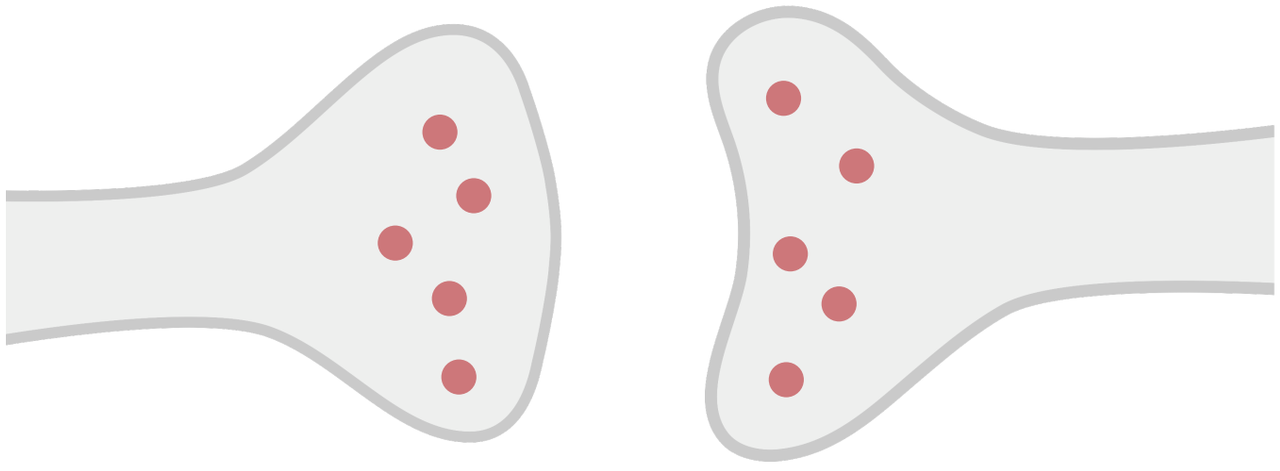
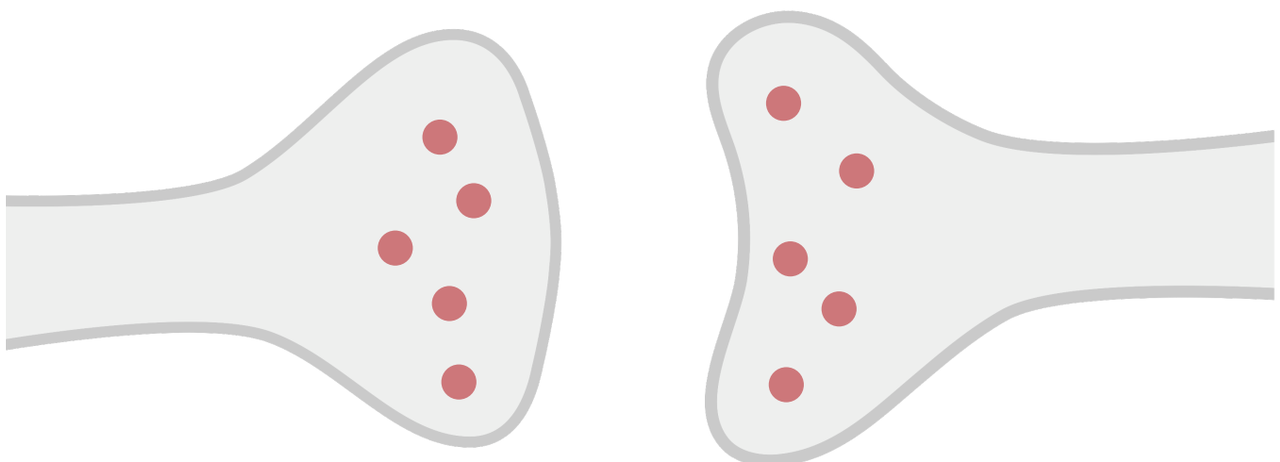


