Targeting Purines as Neuroprotective Therapy for Parkinson's Disease PD

Michael Schwarzschild, MD PhD

MassGeneral Institute for Neurodegenerative Disease
Massachusetts General Hospital
Harvard Medical School

Disclosure

Michael Schwarzschild has no financial conflicts of interest with commercial entities.

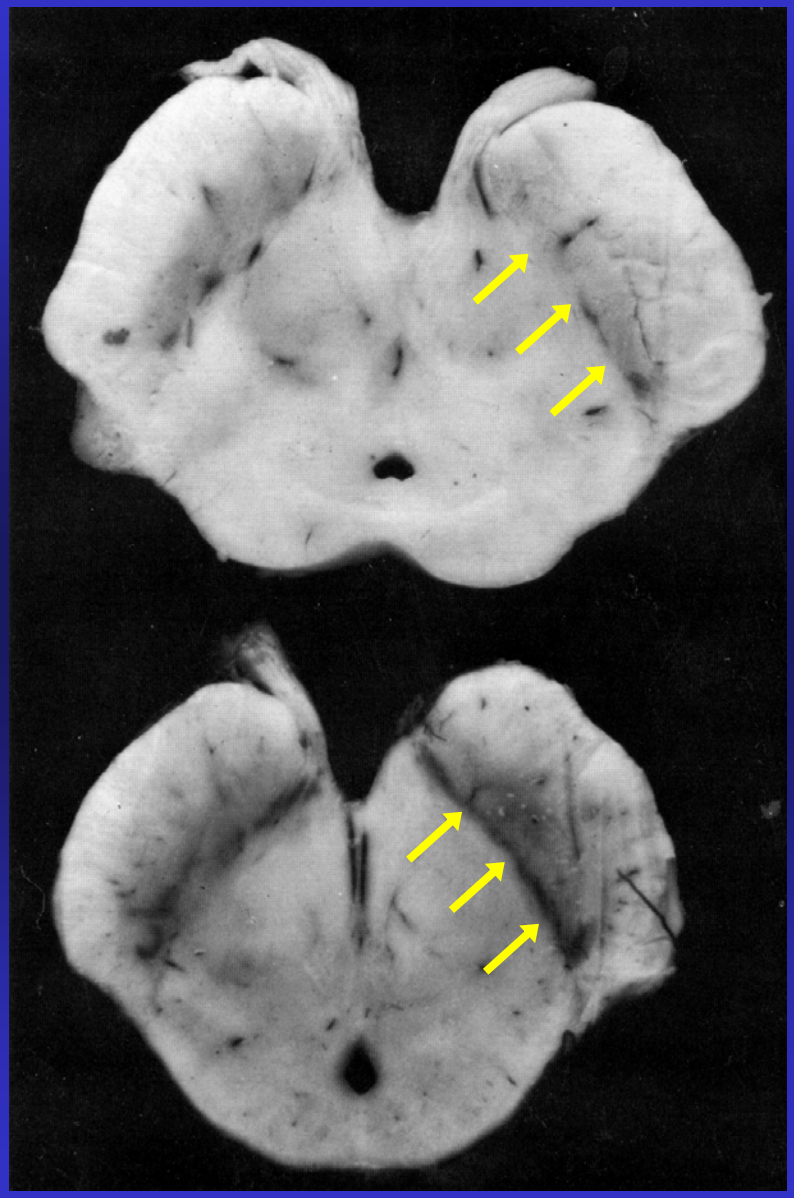
Targeting Purines as Neuroprotective Therapy for Parkinson's Disease PD

