Neuroprotection in Parkinson's Disease

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Current Therapy in PD

- Parkinson's Disease is one of the only "neurodegenerative" diseases in which medications alleviate symptoms
- The advent of carbidopa/levodopa significantly altered longevity in PD patients
- DBS therapy has allowed improved management in a number of patients
- Many years into PD, motor symptoms take a back seat to other problems, and we are more limited in therapies for these problems.

Table 259">

Table 2 *Progression of disability in IPD: latencies to reach successive H+Y stages*

Study	HY 1	HY 2	HY 3	HY 4	HY 5
Pre-levodopa					
Hoehn + Yahr, 1967	3.0	6.0	7.0	9.0	14.0
Marttila + Rinne, 1977	—	2.9	5.5	7.5	9.7
Post-levodopa					
Hoehn, 1983	—	9.0	12.0	12.0	18.0
Hely et al., 1999	—	—	4.0	7.0	6.0
Müller et al., 2000	—	3.0	5.5	14.0	15.0
Lücking et al., 2000	—	11.0	19.0	26.0	40.0

Poewe, W. Neurology 2006;66:S2-S9

Table Predominant problems among surviving subjects at 15 years of follow-up

	Percent of subjects experiencing
Neuropsychiatric	
Cognitive decline	84
Dementia	48
Daytime sleepiness	79
Depression (mostly mild)	50
Hallucinations	21
Axial motor	
Falls	81
Fractures	23
Dysphagia	50
Severe dysarthria	27
Autonomic	
Urinary incontinence	41
Symptomatic postural hypotension	35

Marras, C. et al. Neurology 2008;70:1996-2003

As reported by Hely et al.[29]

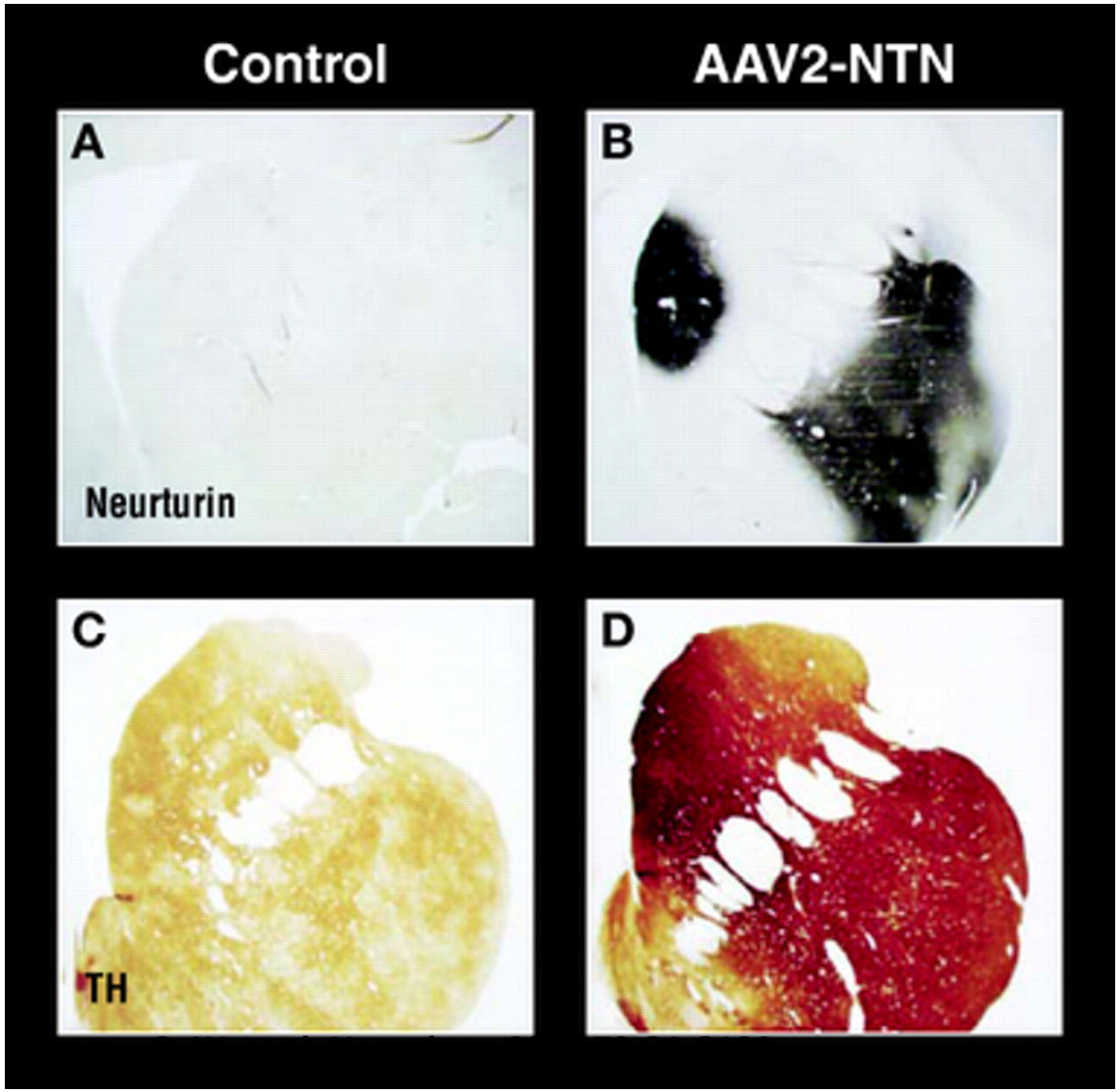
What are people doing to slow down PD?

