

Novel targeted LNP delivery achieved *in vivo* CAR T cell generation resulting in therapeutically relevant B-cell depletion

P0361

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Editas Medicine, Cambridge, MA, USA

See poster P0781 for tLNP manufacturing process, Second Floor, Foyer D-F

Introduction

Background

- Chimeric antigen receptor (CAR) T-cell therapies have seen significant medical advancement in oncology and are achieving breakthrough clinical efficacy in autoimmune diseases

Challenges

- Implementation of CAR-based autoimmune therapy remains limited, partly due to the difficulties of *ex vivo* CAR T-cell manufacturing, which constrains scalability and accessibility

Editas' Immune Cell Targeted LNP for *In Vivo* CAR T-Cell Therapy

Lead T-Cell Targeted LNP

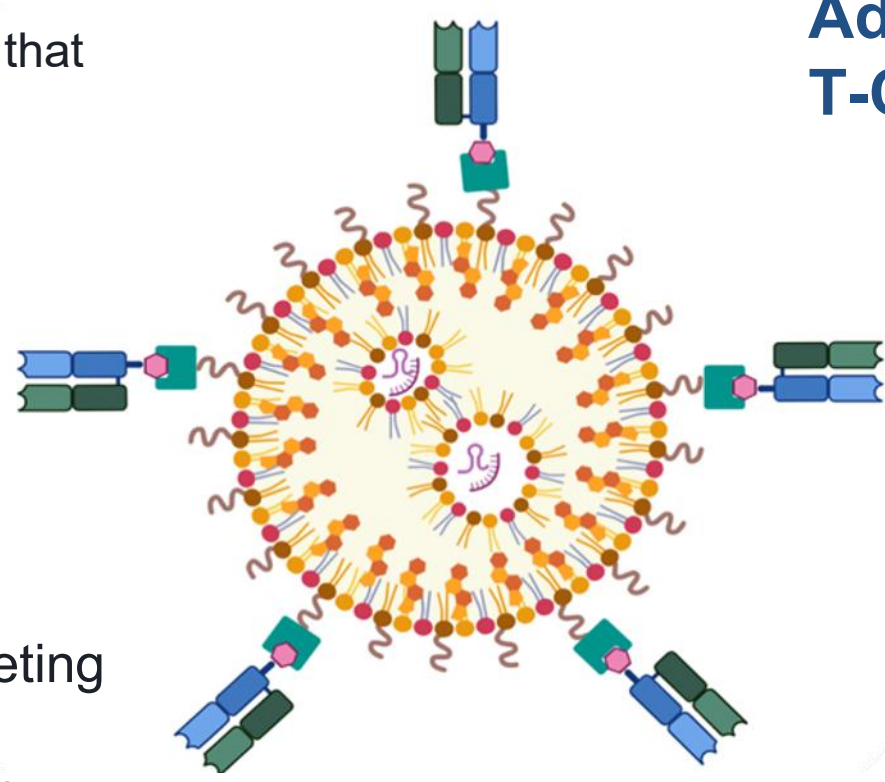
High potency, CD8-targeted LNP composition that integrates Editas' proprietary technology

Modular Delivery Platform

- "Cargo-ready" flexibility for swapping mRNA cargos of choice
- Targeting moieties changeable for cell-specificity of choice

Proprietary Formulation

- Optimized composition for liver de-targeting and increases plasma circulation
- Highly specific and scalable conjugation chemistry

