

Could Stem Cell Research Provide a Treatment for PSP?

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The use of cell therapies for the treatment of disorders of the central nervous system has evolved over the last thirty years to the level of early clinical trials. These trials have mainly used cells derived from the developing fetal brain which are then allografted into patients with moderately advanced neurological disorders. Such disorders include Parkinson's disease and fetal ventral mesencephalic allografts; Huntington's disease and fetal striatal allografts and more recently studies have commenced with stem cells in stroke and multiple sclerosis. To date the fetal allograft trials have produced conflicting results with some patients doing extremely well for many years while others have developed complications from the transplant. Whilst these disparate results are seeking an explanation it is clear that in the laboratory the ability to engineer stem cells to specific fates is becoming increasingly feasible. Thus in the foreseeable future it is likely that stem cells will be considered for grafting into the brains of patients with neurodegenerative disorders including possibly PSP. In this talk I shall summarise what has been achieved to date with neural transplants and neurological disorders of the central nervous system and how these results could be exploited for the treatment of PSP with stem cells.

Lithium in the Tauopathies

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One challenge for assessing the effects of potential therapies in neurodegenerative diseases such as the tauopathies is choosing which measures to use for assessment. Recent studies using the boundary shift integral (BSI) method from serial MRI, in which whole brain volume (WBV) and ventricular volume (VV) are measured sequentially over time, have shown relatively linear rates of decreased WBV (ie, atrophy) and increased VV (ie, ex vacuo dilatation) in patients with pathologically-proven Alzheimer's disease, frontotemporal lobar degeneration with ubiquitin-positive inclusions, corticobasal degeneration, and progressive supranuclear palsy. Similar data from collaborators at Mayo Clinic Rochester are presented, in which relatively linear rates of decreased WBV and increased VV have been found in patients with frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) due to the +3 in exon 10, +16 in exon 10, P301L, and S305N mutations in the microtubule associated protein tau (*MAPT*). Furthermore, data are presented in two siblings with the S305N mutations before and after commencement of lithium carbonate (an inhibitor of glycogen synthase kinase-3 beta or GSK-3B), in which lithium administration was associated with >50% reductions in the rates of decreased WBV and increased VV. Finally, preliminary tolerability data on the use of lithium carbonate in patients with the corticobasal syndrome (CBS) are presented, with poor tolerability achieved in eight patients with the CBS leading to discontinuation of the drug within three months in all subjects. These findings suggest the following: 1) the BSI technique may be a good objective measure for monitoring the effect of any potentially disease-altering treatment in various neurodegenerative diseases, 2) lithium therapy was associated with decreased rates of whole brain atrophy and ventricular dilatation in the FTDP-17 S305N sibs; whether this agent is truly disease-altering or has nonspecific effects on tissue water content (or both) will require further study, and 3) although lithium has inherent limitations due to its side-effect profile, this and other GSK-3B inhibitors are worthy of further study in the tauopathies

Is the Evidence Strong Enough for Lithium Trials – Pros and Cons

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Symptomatic treatment is of negligible benefit in Progressive Supranuclear Palsy (PSP). Attempts have been made to correct known neurotransmitter deficiencies, notably dopamine and acetylcholine, but with largely negative results. To date, no drug has been shown to slow down the progression of the disorder, and it seems clear that to make a significant therapeutic break-through a disease-modifying approach will be required. Several enzymes determine the phosphorylation state of tau, including glycogen synthase kinase-3 (GSK-3). Neuronal over-expression of GSK-3 β induces tau hyperphosphorylation, and transgenic mice over-expressing GSK-3 β exhibit pretangle-like deposits of hyperphosphorylated tau, neuronal loss and glial reactivity. In PSP, GSK-3 β is associated with neuronal and glial hyperphosphorylated tau while the inactive form of the enzyme co-localises with abnormal tau.

Recent *in vitro* and *in vivo* studies indicate that lithium may be neuroprotective. Lithium dose-dependently blocks tau phosphorylation in cultured neuronal-like human cell lines and primary cultures of rat hippocampal neurones and induces phosphorylation of the serine 9 residue of GSK-3 β , inhibiting tau phosphorylation on the PHF-1 epitope in a variety of *in vitro* cell lines.