- Other therapies further treat symptoms.
- Some are thought to be neuroprotective and efforts are being made to prove this (selegiline, rasagiline, Mirapex and Mirapex LA
- Tons of studies as seen below…..but.

TABLE 1. *Randomized trials of neuroprotective agents in Parkinson's disease*[a]

Trials	Active agents	Putative mechanisms	N	Primary outcomes*
Completed, Published Trials				
1. Tetrud and Langston[15]	selegiline	antioxidant/anti-apoptotic	54	Time to levodopa Rx
2. DATATOP[4]	selegiline and tocopherol	antioxidant/anti-apoptotic	800	Time to levodopa Rx
3. SINDEPAR[16]	selegiline[b]	antioxidant/anti-apoptotic	101	Change in UPDRS
4. ROADS[17]	lazabemide (4 dosages)	antioxidant/anti-apoptotic	321	Time to levodopa Rx
5. Swedish Selegiline[18]	selegiline	antioxidant/anti-apoptotic	157	Time to levodopa Rx
6. Norwegian-Danish[19]	selegiline	antioxidant/anti-apoptotic	163	Change in UPDRS
7. QE2[20]	coenzyme Q10 (3 dosages)	antioxidant/mitochondrial stabilizer	80	Change in UPDRS
8. Jankovic and Hunter[21]	riluzole	NMDA antagonist	20	Change in UPDRS
9. TEMPO[22]	rasagiline (2 dosages)	antioxidant/anti-apoptotic	404	Change in UPDRS
10. ELLDOPA[5]	levodopa (3 dosages)	dopaminergic	361	Change in UPDRS
11. U.K. Low-dose Pergolide[23]	pergolide	antioxidant	106	Time to levodopa Rx
12. NET-PD futility #1[24]	minocycline, creatine	anti-inflammatory, mitochondrial stabilizer	200	Change in UPDRS
13. TCH346[25]	TCH346 (3 dosages)	anti-apoptotic	301	Time to dopaminergic Rx
14. NET-PD futility #2[26]	GPI-1485, coenzyme Q10	trophic factor antioxidant, mitochondrial stabilizer	213	Change in UPDRS
15. PRECEPT[27]	CEP-1347 (3 dosages)	anti-apoptotic	806	Time to dopaminergic Rx
Ongoing or Unpublished Trials				
16. NIL-A[c] (completed 2002)	GPI-1485 (2 dosages)	trophic factor	300	Change in UPDRS motor
17. Riluzole[c] (completed 2002)	riluzole (2 dosages)	NMDA antagonist	1084	Time to dopaminergic Rx
18. Guilford GPI-1485[d] (completed 2006)	GPI-1485	trophic factor	~200	Change in UPDRS
19. MitoQ trial[e] (completed 2007)	mitoquinone (2 dosages)	mitochondrial antioxidant	120	Change in UPDRS
20. QE3[f]	coenzyme Q10 (2 dosages)	antioxidant/mitochondrial stabilizer	600	Change in UPDRS
21. ADAGIO[g] (completed 2008)	rasagiline (2 dosages)	antioxidant/anti-apoptotic	1176	Change in UPDRS
22. NET-PD LS Creatine[h]	creatine	mitochondrial stabilizer	1720	Global statistic
23. PROUD[i]	pramipexole	dopaminergic	535	Not reported

