LA NEUROSONOLOGIA NELLE PATOLOGIE DEGENERATIVE E VASCOLARI CEREBRALI

Malattia di Parkinson: patogenesi molecolare e nuove strategie terapeutiche

Giuseppe De Michele

Presentation Outline

Two hundreds years since first description

The Levodopa story

The α-synuclein story

Monogenic parkinsonism

Neuronal dysfunction

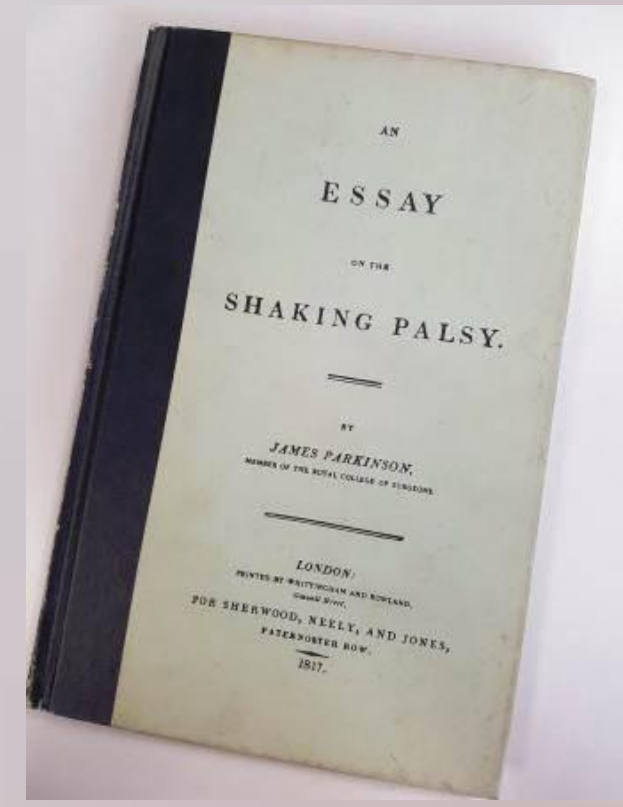
The Braak's model

The prion-like propagation of synucleinopathy

Immunotherapy

Two hundreds years since James Parkinson's first description

Home of J. Parkinson, No.1 Hoxton Square, Shoreditch/London.
(Courtesy Prof. W. Poewe, Innsbruck/Austria)


AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,

LONDON:

FOR SHERWOOD, NEELY, AND JONES,

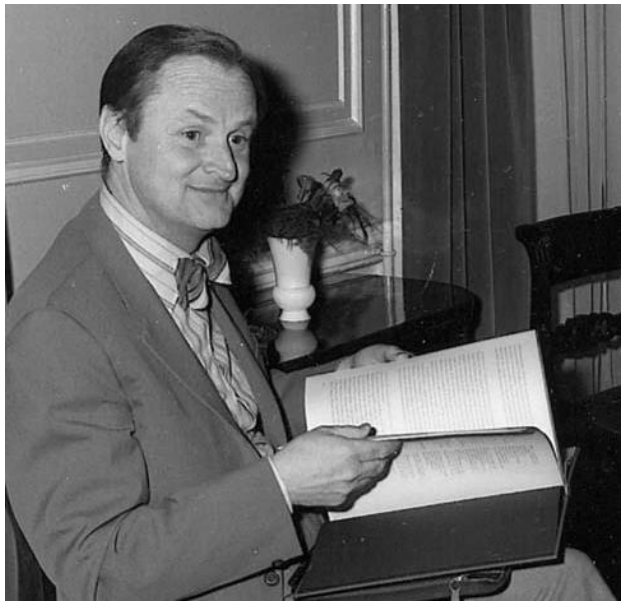
PATERNOSTER ROW.

1817.

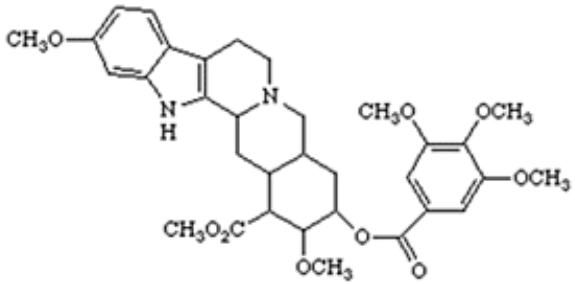
Two hundreds years since James Parkinson's first description

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

The levodopa story



I. In 1957, Arvid Carlsson showed that dopamine was a neurotransmitter, with highest regional concentration in the basal ganglia, that reserpine depleted dopamine and produced parkinsonism, and finally that L-dopa, a precursor of dopamine, could alleviate the symptoms in animals.



Reserpine

The levodopa story

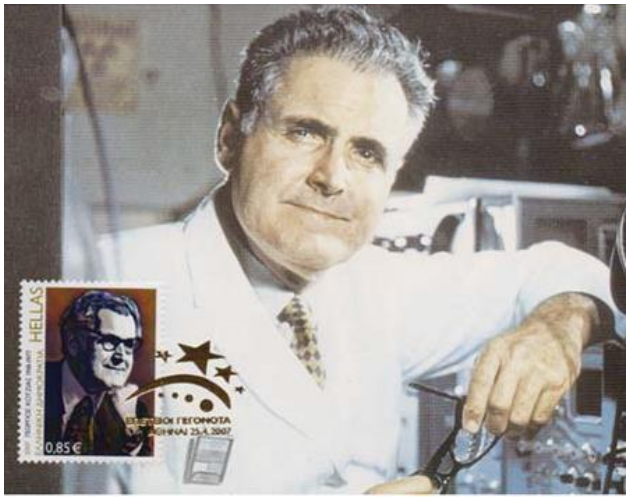
II. Three years later Oleh Hornykiewicz obtained postmortem material from 6 PD patients and showed a marked striatal depletion of dopamine. In 1961, together with Walther Birkmayer he injected L-dopa into PD patients, obtaining a temporary benefit.

"Bedridden patients who were unable to sit up, patients who could not stand up when seated, and patients who when standing could not start walking performed after L-dopa all of these activities with ease. They walked around with normal associated movements, and they could even run and jump. The voiceless, aphonic speech, blurred by palilalia and unclear articulation, became forceful and clear as in a normal person."

Birkmayer and Hornykiewicz, 1961

The levodopa story

III. In 1967, George Cotzias demonstrated a dramatic effect of oral L-dopa in reversing the symptoms in PD patients. Cotzias gradually increasing doses of L-dopa up to large doses proved critical for achieving therapeutic success.



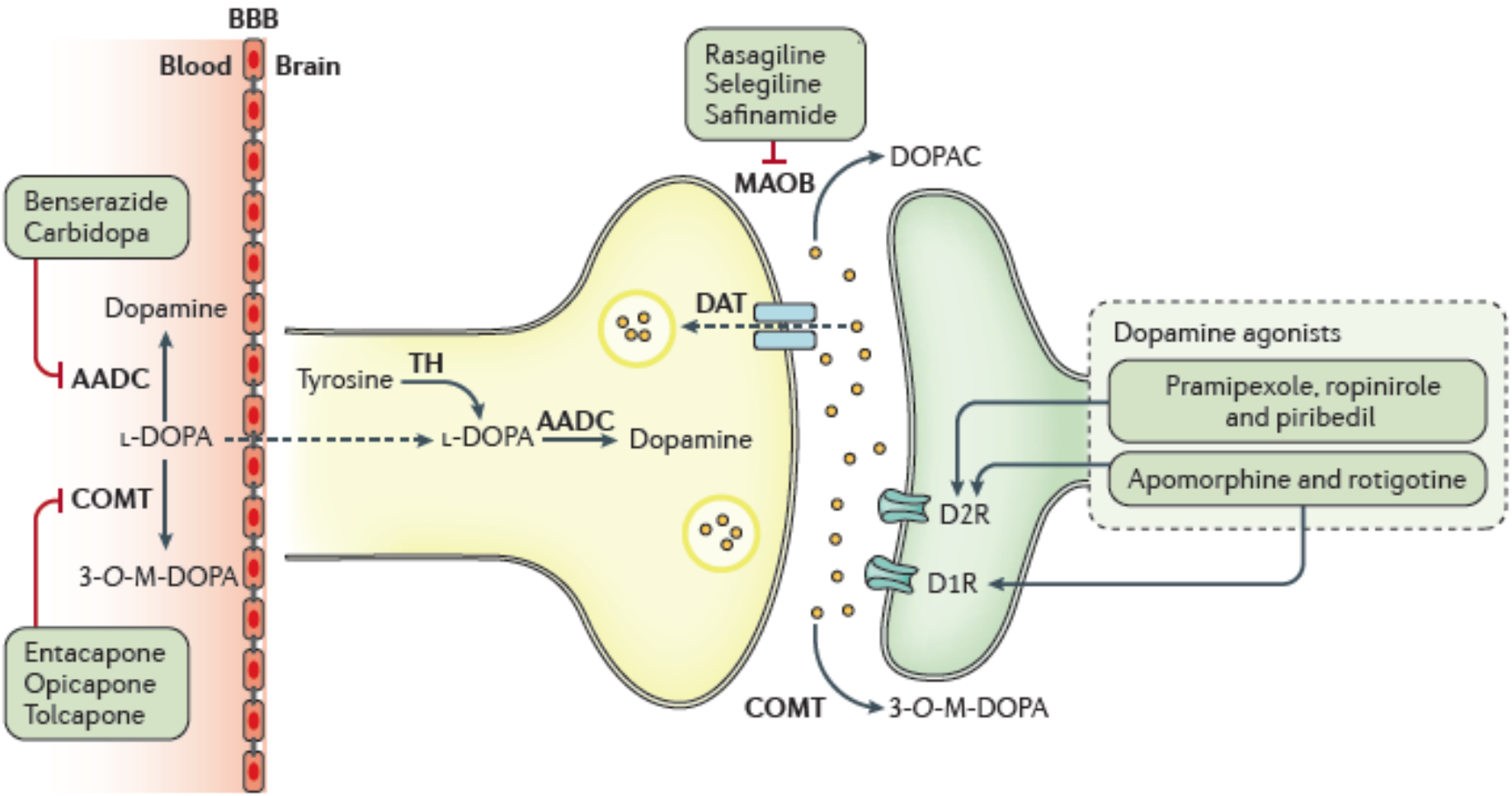
THE NEW ENGLAND JOURNAL OF MEDICINE Feb. 16, 1967

