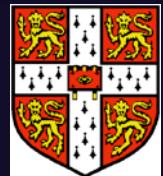


The role of Alpha-synuclein Aggregates in the Pathogenesis of Lewy Body and Parkinson's Disease

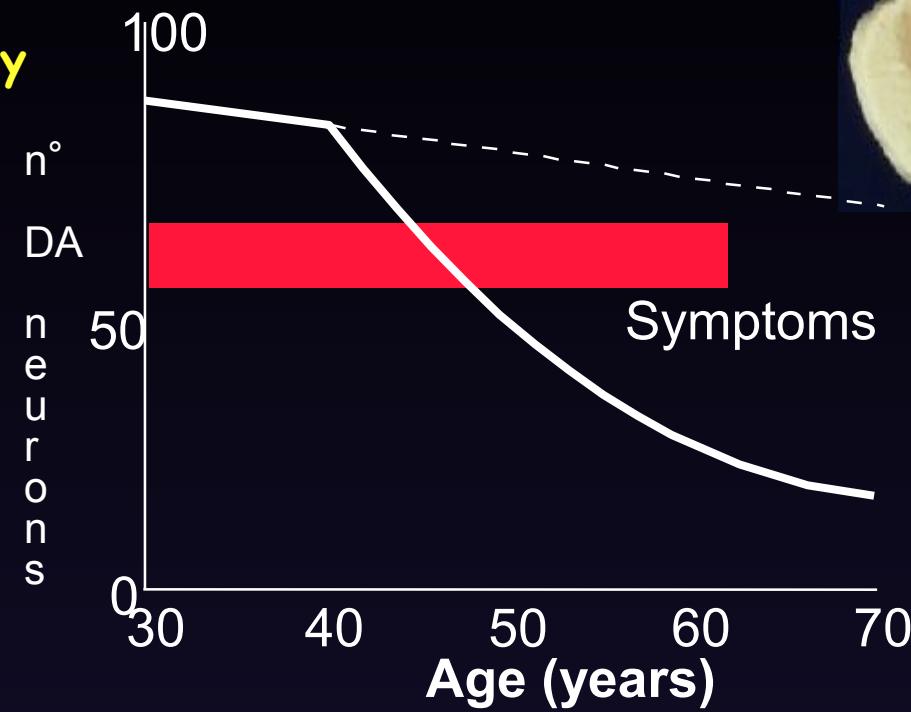
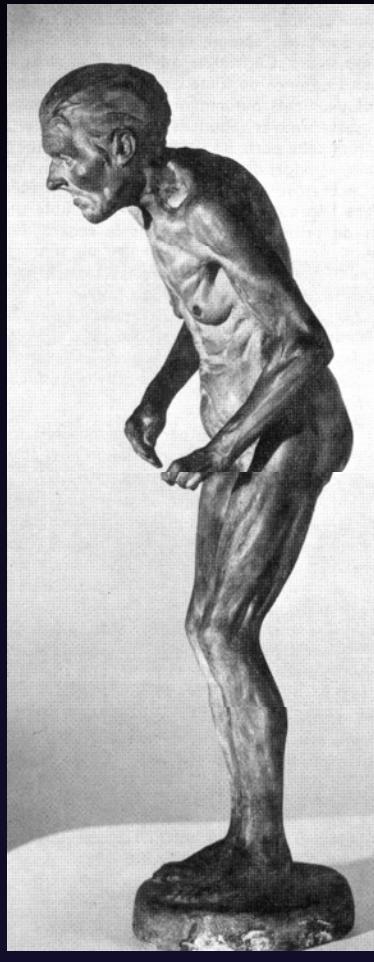
Maria Grazia Spillantini

William Scholl Professor of Molecular Neurology
The Clifford Allbutt Building
Department of Clinical Neurosciences
University of Cambridge

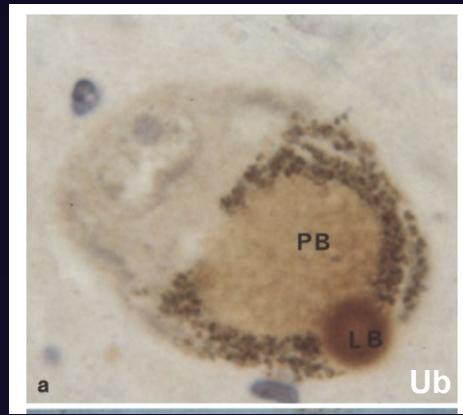


PARKINSON'S DISEASE

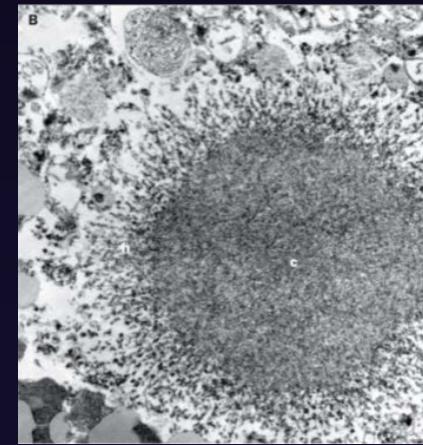
- Rigidity
- Resting tremor
- Bradykinesia
- Postural instability



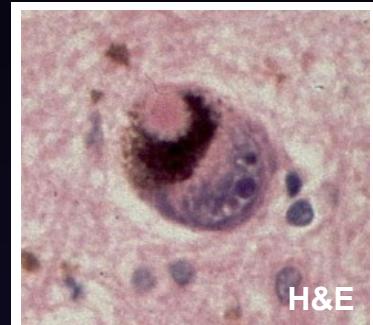
Schulzer et al. *Brain* 1994;117:509-516



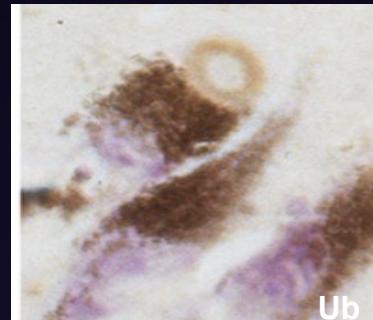
Dale et al. 1992



Duffy & Tennyson 1966

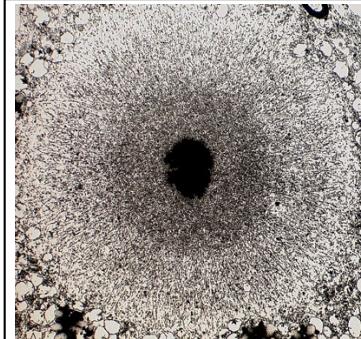
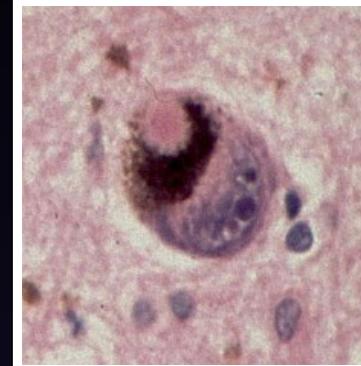
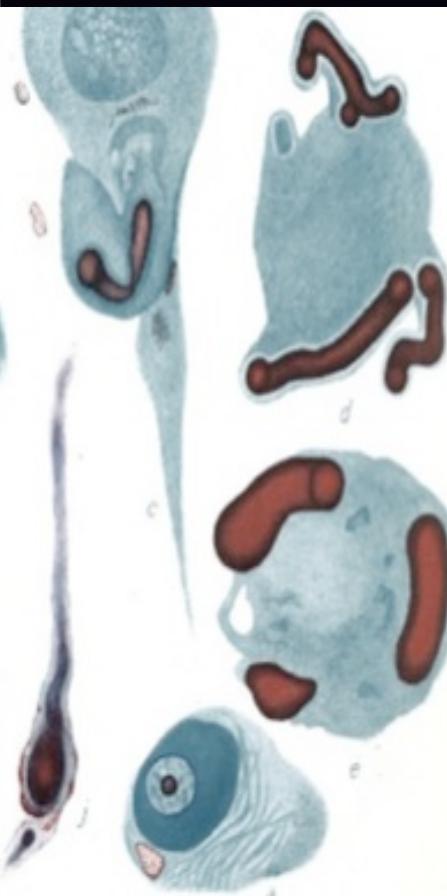


H&E

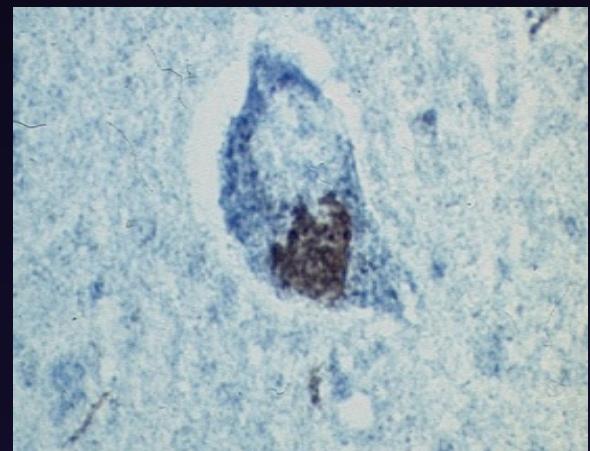


Ub

The Lewy Body



Forno 1990



F. Lewy describes the Lewy bodies in 1912

All sporadic PD cases and the majority of familial cases have LB

The Synucleins and Lewy body



Ross Jakes

Michel Goedert

FEBS Letters 345 (1994) 27–32

FEBS 14009

Identification of two distinct synucleins from human brain

Ross Jakes*, Maria Grazia Spillantini, Michel Goedert

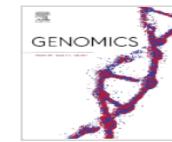
MRC Laboratory of Molecular Biology, Hills Road, Cambridge CB2 2QH, UK

Received 1 April 1994



Genomics

Volume 27, Issue 2, 20 May 1995, Pages 379–381



Brief Reports

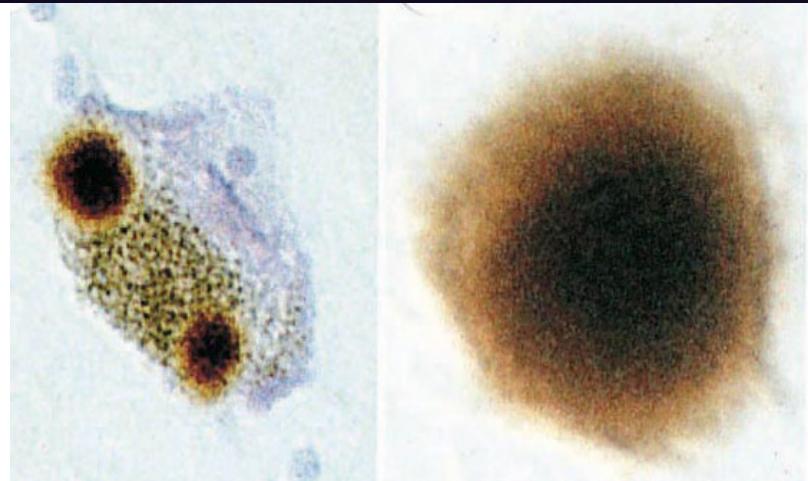
Assignment of Human α -Synuclein (SNCA) and β -Synuclein (SNCB) Genes to Chromosomes 4q21 and 5q35

