131 LEDGF PWWP chromatin tethering

Asset Overview

Product Type	Small Molecule
Indication	Oncology
Current Stage	Hit
Target (MoA)	Inhibition of LEDGF-MLL OR PWWP chromatin binding
Brief Description	LEDGF/p75 is a transcriptional co-activator involved in stress response and critical for the clonal expansion. As full structural characterization is available for LEDGF/P75, inhibition of LEDGF-MLL interaction or PWWP chromatin binding may inhibit oncogenic activity of MLL.
Organization	Center for Drug Design and Discovery

Differentiation

□ **Unmet Needs**

- LEDGF/p75 is a transcriptional co-activator involved in stress response and critical for the clonal expansion. In HoxA9 transcription driven leukemias, function of LEDGF/p75 is critical. Translocations of mixed lineage leukemia (MLL) gene results in acute leukemia with very poor prognosis. MLL, LEDGF/p75, and MENIN form a triple complex that promote leukemogenic activity of MLL-AF9 pairing

□ **Innovations**

- LEDGF/p75 knockout in the hematopoietic system is viable
- The LEDGF/p75-menin binding of fusions is essential for the clonal expansion
- Full structural characterization available
- Could be a promising strategy to inhibit LEDGF/p75/Menin/MLL complex activity that is critical for retaining undifferentiated and highly proliferative state of MLL

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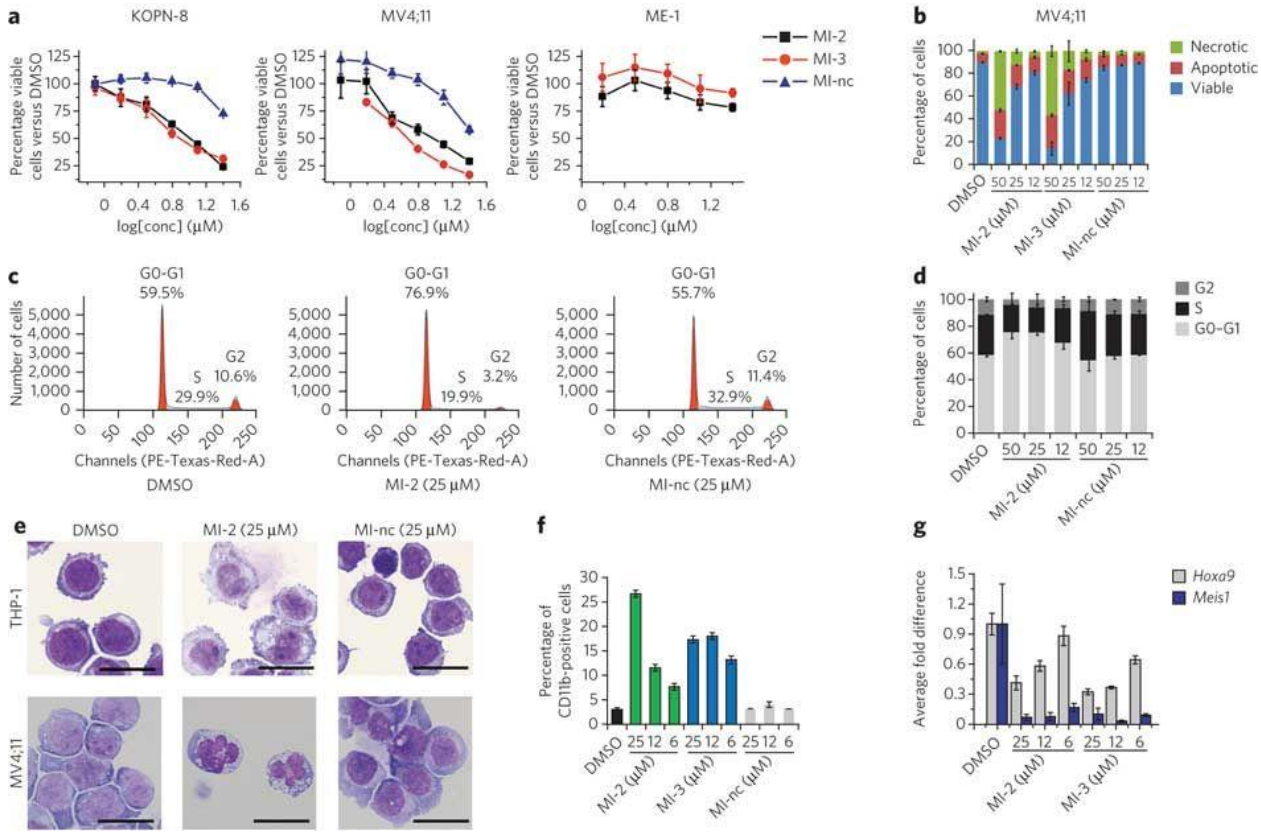
Key Data

Experiments and Results



(a) MTT cell viability assay in the MLL leukemia cells KOPN-8 and MV4;11 treated with MI-2, MI-3 and MI-nc for 72 h. The non-MLL leukemia cell line ME-1 is shown for comparison. Data represent mean values for four samples ± s.d. Experiment was performed three times. (b) Apoptosis and cell death induced by MI-2, MI-3 and MI-nc in MV4;11 cells as detected by flow cytometry using annexin V–propidium iodide staining. Data represent mean values for triplicates ± s.d. (c) Selected histograms from cell cycle analysis performed by FACS after propidium iodide staining in MV4;11 cells treated with DMSO, MI-2 or MI-nc. (d) Dose-dependent effect of MI-2 on cell cycle progression measured by FACS in MV4;11 cells after propidium iodide staining, with MI-nc as a negative control. Data represent mean values for triplicates ± s.d. (e) Wright-Giemsa–stained cytospins on THP-1 and MV4;11 cells after 10 d of treatment with DMSO, MI-2 or MI-nc. Scale bars are 20 μm. (f) Detection of CD11b expression in THP-1 cells assessed by flow cytometry after 6 d of treatment with DMSO, MI-2 or MI-nc. Data represent mean values for triplicates ± s.d. (g) Expression of the HOXA9 and MEIS1 genes normalized to 18S rRNA determined by quantitative RT-PCR in THP-1 cells treated for 6 d with MI-2 and MI-3. Data represent mean values for duplicates ± s.d. Experiment was performed three times. *Nature Chemical Biology* volume 8, pages277–284(2012)

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Intellectual Property

Patent No.	
Application Date	
Status	
Country	

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