AROMATIC AMINO ACIDS AND MODIFICATION OF PARKINSONISM*

GEORGE C. COTZIAS, M.D.,† MELVIN H. VAN WOERT, M.D.,‡ AND LEWIS M. SCHIFFER, M.D.‡

UPTON, NEW YORK

Dopaminergic Treatment in PD



The α-synuclein story
(an emigration story?)

Patrasso

Contursi Terme

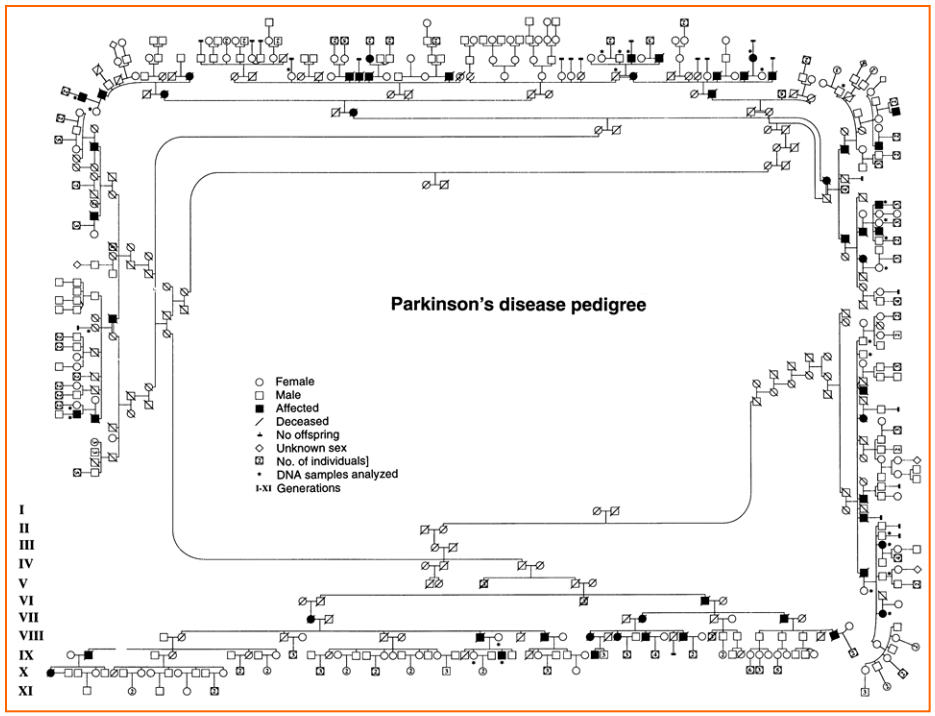
Maria Grazia Spillantini

The α-synuclein story

Mutation in the α-Synuclein Gene Identified in Families with Parkinson's Disease

Mihael H. Polymeropoulos,* Christian Lavedan†, Elisabeth Leroy†, Susan E. Ide, Anindya Dehejia, Amalia Dutra, Brian Pike, Holly Root, Jeffrey Rubenstein, Rebecca Boyer, Edward S. Stenroos, Settara Chandrasekharappa, Aglaia Athanassiadou, Theodore Papapetropoulos, William G. Johnson, Alice M. Lazzarini, Roger C. Duvoisin, Giuseppe Di Iorio, Lawrence I. Golbe, Robert L. Nussbaum

SCIENCE • VOL. 276 • 27 JUNE 1997



α-Synuclein in Lewy bodies

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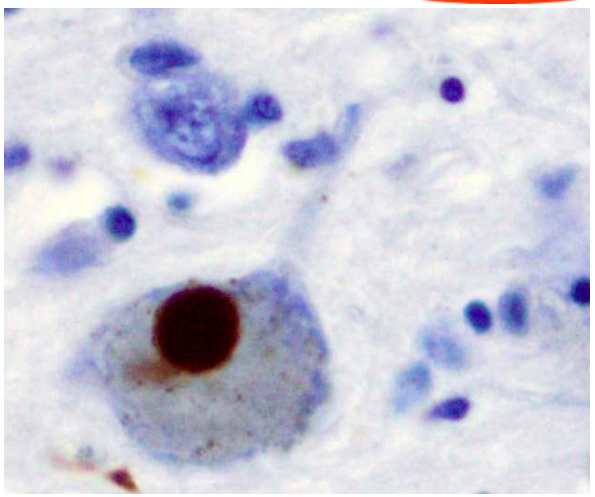
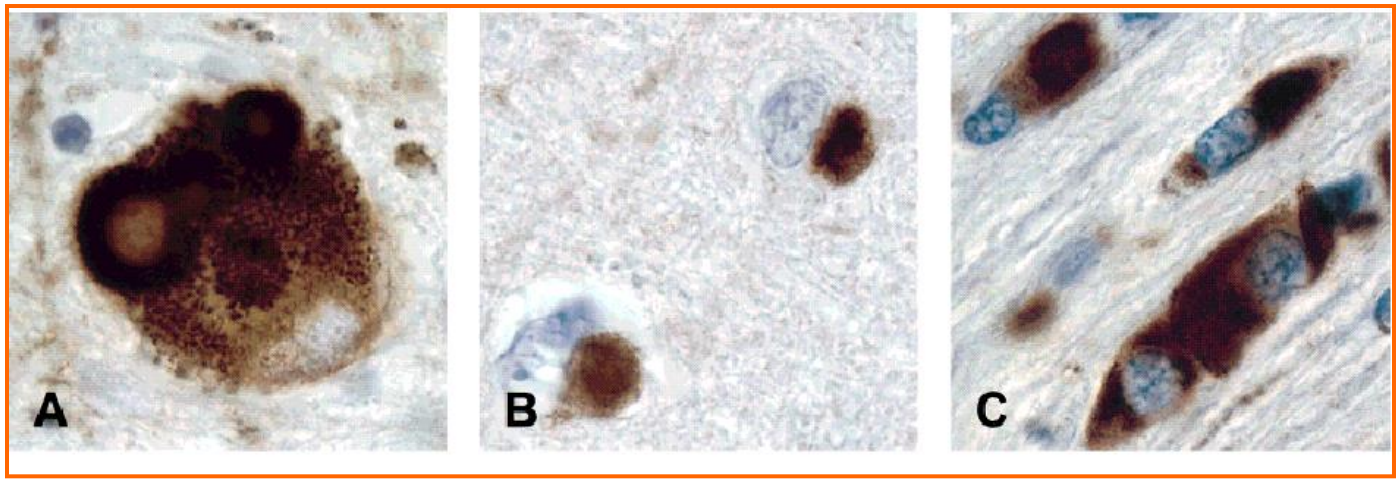
Nature **388**, 839-840 (28 August 1997)



α-synuclein

a-synuclein is the major filamentous component of:
Lewy Bodies (PD, LBD) and Glial Cytoplasmic Inclusions (MSA)



Idiopathic Parkinson's disease
Genetic Parkinson's disease
Dementia with Lewy bodies
Multiple system atrophy
Pure autonomic failure
REM behavior disorder

SYNUCLEINOPATHIES

Monogenic Parkinsonisms

Autosomal Dominant Parkinsonisms

	Disease	Location	Gene	Phenotype	Pathology
1997	PARK1/4	4q22.1	*SNCA*	Early onset -rapid progression	LB+
2004	PARK8	12q12	*LRRK2*	Typical PD	LB±, NFT

