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TISSUE-TARGETED LIPID NANOPARTICLE DELIVERY FOR MRNA ENCODING BISPECIFIC T-CELL ENGAGER DEMONSTRATED POTENT ANTITUMOR EFFECTS ON BOTH HEMATOLOGICAL MALIGNANCIES AND SOLID TUMORS

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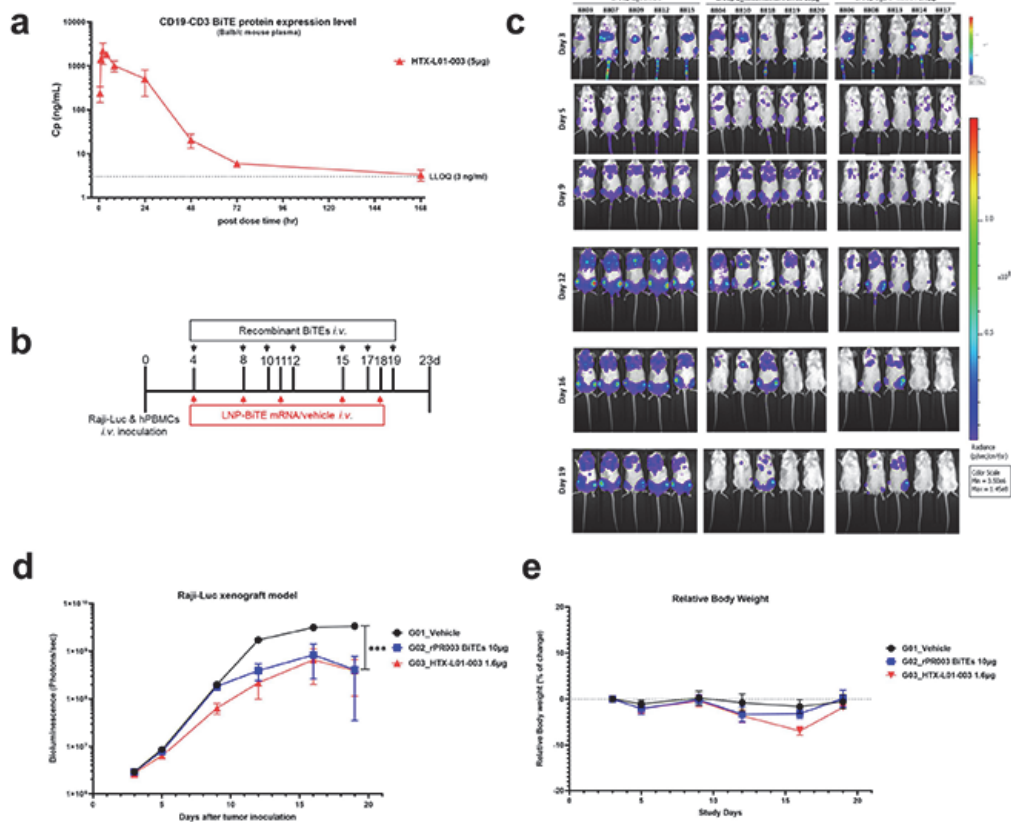
Background The recent clinical success of LNP-mRNA based COVID vaccine has accelerated the development of lipid nanoparticles (LNP) as safe and effective deliver approach for next wave of genomic medicine. Bispecific T cell engager (BiTE) therapy is an approved immunotherapy to treat hematological malignancies, such as ALL, by redirecting cytotoxic T-cells to eliminate cancer cells. However, the relatively short serum half-life of recombinant BiTE, and reported CRS and neurotoxicity have limited its applications. Here, we describe tissue targeted LNP-mRNA encoding BiTE that expressed long-lasting and therapeutic levels of BiTE protein at the targeted tumor sites. The results from the preclinical studies have demonstrated activation of T-cells to eliminate tumor cells in hematological malignancy and solid tumor mouse models and deplete circulating B-cell in a NHP model.

