Safety and clinical effects of NTCELL® (immunoprotected [alginate-encapsulated] porcine choroid plexus cells for xenotransplantation) in patients with Parkinson's disease (PD): 26 weeks follow-up.

Barry J Snow, *MBChB, FRACP[1],* ***Jon A Stoessl,*** *CM, MD, FRCPC, FAAN[2],* ***Arnold Bok,*** *MBChB, FRACP[1],* ***Mark Simpson,*** *MBChB, FRACP[1],* ***David McAuley,*** *MBChB, FRACP[1],* ***Lorraine Macdonald,*** *RN[1],* ***Vesna Sossi,*** *PhD[2],* ***Katie Dinelle,*** *MSc[2],* ***Jess McKenzie,*** *LPN[2],* ***Kathleen Durbin,*** *PhD[3],* ***Jenny Han,*** *BPharm[3],* ***Hai Lin,*** *MD[3],* ***Janice Lam,*** *PhD[3],* ***Jackie Lee,*** *PhD[3],* ***Ken M Taylor,*** *PhD[3].*

1. Departments of Neurology and Neurosurgery, Auckland City Hospital, Auckland, New Zealand; 2. Pacific Parkinson's Research Center & National Parkinson Foundation Centre of Excellence, University of British Columbia Hospital, Vancouver, BC, Canada; 3. Living Cell Technologies New Zealand Ltd, Auckland, New Zealand.

Introduction

Cerebrospinal fluid (CSF) contains a variety of neurotrophic and neuro-protective factors that play critical roles in maintaining the health of the brain. Our pre-clinical studies with NTCELL in animal models of PD indicate that a continuous local production of CSF by NTCELL can result in restoration of degenerated neural functions, thereby supporting the application of NTCELL as a disease-modifying cell-based therapy for neurodegenerative diseases.

We conducted a Phase I/IIa clinical study at Auckland City Hospital (Auckland, New Zealand), in four patients with Parkinson's disease (PD), in order to assess the safety and clinical effects of NTCELL implanted into the putamen, we present the follow-up data up to 26 weeks post-implant.

Background

NTCELL comprises of neonatal porcine choroid plexus cells encapsulated in alginate microcapsules. The Auckland Island pigs, which are the source of the choroid plexus cells, are extensively studied and screened for pathogens. NTCELL is effectively a neurochemical factory capable of sustained CSF production, and secretion of multiple neuroactive agents.

Our pre-clinical studies with NTCELL implanted into the striatum of rats and non-human primates show the following:

- **SAFETY**
  - Absence of Porcine Endogenous Retrovirus (PERV) transmission in rats and non-human primates
  - No major organ toxicity or shortening of lifespan in rats compared to age-matched controls
- **LONGEVITY**
  - Survival of NTCELL for 18 months in rats (the normal duration of their lifespan)
- **EFFICACY**
  - Histological evidence of increased neuronal growth in rats *(data on file, LCT)*
  - Improvement of neurological function and histological evidence of corresponding increase in dopamine fibre (TH+) density in the striatum as seen in Figure 1, in an MPTP-treated non-human primate model of PD *(Luo et al., 2013)*.

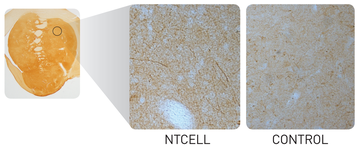


Figure 1: Increased TH staining in the striatum of MPTP-treated non-human primates 6 months after NTCELL implantation

Methods

Our clinical trial was approved by the Ministry of Health and the Northern A Health and Disability Ethics Committee in New Zealand (12/NTA/64).

The trial is registered with ClinicalTrials.gov (NCT01734733). An extensive and enhanced written informed consent procedure was completed prior to four patients participating in this trial.

Patients aged between 40 and 70 years who had previously been accepted for Deep Brain Stimulation according to the Australasian Guidelines were eligible for this trial. We implanted 40 NTCELL microcapsules (approx. 40,000 choroid plexus cells) into the putamen on the side contralateral to that of the greatest clinical deficit in each of the four patients.