Maria Grazia Spillantini, Aspasia Divane, Michel Goedert

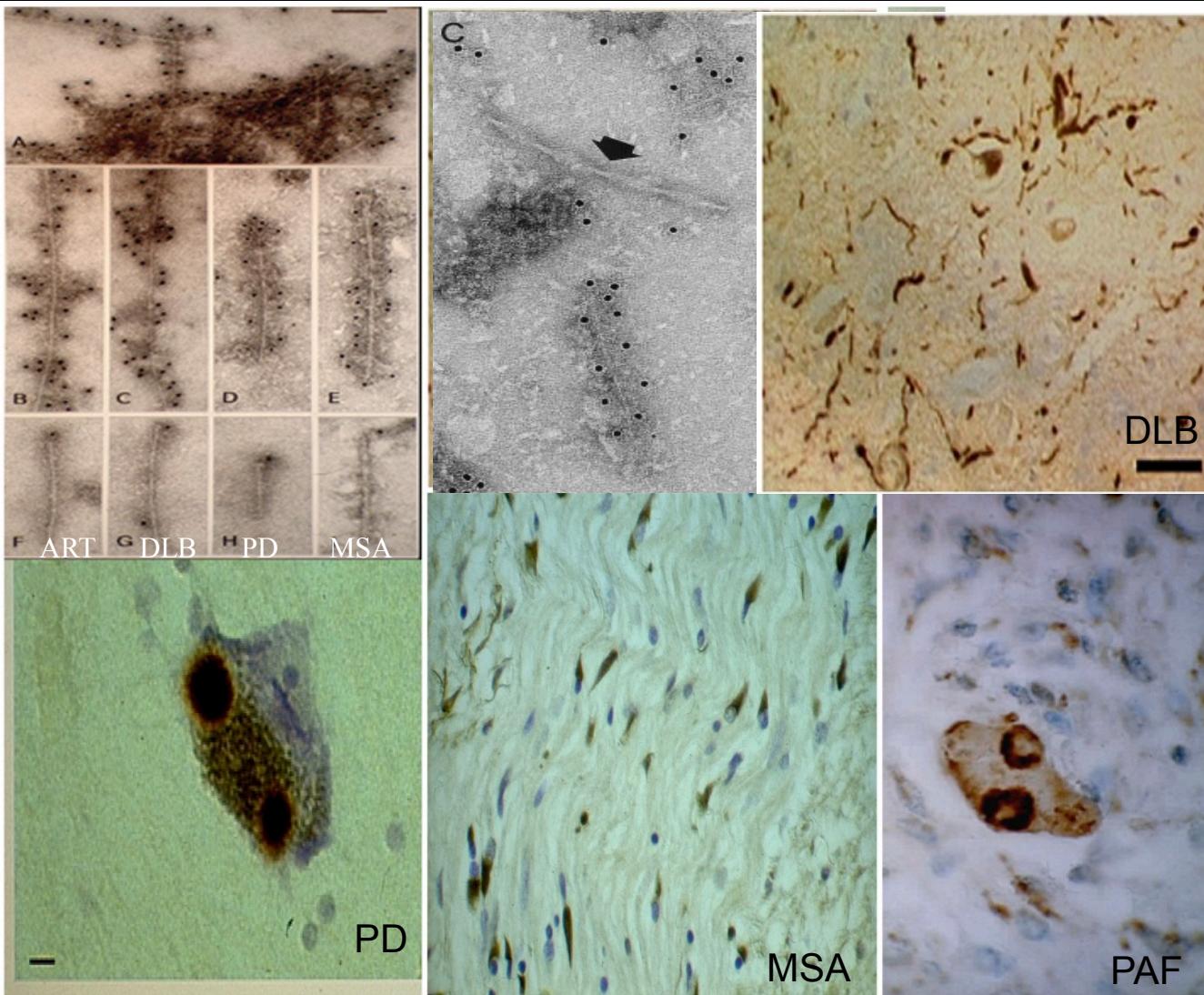
Nature 388, 839–840 (28 August 1997) |

α -Synuclein in Lewy bodies

Maria Grazia Spillantini¹, Marie Luise Schmidt²,
Virginia M.-Y. Lee², John Q. Trojanowski², Ross
Jakes³ & Michel Goedert³



