LUNAR®-CF, an aerosolized mRNA replacement Therapy for Cystic Fibrosis Lung Disease

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LUNAR®-CF Overview

LUNAR®-CF is an aerosolized mRNA replacement therapy to treat Cystic Fibrosis (CF) Lung Disease, a therapeutic approach agnostic to a patient’s genotype. A healthy copy of the human CFTR mRNA is encapsulated into lipid nanoparticles (LUNAR®-hCFTR), aerosolized to patient’s airways using a vibrating mesh nebulizer to directly deliver a de novo human CFTR mRNA into epithelial cells. This human CFTR mRNA encodes a fully functional human CFTR protein that will be beneficial to facilitate mucociliary clearance and improve CF lung disease.

Results

1. Aerosolized LUNAR®, A Delivery Platform for Lung

Aerosolized LUNAR® droplets (2.3 microns) are highly breathable and optimal for lung delivery. To determine if LUNAR® formulations are biologically active as an aerosol, LUNAR®-EGFP mRNA formulations were nebulized, pre- and post-nebulized fractions were collected and used to transduce HBE cells. After a 6h incubation, EGFP expression was visualized under the microscope with similar levels of EGFP expression in both fractions, indicating that the functional properties of LUNAR®-EGFP mRNA were maintained as an aerosol. C: LUNAR®-Luciferase mRNA was nebulized in WT mice and IVIS system was used for imaging. Luminiscence was observed in lower and upper airways. PBS controls were negative.

2. Codon-Optimized mRNAs Generate C-Band Glycosylated Plasma Membrane Proteins

A: WB and quantitation of CFTR C-band expression levels in transfected CBE cells. B: CBE cells were transfected with an optimized hCFTR mRNA, followed by fractioning and de-glycosylation. hCFTR expression was only observed in the plasma membrane fraction of transfected cells. C-band transitioning to A-band was observed in the de-glycosylated samples.

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Conclusions

- Codon optimization is a feasible approach to develop improved hCFTR sequences with higher protein levels and active chloride channels that might be beneficial for mucociliary clearance in CF-patients’ lungs.
- Efficient LUNAR®-mediated delivery of mRNA into ciliated lung epithelial cells has been demonstrated in rodents (mice, rats) and non-rodents (ferrets, NHPs).
- LUNAR® delivery platform is optimal for lung therapeutics such as CF Lung Disease.