Parkinson's Disease: Clinical Trials Update 2019

Stephen L. Lee MD PhD
Co-Medical Director of Movement Disorders Center
Assistant Professor of Neurology
Dartmouth Hitchcock Medical Center

Dartmouth-Hitchcock | Dartmouth GEISEL SCHOOL OF MEDICINE

Financial Disclosures

Served on Advisory Board for Abbvie

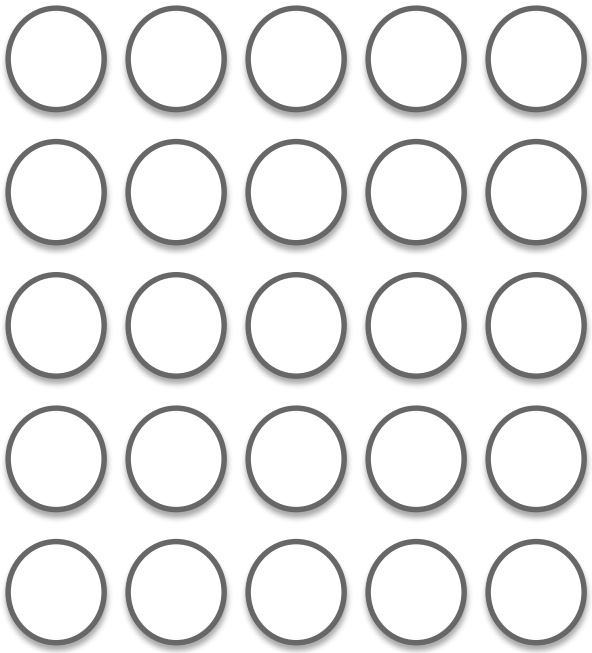
Dartmouth-Hitchcock | Dartmouth GEISEL SCHOOL OF MEDICINE

Objectives

- Clinical Trials Update
  - Risk/Protective Factors
  - Stem Cells
  - Symptomatic Treatment
  - Disease Modification

The epidemiology of Parkinson's disease: risk factors and prevention

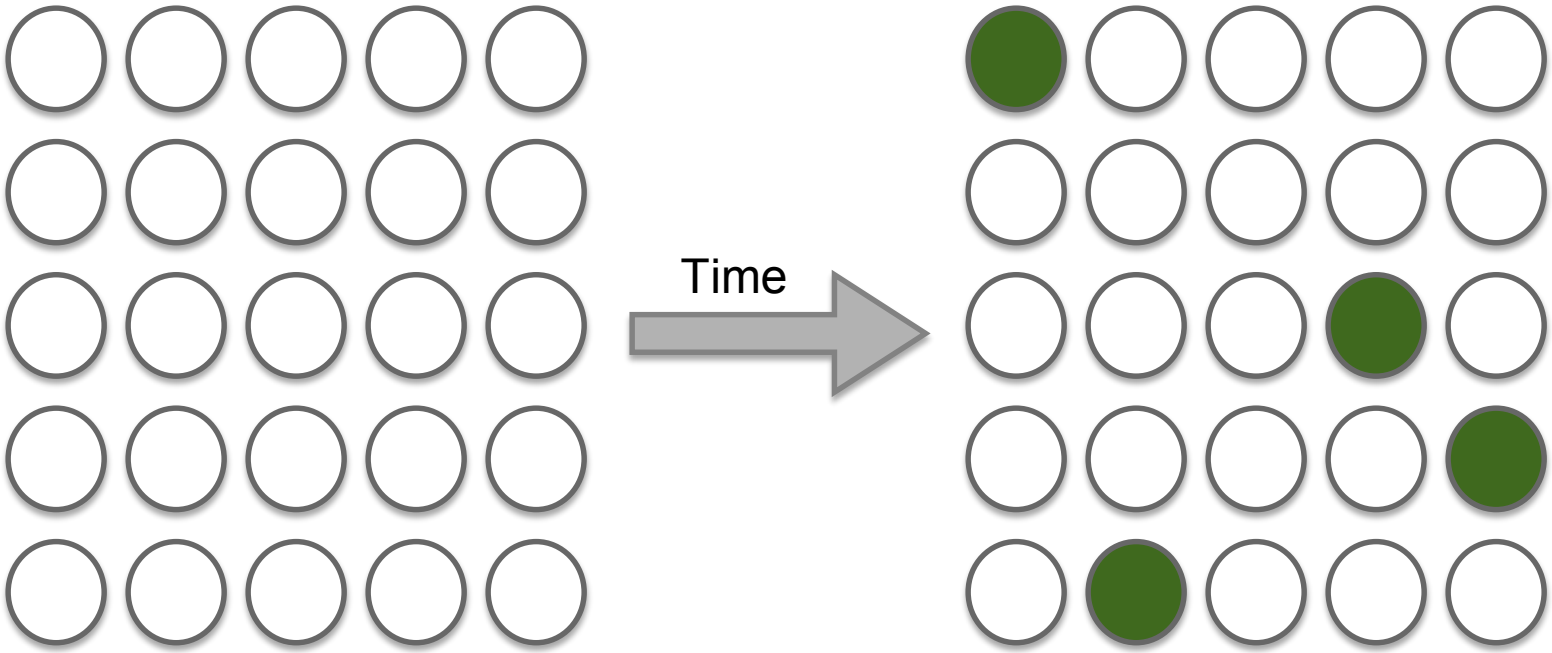
Alberto Ascherio, Michael A Schwarzschild



Dartmouth-Hitchcock | Dartmouth GEISEL SCHOOL OF MEDICINE

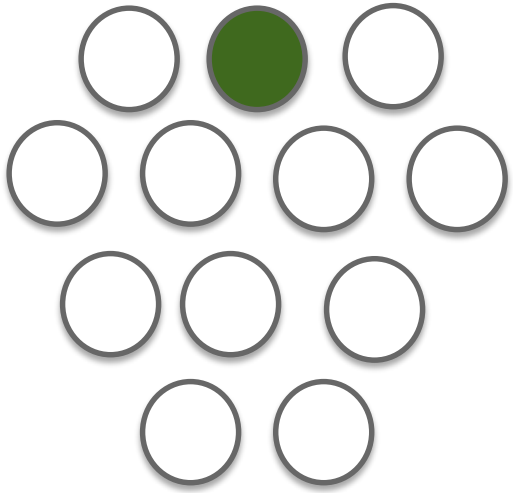
The epidemiology of Parkinson's disease: risk factors and prevention

Alberto Ascherio, Michael A Schwarzschild

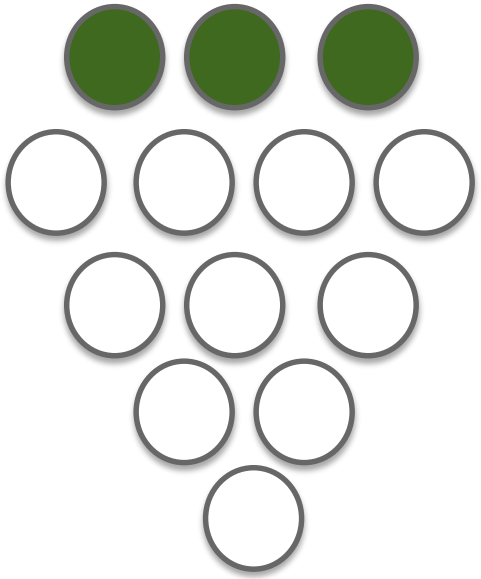


Dartmouth-Hitchcock | Dartmouth GEISEL SCHOOL OF MEDICINE

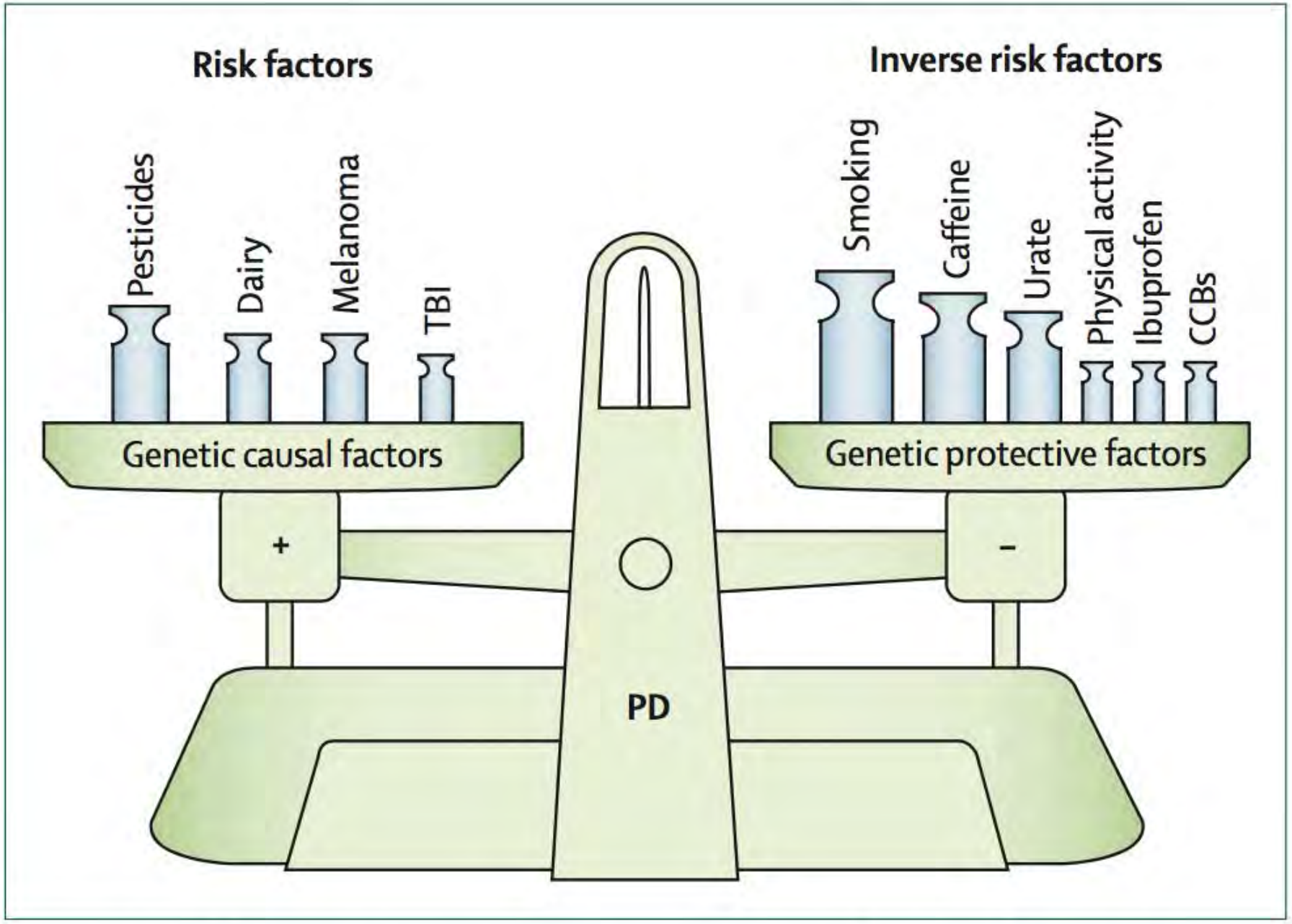
Smokers



Nonsmokers



Honolulu-Asia Ageing Study (HAAS)	7 504 men
Nurses' Health Study	51 500 women
Rotterdam Study	121 700 women
FAME (Agricultural Health Study)	147 000 (45% women)
Finnish cohort	84 739 (72%men)
National Institutes of Health AARP	309 619 (42% women)
Atherosclerosis Risk in Communities (ARIC)	15 792 (57% women)
Physician Health Study (PHS)	63 257 (55% women)


Risk factors
Inverse risk factors
Pesticides
Dairy
Melanoma
TBI
Smoking
Caffeine
Urate
Physical activity
Ibuprofen
CCBs
Genetic causal factors
Genetic protective factors
+
–
PD

What about exercise?

