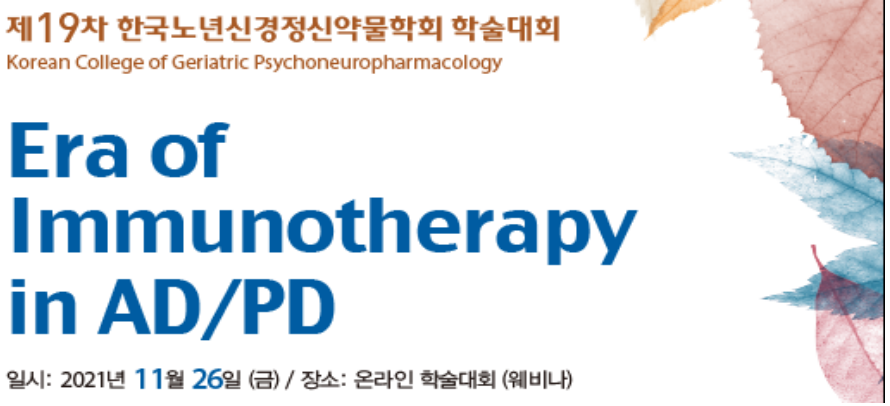

Current Status of Anti-α-synuclein Strategies for Parkinson's Disease

SNUH
SMG-SNU BORAMAE MEDICAL CENTER

2021. 11. 26.

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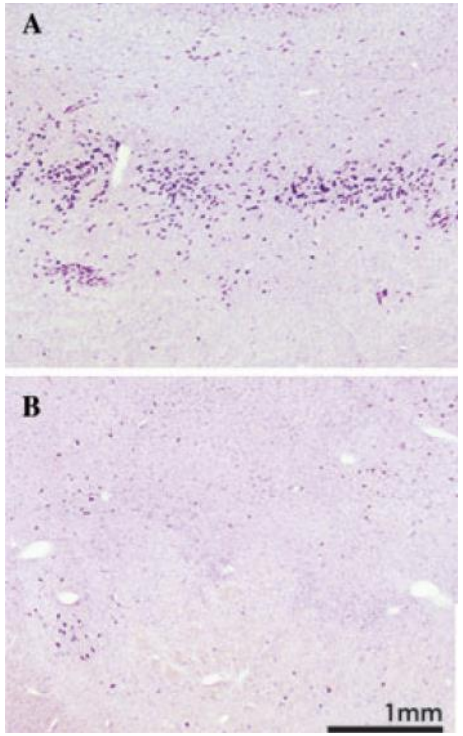
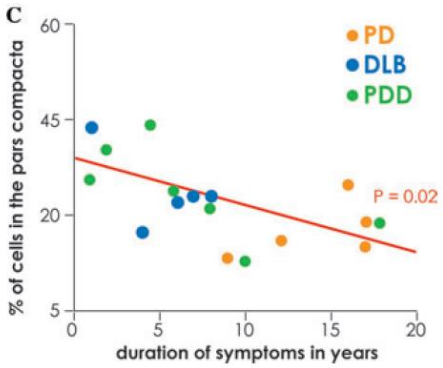
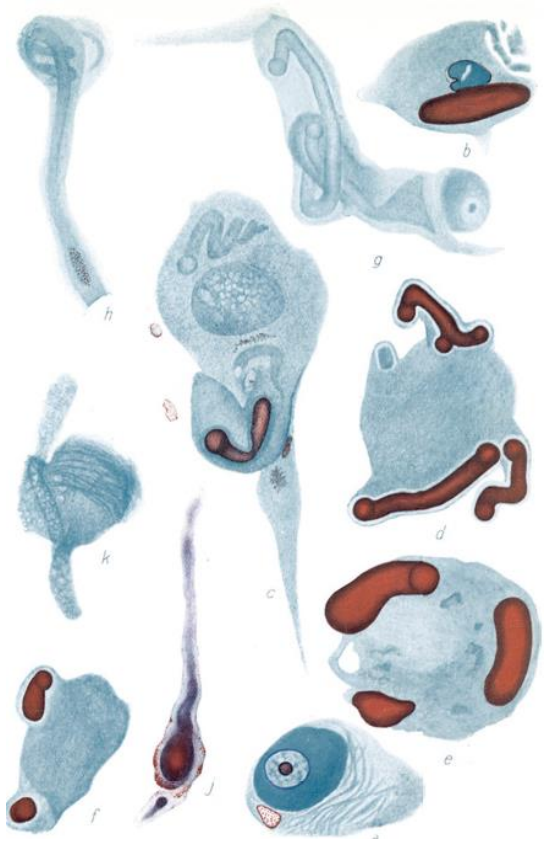
Department of Neurology, Seoul National University Medical College
Department of Neurology, SMG-SNU Boramae Medical Center

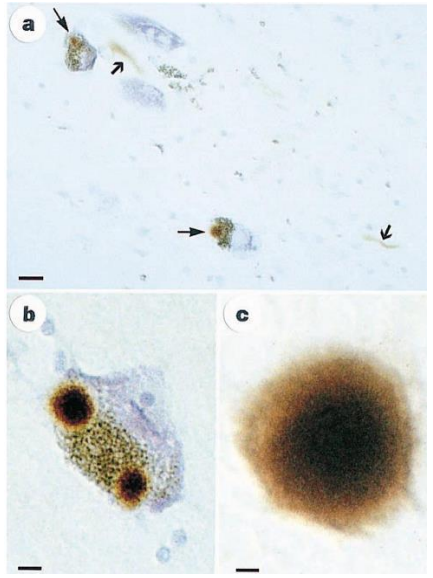
Characteristic pathology of Parkinson's disease





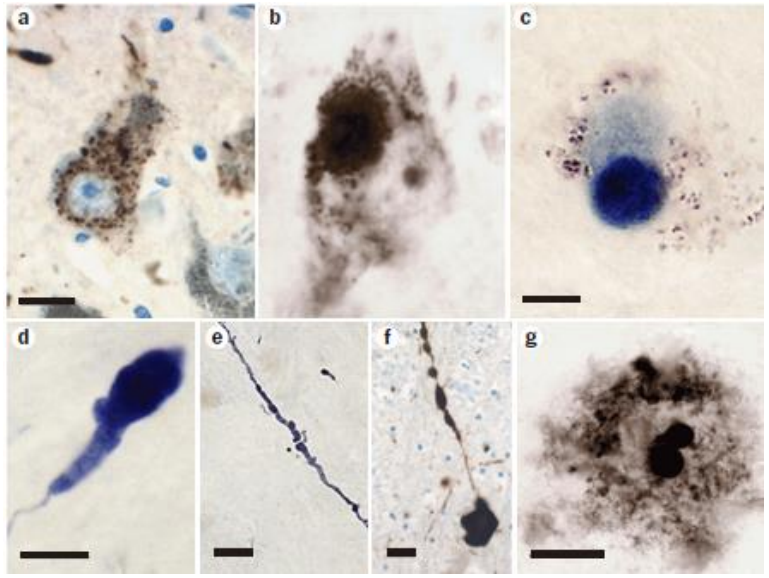


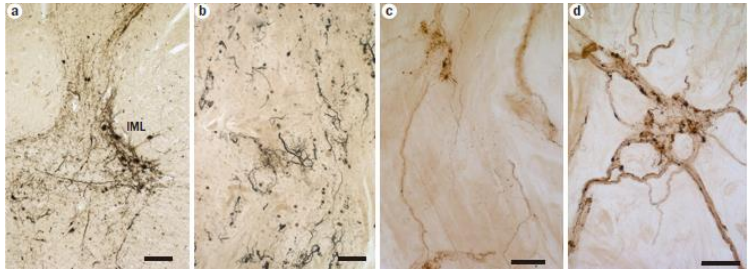
Lewy, F. H. Die Lehre vom Tonus und der Bewegung. (Springer-Verlag, Berlin, 1923).



NATURE | VOL 388 | 28 AUGUST 1997

Spillantini, Schmidt, Lee, Trojanowski, & Goedert.

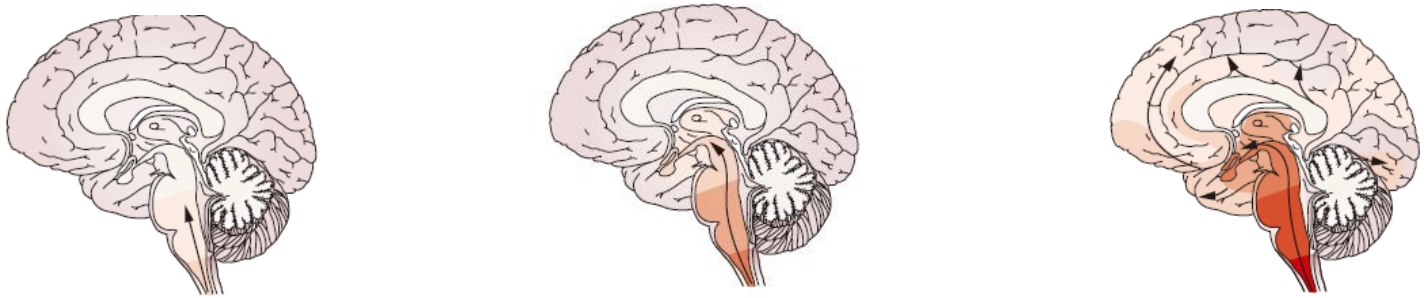


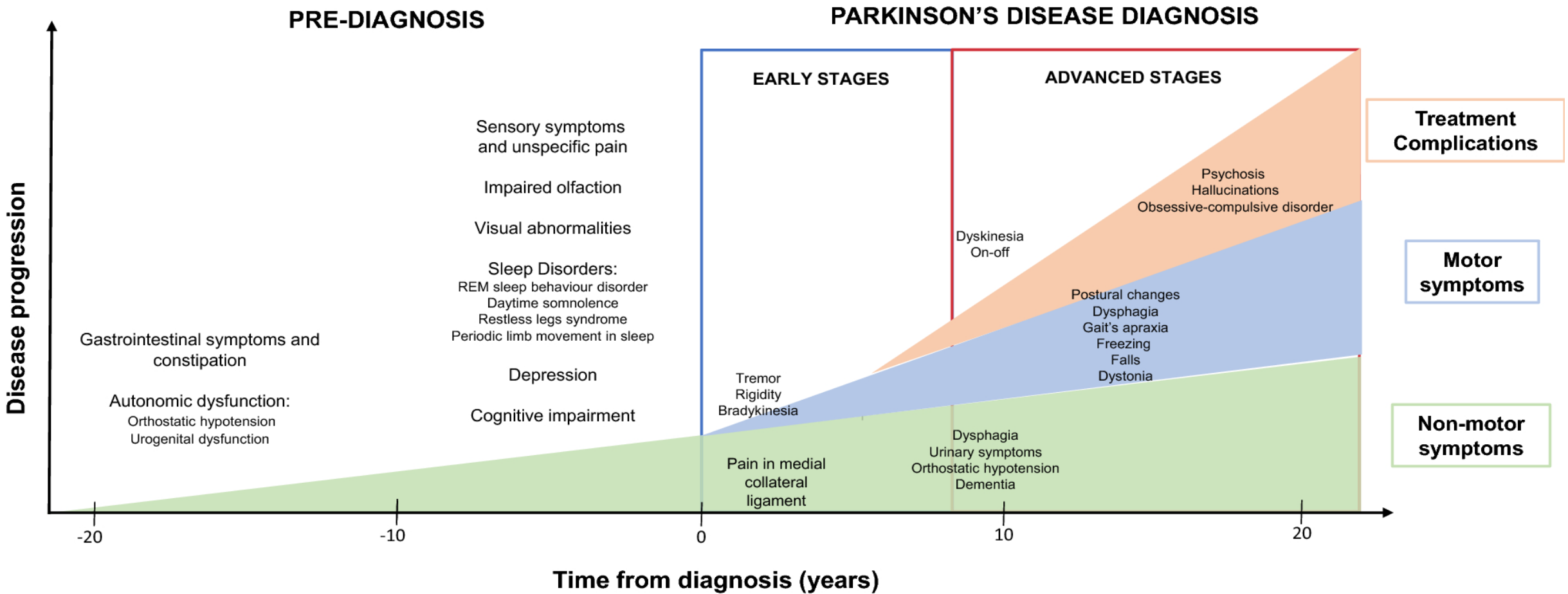


Braak, H. & Del Tredici, K. Neuroanatomy and pathology of sporadic Parkinson's disease. *Adv. Anat. Embryol. Cell Biol.* 201, 1–119 (2009)

Parkinson's disease

A progressive syndrome with bradykinesia, rigidity, flexed posture, resting tremor, and loss of postural reflex.



