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Novel therapeutic approach to improve hematopoiesis by targeting MDSCs with the novel Fc-engineered CD33 antibody BI 836858 in MDS

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We recently reported that, the accumulation of myeloid-derived suppressor cells (MDSCs), defined as $CD33^{+}HLA\text{-}DR^{-}Lin^{-}$, play a direct role in the pathogenesis of myelodysplastic syndrome (MDS). In particular, CD33 is greatly expressed in MDSC isolated from patients with MDS and plays an important role in MDSC-mediated hematopoietic suppressive function through its activation by its ligand S100A9. Therefore, we tested the hypothesis that blocking this interaction with a fully human, Fc-engineered monoclonal antibody against CD33 (BI 836858) suppresses CD33-mediated signal transduction and improves the bone marrow microenvironment in MDS. We found that BI 836858 can reduce MDSC by antibody-dependent cytotoxicity (ADCC), which correlated with an increase in granule mobilization and increased cytotoxicity. BI 836858 can also block CD33's downstream signaling and prevent immune-suppressive cytokine secretion, which correlates with a significant increase in the formation of colony-forming unit granulocyte-macrophage (CFU-GM) and burst-forming unit erythroid (BFU-E) colonies. Activation of the CD33 pathway can cause reactive oxygen species (ROS)-induced genomic instability but BI 836858 reduced both ROS and the level of double strand breaks and adducts (measured by comet assay, γH2AX and 8-oxoguanidine). This work provides the ground for the development of a novel group of therapies aimed at MDSC and their signaling with the long term goal of improving hematopoiesis.

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