# ARCTURUS THERAPEUTICS

Building Next Generation of the RNA Medicines

LUNAR®-CF, an aerosolized mRNA therapy for CF lung disease

Carlos G. Perez-Garcia, Ph.D.

ASGCT, May 2020

# FORWARD LOOKING STATEMENTS



This presentation contains forward-looking statements. These statements relate to future events and involve known and unknown risks, uncertainties and other factors which may cause our actual results, performance or achievements to be materially different from any future performances or achievements expressed or implied by the forward-looking statements. Each of these statements is based only on current information, assumptions and expectations that are inherently subject to change and involve a number of risks and uncertainties. Forward-looking statements include, but are not limited to, statements about: expectations regarding our capitalization and resources; the adequacy of our capital to support our future operations and our ability to successfully initiate and complete clinical trials; our strategy and focus; the development and commercial potential of any of our product candidates; the timing and success of our development efforts; the success of any of our trials and our ability to achieve regulatory approval for any product candidate; the entry into or modification or termination of collaborative agreements and the expected milestones and royalties from such collaborative agreements ; the potential market or clinical or commercial success of the clinical development programs of Arcturus; and any statements other than statements of historical fact, including those related to Arcturus' future cash, market or financial position.

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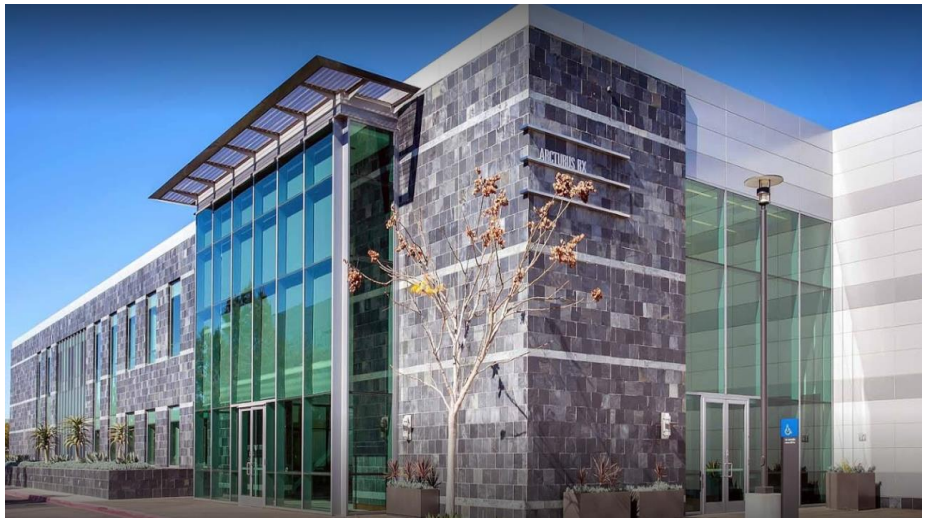
# Company Highlights

BUILDING INNOVATIVE
RNA MEDICINES

## Arcturus is a Clinical-Stage mRNA Medicines and Vaccines Company

### Publicly Traded (NASDAQ:ARCT)

- Headquarters: San Diego, CA
- Number of Employees: 90
- Founded: 2013



### Strong Intellectual Property Technology Portfolio

- 188 Patents & Patent Applications
- LUNAR® Delivery Technology
- STARR™ RNA Manufacturing Process
- Drug Product (LUNAR® + STARR™) Manufacturing Process

### Arcturus Technologies Validated by Multiple Strategic Partners

Johnson & Johnson · Takeda · ultragenyx pharmaceutical · CYSTIC FIBROSIS FOUNDATION · DukeNUS Medical School

# Arcturus Pipeline of mRNA Medicines

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| Name | Indication | IND/CTA Estimated Timing | Clinical Stage | Route of Administration | Target Organ | Target Cells | Prevalence Worldwide |
|---|---|---|---|---|---|---|---|
| **LUNAR-OTC (ARCT-810)** | Ornithine Transcarbamylase (OTC) Deficiency | IND & CTA: Trials Allowed to Proceed | U.S. Phase 1b N.Z. Phase 1 | Intravenous (i.v.) | Liver | Hepatocytes | > 10,000 |
| **LUNAR-COV19** | COVID-19 Vaccine | CTA Summer 2020 | Preclinical | Intramuscular (i.m.) | Muscle | Myocytes Dendritic Cells | Global |
| **LUNAR-CF** | Cystic Fibrosis | IND 2021 | Preclinical | Inhaled Aerosol | Lung | Bronchial Epithelial Cells | > 70,000 |
| **LUNAR-CV** | Rare Cardiovascular Disease | IND 2022 | Preclinical | Intravenous (i.v.) | Liver | Hepatocytes | Undisclosed |
| **LUNAR-MD** | Rare Metabolic Disease | IND 2022 | Preclinical | Intravenous (i.v.) | Liver | Hepatocytes | Undisclosed |

- **LUNAR-OTC (ARCT-810): Phase 1b & Phase 1 Clinical Trials Allowed to Proceed Under IND & CTA, Respectively**
- **LUNAR-COV19: CTA Filing Target Summer 2020**
- **LUNAR-CF: IND Application Filing Target 2021**

ARCTURUS THERAPEUTICS

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RNA MEDICINES

# LUNAR® Lipid-Mediated Delivery

## Versatile

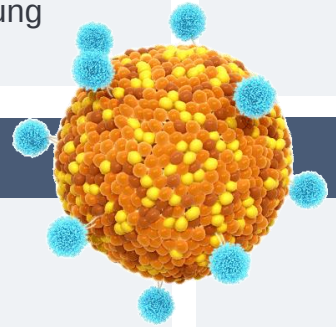
| Feature | Benefit |
|---|---|
| Compatibility | Formulated with multiple RNA modalities |
| Route of Administration | IV, IM, Nebulization |
| Cell Type | Hepatocytes, Stellate cells, Myocytes & Lung Epithelial cells |

## Proprietary

**Diverse Library of over 200 Proprietary Lipids**

Rational Design to Maximize Efficacy and Increase Tolerability

Formulation Compositions Customized for Application and Cell Type of Interest



## Biodegradable

**No Accumulation of Lipids**

## Manufacturing Efficiency

**Scalable and Reproducible Production Process**

**Arcturus LUNAR® is Enabling the Next Generation of RNA Medicines**

# RNA Therapy

## Endothelial

## Epithelial

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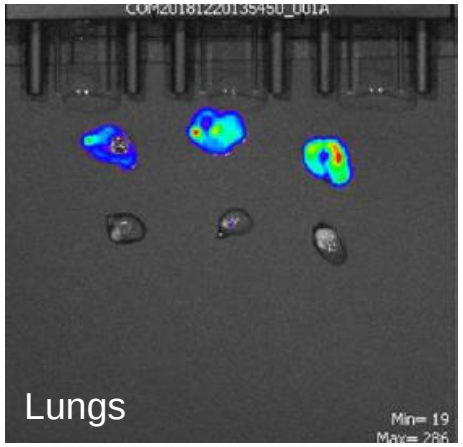
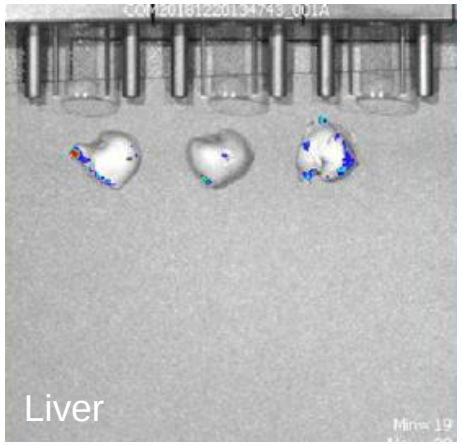
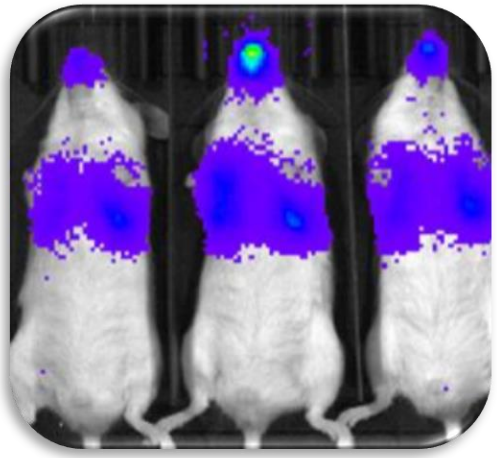
### *Intravenous*



