Autologous iPSC-Derived Midbrain Dopaminergic Progenitors (BXT-110) Demonstrate Reproducible Efficacy and Safety in Preclinical Models of Parkinson's Disease

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INTRODUCTION

Parkinson's disease (PD), the second most common neurodegenerative disorder, is characterized by the progressive loss of dopaminergic neurons. Current therapies primarily alleviate symptoms but do not slow or reverse disease progression, and while cell-replacement approaches in clinical trials have demonstrated safety, robust efficacy data remain limited. To address this unmet need, we aim to establish and validate BXT-110, an autologous induced pluripotent stem cell (iPSC)–derived midbrain dopaminergic progenitors (mDAPs) therapy, as a personalized, disease-modifying treatment for PD and to demonstrate its safety, efficacy and reproducibility in preclinical models.

METHODS

Skin biopsies from PD patients were reprogrammed to iPSCs via mRNA technology, banked, and screened for genetic integrity (Karyostat, aCGH) and PD mutations. Five PD lines were differentiated into mDAP drug products (DPs). Two PD lines (PD2.2, PD116.7) were transplanted into unilateral 6-OHDA–lesioned immunodeficient RNU rats. In-vitro differentiation was assessed by tyrosine hydroxylase (TH) and dopaminergic markers. In vivo efficacy was measured by amphetamine-induced rotation for up to 24 weeks. Ex vivo stereology quantified human nuclear antigen (HNA)+ and HNA+/TH+ cells, neurite projections, and off-target markers (Ki67, TPH2). A non-GLP safety study infused BXT-110 or controls into naïve RNU rats and assessed tolerability, tumorigenicity, and engraftment at 4 and 26 weeks.

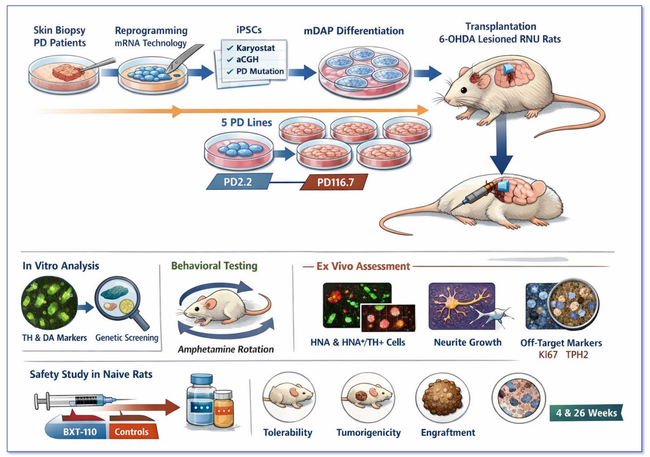

Figure 1. Preclinical experimental design for safety and efficacy assessment of BXT-110

RESULTS

Induction of highly enriched mDAPs from PD donor-derived iPSCs

Differentiation of iPSCs from five PD donors robustly generated highly enriched mDAPs, consistently yielding >30% TH+ dopaminergic neurons with strong lineage fidelity, reproducible on-target/off-target profiles, and >90% viability across all donor lines (Fig. 2).

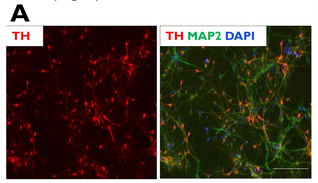

Figure 2. Characterization of mDAP induction from PD donor-derived iPSC. A & B, Immunofluorescence and quantification of TH and MAP2. N=5, error bars = Mean ± SEM. Scale bar = 200 µm

BXT-110 Demonstrates consistent functional recovery as early as 12 weeks post treatment in the 6-OHDA model

Intrastriatal administration of BXT-110 derived from two PD donor lines produced significant behavioral recovery in the 6-OHDA rat model (Fig. 3A). Both PD 116.7 and PD 2.2 grafts reduced amphetamine-induced rotational asymmetry as early as 12 weeks post-transplant, with sustained effects over time (Fig. 3B). Vehicle-treated controls showed no improvement, confirming BXT-110-specific dopaminergic restoration (Fig. 3C).

