Deep TLR Primed™ T cells induce potent anti-tumor activity without systemic toxicity

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Publication date: 2019

Document Version
Publisher's PDF, also known as Version of record

Link back to DTU Orbit

Citation (APA):
Deep TLR Primed™ T cells induce potent anti-tumor activity without systemic toxicity

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Abstract

TLR agonists have been shown to augment immune responses in the tumor microenvironment (TME). The agonists work primarily through two mechanisms: antigen presenting cell (APC) engagement and enhancement followed by T cell co-stimulation. However, multiple TLR agonists, including TLR7/8 agonists, have displayed considerable toxicities upon systemic administration. To circumvent this problem, we developed a T cell mediated delivery system of TLR agonists that can target the TME and lymphoid organs to maximize efficacy while avoiding systemic toxicities. Torque’s Deep Primed™ T cell technology enhances T cell function by tethering systemic immunomodulators to the T cell before adoptive cell transfer (ACT) and by using Torque’s multi-targeted T cell (MTC) platform that primes the T cells against multiple tumor antigens. Herein, we screened several liposomal formulations containing different TLR agonists for both in vitro agonist loading and release in mousse and human T cells followed by in vivo testing in a mouse melanoma model.

Introduction

Deep TLR Agonist

TLR Agonist

TLR Primed™ T cell

TLR Agonist

TLR Primed T cells

TLR Agonist

TLR Primed T cell

TLR Agonist

TLR Primed T cell

2. Optimal liposome formulation maximizes agonist loading and extends drug release

3. Deep TLR loaded T cells retain viability and extend TLR agonist release

4. Deep TLR Primed™ T cells increase cell expansion and tumor control in vivo

Results

Figure 1. Agonist release from Deep TLR Primed™ MTCs in vitro. A) Agonist release from Deep TLR Primed™ MTCs using Torque’s Deep Priming process were loaded with Deep TLR and then frozen. The next day, the cells were thawed and stimulated with TLR7 agonist. Agonist release was monitored using HBSS after cell lysis and protein precipitation to determine agonist concentration. B) Agonist release extended weeks and followed the model used for TLR7 agonist 1. C) Drug release over 40h in vitro. Drug release is measured twice weekly along with weight.

Figure 2. BNLI mice were injected with 1.5 × 10³ PMEL cells and drug by tail vein of cyclopentamide under anesthesia. A) Tumor growth of Torque’s Deep Primed™ T cells supplemented with systemic agonist treatment. B) PMEL cells supplemented with systemic agonist treatment. C) Drug release over 40h in vivo. D) Drug release is measured twice weekly along with weight. T cells supplemented with systemic agonist treatment. E) Drug release is measured twice weekly along with weight. T cells supplemented with systemic agonist treatment. F) Drug release is measured twice weekly along with weight. T cells supplemented with systemic agonist treatment. G) Drug release is measured twice weekly along with weight. T cells supplemented with systemic agonist treatment. H) Drug release is measured twice weekly along with weight. T cells supplemented with systemic agonist treatment. I) Drug release is measured twice weekly along with weight. T cells supplemented with systemic agonist treatment.