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# POSTER ABSTRACTS

## 651.MULTIPLE MYELOMA AND PLASMA CELL DYSCRASIAS: BASIC AND TRANSLATIONAL

### The Role of Macrophage Migration Inhibitory Factor (MIF) in Regulation of T-Cell Activity in Multiple Myeloma

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*Background:* Multiple myeloma (MM) is the second most common hematological malignancy associated with the overproduction of light chain or monoclonal immunoglobulin. MM remains incurable, with high relapses and refractory disease rates after first-line treatment. Hence, novel therapeutic approaches are needed to improve immune responses to prevent relapses or drug resistance after initial therapies. Immune responses are shaped by several factors, including mutations, pro- and anti-inflammatory cytokines and chemokines, and activation of immune checkpoints in the tumor microenvironment (TME) (Gonzalez et al., 2018). Macrophage migration inhibitory factor (MIF) as a soluble pro-inflammatory cytokine has become one of the most puzzling regulators of innate and adaptive immune responses. In myeloma, MIF was found to be significantly higher in MM cells from relapsed patients than those responding to the treatment. MIF has been implicated in drug resistance and suggested as a biomarker for predicting MM patient responses to proteasome inhibitors (Wang et al., 2020). We previously reported that MIF is highly expressed in MM and regulates CD84 (SLAMF5) expression in MM TME. We showed that MIF secreted from MM cells regulates PD-L1 expression through CD84 on CD14 $^{+}$ monocytic cells in the TME. Inhibition of MIF significantly reduced CD84 and PD-L1 expressions on human CD14 $^{+}$ cells and on myeloid-derived suppressor cells of the mice bearing MM (Lewinsky and Gunes et al., 2021). However, whether MIF directly regulates T-cell activity in MM TME has yet to be explored.

*Methods and Results:* The current study reports that MIF may play a pivotal role in T-cell exhaustion in MM. Ouranalyses in published MM transcriptomic databases show that MM patients with low *MIF* had significantly longer overall and post-progression survival, indicating the therapeutic potential of MIF in MM. We also noted upregulated *MIF gene* expression in relapsed or refractory MM (R/RMM) patients *(n=2)* compared to that in newly diagnosed MM patients *(n=7)* and healthy individuals *(n=9)* in our and publicly available MM single-cell RNA sequencing datasets. We detected a profound *MIF* expression in MM cells and myeloid cell fractions, including monocytes, macrophages, and dendritic cells from the patients' bone marrow (BM) specimens. We previously reported that human MM cell lines highly express MIF. In this study, we assessed the impact of MIF secreted by MM cells on the immune cells, specifically CD8 $^{+}$ T cells. Our results showed that inhibition of MIF reduced the elevated T-cell exhaustion markers, PD1 and CTLA-4, on CD8 $^{+}$ T cells in healthy donors (HDs) peripheral blood mononuclear cells (PBMCs) following the coculturing with MM1.S cells *(n=3 $^{*}P < 0.05$ )*. We also found that MIF inhibition induced the T-cell activation marker, LAMP1, on CD8 $^{+}$ T cells in this coculturing setting *(n=3, $^{**}P < 0.01$)*. Furthermore, we noted MIF inhibition reduced PD1 expression on CD8 $^{+}$ T cells in HDs PBMCs *(n=3, $^{**}P < 0.01$)*, suggesting MIF may regulate the exhaustion profile of CD8 $^{+}$ T cells. MIF can conduct paracrine or autocrine signalings by binding to its receptors, including CD74 and CD44, and lead to intracellular signaling cascades. Hence, we assessed *CD74* gene expression as the counterpart of MIF in R/RMM, MM, and healthy patients. We noted significantly upregulated *CD74* expression in R/RMM patients compared to newly diagnosed MM patients and healthy individuals. We also noted higher *CD74* expression in CD8 $^{+}$ T cells than in CD4 $^{+}$ T cells in R/RMM patients, suggesting that MIF/CD74 axis may be a potential target to enhance CD8 $^{+}$ T cell-mediated immunity in R/RMM. To further explore the impact of MIF inhibition on MM progression, we performed a pilot in vivo study by inoculating murine 5TGM1 cells into two groups of syngeneic C57BL/KaLwRijHsd mice. After two weeks, the mice were injected with either sterile PBS as a control or a MIF inhibitor. The results of this pilot study showed that MIF inhibition significantly decreased MM cells in BM and PB of myeloma-bearing mice and reduced T-cell exhaustion markers on CD8 $^{+}$ T cells compared to that in the control mice *(n=3-4, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$)*.

*Conclusion:* Overall, our preliminary data indicate that MIF may have a crucial role in T-cell activity by regulating T-cell exhaustion markers in MM. Further studies are needed to explore the therapeutic potential of MIF to reduce T-cell exhaustion to improve anti-tumor immunity in MM.

**Disclosures Rosen:** *Exicure:* Current holder of *stock options* in a privately-held company; *Pepromene Bio, Inc:* Current holder of *stock options* in a privately-held company; *Pepromene Bio, Inc:* Membership on an entity's Board of Directors or advisory committees; *NeoGenomics:* Membership on an entity's Board of Directors or advisory committees; *Verastem, Inc:* Consultancy; *Trillium Therapeutics, Inc:* Consultancy; *PharmaGene, LLC:* Consultancy; *Apobiologix/Apotex Inc:* Consultancy; *Exicure:* Consultancy; *Pheromone Bio, Inc:* Consultancy; *January Biotech:* Current holder of *stock options* in a privately-held company; *Trillium Therapeutics:* Current holder of *stock options* in a privately-held company; *SLAM BIOTHERAPEUTICS, INC:* Current holder of *stock options* in a privately-held company, Membership on an entity's Board of Directors or advisory committees.

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