Thyromimetics improve disease endpoints and modulate potential target engagement biomarkers in rodent models of AMN and MS

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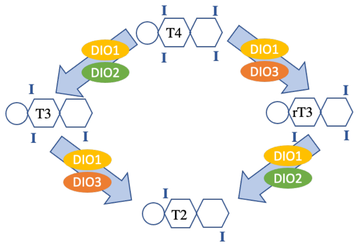
Introduction

- ABX-002 is a fatty-acid amide hydrolase (FAAH) activated prodrug of ABX-002A, a potent TRβ-selective thyromimetic
- Similar to T_3, ABX-002A enhances oligodendrocyte precursor cell differentiation and induces T_3-regulated genes in vitro (MacKenna, AAN, 2021)
- ABX-002 & analogs have in vivo activity in animal models of multiple sclerosis (MS) & adrenomyeloneuropathy (AMN) (Woerner, SFN, 2021; MacKenna, AAN, 2021)
- **Objective of these studies:** Identify relevant & practical biomarkers for TRβ action in the CNS that can translate into early clinical studies

ABX-002 readily crosses the BBB where it is activated by FAAH to active molecule ABX-002A

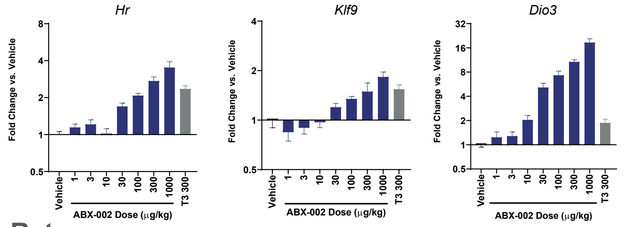
Graphic representation of activation and inactivation of thyroid hormone by deiodinase family



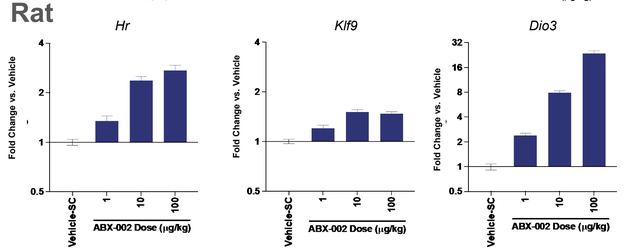
ABX-002 demonstrates dose-dependent target engagement in rodent brain

- TE in mouse brain: increased expression of T_3 target genes *Hr, Klf9 & Dio3*
- Dio3 is required for inactivation of thyroid hormone or attempts at suppressing thyroid hormone signaling, though conversion of T4to rT3or T3to T2

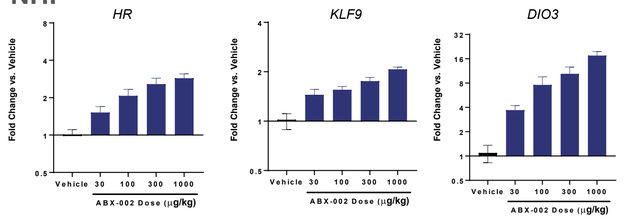
Mouse



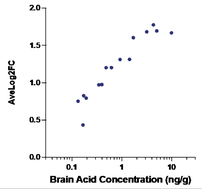
Rat



NHP



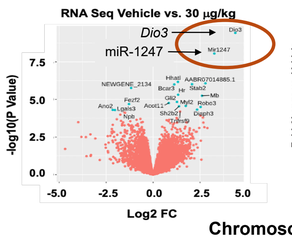
PK/PD in Cortex of NHP

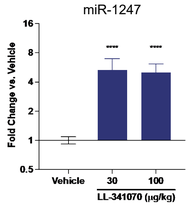


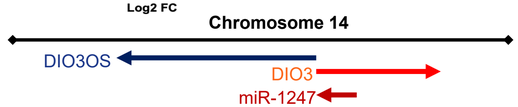
- *HR*, *KLF9*, *DIO3* & miR-1247 are all conserved across mouse, rat & NHP
- *DIO3* is most sensitive T_3-target gene
- miR-1247 increases in parallel with *DIO3*
- Brain delivery of active metabolite is robust & predicts target gene induction