Disappointing Gene Therapy Trials



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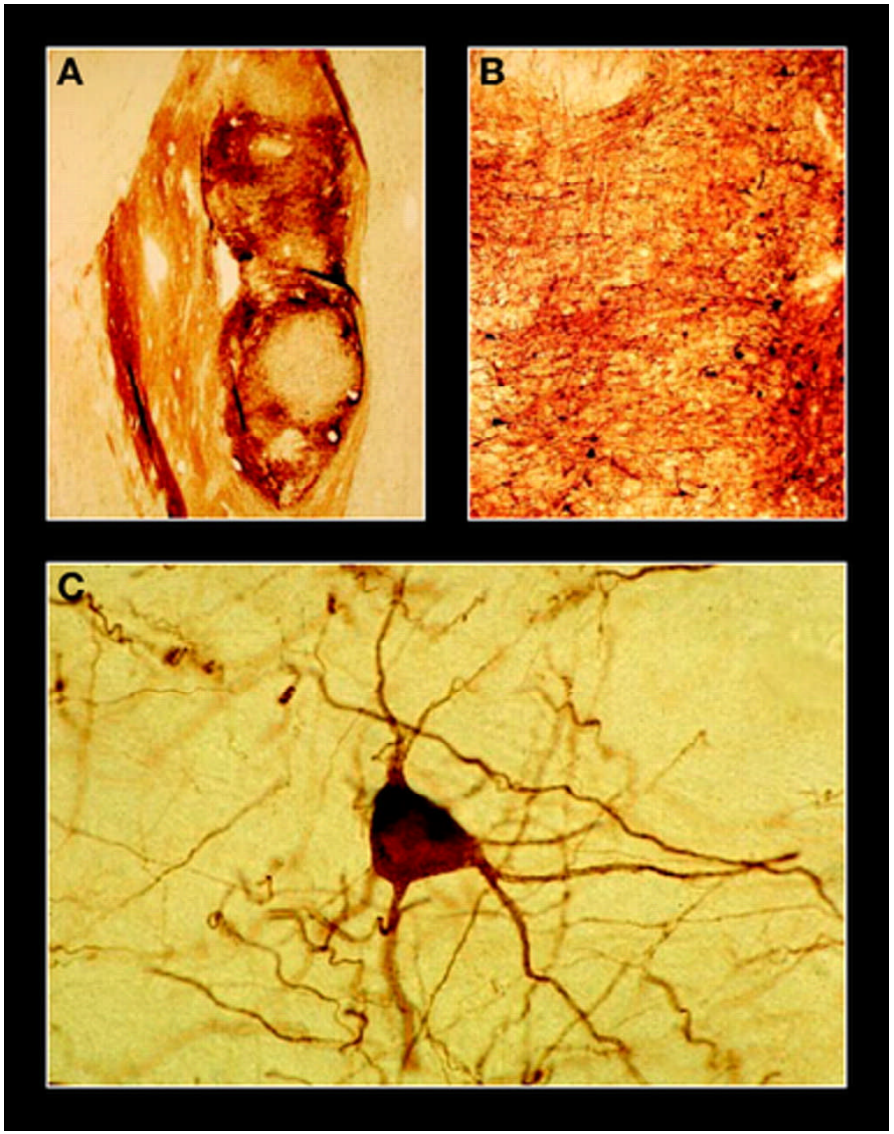
Disappointing Stem Cell Trials