Invited Commentary | Neurology

September 21, 2018

Physical Activity and Parkinson Disease Risk

An Intriguing Link

Lorene M. Nelson, PhD, MS[1]

» Author Affiliations | Article Information

JAMA Network Open. 2018;1(5):e182633. doi:10.1001/jamanetworkopen.2018.2633

Dartmouth-Hitchcock | Dartmouth GEISEL SCHOOL OF MEDICINE

Original Investigation | Neurology

September 21, 2018

Association of Levels of Physical Activity With Risk of Parkinson Disease

A Systematic Review and Meta-analysis

Xuexian Fang, PhD[1,2]; Dan Han, MS[1]; Qi Cheng, BS[1]; et al

Author Affiliations | Article Information

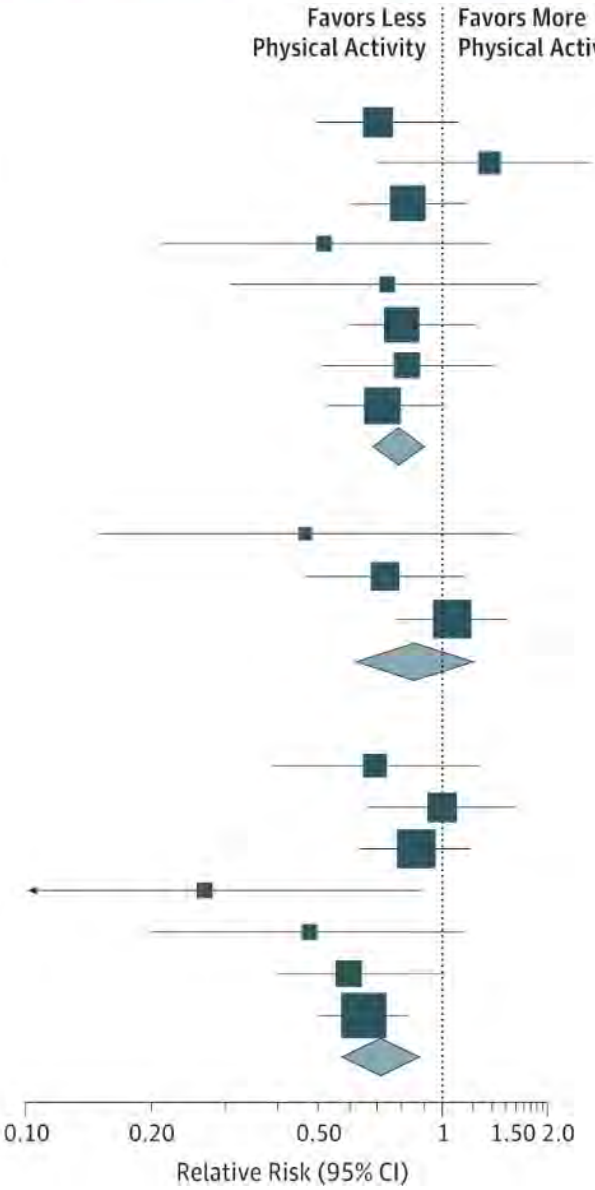
[1]School of Public Health, The First Affiliated Hospital, Institute of Translational Medicine, Zhejiang University School of Medicine, Hangzhou, China

[2]Precision Nutrition Innovation Center, School of Public Health, Zhengzhou University, Zhengzhou, China

[3]State Key Laboratory of Industrial Control Technology, College of Control Science and Engineering, Zhejiang University, Hangzhou, China

JAMA Network Open. 2018;1(5):e182421. doi:10.1001/jamanetworkopen.2018.2421

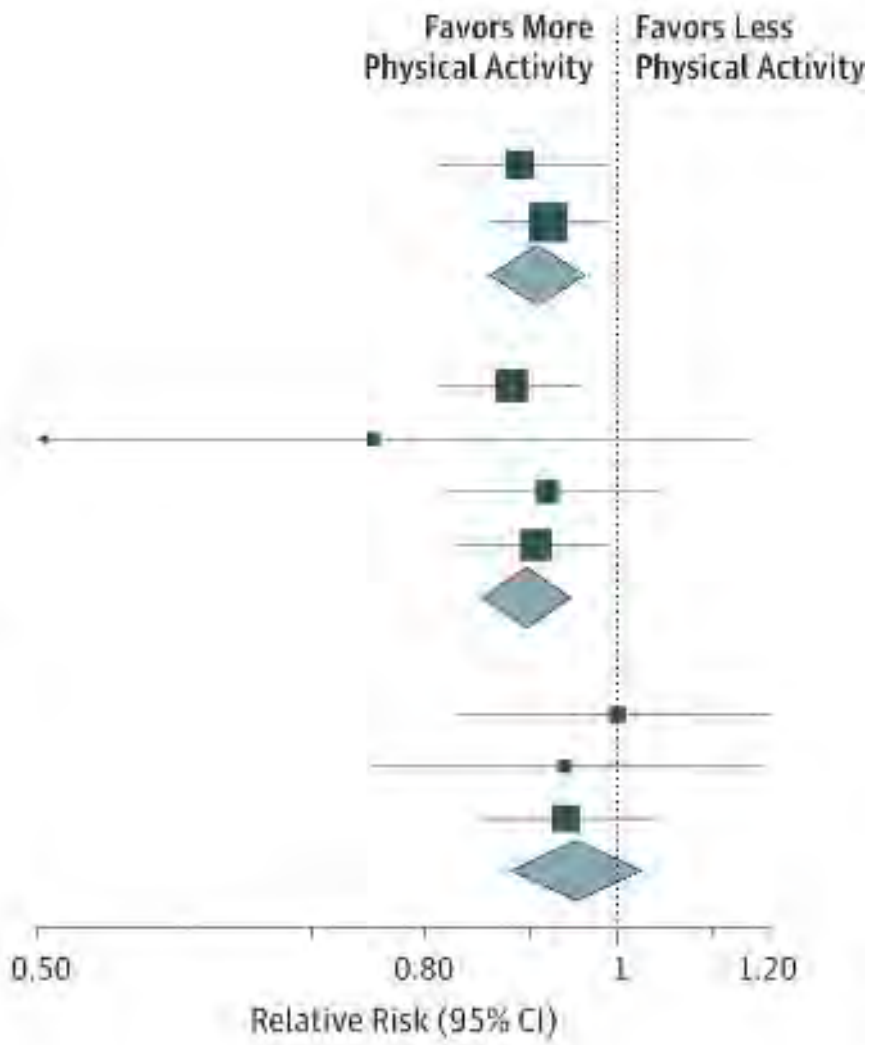
Source	Participants, No.	Relative Risk (95% CI)
Total physical activity		
Chen et al,[18] 2005 (HPFS)	48574	0.70 (0.50-1.10)
Chen et al,[18] 2005 (NHS)	77254	1.30 (0.70-2.30)
Logroscino et al,[19] 2006	10714	0.83 (0.60-1.15)
Sääksjärvi et al,[20] 2014	6715	0.52 (0.21-1.31)
Sasco et al,[21] 1992	685	0.74 (0.31-1.70)
Thacker et al,[22] 2008	143325	0.80 (0.60-1.20)
Xu et al,[23] 2010	213701	0.82 (0.51-1.33)
Yang et al,[24] 2015	43368	0.72 (0.53-0.99)
Subtotal (I^2 = 0.0%)		**0.79 (0.68-0.91)**
Light physical activity		
Logroscino et al,[19] 2006	10714	0.47 (0.15-1.48)
Sääksjärvi et al,[20] 2014	6715	0.73 (0.47-1.13)
Xu et al,[23] 2010	213701	1.06 (0.78-1.44)
Subtotal (I^2 = 37.5%)		**0.86 (0.60-1.23)**
Moderate to vigorous physical activity		
Chen et al,[18] 2005 (HPFS)	48574	0.69 (0.39-1.22)
Chen et al,[18] 2005 (NHS)	77254	1.00 (0.66-1.50)
Logroscino et al,[19] 2006	10714	0.87 (0.64-1.17)
Sääksjärvi et al,[20] 2014	6715	0.27 (0.08-0.90)
Sasco et al,[21] 1992	685	0.48 (0.20-1.13)
Thacker et al,[22] 2008	143325	0.60 (0.40-0.99)
Xu et al,[23] 2010	213701	0.65 (0.51-0.83)
Subtotal (I^2 = 30.7%)		**0.71 (0.58-0.87)**



Dartmouth-Hitchcock | Dartmouth GEISEL SCHOOL OF MEDICINE

A Total physical activity

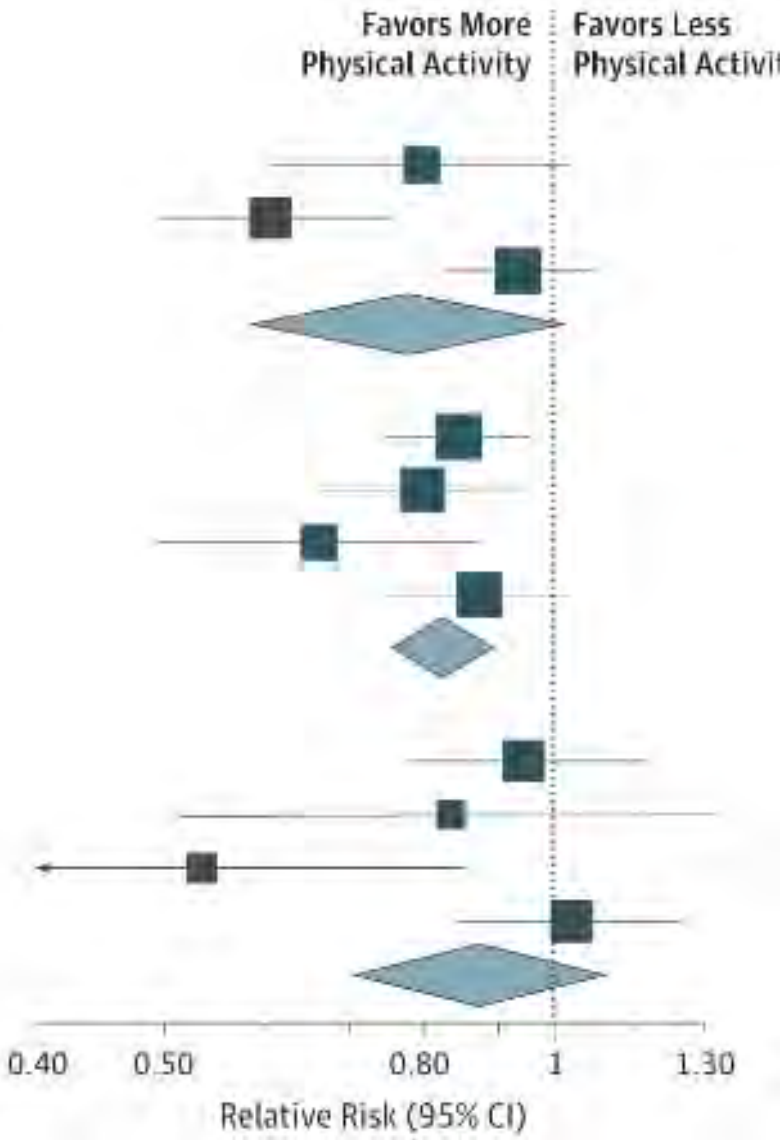
Source	Participants, No.	Relative Risk (95% CI)
Mixed		
Thacker et al,[22] 2008	143325	0.89 (0.81-0.99)
Yang et al,[24] 2015	43368	0.92 (0.86-0.99)
Subtotal (I^2 = 0.0%)		**0.91 (0.86-0.96)**
Male		
Chen et al,[18] 2005 (HPFS)	48574	0.88 (0.81-0.96)
Sasco et al,[21] 1992	685	0.75 (0.48-1.17)
Thacker et al,[22] 2008	63348	0.92 (0.82-1.05)
Yang et al,[24] 2015	15505	0.91 (0.83-0.99)
Subtotal (I^2 = 0.0%)		**0.90 (0.85-0.95)**
Female		
Chen et al,[18] 2005 (NHS)	77254	1.00 (0.83-1.20)
Thacker et al,[22] 2008	79977	0.94 (0.75-1.19)
Yang et al,[24] 2015	27863	0.94 (0.85-1.05)
Subtotal (I^2 = 0.0%)		**0.95 (0.87-1.04)**



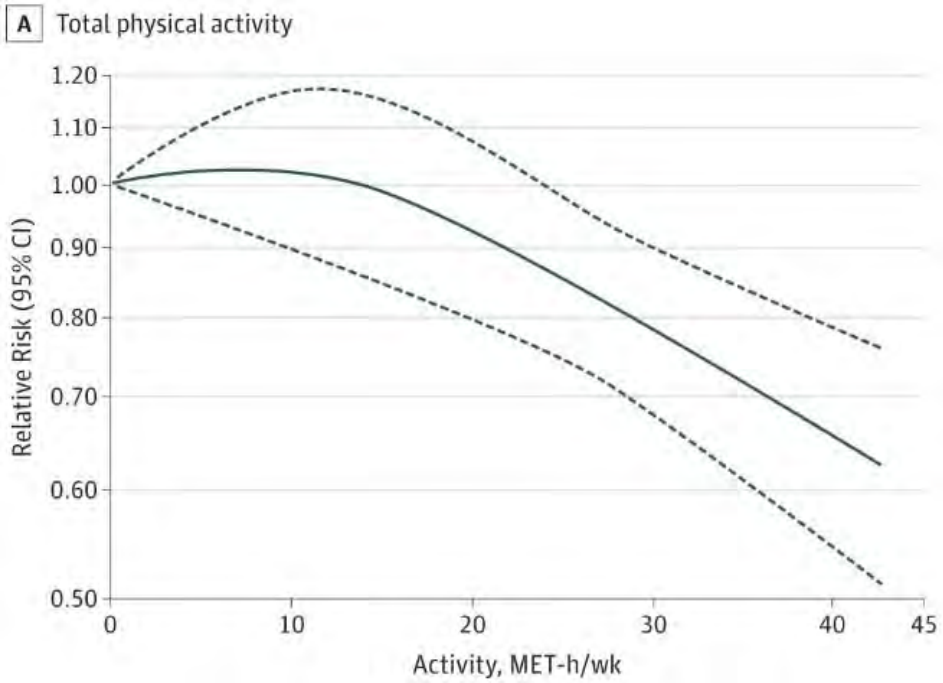
Dartmouth-Hitchcock | Dartmouth GEISEL SCHOOL OF MEDICINE

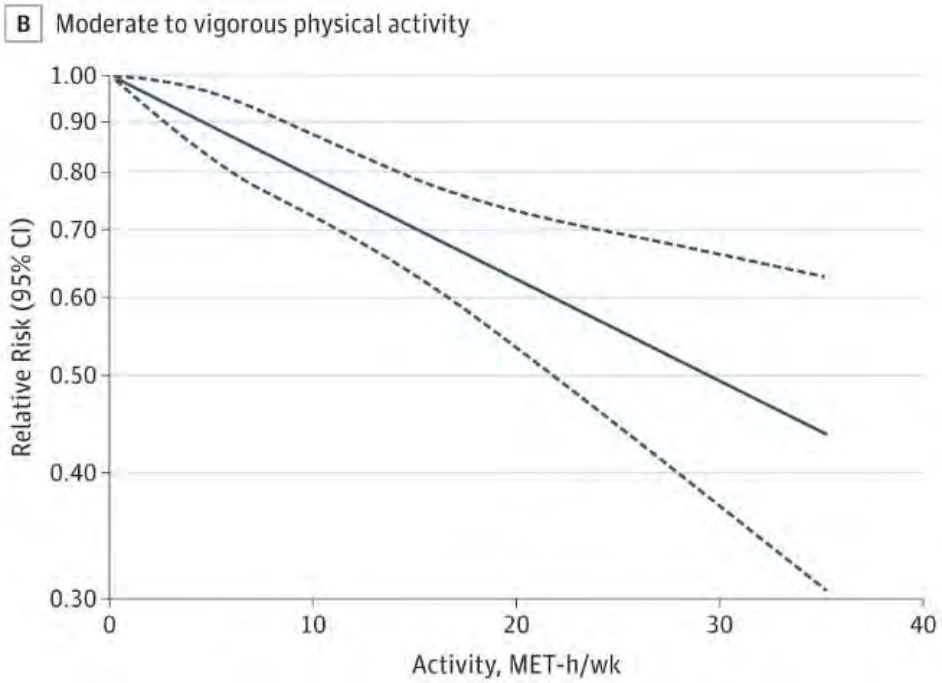
B Moderate to vigorous physical activity