Autosomal Recessive Parkinsonisms

	Disease	Location	Gene	Phenotype	Pathology
1998	PARK2	6q25.2-27	*parkin*	Early-onset PD	LB±, NFT
2004	PARK6	16q11.2	*PINK1*	Early-onset PD	LB±
2003	PARK7	1p36.23	*DJ-1*	Early-onset PD	LB+

Park8 – *Leucine-rich repeat kinase 2 LRRK2*

Western countries	1-4%
North African Arab	36-39%
Ashkenazi Jewish	10-28%
Asian	0.1%

Neuron, Vol. 44, 601–607, November 18, 2004, Copyright ©2004 by Cell Press

Mutations in *LRRK2* Cause Autosomal-Dominant Parkinsonism with Pleomorphic Pathology

Alexander Zimprich,[1,2,11] Saskia Biskup,[3,11]
Petra Leitner,[1] Peter Lichtner,[3] Matthew Farrer,[4]
Sarah Lincoln,[4] Jennifer Kachergus,[4] Mary Hulihan,[4]
Ryan J. Uitti,[5] Donald B. Calne,[6] A. Jon Stoessl,[6]
Ronald F. Pfeiffer,[7] Nadja Patenge,[1]
Iria Carballo Carbajal,[1] Peter Vieregge,[8]
Friedrich Asmus,[1] Bertram Müller-Myhsok,[9]
Dennis W. Dickson,[4] Thomas Meitinger,[3,10,*]
Tim M. Strom,[3,10] Zbigniew K. Wszolek,[5,*]
and Thomas Gasser[1,*]

Neuron, Vol. 44, 595–600, November 18, 2004, Copyright ©2004 by Cell Press

Cloning of the Gene Containing Mutations that Cause *PARK8*-Linked Parkinson's Disease

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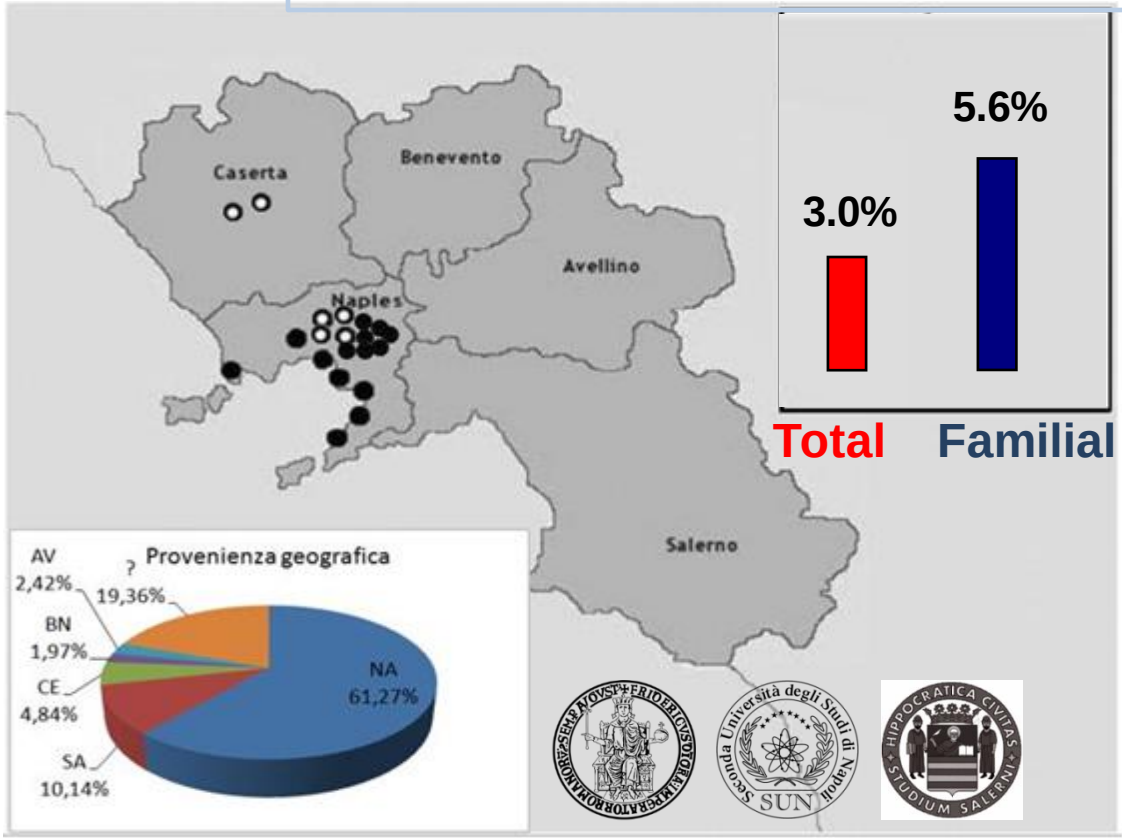
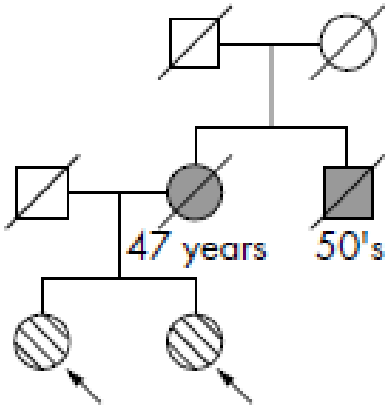
E. Whitney Evans,[4] William P. Gilks,[3] Javier Simón,[1]
Marcel van der Brug,[5] Adolfo López de Munain,[6,7]
Silvia Aparicio,[1] Angel Martínez Gil,[8]
Naheed Khan,[3] Janel Johnson,[4]
Javier Ruiz Martinez,[9] David Nicholl,[10]
Itxaso Marti Carrera,[7] Amets Saénz Peña,[6]
Rohan de Silva,[3] Andrew Lees,[3]
José Félix Martí-Massó,[7] Jordi Pérez-Tur,[1,*]
Nick W. Wood,[2,*] and Andrew B. Singleton[4,*]



Glucocerebrosidase mutations in PD



SHORT REPORT

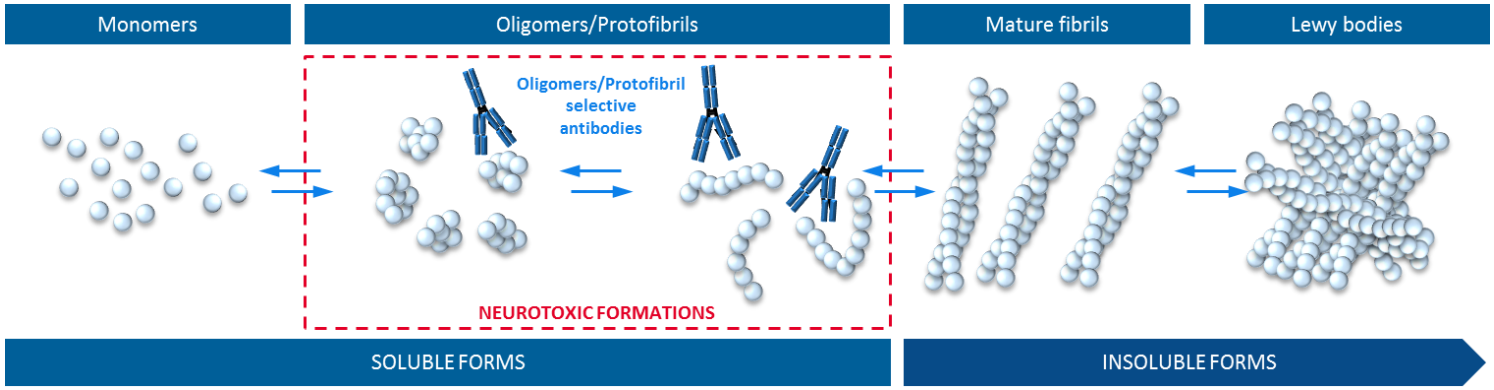
Parkinsonism among Gaucher disease carriers

