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# Cucurbitacin B: A novel agent for inducing tumor-immune response.

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## Recommended Citation

Alvi, Sahir S.; Anning, Emmanuel; Ahmad, Mudassier; Perez, Carlos; Chaib, Mehdi; Chuahan, Subhash C.; Merghoub, Taha; and Hafeez, Bilal B., "Cucurbitacin B: A novel agent for inducing tumor-immune response." (2024). *Research Symposium*. 77.
https://scholarworks.utrgv.edu/somrs/2024/posters/77

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**Cucurbitacin B: A novel agent for inducing tumor-immune response.**

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**Abstract:**

Despite the emergence of immunotherapy as a potential breakthrough in cancer treatment, it showed only a marginal response in pancreatic and liver cancers. Thus, novel strategies are highly desirable to take full advantage of immunotherapy in the treatment of these cancers. One of the critical factors that influence the efficacy of immunotherapy is the increased infiltration of myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAM) into tumors that alter the immune landscape and serve as facilitators of tumor proliferation, metastatic growth, and immunotherapy resistance. Thus, we believe that selecting a potent molecule that has the ability to suppress the function or revert the phenotypes of TAM and MDSCs will have a more significant impact in enhancing tumor immunotherapy response. Cucurbitacin B (Cuc B) is a potent inhibitor of Stat3, CSF-1R, and PI3Kγ and has shown its chemopreventive and therapeutic effects against various cancers but is limitedly explored for its application in modulating tumor immune response. In this study, we investigated the molecular effects and underlying molecular mechanisms of Cuc B on TAM and MDSCs. Cuc B significantly ($P<0.01$) decreased the expression of M2 markers (Arginase I, YM1 FIZZ1, PPARγ and TGFβ in M2 polarized BMDMs and increased M1 markers (NOS2, IL-6, and CD11C) compared to IL-4 alone treatment group. It has been demonstrated that TAMs secrete PDL-1 which neutralizes the function of T-cells. Cuc B treatment significantly ($P<0.001$) decreased PDL-1 expression in IL-4-treated RAW264.7 cells. Surprisingly, we observed that Cuc B treatment abolished the protein levels of PI3Kγ in IL-4 treated macrophages as determined by confocal microscopy and Western blot analysis. Cuc B treatment of bone marrow-derived MDSCs significantly ($P<0.01$) decreased the expression of Arginase-1, IL-10, PDL-1, and Stat3. We observed that IL-4-treated BMDMs inhibited phagocytic capacity which was significantly restored upon Cuc B treatment. We observed that Cuc B is a more potent molecule than a pharmacological inhibitor of PI3Kγ (IPI-549) in suppressing key signaling components of TAM and MDSCs. We are performing in vivo study to investigate Cuc B potential to enhance checkpoint blockade immunotherapy response in clinically relevant mouse models of cancer. These results suggest that Cuc B is a novel therapeutic agent which has the potential to suppress or revert TAMs and MDSCs phenotypes. Cuc B may be used as an adjuvant drug molecule in combination with PD1 or CTLA-4 antibodies for improving immunotherapy response against less responsive tumors.