Source	Participants, No.	Relative Risk (95% CI)
Mixed		
Thacker et al,[22] 2008	143325	0.80 (0.62-1.03)
Xu et al,[23] 2010	213701	0.62 (0.51-0.76)
Yang et al,[24] 2015	43368	0.94 (0.83-1.07)
Subtotal (I^2 = 83.3%)		**0.78 (0.60-1.02)**
Male		
Chen et al,[18] 2005 (HPFS)	48574	0.85 (0.75-0.96)
Thacker et al,[22] 2008	63348	0.80 (0.67-0.96)
Xu et al,[23] 2010	122489	0.67 (0.51-0.88)
Yang et al,[24] 2015	15505	0.88 (0.75-1.03)
Subtotal (I^2 = 6.1%)		**0.83 (0.76-0.90)**
Female		
Chen et al,[18] 2005 (NHS)	77254	0.95 (0.78-1.17)
Thacker et al,[22] 2008	79977	0.84 (0.53-1.32)
Xu et al,[23] 2010	89830	0.55 (0.35-0.86)
Yang et al,[24] 2015	27863	1.03 (0.85-1.24)
Subtotal (I^2 = 54.5%)		**0.88 (0.71-1.09)**



Dartmouth-Hitchcock | Dartmouth GEISEL SCHOOL OF MEDICINE





Dartmouth-Hitchcock | Dartmouth GEISEL SCHOOL OF MEDICINE

Dartmouth-Hitchcock

DHMC Campus Parking

PATIENT PARKING: If your appointment is at the Medical Center follow signs to the Main Entrance, the Faulkner Building, or Parking Garage. The Parking Garage has a direct entrance to the fourth level of the Faulkner Building. If your appointment is scheduled at the Outpatient Surgery Center please park in the Outpatient Surgery Center parking lot. Please remember your vehicle location by the signs on the light poles.

VISITOR PARKING: Follow signs to North Entrance Visitor Parking.

ACCESSIBLE PARKING: A number of accessible parking spaces are available at all entrances.

PAR ecurity staff is
avail onday through
Frida o have trouble
walk ng from their car
and i am to 4:30pm.

WH CE: Wheelchairs
are a ces. To protect your
safet wheelchairs in the
parki

PAR

Please Note:
Loop Road Construction In Progress

Construction will occur in 5 phases. See color coding for construction areas. Dates for each phase are subject to change.
Visit go.d-h.org/looproad for the latest information.

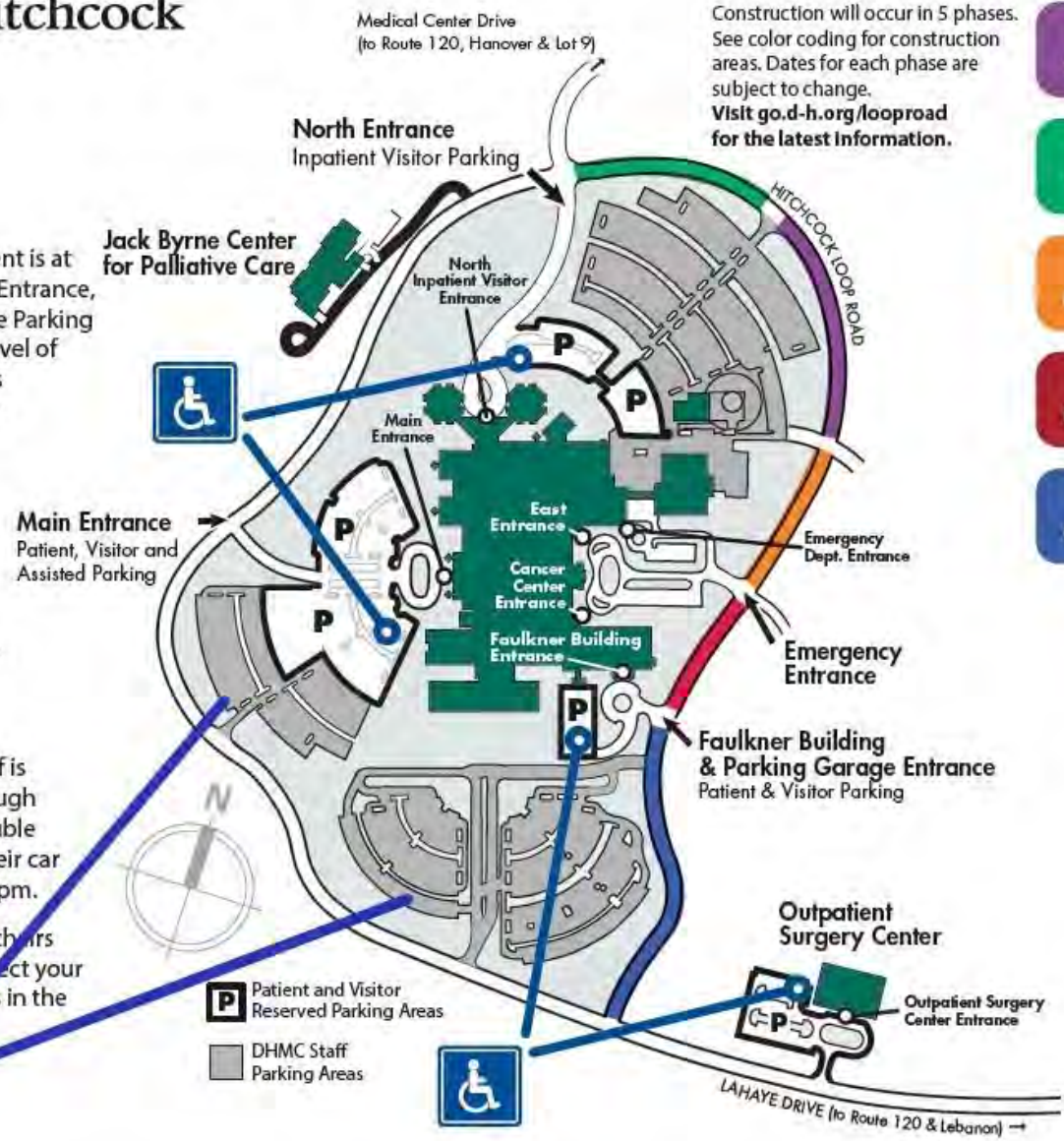
Phase 1 5/12 to 5/24

Phase 2 5/28 to 6/7

Phase 3 6/10 to 6/19

Phase 4 6/20 to 6/27

Phase 5 6/28 to 7/10



Welcome to DHMC – Please drive carefully. **Visit us online at Dartmouth-Hitchcock.org**

REVISED MAY 2019

Objectives

- Clinical Trials Update
  - Risk/Protective Factors
  - Stem Cells
  - Disease Modification
  - Symptomatic Treatment

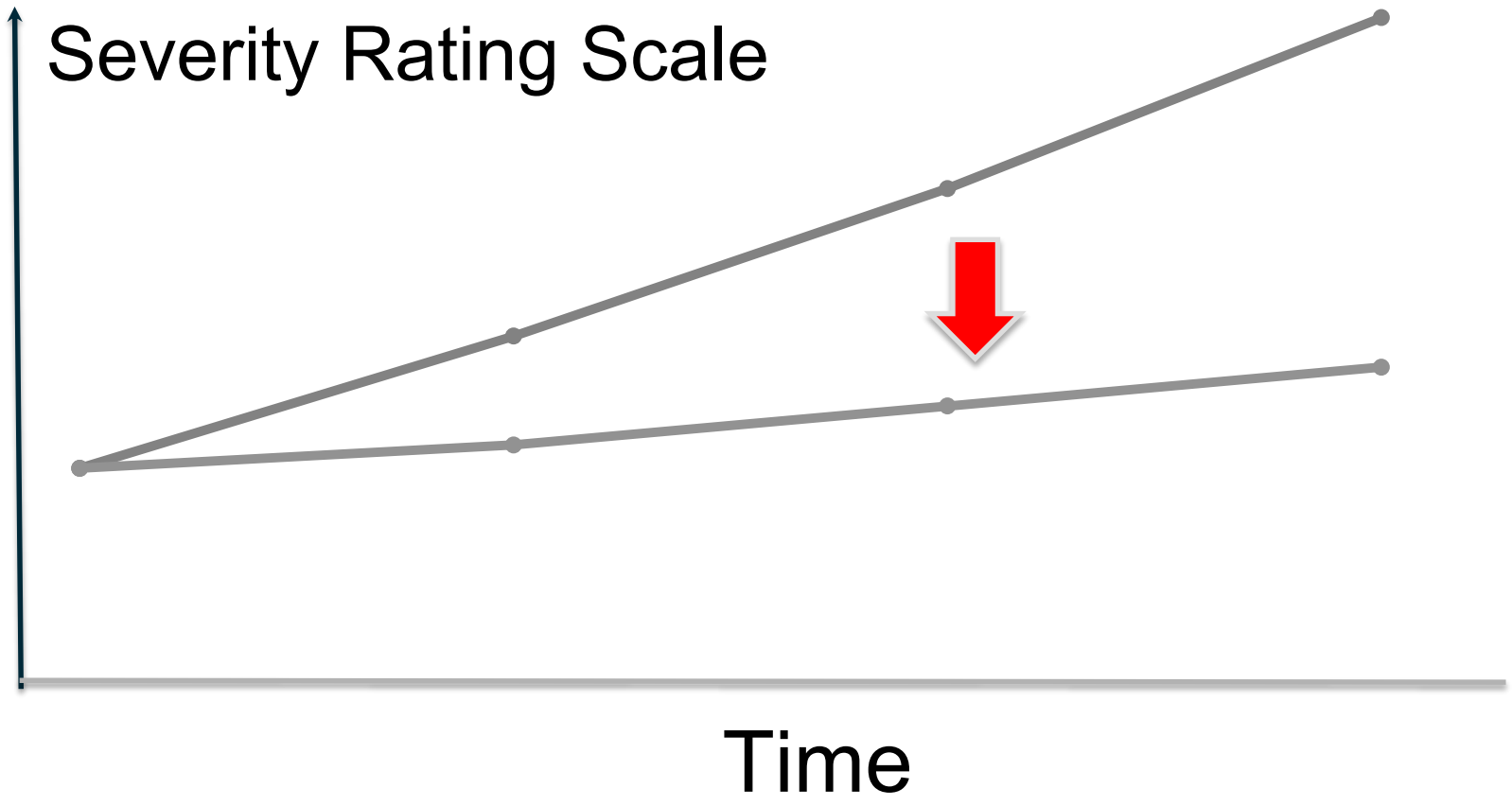
Mesenchymal Stem Cell

- University of Texas Houston (Mya Schiess MD, PI)
  - 20 participants
  - Allogeneic bone marrow derived stem cells
  - Intravenous delivery
  - Recent abstract at AAN 2019:
    - No safety issues

Objectives

- Clinical Trials Update
  - Risk/Protective Factors
  - Stem Cells
  - Disease Modification
  - Symptomatic Treatment

Disease Modification



Neuroprotection Pipeline: disease modification

Here at Dartmouth-Hitchcock:

Isradapine: STEADY PD III trial: NIH sponsored study to show disease modification

- **Calcium channel blockers associated with a reduced risk of developing PD**
- **Isradapine has been shown to protect SNpc neurons from 6-OHDA toxicity in a rodent model**
- **Ongoing for 36 months.**
- **Double blinded, placebo controlled study.**

Dartmouth-Hitchcock | Dartmouth GEISEL SCHOOL OF MEDICINE

Neuroprotection Pipeline: disease modification

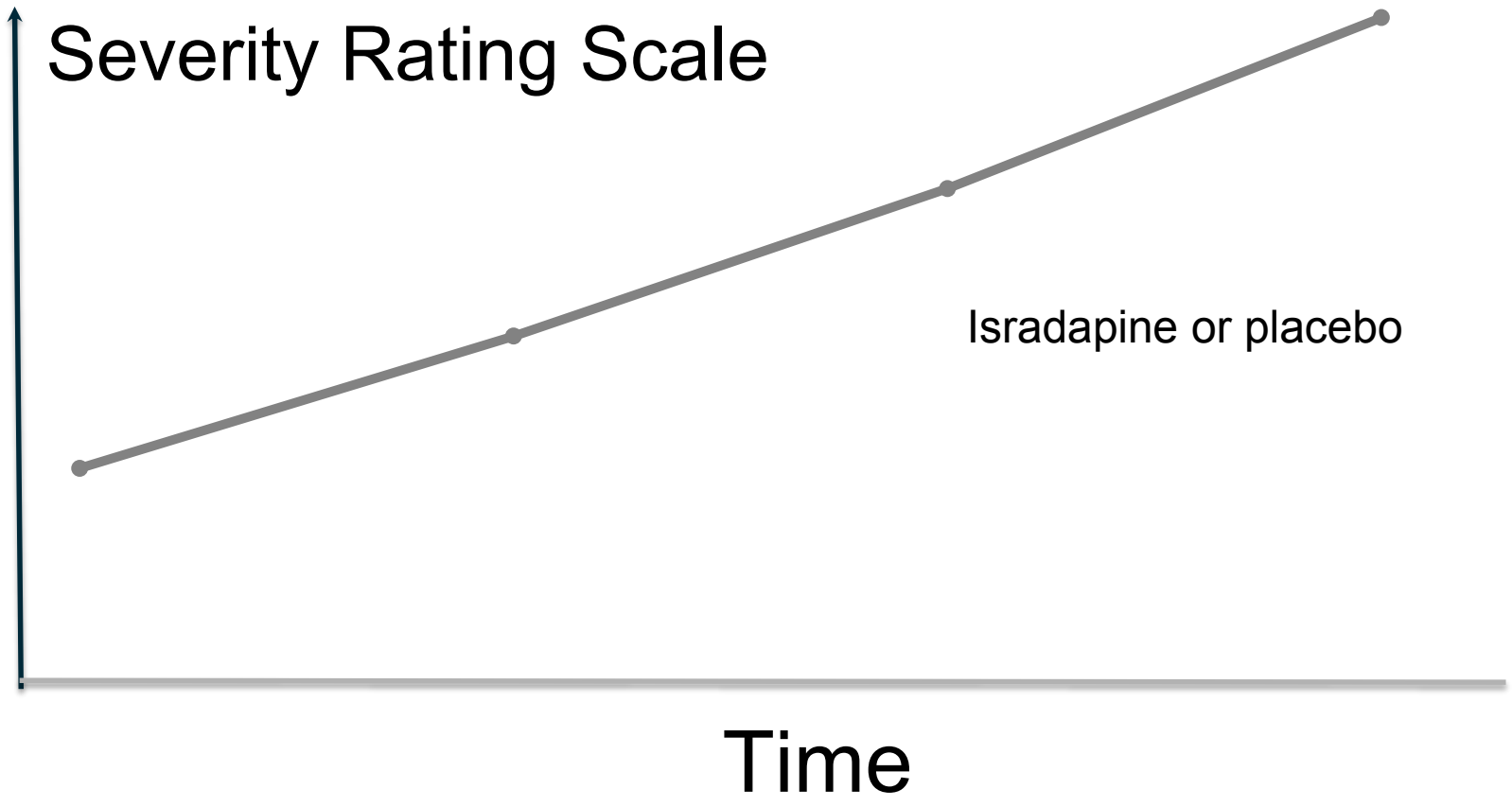
Here at Dartmouth-Hitchcock:

