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Kuntal Bhowmick  
Rowan University

Kristy K. Patel  
Rowan University

Suman Pathi  
Rowan University

Subash Jonnalagadda  
Rowan University

Tulin Budak-Alpdogan  
Rowan University

See next page for additional authors  
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**Development of novel dual inhibitor of CXC Chemokine receptor 4 and Mcl-1 against Multiple Myeloma**

Kuntal Bhowmick1, Kristy K. Patel1, Suman Pathi2, Subash Jonnalagadda3-5, Tulin Budak-Alpdogan1, and Manoj K. Pandey1

1Department of Biomedical Sciences, Cooper Medical School of Rowan University, Camden, NJ; 2Department of Chemistry and Biochemistry, Rowan University, Glassboro, NJ; 3Department of Molecular and Cellular Biosciences, Rowan University, Glassboro, NJ; 4Department of Hematology and Oncology, MD Anderson Cancer Center at Cooper, Camden, NJ

Multiple myeloma (MM) is a neoplastic plasma-cell disorder. It is characterized by clonal proliferation of malignant plasma cells in the bone marrow (BM) microenvironment, monoclonal protein in blood or urine, and associated organ dysfunction. The treatment options approved by FDA are immune-modulatory agents, proteasome inhibitors, and autologous stem cell transplantation (ASCT). Unfortunately, MM remains uniformly fatal owing to intrinsic or acquired drug resistance and the median survival time is 3 to 5 years. Thus, there is a great need for novel strategies to combat MM. The intimate relationship of myeloma cells to BM microenvironment is “hallmark of myeloma”. The homing of MM cells to the BM, mediated by the chemokine stromal cell-derived factor-1α (SDF-1α) and its receptor CXCR4 has important functional sequelae. The BM microenvironment constituting cells secrete chemokines, cytokines, and growth factors such as interleukin 6 (IL6), vascular endothelial growth factor (VEGF), SDF-1α, and tumor necrosis factor α (TNFα) etc.1

These growth factors contribute in activation of several signaling pathways including nuclear factor-κB (NF-κB), phosphatidylinositol 3-kinase (PI3K)/Akt, Ras-Raf-MAPK kinase (MEK) extracellular signal regulated kinase (ERK), and the Janus kinase 1 (JAK1) signal transducer and activator of transcription (STAT1). Activation of these pathways has been associated with increased expression of several anti-apoptotic proteins such as Bcl-xL, Bcl-2, XIAP, and MIP-1. Collectively, these discoveries highlight that interaction of MM cells to BM microenvironment not only promote growth, survival and migration of MM cells, but also confer resistance to conventional chemotherapy. We hypothesized that an agent capable of inhibiting the migration of myeloma cells to bone marrow and suppressing the expression of survival protein MM1 would be a better option for MM treatment. We synthesized a novel dual inhibitor of CXCR4 and Mcl-1. In vitro data suggests this molecule inhibits the expression of CXCR4 and Mcl-1 and survival of MM cells.

**Gambogenic acid - A hope for MM**

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**Hypothesis**

- MM cells are highly dependent on the bone marrow (BM) microenvironment for growth and survival.1
- Migration of cells through the blood to the BM niches requires active navigation, a process termed homing.
- One of the most extensively studied chemokines in homing is stromal cell-derived factor-1α (SDF-1α) also known as CXCL12 chemokine ligand 12 (CCL12) and its receptor, CXCR4.2
- The BM microenvironment constituting cells secrete chemokines, cytokines, and growth factors such as interleukin 6 (IL6), vascular endothelial growth factor (VEGF), SDF-1α, and tumor necrosis factor α (TNFα) etc.1

These growth factors contribute in activation of several signaling pathways including nuclear factor-κB (NF-κB), phosphatidylinositol 3-kinase (PI3K)/Akt, Ras-Raf-MAPK kinase (MEK) extracellular signal regulated kinase (ERK), and the Janus kinase 1 (JAK1) signal transducer and activator of transcription (STAT1). Activation of these pathways has been associated with increased expression of several anti-apoptotic proteins such as Bcl-xL, Bcl-2, XIAP, and MIP-1. Collectively, these discoveries highlight that interaction of MM cells to BM microenvironment not only promote growth, survival and migration of MM cells, but also confer resistance to conventional chemotherapy. We hypothesized that an agent capable of inhibiting the migration of myeloma cells to bone marrow and suppressing the expression of survival protein MM1 would be a better option for MM treatment. We synthesized a novel dual inhibitor of CXCR4 and Mcl-1. In vitro data suggests this molecule inhibits the expression of CXCR4 and Mcl-1 and survival of MM cells.

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**Results**

- **Figure 2. A.** GA interacts with CXCR4 and modulates the expression of CXCR4 protein of MM cells
- **Figure 3. A.** GA analog reduces the survival of MM cells. MM cells (RPMI 826 and U266) were treated with different concentration of GA, and its analogs for 8h. Cell viabilities were assessed using MTT assay. As shown in the figure treatment of GA and its analog effectively kill MM cells. Prism software was used to plot the graph. B. Effect of GA on survival protein with the BM microenvironment. MM human RPMI 826 cells were treated with the indicated amount of GA analog for 14h. Treatment of GA analog modulates expression of anti-apoptotic proteins such as Mcl-1, Bcl-xL, and caspase 3.

**Conclusion and future directions**

- **Figure 4.** Our data showed that GA and its analog mediate their effects by targeting MM cells and the BM microenvironment. (A) GA targets CXCR4 receptor, (B) directly inhibits MM cell growth, (C) inhibits angiogenesis, (D) decrease cytokine production and sequestrum such as osteoclastogenesis, and whether inhibits MM cell adhesion to BM accessory cells (E) will be explored.

**References**