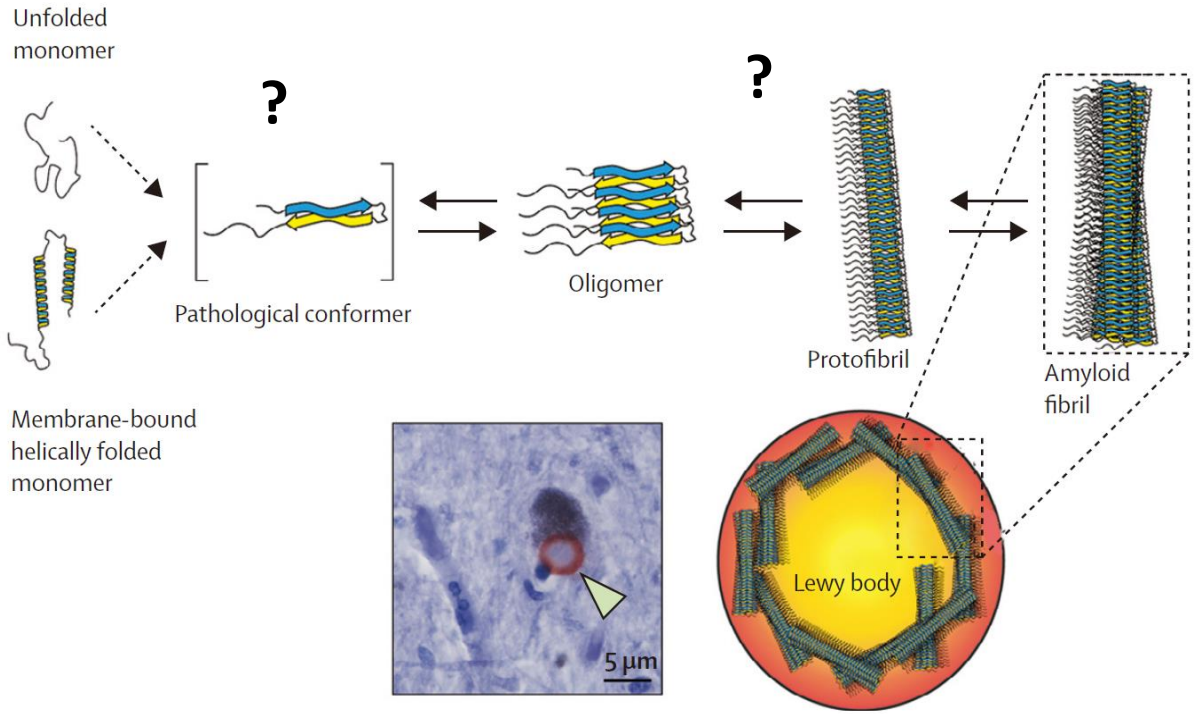


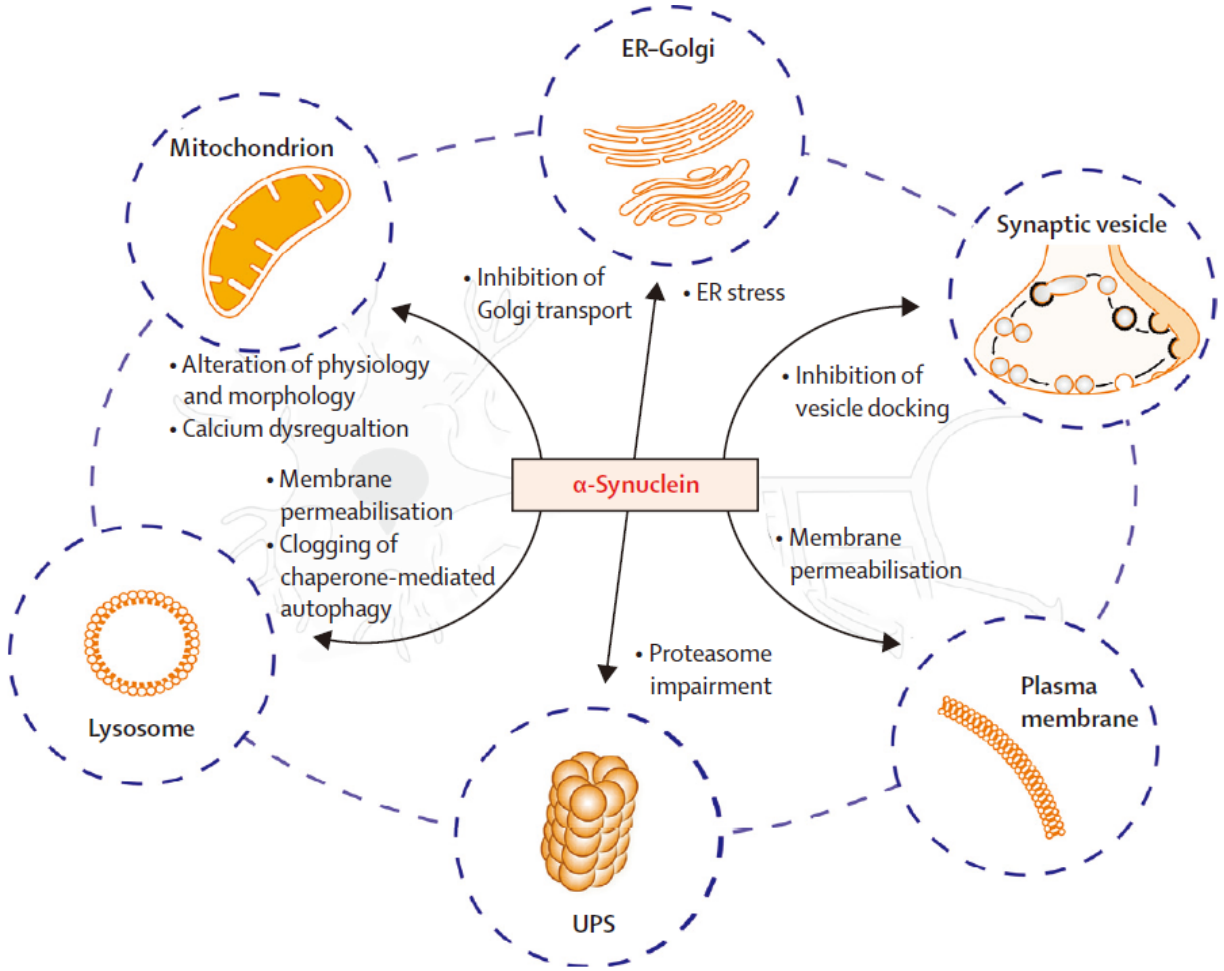
Modifying disease progression in PD

- Restoration of dying cells/prolong the survival of neurons/block the propagation of pathology → modification of the disease course

- Detection of PD pathology as early as possible and starting disease modifying therapy: ideal treatment of PD

Alpha-synuclein cascades in the pathogenesis of PD

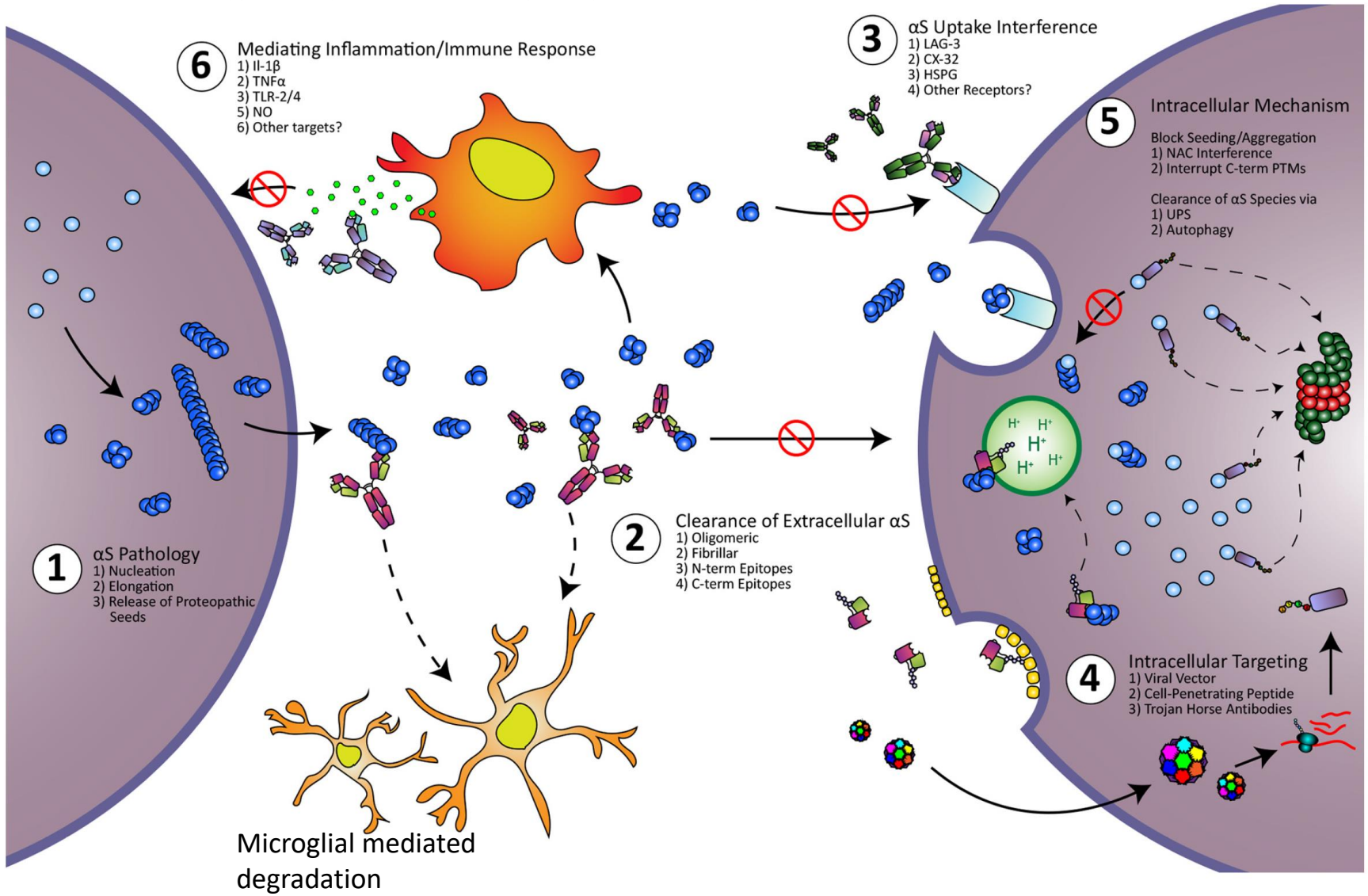




Schematic diagram of the α-synuclein aggregation pathway

Anti-alpha-synuclein strategy in PD

Antibodies targetting cytokines released from activated microglia or reactive astrocytes to modulate inflammatorypathways that enhance protepathic seeding and release



Intrabodies

Enhance intracellular clearance system

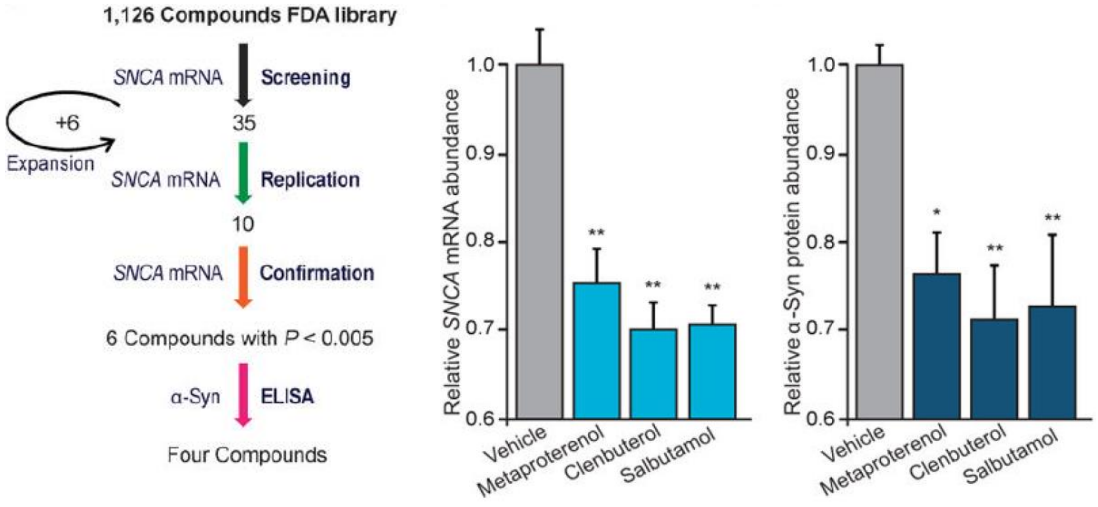
engineered antibody fragments can hijack cellular uptake machinery for enhanced cellular penetrance