Isradapine: STEADY PD III trial: NIH sponsored study to show disease modification

- **announced at the AAN in May 2019**
- **No difference between Isradapine vs Placebo when followed over 3 years.**

Dartmouth-Hitchcock | Dartmouth GEISEL SCHOOL OF MEDICINE

Disease Modification



Disease modifying therapy trials

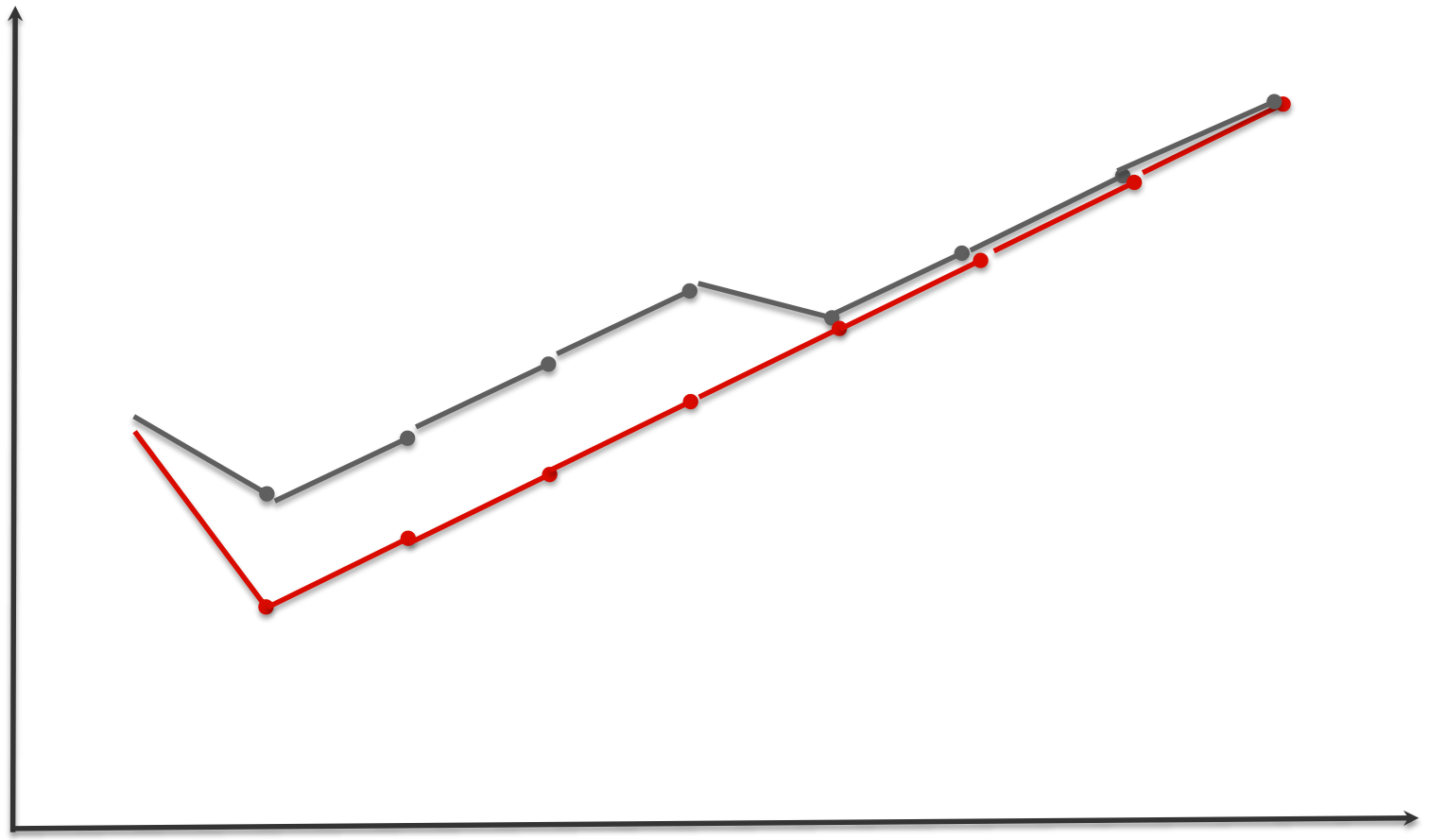
- Creatine
- Co-Q10
- Inosine (urate)
- Pioglitazone
- Isradapine

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 24, 2019 VOL. 380 NO. 4

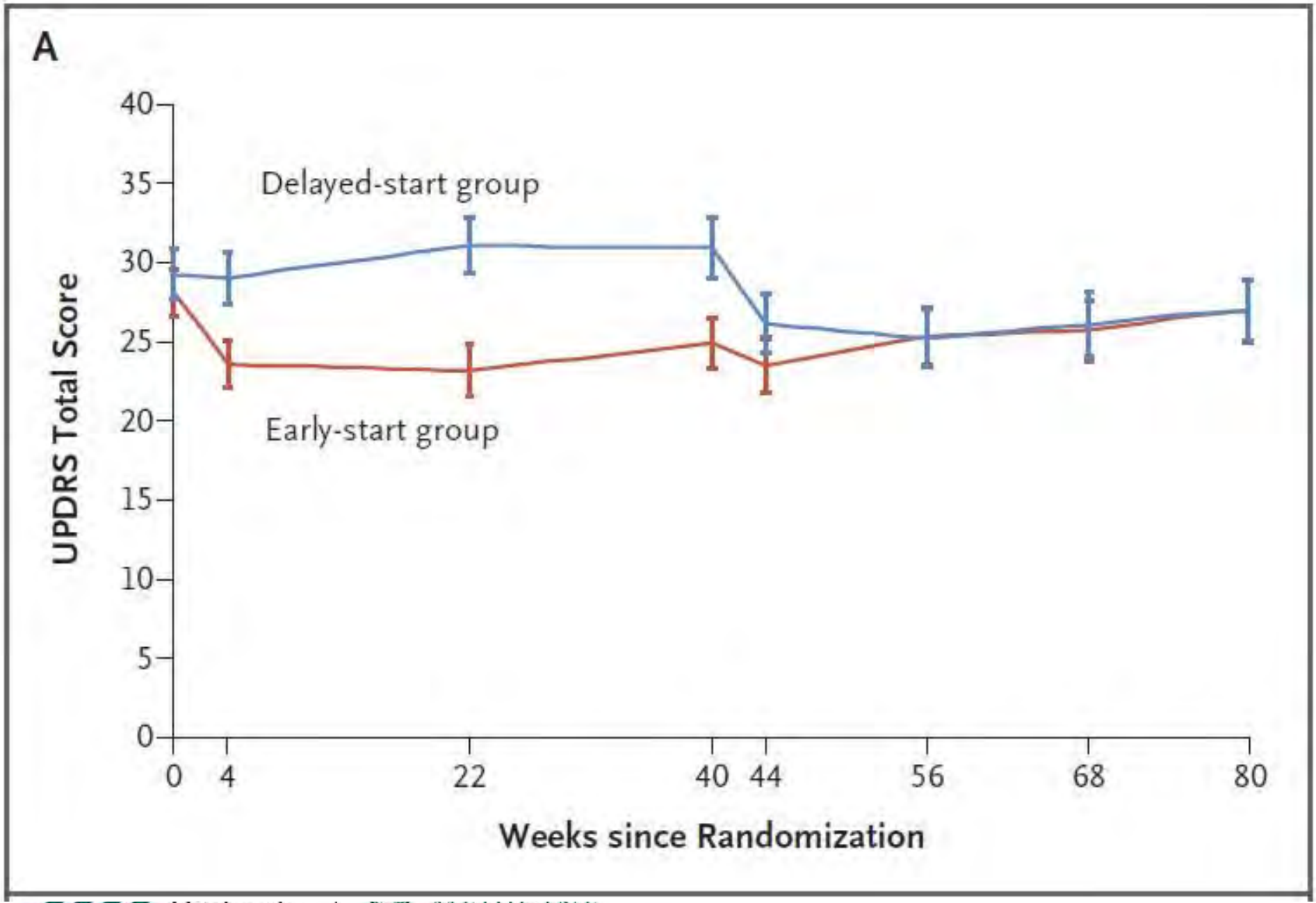
Randomized Delayed-Start Trial of Levodopa in Parkinson's Disease

C.V.M. Verschuur, S.R. Suwijn, J.A. Boel, B. Post, B.R. Bloem, J.J. van Hilten, T. van Laar, G. Tissingh, A.G. Munts, G. Deuschl, A.E. Lang, M.G.W. Dijkgraaf, R.J. de Haan, and R.M.A. de Bie, for the LEAP Study Group*



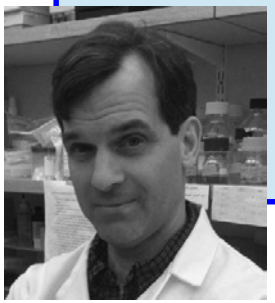
Dartmouth-Hitchcock

Dartmouth GEISEL SCHOOL OF MEDICINE

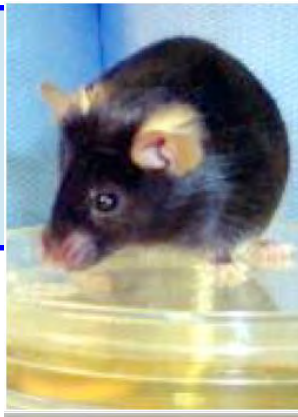

A
UPDRS Total Score
40
35
30
25
20
15
10
5
0
Delayed-start group
Early-start group
0
4
22
40
44
56
68
80
Weeks since Randomization

Take home message from the LEAPS trial

- Levodopa does not appear to accelerate PD
- Levodopa does not appear to increase risk for dyskinesia



Chronic Rotenone in Mice



Matthew C. Havrda PhD

Mus musculus

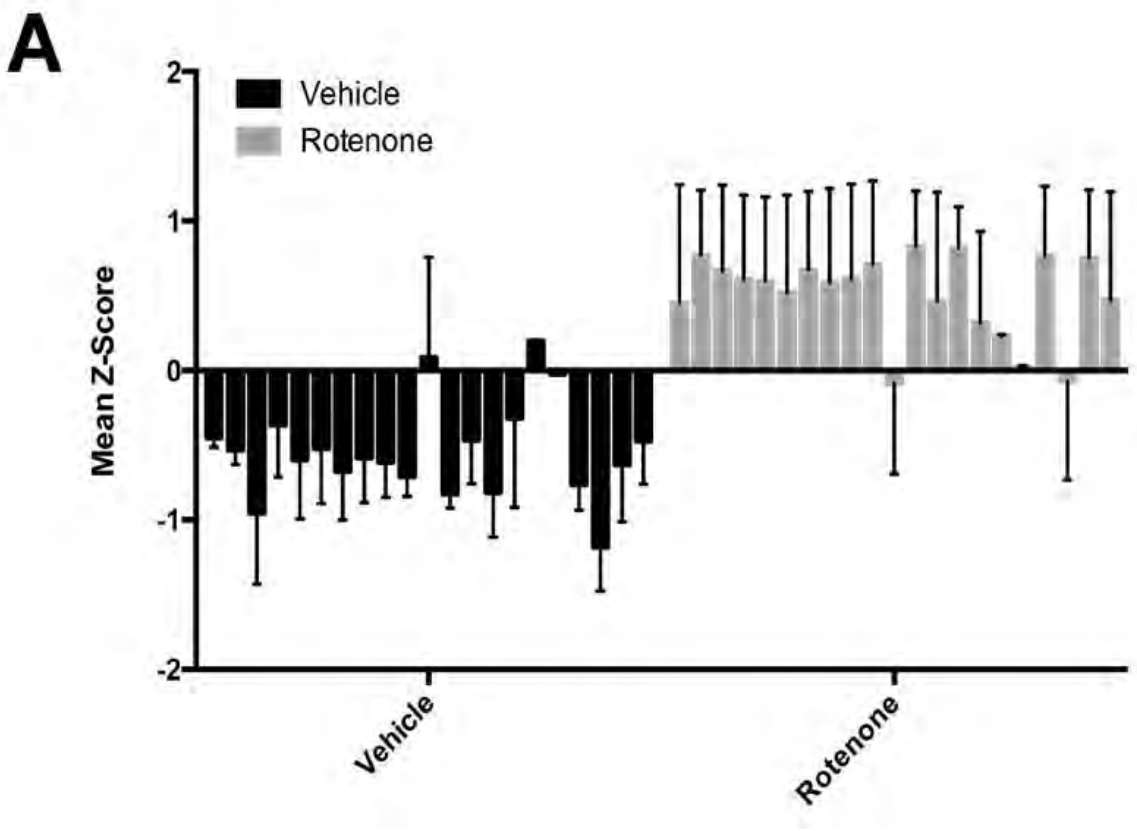


Table 1

Analyte	p value
G-CSF	0.32078
IL1b	0.04369
IL6	0.03002
Cxcl1	0.0063
IFNg	0.01068
IL1a	0.23858
IL7	0.09383
IL9	0.17032
IL10	0.14429
IL12p40	0.06895
IL12p70	0.86272
IL13	0.01301
IL15	0.30244
IL17	0.01614
IP10	0.49807
MCP-1	0.08382
M-CSF	0.02216
Cxcl9	0.03805
RANTES	0.20015
TNFa	0.08239
VEGF	0.29733

