Mission
CurePSP’s mission is to increase awareness of progressive supranuclear palsy, corticobasal degeneration, and other atypical Parkinsonian disorders; fund research toward treatment, cure and prevention; educate healthcare professionals; and provide support, information and hope for affected persons and their families.

Response
CurePSP has advanced the understanding of PSP, CBD and closely related brain diseases by funding research focusing on: identifying the causes and risk factors for these disorders; developing early stage diagnostic tests and disease biomarkers; and developing treatments or interventions to ameliorate symptoms and to prevent, slow, halt or reverse disease progression. This research has generated several new avenues of potential treatments for these disorders including potential neuroprotective or disease-modifying treatments that may possibly slow progression and better methods to ameliorate symptoms. Since 1997, CurePSP has funded 160 research grants valued at $13 million and assembled an international genetics consortium that has searched the human genome for genes related to PSP and CBD. Supporting this work, the Foundation has also established a brain bank providing autopsy-confirmed brain tissue and DNA samples to researchers worldwide at no cost to them. CurePSP consistently re-evaluates its research goals as prompted by the latest scientific developments and holds an annual international research symposium to publicize its findings. The Foundation avails itself of the advice of a Scientific Advisory Board composed of some of the world’s leading neuroscientists. CurePSP continuously seeks opportunities to collaborate with existing research groups with similar and complementing goals. The Foundation continues to emphasize the biological similarities between PSP/CBD and the more common neurodegenerative disorders in an attempt to create scientific and funding synergies.

New Direction
CurePSP recognizes that the fight against PSP can now take a new direction, capitalizing on recent discoveries, exciting ongoing work and new hypotheses. We propose to fund research initiatives in five areas that in many cases can proceed in parallel. They can take place in academia or industry and would be awarded via a competitive, peer-reviewed process. CurePSP Research Road Map 1 These areas are Genes, Prions, Proteins, Models and Markers. The first three are new hypotheses. The last two are new experimental tools.
Genes

PSP research can now follow up on the discoveries of our CurePSP Genetics Consortium, funded by our Charles D. Peebler, Jr. PSP Genetics Program. In 2011, the Consortium published the results of its genome-wide association study (GWAS), which used “snip chips” to find genes not previously known to be associated with PSP. It found three such genes with very strong associations, STX6, EIF2AK3 and MOBP. It also confirmed the known association of one variant in MAPT (the tau gene) and found a second, new Tau gene variant. This work has now been extended, via funding from the Morton and Marcine Friedman Foundation, using a technique called whole-exome sequencing analysis. Already, exome sequencing has identified additional PSP-associated genes that escaped the earlier analysis.

Plan: Once the whole-exome sequencing study is completed in the first half of 2014, CurePSP will move on to supporting biochemical studies of these genes to determine their normal function and to understand how the PSP-associated mutations damage brain cells.

Cost: We will study the 10-15 most promising genes at $200,000 per gene or $2 million to $3 million.

Prions

Work in the 1970s showed that the rapidly progressive neurodegenerative disorder Creutzfeldt Jakob disease and a few others were caused by a newly discovered brain protein that assumed an abnormal folding pattern that was toxic to the cells. This misfolded “prion protein” then induced nearby normal prion protein molecules to similarly misfold, creating a chain reaction that spread throughout the brain. Evidence over the past five years now suggests that a similar mechanism, albeit operating more slowly and affecting different proteins, is at work in other neurodegenerative diseases, possibly including PSP.
**Plan:** Results of ongoing research on treatment of prion disorders can be used to jumpstart a similar effort focused on PSP. Initial steps along this research pathway include creation of cell culture and animal models of PSP that show characteristics of prion disorders such as cell-to-cell spreading of misfolded protein. Subsequent steps will focus on identifying drugs or other interventions that interfere with the misfolding/propagation process.

**Cost:** Initial model development to test the prion disorder mechanism using five cell culture/animal models at $200,000 to $1 million; followed by characterization of 10-15 treatment targets at $200,000 per target or $2 million to $3 million.

**Proteins**
Defects in how brain cells handle various proteins, even in the absence of a prion-like mechanism, may be central to the development of PSP and the other neurodegenerative diseases. Examples of such defects in protein handling are overproduction, inappropriate folding, and deficiencies in disposal of worn, defective or excess proteins. Many potential drug targets exist in the complicated protein handling systems in brain cells.

**Plan:** Identify treatment targets by studying protein handling mechanisms in PSP. As part of this, we will use new PSP-specific laboratory models (see below) to evaluate drugs modifying protein production and turnover that are already under development for other disorders such as cystic fibrosis.

**Cost:** 10-15 targets at $200,000 per target or $2 million.

**Models**
Once drug candidates are identified, they must be tested in animal models. There are several laboratory models for PSP, ranging from brain cells in a “dish” to roundworms, fruit flies, zebrafish and mice. Most of these models rely on insertion of a tau gene with a single mutation that occurs in some people with a different tau disorder, hereditary frontotemporal dementia. We need models that are created by methods similar to what is causing human PSP itself. The new genetic discoveries mentioned above, and advanced in preparing patient-derived stem cells may provide that opportunity.

**Plan:** Create models in established lab animals and in cell lines using genes, alone or in combination, that have been found to be associated with PSP. Alternatively, make induced pluripotent stem cell lines (iPS) directly from patient samples with specific defined mutations associated with PSP. Then characterize these models to determine their utility in evaluating treatments.

**Cost:** Five models at various phylogenetic levels at $200,000 per model or $1 million.

**Markers**
Drug candidates that prove safe and effective in animal models are then tested in humans. These would be drugs to slow or stop progression, not merely to blunt symptoms. Initiating treatment at the earliest possible stage of disease would be most effective. Furthermore, we need more sensitive ways of measuring effectiveness of such drugs in PSP in order to minimize the necessary size, duration, and therefore cost of drug trials.

**Plan:** To find one effective principal outcome measure for neuroprotection trials in PSP, we will have to evaluate multiple ideas. These may be tests of tau or other proteins in the spinal fluid or blood, imaging procedures using novel MRI techniques or radiotracer ligands, physiological test batteries, or ideas yet to be developed.

**Cost:** Evaluate ten candidate markers at $500,000 per marker or $5 million.
Cost and Time
It is estimated that the cost to complete the projects in the Research Road Map will be $13 million to $15 million over a seven-year period.

Results
We expect that of the 30-45 drug (or other treatment technique) candidates tested, perhaps five or six will demonstrate potential value for commercial development. At that point, the pharmaceutical industry may take over or partner with academia, using its resources for the very expensive Phase 2 and 3 clinical trials. CurePSP consistently looks for opportunities to achieve its vision of a world free of PSP, CBD and related brain diseases through good science, technology and human talent. We are on the verge of significant breakthroughs that will not only clarify the causes of these devastating illnesses but identify much-needed treatments that will in the end cure PSP, CBD and other atypical Parkinsonian disorders. The timing has never been better to unlock the secrets of neurodegenerative brain disease.