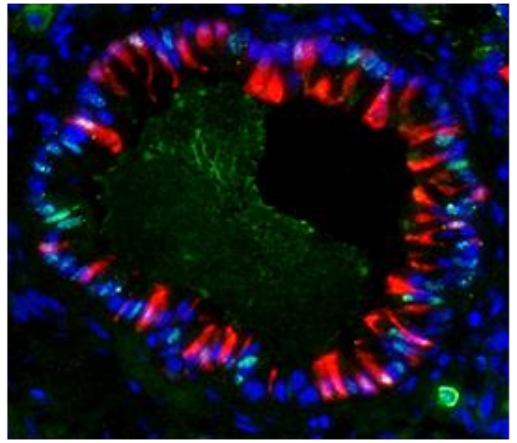




**Selective delivery of LUNAR® to mouse lungs, with minimal delivery to the liver via IV**

### *Nebulization*



**Nebulization of LUNAR®-mRNA**

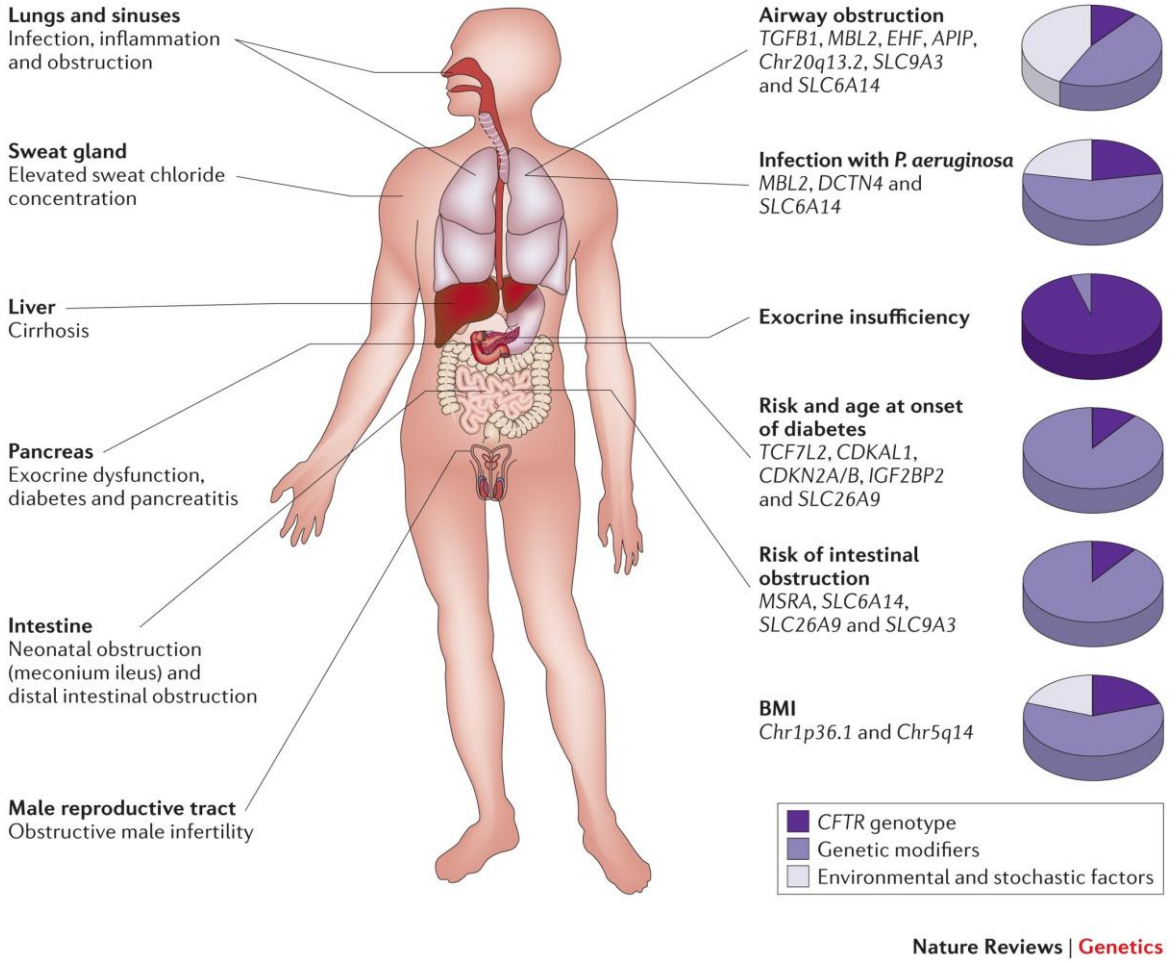


**Ciliated epithelial cells targeted in the mice airways**

*LUNAR® composition can be modulated to be utilized via Nebulization or Intravenous to treat lung diseases*

# What is Cystic Fibrosis (CF)?

- CF is a rare and inherited disease
- CF is considered a multi-systemic disease affecting multiple organs
- CF mainly affects children and young adults.
- People with CF can still live an active life when the condition is properly managed (e.g. modulators therapy if suitable)
- Epidemiology:
  - 30,000 patients in US
  - 70,000 patients worldwide
  - ~1,000 cases diagnosed annually
  - 1/29 Americans are carriers of a defective copy of CFTR
- ~40 years is current life expectancy




(Cutting, 2014)

# Disease Profile

- Significant Unmet Needs
  - Mucus buildup in the multiple organs
  - Mucociliary clearance failure, increase in infections and exacerbated inflammatory responses
  - Mortality is primary driven by progressive decline in lung function
  - Current treatments are palliative (mutation-specific)
  - Physiological and psychological burdensome
  - No cure

- Standard-of-Care (1-2x/day, 2-3h/day)
  - Inhaled medicines:
    - Antibiotics
    - Mucolytics
  - Inflatable vests
  - Pancreatic enzyme supplement
  - Multivitamins

- Current Therapies:
  - Small molecule modulators (e.g. Trikafta), daily
    - Gene mutation specific (F508del/X)

## Cystic Fibrosis

*Genetic mutations in Cystic Fibrosis Transmembrane Regulator (CFTR) result in dysfunctional or absent CFTR protein*