WPA-Dartmouth Biorepository

- Collaboration between Neuropathology (C. Harker Rhodes) & Bill Hickey and the Wisconsin Parkinson Association (WPA)

- 96 brain specimens
- 1 hemisphere cryopreserved
- Other hemisphere formalin fixed

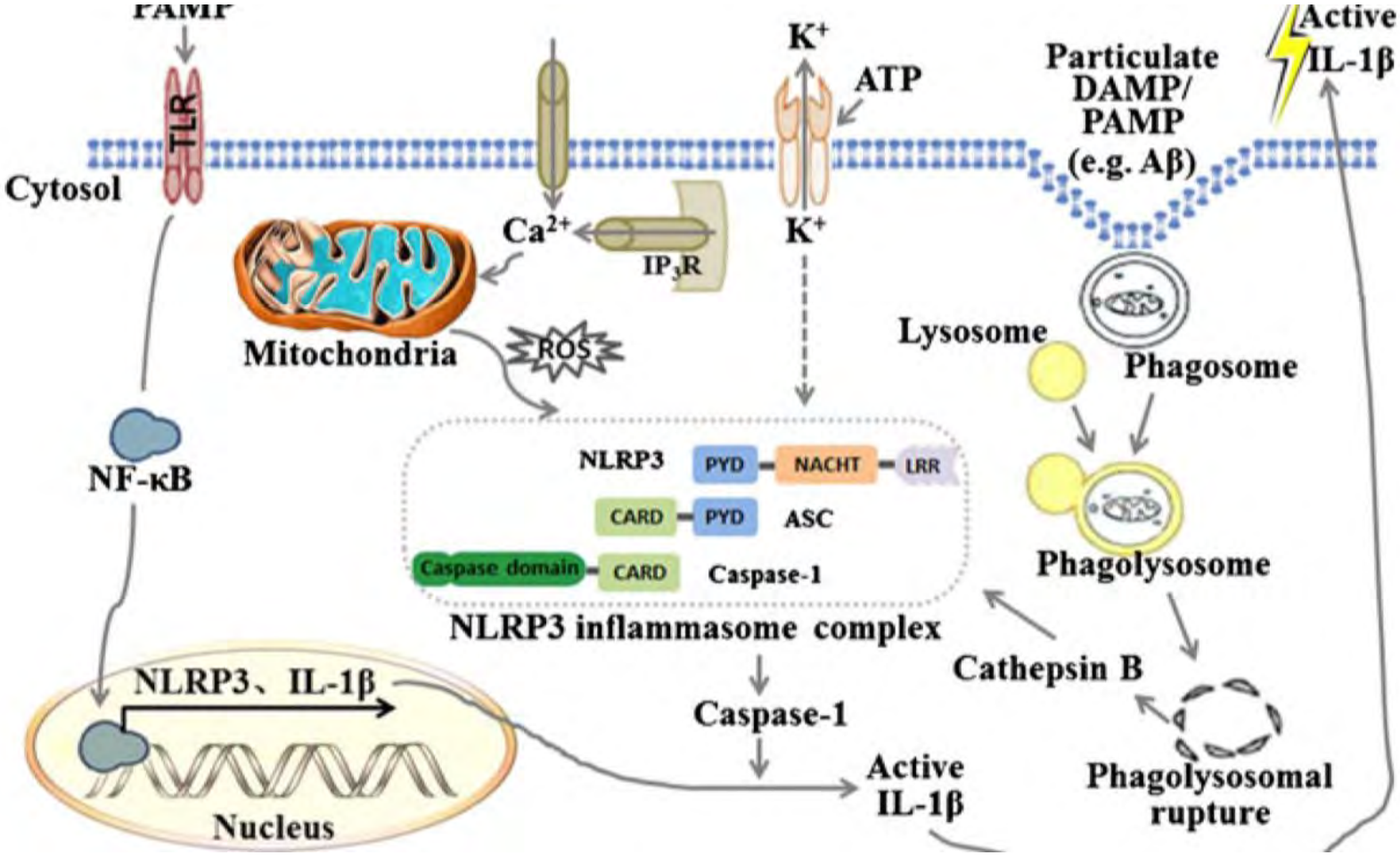
C Harker Rhodes

Bill Hickey

DHMC Parkinson's group

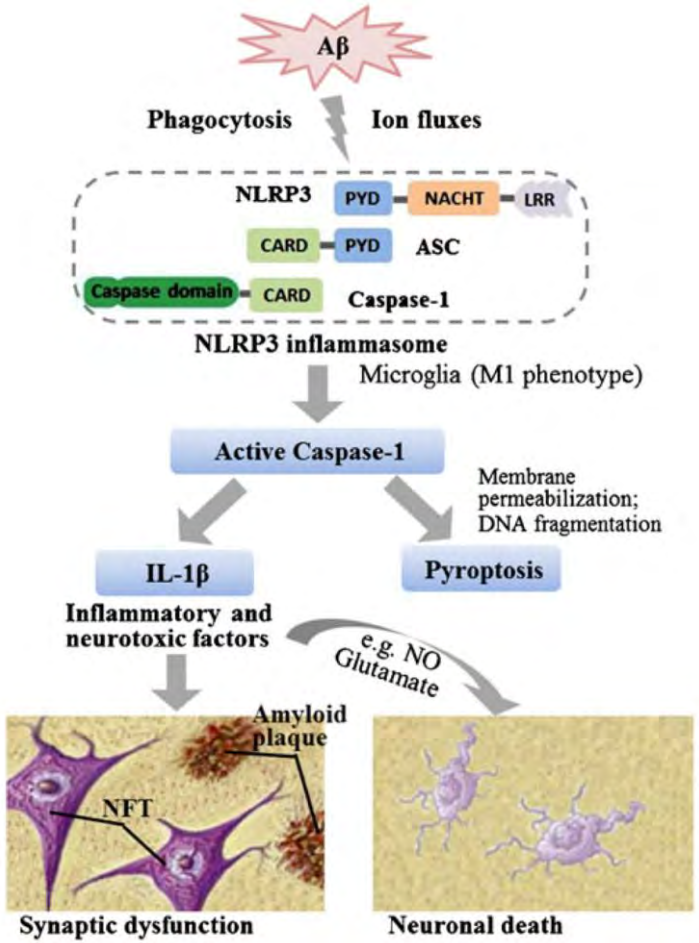
Dartmouth-Hitchcock | Dartmouth GEISEL SCHOOL OF MEDICINE

Inflammasomes in AD and PD



Tan et al., Mol Neurobiol 2013

Inflammasomes in AD and PD

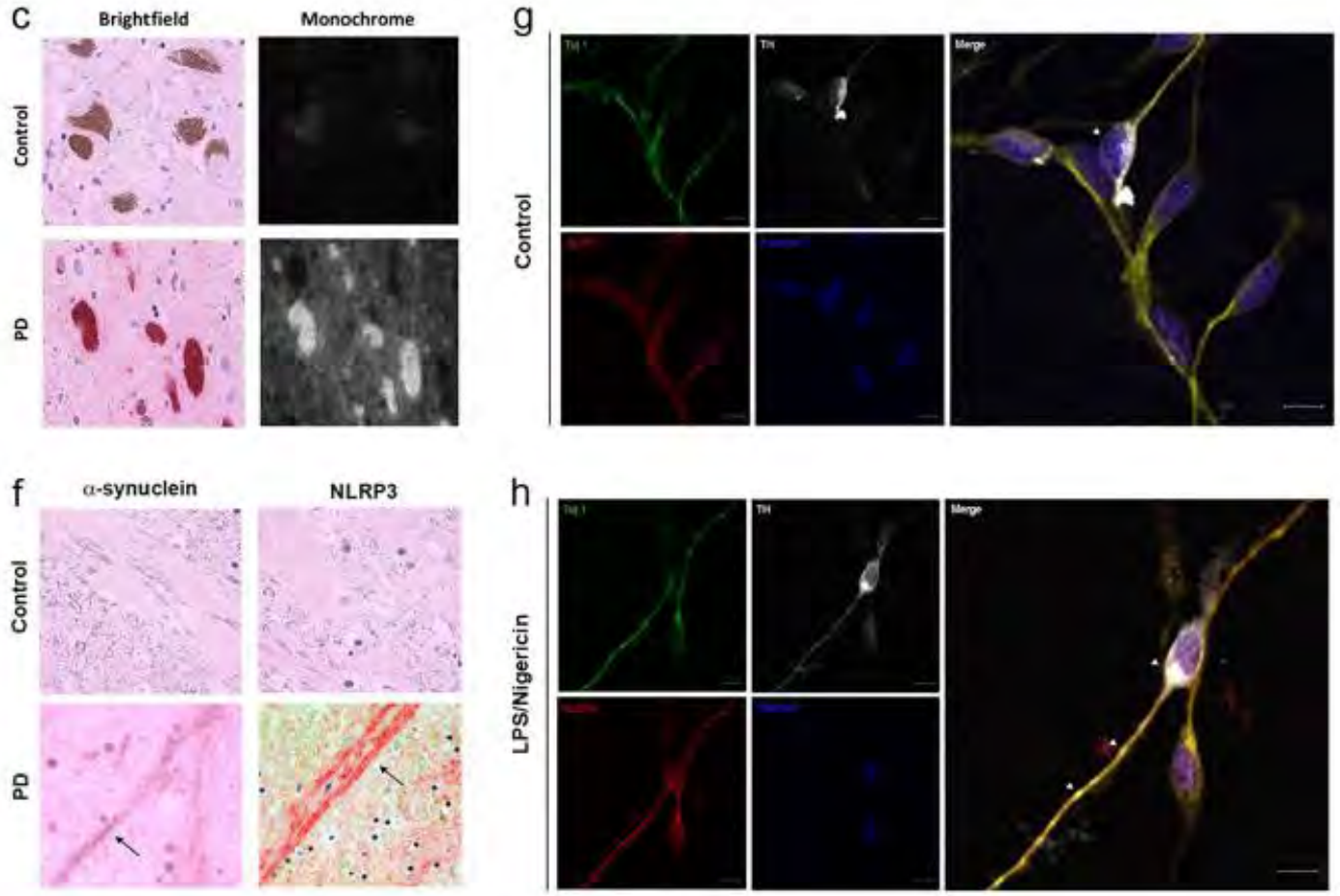


Tan et al., Mol Neurobiol 2013

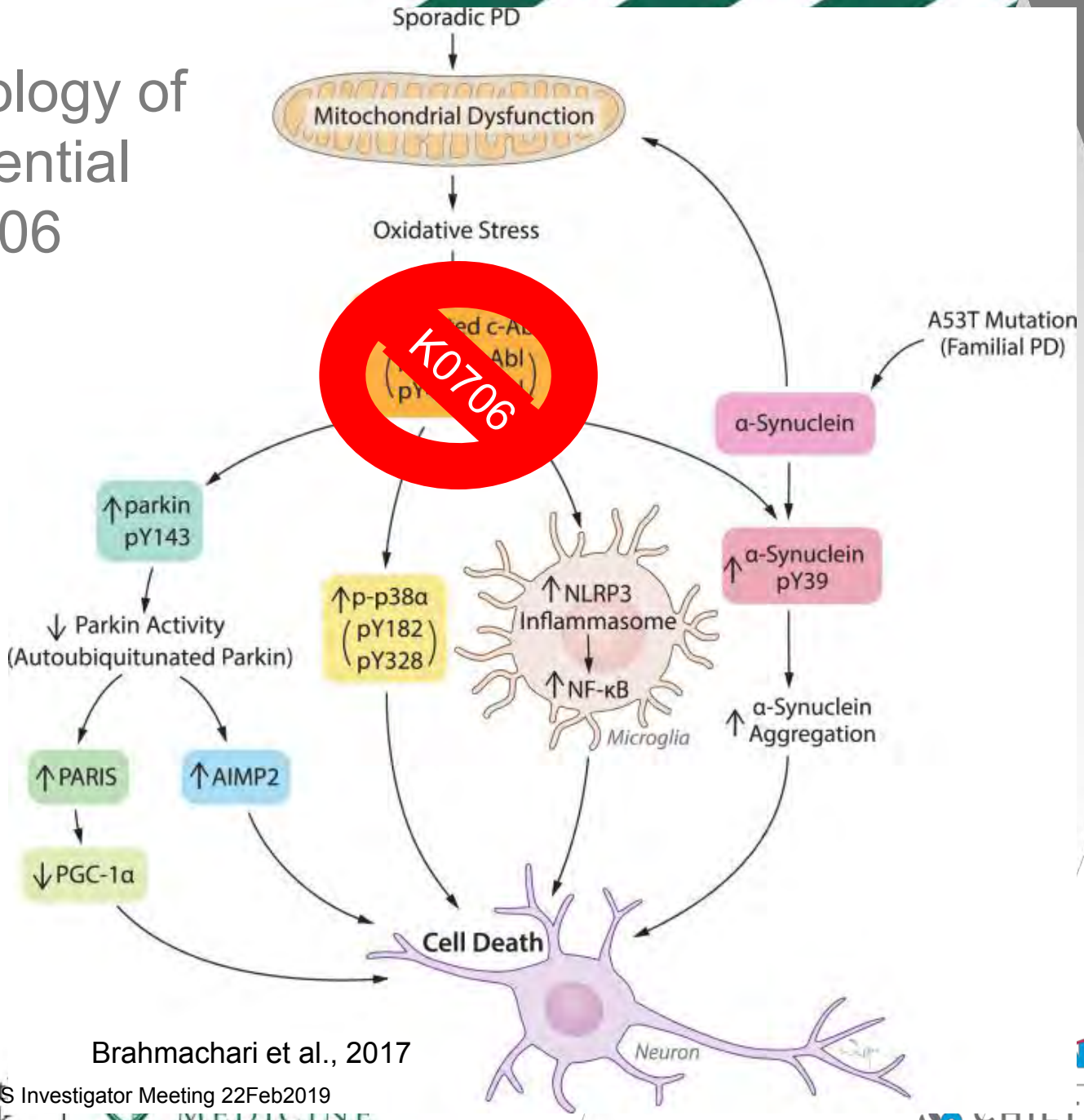
NLRP3 expression in mesencephalic neurons and characterization of a rare *NLRP3* polymorphism associated with decreased risk of Parkinson's disease