Lewy pathology from healthy WT neurons

Volpicelli-Daley, L. A. *et. al. Neuron* **2011**, *72*, 57

Preformed Fibrils Can Initiate Aggregation



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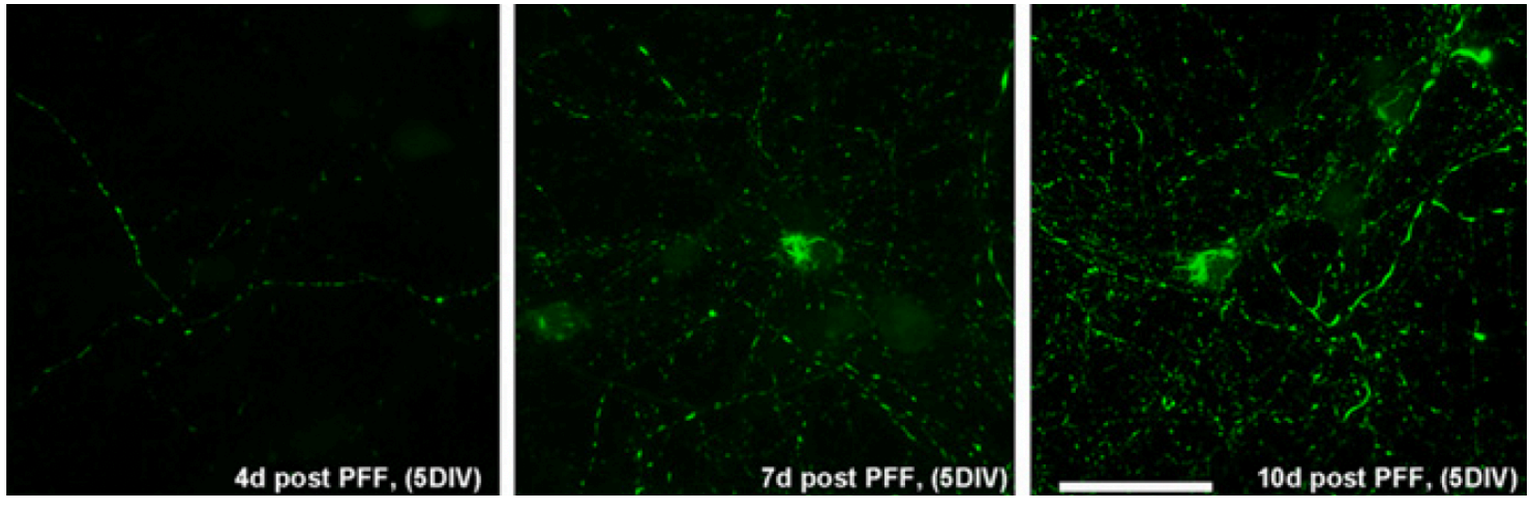
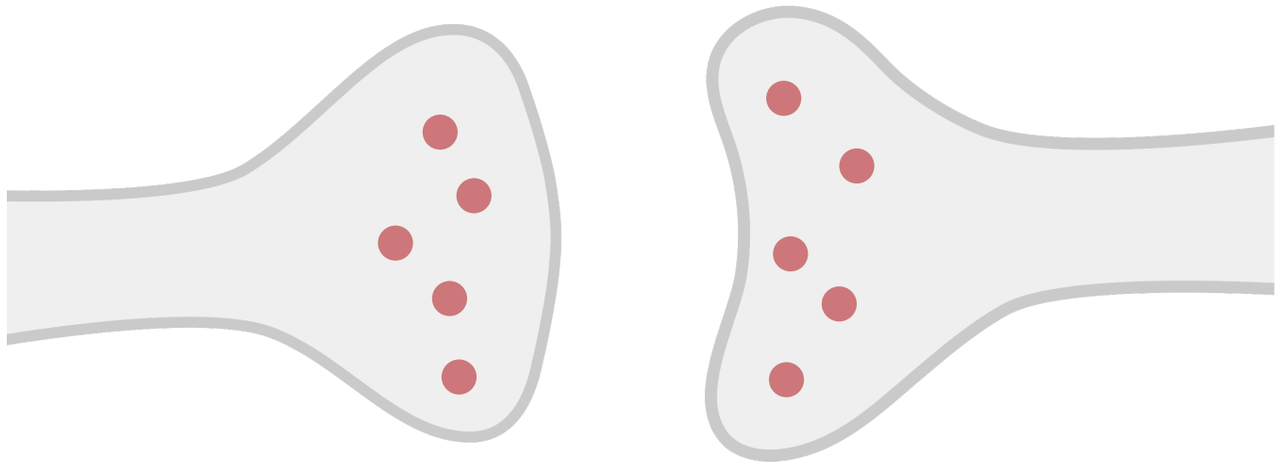


