

Development of a configurable, GMP-ready manufacturing platform for targeted LNP therapeutics

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Editas Medicine, Cambridge, MA, USA

See poster P0361
for non-human primate data,
Ground floor, Foyer 4

Introduction

- LNP platform:** Lipid nanoparticles are a clinically proven delivery system established for liver-directed targeting across mRNA vaccines, siRNA, and gene-editing medicines (**Figure 1**)
- Challenge:** Extending that platform from passive liver delivery to targeted extrahepatic tissues raises manufacturing complexity and demands tighter process control
- Process design:** Modular architecture enables flexible scaling, streamlined technology transfer, and seamless transition from development to GMP-compliant manufacturing (**Figure 2**)
- Consistency:** The resulting process maintains particle size, polydispersity index, encapsulation, and conjugation from 10 mg to 100 mg and across different binders (**Figure 3**), with potency retained through 5 freeze/thaw cycles (**Figure 4**)
- Case study:** Applied to chimeric antigen receptor (CAR) mRNA delivery to T cells, the platform gives scale-independent potency *in vitro* (**Figure 5**) and dose-dependent CAR expression and B-cell depletion *in vivo* in NSG mice (**Figure 6**)

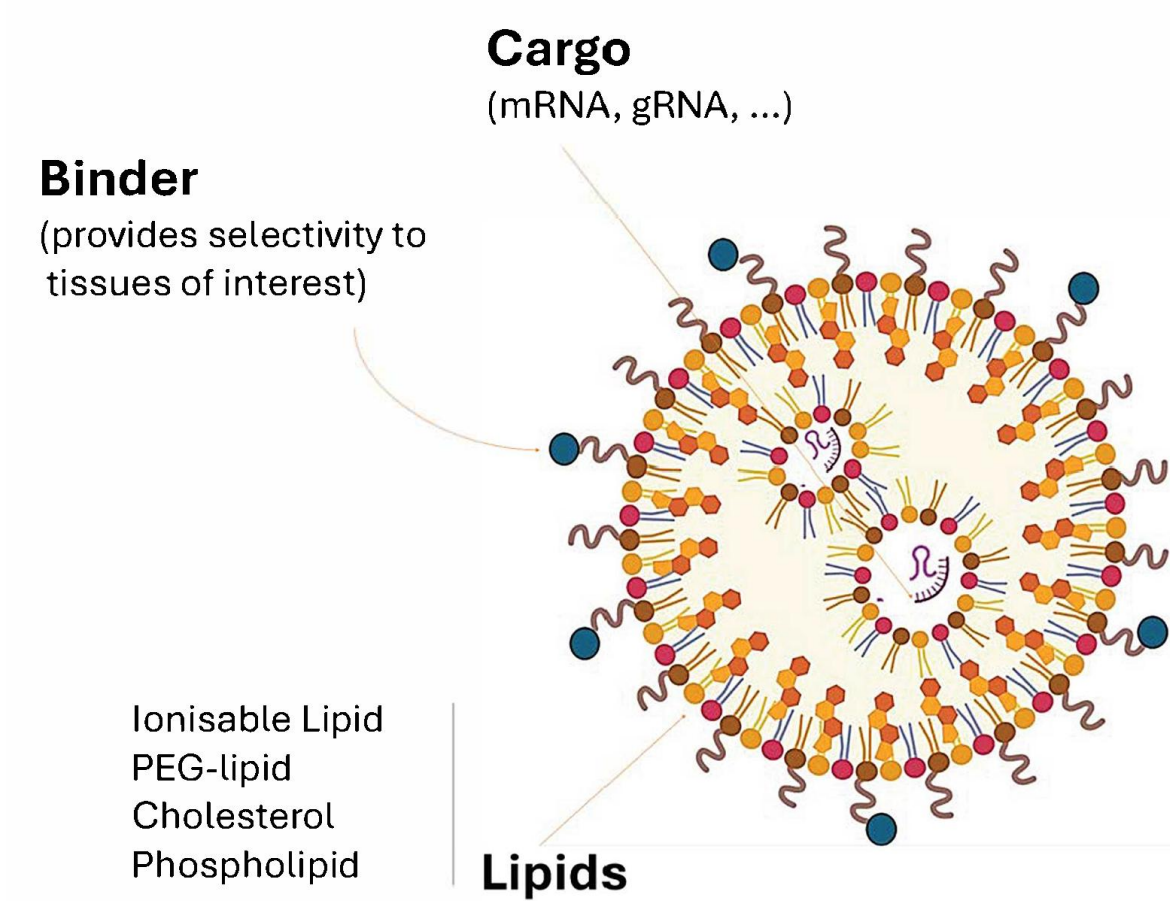


Figure 1. Targeted LNP structure

LNP Manufacturing Process and Analytics

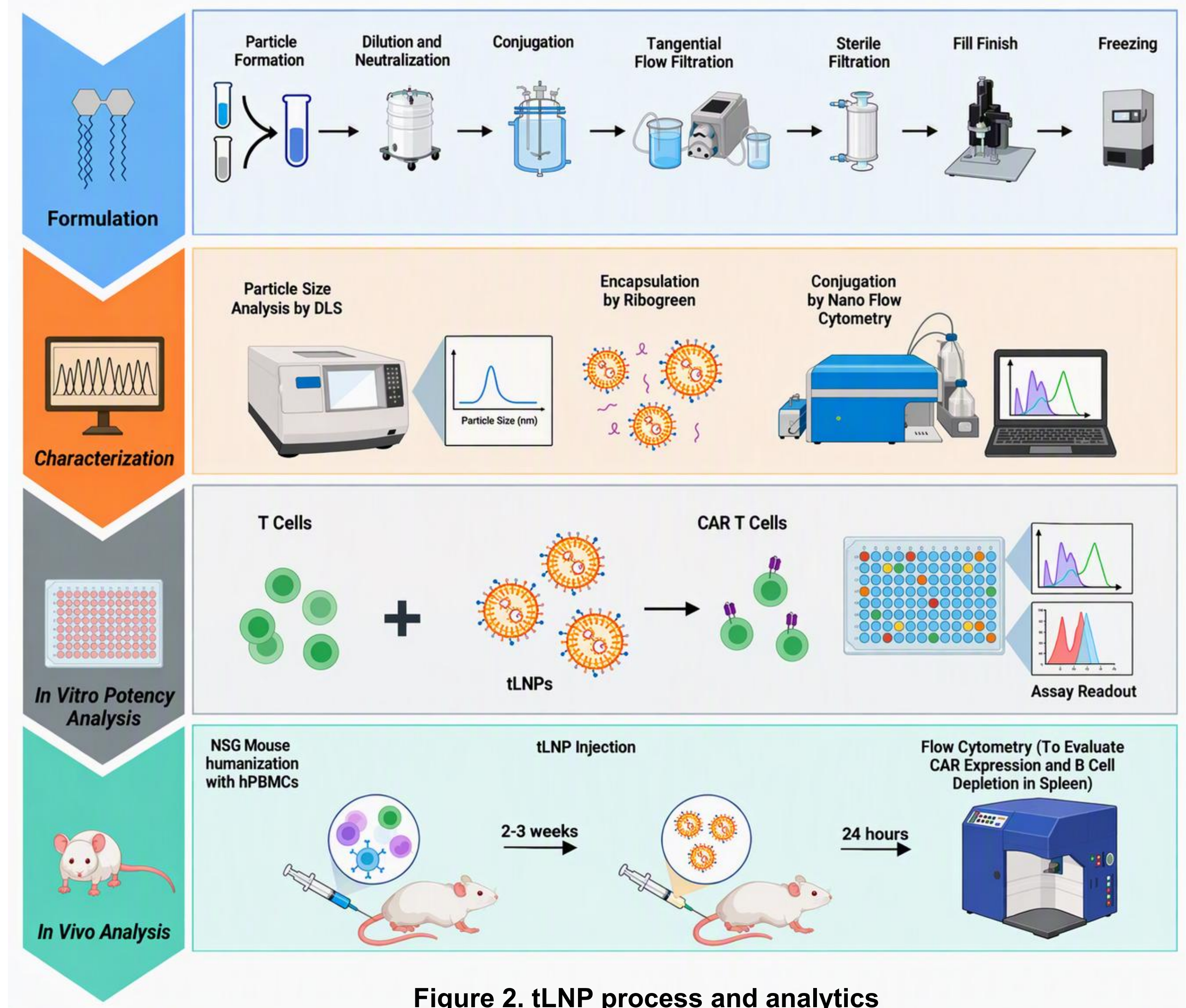


Figure 2. tLNP process and analytics

In this modular architecture design, the overall manufacturing process is composed of discrete, standardized unit operations, each performing a specific function.

Consistent Process Performance and tLNP Product Quality

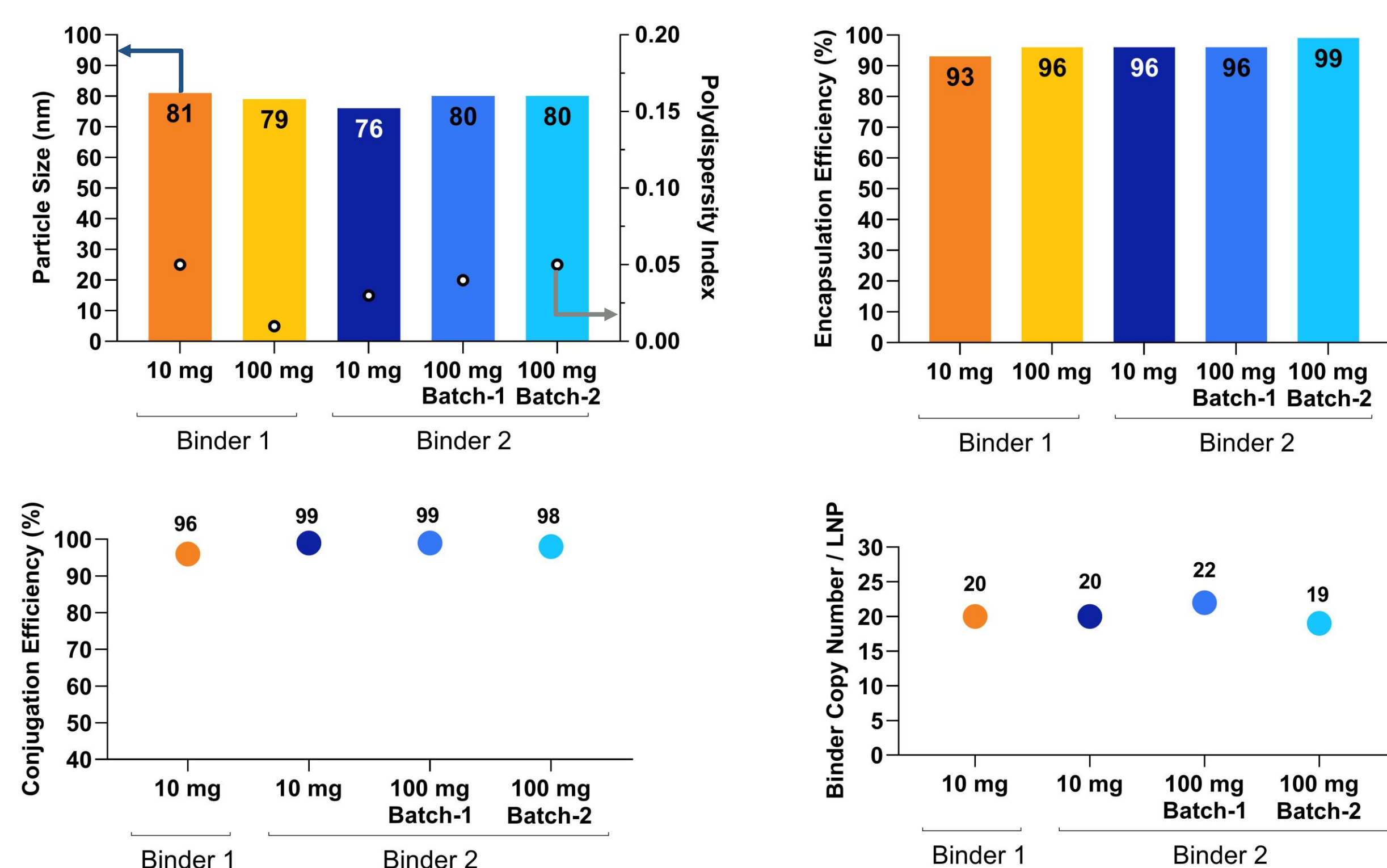


Figure 3. Particle quality for tLNP batches at various scales using different binders

