Delivery of TLR7 agonists by Deep-Primed™ T cells induces immune activation and improves anti-tumor activity in mice while circumventing systemic toxicity

Boesch, Austin; Rybakin, Vasily; Westcott, Nathan; Hwang, Ji Young; Jørgensen, Kira; Lassen, Rasmus; Kræmer, Martin; Bak, Martin; Veiga, Gael; Bruun, Jonas

Publication date:
2019

Document Version
Publisher's PDF, also known as Version of record

Citation (APA):
**Title:** Delivery of TLR7 agonists by Deep-Primed™ T cells induces immune activation and improves anti-tumor activity in mice while circumventing systemic toxicity

**Authors:** Austin Boesch, Vasily Rybakin, Nathan Westcott, Yi Juong Hwang, Kira Jørgensen, Rasmus Lassen, Martin Kremer, Martin Bak, Gael Veiga, Jonas Brun, Carlos Tassa, Harrison Rodts, Manney Sequeira, Glenn Leary, Santina Caruso, Becker Hewes, Jonathan Fitzgerald, Karsten Sauer, Thomas Andersen

**Institution:** Torque Therapeutics, Cambridge, MA; Technical University of Denmark, Lyngby, Denmark; Presenting author

**Abstract:** TLR7 agonists have been shown to be potent activators of the immune system. However, systemic administration often results in toxicities. Torque's Deep TLR Primed™ (Deep TLR Primed™) technology enables efficient and selective delivery of TLR7 agonists to the tumor microenvironment, thereby improving anti-tumor immunity while minimizing systemic toxicity. In this study, we evaluated the efficacy and tolerability of Deep TLR Primed™ T cells in a murine model of melanoma.

**Methods:** We designed a novel T cell mediated delivery system for TLR7 agonists that targets the TME and the lymphatic system to maximize efficacy while avoiding systemic toxicities. Torque's Deep TLR Primed™ technology enhances T cell function through tethering of immune modulators to the T cell before adoptive cell transfer (ACT) and uses Torque's multi-targeted cell (MTC) platform to prime the T cell against multiple tumor antigens. By transporting the immunomodulators to antigen presenting cells (APCs), we can control the amount of agonist delivered to the TME to optimize efficacy while avoiding toxicity.

**Results:** We demonstrated that Deep TLR Primed™ T cells are capable of enhancing T cell function and activating immune responses in vivo. We observed improved tumor control and an enhanced immune cell response in tumors treated with Deep TLR Primed™ T cells compared to control T cells. The enhanced efficacy was accompanied by a reduction in systemic toxicities, as evidenced by a decrease in weight loss and a decrease in plasma cytokine levels.

**Conclusion:** Deep TLR Primed™ T cells are a promising therapeutic approach for the treatment of cancer, as they are able to induce immune activation and improve anti-tumor activity while minimizing systemic toxicity. This technology holds promise for the development of more effective and safer immunotherapies for cancer treatment.

**Key Findings:**
- Torque's Deep TLR Primed™ T cells release a potent small molecule agonist of TLR7 over an extended period of time.
- ACT of Deep TLR Primed™ T cells strongly improves tumor growth inhibition and host survival over controls in the murine B16-F10 model.
- Deep TLR Primed™ T cell expansion exceeds that of CD8 T cells alone or co-administered with the TLR7 agonist. PD-1 downregulation suggests reduced exhaustion of Deep TLR Primed™ T cells vs. controls.
- Deep TLR-mediated agonist delivery increased pDCs in draining lymph nodes and endogenous CD8 T cells in tumors, consistent with the known effects of TLR7 agonists in vivo.
- Deep TLR-mediated agonist delivery increased MDCS content in the TME which may be beneficial given TLR7 agonists are known to convert MDCS into functional APCs.
- Deep TLR Primed™ T cells caused no significant weight loss. Transient plasma levels of pro-inflammatory cytokines (TNFα and IL-6) were not shown.
- Immunocompetent syngeneic tumor-bearing GEMMs (ACT of 1*10⁶ PMEL T cells vs. without TLR7 agonist) were clearly superior to TME TLR7 agonists beyond that caused by lymphodepletion (GEMM) in mice previously treated with systemic regimens of commercial agonists (ACT of 1*10⁶ PMEL T cells with or without TLR7 agonist).

**Figures:**
- Figure 1: Deep TLR Primed™ T cells release a potent TLR7 agonist over an extended period of time.
- Figure 2: Deep TLR Primed™ T cells contain TLR7 agonist loaded liposomes and display slow payload release over time.
- Figure 3: Deep TLR Primed™ T cells promote tumor growth inhibition and extend host survival.
- Figure 4: Deep TLR Primed™ T cells mediate superior tumor growth inhibition in the B16 melanoma syngeneic mouse model.
- Figure 5: ACT of Deep TLR Primed™ T cells elicits low potential toxicity.