There have been no studies of lithium to date in PSP patients. There are conflicting data as to whether lithium slows down cognitive deterioration in patients prescribed it for other indications (mainly bipolar affective disorder). Previous trials of lithium in Alzheimer's disease have yielded mixed results but these studies used smaller than usual doses of the drug and included severely demented patients. Nevertheless, the issue of tolerability in an older and frailer population, more likely to be taking drugs for co-morbidities that could interact with lithium is of concern for potential trials of this agent in PSP. Additionally, lithium may exacerbate or cause tremor and extrapyramidal features and predispose to delirium.

In the face of biological plausibility, and absence of a less toxic current alternative, it seems reasonable to undertake a lithium trial in PSP. Any study of this agent in PSP, which would be phase II, should, however, use tolerability as a primary outcome measure. Additional biomarker data and perhaps limited efficacy data could also be simultaneously gathered. Just because we have to deal with a brutal and aggressive neurodegenerative disease should not mean that our default position is to try anything rather than nothing.

How DeNDRoN can Facilitate Trials in PSP

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The Dementias & Neurodegenerative Diseases Research Network (DeNDRoN) is a topic-specific network within the UK Clinical Research Network (CRN) co-directed by Professor Martin Rossor (London) and Professor Ian McKeith (Newcastle). The aim of DeNDRoN is to provide a world-class health service infrastructure to support clinical neurodegeneration research and remove barriers to its conduct, thereby facilitating randomised prospective trials and other well-designed studies, including those for prevention, diagnosis and treatment. In England, DeNDRoN has established seven Local Research Networks (LRNs). The LRNs coordinate the recruitment of patients, participants and clinical teams for both the large-scale multi-centre research and local/pilot studies.

Within DeNDRoN there are four Clinical Studies Groups (CSGs) that provide the primary route through which studies are adopted by the Network, and through which new ideas for clinical trials are developed. These comprise Dementia, Parkinson's disease (PD), Motor Neurone Disease and Huntington's Disease. In common with the other CSGs, the PD CSG, chaired by Professor Andrew Lees, is charged with the development of a portfolio of national multi-centre and local/pilot clinical trials and other well-designed studies. For a non-commercial

study to be adopted by DeNDRoN, it must be funded in open competition and have undergone peer-review. If the CSG recommends that the study be adopted, it may then utilise the service support structure of the LRNs.

With regard to Progressive Supranuclear Palsy (PSP), any trials wishing to be adopted by DeNDRoN would be best dealt with currently via the PD CSG (the name of which may need to change in future to reflect its broader remit). Within the CSG there are several researchers currently active in the PSP field, whilst there is also expertise available, if required, in relevant areas such as neuroepidemiology, trial design and genetics. Although DeNDRoN does not fund trials *per se*, an established, geographically dispersed network of committed workers via the LRNs could undoubtedly enhance trial recruitment (one of the overarching aims of the CRN is to increase patient and public involvement in research). Furthermore, access to the service infrastructure would also lead to considerable savings in trial support costs. PSP research conducted through DeNDRoN could also benefit, where appropriate, from recently established "cross-cutting" study groups, including Methodology (Outcome Measures etc), Brain-Banking and Neuropalliative Rehabilitation.

These are exciting and busy times for clinical research in the UK. It is essential that PSP researchers engage with DeNDRoN so that more patients may benefit from a dynamic and developing organisation that is dedicated to facilitating high class studies.

Sodium Valproate for Slowing Down Disease Progression in Progressive Supranuclear Palsy. A French Multicenter Randomized Placebo-controlled Study

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Background. Hyperphosphorylation of tau protein might be involved in the abnormal aggregation observed in the brain of patients suffering from progressive supranuclear palsy (PSP). The anticonvulsant drug sodium valproate (VPA) is an inhibitor of glycogen synthase kinase 3 β , one of the main kinases responsible for tau phosphorylation. Reduction of tau phosphorylation might thus lead to a slowing down of neurodegeneration in PSP.

