Elucidating causative mechanisms and trying to slow Parkinson's disease progression

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National Medical Research Council of Singapore
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Today's talk

- What is Parkinson's disease (PD)?
- What are the causes of PD?
- Can new targets result in slower disease progression?
- Can better animal models help?
- Is drug repurposing one way forward?

Parkinson’s symptoms

- Motor symptoms (stiffness, slowness, tremor)
- Non-motor issues (depression, dementia, loss of sense of smell, constipation, sleep disorder, etc)
- Some symptoms precede motor symptoms by over a decade - “prodromal” Parkinson’s exists!

Parkinson's - societal impact

- 1 million US patients and 10 million worldwide
- $25 billion cost annually in US alone

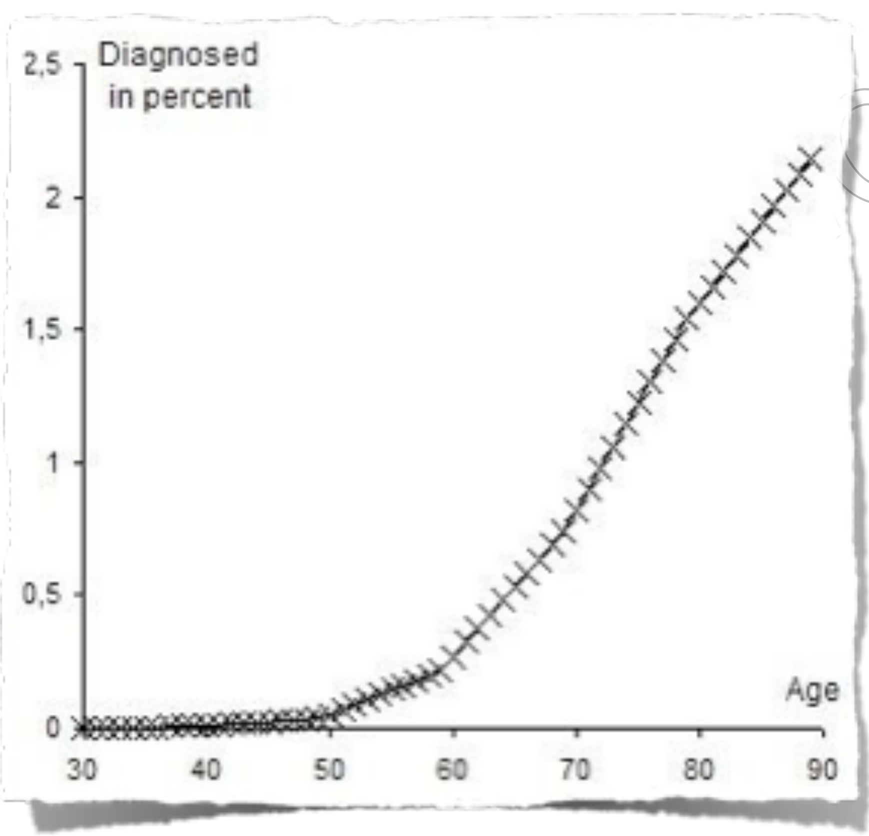
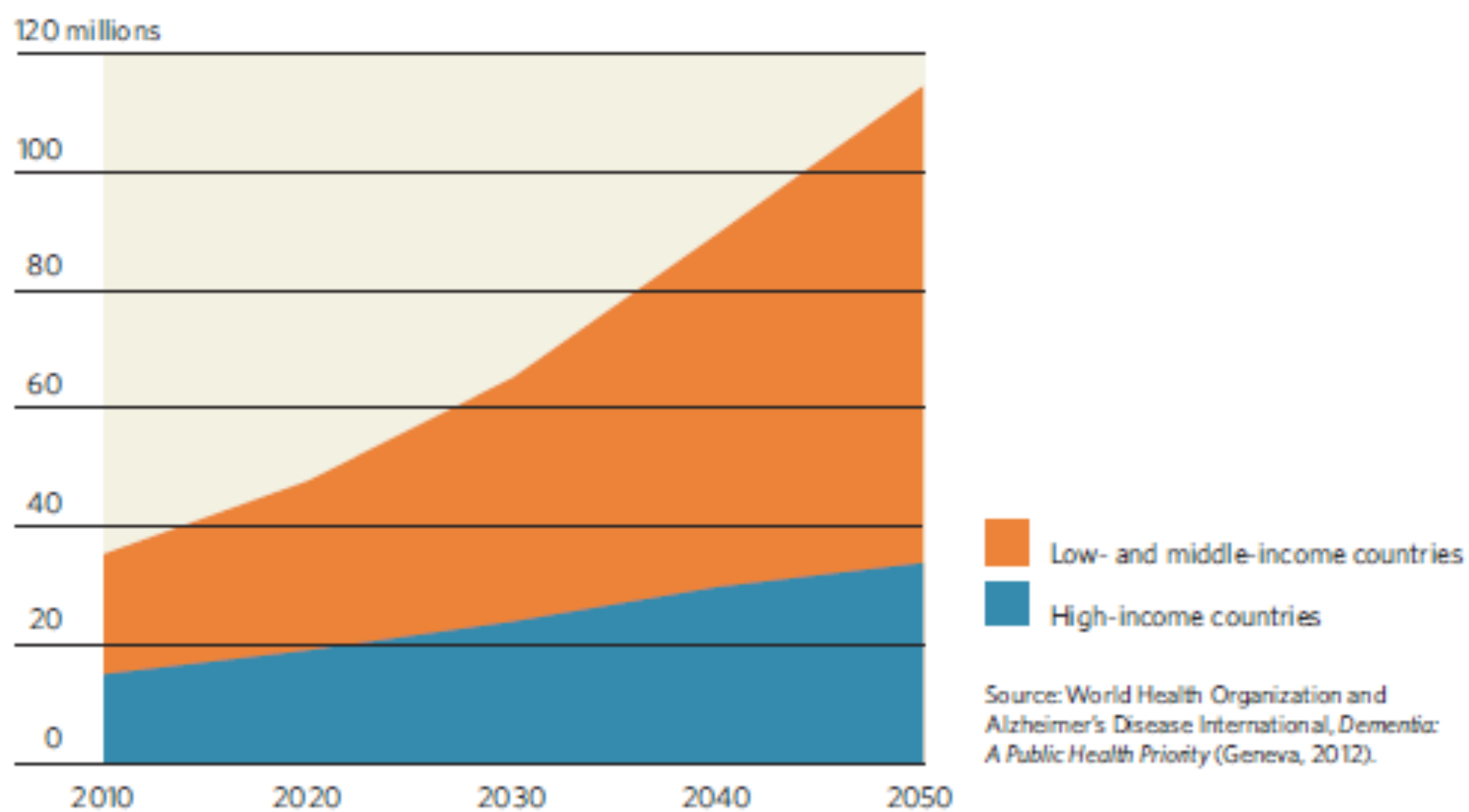
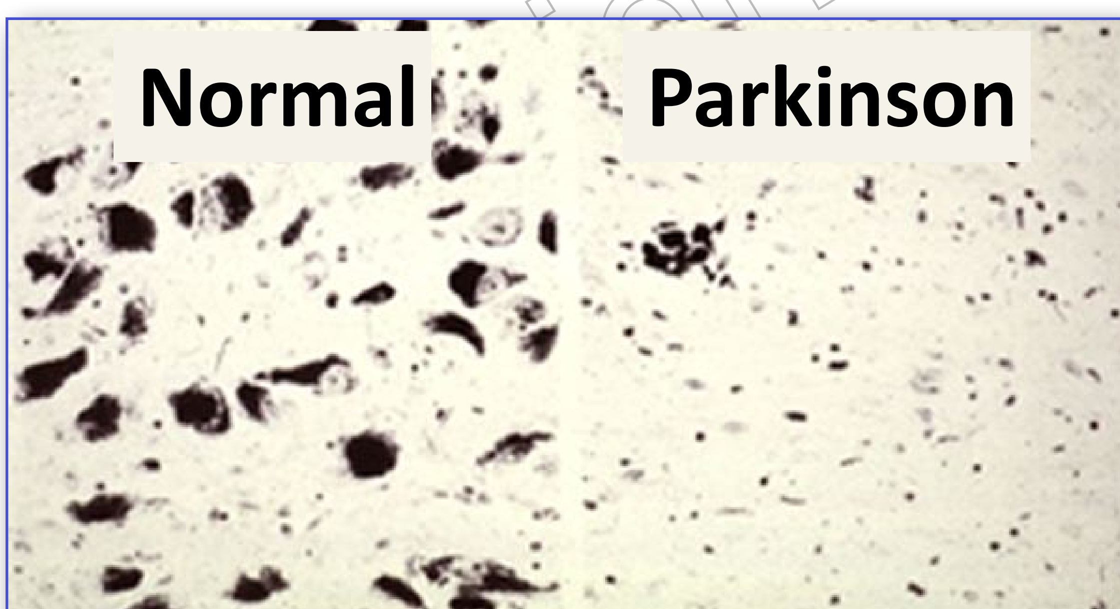


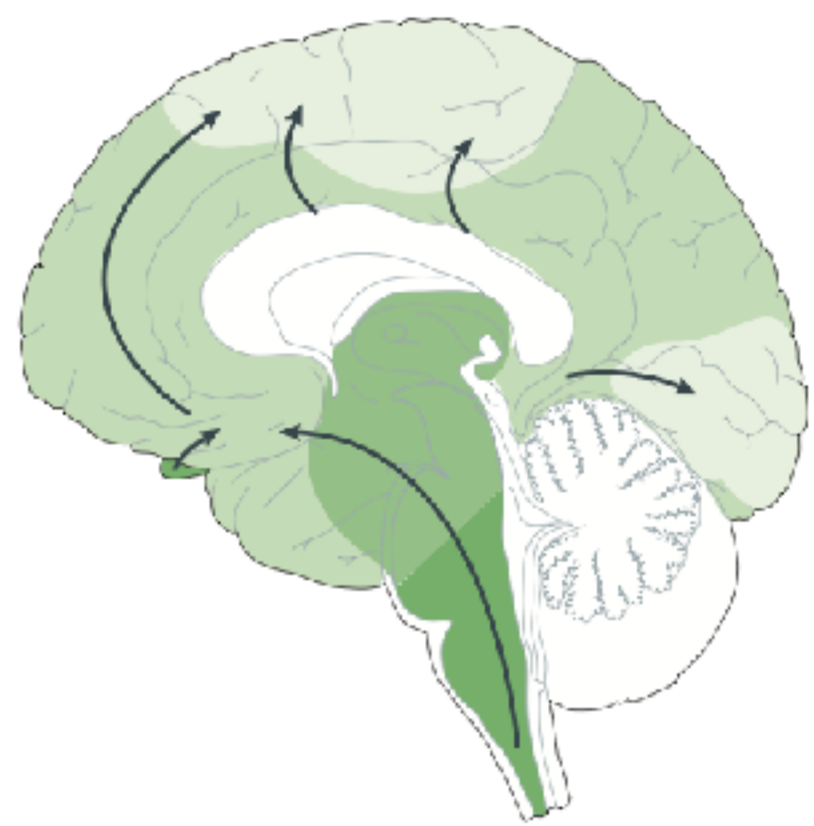
Figure 5: Growth in numbers of people with dementia in high-income and low- and middle-income countries



Parkinson’s pathology

- Death of dopamine neurons is key to motor symptoms
- Lewy bodies (protein aggregates) a salient feature
- Many brain regions are progressively affected





Unmet medical needs

- Dopamine-replacement therapies treat motor symptoms well for several years
- Non-motor symptoms lack effective therapies
- No therapies effectively slow PD progression

Do we need to know the cause(s) of PD?

Four approaches to disease-modifying therapy:

- Identify the root cause, and fix it
- Target an "intermediary step" in the disease process
- Guess the cause, and target it
- Fire a shotgun, pray, and hope you hit something!

Overview of targets for disease-modification

Neuroinflammation

Protein aggregation

Energy deficiency

Oxidative stress

Overview of targets for disease-modification

Energy deficiency

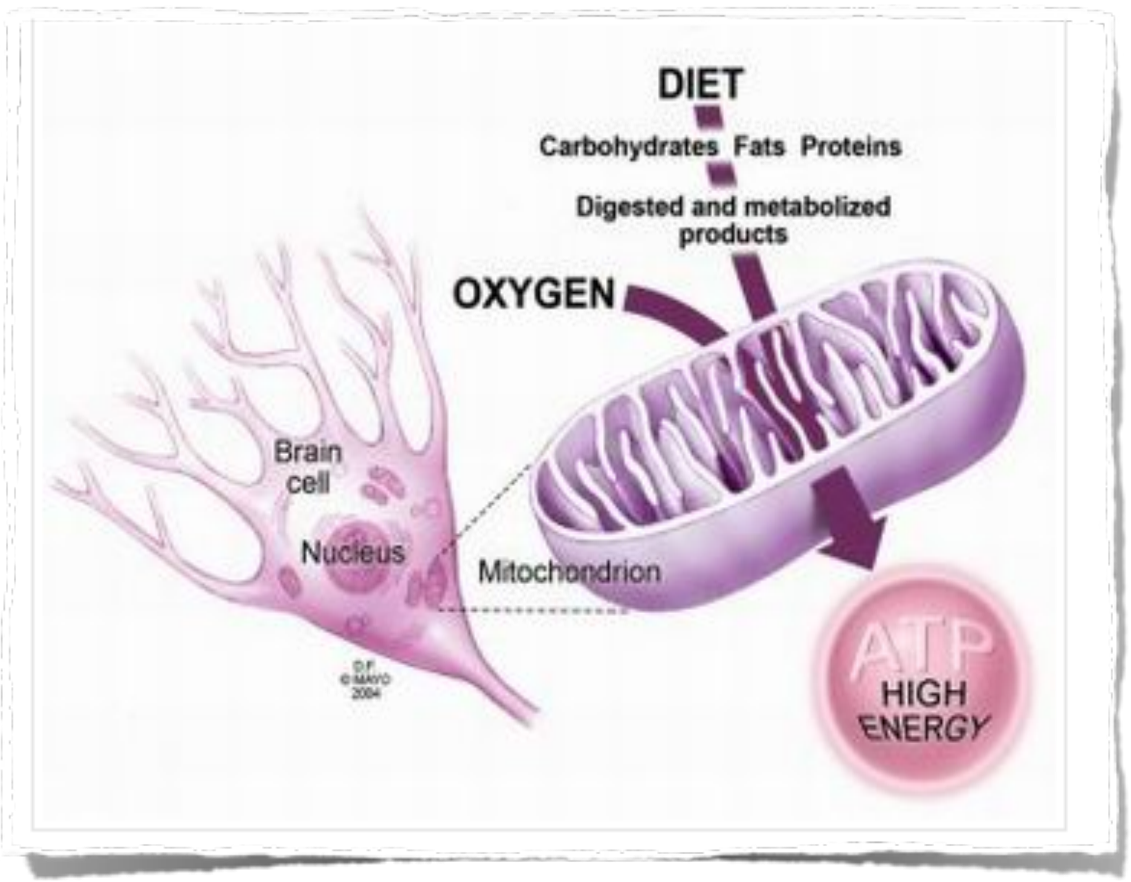
Oxidative stress

Protein aggregation

Neuroinflammation

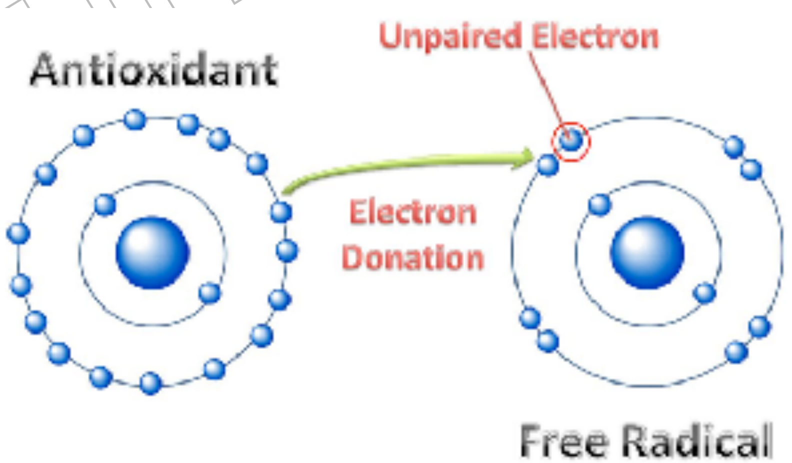
Energy deficiency and oxidative stress

- Gene expression changes implicate energy metabolism
- Rare mutations linked to mitochondria cause PD
- Mitochondrial toxins cause PD-like changes
- Free radical stress - byproduct of mitochondrial failure?



