

POSTER PRESENTATION

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# Purine nucleoside phosphorylase inhibitors - an immunotherapy with novel mechanism of action for the treatment of melanoma

Shanta Bantia

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## Introduction

Contrary to expectations based on the immuno-compromised clinical phenotype of the PNP-deficient patients, the present study demonstrates that PNP inhibitors (PNPi) can activate immune cells that can help mount a robust antitumor response. PNP deficiency in humans lead to elevation of plasma guanosine [1]. In the present study, we demonstrate that guanosine can activate toll like receptor 2 (TLR2) and TLR4. Powerful immune-stimulatory properties of TLR2 and TLR4 agonist have been exploited for their potential as anti-cancer agents and as an adjuvant in cancer vaccines.

## Method

TLR stimulation is tested in-vitro by assessing NF- $\kappa$ B activation in HEK293 cells expressing a given TLR. In mouse melanoma model, cancer cells were injected subcutaneously and treatment with the NTR001 was initiated on day 6 after injection of tumor cells. Tumor volume and survival were recorded every 3-4 days. Mouse tetanus toxoid vaccine model was used to evaluate the adjuvant effect of NTR001.

## Results

Guanosine (100  $\mu$ M) exhibits a significant stimulatory effect on human TLR2 and TLR4 ( $p < 0.0001$  vs vehicle), alone and in combination with PNPi, NTR001 (10  $\mu$ M). Guanosine demonstrates no effect on TLR3, TLR5, TLR7, TLR8 and TLR9. NTR001 as single agent demonstrates no effect on any of the TLRs. Treatment with NTR001 at doses 30 mg/kg every other week given p.o. and 5 mg/kg given every day in drinking water resulted in a significant decrease in tumor volume compared to

the vehicle treated group (30 mg/kg and 5mg/kg  $p < 0.05$  vs vehicle). Twenty percent of mice survived in the 5 mg/kg dose group whereas no mice survived in the vehicle and 30 mg/kg dose groups. The immune potentiating effect of NTR001 was further confirmed in mouse tetanus toxoid model where it demonstrated increase in both antibody titers and interferon-g levels.

## Conclusion

PNP inhibitors represent a novel approach, to enhance the immune system through activation of TLR2 and TLR4, for the treatment of melanoma and other malignancies. Combinations of NTR001 and/or guanosine with other cancer immunotherapies such as checkpoint modulators, CTLA-4 antagonist, PD-1 antagonist, and IDO-1 inhibitors will be explored further.

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Nitor Therapeutics, Birmingham, AL, USA



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