Efficacy and Mechansim of Action of the Novel Bromodomain Inhibitor, PLX51107, in B Cell Malignancies

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Background

- BRD4 functions as an important epigenetic regulator of oncogenic transcription pathways.
- Inhibition of BRD4 with small molecule inhibitors has demonstrated activity in B cell malignancies, but the exact mechanism of action is unclear.
- Here we demonstrate the efficacy of PLX51107 across a spectrum of B cell malignancies and the pathways involved

Methods

• A panel of 22 human multiple myeloma (MM) cell lines and 56 B cell lymphoma (BCL) cell lines were evaluated for the effects of PLX51107 on cell proliferation after 5 days of drug exposure.

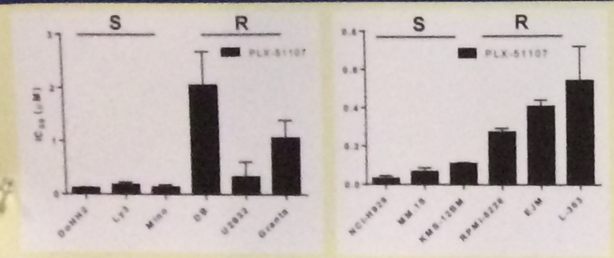
•Sensitive (S) MM (NCI-H929, MM.1S, KMS-12BM) and matched resistant (R) MM (RPMI, EJM, L363); along with sensitive BCL (DoHH2- DLBCL GCB subtype, Ly3- DLBCL ABC subtype, MINO-mantle cell) and matched resistant BCL (DB, U2932, GRANTA) cell lines were selected for mechanism of action studies.

• Cell cycle analysis and induction of apoptosis was performed by FACS after PI or Annexin V FITC staining respectively on cells treated for 72 hours.

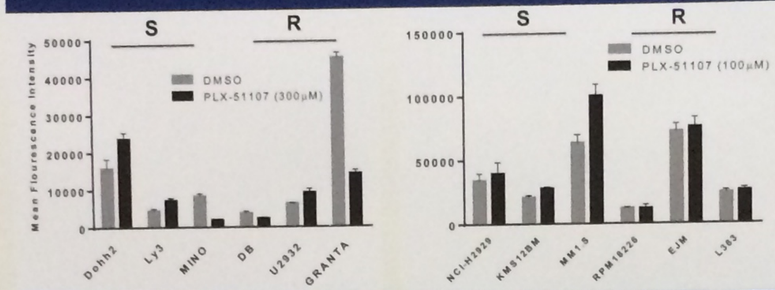
•Cellular senescence was determined by measurement of β-galactosidase activity in cells treated for 7 days (BCL) or 5 days (MM).

•Western blot analyses for c-myc, p-IRAK, p-Iκβα, and p-MAPK Erk1/2 were performed at 4 and 24 hours post treatment.

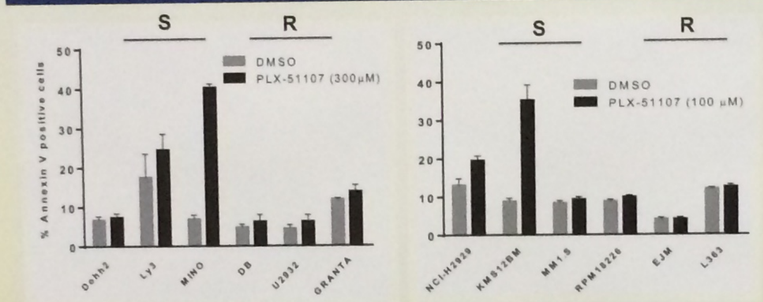
Cell Proliferation



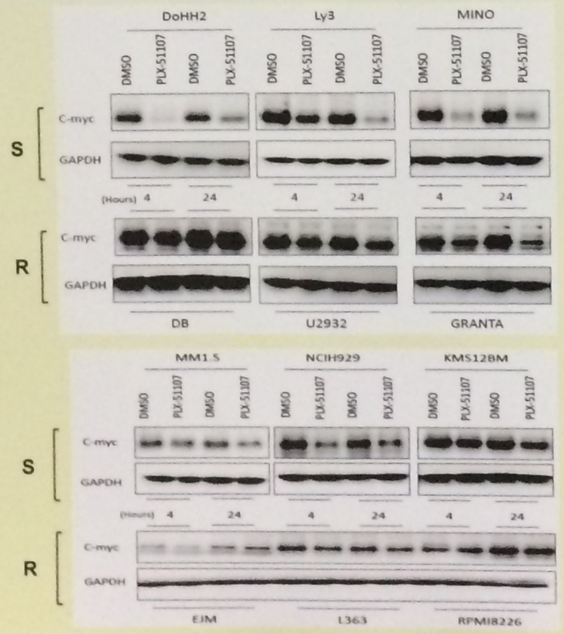
Senescence



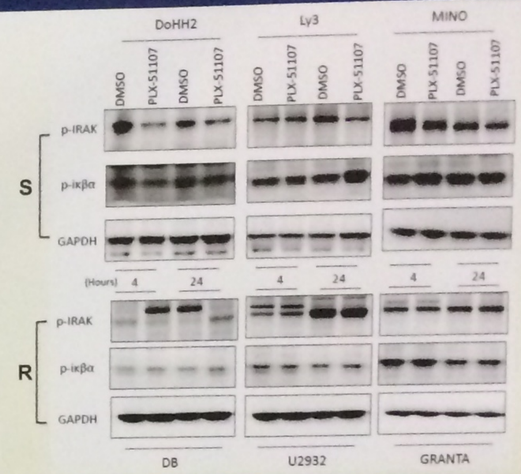
Apoptosis



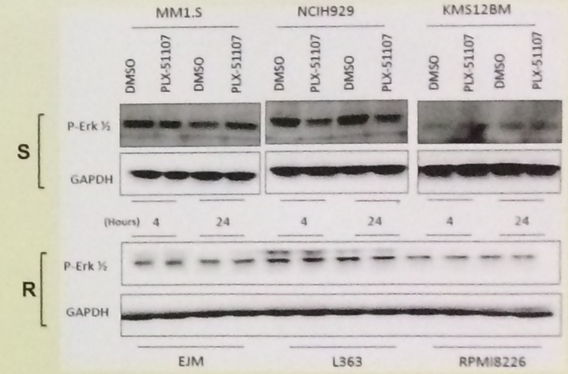
C-myc expression



Lymphoma-MYD88-dependent TLR pathway



Multiple myeloma: NFκB pathway



Conclusions

- PLX51107 demonstrates *in vitro* efficacy through differential mechanisms across a maturational spectrum of B-cell malignancies.
- Treatment of BCL and MM cell cultures results in downregulation of c-myc in sensitive cell lines, consistent with findings from previous BRD4 inhibitors.
- These data suggests treatment with PLX51107 affects the MyD88-dependent toll-like receptor pathway in the BCL cell cultures, while the NFκB pathway is changed in MM cell cultures.

Acknowledgements:
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