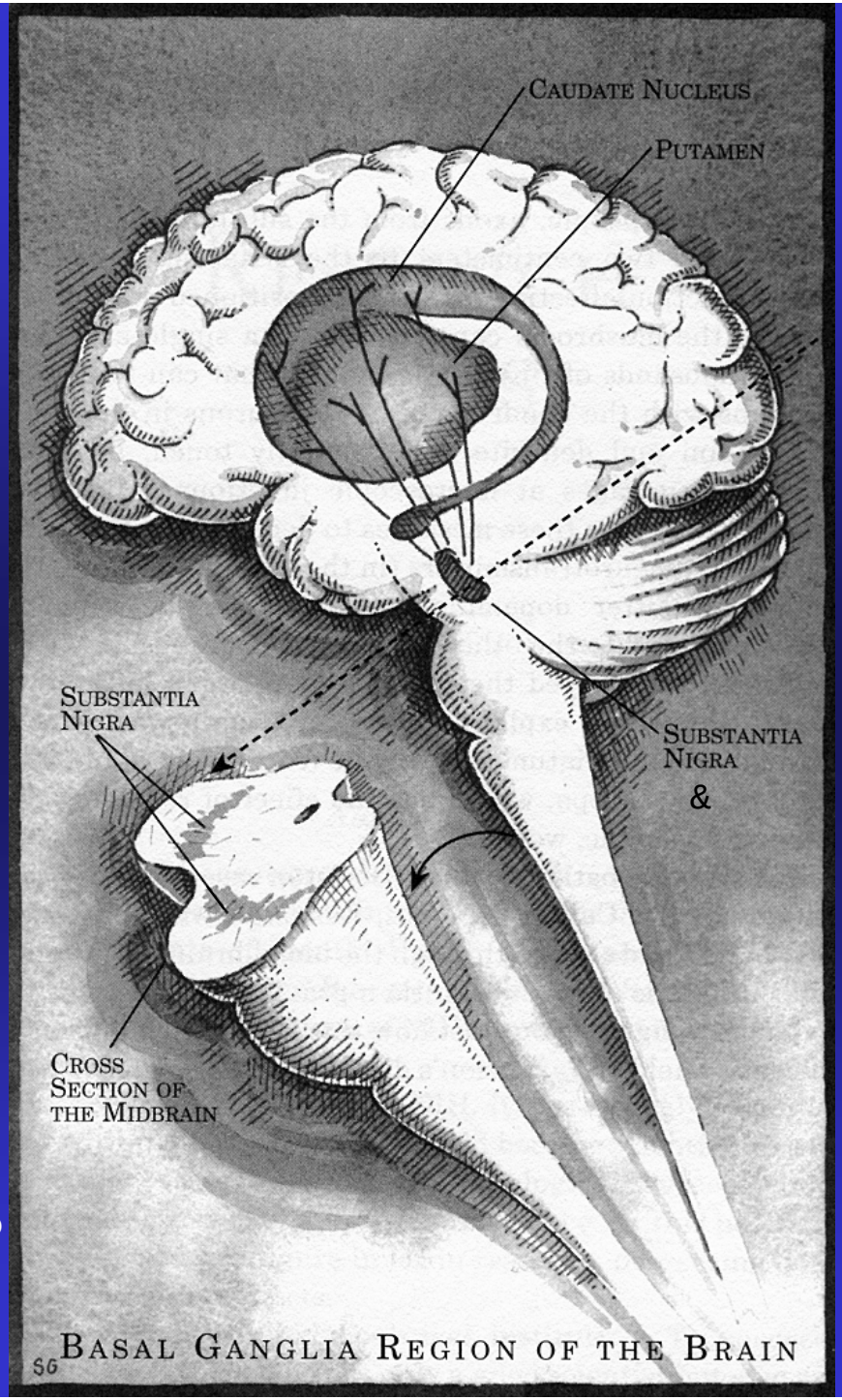
Michael Schwarzschild, MD PhD

MassGeneral Institute for Neurodegenerative Disease

Charlestown Navy Yard, Boston

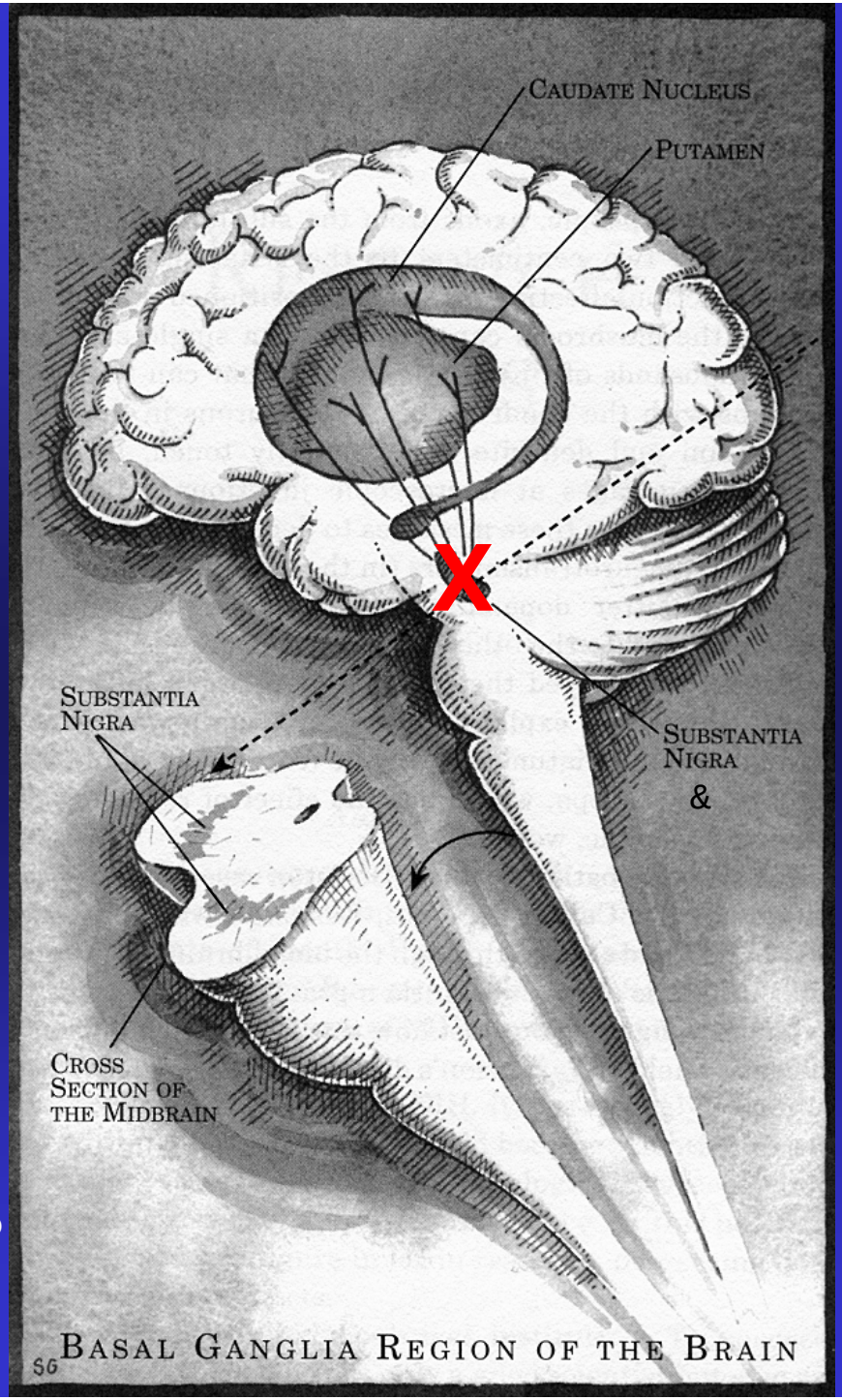
F. Netter





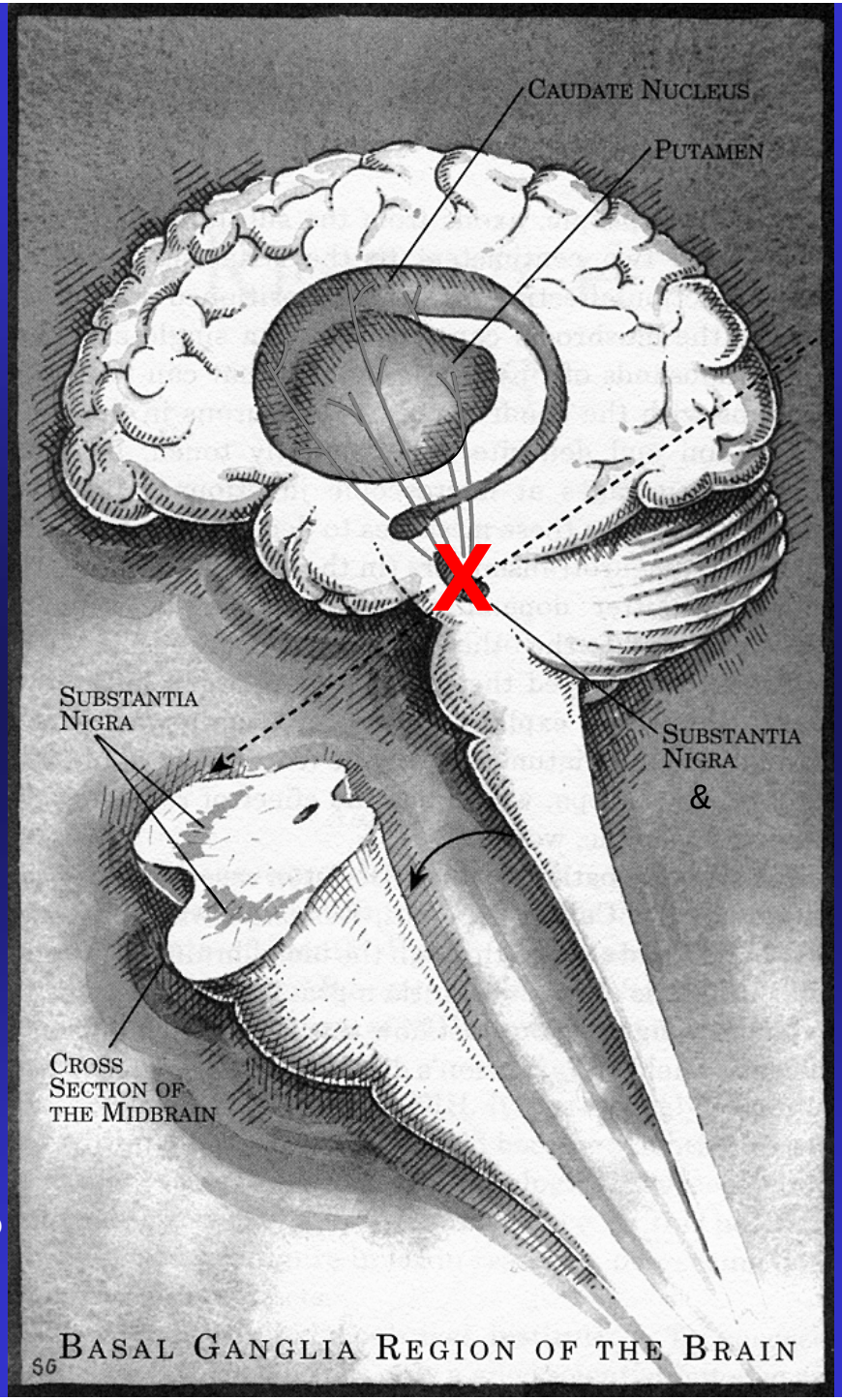
Scott Gagne

from JW Langston & J Palfreman (1995)
The Case of the Frozen Addicts,
NewYork:Pantheon Press.



Scott Gagne

from JW Langston & J Palfreman (1995)
The Case of the Frozen Addicts,
NewYork:Pantheon Press.



Scott Gagne

from JW Langston & J Palfreman (1995)
The Case of the Frozen Addicts,
NewYork:Pantheon Press.

Don Eyles *November 2001*

Purines as PD Protectants

--Translational themes--

- Epidemiology → PD R_x:
  Two purines (caffeine, urate) are major *inverse* risk factors
- Adenosine A_{2A} antagonists:
  Realistic & multi-faceted potential new R_x for PD
- Inosine to raise urate in PD:

Don Eyles *November 2001*

Purines as PD Protectants

--Translational themes--

- Epidemiology → PD R_X:
  Two purines (caffeine, urate) are major *inverse* risk factors
- Adenosine A_{2A} antagonists:
  Realistic & multi-faceted potential new R_x for PD
- Inosine to raise urate in PD:
  Clinic

Don Eyles *November 2001*

Purines as PD Protectants

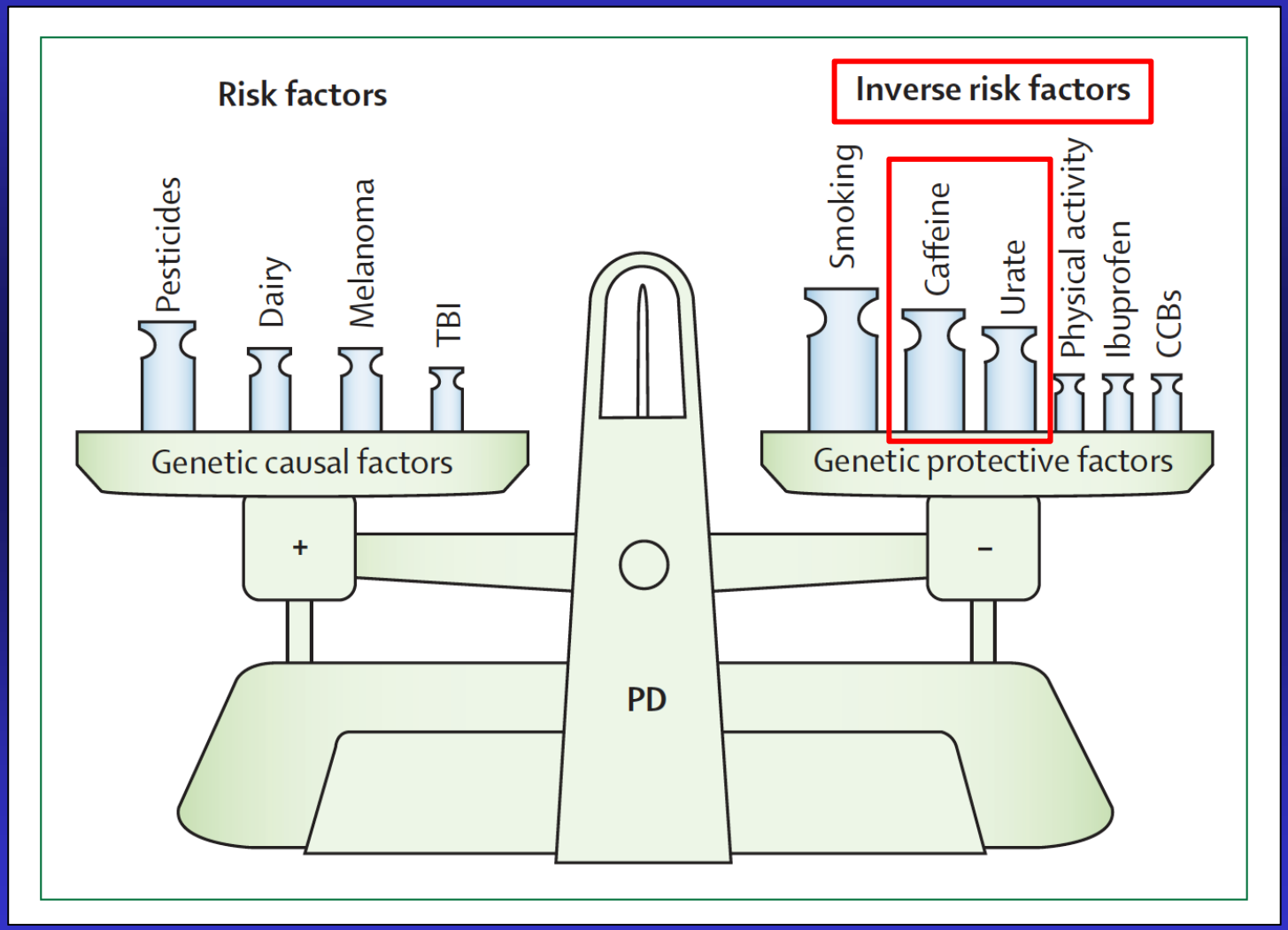
--Translational themes--

- Epidemiology → PD R_X:
  Two purines (caffeine, urate) are major *inverse* risk factors

- Adenosine A_{2A} antagonists:
  Realistic & multi-faceted potential new R_x for PD

- Inosine to raise urate in PD:
  Acute → Urate ↔ Renal
  Clinic

Balance of environmental and genetic factors linked to PD occurrence



Ascherio A & Schwarzschild MA. *Lancet Neurology*. Nov. 2016. 15:1257-72.

Don Eyles *November 2001*

Purines as PD Protectants

--Translational themes--

- Epidemiology → PD R_X:
  Two purines (caffeine, urate) are major *inverse* risk factors

- Adenosine A_{2A} antagonists:
  Realistic & multi-faceted potential new R_x for PD

- Inosine to raise urate in PD:
  Acute → Chronic ↔ Pilot
  ↘ ↙
  Clinic

Don Eyles *November 2001*

Purines as PD Protectants

--Translational themes--

- Epidemiology → PD R_X:
  Two purines (caffeine, urate) are major *inverse* risk factors

- Adenosine A_{2A} antagonists:
  Realistic & multi-faceted potential new R_x for PD

- Inosine to raise urate in PD:
  Acute → Chronic ↔ Trials
  Clinic

Don Eyles *November 2001*

Purines as PD Protectants

--Translational themes--

- Epidemiology → PD R_X:
  Two purines (caffeine, urate) are major *inverse* risk factors
- Adenosine A_{2A} antagonists:
  Realistic & multi-faceted potential new R_x for PD
- Inosine to raise urate in PD:

Don Eyles *November 2001*

Purines as PD Protectants

--Translational themes--

- Epidemiology → PD R_X:
  Two purines (caffeine, urate) are major *inverse* risk factors

- Adenosine A_{2A} antagonists:
  Realistic & multi-faceted potential new R_x for PD

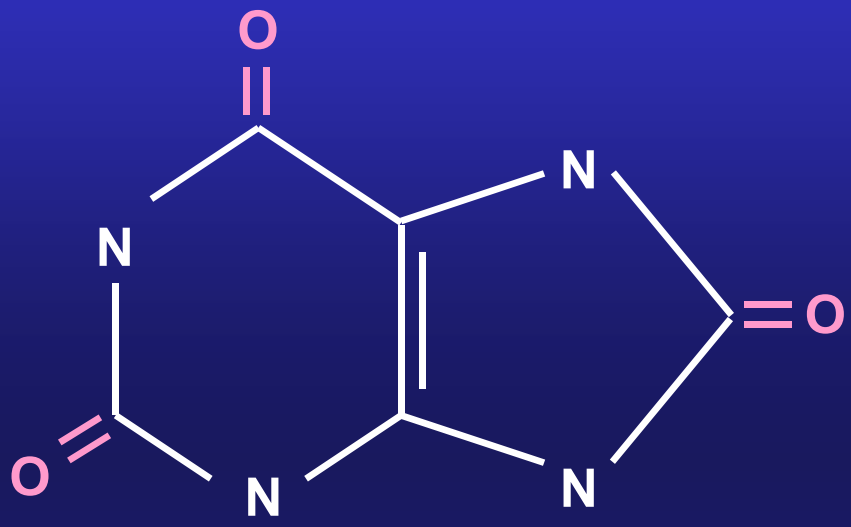
- Inosine to raise urate in PD:

Apes ⟶ Lab ⟷ Epi

↘ ↙

Clinic

Don Eyles *November 2001*



urate

(trioxy-purine)

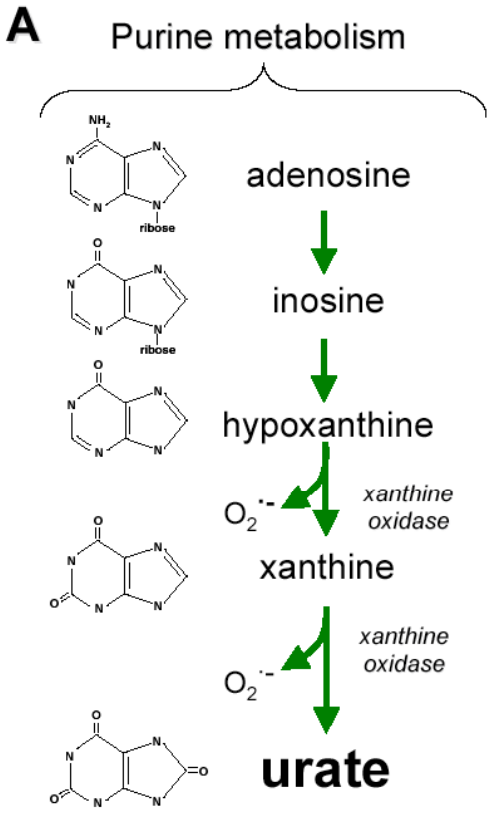
Don Eyles *November 2001*

Targeting Urate in PD

--Translational themes--

- Evolutionary genetics
  - → Urate a major antioxidant
- Epidemiology of PD
  - → Urate an inverse risk factor
  - → Urate a prognostic biomarker
- Neurobiology of PD
  - → Neuroprotection by urate
  - → Astrocytic Nrf2 activation
- Therapeutic Development
  - → Inosine for PD, phase 2 – ✓
  - → Inosine Rx, phase 1 – ✓
  - → Inosine, phase 3 → 2016-2020

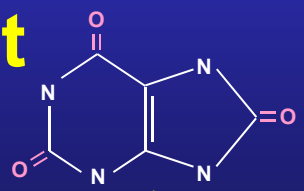
Urate oxidase mutations during primate evolution



…a selective advantage of higher urate in hominoid evolution?

