Parkinson's disease:
causes & cures

European Parliament, 8 November 2018

S&D EuChemS European Chemical Society EFMC European Federation for Medicinal Chemistry

Centro Specialistico Ortopedico Traumatologico Gaetano Pini-CTO

Sistema Socio Sanitario Regione Lombardia

ASST Gaetano Pini

UNIVERSITÀ DEGLI STUDI DI MILANO BICOCCA

Causes for Parkinson's Disease

Roberto Cilia, M.D.

Parkinson Institute
ASST G. Pini-CTO
Milano, ITALY

Email: roberto.cilia@gmail.com

VIEWPOINT

The Parkinson Pandemic—A Call to Action

Why shall we talk about PD?

Prevalence will double by 2040 (surpassing Alzheimer's)
due to ↑ Ageing, ↑ Diagnosis, ↓ Smoking

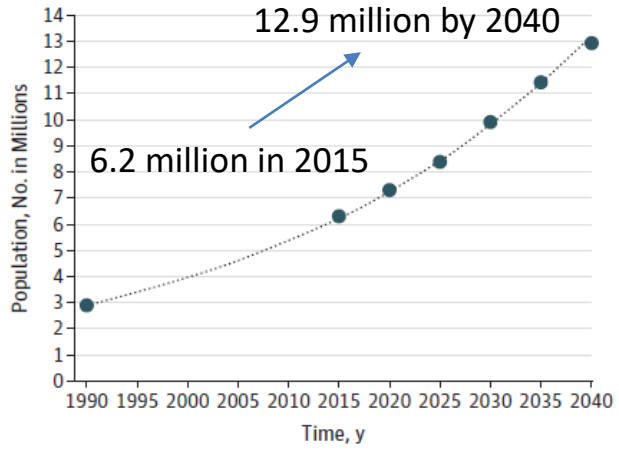
↑ Disability -> ↑ Personal, Societal, Economic Burden

Need to understand the complex pathogenesis of PD

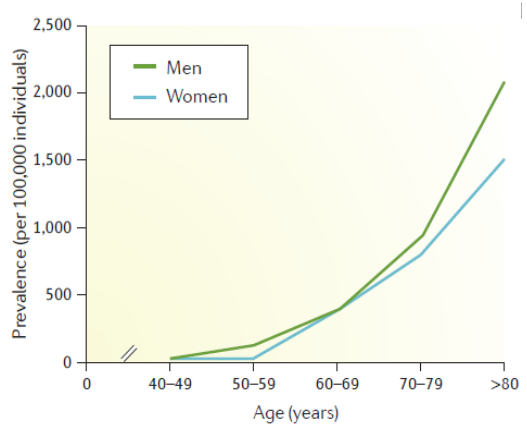
PD development is likely to require the simultaneous failure of multiple cellular homeostatic/protective mechanisms.

Find targeted and effective 'Neuroprotective' therapies to be started at early prodromal PD stages

Figure. Estimated and Projected Number of Individuals With Parkinson Disease, 1990-2040



Sources: Global Burden of Disease Study (1990 and 2015) and projections based on published[2] and public[3] sources.

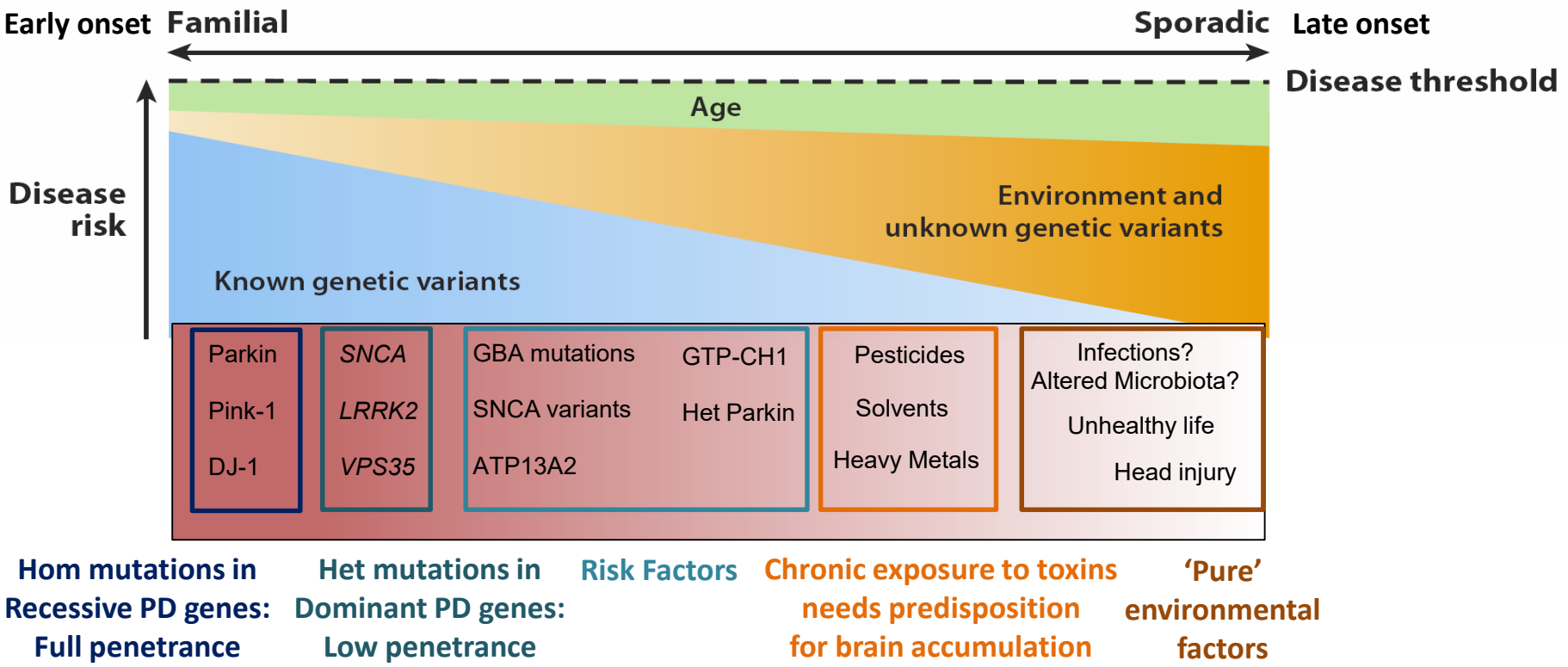


Dorsey and Bloem, JAMA Neurol 2018 (referring to D. France's book *How to survive a Plague*)