Katharine M. von Herrmann[1], Lucas A. Salas[1,2,3], Eileen M. Martinez[1], Alison L. Young[1], Joseph M. Howard[1], Mary S. Feldman[4], Brock C. Christensen[1,2,3], Owen M. Wilkins[1,2], Stephen L. Lee[5], William F. Hickey[5,6] and Matthew C. Havrda[1]

NLRP3 in mesencephalic neurons



Pathophysiology of PD and Potential Role of K0706



Brahmachari et al., 2017

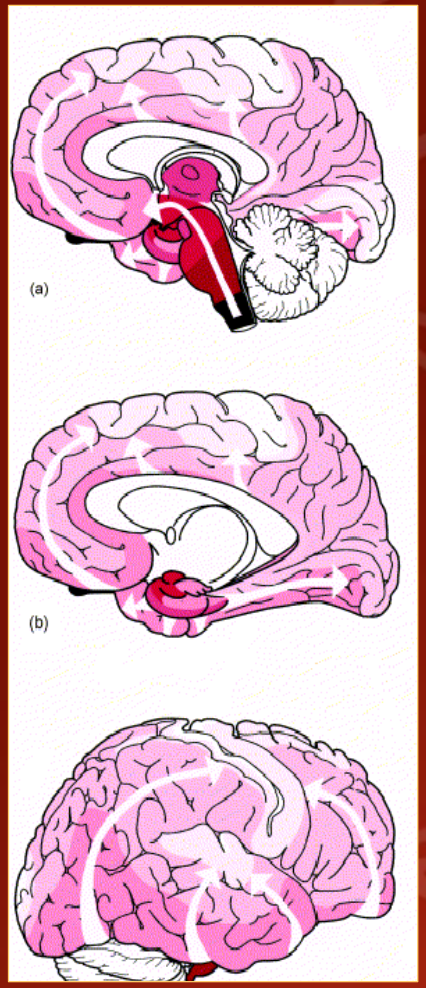
What is the Evidence of K0706 Slowing PD?

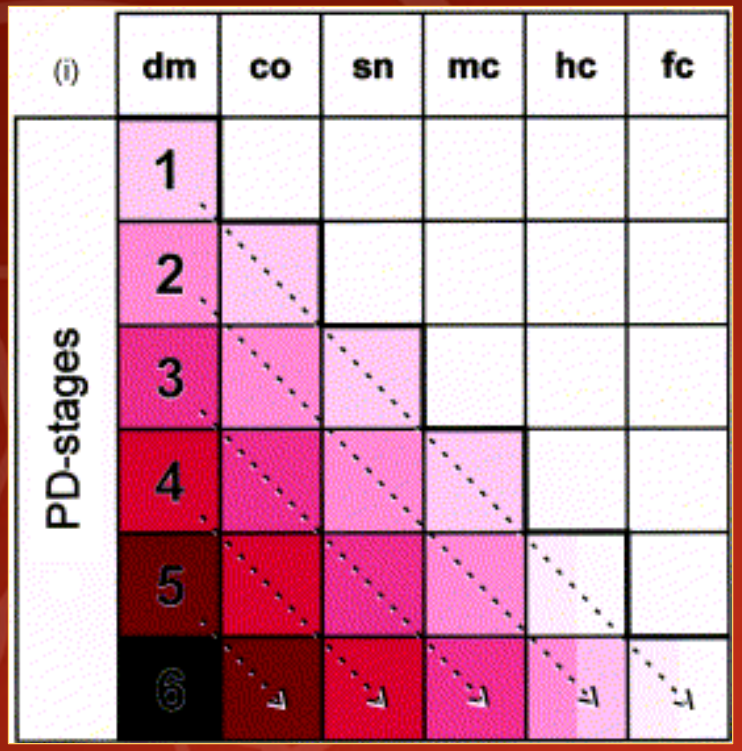
- No clinical data confirming that K0706 or other Abl TKIs slow disease progression in Parkinson's disease
- Multiple animal models have shown slowing of disease with multiple Abl-TKIs including K0706 (next slides)
- One published case series of 12 subjects with PD Dementia or Dementia with Lewy Bodies treated with nilotinib (Pagan et al., 2016). Drug was associated with hallucinations and reduced need for dopamine medication suggesting symptomatic effect. Two ongoing phase 2 studies of nilotinib in mid-stage PD subjects.
- Two ongoing phase 2 studies of nilotinib in mid-stage PD subjects.

Target validation in PD

- Confirm inflammasome activity in our biorepository.
- Evaluate for serum or CSF markers of inflammasome activity in PD patients

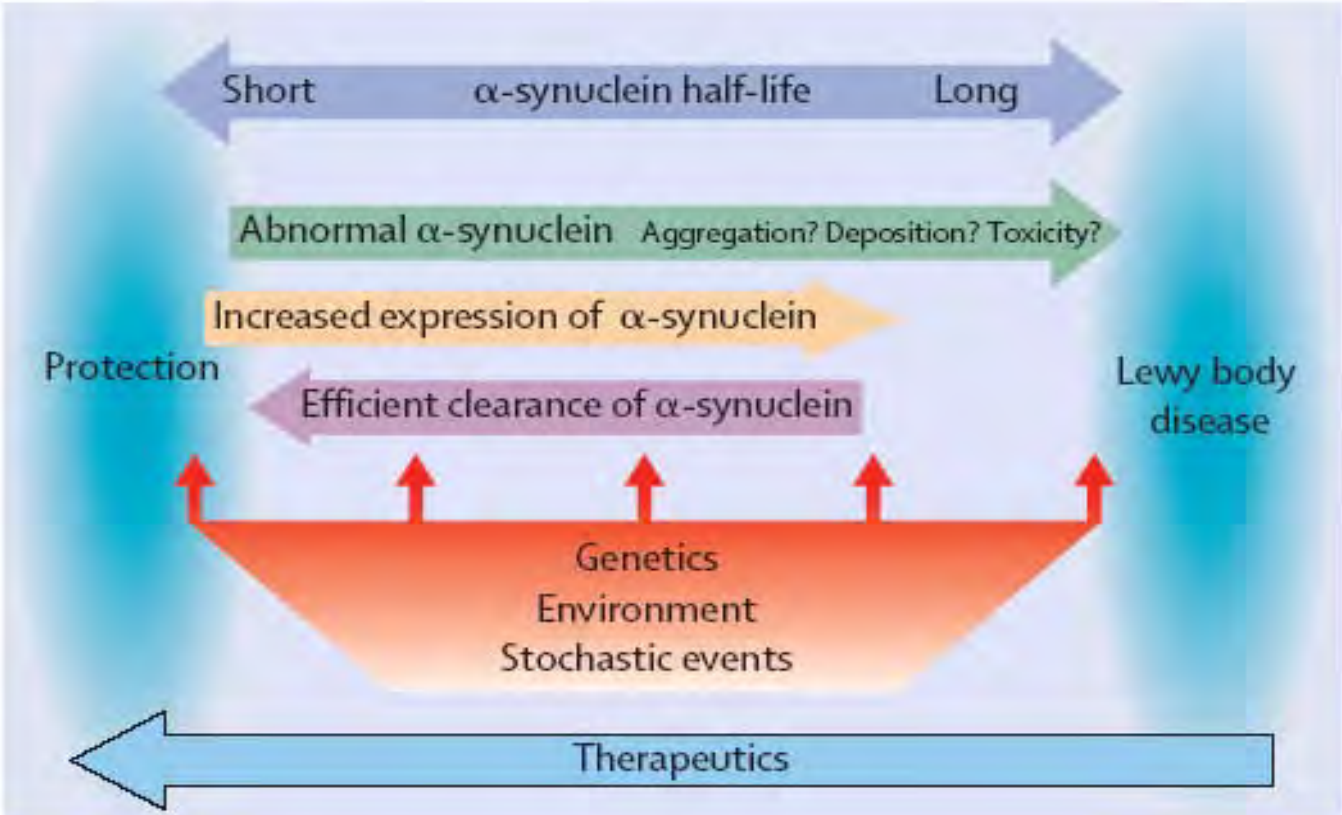
Lewy Body Pathology in PD





Braak et al. Neurobiol Aging 2003;24:197-211

α-synuclein: a matter of dose?



Singleton, Lancet 2004

FEATURED ARTICLE

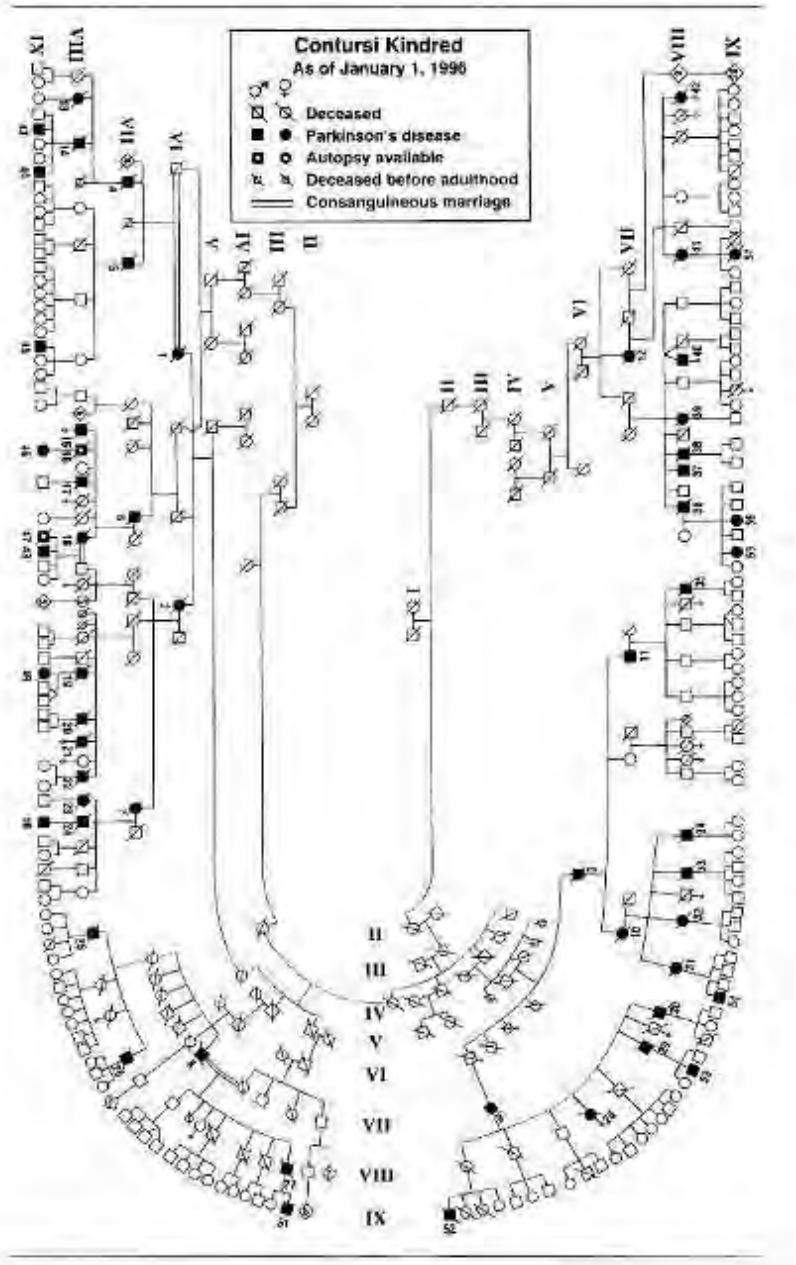
Is Alpha-Synuclein in the Colon a Biomarker for Premotor Parkinson's Disease? Evidence from 3 Cases

Kathleen M. Shannon, MD,[1]* Ali Keshavarzian, MD,[2] Hemraj B. Dodiya, MS,[3] Shriram Jakate, MD,[4] and Jeffrey H. Kordower, PhD[3]

[1]*Department of Neurological Sciences, Rush Medical College, Chicago, Illinois, USA*
[2]*Department of Gastroenterology and Nutrition, Rush Medical College, Chicago, Illinois, USA*
[3]*Department of Center for Brain Repair, Rush Medical College, Chicago, Illinois, USA*
[4]*Department of Pathology, Rush Medical College, Chicago, Illinois, USA*

