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

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.1-4 However, multiple TLR agonists, including TLR7/8 agonists, have displayed considerable toxicities upon systemic administration.5 To circumvent this problem, we developed a T cell mediated delivery system of TLR7 agonist 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 administration.

In a mouse melanoma model, we screened several liposomal formulations containing immune modulators to the T cell before adoptive cell transfer to leverage the immune stimulating potential of TLR agonists to 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 immunotherapy treatment.

Introduction

TLR7 agonist

Deep TLR Primed T cell

Loading onto antigen-specific CD8 T cells

Deep TLR Primed T cells

Reaching the tumor microenvironment (TMEM)

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 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 TLR7 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 immunotherapy treatment.

References


Acknowledgments

We would like to thank our Torque colleagues for productive discussions and criticisms.