The Bromodomain And Extraterminal Domain Protein Inhibitor Apabetalone Inhibits The Neurotoxic Kynurenine Pathway In Monocytes And Brain Endothelial Cells

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Background

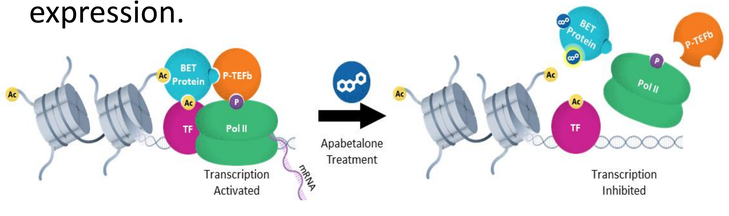
The kynurenine pathway (KP) is activated in several neurodegenerative and neuropsychiatric disorders including Alzheimer's disease. Peripheral chronic inflammation, induces the KP pathway in multiple cell types, with monocytes being the most active producers of KP metabolites. Proinflammatory cytokines induce the expression of two KP rate-limiting enzymes: indoleamine 2,3-dioxygenase 1 (IDO1) responsible for the conversion of tryptophan to kynurenine, and kynurenine 3-monooxygenase (KMO) that facilitates conversion of kynurenine into 3-hydroxykynurenine. Kynureninase (KYNU) converts kynurenine into anthranilic acid. These metabolites can cross the blood brain barrier where they are processed by brain cells into neuroactive molecules, the ratio of which can either be neuroprotective or neurotoxic. The kynurenine-to-tryptophane ratio, an indicator of IDO1 peripheral activity, is elevated in patients with neurodegenerative disease. Reducing the activity of the KP pathway in the circulation favorably alters the ratio of KP metabolites in blood and the brain and has been shown to improve disease outcomes in mouse models of Huntington's disease and Alzheimer's disease.

Objectives

Epigenetic regulators bromodomain and extraterminal domain (BET) proteins control responses to cytokines in monocytes, endothelial cells and hepatocytes. Here, we tested the ability of a clinical-stage BET inhibitor (BETi) apabetalone (also called RVX-208) to counter the cytokine-dependent production of KP enzymes and kynurenine in cultured human cells.

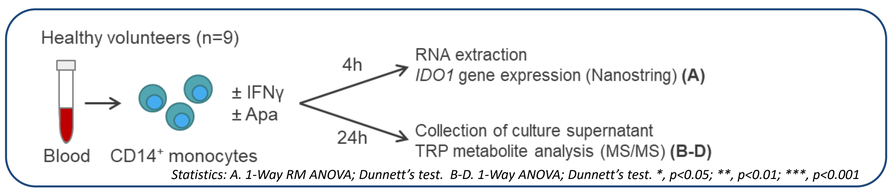
Drug Mechanism of Action

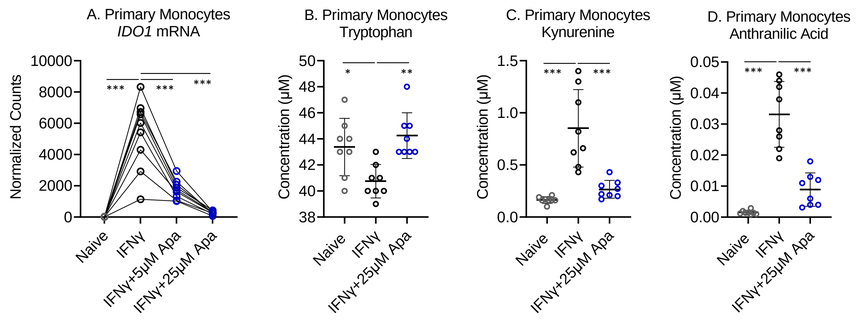
Apabetalone binds competitively to bromo-domains in histone acetylation "readers" termed BET proteins, causing their release from chromatin and downregulation of BET sensitive gene expression.