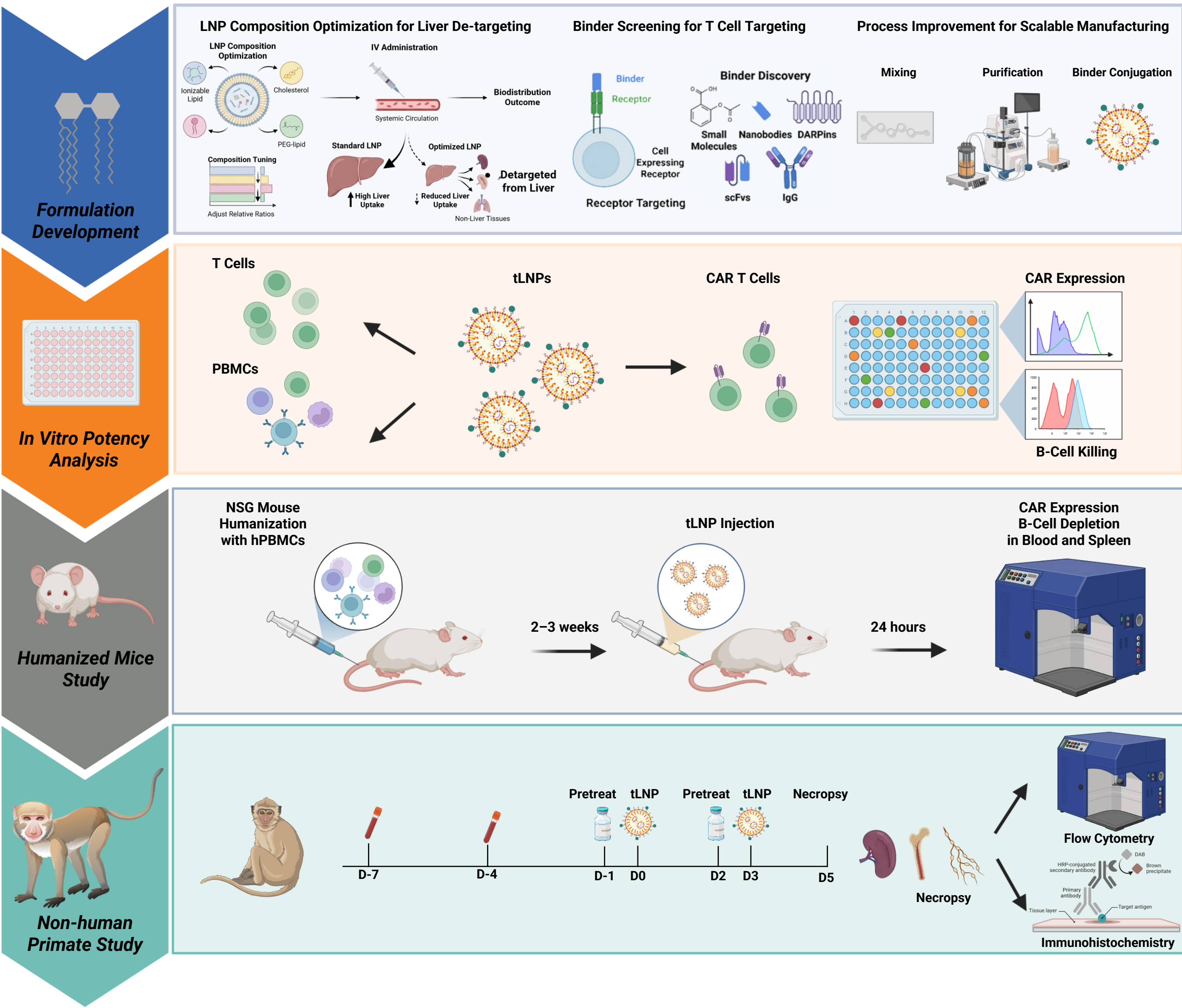


Advantages of Editas' *In Vivo* CAR T-Cell Therapy with anti-CD19 CAR*

- ✓ Re-dosable
- ✓ Off-the-shelf
- ✓ Transient and rapid
- ✓ Deep B-cell depletion
- ✓ No lympho-depletion

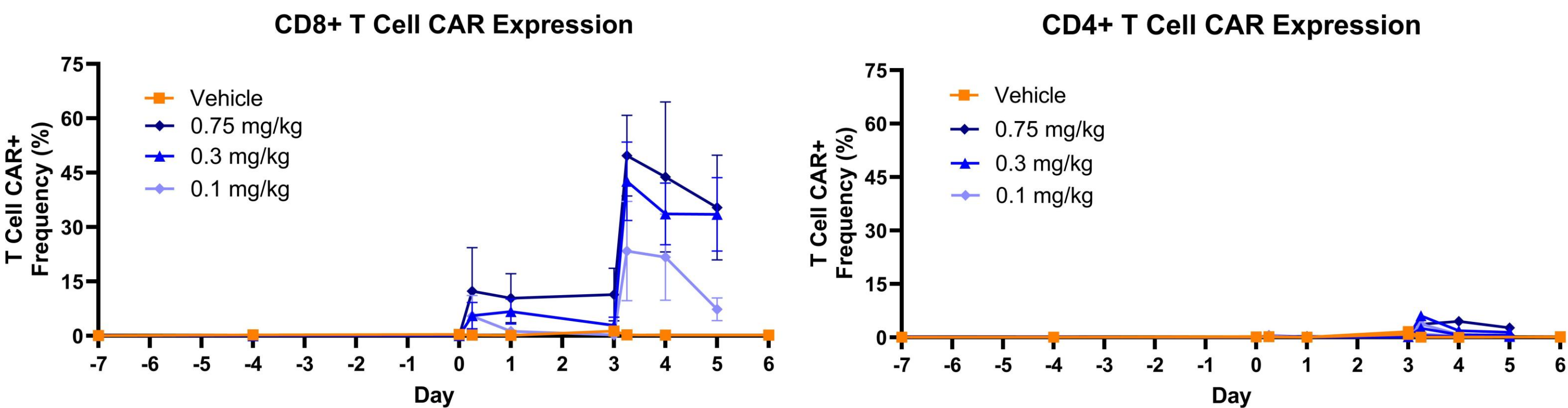
*Anti-CD20 CAR payload was used as a surrogate because of the lack of CD19 cross-reactivity between human and NHP.