Olanow, C. W. et al. Neurology 2009;72:S1-S136

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I can't get no satisfaction

Still no neuroprotection for Parkinson disease

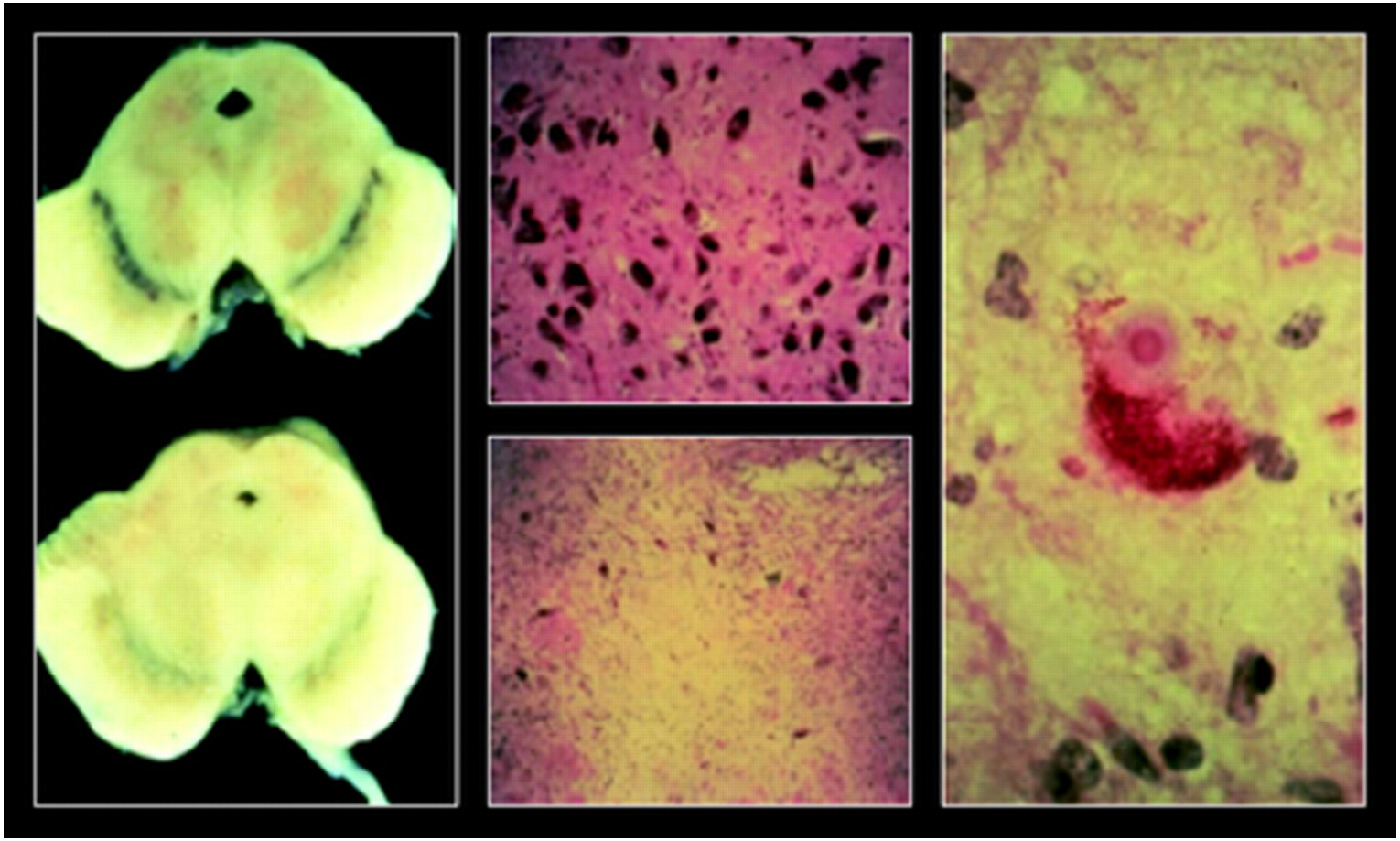
- Editorial written following PSG Trial based on CEP-1347, an anti-apoptotic therapy in PD
- 2 points made in this editorial
  - ?Animal Models for PD
  - ?simplification of apoptosis vs. necrosis of cells

J. Eric Ahlskog
Neurology 2007;69;1476-1477

Back to the Drawing Board!

