“Which Neurological Disorders are Primed for Key Advances in Biomarker Development?”

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University of Rochester
Rochester, NY, USA
Not sure, but likely disorders characterized by:

- Knowledge of etiopathogenesis
- Active clinical trials and observational studies
- Would be helpful to inventory and track biomarker projects, but more than 600 neurological disorders
Urate as a Predictor of Progression of Parkinson’s Disease
Alberto Ascherio & Michael A. Schwarzschild
and the Parkinson Study Group

The Gout by James Gillray (1799)
purine / adenosine metabolism

~14 million years ago

adenosine

- adenosine deaminase

inosine

- nucleoside phosphorylase

hypoxanthine

- xanthine oxidase

xanthine

- xanthine oxidase

urate

- uricase

allantoin
Parkinson’s Disease (PD)

- Oxidative mechanisms are implicated in pathogenesis of PD.
- Uric acid exerts anti-oxidative effects against reactive nitrogen and oxygen species.
- Three large prospective epidemiological studies link higher blood urate to a lower risk of PD (Weisskopf MG et al, Health Professional Follow-Up Study).
Relative risk for PD for each standard deviation increase in urate concentration: Meta-analysis of cohort studies

- **HPFS**: RR (95% CI) 0.76 (0.61-0.95)
- **Honolulu Heart**: RR (95% CI) 0.8 (0.7-1.0)
- **Rotterdam**: RR (95% CI) 0.71 (0.51-0.98)

**Combined**: RR (95% CI) 0.80 (0.71-0.90) *p < 0.0001
PRECEPT Clinical Trial
Shoulson I and the Parkinson Study Group (PSG) PRECEPT Investigators
Neurology 2006; 67:185

- CEP-1347 inhibits mixed lineage kinases that activate apoptotic pathways implicated in the pathogenesis of Parkinson’s disease (PD).
- 806 patients with early PD, randomized to one of 3 dosages of CEP-1347 or placebo, were evaluated clinically (disability requiring dopaminergic therapy) and by dopamine transporter β-CIT SPECT imaging over 21.4 months (trial was concluded prematurely based on pre-specified futility analysis)
- But, we found that baseline serum uric acid concentration was inversely related to clinical and radiographic measures of PD progression.
### Hazard ratios (HR)† for reaching the PD disability endpoint in PRECEPT according to baseline serum urate


<table>
<thead>
<tr>
<th>Serum urate quintile</th>
<th>Median serum urate (mg/dL)</th>
<th>All (n=804)</th>
<th>Men (n=517)</th>
<th>Women (n=287)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR (95% CI)</td>
<td>p value</td>
<td>n</td>
</tr>
<tr>
<td>1</td>
<td>3.8</td>
<td>1.00 (Ref)</td>
<td>-</td>
<td>45</td>
</tr>
<tr>
<td>2</td>
<td>4.8</td>
<td>0.80 (0.60-1.07)</td>
<td>0.12</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td>5.5</td>
<td>0.85 (0.63-1.15)</td>
<td>0.29</td>
<td>110</td>
</tr>
<tr>
<td>4</td>
<td>6.3</td>
<td>0.65 (0.47-0.88)</td>
<td>0.006</td>
<td>143</td>
</tr>
<tr>
<td>5</td>
<td>7.5</td>
<td>0.51 (0.37-0.72)</td>
<td>&lt;0.0001</td>
<td>132</td>
</tr>
<tr>
<td>p, for trend</td>
<td></td>
<td>0.0002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p, for gender-urate interaction</td>
<td></td>
<td>0.15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

†Adjusted for age and gender

- 492 of 804 subjects reached disability endpoint over mean 21 months.
- Associations not appreciably affected by controlling for smoking, BMI, CEP-1347 and other potential confounders.
SPECT images of $[^{123}\text{I}]\beta$-CIT uptake over 3 years demonstrates progressive dopamine transporter loss in PD

adapted from Marek, K. et al. (2001) *Neurology* 57:2089-2094
Higher serum urate at baseline indicates 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.
• Deprenyl (selegiline) and tocopherol exert anti-oxidative effects implicated in the pathogenesis of Parkinson’s disease (PD).
• 800 patients with early PD were randomized in 2X2 factorial design to deprenyl and/or tocopherol and evaluated clinically over 18+ months when the trial was modified because of robust efficacy of deprenyl.
Hazard ratios of reaching primary endpoint of disability requiring levodopa therapy according to serum urate at DATATOP baseline