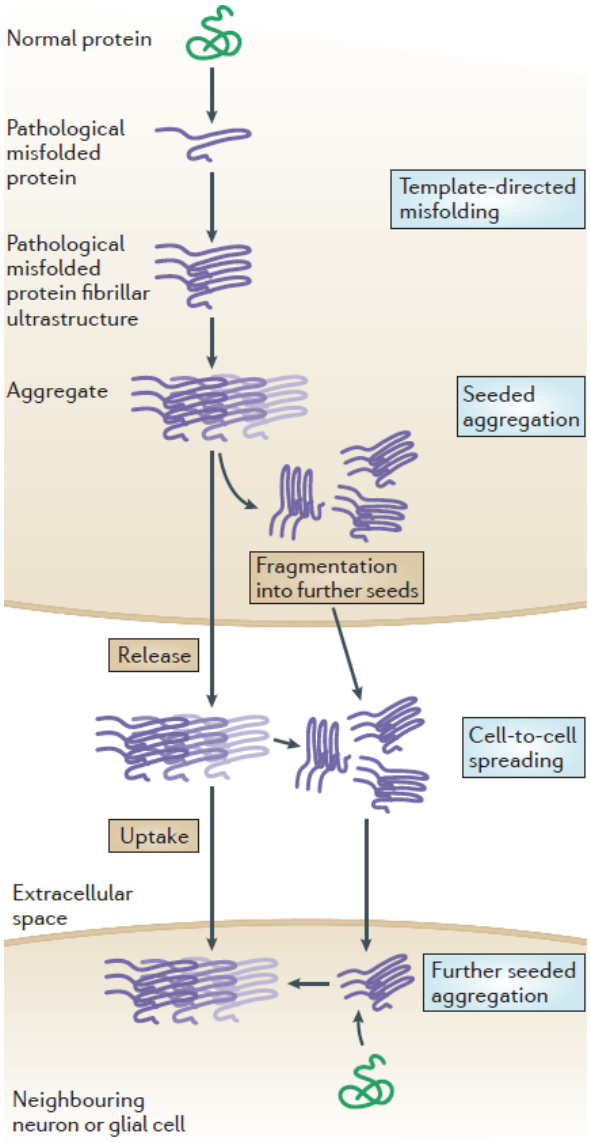
PD as model of *Multifactorial Disease*

- Heritable (Mendelian) 5-10% vs. Idiopathic PD ≈ 90%
- Idiopathic PD is caused by the interaction between 3 factors:

1) Ageing
2) Genetic Predisposition
3) Environmental Factors

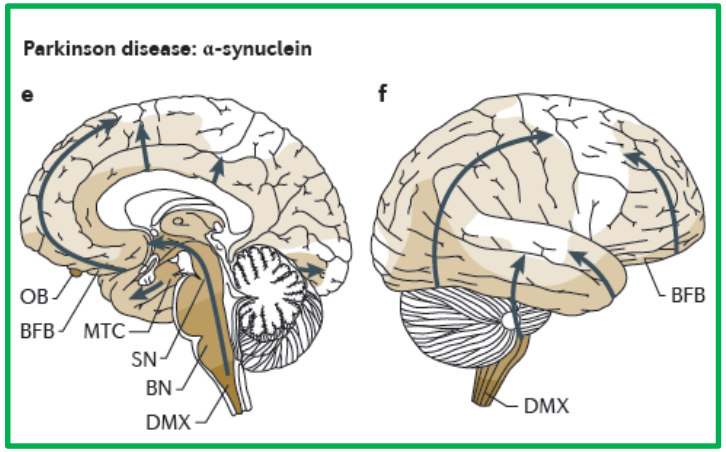


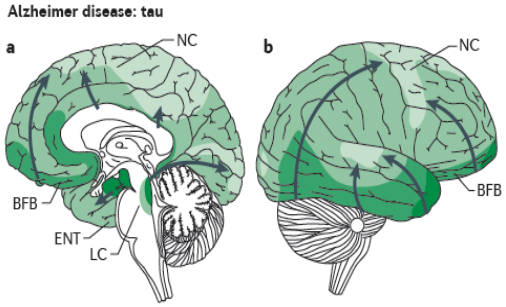
Cell-to-Cell propagation of α-syn pathology

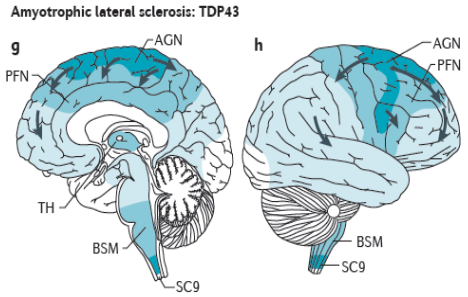


From the discovery of the α-syn gene (SNCA) and the presence of α-syn in Lewy Bodies (1997), research found strong evidence for a cell-to-cell propagation of pathology in PD (also AD, ALS).

WHAT IS THE TRIGGER of α-SYN PATHOLOGY?



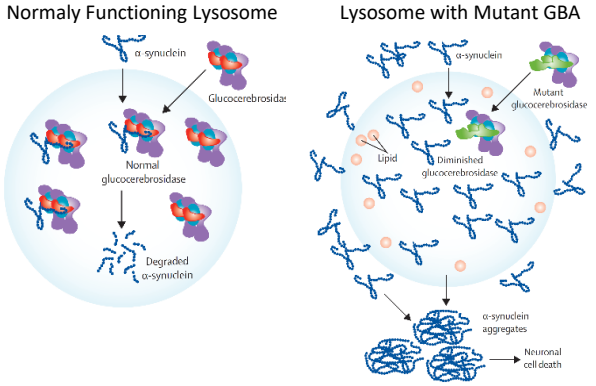


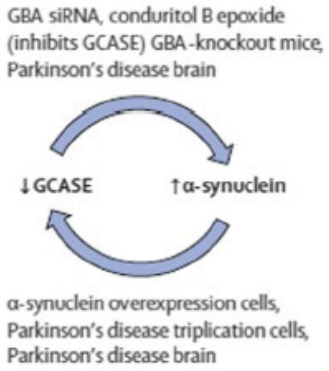


Desplats et al., PNAS 2009; Luk et al., Science 2012; Goedert, Science 2015; Brettschneider, Nat Rev Neurosci 2015

What is the Trigger of initial α-syn aggregation?
(1) Genetics

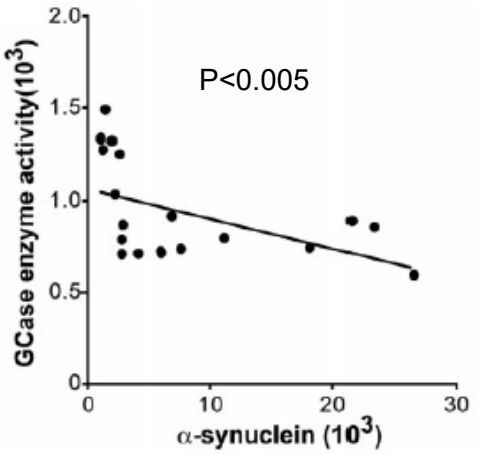
(a) GBA





GBA1 mutations (10-11% of PD) reduce neuronal ability to degrade α-syn. Risk for Dementia 3-fold higher than for PD -> diffuse α-syn pathology.