Dartmouth-Hitchcock | Dartmouth GEISEL SCHOOL OF MEDICINE

The Contursi Kindred

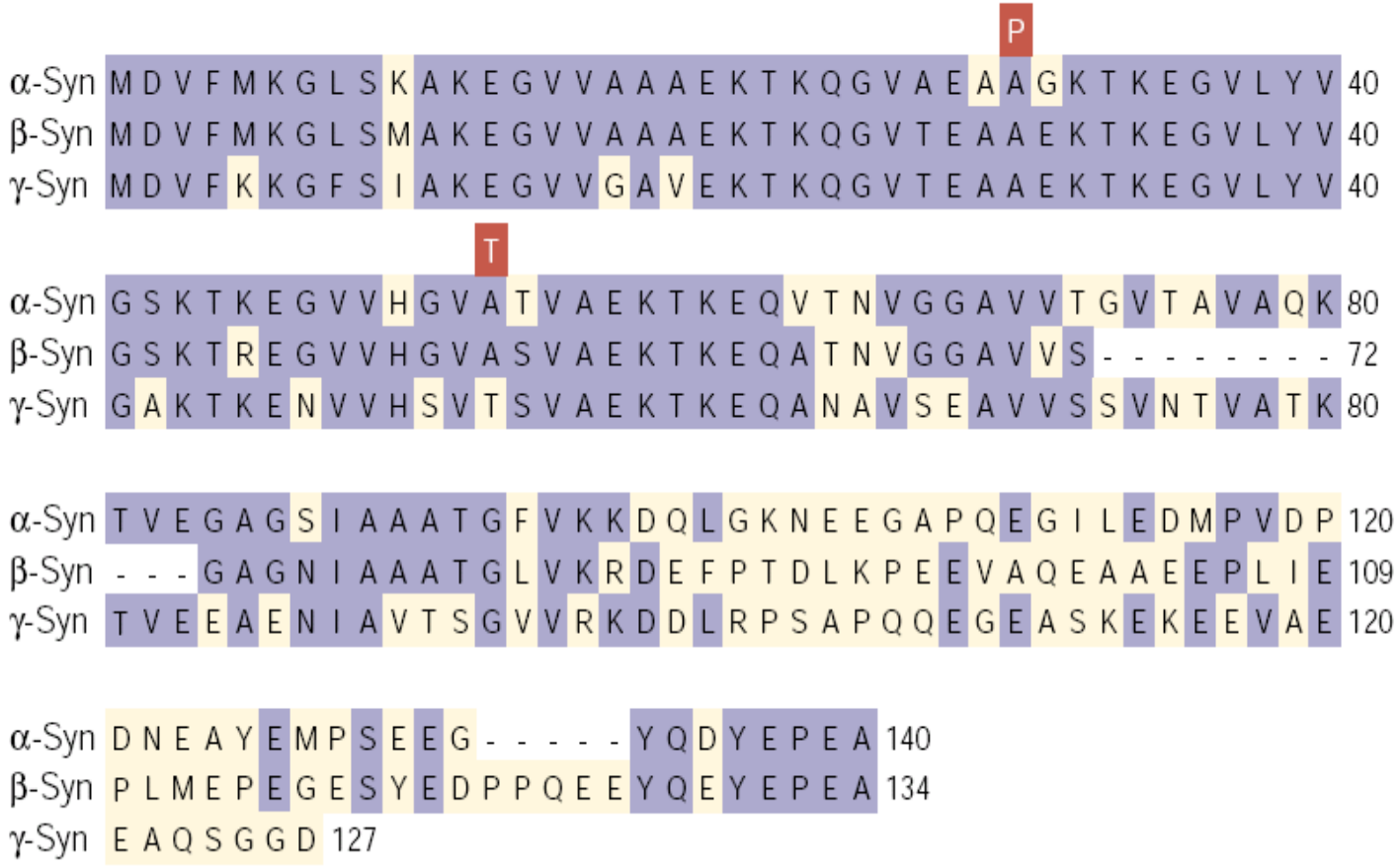


- Family studies
  - In very rare cases, PD tends to run in families.
  - Inheritance: AD with variable penetrance
  - Pathology: LB
  - Clinical presentation: Variable
  - Linkage analysis Chr 4p
  - D4s2380 Zmax 6.00

Mapping of a gene for Parkinson's disease to chromosome 4q21-q23.
Polymeropoulos et al. Science 1996

Mutation in the alpha-synuclein gene identified in families with Parkinson's disease

Polymeropoulos *et al. Science* 1997 276:2045-7.
Kruger et al. *Nat Genet* 1998 18:106-8.

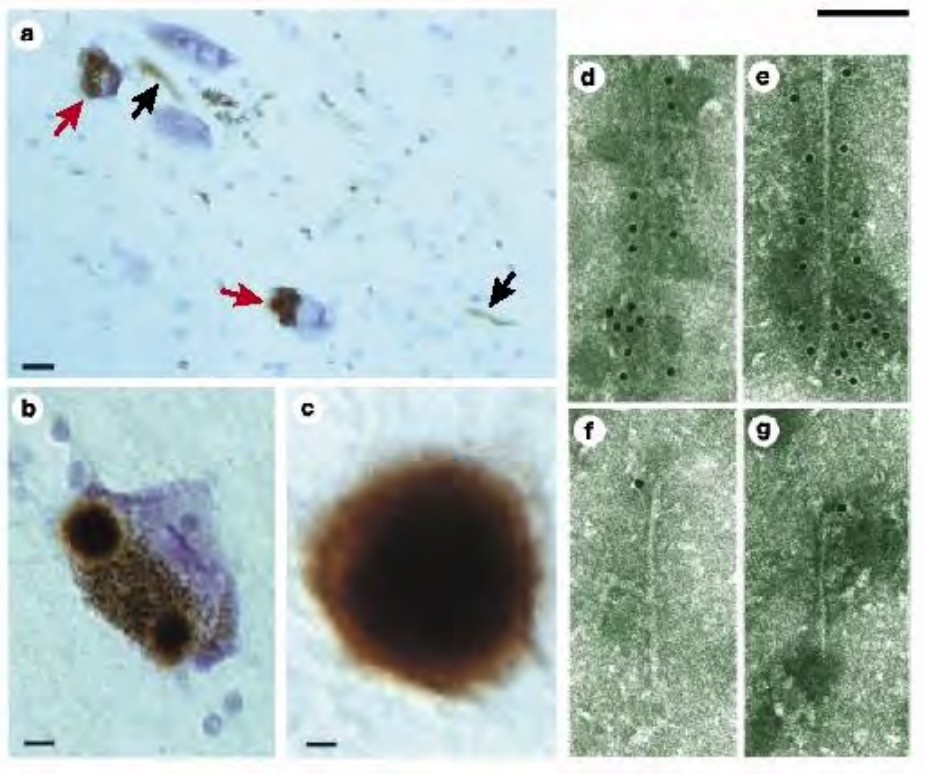


Goedert, Nat Rev Neurosci 2001.

PARK1: Alpha Synuclein

(Polymeropoulos et al., *Science* 1997)

- Autosomal dominant with variable penetrance
- A30P and A53T mutations discovered in Italian, Greek and German pedigrees.
- Exhaustive search for mutations in common forms of PD have been negative.
- Discovery of this gene facilitated the key discovery that alpha synuclein was a key component of Lewy bodies.



(Spillantini et al. *Nature* 1997)

Mapping PD loci: Elucidating a common molecular pathogenesis ?

Gene	Chr	Gene	Family	Clinical features	LB	Yr
PARK1	4p	αSyn	Contursi and Greek kindreds, a German kindred	AD, penetrance 85%, also in MSA	+	1997
PARK2	6q25	Parkin	Several consanguineous Japanese families	AR juvenile onset	-	1998
PARK3	2p13	Unknown	Several European kindreds	AD, reduced penetrance	+	1998
PARK4	4p14-16.3	αSyn	Iowa Kindred	AD, early onset	+	1999, 2003
PARK5	4p14	UCH-L1	A single German family		?	1999
PARK6	1p35-36	PINK1	A large Italian family	AR	?	2004
PARK7	1p36	DJ-1	Dutch family, Italian family	AR	?	2002
PARK8	12p11.2-q13.1	LRRK2	Japanese, Basque, Canadian-American (NE)	AD (Variable, DLB)	-/+	2004
PARK10	1p32	Unknown	DeCode, Icelandic ASP study	Late onset IPD	?	2002
PARK11	2q36-37	Unknown	Parkin negative N.A. ASPs	Late onset IPD	?	2002
FTDP-17	17q21.1	Tau	Multiplex families of iPD	FTDP-17 and PSP PD?		
NR4A2	2p22	Nurr1				2003

TABLE 1. Clinical features of PD patients

Case No./Gender	Age At Biopsy	Age At PD Symptom Onset
1/M	69	71
2/F	60	62
3/F	80	85

Abbreviations: M, male; F, female.

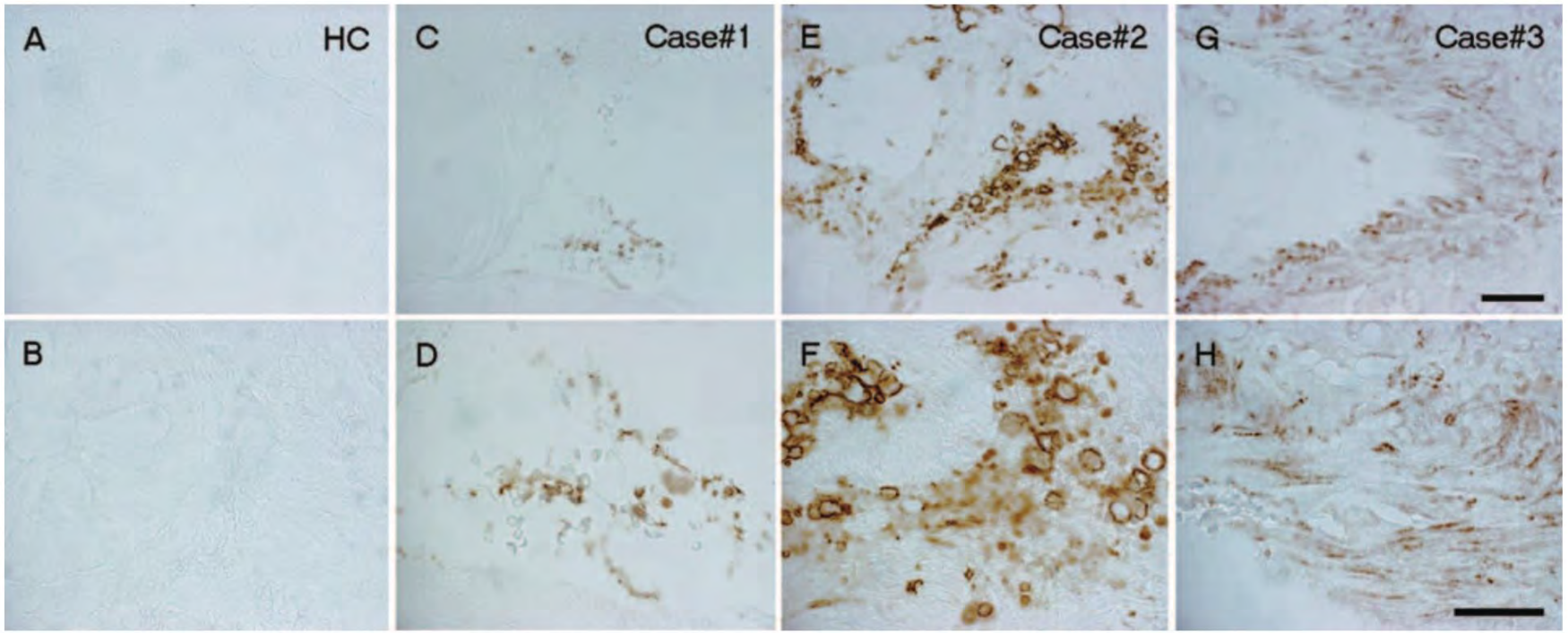


FIG. 1. Low- (A, C, E, and G) and high-power (B, D, F, and H) photomicrographs showing α-SYN histology through the colon from a healthy control (A and B), case 1 (2 years pre-PD diagnosis) (C and D), case 2 (2 years pre-PD diagnosis) (E and F), and case 3 (5 years pre-PD diagnosis) (G and H). Scale bar in (A, C, E, and G) represents 50 um and in (B, D, F, and H) represents 30 um.

Acta Neuropathol (2014) 127:235–241
DOI 10.1007/s00401-013-1214-6

ORIGINAL PAPER

Accumulation of α-synuclein in the bowel of patients in the pre-clinical phase of Parkinson's disease

David Hilton · Madeleine Stephens · Leanne Kirk · Philip Edwards · Ross Potter · John Zajicek · Ellie Broughton · Hannah Hagan · Camille Carroll

Received: 2 October 2013 / Revised: 8 November 2013 / Accepted: 9 November 2013 / Published online: 17 November 2013

Neuroprotection Pipeline: disease modification

Immunization against α-synuclein

- **α-synuclein is an abundant protein in the brain and blood, normal physiologic functions poorly understood**
- **? Which α-Syn aggregate species are most toxic to the neurons in PD**
- **Develop an immunization (passive/active immunity) against those toxic aggregates**

Neuroprotection Pipeline: disease modification

<u>Immunization against α-synuclein</u>

4 Clinical Trials underway currently, clinicaltrials.gov:

- NCT02216188 (active immunization)
- NCT01885494 (active immunization)
- NCT02267434 (active immunization)
- NCT02157714 (passive immunization)

Dartmouth-Hitchcock | Dartmouth GEISEL SCHOOL OF MEDICINE

Design and Status of the BIIB054 SPARK Trial

Parkinson Study Group, A. Siderowf (NY, USA)

Meeting: 2018 International Congress

Objective: To describe the design and status of the BIIB054 SPARK trial of the safety and potential efficacy of a monoclonal antibody (mAb) targeting alpha-synuclein (α-syn).

Background: Aggregated α-syn is a major constituent of Lewy bodies and is thought to play a central role in the pathology and progression of Parkinson's disease (PD). BIIB054 is a mAb that binds with sub-nanomolar affinity to the N-terminal region of aggregated α-syn with much lower affinity for the monomer. Favorable toxicology has been observed in chronic exposure studies in rats and monkeys. A first-in-human, single ascending dose study of BIIB054 in healthy controls and PD patients demonstrated a favorable safety and pharmacokinetic profile.