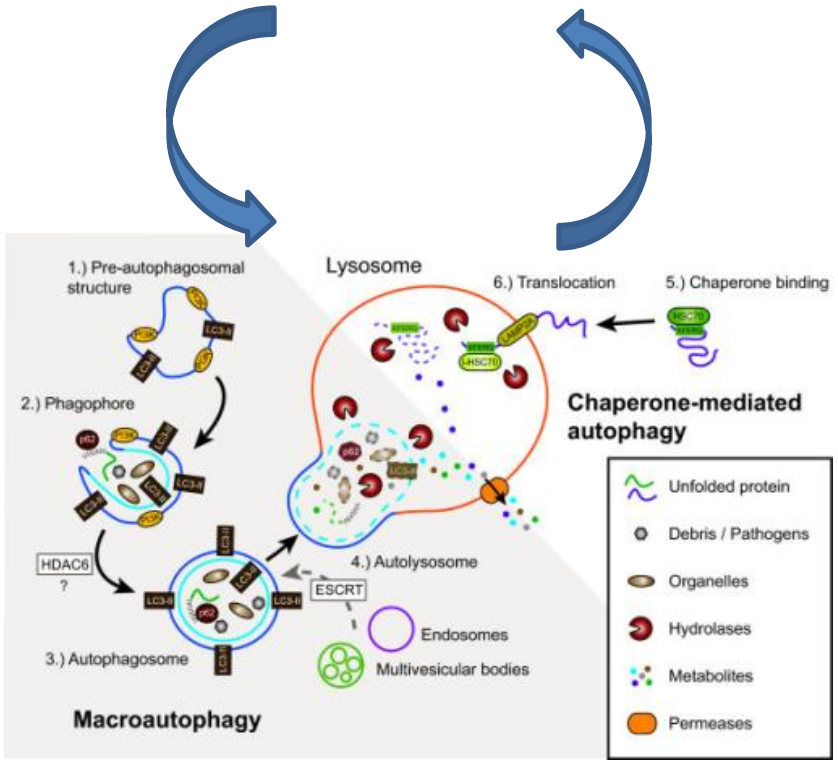
O Goker-Alpan, R Schiffmann, M E LaMarca, R L Nussbaum, A McInerney-Leo, E Sidransky

J Med Genet 2004;**41**:937–940. doi: 10.1136/jmg.2004.024455

- GBA mutations were detected in 71/605 (11,4%) Italian probands.
- The two recurrent mutations (L44P, N370S) account for only 39% of cases.
- GBA mutations more frequent in: early-onset PD, familial cases, cases with dementia

α-Synuclein degradation

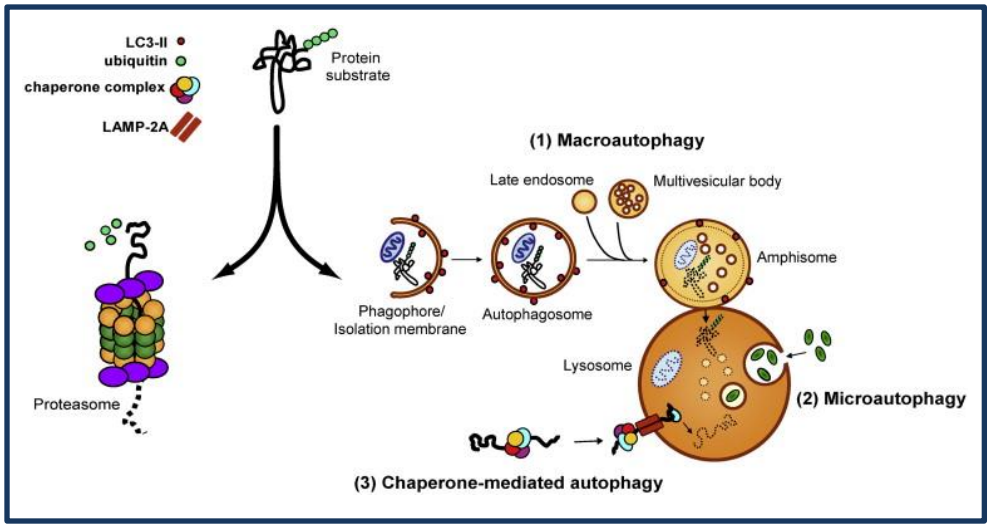




Disrupted proteostasis leads to α-synuclein accumulation, which in turn leads to defective α-synuclein degradation.

The Lysosomal Autophagy System

α-synuclein olygomers and aggregates inhibit LAS and the ubiquitin–proteasome system



The G2019S mutation in the *LRRK2* gene (PARK8) is associated with impaired LAS and increased aggregation of α-synuclein in dopaminergic neurons

Heterozygous mutations in the *GBA* gene are coupled to reduced LAS function

Ambroxol

Ambroxol has been shown to improve the function of glucocerebrosidase in neuron

RESEARCH ARTICLE

Ambroxol Effects in Glucocerebrosidase and α-Synuclein Transgenic Mice

Anna Migdalska-Richards, PhD,[1] Liam Daly, MSci,[1] Erwan Bezard, PhD,[2,3] and Anthony H. V. Schapira, MD, DSc, FRCP, FMedSci[1]

NIH U.S. National Library of Medicine

ClinicalTrials.gov

Home > Study Record Detail

Ambroxol as a Treatment for Parkinson's Disease Dementia

This study is currently recruiting participants.

A Phase 2 study is recruiting. Main aim is drug safety and ability to penetrate the blood brain barrier. Cognitive functions, MRI, and a number of biomarkers will be examined to characterize the potential beneficial action of the drug.

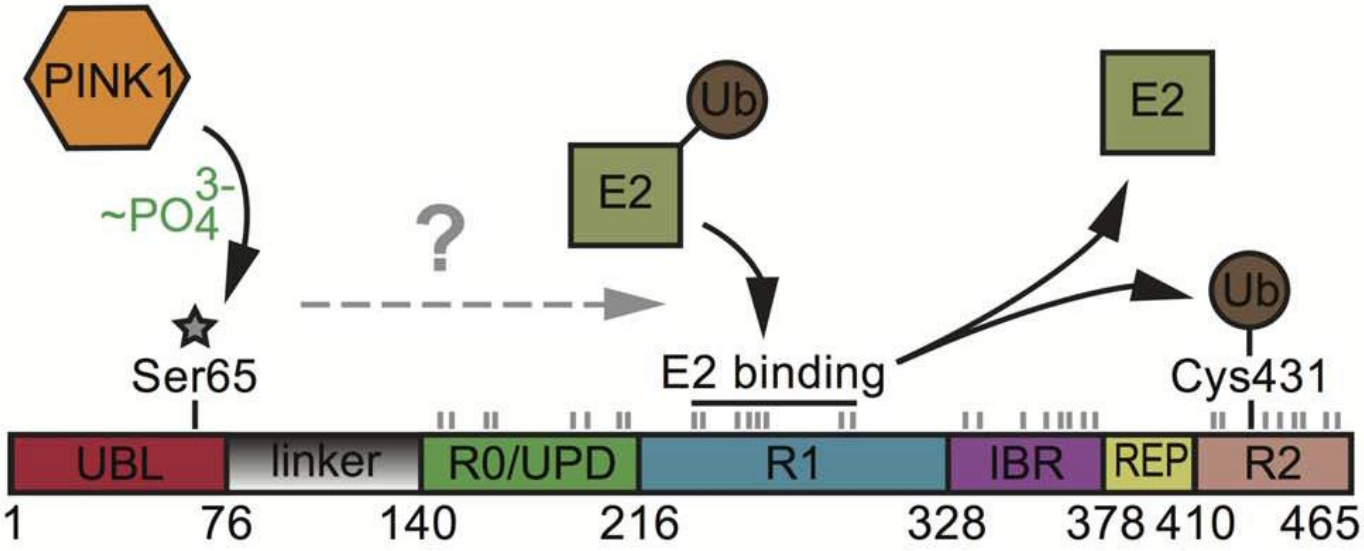
Early-Onset Parkinsonism

		% EOPD cases
PARK2	*parkin*	*8.6*
PARK6	*PTEN-induced putative kinase 1 (PINK-1)*	*3.7*
PARK7	*Daisuke-Junko-1 (DJ-1)*	*0.4*

- Autosomal recessive transmission
- Onset before 50 years
- Slow progression
- Dystonia at onset, motor fluctuations, increased tendon reflexes
- Psychiatric symptoms
- Good L-Dopa response, drug-induced dyskinesias

