Multiple myeloma (MM) remains incurable despite novel therapies, highlighting the need for further identification of factors mediating disease progression and drug resistance. The bone marrow (BM) microenvironment confers growth, survival, and drug resistance on MM cells. Our recent study utilized in vitro and in vivo MM xenograft models to show that plasmacytoid dendritic cells (pDCs) were significantly increased in MMBBM and promote MM growth (Chauhan et al., Cancer Cell 2009, 16:309-322). Importantly, we found increased IL-3 levels upon pDC-MM interaction, which in turn, trigger MM cell growth and pDCs survival. IL-3R is highly expressed on pDCs. We utilized SL-401, a novel biologic conjugate that targets IL-3R, to examine whether abrogation of IL-3–IL-3R signaling affects pDC-MM interaction and its tumor promoting sequelae. MM cell lines, patient MM cells, and pDCs from healthy donors or MM patients were utilized to study the anti-MM activity of SL-401. MM cell lines and pDCs were cultured alone or together in the presence or absence of SL-401, followed by analysis of cell growth or viability. SL-401 significantly decreased the viability of pDCs at low concentrations (C50: 0.93 ng/ml; P < 0.005, n = 3). SL-401 also decreased the viability of MM cells at concentrations that can be achieved clinically achievable doses. Co-culture of pDCs with MM cells induced growth of MM cell lines; and importantly, low doses (0.8 ng/ml) of SL-401 blocked MM cell growth-promoting activity of pDCs. MM patient-derived pDCs induced growth of MM cell lines and primary MM cells as well; conversely, SL-401 inhibited pDC-triggered MM cell growth (P <0.005, n= 5). Tumor cells from 3 of the 5 patients were from patients whose disease was progressing while on bortezomib, dexamethasone, and Revlimid therapies. In agreement with these results, SL-401 blocked pDC-induced growth of Dexamethasone-resistant MM cell lines. Our study therefore provides the basis for directly targeting pDCs or blocking the pDC-MM interaction, as well as targeting MM in novel therapeutic strategies with SL-401 to enhance MM cytotoxicity, overcome drug resistance, and improve patient outcome.

**Results**

SL-401 is a recombinant protein expressed in E. coli from a hybrid gene comprised of the DNA sequence of human IL-3 fused to the DNA sequence of truncated DT consisting of its catalytic and translocation, but not binding, domains. The IL-3 domain of SL-401, which replaces the binding domain of DT, targets SL-401 to cells that over-express the IL-3R.

**Material and Methods**

**Isolation of pDCs, MNCs, and MM cells** All studies involving human samples were performed under IRB-approved protocols at Dana-Farber Cancer Institute (Boston), and Brigham and Womens Hospital (Boston) through which informed consent was obtained and de-identified samples were utilized. pDCs were separated from MM BM and PB using magnetic bead separation (BioLegend, San Diego, CA) and plastic adherence (Milenyi Biotech, Auburn, CA) as described in previous study (Chauhan et al., Cancer Cell 2009, 16:309-322). BDCA-4-positive pDCs derived in this way are lineage (CD3, CD14, CD11c)-negative, MHC II-positive, as well as CD122 and CD62d positive. MM cells from patients were isolated by CD138-positive selection using CD138 microbeads and the Auto MACS magnetic cell sorter. SL-401 was obtained from Stemline Therapeutics, Inc.

**Conclusion**

Our recent findings identified an integral role of pDCs in MM pathogenesis (Chauhan et al., Cancer Cell 2009, 16:309-322). In the present work, we provide the basis for targeting pDC-MM interactions with SL-401 as a novel therapeutic strategy to increase MM cytotoxicity, overcome drug-resistance, and improve patient outcome in MM.