# Classes of mutations in the CFTR gene

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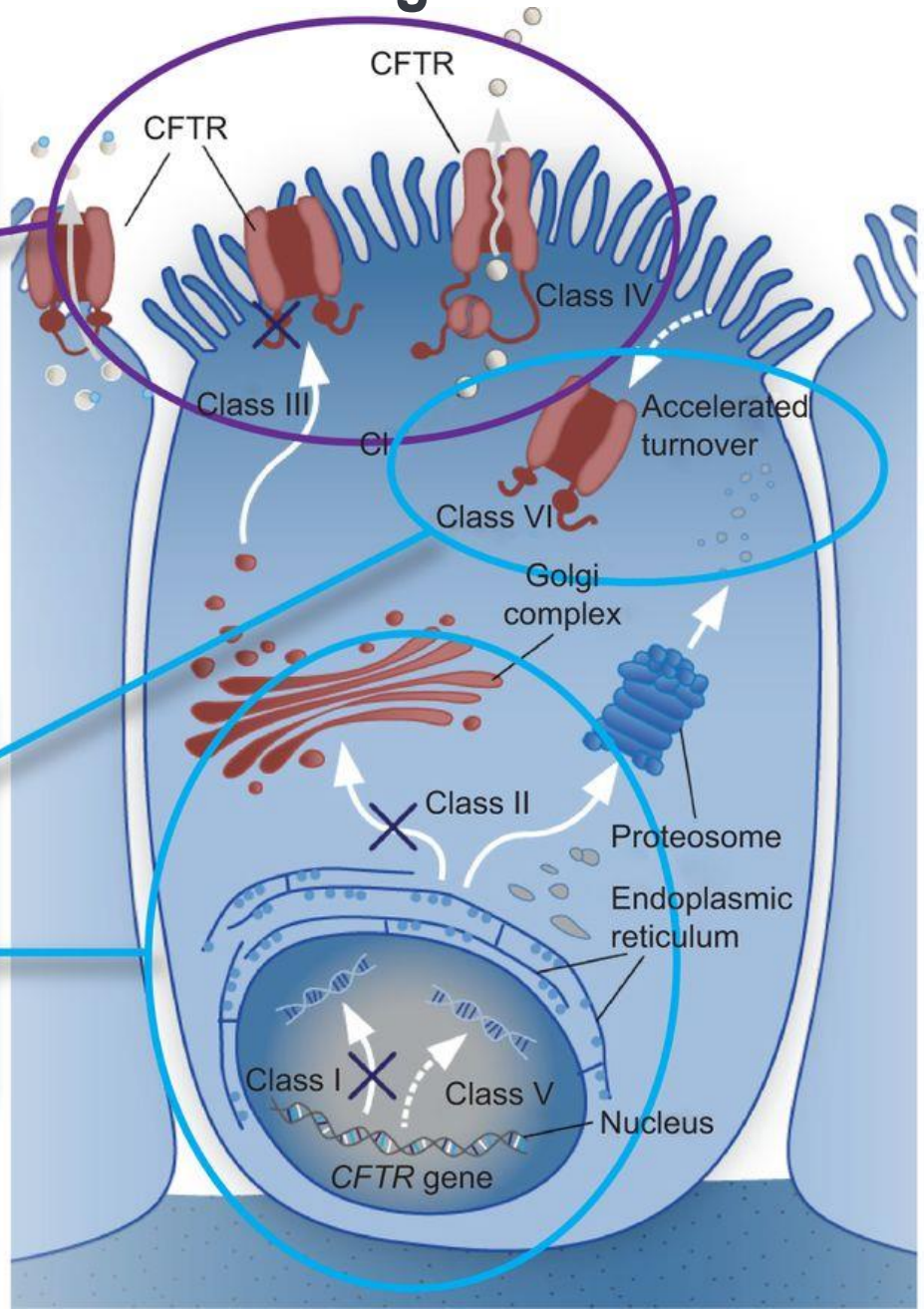
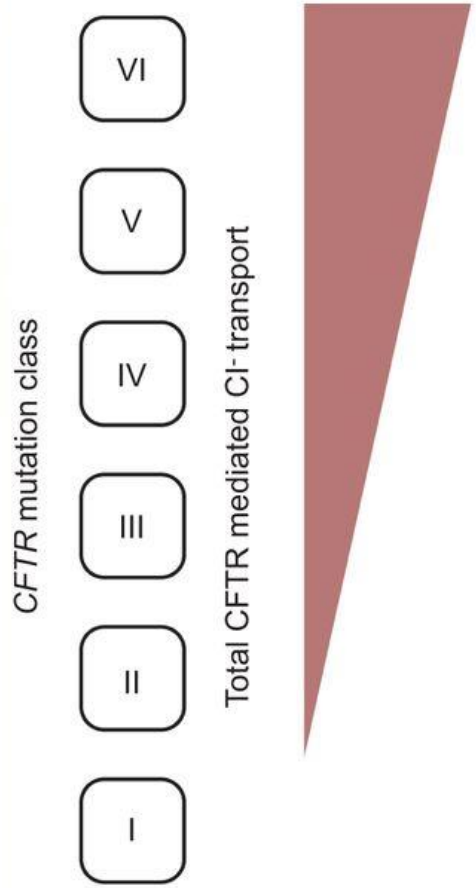
Mutations that reduce the FUNCTION of CFTR proteins at the cell surface (including gating and conductance)

Mutations that reduce the QUANTITY of functional CFTR proteins that reach the cell surface

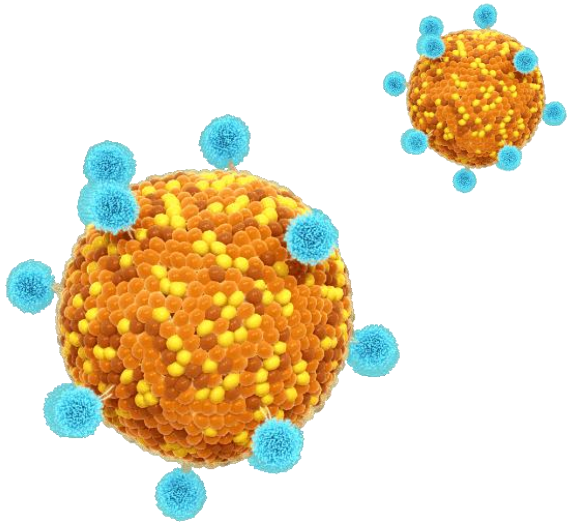


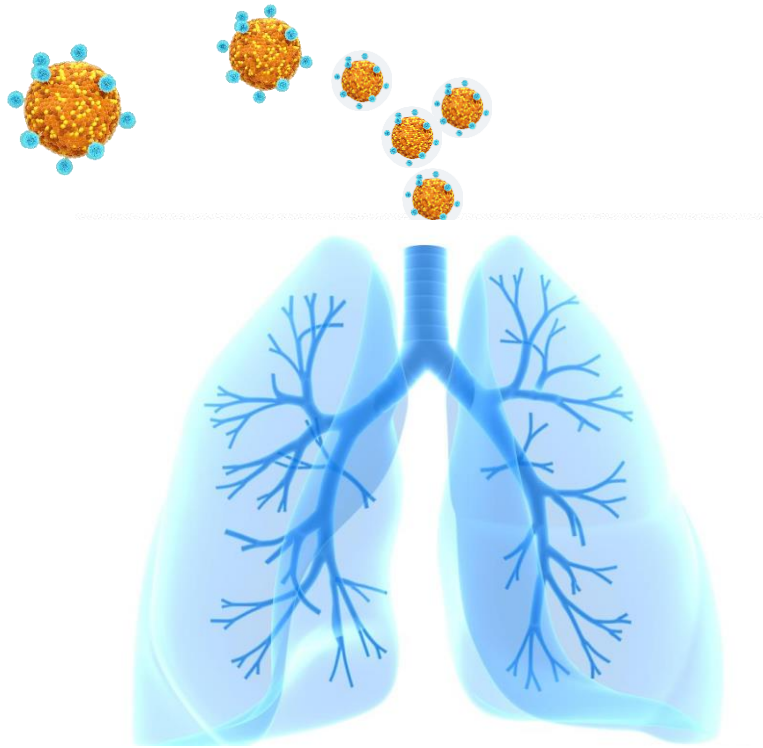




(Derichs, 2013)

# LUNAR®-CF Drug

mRNA Replacement Therapy



Cargo: mRNA

Delivery vehicle: LUNAR®

Delivery format: Aerosol

**Targeted Patient Population** *Patient-agnostic*

LUNAR®-CF

# KEY PRECLINICAL MILESTONES TO SUPPORT FIH

- ✓ In vitro: FRT and HBE cells
- ✓ Aerosol Development for LUNAR®
- ✓ Achieved delivery of LUNAR® formulations in epithelial airways
  - ✓ Rodents: WT and disease models (mice, rat)
  - Non-rodents:
    - ✓ Ferrets
    - NHP (ongoing)
- ✓ Achieved Delivery of LUNAR® formulations in ciliated epithelial cells
  - ✓ Rodents: lung and nasal
  - ✓ Ferret
- ✓ Achieved efficacy in disease model
- ✓ Delivery POC to human lung explants

# LUNAR®-CF: Aerosol Development

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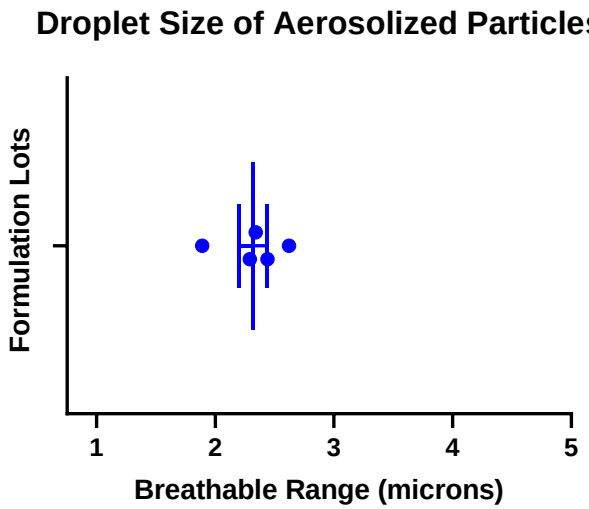
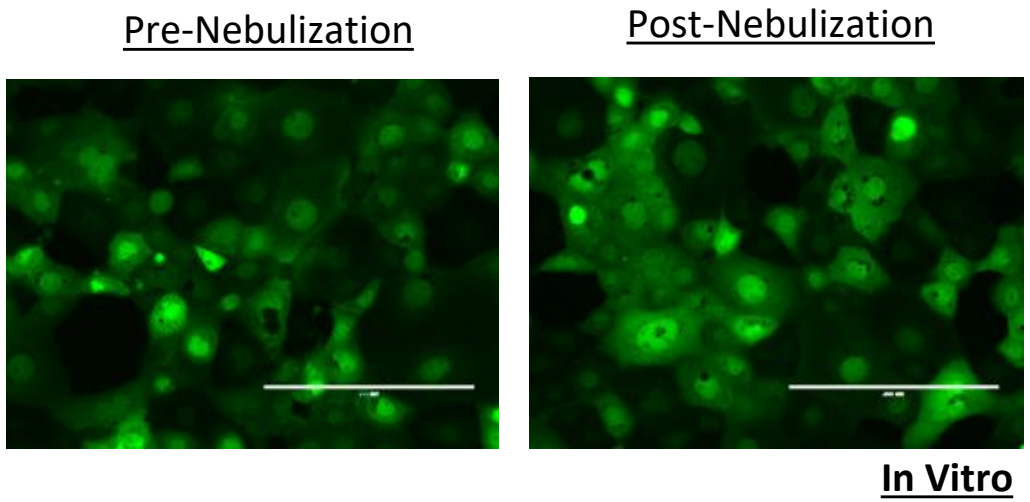
## *Aerosolized LUNAR® particles are breathable*




