

Title: B7-H3 Tri-specific Killer Engager Elicits Robust Prostate Cancer Patient NK Cell Activity in vitro

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Introduction: Prostate cancer (PCa) is the leading cause of cancer deaths in men. PCa therapy includes androgen deprivation (ADT). While some patients initially respond to ADT(hormone sensitive), eventually PCa becomes hormone-resistant. There is growing interest for immune engagers to treat PCa patients. Although PCa is a typically immunologically cold environment, we recently published that NK cells are still able to infiltrate and improve patient overall survival (OS). We developed a NK cell engager to improve tumor infiltration and killing. The Tri-specific Killer Engager (TriKE) utilizes an anti-CD16 component to engage NK cells and stimulate cytokine activity, an IL-15 moiety to stimulate NK cell proliferation, and an anti-tumor component to direct the NK cell to its target. Our molecule targets B7-H3 on the tumor; a highly expressed antigen that is rarely expressed in normal tissue.

Methods: We compared B7-H3 TriKE's ability to elicit a robust NK cell response in healthy, hormone-sensitive, and hormone-resistant donor PBMCs. Experiments performed included NK cell inflammatory cytokine production and degranulation assays to determine functional response, as well as proliferation assays to determine NK cell expansion. Additionally, a 42-panel cytometry time-of-flight (CyTOF) was performed to detect differences in NK cell surface marker expression between donor groups.

Results: We found that between PCa patient groups, there are few differences between the surface marker expression of NK cells. However, we were able to detect a trend towards an increase of NKG2A in hormone-resistant NK cells, a surface marker responsible for inhibiting NK cell effector response. We also saw that B7-H3 TriKE was able to elicit robust cytokine production, degranulation, and proliferation of NK cells between donor groups, indicating that B7-H3 TriKE is able to rescue NK cell function across both hormone states of PCa.

Conclusions: While hormone-resistant patients tend to have poorer prognosis, and may have an increase in NK cell inhibition markers, the B7-H3 TriKE is able to rescue lost function that may come with the state of the disease, holding promise for potential future treatment. Further experiments to demonstrate any differences in the cytotoxic effect of donor NK cells between groups are pending, including whether B7-H3 TriKE can initiate a strong killing effect like that seen with healthy donor PBMCs.