Title: ***Predicting PD Progression Subtypes by CSF Urate Pathways***

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Abstract: Urate is as a major antioxidant as well as the enzymatic end product of adenosine metabolism in humans. Findings from a large prospectively followed cohort of 18,000 men (in the Harvard HPFS) substantiated a strong predictive association between plasma urate and a reduced risk of later developing PD. This emerging link between urate and PD risk in healthy populations led us to collaborate with the leadership of two major Parkinson Study Group (PSG) studies in order to explore the relationship between urate and disease progression amongst some 1,600 early PD patients. In the PRECEPT and DATATOP cohorts, higher (but still normal) levels of serum urate at baseline were associated with a highly significant reduction in the rate of disease progression as gauged by clinical (time to dopaminergic therapy) or neuroimaging (loss of striatal DAT ligand binding) measures. Analysis of previously measured urate concentrations in a subset of CSF samples from DATATOP suggested an even greater predictive value of CSF (compared to serum) urate regarding the pace at which PD progresses.

We propose to determine whether the rate of PD progression can be predicted based on their CSF urate pathway profiles. For this purpose, we plan to mine the DATATOP CSF repository and outcomes database to 1) confirm the correlations between CSF urate, serum urate and clinical progression of PD and clarify whether they occur in women as well men; 2) characterize the predictive value of another major soluble antioxidant ascorbate, as well as other purine metabolites in urate's metablolic pathway (hyoxanthine-->xanthine-->urate). The findings may help explain why PD progresses more slowly and in some patients, and may be directly translated into the design of clinical neuroprotection trials for PD.

Funding provided by the PSG/PDF data-mining program will allow to initiate the project, and clarify the urate-PD relationship in women.