Mechanism of action of adrabetadex for treatment of Niemann-Pick disease type C

Poster 18.1

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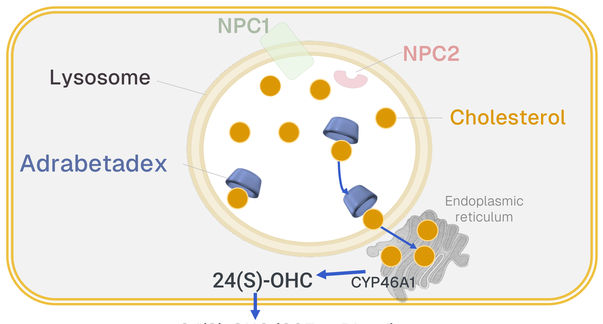
BACKGROUND

- Niemann-Pick disease type C (NPC) is a rare neurodegenerative disorder in which defective intracellular cholesterol trafficking drives progressive cholesterol accumulation within late endosomes and lysosomes.[1-3]
- Impaired lysosomal function and insufficient cholesterol availability reduce neuronal function and survival.[1-3]
- 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.
- Adrabetadex is also the only therapy shown to clinically improve survival in both early and late I-NPC.[4]

MECHANISM OF ACTION



24(S)-OHC (CSF -> Blood):
≥85% of CNS cholesterol efflux

OBJECTIVES

To characterize the pharmacokinetic and mechanistic basis for centrally administered adrabetadex as a foundational disease-modifying approach in I-NPC through evaluation of CNS distribution, duration of therapeutic exposure, and target engagement.

METHODS

Distribution and PK:

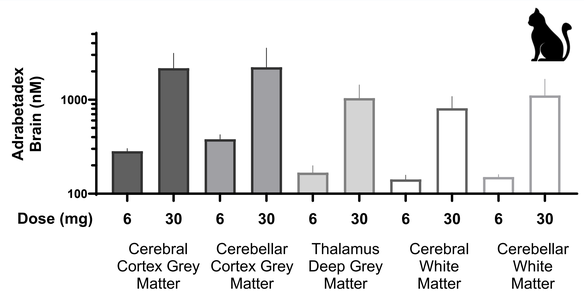
- *Npc1*$^{+/-}$ mice received a single 0.2 or 0.8 mg dose of adrabetadex intracerebroventricularly (ICV) and were evaluated for 2 wks.
- *NPC1*$^{C955S/+}$ cats aged 11–22 wks were dosed with single 6 mg or 30 mg of adrabetadex via intracisternal (IC) route and evaluated for 2 wks.
- Plasma, CSF and brain samples were analyzed for adrabetadex levels by LC-MS/MS.

Target Engagement:

- Profoundly symptomatic I-NPC model mice (7-wk old *Npc1*$^{-/-}$ mice) were dosed ICV with 0.8 mg of adrabetadex twice, two wks apart, and sacrificed at 9-9.5 wks. Brain levels of 24(S)-hydroxycholesterol (24[S]-OHC) were assessed by GC-MS/MS by Dr. D Lütjohann.
- I-NPC cats (*NPC1*$^{C955S/C955S}$) were dosed every 2 wks IC pre-symptomatically beginning at 3 wks of age. Untreated cats were sacrificed at 24 wks, treated cats were sacrificed at 27 & 78 wks for cats receiving 3.8 mg or 7.5 mg and 30 mg, respectively. See Vite 2015 for filipin staining technique.[5]

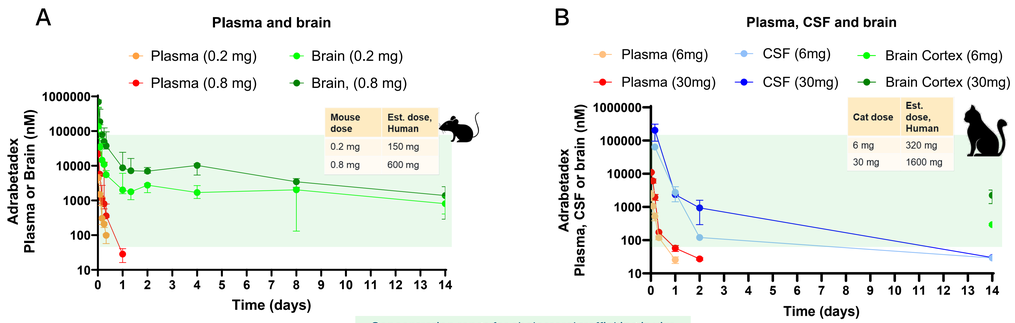
DISTRIBUTION: Centrally administered adrabetadex distributes to the entire brain and sustains therapeutic levels for ≥2 weeks