Antibody constructs can also be delivered as transduced genes by viral vectors

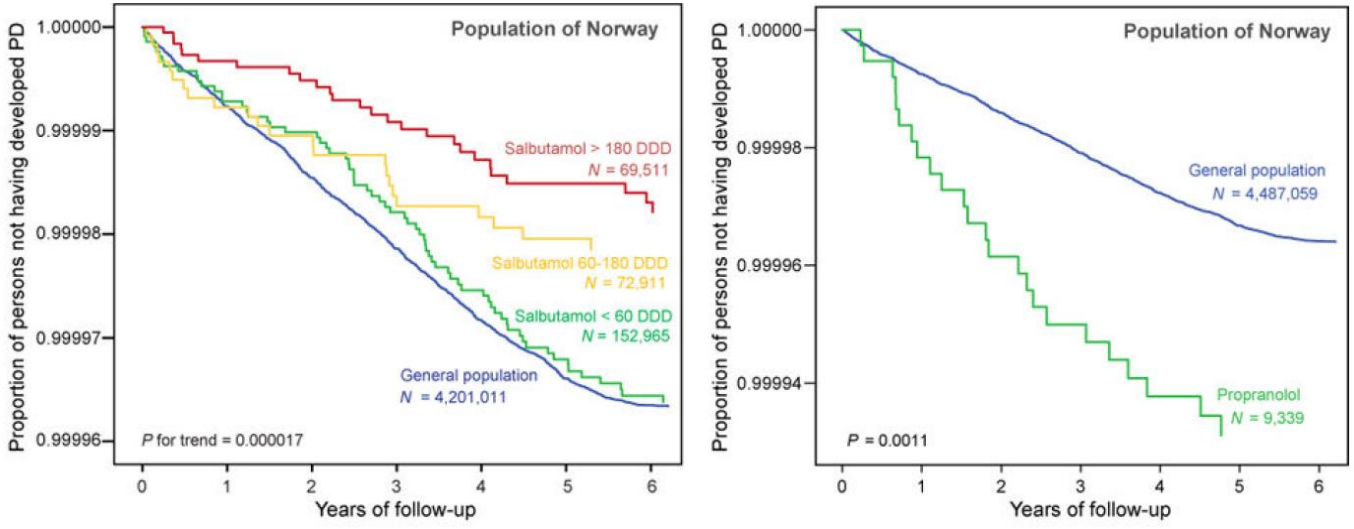
1) Reducing aSC production at the transcriptional or translational level

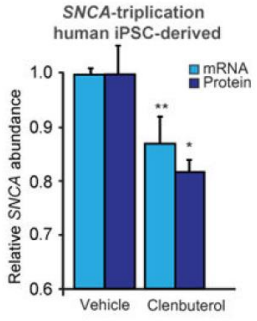
- Backgrounds: a-syn gene duplication, triplication causing PD, accummulation of non-aggregated a-syn associated with decreased dopamine level (but not nigral neuronal loss)
- Strategy: reducing a-syn production prior to its aggregation

Modifying transcription of a-syn gene
beta-2-adrenoreceptor agonism as
a mechanism to reduce a-syn gene expression



Mittal S, et al. Science. 2017;357(6354):891-898.





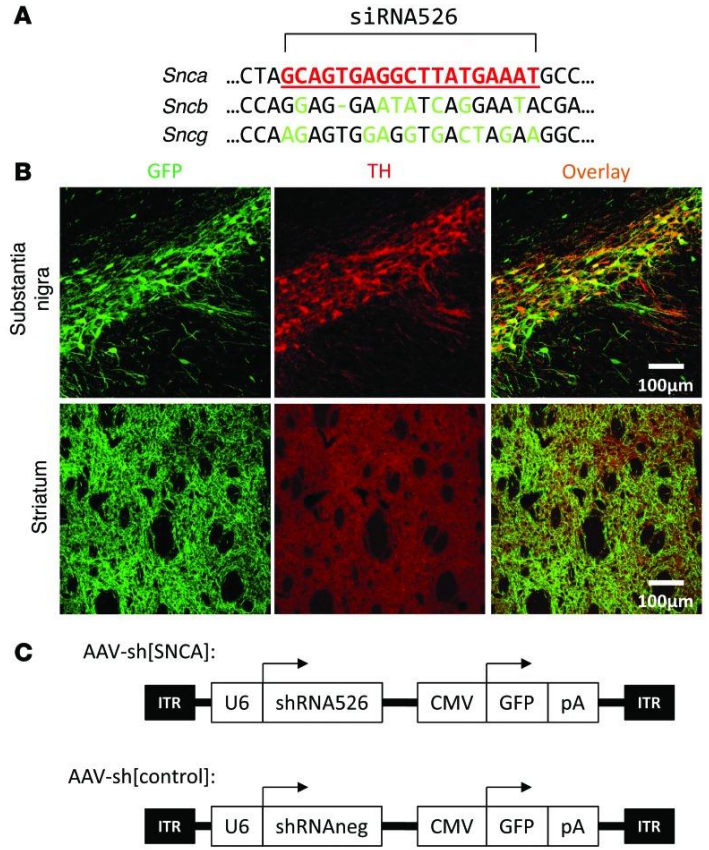
	Users	Cases	Person-years	RR (95% CI) Age-, sex- adjusted	RR (95% CI) Multivariate adjusted[a]
Salbutamol					
Never user	4,066,119	4,398	36,700,554	1 (ref)	1 (ref)
Ever user	619,863	236	3,135,956	0.65 (0.57–0.74)	0.66 (0.58–0.76)
Propranolol					
Never user	4,671,188	4,593	39,770,912	1 (ref)	1 (ref)
Ever user[b]	14,794	41	65,598	2.16(1.59–2.94)	2.20 (1.62–3.00)

1) Reducing aSC production at the transcriptional or translational level

- Backgrounds: a-syn gene duplication, triplication causing PD, accummulation of non-aggregated a-syn associated with decreased dopamine level (but not nigral neuronal loss)
- Strategy: reducing a-syn production prior to its aggregation

RNA interference (RNAi)
Short hairpin a-syn RNA (shRNA) delivered via lentiviral ventor silencing ectopic expression of human a-syn
Small interfering RNA (siRNA) against a-syn infusion

A safe degree of knockdown !

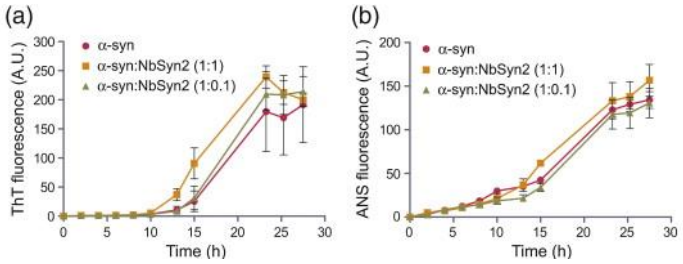


However, Manfredsson and coworkers reported that when using viral vectors to achieve marked (> 90%) reductions of a-syn in the substantia nigra of rats and nonhumans primates, the nigrostriatal system degenerates.

2) Inhibiting intracellular aSC aggregation with small molecules

- Backgrounds: preventing the aggregation of a-syn while maintaining normal function, will prevent the toxicity from misfolded a-syn

- Intrabodies: a small antibody fragment, binding to a-syn monomers to prevent oligomerization
- intrabodies may be neuroprotective by attenuating/neutralizing/modulating aggregated a-syn, possibly by interfering with the aggregation prone region (NAC)



Intranigral injection with viral vector overexpressing a-syn: Nanobody VH14*PEST (target for the NAC of α-syn), nanobody NbSyn87 (target for both the C-terminal of a-syn and fibrillar forms). both of the two intrabodies completely eliminated aggregated a-syn, restored striatal dopamine, and improved motor function as assessed on the stepping test (De Genst et al., 2010).

A challenge for the clinical application of intrabodies: how to achieve high levels in the CNS for prolonged periods

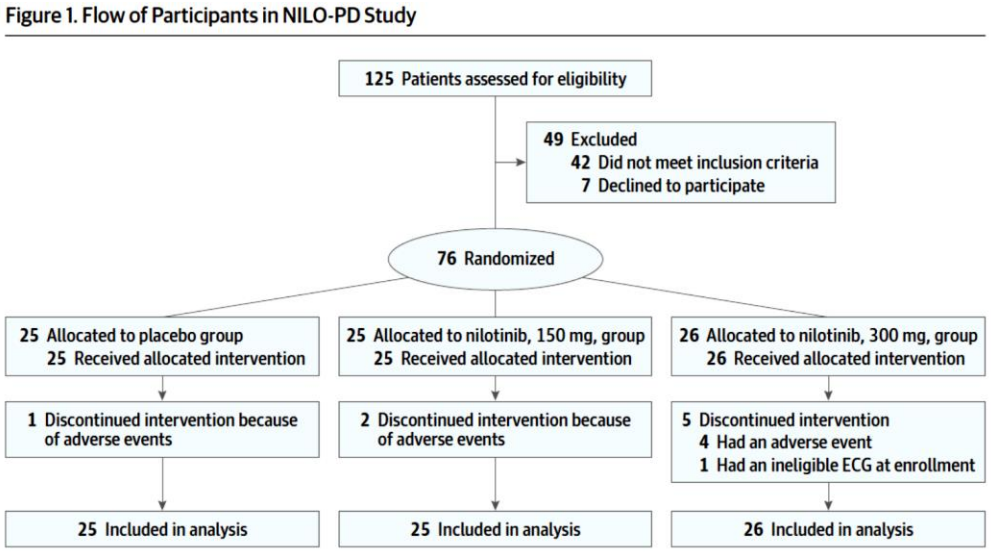
New vectors using systemic injection are under-developing (Chan et al., 2017)

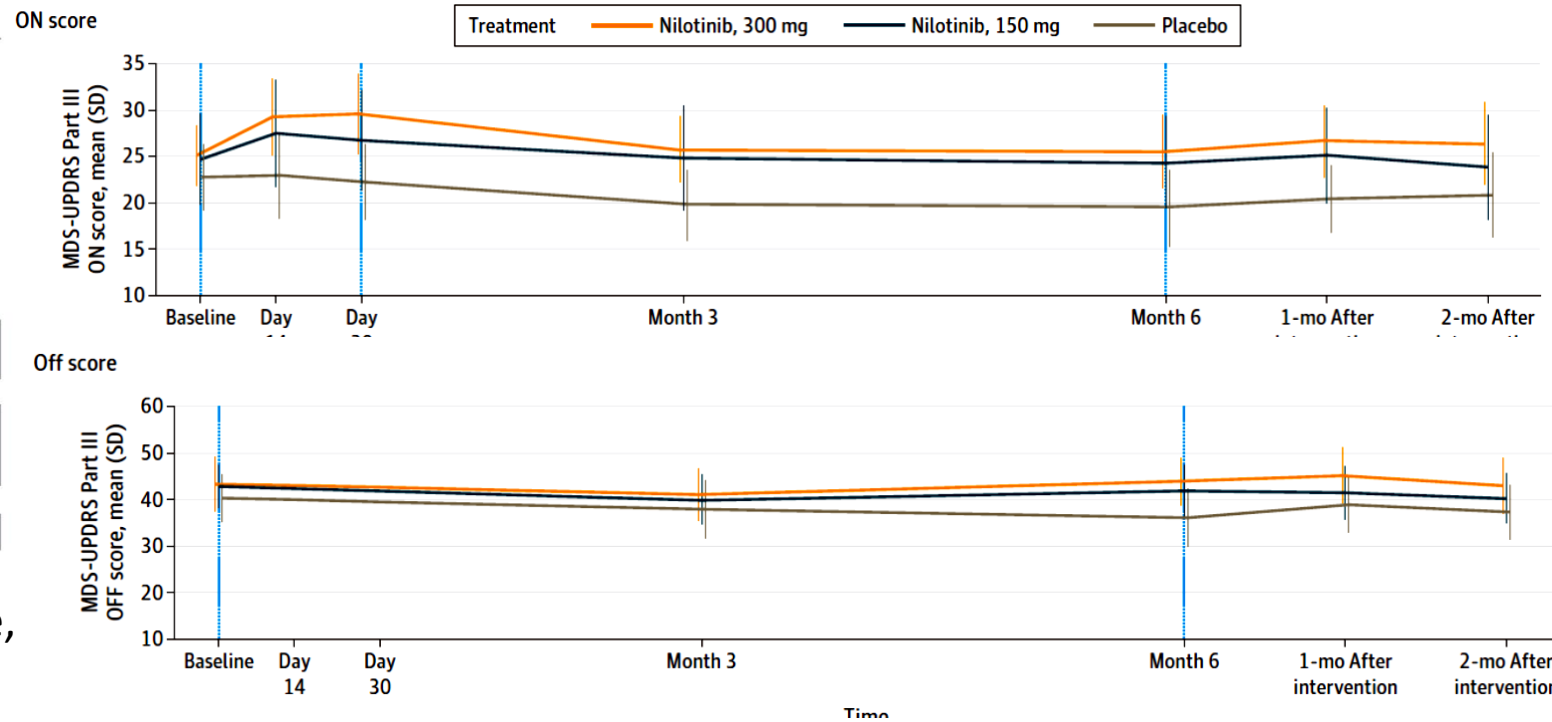
3) Promoting degradation of intracellular aSC aggregates through autophagy-lysosomal system