- **Aerosolized LUNAR® droplets are highly breathable**

## *Aerosolized LUNAR ®-mRNA (EGFP) maintains activity*




- **LUNAR®-EGFP mRNA maintains its functional properties as an aerosol**

**Aerosolized LUNAR® droplets (2-3 microns) are in the optimal breathable range for lung delivery**
**Aerosolized LUNAR® maintains physicochemical properties**

# LUNAR®-CF

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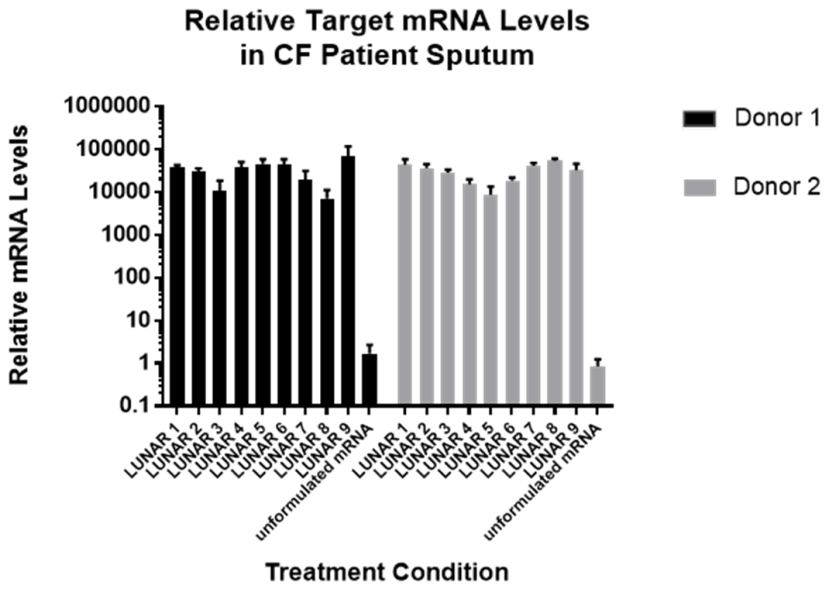
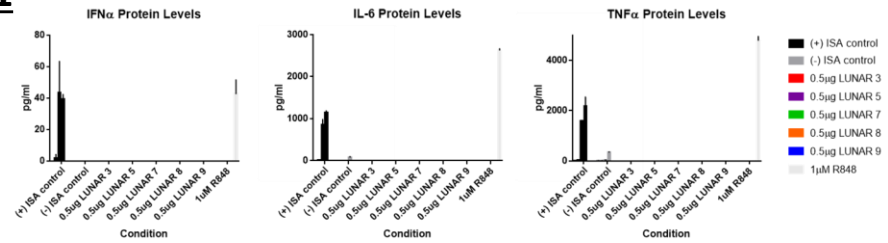
## CF Sputum Stability



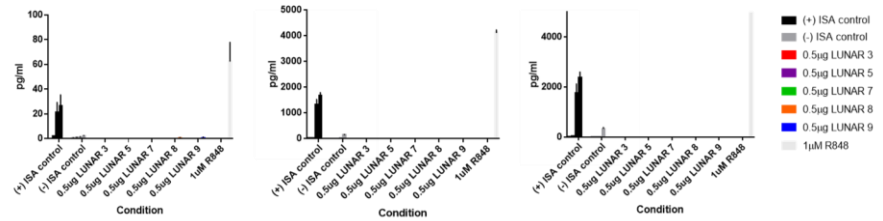

- **LUNAR® protects the mRNA from degradation in CF patient sputum**

## Immunostimulatory Activity In Vivo

**Donor #1**




**Donor #2**




- **LUNAR®-mRNAs show minimal immunostimulatory activity**

**LUNAR®-mRNAs shields the mRNA with minimal immunostimulatory activity**

# SCREENING OF CODON-OPTIMIZED MRNAS

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*Arcturus' proprietary mRNA optimization platform*

*In vitro Screening*

A

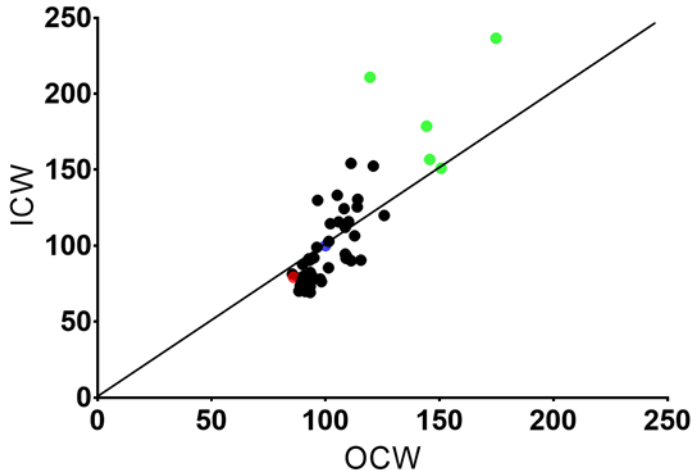
***Optimized conditions***

- mRNA sequence
- Chemistry
- Process optimization

→

- Improved protein expression and duration
- Improved functional activity


B

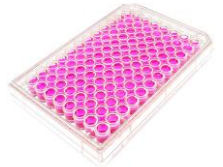



- Codon optimized sequences were generated and screened in CFBE cells in vitro
- Expression levels are several fold higher than the natural sequence (blue dot)

**hCFTR protein expression is improved with codon optimized leads**

Screening

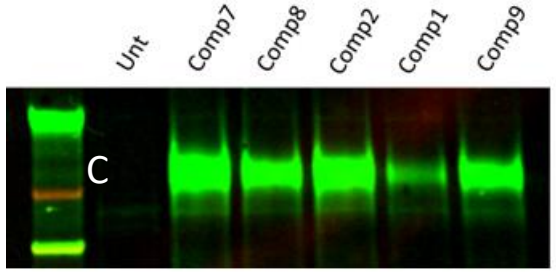
# EFFICACY IN VITRO



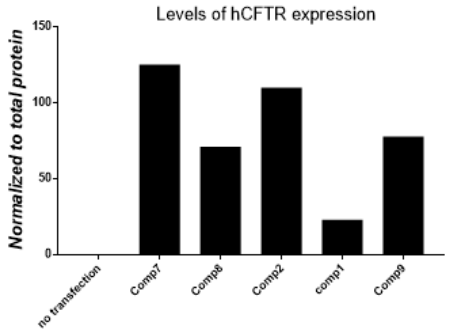
BUILDING INNOVATIVE RNA MEDICINES

## *Expression of mature hCFTR protein in vitro*

A



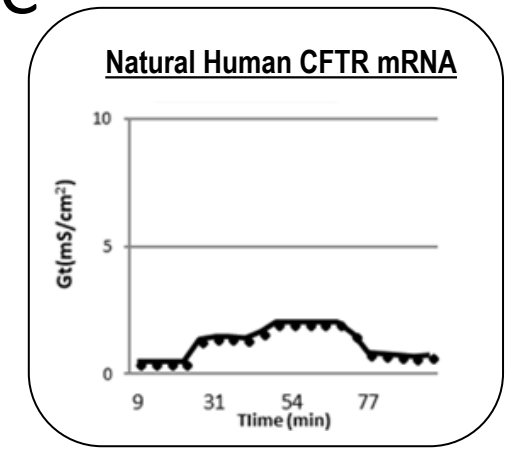

B




- **Codon optimized hCFTR and human natural sequence mRNAs were transfected in CFBE cells.**
- **Protein analysis was performed by WB with a human specific CFTR antibody**
- **Codon optimized hCFTR mRNAs (Comps 2, 7, 8, 9) express higher levels of mature protein (C-band) than the natural sequence (Comp1), as observed in A-B.**