RNA sequencing reveals induction of *Dio3* & congenic microRNA, mir-1247, in rat brain

- Transcriptomic profiling confirmed that *Dio3* is most highly upregulated gene in rat brain and identified miR-1247 as 2nd most robustly induced target
- miR-1247 is transcribed from the *DLK1-DIO3* locus on the reverse strand of human chromosome 14, overlapping with the intergenic non-coding RNA *DIO3OS*.
- microRNAs can serve as TE biomarkers because of their excellent stability and accessibility in biofluids



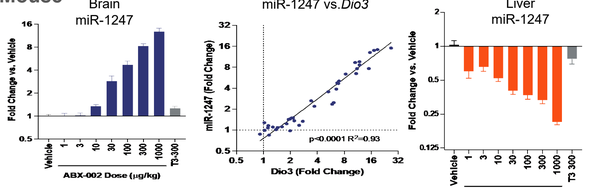




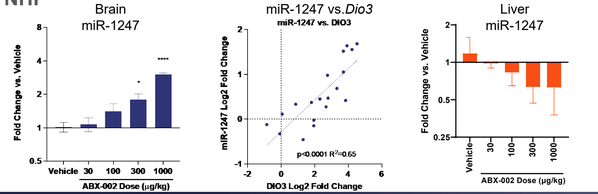
miR-1247 is conserved as a thyromimetic target across species and correlates with DIO3 in brain but not periphery

- miR-1247 is conserved in the *DIO3* locus from mouse to human
- miR-1247 increases in brain and decreases in liver

Mouse

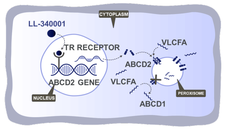


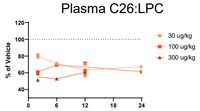
NHP

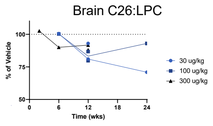


ABX-002 dose-dependently reduces VLCFAs in AMN disease model

- 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), which can replace *ABCD1* in VLCFA transport; *ABCD2* is a direct target gene of T_3.
- Increasing thyroid hormone tone in the brain should increase ABCD2 expression & reduce VLCFAs.

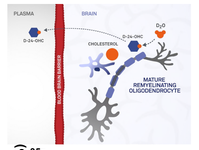


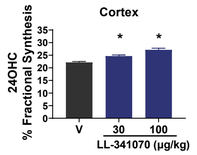


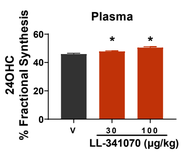


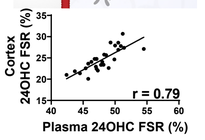
ABX prodrugs enhance fractional synthesis rate of *de novo* cholesterol synthesis in rat cuprizone MS model

- LL-341070 (ABX-002 analog) treatment enhances incorporation of ^2H label into 24-OHC in both brain & plasma in rat cuprizone model during remyelination
- Plasma 24-OHC synthesis can be used as a biomarker of brain activity using ^2H_2O labeling









Conclusions

- ABX-002 induces T_3-regulated gene expression in brain of mouse, rat, & non-human primate with the same genes in brain of all species
- miR-1247 expression, a novel miRNA in the same gene loci as *DIO3*, strongly correlates with *DIO3* accelerated expression in brain
- ABX-002 treatment shows efficacy in disease models, including increased 24-OHC synthesis, a marker of brain cholesterol synthesis in a MS model, and VLCFA lowering in an AMN mouse model
- Target mRNAs & novel biomarker miR-1247 may serve as target engagement biomarkers while plasma 24-OHC synthesis may serve as an early efficacy biomarker of remyelination

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