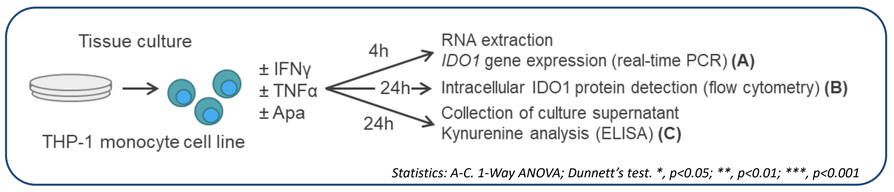


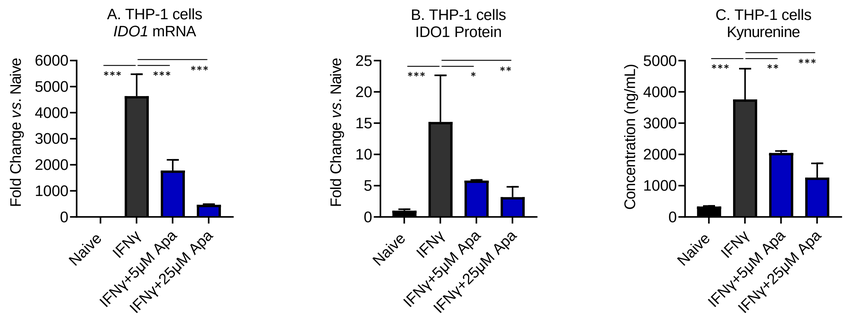
BET: bromodomain and extraterminal proteins; ac: acetylated lysine residue on DNA associated proteins; BD: bromodomain; TF: transcription factor

Apabetalone Downregulates IDO1 Expression and Activity in Human Monocytes

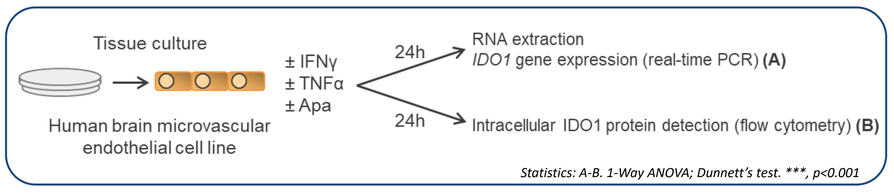


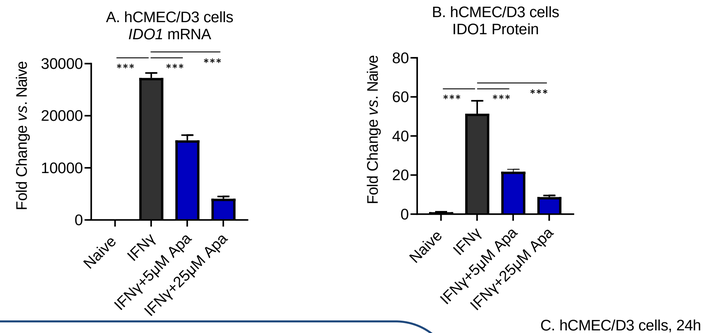


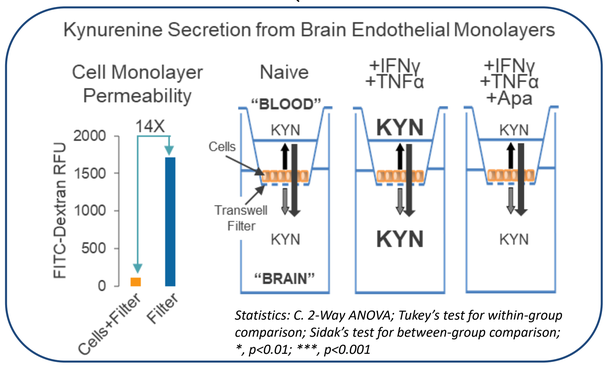


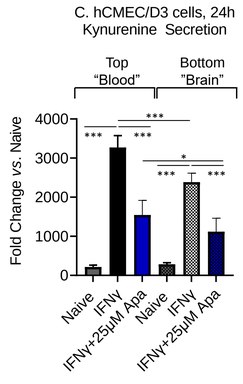


Apabetalone Downregulates IDO1 Expression and Activity in Brain Endothelial Cells