Objective. To assess the efficacy of VPA for slowing down PSP progression. Study design. Multicenter randomized double-blind placebo-controlled trial.

Method. The plan is to include 36 patients: 18 to receive a daily dose of 1,500 mg VPA (500 mg/week titration) and 18 to receive a placebo. The primary outcome measure is the change in score of the PSP Rating Scale after 24 months of treatment. Other outcome measures are the Mattis Dementia Rating Scale, the Minimal Mental Test, various scales for frontal lobe assessment and the Neuropsychiatric Inventory.

Preliminary results. Inclusion started in November 2006. By June 2007, 19 patients had been included. No marked motor or cognitive improvement has yet been observed in any of the patients. Eight patients developed sleepiness and delirium especially during the first weeks of treatment, but all but one were able to receive 1,500 mg of VPA or placebo daily. Hallucination was observed in two patients, a side-effect that was resolved after adjustment of the antiparkinsonian drug treatment (withdrawal of Amantadine).

Conclusion. Several lines of evidence support the putative interest of VPA as a means of slowing down disease progression in PSP. A multicenter placebo-controlled trial is being conducted to test this hypothesis. The results of the study are expected by the end of 2009.

GSK3 as a Pathogenic Kinase in Tauopathy and the use of GSK3 Inhibitors such as Lithium as a Therapeutic

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PSP is characterized by the presence of neurofibrillary tangles (NFTs) in the brain. Tangles are composed primarily of an insoluble, filamentous form of the microtubule binding protein tau that has undergone extensive hyperphosphorylation at some stage in the pathogenic processes. We have examined the impact of aberrant phosphorylation on tau biology, especially its contribution to the initiation and progression of tauopathies. Using genetic and pharmacological models, we have primarily examined the impact of the kinases GSK3 and cdk5 in the pathogenic process. We have shown that GSK3 is the predominant tau kinase *in vivo* and it is especially active in the aged brain. Using mouse models of tauopathy, we have shown that administration of the GSK3 inhibitor Lithium can ameliorate disease progression suggesting that this drug may have therapeutic value in the treatment of patients with tauopathies.

Inhibitors of Tau Phosphorylation

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Hyperphosphorylation of tau is a characteristic feature of the tauopathies including progressive supranuclear palsy (PSP). There are numerous phosphorylation sites along tau, and this protein is the substrate for several kinases and phosphatases. The sites on tau which are hyperphosphorylated in PSP are the same as in Alzheimer's disease (AD) suggesting that agents which decrease tau phosphorylation in AD may also be effective for PSP. This similarity is an important consideration for the development of therapeutics for PSP.

Tau is hyperphosphorylated in response to an imbalance in kinase/phosphatase activity and, therefore, targets for tau therapeutics include decreasing kinase activity or increasing phosphatase activity. Three of the most studied tau kinases are glycogen synthase kinase 3 β (GSK-3 β), cyclin-dependent kinase 5 (CDK5), and the mitogen activated protein kinase ERK2. Each of these kinases has been shown to be relevant to the tauopathies, with phosphorylation of the appropriate epitopes of tau and localization to neurofibrillary tangles. There are several known inhibitors of these kinases, including the commonly used agents lithium and valproic acid which inhibit GSK-3 β . Yet, it is important to keep in mind the limitations of the current kinase inhibitors: they lack selectivity, and may therefore result in off-target effects, and they also may have other activities in addition to kinase inhibition.

An alternate approach to decreasing tau phosphorylation is to increase phosphatase activity. As it is more difficult to upregulate an enzyme than to inhibit an enzyme, this approach has received less attention. In AD, there is a decrease in the activity of some phosphatases, and an endogenous phosphatase inhibitor has been identified. As phosphatases have diffuse actions, off-target effects of phosphatase inhibition need to be characterized.