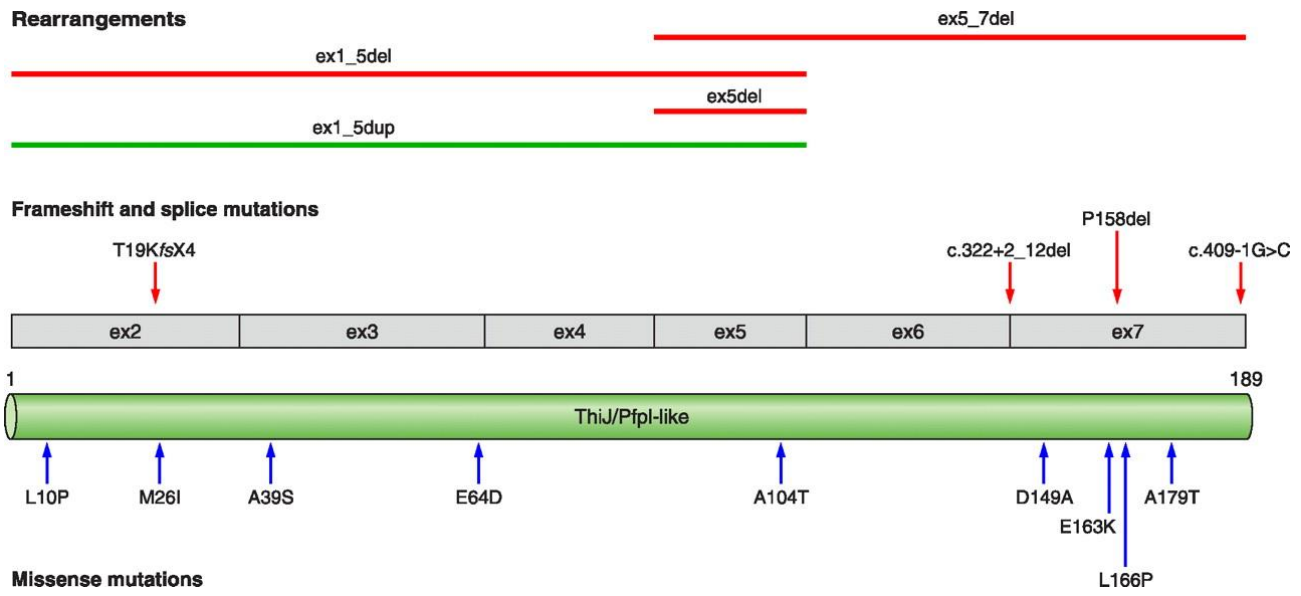
Parkin (PARK2) and PINK1 (PARK6) interact

•Parkin is a 465-AA E3 ubiquitin ligase with an ubiquitin-like domain and two RING domains.
•Parkin has a generally cytosolic localization. In the context of mitochondrial damage it is phosphorylated by PINK and traslocated to mitochondria to ubiquitinate mitochondrial membrane proteins, signaling that the damaged mitochondria must undergo mitophagy.

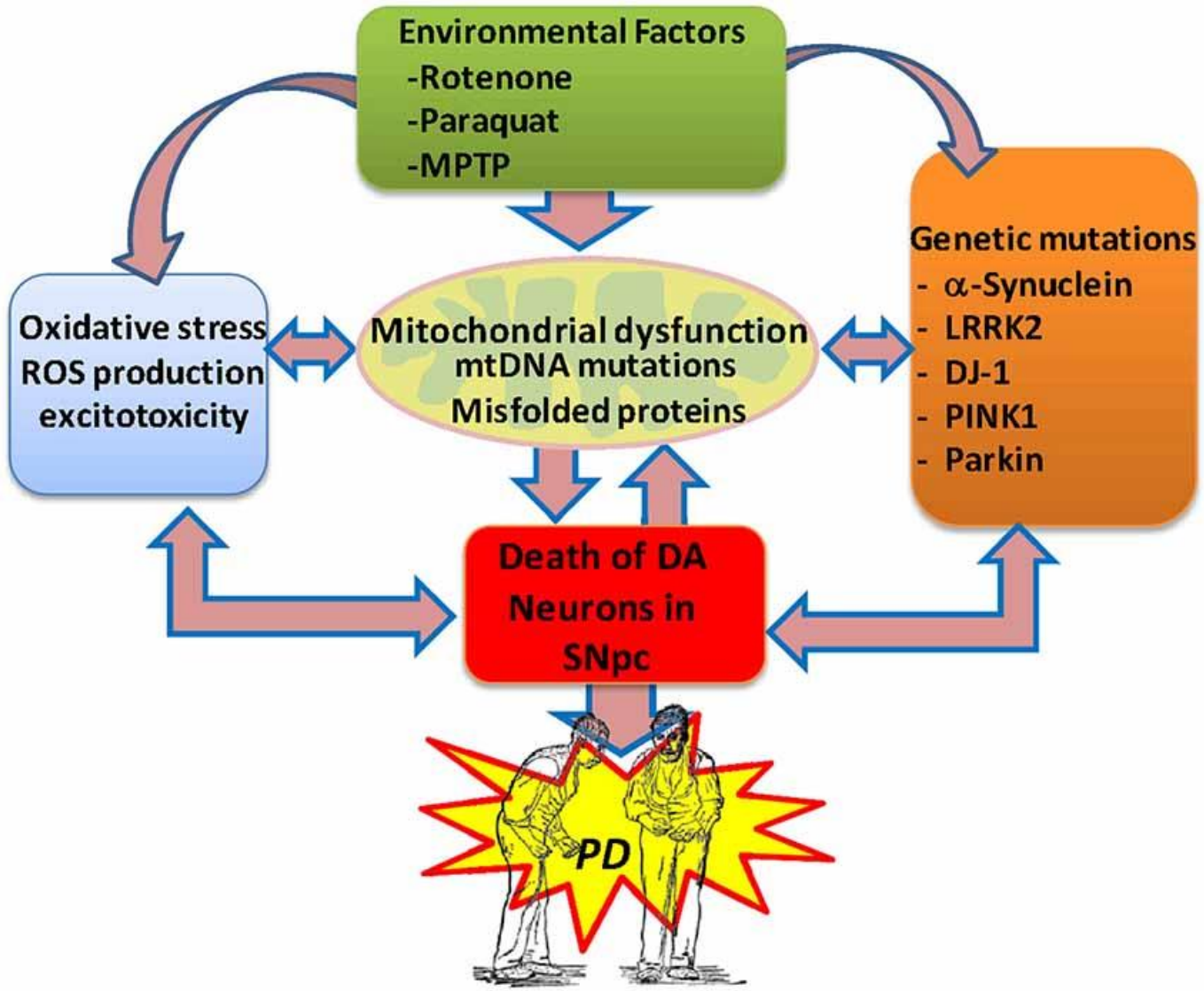


DJ-1 (PARK7) is protective against oxidative stress

- DJ-1 translocates to mitochondria in response to oxidative stress
- DJ-1 protects cells against oxidative stress and plays a role in maintaining normal dopaminergic function in the nigrostriatal pathway



Mitochondrial dysfunction-Oxidative stress



Mitochondrial dysfunction-Oxidative stress

Activity of complex I is reduced in several tissues isolated from patients with PD

Pesticides (paraquat) and toxins that inhibit complex I (MPTP, rotenone) impair mitochondrial energy production, leading to oxidative stress and deficits in ATP

Parkin and PINK1 cooperate in the clearance of damaged mitochondria through mitophagy

Mutations in DJ1 are associated with increased cellular oxidative stress

Accumulation of α-synuclein inside mitochondria leads to mitochondrial complex I deficits and oxidative stress

LRRK2 mutations (PARK8) are associated with mitochondrial impairment

Increased levels of dopamine and its metabolites can cause oxidative stress

Treatment of mitochondrial dysfunction and oxidative stress

Improvement has been observed after creatine and CoQ10 supplementation in mouse models of PD

Trials in humans failed to show significant effects of both drugs

A double blind study using MitoQ (a powerful mitochondrial antioxidant) did not slow the progression of the disease

Movement Disorders
Official Journal of the International Parkinson and Movement Disorder Society
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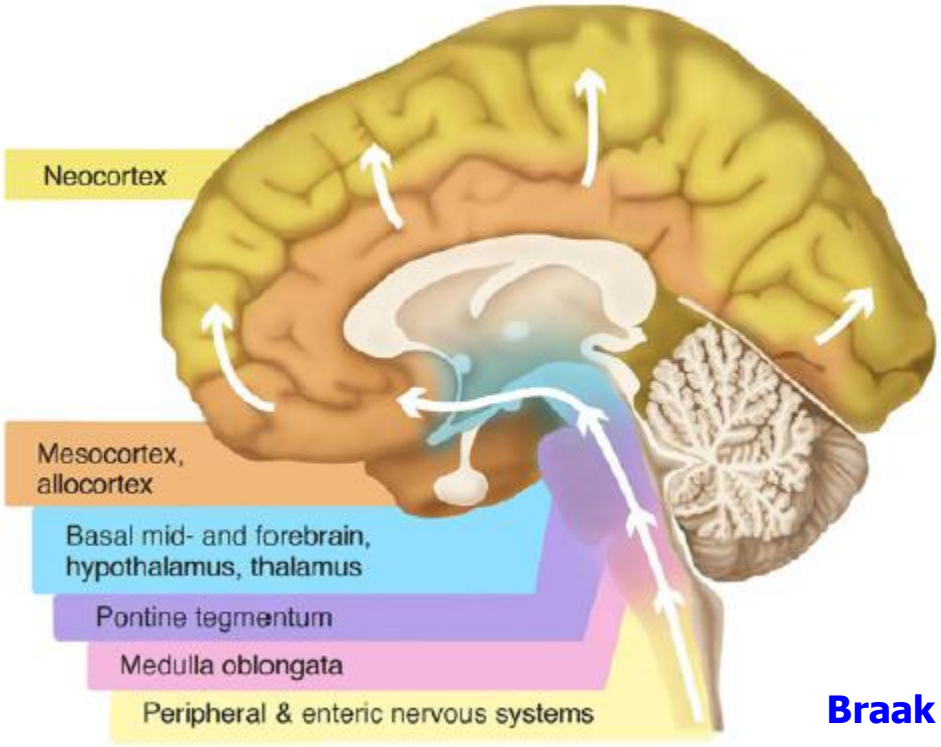
Research Article

