

# ARCTURUS THERAPEUTICS

Building the Next Generation of RNA Medicines

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# FORWARD LOOKING STATEMENTS

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# Company Highlights



BUILDING INNOVATIVE  
RNA MEDICINES

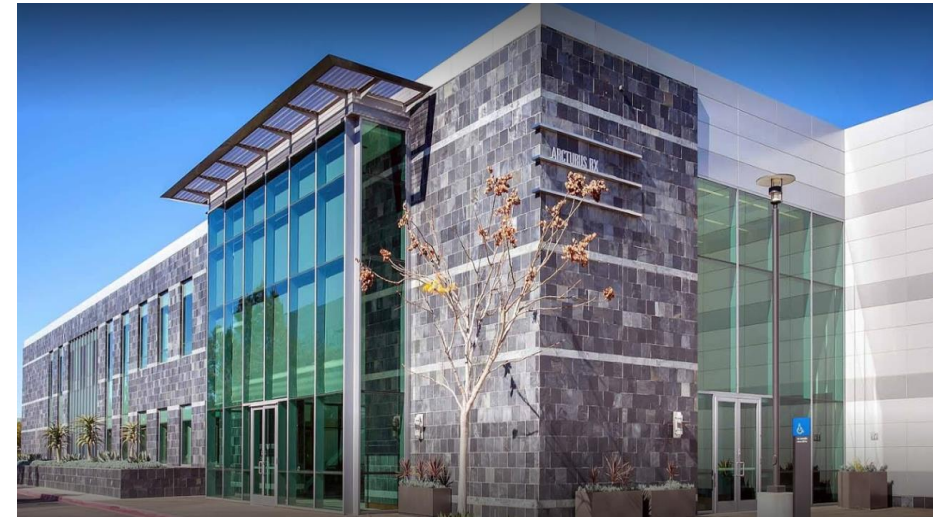
**Arcturus is an mRNA Medicines and Vaccines Company**

## Publicly Traded (NASDAQ:ARCT)

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

## Strong Intellectual Property Technology Portfolio

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



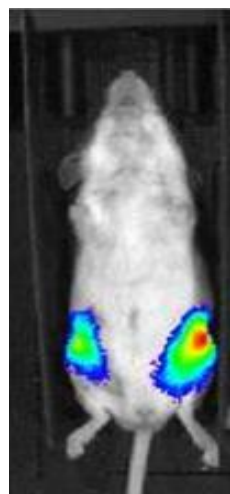
**Arcturus Technologies Validated by Multiple Strategic Partners**



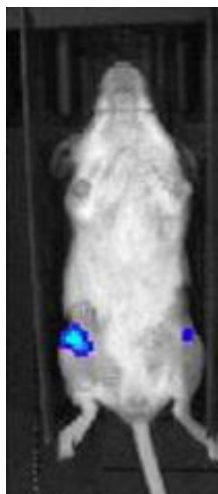
# STARR™ mRNA Superior to Conventional mRNA

*Self-Transcribing and Replicating mRNA (STARR) delivered with LUNAR® provides higher protein expression and potentially longer-lasting duration of protein expression in mouse*

**STARR™ Technology**  
**30-Fold Higher Protein Expression**



**STARR™  
Technology**



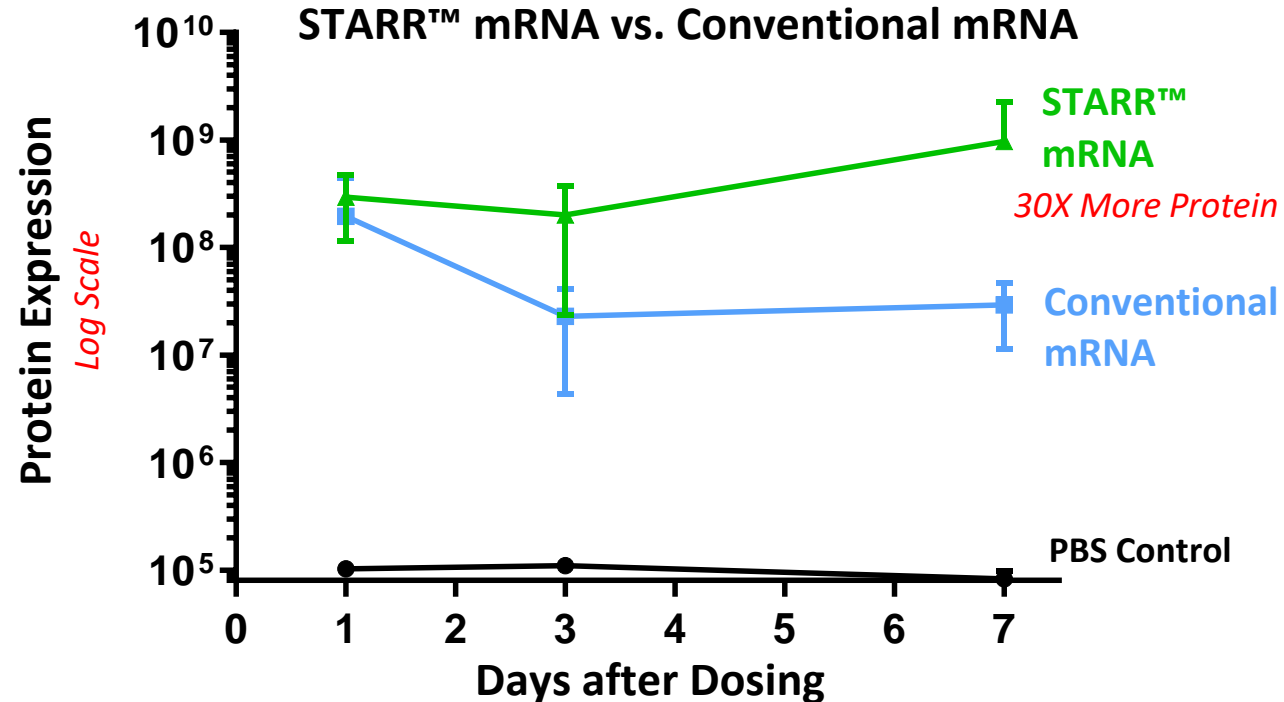
**Conventional  
mRNA**



**PBS  
Control**

## Protein Expression Over 7 days

### STARR™ mRNA vs. Conventional mRNA



**Single Dose of STARR™ mRNA with LUNAR® Delivery Provides Enhanced Protein Expression**



# Arcturus COVID-19 Vaccine has Significant Advantages



## Very Low Dose

- Result of combining Arcturus' LUNAR® and STARR™ technologies
- Means potentially more people vaccinated per manufactured batch

