

1170 **EGFR-TA:RNA: MULTIMODAL MECHANISM OF ACTION POTENTIATES IMMUNE CHECKPOINT INHIBITOR ACTIVITY**

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Background The discovery and development of immune checkpoint inhibitors (ICIs) revolutionized cancer treatment and cancer immunotherapy. However, the majority of patients with metastatic disease do not achieve durable response following treatment with ICIs, highlighting the unmet need for effective cancer therapeutics. TargImmune's novel platform technology, Ta:RNAs, consists of targeted nanoparticle drugs, in which polyinosinic polycytidylic acid (pIC), a Pattern Recognition Receptor (PRR) agonist, is formulated with a non-viral vector. The non-viral vector comprises linear polyethyleneimine (LPEI) and polyethylene glycol (PEG), linked to the tumor-targeting moiety EGF. Unlike other PRR inducers under development, which are delivered intratumorally or intramuscularly, the Ta:RNA polyplex is designed for systemic administration: the nanoparticles are targeted to tumors that overexpress EGFR, and the pIC enters the cancer cells by receptor-mediated internalization. Furthermore, while other PRR agonists act as adjuvants, the Ta:RNA polyplex has strong cytotoxic and immunomodulatory effects, displaying a multimodal mode of action that harnesses the body's antiviral defenses to fight cancer.

Methods The anti-tumor efficacy and complex mode of action of EGFR-targeted Ta:RNA polyplex (EGFR-Ta:RNA) were extensively studied *in vitro* and *in vivo*. *In vitro*, EGFR-Ta:RNA potency and specificity was established by comparing the responses of high-EGFR-expressing cancer cells versus low-EGFR-expressing control cells using a cytotoxicity assay. The effects of EGFR-Ta:RNA alone or in combination with Nivolumab on human PBMC activation were also measured. *In vivo* efficacy was studied in an aggressive syngeneic experimental lung metastasis mouse model overexpressing human EGFR, in which EGFR-Ta:RNA alone was compared to the combination of EGFR-Ta:RNA with anti-PD-1 antibody treatment.

Results

Our EGFR-TA RNA nanoparticles induced cytotoxicity and proinflammatory cytokine (RANTES/CCL5, IP-10) secretion selectively in EGFR-overexpressing cancer cells, *in vitro*. Supernatant from EGFR-overexpressing cancer cells treated with EGFR-Ta:RNA enhanced the activation of human PBMCs, and this was further potentiated by combination treatment with anti-PD-1 antibody Nivolumab, demonstrated by increased INF γ secretion. Systemic administration of EGFR-Ta:RNA in the experimental lung metastasis mouse model led to potent anti-tumor activity, while anti-PD-1 antibody as a single therapy did not have any effect on mouse survival. In contrast, the combination of EGFR-Ta:RNA with an anti-PD-1 antibody exerted a profound effect and further increased the survival of the mice in comparison to EGFR-Ta:RNA alone.

Conclusions

EGFR-Ta RNA nanoparticles provide a multimodal anti-tumor approach by inducing targeted tumor cytotoxicity and anti-tumor immunity. This approach has been shown to potentiate anti-PD-1 antibodies in an experimental lung metastasis mouse model.

Ethics Approval This study was approved by the Hebrew University of Jerusalem Institutional Animal Care and Use Committee, approval number: NS-20-16089-5

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