fibrillar **aSyn seeds propagate** and

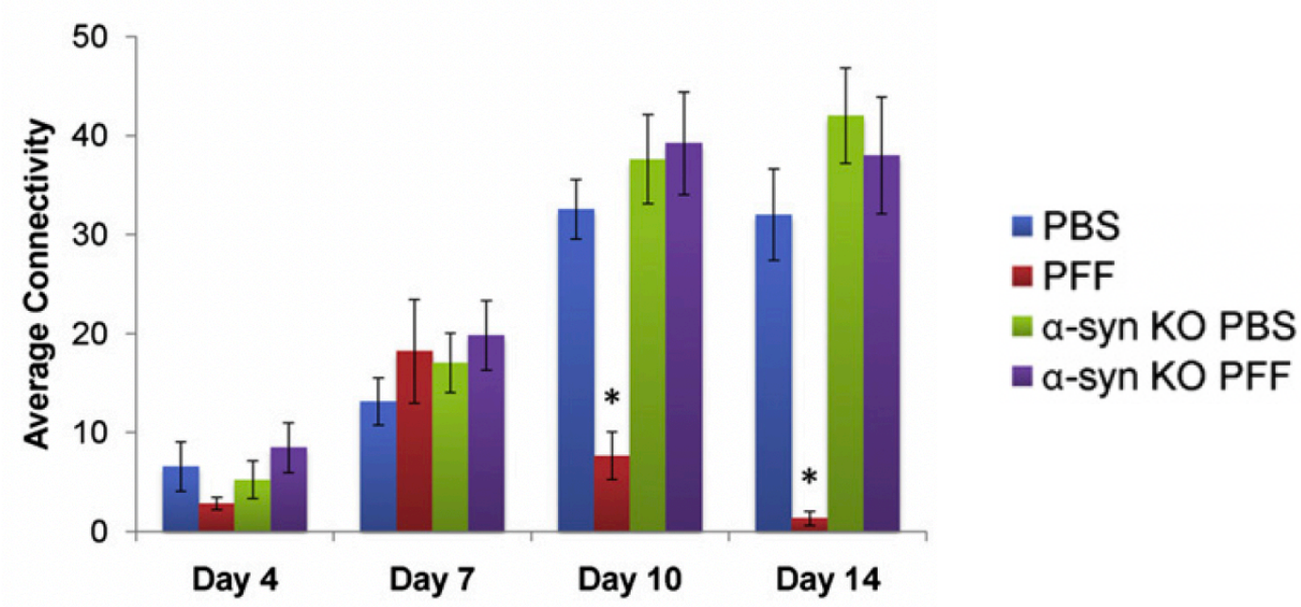
initiate aggregation of endogenous aSyn

Volpicelli-Daley, L. A. *et. al. Neuron* **2011**, *72*, 57

Preformed Fibrils Can Initiate Aggregation



Lewy pathology from healthy WT neurons



fibrillar aSyn seeds **initiate defective neuron function** and ultimately lead to **cell death**

Volpicelli-Daley, L. A. *et. al. Neuron* **2011**, *72*, 57

Prion Hypothesis

Prion Like Propagation of Fibrils

aSyn oligomers are **released in to the extracellular environment** and **taken up by healthy neurons**

⇩

aSyn oligomers **initiate misfolding** and aggregation of native, soluble, monomeric aSyn