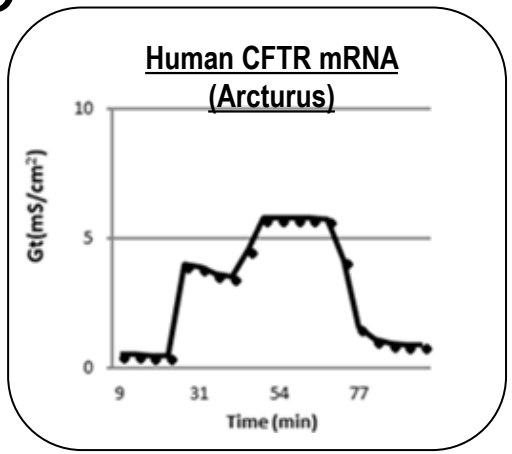
## *Air-Liquid Interface in FRT cells*

C




D

Representative image




- **Codon optimized hCFTR and human natural sequence mRNAs were tested in ALI using FRT cells**
- **Polarized FRT cells were treated with benzamil to inhibit ENaC, followed by Forskolin/VX770 to activate specific-CFTR channel responses**
- **The data generated indicates that codon optimized hCFTR mRNAs are several fold more active than the natural sequence**

**Codon optimized hCFTR mRNAs are highly expressed and are biologically active**

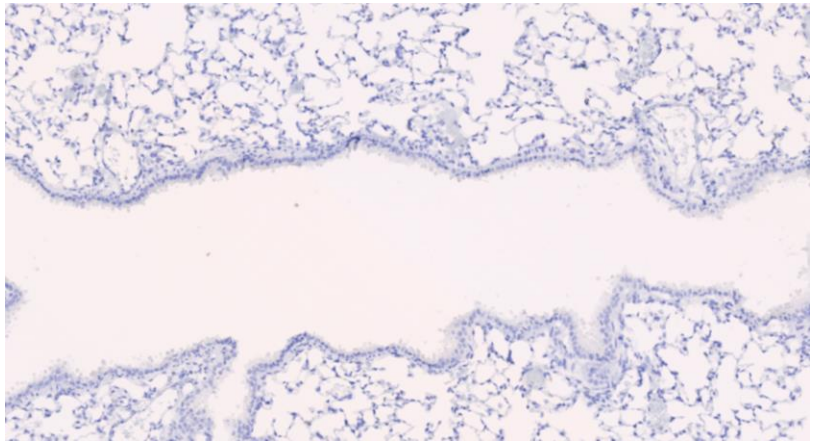
Efficacy

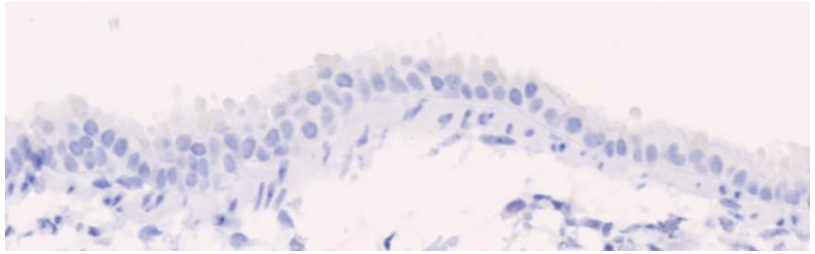
# LUNAR® TARGETING THE LUNG (RODENT)

BUILDING INNOVATIVE
RNA MEDICINES

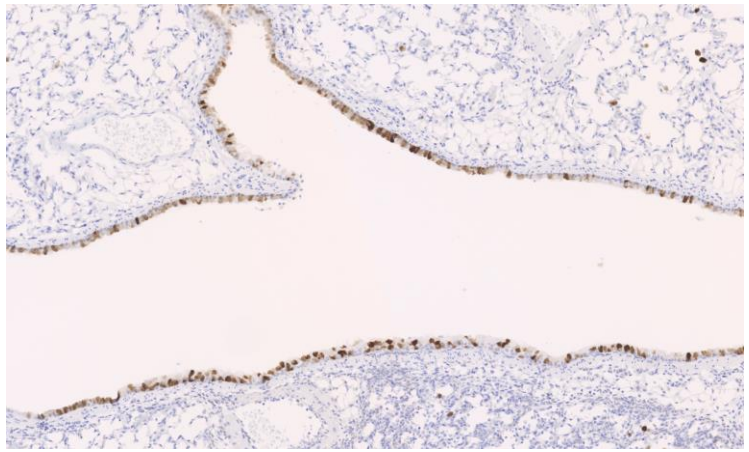
*Delivery of LUNAR®-mRNA into lung epithelial airways*

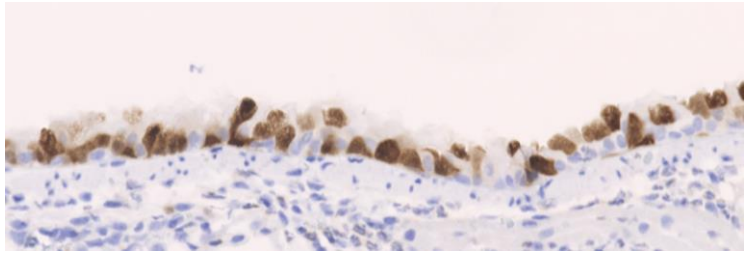
*PBS-treated*





*LUNAR®-TdTomato-treated*





- **LUNAR®-TdTomato mRNA was administered to WT mice**
- **The presence of TdTomato protein (IHC) indicates that LUNAR® can target epithelial airways in rodent**