## Potential Single Shot

- Small, single intramuscular injection
- Simpler logistics for vaccinating large populations

## Utilizes STARR™ mRNA

- STARR™ mRNA produces 30X more protein than conventional mRNA
- Lasts longer, booster shot may be unnecessary

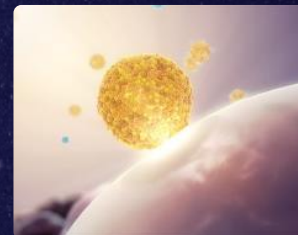
## Contains No Viruses or Viral Material

- No dead viruses, no attenuated viruses, no virus or viral vectors (AAVs) used to deliver the RNA vaccine
- LUNAR® Delivery Technology is Non-Viral

# LUNAR<sup>®</sup> Delivery Technology



**LUNAR Associates  
with Cell Membrane**



Enters Cell  
Via Endocytosis

**Lipid Particle in  
Endosome**



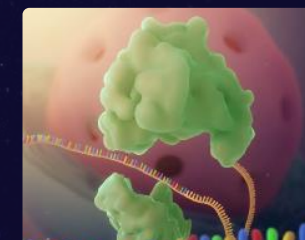
Increased Acidity as  
Endosome Ages

**pH-Mediated  
Disruption**







Rapid Biodegradation  
of Vehicle

**RNA  
in Cytosol**



RNA Processing  
and Translation

# Arcturus Platform: Enabling Genetic Medicines

Program	Partner	Indication	Arcturus Chemistry	Arcturus Delivery	Program Status
LUNAR-GSD3		Glycogen Storage Disease Type III	mRNA	LUNAR® Hepatocytes	Target IND 2020+
LUNAR-RARE		Undisclosed Rare Disease	mRNA	LUNAR® Hepatocytes	Preclinical
LUNAR-HBV		Hepatitis B	RNA	LUNAR® Hepatocytes	Preclinical
LUNAR-NASH		NASH	RNA	LUNAR® Stellate Cells	Preclinical
LUNAR-RPL	Large Pharma	Infectious Disease Prophylactic Vaccines	SGL's Replicon RNA	LUNAR®	Preclinical
LUNAR-AH	Large Animal Health Pharma	Infectious Disease Prophylactic Vaccines	SGL's Replicon RNA	LUNAR®	Preclinical

- Greater than \$1 Billion in Potential Milestones & Royalties
- Enabling Different Types of RNA – Messenger RNA, Gene Editing RNA, Replicon RNA
- Multiple Cell Types Targeted
- LUNAR-GSD3 (UX053) partnered with Ultragenyx – IND Target 2020+



# Arcturus Pipeline of mRNA Medicines

Name	Indication	Expected Regulatory Filing Date	Route of Administration	Target Organ	Target Cells	Prevalence Worldwide
<b>LUNAR-COV19</b>	Coronavirus COVID-19 Vaccine	H2 2020 (CTA, Singapore)	Intramuscular (i.m.)	Muscle	Myocyte	Global
<b>LUNAR-OTC (ARCT-810)</b>	Ornithine Transcarbamylase (OTC) Deficiency	IND Filed March 2020	Intravenous (i.v.)	Liver	Hepatocytes	> 10,000
<b>LUNAR-CF</b>	Cystic Fibrosis	2021	Nebulized Aerosol	Lung	Bronchial Epithelial Cells	> 70,000
<b>LUNAR-CV</b>	Rare Cardiovascular Disease	Preclinical	Intravenous (i.v.)	Liver	Hepatocytes	Undisclosed
<b>LUNAR-MD</b>	Rare Metabolic Disease	Preclinical	Intravenous (i.v.)	Liver	Hepatocytes	Undisclosed

- **LUNAR-COV19: CTA (Singapore) Filing Target H2 2020**
- **LUNAR-OTC (ARCT-810): IND Filed; Next Milestone Human Data**
- **LUNAR-CF (Funded by the Cystic Fibrosis Foundation): IND Filing Target 2021**



# Arcturus Developing COVID-19 Vaccine with Duke-NUS



## Partnership Initiated March 4, 2020

- Funded, up to \$10M



## Arcturus COVID-19 Vaccine Benefits From Duke-NUS Genetic Correlation System

- Helps Arcturus learn more quickly about the LUNAR-COV19 efficacy and safety profile
- Specific gene changes correlate with efficacy and safety
  - Level of neutralizing antibody titers
  - Safety-related adverse events (headache, fever)
- Gene expression changes can be measured within the first 5 days following vaccination

- Duke-NUS data helps Arcturus learn more quickly about LUNAR-COV19 efficacy and safety profile
- Potentially accelerating development timeline

# OTC Deficiency Market Opportunity



## **Ornithine Transcarbamylase (OTC) Deficiency: The most common urea cycle disorder**

- The urea cycle converts neurotoxic ammonia to water-soluble urea that can be excreted in urine
- Deficiency in OTC causes elevated blood ammonia, which can lead to neurological damage, coma, and death
- 10,000 worldwide prevalence



## **Unmet Medical Need**

- Present standard of care involves a strict diet (low protein, high fluid intake) plus ammonia scavengers (sodium phenylbutyrate)
- Present standard of care does not effectively prevent life-threatening spikes of ammonia
- Severe OTC Deficiency patients are typically referred for liver transplant, currently the only cure