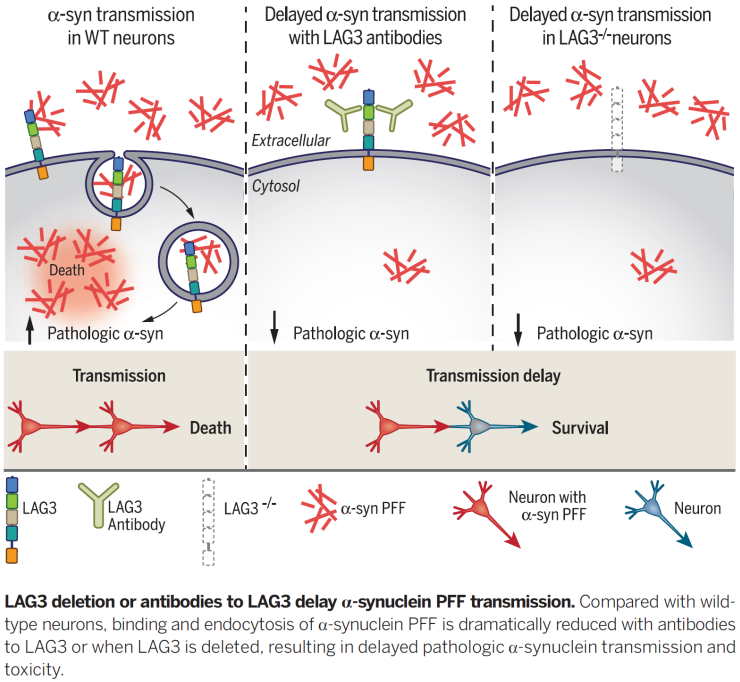
↓ GCase activity also in **sporadic PD without GBA1 mutations associated with ↑ α-syn accumulation**



GCase as potential target of 'disease-modifying' therapies in the whole PD population.

(b) LAG-3

Pathological α-synuclein transmission initiated by binding lymphocyte-activation gene 3



LAG3 deletion or antibodies to LAG3 delay α-synuclein PFF transmission. Compared with wild-type neurons, binding and endocytosis of α-synuclein PFF is dramatically reduced with antibodies to LAG3 or when LAG3 is deleted, resulting in delayed pathologic α-synuclein transmission and toxicity.

Mao et al., Science 2016; Murphy et al., Brain 2014; Cilia et al., Ann Neurol 2016

What is the Trigger of initial α-syn aggregation?
(2) Environmental Causes

Exposure to pesticides or solvents and risk of Parkinson disease

Gianni Pezzoli, MD
Emanuele Cereda, MD, PhD

Neurology® 2013;80:2035-2041

In a meta-analysis, high-quality case-control studies evidence that exposure to any-type pesticides, herbicides, and solvents, increase the risk for PD.

Exposure to Paraquat and Maneb/Mancozeb -> 2-fold increased risk.

FEBS 25011 FEBS Letters 500 (2001) 105–108

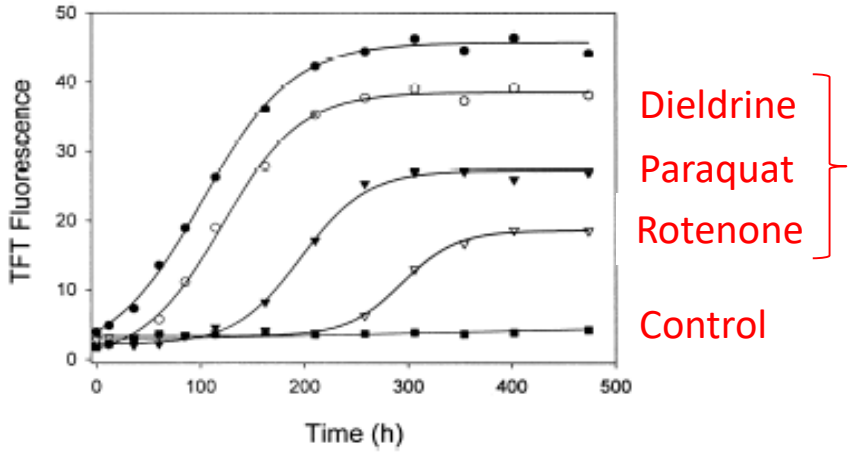
Oral Exposure to Paraquat Triggers Earlier Expression of Phosphorylated α-Synuclein in the Enteric Nervous System of A53T Mutant Human α-Synuclein Transgenic Mice

Nicolas Naudet, MSc, Emilie Antier, BS, Damien Gaillard, BS, Eric Morignat, MSc, Latifa Lakhdar, PhD, Thierry Baron, DVM, PhD, HDR, and Anna Bencsik, PhD, HDR

Pesticides (Paraquat) are able to trigger α-syn aggregation in the gut and to accelerate the formation of toxic oligomers.

