Disease modifying effects of centrally administered adrabetadex for treatment of Niemann-Pick disease type C

Poster 18.2

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BACKGROUND

- Niemann-Pick disease type C (NPC) is a rare neurodegenerative disorder caused by pathologic variants in *NPC1* or *NPC2*, resulting in intracellular cholesterol accumulation within late endosomal and lysosomal compartments and impaired cholesterol availability across the cell.[1,2]
- Impaired cholesterol trafficking affects all CNS cell types, contributing to axonal degeneration, myelination deficits, neuroinflammation, neuronal damage, and cell death.[3-7]
- Adrabetadex is an investigational intrathecal therapy for infantile-onset NPC (I-NPC; neurological onset <6 years of age) and the only therapy designed to directly target accumulated intracellular cholesterol in the CNS, the central pathogenic driver of NPC, by increasing cholesterol redistribution from late endosomal and lysosomal compartments.
- As described in the companion poster (APMRF #18.1), central adrabetadex administration achieves broad and durable CNS exposure and drives clearance of accumulated cholesterol from deep and superficial brain regions at therapeutically relevant concentrations, providing the pharmacokinetic foundation for the functional disease-modifying effects described here.

OBJECTIVES

To characterize the functional consequences of re-establishing cholesterol trafficking by centrally administered adrabetadex (APMRF Poster #18.1), assessed through effects on myelination, neurodegeneration, and survival, supporting its potential as a foundational disease-modifying therapy for I-NPC.

METHODS

In vitro assay for growth and development of neurons and myelin

- Primary embryonic neuron-glia co-cultures derived from *Npc1-/-* mice were injured with lipopolysaccharide (LPS, 50 ng/mL) for 30 min prior to treatment with adrabetadex from day 24 to day 27, followed by immunocytochemistry as described in Hauser, 2020. See APMRF Poster 2 for additional information.

I-NPC models

- Homozygous *Npc1-/-* mice were dosed every 2 wks beginning at 5 wks (post-symptomatic) intracerebral ventricularly (ICV) with 0.2 or 0.8 mg of adrabetadex. Immunofluorescent histology and clinical measures were assessed at 9.5 wks (after 3 doses). NPC mouse neurological score was determined based on Yerger, 2022 and analyzed by nonlinear regression.[8] Mean survival rate was analyzed by log-rank test.

Histoimmunofluorescence

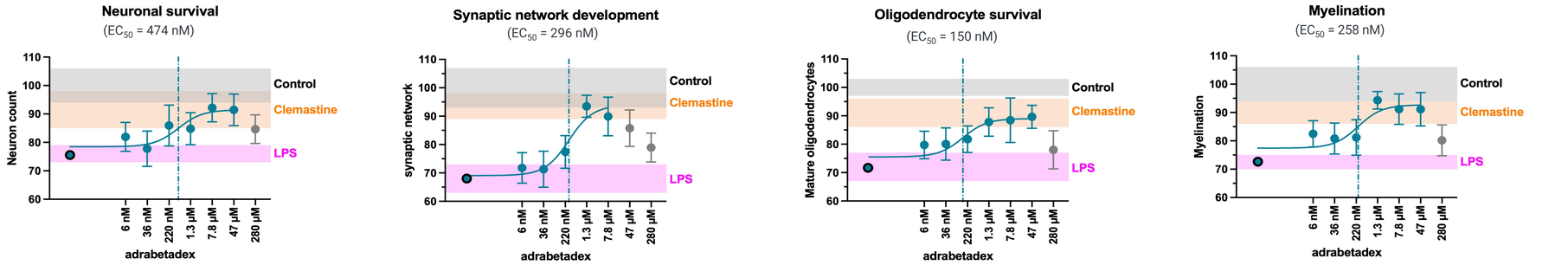
- Myelin basic protein, Calbindin D and fatty acid binding protein 3 (FABP3) were analyzed by immunofluorescence in brain sagittal sections. Imaging was conducted by confocal microscopy. Representative brain sections from 1 mouse per group are shown. Analysis was performed by multiple regression models.

Biomarkers

- FABP3 was assessed in CSF by Meso Scale Discovery (MSD) electrochemiluminescence (ECL) in a custom assay (PPD) validated under M10 guidelines (ICH, 2022).

Re-established cholesterol trafficking improves synaptic network, myelination & cell survival *in vitro*

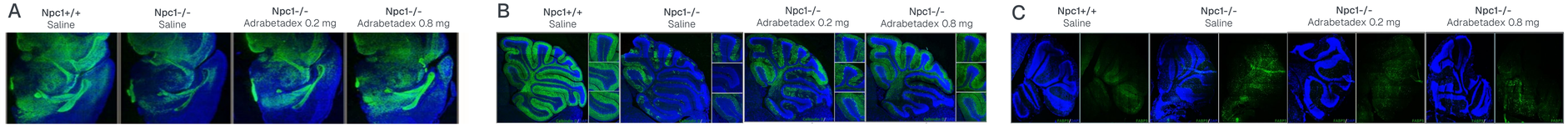
Figure 1. Adrabetadex dose-dependently increases cholesterol trafficking under neuroinflammatory conditions in NPC$^{-/-}$ mouse brain co-cultures, increasing myelination and synaptic network formation, and improving oligodendrocyte and neuronal survival



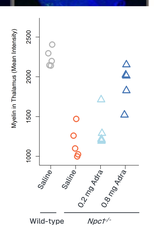
The vertical dashed line represents the EC_{50} value. Concentrations excluded from EC_{50} calculation are plotted in gray. An artificial data point (black circle) was added at a concentration near 0 to stabilize the estimate of the lower asymptote.

