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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™ T cell technology enhances T cell function through tethering of immune modulators to systemic toxicities. Torque’s Deep™ TME and the lymphatic system to maximize efficacy while avoiding

Materials and experimental design

TLR7 agonists and several liposomal formulations were screened for optimal T cell tethering and release, measured by HPLC. Formulations with desired characteristics were furthered to mature PMEL CD8 T cell specific for the B16-F10 melanoma antigen gp100 to generate Deep TPRIMED T cells. Following ACT into an immunocompetent syngeneic mouse model, the T cell product was evaluated for efficacy and immune cell activation.

Key findings

Torque’s Deep-Primed T cells release a potent small molecule agonist of TLR7 over an extended period of time (Fig. 1). TLR7 agonist A displays a high potency in stimulating CD8+ presentation in vivo even in the presence of endogenous CD8+ T cells. Deep™ T cells mediate delivery of TLR7 agonist to the TME which may be beneficial given TLR7 agonism in vivo (Mouries et al. 2008). Deep™ T cells promote tumor growth inhibition and extend host survival (Fig. 4). Deep-Primed™ T cells mediate superior tumor growth inhibition in the B16 melanoma syngeneic mouse model. Experimental setup as in Fig. 2. PD-1 downregulation suggests reduced exhaustion of Deep PRIMED T cells vs. controls. Deep™ T cells mediated agonist delivery increased pDCs in draining lymph nodes and endogenous CD8 T cells in tumors, consistent with the known effects of TLR7 agonism in vivo (Mouries et al. 2008). Deep™ T cells caused no significant weight loss. Transient plasma levels of pro-inflammatory cytokines (TNFs and IL-6 not shown) remained below 5% of known toxic levels (Borsboom et al. 2014, Brand et al. 2009, Tateda et al. 1996). This suggests that our Deep PRIMED T cell therapy has the potential to be efficacious and well tolerated.

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Figure 1. Deep TLR Primed T cells release a potent TLR7 agonist over an extended period of time. A) Torque TLR7 agonist A displays a high potency in stimulating CD8+ presentation in vivo even in the presence of endogenous CD8+ T cells. Deep™ T cells mediate delivery of TLR7 agonist to the TME which may be beneficial given TLR7 agonism in vivo (Mouries et al. 2008). B) Deep™ T cells promote tumor growth inhibition and extend host survival (Fig. 4). Deep-Primed™ T cells mediate superior tumor growth inhibition in the B16 melanoma syngeneic mouse model. Experimental setup as in Fig. 2. PD-1 downregulation suggests reduced exhaustion of Deep PRIMED T cells vs. controls. Deep™ T cells mediated agonist delivery increased pDCs in draining lymph nodes and endogenous CD8 T cells in tumors, consistent with the known effects of TLR7 agonism in vivo (Mouries et al. 2008). Deep™ T cells caused no significant weight loss. Transient plasma levels of pro-inflammatory cytokines (TNFs and IL-6 not shown) remained below 5% of known toxic levels (Borsboom et al. 2014, Brand et al. 2009, Tateda et al. 1996). This suggests that our Deep PRIMED T cell therapy has the potential to be efficacious and well tolerated.

Figure 2. Deep TLR Primed™ T cells mediate superior tumor growth inhibition in the B16 melanoma syngeneic mouse model. Experimental setup as in Fig. 2. PD-1 downregulation suggests reduced exhaustion of Deep TPRIMED T cells vs. controls. Deep™ T cells mediated agonist delivery increased pDCs in draining lymph nodes and endogenous CD8 T cells in tumors, consistent with the known effects of TLR7 agonism in vivo (Mouries et al. 2008). Deep™ T cells caused no significant weight loss. Transient plasma levels of pro-inflammatory cytokines (TNFs and IL-6 not shown) remained below 5% of known toxic levels (Borsboom et al. 2014, Brand et al. 2009, Tateda et al. 1996). This suggests that our Deep PRIMED T cell therapy has the potential to be efficacious and well tolerated.

Figure 3. Deep TLR Primed™ T cells mediate superior tumor growth inhibition and extend host survival (Fig. 4). Deep-Primed™ T cells mediate superior tumor growth inhibition in the B16 melanoma syngeneic mouse model. Experimental setup as in Fig. 2. PD-1 downregulation suggests reduced exhaustion of Deep PRIMED T cells vs. controls. Deep™ T cells mediated agonist delivery increased pDCs in draining lymph nodes and endogenous CD8 T cells in tumors, consistent with the known effects of TLR7 agonism in vivo (Mouries et al. 2008). Deep™ T cells caused no significant weight loss. Transient plasma levels of pro-inflammatory cytokines (TNFs and IL-6 not shown) remained below 5% of known toxic levels (Borsboom et al. 2014, Brand et al. 2009, Tateda et al. 1996). This suggests that our Deep PRIMED T cell therapy has the potential to be efficacious and well tolerated.