ABX-002: A fatty-acid amide hydrolase (FAAH)-activated prodrug enhances functional delivery of a potent TRβ selective thyromimetic to the brain and demonstrates biological activity in models of X-linked Adrenoleukodystrophy

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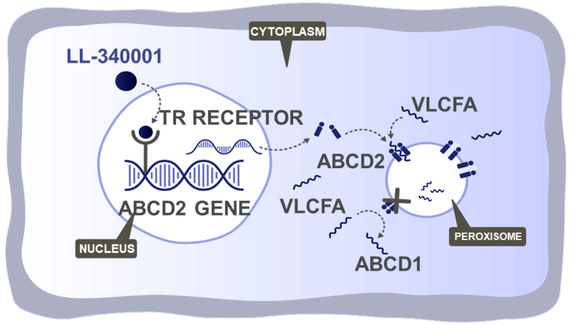
Introduction

- Adrenomyeloneuropathy (AMN) is caused by genetic defects in *ABCD1*, which encodes for adrenoleukodystrophy protein (ALDP), a peroxisomal transporter of very long chain fatty acids (VLCFAs). Loss of ALDP causes neurotoxic accumulation of VLCFAs.
- *ABCD2* encodes for ALDP related protein (ALDPR), another peroxisomal transporter, which can replace *ABCD1* in VLCFA transport; *ABCD2* is a direct target gene of thyroid hormone, T_3.
- Increasing thyroid hormone tone in the brain should increase *ABCD2* expression and reduce VLCFAs.
- ABX-002 is a clinical-stage thyromimetic prodrug intended for treating patients with AMN. ABX-002 is a FAAH-activated prodrug of the thyromimetic LL-340001.

- Graphic representation of ALDPR/*ABCD2* substituting for ALDP/*ABCD1* in peroxisomal VLCFA transport.

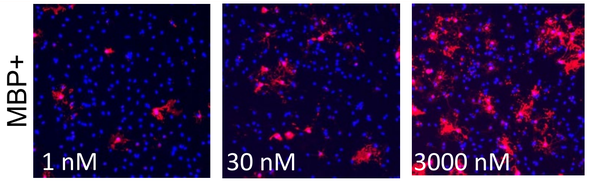


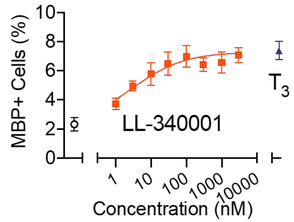
TRβ Potency and Selectivity

Profile	Prodrug ABX-002 (nM)	Active LL-340001 (nM)
TRβ EC_{50}	>10,000	95
TRα EC_{50}	>10,000	260
Selectivity*	n/a	16x

*Selectivity adjusted to TRα-bias of T_3 in the assays.

OPC Differentiation

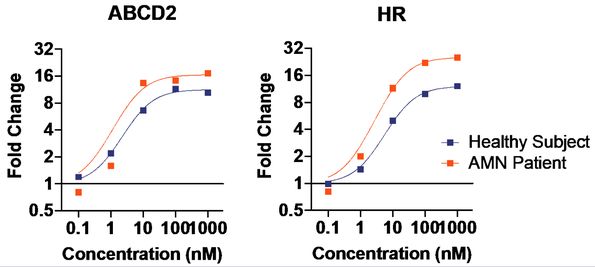




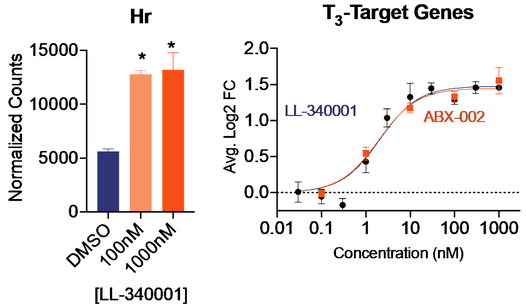
LL-340001 enhances mouse oligodendrocyte progenitor cell (OPC) differentiation in vitro (MBP staining after 7D Tx; n=6/concentration) with EC_{50} values of 2.2 nM.

ABCD2 and T_3-Target Gene Expression

LL-340001 increases *ABCD2* & Hairless (HR) mRNA (RT-PCR) expression in primary skin from healthy subjects and patients with AMN (48-hour treatment).

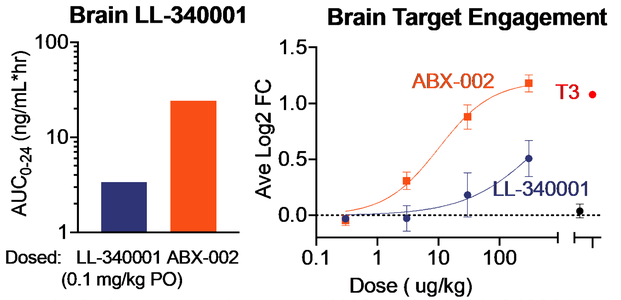


T_3-Target Gene Expression



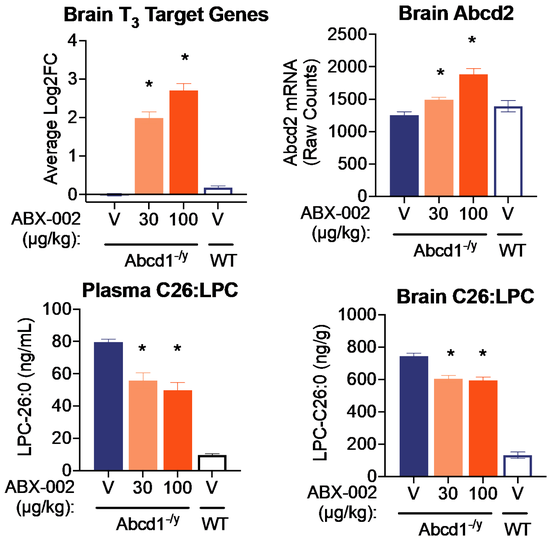
ABX-002 and LL-340001 induce T_3-regulated gene expression (Nanostring) ex vivo in precision-cut brain slices from P7-P10 mice with EC_{50} values ~2 nM (5D Treatment; n=5/dose).

Tissue Distribution & Target Engagement



- **Left**: Area under the curve (AUC) of brain LL-340001 exposure after dosing of LL-340001 or ABX-002 (PO). Delivery of LL-340001 is enhanced by ABX-002. Brain-to-plasma ratios of LL-340001 increase from 0.03 to 1.1 (not shown).
- **Right**: Average Log_2-fold change of 6 T_3-regulated genes in brain at 8 hours after oral dosing of ABX-002 or LL-340001. ABX-002 increases expression of T_3-regulated target genes in brain at ~30x lower doses than LL-340001. RNA analyzed by Quantiplex technology.

Efficacy in *Abcd1*$^{-/y}$ Mouse Model



ABX-002 increases T_3-regulated target gene expression, including *Abcd2* (Nanostring) and reduces C26:0-LPC (LC-MS) in plasma and brain of *Abcd1*$^{-/y}$ mice (PO, QD 12W; n=5-11/group).

Conclusions

- LL-340001 induces T_3-regulated gene expression, including *ABCD2*, and differentiates OPCs *in vitro*, consistent with known T_3 biology.
- By enhancing delivery of LL-340001 to the brain, ABX-002 increases T_3-target gene and *Abcd2* expression in an AMN disease model, which reduces VLCFAs in both plasma and brain.
- Collectively, these data support advancement of ABX-002 into clinical development for patients with AMN.

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