## **LUNAR-OTC Aims to Restore Enzyme Function**

- Expression of OTC enzyme in liver has potential to restore normal urea cycle activity to detoxify ammonia, preventing neurological damage and removing need for liver transplantation

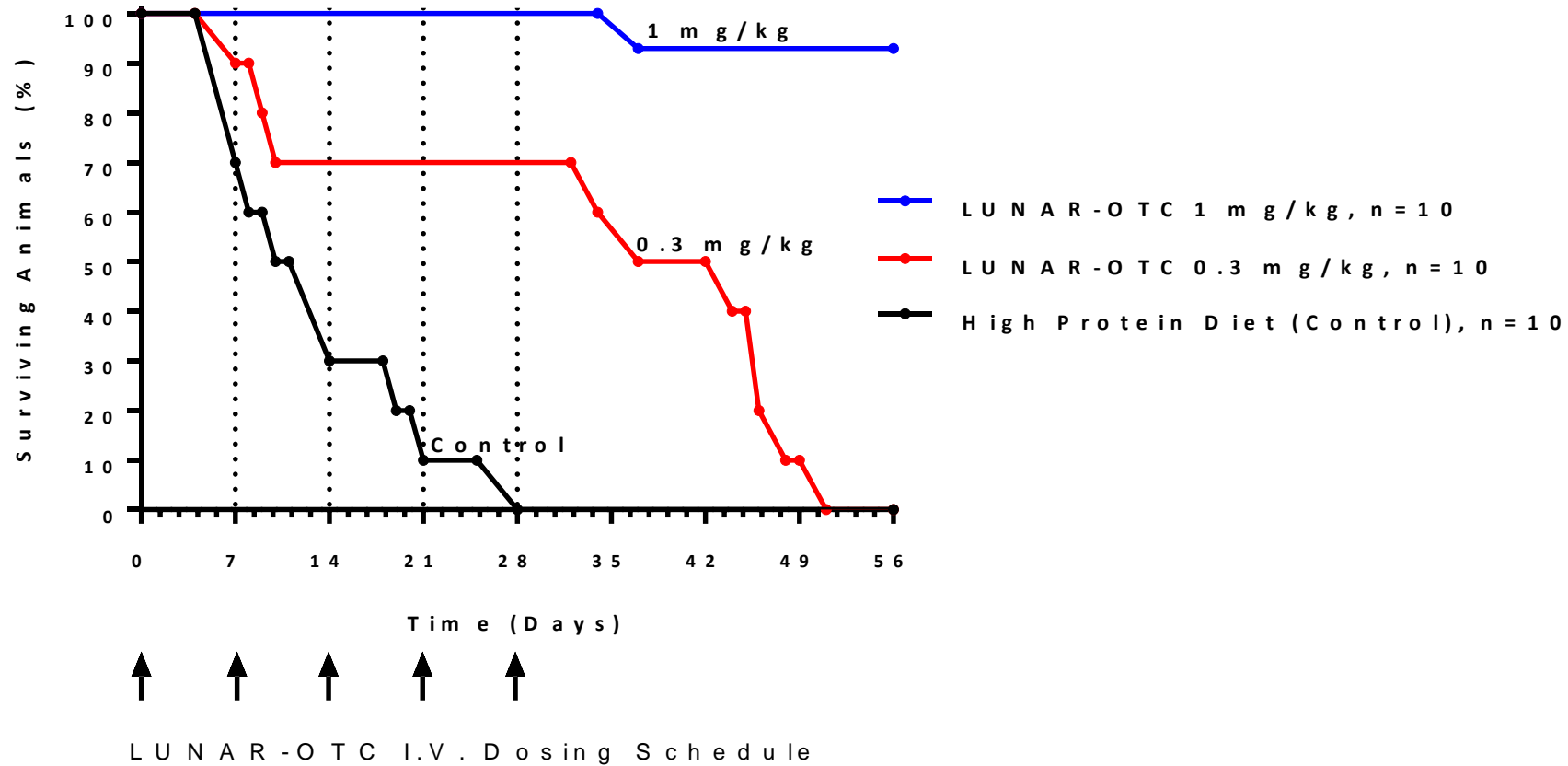
# LUNAR<sup>®</sup>-OTC

Disease Normalization Following Single and Repeat Dosing in OTC Mouse Model



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## Survival of OTC-deficient Mice on High Protein Diet - Weekly LUNAR-OTC Treatment