Central adrabetadex administration improves myelination & decreases markers of neurodegeneration in *Npc1-/-* mice

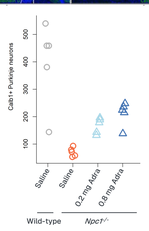
Figure 2. Histoimmunofluorescence shows central adrabetadex administration (A) increases myelination (MBP), (B) preserves cerebellar Purkinje neurons (calbindin D) and (C) reduces neurodegeneration (FABP3) in *Npc1-/-* mice



Npc1-/- mice showed significantly less myelination than wild type controls (P<0.0001).
Adrabetadex increases MBP (P<0.0001);
mid-sagittal brain sections, 10x tile
- green: MBP; blue: cell nuclei (above, and near right)

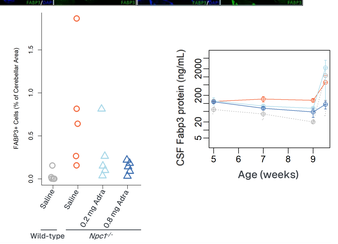


Npc1-/- mice showed significantly fewer calbindin D-positive Purkinje neurons than wild type controls (P<0.0001).
Adrabetadex increases calbindin D-positive Purkinje neurons (P=0.00065);
midline sagittal cerebellar sections, 10x tile
- green: calbindin D; blue: cell nuclei (above, and near right)



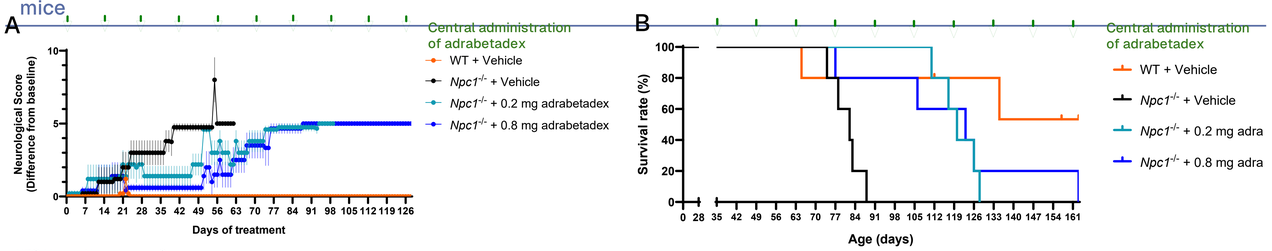
Npc1-/- mice showed a significantly greater FABP3-positive cerebellar area than wild type controls (P<0.0001) and decreases with adrabetadex treatment (P=0.031);
midline sagittal cerebellar sections, 20x tile
- green: FABP3; blue: cell nuclei (above, and near right)

Npc1-/- mice treated with ICV adrabetadex showed a significant (P= 0.038), dose-dependent decrease in CSF FABP3 (far right)



Functional translation: slowed neurological progression and improved survival in *Npc1-/-* mice

Figure 3. Central adrabetadex significantly (A) slows neurological progression and (B) extends survival in symptomatic *Npc1-/-* mice



NPC Mouse Neurological Score

Criterion	Value
Presence of righting reflex, normal movement	0
Slight incoordination, slight-moderate tremor	1
High-level of tremor, uncoordinated movement	5
Reduced righting reflex	10
Body weight loss >1 g within 24h, loss of righting reflex	20

Symptomatic *Npc1-/-* mice treated every 2 wks with ICV adrabetadex showed significant (P<0.0001), dose-dependent slowing in symptomatic neurological scores relative to those treated with saline (upper left, A), with measurement limited by the scale (lower left, A). Adrabetadex significantly increased survival (0.2 mg adrabetadex: median survival = 120 days, P = 0.0018); 0.8 mg adrabetadex: median survival = 123 days, P = 0.0269) relative to those treated with saline (median survival = 82 days) (right, B).

CONCLUSIONS

- Adrabetadex re-establishes intracellular cholesterol trafficking, enabling improved synaptic network development, myelination, and cell survival in NPC models.
- Central adrabetadex administration preserves neuronal integrity, increases myelination, and reduces neurodegeneration, demonstrating disease-modifying effects *in vivo*.
- These biological effects translate to functional benefit, with central administration slowing neurological progression and extending survival in I-NPC mice, with post-symptomatic treatment.
- These findings support the observed clinically meaningful outcomes of slowed disease progression and improved survival.
- Adrabetadex may serve as a foundational therapy targeting the causal biology of NPC, with the potential for layering complementary therapies that address additional mechanisms (see APMRF Poster 2)

References

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Acknowledgments

This study was funded by Beren Therapeutics P.B.C. Medical writing support was provided by Ana Mata, PhD, and Tiago Silva, PharmD, PhD, CMPP, of Med Communications, Inc, and Paula Stuckart, of Helios Global Group, with funding from Beren Therapeutics P.B.C. The authors gratefully acknowledge Dr. N. Callizot at Neuro-Sys for her contributions to experimental data generation, analysis, and interpretation for this work.

We thank the patients and their families for their participation in the adrabetadex development program.