Methods

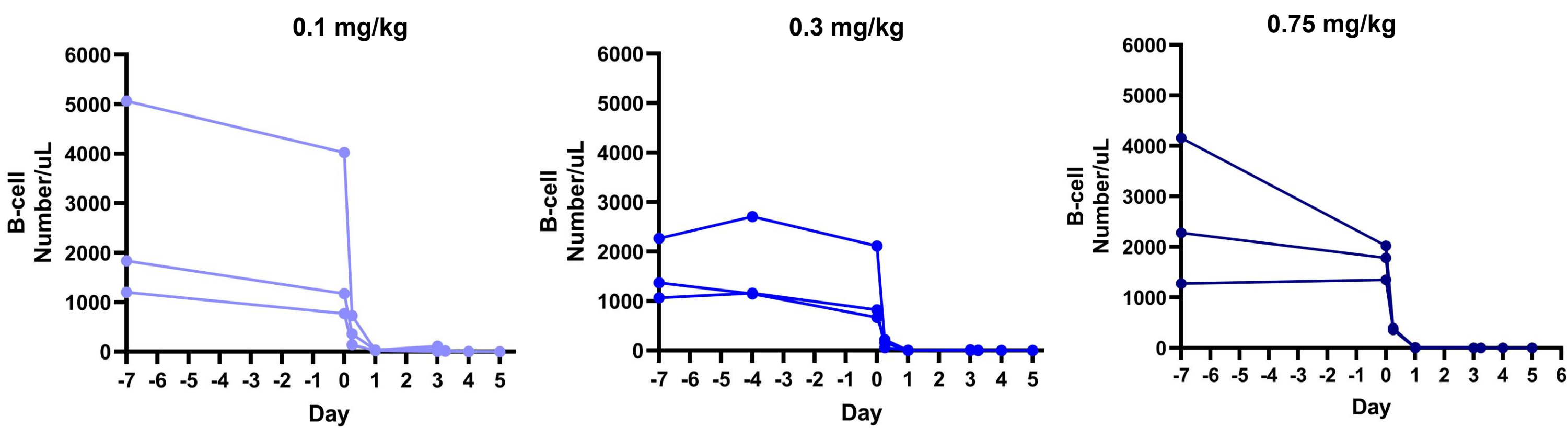


Results

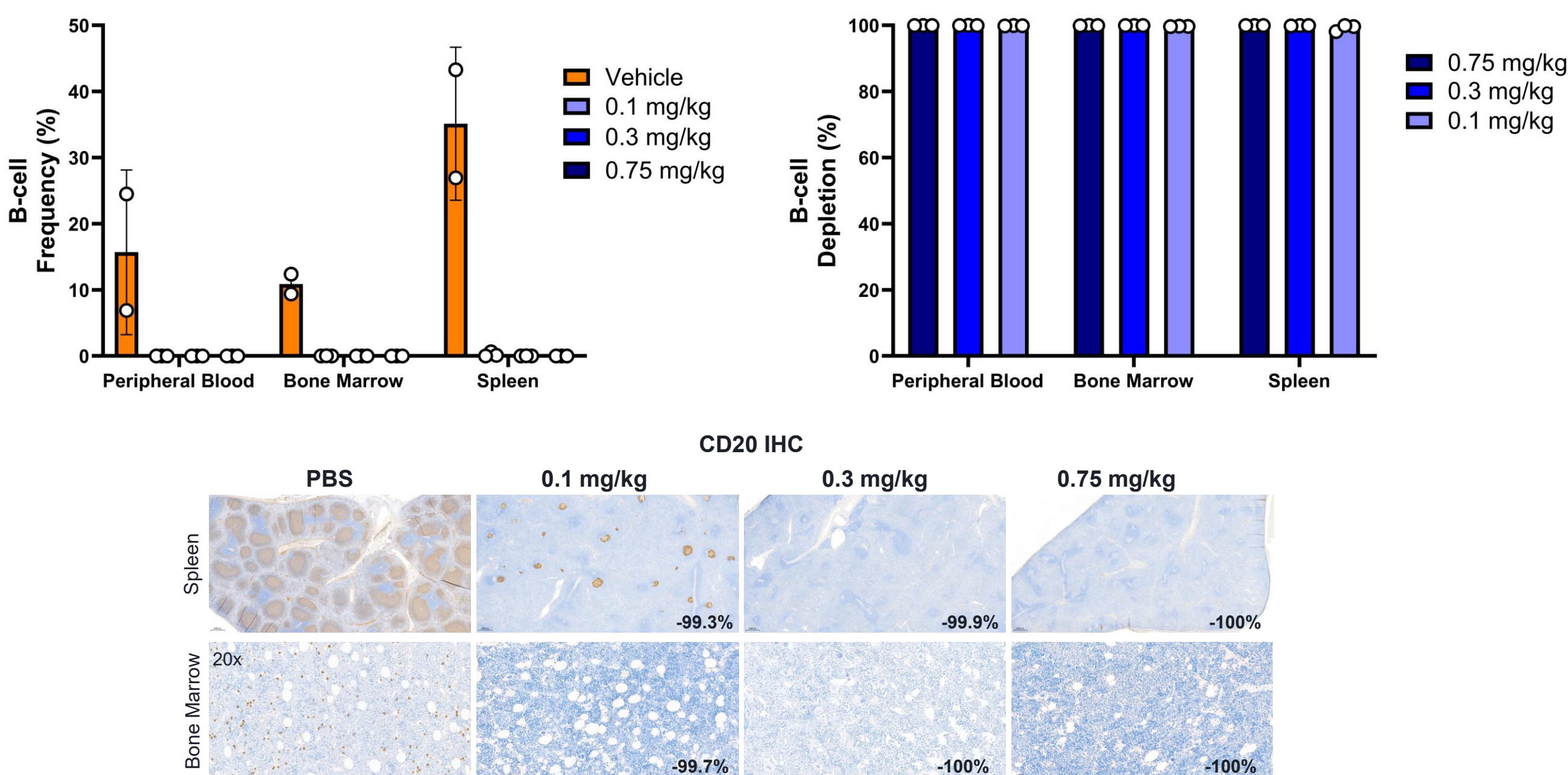
Anti-CD8/CD20 CAR tLNP Proof of Delivery Demonstrated by Dose-Dependent CAR