Tau kinases and phosphatases may be potential therapeutic targets for inhibiting tau hyperphosphorylation, yet several issues remain. There are concerns about limited specificity and the possibility of off-target effects. Yet, with an increased understanding of the structural determinants for selectivity, small molecule development may be optimized. Importantly, for any novel therapy, the safety and tolerability in the PSP population will need to be determined.

The Natural History of PSP

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In planning clinical trials of neuroprotection for PSP, understanding the natural history of the disorder can help in planning the required duration of observation and sample size and can estimate the dropout

rate. For futility studies, historical data on the course of the illness are imperative.

In most series, the actuarially corrected median survival from symptom onset is 7 to 7.5 years. In our series, survival for the middle 50% ranged from 5.3 to 10.1 years. For the oldest onset age group, with onset after age 75, the middle 50% survival ranged from 3.7 to 7.0, while for the youngest onset age group, with onset before age 65, the corresponding range was 6.3 to 9.8 years.

Survival can also be estimated from the PSP Rating Scale score at the time of initial examination. For example, patients with scores in the 20s (0=normal, 100=worst possible), median survival is 3.3 years, while for those scoring in the 40s, it is 2.5 years and in the 60s, 2.0 years.

Disability milestones can also be used as outcome variables. For example, the fraction of patients who retain some gait ability (<4 on PSPRS item 26) 12 months later is 76% (95% CI 68-87%) for patients with initial PSPRS scores in the 20s, 52% (40-67%) for those in the 40s and 21% (10-46%) for those in the 60s.

Survival in the advanced stages of PSP is importantly prolonged by energetic nursing care and by PEG placement. Therefore, time to disease milestones as the dependent variable in treatment trials may require smaller sample sizes and shorter observation, than using survival duration.

Towards therapeutics for PSP

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Identification of MAPT mutations in FTD, followed quickly by the characterisation of the association between MAPT haplotypes and PSP and CBD firmly placed tau biology at the centre of the pathogenesis of these diseases. Many FTD causing MAPT mutations increase the proportion of 4 repeat tau, and the associated PSP haplotype, H1c, also causes an increase in expression of this isoform. In addition, finding MAPT mutations allowed the creation of transgenic mouse models of tangle formation and cell loss and thus it also allowed the testing of tau-based therapies. The initial ones of these focussed naturally on tau phosphorylation since this has long been suspected to be an initiating factor. The GSK inhibitor, Li, long a therapeutic in bipolar disorder slowed tangle formation in transgenic mice and is thus now a credible trial therapeutic for tangle diseases. The challenge now is for the development of a credible therapeutic trial strategy with which we can test these plausible agents in the clinic.

Neuroprotection and Natural History in Parkinson Plus Syndromes (NNIPPS): Validation of a survival approach to phase 3 trials of neuroprotection in PSP and MSA.

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Objective: To test the efficacy of riluzole in progressive supranuclear palsy (PSP) and multiple system atrophy (MSA) and to investigate the natural history of PSP and MSA presenting as 'parkinson's plus' syndromes.

Background: PSP and MSA often present as 'parkinson plus' syndromes. Excitotoxicity may contribute to neuronal damage. We investigated the effect of riluzole, a glutamate release inhibitor, on survival and function and acquired prospective data on diagnostic criteria, natural history, MRI changes, and pathology. A brain tissue bank and DNA resource was established.

Methods: NNIPPS is an European multicentre, stratified, randomized (PSP or MSA) parallel-group trial of riluzole (50mg-200mg daily) versus placebo in patients with PSP and MSA. The primary outcome measure was survival at 36 months. The study was powered to detect a 40% decrease in relative risk of death at 36 months (two-sided $\alpha=0.05$; $\beta=0.80$). Secondary outcome measures included functional

status, cognition, quality of life, service costs, and MRI abnormalities. Power calculations were based on published estimates of survival. The primary analysis was intent-to-treat. Treatment effect was analysed by the Kaplan-Meier method using a stratified Log-Rank test, and the Cox proportional hazards model.