Higher CSF urate and slower PD progression in DATATOP


<table>
<thead>
<tr>
<th>CSF urate quintile</th>
<th>Median CSF urate (mg/dL)</th>
<th>ALL (n=290)</th>
<th></th>
<th>p value</th>
<th>Men (n=196)</th>
<th></th>
<th>p value</th>
<th>Women (n=94)</th>
<th></th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR (95% CI)</td>
<td></td>
<td></td>
<td>HR (95% CI)</td>
<td></td>
<td></td>
<td>HR (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.47</td>
<td>1.00 (Ref)</td>
<td>-</td>
<td></td>
<td>0.60</td>
<td>1.00 (Ref)</td>
<td>-</td>
<td></td>
<td>0.38</td>
<td>1.00 (Ref)</td>
</tr>
<tr>
<td>2</td>
<td>0.67</td>
<td>0.76 (0.50 – 1.15)</td>
<td>0.20</td>
<td></td>
<td>0.79</td>
<td>0.89 (0.54 – 1.48)</td>
<td>0.66</td>
<td></td>
<td>0.50</td>
<td>0.64 (0.29 – 1.44)</td>
</tr>
<tr>
<td>3</td>
<td>0.86</td>
<td>0.80 (0.52 – 1.25)</td>
<td>0.49</td>
<td></td>
<td>0.92</td>
<td>0.82 (0.50 – 1.35)</td>
<td>0.44</td>
<td></td>
<td>0.66</td>
<td>0.47 (0.20 – 1.09)</td>
</tr>
<tr>
<td>4</td>
<td>1.04</td>
<td>0.66 (0.43 – 1.03)</td>
<td>0.15</td>
<td></td>
<td>1.09</td>
<td>0.74 (0.45 – 1.23)</td>
<td>0.25</td>
<td></td>
<td>0.78</td>
<td>0.67 (0.30 – 1.50)</td>
</tr>
<tr>
<td>5</td>
<td>1.39</td>
<td>0.52 (0.33 – 0.81)</td>
<td>0.004</td>
<td></td>
<td>1.44</td>
<td>0.53 (0.32 – 0.90)</td>
<td>0.02</td>
<td></td>
<td>1.18</td>
<td>0.43 (0.19 – 0.98)</td>
</tr>
</tbody>
</table>

†Adjusted for age, gender, and treatment group (deprenyl or placebo) 1 standard deviation (SD = 0.37 mg/dL)
Conclusions & Biomarker Implications

- Higher serum (CSF) urate is associated with reduced risk and slower progression of PD, assessed clinically and radiographically in two large longitudinal studies.

- Urate is the first molecular factor linked to the progression of PD.

- Urate and purine metabolism provide phenotypic clues to the pathogenesis of PD.

- Urate or its determinants may have therapeutic implications for modifying the progression of PD.
Serum urate and the 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 and DATATOP Investigators

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

• NIH (NINDS, NHGRI, NCCAM)
• Somerset Pharmaceuticals (DATATOP)
• Cephalon and Lundbeck (PRECEPT)
• FDA (Orphan Drug Division)
• Parkinson Study Group (www.parkinson-study-group.org)
• Huntington Study Group (www.huntington-study-group.org)
Huntington’s Disease (HD)

- Oxidative mechanisms are implicated in pathogenesis of HD, which is caused by a trinucleotide repeat (CAG<sub>n</sub>) gene mutation.
- Nucleic acid oxidation may be a marker of oxidative stress.
- Indices of nucleic acid oxidation can be examined in prospective observational studies (PHAROS, PREDICT-HD) and clinical trials (2-CARE) involving HD gene carriers (pre-manifest, manifest).
Peripheral Biomarkers of Oxidative DNA and RNA Damage in HD

Steven Hersch, MD, PhD
MassGeneral Institute for Neurodegenerative Disease
Massachusetts General Hospital, Harvard Medical School
Nucleic Acid Oxidation as a Biomarker of Oxidative Stress

Guanosine 8-hydroxy-2’-deoxyguanosine
8OH2’dG and 8OHrG Production

DNA

RNA

oxidation

excision repair

degradation

8OH2’dG

8OHrG
$8\text{OH}_2'd\text{G}$ and $8\text{OHrG}$ as Biomarkers of Oxidative Damage

- Carcinogenesis
- Aging and senescence
- Toxicology
- Neurodegenerative disorders (AD, PD, ALS)
- Ischemic vascular disease
8OH2’dG is Elevated in HD Postmortem Brain

Polidori et al. 1999

Fig. 2. Amounts of OH²dG in mtDNA extracted from frontal cortex of HD (n = 22) and control (n = 15) subjects (n.s.).

Fig. 3. Amounts of OH²dG in mtDNA extracted from parietal cortex of HD (n = 17) and control (n = 10) subjects (P < 0.001).
8OH2’dG Elevated in R6/2 Transgenic Mice

- Present in DNA and CSF in brain
- Present in serum, urine
- Brain may be major source of peripheral levels
- Responds to some classes of neuroprotective therapies.

8OH2’dG is Elevated in HD Knock-In Mice
8OH2’dG is Elevated in Early Symptomatic HD (TFC 13-7)

<table>
<thead>
<tr>
<th>Controls</th>
<th>HD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean=13.5</td>
<td>Mean=45.3</td>
</tr>
<tr>
<td>SD=4.04</td>
<td>SD=14.62</td>
</tr>
</tbody>
</table>
8OH2’dG is Elevated in Pre-Manifest HD

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Pre-Manifest</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13.4</td>
<td>18.1</td>
</tr>
<tr>
<td>2</td>
<td>1.531078234</td>
<td>5.609367802</td>
</tr>
<tr>
<td>p</td>
<td>0.00271792</td>
<td></td>
</tr>
</tbody>
</table>
8OH2’dG Levels May Mark The HD Prodrome and Phenoconversion