Energy deficiency and oxidative stress

- Reduce free radical stress
  - Consult your local health care store…
  - Glutathione



- Improve mitochondrial function
  - Pioglitazone
  - Exenatide

Treating energy deficits

doi:10.1093/brain/aws009

Brain 2012: Page 1 of 11 | 1

BRAIN
A JOURNAL OF NEUROLOGY

REVIEW ARTICLE

Parkinson's disease, insulin resistance and novel agents of neuroprotection

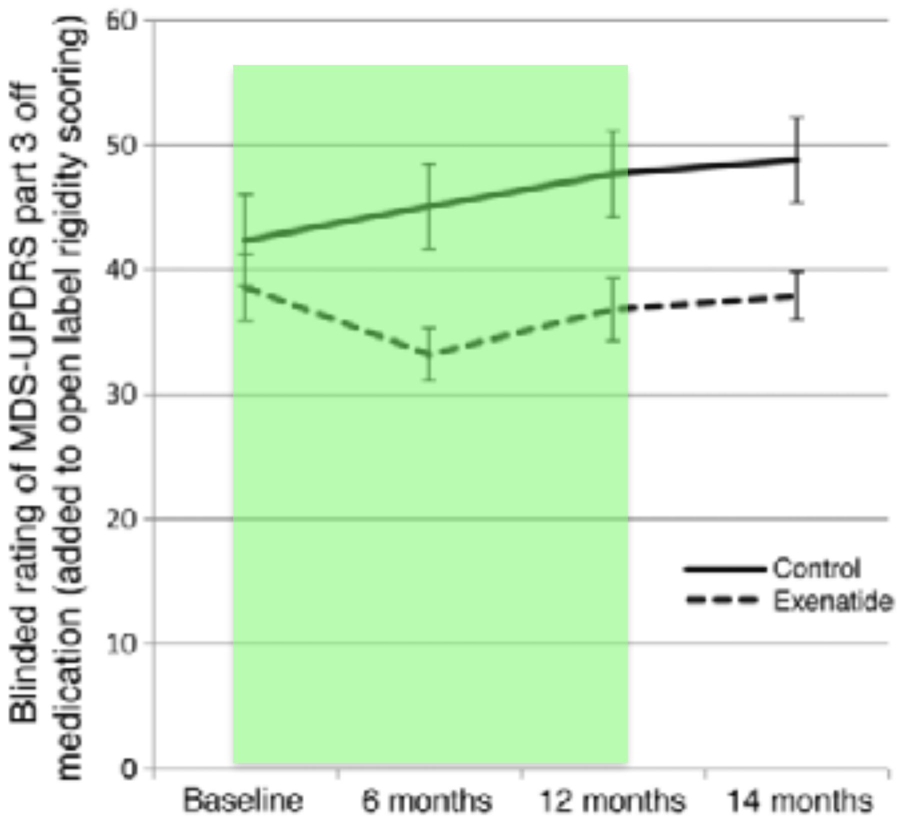
Iciar Aviles-Olmos,[1] Patricia Limousin,[1] Andrew Lees[2] and Thomas Foltynie[1]

Treating energy deficits

Exenatide and the treatment of patients with Parkinson's disease

Iciar Aviles-Olmos,[1] John Dickson,[2] Zinovia Kefalopoulou,[1] Atbin Djamshidian,[3] Peter Ell,[2] Therese Soderlund,[2] Peter Whitton,[4] Richard Wyse,[5] Tom Isaacs,[5] Andrew Lees,[3] Patricia Limousin,[1] and Thomas Foltynie[1]

J Clin Invest 2013



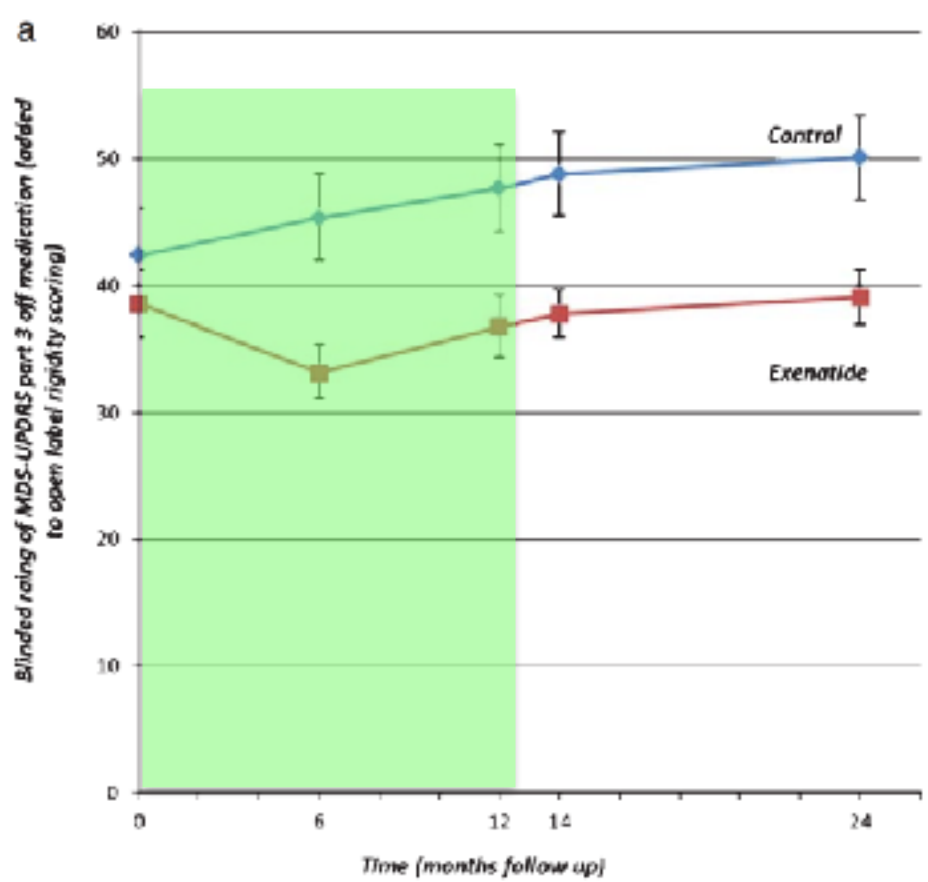
Treating energy deficits

Journal of Parkinson's Disease 4 (2014) 337–344
DOI 10.3233/JPD-140364
IOS Press

Research Report

Motor and Cognitive Advantages Persist 12 Months After Exenatide Exposure in Parkinson's Disease

Iciar Aviles-Olmos[a], John Dickson[b], Zinovia Kefalopoulou[a], Atbin Djamshidian[c], Joshua Kahan[a], Peter Ell[b], Peter Whitton[d], Richard Wyse[e], Tom Isaacs[e], Andrew Lees[c], Patricia Limousin[a] and Thomas Foltynie[a,*]



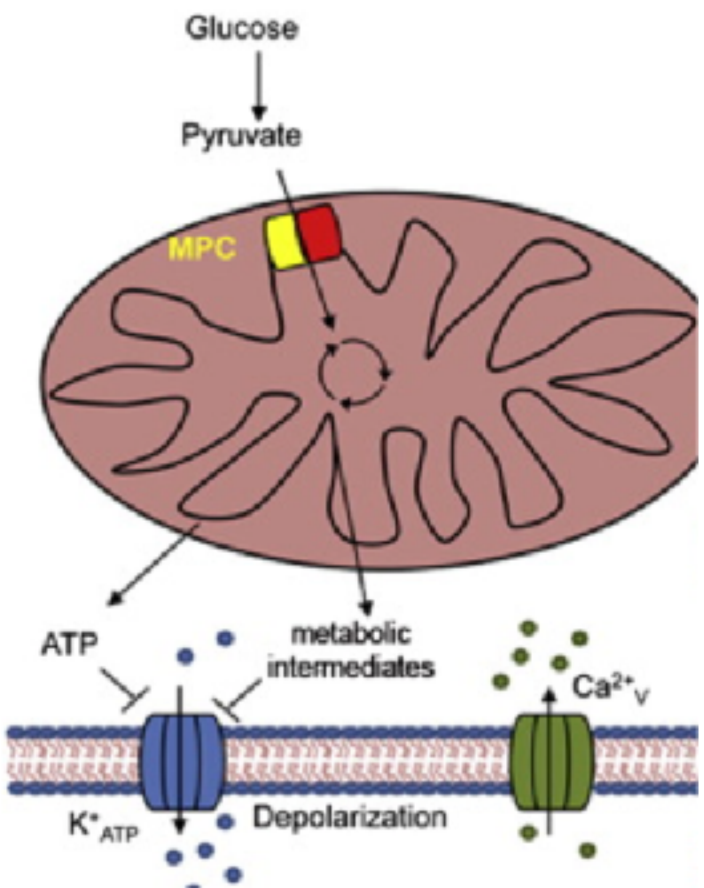
Treating energy deficits

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

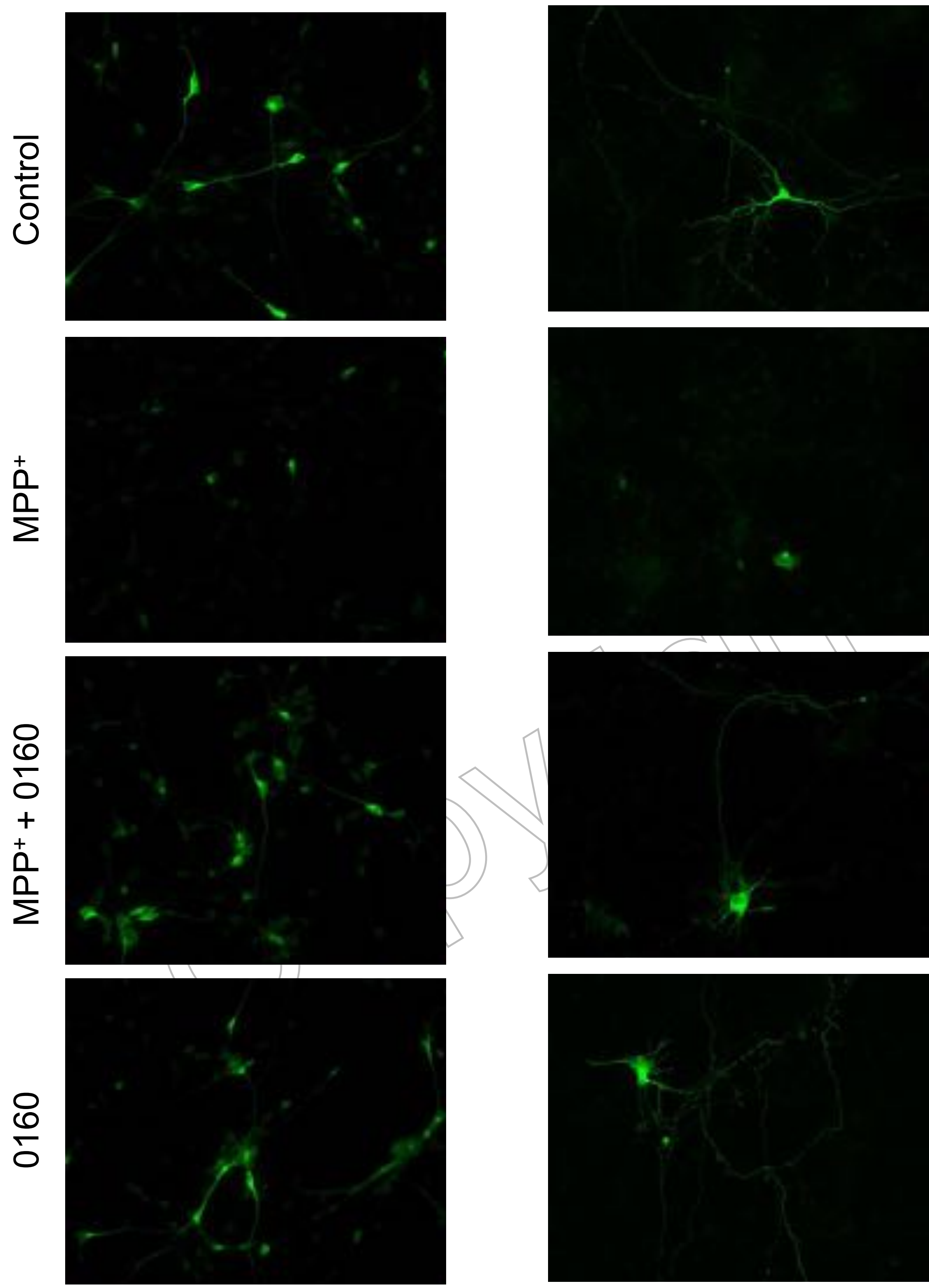
PARKINSON'S DISEASE

Mitochondrial pyruvate carrier regulates autophagy, inflammation, and neurodegeneration in experimental models of Parkinson's disease