**LUNAR® formulations can efficiently target the epithelial airways in the rodent**

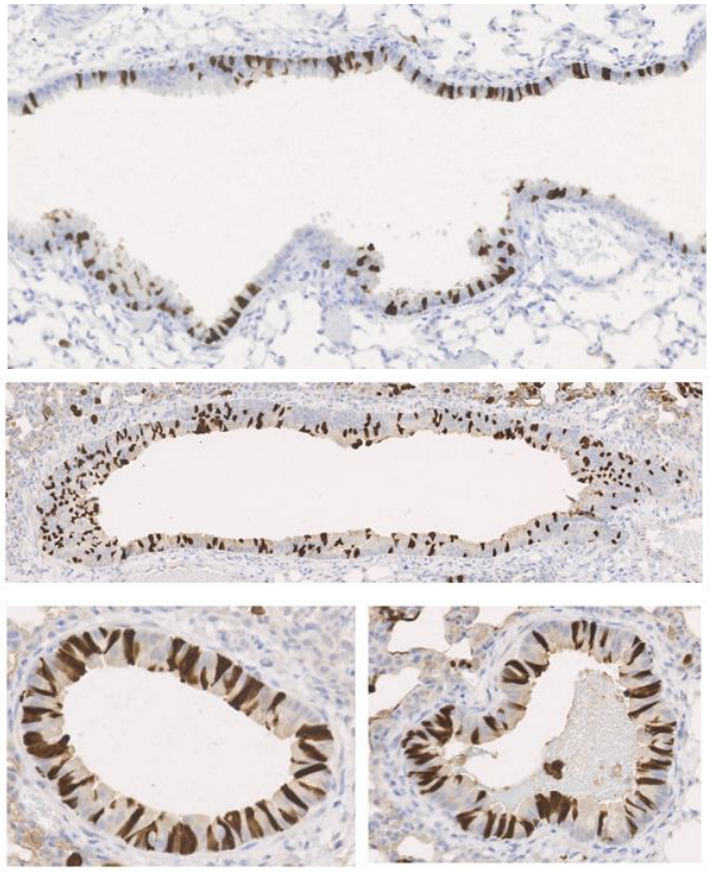
Lung Deposition

# LUNAR® TARGETING CILIATED CELLS (LUNG)

UNLEASHING INNOVATIVE A MEDICINES

*Delivery of LUNAR®-mRNA targeting ciliated epithelial cells*

A



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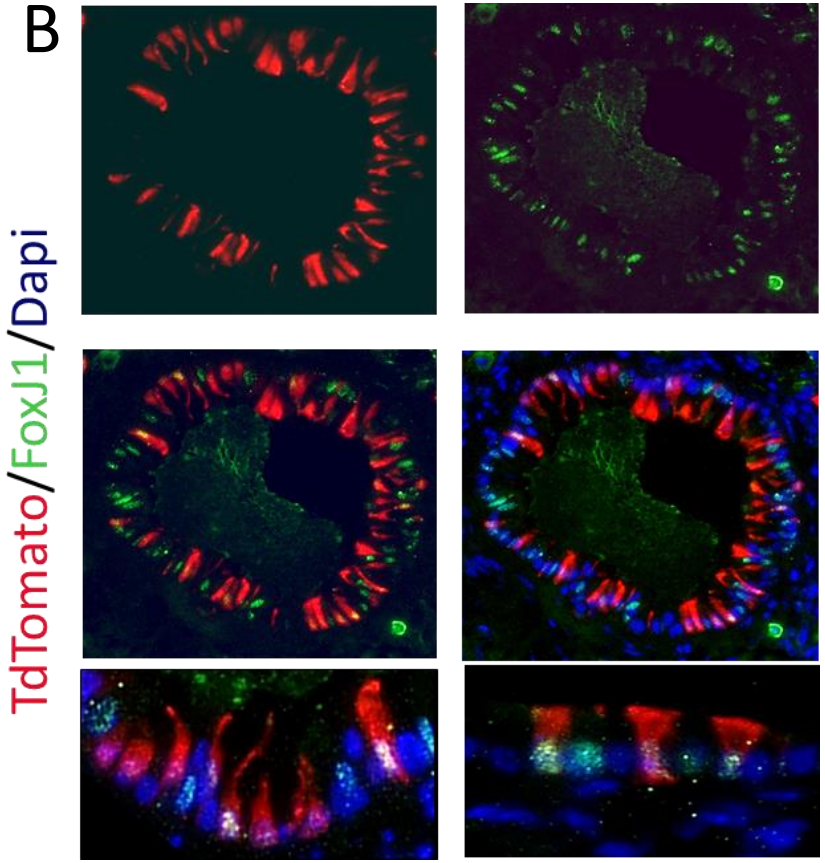



- **LUNAR®-Cre mRNA was asministered to Floxed-TdTomato transgenic mice**
- **TdTomato protein (IHC) is detected in large and small epithelial airways (A)**
- **Co-localization with FoxJ1 (immunofluorescence, B) confirms the targeting of ciliated epithelial cells**

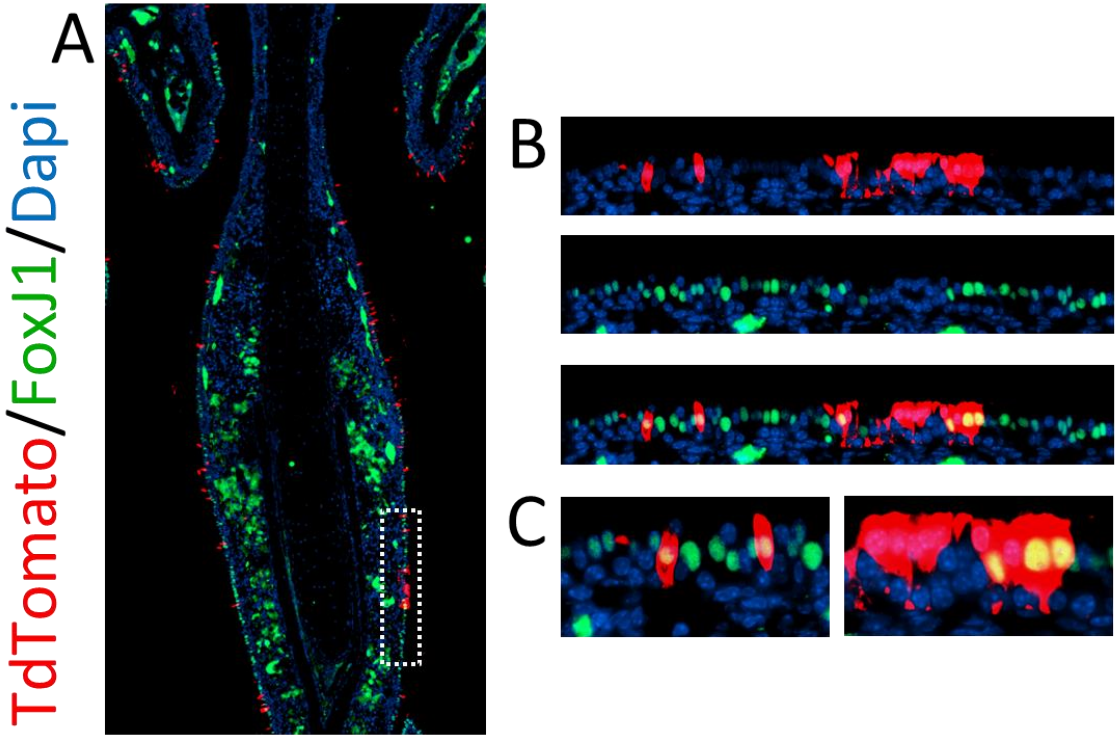
**LUNAR® selective delivery to lung ciliated epithelial cells in the rodent airways**

Lung Deposition

# LUNAR® TARGETING CILIATED CELLS (NASAL)

BUILDING INNOVATIVE MEDICINES

*Delivery of LUNAR® formulations in the nasal epithelia*




- **LUNAR®-Cre mRNA delivered IN to Floxed-TdTomato transgenic mice**
- **TdTomato protein (IHC) is detected in the nasal epithelial airways in mice**
- **Co-localization with FoxJ1 (immunofluorescence) confirms targeting ciliated epithelial cells**
- **~60% of TdTomato positive cells targeted are ciliated (D)**

Nasal Deposition

**LUNAR®-mRNA formulations target ciliated cells in both nasal and lung epithelial airways**

IN: intra-nasal

# EFFICACY IN VIVO

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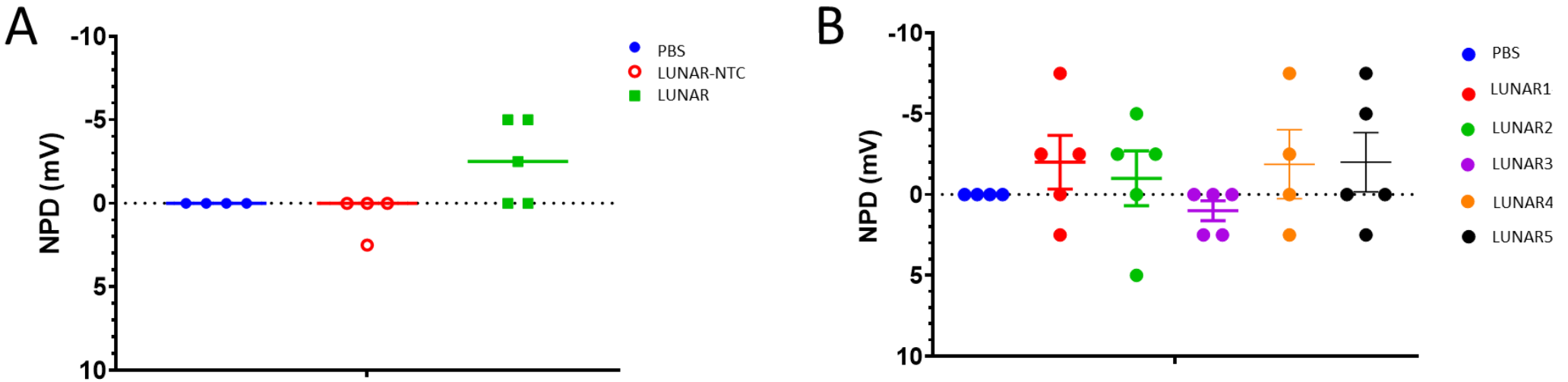
RNA MEDICINES

## *Nasal Potential Difference: Class I CFTR KO mice*

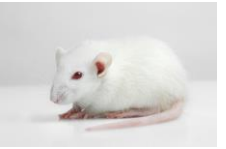



- **Efficacy of LUNAR® formulations encapsulating hCFTR mRNA were tested in the nasal epithelia of a Class I CFTR KO mice model (G542X, Hodges et al., 2018)**
- **Demonstrated consistent efficacy of LUNAR® -hCFTR mRNA in five consecutive studies in a Class I CFTR KO mice (representative images shown in A-B)**