α -Synucleinopathies



Idiopathic Parkinson's disease

Dementia with Lewy Bodies

Pure autonomic failure

Lewy body dysphagia

Inherited Lewy body diseases

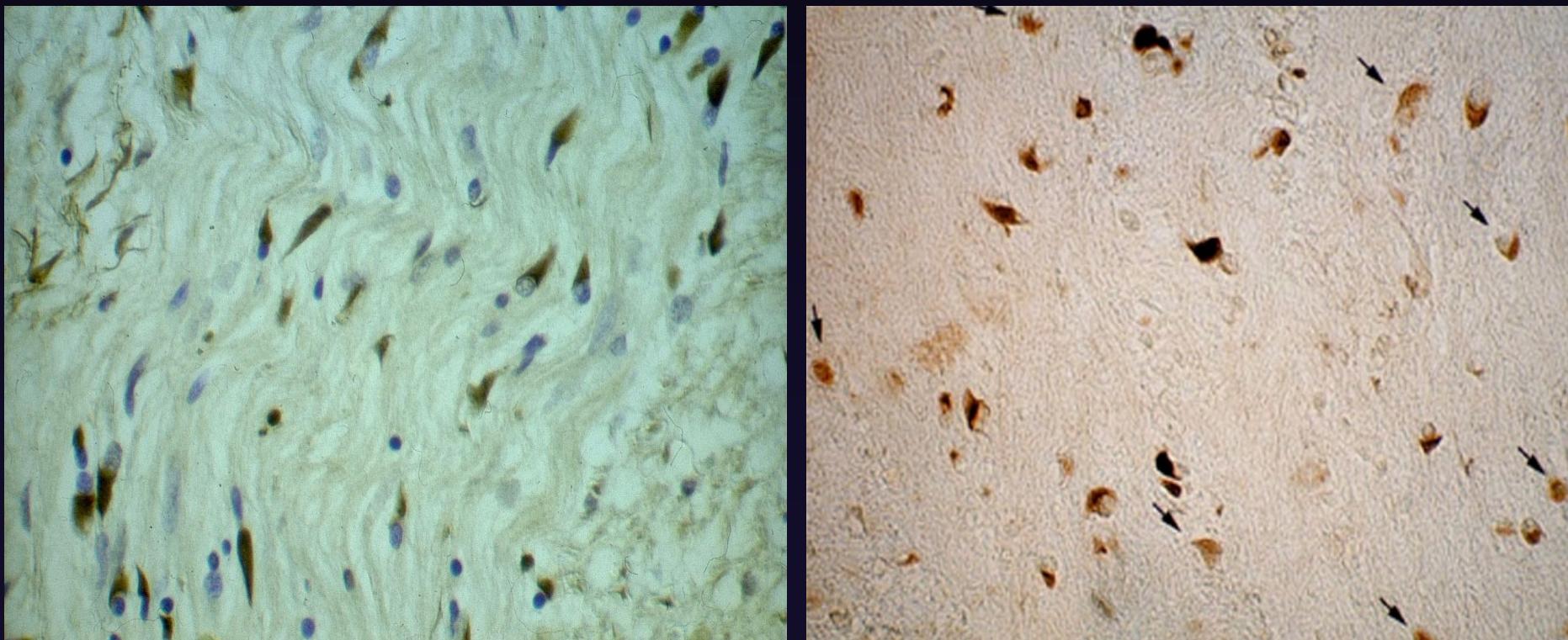
REM Sleep Disorder

Multiple system Atrophy

α -Synuclein as marker for Lewy bodies instead of ubiquitin

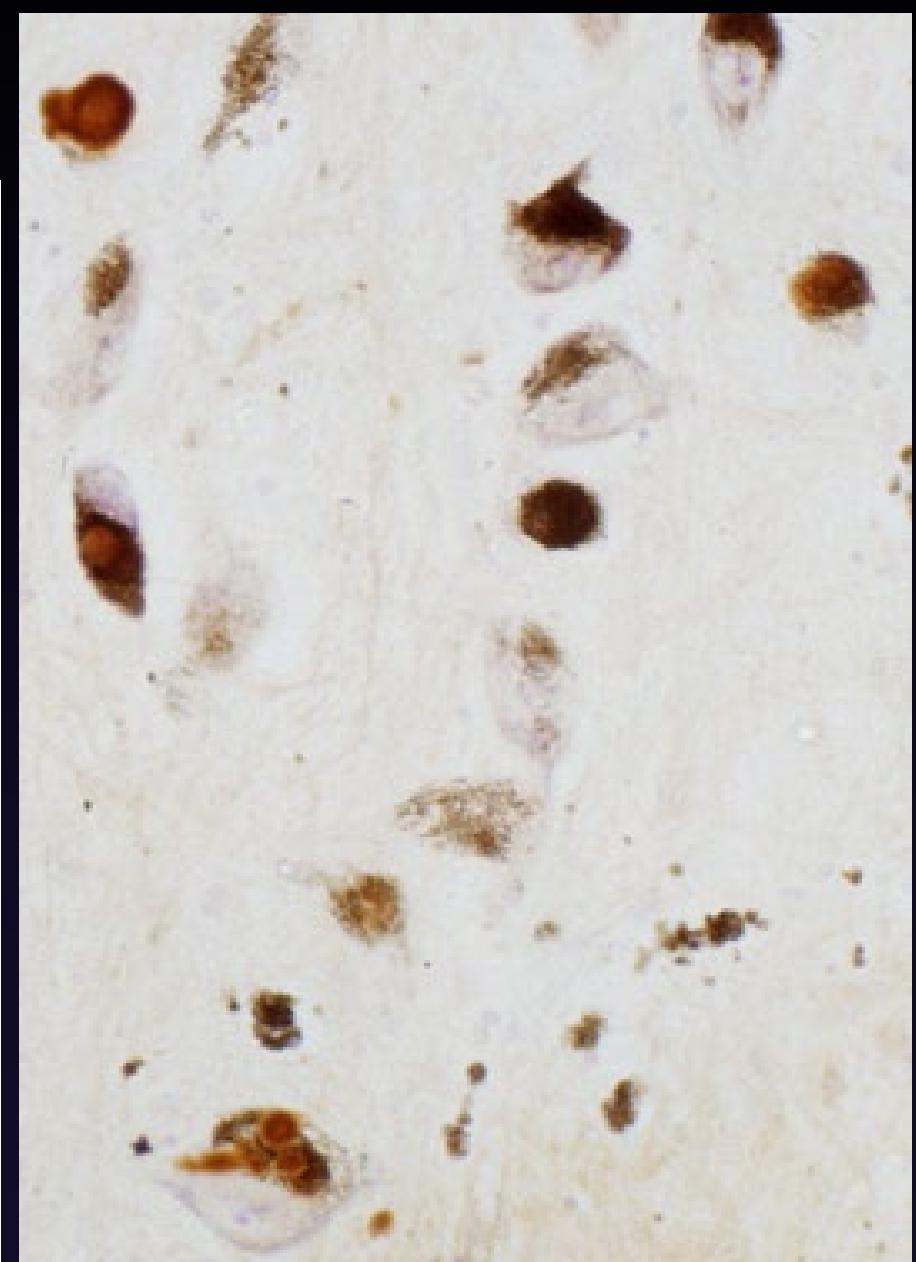
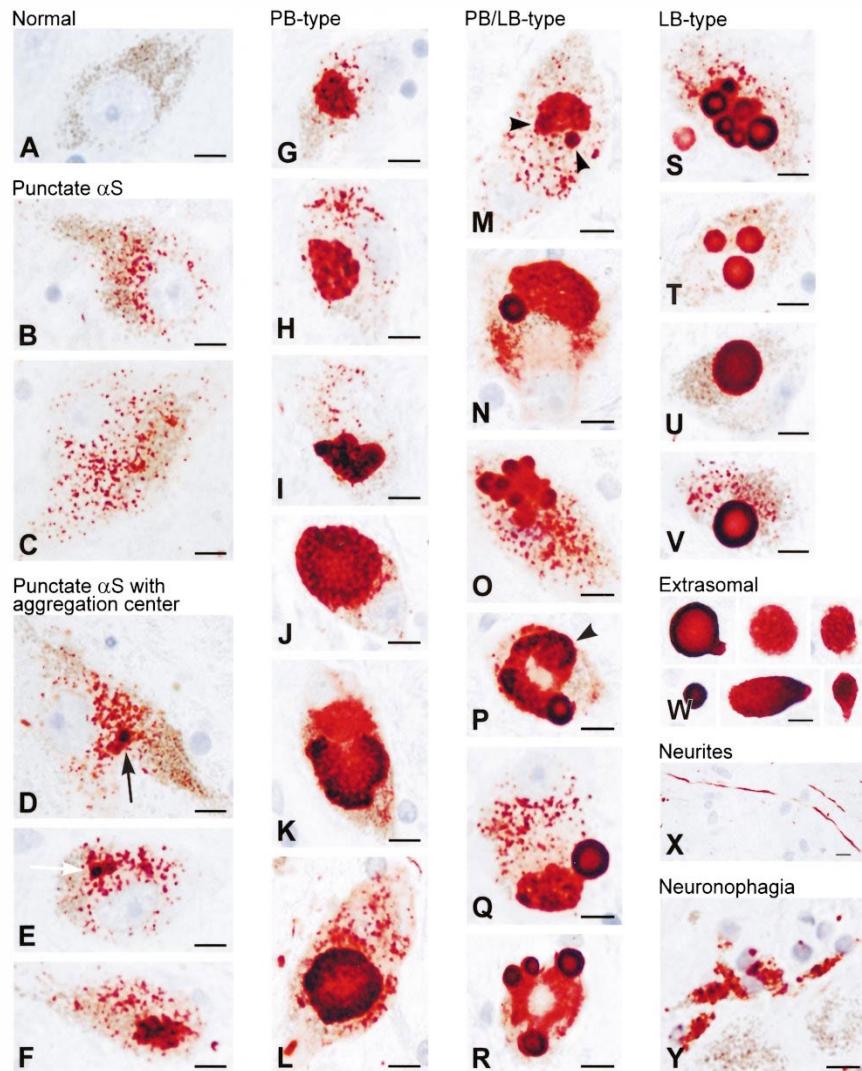


25% more GCI in MSA detected with α -syn than ubiquitin

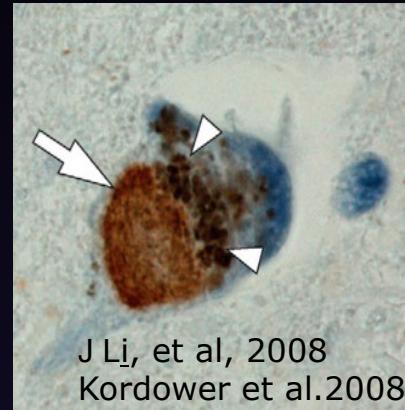
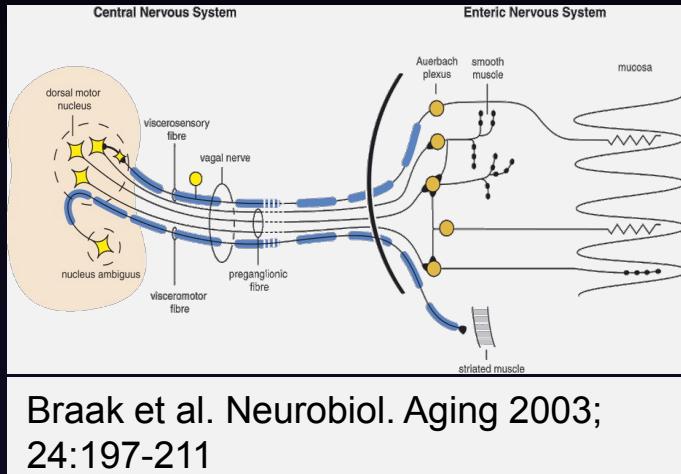


Morphogenesis of Lewy Bodies: Dissimilar Incorporation of α -Synuclein, Ubiquitin, and p62

ERKKI KUUSISTO, MSC, LAURA PARKKINEN, MSC, AND IRINA ALAFUZOFF, MD, PhD



α -Synuclein aggregates spreading are associated with symptomatology.



Panel 2: Non-motor symptoms suggested as preclinical (motor) characteristics in Parkinson's disease

Strong evidence

Constipation

Olfactory deficit

REM sleep behaviour disorder

Depression

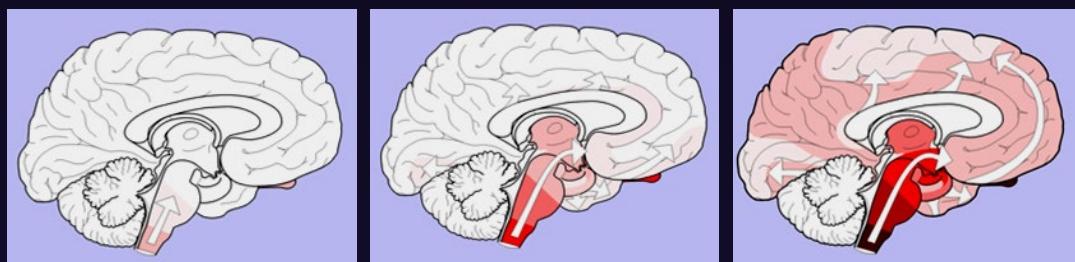
Suggested links (poor evidence base)

Restless-legs syndrome

Apathy

Fatigue

Anxiety

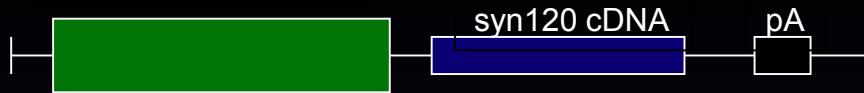


Incidental LBD

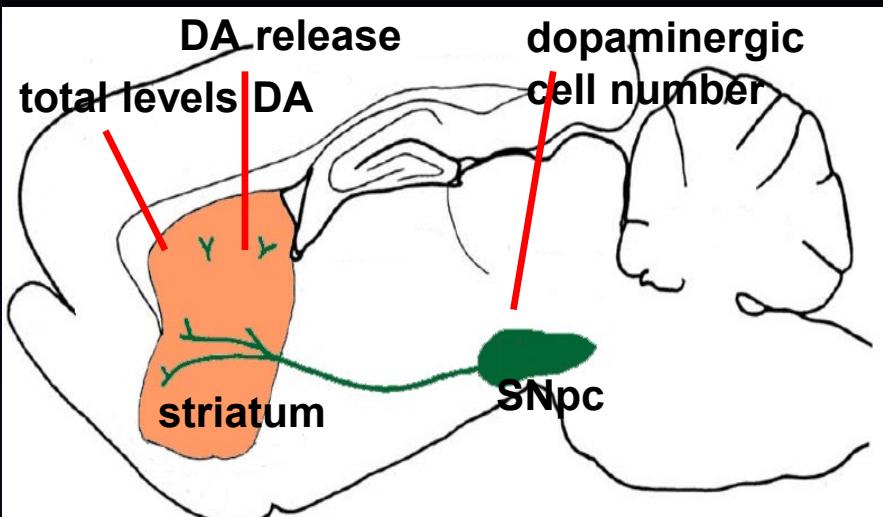
Parkinson's disease

DLB

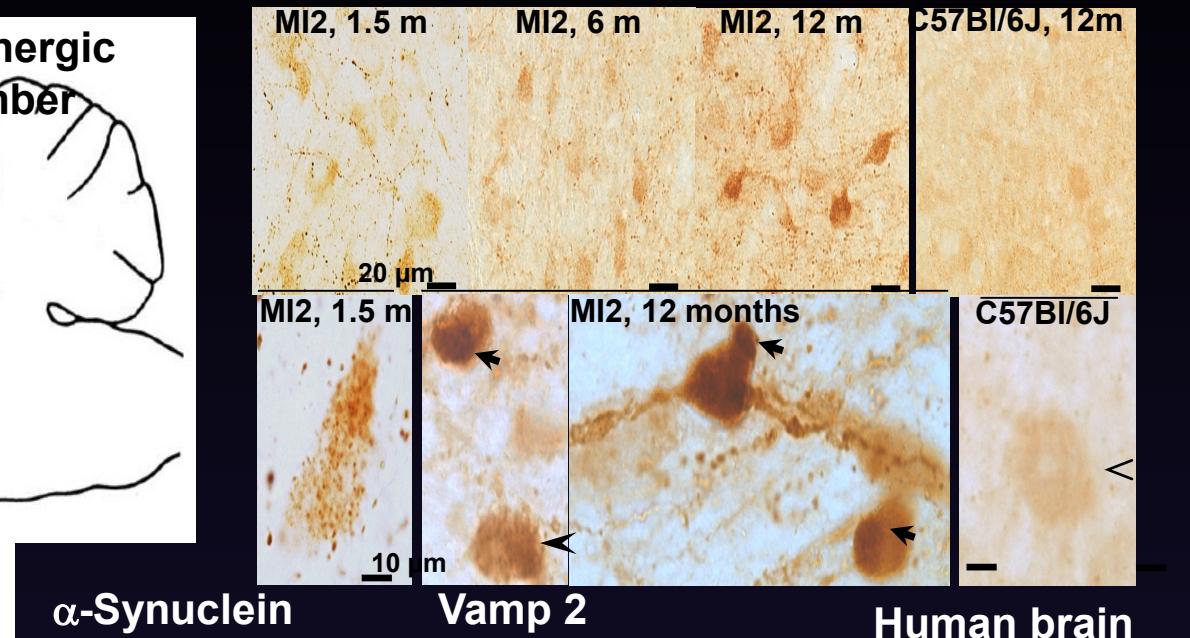
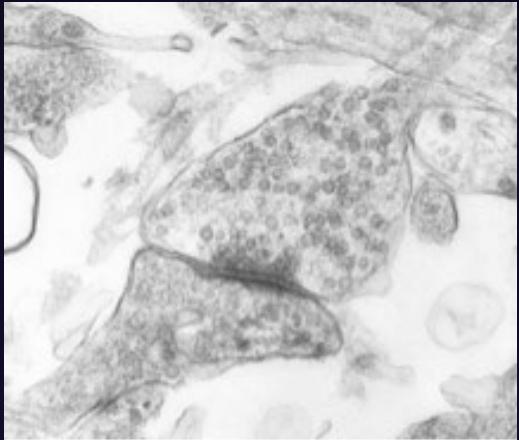
TH-promoter (9kDa)



