**Introduction**

Multiple myeloma (MM) is considered a chronic and incurable disease due to its highly complex and heterogeneous molecular abnormalities and the support from myeloma microenvironment factors. Macrophages are an abundant component of the stromal cell compartment and are believed to support proliferation, survival, and drug resistance of MM cells. Conversely, macrophages are key immune effector cells for the therapeutic effect of monoclonal antibodies and can directly eliminate tumor cells. However, myeloma-associated macrophages (MAMs) regularly fail to exert direct effector functions. Given their abundance in MM, an attractive therapeutic approach would be to stimulate their tumoricidal activity in order to promote antitumor immunity.

Lenalidomide, an immunomodulatory agent that enhances antibody dependent cell mediated cytotoxicity (ADCC), has the potential to synergize with MOR202, an anti-CD38 monoclonal IgG1 antibody currently in phase I/II for the treatment of MM.

Furthermore, vitamin D plays a key role in regulating effector functions of human macrophages. This is closely linked to the expression of the vitamin D-1-hydroxylase CYP27B1, which catalyzes the conversion of 25-hydroxyvitamin D (25D) to the bioactive 1,25-dihydroxyvitamin D (1,25D). We have previously shown, that vitamin D promotes tumoridal activity of macrophages and improves the efficacy of rituximab-dependent cytotoxicity [1, 2].

**Hypothesis**

Combination of MOR202 with lenalidomide and vitamin D enhance MOR202-dependent macrophage-mediated effector functions against myeloma cells.

**Results**

1. **Myeloma-associated macrophages exhibit an altered vitamin D metabolism**

   - **A** Myeloma patient or Control (after SCT)
   - Bone marrow
   - Flow cytometry

2. **Lenalidomide treatment increases the expression of CYP27B1 and CAMP in human macrophages**

   - **A** Vitamin D (25D)
   - Control
   - VDR
   - CYP27B1
   - CAMP

3. **MOR202-dependent elimination of myeloma cells is enhanced by pre-treatment with lenalidomide and vitamin D**

   - **A** Myeloma cell line
   - VDR
   - CYP27B1
   - CAMP

**References**

1. Vitamin D-dependent induction of vulnerability in human macrophages results in phagocytosis by targeted high-grade solid tumors shown et al., Journal of Immunology Research, 2013.

**Conflict of interest disclosure:** There are no relevant conflicts of interest to disclose.