A double-blind, placebo-controlled study to assess the mitochondria-targeted antioxidant MitoQ as a disease-modifying therapy in Parkinson's disease

Barry J. Snow MD, Fiona L. Rolfe BSc, Michelle M. Lockhart MM, Christopher M. Frampton PhD, John D. O'Sullivan MD, Victor Fung PhD, FRACP, Robin A.J. Smith PhD, Michael P. Murphy PhD, Kenneth M. Taylor PhD

First published: 21 June 2010 Full publication history

Staging of Lewy pathology according to the Braak's model

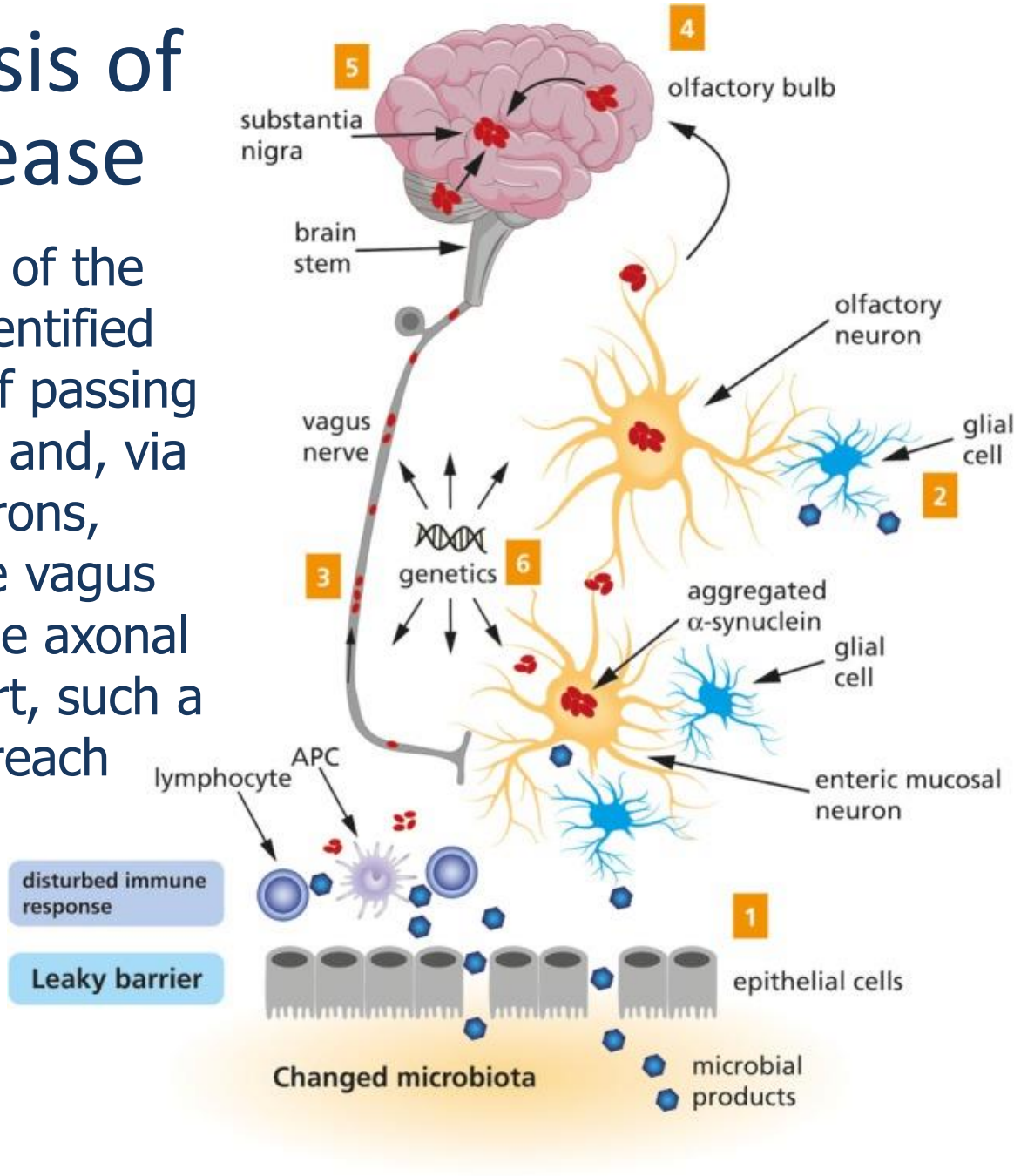


Braak et al Neurobiol Aging. 2003

According to the Braak's model, α-synuclein deposits in a stereotypic, temporal pattern ascending caudo-rostrally from the lower brainstem through susceptible regions of the midbrain and forebrain and into the cerebral cortex

Braak's hypothesis of Parkinson's disease

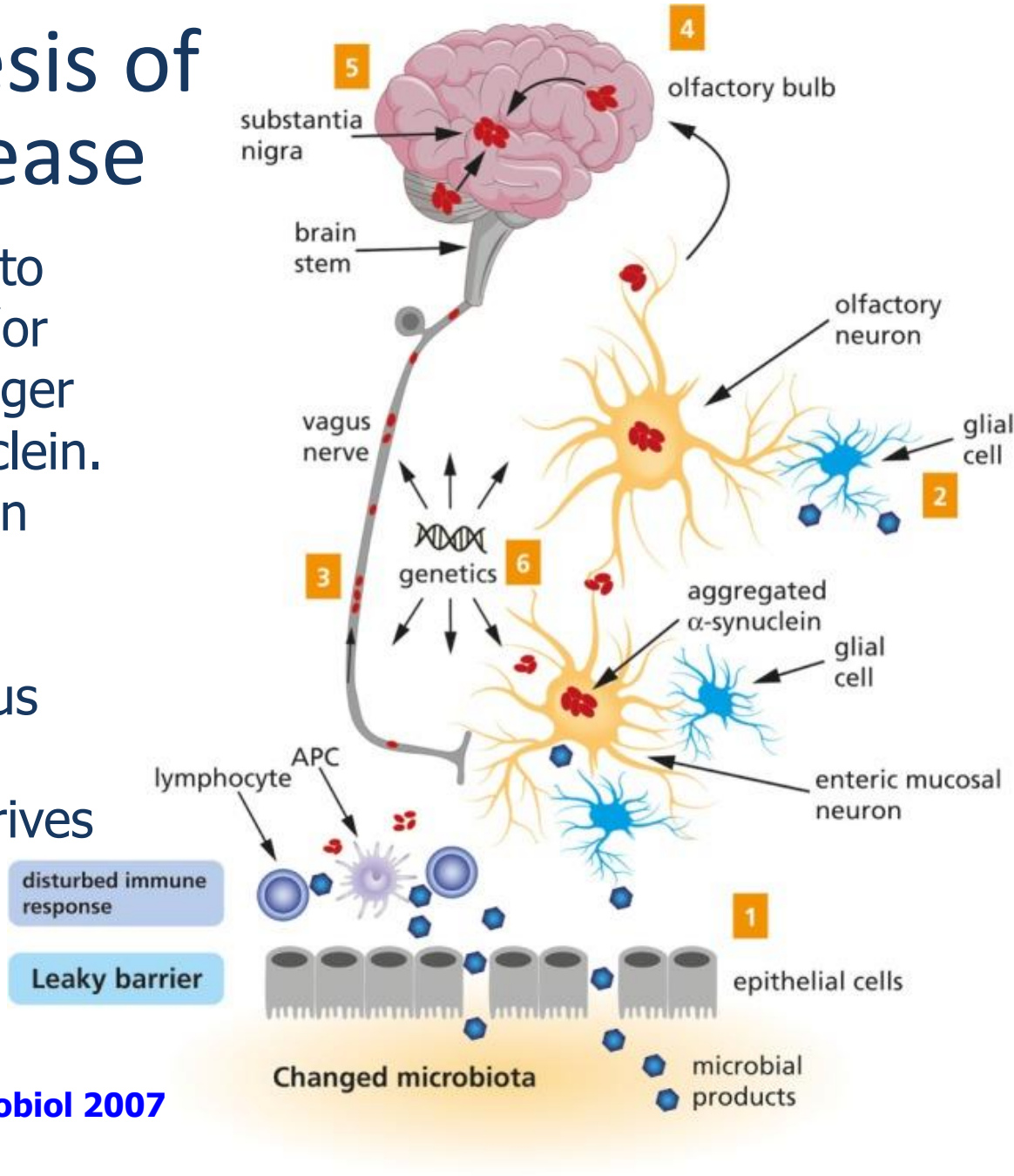
PD might originate outside of the CNS, caused by a yet unidentified pathogen that is capable of passing the gastrointestinal barrier and, via postganglionic enteric neurons, entering the CNS along the vagus nerve. By way of retrograde axonal and transneuronal transport, such a causative pathogen could reach selectively vulnerable subcortical nuclei and the cerebral



Braak et al J Neural Transm 2003

Dual-hit hypothesis of Parkinson's disease

Microbial products come into contact with olfactory and/or enteric neurons, which trigger the aggregation of α-Synuclein. The aggregated α-Synuclein spreads toward the central nervous system via the olfactory bulb and the vagus nerve. Eventually, the aggregated α-Synuclein arrives at the substantia nigra.



