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Novel LNP delivered mRNA vaccine elicits potent immune responses and cures established tumor in mice

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INTRODUCTION

Lipid nanoparticle (LNP)-based mRNA vaccines have recently gained traction as an attractive modality for cancer therapies. However, inducing an effective anti-tumor response often requires the induction of a T cell response breaking self-tolerance mechanisms, a challenge for current therapies. Providence Therapeutics has developed next-generation LNP formulations, which can break self-tolerance and have the potential to be utilized for therapeutic LNP/mRNA cancer vaccines. Here, we report one such LNP formulation, LNP01, in the well characterized mouse syngeneic colorectal cancer model (MC38gp). Intramuscular administration of this next generation LNP formulation encapsulating mRNA expressing model glycoprotein antigens (3gp) from lymphocytic choriomeningitis virus (LCMV) elicited potent innate and adaptive immune responses. When it was used as a monotherapy in a therapeutic setting after tumor inoculation, LNP01-3gp mRNA significantly delayed tumor growth and cleared tumors in 52% of treated mice. The data suggests the possible applicability of our next generation LNP formulations for the development of effective therapeutic mRNA cancer vaccines for multiple solid tumors.

Methodology

1. *In vivo* immunogenicity – mRNA encoding 3 immunodominant epitopes to LCMV (3gp: gp33, gp61 and gp276) was formulated into LNP01 and injected intramuscularly to C57BL/6 animals to evaluate the induction of innate immune response and antigen specific $CD8^+$ T cells.
2. Tumor control – LNP01-3gp mRNA was further tested in a therapeutic setting as a monotherapy for the colon adenocarcinoma model (MC38gp) to assay potential for cancer therapeutics.

Providence Therapeutics LNP Development Programs

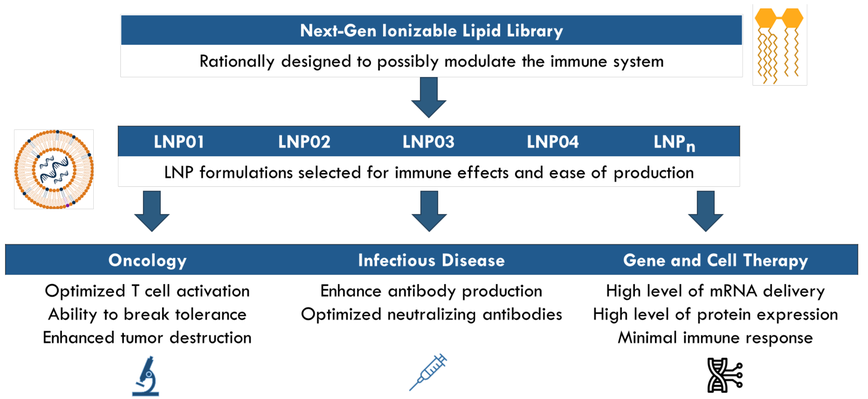

Figure 1. Providence Therapeutics LNP development programs
Providence therapeutics has developed multiple proprietary LNP formulations that are tailored to different clinical utilizations.

Immunization with next-generation LNP can induce potent immune responses

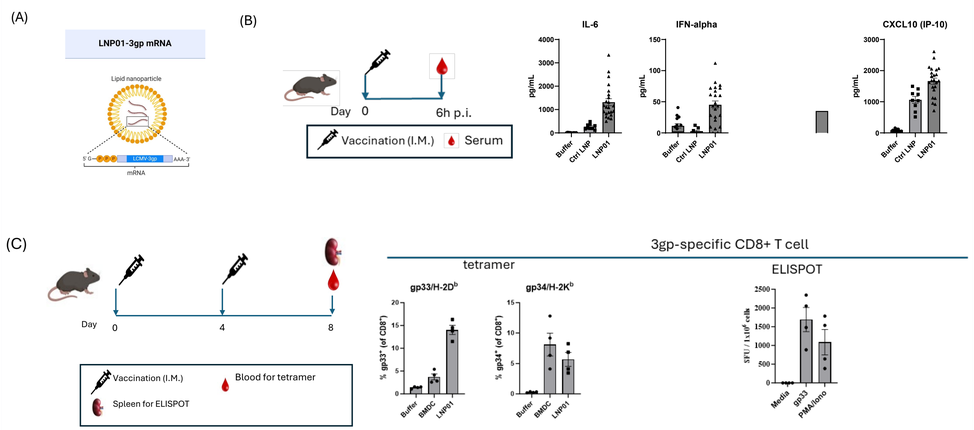

Figure 2. LNP01 encapsulated 3gp mRNA induced potent immune responses
Female C57BL/6 mice were immunized with 50µL of LNP01-3gp mRNA in the biceps-femoris. (A) Schematic representation of LNP01-3gp mRNA. (B) Innate immune response. Serum samples collected 6 hours p.i. were used to measure cytokines and chemokines. (C) T cell immune response. Peripheral blood was stained for antigen specific CD8+ T cells using tetramers to gp33/H-2Db and gp34/H-2Kb. BMDC group mice received bone marrow derived dendritic cells , matured with CpG and pulsed with gp33, gp61 and gp276 peptides delivered i.p. on days 0, 2 & 4 ($5x10^5$ cells/injection). In ELISPOT, splenocytes from LNP01-3gp mRNA vaccinated mice were stimulated with gp33 peptide or media as negative control or PMA plus Ionomycin as positive control.

Immunization with next-generation LNP inhibited tumor growth and cured established tumor in MC38gp tumor model

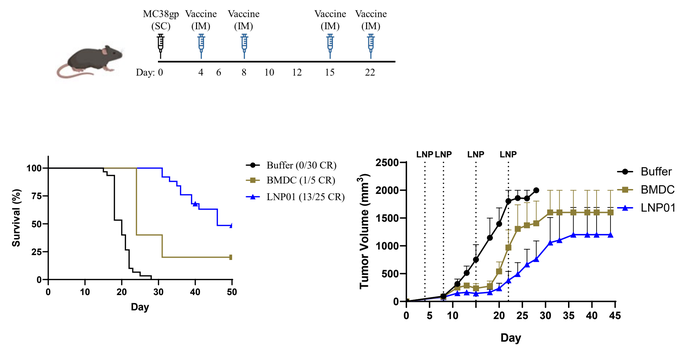

Figure 3. LNP01-3gp mRNA immunization cured tumor in MC38gp model
Female C57BL/6 mice were inoculated s.c. with $1x10^6$ MC38gp tumor cells on day 0 and treated with LNP01-3gp mRNA on days 4, 8, 15 & 22 (12.5µg/50µl/dose). BMDCs matured with CpG and pulsed with gp33/61/276 peptides were used as a positive control and delivered i.p. on days 4, 6 and 8 ($5x10^5$ cells/dose). Tumor volume was measured using digital calipers and calculated as $Width^2xLength/2$. Animals clearing established tumor were deemed to have a complete response (CR).

CONCLUSIONS

- Multiple next generation LNP formulations tailored to different clinical applications are under development at Providence Therapeutics (Fig. 1).
- A novel next generation LNP formulation, LNP-01, developed for use as a cancer treatment, was evaluated in mouse models (Fig. 2 and Fig. 3).
- LNP01-mRNA vaccines are capable of breaking self-tolerance (AACR 2024, Abstract # 6740) and inducing potent immune responses in mice (Fig. 2).
- LNP01-mRNA vaccines cured established MC38gp tumors (Fig. 3) and glioblastomas in mice (AACR 2024, Abstract # 5002).

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