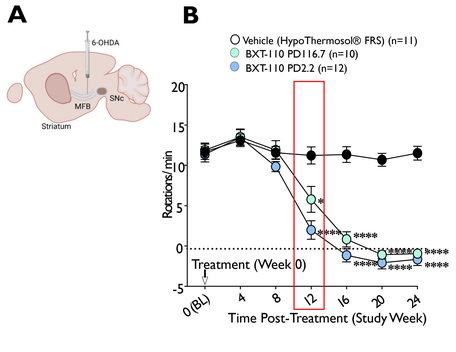

Figure 3. Efficacy of BXT-110 in the 6-OHDA PD rat model. (A) Schematic and validation of 6-OHDA unilateral lesion in RNU rats. (B&C) BXT-110 grafts from PD 116.7 and PD 2.2 significantly reduced amphetamine-induced rotations vs. vehicle (*p < 0.05; ***p < 0.0001; two-way RM ANOVA, Tukey post hoc). Data = Mean ± SEM.

BXT-110 Grafts exhibit robust survival and minimal off-target differentiation

At 26 weeks post-transplantation, stereological analysis of BXT-110 grafts showed volumes of 2.1 mm³ (PD116.7) and 1.3 mm³ (PD2.2), with greater than 60% survival of HNA$^+$ dopaminergic progenitors in both PD donor lines (Fig. 4A,B). The grafts exhibited extensive TH$^+$/hNCAM$^+$ projections extending ≥1.4 mm into the host striatum, along with comparable levels of dopaminergic maturation, as indicated by 21–28% TH$^+$/HNA$^+$ cells (Fig. 4C–E). Proliferative (Ki67$^+$) and serotonergic (TPH2$^+$) cell populations were minimal, accounting for <0.05% and <0.005% of HNA$^+$ cells, respectively. These low proportions of Ki67$^+$/HNA$^+$ proliferating cells and TPH2$^+$/HNA$^+$ off-target serotonergic cells confirm stable engraftment with minimal unintended differentiation (Fig. 4F,G).

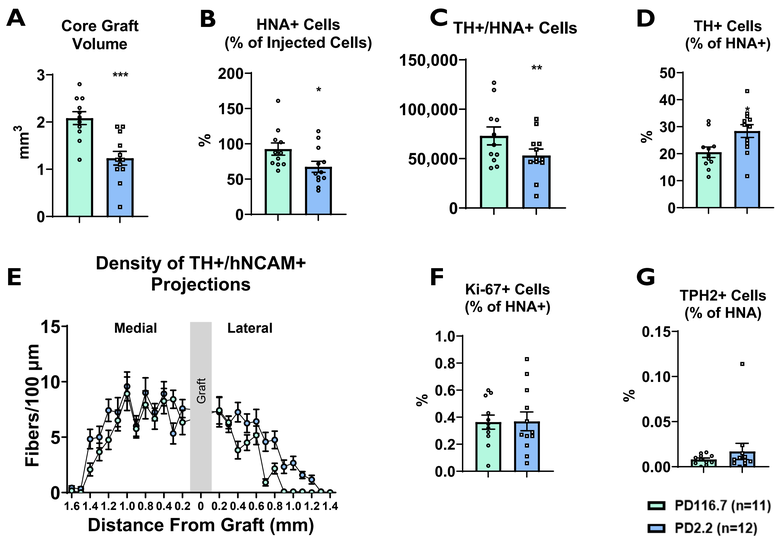

Figure 4. Quantification of graft survival and off-target markers at 26 weeks post-transplantation. (A&B) HNA$^+$ graft volume and survival rate (**p < 0.001, unpaired t-test). (C&D) TH$^+$/HNA$^+$ neurons (>20%, p<0.05). (E) Comparable medial and lateral TH$^+$/hNCAM$^+$ fiber projections into the striatum. (F&G) Ki67$^+$/HNA$^+$ and TPH2$^+$/HNA$^+$ quantification in BXT-110 grafts from PD 116.7 and PD 2.2. Error bars = mean ± SEM.

