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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Deep TLR Agonist

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 is achieved. Multiple TLR7 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 technology enhances T cell function through tethering of immune modulators to the T cell before adoptive cell transfer (ACT) and uses Torque’s multi-channel delivery system, Torque’s Deep TLR Primed™ T cells, to deliver the T cell before adoptive cell transfer (ACT) and uses Torque’s multi-channel delivery system. An Agonist release from Deep TLR Primed™ T cells, performed using Torque’s Priming process, was determined by HPLC. The next day, the cells were thawed and activated using Torque’s Priming process, performed using Torque’s Priming process, to determine the mass balance over time. The metabolization of the agonist remained negligible.

Materials and experimental design

TLR7 agonists and several liposomal formulations were screened for agonist release. The agonist release from Deep TLR Primed™ T cells, performed using Torque’s Priming process, was determined by HPLC. The next day, the cells were thawed and activated using Torque’s Priming process, performed using Torque’s Priming process, to determine the mass balance over time. The metabolization of the agonist remained negligible. TLR7 agonists were isopropyl dimethylammonium phosphonoformate (R3) KRJ2-110, PMEL only, and soluble KRJ2-110. Agonist release from Deep TLR Primed™ T cells was determined by HPLC to determine the mass balance over time. The metabolization of the agonist remained negligible.

Key findings

• Torque’s Deep TLR Primed™ T cell product targets 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 product expands that of CD8 T cells alone or co-administered with the TLR7 agonist. PD-L1 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 agonist in vivo (Mourias et al. 2008).

• Deep TLR-mediated agonist delivery increased MDCS content in the TME which may be beneficial given TLR7 agonist is known to convert MDCS into functional APCs (Sinistri 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 (Bosom 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.