- What are we protecting from?
- Retrospective thinking
- Faulty logic based on grossly incomplete models of PD
- Measurements of PD progression very limited
- Inability to “screen” good compounds based on poor animal models

Parkinson's as we were taught



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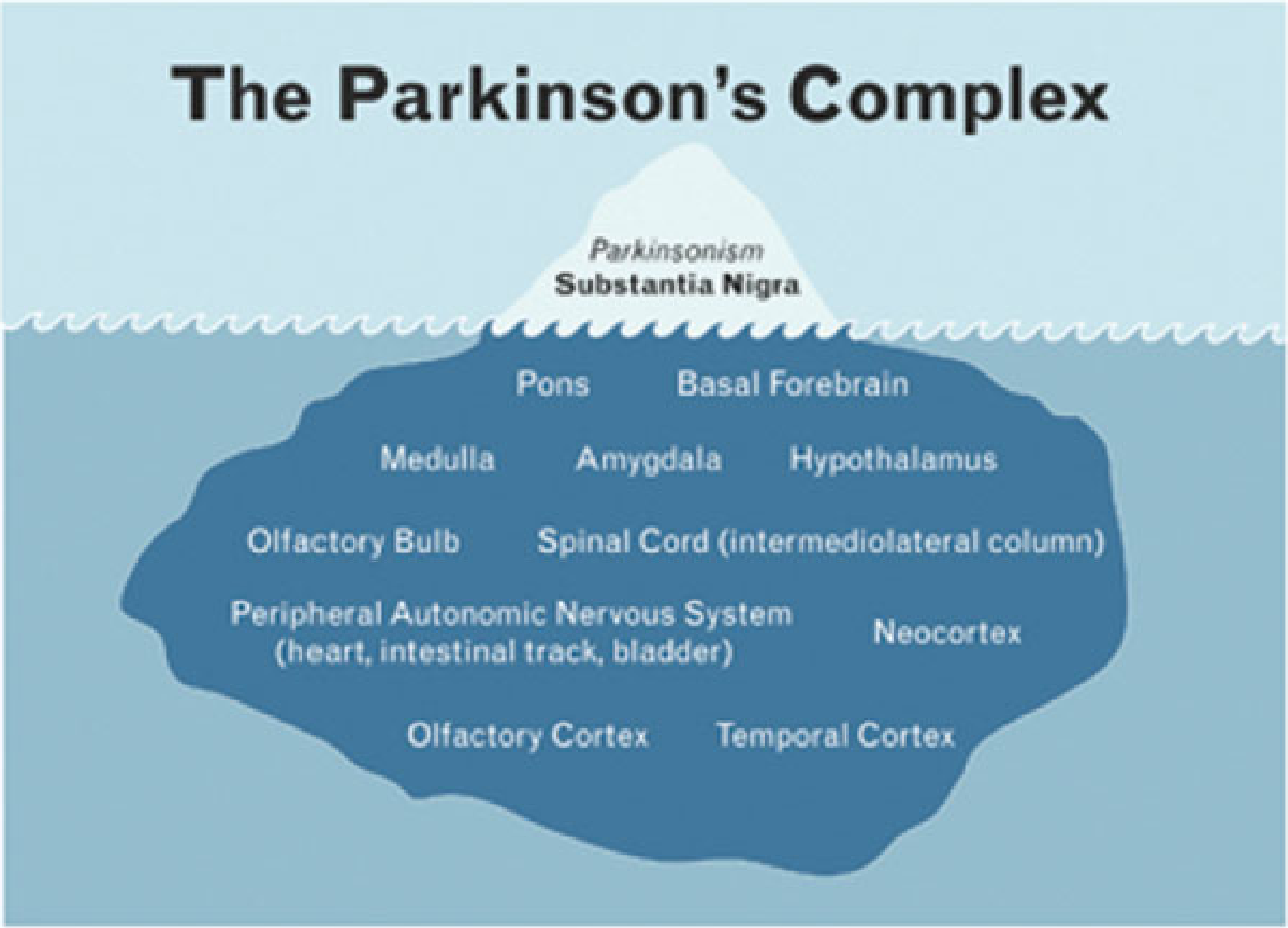
Parkinson's as a Multi-system Disease