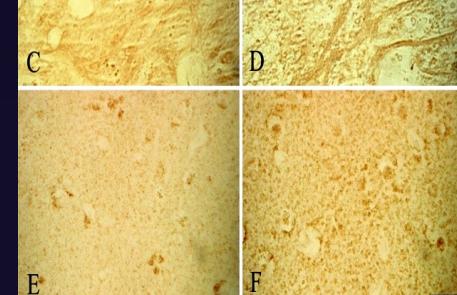
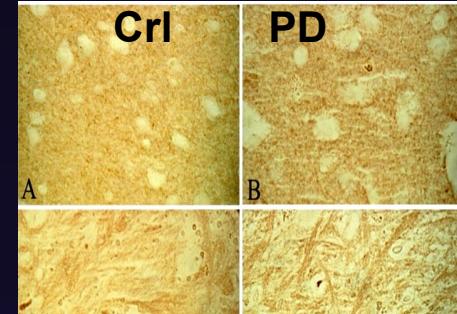
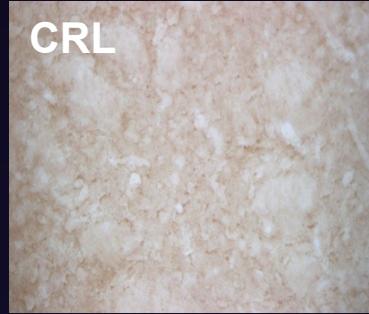
α -Synuclein expression in 1-120 MI2 α -synuclein transgenic mice



Associated with
 α -Synuclein expression



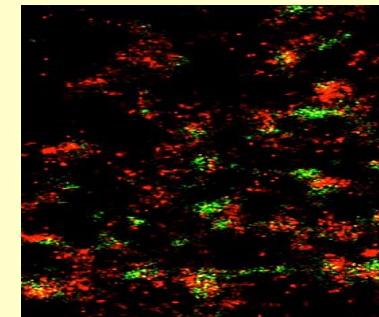
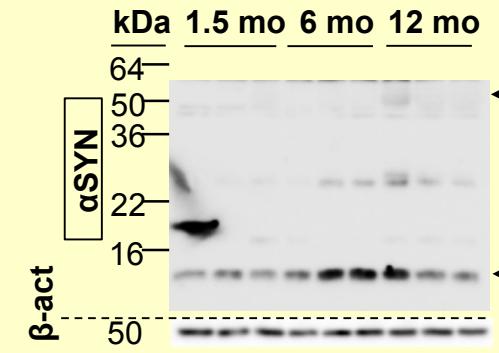
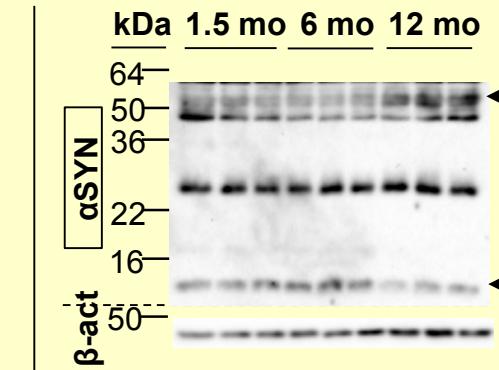
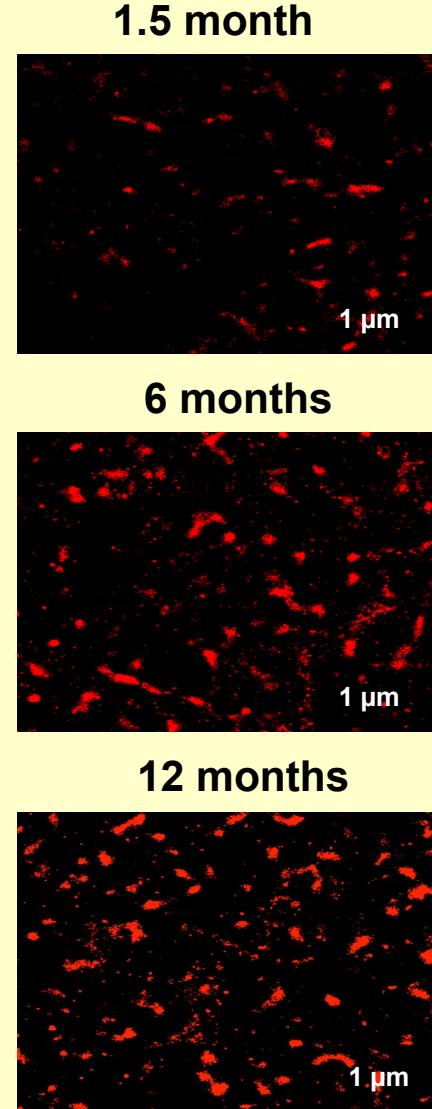
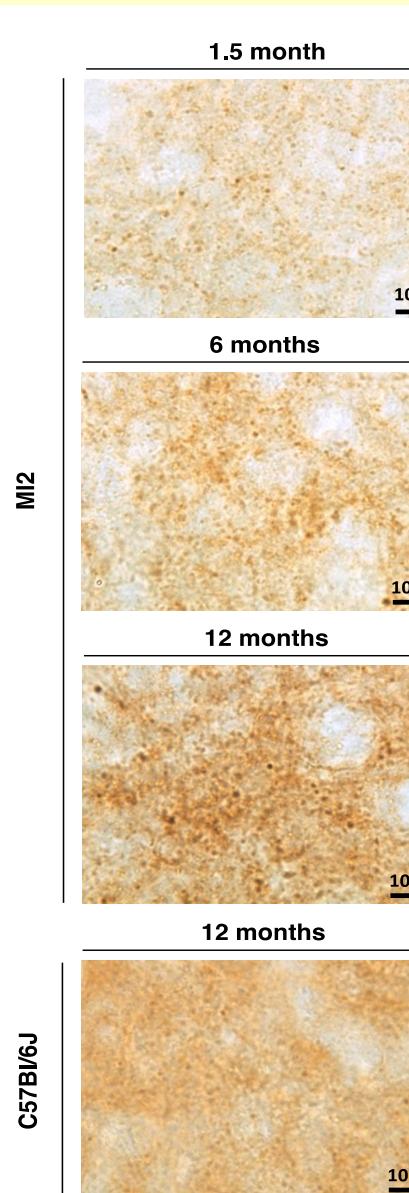
α -Synuclein Vamp 2 Human brain



