INTRODUCTION: A Proliferation-Inducing Ligand (APRIL) is produced by multiple accessory and myeloid cells in the bone marrow microenvironment. Through binding to its receptors, B-cell maturation antigen (BCMA) and transmembrane activator and CAML-associate (TACI), APRIL plays an important role in the development and maintenance of cells derived from the B cell lineage. Both APRIL and its receptors have been identified on subsets of multiple myeloma (MM) cells that is characterized by malignant proliferation in cells in the bone marrow. We have shown that BION-1301, a first-in-class APRIL-targeting humanized antibody, blocks APRIL-induced MM cell survival and the tumor microenvironment (TMEM). Despite availability of a broad range of new therapies for MM, this type of cancer remains incurable as patients relapse and eventually become refractory to the current therapeutic regimens. We have previously shown that the presence of high levels of APRIL in the bone marrow of patients with MM establishes a protected environment favoring tumor cell survival and proliferation. These effects include the induction of an immunosuppressive environment, secretion of BM niche regulating chemokines and upregulation of anti- apoptotic signaling in the MM cell. We further hypothesize that engaging APRIL with BION-1301 sensitizes MM cells for other MM-targeting therapeutic agents.

Here we present an insight into the mode of action of the BION-1301 parental antibody: anti-APRIL 01A.

Figure 1. anti-APRIL 01A blocks APRIL induced anti-apoptotic signaling

We have generated a panel of APRIL-responsive cell lines, including MM cell lines, and identified a subset of cell lines that were responsive to APRIL treatment. The effect of APRIL treatment on these cell lines was assessed using a variety of functional assays, including cell viability, apoptosis, and cytokine secretion. The results showed that APRIL treatment induced a significant increase in cell viability and a decrease in apoptosis, as measured by Annexin V staining and caspase activity. The selective inhibition of APRIL with anti-APRIL 01A led to a dramatic reduction in cell viability and an increase in apoptosis. These results are consistent with previous reports showing that APRIL is a potent survival factor for MM cells and that APRIL blockade can induce cell death.

Figure 2. anti-APRIL 01A reverses APRIL mediated protection from bortezomib induced MM cell toxicity

Figure 2 demonstrates the effect of APRIL on MM cell viability and sensitivity to bortezomib, a proteasome inhibitor that is commonly used in the treatment of MM. APRIL treatment significantly increased cell viability and protected MM cells from the cytotoxic effects of bortezomib. However, co-treatment with anti-APRIL 01A and bortezomib completely reversed the protective effect of APRIL, restoring cell viability to levels observed in control cells. These results suggest that APRIL may be a key mediator of MM cell survival and that blocking APRIL can sensitizes MM cells to the cytotoxic effects of bortezomib.

CONCLUSIONS: Together, these findings support the potential role of APRIL as a therapeutic target in MM and provide a rationale for the development of APRIL antagonists for the treatment of MM.

Figure 3. APRIL induces immune suppression through IL-10 and PD-L1

Figure 3 shows the effect of APRIL on the production of IL-10 and PD-L1, two key immune suppressive cytokines. APRIL treatment increased the production of IL-10 and PD-L1 in MM cells, which was blocked by anti-APRIL 01A. These results suggest that APRIL may act through the production of IL-10 and PD-L1 to suppress immune responses in MM.

Figure 4. anti-APRIL 01A blocks APRIL induced osteolytic chemokine expression

Figure 4 demonstrates the effect of APRIL on the production of osteolytic chemokines, including MIP-1α and IL-8, which are known to promote bone destruction in MM. APRIL treatment increased the production of MIP-1α and IL-8, which was blocked by anti-APRIL 01A. These results suggest that APRIL may be a key mediator of bone destruction in MM and that blocking APRIL can prevent bone destruction.

Model of Action of BION-1301

BION-1301 blocks APRIL-induced anti-apoptotic signaling, immune suppressive phenotype, and chemokine production associated with multiple myeloma.

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