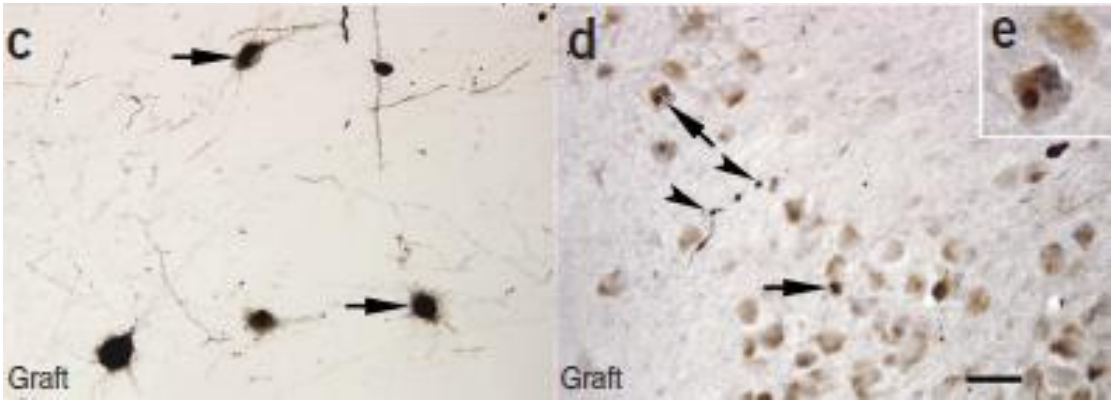
Hawkes et al Neuropathol Appl Neurobiol 2007

Lewy body–like pathology in long-term embryonic nigral transplants in Parkinson's disease

Jeffrey H Kordower[1], Yaping Chu[1], Robert A Hauser[2], Thomas B Freeman[3] & C Warren Olanow[4]

nature medicine

VOLUME 14 | NUMBER 5 | MAY 2008



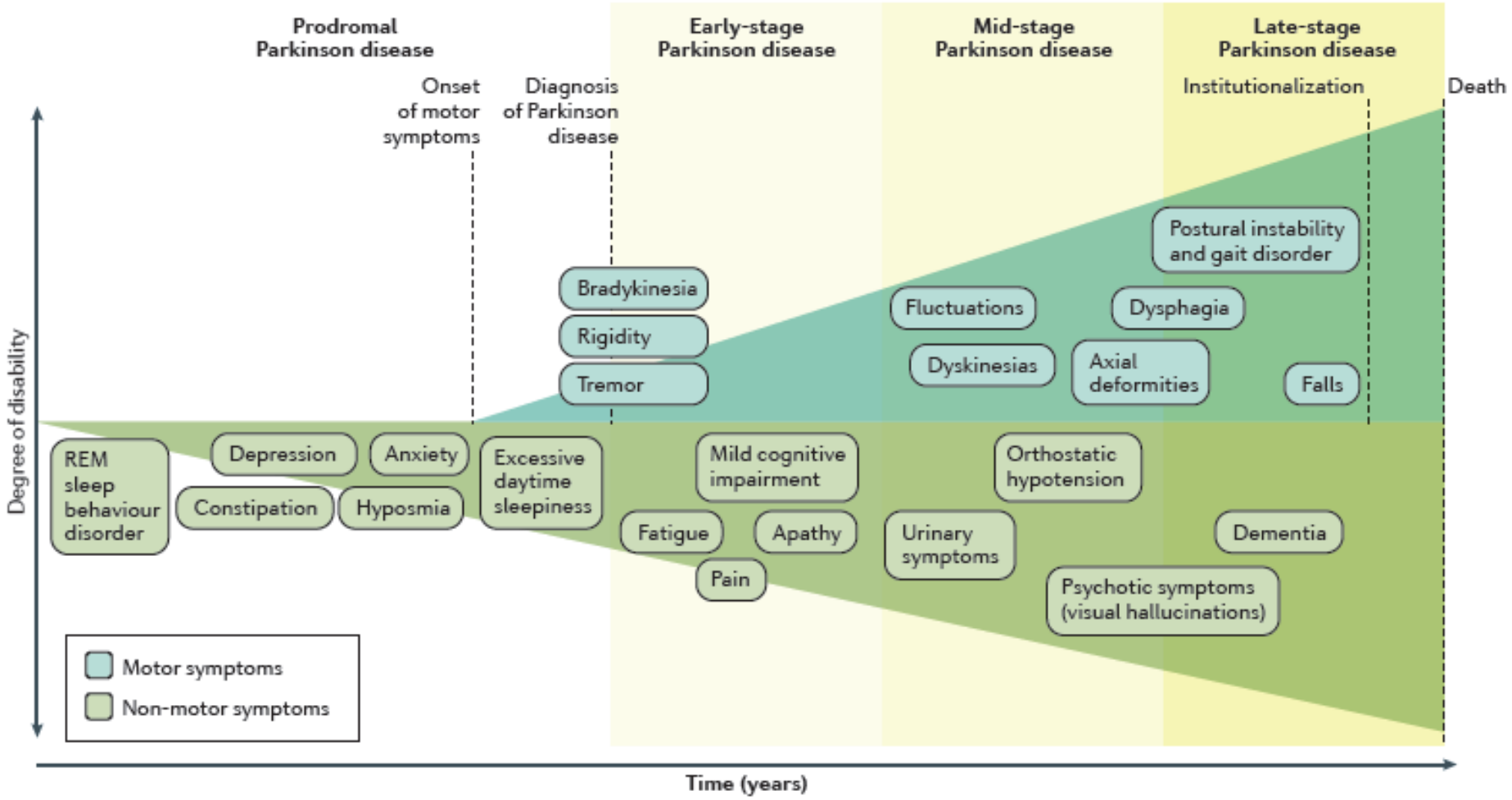
Movement Disorders
Vol. 23, No. 16, 2008, pp. 2303–2306
© 2008 Movement Disorder Society

Transplanted Dopaminergic Neurons Develop PD Pathologic Changes: A Second Case Report

Jeffrey H. Kordower, PhD,[1]* Yaping Chu, MD,[1] Robert A. Hauser, MD,[2] C.Warren Olanow, MD,[3] and Thomas B. Freeman, MD[4]

After long-term transplantation, into the striatum of two individuals with PD, grafted nigral neurons were found to have Lewy body-like inclusions that stained positively for alpha-synuclein and ubiquitin

