SEL120-34A is a selective, nanomolar inhibitor of CDK8

SEL120-34A selectively binds and inhibits CDK8 in a type I mode (Ryzmski et al., Oncotarget, 2017) showing similar activity to other specific CDK6 inhibitors under development: SNK2 (1,567 patent WO2014131518A1) and CCT251454 (Dale et al., Nature Chemical Biology, 2015).

SEL120-34A targets AML cell lines with leukemia stem cell properties

Activated STAT signaling and CD4 expression were previously described as features of leukemia stem cells (LSC) (Kato et al., JMM, 2005; Thomas & Majeti, Blood, 2017) that contribute to AML relapse through expansion of treatment resistant clones. Here, we show that SEL120-34A is especially effective in AML cell lines with characteristics resembling leukemia stem cells where we have low nanomolar activity.adden enrichment analysis (DEAS) of cell lines sensitive to SEL120-34A also shows upregulation of LSC-associated genes that have been linked to intrinsically aggressive disease and survival in AML patients (Rippe et al., Nature Medicine, 2017; Gevensky et al., JAMA, 2015).

SEL120-34A specifically depletes CD34 positive cells and leads to differentiation

Treatment with SEL120-34A results in decreases of CD44 and increase of CD44 surface levels, linking the mechanism of action of SEL120-34A to differentiation. Additionally, gene expression analysis of a LSC-like AML cell line (Wenner et al., Leukemia, 2007) shows that 6 day treatment with the inhibitor leads to decreased expression of LSC-linked genes (EED and LMBR2) downregulation of LSC genes, increased expression of differentiation markers and immune response genes.

SEL120-34A works in synergy with chemotherapy

Clinically relevant, selective treatment with Ara-C followed by SEL120-34A leads to increased death of cancer cells and decreased CD44 after initial evolution of this marker due to chemotherapy treatment.

SEL120-34A is highly active in CD34+ tumors

Efficacy of SEL120 was tested in CD34 enriched or depleted NOLM-16 subcutaneous tumor models. CD34 positive cells initiate most robust tumor growth and SEL120-34A is highly active in those tumors.

SUMMARY

We have shown strong efficacy of SEL120-34A in CD34-positive AML models with molecular characteristics resembling leukemia stem cells.

Mechanism of action of SEL120-34A is factuated through complex transcriptional effects that reprogram LSC-like cells towards differentiation.