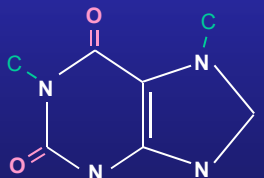
Advantage of higher urate?

- **Possible cognitive benefit**



urate

?
~



caffeine

- **Possible hypertensive benefit**

- **Possible antioxidant benefit**

– Proctor P (1970) Similar functions of uric acid and ascorbate in man. *Nature* 228:868.

– Ames B *et al*. (1981) Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: A hypothesis. *PNAS* 78:6858.

Don Eyles *November 2001*

Targeting Urate in PD

--Translational themes--

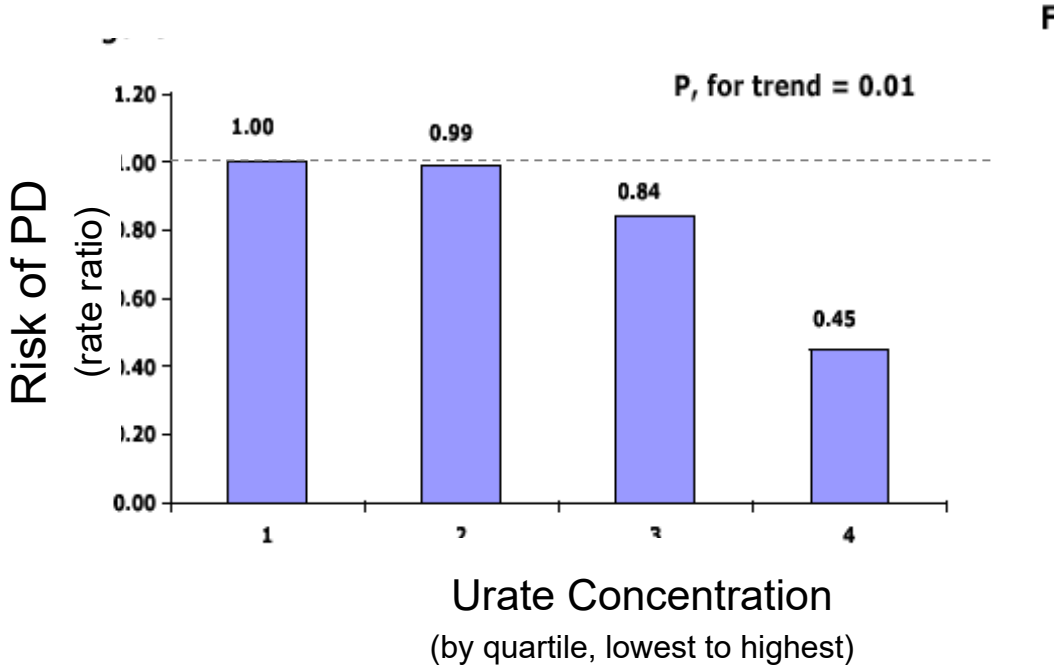
- Evolutionary genetics
  - → Urate a major antioxidant
- Epidemiology of PD
  - → Urate an inverse risk factor
  - → Urate a prognostic biomarker
- Neurobiology of PD
  - → Neuroprotection by uyrate
  - → Astrocytic Nrf2 activation
- Therapeutic Development
  - → Inosine for PD, phase 2 → 3
  - → Inosine, phase 3 → 2016

MGH Molecular Neurobiology Lab - HSPH Neuroepi group

Mass MoCA retreat 2007

Epidemiology of urate and PD

Higher blood urate linked to a lower risk



from Weisskopf, O'Reilly, Chen, Schwarzschild & Ascherio. *Amer. J. Epidem.* (2008)

Observation

Among healthy individuals a higher urate predicts an *reduced* risk of PD.

Hypothesis

Among PD patients higher urate predicts a *slower* rate of PD progression.

MassGeneral Institute for Neurodegenerative Disease

Parkinson Study Group (PSG)

Investigators, 1987

Serum urate predicts progression of Parkinson's disease

Michael A. Schwarzschild, MD PhD, Steven R. Schwid, MD, Kenneth Marek, MD, Arthur Watts, PhD, Anthony E. Lang , MD, David Oakes, PhD, Ira Shoulson, MD, and Alberto Ascherio, MD

& the Parkinson Study Group PRECEPT Investigators

Harvard University (HSPH and MGH) and the Parkinson Study Group

Results: Hazard ratios (HR)† for reaching the PD disability endpoint according to quintiles of baseline serum urate in 804 subjects in the PRECEPT study

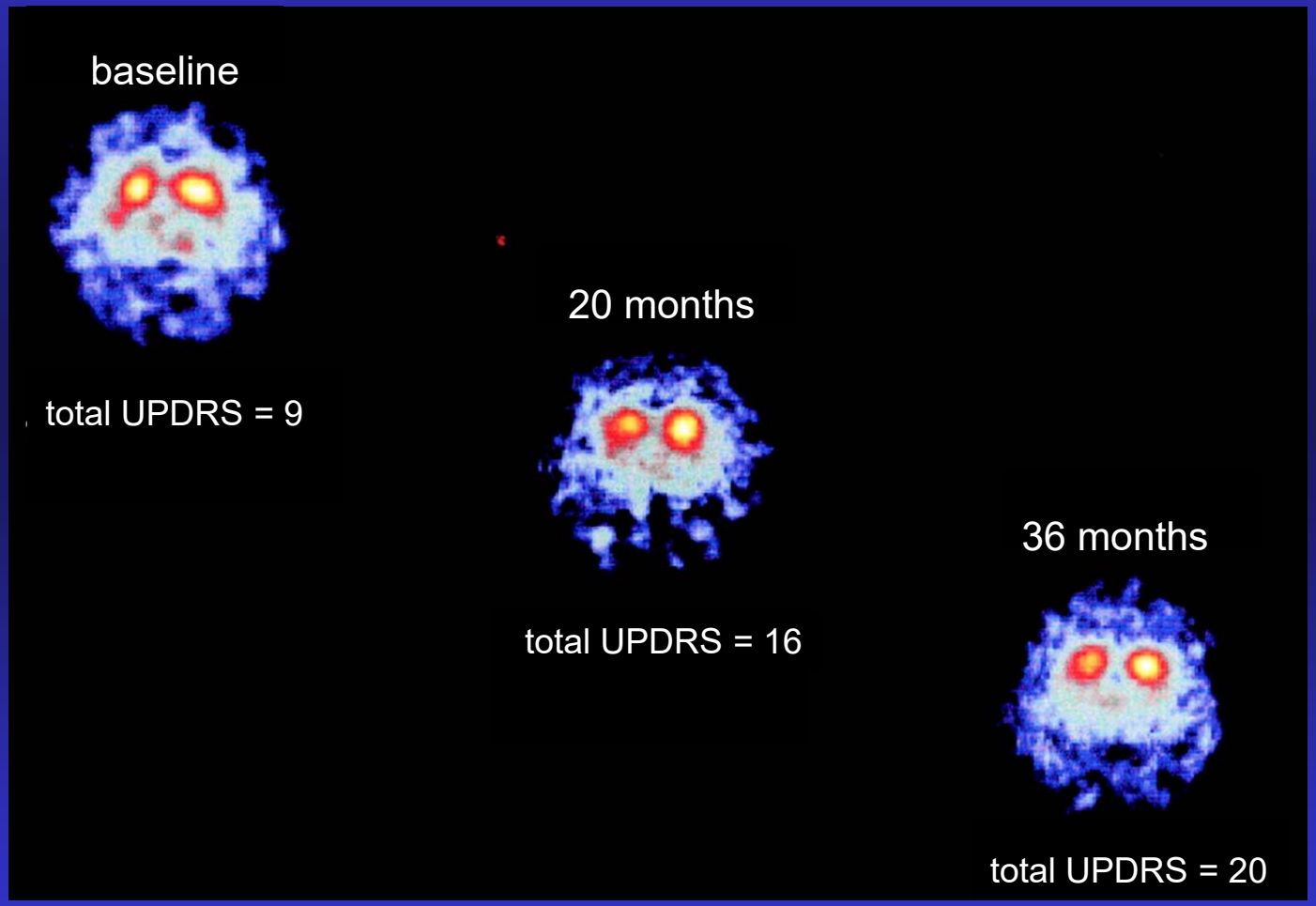
Serum urate quintile	Median serum urate (mg/dL)	**All** (n=804)		**Men** (n=517)			**Women** (n=287)		
		HR (95% CI)	p value	n	HR (95% CI)	p value	n	HR (95% CI)	p value
1	3.8	1.00 (Ref)	-	45	1.00 (Ref)	-	132	1.00 (Ref)	-
2	4.8	0.80 (0.60-1.07)	0.12	87	0.61 (0.40-0.94)	0.03	70	0.93 (0.63-1.37)	0.70
3	5.5	0.85 (0.63-1.15)	0.29	110	0.66 (0.44-1.00)	0.05	37	1.00 (0.61-1.64)	0.99
4	6.3	0.65 (0.47-0.88)	0.006	143	0.51 (0.34-0.76)	0.001	26	0.76 (0.41-1.39)	0.37
5	7.5	0.51 (0.37-0.72)	<0.0001	132	0.39 (0.26-0.60)	<0.0001	22	0.77 (0.39-1.50)	0.44
p, for trend			**0.0002**			**<0.0001**			**0.33**
p, for gender-urate interaction			0.15						

†Adjusted for age and gender

Schwarzschild *et al*. (2008) *Arch. Neurol*. 65:716-23.

MassGeneral Institute for Neurodegenerative Disease

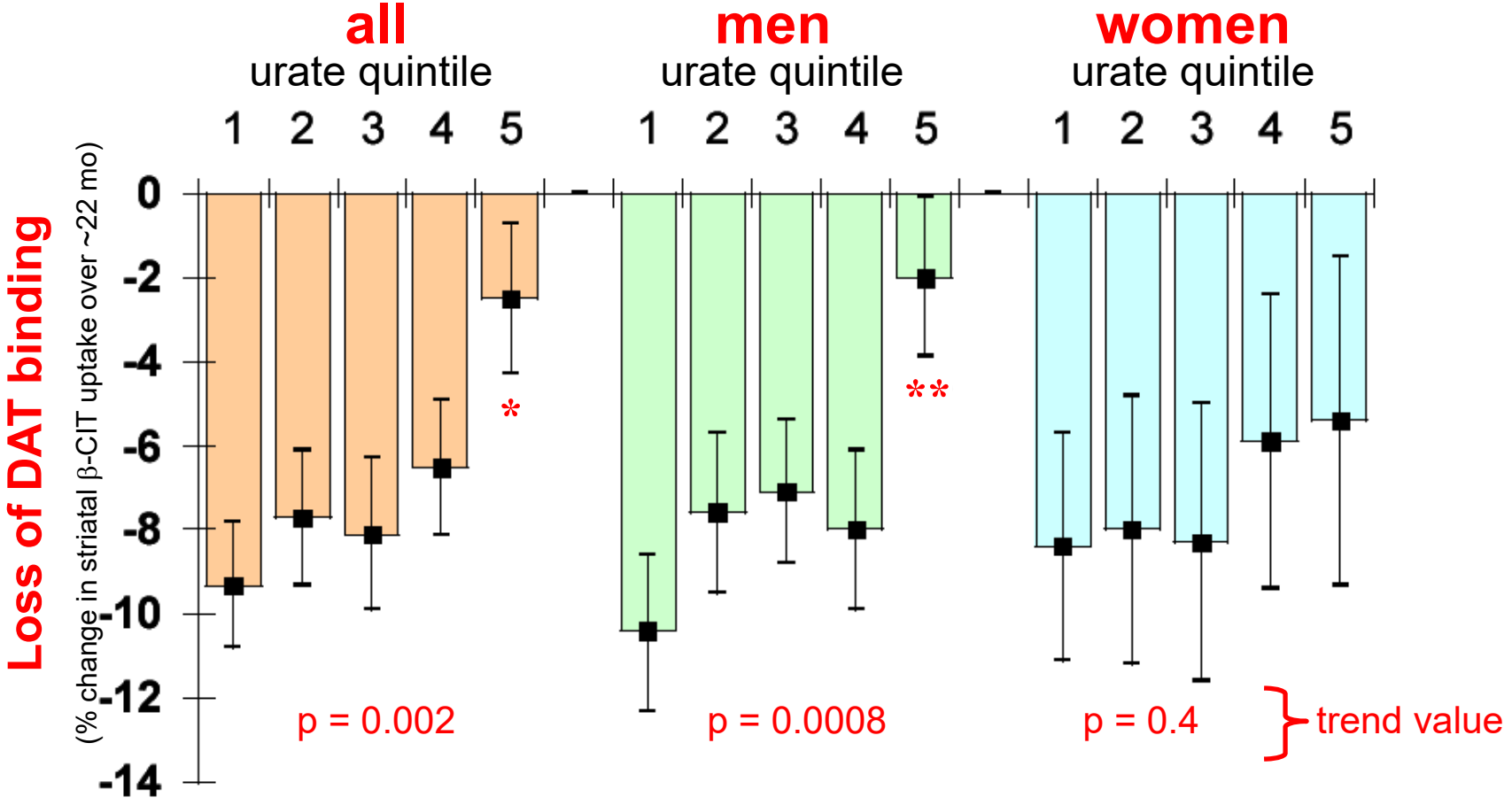
SPECT images of [^{123}I]β-CIT uptake over a 3 years demonstrates progressive dopamine transporter loss in PD



adapted from Marek, K. et al. (2001) *Neurology* 57:2089-2094

MassGeneral Institute for Neurodegenerative Disease

Higher serum urate at baseline predicts a slower rate of losing DA transporter binding sites in PD



Age-adjusted % change in striatal [123]β-CIT uptake by overall and gender-specific quintiles of baseline serum urate; n=399.