- Backgrounds: targeting enhancement of autophagic processes would lead to increase clearance of pathological a-syn

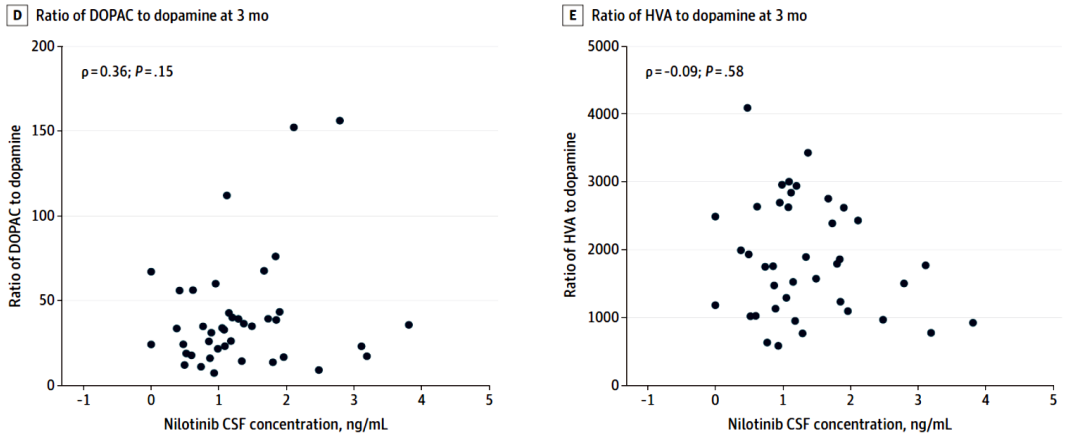
- Rapamycin and analogues: act via the mammalian target of rapamycin (mTOR) to increase macroautophagy function: reduce a-syn aggregation and resulting toxicity in various overexpression-based cellular and animal models, lack of specificity and side-effects have limited the potential use if these drugs in the treatment of patients.
- **mTOR inhibition** by reducing pyruvate transport into mitochondria using a modulator of the mitochondrial pyruvate carrier (MPC) : reports only in rodent models
- Nilotinib: **targeting c-abl**. c-abl activity is enhanced in brain tissue of PD patients, increased c-abl activity leads to a downstream increase in phosphorylation and aggregation of a-syn. Increased c-abl activity also reduced function of Parkin, a key protein involved in mitochondrial biogenesis
- Increase the expression, stability, and delivery of lysosomal enzyme **β-glucocerebrosidase (GCase)**: a correlation between the decreased Gcase activity and accumulation of a-syn: compound GZ/SAR402671
- Use **small-molecule chaperones** that would drive correct folding of mutant GCase molecules in the ER, resulting in efficient transport to the lysosomes and increased GCase activity: ambroxol

c-Abl tyrosine kinase inhibitors for PD





Also, no difference in the CSF levels of dopamine, DOPAC, HVA among the three groups.

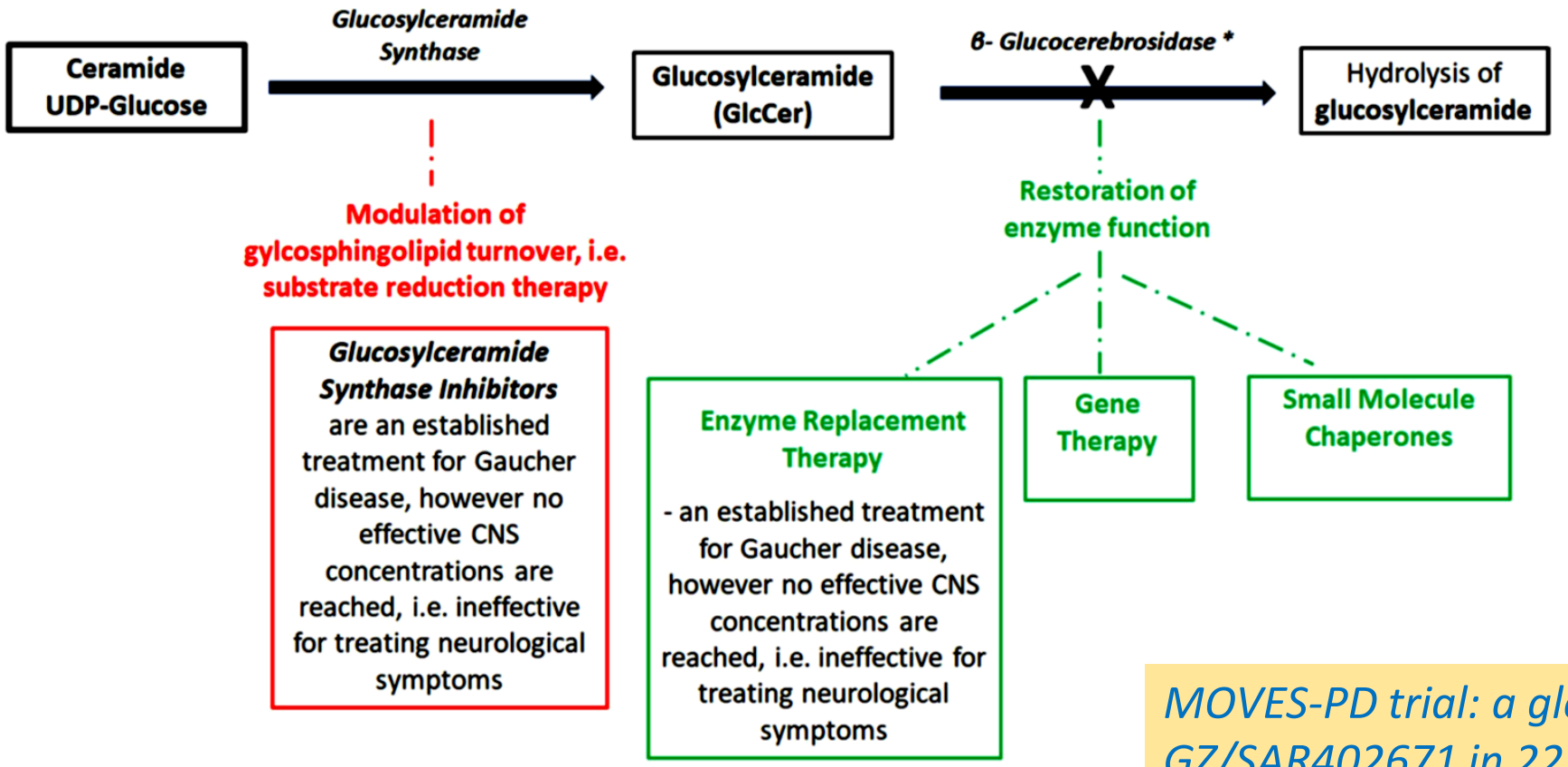


Both the clinical efficacy measures and biomarker changes ***did not show any benefit*** *from nilotinib in PD*

There is an on-going large (N=504) multicenter phase 2 trial of K0706, a brain penetrant c-Abl inhibitor (NCT03655236) in US, Europe, and India

Simuni, T. et al. JAMA Neurol. 2021;78:312-320

Therapeutic targets under development for GBA-PD

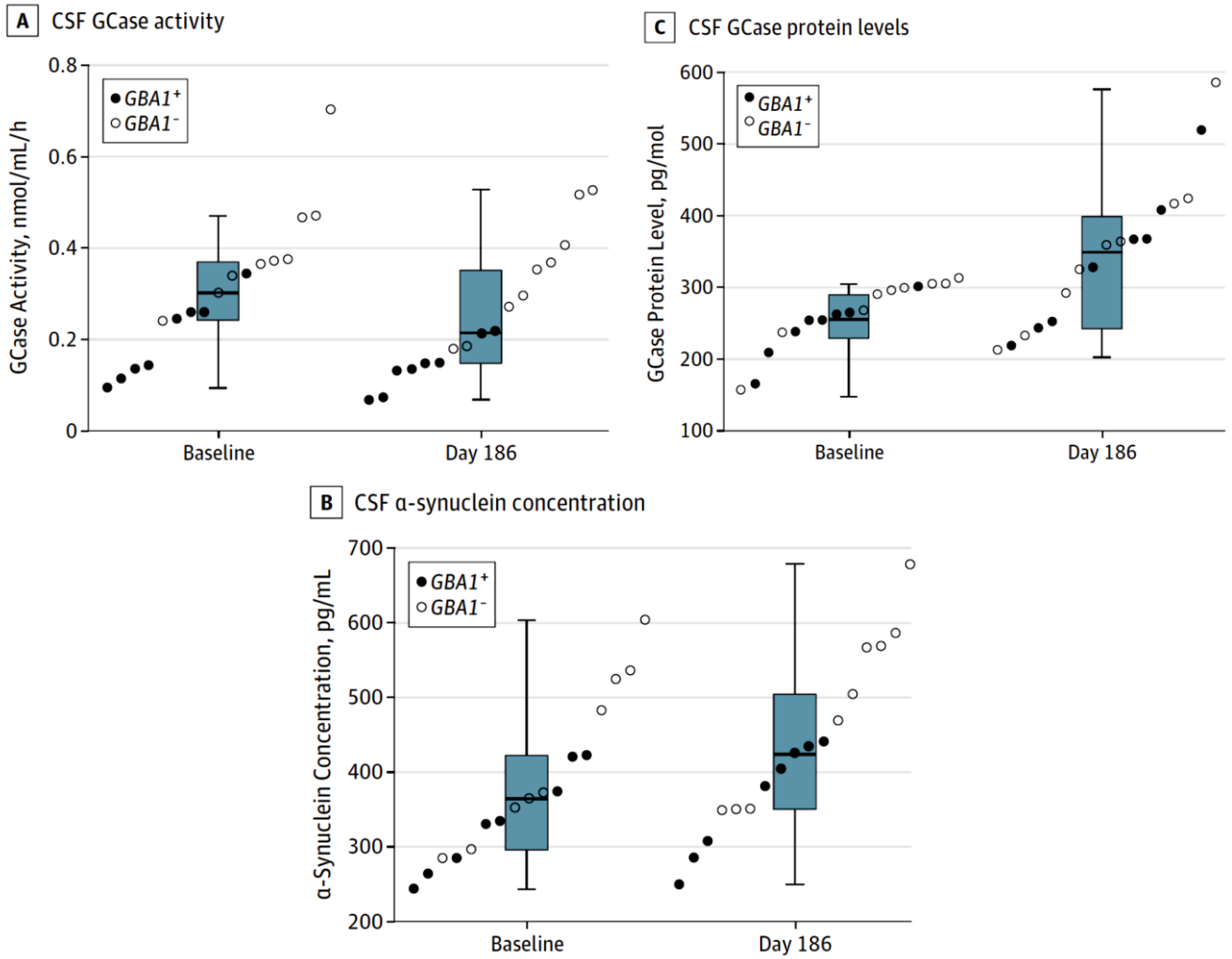


Development scheme by Schneider SA, et al. J Neurol 2020; 267: 860-869

MOVES-PD trial: a global phase 2 trial of GZ/SAR402671 in 221 GBA-PD patients, recently reported that the investigational drug showed no impact on the progression of PD as measured by MDS-UPDRS II+III.