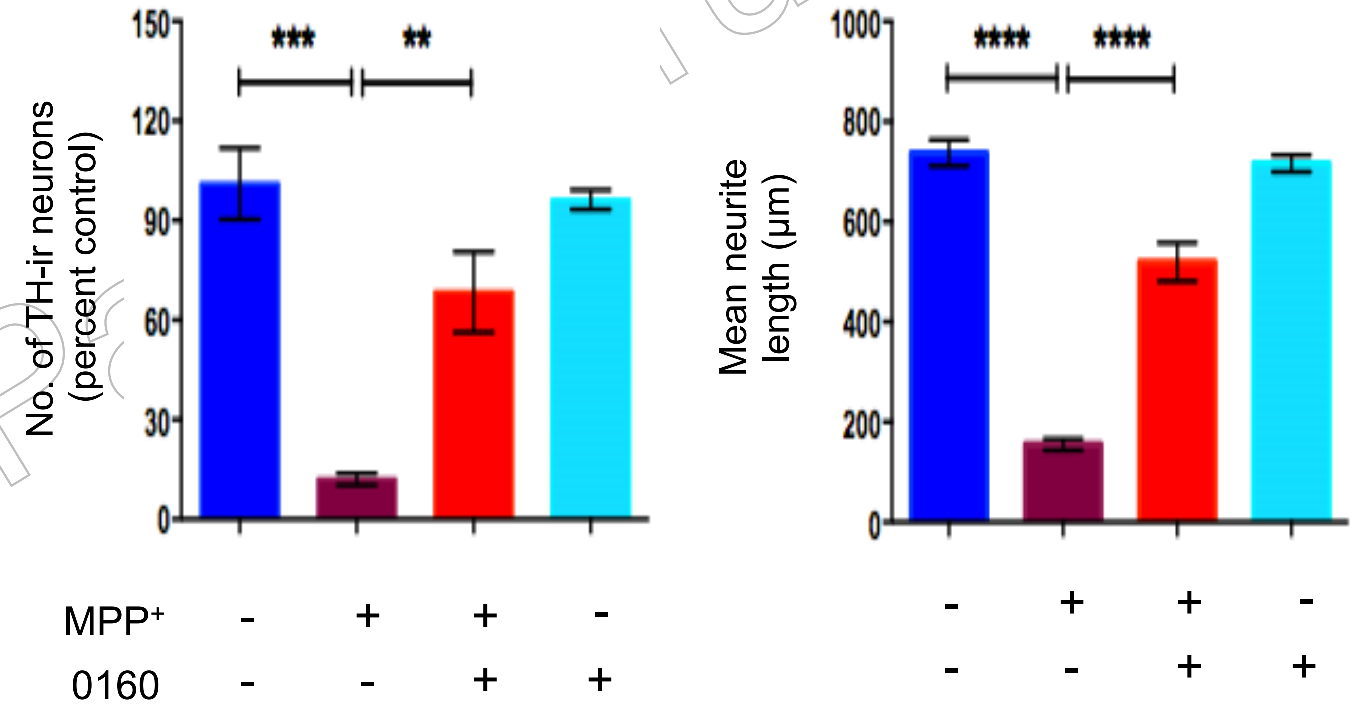
Anamitra Ghosh,[1] Trevor Tyson,[1] Sonia George,[1] Erin N. Hildebrandt,[1] Jennifer A. Steiner,[1] Zachary Madaj,[2] Emily Schulz,[1] Emily Machiela,[1] William G. McDonald,[3] Martha L. Escobar Galvis,[1] Jeffrey H. Kordower,[1,4] Jeremy M. Van Raamsdonk,[1] Jerry R. Colca,[3] Patrik Brundin[1]*

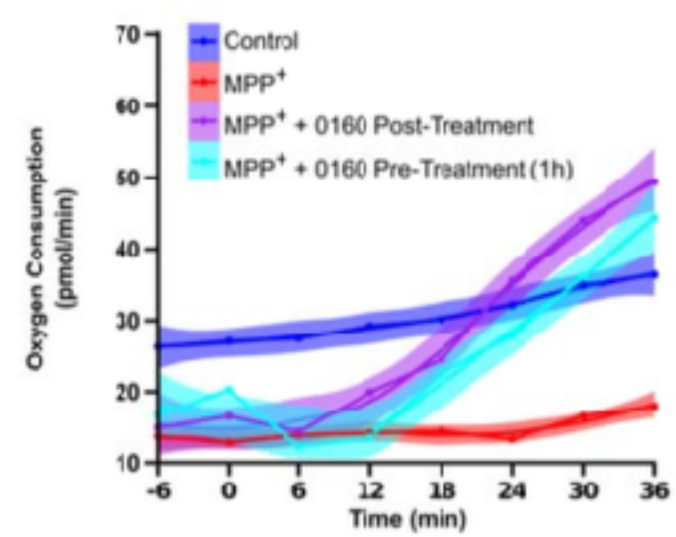


MSDC-0160 (MPC modulator) protects cultured human dopamine neurons



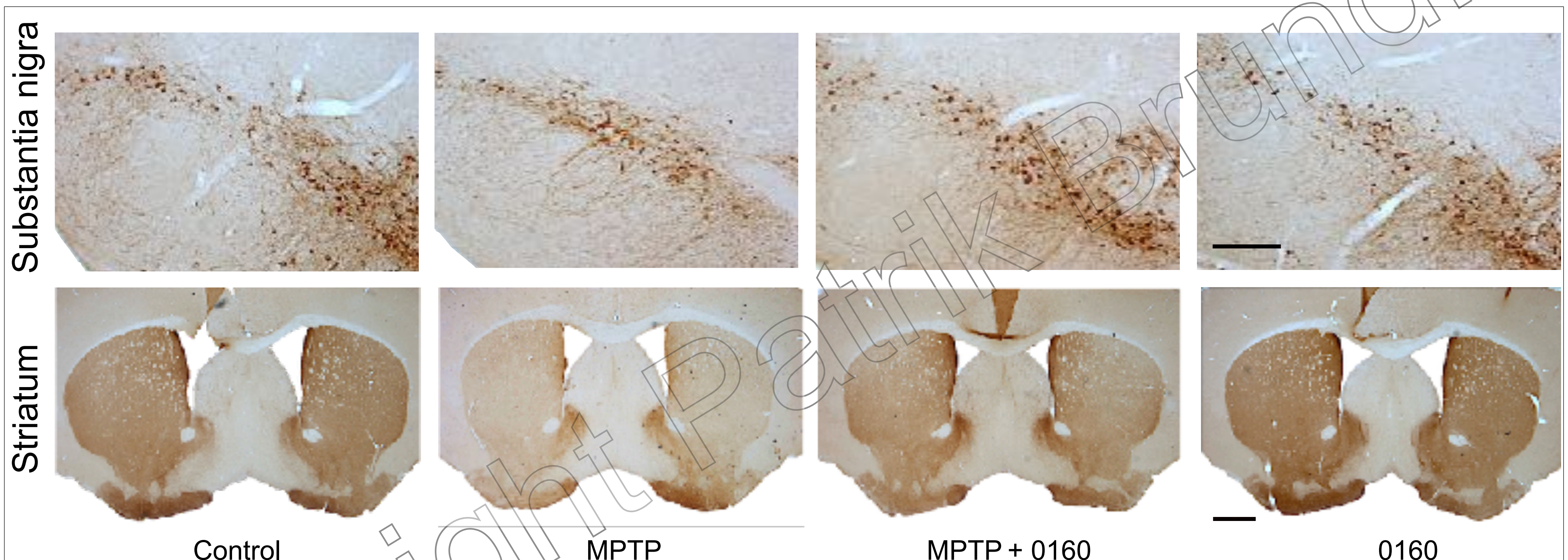
Human dopamine neurons



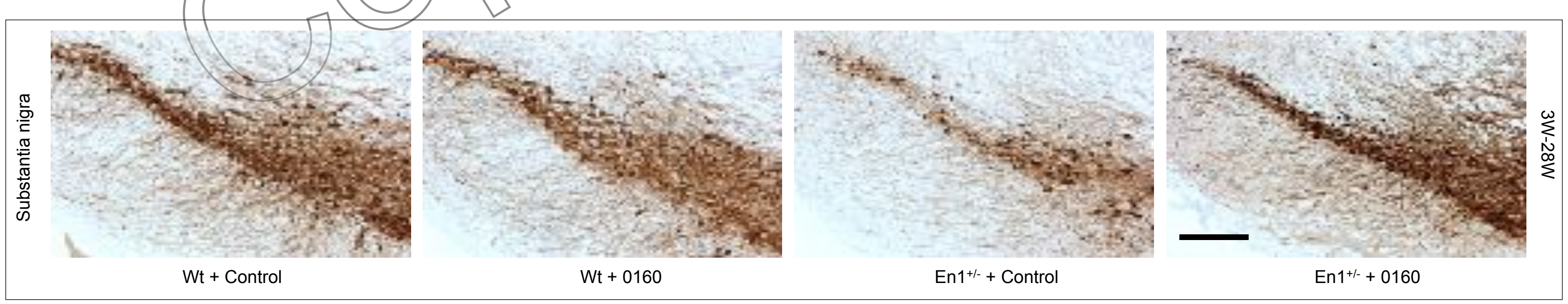


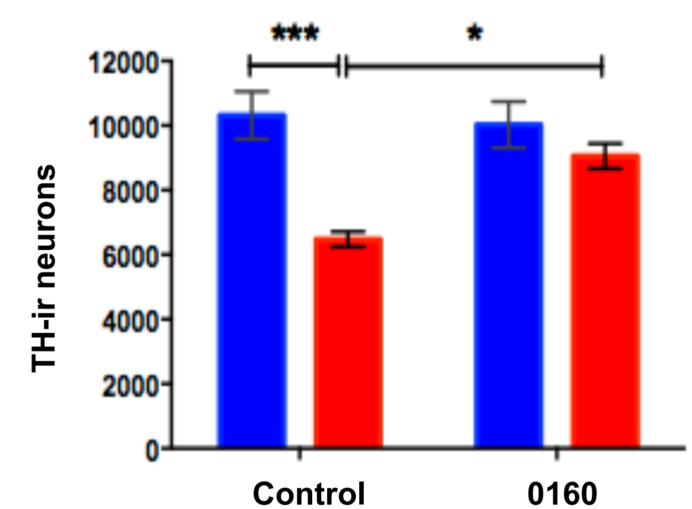
Ghosh et al 2016

MSDC-0160 protects dopamine neurons in mouse PD models



MPTP





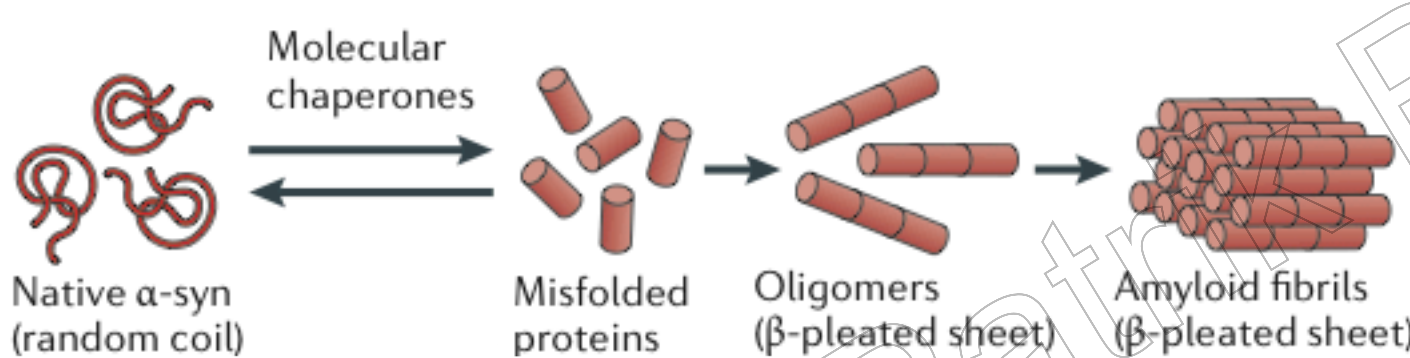
Engrailed1 +/-

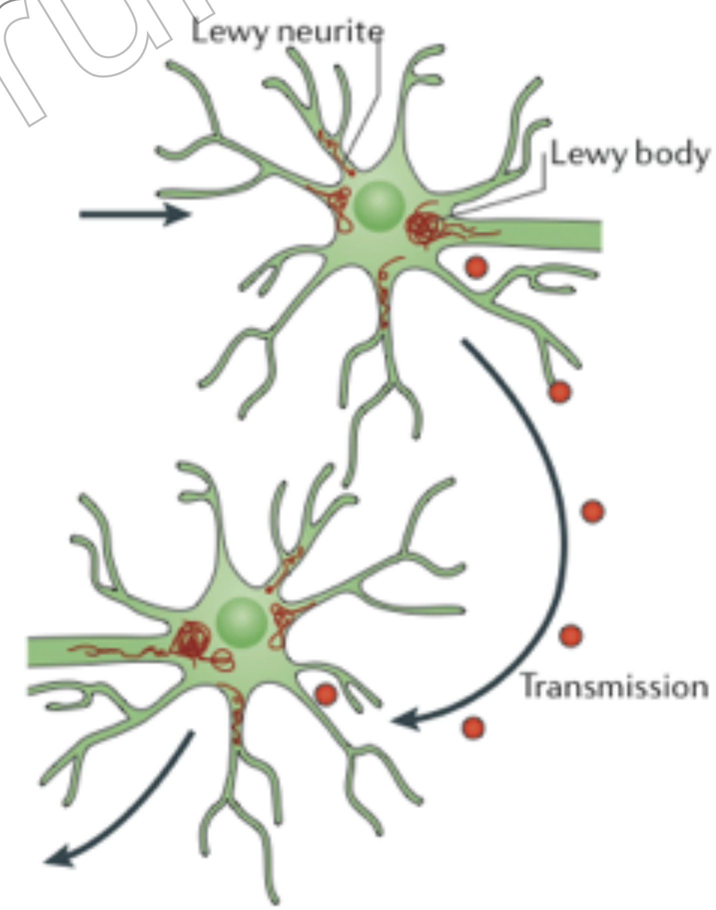
Ghosh et al 2016

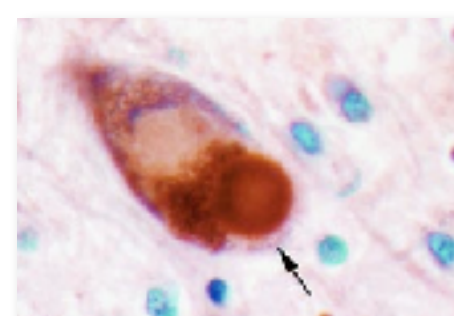
Protect against bad proteins?