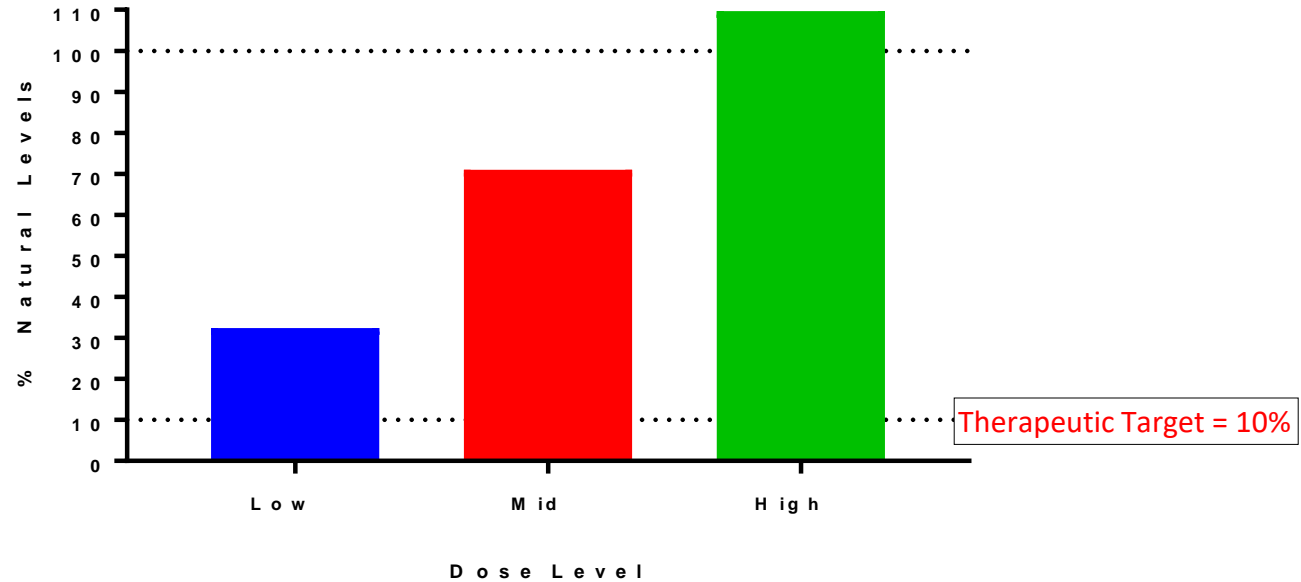
# LUNAR-OTC



Exceeds Therapeutic Target of 10% Enzyme Replacement at all Doses in OTC-Deficient Mouse Model

- OTCD impacts ureagenesis (ammonia detoxification)
- The main site of ureagenesis is the periportal region of the liver\*
- Establishing 10% of natural enzyme levels is expected to be therapeutically significant

Periportal Expression in the Liver of OTC Protein



\*Li, L. et al. PGC-1 $\alpha$  Promotes Ureagenesis in Mouse Periportal Hepatocytes through SIRT3 and SIRT5 in Response to Glucagon. Scientific Reports. 6:24156 | DOI: 10.1038/srep24156, April 2016

\*Lamers, W.H., Hakvoort, T.B.M., and Köhler, E.S. 'Molecular Pathology of Liver Diseases' in Monga S.P.S. (ed.), MOLECULAR PATHOLOGY LIBRARY SERIES, Springer Publishing, New York, pp. 125-132 | DOI: 10.1007/978-1-4419-7107-4

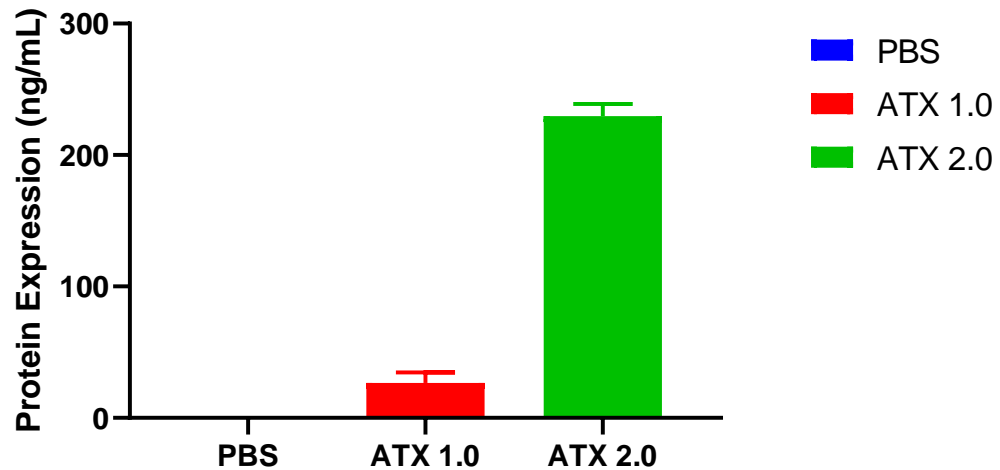
**LUNAR-OTC treatment increases OTC expression in mouse periportal hepatocytes (main site of ureagenesis)**



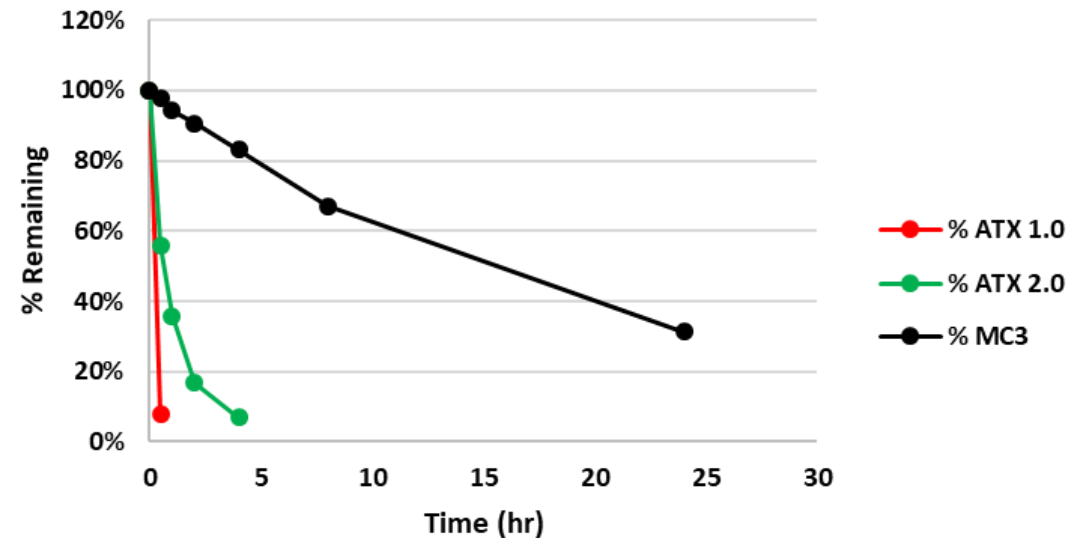
# ATX Lipids are Effective and Degrade Rapidly

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### Protein Expression (*in vivo*)