Glucocerebrosidase targeting therapeutics

A total 20 (9 GBA1+ and 11 GBA1-) patients received ambroxol treatment, and final analysis included 18 patients



The open-label proof-of-concept trial showed "ambroxol has potential as a drug to target the GCase pathway in PD" and ***increase GCase activity in the brain.***

Mullin, S. et al. JAMA Neurol 2020;77(4):427-434

A phase 2, single-center, DB, PC trial for PD dementia for 52 weeks tx with ambroxol high-dose (1050 mg/day), low-dose (525mg/day), or placebo for 52 weeks and a 6-mo open label extension (NCT02914366) in Canada: on-going

4) Increasing extracellular aSC degradation by active and passive immunization

- Backgrounds: targeting extracellular a-syn

Neuron, Vol. 46, 857–868, June 16, 2005, Copyright ©2005 by Elsevier Inc. DOI 10.1016/j.neuron.2005.05.010

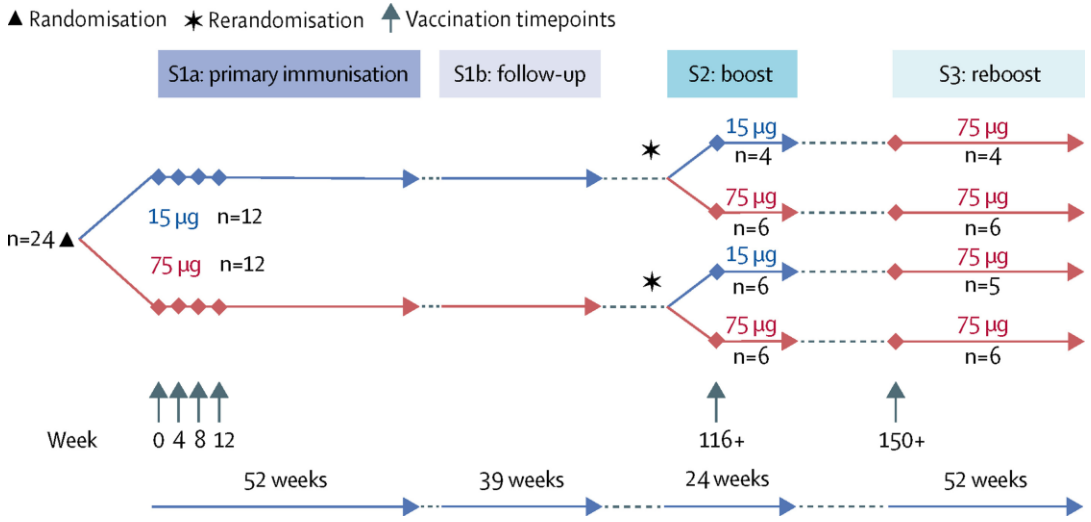
Effects of α-Synuclein Immunization in a Mouse Model of Parkinson's Disease

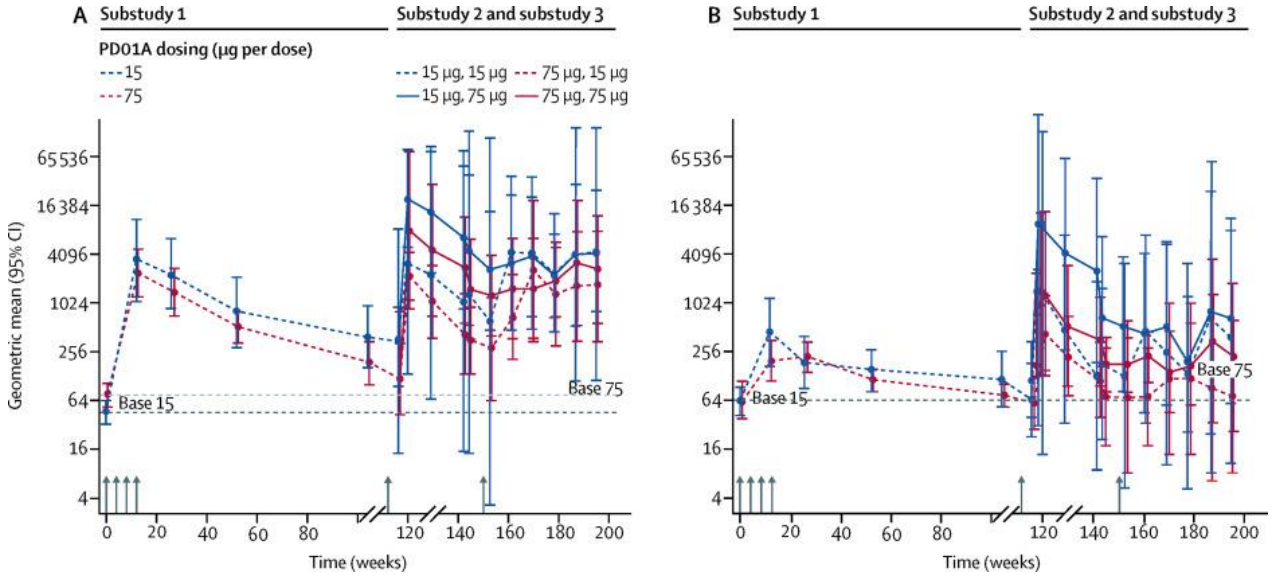
- **Strategy:**
  - ✓ Active immunization: stimulation of immune system to produce antibodies against target proteins
  - ✓ Passive immunization: administration of temporary antibodies for degradation
- **Caveats:**
  - ✓ the potential to trigger off-target responses, non-specific inflammatory reactions
  - ✓ the need for repetitive administration
  - ✓ lack of response due to senescence of the innate immune system
  - ✓ limited penetration of antibodies into the CNS
  - ✓ It is unclear how immunotherapies that are efficacious in animal models of PD will work in the specific form of inflammation and glial activation that is present in advanced PD patients.

Investigational products ..

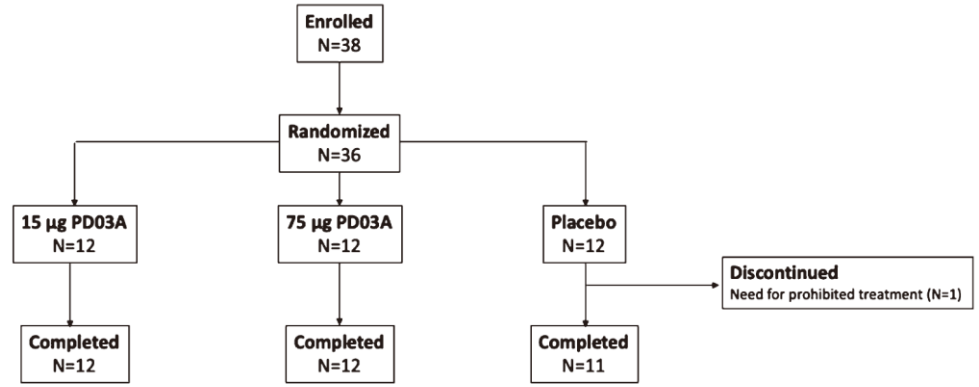
- AFFITOPE® PD01A, PD03A: subcut injection: dose-dependent immune response against the peptide and cross reactivity against a-syn, (potentially targeting oligomeric a-syn)
- Cinpanemab: N-terminus of a-syn (stopped due to lack of benefit, phase 2 SPARK study)
- Prasinezumab: C-terminus of a-syn
- Other C-terminal-targeting antibodies in phase 1 trial: MEDI1331, LuAF82422, UCB7853
- ABBV-0805(BAN0805): antibodies targeted for oligomeric a-syn, entered phase 1 in Mar 2020, but stopped in July 2020

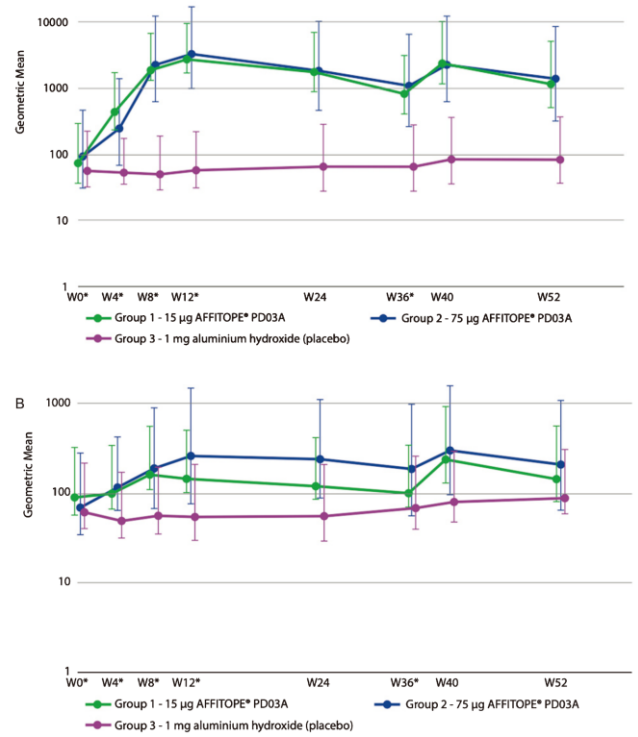
Phase 1 trial of PD01A and PD03A in early PD





Volc D, et al. Lancet Neurol. 2020;19(7):591-600



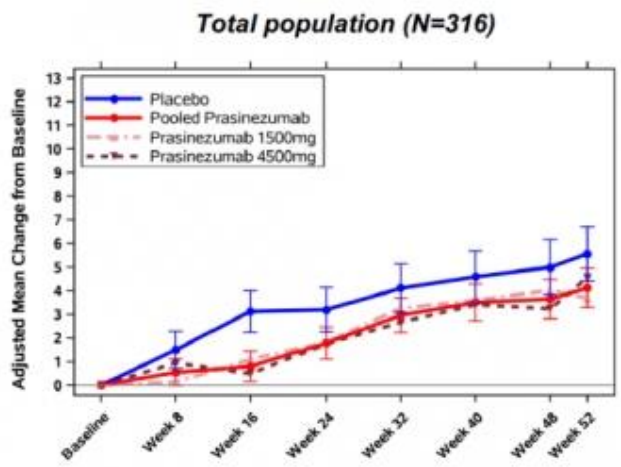


Differences in titers between both active groups versus placebo were statistically significant from the second immunization at Week-8 until Week-52.

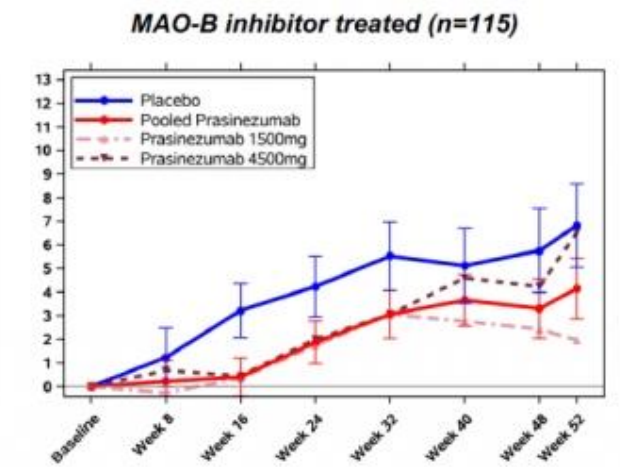
Poewe W, et al. J Parkinsons Dis. 2021;11(3):1079-1089.

The only promising result of Ab trials so far..

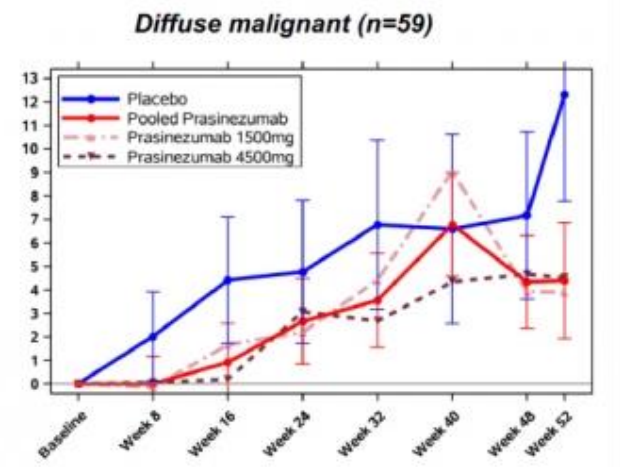
The primary outcome was not met: either that α-synuclein pathology is not so central in pathogenesis, or that the trial did not target the toxic α-synuclein species, and that other antibodies may be necessary.



