Delivery of TLR7 agonists by Deep-Primed™ T cells induces immune activation and improves anti-tumor activity in mice while circumventing systemic toxicity

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Introduction

TLR7 agonists boost immune responses in the tumor microenvironment (TME), primarily through dendritic cell (DC) engagement, enhancement of antigen presentation and T cell co-stimulation. However, multiple TLR agonists have displayed unfavorable PK/PD profiles and considerable toxicities upon systemic administration. To overcome these limitations, we designed a T cell mediated delivery system for TLR7 agonists that targets the TME and the lymphatic system to maximize efficacy while avoiding systemic toxicities. Torque’s Deep TLR Priming™ T cell technology enhances T cell function through tethering of immune modulators to the T cell before adoptive cell transfer (ACT) and uses Torque’s multi-targeted T cell (MTC) platform to prime the T cells against multiple tumor antigens. By transporting the immunomodulators to antigen-expressing tissues, Deep-Primed™ MTCs focus their effect on desired locations. Here, we show how Deep TLR Primed T cells delivering TLR7 agonists induce potent immune cell activation in the TME and elicit exquisite anti-tumor efficacy without overt toxicity.

Materials and experimental design

TLR7 agonists and several liposomal formulations were screened for optimal T cell tethering and release, measured by HPLC.

1. Deep TLR7 agonist T cells contain TLR7 agonist loaded liposomes and display slow payload release over time

2. Deep TLR Priming increases T cell expansion in vivo and reduces PD-1 expression

3. TLR7 agonist delivery enriches pDCs in draining LNs as well as endogenous CD8 T cells and MDCSCs in tumors

4. Deep TLR Primed T cells promote tumor growth inhibition and extend host survival

Key findings

• Torque’s Deep TLR Primed T cells release a potent small molecule agonist of TLR7 over an extended period of time.

• Deep TLR Primed T cells strongly improves tumor growth inhibition and host survival over controls in the murine B16-F10 model.

• Deep TLR Primed T cell expansion exceeds that of CD8 T cells alone or co-administered with TLR7 agonist. PD-1 downregulation suggests reduced exhaustion of Deep TLR Primed T cells vs. controls.

• TLR7-mediated agonist delivery increased pDCs in draining lymph nodes and endogenous CD8 T cells in tumors, consistent with the known effects of TLR7 agonist in vivo (Mouriès et al. 2008).

• Deep TLR7-mediated agonist delivery increased MDCSC content in the TME which may be beneficial given TLR7 agonist is known to convert MDCSCs into functional APCs (Spinetti et al. 2016).

• Deep TLR Primed T cells caused no significant weight loss. Transient plasma levels of pro-inflammatory cytokines (TNFα and IL-6 not shown) remained below 5% of known toxic levels (Kolar et al. 2014, Bandell et al. 2009, Tateishi et al. 1996). This suggests that our Deep TLR Primed T cell therapy has the potential to be efficacious and well tolerated.