Apabetalone, an Epigenetic BET Inhibitor in a Phase 3 Trial, Inhibits Vascular Inflammation and Cellular Adhesion Leading to Beneficial Outcomes in CVD Patients

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Abstract

Background: Apabetalone (RVX-208) is a small molecule bromodomain & extranuclear (BET) protein inhibitor, targeting the second bromodomain (BD2) of BET proteins. In cardiovascular disease (CVD) patients enrolled in phase 2 trials apabetalone treatment reduced the relative risk of a CV event by 44% (Nicholls 2017). Elevated cytokines, such as TNFα, promote vascular inflammation (VI) and monocyte adhesion in CVD and Diabetes Mellitus, driving atherosclerosis. Here we test the impact of apabetalone on cell types that contribute to atherosclerosis.

Methods: Human endothelial cells (HUVECs) and THP-1 monocytes were stimulated with TNFα and treated with apabetalone or MZ-1 PROTAC-mRNA (pPRC, NMDR) and protein levels (FACS, western blot) were compared. HUVEC-THP-1 adhesion assays assessed the functional consequences of TNFα stimulation and apabetalone treatment. The phase 2 ASSURE CVD patient plasma proteome (SOMAscan®) was analyzed using Ingenuity® Pathway Analysis (IPA®) to predict canonical and upstream regulator pathways impacted by apabetalone.

Results: Apabetalone repressed transcription of inflammatory and adhesion genes in TNFα-stimulated HUVEC and THP-1 cells. Corresponding HUVEC protein abundance was also reduced. MZ-1 BET protein degradation blocked TNFα responses, indicating BET-dependency. Functionally, apabetalone suppressed monocyctic THP-1 cell adhesion to inflamed endothelial cells. CVD patient plasma proteome analysis revealed that apabetalone reduced key players in adhesion (VCAM-1, ICAM-1) and plaque stability (MMP-3, MMP12). IPA® analysis of the clinical proteome data predicted that apabetalone inhibits pro-atherogenic mediators and inflammation pathways.

Conclusion: Apabetalone attenuates VI through the epigenetic regulation of inflammatory and adhesion gene transcription. Downregulation of VI by apabetalone may contribute to the reduction in CVD events observed in phase 2 studies. The ability of apabetalone to prevent major adverse cardiac events in post-acute coronary syndrome patients with type 2 diabetes mellitus (DM) and low HDL-C is being assessed in phase 3 trial (BETonMACE).

Results

Apabetalone lowers MACE, phase 2b analysis

Pro-inflammatory gene expression is BET-dependent

Apabetalone suppresses pro-atherogenic and plaque rupture mediators in CVD patient plasma

Summary

Apabetalone downregulates pro-atherogenic gene expression in endothelial and monocyctic cells.

1Disclosure: Resverlogix employees received salaries & stock options from RVX.