

# Inhibition of NAMPT increases the sensitivity of leukemia cells for etoposide

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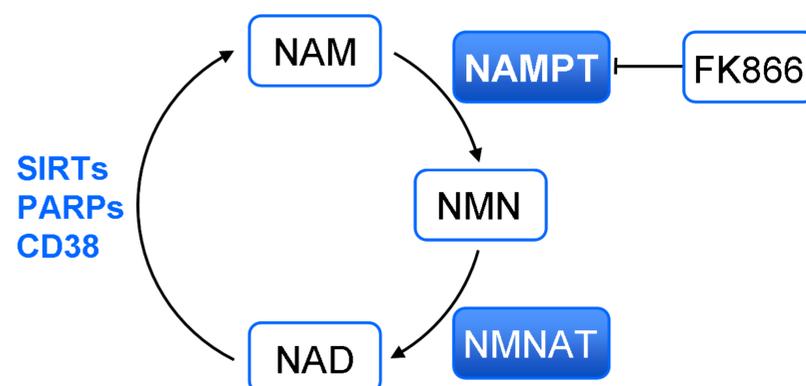
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We have nothing to disclose.

## Background

NAMPT (Nicotinamide phosphoribosyltransferase) catalyzes the rate-limiting step in the NAD-biosynthetic pathway starting from nicotinamide, regulates intracellular NAD concentrations and therefore the activity of NAD-dependent enzymes. Cancer cells are highly dependent on NAD for energy metabolism and DNA repair and are expected to be more susceptible to an inhibition of the NAD synthesis than non-transformed cells.

**Does an inhibition of NAMPT by its specific inhibitor FK866 sensitize leukemia cells for etoposide?**



## Results

### NAMPT expression & activity

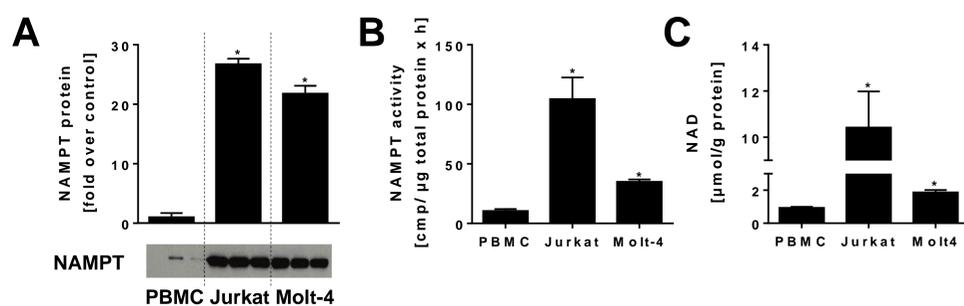


Fig. 1: NAMPT protein level (A), activity (B) and NAD levels were higher in leukemia cell lines than in normal PBMCs (peripheral blood mononuclear cells). \* $p < 0.05$  compared to PBMCs.