Expression in NHP CD8+ T Cells in Peripheral Blood



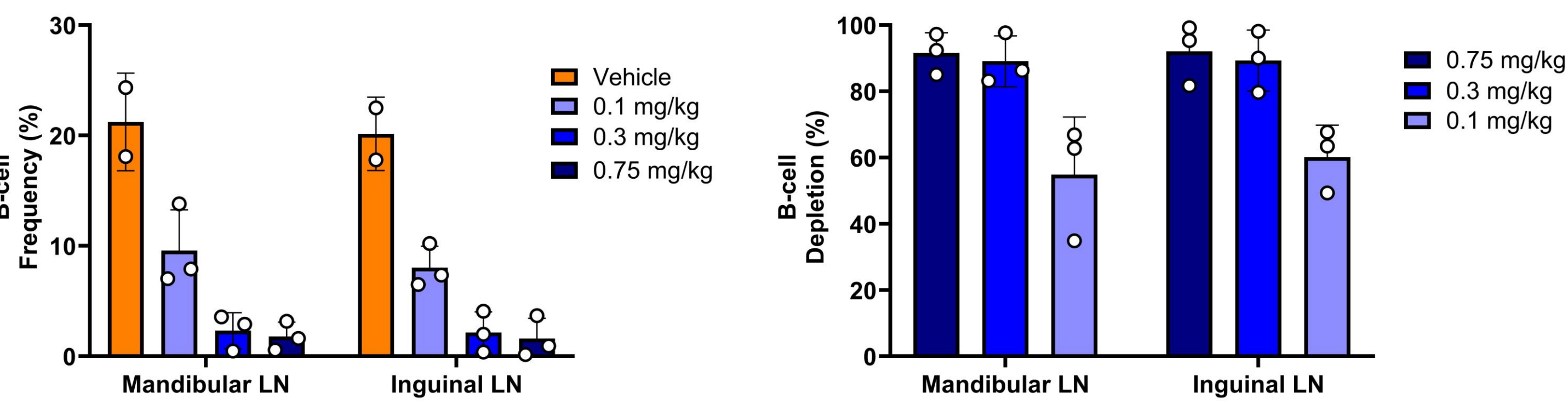
B-Cell Depletion of ≥99% in NHP Peripheral Blood with Doses as Low as 0.1 mg/kg