The primary endpoints of this trial were:

- Occurrence of adverse events and serious adverse events reported over the duration of the study
- Clinical and laboratory evidence of PERV transmission in implant recipients and partners

The secondary endpoints of this trial included:

- Unified Parkinson's Disease Rating Scale (UPDRS) in the 'on' and 'off' states
- Unified Dyskinesia Rating Scale (UDysRS) in the 'on' and 'off' states
- Parkinson's Disease Quality of Life Questionnaire (PDQ-39) score
- Positron Emission Tomography (PET) with [18F]-fluorodopa and [11C]-tetrabenazine

The results at Week 26 following implantation were compared with those at baseline.

MRI was performed on the day following implantation, and at Weeks 8 and 26. Laboratory tests including biochemistry, haematology, and PERV were performed at intervals throughout this period. All trial data at time points as defined by the protocol were reviewed by an independent Data Safety Monitoring Board (DSMB).

Whilst this was an open label study, the assessor did not have access to previous observation results when performing subsequent observations.

Results

Patient demographics

Table 1: Patient demographics

PATIENT NUMBER	001	002	003	004
Age at consent (years)	59	61	60	68
Gender	Female	Female	Male	Male
Disease duration (years)	23	11	6	10
UPDRS at baseline (off)	87	53	74	78
UPDRS at baseline (on)	27	25	32	29

All testing for PERV transmission in patients was negative and there was no evidence of PERV transmission in partners.

MRI

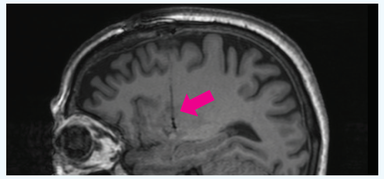


Figure 2: Saggital MRI showing the cannula tract. Implanted NTCELL micro-capsules can be seen distributed through the putamen at the end of the tract.

Adverse events

There were no serious adverse events in any of the four patients after 26 weeks follow-up. There were a total of 8 treatment emergent adverse events that were considered related to the implant procedure, rather than NTCELL (Table 1). The MRI assessments showed no evidence of inflammation.

Table 2: Adverse events related to the implant procedure

ADVERSE EVENT DESCRIPTION	NUMBER OF EVENTS	SEVERITY
Small area of implant site ischaemia	2	Mild
Inflammation of scalp wound	1	Mild
Subdural haematoma (up to 5mm thick)	1	Mild
Increased dyskinesia	1	Mild
Transient headache	1	Mild
Transient memory impairment	1	Mild
Cannula pass through pallidum	1	Mild

One patient received a pallidal lesion during the implant procedure due to the inaccuracy of the first needle pass. This may have had an effect on the UDysRS when assessed in the 'on' state.
The increased dyskinesia in Patient 001 was resolved by a reduction in their levodopa dosage. The dosage remained the same in the other three patients.

Table 3: Patient 001 change in levodopa dosage

START	STOP	TOTAL DAILY LEVODOPA DOSAGE (MG)
Baseline	Week 1	1800
Week 1	Week 2	900 - 1600
Week 2	Week 3	1100 - 1800
Week 3	Continuing	600 - 1200

PET

At Week 26 post-implant there was no consistent change compared to baseline measurements.

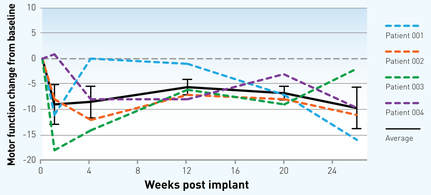
Table 4: PET results with [18F] - fluorodopa from the putamen region of the brain ipsilateral to the side of NTCELL implant

		RATIO TO AGE MATCHED NORMAL (PATIENT/HEALTHY)	
PATIENT NUMBER	BASELINE	WEEK 26 POST-IMPLANT	CHANGE FROM BASELINE
001	0.28	0.29	0.01
002	0.37	0.32	-0.05
003	0.07	0.27	0.20
004	0.28	0.12	-0.16
Mean	0.25	0.25	0

UPDRS part III motor function

There was a significant mean change from baseline to Week 26 ($p<0.05$) for UPDRS Part III motor function (Figure 3), this happened immediately following NTCELL implant.

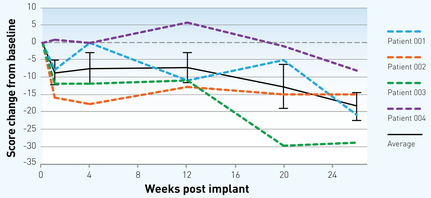
Figure 3: UPDRS part III motor function change from baseline



UDysRS ON

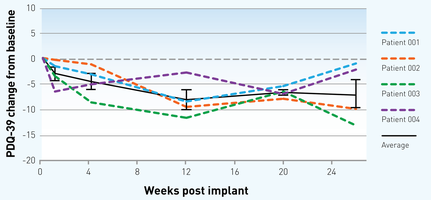
There was a significant mean change from baseline to Week 26 ($p<0.05$) for UDysRS in the 'On' state (Figure 4).

