A Bi-Functional Mechanism of Action: Activating the NLRP3 Inflammasome in Macrophages and Triggering Apoptosis in Cancer Cells via HK2/VDAC Modulator

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**BACKGROUND**

- Metabolic re-programming to aerobic glycolysis, known as the Warburg effect, allows cancer cells an efficient conversion of glucose to biomass and energy required for rapid cell growth and proliferation.
- Similar metabolic re-programming occurs in some activated immune cells.
- A key enzyme in glycolysis is hexokinase (HK), which catalyzes the first step of glucose metabolism.
- Many cancer types express high levels of HK2, whereas the HK1 isozyme is ubiquitously expressed in normal cells.
- In cancer cells, HK2 attaches to the outer mitochondrial membrane via interaction with the VDAC1 channel.
- VDAC1/HK2 association results in apoptosis prevention and a high rate of glycolysis, by blocking pro-apoptotic signals and allowing a continuous flux of mitochondrial ATP to HK.
- Transient high HK expression, and binding to VDAC1, is also found in a variety of activated immune cells to support their changing metabolic needs.
- It has been recently published that detachment of HK2 from VDAC is one of the first events leading to NLRP3-inflammasome activation, resulting in IL-1β and IL-18 secretion from macrophages (Cell 2016; 166:624).
- VDA-1102 is a novel small-molecule HK2 modulator that selectively detaches HK2 from VDAC1, triggering apoptosis in cancer cells while promoting an anti-tumor immune response.

**MOA of VDA-1102 (Biochemical)**

**RESULTS**

**HK Levels in Bone Marrow-Derived Macrophages (BMDM)**

**VDA-1102 Induces Apoptosis in Cancer Cells**

**VDA-1102 Selectively Detaches HK2 from VDAC**

**Effects of VDA-1102 on Cancer Cells**

**Anti-Clandegic Effects of VDA-1102 on Human Tumors**

**VDA-1102 Mechanism of Action (MOA)**

Effects of VDA-1102 on Cancer Cells:

- VDA-1102 Induces Apoptosis in Cancer Cells:
- VDA-1102 Selectively Detaches HK2 from VDAC
- HK2 protein levels are up-regulated in activated macrophages
- HK2 dissociation from VDAC is essential for activation of NLRP3 inflammasome

**VDA-1102 Activates M1 Macrophages In Vitro**

**VDA-1102 Reduces Glutathione in Cancer Cells**

**VDA-1102 Reduces M2 Macrophage In Vitro**

**VDA-1102 Increases NOX Expression and Activity**

**VDA-1102 Suppresses M2 Macrophage in Vitro**

**VDA-1102 Reduces M2 Marker Gene Expression**

**VDA-1102 Reduces the M2 Marker COX26**

**Effects of VDA-1102 on Macrophages:**

- VDA-1102 Mechanism of Action (MOA)
- Effects of VDA-1102 on Cancer Cells:
- Effects of VDA-1102 on Macrophages:
- VDA-1102 Reduces Glutathione in Cancer Cells
- VDA-1102 Reduces M2 Macrophage In Vitro
- VDA-1102 Increases NOX Expression and Activity
- VDA-1102 Suppresses M2 Macrophage in Vitro
- VDA-1102 Reduces M2 Marker Gene Expression
- VDA-1102 Reduces the M2 Marker COX26

**SUMMARY**

- VDA-1102 is a novel selective small-molecule HK2 modulator that targets cancer cells as well as the innate immune system.
- VDA-1102 stimulates multiple anti-tumor mechanisms: triggers apoptosis within cancer cells, increases anti-tumor immune responses (activating NLRP3 inflammasome in M1 macrophages) and decreases immune suppression (suppressing M2 macrophages).
- Our findings support further development of VDA-1102 to evaluate its potential as an anti-cancer therapy, both as a monotherapy and in combinations.