Schwarzschild *et al*. (2008) *Arch. Neurol*. 65:716-23.

MassGeneral Institute for Neurodegenerative Disease

Urate in PRECEPT Study

- Higher serum urate predicts slower progression of PD assessed clinically and radiographically in a large longitudinal study.

- The findings identify serum urate as the first molecular factor directly linked to the progression of typical PD.

- They suggest that targeting urate or its determinants could be an effective disease modifying therapy in PD.

MassGeneral Institute for Neurodegenerative Disease

Parkinson Study Group (PSG)

Investigators, 1987

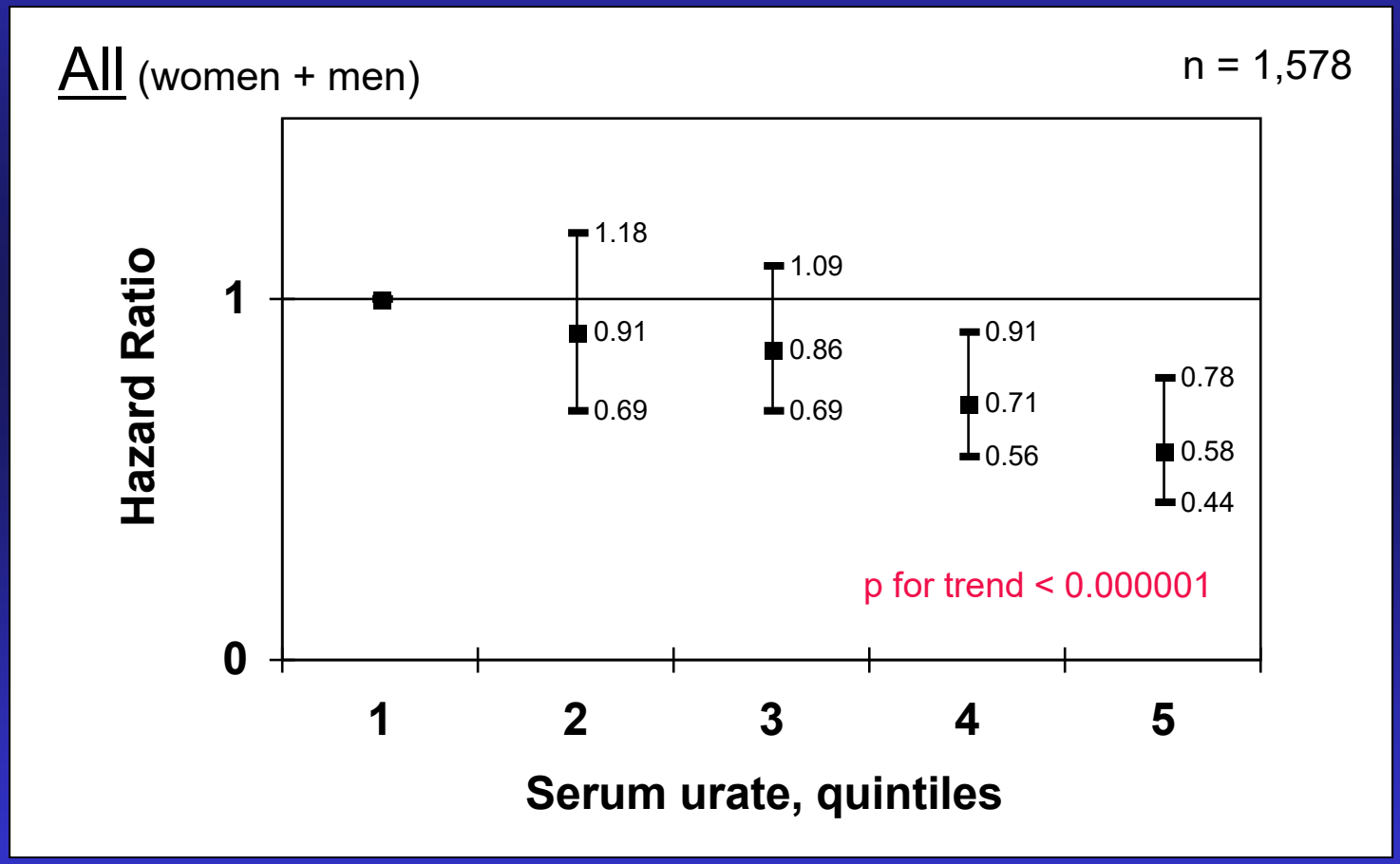
CSF and serum urate as predictors of progression of Parkinson's disease

Alberto Ascherio, M.D., Peter A. LeWitt, M.D., Arthur Watts, Ph.D., Wayne R. Matson, Ph.D., Connie Marras, M.D., Karl Kieburtz, M.D., Alice Rudolph, Ph.D., Steven R. Schwid, M.D., Marsha Tennis, R.N., Caroline M. Tanner, M.D., Ph.D., M. Flint Beal, M.D., Anthony E. Lang, M.D., David Oakes, Ph.D., Stanley Fahn, M.D., Ira Shoulson, M.D., and Michael A. Schwarzschild, M.D., Ph.D.

on behalf of the PSG DATATOP investigators

Harvard University (HSPH and MGH) and the Parkinson Study Group

Hazard ratios of reaching primary endpoint
(of progression sufficient to require dopaminergic therapy)
according to serum urate at baseline



MassGeneral Institute for Neurodegenerative Disease

Urate in PD: Summary and translational potential

- Convergent epi and clinical data identify urate as a

  predictor of both risk and the rate of PD

- Biological plausibility of neuroprotection by urate
  - –Major antioxidant
  - –Protects DA neurons in culture

- Therapeutic potential for neuroprotection
  - –Urate pathway amenable to pharmacological manipulation
    - increasing precursors (e.g., inosine)
    - decreasing clearance (e.g., thiazides)

Don Eyles *November 2001*

Targeting Urate in PD

--Translational themes--

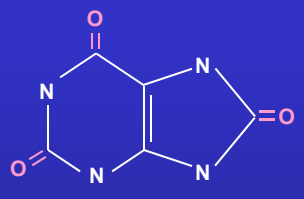
- Evolutionary genetics
  - → Urate a major antioxidant
- Epidemiology of PD
  - → Urate an inverse risk factor
  - → Urate a prognostic biomarker
- Neurobiology of PD
  - → Neuroprotection by uyrate
  - → Astrocytic Nrf2 activation
- Therapeutic Development

Don Eyles *November 2001*

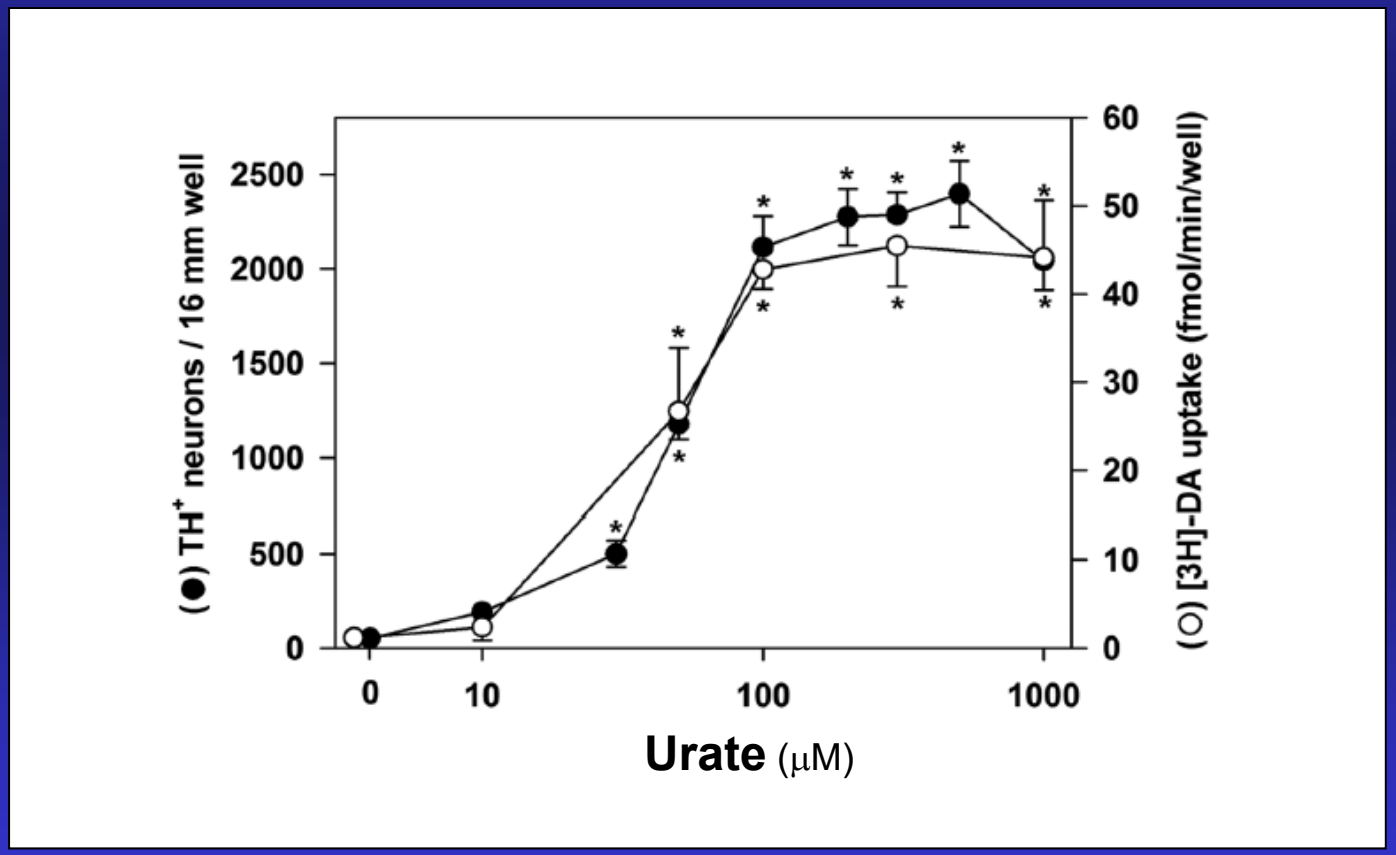
Targeting Urate in PD

--Translational themes--

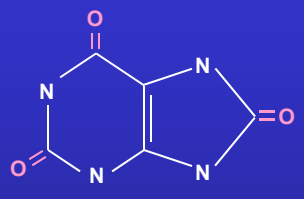
- Evolutionary genetics
  - → Urate a major antioxidant
- Epidemiology of PD
  - → Urate an inverse risk factor
  - → Urate a prognostic biomarker
- Neurobiology of PD
  - → Neuroprotection by uyrate
  - → Astrocytic Nrf2 activation
- Therapeutic Development



