# Immuno-Engineering

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## 1202 IN VIVO ENGINEERING OF CAR T CELLS USING A NOVEL TARGETED LNP-MRNA TECHNOLOGY

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**Background** Autologous chimeric antigen receptor (CAR) T cell therapies have revolutionized the treatment of some cancers and are now demonstrating effects in autoimmune disease. With several approved therapies on the market and cure rates approaching 50% in various hematologic malignancies, access to these life-saving therapies is paramount. However, challenges with cell manufacturing, scaling, and the need for inpatient treatment necessitate a truly off-the-shelf solution, especially for non-oncology indications. Utilizing the success of mRNA lipid nanoparticles (LNP) as COVID vaccines, Capstan Therapeutics has developed a novel targeted LNP (tLNP) platform that is purpose-built for specific delivery of therapeutic mRNAs to immune cells through functionalization with a targeting antibody.

**Results** Capstan has developed rationally designed proprietary LNPs that exhibit significantly reduced delivery to liver compared to conventional LNPs and effectively deliver to T cells when functionalized with a T cell specific targeting antibody. These Capstan proprietary tLNPs were well tolerated following a single intravenous dose up through 6mg/kg in male Sprague Dawley rats, a highly sensitive species for evaluating LNP toxicity. In vitro screens for the optimization of payload mRNA components, including UTR sequences and codon usage, resulted in a several fold increase in CAR expression and promoted improved tumor cell killing. CD5 and CD8 antibody tLNPs delivered a reporter gene mRNA payload to human cells in vivo in a humanized mouse model at high efficiency and specificity. CD8 tLNPs specifically reprogrammed CD8 T cells effectively with minimal reporter expression in CD4 T cells, whereas CD5 tLNPs reprogrammed both CD8 and CD4 T cell populations. Delivery of an anti-CD19 mRNA CAR construct by both CD5 and CD8 tLNPs into a human PBL-engrafted Nalm6 tumor-bearing mouse model resulted in rapid clearance of the tumor. Repeat doses of tLNPs (BIWx5) at dose levels up through 30 μg/animal were well tolerated and the CAR was expressed on T cells in vivo after single and repeat dosing.

**Conclusions** Capstan's tLNPs can specifically target and deliver a therapeutic CAR payload in vivo resulting in functional anti-tumor CAR T cells. This non-viral, redosable approach promises to improve access, efficacy, and safety, owing in part to lack of harsh lymphodepletion conditioning. Due to the versatility of this platform, treatments for various disease categories can be envisioned using different targeting binders to deliver a broad set of payloads to diverse cell populations.

**Ethics Approval** This study complied with all relevant ethical regulations and all animal protocols were approved by the Explora BioLabs (AAALAC-accredited) Institutional Animal Care and Use Committee (IACUC).