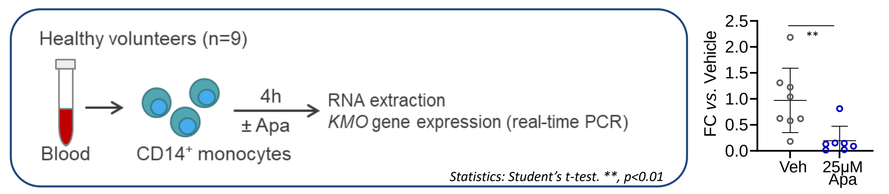


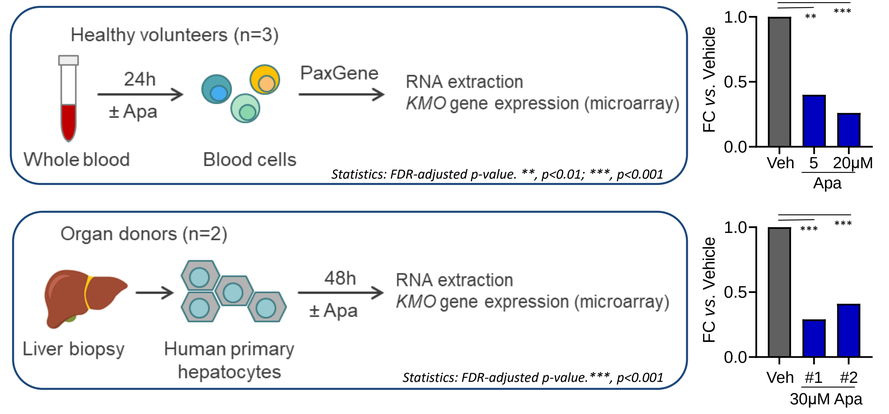




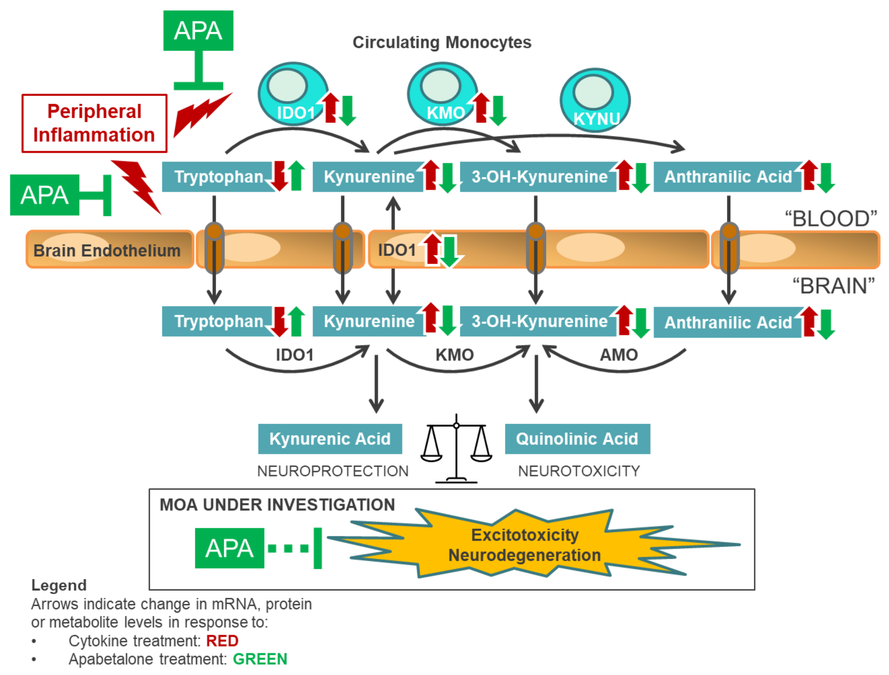


Apabetalone Downregulates KMO Gene Expression in Blood and Liver Cells





Apabetalone Reduces KP Metabolites, Potentially Impacting Neurotoxicity



Summary and Conclusions

- **Apabetalone decreases activation of the KP in monocytes and brain endothelial cells. Reduced peripheral KP activity may reduce neurotoxicity in the brain through reduced transport of KP metabolites across the BBB.**
- **These findings provide mechanistic insights into the beneficial effects of apabetalone on cognition that were demonstrated in a phase 3 clinical trial (BETonMACE): patients with type 2 diabetes and high-risk CVD with baseline MoCA scores ≤21 experienced a significant 1.8-unit improvement in MoCA scores following apabetalone treatment versus placebo (p=0.02) over 24 months.**

Disclaimer: JK and ESGS have nothing to declare. All other authors are employees and stockholders of Resverlogix Corp.