Langston, 2006

Parkinson's as we think about it now

Olanow, C. W. et al. Neurology 2009;72:S1-S136

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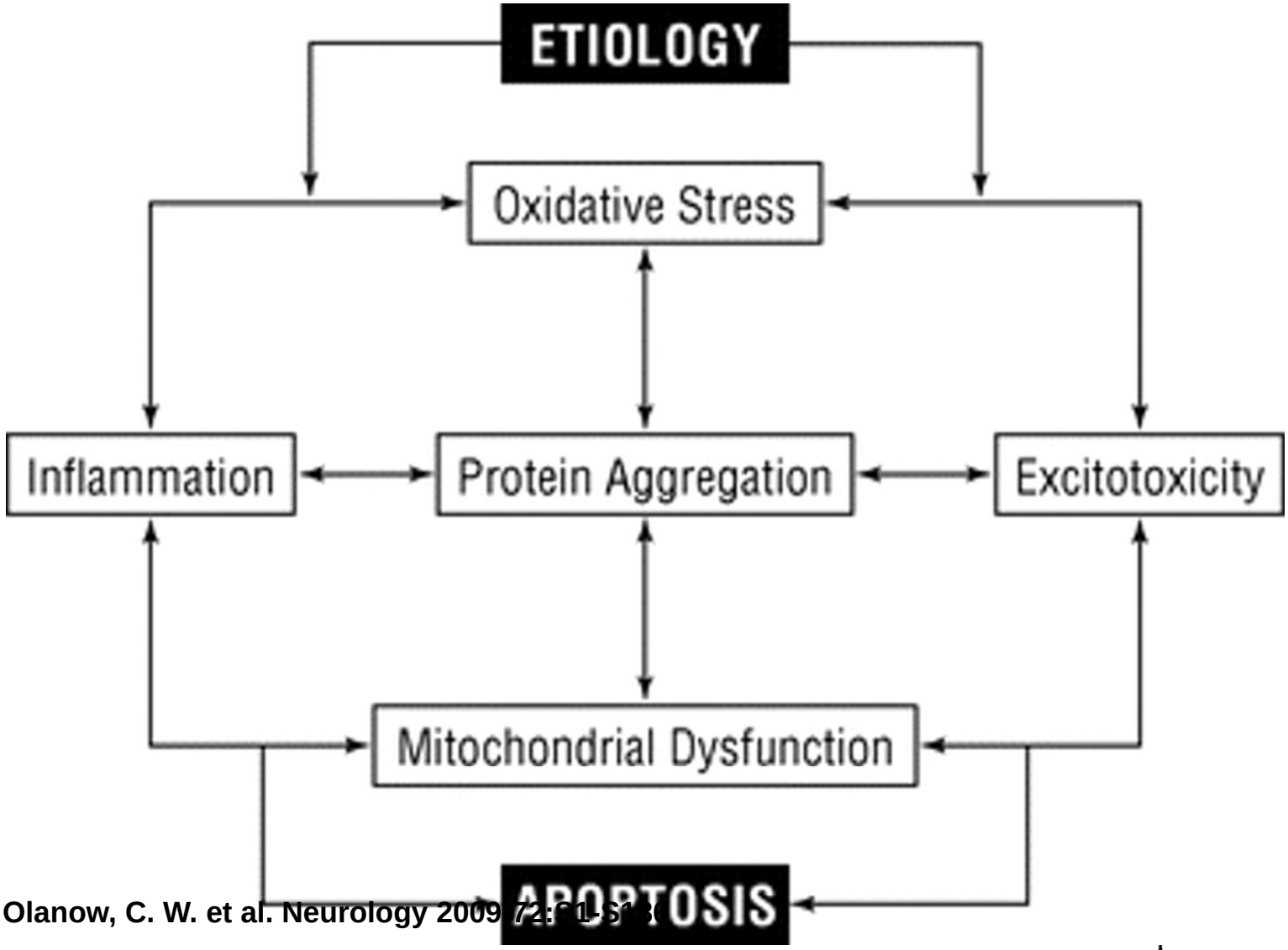
Does everyone with “pre-clinical” PD end up getting PD?

Incidental Lewy Body Disease and Preclinical Parkinson Disease

Anthony DelleDonne, PhD; Kevin J. Klos, MD; Hiroshige Fujishiro, MD, PhD; Zeshan Ahmed, BSc Joseph E. Parisi, MD; Keith A. Josephs, MD, MST; Roberta Frigerio, MD; Melinda Burnett, MD; Zbigniew K. Wszolek, MD; Ryan J. Uitti, MD; J. Eric Ahlskog, PhD, MD; Dennis W. Dickson, MD

- 8-17% of patients who pass away without ever having a PD symptom are discovered to have “pre-clinical PD
- iLB’s are found in various tissues in the nervous system.