Results: 766 subjects (363 PSP, 403 MSA) were recruited in UK, France, and Germany, randomized over 3 years and followed double-blind for up to 36 months. 760 patients qualified for the intent-to-treat analysis. Pathological diagnosis in 112 cases showed ~90% sensitivity and specificity for PSP and MSA using NNIPPS diagnostic criteria. Median survival from onset was 7.8 years for PSP and 8.7 for MSA. There was no significant difference in survival between PSP and MSA from randomization, despite the observation that PSP patients deteriorated more rapidly than MSA patients. The study had adequate power to detect the predicted difference in survival. PSP subjects were more impaired on measures of clinical and cognitive function. There was no evidence of a significant treatment effect of riluzole in the population as a whole, or in the PSP or MSA strata.

Conclusions: Riluzole has no neuroprotective effect in PSP or MSA, but survival can be used as a primary outcome measure for trials in early-stage PSP and MSA ('parkinson's plus' syndromes). The NNIPPS diagnostic criteria performed well in this context. Functional measures including the PPS Scale developed for NNIPPS are useful for assessing disease severity. NNIPPS provides a unique resource for understanding motor, cognitive, neuroimaging, and genetic factors in MSA and PSP.

Surrogate Markers for PSP

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Surrogate markers of disease progression in Progressive Supranuclear Palsy (PSP) will be essential for clinical trials of novel therapeutic agents which affect the underlying pathological processes. We have identified two key areas of interest with potential to fulfil this role.

Cerebrospinal fluid (CSF) markers for PSP

CSF reflects biochemical changes in brain and pathological processes in the Central Nervous System. Pathological and biochemical data consistently show that PSP is associated with an elevated four repeat tau (4R-tau) in brain. In such cases, the quantity and ratio of 3R-tau and 4R-tau isoforms could be reflected in CSF and could potentially serve as an early diagnostic biomarker to support clinical diagnosis of the disorder. We have currently developed a sandwich ELISA for these tau isoforms with sensitivity of 200pg/mL for 3R-tau and 1000pg/mL for the 4R-tau. Based on this ELISA model, a feasibility study has been carried out using the PCR-ELISA Imperacer™ approach and preliminary results have shown a significant increase in sensitivity for both 3R-tau and 4R-tau isoforms that are relevant at the CSF levels in PSP patients. Other studies have also suggested the potential use of orexin A and heavy chain neurofilament as candidate markers for PSP. The usefulness of 3R-tau: 4R-tau ratio as well as in combination with other potential markers including other CSF biomarkers and neuroimaging techniques for PSP, should be investigated in the future for predictive, diagnostic, or treatment evaluation purposes.

Neuroimaging

Neuroimaging is evolving rapidly. Although conventional Magnetic Resonance Imaging (MRI) techniques are the mainstay of current practice, there are many newer techniques on the verge of breakthrough. Using volumetric MRI, the rate of whole-brain atrophy has been measured in pathologically proven cases of PSP. Regional rates of atrophy are significantly greater, and it has been estimated that using midbrain atrophy rates in trials (looking for a treatment effect of 30% reduction in atrophy in PSP), would reduce the number of patients in each treatment arm from 499 (using whole-brain atrophy rates) to 183. More advanced quantitative MRI techniques such as diffusion weighted imaging (DWI) and magnetization transfer imaging (MTI) have the potential to provide quantitative assessment of disease pro-

gression. Quantitative increases in relative Apparent Diffusion Coefficient (rADC) in the putamen in Multiple System Atrophy-Parkinsonian variant (MSA-P) correlate with the topographical distribution of pathology and clinical severity. Serial study shows progression both in clinimetric severity and rADC. MTI has also shown quantitative differences compatible with underlying pathology of PSP, MSA-P and PD and segmented inversion recovery has shown disease specific changes in the Substantia Nigra in PD and PSP, and severity of clinical findings correlates with a radiological index in PD. Serial study in PSP of these markers has not yet been undertaken. High field MRI will enable higher resolution images of structures involved in PSP, and has been used to see plaques in Alzheimer's disease in pathological specimens, and much better image resolution of the midbrain and associated structures in vivo. These techniques are promising in the quest to develop an objective surrogate marker of disease progression in vivo.