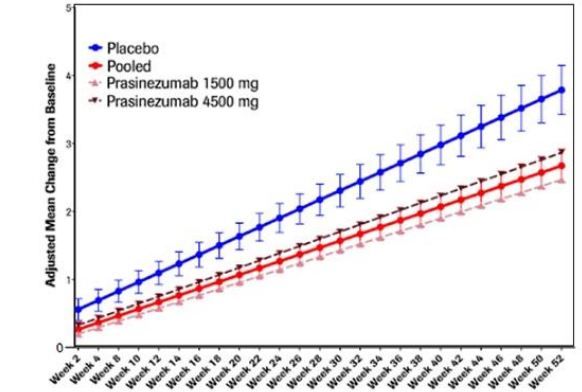
Pooled: –1.44, 80% CI=(–2.83, –0.06); **–25.0%**
Prasinezumab 1500 mg: –1.88, 80% CI=(–3.49, –0.27); **–33.8%**
Prasinezumab 4500 mg: –1.02, 80% CI=(–2.64, 0.61); **–18.2%**



Pooled: –2.66, 80% CI=(–4.87, –0.45); **–39.0%**
Prasinezumab 1500 mg: –4.85, 80% CI=(–7.33, –2.37); **–71.1%**
Prasinezumab 4500 mg: –0.28, 80% CI=(–2.82, 2.25); **–4.0%**



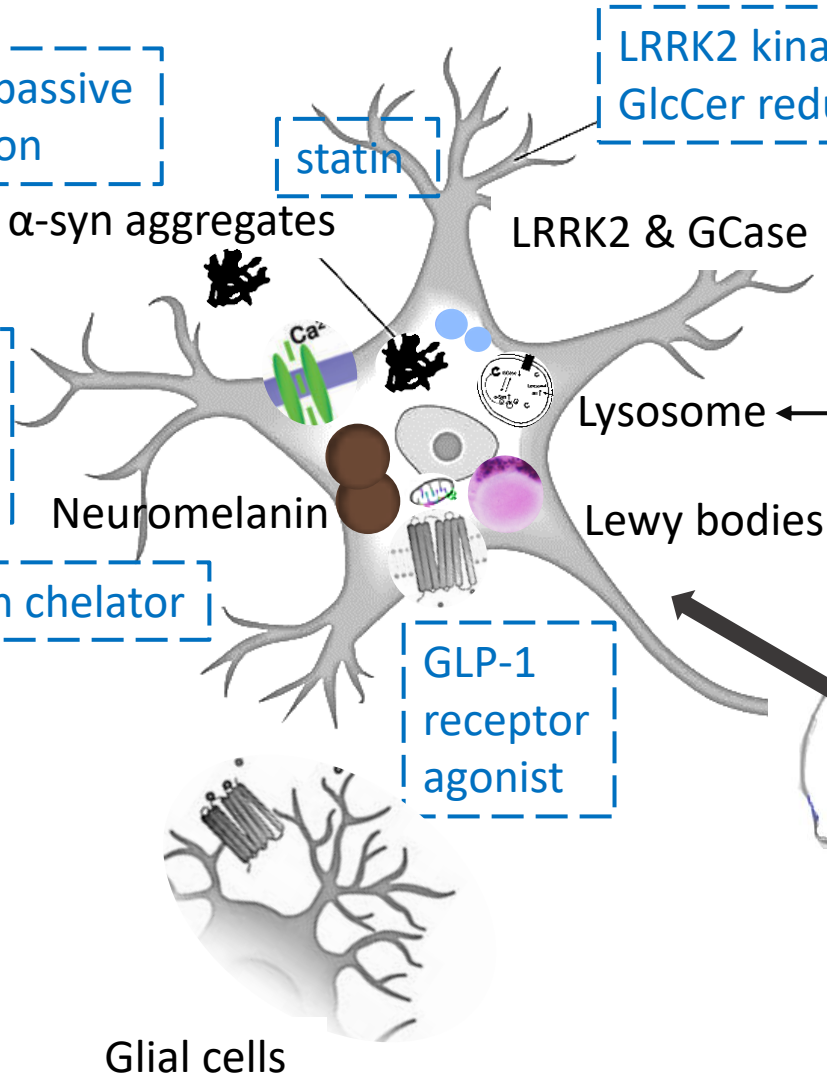
Pooled: –7.86, 80% CI=(–12.9, –2.82); **–63.9%**,
Prasinezumab 1500 mg: –8.4, 80% CI=(–14.2, –2.59); **–68.3%**
Prasinezumab 4500 mg: –7.77, 80% CI=(–13.4, –2.14); **–63.2%**



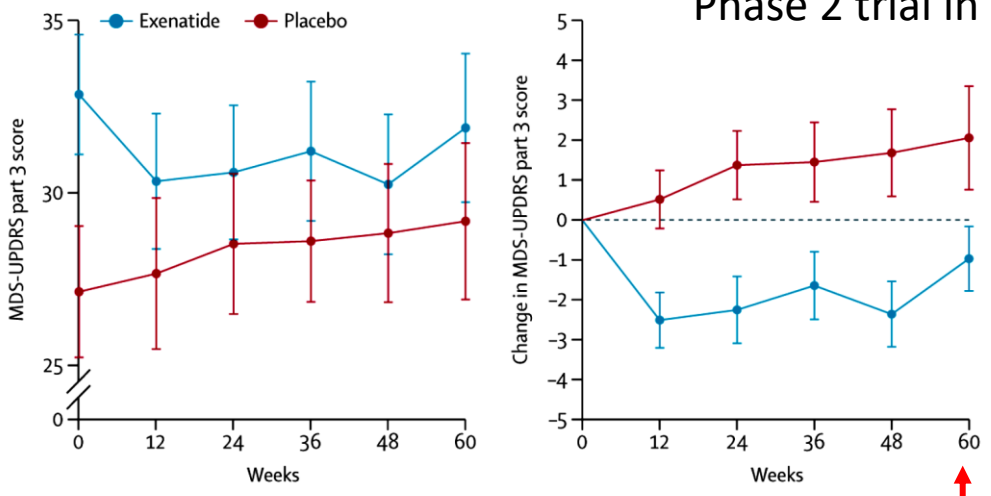
Pooled: –0.030, 80% CI=(–0.050, –0.010); **–25.0%**
Prasinezumab 1500 mg: –0.040, 80% CI=(–0.063, –0.017); **–30.3%**
Prasinezumab 4500 mg: –0.029, 80% CI= (–0.052, –0.006); **–21.5%**

Prasinezumab recognizes the C-terminus of α-synuclein, and binds preferentially to aggregated forms.
In Phase 1, the antibody entered the central nervous system but did not affect monomeric, physiological α-syn.
The Phase 2 trial enrolled 316 newly diagnosed with PD patients without dopamine replacement therapy, but one-third took monoamine oxidase-B inhibitors.

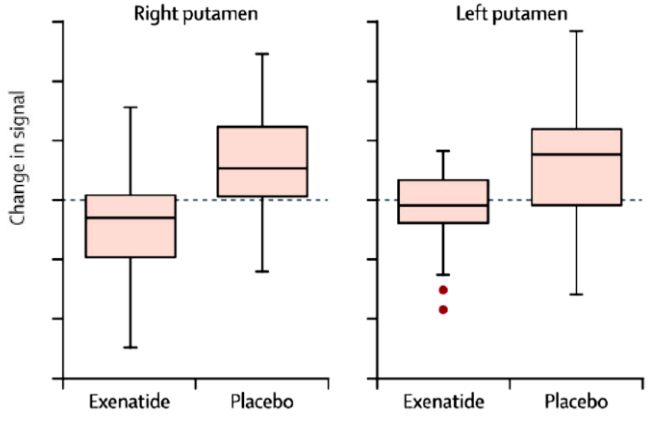
Potential disease modifying targets under development



Glucagon-like peptide 1 (GLP1) receptor agonists trials

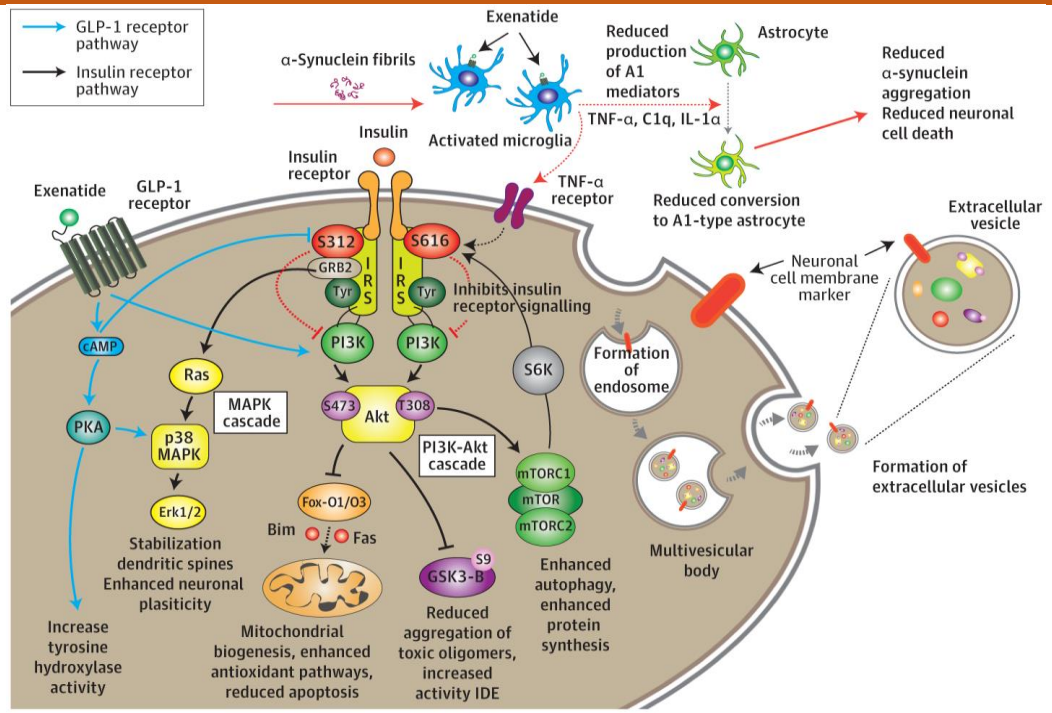


Phase 2 trial in UK



After 12wks' wash-out, MDS-UPDRS part 3 (off) improved by 1.0 [−2.6 to 0.7] in the exenatide group & worsened by 2.1 [−0.6 to 4.8] in the placebo group.

adjusted mean difference = −3.5 points (p=0·0318).



Peripherally administered exenatide may engage and normalize brain insulin signaling in association with activation of Akt and mTOR cascades in PD

Aviles-Olmos, I. et al. J Clin Invest 2013; 123: 2730–2736

Athuada, D., et al. Lancet 2017;390:1664-1675

Aviles-Olmos, I. et al. J Parkinson's Dis 2014; 4:337-344.

Athuada, D., et al. J Parkinson's Dis 2018; 8:247-258.

Athuada, D., et al. JAMA Neurol 2019;76: 420-429.

Glucagon-like peptide 1 (GLP1) receptor agonists and other anti-diabetic agents

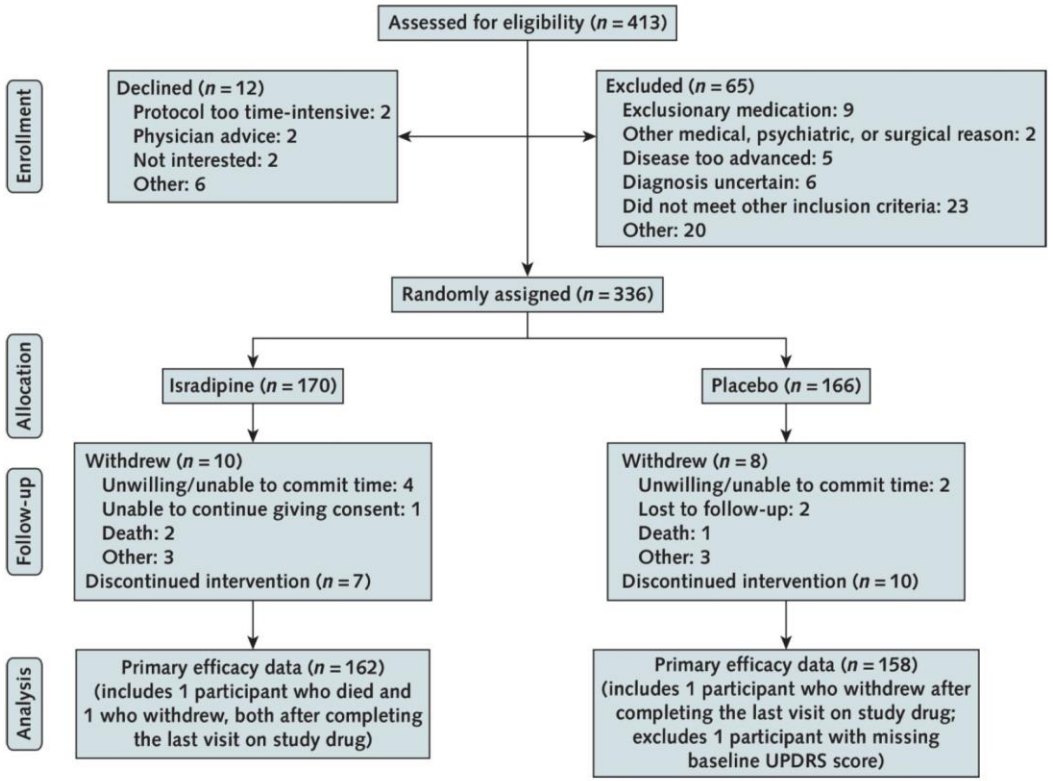
Investigational Agents	Trial Phase	Target	Primary outcome	Special outcomes	Sponsor/organization	Comments
Exenatide	II	Early PD (N=60)	Changes in metabolic network (FDG-PET)	Changes in MDS-UPDRS part 3 at OFF, accelerometer-based activity, blood/csf	Stockholm Health Services/Karolinska Institutet,	18 mo tx, 3 mo washout
Exenatide	III	Early PD (N=200)	Changes in MDS-UPDRS part 3 at off (at 96 wk)	Other scales covering nonmotor aspects, QOL	University College London	Over 2 yr, 2mg SC once weekly
Exenatide SR	II	Early PD (N=99)	Changes in MDS-UPDRS part 3 at off	Changes in DAT SBR (FP-CIT PET), blood/csf, Ab	Peptron, Inc./ C.I. Seoul National University, Korea	2mg once weekly vs. 2.5mg every 2 wks
NLY01	II	Early tx naïve PD (N=240)	Changes in MDS-UPDRS part 2+3	Including SCOPA-COG, DaTscan, Ab, PK, safety/tolerability	Neuraly, Inc./US, Toronto	Pegylated form, 36wks tx, 2.5mg vs 5mg
Semaglutide	II	Early PD (N=120)	Changes in MDS-UPDRS part 3 at off at 48 mo	DaTscan, blood/csf	Oslo University Hospital	Doubleblind 2 yr+ Open-label 2yr
Liraglutide	II	Early PD (N=57)	MDS-UPDRS part3, NMSS, MADRS-2	Insulin resistance	Cedars-Sinai Medical Center	Once daily
Lixisenatide	II	Early PD (N=158)	Changes in MDS-UPDRS part 3 at on at 12mo		University Hospital Toulouse	Once daily ,12mo tx + 2mo washout

