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

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Introduction

TLR7 agonists have been shown to augment immune responses in the tumor microenvironment (TME). The agonist work primarily through two mechanisms: antigen presenting cell (APC) engagement and enhancement followed by T cell co-stimulation.1–3 However, multiple TLR agonists, including TLR7/8 agonists, have displayed considerable toxicities upon systemic administration.4 To circumvent this problem, we developed a T cell mediated delivery system of TLR7 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 immune modulators to the T cell before adoptive cell transfer (ACT), and by using Torque’s multi-platform that primes the T cells against multiple tumor antigens.

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Abstract

TLR7 agonists have been shown to augment immune responses in the tumor microenvironment (TME). The agonist work primarily through two mechanisms: antigen presenting cell (APC) engagement and enhancement followed by T cell co-stimulation.1–3 However, multiple TLR agonists, including TLR7/8 agonists, have displayed considerable toxicities upon systemic administration.4 To circumvent this problem, we developed a T cell mediated delivery system of TLR7 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 immune modulators to the T cell before adoptive cell transfer (ACT), and by using Torque’s multi-platform that primes the T cells against multiple tumor antigens.

Results

1. TLR agonists 1 and 2 are specific for TLR7?

![Figure 1.](image1.png)

**A** TLR agonist 1 and 2 are specific for TLR7.

**B** TLR agonist 1 and 2 are specific for TLR7.

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

![Figure 2.](image2.png)

**A** Optimal liposome formulation maximizes agonist loading and extends drug release.

**B** Optimal liposome formulation maximizes agonist loading and extends drug release.

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

![Figure 3.](image3.png)

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

**B** 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

![Figure 4.](image4.png)

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

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

Conclusions

- Torque’s Deep TLR Primed T cells released a potent small molecule agonist of TLR7 over an extended period of time.
- Two TLR7-specific agonists capable of liposome encapsulation were identified.
- Formulation optimization enabled high concentrations of two different TLR agonists to be loaded on both mouse and human T cells with extended release.
- The optimal liposomal formulation enabled encapsulation of high concentrations of TLR agonist loaded onto MITCs with minimal effect on viability and proliferative capacity.
- Deep TLR Primed T cells remain viable and release TLR agonist slowly over 10 days.
- Deep TLR Primed T cell expansion exceeds that of CD8 T cells alone or co-administered with systemic TLR7 agonist.
- ACT with Deep TLR Primed T cells provides a novel avenue to leverage the immune stimulating potential of TLR agonists for superior anti-tumor efficacy while avoiding systemic exposure and toxicities - key current bottlenecks to successful TLR therapy.
- In the future, agonist delivery via Deep-Primed™ tumor antigen-specific autologous T cells could target a wide variety of tumors and their distant metastases, enabling a new immunotherapeutic strategy.

References


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