In vivo efficacy of the PAK4 Allosteric Modulator, KPT-9274, against a triple negative breast cancer model.

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INTRODUCTION

The p21-activated kinases (PAKs) belong to a family of serine threonine kinases that promote cell survival and play an important role in cell proliferation, cell cycle regulation, and cell shape determination. There are six mammalian PAK proteins which can be subdivided into two groups by sequence homology and mode of activation. Group A PAKs consisting of PAK 1, 2 and 3 and Group B PAKs consisting of PAK 4, 5 and 6. We have found that PAK4 protein levels are elevated in breast cancer, including Her2 positive and triple negative breast cancers. When it is expressed at low levels in normal mammary tissue, making it an attractive drug target. PAK inhibitors are being tested for effectiveness against solid tumors, but generation of highly specific PAK4 inhibitors has been a challenge. Furthermore, PAK4 has been reported to have kinase-independent functions. Therefore inhibiting its kinase activity alone might not be sufficient in blocking its lymphotoxic potential. Our lab has previously reported the effectiveness of PAK4 allosteric modulators (KPT-8752 and KPT-9274) against multiple breast cancer cell lines. These novel PAK4 inhibitors reduce steady state protein levels and were able to block cell growth cell migration and induce apoptosis in breast cancer cell lines, without affecting the control cells. Here, we tested the efficacy of 1 of our genetically modified PAK, KPT-9274 against tumors formed by the triple negative breast cancer cell line, MDA-MB-231. Following six weeks of treatment with orally administered KPT-9274 (150 mg/kg bidx4), there was almost a five-fold reduction in tumor volume and tumor weight in the treatment group as compared to the control group (Average Tumor Volume in Control group, 533 ± 93 mm³, S.E., Average Tumor Weight in Treatment group, 120 ± 15 mg, S.E.; Average Tumor Weight in Control group, 36 ± 15 mg, S.E.). Average Tumor Weight in Treatment group, 61.4 ± 4.6 S.E.).

PAK4 protein levels upregulated in triple negative breast cancer cell lines

Fig 1. PAK4 protein levels upregulated in triple negative breast cancer cell lines

PAK4 Allotrophic Modulators block cell growth in triple negative breast cancer cell lines

Fig 2. Treatment with PAMs block cell growth of triple negative breast cancer cells

PAK4 Allotrophic Modulators induce apoptosis in triple negative breast cancer cells

Fig 3. PAMs induce apoptosis in triple negative breast cancer cells

PAK4 Allotrophic Modulators block cell migration in triple negative breast cancer cell lines

Fig 4. Treatment with PAMs impair motility of triple negative breast cancer cells

CONCLUSIONS

- PAK4 plays an important role in driving MDA-MB-231 tumor growth.
- Treatment with orally administered KPT-9274 blocks PAK4 protein levels and significantly reduces tumor load in athymic mice.
- Triple negative breast cancer cells, MDA-MB-468 and SUM159, expressing high levels of PAK4 respond effectively to KPT-9274. In vivo with significant reduction in cell proliferation, cell migration, and induction of apoptosis.
- Orally available PAK4 inhibitor KPT-9274 can be utilized as a potential clinical agent for triple negative breast cancer treatment which form aggressive tumors and have a poor prognosis.

FUTURE DIRECTIONS

- Understand the mechanism of action of PAK4 driving tumor growth in breast cancer.
- Analyze in vivo efficacy of KPT-9274 on additional triple negative breast cancer models.
- Validate the use of PAK4 targeting compounds as a clinical method for triple negative breast cancer treatment.