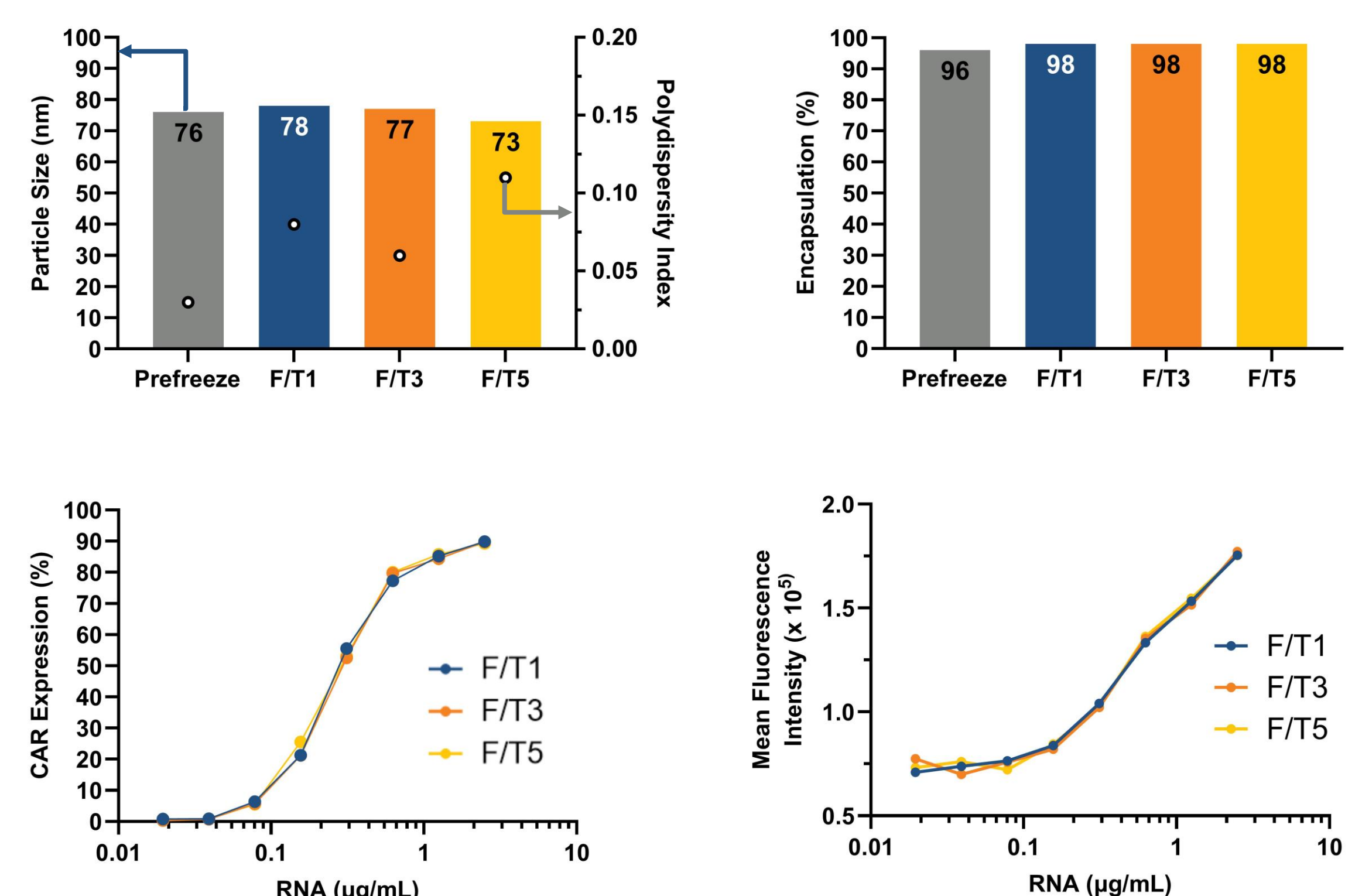


Figure 4. tLNP stability through freeze/thaw cycles*

*F/T1, F/T3, and F/T5 indicate following 1, 3, or 5 freeze/thaw cycles, respectively.