Malattia di Parkinson: decorso clinico



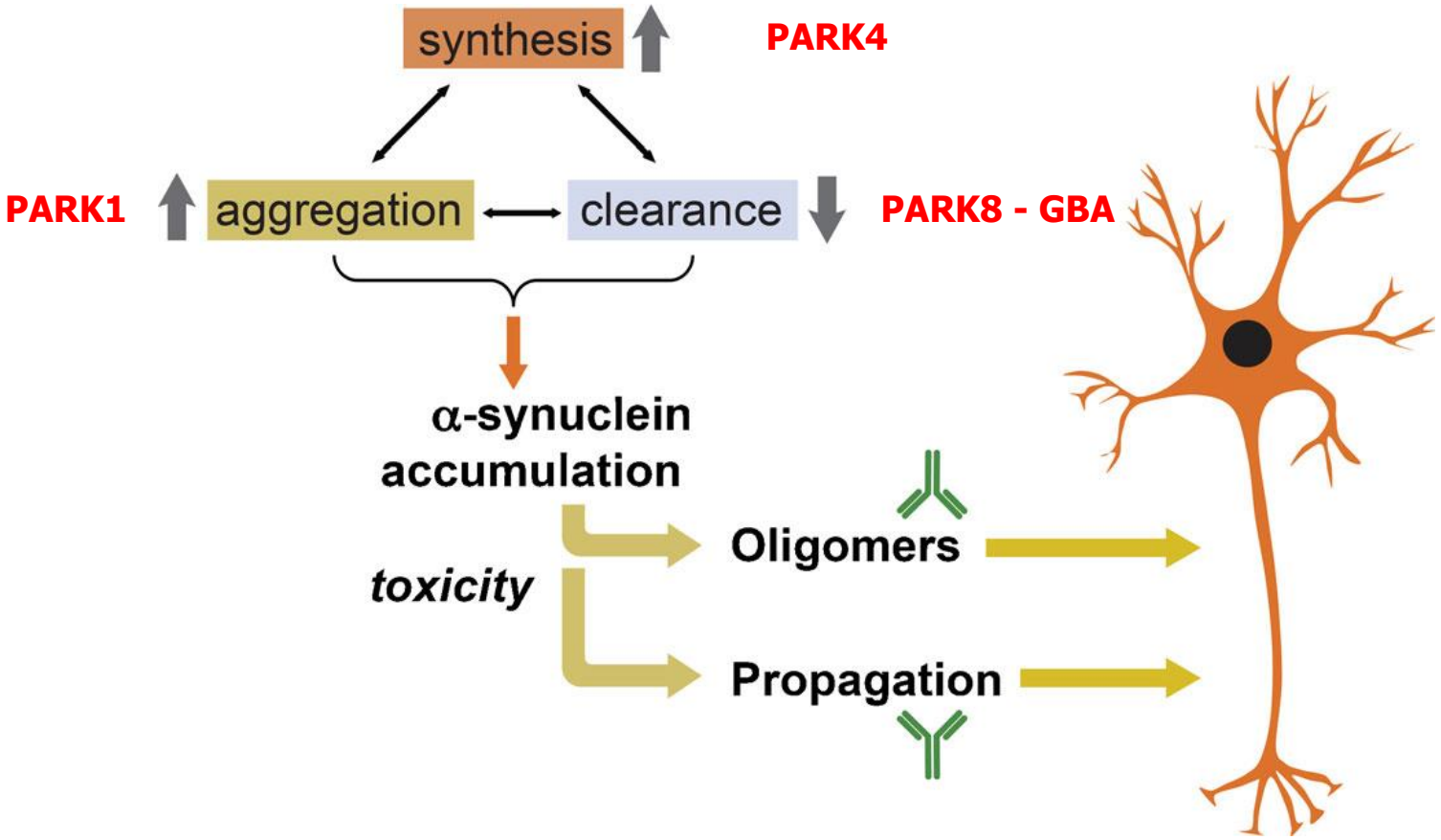
Prion-like propagation of α-synuclein

According to the prion-like hypothesis, once α-synuclein aggregates have formed in a neuron, they can be transported intra-axonally to other brain regions, be released into the extracellular space, be taken up by neighbouring neurons and seed aggregation of endogenous α-synuclein once inside their new cellular host

This model is consistent with the idea that α-synuclein pathology gradually engages more brain regions as the disease progresses, as suggested by Braak

This is also consistent with the idea that the first sites of α-synuclein aggregation might be in the gut enteric nerves and the olfactory bulb, causing some prodromal PD features (anosmia and constipation) before they spread to substantia nigra, leading to motor dysfunction

Toxicity of α-synuclein in PD



Therapeutic stategies against α-synuclein aggregation

Therapeutic strategies for PD might require reducing the synthesis, preventing the aggregation and/or enhancing the clearance of α-syn.

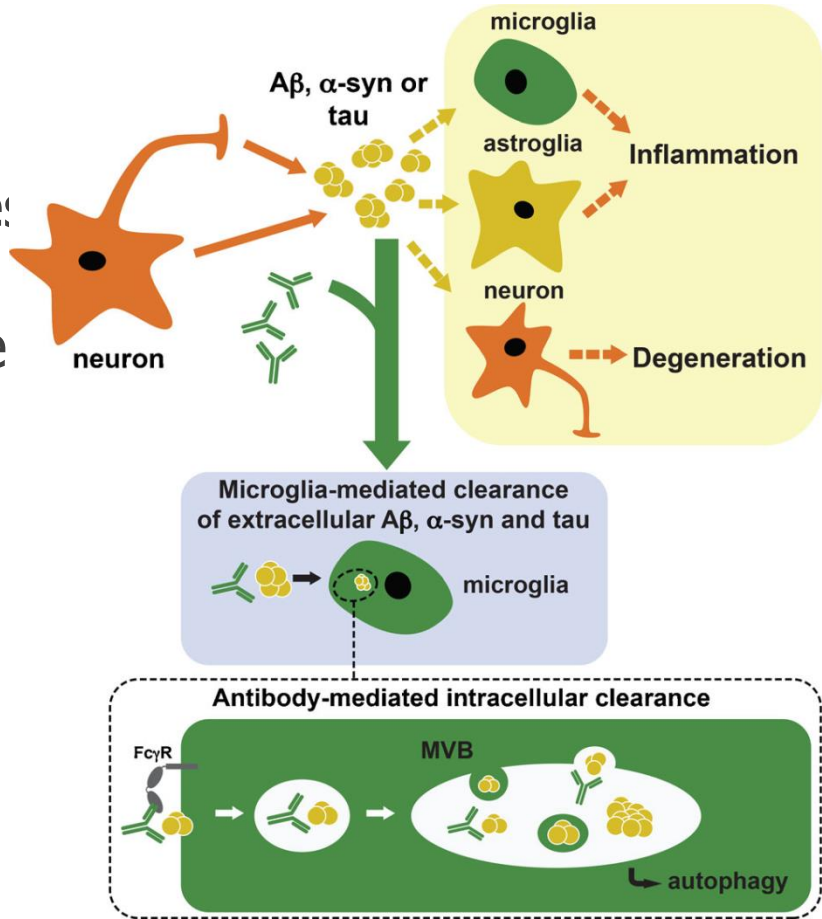
Numerous strategies directed at reducing the accumulation of these proteins have been developed, including the use of small interfering RNA, antisense RNA degrading enzymes, chaperone-like molecules that modulate aggregation state, anti-aggregation compounds, and immunotherapy.

Concerning the development of immunotherapeutic approaches targeting α-syn, both humoral (active and passive) and T-cell-based approaches have been explored.

Therapeutic immunotherapy

Therapeutic immunotherapy has been shown to induce a physiological microglial response and to reduce the production of proinflammatory cytokines, thus exerting an anti-inflammatory effect in neurodegenerative disorders.

Disadvantages of immunotherapy are the potential for autoimmune responses, inflammatory reactions such as perivascular edema, need for repetitive administration, lack of response due to senescence of the innate immune system, and limited penetration of antibodies into the central nervous system.



Active and passive immunotherapy

Immunotherapy may be pursued by active immunization or by a passive immunization approach.

The costs associated with active vaccination are lower with easier and less frequent administration. On the other hand, this approach requires the patients' immune system to be able to produce antibodies with the right specificity and in high enough amounts to be efficacious.

Passive immunization will be more expensive and require more frequent administration by specialized personnel. However, the advantage with this approach is the ability to control antibody levels in plasma and brain and select the antibody with well-documented affinity, physical properties, brain exposure, and efficacy in preclinical models.

Active immunotherapy targeting α-synuclein

AFFITOPEs are synthetic peptides that mimics the C-terminus region of α-syn and are able to elicit an immune response specific to α-syn oligomers in animal models of PD.

Vaccination with AFFITOPEs resulted in high antibody titers against α-syn aggregates, decreased accumulation of α-syn oligomers, reduced degeneration of tyrosine hydroxylase fibers in the striatum, and improved motor and memory deficits in α-syn transgenic models.

Antibodies against α-syn are currently being tested in phase 1 trials.

Passive immunotherapy targeting α-synuclein

Antibodies that recognize an epitope in the C-terminus of α-syn are more effective at ameliorating the pathology in transgenic mouse models of PD, as they clear intracellular aggregates, inhibit α-syn propagation, and prevent C-terminus cleavage of the protein, which may lead to increased aggregation

Antibodies against the N-terminus are also effective at clearing α-syn aggregates, reducing their propagation, and diminishing motor dysfunctions

The C-terminus antibody PRX002 (AFFiRiS AG) and the antibody BIIB054 (Biogen) are currently being tested in phase I clinical trials

RESEARCH ARTICLE

First-in-Human Assessment of PRX002, an Anti–α-Synuclein Monoclonal Antibody, in Healthy Volunteers

Dale B. Schenk, PhD,[1†] Martin Koller, MD, MPH,[1] Daniel K. Ness, DVM, PhD,[1] Sue G. Griffith, MD, PhD, MRCP,[2] Michael Grundman, MD, MPH,[3,4] Wagner Zago, PhD,[1] Jay Soto, BS,[1] George Atiee, MD,[5] Susanne Ostrowitzki, MD, PhD,[6] and Gene G. Kinney, PhD[1*]

Movement Disorders, Vol. 32, No. 2, 2017

This first-in-human, randomized, double-blind, placebo-controlled, phase 1 study assessed the impact of PRX002 administered to 40 healthy participants.

No serious adverse events, discontinuations as a result of adverse events, or dose-limiting toxicities were reported.

Significant dose-dependent reduction in free serum a-synuclein was apparent within 1 hour after PRX002 administration.

Disease-Modifying Therapies in PD

1817 → 2017