# Background

MLN4924 is a potent and selective small molecule NAE inhibitor. In most cancer cells tested, inhibition of NAE leads to induction of DNA repair proteins, resulting in DNA damage and cell death. NEDD-activating enzyme (NAE) is an essential component of the NEDDS contentious pathway that controls the activity of the cullin-RING ubiquitin ligase, thereby affecting the turnover of a subset of proteins that control cell growth and survival pathways. Substrates of cullin-RING ligases have important roles in cellular processes associated with cancer cell growth and survival pathways. The activity of MLN4924 was evaluated against PTPP's in vitro and in vivo panels.

# Methods

The PTPP includes a molecularly characterized panel of xenografts (n=61) representing most of the common types of childhood solid tumors and acute leukemias. The PPTP cell lines was 143 nM (range 15 nM to 678 nM).

# Results

- MLN4924 demonstrated intermediate activity to the response-relative fluorescence values vs. the concentration-response curve for each xenograft.

# Conclusion

- The rIC50 value for the Ewing panel (31 nM) was significantly lower than the median for the other PPTP cell lines.

# Abstract

**ABSTRACT**

**MLN4924 IN VITRO ACTIVITY**

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The median rIC50 value for the Ewing panel (31 nM) was significantly lower than the median for the other PPTP cell lines.

**MLN4924**

- D465 (glioblastoma)
- D458 (glioblastoma)
- GBM2 (glioblastoma)

**D465 (glioblastoma)**

- Controls (gray lines)
- Treatment (black line)

**IN VITRO AND IN VIVO TESTING METHODS**

**PPTP IN VITRO & IN VIVO TESTING METHODS**

- In vitro: In vitro testing was performed using D.M.S.A., a semiconductor fluorescence-based digital image microscopy system that quantifies viable (using fluorescein diacetate dye) and non-viable cells (using ethidium homodimer dye).
- In vivo: Standard PPTP methods for in vivo testing were employed (see "In vivo: Standard PPTP methods for in vivo testing were employed)."

**MLN4924**

- Reduced the overall levels of neddylation in solid tumor xenografts: A single dose of MLN4924 (100 mg/kg S.C.) was administered to mice and tumors harvested at the times shown. Neddylated cullin protein levels were determined by immunoblotting & normalized against β-actin as previously described (Shoos et al, Nat Med 16:320-31, 2010).

**IN VITRO RESULTS AND CONCLUSIONS**

- MLN4924 was well tolerated (4.6% mortality) at the dose (100 mg/kg SQ) and schedule (twice-daily 5x days x 3 weeks) evaluated, and 42 of 45 xenograft models were considered evaluable for activity.
- MLN4924 was determined to have a range from 15 nM to 678 nM. The median relative IC50 value for the Ewing panel (31 nM) had greater observed Ymin values (10.3% and 15.7%, respectively) than the Ewing and ALL cell lines (0.6% and 0.1%, respectively).
- The PPTP's in vitro and in vivo panels.

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The poster will be available at ptp.nchresearch.org