Protect against proteins aggregates

α-synuclein - the bad guy





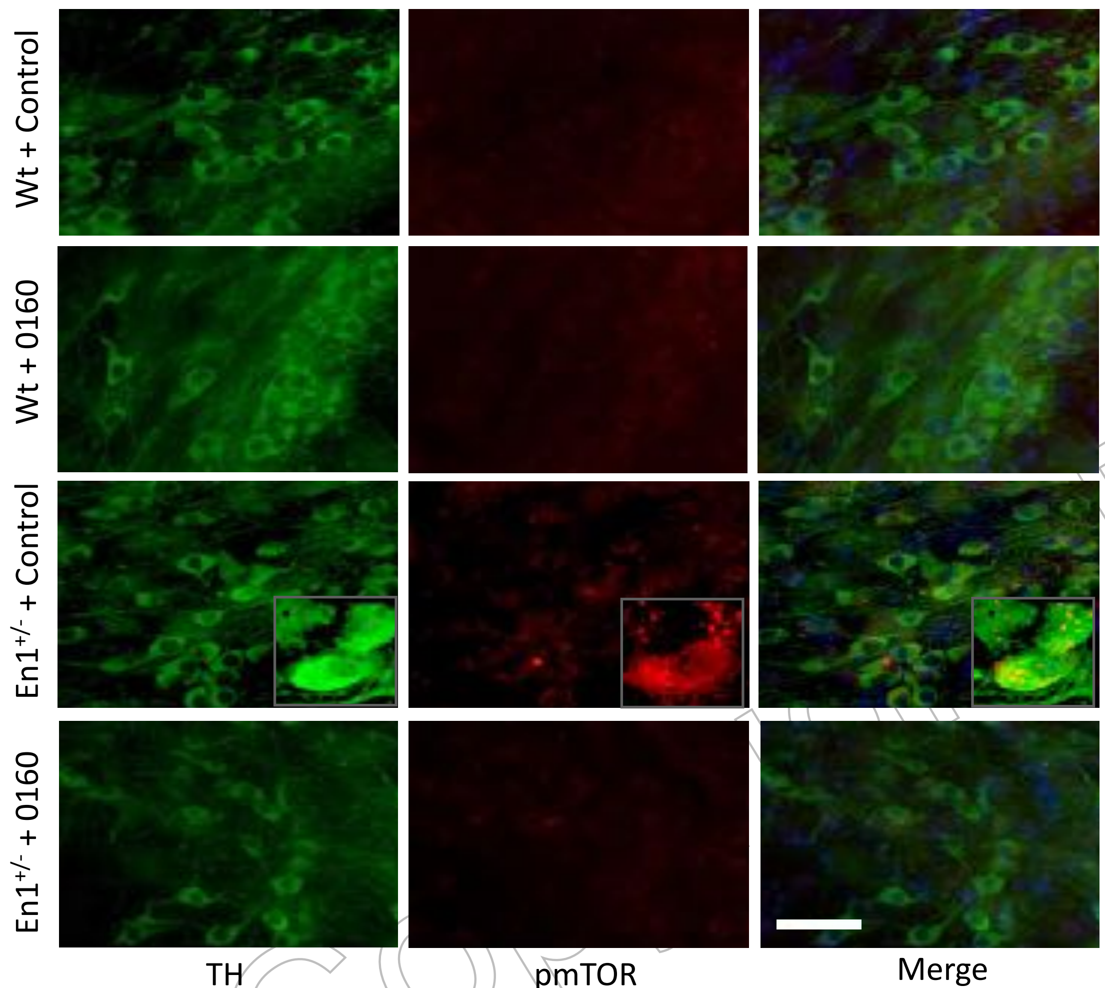


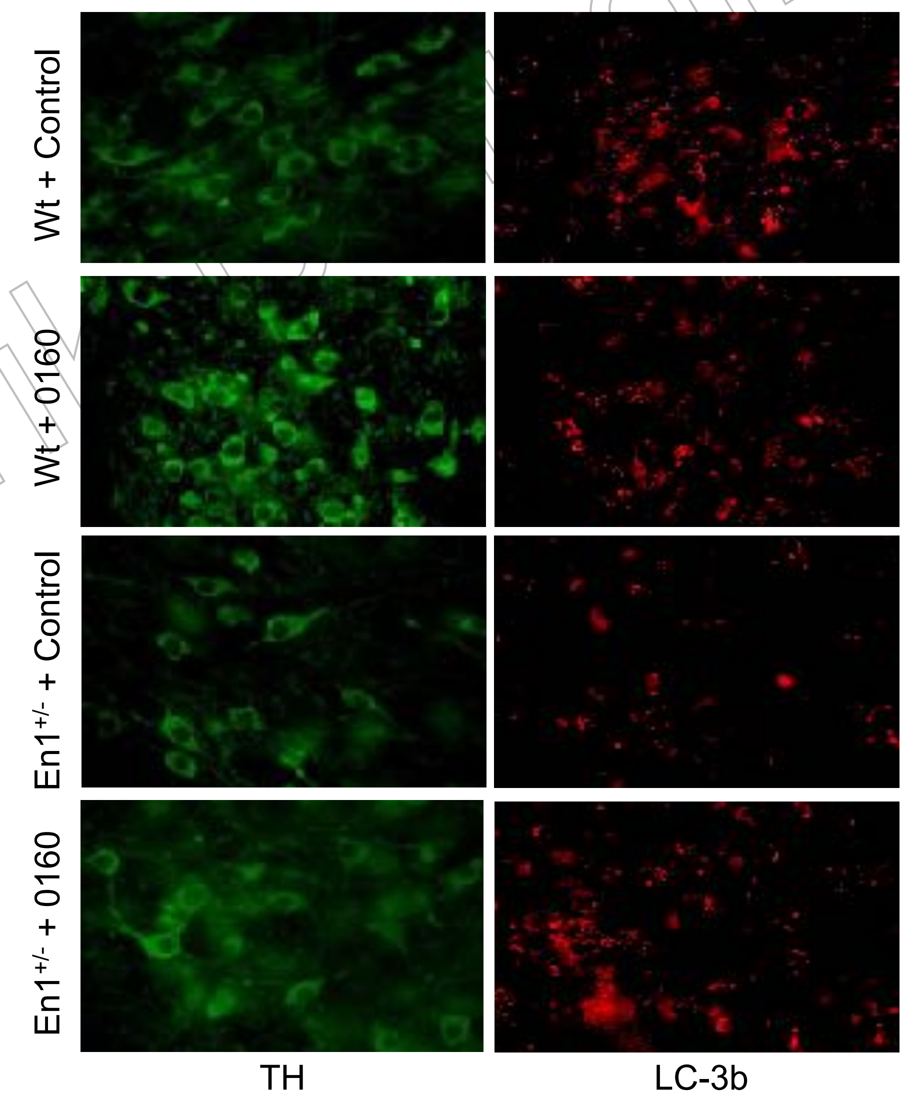
Lewy body

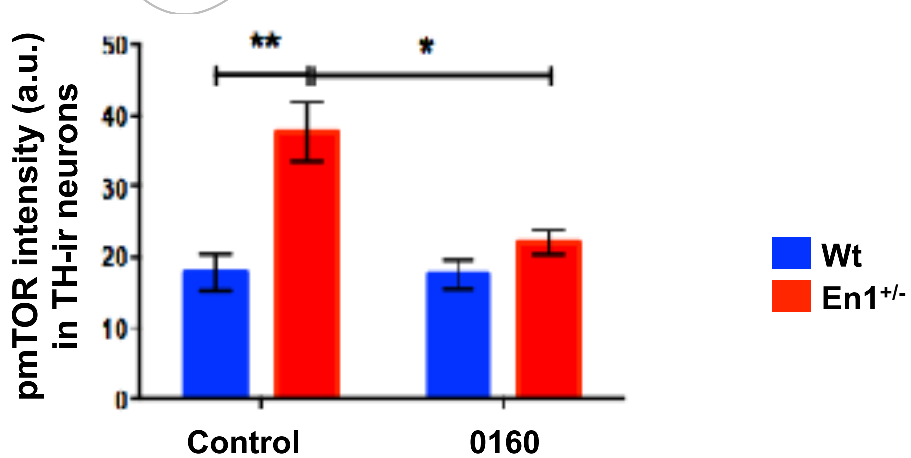
Irwin et al 2013

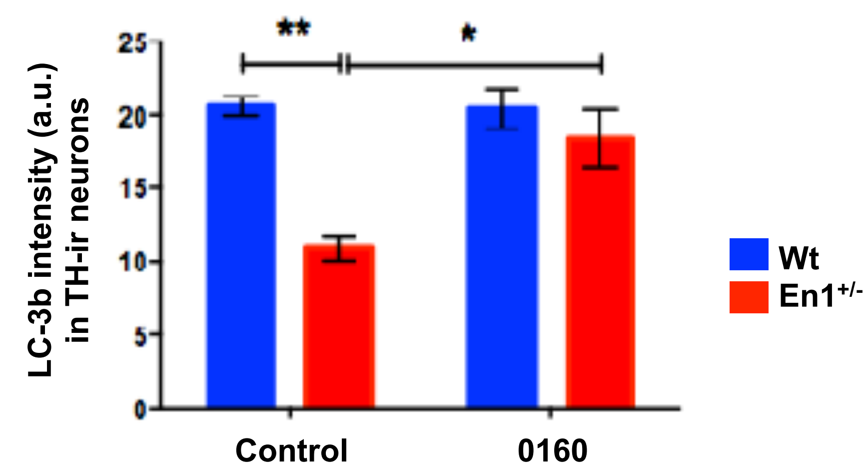
MSDC-0160 normalises autophagy in mouse PD model

Ghosh et al 2016

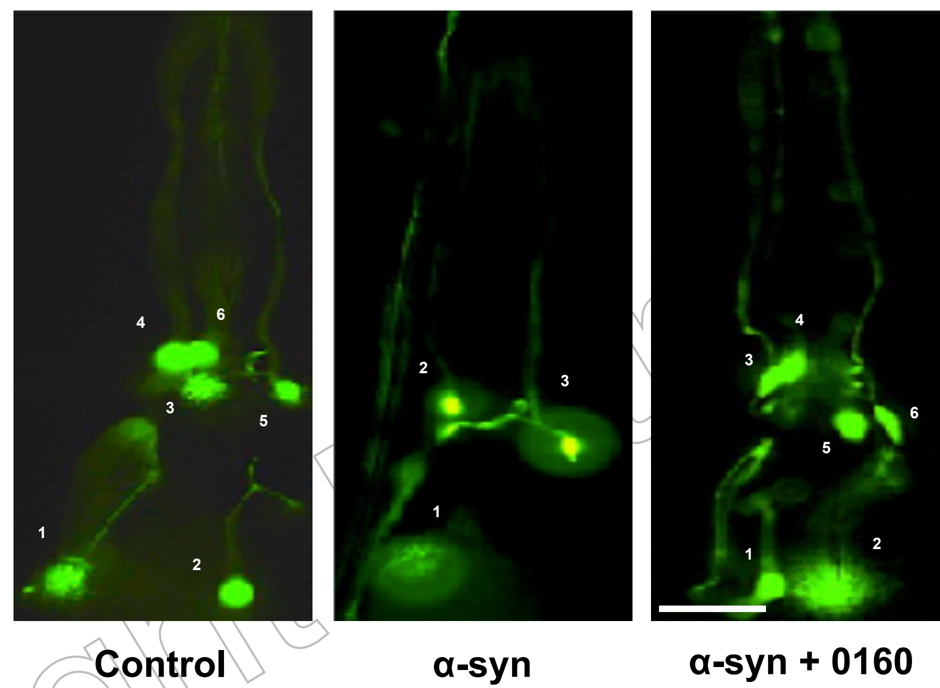


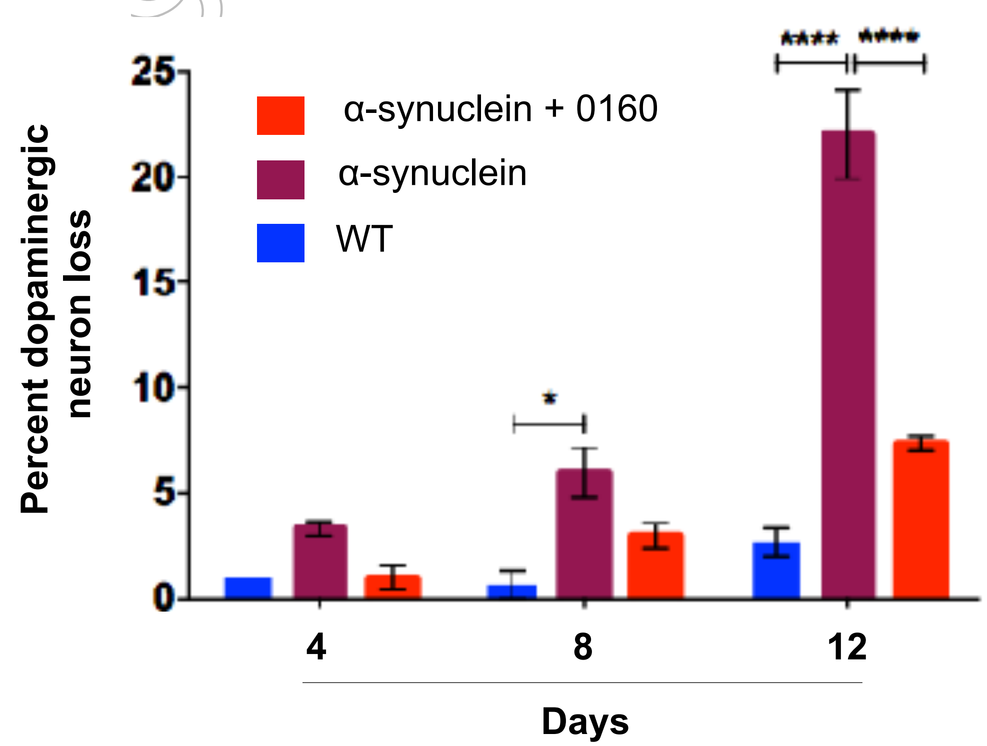






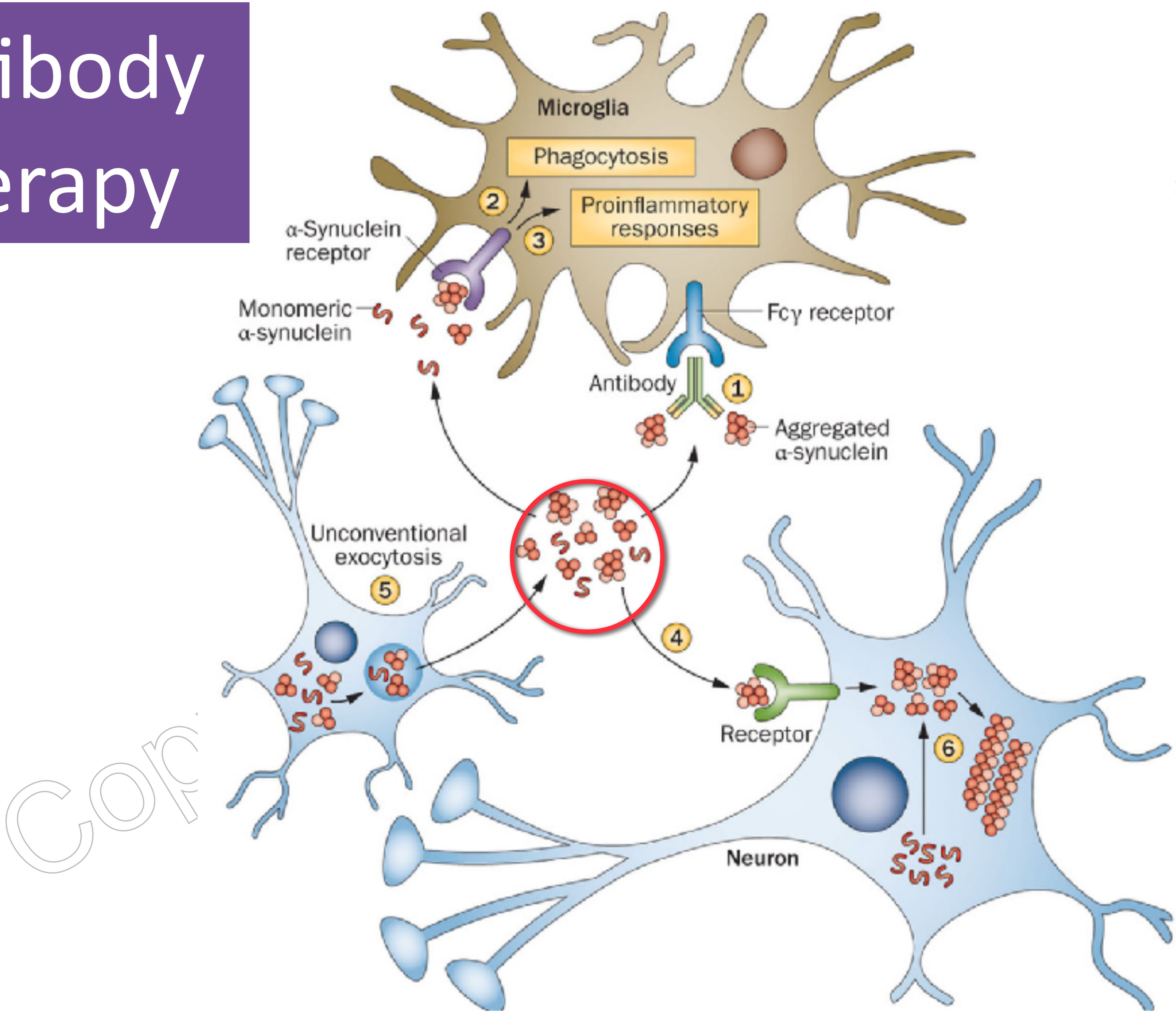
MSDC-0160 reduces α-synuclein accumulation in worm PD model





