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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Torque Deep TLR Primed™ T cell product

Deep TLR Primed T cell

Introduction

TLR 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 stimulation. However, multiple TLR agonists have displayed unfavorable PK/PD profiles and considerable toxicities upon stimulation. In vivo tumor efficacy without overt toxicity.

Figure 1. Deep TLR Primed T cells release a potent TLR agonist over an extended period of time. (A) Torque TLR agonist A displays single-potency in stimulating CD4+ T cells in ex vivo antigen-presenting cells. Each group represents the mean ± SEM of 3 separate experiments. n = 3. (B) PMEL CD8 T cells specific for the B16 mouse melanoma. CD8 T cells were stimulated with Torque Priming POM (10 μg/mL) for 7 days. The total cell yield was confirmed by trypan blue exclusion. (C) CD8 T cells were cultured with Torque Priming POM (10 μg/mL) and LPS (100 ng/mL) for 24 h. IFNγ levels were assessed by immunoassay. Data are shown as mean ± SEM of 3 separate experiments.

Materials and experimental design

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

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

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

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

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

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

5. Deep TLR shows low potential toxicity

Key findings

- Torque’s Deep TLR Primed T cells release a potent small molecule agonist of TLR7 over an extended period of time.
- ACT of 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 the TLR agonist. PD-1 downregulation suggests reduced exhaustion of Deep TLR Primed T cells vs. controls.
- Deep TLR-mediated agonist delivery increased pDCs in draining lymph nodes and endogenous CD8 T cells in tumors, consistent with the known effects of TLR7 agonists in vivo (Mouries et al. 2003).
- Deep TLR-mediated agonist delivery increased MDSC content in the TME which may be beneficial given TLR7 agonist is known to convert MDSCs into functional APCs (Spinetti et al. 2016).
- Deep TLRPrimed 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 (Boroujerdi et al. 2014, Brand et al. 2009, Tateda et al. 1996). This suggests that our Deep TLR Primed T cell therapy has the potential to be efficacious and well tolerated.

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