Abstract # 1358

p21 activated kinase 4 (pak4) as a novel therapeutic target for non-hodgkin's lymphoma

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ABSTRACT

The p21-activated kinase 4 (PAK4) is a key downstream effector of the Rho GTPase family and is over-expressed in many different cancer types[1]. PAK4, by virtue of its ability to engage multiple ligands, regulates a repertoire of signaling pathways. A survey of non-Hodgkin's lymphoma (NHL) cell lines shows that there is an increase in PAK4 mRNA and protein expression not in normal peripheral lymphocytes (PBL). PAK4 RNA interference suppresses lymphoma cell proliferation indicating to a novel role for PAK4 in promoting NHL cell growth. Here we examined the impact of the dual PAK4 and NAMPT allosteric modulators (KPT-8752 and KPT-9274) on NHL proliferation both in vitro and in vivo.

METHODS

WSU-FSCCL (representing follicular small cell cleaved lymphoma) and WSU-DLCL2 (diffused large B-cell lymphoma) were exposed to increasing concentrations of different compound analogs in the presence or absence of CHOP (used at IC_{25}) for 72 hrs. Following combination treatment viability was evaluated using Trypan Blue and apoptosis was analyzed using 7AAD. Molecular changes were evaluated using immunoblotting and RT-PCR. The efficacy of these compounds were evaluated in sub-cutaneous and disseminated xenograft models of NHL.

RESULTS

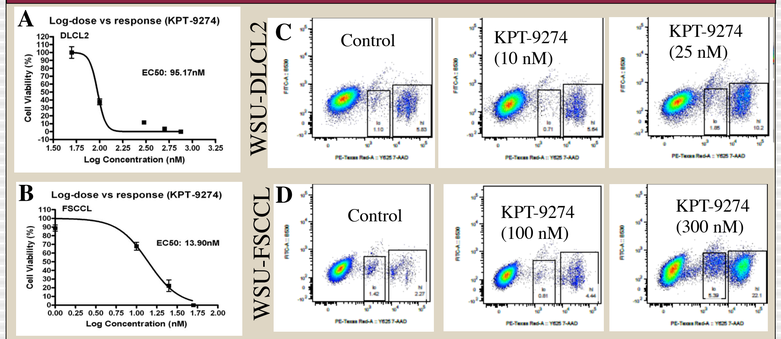

Figure 1. KPT-9274 suppress growth and induce apoptosis in NHL cell lines. [A and B] WSU-DLCL2 and WSU-FSCCL were seeded in duplicate in 24 well plates at $2x10^5$ cells/ml. and were exposed to different concentrations of KPT-9274. Cell viability was plotted against concentration after being counted daily for 72 hours using Trypan Blue. **[C and D]** Apoptosis analysis using 7AAD assay.

RESULTS

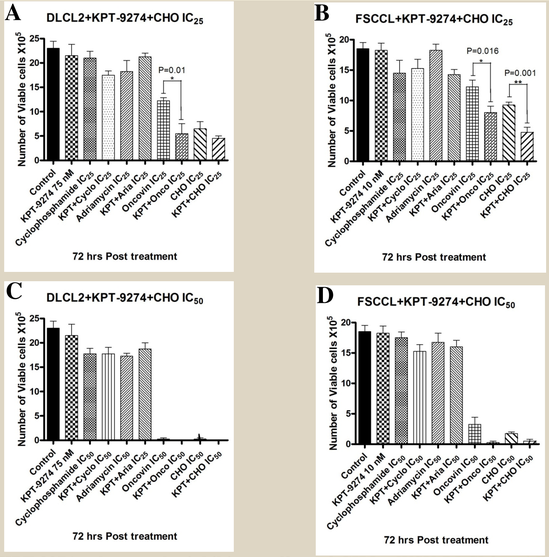

Figure 2. KPT-9274 enhances the inhibitory effect of CHO. WSU-DLCL2 and WSU-FSCCL were seeded in duplicate in 24 well plates at $2X10^5$ cells/ml. Viability was evaluated using Trypan blue exclusion test. **[A and B]** CHO used at IC_{25}; **[C and D]** CHO used at IC_{50}

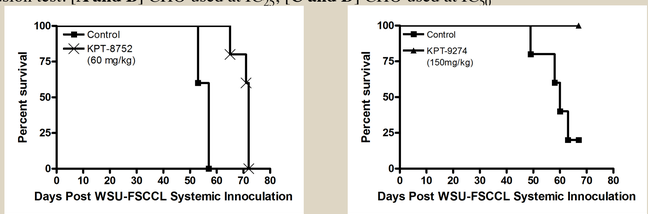

Figure 3. KPT-8752 and KPT-9274 increase host life span of NHL brain- disseminated model. WSU-FSCCL cells was inoculated in the tail vein of mice at a density of $10x10^5$ cells per mouse. One week later, eight mice each were treated with either vehicle or as indicated. (KPT-9274 study still ongoing)

RESULTS

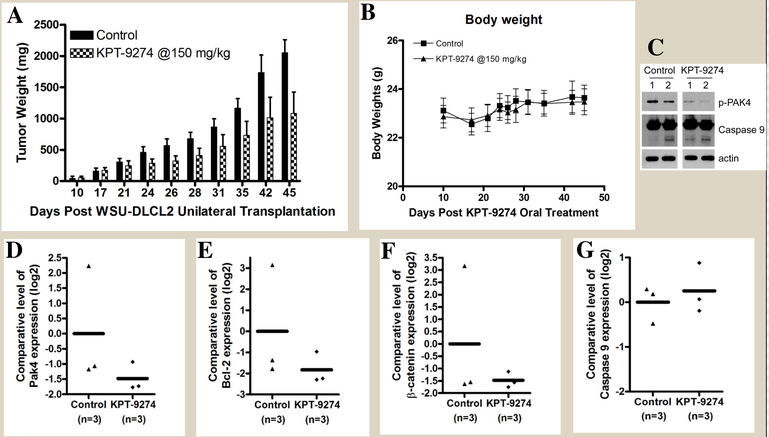

Figure 4. KPT-9274 significantly delayed NHL tumor growth. **[A and B]** WSU-DLCl2 tumors were implanted subcutaneously into the flank of 12 female ICR-SCID mice. Ten days post implantation, mice were divided into two groups. KPT-9274 was administered to 6 mice at a dose of 150 mg/kg orally daily for five days per week for four weeks. Tumor and Body weight was recorded 3 days per week. Three days post treatment, protein and RNA was isolated from 4 tumors (data for three shown here) in each group and subjected to western blot **[C]** and RT-PCR analysis **[D-G]**.

CONCLUSIONS

This is the first study demonstrating a role for PAK4 in diffused large B-cell and follicular small cell cleaved NHL

Our data shows that inhibition of PAK4 could become a viable therapy for NHL either alone or in combination with CHOP

Reference: Aboukameel A et al. Mol Cancer Ther. 2017 ;16(1):76-87

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