Alpha-synuclein aggregation in synapse in the striatum

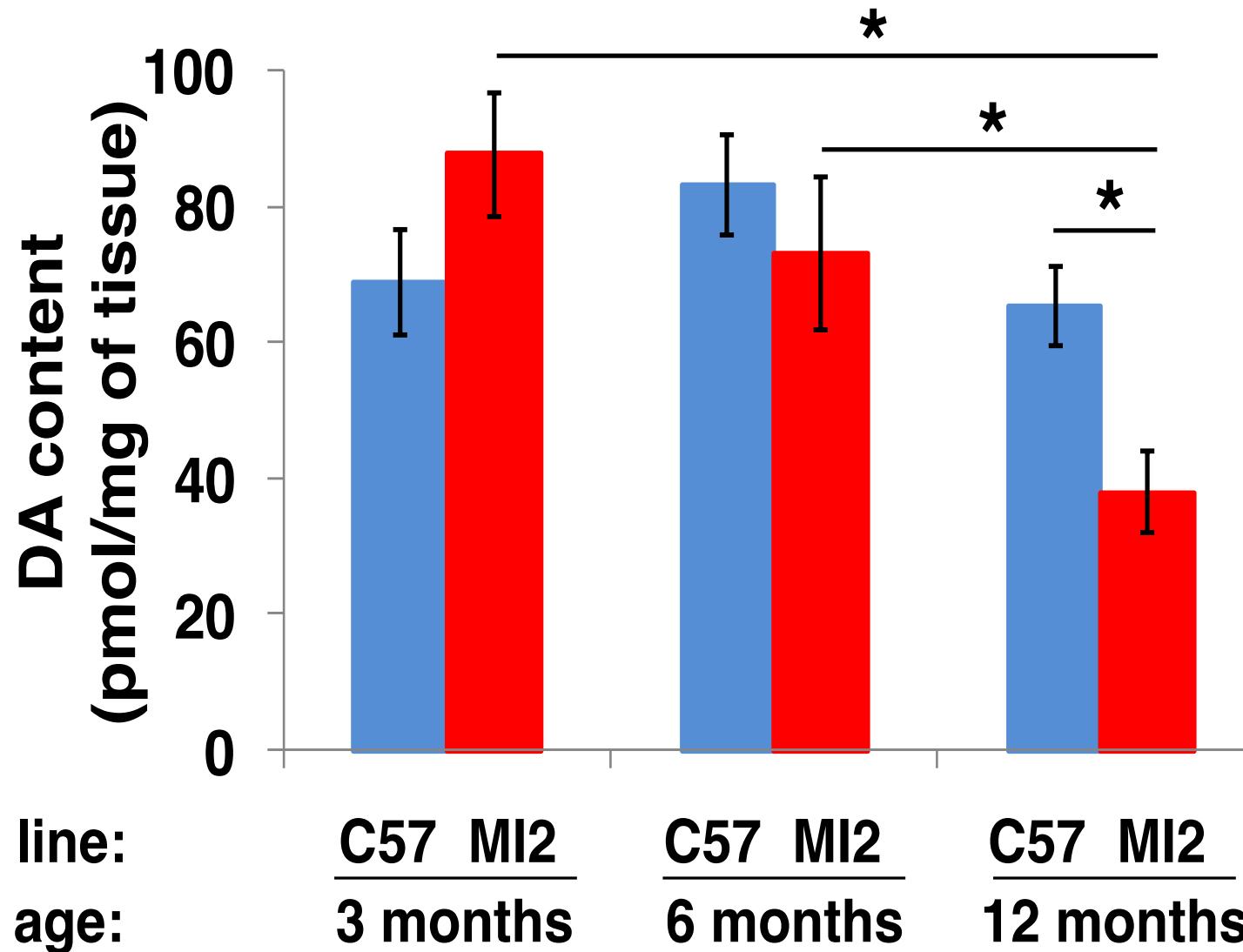
B

striatum



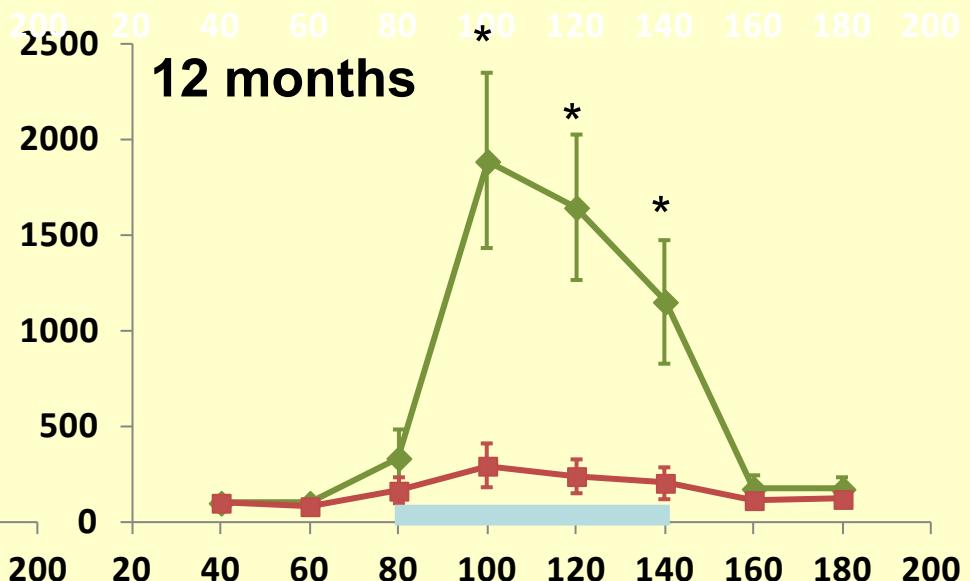
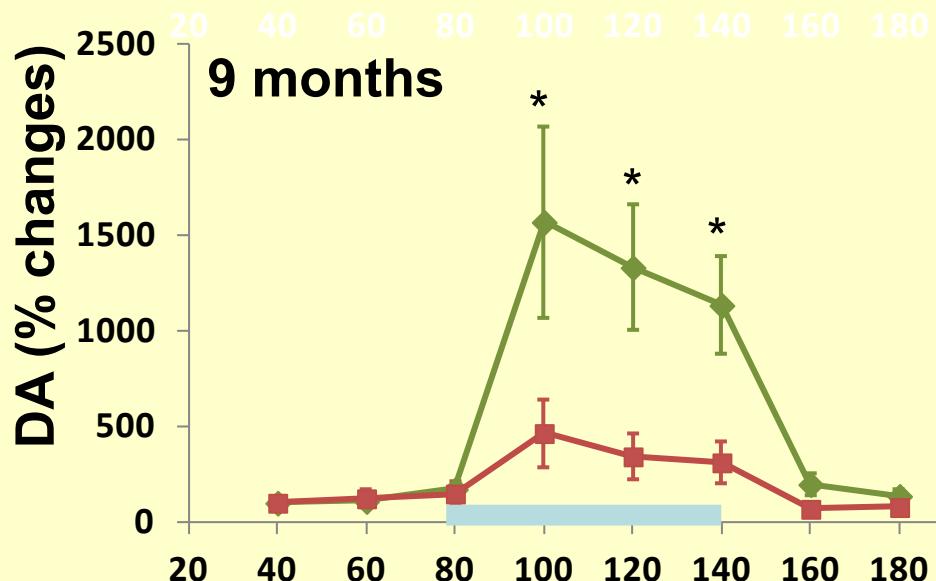
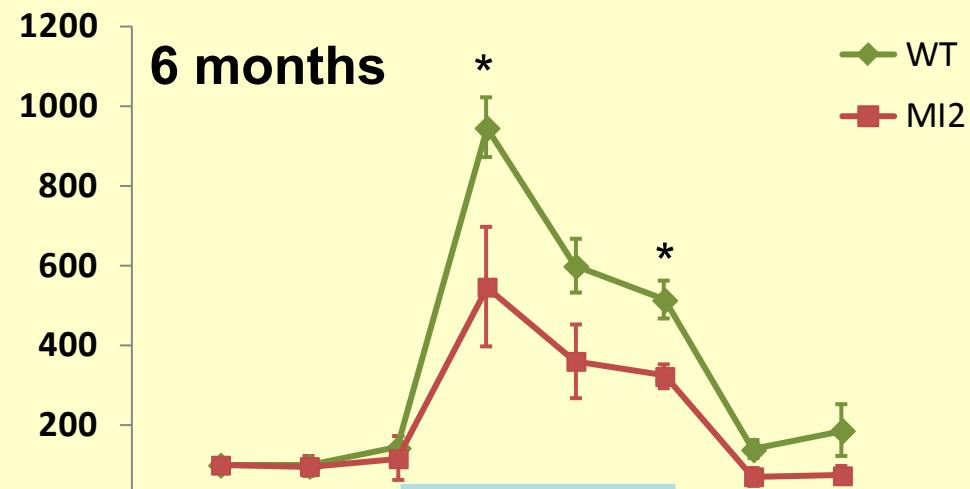
α-synuclein
Vamp 2

Reduction of DA levels in striatal tissue at 12



*

Progressive DA release impairment in striatum in MI2 mice



50 mM K⁺

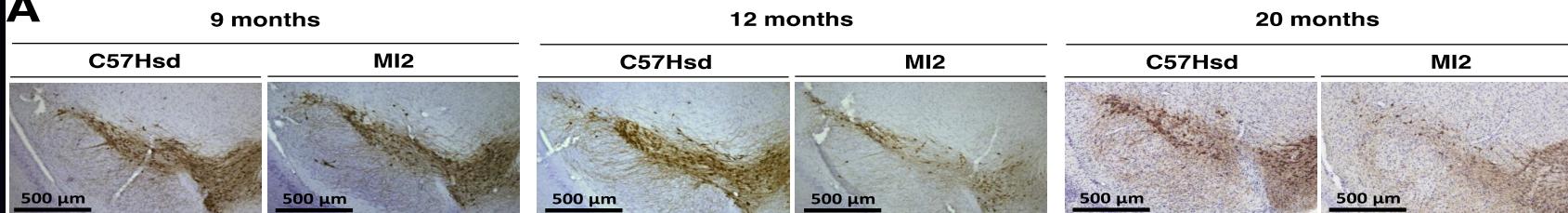
time [min.]

50 mM K⁺

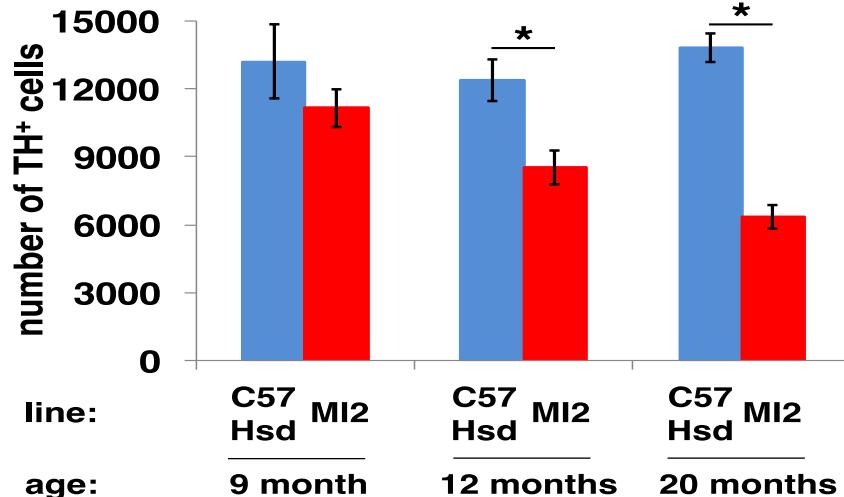
* p<0.05 WT vs MI2

Progressive dopaminergic neuron loss in SNpc

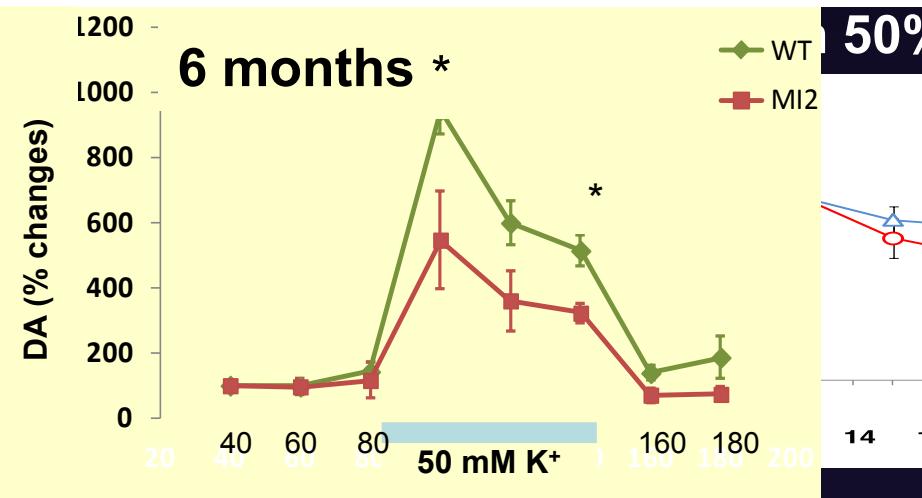
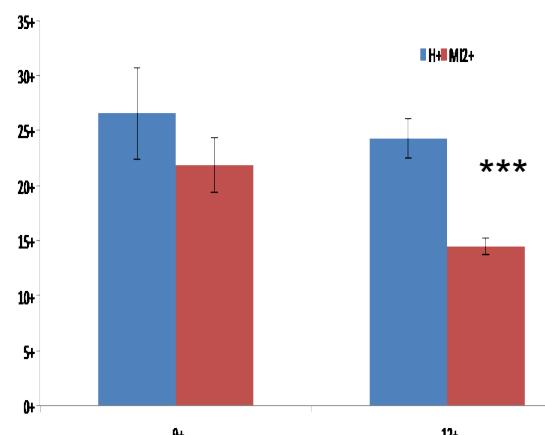
A