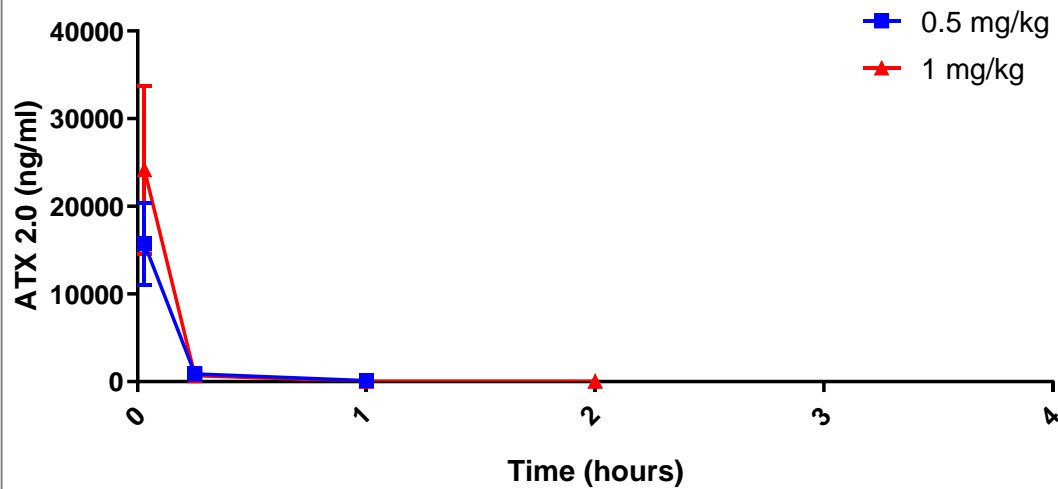
### Esterase Catalyzed Degradation (*in vitro*)



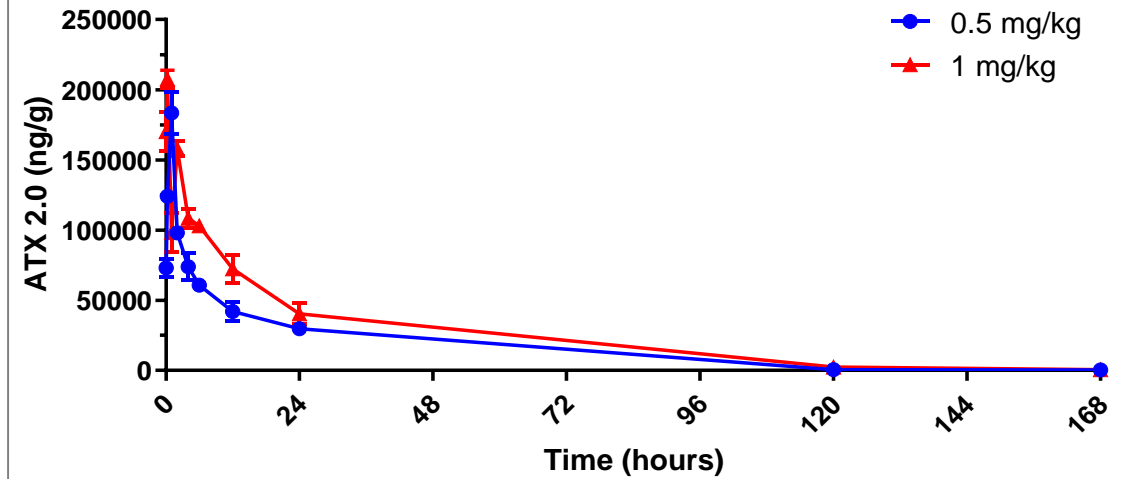
Next Generation ATX Lipids Retain Degradability & Improve Delivery Efficiency

# ATX 2.0 Lipid Rapidly Clears *in vivo*

## Plasma



## Liver



- ATX Lipid (the major component in LUNAR® technology) is rapidly degraded *in vivo*
- ATX Lipid Half-Life in the Liver is Approximately 20 hours

# Arcturus Safety Profile



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## External Validation

- Multiple strategic partnerships over many years confirms the positive safety profile of Arcturus LUNAR® and mRNA

## Arcturus is committed to developing safe mRNA products

- 15 studies over several years with strategic partners

## Top Safety Concern for RNA Medicines is Delivery

### Arcturus LUNAR® Delivery Technology is well tolerated in non-human primates (NHPs)

- ✓ @ 15 mg/kg single dose of non-coding siRNA
- ✓ @ 3 mg/kg x eight (8) weekly doses of non-coding siRNA (total of 24 mg/kg over 2 months)

## Arcturus mRNA chemistry shows promising efficacy and tolerability data

- Efficacy of OTC mRNA in mouse model @ 0.1 – 1 mg/kg

# Cystic Fibrosis Market Opportunity



## **Cystic Fibrosis: The most common rare disease in the United States**

- Caused by genetic mutations in the CFTR gene, resulting in aberrant flux of ions in and out of cells, causing thick mucus buildup in lung airways
- Chronic airway obstruction leads to infection and inflammation, which causes permanent tissue scarring and respiratory failure
- 70,000 worldwide prevalence



## **Unmet Medical Need**

- No CFTR functional corrector is approved for treatment of all patients
- Present standard of care does not effectively prevent long-term effects of mucus accumulation. CF patients with late-stage loss of respiratory function require lung transplant



## **LUNAR-CF Aims to Restore CFTR Function**

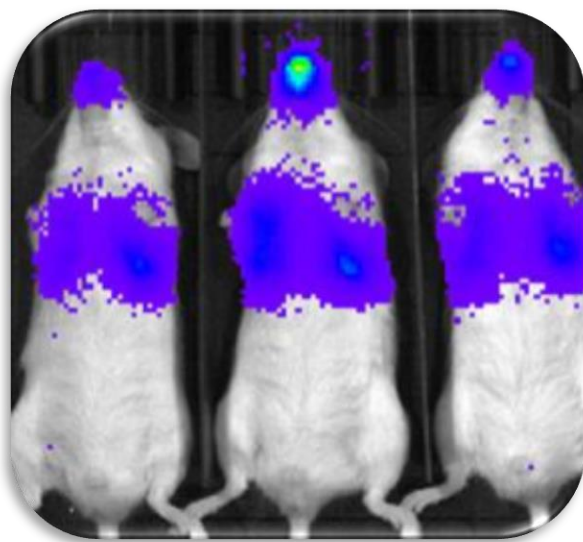
- An mRNA replacement therapy has the potential to deliver a new copy of CFTR into the lungs of CF patients, independent of any genotype
- A functional CFTR protein can restore chloride channel efflux in the airways, reducing mucus accumulation, tissue scarring and minimizing the progressive respiratory dysfunction observed in CF patients



