Published in final edited form as:

Mov Disord. 2010 ; 25(Suppl 1): S152–S154. doi:10.1002/mds.22790.

Therapeutic Directions for Parkinson Disease

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The recent failures of novel experimental treatments aimed at slowing the progression of Parkinson disease (PD) have raised questions about the vitality of the research pipeline, the identification of suitable therapeutic targets, the 'druggability' of potential lead compounds, the availability of predictive animal models, and the unmet need for biological markers that might better inform about mechanisms and the underlying neurodegenerative process^{1–3}. There are lingering concerns that rational experiment treatments may not affect the desired target or mechanism. The relationship of clinical outcomes to neuronal degeneration may not be straightforward because clinical progression reflects neurochemical and regenerative compensatory mechanisms as well as neuronal vitality or function⁴.

So too, PD clinical trial methodology for detecting so-called 'neuroprotective' effects has been criticized because of poor sensitivity and high variability of clinical outcomes, failure to measure patient-reported outcomes, large placebo effects, diagnostic imprecision, lack of informative biomarkers, large sample size requirements, need for long duration of observation, and high costs. Is the experimental therapeutics of PD in a funk? Hardly! Rather, the high expectations for quantum therapeutic advances have overshadowed the incremental gains that have been gradually achieved⁵.

The PRECEPT clinical trial is a case in point¹. CEP-1347 inhibits mixed lineage kinases that activate apoptotic pathways implicated in the pathogenesis of Parkinson's disease⁶. Following preliminary, safety, tolerability and dose-ranging studies⁷ and considerable planning, Parkinson Study Group (PSG) investigators at 65 sites in the United States and Canada enrolled 806 patients with early PD who were randomized to one of 3 dosages of CEP-1347 or matching placebo and evaluated clinically and by dopamine transporter β -CIT imaging⁸. The trial was concluded prematurely after 21.4 months when pre-specified endpoints of futility were reached and experimental treatments discontinued. Despite the disappointing treatment outcome, the PRECEPT trial has led to informative biomarker findings, and research patients continue to be followed systematically as the core of an expanding biomarker project.

From the accrued data in the PRECEPT trial, it was discovered that baseline serum uric acid concentration of research participants was inversely related to clinical and radiographic measures of PD progression, notwithstanding randomized allocation of CEP-1347 treatments⁹. This observation that higher blood urate levels were associated with slower clinical progression was subsequently confirmed by analyses of DATATOP trial data that were generated 20 years earlier, and extended to cerebrospinal fluid urate concentrations obtained from stored DATATOP samples¹⁰. Shortly before these findings emerged, collective analyses of epidemiological data indicated that serum uric acid was inversely related to the risk of developing PD¹¹. These observations have also prompted safety and dose-finding studies of inosine, a precursor of uric acid, in order to gauge whether

pharmacologic elevation of blood and CSF urate may be a feasible strategy to slow the progression of PD [SURE-PD clinicaltrials.gov registration # pending]. Taken together, extended analyses of well-characterized clinical trial cohorts like PRECEPT and DATATOP have provided important clues to unraveling pathogenesis and therapeutic leads to favorably altering the course of PD.

Re-engineering of the clinical research enterprise has taken on substantive meaning and support in the form of the NIH Roadmap for Clinical Research¹². Rather than discard or dismantle clinical trial resources after the interventional phase has concluded, seize the opportunity to follow consenting research participants so that the valuable investments of human and financial resources can be recycled and applied to inform the direction of experimental therapeutics. In so doing, extended and systematically accrued longitudinal data can be made available for public access, retrieved for analyses, and in turn applied to inform about more efficient and relevant clinical outcomes, improved diagnostic precision, biomarkers applicable to the trait and state of PD, and promising therapeutic interventions.

The PRECEPT clinical trial cohort has been gradually transformed into the PostCEPT observational study aimed at longitudinal follow up of clinical and imaging (β -CIT SPECT of DA transporter) outcomes and the development of biomarkers for PD. About 75% of the 713 potentially eligible PRECEPT participants have consented to enroll in PostCEPT, and systematically collected longitudinal clinical and imaging data from PRECEPT are now linked to ongoing annual in-person assessments in PostCEPT. β -CIT SPECT imaging of PostCEPT participants is ongoing, comprising standardized follow-up scans for up to 4 years of longitudinal assessment since enrollment in the PRECEPT trial. Neuroimaging data include subjects who have 'scans without evidence of dopamine deficiency' (SWEDDs) in order to learn more about these participants and how they might differ from the natural history of PD. The PostCEPT observational study now represents the largest 'live' cohort of PD patients that is actively being followed in North America.