Pesticides directly accelerate the rate of α-synuclein fibril formation: a possible factor in Parkinson's disease

Vladimir N. Uversky, Jie Li, Anthony L. Fink*



Uversky et al., FEBS Letters 2008; Cereda and Pezzoli, Neurology 2013; Naudet et al., J Neuropathol Exp Neurol 2017

CME

Hydrocarbon exposure and Parkinson's disease

G. Pezzoli, MD; M. Canesi, MD; A. Antonini, MD; A. Righini, MD; L. Perbellini, MD; M. Barichella, MD; C.B. Mariani, MD; F. Tenconi, MD; S. Tesei, MD; A. Zecchinelli, MD; and K.L. Leenders, MD

Article abstract—*Background:* Single cases of parkinsonism have been associated with hydrocarbon solvents. *Objective:* To determine whether exposure to hydrocarbon solvents is related to PD. *Methods:* Cohort study of 990 patients with PD according to Core Assessment Program for Intracerebral Transplantations (CAPIT) criteria, selected from 1455 consecutive subjects presenting at a referral center; case–control study assessing Unified PD Rating Scale scores (motor score as primary endpoint) in all subjects with positive history of hydrocarbon solvent exposure (n = 188), matched for duration of disease and gender to 188 subjects selected from the remaining 802 with a negative history. Two subgroups in the case–control study included the following: 1) response to apomorphine (n = 26); 2) brain MRI (n = 15). PET imaging (n = 9) was compared with that of historic controls. *Results:* Exposed patients were younger (61.0 ± 9.4 versus 64.7 ± 9.4 years, $p = 0.002$), predominantly male (76.4% versus 45.2%, $p = 0.0001$), less educated (8.4 ± 4.2 versus 10.1 ± 4.4 years, $p = 0.0001$), and younger at onset of disease (55.2 ± 9.8 versus 58.6 ± 10 years, $p = 0.014$). Exposure to hydrocarbon solvents directly correlated to disease severity ($r = 0.311$) and inversely correlated to latency period ($r = -0.252$). Nine blue-collar occupations accounted for 91.1% of exposures. *Conclusions:* Occupations involving the use of hydrocarbon solvents are a risk factor for earlier onset of symptoms of PD and more severe disease throughout its course. Hydrocarbon solvents may be involved in the etiopathogenesis of PD, which does not have a major genetic component.

NEUROLOGY 2000;55:667–673

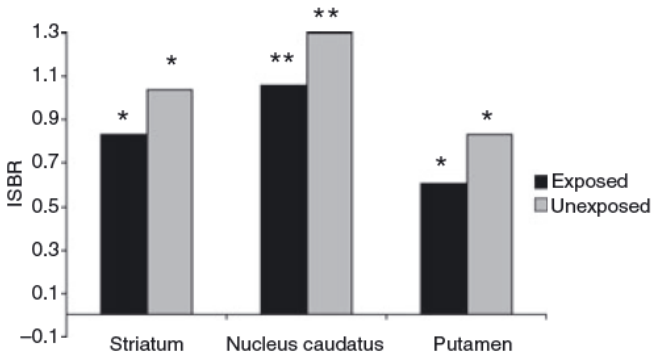
Solvents exposure (hydrocarbon) increase the risk for PD.
Earlier age at onset and more aggressive disease (clinical and SN terminals loss at imaging).

Association between PD and reduced n-hexane metabolism (Genetically-inherited? Secondary to PD pathology?)

Striatal dopamine transporter binding in patients with Parkinson's disease and severe occupational hydrocarbon exposure

M. Canesi[a], R. Benti[b], G. Marotta[b], R. Cilia[a], I. U. Isaias[a], P. Gerundini[b], G. Pezzoli[a] and A. Antonini[a]

European Journal of Neurology 2007, **14:** 297–299

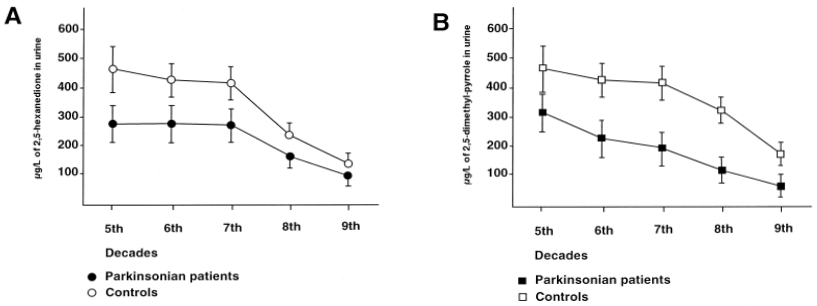


J Neurol (2003) 250 : 556–560
DOI 10.1007/s00415-003-1035-y

ORIGINAL COMMUNICATION

Poor metabolization of n-hexane in Parkinson's disease

M. Canesi
L. Perbellini
L. Maestri
A. Silvani
L. Zecca
L. Bet
G. Pezzoli



Gene-Environment Interactions (1)

Genetic and Epigenetic Predisposition

CYP2D6 Polymorphism, Pesticide Exposure, and Parkinson's Disease

Alexis Elbaz, MD, PhD,[1] Clotilde Levecque, MSc,[2] Jacqueline Clavel, MD, PhD,[3] Jean-Sébastien Vidal, MD,[4] Florence Richard, MD, PhD,[2] Philippe Amouyel, MD, PhD,[2] Annick Alpérovitch, MD, MSc,[1] Marie-Christine Chartier-Harlin, PhD,[2] and Christophe Tzourio, MD, PhD[1]

Ann Neurol 2004;55:430–434

Genetic Modification of the Association of Paraquat and Parkinson's Disease

Samuel M. Goldman, MD, MPH,[1*] Freya Kamel, PhD, MPH,[2] G. Webster Ross, MD,[3] Grace S. Bhudhikanok, PhD,[1] Jane A. Hoppin, ScD,[2] Monica Korell, MPH,[1] Connie Marras, MD, PhD,[4] Cheryl Meng, MS,[1] David M. Umbach, PhD,[5] Meike Kasten, MD,[6] Anabel R. Chade, MD,[7] Kathleen Comyns, MPH,[1] Marie B. Richards, PhD,[8] Dale P. Sandler, PhD,[2] Aaron Blair, PhD,[9] J. William Langston, MD,[1] and Caroline M. Tanner, MD, PhD[1]

High PD risk from paraquat exposure in individuals with **Glutathione S-transferase** (GSTT1*0) genotype, which is common and identifies a large subpopulation at high risk of PD from oxidative stressors.

ORIGINAL ARTICLE

Gene-environment interactions in parkinsonism and Parkinson's disease: the Geoparkinson study

F D Dick, G De Palma, A Ahmadi, A Osborne, N W Scott, G J Prescott, J Bennett, S Semple, S Dick, P Mozzoni, N Haites, S Bezzina Wettinger, A Mutti, M Otelea, A Seaton, P Soderkvist, A Felice, on behalf of the Geoparkinson Study Group

Occup Environ Med 2007;64:673–680. doi: 10.1136/oem.2006.032078

Glutathione S-transferase M1 (GSTM1) null subjects heavily exposed to solvents are at increased risk of PD

Microrna. 2017 Dec 6;6(3):157-165. doi: 10.2174/2211536606666170811151503.