**LUNAR®-hCFTR mRNA is biologically active in a Class I CFTR KO mouse model**

Efficacy

# AEROSOLIZED LUNAR®-MRNA TARGETING THE LUNG

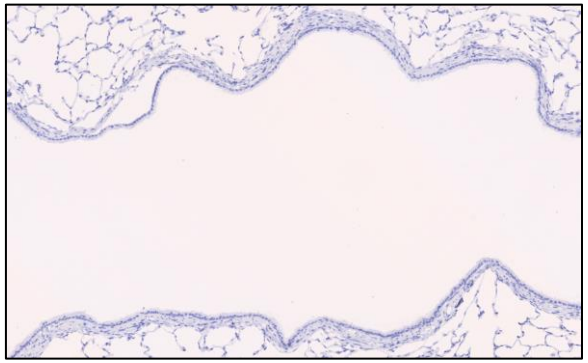


BUILDING INNOVATIVE MEDICINES

## *Aerosolized LUNAR®-TdTomato mRNA delivery in Rat*

| *PBS-treated* | *LUNAR®-TdTomato-treated* |
|---|---|

A



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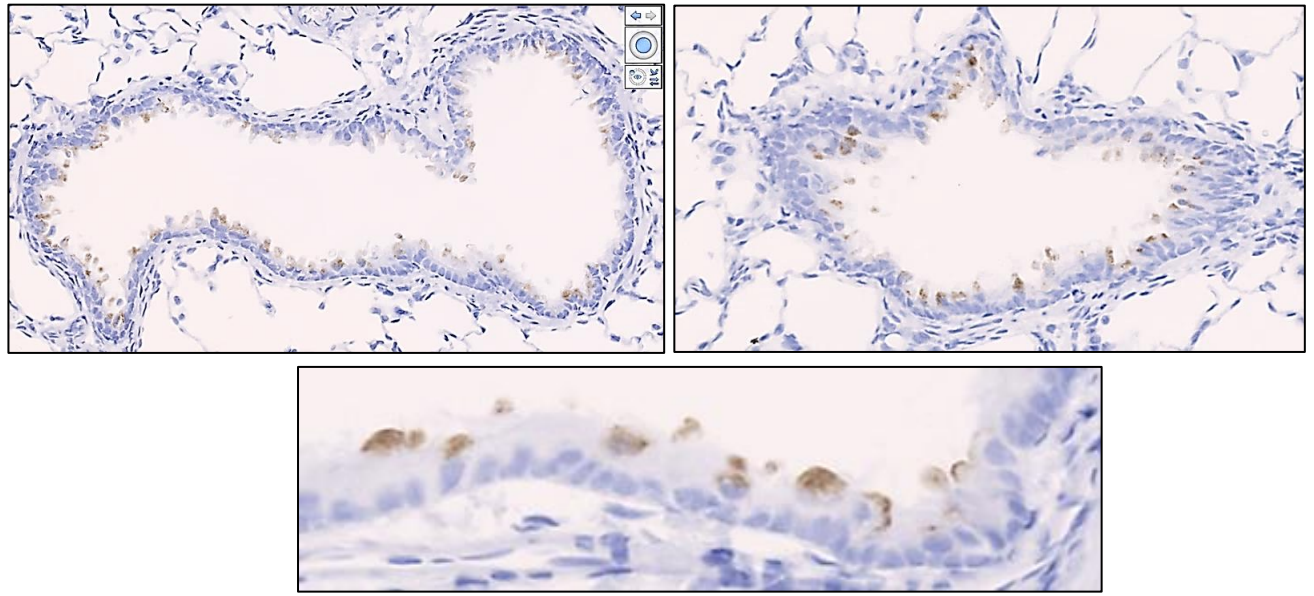


- **WT Rats were aerosolized with either PBS or LUNAR®-TdTomato mRNA using a nose-only exposure chamber**
- **48h post-dose, animals were sacrificed and lungs were processed and analyzed for IHC using a TdTomato antibody**

## *Aerosolized LUNAR®-TdTomato mRNA is efficiently delivered to WT Rat epithelial airways*

Lung Deposition

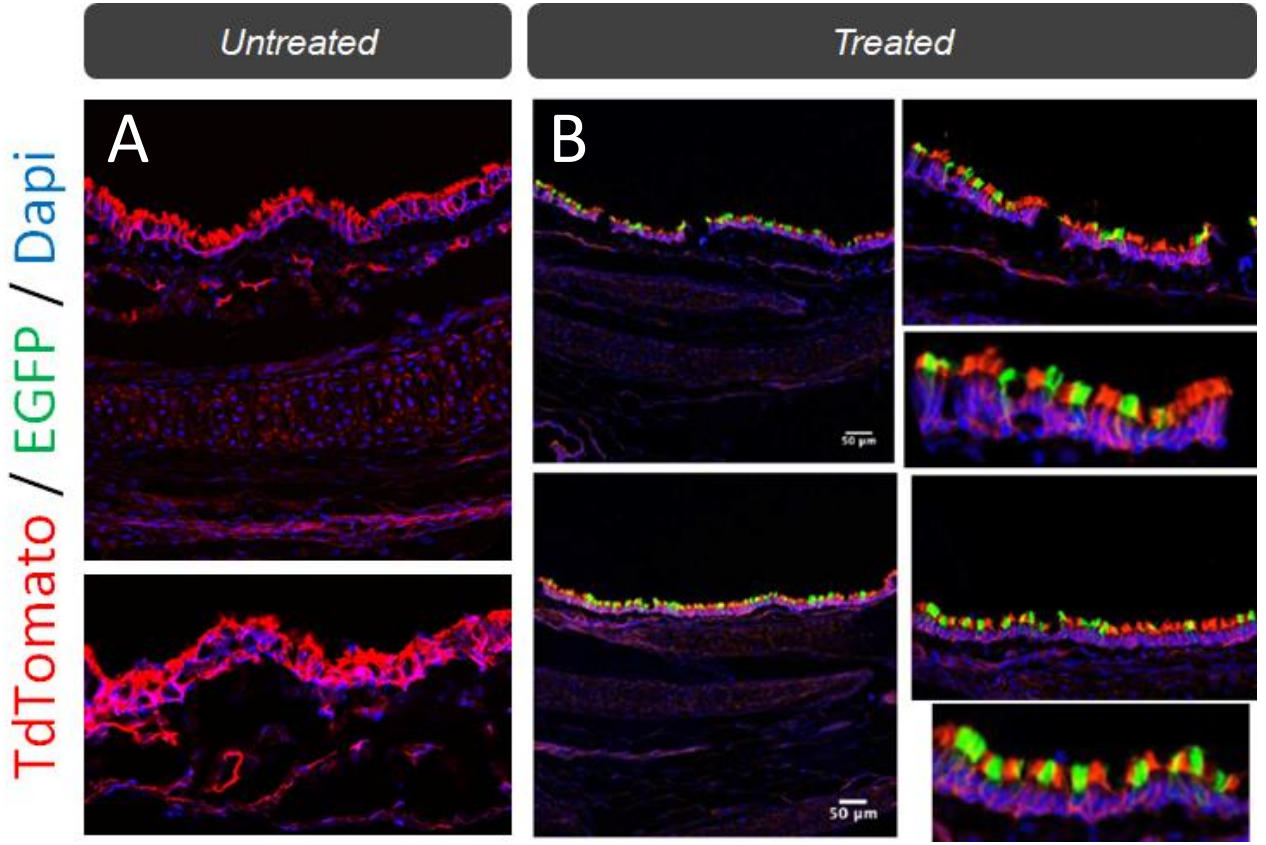
# LUNAR® TARGETING CILIATED CELLS (NON-RODENT)

BUILDING INNOVATIVE MEDICINES

***Effective EGFP conversion in tracheal epithelial airways was observed in the ROSA26TG Ferret model***

- **Novel LUNAR® formulations carrying a Cre mRNA (LUNAR®-Cre mRNA) were tested in the transgenic ROSA26TG ferret model**
  - **An efficient cellular uptake will imply the genetic recombination and activation of EGFP expression:**

  **TdTomato: TURN OFF, EGFP: Turn ON**
- **The data generated in trachea suggest that we are targeting tracheal epithelial airways**




**In collaboration with John Engelhardt**

Airway deposition (non-rodent)