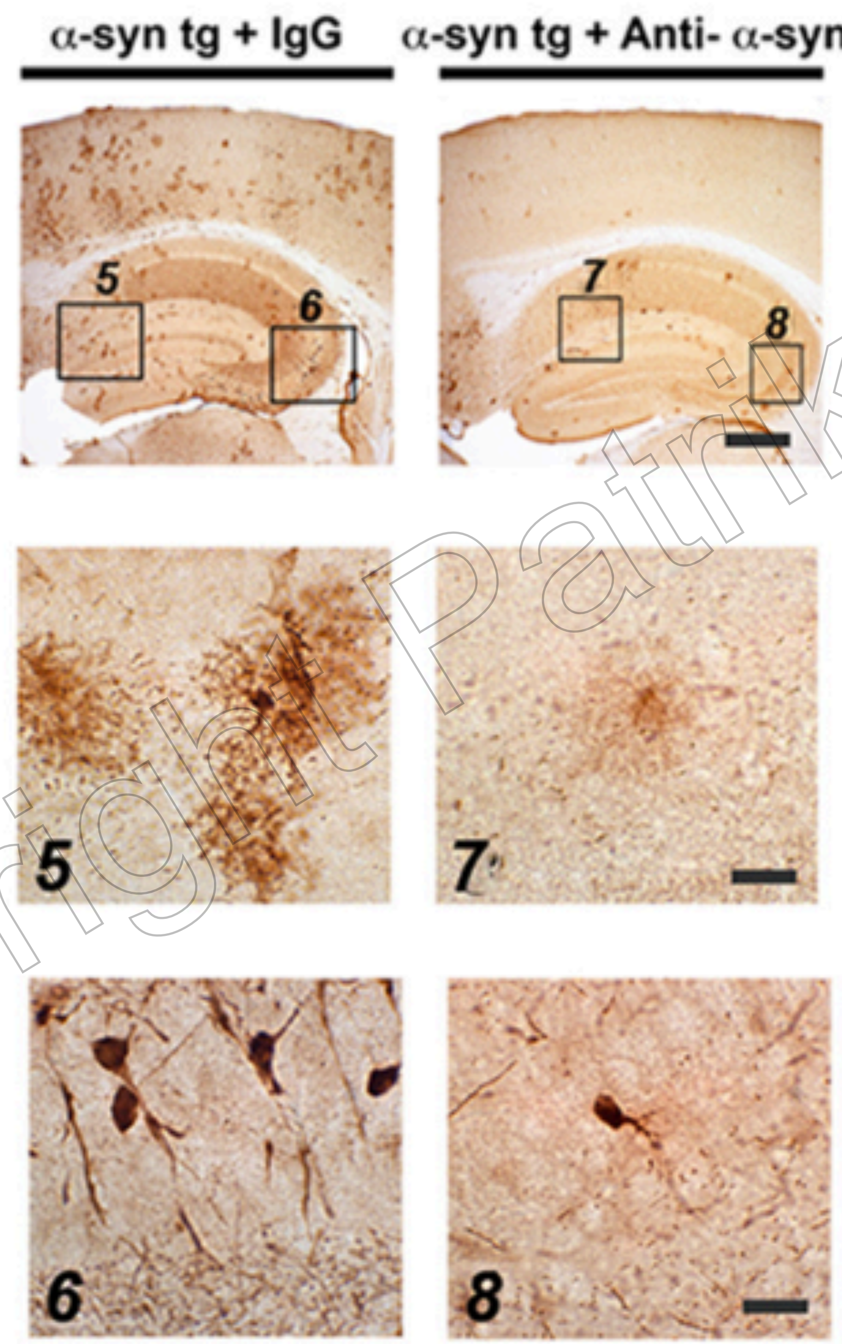
Ghosh et al 2016

Antibody therapy



Bae et al 2014, Nat Rev Neurol

Injection of antibodies against α-synuclein



Reduces α-synuclein aggregates in brain cells

Bae et al 2012

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

prothena®

Mar 19, 2015

- **PD01A was Safe and Well Tolerated: Prim...**
- **Immune Response was S... Rate after ...**

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

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*]

...ry Objective of Phase 1 Single Ascending Dose

...duction of Free Serum Alpha-Synuclein, Potential Disease-

... -- Prothena Corporation plc (Nasdaq:PRTA), a late-stage clinical biotechnology company ...mercialization of novel protein immunotherapy programs, today announced positive results ...dy of PRX002, a monoclonal antibody for the potential treatment of Parkinson's disease and other ...is the focus of a worldwide collaboration between Prothena and Roche.

The Michael J. ... $1.5 million grant, and ...

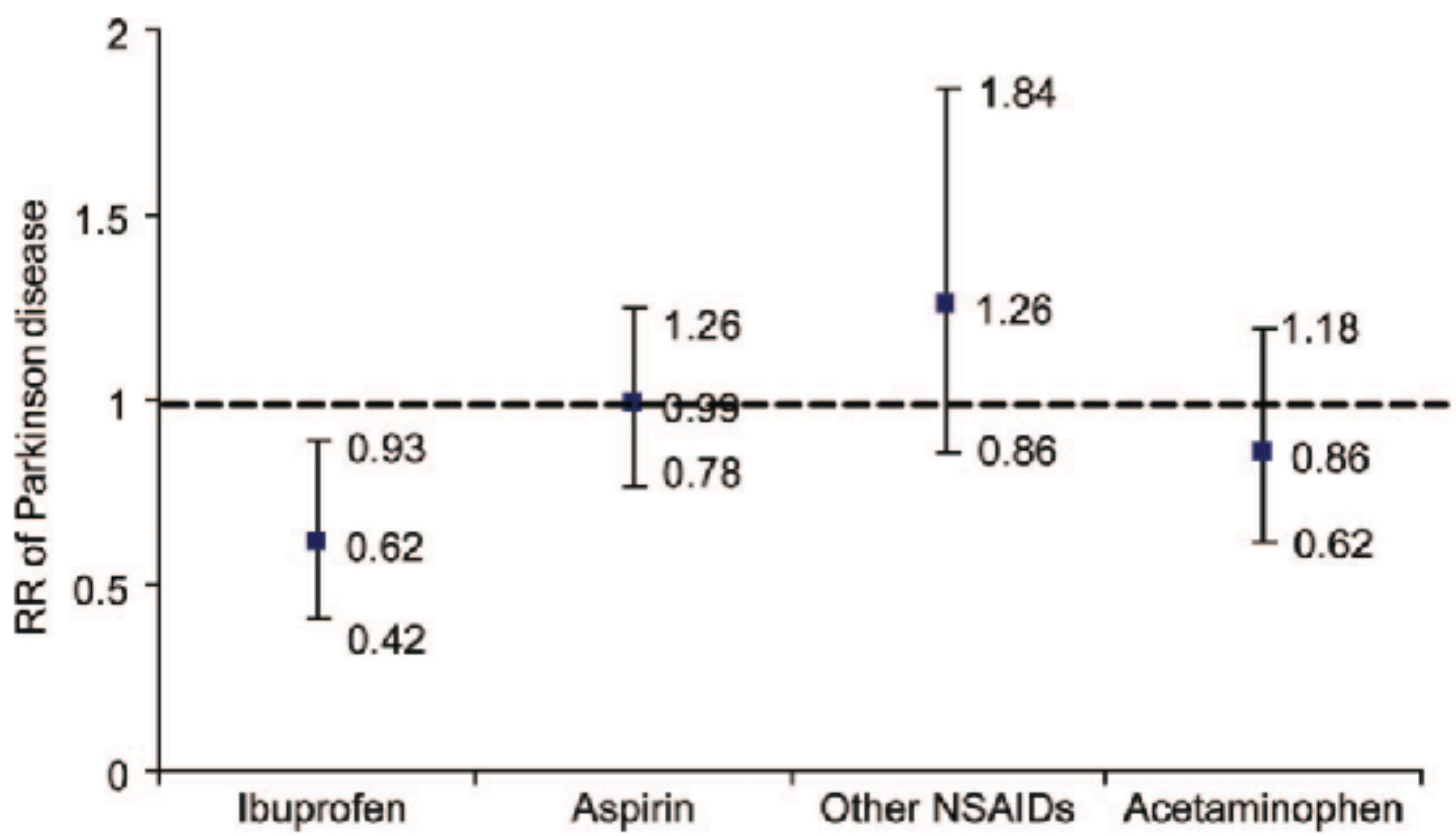
Neuroinflammation

Inflammation ⇄ Nerve cell death

Epidemiological evidence

Ibuprofen intake associated with reduced PD risk in 136,197 health professionals

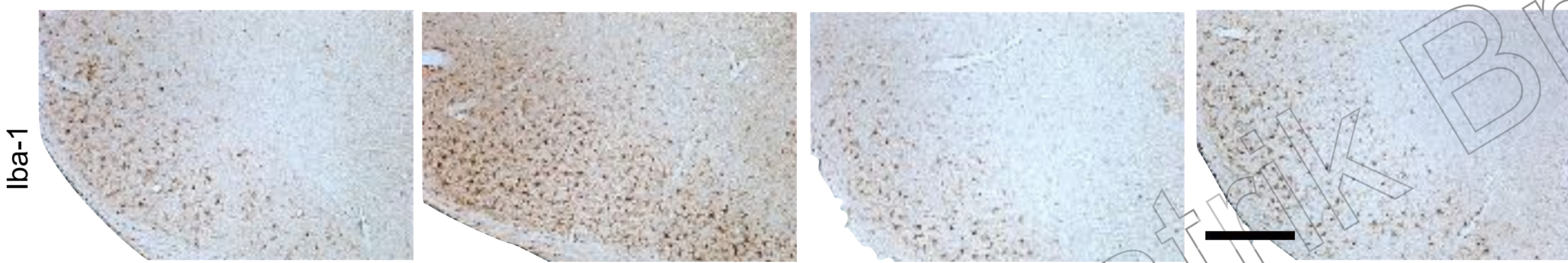
Figure 1 Combined relative risks (RRs) of Parkinson disease according to use of each type of nonsteroidal anti-inflammatory drug (NSAID) or acetaminophen



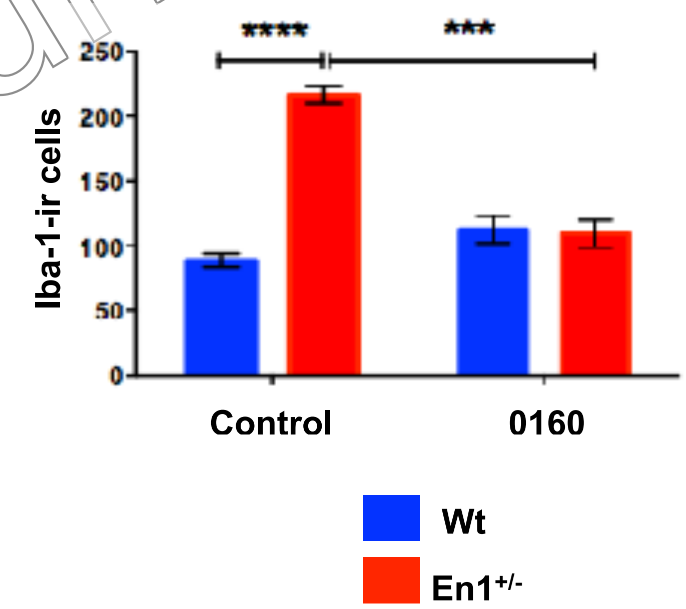
Gao et al, 2011

MSDC-0160 reduces neuroinflammation in mouse PD model

Microglia

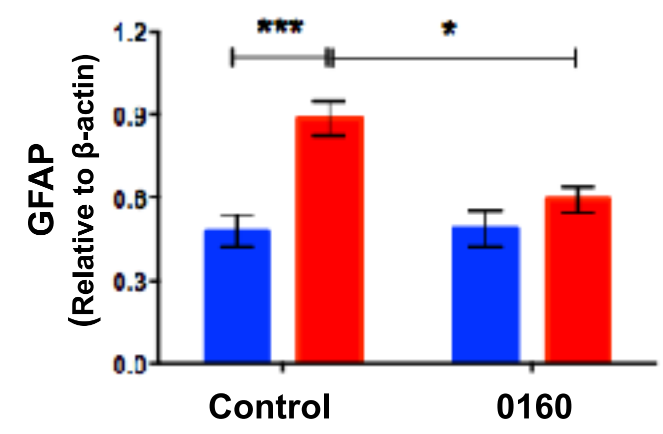


Wt + Control | En1$^{+/-}$ + Control | En1$^{+/-}$ + 0160 | Wt + 0160



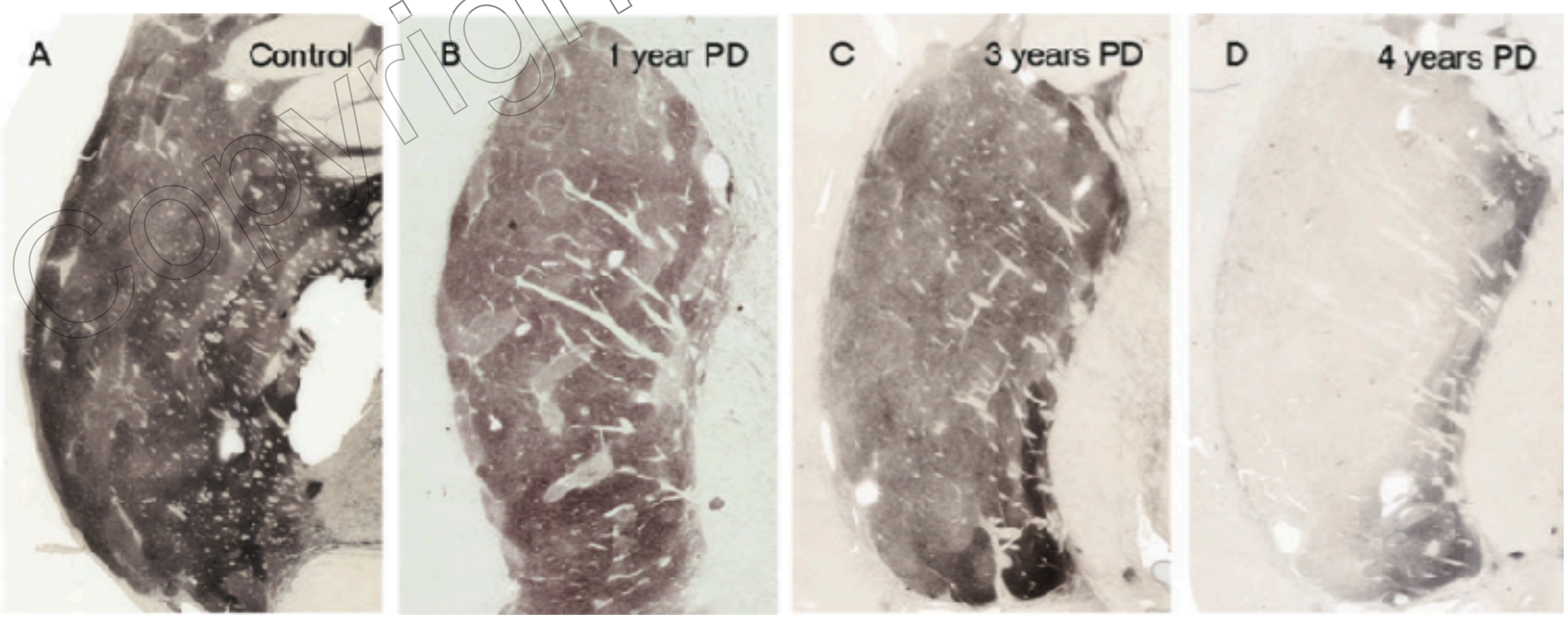
Astroglia

Wt + Control | En1$^{+/-}$ + Control | En1$^{+/-}$ + 0160 | Wt + 0160



Why still no disease-modifying treatment?

