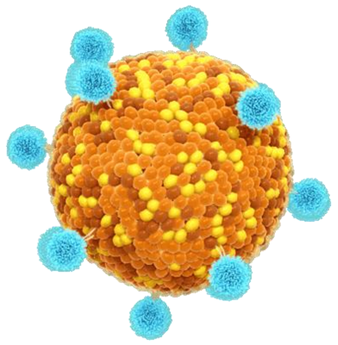
mRNA THERAPY FOR ORNITHINE TRANSCARBAMYLASE DEFICIENCY

Marciano Sablad, Yanjie Bao, Jerel Vega, Hari Bhaskaran, Carlos Perez-Garcia, Jose Gonzalez, Thanhchau Dam, Patty Limphong, Jared Davis, Priya Karmali, Suezanne Parker, Pad Chivukula

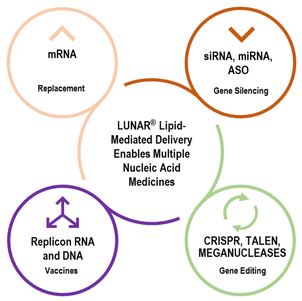
Arcturus Therapeutics, Inc., San Diego, CA, USA

Contact: Marciano R Sablad, marciano@arcturusrx.com

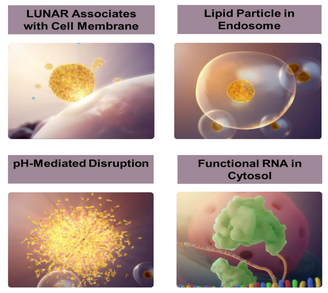


INTRODUCTION

Arcturus Therapeutics is a nucleic acid medicines company focused on developing RNA therapeutics to treat rare diseases. Our proprietary LUNAR® lipid-mediated delivery technology enables the efficient delivery of any mRNA into a variety of cell types and tissues, and can be optimized for multiple routes of administration.



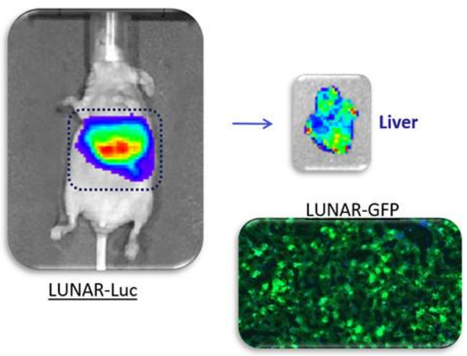
LUNAR® lipid nanoparticles carrying the mRNA payload reaches the target cell, where it fuses with the plasma membrane forming an intracellular endosome. This endosomic particle undergoes a pH-mediated disruption that causes the breakdown of the biodegradable nanoparticle and the delivery of the mRNA into the cytoplasm. The mRNA then follows the cells endogenous translational and post-translational routes to generate the protein of interest.



LUNAR®-OTC treats patients suffering from ornithine transcarbamylse deficiency (OTCD) using mRNA to replace the wild-type human enzyme. OTCD is a rare metabolic disease in which the urea cycle cannot efficiently convert ammonia into urea. The efficacy of LUNAR®-OTC was evaluated in an animal model of OTCD ameliorating certain OTCD disease phenotypes in mice.

