Apabetalone, a BET inhibitor, attenuates inflammation induced by viral RNA mimetic and reduces SARS-CoV-2 spike protein binding regardless of variants


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Background/Introduction: Hyperinflammatory responses to SARS-CoV-2 can cause myocarditis and cardiac dysfunction including congestive heart failure [1]. SARS-CoV-2 RNA induces type I interferon (IFN-I), activating IFN regulatory factors (IRFs) and downstream IFN stimulated genes (ISGs) to initiate inflammatory processes. SARS-CoV-2 variants may develop immune escape, undercutting benefits of vaccinations. These challenges highlight the need of variant-independent therapies to improve COVID-19 outcomes. Apabetalone is an epigenetic B02-selective BET inhibitor in phase 3 trials for cardiovascular disease [2]. Apabetalone has the potential to treat COVID-19. It counters inflammatory signals caused by cytokine storm (CS), preventing cardiac dysfunction associated with severe COVID-19 symptoms in cardiac organoids [3]. It also downregulates angiotensin-converting enzyme 2 (ACE2) expression, the main host cell receptor for SARS-CoV-2 spike protein thus impeding propagation of wild-type SARS-CoV-2 [3,4].

Purpose: 1) Evaluate apabetalone’s effect on inflammatory processes induced by viral-RNA mimetic in human lung cells; 2) Assess apabetalone’s ability to prevent binding of the highly contagious delta variant spike protein to human lung cells.

Methods: Inflammatory gene expression was examined by real-time PCR in apabetalone treated human bronchial epithelial cells (Calu-3) stimulated with poly I:C, a well-accepted viral RNA mimetic that elicits inflammatory signals similar to SARS-CoV-2 RNA [5]. Binding of SARS-CoV-2 delta or wild-type spike protein to apabetalone treated Calu-3 cells was determined by flow cytometry.

Results: In Calu-3 cells, apabetalone dose-dependently downregulated poly I:C induced transcription of key COVID-19 associated cytokines (IL6, CXCL10, CCL2) to a similar extent as baricitinib (up to 86%, \( p < 0.0001 \)), an anti-inflammatory agent in emergency use for COVID-19 treatment. Moreover, apabetalone but not baricitinib diminished IL1B mRNA levels (up to 66%, \( p < 0.0001 \)). Apabetalone and baricitinib opposed poly I:C induced expression of IFNB1 (an IFN-I), IRF1 and IRF9 (upstream regulators) as well as IFIT1 and IFIT2 (downstream ISGs that regulate CXCL10 expression; up to 90%, \( p < 0.0001 \)). Clinically relevant doses of apabetalone did not alter expression of anti-viral IFITM2, an ISG that blocks SARS-CoV-2, particularly omicron, endosomal entry [6]. Therefore, apabetalone counters the expression of inflammatory factors with roles in CS and IFN-I signaling in response to poly I:C. Additionally, apabetalone reduced delta and wild-type spike protein binding to unstimulated Calu-3 cells (up to 72%, \( p < 0.0001 \)).

Conclusions: Apabetalone’s dual anti-viral and anti-inflammatory mechanism positions it as a variant-independent COVID-19 therapeutic. Together with an established safety profile from >2000 treatment-years with apabetalone, the data provide rationale for an ongoing clinical trial (NCT04894266) which includes analysis of cardiac damage.