# LUNAR<sup>®</sup> Delivery of mRNA to Lung (Mouse)

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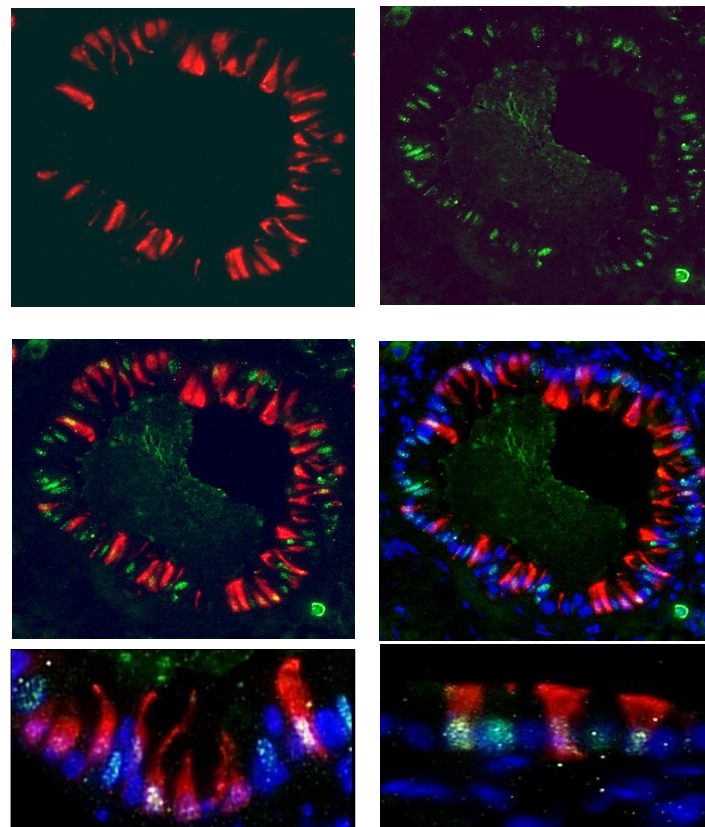
## Nebulization



LUNAR<sup>®</sup> + Luciferase mRNA

## LUNAR<sup>®</sup> Delivery of mRNA into Bronchial Epithelial Cells (BECs)

TdTomato / FoxJ1 / Dapi

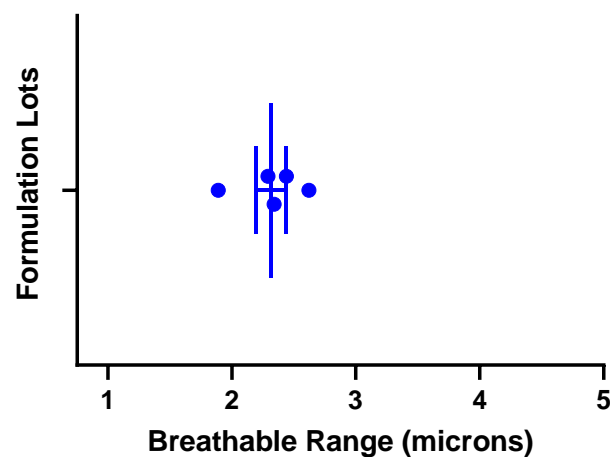


Functional Nebulized Delivery of LUNAR<sup>®</sup>+ mRNA into Lung Epithelial Cells

# Aerosolized LUNAR<sup>®</sup>

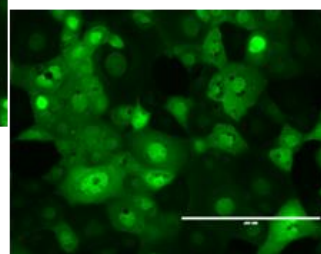
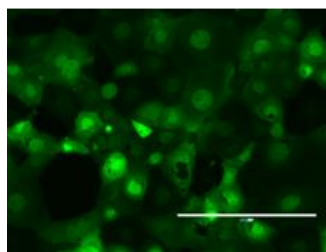
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Aerosolized LUNAR<sup>®</sup>  
Particles are Breathable



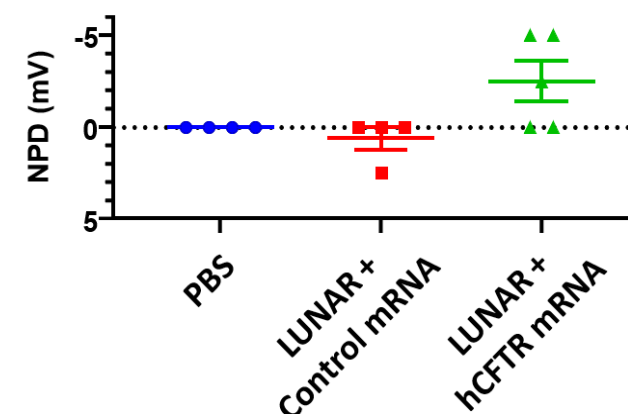
Aerosolized LUNAR<sup>®</sup> -mRNA (GFP)  
maintains activity

Pre-Nebulization



Post-Nebulization

Aerosolized LUNAR<sup>®</sup> -CF  
is functional *in vivo* (mouse)



Aerosolized LUNAR<sup>®</sup> Droplets are in the Optimal Breathable Range (2-3 microns)

Aerosolized LUNAR<sup>®</sup> Maintains Function as Measured by GFP Protein Expression & Nasal Potential Difference (NPD)

