Targeting E-selectin with GMI-1271 Overcomes Microenvironment-mediated Resistance to Venetoclax/HMA Therapy

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Disclosures

- Research supported by GlycoMimetics, Inc. and a NCI-CTEP grant.
E-Selectin in AML

- Endothelial (E)-selectin: vascular adhesion molecule expressed by endothelial cells (EC) in response to IL-1, lipopolysaccharide, TNF-α, or IFNγ. Bevilacqua MP. et al., PNAS 1987.


- Elevated soluble E-selectin levels detected in relapsed AML. Aref S. et al., Hematology 2002.


- GMI-1271 (uproleselan) mimics the bioactive conformation of sLeα/β, binds to E-selectin with high affinity (K_D 0.45µM).

- Phase 3 clinical trial ongoing.
Venetoclax (Ven), the highly potent and selective Bcl-2 inhibitor + hypomethylating agents, has revolutionized treatment of AML (FDA approved).

- 60-90% of patients achieve CR (previously 15-30%), but median survival remains unsatisfactory for most patients.
- Bone marrow microenvironment plays critical roles in leukemia initiation, progression and drug resistance.
- LSC survive in the BM niche resulting in subsequent relapse.
Hypothesis

Targeting the BM microenvironment by inhibition of E-selectin in the vascular niche with GMI-1271 improves Ven/HMA therapy in AML.
In Vivo PDX-AML Model (Ven/HMA-resistant)

A PDX model derived from an AML patient harboring FLT3-ITD, NRAS, and GATA2 mutations who initially responded to venetoclax/HMA therapy and then relapsed.
Co-targeting E-selectin and Bcl-2 Significantly Reduces Circulating Leukemia Cells in AML-PDX Model From Patient with Acquired Resistance to Ven/HMA

*\(p<0.05\); **\(p<0.01\); ***\(p<0.001\), Student’s t-test for experiments that compare two groups.
GMI-1271 Combination Significantly Extends Survival in AML-PDX Model From a Patient with Acquired Resistance to Ven/HMA Therapy

Mean survival: VC (86 days), GMI-1271 (91 days), Ven+5Aza (81.5 days), and Combination (106.5 days)

\[ P = 0.015, \text{VC vs. Comb} \]
\[ P = 0.0009, \text{Ven+5Aza vs. Comb} \]
\[ P = 0.03, \text{GMI vs. Comb} \]
Differences in Leukemia Cell Infiltration Confirms Anti-Leukemia Efficacy of the Combination Treatment

Organs (from 3 mice per group) collected one day after last Rx
Co-targeting E-selectin and Bcl-2 Reduces LSC Population

Gated: total hCD45+

CyToF: BM collected one day after last Rx
Combination Treatment is Highly Effective in AML Cells with High Expression of E-selectin Ligand

Gated: total hCD45+

CyToF: BM collected one day after last Rx
Inhibition of E-selectin Decreases Proliferation in Residual Cells after Ven/Aza Treatment

Gating: hCD45+

CyToF: BM collected one day after last Rx
Treatment-Resistant AML Blasts Show Distinct Signaling Pathways

Gating: hCD45+

CyToF: BM collected one day after last Rx

Abstract #2865 (ASH 2020) Zhang W et al
In Vivo PDX-AML Model (Short Term Treatment for 2 days)

- Second AML PDX model (Flt3-ITD and WT1 mutations, sorafenib-resistant)
- PDX mice bearing advanced AML (> 20% human AML cells in circulation)
- Treatment x 2 days only

• AML-PDX injection
• AML Progression (Avg. 21.6% hCD45+)
• CyTOF

Days 0 Post injection  

- Covid19 outbreak: Research suspension
- Rx
- Days 103 117 118 119

- Vehicle control
- GMI-1271
- Ven/HMA(5Aza)
- GMI-1271 + Ven/HMA (5Aza)
E-selectin Inhibition Alters Proliferation of AML Blasts and AML Pro-Survival Signaling Signatures

BM cells were collected after 2 times of Rx
E-selectin Antagonist Mediates Signaling Alterations in AML BM Microenvironment

BM cells were collected after 2 times of Rx.
Summary

- **Co-targeting E-selectin with GMI-1271 and Bcl-2 with Ven/HMA**
  1) reduced AML LSC and AML blasts with high E-selectin ligand expression.
  2) prolonged survival of AML-PDX mice derived from a patient who acquired resistance to Ven/HMA.
  3) Decreased expression of Bcl-xL and Mcl-1 in AML blasts, suggesting a mechanism of overcoming cell intrinsic drug resistance.

- **Inhibition of E-selectin may protect BM niches:**
  1) by blocking NO production through reduction of PI3K-AKT-eNOS phosphorylation in EC.
  2) by promoting MSC pro-survival signaling pathways that can support nonmalignant HSC, resulting in faster recovery and perhaps longer remission duration following Ven/HMA treatment.

- **E-selectin targeting strategy can partially overcome microenvironmental resistance to Ven/HMA-based therapy in AML by leukemia cell autonomous and non-autonomous mechanisms in the BM vascular niche.**
Acknowledgement

MDACC
Michael Andreeff
Bing Z Carter
Muharrem Muftuoglu
Weiguo Zhang
Mahesh Basyal
Po Yee Mak
Lauren Ostermann
Wenjing Tao

GlycoMimetics, Inc.
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