BrainOnly Pharmacology Enables Brain-Specific mTOR Inhibition to Restore Autophagy in the Brain

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Abstract

Dysregulated autophagy is increasingly recognized as a central driver of neurological diseases, contributing to the accumulation of damaged organelles, misfolded proteins, and toxic aggregates. While inhibition of mTOR represents a powerful way to activate autophagy, systemic mTOR inhibitors, such a rapalogs, are limited by dose-limiting peripheral toxicities, preventing their long-term use in CNS indications. Montara's BrainOnly™ platform provides a solution by combining an FKBP12-competitive "Peripheral Blocker" (MT1110) with FKBP12-dependent rapalog mTOR inhibitors to achieve brain-selective pharmacology. MT1110 competes for FKBP12 binding sites in peripheral tissues, thereby preventing drug activity outside the CNS while maintaining robust mTOR inhibition in the brain. This approach should enable selective induction of autophagy in the CNS, offering a path forward for diseases such as Alzheimer's disease, Parkinson's disease, and other neurodegenerative disorders where aberrant proteostasis plays a pathogenic role.

mTOR is a Central Regulator of Autophagy

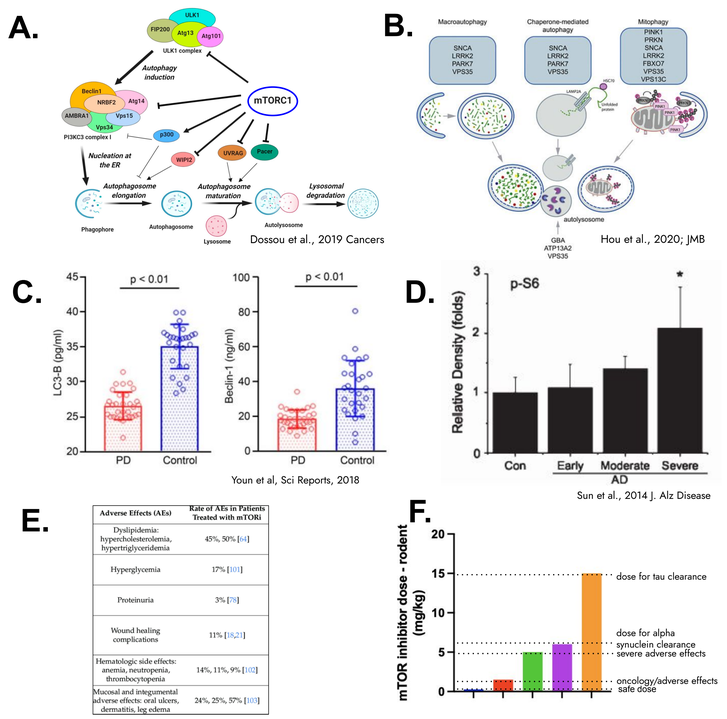

Figure 1. Role of mTOR in Autophagy. (A) Schematic illustrating the mTOR signaling pathway and role in autophagy. (B) Different types of autophagy associated with human genetic causes of neurodegeneration (C) Decreased autophagy pathway markers LC3-B and Beclin-1 in PD patients. (D) increased mTOR marker pS6 in AD patients. (E) Summary of AEs in patients treated with mTORi. (F) Illustration of relative efficacious and toxic doses of mTOR inhibitors in rodents

BrainOnly mTOR Inhibition

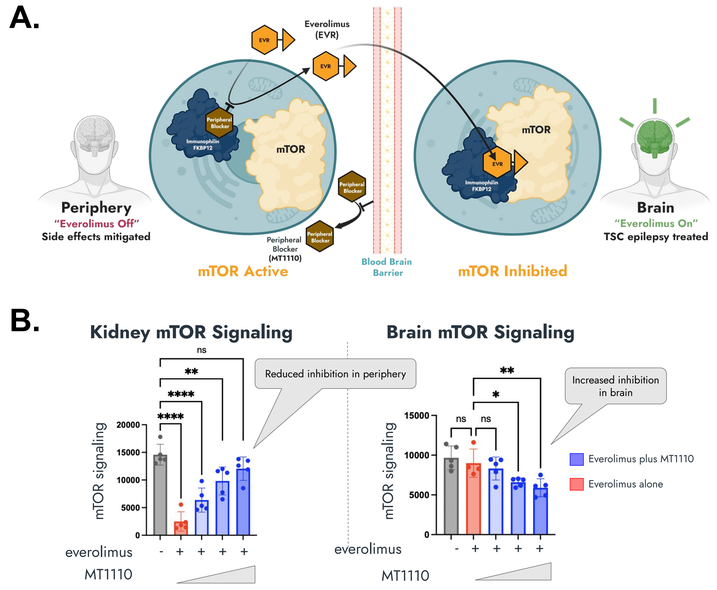

Figure 1. Overview of the BrainOnly Platform. (A) Schematic illustrating the brain-selective rapalog pharmacology enabled by the BrainOnly Platform. (B) In mice, co-treatment with MT1110 and everolimus enhances inhibition of signaling in the brain while preserving signaling in peripheral tissues.

