Resminostat is a novel epigenetic modulator with inhibitory potency against HDAC class I, IIb and IV with pronounced activity on HDAC6. The compound is in phase II clinical development and was evaluated in Hodgkin’s lymphoma, hepatocellular carcinoma, colorectal cancer, non-small-cell lung cancer, pancreatic and biliary tract cancer, and demonstrated favorable safety profile and clinical efficacy. Resminostat has the potency to affect the immune response at different levels on tumor as well as immune cells. It reduced the expression of immunosuppressive enzymes, IDO1 and ARG1, which deplete the tumor microenvironment of amino acids essential for T cell activity. Further, resminostat enhanced the expression of various tumor associated antigens as well as MHC class I molecules and upregulated the immunogenic cell death (ICD) marker and dendritic cell engulfment signal Calreticulin. Furthermore, resminostat increased NK cell activating ligands on tumor cells resulting in enhanced NK cell-mediated tumor cell cytotoxicity. In MDSC culture, resminostat not only reduced the number of HLA-DR<sup>low</sup> cells but also diminished the immunosuppressive arginase activity of these cells.

Resminostat enhances tumor immunogenicity

A. Tumor-associated antigens (TAA) are expressed on tumor but silent in normal cells. The anti-tumoral T cell response can be enhanced by up-regulation of TAA expression upon resminostat treatment as detected in various tumor cell lines, B. Resminostat increased the exposure of the dendritic cell engulfment signal Calreticulin, a marker of immunogenic cell death on the surface of K562 cells.

Reduction in arginase activity in MDSC culture and number of HLA-DR<sup>low</sup> MDSC

Myeloid-derived suppressor cells (MDSC) expand during neoplastic diseases and serve to limit T cell responses via different immunosuppressive mechanisms such as arginase expression and subsequent upregulated arginine metabolism. CD33<sup>+</sup> HLA-DR<sup>low</sup> MDSC were generated by co-culture of PBMC with Caki-2 tumor cells. A. Increased arginase activity in MDSC was reduced upon 2 µM resminostat treatment. B. In the presence of resminostat, also the number of HLA-DR<sup>low</sup> CD33<sup>+</sup> cells was diminished.

Resminostat reduces expression of immunosuppressive enzymes arginase and IDO

Resminostat inhibited inducible as well as constitutive IDO1 and Arginase1 expression in different tumor cell lines. Both enzymes significantly contribute to immunosuppressive microenvironment by depletion of arginine and tryptophan, respectively, which are essential for T cell function.

Resminostat exerts pleiotropic immunomodulating effects

A. Resminostat displays diverse immunomodulating effects both on tumor as well as on immune cells. B. These effects suggest potential synergism with different immunotherapy approaches such as immune checkpoint blockers or opsonizing antibodies.