What triggers PD Pathology?



Olanow, C. W. et al. Neurology 2009; 72: S1-S13

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Where Should We be Focusing

- Back to the Basics—trying to figure out what we are actually treating rather than “throwing the kitchen sink” disease progression
- Focus on relevant animal models
- Focus on potential biomarkers for PD
- Rational drug design with solid study design
- Refuse to “re-invent” the wheel!

The Good News

TABLE 1. *Funding for Parkinson disease research, 2003 to 2005 (in millions of US dollars)*

Source	2003	2004	2005
US-based foundations	$15	$22	$20
US Federal Government*	$261	$224	$236
Industry	$785	$882	$948
Total	$1,061	$1,128	$1,204

*Includes the US National Institutes of Health and the Department of Defense.

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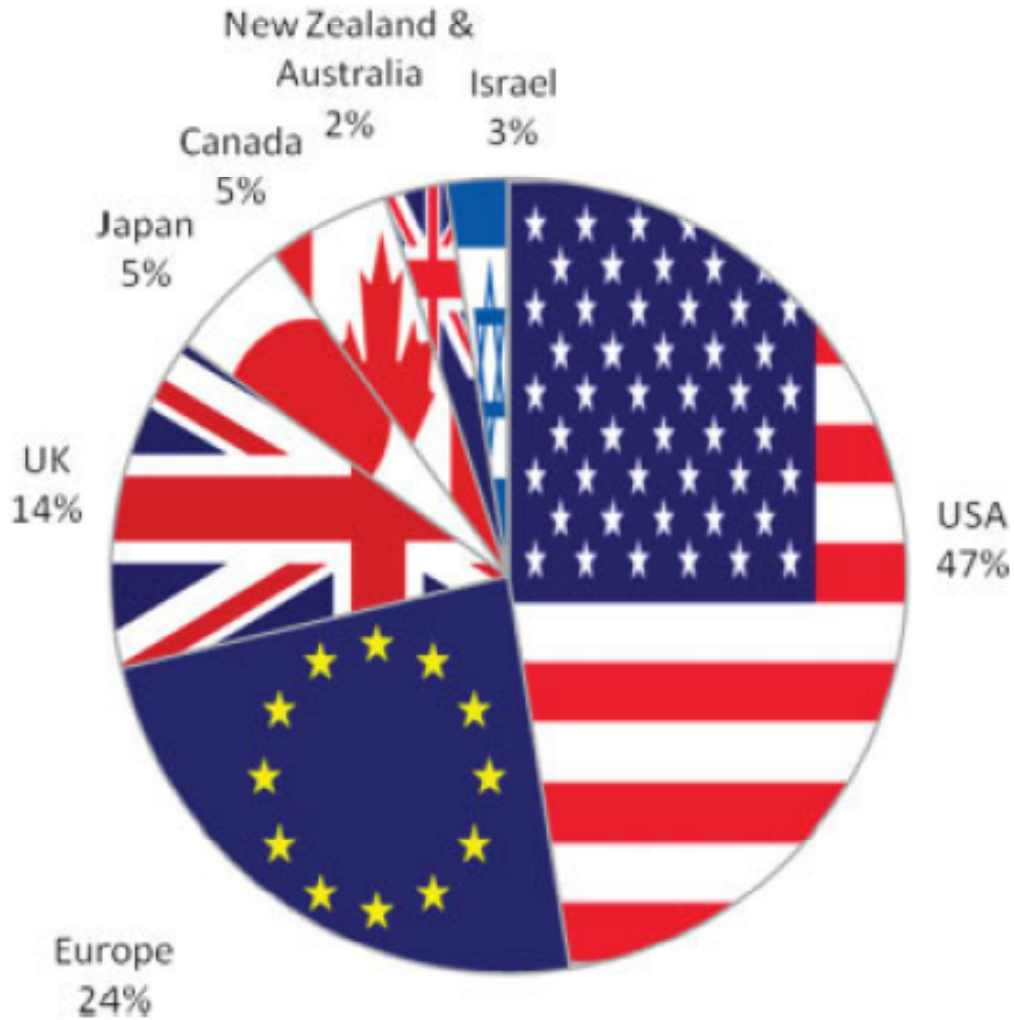