In vivo activity of MTX-E1

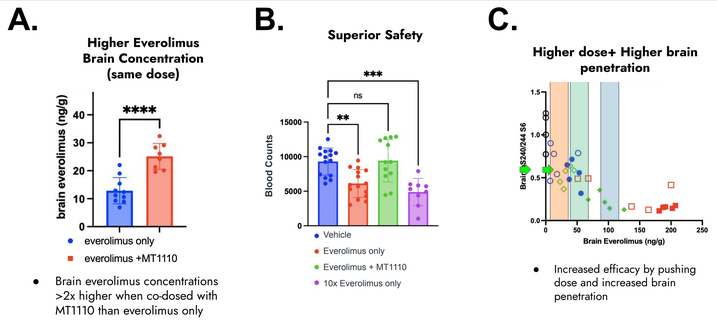

Figure 3. Co-dosing with MT1110 improved the therapeutic profile of rapalog Everolimus (A) Co-dosing with MT1110 increase the brian exposure of total Everolimus in Mice. (B) Co-dosing with MT1110 reverses the immunosuppressive effect of Everolimus in mice. (C) Increased total Everolimus in the brains of mice result in increases mTOR inhibition as measured by pS6 levels.

Thanks!

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The presenters are employees and shareholders of Montara Therapeutics, Inc. Accordingly, the data presented here could influence the value of the company's shares.

Biomarker

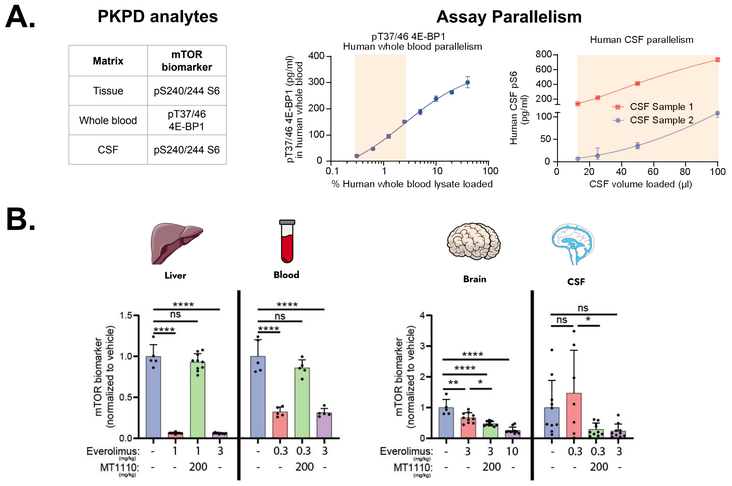

Figure 4. mTOR Biomarker Assays Demonstrate Correlation Between Biofluid and Tissue Biomarkers. (A) Indication of mTOR biomarker assays developed and parallelism range (shaded area) of the assays for human biofluids. (B) In everolimus ± MT1110–treated mice, mTOR biomarkers in peripheral tissues correlate with whole blood, and brain mTOR biomarkers trend with CSF

In vivo evidence for mTOR inhibition in AD/PD

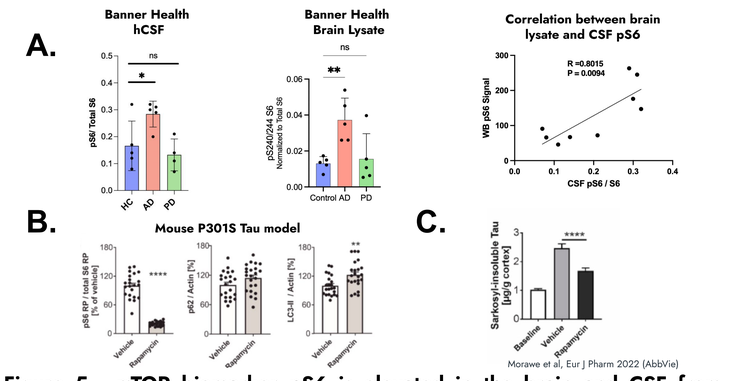

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Figure 5. mTOR biomarker pS6 is elevated in the brain and CSF from Alzheimer's Disease patients - Potential for disease modification. (A) CSF and brain lysates from AD patients show elevated levels of pS6. There is good correlation between CFS and Brain levels, supporting CSF as a relevant biomarker. (B) Treatment with Rapamycin inhibited mTOR pS6, increased p62 and LC3, markers of autophagy (C) Rapamycin dosing reduced insoluble Tau in P301S Tau mice

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