Discovery of novel menin-MLL small molecule inhibitors that display high potency and selectivity \textit{in vitro} and \textit{in vivo}


Abstract

Chromosomal translocations that affect the Mixed Lineage Leukemia (MLL) gene result in aggressive acute myeloid and lymphoid leukemias that are resistant to standard chemotherapy. MLL leukemias constitute approximately 5-10\% of acute leukemias and 70\% of acute leukemias in adults and infants, respectively. MLL fusion proteins require menin for leukemogenic activity, and selective disruption of the menin-MLL interaction represents a potential therapeutic approach for the treatment of acute leukemias with MLL rearrangements. Here we describe the characterization of KO-382, a small molecule inhibitor of the menin-MLL interaction, in biochemical, cellular and \textit{in vivo} activity assays.

KO-382 is a potent inhibitor of menin-MLL interaction that binds to menin with a Kd of \(-30\text{ nM}\). It potently inhibits the proliferation of MLL-AF9 transformed leukemic cells with GI50 of \(-30\text{ nM}\) and MLL-fusion cell line MV4-11 with GI50 of \(-30\text{ nM}\). KO-381, an enantiomer of KO-382, is approximately 25-fold less potent, which underscores the specificity of the interaction. KO-382 displays a greater than 50-fold reduction in growth of non-MLL fusion leukemic cell lines and induces regression in a MLL-AF11 mouse xenograft model while KO-381 displays limited activity in the same settings. The anti-tumor activity of KO-382 correlates with target engagement in the tumors. KO-382 demonstrates potent efficacy in an aggressive disseminated leukemic model as measured by significant extension of survival, inhibition of HOXA9 and MEIS1 gene expression and induction of differentiation, as measured by CTD10 expression.

KO-382 is a highly potent and selective inhibitor of the menin-MLL interaction with robust efficacy in subcutaneous and disseminated models of MLL-fusion leukemias. These results demonstrate the potential clinical utility of menin inhibitors in MLL leukemias.

Characterization of the menin-MLL complex

KO-382 demonstrates robust efficacy \textit{in vivo} in MLL-r leukemia model (MV4;11 xenograft)

- Significant efficacy at well-tolerated doses for KO-382 (oral dosing)
  - Regression at 200 mg/kg BID
  - Similar efficacy with QD (200 mg/kg) vs. BID (150 mg/kg/day + 200 mg/kg/day)

- KO-382 displays greater activity than the less active enantiomer KO-381
- Demonstrates that the antitumor activity is result of target inhibition
- KO-381 and KO-382 have similar in vivo exposure

Efficiency in \textit{vivo} correlates with target engagement in tumors

KO-382 demonstrates robust survival benefit in disseminated models of leukemia

Background

MLL-Leukemias are an aggressive type of blood cancer. Predominantly in children and therapy-related leukemias in adults. Chromosomal translocations in the KMT2A (MLL) gene at 11q23 result in MLL fusions with any of 50 partner genes. MLL fusion proteins drive leukemogenesis through de-repression of HOX genes. The leukemogenic activity of MLL fusion proteins is critically dependent on menin binding.

KO-382 is a potent and selective menin inhibitor

- KO-382 is a potent inhibitor of menin-MLL binding and potently inhibits growth of cell lines containing MLL fusions
- KO-382 is selective >50 fold more potent in MLL-r leukemia cell lines
- KO-381 is a less potent enantiomer of KO-382

Efficacy in \textit{vivo} correlates with target engagement in tumors

KO-382 demonstrates robust survival benefit in disseminated models of leukemia

- KO-382 is a potent and selective inhibitor of the menin-MLL interaction.
- KO-382 demonstrates robust, sustained tumor inhibition in subcutaneous and disseminated models of MLL-r leukemias that correlates with target engagement and inhibition of target gene expression.
- Additional efforts underway to assess potential utility of menin-MLL inhibitors in additional hematological malignancies and solid tumor models.

Conclusions

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Chromosomal translocations that affect the Mixed Lineage Leukemia (MLL) gene result in aggressive acute myeloid and lymphoid leukemias that are resistant to standard chemotherapy. MLL leukemias constitute approximately 5-10\% of acute leukemias and 70\% of acute leukemias in adults and infants, respectively. MLL fusion proteins require menin for leukemogenic activity, and selective disruption of the menin-MLL interaction represents a potential therapeutic approach for the treatment of acute leukemias with MLL rearrangements. Here we describe the characterization of KO-382, a small molecule inhibitor of the menin-MLL interaction, in biochemical, cellular and \textit{in vivo} activity assays.

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