On the Link Between α-synuclein and Parkinson's Disease

I. Evidence for aSyn neurotoxicity

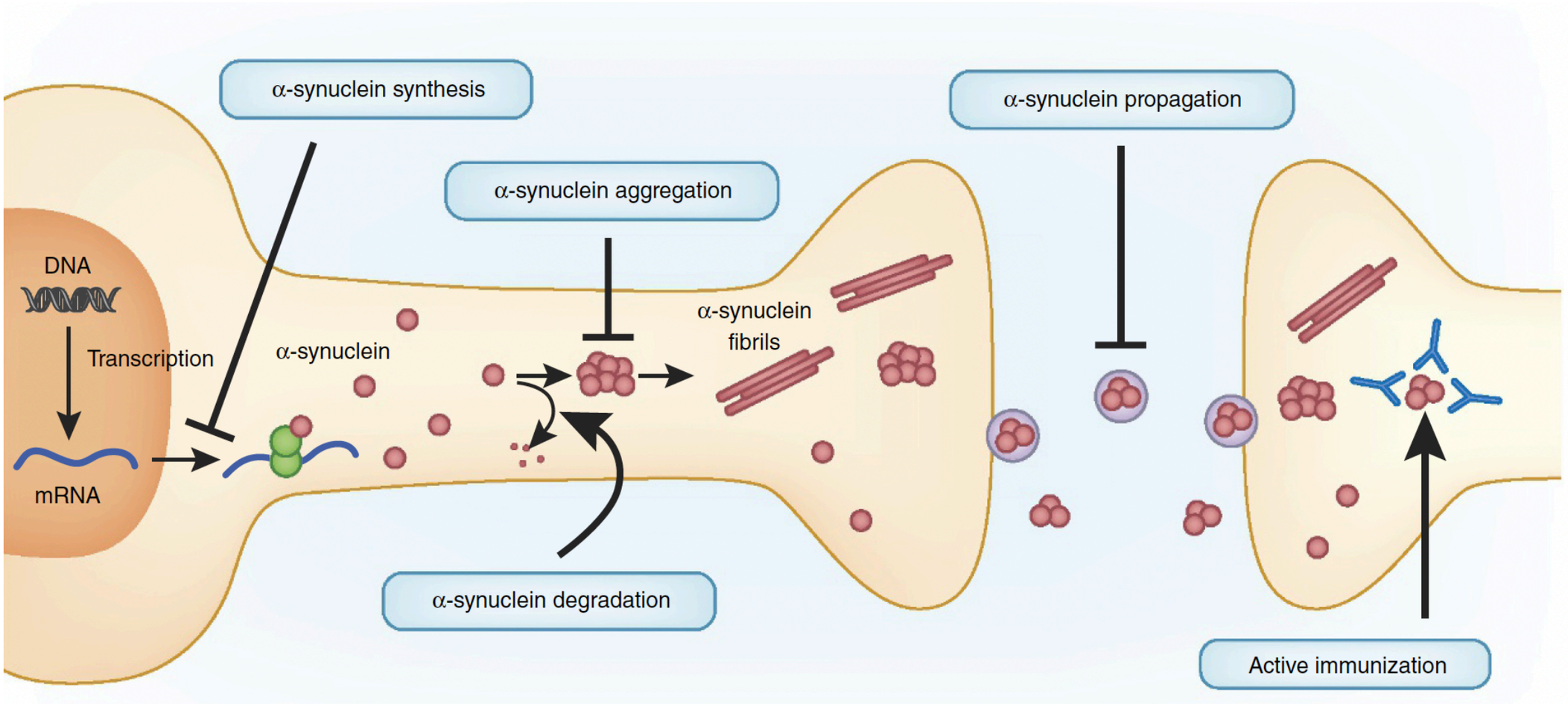
- *Evidence for aSyn toxicity*
- *aSyn structural polymorphism*

II. Link between aSyn function and neurodegeneration

- *Synaptic vesicle trafficking*
- *Autophagy/lysosomal disfunction*
- *Prion hypothesis*