L-type calcium channel blocker trial in PD

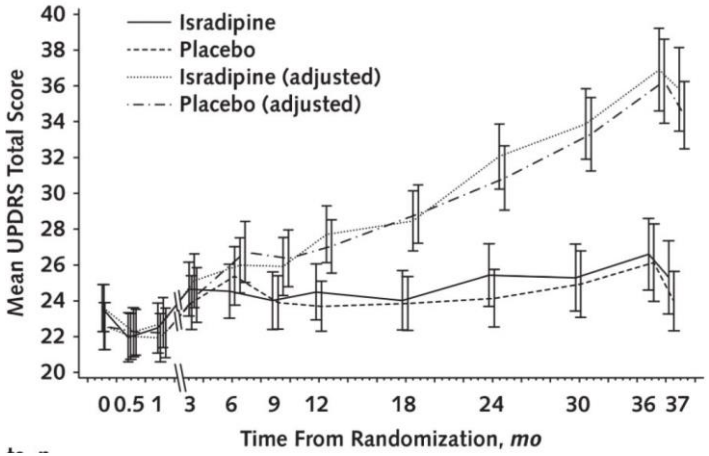
Isradipine Versus Placebo in Early Parkinson Disease A Randomized Trial

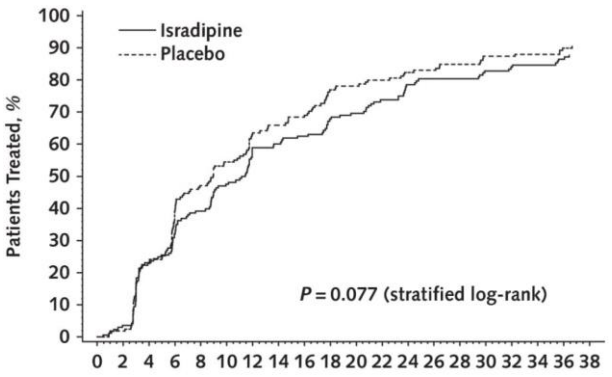
The Parkinson Study Group STEADY-PD III Investigators*

Early PD <5 yr, naïve to dopaminergic tx
5 mg of isradipine twice daily (n = 170) or placebo (n = 166) for 36 mo



Time to anti-parkinson therapy



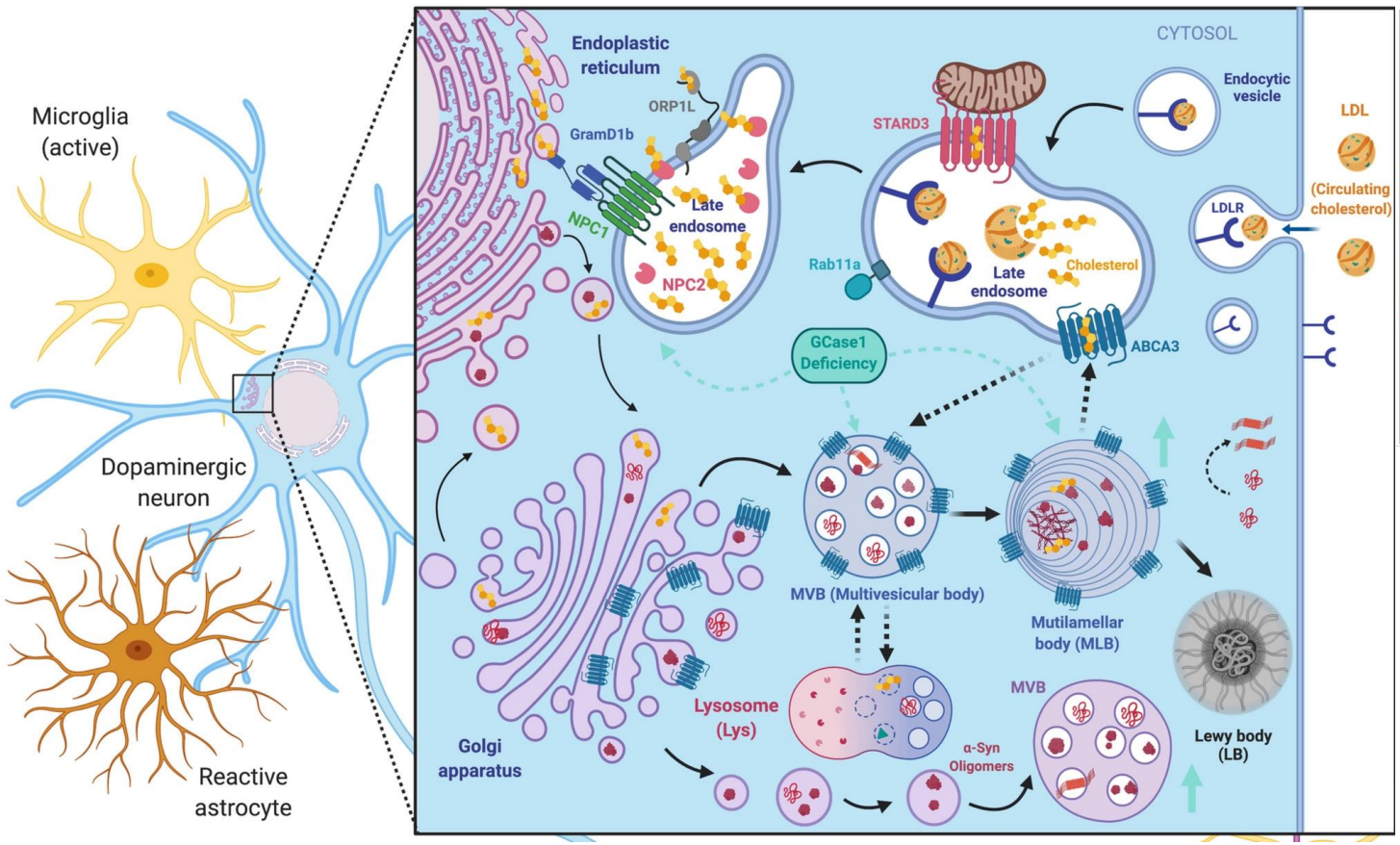


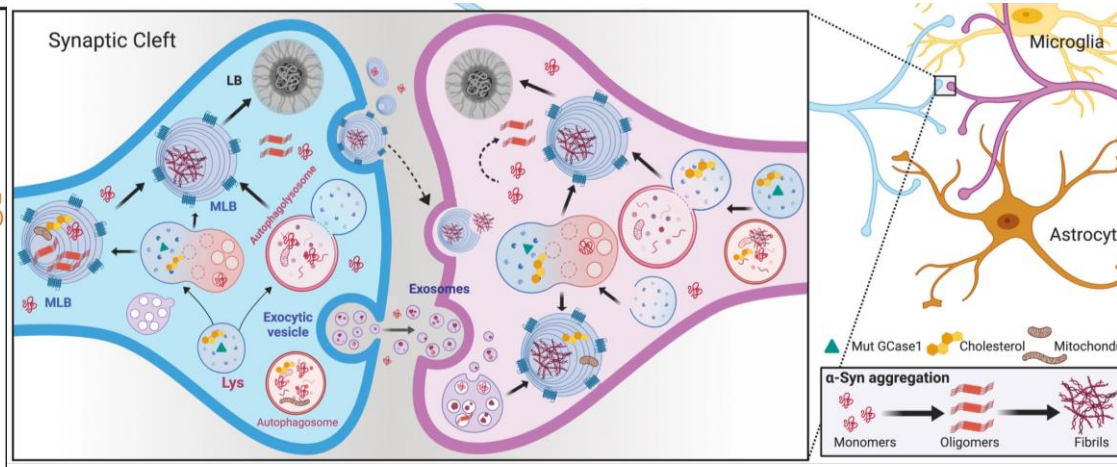
Immediate release isradipine twice daily treatment **failed to slow** progression in early-stage PD.

A lack of target engagement in the brain?
A lack of biomarkers to show target engagement?
Inadequate outcome measure?

Ann Intern Med. 2020; 172(9): 591–598

Cholesterol and α-syn aggregation & propagation in PD





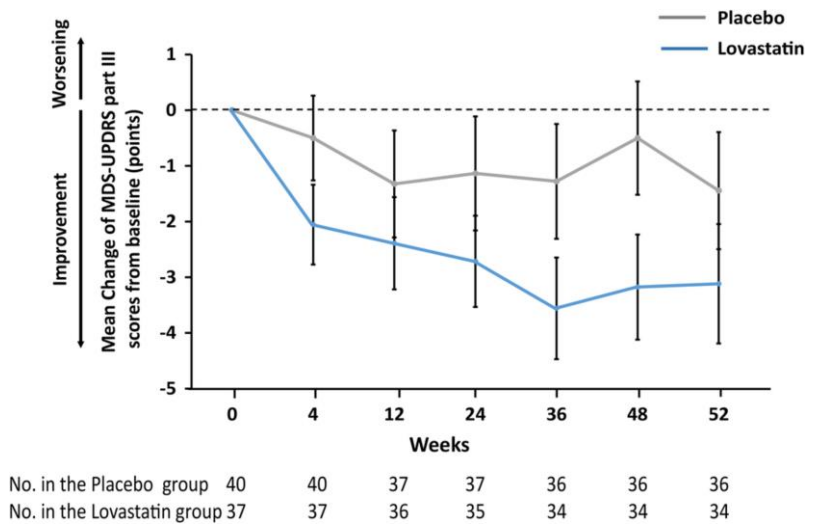
A hypothesized model of transneuronal propagation of pathogenic α-syn through multilamellar bodies (MLB) in PD.

Intracellular trafficking of LDL cholesterol into MLB. GCase lysosomal dysfunction increases the amount of multivesicular endosomes.

García-Sanz, et al. Mov Disord 2021; 36(5): 1070-1085

Does lipophilic statin help in Parkinson's disease?

A single center, double-blind, placebo-controlled trial in Taiwan in early PD patients (HY ≤2)