Figure 4: UDysRS in the 'On' state score change from baseline



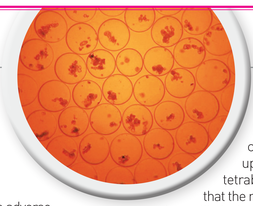
PDQ-39

Figure 5: PDQ-39 change from baseline



The DSMB confirmed the investigator's recommendation that none of the four patients required either deep brain stimulation or a second implant of NTCELL, which were options defined by the protocol following 26 weeks follow-up.

Discussion



The primary endpoint of this clinical trial was to demonstrate the safety of NTCELL implantation. This endpoint has been met. All adverse events were attributable to the implant procedure, and there were no adverse events attributable to the implanted NTCELL.

The secondary endpoint of efficacy as measured by validated neurological rating scales and questionnaires provides evidence of a consistent and significant mean improvement from baseline. The cause of this change is unclear and must not be over-interpreted in only four patients in an open-label study.

The marked improvement immediately after the procedure could relate to a lesion effect. Similar changes were not shown in a previous foetal transplantation study where there was a similar cannula trajectory and implantation of tissue into similar locations in the putamen (Olanow 2003). This raises the possibility of a placebo effect or some immediate effect of NTCELL in our clinical study.

The sustained improvement at Week 26 post-implant in all four patients is less easily explained as a lesion or placebo effect.

The improvement at this time would be consistent with the histological improvement seen in animal studies. Moreover, the improvement in the neurological scores in the first patient remain evident at Week 74 post-implant.

PET scans showed no consistent change in the uptake of levodopa and tetrabenazine. This indicates that the mechanism of improvement is not likely due to re-sprouting of dopaminergic nerve terminals.

Efficacy could be the result of recovery in function of other types of neurons involved in neuro-degeneration and compensatory mechanisms known to occur in the striatum of PD patients.

NTCELL is encapsulated choroid plexus cells which after implantation will receive incoming signals that will trigger the release of neurotrophic factors that are appropriate to the demand in each individual patient. Such plasticity and pleiotropy would support the specific individual responses seen in this study.

It is tempting to relate efficacy in this preliminary study to the main function of the choroid plexus, a localised increment in the production of CSF leading to increased neuronal restoration and removal of waste products such as amyloids and proteins.

If this is confirmed by future studies, then NTCELL would have considerable potential as a disease modifying agent in PD and other neurodegenerative conditions, due to a pleiotropic effect within the brain.

Conclusion

NTCELL implantation was safe and well tolerated.

NTCELL administered via unilateral implantation into the putamen of four patients with PD is safe and well tolerated. There were eight adverse events considered related to the implant procedure, none were considered related to NTCELL. There was no clinical or laboratory evidence of PERV transmission in patients or partners.

NTCELL implantation improved clinical features of PD.

Data suggests sustained improvement on clinical features as seen in the UPDRS, UDysRS and PDQ-39.

Encouraging results justify a confirmatory study.

While the study is small in scale, the results obtained are sufficiently encouraging to warrant further studies with this novel treatment. The results of this study will be used in the design of a second clinical trial of NTCELL to further explore its potential as a disease modifying treatment for patients with PD.

REFERENCES: *1. Luo XM, Lin H, Wang W, Geaney MS, Law L, Wynyard S, Shaikh SB, Waldvogel H, Faull RL, Elliott RB, Skinner SJ, Lee JE, Tan PL. (2013) Recovery of neurological functions in non-human primate model of Parkinson's disease by transplantation of encapsulated neonatal porcine choroid plexus cells. J Parkinsons Dis. 3(3):275-291.*
2. Olanow CW, Goetz CG, Kordower JH, Stoessl AJ, Sossi V, Brin MF, Shannon KM, Nauert GM, Perl DP, Godbold J, Freeman TB. (2003) A double-blind controlled trial of bilateral fetal nigral transplantation in Parkinson's disease. Ann Neurol. 54(3):403-14.