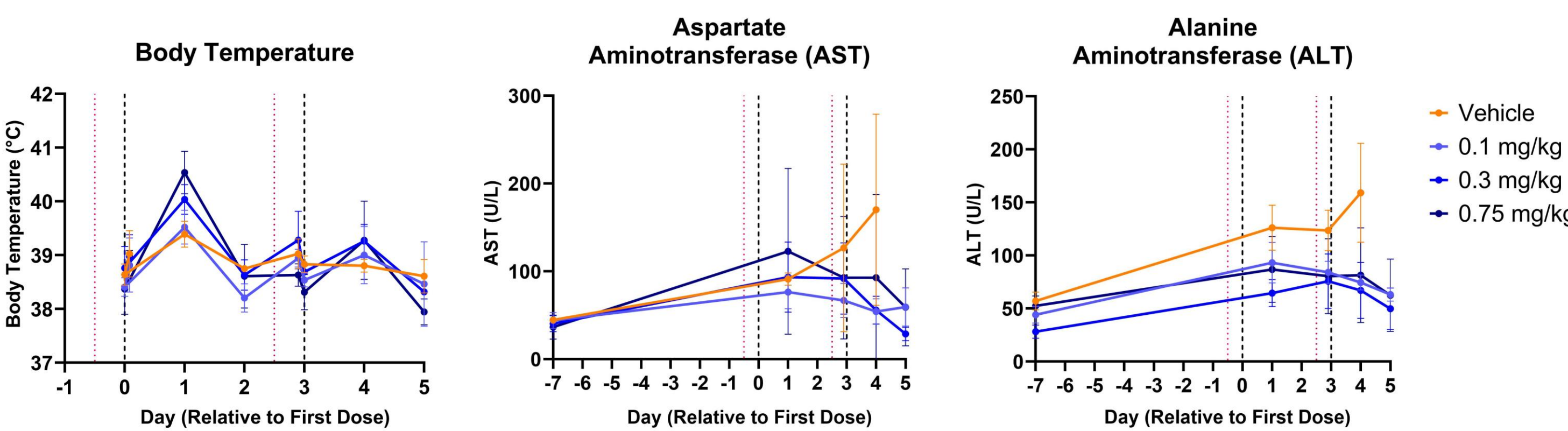
B-Cell Depletion of ≥99% in NHP Peripheral Blood, Bone Marrow, and Spleen with Dose as Low as 0.1 mg/kg