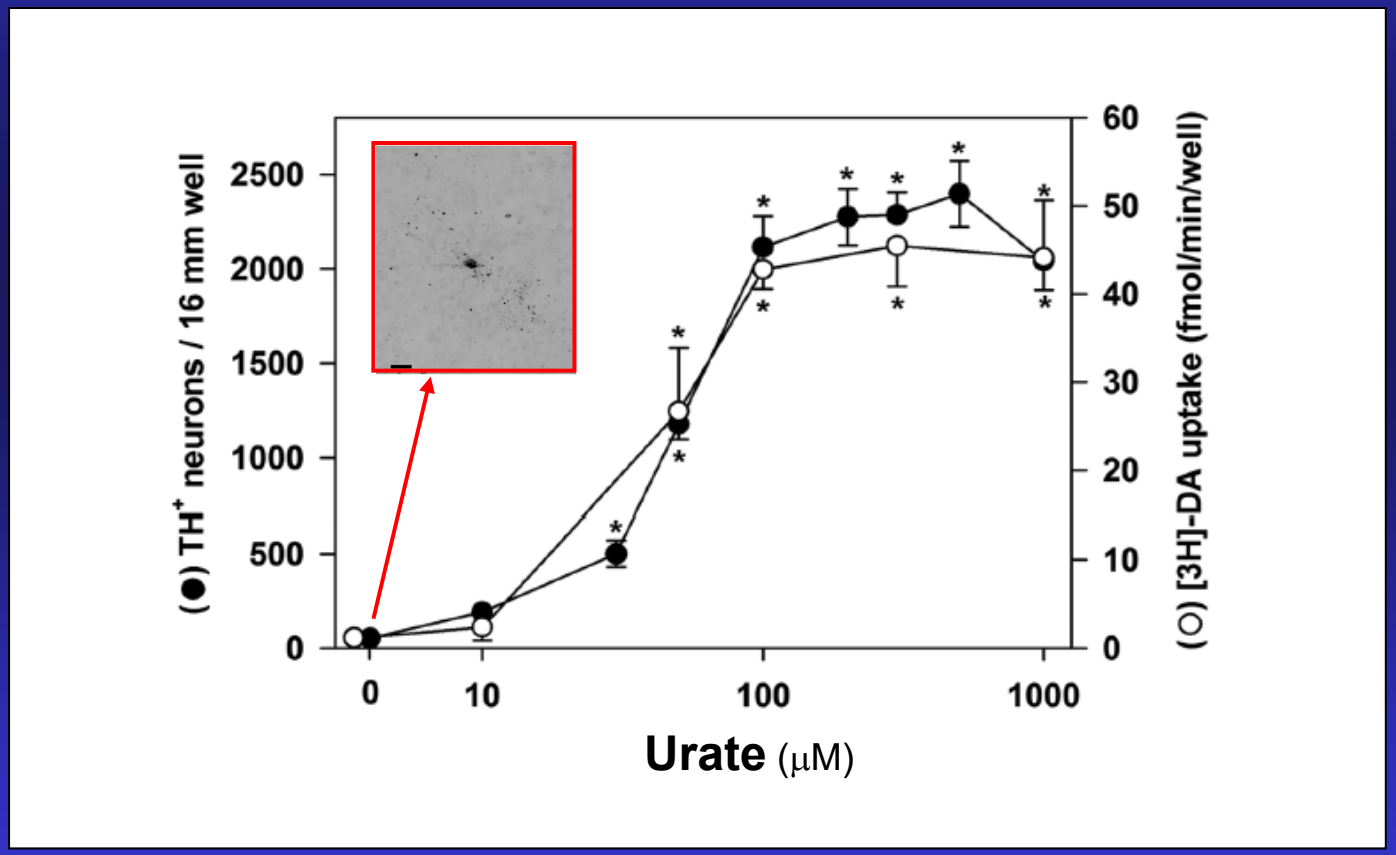
Urate prevents dopaminergic neuron death in primary cultures of midbrain neurons



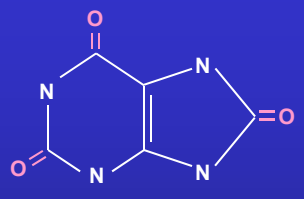
adapted from Guerreiro (2009) *J Neurochem*. 109:1118-1128



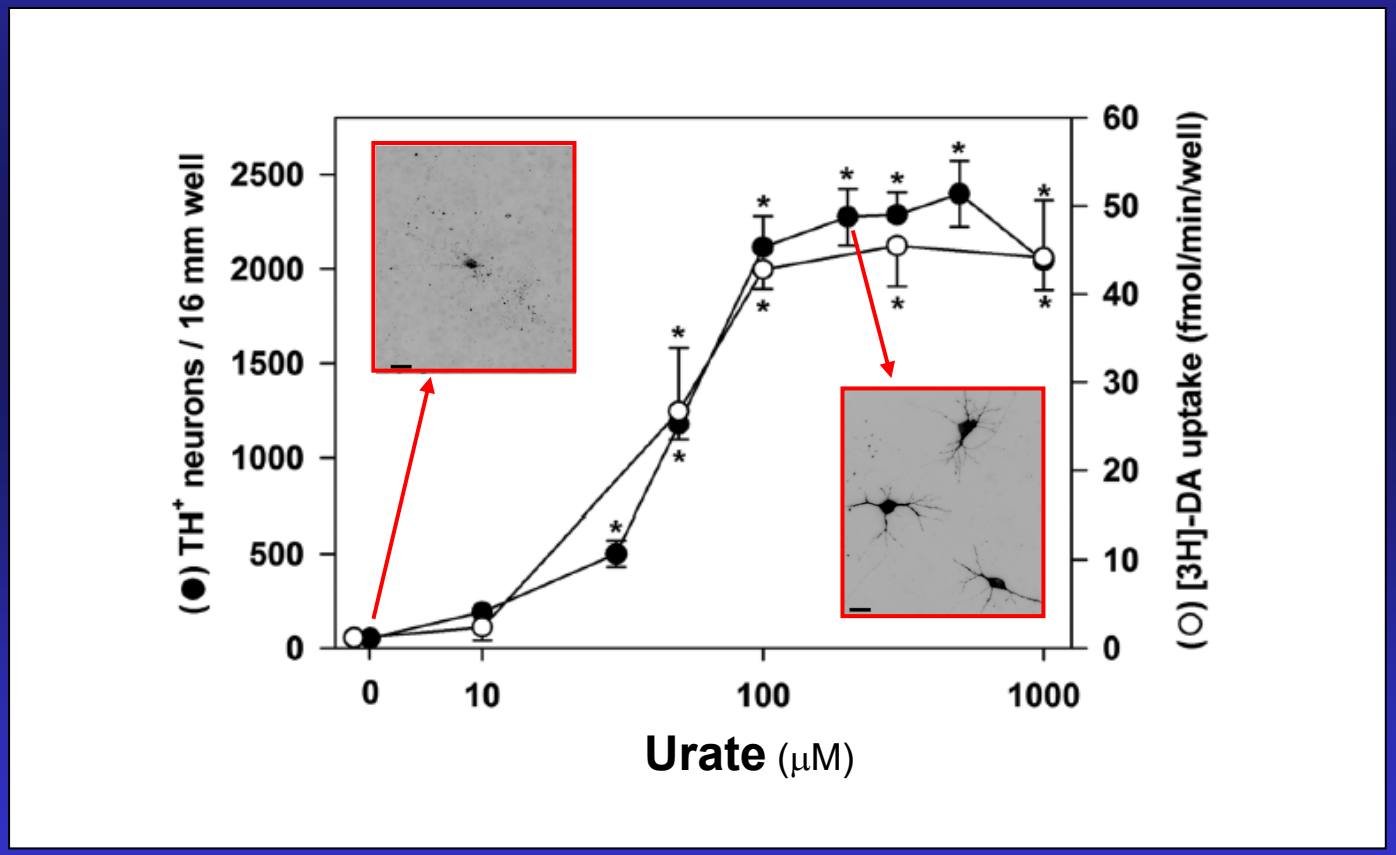
Urate prevents dopaminergic neuron death in primary cultures of midbrain neurons



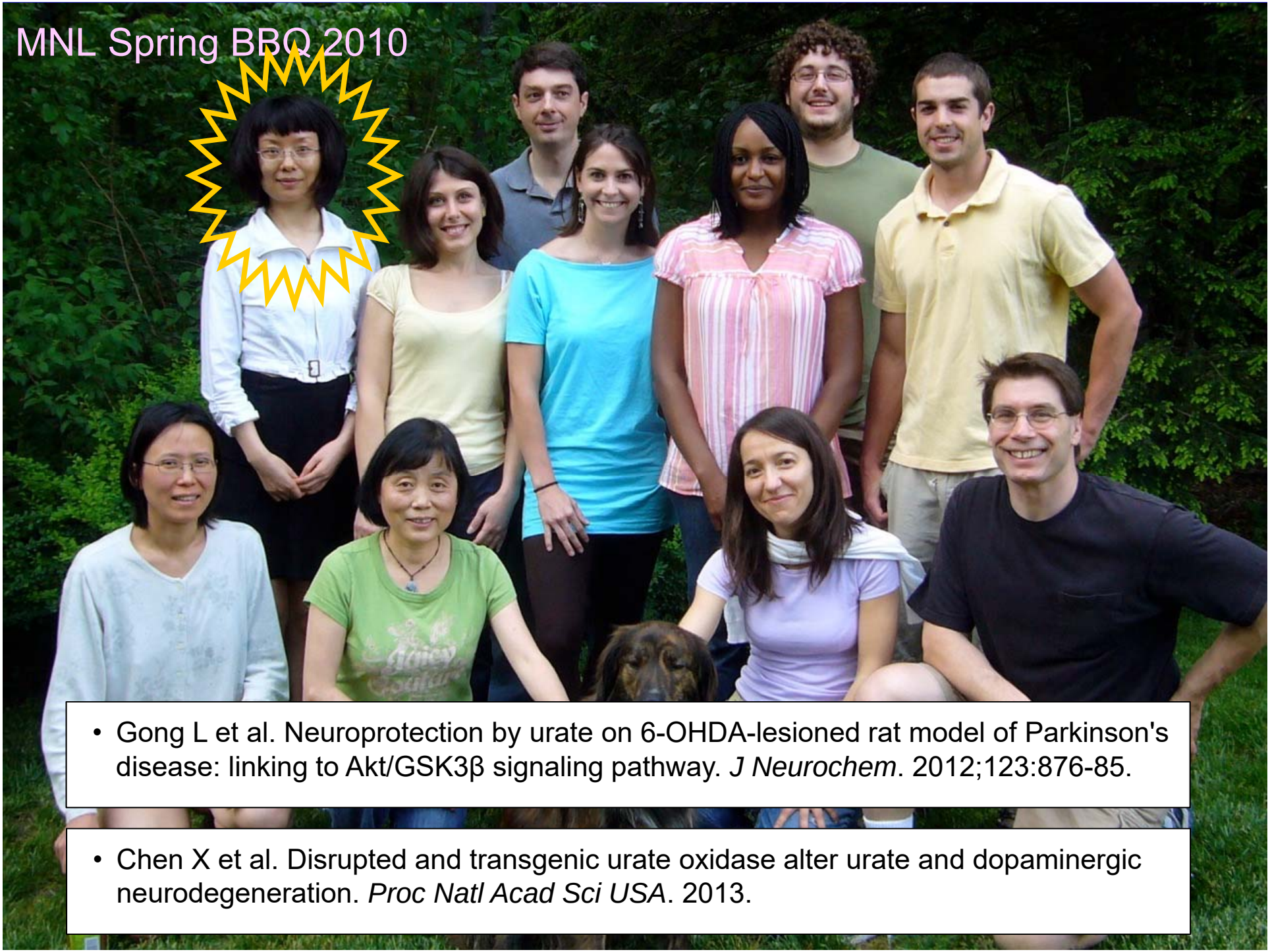
adapted from Guerreiro (2009) *J Neurochem*. 109:1118-1128



Urate prevents dopaminergic neuron death in primary cultures of midbrain neurons



adapted from Guerreiro (2009) *J Neurochem*. 109:1118-1128



- Gong L et al. Neuroprotection by urate on 6-OHDA-lesioned rat model of Parkinson's disease: linking to Akt/GSK3β signaling pathway. *J Neurochem*. 2012;123:876-85.

- Chen X et al. Disrupted and transgenic urate oxidase alter urate and dopaminergic neurodegeneration. *Proc Natl Acad Sci USA*. 2013.

- Cipriani et al. Protection of dopaminergic cells by urate requires its accumulation in astrocytes. *J Neurochem*. 2012.
- Cipriani et al. Urate and its transgenic depletion modulate neuronal vulnerability in a cellular model of Parkinson's disease. *PLoS One*. 2012.

- Bakshi et al. Neuroprotective effects of urate are mediated by augmenting astrocytic glutathione synthesis and release. *Neurobiol Dis*. 2015.