Environment and Neurodegenerative Diseases: An Update on miRNA Role.

Ferrante M[1], Conti GO[1].

miRNAs may contribute to neurodegeneration process in response to environmental risks (influencing gene expression).
Environmental chemicals (eg pesticides) cause miRNA alterations via increasing oxidative stress and/or triggering inflammatory responses.

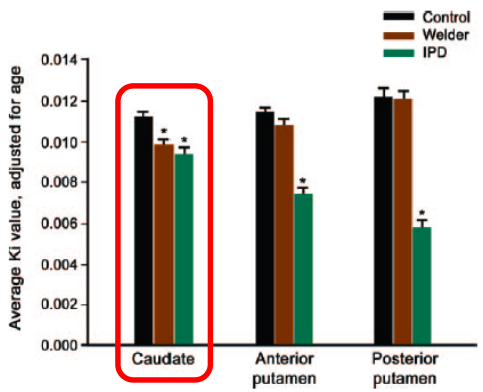
Elbaz et al., Ann Neurol 2004; Dick et al., Occup Environ Med 2007; Goldman et al., Mov Disord 2012; Ferrante and Conti, Microrna 2017

Gene-Environment Interactions (2)

a) Occupation-related Risk

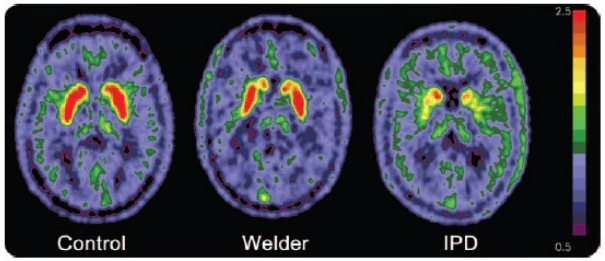
Reduced uptake of [^{18}F]FDOPA PET in asymptomatic welders with occupational manganese exposure

Figure 1 Average FDOPA PET K_i by region by group adjusted for age



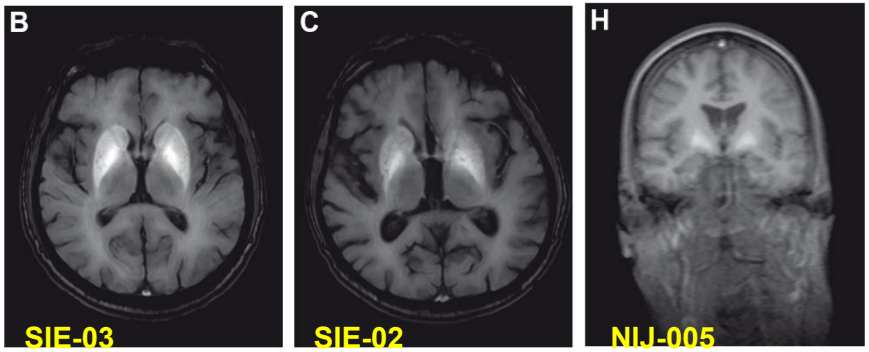
Average FDOPA PET K_i by region for controls, welders, and subjects with idiopathic Parkinson disease (IPD) adjusted for age. *Different from controls, $p < 0.01$.

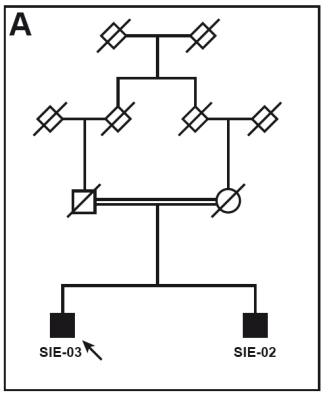
Figure 2 FDOPA PET images of decay-corrected counts from 24 to 94 minutes

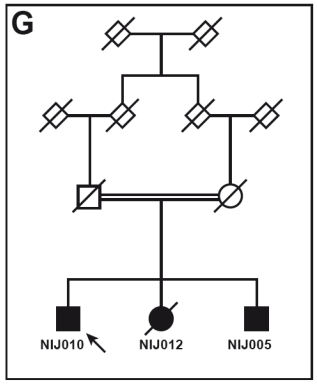


Criswell et al., Neurology 2011;

b) Inherited defect of Manganese excretion (SLC30A10 gene)







- **Parkinsonism, Distonia**
- Hypermanganesaemia
- Polycythaemia
- Chronic Liver Disease

Quadri et al, Am J Hum Genet 2012; Tuschl et al, Am J Hum Genet 2012

Other Environmental Risk *vs.* Protective Factors

- **RISK FACTORS**
  - **Dairy products** (Urate-lowering effects. Contamination by heptachlor epoxide?)
  - Melanoma
  - Traumatic Brain Injury
  - Methamphetamine use