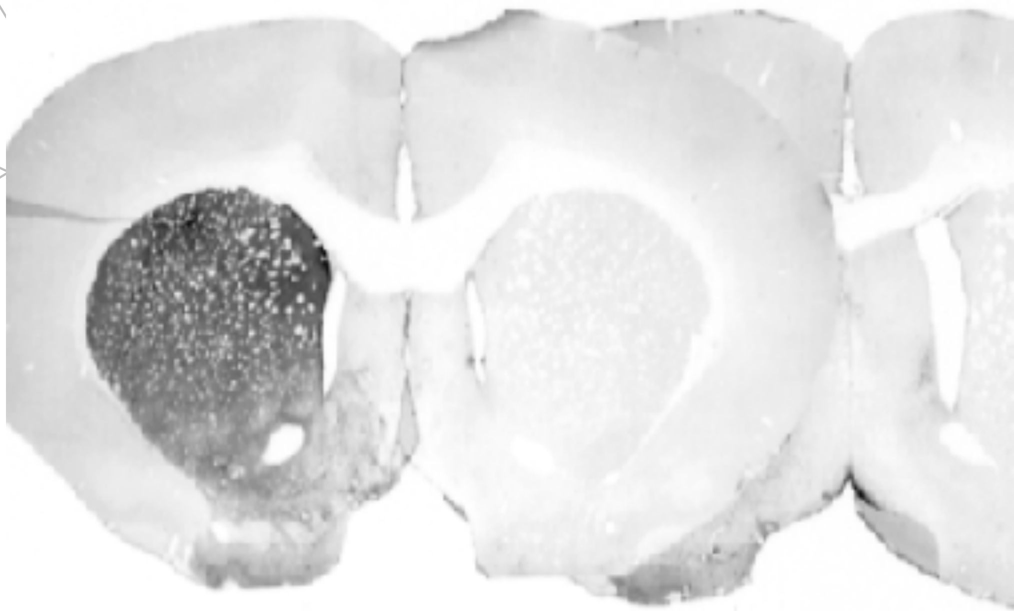
- Are we starting treatments too late?
- Has engagement of molecular targets been poor? (poor BBB penetration, pharmacokinetics etc)
- Are cell and animal models of PD flawed?



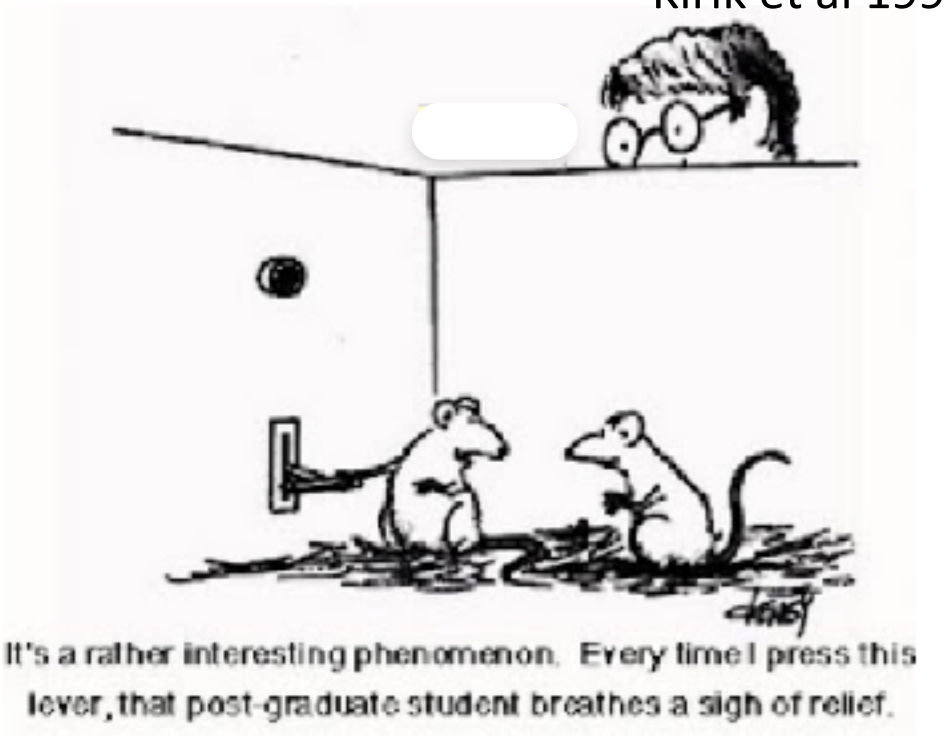
Kordower et al 2013

What's wrong with the models?

- Models typically exhibit severe <u>acute</u> cell death (toxin models) or <u>no</u> cell death at all (gene models)
- Many treatments that have 'worked' in cell cultures and rodents failed in clinical trials
- Current models are poor predictors of clinical success

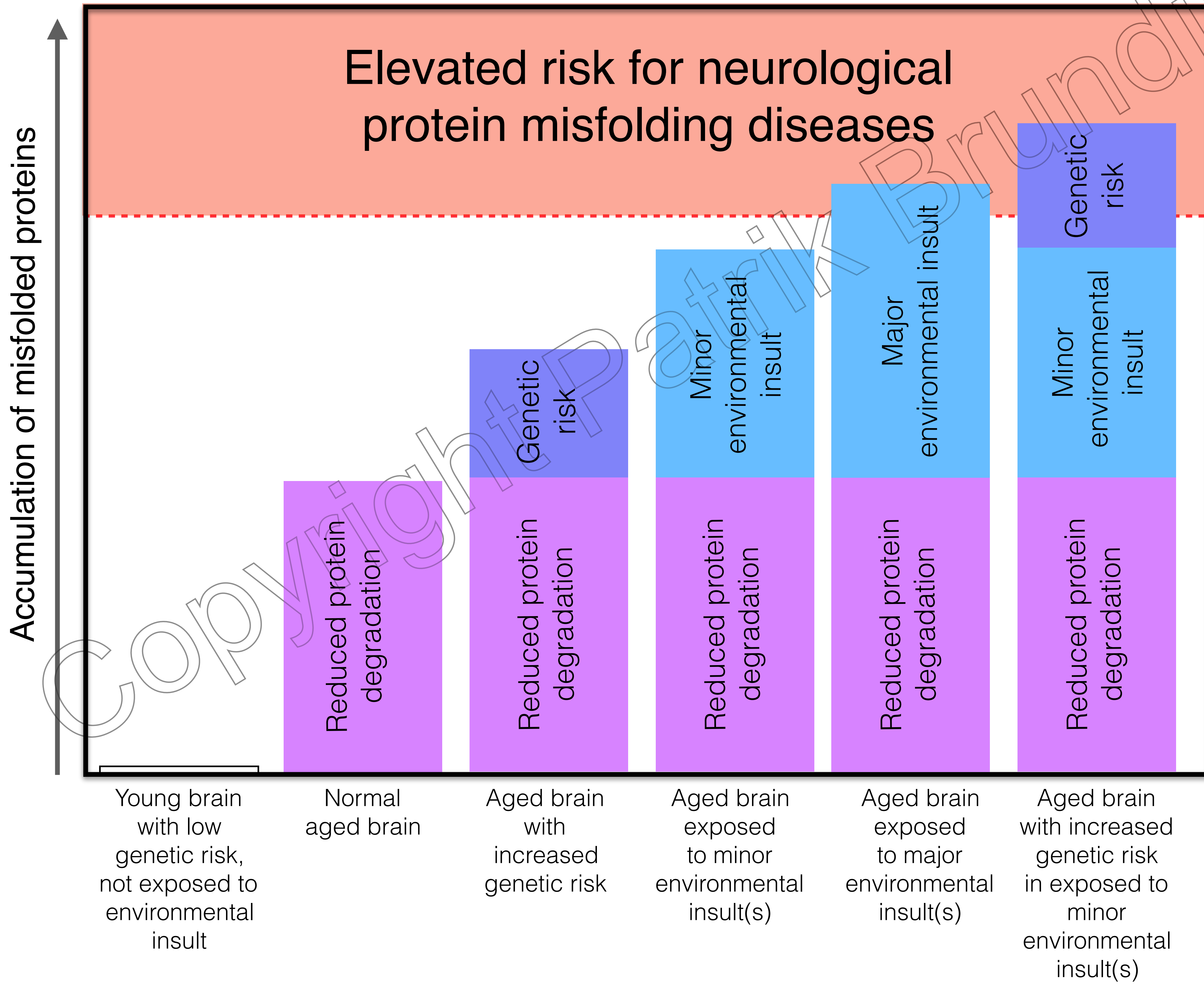


Kirik et al 1998



A multifactorial disease

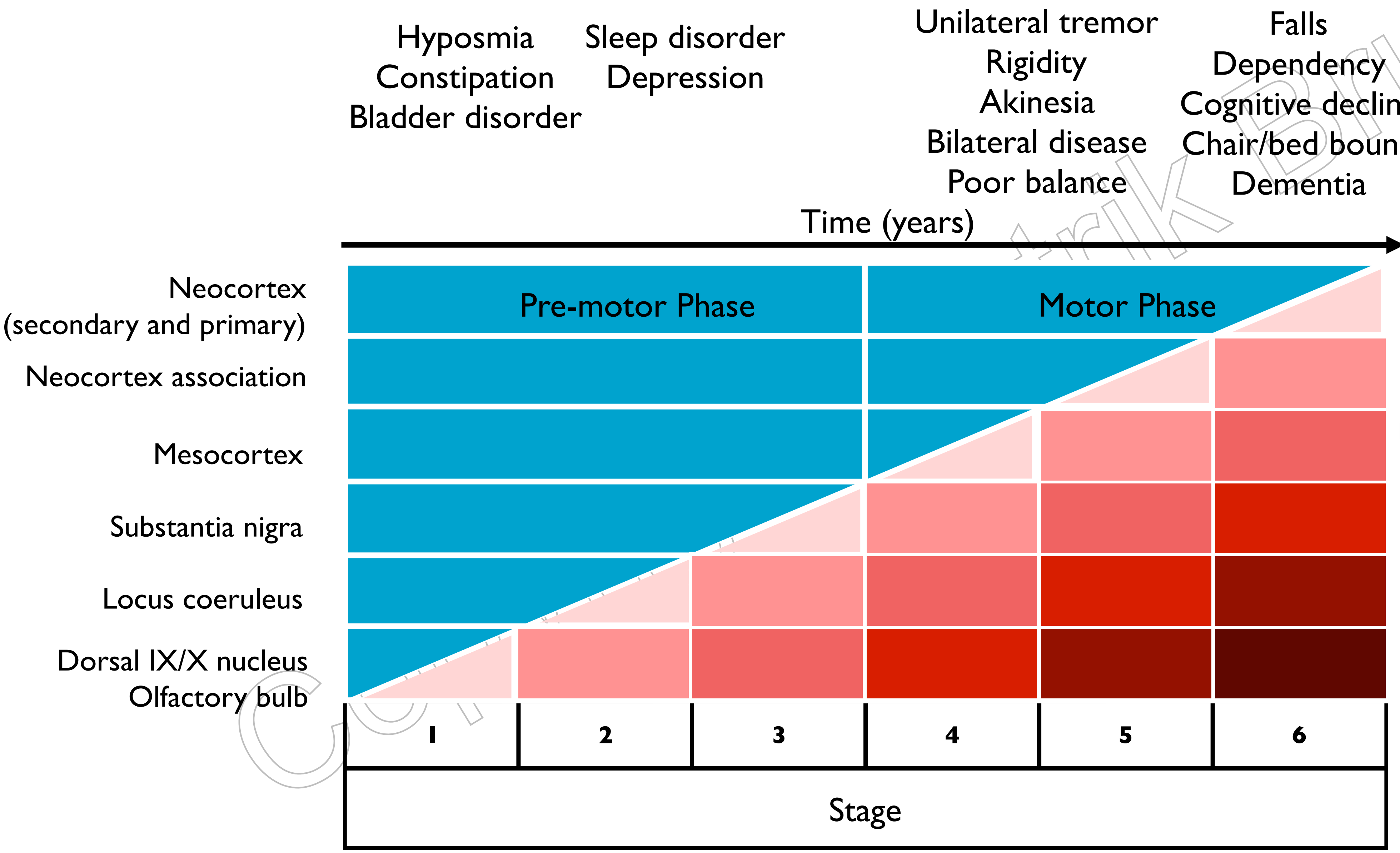
George and Brundin 2017

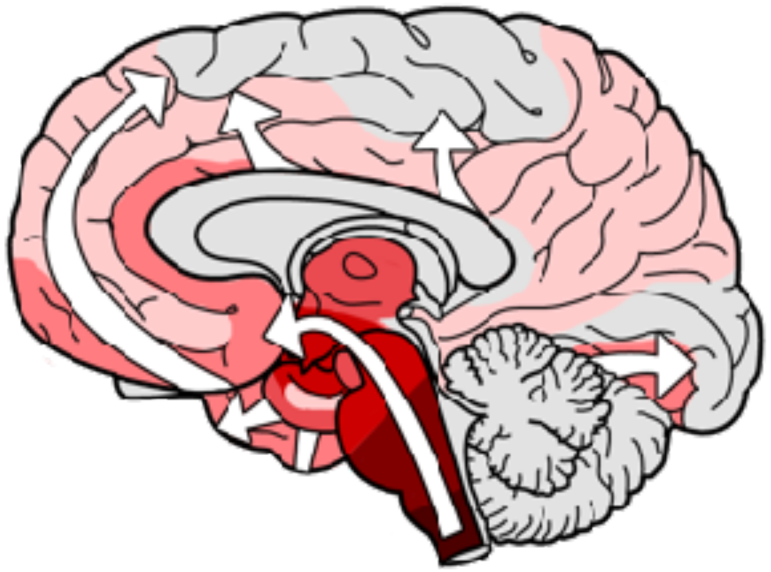


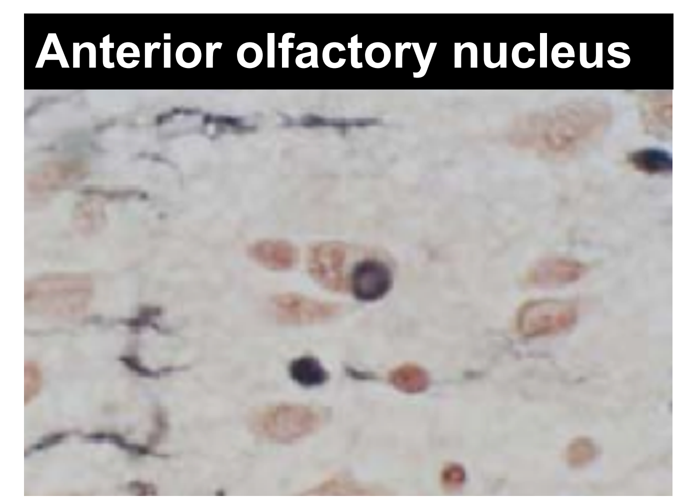
What's should an ideal model exhibit?