Methods The LNP formulated with Hopewell's proprietary ionizable lipid HTX-L01 was selected through *in vitro* biophysical characterization and *in vivo* screening. HTX-L01-003 and HTX-L01-008 encapsulated with mRNA encoding optimized single chain sequence of CD19-CD3 and GPC3-CD3 respectively, were evaluated for their PK/PD profile, bio-distribution and bio-tolerability in WT mice and NHP (dose

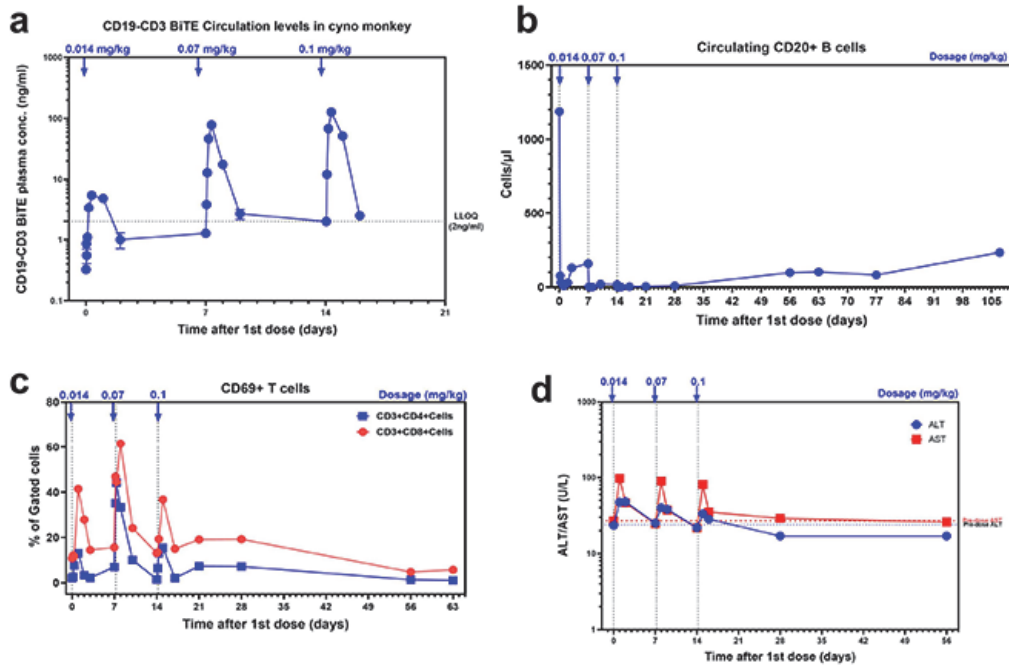
escalating at 0.014, 0.07 and 0.1 mg/kg). The tumor control activities were assessed in the Raji-xenograft non-Hodgkin lymphoma (NHL) model for HTX-L01-003 at the dose of 0.08 mg/kg and Hep3B-orthotopic hepatocellular carcinoma (HCC) model for HTX-L01-008 at the dose of 0.5 mg/kg.

Results LNP-mRNA formulated with HTX-L01 primarily targets liver, spleen, and less extent BM via intravenous injection. Specifically high level of transfection in hepatocytes, Kupffer cells and immune cells were achieved. In a hPBMC-reconstituted Raji-luc xenograft model, a much lower dosage and less frequent injection of HTX-L01-003 achieve the equivalent tumor regression/elimination efficacy as recombinant BiTEs (figure 1) in NHP studies, dose-dependent protein expression was observed in 3-week repeat dosing and resulted in transient T-cell activated and complete and sustained B-cell depletion (figure 2). HTX-L01-008 maintained the extended GPC3-CD3 BiTE protein expression, and successfully eliminates orthotopic HCC tumors in mice (figure 3).