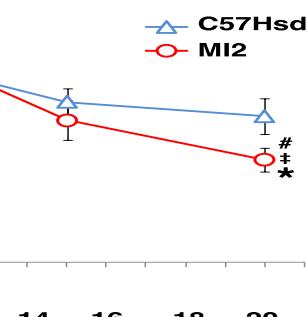
B



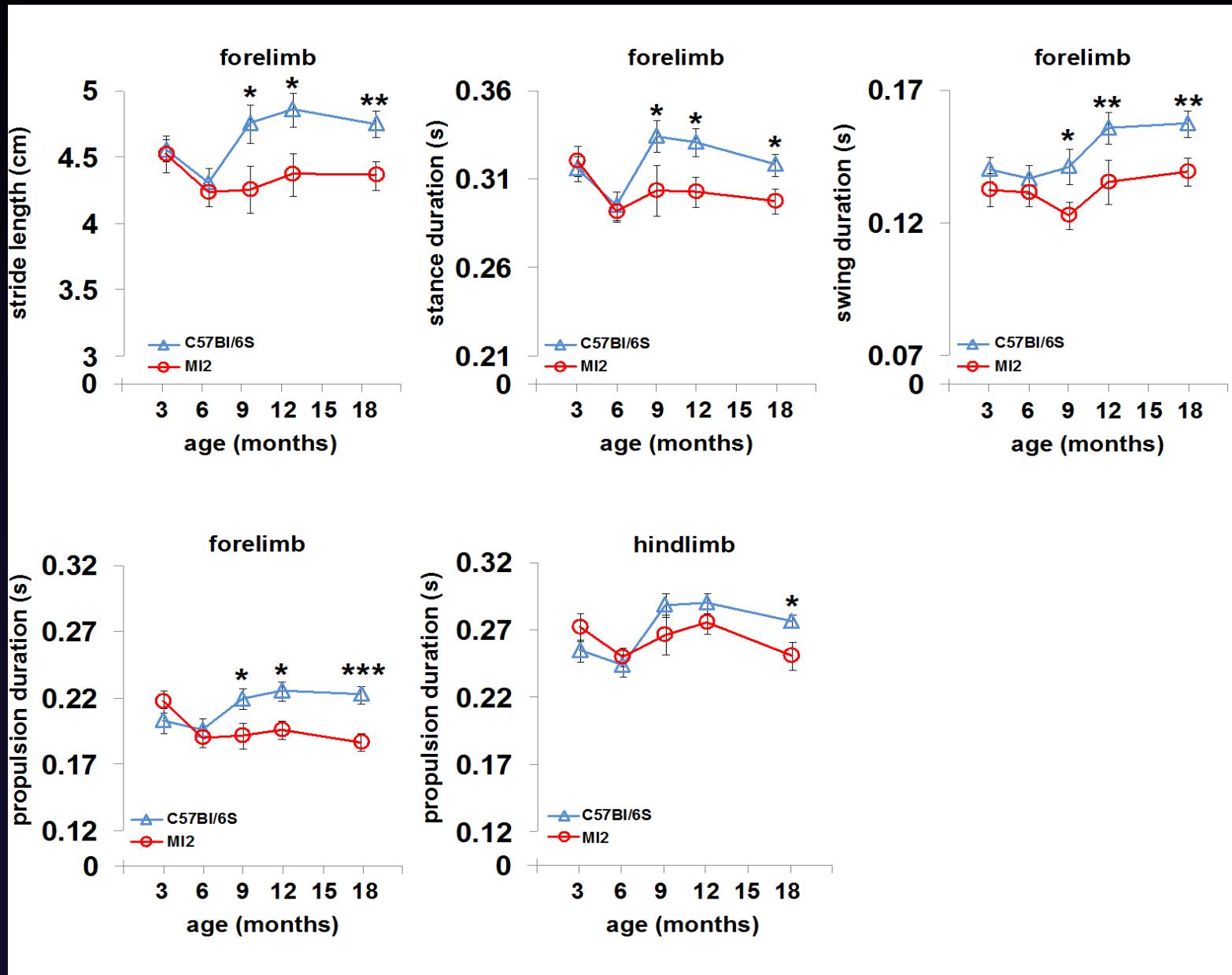
TH⁺ neurites are progressively reduced in striatum of MI2 mice



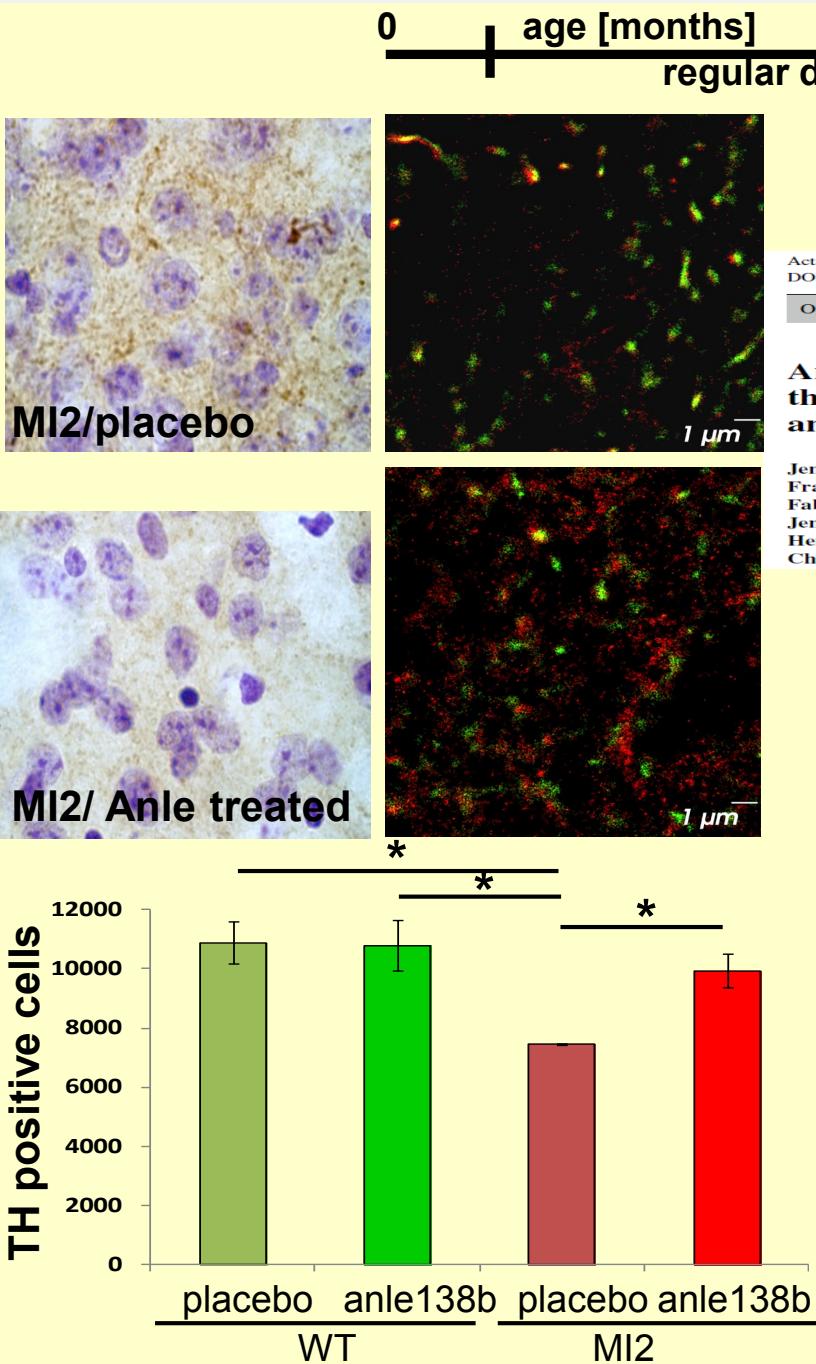
50% of neurons are lost



Progressive motor impairment in MI2 mice is observed earlier with DIGIGAIT



Anle138b treatment rescues Dopamine deficit and neuronal death

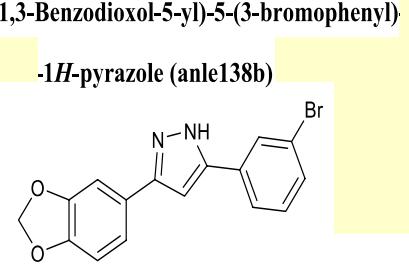
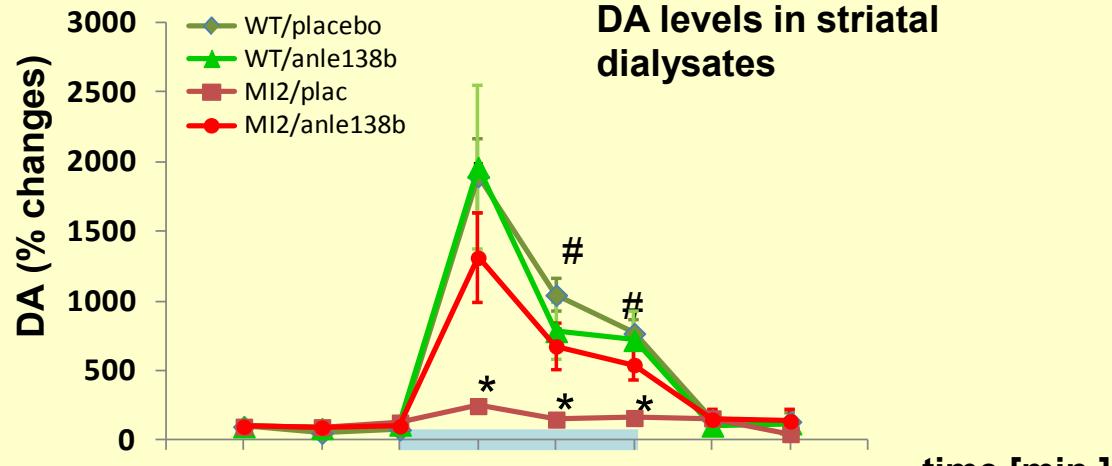


