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

Nathan Westcott¹, Austin Boesch¹, Vasily Rybakin¹, Ji Young Huang¹, Kira Jørgensen², Rasmus Lassen³, Martin Kraemer², Martin Bak⁴, Gael Veiga⁵, Jonas Bruun⁶,
Carlos Tassa¹, Harrison Rodts¹, Manly Sequeira¹, Karsten Sauer¹, Thomas L. Andresen¹
¹Torque Therapeutics, Cambridge, MA; ²Technical University of Denmark, Lyngby, Denmark

Abstract
TLR7 agonists have been shown to augment immune responses in the tumor microenvironment (TME). However, multiple TLR agonists, including TLR7/8 agonists, have displayed considerable toxicities upon stimulation. TLR7 agonists have been shown to augment immune responses in vitro but currently lack evidence in vivo. In the present study, we aimed to characterize the potential of a novel TLR agonist-DNA-liposome delivery platform for in vivo adoptive T cell therapy, without inducing systemic toxicity.

Introduction
TLR agonists can be delivered intratumorally to augment immune responses in the TME. However, multiple TLR agonists have displayed considerable toxicities upon stimulation. TLR7 agonists have been shown to augment immune responses in vitro but currently lack evidence in vivo. In the present study, we aimed to characterize the potential of a novel TLR agonist-DNA-liposome delivery platform for in vivo adoptive T cell therapy, without inducing systemic toxicity.

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

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