The Epigenetic Inhibitor Apabetalone Downregulates Brain Endothelial and Microglial Cell Activation that Contributes To Neurodegenerative Disease

**Background**

Systemic or localized peripheral inflammatory injury can lead to transmission of neural signals as well as infiltration of peripheral molecules and immune cells into the central nervous system (CNS). This contributes to microglial pro-inflammatory activation and neurodegeneration. Apabetalone is an orally available small molecule in phase 3 trials for cardiovascular disease (CVD). As an inhibitor of bromodomain and extrathorinal domain (BET) proteins, apabetalone regulates gene expression through an epigenetic mechanism. Clinical trials in CVD patients and preclinical models demonstrate peripheral anti-inflammatory effects of apabetalone treatment.

**Objective**

We evaluated the therapeutic potential of apabetalone in pre-clinical models of neuroinflammation.

**Methods**

Human brain microvascular endothelial cells (HBMVECs) were stimulated with cytokines TNFα and IFNγ ± apabetalone or JQ1 (BETi) and assayed for gene expression, surface protein levels, and THP-1 monocyte adhesion under flow. BV-2 microglial responses to lipopolysaccharide (LPS) and IFNγ ± BETi were examined. C57BL/6J mice treated with 150 mg/kg apabetalone for 7 days received 10 μg LPS intraperitoneally, followed by brain mRNA analysis on day 8.

**Results**

In cytokine-stimulated HBMVECs, apabetalone dose-dependently reduced the induction of vascular activation marker mRNAs including IL-6, IL-1β, MCP-1, VCAM1 and E-selectin. Surface expression of VCAM1 and E-selectin was also reduced, leading to decreased adhesion of HBMVECs with THP-1 monocytes under laminar flow. In BV-2 microglial cells, apabetalone opposed LPS and IFNγ mediated induction of IL-6, IL-1β, complement C3 and C1q. Peripheral LPS injection in mice provokes inflammatory responses in the brain, where apabetalone attenuated the LPS-induced mRNA expression of endothelial, monocyte and macrophage adhesion molecules E-selectin, ICAM, CCR2, and CD68.

**Mechanism of Action**

Apabetalone reduces monocyte adhesion to cytokine-activated HBMVECs.

**Conclusions**

- In CNS cell models and endotoxia mice, the epigenetic inhibitor apabetalone can counter inflammatory expression of cytokines, chemokines and markers of endothelial and microglial activation associated with neuroinflammation and cognitive dysfunction.
- The effect of apabetalone on cognition is currently being evaluated with MoCA in participants ≥70 years of age enrolled in the phase 3 BETonMACE trial focusing on cardiovascular outcomes in patients with CVD and diabetes.