Targeting E-Selectin with GMI-1271 Overcomes Microenvironment-Mediated Resistance to Venetoclax / HMA Therapy

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Introduction
Acute myeloid leukemia (AML) is an aggressive heterogeneous hematologic disease with high mortality in patients older than 60 years. Clinical studies have proven that combinations of FDA-approved Bcl-2 inhibitor, venetoclax and hypomethylating agents (HMA) are highly effective in elderly patients with AML (D’Nardo et al., 2019). Despite improved remission rates, the duration of response is still short. Adhesion to the bone marrow (BM) niche is critical for AML initiation, progression and leukemic stem cells (LSC) survival after induction therapy. The vascular adhesion molecule, E-selectin (E-sel) has crucial roles in BM homing and engraftment in leukemia (Krause et al., 2006). Our hypothesis is that targeting the vascular niche in the BM microenvironment by inhibition of E-sel with GMI-1271 can further improve the venetoclax/HMA therapy for patients with AML. Here, we analyzed the underlying mechanisms of E-sel in AML and AML BM niches.

Models
In vitro
Human AML cells lines
Human umbilical vein endothelial cells (HUVEC)
Human healthy donor derived-mesenchymal stromal cells (MSC)
In vivo
AML-PDX derived from a venetoclax/HMA resistant AML patient harboring FLT3-ITD, NRAS, and GATA2 mutations.

Results

- E-Selectin binding reduces proliferation and increases AML cell dormancy
- E-selectin modulates CKI4/6 expression in AML
- E-selectin modulates AKT activation in EC
- CD44 surface expression in MSC is induced by soluble E-selectin binding

Conclusions
- AML upregulates expressions of E-sel and its active binding molecule, CD15s in EC.
- E-sel binding reduces CDK4/6 expression in AML resulting in diminished AML proliferation and augmented G0G1 cell cycle arrest.
- E-sel modulates BM niche component cells: eNOS in EC and CD44 in MSC.
- Targeting E-sel mobilizes human AML cells and sensitizes them to venetoclax/HMA in a PDX model derived from a patient who had developed resistance to venetoclax/HMA therapy.