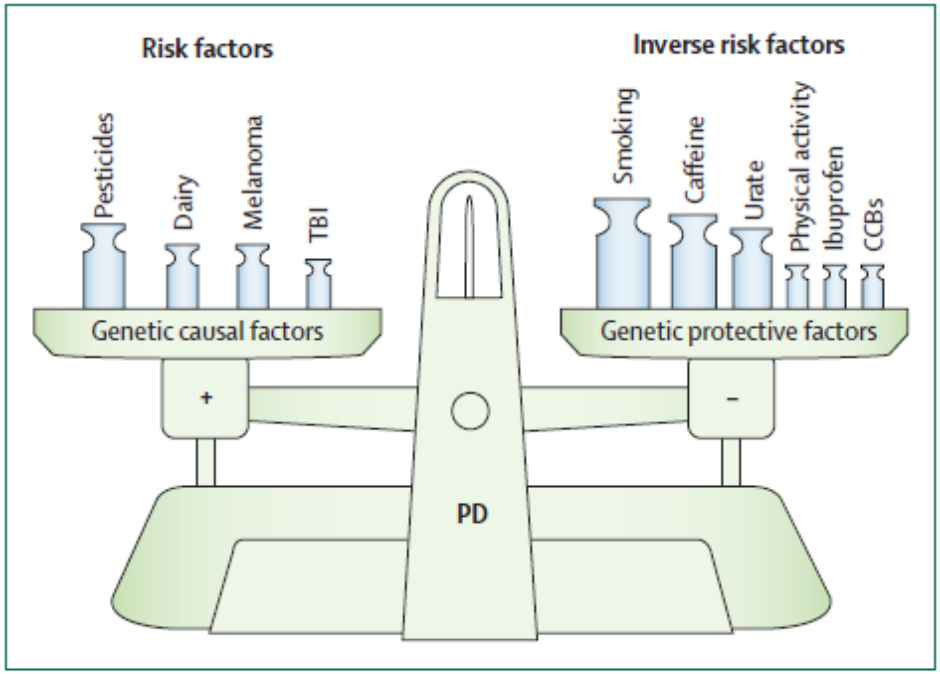


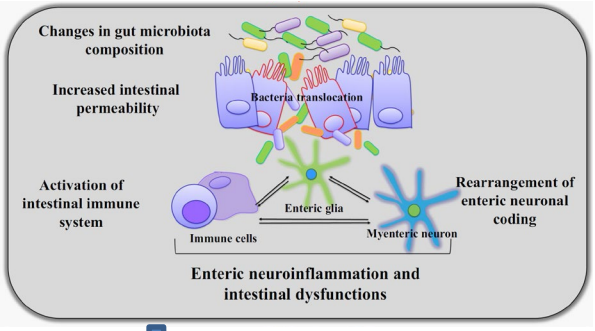
Figure 4: The balance of genetic and environmental factors that underlie Parkinson's disease occurrence

- **PROTECTIVE FACTORS**
  - **Physical Activity** (↑DA, ↑BDNF)
  - **Smoking**
  - **Coffee and Tea**
  - **Urate** (↑ Nrf2/antioxidant response)
  - Alcohol (urate-elevating effects)
  - Female gender
  - NSAIDs
  - Calcium Channels Blockers

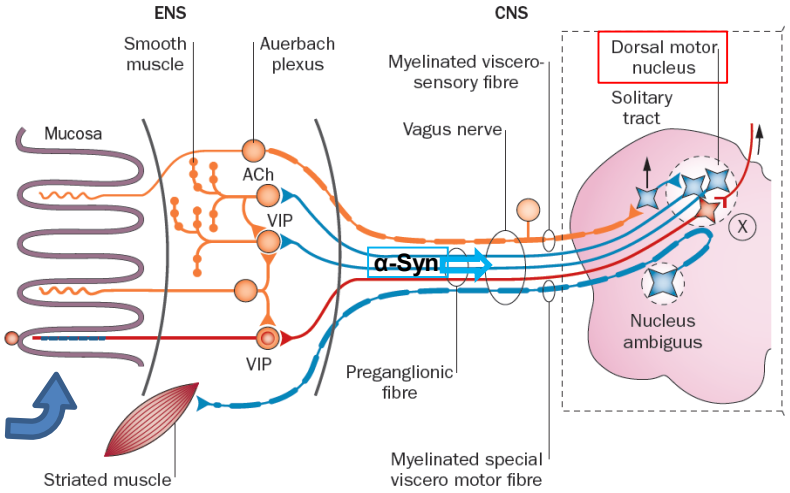
Ascherio and Schwarzschild, Lancet Neurol 2016.

What is the Trigger of initial α-syn aggregation?
(3) *Microbiota and the gut-to-brain propagation*

1) A **pathogen** passes the GI mucosal lining (increased epithelial permeability?)

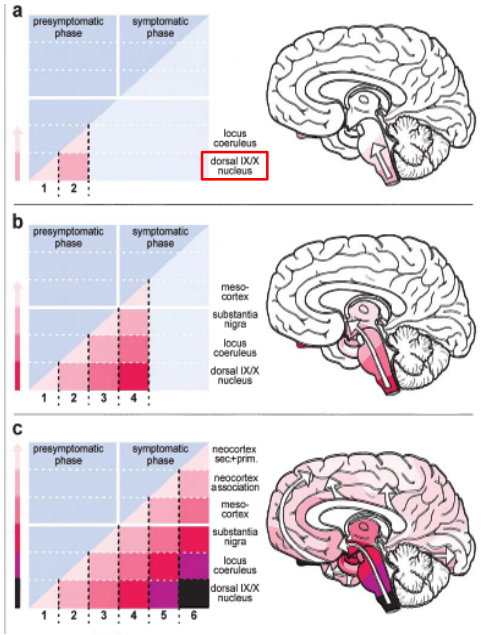


2) Triggers **α-Syn misfolding** in post-ganglionic ENS terminals



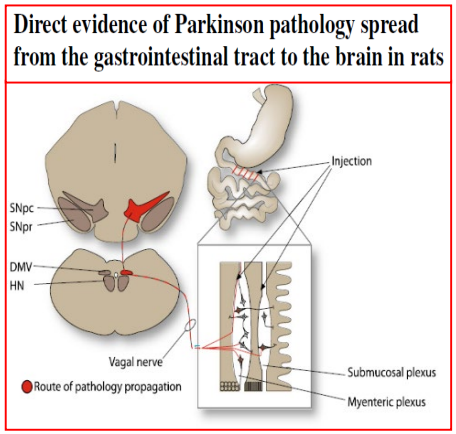
3) α-Syn retrogradely propagates along the vagus nerve

4) α-Syn reaches the DMV



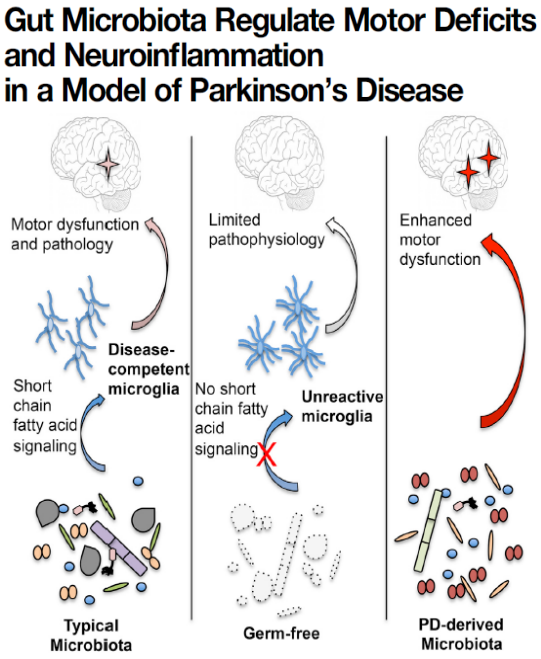
5) α-Syn spreads and aggregates in LB throughout the CNS