MGH-HSPH collaborative PD research retreat -- Chatham 2013

Urate in PD: Summary and translational potential

- Convergent epi and clinical data identify urate as a

  predictor of both risk and the rate of PD

- Biological plausibility of neuroprotection by urate
  - –Major antioxidant
  - –Protects DA neurons in culture and *in vivo*

- Therapeutic potential for neuroprotection
  - –Urate pathway amenable to pharmacological manipulation
    - increasing precursors (e.g., inosine)
    - decreasing clearance (e.g., thiazides)

Urate in PD: Summary and translational potential

- Convergent epi and clinical data identify urate as a ***predictor of both risk and the rate of PD***

- Biological plausibility of neuroprotection by urate
  - –Major antioxidant
  - –Protects DA neurons in culture

- Therapeutic potential for neuroprotection
  - –Urate pathway amenable to pharmacological manipulation
    - increasing precursors (e.g., inosine)
    - decreasing clearance (e.g., thiazides)

Don Eyles *November 2001*

Targeting Urate in PD

--Translational themes--

- Evolutionary genetics
  - → Urate a major antioxidant
- Epidemiology of PD
  - → Urate an inverse risk factor
  - → Urate a prognostic biomarker
- Neurobiology of PD
  - → Neuroprotection by urate
  - → Astrocytic Nrf2 activation
- Therapeutic Development
  - → Inosine for PD, phase 2 – ✓
  - → Inosine Rx, phase 1 – ✓
  - → Inosine, phase 3 → 2016-2020

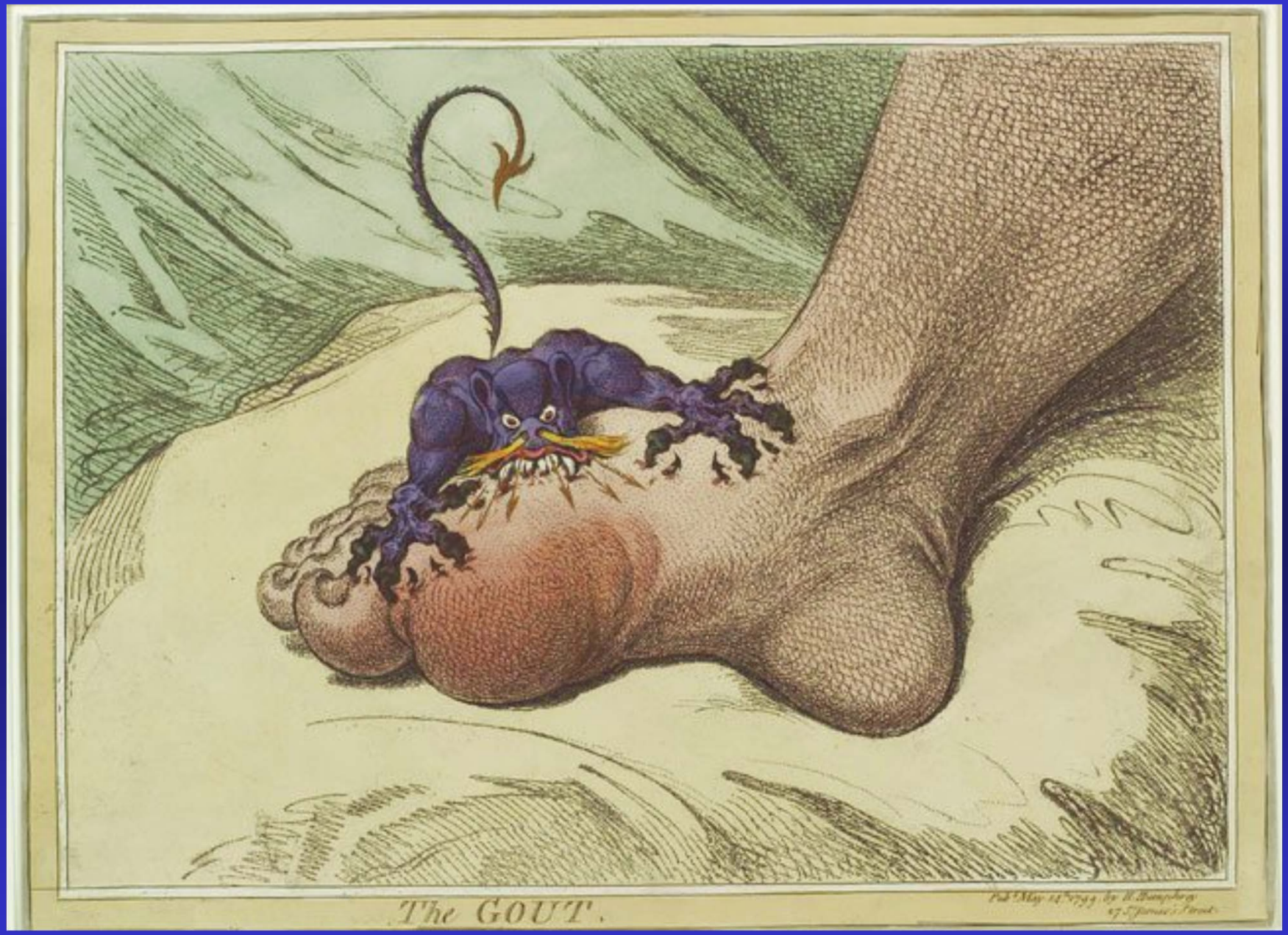
Safety of URate Elevation in PD

SURE-PD

A randomized, double-blind, placebo-controlled, dose-ranging trial of oral inosine to assess safety and ability to elevate CSF urate in early PD

Michael J. Fox Foundation for Parkinson's Resarch

MGH, HSPH and the Univ Rochester

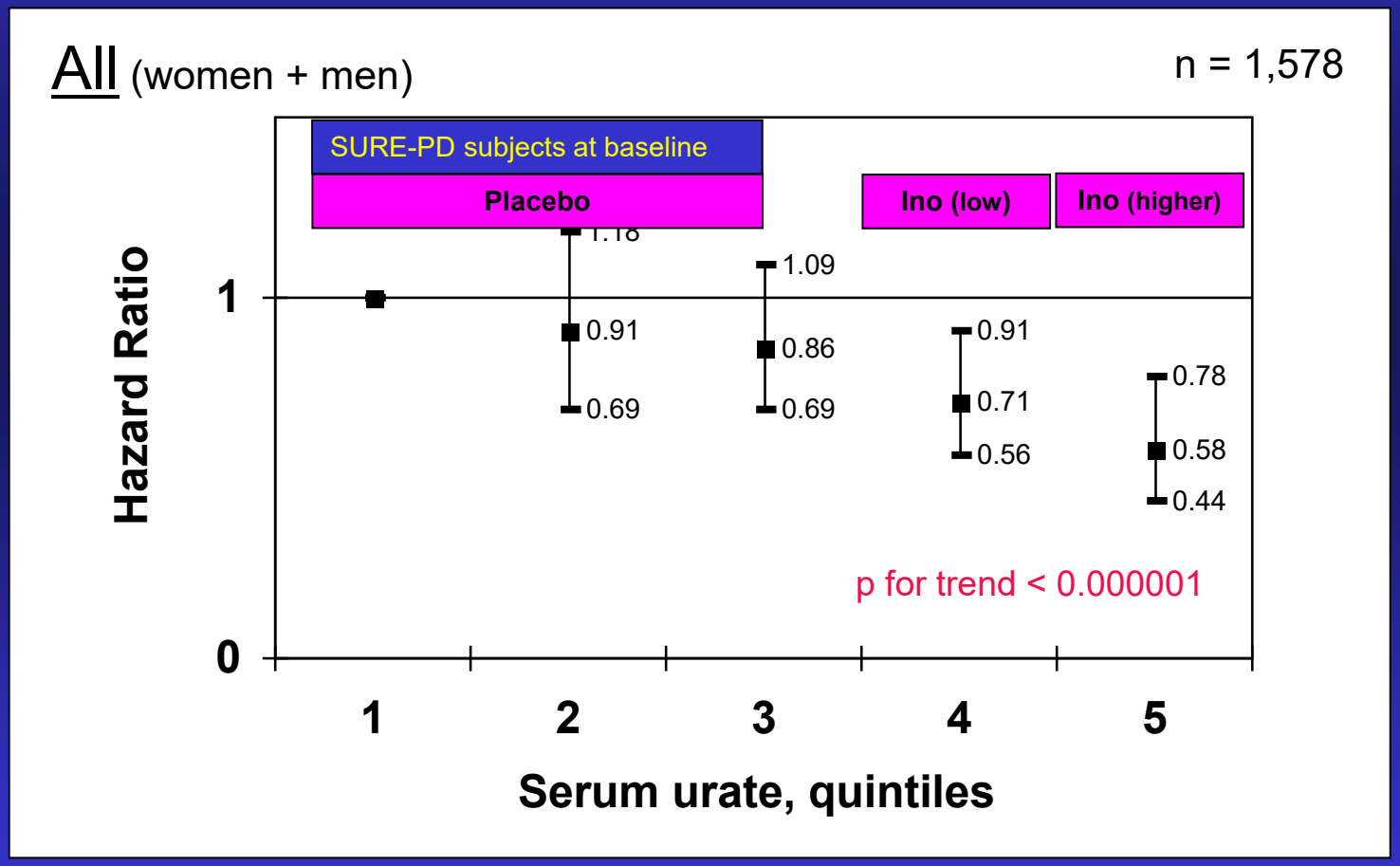


The Gout by James Gillray (1799)

MassGeneral Institute for Neurodegenerative Disease

Serum urate is a predictor of progression in PD
(pooled cohorts of DATATOP and PRECEPT)

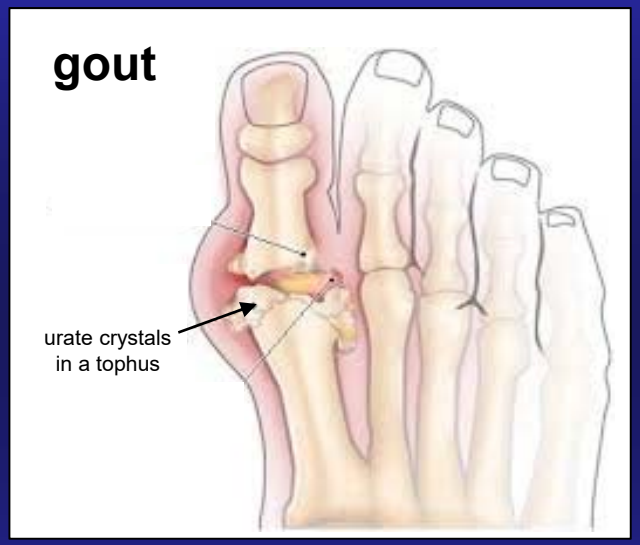
HR of reaching primary endpoint (of progression sufficient to require dopaminergic therapy)
according to quintile of serum urate at baseline

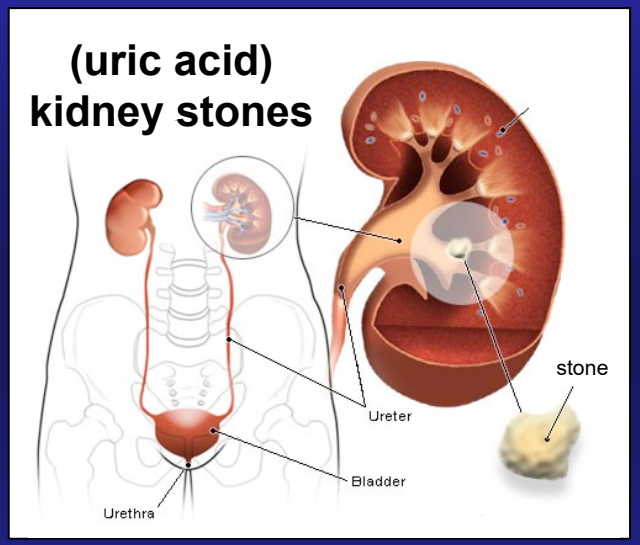


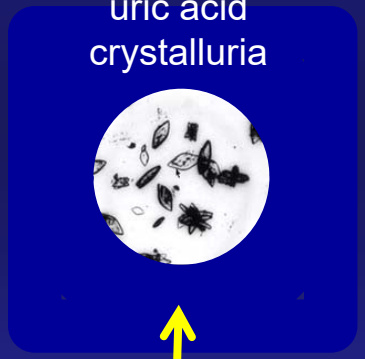
MassGeneral Institute for Neurodegenerative Disease

Safety – serious adverse events (SAEs) occurred at lower rates on inosine compared to placebo.

