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

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**Abstract**

TLR7 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 agonists, have displayed considerable toxicities upon systemic administration. To circumvent this problem, we developed a T cell mediator delivery system of TLR7 agonists that can target the TME and lymphoid organs to maximize efficacy while avoiding systemic toxicities. Torque’s Deep-Primed™ 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-targeted T cell (MTC) platform that primes the T cells against multiple tumor antigens. Herein, we screened several liposome formulations containing two different TLR7 agonists for both in vitro agonist loading and release in mouse and human T cells followed by in vivo testing in a mouse melanoma model.

**Introduction**

Deep TLR Agonist

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 agonists, have displayed considerable toxicities upon systemic administration. To circumvent this problem, we developed a T cell mediator delivery system of TLR7 agonists that can target the TME and lymphoid organs to maximize efficacy while avoiding systemic toxicities. Torque’s Deep-Primed™ 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-targeted T cell (MTC) platform that primes the T cells against multiple tumor antigens. Herein, we screened several liposome formulations containing two different TLR7 agonists for both in vitro agonist loading and release in mouse and human T cells followed by in vivo testing in a mouse melanoma model.

**Results**

1. TLR agonists 1 and 2 are specific for TLR7

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

**Conclusions**

- Torque’s Deep TLR Primed™ T cells released a potent small molecule agonist of TLR7 over an extended period of time.
- Two TLR-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 MTCs 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 option.

**References**

3. Dendritic Cell Based Advances in the Discovery and Delivery of TLR7 Agonists as Vaccine Adjuvants. ImmuneNet 2018. 2:145-197

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