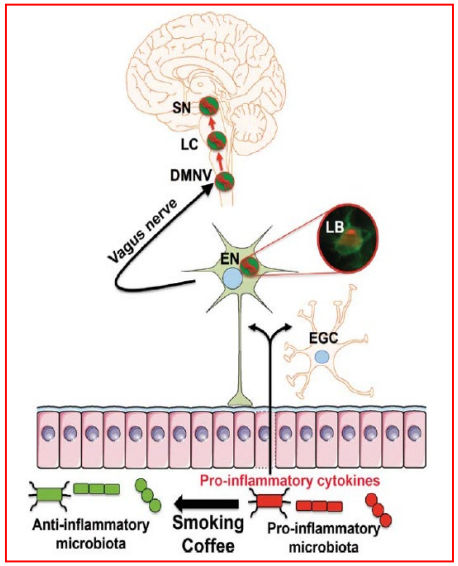
6) LB induce neuronal death and PD symptoms/signs



Braak et al, Neurobiol Aging 2003; Holmqvist et al, Acta Neuropathol 2014 Klingelhoefer & Reichmann, Nature Rev 2015; Pellegrini et al, Acta Neuropathologica 2018

How does Gut Microbiota influence PD?





In α-syn overexpressing mouse model of PD:

- **Typical Microbiota** promote α-synuclein pathology
- Depletion of gut bacteria (**Germ-Free**) reduces microglia activation and α-syn pathology
- **Human gut microbiota from PD cases** (but not from HC) enhances motor dysfunction

May Microbiota-induced changes provide a potential explaination of
*- **Initial α-syn misfolding** and aggregation triggering PD pathology?*
*- **Protective effects** associated with smoking and coffee?*

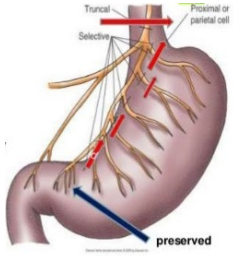
HOWEVER:
Change in Microbiota alone is not sufficient to trigger α-syn pathology in the ENS: **SCFAs signaling -> Microglia activation is needed**
-> Oral feeding by SCFAs induces α-syn pathology without microbiota colonization.

OPEN QUESTIONS:

- *What is the role of **SCFAs**? (..protective and anti-inflammatory..)*
- *Is the **systemic route** associated to Microbiota-induced changes (rather than the vagus nerve)?*

Sampson et al, Cell 2016; Visanji, Mov Disord 2014

Does Truncal Vagotomy reduce the risk of PD?
(What if the 'spreading' involves systemic routes?)



Vagotomy and Subsequent Risk of Parkinson's Disease

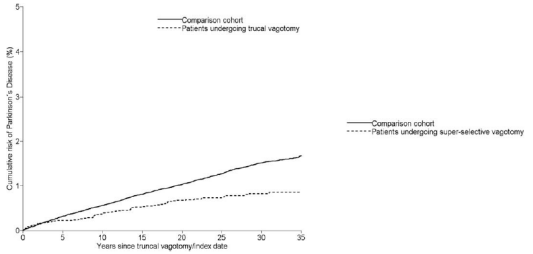


FIGURE 1: Cumulative incidence curves of Parkinson's disease for patients who underwent truncal vagotomy compared to a matched general population cohort.

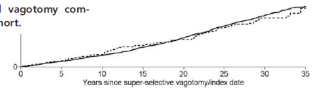


FIGURE 2: Cumulative incidence curves of Parkinson's disease for patients undergoing superselective vagotomy compared to a matched general population cohort.

Danish registry. Follow-up 1977-1995
Nonsignificant lower PD risk at 5 years F-up
(adjusted HR 0.85; 95% CI: 0.56–1.27)
Marginal significance only >20-y F-up (HR 0.53, 95% CI 0.53–0.99)
«limited statistical precision, wide associated CIs»

Does Vagotomy Reduce the Risk of Parkinson's Disease?
Ole-Bjørn Tysnes, MD, PhD,[1,6] Line Kenborg, MSc, PhD,[2] Karen Herlofson, MD, PhD,[3] Marianne Steding-Jessen, MSc,[2] Arild Horn, MD, PhD,[4] Jørgen H. Olsen, DMSc,[2] Heinz Reichmann, MD, PhD[5]

Same Danish population with extended Follow-up 1977–2011
Truncal vagotomy -> nonsignificantly lower PD risk (HR 0.88, 95% CI 0.55–1.21)
Nonsignificantly elevated PD risk >20 years after the surgery (HR 1.14, 95% CI 0.23–2.05)

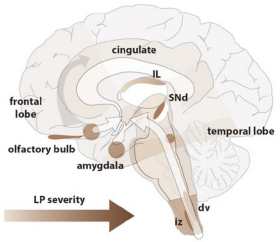
Vagotomy and Parkinson disease
A Swedish register–based matched-cohort study

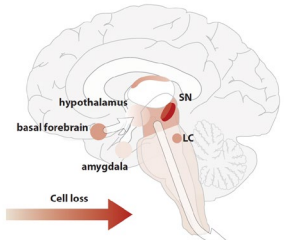
9,430 vagotomized patients (3,445 truncal and 5,978 selective) Follow-up 1970-2010
N = 4,930 incident PD during 7.3 million person-years of follow-up.
Truncal vagotomy -> nonsignificantly lower PD risk (HR 0.78, 95% CI 0.55–1.09)

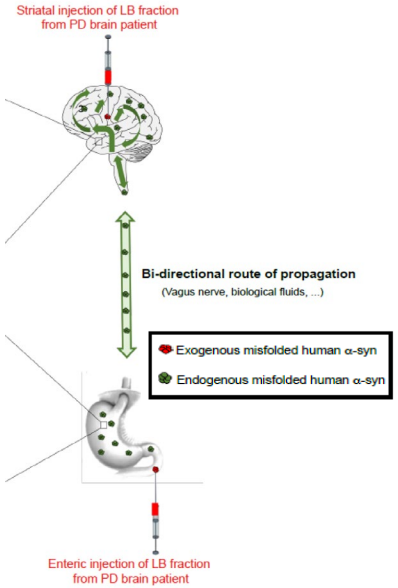
CONCLUSIONS:
- Nonsignificant Risk Reduction (CIs > 1.0)
- Conflicting Data at 20-y F-up

Svensson et al., Ann Neurol 2015; Tysnes et al., Ann Neurol 2015; Liu et al., Neurology 2017

Limitations of the Braak's Hypothesis and Open Questions







1) « Conjecture that LB would be followed by cell death »