Figure 1. Adrabetadex is observed in deep and superficial brain regions 2 weeks post dose



Superficial, cortical regions show 2.3x higher levels of adrabetadex two weeks post-dose than deep grey matter and white matter

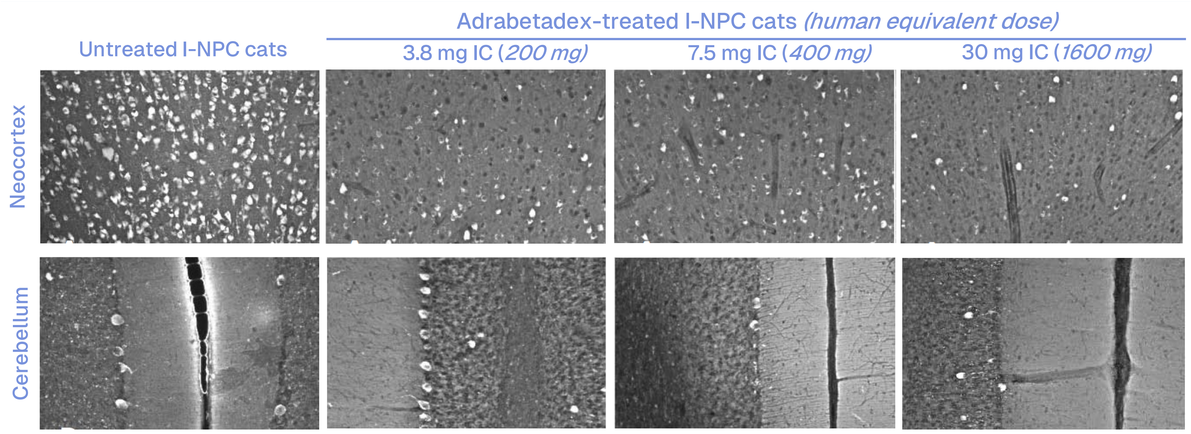
Figure 2. A single central dose of adrabetadex achieves CNS concentrations necessary to maintain cholesterol trafficking concentrations for ≥2 weeks in (A) *Npc1*$^{+/-}$ mice and (B) *NPC1*$^{C955S/+}$ cats



Concentration range for cholesterol trafficking *in vivo*

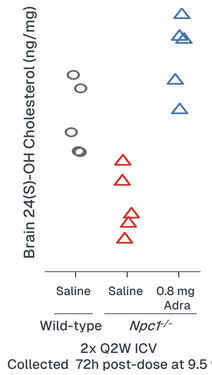
TARGET ENGAGEMENT: Centrally administered adrabetadex achieves necessary concentrations to dose-dependently reduce accumulated cholesterol in deep and superficial brain regions and enable efflux of excess brain cholesterol

Figure 3. Presymptomatic I-NPC cat model shows dose-dependent filipin clearing of cholesterol in cerebrum and cerebellum



Unesterified cholesterol is detected in post-mortem brain sections using filipin stain, seen as intracellular white areas In these single-channel images.

Figure 4. Centrally administered adrabetadex increases brain 24(S)-OHC production in *Npc1*$^{-/-}$ mice



- Profoundly symptomatic 7-week-old I-NPC model mice produce significantly less 24(S)-OHC in the brain than wild-type mice ($p<0.0001$).
- Adrabetadex treatment significantly increased brain 24(S)-OHC ($p=0.0008$), 72 hours after the second 0.8 mg ICV dose.

24(S)-OHC production is proportional to both trafficking capability and the size of the accumulated cholesterol pool, indicating the need for repeated and frequent administrations to counteract the rate of ongoing cholesterol accumulation in I-NPC.

CONCLUSIONS

- Adrabetadex re-establishes intracellular cholesterol trafficking within the CNS, addressing the central pathogenic defect in I-NPC and supporting its potential as foundational therapy.
- Central administration distributes adrabetadex broadly throughout the CNS, reaching deep and superficial brain regions at human-equivalent doses.
  - Sustained CNS concentrations support once-every-2 weeks dosing to counter ongoing cholesterol accumulation.
- Target engagement is directly linked to CNS exposure: adrabetadex dose-dependently reduces intracellular cholesterol across brain regions and increases 24(S)-OHC, consistent with enhanced efflux of accumulated cholesterol from the CNS.
  - Sufficient exposure is required to reach deep brain regions such as the cerebellum.
- Companion poster (APMRF #18.2) characterizes the disease-modifying consequences of re-established cholesterol trafficking through evaluation of myelination, neurodegeneration, and survival.

References

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