# Drug Substance: mRNA Design

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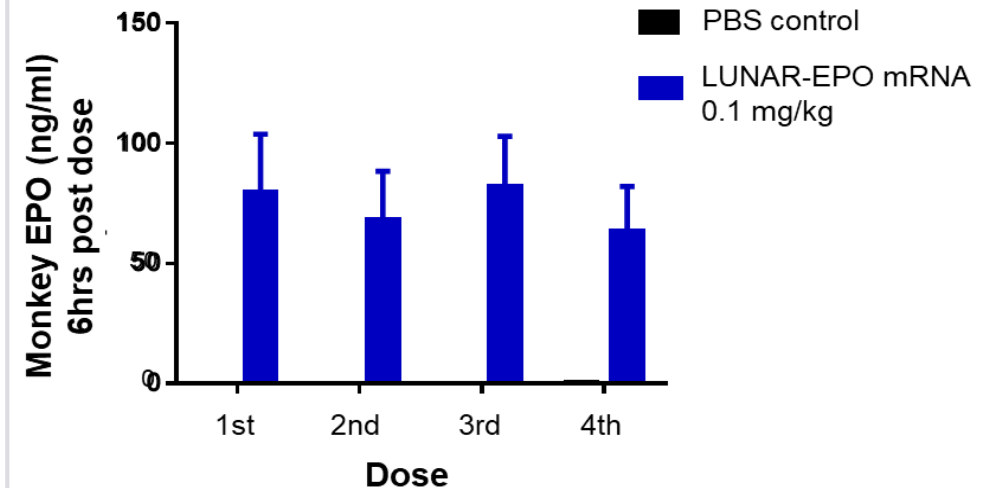
Optimize  
mRNA sequence  
Chemistry  
Process



Improve  
Protein Expression  
Duration  
Functional Activity



## Weekly Dosing in Non-Human Primates (NHPs)

**Proprietary mRNA Optimization Platform Demonstrates Sustained Activity Upon Repeat Dosing in NHPs**

# Drug Substance (mRNA) Manufacturing

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Features	Benefits
Optimized IVT Method	Reduced Cost; Higher Purity
Improved Capping Reaction	Reduced Cost of Goods
Proprietary Purification Process	Higher Purity in a Shorter Time
Efficient	Entire Process Less Than One Week
Scalable to > 1Kg	Access Large Patient Populations
Adaptable	Can Utilize a Variety of Modifications

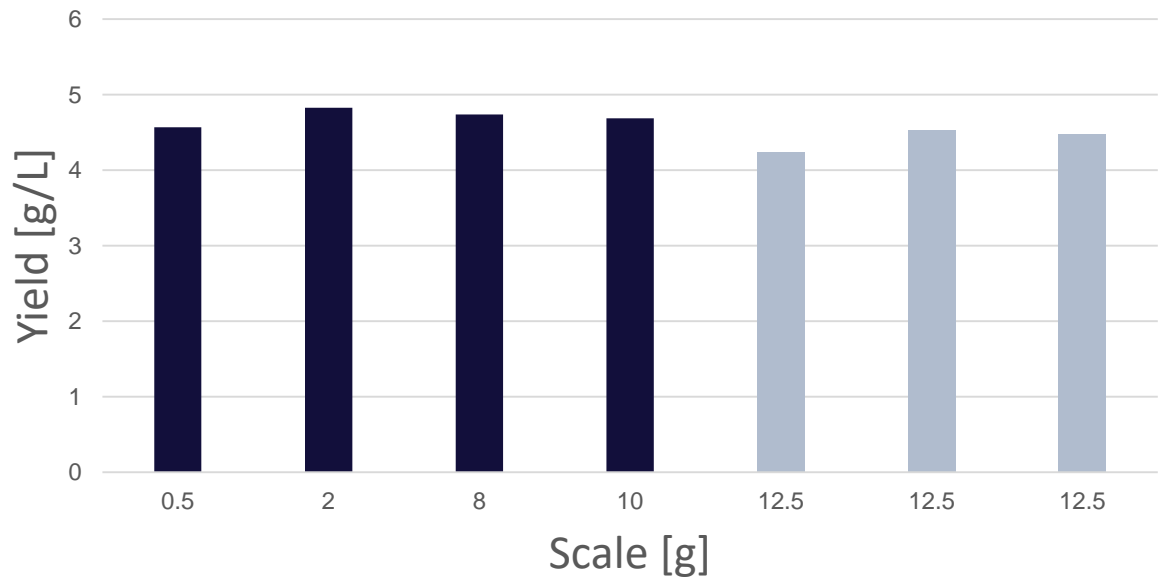
**Arcturus Internal non-GMP mRNA Production Capabilities: Up to 30 g in Less Than One Week**