- Key neuropathological features
- Slow progression
- Evidence of the likely pathogenetic mechanisms
- A “prodromal phase”

Creating a model of prodromal PD







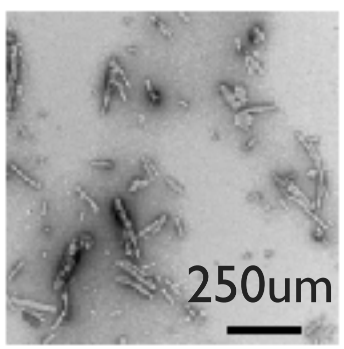
Beach et al. 2008.

Creating a model of prodromal PD

Create a model of progressive pathology of direct relevance to the "Braak model"

Can preformed α-synuclein fibrils induce spread of pathology in the olfactory system?

Are there associated olfactory deficits?

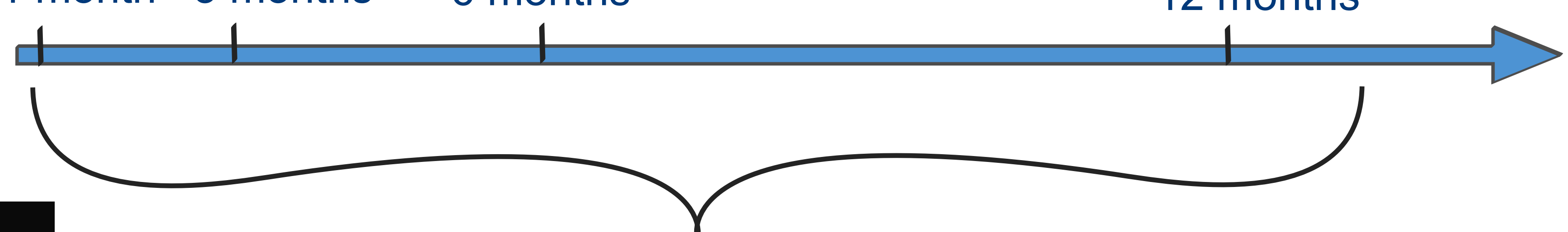


Sonicated preformed α-synuclein fibrils (PFFs)

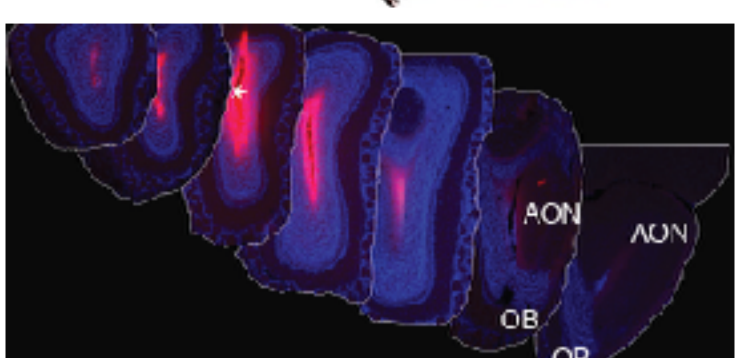
[monomer and PBS as controls]

Injection into the olfactory bulb

Wild type mice

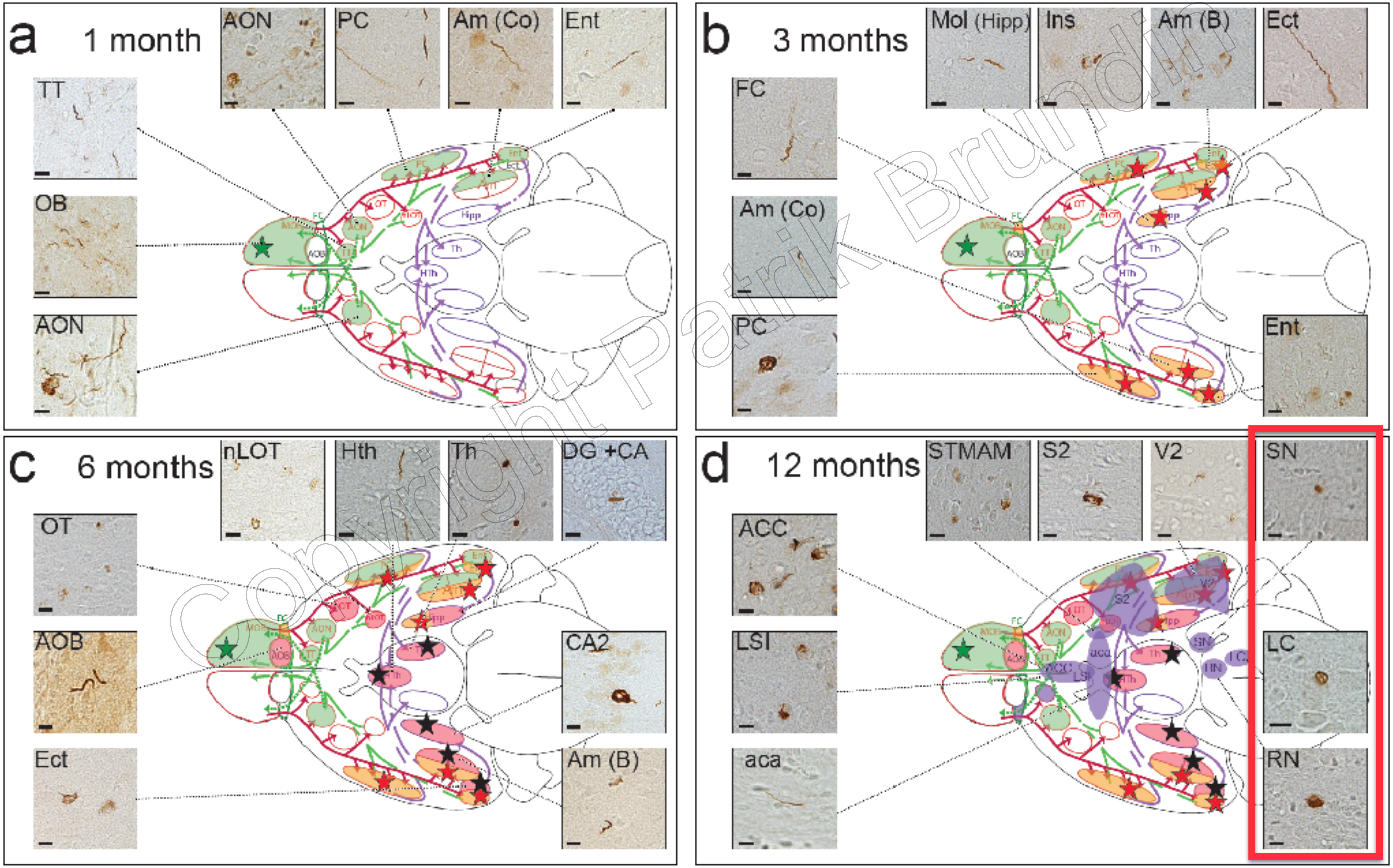


Olfactory tests
α-synuclein neuropathology



Rey et al, J Exp Med, in press

Slow spreading of Pser129 α-synuclein in brain



Olfactory dysfunction in prodromal PD

Appears > 4 years before motor symptoms

Occurs in 90-96% of PD patients

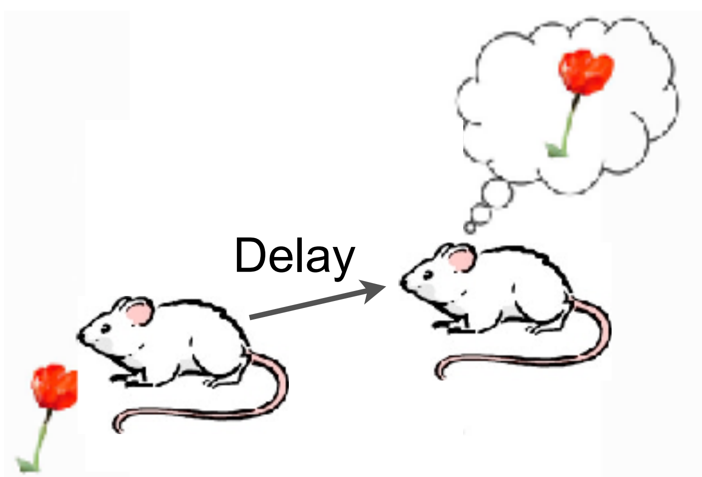
Olfactory system pathology as a model of Lewy neurodegenerative disease

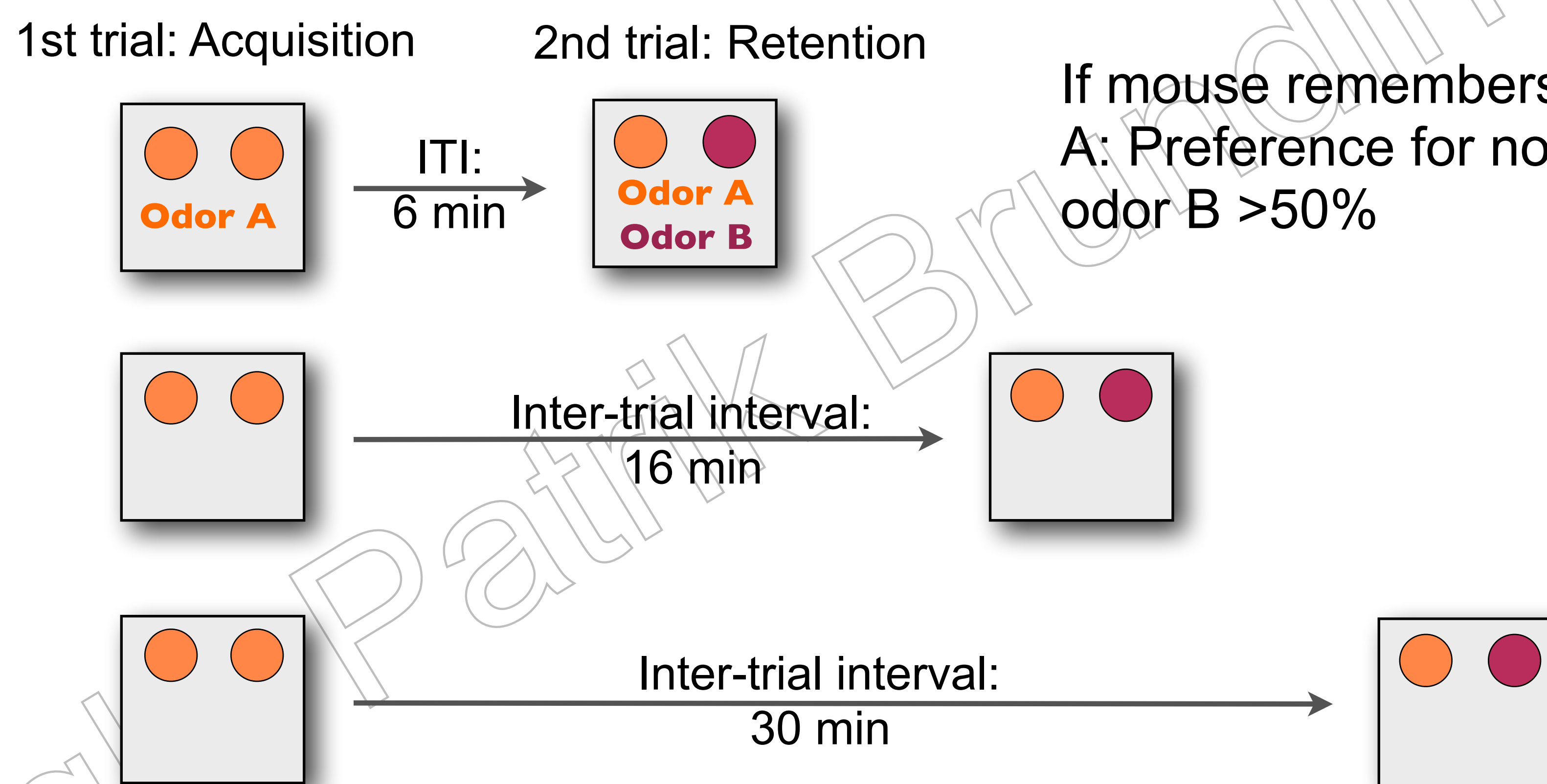
John E. Duda *

Association of Olfactory Dysfunction with Risk for Future Parkinson's Disease

G. Webster Ross, MD,[1–5] Helen Petrovitch, MD,[1–5] Robert D. Abbott, PhD,[4–8] Caroline M. Tanner, MD, PhD,[9] Jordan Popper, MD,[1,2] Kamal Masaki, MD,[3–5] Lenore Launer, PhD,[10] and Lon R. White, MD, MPH[1–5]

