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

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

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Abstract

TLR3 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.1-3 However, multiple TLR agonists, including TLR7/8 agonists, have displayed considerable toxicities upon systemic administration.1 To circumvent this problem, we developed a T cell mediated delivery system of TLR3 agonist that can target the TME and lymphed 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-targeted T cell (MTC) platform that primes the T cells against multiple tumor antigens. Henceforth, we screened several liposome combinations containing two different TLR3 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

Loading onto antigen-specific CD8 T cells

Deep TLR Primed™ T cell

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

References

3. Developing TLR Based Adjuvants. The Discovery and Delivery of TLR7 agonists as Vaccine Adjuvants. ImmunoHorizons 2018:2-165-197

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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 TLR7 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 approach.