The PSG 'Follow-Up of Persons with Neurologic Disease' (FOUND) project¹³, which provides centralized and systematic bi-annual follow up and clinical assessments through mail and telephone, was also adapted and applied to PostCEPT. Consenting subjects provide contact information as well as information about disease status. A benefit of enrolling subjects into FOUND is the opportunity for long-term follow up, even for subjects who withdraw from in-person follow up at study centers. FOUND also provides PostCEPT with an important safety net to enhance retention and longitudinal data collection.

PostCEPT participants have also provided blood samples to the NINDS Human Genetics DNA and Cell Line Repository at Coriell Institute for Medical Research repository (<http://ccr.coriell.org/Sections/Collections/NINDS/?SsId=10>) for future DNA scientific research. De-identified samples of extracted DNA will be genotyped for LRRK2, Rep 1 allele and other potential PD-related mutations.

A sub-study of alpha-synuclein and RNA biomarkers, referred to as PROBE, is underway at 22 PostCEPT sites. Through PROBE, healthy volunteers (N=50) as well as 25 patients with multi-system atrophy (MSA) and 25 patients with progressive supranuclear palsy (PSP) are joining observational research participation in PostCEPT. Additional biomarker studies are being undertaken in this well-characterized cohort of PD patients and control groups.

Public sharing of data has been an abiding principle in this observational study. A core set of the PostCEPT data that has been compiled at the PSG coordination center now resides on the public PD-DOC website (<http://www.pd-doc.org>), which is sponsored by NINDS through the Udall Center program. The PD-DOC website provides standardized, de-identified clinical data in order to share data, provide public access and enhance the ability

of researchers to correlate clinical, imaging and genotype data (<http://ccr.coriell.org/Sections/Collections/NINDS/?SsId=10>).

By working together, the PSG has been successful in ensuring the transition of our PRECEPT research participants from a clinical trial into an unprecedented observational and biomarker study for PD. This accomplishment is in keeping with the NIH Roadmap `clinical research re-engineering` mission to more efficiently utilize existing resources (human, clinical data, biomarker samples) to generate new pathogenetic and therapeutic knowledge. As the cohort is followed over time, it will take on added value as a living laboratory to examine the natural history of PD.

A major limitation in the experimental therapeutics of PD has been the relatively short duration of prospective and systematic follow up, linked to biomarker research and genotypic correlations. The ongoing follow up of the original DATATOP cohort is the closest approximation of the value of such longitudinal and systematic research^{14, 15}. To this day, the information from the `cold` DATATOP cohort continues to provide valuable new knowledge about PD. It is anticipated that an ongoing and systematically observed `live` cohort of remarkably well-characterized research participants will provide a continuously enriched living laboratory to expand applicable knowledge about PD.

As science progresses and biomarker opportunities expand, appropriate biological material can be collected from consenting research participants to enhance the prospects of developing a variety of biological hallmarks and characteristics of PD. The availability of corresponding and de-identified genetic data is expected to further enrich the knowledge in this advancing field of inquiry.

Biomarkers are expected to improve the efficiency and informativeness of clinical trials aimed at modifying the underlying disease process. However, biomarkers will not substitute for relevant clinical outcomes, such as sustained functional capacity or employability, slowing of accrued disability, sustained quality of life, reduced mortality, and eventually postponing the onset of illness in pre-manifest PD.

Clinical investigators might best abandon or minimize use of terms such as `neuroprotective` and `disease-modifying`, which are appropriate for scientists examining basic mechanisms of pathogenesis. Instead, clinical researchers should pursue relevant clinical outcomes and corresponding biomarkers that ultimately require validation in clinical trials. What is now needed are large-scale and multi-year, multi-site studies of sufficient duration that examine clinically relevant outcomes and potential biomarkers. This effort will be enhanced by a concerted effort at data sharing, data mining and public reporting

Acknowledgments

- Funding Sources (Uric acid biomarker discovery and development):
 - NIH/NINDS NS24778 (original DATATOP sponsor)
 - NIH/NINDS R01 NS048517, NS054978
 - NIH/NIEHS R01 ES010804
 - Parkinson Study Group
 - Michael J Fox Foundation
- PRECEPT sponsors: Cephalon, Inc., H. Lundbeck A/S
- PostCEPT sponsors: NINDS (Udall Centers/PD-DOC), Department of Defense NTERP Program (Imaging, PROBE Biomarkers) Cephalon, Inc., H. Lundbeck A/S, Parkinson's Disease Foundation (FOUND)

- PRECEPT/DATATOP study patients and families

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