FIG. 3. Companies with at least one compound in development for Parkinson disease in 2007 by country. 100% = 80 companies. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

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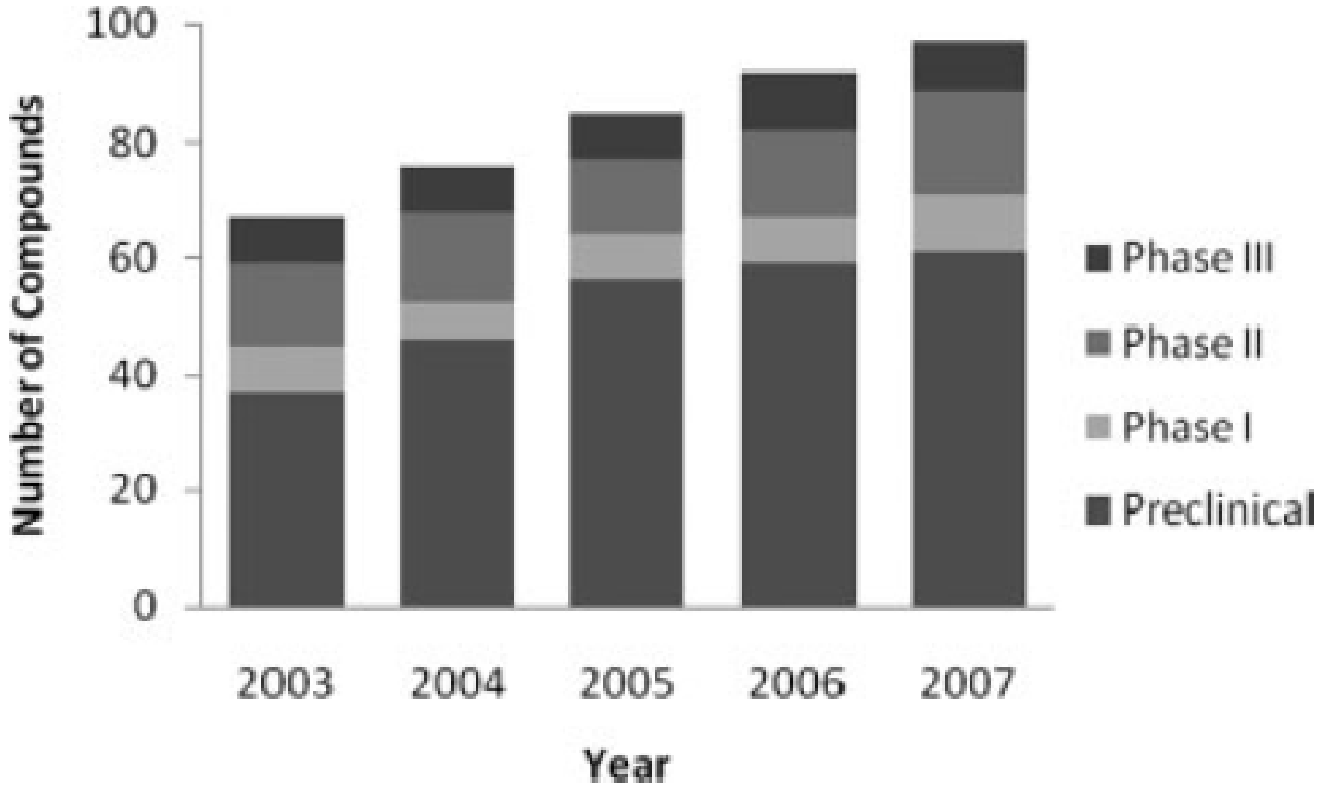

FIG. 1. Number of compounds in development for Parkinson disease by phase of development, 2003–2007.

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Conclusions

- There is an unprecedented amount of funding going to PD research .
- Our “tool set” to attack the disease is greater than it has ever been.
- Although it is reasonable to look into “existing” compounds, the bulk of our focus should be devoted to fundamental questions that remain unanswered and will guide therapy!

thank you
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