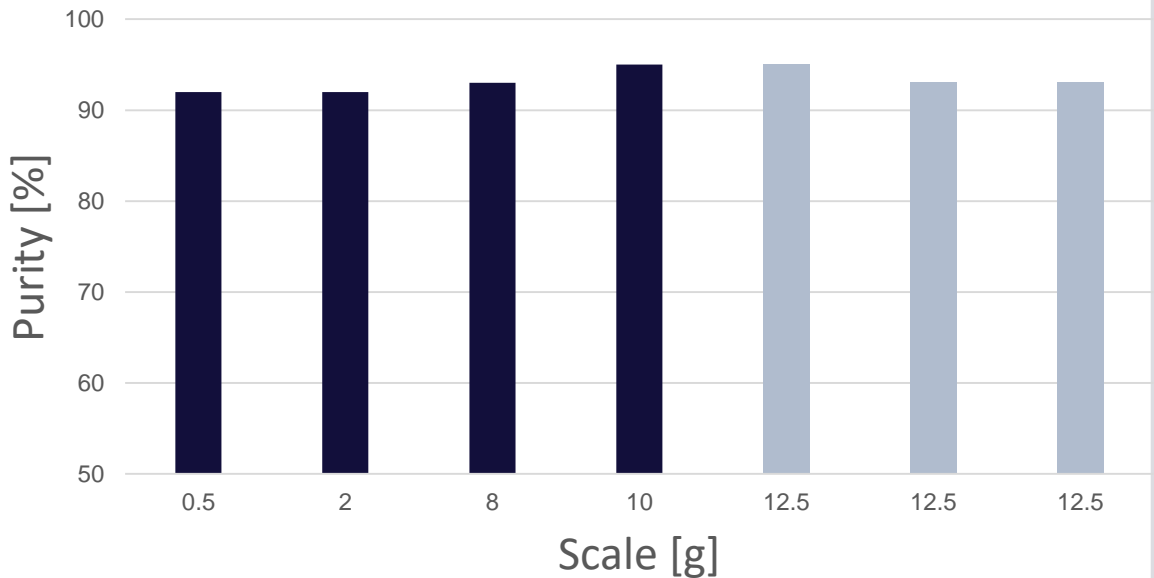
# Drug Substance (mRNA) Manufacturing



RNA Yield



RNA Purity



- Non-GMP Lots Produced at Arcturus
- GMP Lots Produced at CMO as part of recent GMP campaign

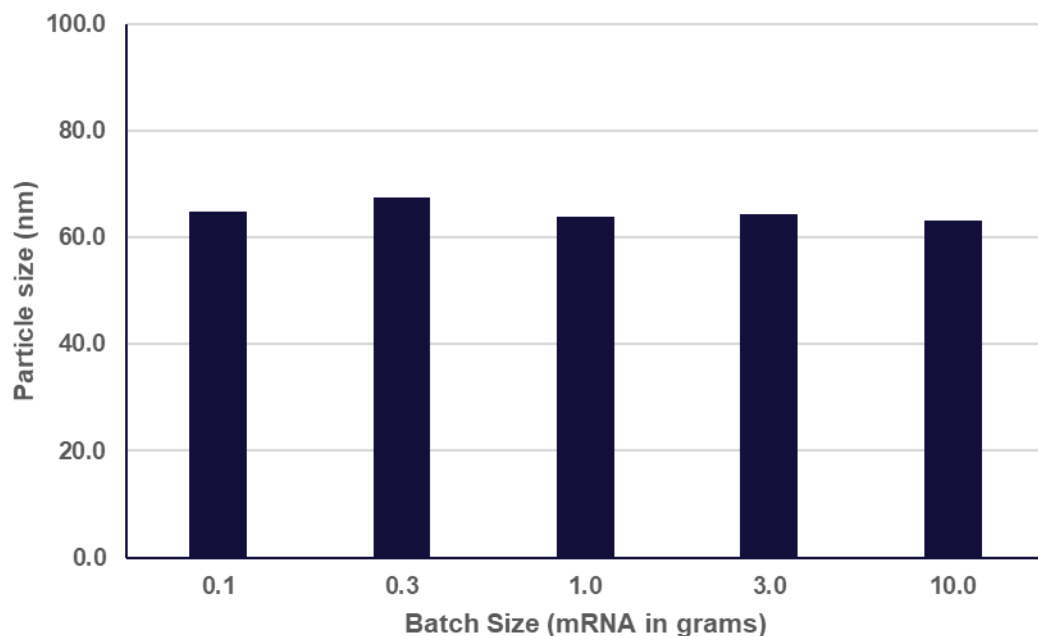
Three 12.5 g lots produced in recent GMP campaign are of equivalent quality and yield

# Drug Product (LUNAR<sup>®</sup> + mRNA) Manufacturing

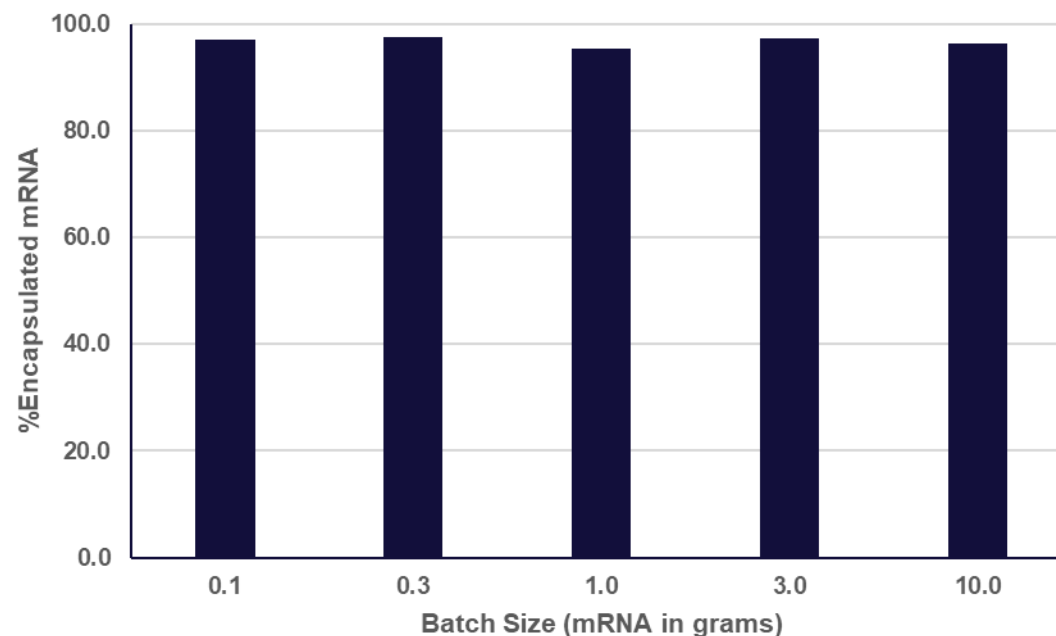


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Particle Size



%Encapsulated mRNA



- Manufacturing of Drug Product Demonstrated up to Multigram Scale with Yields  $\geq 85\%$
- GMP Batch of LUNAR<sup>®</sup>-OTC (ARCT-810) Drug Product Manufactured and Released

# Board of Directors



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