BXT-110 Demonstrates a well characterized safety profile in a non-GLP in vivo pilot study

A pilot tolerability, tumorigenicity, and brain distribution study was conducted in naïve adult RNU rats. Animals received a single bilateral intrastriatal injection of HypoThermosol FRS, BXT-110, BXT-110 with 0.1% iPSC spike-in, or 100% iPSCs. Acute (4-week) and chronic (26-week) endpoints were assessed, including monitoring for health abnormalities, tumor formation, graft proliferation, cell survival, off-target cell contamination, and TH$^+$ dopaminergic content. The study also informed surgical procedures for the subsequent GLP toxicology study.

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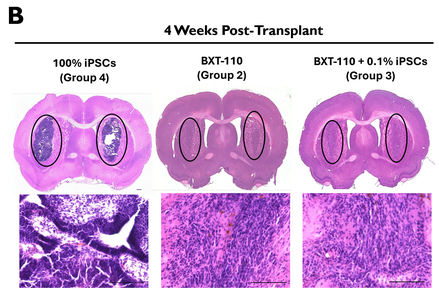
Group	Condition	Number (N) per Time Point		Total (N)
		4-6 weeks	26 weeks	
1	HypoThermosol Vehicle	2 (1M+1F)	2 (1M+1F)	4
2	BXT-110	4 (2M+2F)	4 (2M+2F)	8
3	BXT-110 + 0.1% iPSC	4 (2M+2F)	4 (2M+2F)	8
4	100% iPSCs	6 (3M+3F)	--	6



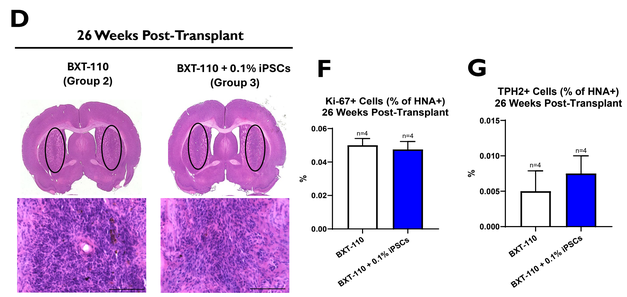


Figure 5. Non-GLP safety evaluation of BXT-110. (A) Study groups included: vehicle, BXT-110, BXT-110 + 0.1% iPSC spike-in, and 100% iPSCs. (B-G) At 4 and 26 weeks, BXT-110 and BXT-110 + 0.1% iPSCs displayed normal graft morphology, no adverse health findings, and minimal proliferation. (p>0.05 One-way ANOVA, Tukey's post-hoc test. Scale bar = 1 mm (H-J)The 100% iPSC group exhibited early mortality, abnormal histology, and teratoma-like features, confirming assay sensitivity. No significant differences were detected between Groups 2 and 3 in HNA$^+$ cell counts, HNA$^+$Ki-67$^+$ proliferating cells (<0.05%), or HNA$^+$TPH2$^+$ serotonergic cells (<0.01%). Quantification showed comparable HNA$^+$TH$^+$ dopaminergic neurons (~30%) between BXT-110 groups at 26 weeks, demonstrating clean lineage fidelity and absence of tumorigenic behavior (p>0.05 unpaired t-test; error bars = mean ± SEM). (*p<0.05 unpaired t-test; error bars = mean ± SEM). Scale bar = 1mm

CONCLUSIONS

BXT-110, an autologous iPSC-derived mDAP therapy, demonstrates reproducible and durable functional recovery with robust host integration in a PD rat model. BXT-110 engrafts without tumor formation or concerning preliminary safety effects, supporting the potential as a best-in-class personalized neuronal replacement therapy for clinical translation.

CIRM CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE
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