Case Study: Immune Cell Targeting Efficacy

In Vitro Potency

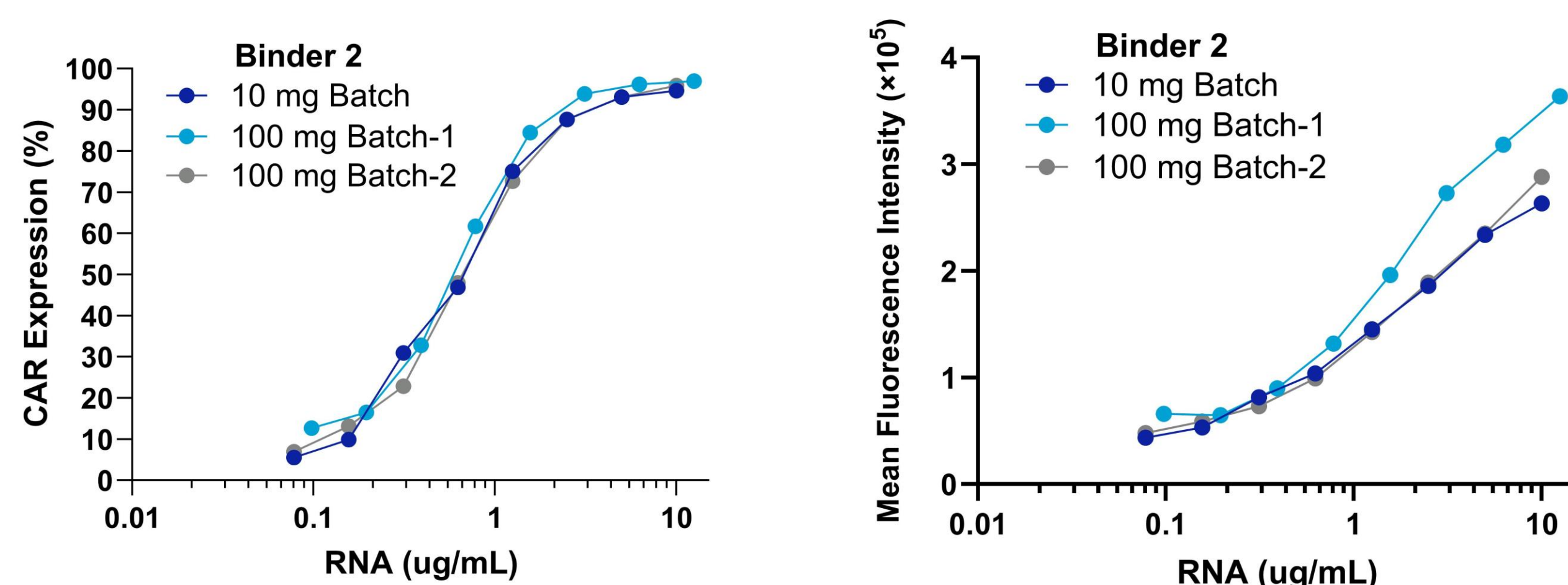


Figure 5. CAR expression (left) and mean fluorescence intensity (right) of T cells transfected by tLNP batches

