Apabetalone (RVX-208) attenuates inflammatory milieu underlying adhesion of monocytes to endothelial cells in T2DM with CVD patients

Maura L. Tsujikawa1, Brooke D. Rakal1, Li Fu1, Shovan Das1, Christopher Halliday1, Chris Sarsons2, Emily Daze1, Sylvia Wasilak1, Dean Gilham1, Kristina D. Rinker1, Jan O. Johannsson1, Michael Sweeneyey, Norman C. Wong1 and Ewelina Kulikowski1

Resverlogix Corp. Calgary, AB, Canada, 2San Francisco, USA, and 3Department of Chemical and Petroleum Engineering, University of Calgary, AB, Canada

**Summary**

- Apabetalone suppresses all pro-atherogenic mediators shown above.
- BET-dependent downregulation of vascular inflammation and cell adhesion by apabetalone may contribute to the reduction in MACE, a hypothesis currently being tested in the phase 3 cardiovascular outcomes trial BETonMACE in post-Acute Coronary Syndrome patients with diabetes mellitus and low HDL-c.

**Results**

- Apabetalone reduces MACE, phase 2b post-hoc analysis
- Apabetalone reverses high glucose impact on major inflammatory gene sets in endothelial cells
- IPA® predicts apabetalone inhibition of TNFα and pro-atherogenic pathways in ASSERT CVD patient proteome

**Mechanism of Action**

- Apabetalone inhibits high glucose induced pro-atherogenic gene expression in monocytes and endothelial cells

**Results**

- Apabetalone reverts high glucose impact on major inflammatory gene sets in endothelial cells

**GSEA**

- Broad Institute software: Hallmark, Curated (Bicarta, KEGG, Reactome), GO (biological process, molecular function, cellular compartment), and immunologic gene sets

**GO: Gene ontology - Molecular function (MF)**

- Top 5 GO gene sets impacted are: GO molecular function, GO biological processes, GO cellular components, GO disease ontology, GO gene ontology.

**Cytokines & Chemokines**

- TLR signaling
- TGFb signaling
- TNF signaling

**Table**

<table>
<thead>
<tr>
<th>Glucose</th>
<th>5uM</th>
<th>20uM</th>
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<tbody>
<tr>
<td>CCL20</td>
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<td>-20</td>
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<tr>
<td>CSF3</td>
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<tr>
<td>CXCL10</td>
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<td>-44</td>
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<tr>
<td>CYSLTR2</td>
<td>1.4</td>
<td>-91</td>
</tr>
</tbody>
</table>

**Tables**

- Table 1: Summary of gene expression changes.
- Table 2: Inflammation, immune function, and cell adhesion.

**Figure**

- Apabetalone reduces MACE, phase 2b post-hoc analysis
- Apabetalone reverses high glucose impact on major inflammatory gene sets in endothelial cells
- IPA® predicts apabetalone inhibition of TNFα and pro-atherogenic pathways in ASSERT CVD patient proteome

**Disclosure**

- Authors were employed by Resverlogix & Disclosure form for each author.

**Target gene expression changes**

- Upstream Regulator
- Canonical Pathway
- Acute Phase Response Signaling
- Coagulation System
- Leukocyte Extravasation Signaling

**Bioinformatics [IPA®] Analysis of the Plasma Proteome (SOMAscan)**

- ASCERT phase II trial: Apabetalone treatment vs. placebo

- Inflammation Pathway Analysis
- Regulator/Pathway
- Activation score
- p-value
- # of overlap

- Upstream Regulator (TF)
- Canonical Pathway (IRBP)
- Acute Phase Response Signaling
- Coagulation System
- Leukocyte Extravasation Signaling

- Plasma proteins targets: CCL2 (CXCR2; p=0.00001), CCL3 (CXCR3; p=0.00001), IL-6 (p=0.00001), TNFα (p=0.00001), IL-1β (p=0.00001), IL-8 (p=0.00001), MCP-1 (p=0.00001), IL-10 (p=0.00001), IL-12 (p=0.00001), IL-16 (p=0.00001), IL-18 (p=0.00001).

- Plasmas from 42 patients in the RVX-208 trial (25% treated, 75% placebo)

- Results from these analyses were used to identify potential clinical targets and patient subpopulations that may benefit from apabetalone treatment.

**Authors**

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