PRE-CELL: Preparing for a future planned Phase 1 trial of genetically-modified stem cells over-expressing BDNF in patients with Huntington’s disease

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Background
Mesenchymal stem cells (MSCs) engineered to overexpress brain-derived neurotrophic factor (BDNF) is a proposed therapeutic for neuroprotection in Huntington’s disease (HD). Pre-CELL is the lead-in observational study for a future planned Phase I clinical therapy trial of MSC/BDNF in HD (NCT01597923). The primary objective is to enroll a cohort of up to 40 subjects with early-stage Huntington’s disease (HD) to characterize the rate of change in clinical, neuro-imaging, laboratory and biomarker correlates of disease progression over a 12 – 24 month period.

Methods
Subjects were recruited from July 2013 – June 2015 with the following inclusion criteria: adult man and woman with clinically diagnosed HD, CAGs > 37, TFC 9 – 13, without dementia or unstable psychiatric symptoms, and with a care partner willing to enroll in the study and to report on their status. Exclusion criteria included pre-manifest or prodromal HD, minors, advanced HD clinical, stage, history of substance abuse, unstable psychiatric status, dementia, unstable general health, coagulopathy, history of previous stem cell or cytokine treatment, and contraindication to MRI. Assessments were performed at screening/baseline and then every 6 months, including vital signs, clinical and neurocognitive evaluations, concomitant medication review, UHDRS motor examination, Total Functional Capacity, Functional Examination and Independence scores, cognitive assessment using the CAB-HD battery, Columbia Suicide Rating Scale, Problem Behaviors Assessment-short form, HD Quality of Life, Neuropsychiatric Inventory-Caregiver, E-COG assessment, modified Rankin Scale, serum and CSF biomarkers, structural MRI and safety laboratories. Interim telephone visits are scheduled every 3 months.

Results
Forty-two subjects have been screened and 32 enrolled (Figure 1). Demographics are presented in Figure 2. Interim analysis of study measures for the 32 subjects meeting enrollment criteria was performed in month 23 of the study, with 26-32 subjects completing 6 months of follow-up, 18 completing 12 months, and 7 completing 18 months.

The estimated change rates for selected clinical measures include: Total Functional Capacity score, -0.784 per year, (p-value < 0.0001); Independence Score, -4.254 per year, (p-value < 0.0001); Total Motor Score, 9.1038 per year, (p-value < 0.0001); change rate in square root of total Problem Behavior Assessment score, 0.12942 per year, (i.e., p-value = 0.6521). Additional significant changes were seen in the HD-QOL, 17.089 per year, (p-value = 0.0078), E-COG total score, 6.0312 per year, (p-value = 0.0003), square root of PBA-Apathy sub-score, 0.7518 per year, (p-value < 0.0001). (See Figure 3).

Baseline and longitudinal cognitive assessment scores for the cohort are consistent with those of controls identified as diagnostic in previous studies (Track-2 and CAB-Beta, not shown). Rate of change in selected cognitive measures are presented in Figure 4. Preliminary biomarker analysis revealed significant variability in serum BDNF levels. CSF BDNF analysis is still underway. Detection of mutant Huntingtin (mHtt) protein levels in serum and CSF by the Hersch lab revealed a strong linear relationship between serum mHtt and CSF mHtt (correlation 0.8777, p-value <0.0001). (Figure 5). Cross sectional and longitudinal analysis of imaging data for the cohort shows significant reduction in striatal, putaminal region, and white matter volume and increase in CSF volume detected 6 months (Figure 6), with a significant correlation in rate of change seen with CAP scores.

Conclusions
The PRE-CELL study has successfully enrolled a cohort of subjects with early-stage HD and has characterized the rate of change in clinical, imaging and biomarker measures. The rate of change in TFC, independence score, functional check lists, PBA’s apathy subscore and CAB-HD battery are similar to findings seen in TRACK-HD and CAB-HD studies, while the rate of change in the UHDRS total motor score is greater than that seen in TRACK-HD. Additionally, we have shown that the rate of change in the HD-QOL, E-COG, and the modified Rankin score are also statistically significant. We have detected novel findings in HD serum and CSF biomarkers, and the cross sectional and longitudinal rates of change in structural imaging are robust at 6 months and correlate with CAP scores. This data will be used as a baseline for comparison in subjects who may enroll in the future planned Phase 1 trial once regulatory approval has been obtained and may be generalizable to other studies in early-stage HD.

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