Acta Neuropathol (2013) 125:795–813
DOI 10.1007/s00401-013-1114-9

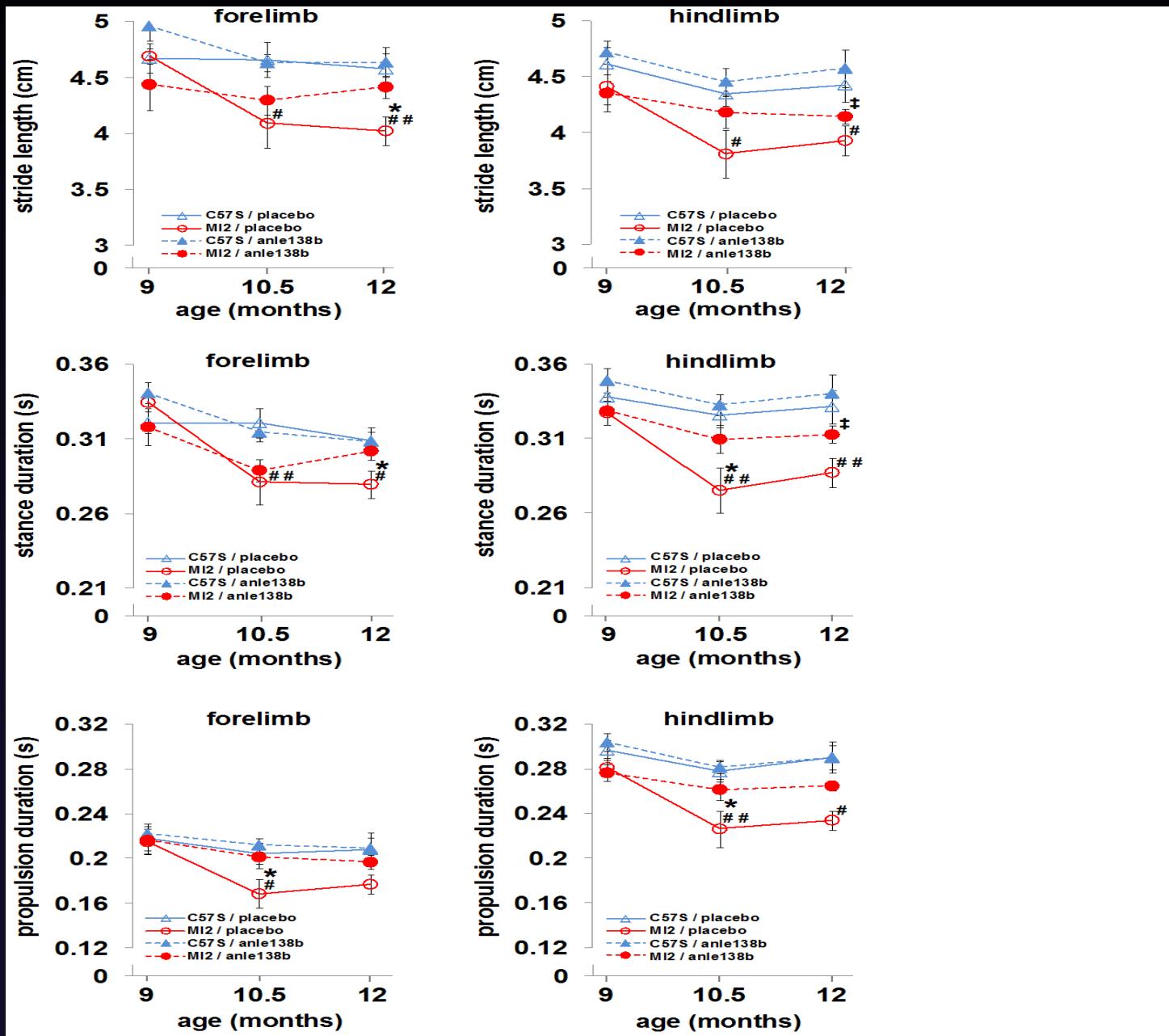
ORIGINAL PAPER

Anle138b: a novel oligomer modulator for disease-modifying therapy of neurodegenerative diseases such as prion and Parkinson's disease

Jens Wagner · Sergey Ryazanov · Andrei Leonov · Johannes Levin · Song Shi · Felix Schmidt · Catharina Prix · Francisco Pan-Montojo · Uwe Bertsch · Gerda Mittelregger-Kretzschmar · Markus Geissen · Martin Eiden · Fabienne Leidel · Thomas Hirschberger · Andreas A. Deeg · Julian J. Krauth · Wolfgang Zinth · Paul Tavan · Jens Pilger · Markus Zweckstetter · Tobias Frank · Matthias Bähr · Jochen H. Weishaupt · Manfred Uhr · Henning Urlaub · Ulrike Teichmann · Matthias Sammer · Kai Bötzelt · Martin Groschup · Hans Kretzschmar · Christian Griesinger · Armin Giese

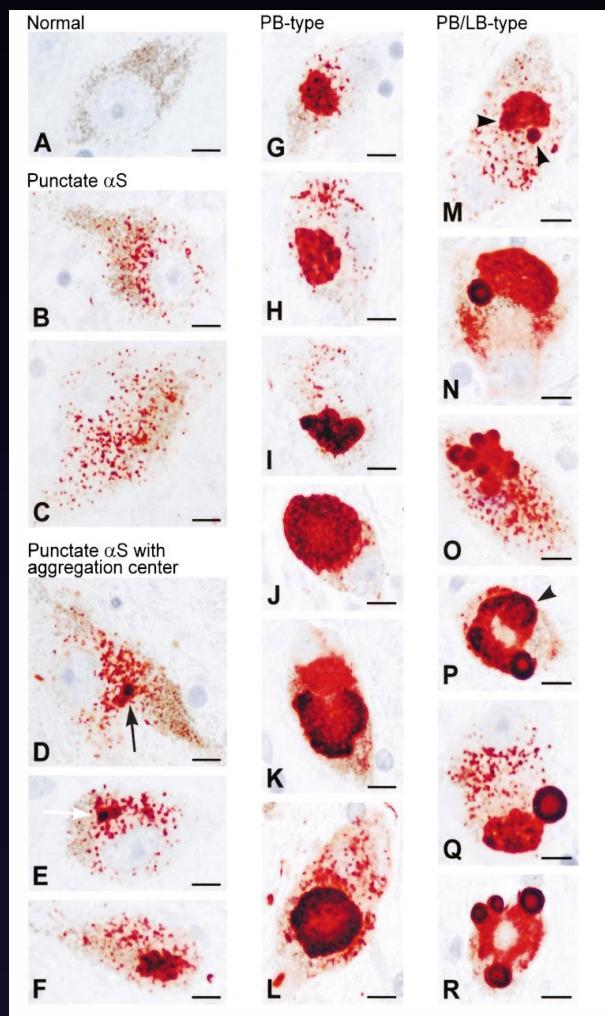


3 month-treatment with Anle138b rescues gait impairment in MI2 mice



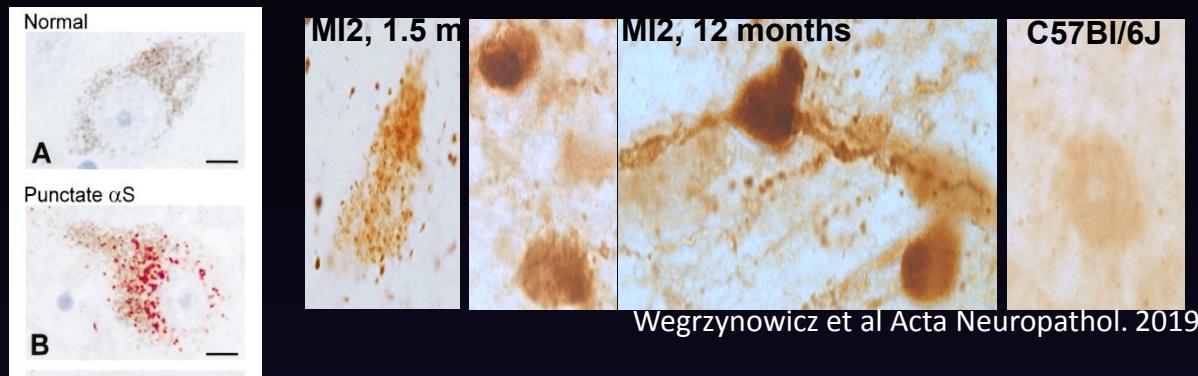
Comparison of Synuclein aggregates in SN of human brain, transgenic mice Human iPSC-derived neurons

Parkinson's human brain



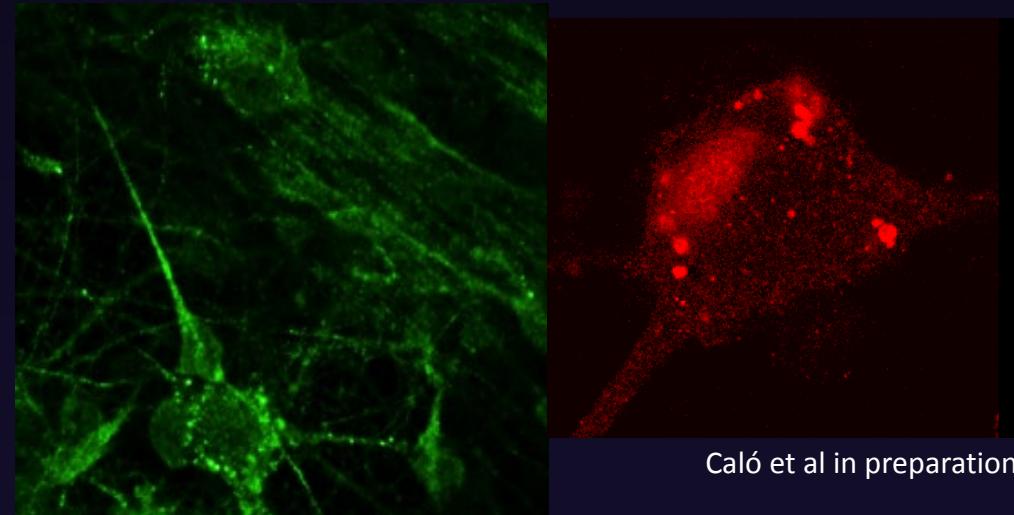
Kuusisto et al. 2003

MI2 transgenic mice



Wegrzynowicz et al Acta Neuropathol. 2019

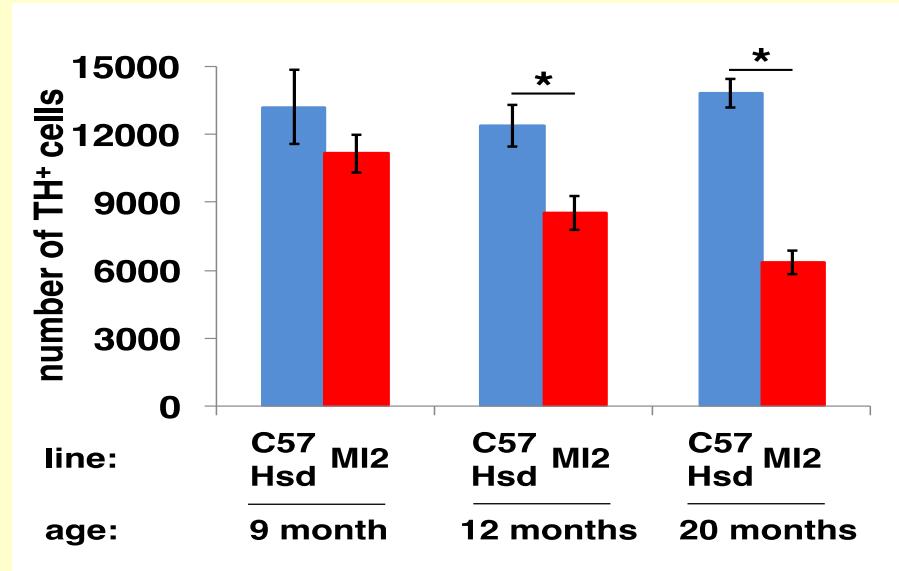
Neurons from IPSC with SNCA triplication