**Partial discrimination of controls from pre-manifest HD suggests that 8OH2’dG elevates during the HD prodrome.**

**Nearly complete discrimination of pre-manifest from manifest HD suggests that 8OH2’dG may elevate as phenoconversion occurs.**
Creatine in Huntington disease is safe, tolerable, bioavailable in brain and reduces serum 8OH2'dG

Abstract—In a randomized, double-blind, placebo-controlled study in 64 subjects with Huntington disease (HD), 8 g/day of creatine administered for 16 weeks was well tolerated and safe. Serum and brain creatine concentrations increased in the creatine-treated group and returned to baseline after washout. Serum 8-hydroxy-2'-deoxyguanosine (8OH2'dG) levels, an indicator of oxidative injury to DNA, were markedly elevated in HD and reduced by creatine treatment.

NEUROLOGY 2006;66:250–252

S.M. Hersch, MD, PhD; S. Gevorkian, MSc; K. Marder, MD, MPH; C. Moskowitz, MS; A. Feigin, MD; M. Cox, MS, RN; P. Como, PhD; C. Zimmerman, RN; M. Lin, MD; L. Zhang, MD; A.M. Ulug, PhD; M.F. Beal, MD; W. Matson, PhD; M. Bogdanov; E. Ebbel; A. Zaleta, BA; Y. Kaneko, BA; B. Jenkins, PhD; N. Hevelone, MPH; H. Zhang, MS; H. Yu, MPH; D. Schoenfeld, PhD; R. Ferrante, PhD, MSc; and H.D. Rosas, MD, MS
Effect of Creatine (8gm/day) on Serum 8-OH2’dG in Huntington’s Disease

Changes in serum 8-OH2’dG levels (pg/ml) in 32 placebo- and creatine-treated subjects with manifest HD. These scatterplots show individual 8-OH2’dG levels after 16 weeks of treatment. The difference in the changes between the placebo and treatment groups was significant (p<0.0042). Hersch S, et al (Neurology 2006; 66: 250-252)
Dose Dependent Suppression of 8OH2’dG by Creatine in Symptomatic HD (CREST-UP)
Oxidized Nucleic Acids as Biomarkers

• Measures the molecular damage caused by an important disease activity.
• Peripheral levels may reflect brain levels.
• Peripheral levels respond to specific therapies.
• Easily measured in plasma or urine with simple specimen preparation.
• Influences like gender, smoking, concomitant medications seem small compared to robust signal in HD.
• Usefulness in assessing Rx activity, dose/response, response maintenance, phenoconversion?
Clinical Studies With Plans to Examine 8OH2’dG and 8OHrG in HD

- Phenylbutyrate (PHEND-HD)
- Creatine (CREST, CREST-UP, CREST-X, PRE-CREST, CREST-E)
- Coenzyme Q10 (PREQUEL)
- PHAROS
- PREDICT
‘Neuro Prevention’

Experimental interventions that postpone or prevent the onset of illness in individuals who are at high risk to develop the (neurodegenerative) disease.
Acknowledgements

• NIH (NINDS, NHGRI, NCCAM)
• Somerset Pharmaceuticals (DATATOP)
• Cephalon and Lundbeck (PRECEPT)
• FDA (Orphan Drug Division)
• Parkinson Study Group (www.parkinson-study-group.org)
• Huntington Study Group (www.huntington-study-group.org)
HSG
HUNTINGTON STUDY GROUP

seeking treatments that make a difference for Huntington’s disease
Higher serum urate predicts slower PD progression

Hazard ratios (HR)† for reaching the endpoint
According to common quintiles of baseline serum urate in DATATOP

<table>
<thead>
<tr>
<th>Serum urate quintile</th>
<th>Serum urate (mg/dL)</th>
<th>All (n=774)</th>
<th>Men (n=510)</th>
<th>Women (n=264)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR (95% CI)</td>
<td>p value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>1</td>
<td>&lt;3.9</td>
<td>1.00 (Ref)</td>
<td>-</td>
<td>1.00 (Ref)</td>
</tr>
<tr>
<td>2</td>
<td>3.9 - 4.7</td>
<td>1.05 (0.75 - 1.46)</td>
<td>0.78</td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td>4.7 - 5.3</td>
<td>0.88 (0.62 - 1.26)</td>
<td>0.49</td>
<td>135</td>
</tr>
<tr>
<td>4</td>
<td>5.3 - 6.3</td>
<td>0.81 (0.56 - 1.17)</td>
<td>0.26</td>
<td>115</td>
</tr>
<tr>
<td>5</td>
<td>&gt;=6.3</td>
<td>0.69 (0.47 - 1.01)</td>
<td>0.06</td>
<td>139</td>
</tr>
<tr>
<td>Serum urate, 1 SD</td>
<td></td>
<td>0.82 (0.73 - 0.93)</td>
<td>0.002</td>
<td>80</td>
</tr>
<tr>
<td>p, for gender-urate interaction</td>
<td></td>
<td>0.50</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

†Adjusted for age, gender, and treatment group (deprenyl or placebo)
1 standard deviation (SD = 1.4 mg/dL)