Small Molecule Inhibitor of CD38 Modulates Its Intra- And Extracellular Functions Leading to Antitumor Activity


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CD38 is a Multi-functional Enzyme and is an NADase

- ADP-ribosyl cyclase that converts NAD+ to ADP-ribose (ADPR) or cyclic ADPR (cADPR) and NAADP
- Present in either an ecto- or endo-catalytic orientation with different sub-cellular localization
- Regulates internal and external pools of NAD+ and its metabolites
- Drives non-canonical generation of adenosine
- Upregulated in various disease conditions and associated with immune dysfunction
- Therapeutic target for cancer, autoimmune and metabolic disorders

RBN013209 Potent and Selective Inhibitor of CD38

- RBN013209 is a potent and selective inhibitor of human and mouse CD38
- High target coverage achieved with oral dosing

Pharmacodynamic Modulation of NAD+ and Metabolites In Vivo

Oral Dosing of RBN013209 in Mice Modulates Liver NAD+ at Multiple Doses and Increased NAD+ for 12 Hours

- RBN013209 PK/PD Time Course
- LCMS based detection of NAD in homogenates from acid preserved tissue. Tissue and tissue collected after 6 hours for time course study and 12, 24 and 48 hours for the time course study. Similar results observed in spleen.

CD38 Inhibition Supports T cell Fitness Enabling Effector Functions

- CD38 is upregulated upon T cell activation
- CD38 inhibition enriches memory effector cell

CD38 inhibition enhances effector cytokine production

- Changes in cytokine production (p<0.05 vs DMSO control for all groups)
- Representation of 2 donors; 3 liver homogenates (summarized in Table 1)

CD38 Is Highly Expressed in Subsets of Lung and Prostate Cancer

- Confirmed CD38 expression in cancer patient samples

- Samples exhibit varying levels of tumor and immune-specific staining patterns

Conclusions

- RBN013209 is a potent and selective CD38 inhibitor with good PKPD properties
- Inhibition of CD38 with a small molecule affects both intra- and extra-cellular CD38 activity and modulates key metabolites playing an important role in immunomodulation
- CD38 is increased by ICI treatment and inhibition of CD38 can lead to antitumor activity

ICI treatment Drives CD38 Upregulation in the Tumor Microenvironment

- MC38: colon cancer model
- B16-F10: melanoma model

- Increases in CD38 expression on tumor cells and infiltrating immune cells in MC38 colon cancer and B16-F10 melanoma, upon immune checkpoint (ICI) blockade inhibitor treatment

RBN013209 in Combination with ICI Treatment Shows Significant Tumor Growth Inhibition in B16-F10

- Single agent activity (~ 40 %) observed in MC38 syngeneic mouse model with oral BID dosing of RBN013209
- Tumor PD observed in terms of modulation of NAD+ and ADPR levels

- Oral treatment with BID dosing of RBN013209 overcomes ICI resistance in B16-F10 tumor model
- Tumor PD observed in terms of modulation of NAD+ levels