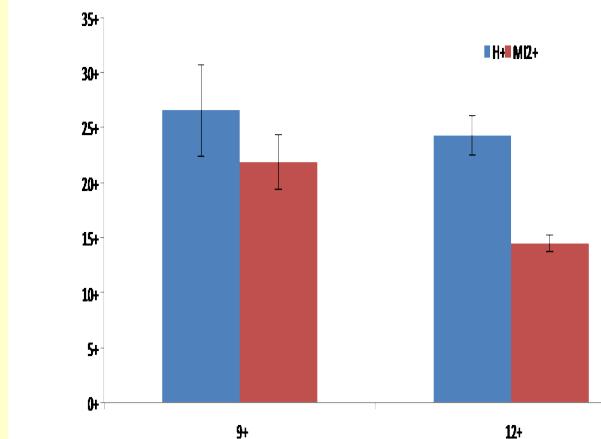
Caló et al in preparation

Whiten et 2018

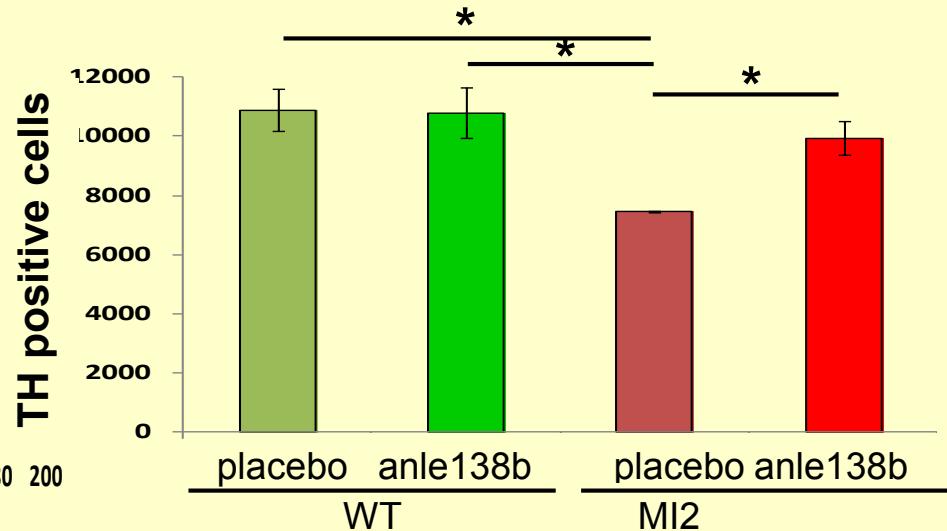
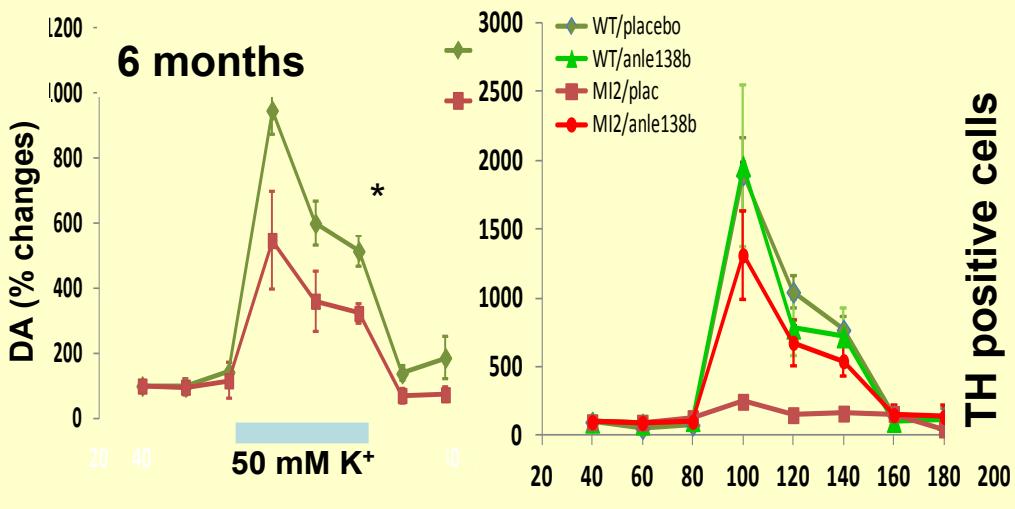
Timing of DA neuron dysfunction and death in MI2 mice



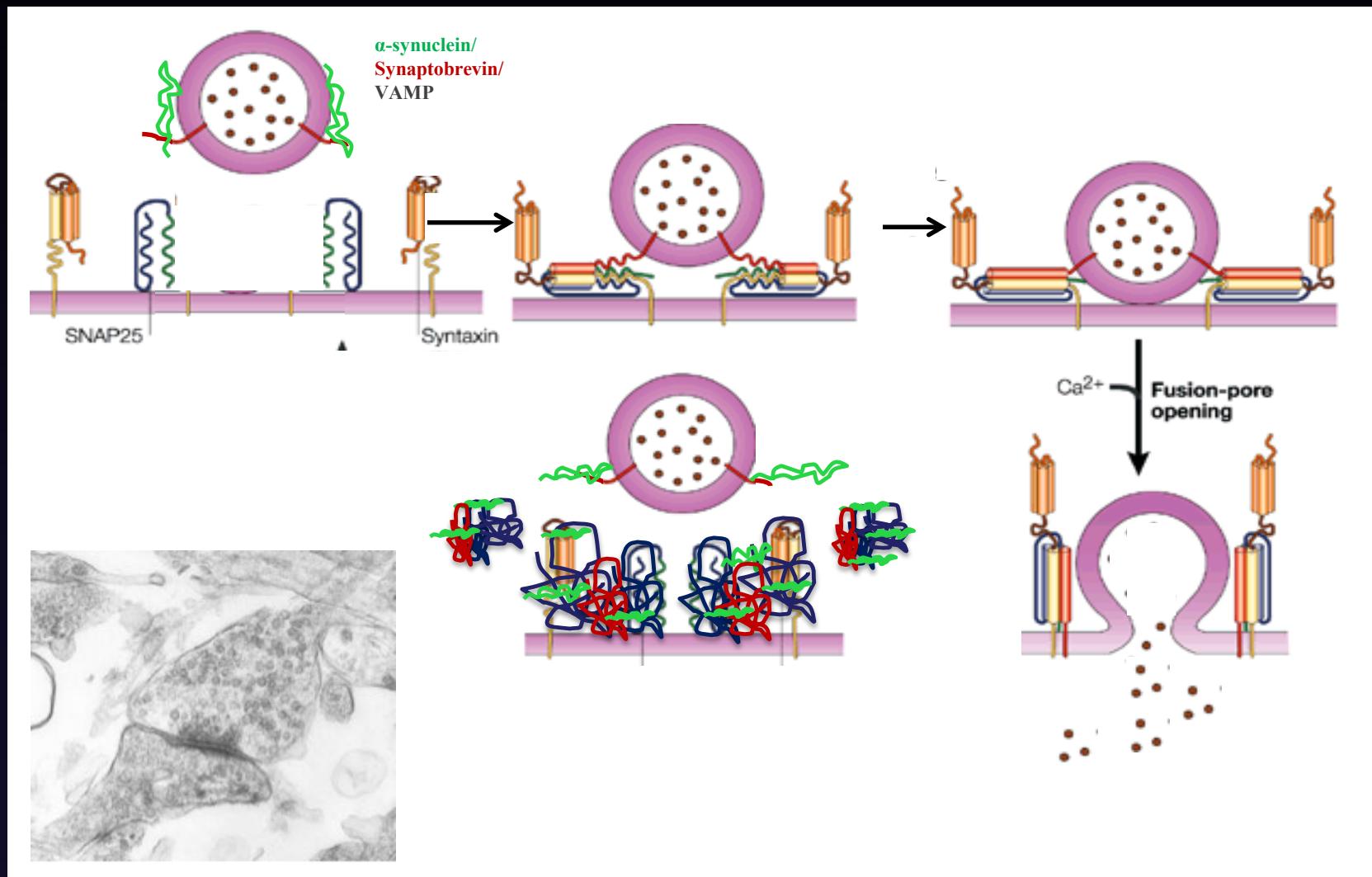
TH⁺ neurites are progressively reduced in striatum of MI2 mice



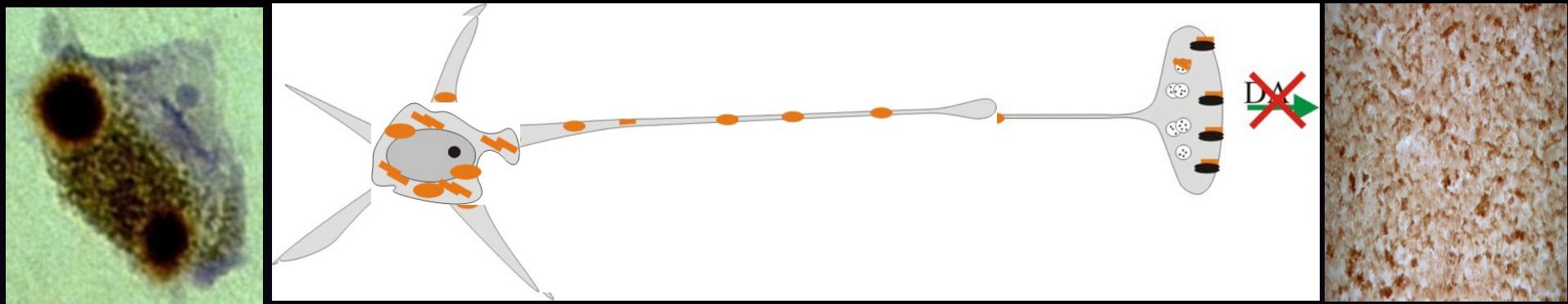
Alterations of DA induced release in striatum are rescued by Anle prevents neuronal death



Alpha-synuclein aggregates disrupt neurotransmitter release in striatal terminals



(JBC 2002)



Conclusions

Overexpression of α -synuclein or its post-translational modifications or mutations lead to its redistribution and aggregation at the synapse with consequent redistribution of SNARE proteins and abnormal dopamine release.

In α -synucleinopathies and alpha-synuclein transgenic mice alteration of synaptic function and dopamine release is an initial event in the pathological process.

Parkinson's disease is a dyeing back pathology starting at the synapse and pale bodies/ Lewy bodies presence could be indicators that a pathological process is taking place in that neuron and they could represent a marker of alpha-synuclein aggregation related synaptic dysfunction.

Michał Wegrzynowicz

Jack Brelstaff

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Methap Bacioglu

Aishwarya Nadadhur

Steven Fagan

Janine Brandes

Joana Domingues

Giorgio Vivacqua

Ellen Tetford

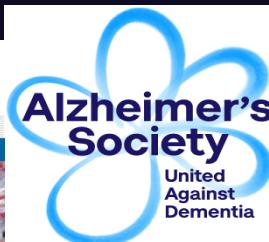
Helen Henson

Emma Carlson

Aviva Tolkovsky

George Tofaris-Oxford

Pablo Garcia Reitböck-UCL



Cambridge Biomedical Research Centre and Brain Bank, The Scholl Foundation

Munich University

Armin Giese

Max Plank Göttingen

Christian Griesinger

Andrei Leonov

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