Potential crystallopathic AEs:







0

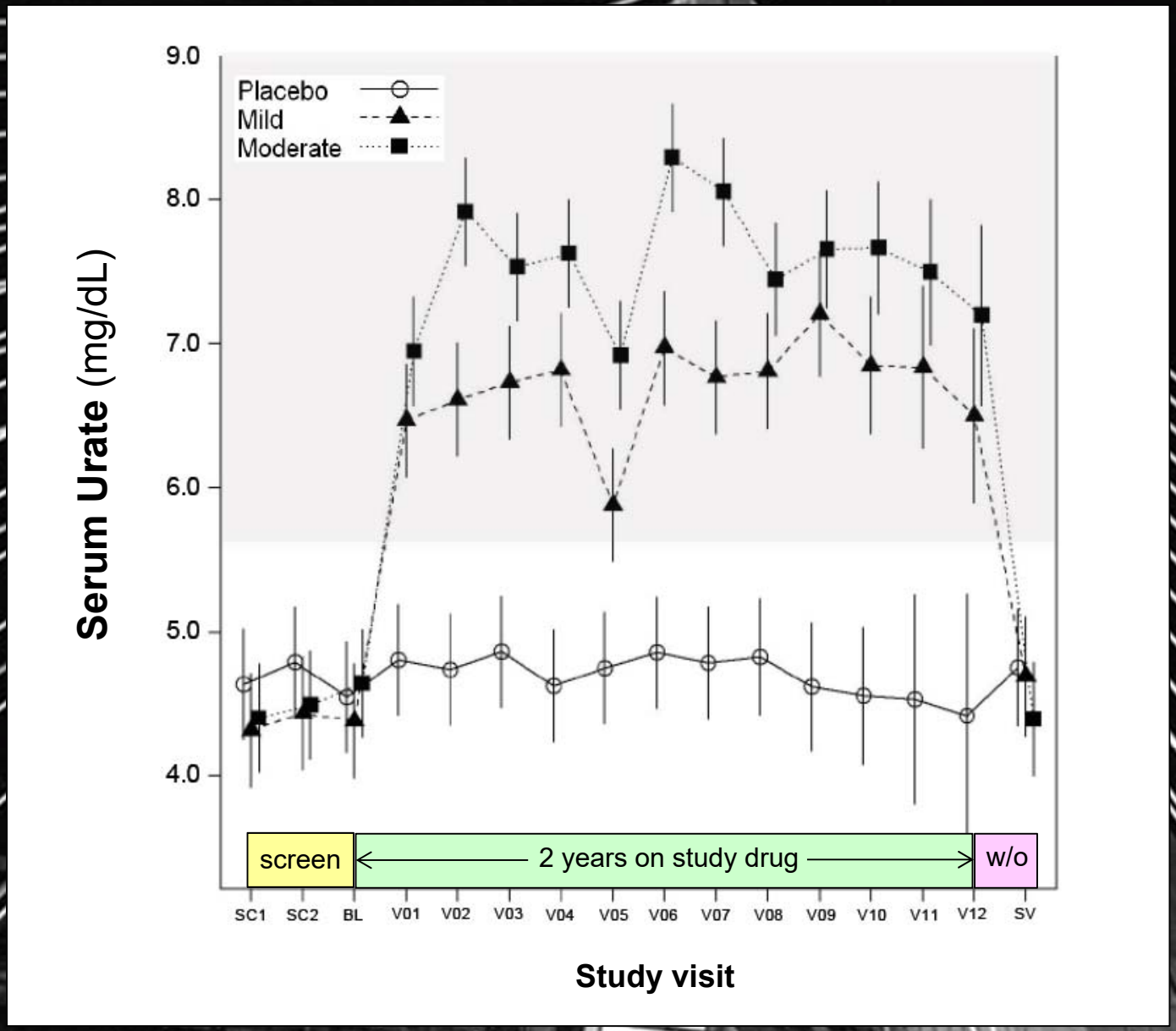
3 stone AEs:

- **0 on placebo**
- **1 on inosine (mild)**
- **2 on inosine (mod)**

routine monitoring of urine sediment + alkalinization may reduce UA stone risk

Tolerability – excellent;
0 dose reductions

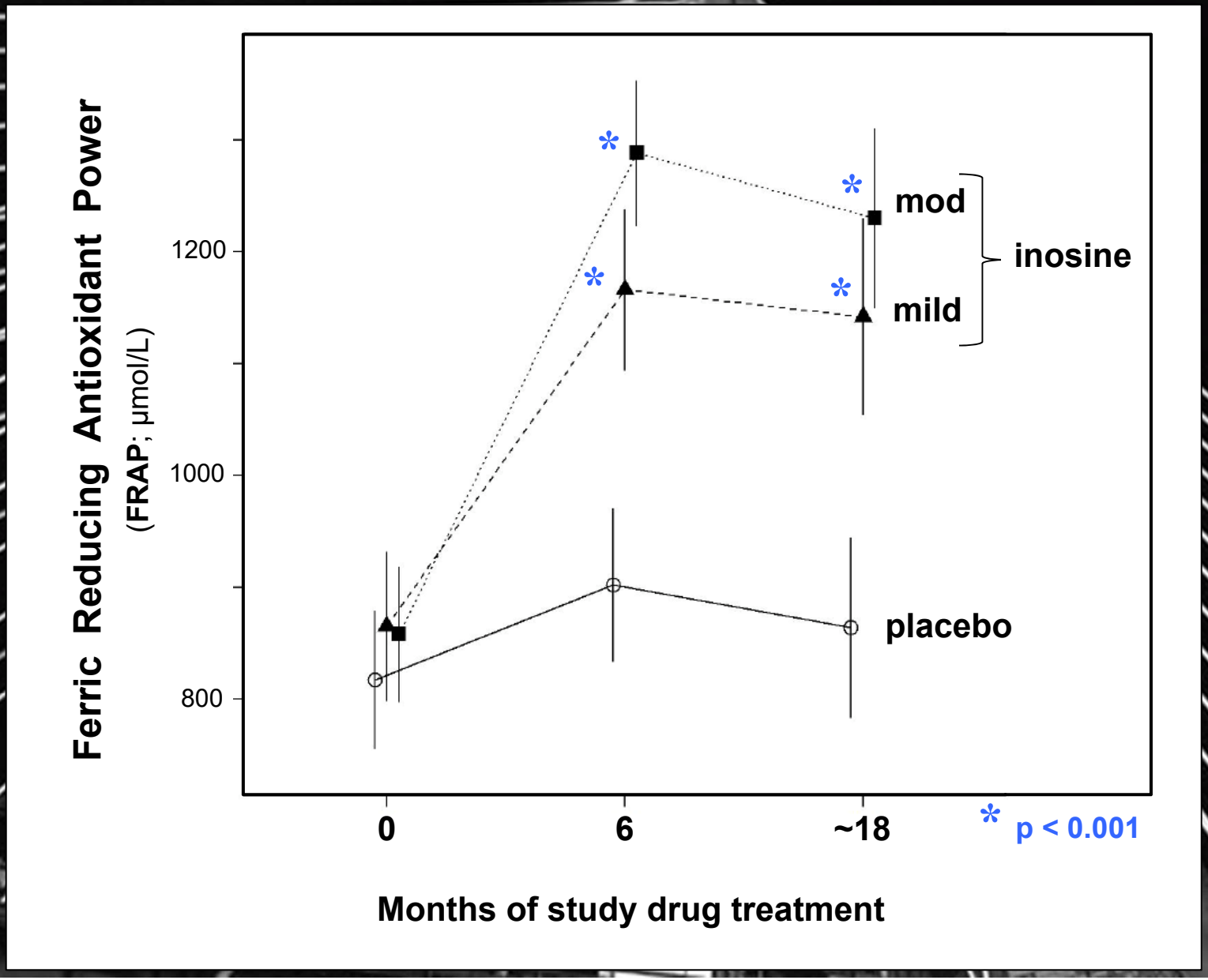
Target engagement: Inosine dose-dependently and chronically elevates serum urate in early PD



Parkinson Study Group. *JAMA Neurology*. 2014; 71:141-50.

Dorsey, January 2001

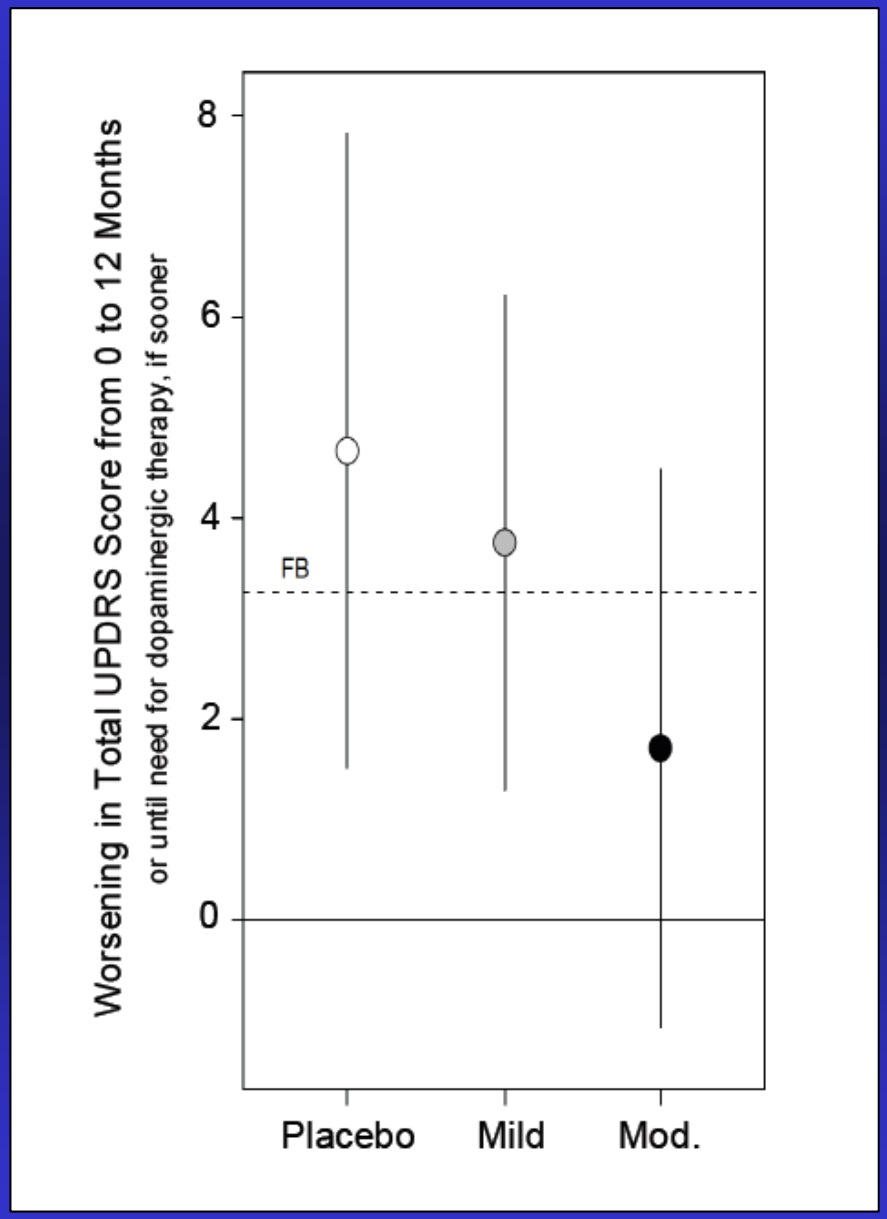
Target engagement: Inosine dose-dependently and chronically elevates plasma antioxidant capacity (measured as FRAP)



Bhattacharyya S, Bakshi R et al. *Mov Disord.* 2016; 31:417-21.

Don Eyles January 2001

SURE-PD: Secondary Results, Clinical Scales



Overall Conclusion:

- Inosine was generally safe, tolerable, and effective in raising serum and CSF urate levels in early PD.
- The findings support advancing to more definitive development of inosine as a potential disease-modifying therapy for PD.

Parkinson Study Group. *JAMA Neurology*. 2014; 71:141-50.