### Cell death

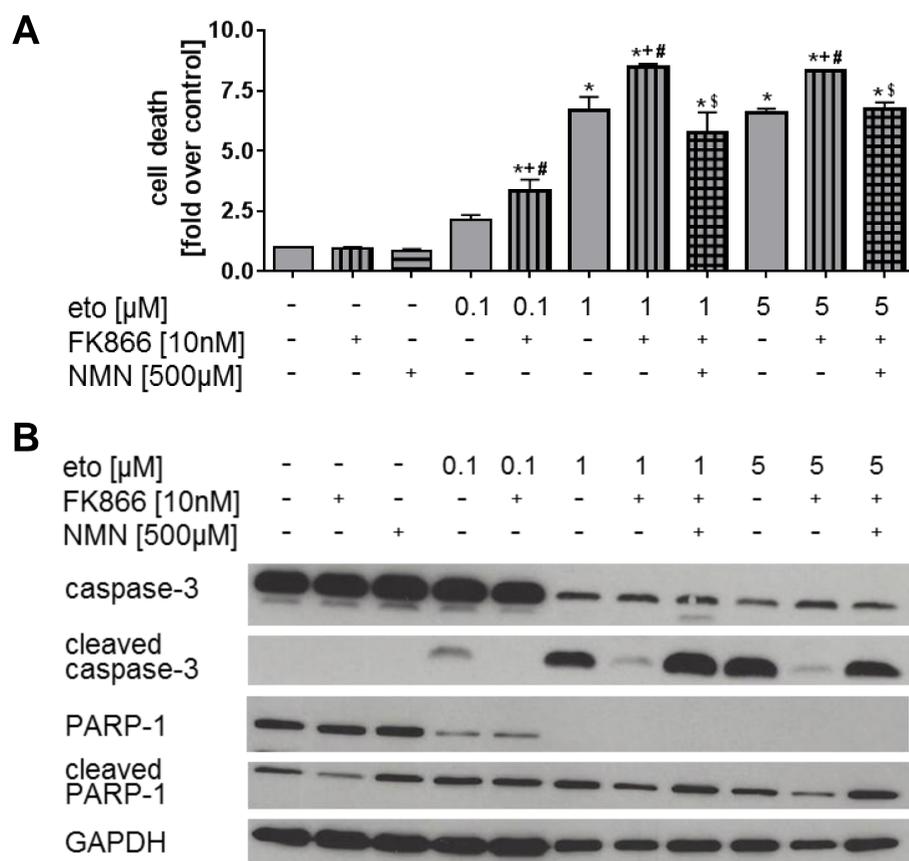


Fig. 2: FK866 increased etoposide-mediated cell death (A) in Molt-4 cells which was not caspase mediated (B). NMN was able to reverse the FK866 effects. Jurkat cells showed the same tendency but were less sensitive to etoposide (not shown). \* $p < 0.05$  compared to control (con), + $p < 0.05$  compared to FK866, # $p < 0.05$  compared to etoposide (eto) alone in equivalent concentration, \$ compared to eto+FK866 in equivalent concentration of eto.

### NAMPT and SIRTUIN expression

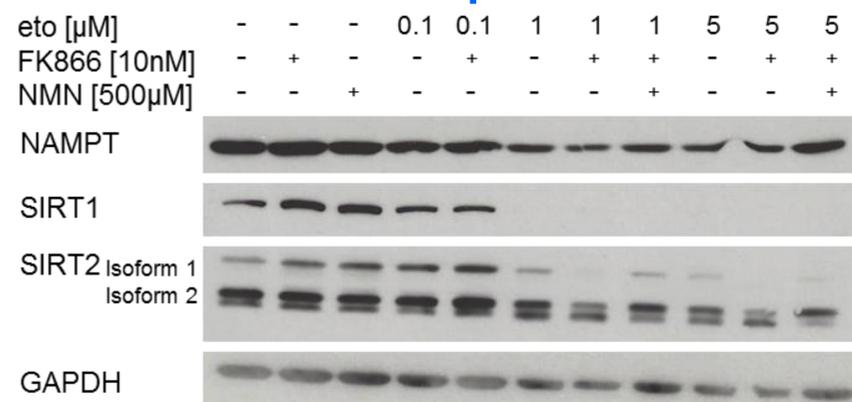


Fig. 3: NAMPT abundance is not influenced after etoposide treatment in Molt-4 cells. Etoposide decreased expression of deacetylases SIRTUIN 1 and 2. The addition of FK866 further decreased expression of SIRTUIN 2 in Molt-4 cells.

### SIRTUIN targets

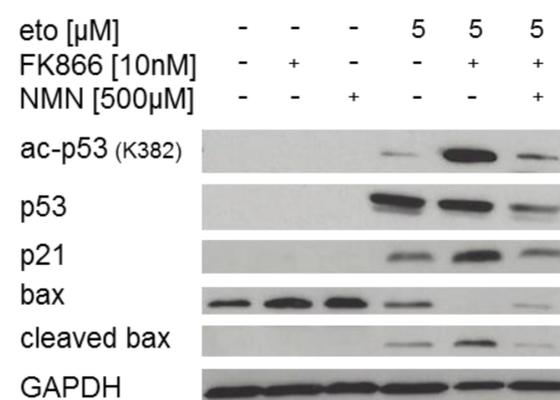


Fig. 4: In etoposide treated Molt-4 cells SIRTUIN2 activated p53 via acetylation and therefore increased the protein level of p21 and cleaved bax. P53 acetylation and the abundance of p21 and cleaved bax were further

increased by the addition of FK866. The effects were counteracted after addition of NMN.

## Conclusion

NAMPT protein level, activity and NAD level were higher in leukemia cell lines than in normal PBMCs. Inhibition of NAMPT in etoposide incubated leukemia cells caused increased cell death compared to etoposide alone. The combination of FK866 and etoposide activated p53 and thus p21 and cleaved bax. Combining FK866 and etoposide could therefore be a novel therapeutic strategy to enhance the efficacy of etoposide against leukemia cells.