Developing a European PSP Network

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The prevalence of PSP means that it is likely that international collaboration will be needed to develop large scale trials of symptomatic and disease modifying treatments. The development of research networks in individual European member states and the funding being made available for trans-European collaboration will enable the development of a European PSP research network. Successful research networks have been set up for several neurodegenerative diseases. The primary role of a PSP network will be to facilitate clinical trials but similarly to other networks it would be desirable to collect standardised clinical including longitudinal studies of natural history, and to support the storage of biological materials.

Options for Disease Modifying Interventions in Progressive Supranuclear Palsy

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Recent years have produced exciting advances in our understanding of the pathophysiology of PSP. The pathogenic mechanisms may be grouped as follows:

1. Mitochondria: Reduced cerebral glucose and energy metabolism have been shown in functional imaging studies in PSP patients. Cybrid cells harboring mitochondrial genes from PSP patients have decreased ATP-levels and complex I activity. Experimentally, chronic systemic exposure of rats to annonacin, a lipophilic complex I inhibitor extracted from *annona muricata*, has been shown to induce a pattern of neurodegeneration and a tau pathology, which closely mimics that of PSP.

2. Oxidative stress: Neuropathological examinations demonstrated indirect evidence for oxidative stress by showing oxidatively caused damage to DNA, RNA, proteins and lipids.

3. Tau metabolism: The neuropathology of PSP is characterized by abundant Tau aggregates in the cytoplasm of neurons, astrocytes and

oligodendrocytes. The pathological Tau isoforms in PSP are preferentially encoded by the H1 haplotype, contain 4 microtubule-binding sites, and are hyperphosphorylated at multiple amino acids.

4. Abnormal axonal transport: Work with transgenic and toxin-induced models of PSP provided evidence suggesting an impaired axonal transport as a consequence of the pathological Tau metabolism, ultimately leading to axonal malnutrition and breakdown.

5. Inflammation: PK11195 PET imaging provided direct in vivo evidence for microglial activation in PSP.

These insights into the pathophysiology of PSP may offer novel targets for therapeutic interventions in PSP, aimed at slowing down the progression of the disease. The following interventions appear reasonable:

1. Enhancers of mitochondrial energy metabolism: e.g. Coenzyme Q10, the physiological electron recipient of complex I; gene therapy with NDI1 yeast NADH-quinone-oxidoreductase.

2. Oxidative radical scavengers: e.g. N-acetyl cysteine or ascorbic acid.

3. Inhibitors of Tau phosphorylation: e.g. Lithium, a potent inhibitor of GSK-3.

4. Microtubule stabilizing agents, e.g. paclitaxel, a drug binding to the Tau-binding site of tubulin, thereby stabilizing microtubules.

5. Anti-inflammatory drugs: e.g. COXII inhibitors.

These interventions are awaiting a systematic evaluation of their putative disease-modifying effects in clinical trials in PSP.

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A Critical Review of Symptomatic Drug Therapies for PSP including Amantadine

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Symptomatic drug therapy for PSP has focussed on cognitive impairment and parkinsonism. Cholinergic deficits in brainstem and basal forebrain have long been recognized as potential targets of replacement therapy. Unfortunately, none of the drug trials, some of them randomized controlled, have shown clinically relevant improvement illustrating both deficiencies in trial design as well disease-related drug resistance. The same applies to dopaminergic substitution therapies targeting the profound dopamine depletion within the nigrostriatal circuitry. Except for 20% of patients with transient benefit there is no meaningful reversal of parkinsonian motor deficits. Again, this poor outcome may reflect deficiencies in trial design including underpowered patient cohorts and failure to recognize clinical heterogeneity (Richardson's syndrome versus PSP-P) as well as true drug resistance due to basal ganglia output failure reflecting extensive subcortical tauopathy. Amantadine is often used in PSP patients, however, there is no convincing trial evidence that it works. The failure of symptomatic therapies highlights the need for neuroprotective interventions aimed at halting the rapid progression of PSP.