Don Eyles *November 2001*

Targeting Urate in PD

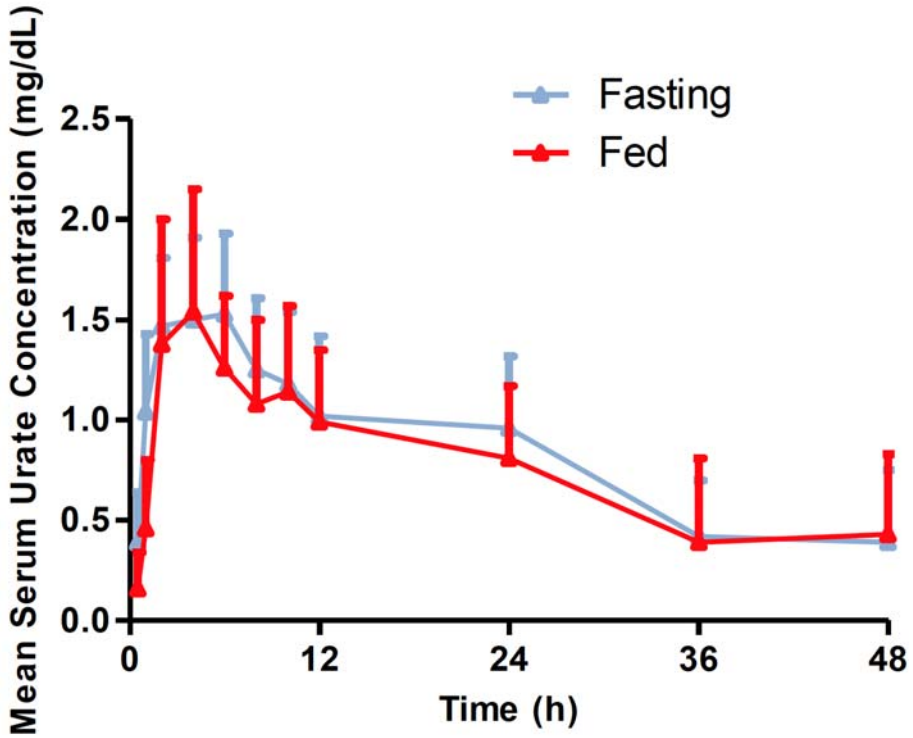
--Translational themes--

- Evolutionary genetics
  - → Urate a major antioxidant
- Epidemiology of PD
  - → Urate an inverse risk factor
  - → Urate a prognostic biomarker
- Neurobiology of PD
  - → Neuroprotection by urate
  - → Astrocytic Nrf2 activation
- Therapeutic Development
  - → Inosine for PD, phase 2 – ✓
  - → Inosine Rx, phase 1 – ✓
  - → Inosine, phase 3 → 2016-2020

Phase 1 Studies of inosine for PD

- **Food-Drug Interaction** → **OK to dose ± food**

Time course of change in serum urate after oral inosine under fasted vs fed condidtions (n=18 healthy men)



- **Drug-Drug Interaction** → **no R_x restrictions**

SURE-PD3

Study of **UR**ate **E**levation in **P**arkinson's **D**isease, phase **3**

PARKINSON STUDY GROUP

Parkinson Study Group

- 130 clinical sites in the US & Canada
- 500 site coordinators & credentialed investigators / movement disorders neurologists, psychiatrists, neurosurgeons, biostatisticians & epidemiologists

Don Eyles *November 2001*

Targeting Urate in PD

--Translational themes--

- Evolutionary genetics
  - → Urate a major antioxidant
- Epidemiology of PD
  - → Urate an inverse risk factor
  - → Urate a prognostic biomarker
- Neurobiology of PD
  - → Neuroprotection by urate
  - → Astrocytic Nrf2 activation
- Therapeutic Development
  - → Inosine for PD, phase 2 – ✓
  - → Inosine Rx, phase 1 – ✓
  - → Inosine, phase 3 → 2016-2020

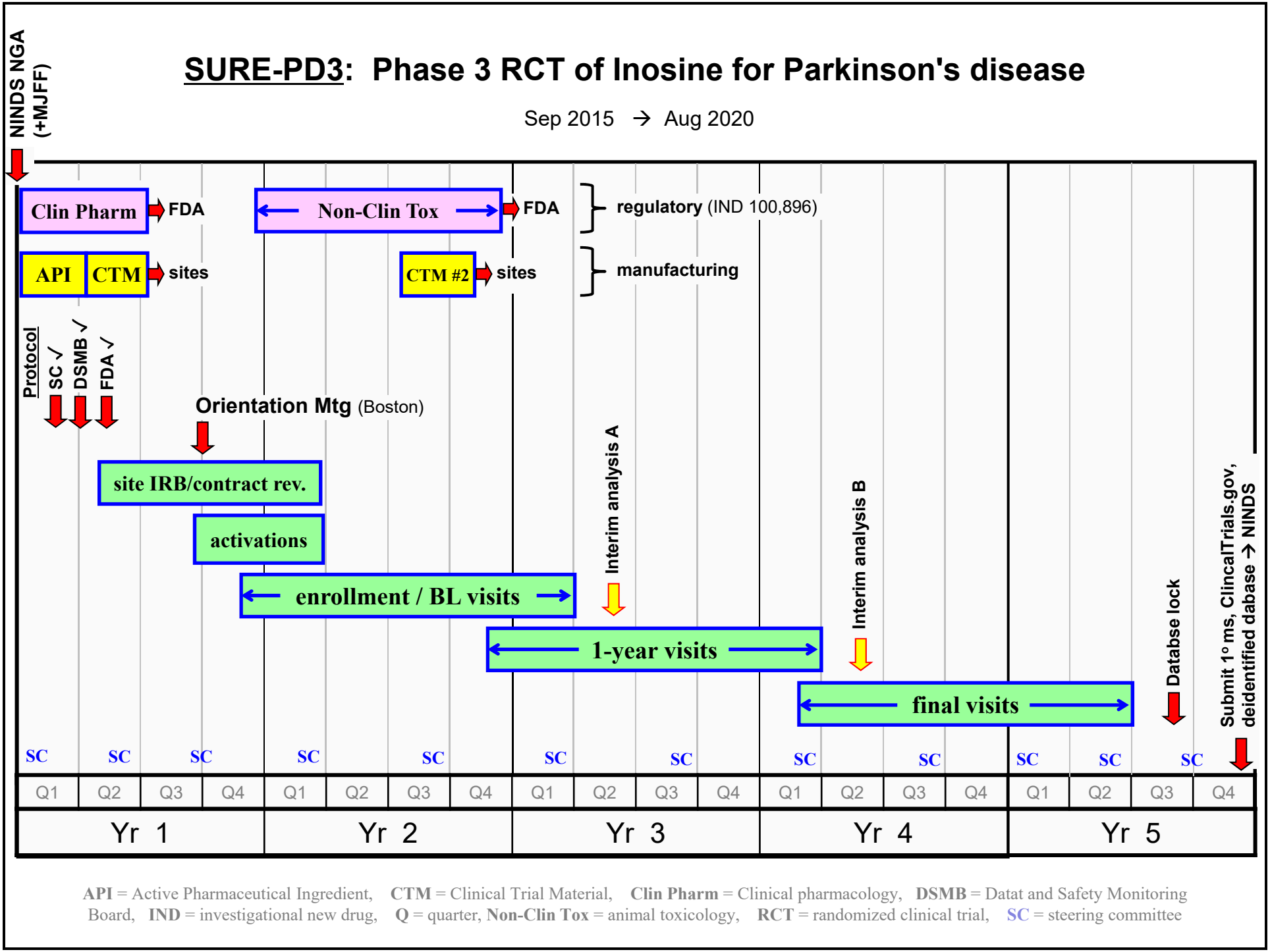
MNL Parkinson's Research Group

at

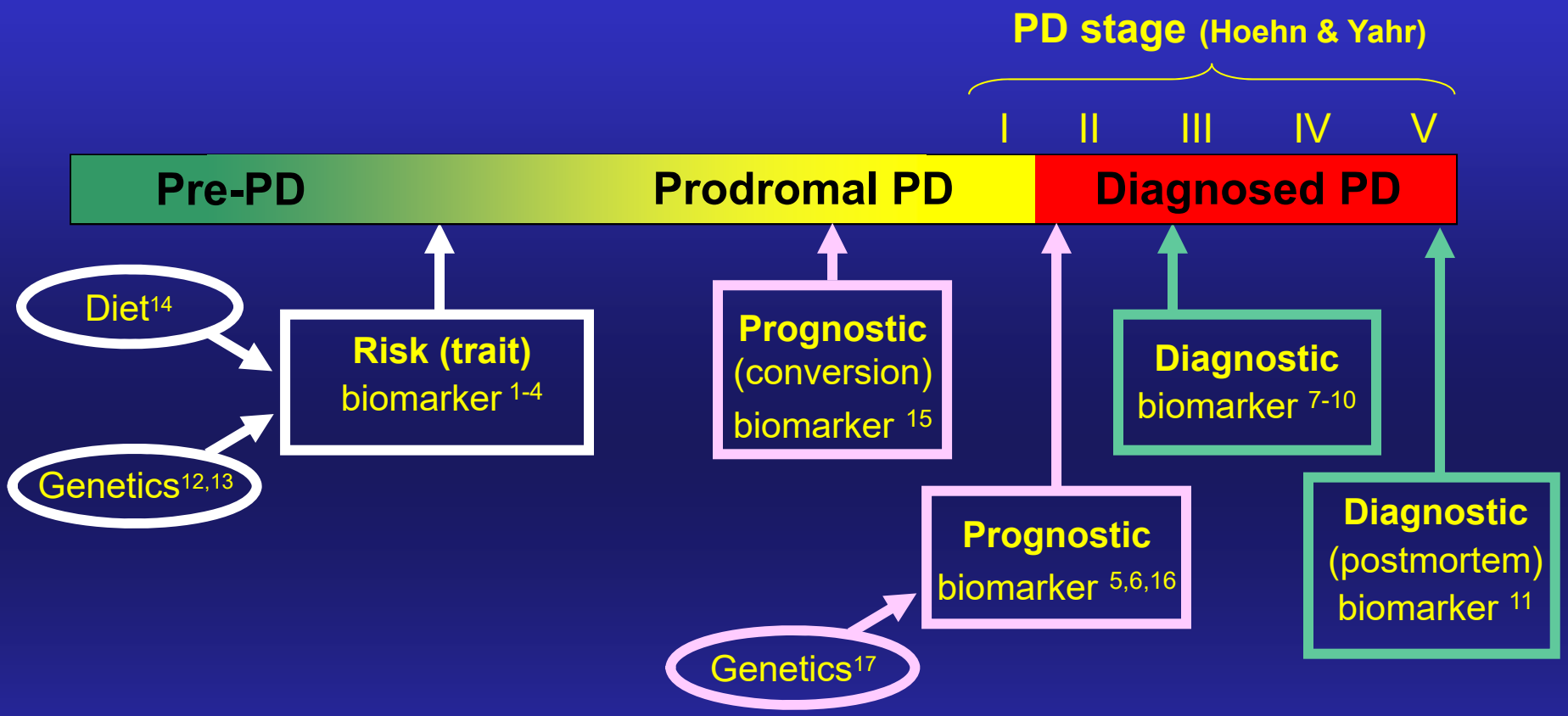
MGH MIND

gratefully acknowledges support from

- **National Inst. of Health** (NINDS, NIEHS)
- **US Dept. of Defense** (NETPR program)
- **Foundations** (**Michael J. Fox Foundation, PDF, APDA, RJG Foundation, and AFAR**)
- **PD Patients & Families**


SURE-PD3: Phase 3 RCT of Inosine for Parkinson's disease
Sep 2015 → Aug 2020
NINDS NGA (+MJFF)
Clin Pharm
FDA
Non-Clin Tox
FDA
regulatory (IND 100,896)
API
CTM
sites
CTM #2
sites
manufacturing
Protocol
SC ✓
DSMB ✓
FDA ✓
Orientation Mtg (Boston)
site IRB/contract rev.
activations
enrollment / BL visits
Interim analysis A
1-year visits
Interim analysis B
final visits
Databse lock
Submit 1° ms, ClincalTrials.gov, deidentified dabase → NINDS
SC
Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4
Yr 1
Yr 2
Yr 3
Yr 4
Yr 5
API = Active Pharmaceutical Ingredient, CTM = Clinical Trial Material, Clin Pharm = Clinical pharmacology, DSMB = Datat and Safety Monitoring Board, IND = investigational new drug, Q = quarter, Non-Clin Tox = animal toxicology, RCT = randomized clinical trial, SC = steering committee

Biomarker Properties of Urate across the Timeline of PD



1 Davis *et al. Am. J. Epidemiol.* 144:480-4 (1996).

2 de Lau *et al. Ann. Neurol.* 58:797-800 (2005).

3 Weisskopf *et al. Am. J. Epidemiol.* 166:561-7 (2007).

4 Chen *et al. Am. J. Epidemiol.* 169:1064-9 (2009).

5 Schwarzschild *et al. Arch. Neurol.* 65:716-23 (2008).

6 Ascherio *et al. Arch. Neurol.* 66:1460-8 (2009).

7 Larumbe Ilundain *et al. Rev. Esp. Salud Publica* 75:43-53 (2001).

8 Annanmaki *et al. Mov. Disord.* 22:1133-7 (2007).

9 Andreadou *et al. Clin. Neurol. Neurosurg.* 111:724-8 (2009).

10 Winquist *et al. Mov. Disord.* 25:932-6 (2010).

11 Church & Ward. *Brain Res. Bull.* 33:419-25 (1994).

12 Facheris *et al. J. Mol. Neurosci.* 43:246-250 (2010).

13 Gonzalez-Aramburu et al. *Mov. Disord. 28*, 1737-1740 (2013).

14 Gao *et al. Am. J. Epidemiol.* 167:831-8 (2008).

15 Uribe-San Martın et al. *Mov. Disord.* [10.1002/mds.25441] (2013).

16 Moccia *et al. Eur. J. Neurol.* [doi:10.1111/ene.12533] (2014).

17 Simon, Eberly, Gao *et al. Ann. Neurol.*. (2014) Sep 25. online.