III. Outlook

Parkinson's Disease Therapeutic Outlook

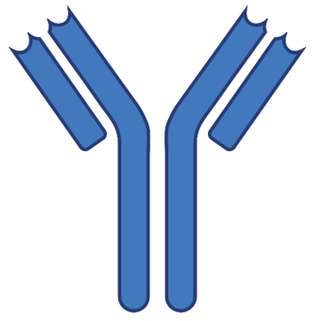


Goal: ***disease modifying therapy***

Wong, Y. C. *Nat. Med.* **2017**, *23*, 1

Parkinson's Disease Therapeutic Outlook

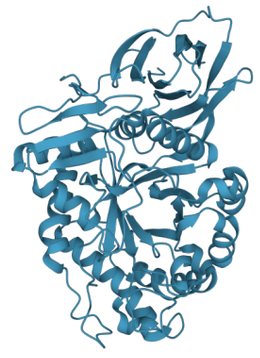
aSyn targeting antibodies



propagation ↓ *aggregation ↓*

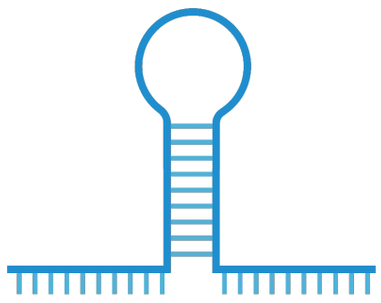
clearance ↑

small molecule GCase activators



clearance ↑ *aggregation ↓*

siRNA



aSyn expression ↓ *aggregation ↓*

aSyn monomer stabilizers

propagation ↓ *aggregation ↓*

Wong, Y. C. *Nat. Med.* **2017**, *23*, 1

Parkinson's Disease Therapeutic Outlook

no clinical success to date

Wong, Y. C. *Nat. Med.* **2017**, *23*, 1

aSyn: Where We Are and What We Need

THE MICHAEL J. FOX FOUNDATION
FOR PARKINSON'S RESEARCH

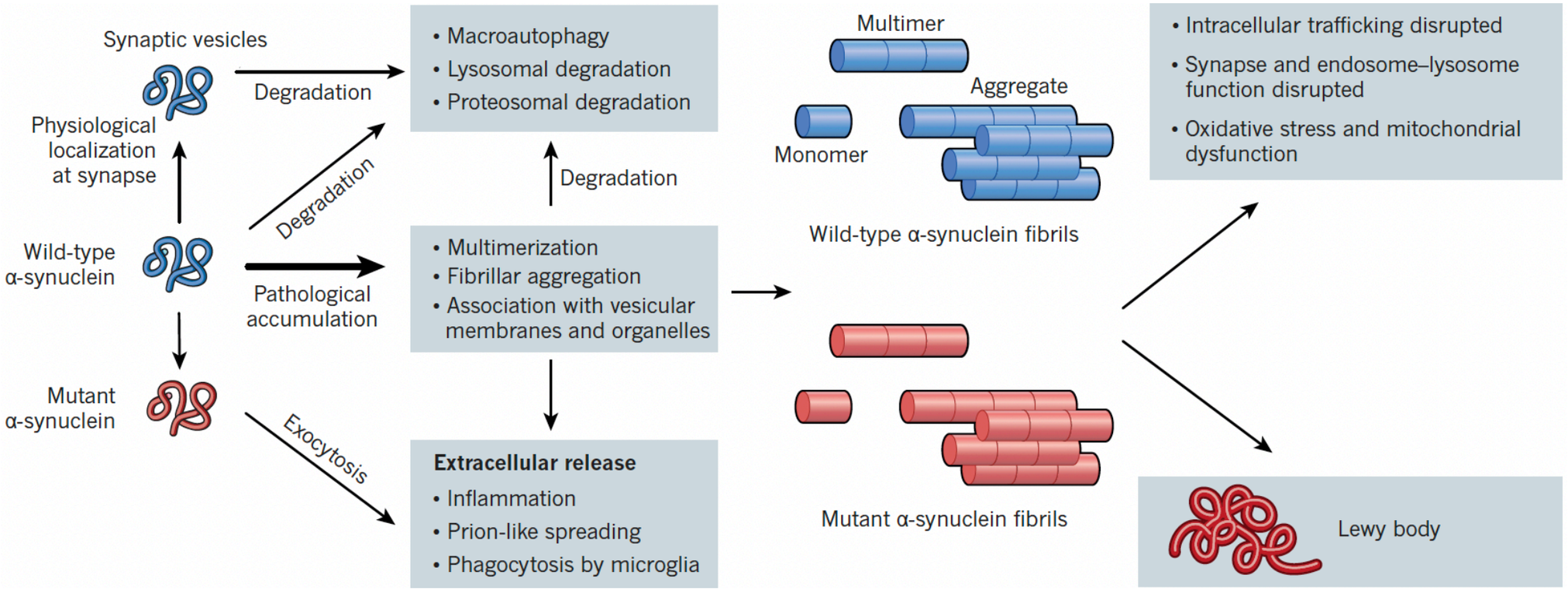
"Ultimately, the nature and extent of the aSyn–PD connection can only be determined by carefully designed clinical experiments in humans" – **MJFF 2021**

SYNUCLEIN MEETING
1-4 September 2019
Porto, Portugal

"After all, a major question we still cannot completely discard…is: are aSyn inclusions relevant or simply a epiphenomenon? Time will tell." – **2020**

Outeiro, F. *et. al. Journal of Neurochemistry* **2020**, *153*, 433
Oliveira, L. M. A. *et. al. NPJ Parkinson's Disease* **2021**, *7*, 65

Questions?



Nick Intermaggio
Group Meeting–Literature Review
Nov. 30th, 2021