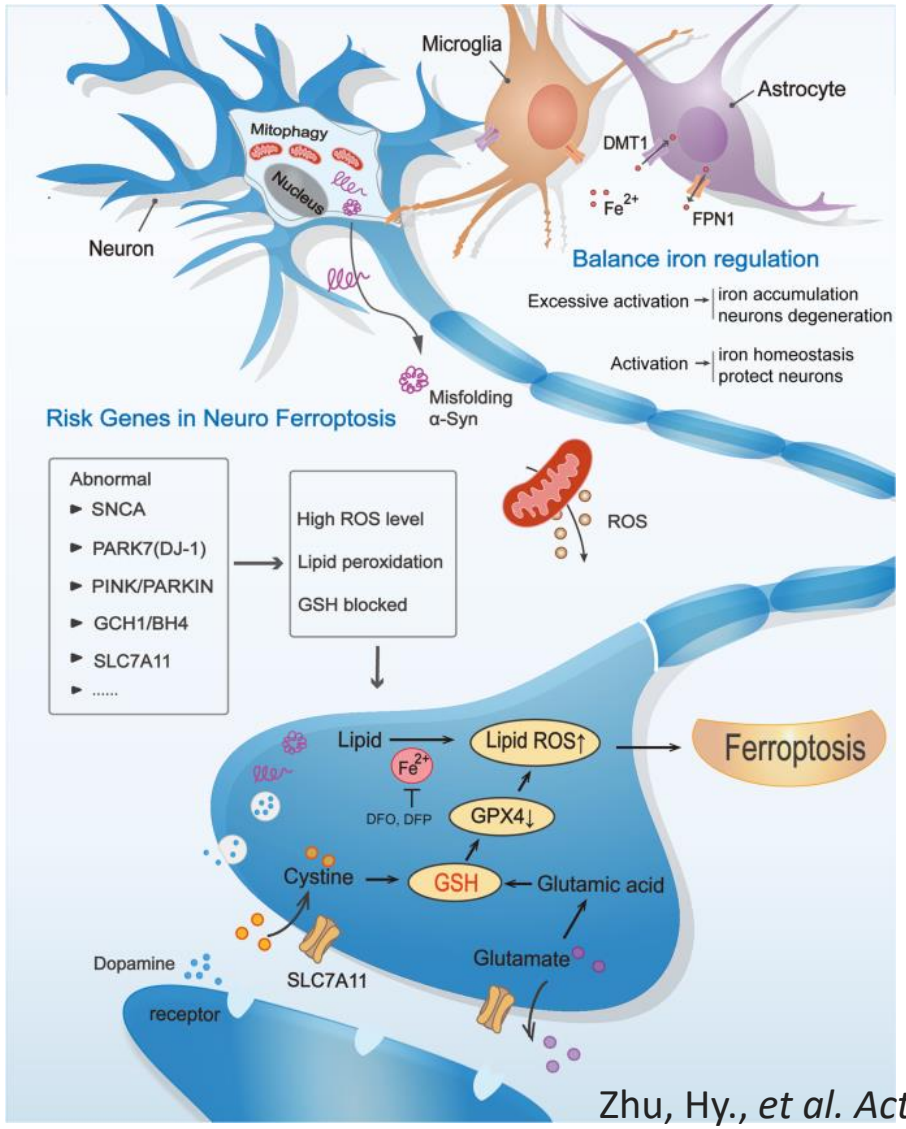
^{18}F-dopa striatum-to-cerebellum ratio	Placebo (N=40)	Lovastatin (N=37)
Dominant side	0-48 wk	0-48 wk
Caudate	-7.1(8.2)%	1.2(7.3)%
Putamen	-6.4(8.1)%	2.3(7.1)%
Nondominant side	0-48 wk	0-48 wk
Caudate	-6.3(10.1)%	0.4(7.1)%
Putamen	-5.2(9.2)%	2.0(8.1)%

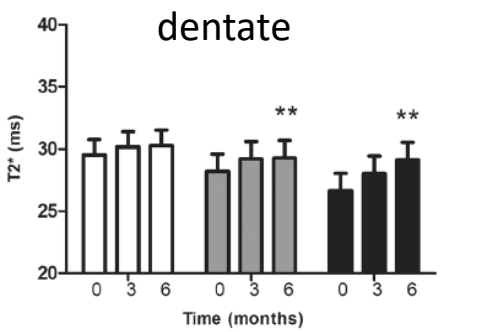
- **Epidemiological** studies report **controversial** effect of statin on the development of PD. (increased vs. lowered risk vs. no difference)

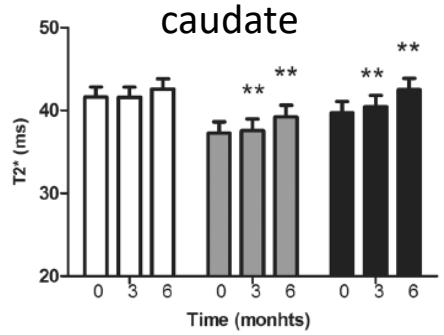
- Simvastatin trial in moderate stage PD patients with wearing-off (**PDSTAT2015**) showed SVS **was futile** at slowing disease progression compared to placebo (NCT02787590) (reported in the MDS 2020).

Lin CH, et al. Mov Disord 2021; 36(5): 1229-1237

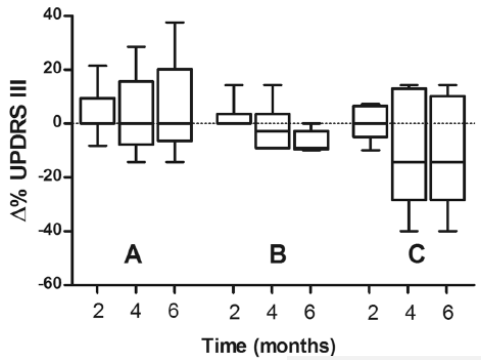
Iron chelation trial in PD







No change was detected in the putamen, nigra, pallidum



A pilot double-blind placebo-controlled phase 2 trial of deferiprone 20mg or 30mg daily for 6 months in 22 early PD patients in UK

Martin-Bastida, A. et al. Sci Rep 2017;7(1):1398

- Conservative Iron Chelation as a Disease-modifying Strategy in Parkinson's Disease. European Multicentre, Parallel-group, Placebo-controlled, Randomized Clinical Trial of Deferiprone (FAIRPARKII) (NCT02655315): 25 sites in Europe led by Devos D. (University Hospital, Lille)
- SP-420, a small molecule next generation iron chelator, under development

Zhu, Hy., *et al. Acta Pharmacol Sin* (2020)

Issues: outcome measures for early PD progression

- NET-PD experience: the MDS-UPDRS part II and III score increases
- Symptomatic effect of LD medication, especially in early stages
- What is the more sensitive and objective measures of clinical changes?
- Definition of disease modifying effect: individual variability in disease progression in the early stage of PD, how long the clinical trial should be required to determine the benefit?

➢ When the clinical measures not significant and imaging parameters are significant, how do we interpret the results?

Issues: what is the best target among the a-syn species

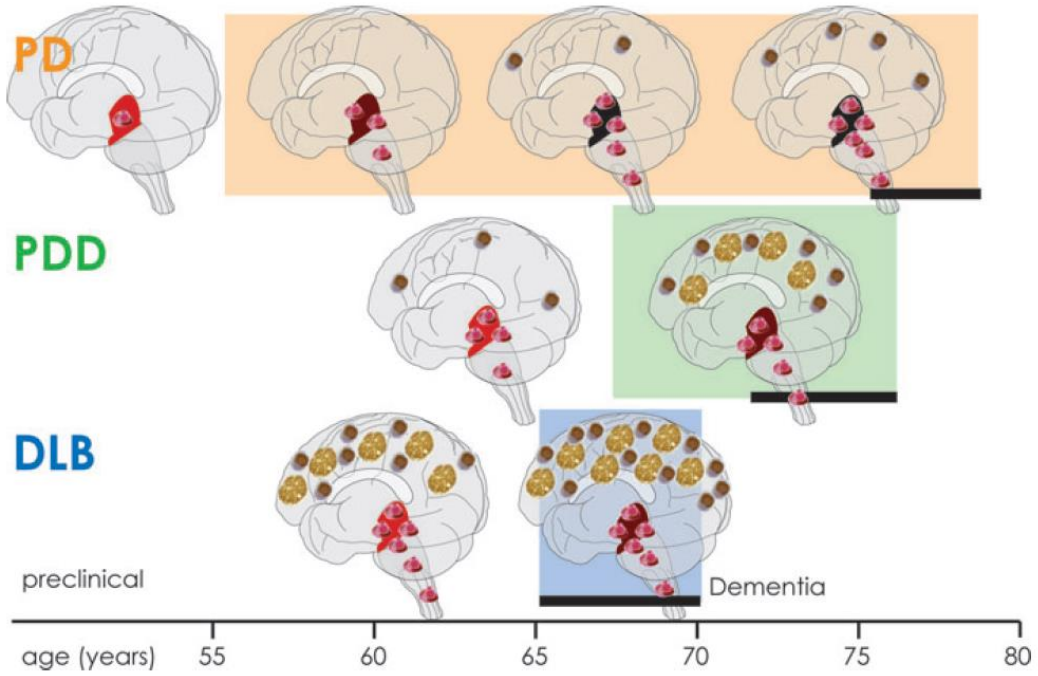
- Due to the nature of a-syn to be an intrinsically disordered protein with extreme conformational diversity, it has been difficult to associate a particular structural species to neuronal toxicity
- It is not clear whether how many monomeric molecules constitute that “toxic” oligomer (a 26-mer, a 113-mer or a 212-mer molecule, etc.), whether toxicity results from a particular post-translational modification or truncated species, or whether aggregation is even necessary for toxicity.
- Individual variations on the type (strain) and amount of multimeric a-syn species (ex. among the PD patients, PD vs MSA patients)

Issues

- No reproducible and validated a-syn imaging, bio-fluid, non-invasive a-syn biomarkers until now: can not exactly check up the target engagement
- Need of Neuroprotective strategy-based approach; composite measures, as well as therapeutics' mechanism-based specific biomarkers
- Need of specific Biomarker-based models?

➢ Lack of objective biomarkers that track with the progression of the disease have led to longer, larger and costlier trials, and ultimately leading to inconclusive testing of the hypothesis and uninformed results.

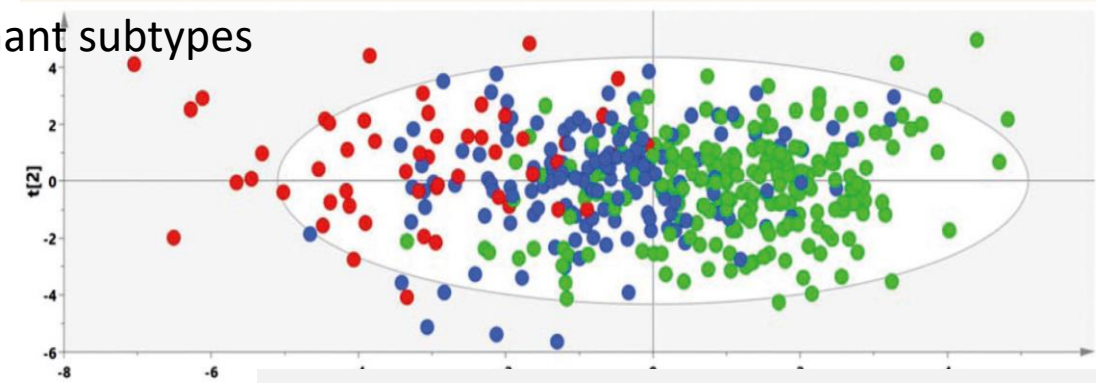
Issues: combined pathologies and phenotypic heterogeneity



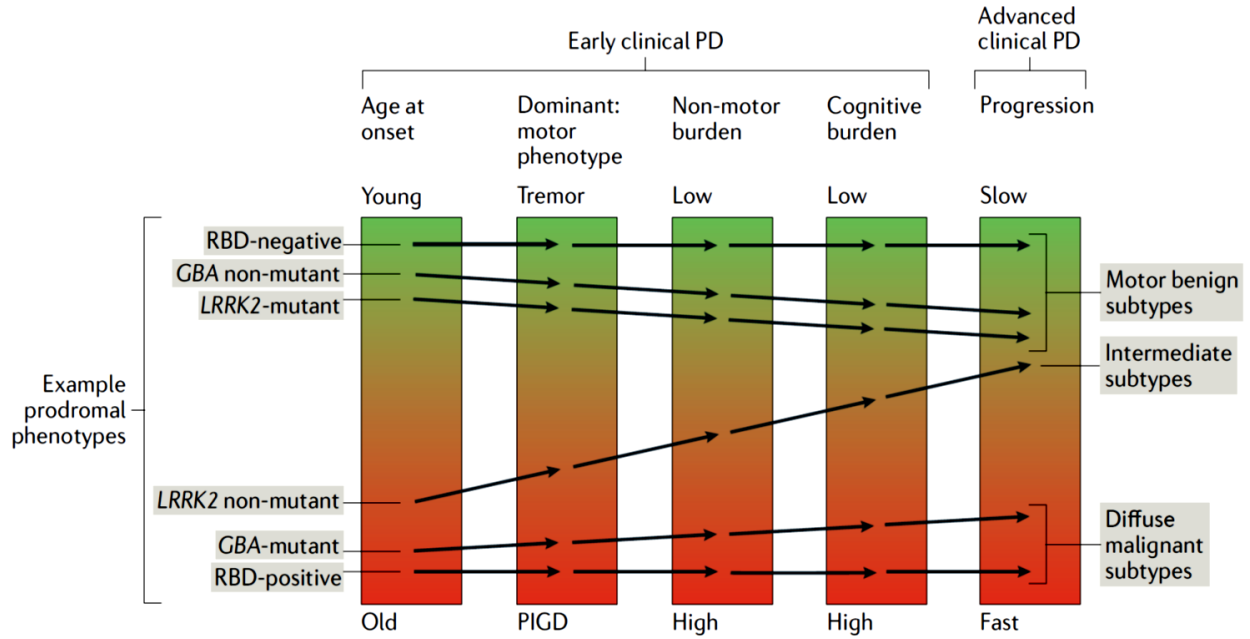
Ann. N.Y. Acad. Sci. 1184 (2010) 188–195

A large heterogeneity of clinical feature and disease progression in PD from the early prodromal phase

predominant motor, intermediate, diffuse malignant subtypes



Fereshtehnejad SM, et al. Brain 2017;140:1959-1976.



Berg D, et al. Nat Rev Neurol 2021; 17: 349-361.

Thank you for your attention!