In Vivo Potency

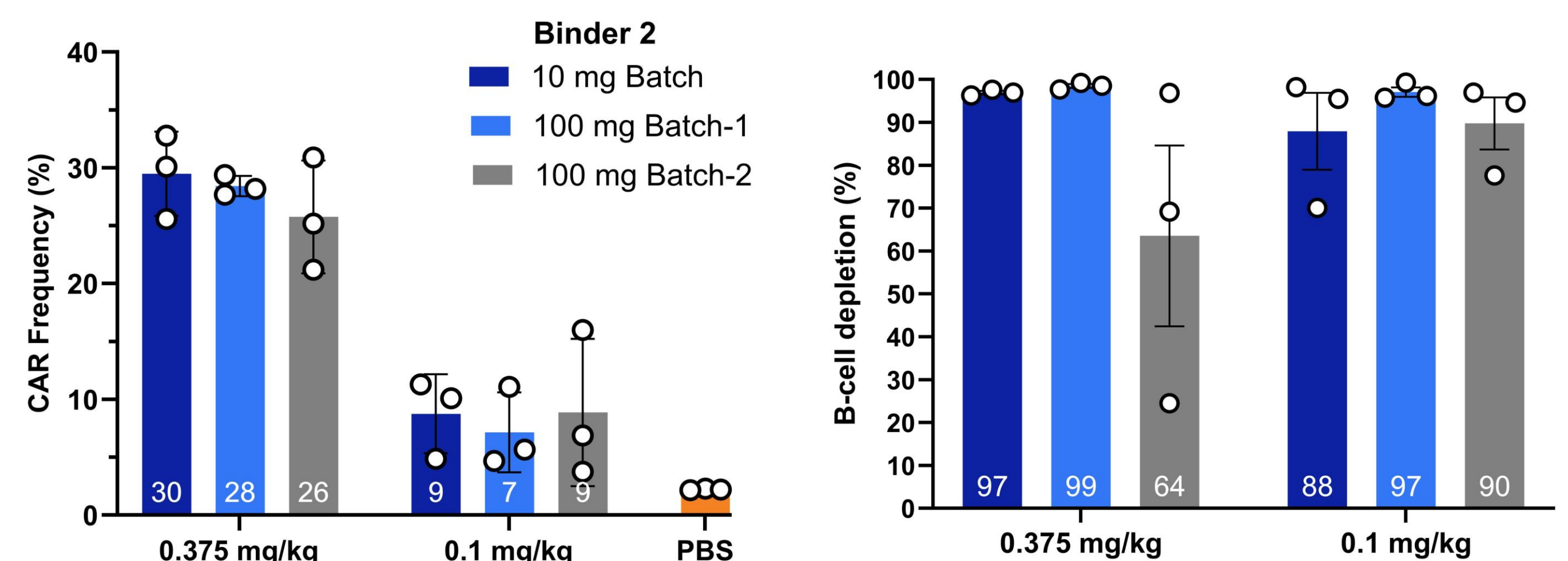


Figure 6. CAR frequency (left) and B-cell depletion (right) in the spleen of NSG mice treated with 2 different doses of tLNPs

Conclusions

- Modular platform enables rapid evaluation of novel binders and cargos
- Consistent tLNP quality attributes were maintained across scales, binders, and batches
- Potency was maintained through multiple freeze/thaw cycles, demonstrating robust formulation stability
- A case study targeting immune cells demonstrated consistent *in vitro* and *in vivo* performance pre- and post-scale-up
- The efficacy of the tLNP was demonstrated through *in vivo* mouse studies with robust generation of CAR T cells as well as potent B-cell depletion

Disclosures
Authors are employees of Editas Medicine. This study was sponsored by Editas Medicine.

Acknowledgments
Medical writing and editorial services have been funded by Editas Medicine and provided by Amanda Weber, RPh, of Porterhouse Medical US.

Abbreviations
CAR, chimeric antigen receptor; DLS, dynamic light scattering; F/T, freeze/thaw cycle; GMP, good manufacturing practice; gRNA, guide RNA; hPBMC, human peripheral blood mononuclear cell; LNP, lipid nanoparticle; NSG, NOD/SCID/IL-2Rγ^{-/-}; mRNA, messenger RNA; PBS, phosphate-buffered saline; PEG, polyethylene glycol; siRNA, small interfering RNA; tLNP, targeted lipid nanoparticle.

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