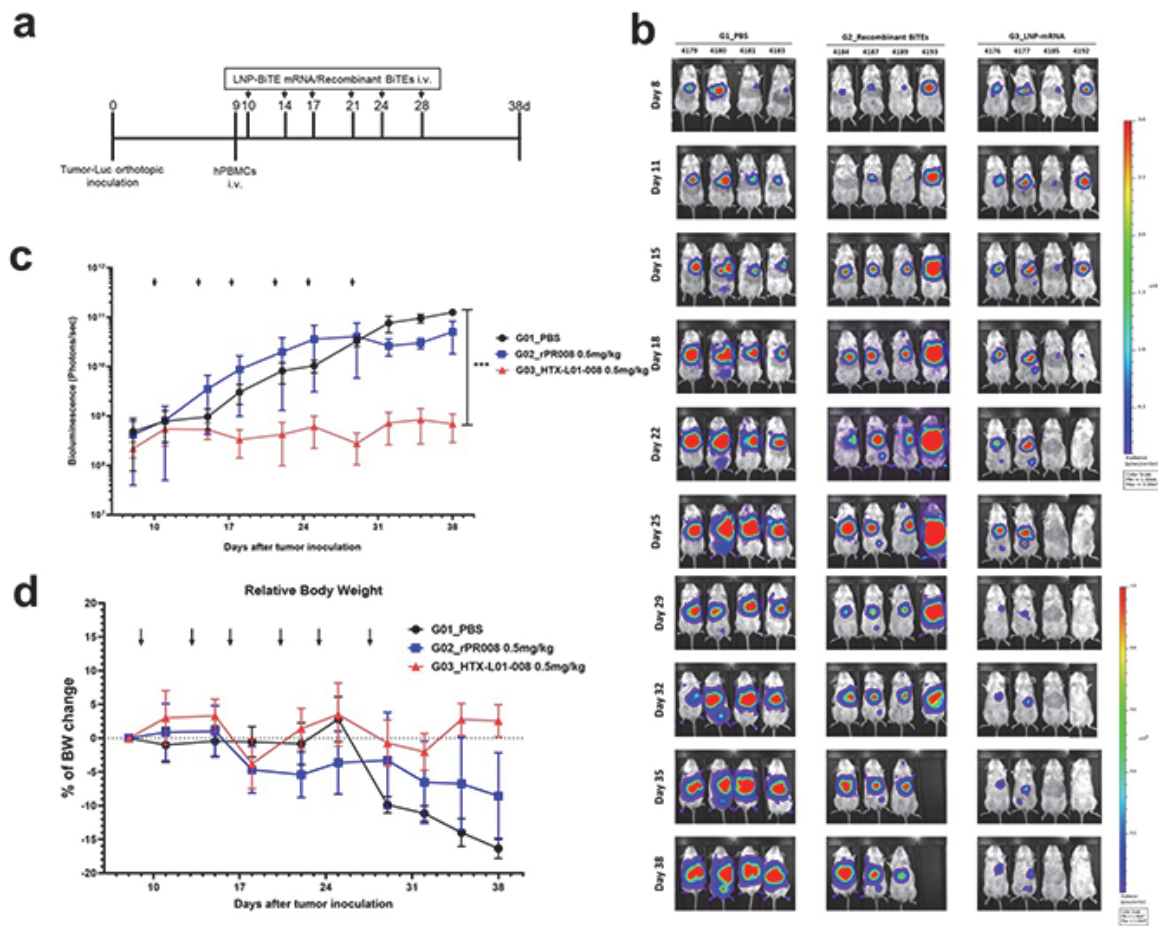
Conclusions Systemic administration of HTX-L01-003 demonstrated in-body and 'local' production of CD19/CD3 BiTE protein which resulted in highly potent and long-lasting depletion of target cells in both mouse and NHP studies. HTX-L01-008 demonstrates the ability to regress solid tumors *in situ* via i.v. injection. The LNP-mRNAs were well-tolerated. Overall, the studies showed the tissue targeting LNP-mRNA encoding BiTE provides a unique platform with enhanced efficacy and reduced toxicity for the treatment of both liquid and solid tumors.



Abstract 1358 Figure 1



Abstract 1358 Figure 2



Abstract 1358 Figure 3

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