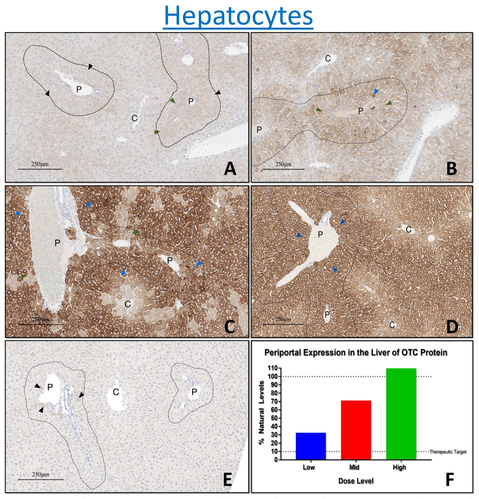
RESULTS

1. LUNAR® -Luciferase and LUNAR®-GFP mRNA Delivery into the Liver



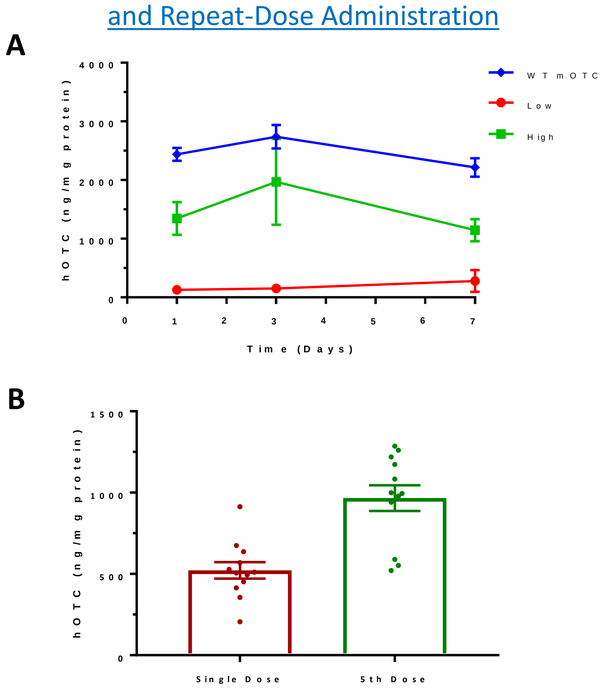
In vivo imaging demonstrated a broad distribution of bioluminescence (LUNAR®-Luciferase) and fluorescence (LUNAR®-GFP) in the liver after intravenous administration in wild type mice.

2. OTC Protein Expression in Periportal Hepatocytes



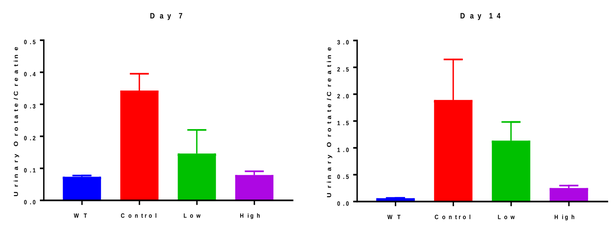
LUNAR®-OTC produced dose related increases in periportal hepatocyte OTC protein expression in OTC *spf-ash* mice. A) Low, B) Mid, C) High, D) Wild Type Control, E) OTC *spf-ash* Control, F) OTC protein IHC staining intensity compared to wild type animals.

3. Human OTC Protein Expression in Liver after Single and Repeat-Dose Administration



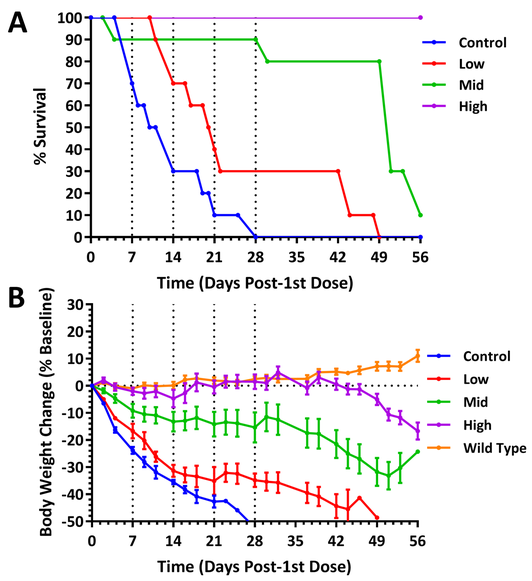
LUNAR®-OTC led to persistent human OTC protein expression in mouse liver after A) Single intravenous dose administration B) 5 weekly intravenous treatments which displayed human OTC protein accumulation (~2-fold) when compared to single-dose in wild type mice.

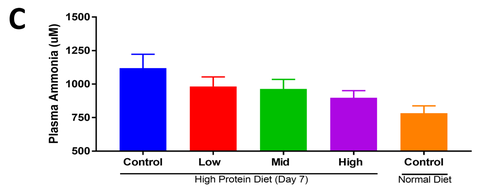
4. Reduction of Urinary Orotate in OTC *spf-ash* Mice after Single-Dose Administration



Single-dose administration of LUNAR®-OTC in OTC *spf-ash* mice led to dose dependent and maintained reduction of urinary orotate, a biomarker for the urea cycle. Normalization of urinary orotate to wild type control levels was observed out to Day 14.

