APABETALONE (RVX-208) REDUCES ACE2 PROTEIN ABUNDANCE AND PREVENTS SARS-COV-2 SPIKE PROTEIN BINDING TO HUMAN LUNG CELLS, A MOA THAT COULD ATTENUATE VIRAL ENTRY

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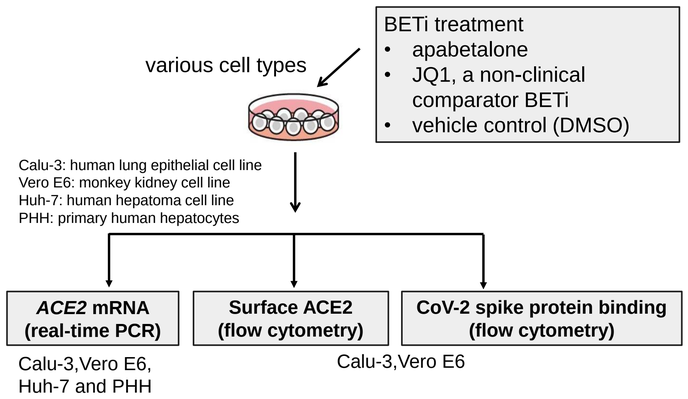
BACKGROUND

- The receptor angiotensin converting enzyme 2 (ACE2) on the surface of host cells is essential for SARS-CoV-2 (CoV-2) virus entry
- ACE2 binds to CoV-2 spike protein to initiate infection
- BET proteins, epigenetic readers that regulate gene transcription in host cell nuclei, have recently been demonstrated to play a role in CoV-2 viral replication
- BET inhibitors (BETi) including apabetalone reduce CoV-2 infection in a human 2-D cardiac myocyte model
- Apabetalone is a well-tolerated BETi evaluated in phase 3 trials for cardiovascular disease (CVD) without adversely affecting blood pressure in patients tested in clinical studies

OBJECTIVES

- Examine potential effect of apabetalone on ACE2 receptor expression in cells derived from the lung and other tissues
- Determine if apabetalone affects the ACE2-CoV-2 spike protein binding as well as CoV-2 infection in cell models

METHODS



Statistical significance was determined with one-way ANOVA followed by Dunnett's multiple comparison test relative to DMSO. *p<0.05, **p<0.01, ***p<0.001

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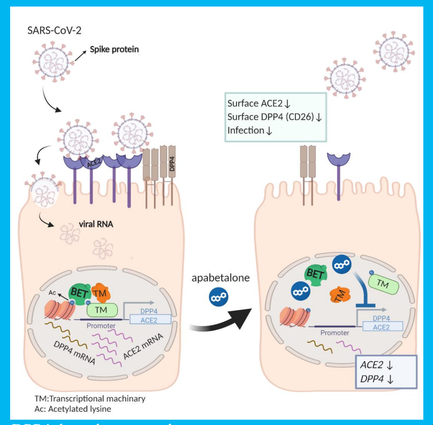
MAIN FINDINGS

- **Apabetalone reduces *ACE2* transcription** in lung and extrapulmonary cells
- **Apabetalone reduces ACE2 protein** abundance and **attenuates binding of CoV-2 spike protein** in human lung cells and monkey kidney cells, both of which can propagate CoV-2
- Results suggest that **apabetalone may mitigate CoV-2 replication/transmission** in multiple organs. Further assessments have shown **apabetalone strikingly inhibits live CoV-2 infection** to levels comparable to anti-viral agents in cultured human lung cells (Dean Gilham et al, 2021, *https://www.mdpi.com/2227-9059/9/4/437/pdf*)
- Apabetalone is a safe well tolerated drug in phase 3 clinical development for CVD with plans to test apabetalone **in clinical studies of COVID-19** underway



DPP4 data please see the paper:
https://www.mdpi.com/2227-9059/9/4/437/pdf

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RESULTS

Figure 1. Apabetalone downregulates *ACE2* gene expression

Gene expression of *hACE2* (A, C-D) or *RhACE2* (B) in various cell types following BETi treatment (up to 96h) determined by real-time PCR. Bar graphs show mean ±SD. apa denotes apabetalone

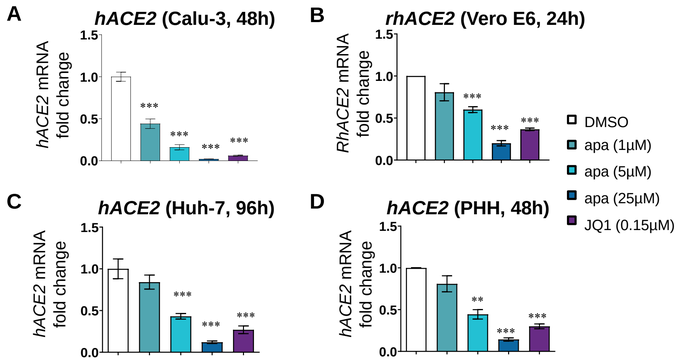


Figure 2. Apabetalone reduces ACE2 surface expression

Flow cytometric analysis of surface ACE2 on Calu-3 (A,B) and Vero E6 cells (C) following 72h or 48h apabetalone treatment, respectively. Bar graphs show mean ±SD. apa denotes apabetalone

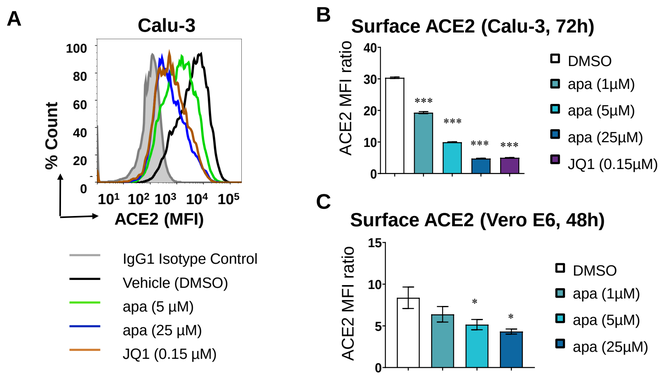
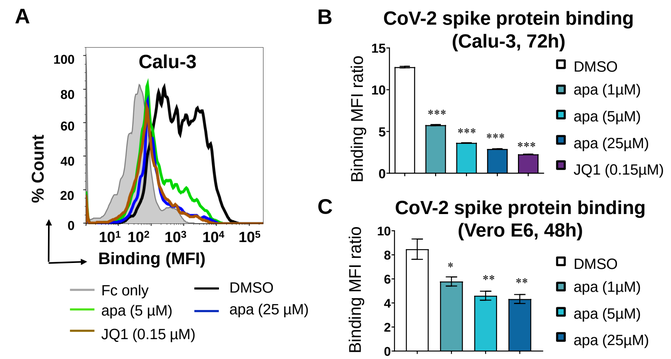


Figure 3. Apabetalone attenuates CoV-2 spike-RBD binding

Flow cytometric analysis of binding of CoV-2 spike protein fragment (spike receptor binding domain [RBD] fused with human IgG1 Fc) to Calu-3 (A,B) and Vero E6 cells (C) following apabetalone treatment . Bar graphs show mean ±SD. apa denotes apabetalone



DISCLOSURE

All authors are employees of Resverlogix & hold stock or stock options.