Neuroprotection Pipeline: disease modification

RECRUITING

Leucine Rich repeat Kinase 2 Inhibitors (LRRK2 inhibitors)

- May slow degenerative process
- May play a pivotal role for the future
- Further investigation needed

Future Drug Therapies for Motor Fluctuations

COMPLETED

For "off periods"

- **Inhaled-Levodopa** (CVT-301) Acorda Pharmaceuticals: in the treatment of "off" episodes in PD. Phase III is now underway. The medication will be inhaled with an actuator, for rapid delivery
- **Inhaled-Apomorphine (VR-040) –** phase III underway, Efficacy and safety of phase II trial were very successful

- **Sublingual Apomorphine (APL-130277)** Cynapsus – phase III currently underway. Another rescue therapy for off periods.

Future Drug Therapies for Motor Fluctuations

Here at Dartmouth-Hitchcock Medical Center, 2016-2017:

COMPLETED

A Phase III, Multicenter, Randomized, Double-Blind, Double-Dummy, Active- Controlled Study Comparing the Efficacy and Safety of Gastric Retentive, Controlled Release Accordion Pill™ Carbidopa/Levodopa (AP-CD/LD) to Immediate Release CD/LD in Fluctuating Parkinson's Disease Patients

- **32 wk study, for fluctuating PD patients currently on Levodopa with approximately 2.5 hours of "off time"**

Dartmouth-Hitchcock | Dartmouth GEISEL SCHOOL OF MEDICINE

Future Drug Therapies for Motor Fluctuations

Treatment of Dyskinesia

- **Amantadine ER** (***Osmolex and Gocovri***)– once daily, glutamate NMDA antagonist (anti-dyskinetic effect) – also increased "on" time, and did not cause insomnia as the immediate release formula did.
- **Eltoprazine** – selective partial agonist at the 5-HT1A/HT1B receptors with antidyskinetic activity, phase II trial underway.
- **Caffeine** – adenosine receptor antagonist; CALM PD study: consumption higher than 12 oz/day associated with less freq dyskinesia as compared with consumers of less than 4 oz/da

Dartmouth-Hitchcock | Dartmouth Geisel School of Medicine

Many other new drugs/Research being done

For **psychosis** (Pimavanserin),

Orthostatic hypotension (Droxidopa – Clinical trial approved by IRB here at DHMC, Mary Feldman, PI, Jeff Cohen, MD)

New meds for **dementia** being investigated,

Gene therapy,

Research into **balance/gait** (Dr. Lee's visual adaptation study underway here at DHMC),

More **targets** for **DBS surgery**

Neuroinflammation (translational study "Inflammasomes in PD" sponsored by Michael J Fox Foundation, Matt Havrda, PhD, PI, Steve Lee, Mary Feldman).

Pathological α-Synuclein in Gastrointestinal Tissues from Prodromal Parkinson Disease Patients

Morten Gersel Stokholm, MD,[1] Erik Hvid Danielsen, MD, PhD,[2]
Stephen Jacques Hamilton-Dutoit, MD, DMSc,[3] and
Per Borghammer, MD, PhD, DMSc[1]

Objective: It has been hypothesized that Lewy pathology initiates in the enteric nervous system years prior to debut of clinical motor symptoms in Parkinson disease patients. This study investigates whether Lewy pathology is present in various gastrointestinal tract tissues from Parkinson disease patients in the prodromal phase.
Methods: We used the Danish National Pathology Registry to identify archived paraffin-embedded tissue blocks from 57 Parkinson disease patients (98 blocks) and 90 control subjects (98 blocks). We employed 2 different immunohistochemistry techniques visualizing aggregated α-synuclein and phosphorylated α-synuclein.
Results: Thirty-nine Parkinson disease patients contributed tissues obtained in the prodromal disease phase, whereas 18 Parkinson disease patients contributed tissues obtained solely after Parkinson diagnosis. Prodromal tissues were obtained on average 7.0 years prior to diagnosis (range = 20 years to 4 months), and postdiagnosis tissue on average 2.8 years after diagnosis (range = 2 days to 18 years). Phosphorylated α-synuclein positivity was seen in 22 of 39 (56%) prodromal Parkinson disease subjects and 30 of 67 (45%) prodromal tissue blocks. These fractions were significantly higher compared to control subjects ($p = 0.0001$ and $p = 0.0032$, respectively). In contrast, no significant difference was seen in the positivity rate between prodromal Parkinson disease patients and controls when using the aggregated α-synuclein immunohistochemistry technique.
Interpretation: We detected Lewy pathology in the gastrointestinal tract of patients up to 20 years prior to their Parkinson disease diagnosis. These findings are in accordance with a hypothesized prodromal disease phase spanning 10 to 20 years.

ANN NEUROL 2016;79:940–949

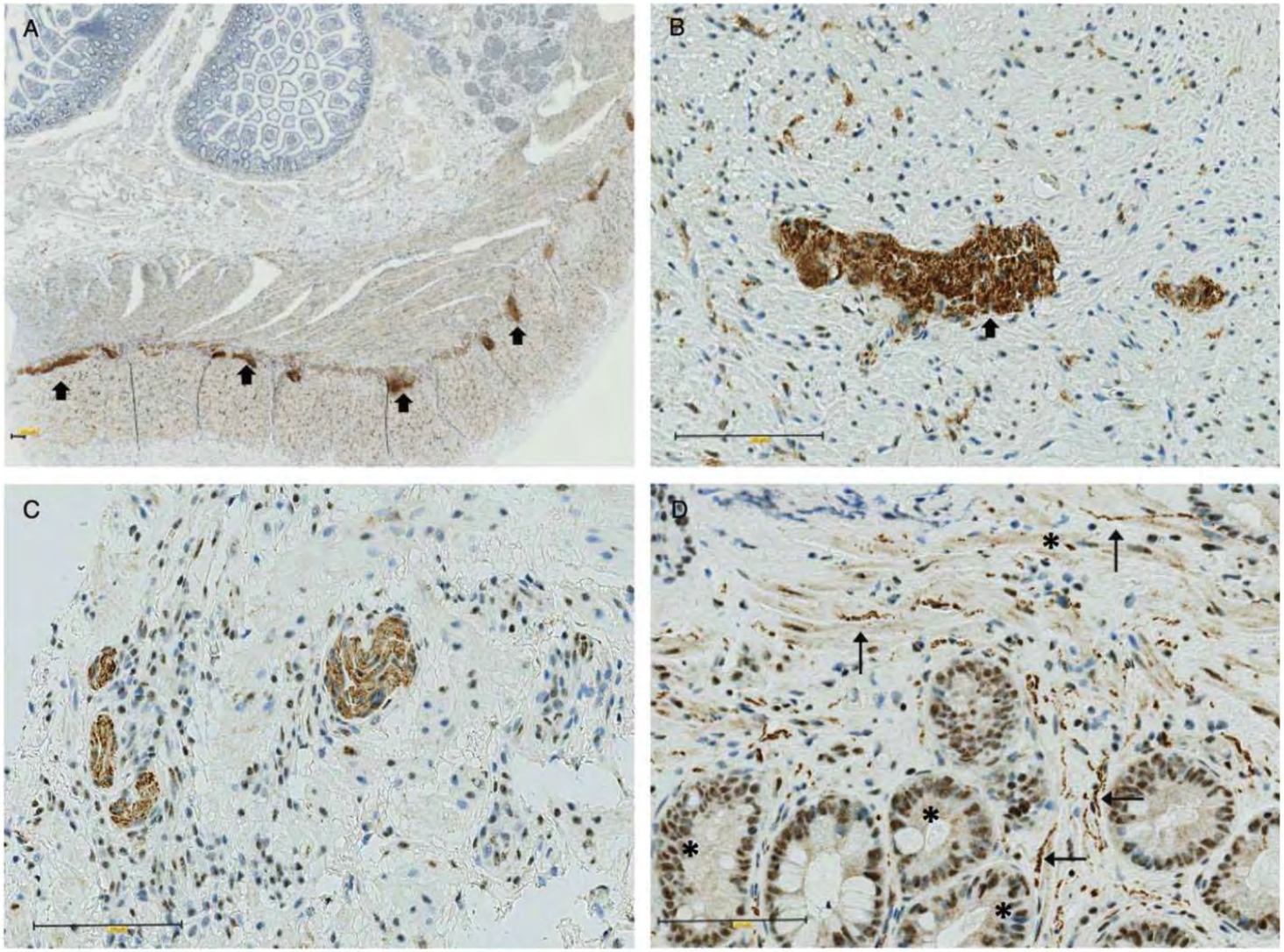


FIGURE 3: Gastrointestinal tract tissues stained with phosphorylated α-synuclein immunohistochemistry. Scale bars represent 100μm; thin and thick arrows indicate positive neurites and plexuses, respectively; asterisks indicate nonspecific staining in non-neural structures. (A) Small intestine, Parkinson disease (PD) patient. (B) Plexus in appendix, control subject. (C) Nerves in stomach, PD patient. (D) Esophagus, PD patient.

STEPS-PD

frontiers in NEUROLOGY

ORIGINAL RESEARCH ARTICLE
published: 28 September 2012
doi: 10.3389/fneur.2012.00132

Moving forward with prisms: sensory-motor adaptation improves gait initiation in Parkinson's disease

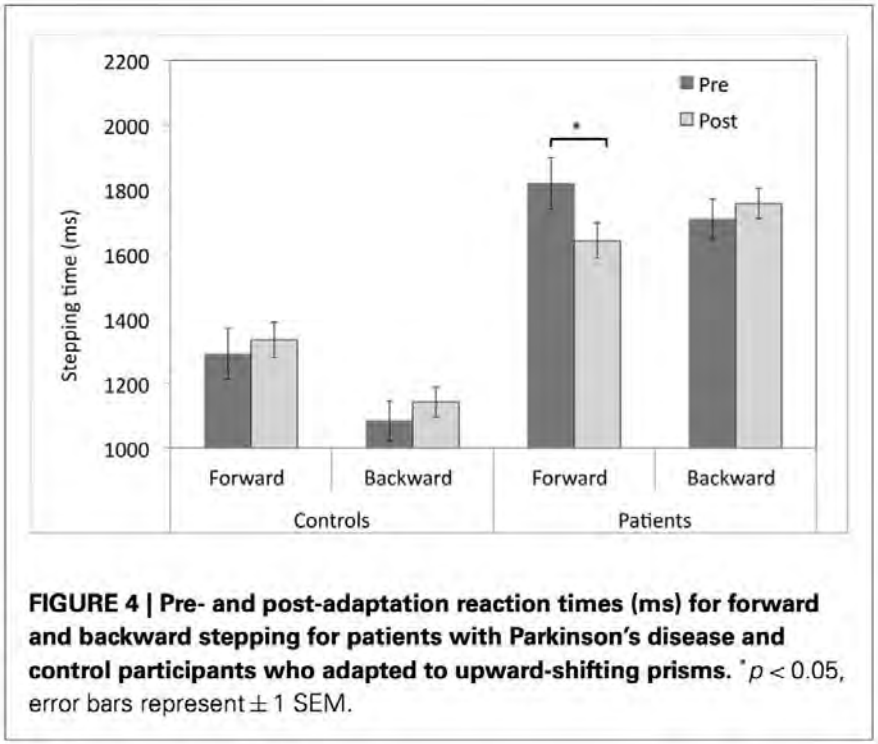
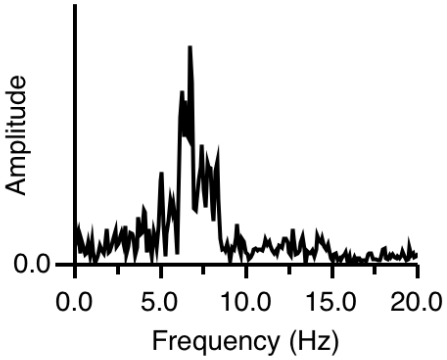


FIGURE 4 | Pre- and post-adaptation reaction times (ms) for forward and backward stepping for patients with Parkinson's disease and control participants who adapted to upward-shifting prisms. $^{*}p < 0.05$, error bars represent ± 1 SEM.

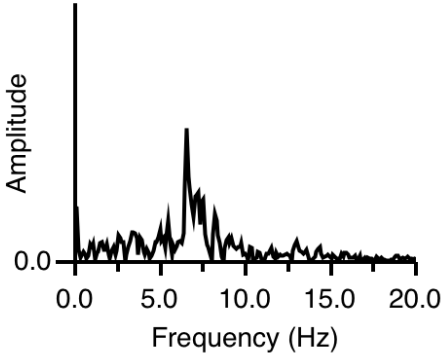
CANNABINOIDS AND PARKINSON'S DISEASE

Dartmouth-Hitchcock | Dartmouth GEISEL SCHOOL OF MEDICINE

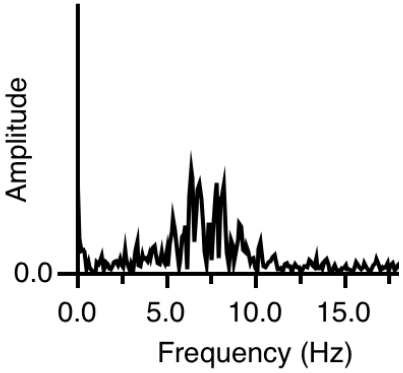
Dominant Frequency: 6.35 Hz



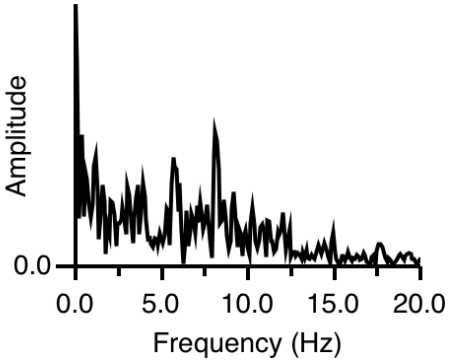
Dominant Frequency: 7.13 Hz



Dominant Frequency: 6.74 H



Dominant Frequency: 8.11 Hz



Conclusions

- Genetic, epidemiologic, and pathologic studies
  - multiple environmental triggers
  - multiple genetic susceptibilities
  - common final pathway of synucleinopathy

Dartmouth-Hitchcock

Dartmouth GEISEL SCHOOL OF MEDICINE

Questions?

Dartmouth-Hitchcock | Dartmouth GEISEL SCHOOL OF MEDICINE