-> No correlation between LB and Neuronal loss in CNS and ENS

- ≈50% clinical PD with brains not consistent with Braak's pattern of LB spread
- Cell death may occur in the absence of α-syn: cases with clinical PD with little/no LB
- No Neuronal Loss in the ENS (Myenteric system) despite LB pathology

What is the role of LBs? *LB have not yet be proven to be harmful: LB may even be protective by sequestering misfolded proteins.*

2) « Involvement of the DMN of the Vagus is mandatory »

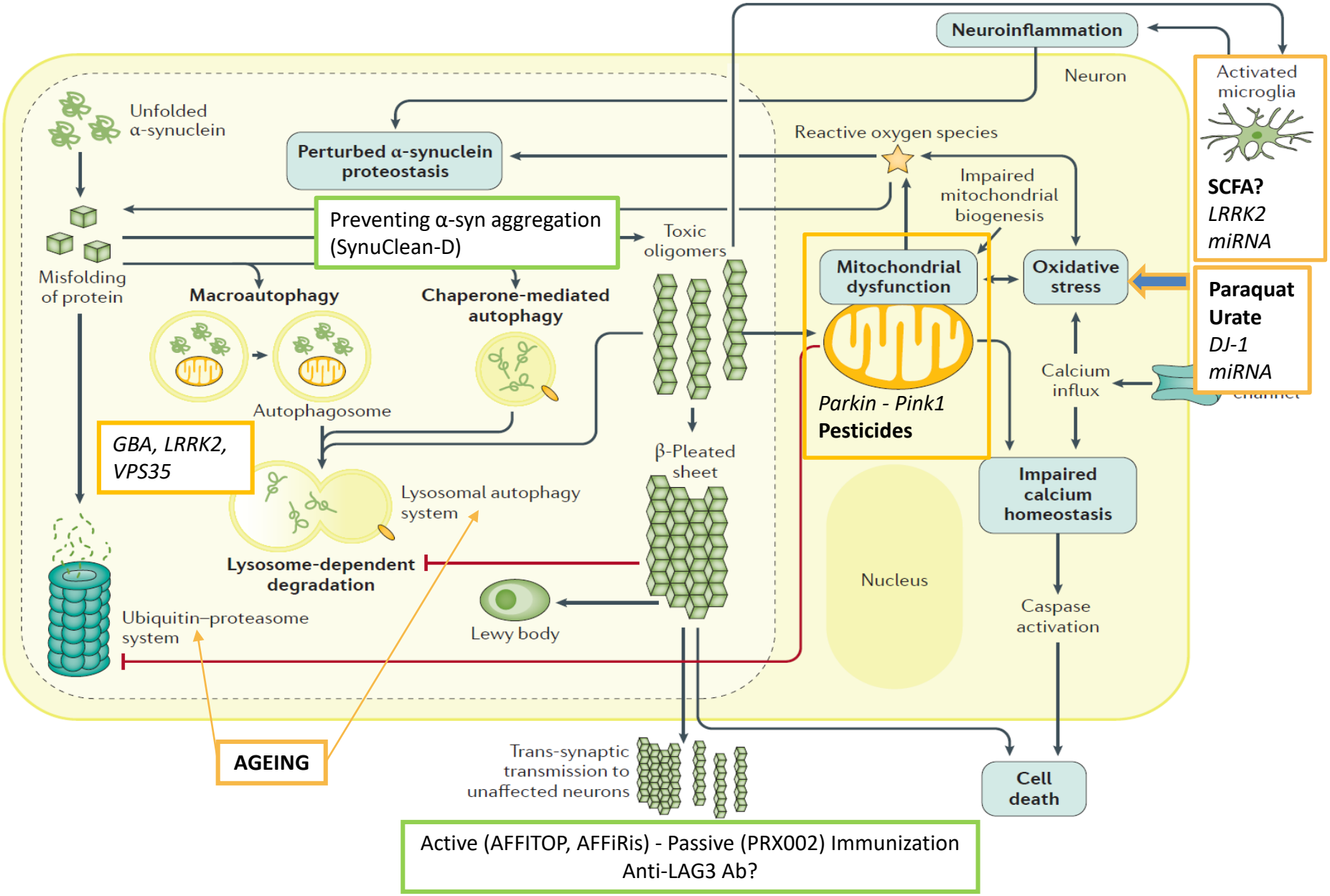
-> Rarely involved in prodromal PD stages

- Healthy elderly with Incidental Lewy Bodies
  -> Only 9% involved DMV (95% with the olfactory bulb as the only site involved)
- *α*-SYN can transported anterogradely and retrogradely with similar efficiency

Where does PD start? *The initial site of α-syn accumulation may occur in different areas and explain different subtypes.*

Burke et al. Ann Neurol 2008; Annerino, Acta Neuropath 2012; Corbillé et al., Neurosci Lett 2017; Surmeier et al. Nat Rev Neurosci 2017; Halliday et al, J Neurosci 2017; Ulusoy, Acta Neuropathol 2016; Anselmi, Gastroenterol 2017; Surmeier and Brundin, J Neurosci 2017; Arotcarena et al., MDS congress 2018 Poster N. 1663

Understanding the CAUSES to find the CURE



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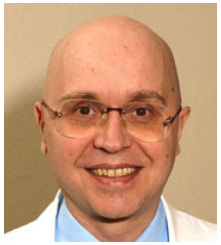

Prof. Gianni Pezzoli, MD
Director of the Parkinson Institute,
ASST G. Pini-CTO, Milan
President of the «Fondazione Grigioni per il Morbo di Parkinson» and the «Associazione Italiana Parkinsoniani»

Neurologists
Dr Del Sorbo Francesca
Dr Mariani Claudio B.
Dr Meucci Nicoletta
Dr Sacilotto Giorgio
Dr Tesei Silvana
Dr Zecchinelli Anna L.
Dr Zini Michela

Michela Barichella, MD
Head of the Nutrion Dept.
Parkinson Institute, Milan
President of Brain & Malnutrition ONLUS

Emanuele Cereda, MD, PhD
Nutrition Specialist
Statistician Consultant
IRCCS San Matteo, Pavia

Parkinson Institute BIOBANK
Prof. Duga Stefano – Humanitas University (MI)
Prof. Asselta Rosanna – Humanitas University (MI)
Dr. Mirella Filocamo – Gaslini Institute (GE)

Parkinson Institute BRAIN BANK
Prof. Cappelletti Graziella – University of Milan

Fondazione Grigioni per il Morbo di Parkinson (Milan, IT)
www. parkinson.it