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):
Herein, we screened several liposomal formulations containing Primed™ T cell technology enhances T cell function by tethering efficacy while avoiding systemic toxicities. Torque's Deep developed a T cell mediated delivery system of TLR7 agonists systemic administration.

However, multiple TLR agonists, including DCs TLR7-4 R848, Resiquimod (A) TLR agonists 1 and 2 are specific for TLR7 and TLR8 HEK reporter assay. The same process were loaded with Deep TLR and then frozen. The next day, the cells were thawed and cultured for 10 d. After Deep TLR loading, viability and cell count were assessed compared to a PBS treated control.

TLR agonist retained within cells and released into the media was assessed by HPLC to determine the mass balance over time. The metabolization of the agonist remained negligible. After adding different concentrations of TLR agonist 1, TLR agonist 2, or the known TLR agonist 2. (B) TLR agonist 1 and (C) TLR agonist 2. (D) TLR agonist 1 and (E) TLR agonist 2. (F) TLR agonist 1 and (G) TLR agonist 2. (H) TLR agonist 1 and (I) TLR agonist 2. (J) TLR agonist 1 and (K) TLR agonist 2. (L) TLR agonist 1 and (M) TLR agonist 2. (N) TLR agonist 1 and (O) TLR agonist 2. (P) TLR agonist 1 and (Q) TLR agonist 2. (R) TLR agonist 1 and (S) TLR agonist 2. (T) TLR agonist 1 and (U) TLR agonist 2. (V) TLR agonist 1 and (W) TLR agonist 2. (X) TLR agonist 1 and (Y) TLR agonist 2. (Z) TLR agonist 1 and (AA) TLR agonist 2. (BB) TLR agonist 1 and (CC) TLR agonist 2. (DD) TLR agonist 1 and (EE) TLR agonist 2. (FF) TLR agonist 1 and (GG) TLR agonist 2. (HH) TLR agonist 1 and (II) TLR agonist 2. (JJ) TLR agonist 1 and (KK) TLR agonist 2. (LL) TLR agonist 1 and (MM) TLR agonist 2. (NN) TLR agonist 1 and (OO) TLR agonist 2. (PP) TLR agonist 1 and (QQ) TLR agonist 2. (RR) TLR agonist 1 and (SS) TLR agonist 2. (TT) TLR agonist 1 and (UU) TLR agonist 2. (VV) TLR agonist 1 and (WW) TLR agonist 2. (XX) TLR agonist 1 and (YY) TLR agonist 2. (ZZ) TLR agonist 1 and (AAbb) TLR agonist 2.

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 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 critiques.