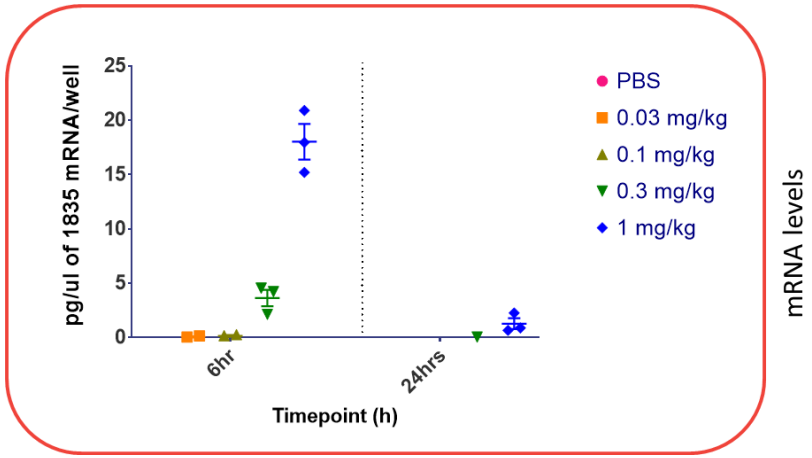
*LUNAR®-CRE mRNA is efficiently delivered in tracheal epithelial airways in a non-rodent model (Ferret)*

# LUNAR®-CFTR MRNA TARGETING LUNG (RODENT)

BUILDING INNOVATIVE
RNA MEDICINES

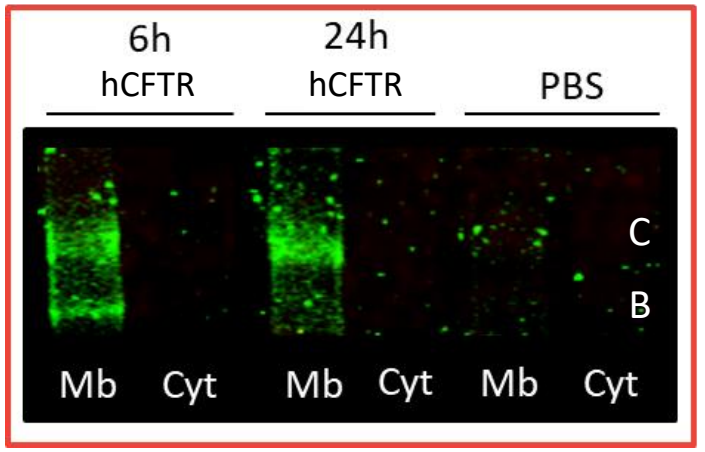
## *Detection of hCFTR in mouse lungs*

A




- LUNAR®-hCFTR mRNA was administered to CFTR KO mice model in a dose response
- mRNA levels were measured at 6h and 24h using QG assay
- A mRNA dose response was observed at 6h, with baseline levels at 24h, which agrees with the short half-life of the mRNA molecules

B




- LUNAR®-hCFTR mRNA was administered to WT mice
- WB analysis was performed on the protein lysates using a hCFTR specific antibody
- Enrichment protocols were performed to detect hCFTR expression associated with the membrane
- B- (core-glycosylated) and C- (fully glycosylated) bands were observed at 6h, whereas at 24h only C-band was observed

**CFTR mRNA and protein detected in WT and CFTR KO mice**

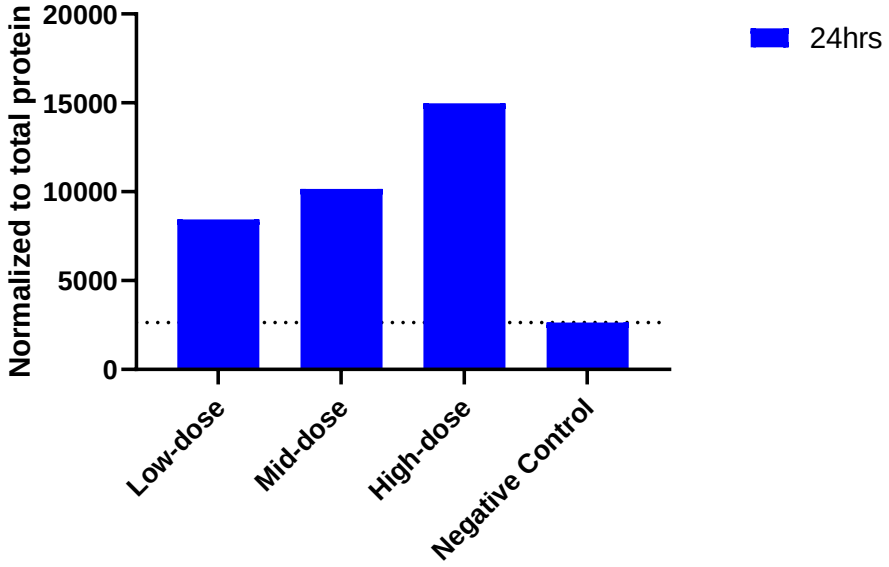
Lung Deposition

# LUNAR®-MRNA TARGETING HUMAN LUNGS EX VIVO

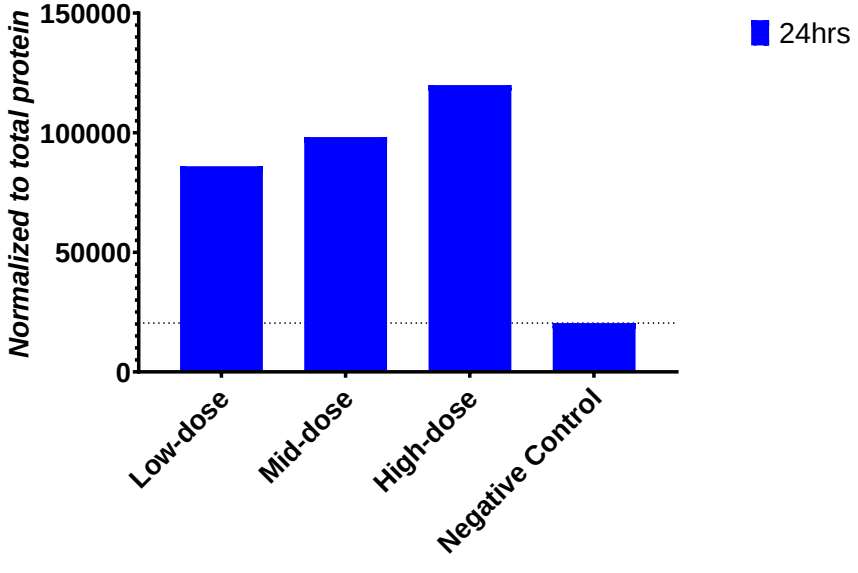
BUILDING INNOVATIVE RNA MEDICINES

*Delivery of LUNAR®-mRNA to a human lung*

*Non-CF*




*CF*



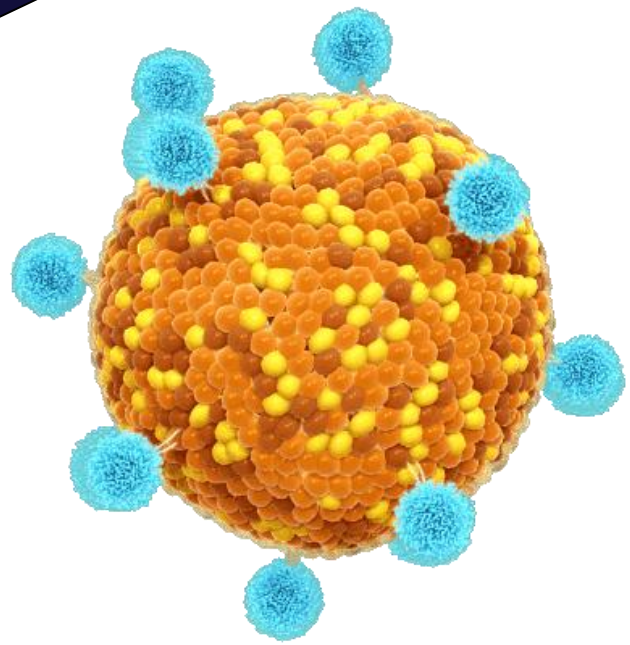

- **Lung slices from normal and CF patients lungs were generated, treated with different LUNAR®-EGFP formulations, and analyzed by WB using a EGFP specific antibody. Cell viability was maintained normal for the duration of the experiment.**
- **A dose response in EGFP protein levels was observed in all samples analyzed**

**LUNAR® formulations can efficiently transfect Non-CF/CF human lung explants in a dose dependent fashion**

Lung Deposition

Arcturus Technology targeting CF

# LUNAR®-CF



LUNAR® formulations are biodegradable and can be optimized for aerosolized delivery

LUNAR® shields the mRNA in CF mucus

LUNAR® can selectively targets epithelial airways, including ciliated cells

Codon optimized hCFTR mRNAs express higher protein levels that are biologically active

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ARCTURUS therapeutics