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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-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 CFU-GM and 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 levels 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

Biography

Jinhong Liu has completed his MD and PhD from University of South Florida and Postdoctoral studies from H. Lee Moffitt Cancer Center. She is a very active physician scientist in the clinical and translational research in the precision medicine.

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