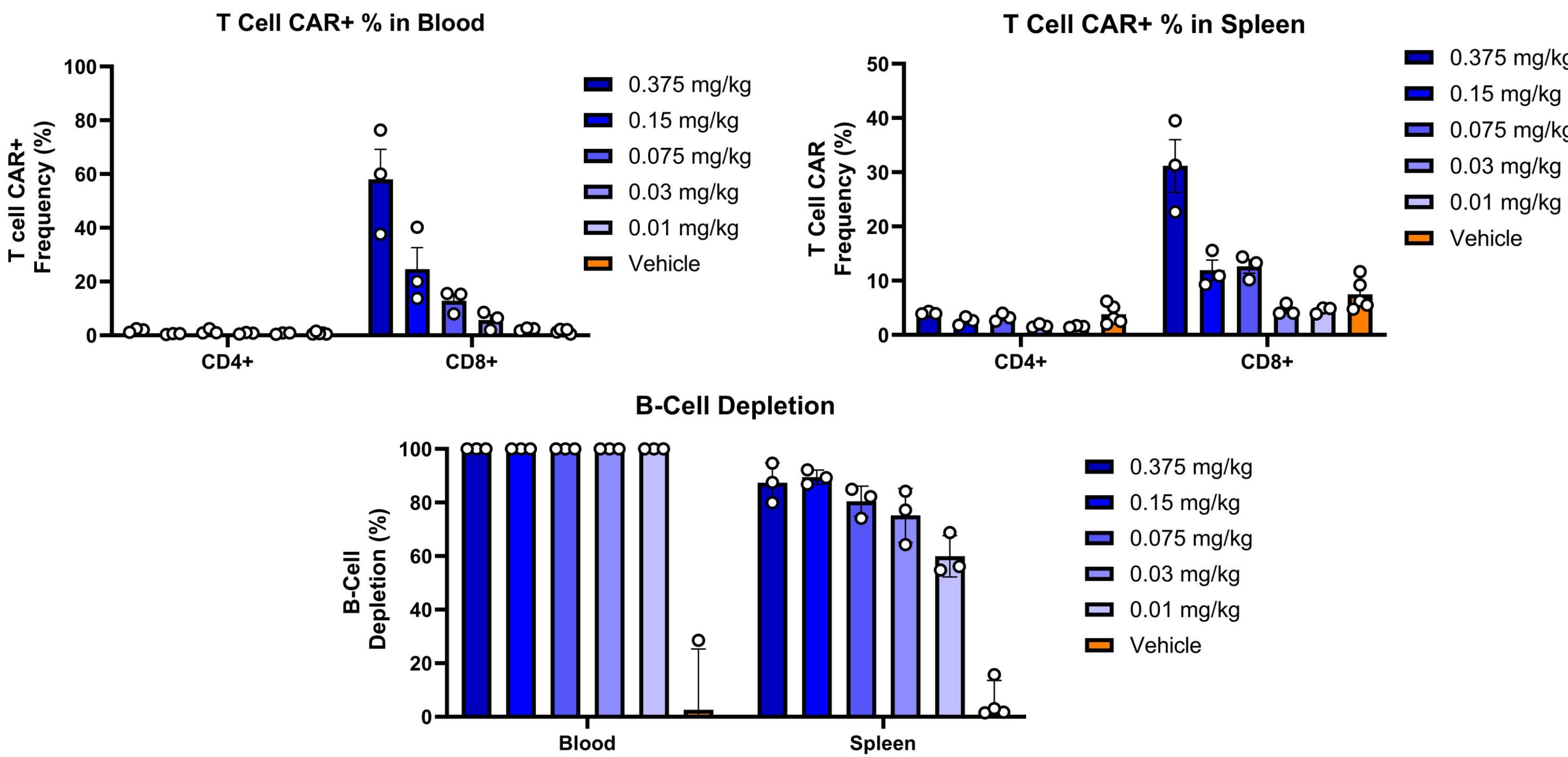
Deep B-Cell Depletion in NHP Lymph Nodes at 0.3 mg/kg



Well Tolerated in NHP with No ALT/AST Elevation Relative to Vehicle



Anti-CD8/CD19 CAR tLNP Demonstrated Dose-Dependent CAR Expression and B-Cell Depletion in Humanized Mice



Conclusions

- We demonstrated robust *in vivo* delivery of mRNA to targeted T cells with our novel, scalable tLNP-based platform
- Transient expression of the CAR in targeted T cells resulted in deep B-cell depletion in the blood within 24 hours post-dose
- Therapeutically relevant B-cell depletion in lymphoid tissues was also observed, creating the potential for clinically meaningful immune reset for autoimmune therapy

Disclosures
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Abbreviations
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAR, chimeric antigen receptor; hPBMC, human peripheral blood mononuclear cell; HRP, horseradish peroxidase; IHC, immunohistochemistry; IgG, immunoglobulin G; IV, intravenous; LN, lymph node; LNP, lipid nanoparticle; PEG, polyethylene glycol; PBMC, peripheral blood mononuclear cell; PBS, phosphate buffered saline; NHP, non-human primate; NSG, NOD/SCID/IL-2Rγ^{-/-}; mRNA, messenger RNA; scFvs, single-chain variable fragments; tLNP, targeted LNP.

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