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# The beta-carboline Harmine sensitives microsatellite stable colorectal cancer mouse model to anti-PD-1 through upregulating MHC-I dependent antigen presentation machinery and improving the infiltration of CD8 T cells into the tumor microenvironment.

**Author Block:** Ruize Gao[1], Kris Van Moer[1], Coralie Puliodo[2], Anaïs Oudin[2], Diane Murera[1], Teresa L. Ramos[1], Margaux Poussard[1], Andreas Schläpfer[3], Annette Ives[3], Christian Auclair[3], **Bassam Janji**[1]

[1]Department of Cancer Research - Tumor Immunotherapy and Microenvironment (TIME) Group, Luxembourg Institute of Health, Luxembourg City, Luxembourg,[2]Department of Cancer Research - Animal Experimental Core facility, Luxembourg Institute of Health, Esch-sur-Alzette, Luxembourg,[3]AC Bioscience SA, Epalinges, Switzerland

**Abstract:**
Colorectal cancer (CRC) is the most common gastrointestinal cancer and the third leading cause of cancer-related death in both sexes. Mismatch repair deficient/microsatellite instability-high (MSI) colorectal cancer patients benefit from immune checkpoint blockades (ICBs)-based immunotherapy; however, this benefit has not been translated into microsatellite stable (MSS) colorectal cancer. It has been proposed that the loss of major histocompatibility complex class I (MHC-I) in tumor cells limits the use of ICB in colorectal cancer. Harmine displays a number of biological and pharmacological properties affecting the immune response and tumor phenotype. Here, we assessed the impact of combining harmine, also referred to as ACB1801 molecule, on improving the responsiveness of ICB in the mouse MSS CRC model. Our results showed that combining ACB1801 significantly improves the therapeutic benefit of anti-PD-1 in the CT26 CRC mouse model by decreasing tumor growth and improving the survival of tumor-bearing mice. The improvement of anti-PD-1-based therapy by combining ACB-1801 was associated with a modification of the immune landscape of tumors as evidenced by an increase in the CD8+ T cells and a decrease in the Treg infiltrations into the tumor microenvironment. By profiling the cytokine/chemokine network, we showed that ACB1801 induced the expression and the release of the proinflammatory chemokine CXCL10 by CRC tumor cells *in vitro*, which could be responsible for driving CD8+ T cells to the tumor microenvironment. Mechanistically, we showed that ACB1801 increased the expression of MHC-I genes, including TAP1 and TAPASIN, and improved the antigen loading on MHC-I in CRC cells *in vitro*. Overall, our study highlights the value of combining ACB1801 and anti-PD-1 as a therapeutic opportunity to convert MSS colorectal cancer into an "immune hot" cancer, which may define the future treatment paradigm of colorectal cancer for which there is a great unmet need.

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