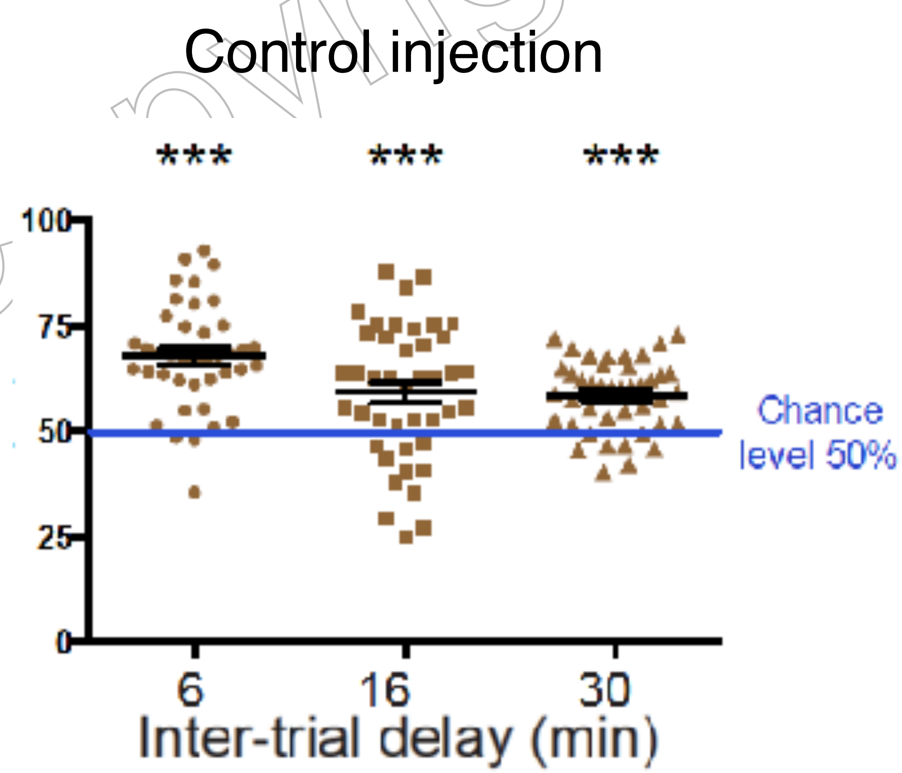
Olfactory dysfunction in mouse model

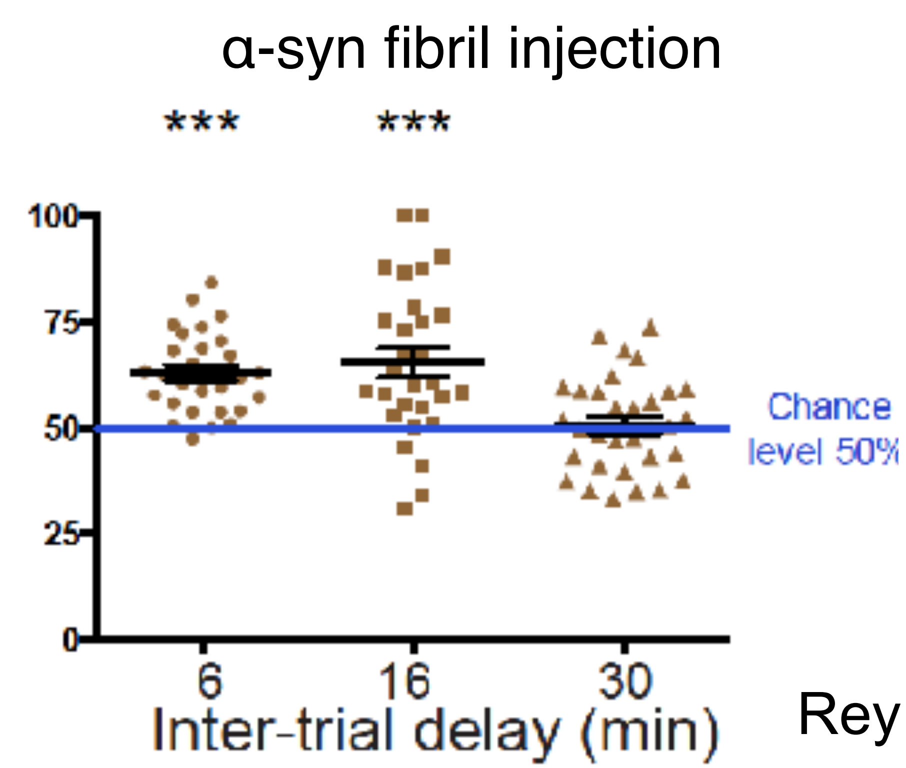




If mouse remembers Odor A: Preference for novel odor B >50%

1 month
after injection





Rey et al, 2016

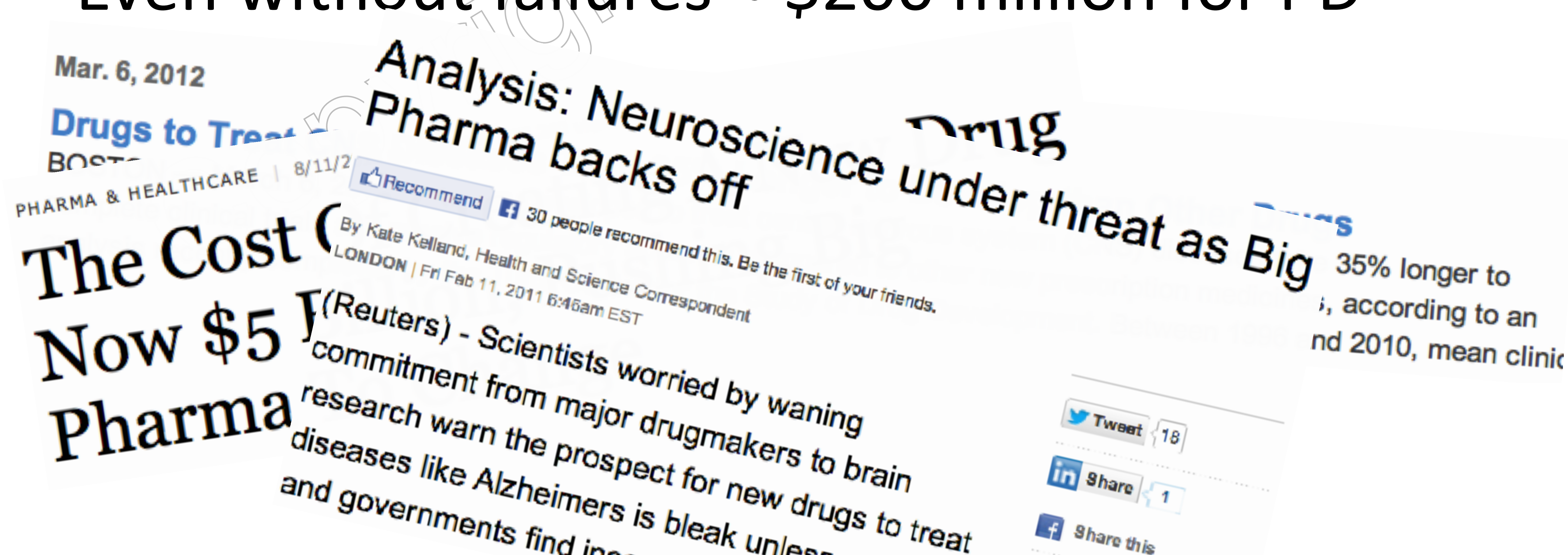
Olfactory mouse model of prodromal PD

- Trigger site (olfactory bulb) is highly relevant to Parkinson's disease
- Progressive pathology develops with a delay (therapeutic window)
- Propagation of α-synuclein pathology is faithful to complex olfactory pathways
- Progressive and specific olfactory deficits relevant to "prodromal" disease

CNS drug discovery is expensive!

The cost is enormous!

- CNS drugs take 35% longer to develop
- Only 8% of CNS drugs "make it"
- Cost for one successful drug, if one includes all research and failed drugs ≈ $5 billion
- Even without failures ≈ $200 million for PD



Can it be done cheaper and faster?

Repurposing existing drugs

Journal of Parkinson's Disease 3 (2013) 231–239
DOI 10.3233/JPD-139000
IOS Press

Review

Linked Clinical Trials – The Development of New Clinical Learning Studies in Parkinson's Disease Using Screening of Multiple Prospective New Treatments

Patrik Brundin[a,1,*], Roger A. Barker[b,1], P. Jeffrey Conn[c,1], Ted M. Dawson[d,1], Karl Kieburtz[e,1], Andrew J. Lees[f,1], Michael A. Schwarzschild[g,1], Caroline M. Tanner[h,1], Tom Isaacs[i], Joy Duffen[i], Helen Matthews[i] and Richard K.H. Wyse[i]

The Cure Parkinson's Trust

We recognise the significance of efficacy and safety in the development of new treatments, but we also recognise the need for greater urgency. The Cure Parkinson's Trust believes the science is out there to make a real breakthrough in the treatment of Parkinson's. We constantly strive to ensure that the pace of transition from science to clinic is not hampered for reasons of excessive regulation or viability.

Linked Clinical Trials

New biochemical thinking has highlighted that drugs from other disease areas can be brought into Parkinson's. The Linked Clinical Trials initiative is a drug repositioning programme designed by The Cure Parkinson's Trust to harness this new opportunity. Because many of these drugs are already in use in man, if proved of value in Parkinson's they could move quickly to the clinic. This initiative not only prioritises potential new therapeutic candidates, but also explores the best way of bringing them into trial, to ensure synergy between trials in the data collected to allow maximum comparison. The Linked Clinical Trials scientific committee has been recruited from across Europe and the USA and is chaired by Dr Patrik Brundin, Director of the Centre for Neurodegenerative Science and Head of the Laboratory for Translational Parkinson's Disease Research at the Van Andel Institute, Grand Rapids,

The Linked Clinical Trials Committee

Professor Patrik Brundin, Chairman

Professor Brundin is Associate Director of Research at the Van Andel Research Institute in Grand Rapids, USA. He is also the co-editor in chief of the Journal of Parkinson's Disease and has coordinated multiple international research programs.

Professor Roger Barker
University of Cambridge, UK

Professor Flint Beal
Cornell University, New York, USA

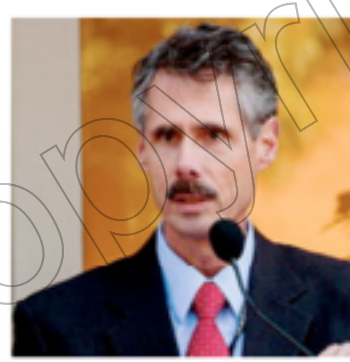
Professor Ted Dawson
Johns Hopkins Institute
Baltimore, USA

Professor Andrew Lees
University College London, UK

Professor Werner Poewe
University of Innsbruck, Austria

Professor Michael Schwarzschild
Massachusetts General Hospital, USA

Professor Jeffrey Conn
Vanderbilt University Medical Center, Nashville, USA



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Repurposing existing drugs

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Review

Linked Clinical Trials – The Development of New Clinical Learning Studies in Parkinson's Disease Using Screening of Multiple Prospective New Treatments

Patrik Brundin[a,1,*], Roger A. Barker[b,1], P. Jeffrey Conn[c,1], Ted M. Dawson[d,1], Karl Kieburtz[e,1], Andrew J. Lees[f,1], Michael A. Schwarzschild[g,1], Caroline M. Tanner[h,1], Tom Isaacs[i], Joy Duffen[i], Helen Matthews[i] and Richard K.H. Wyse[i]

We have reviewed over 100 drugs

About 10 are currently selected for trials

Simvastatin - cholesterol lowering drug
N-acetyl cystein - mucolytic drug
Ambroxol - cough syrup
Exenatide - anti-diabetic drug

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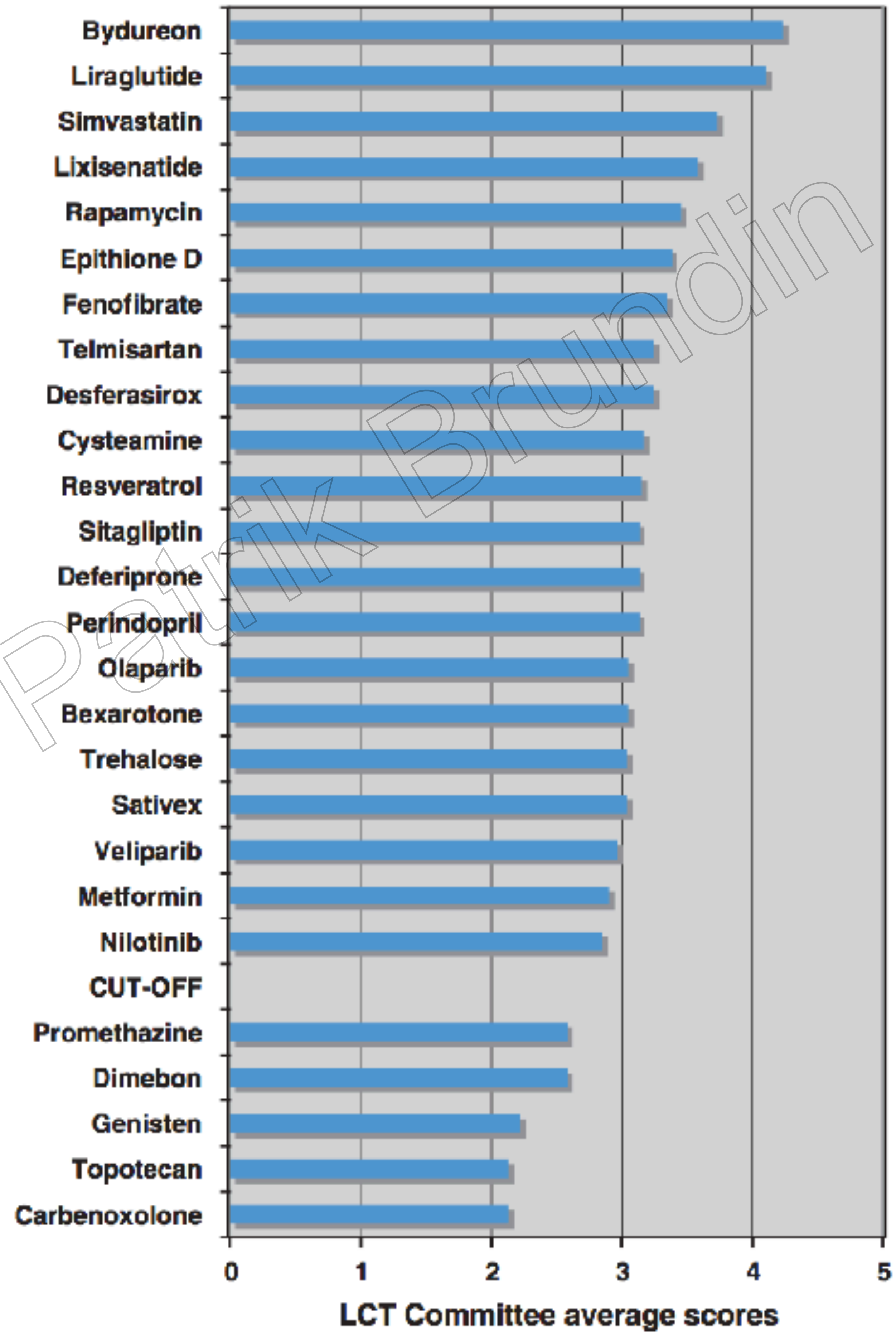

Fig. 1. Pre-prioritization of the initial 26 candidate PD therapies for rapid translation to clinical trials.

Concluding remarks

- Multifactorial etiopathogenesis
- Numerous interesting drug targets exist
- New drug targets remain to be discovered
- New animal models needed
- Drug development cost is prohibitive
- Drug repurposing should be part of the portfolio

Thank you for listening!