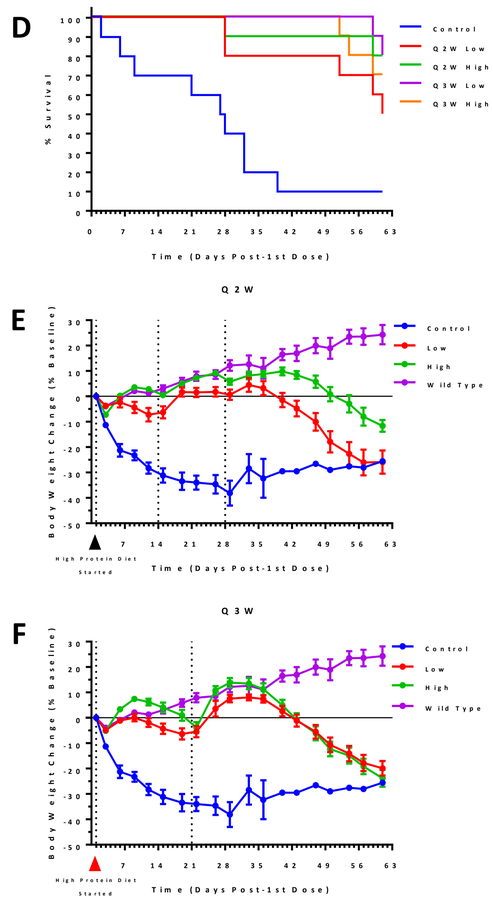
5. LUNAR®-OTC Efficacy in a High Protein Diet Hyperammonemia Model in OTC *spf-ash* Mice





OTC *spf-ash* mice were treated with LUNAR®-OTC and immediately placed on a high protein diet (53%) to induce hyperammonemia. Subsequently, animals were dosed on a weekly basis until Day 28. Control animals showed a rapid decline in survival and dramatic body weight loss. Q1W treatment with LUNAR®-OTC resulted in a dose dependent improvement of A) % survival and, B) body weight change compared to Control animals. Extended efficacy was observed for up to one month after the last dose consistent with previously observed OTC protein accumulation. One week after 1st dose, LUNAR®-OTC dose dependently reduced plasma ammonia levels (C).

In a regimen optimization study, animals were placed on a Q2W (every 2 weeks; Day 0, 14, 28) and Q3W (every 3 weeks; Day 0, 21) dosing regimen



and monitored for survival and body weight changes. LUNAR®-OTC related improvement of survival was observed in the Q2W and Q3W dosing regimens when compared to Control animals (D). Dose related inhibition of body weight loss was observed in the E) Q2W and, F) Q3W treatment groups. Improvements in body weight changes can be seen directly after each dose administration.

All together, these results demonstrate that LUNAR®-OTC has the potential to provide significant benefit to patients with OTCD.

CONCLUSIONS

- LUNAR® targeted reporter mRNA into the liver where bioluminescence and fluorescence was observed.
- LUNAR® -OTC targeted hepatocytes and produced OTC protein within & outside the periportal region of the liver.
- Single-dose administration of LUNAR®-OTC produced prolonged human OTC protein expression in the liver.
- Repeat-dose administration of LUNAR®-OTC resulted in human OTC protein accumulation.
- Urinary orotate levels in OTC *spf-ash* mice were reduced out to 14 days after a single treatment of LUNAR®-OTC.
- Q1W treatment with LUNAR®-OTC protected OTC *spf-ash* mice from high protein diet-induced (hyperammonemia) weight loss and mortality. Efficacy persisted up to 28 days after the cessation of dosing as evidenced by effects on body weight and prolongation of survival.
- Dosing as infrequently as Q3W protected OTC *spf-ash* mice from high protein diet induced weight loss and mortality.
- LUNAR®-OTC has the potential to provide significant benefit to patients with OTCD.