

# ARCTURUS THERAPEUTICS

Building the Next Generation of RNA Medicines

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# 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

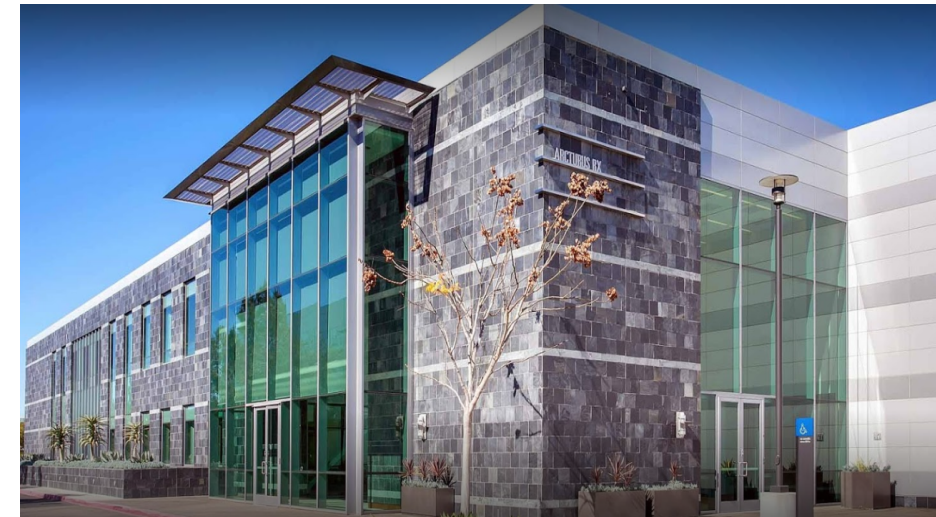
**Arcturus is an mRNA Medicines and Vaccines Company**

## Publicly Traded (NASDAQ:ARCT)

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

## Strong Intellectual Property Technology Portfolio

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



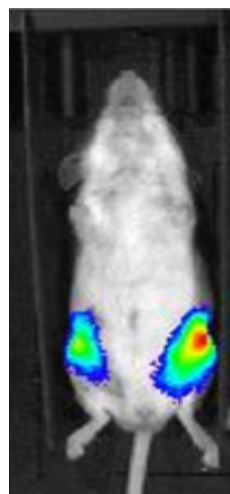
**Arcturus Technologies Validated by Multiple Strategic Partners**



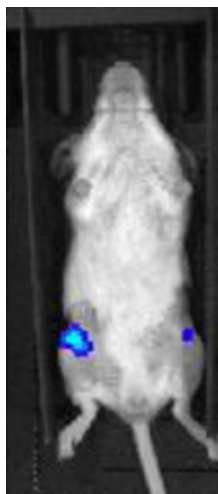
# STARR™ mRNA Superior to Conventional mRNA

*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**



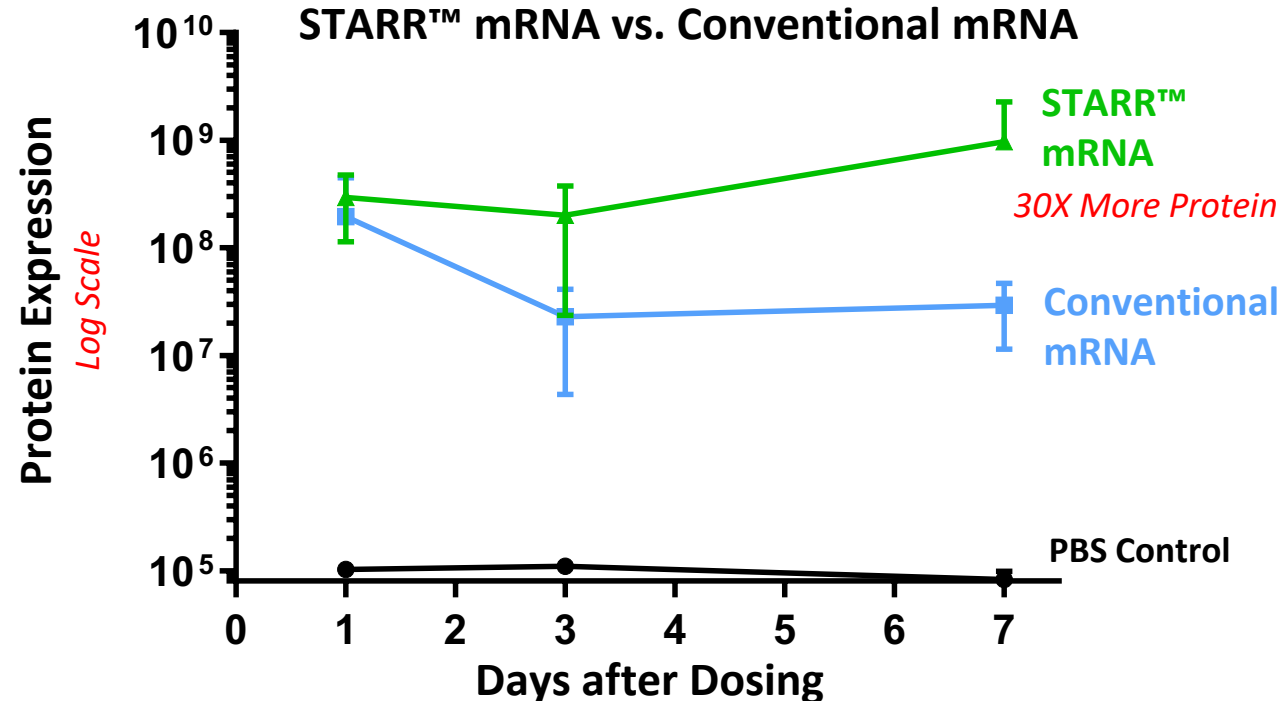
**Conventional  
mRNA**



**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

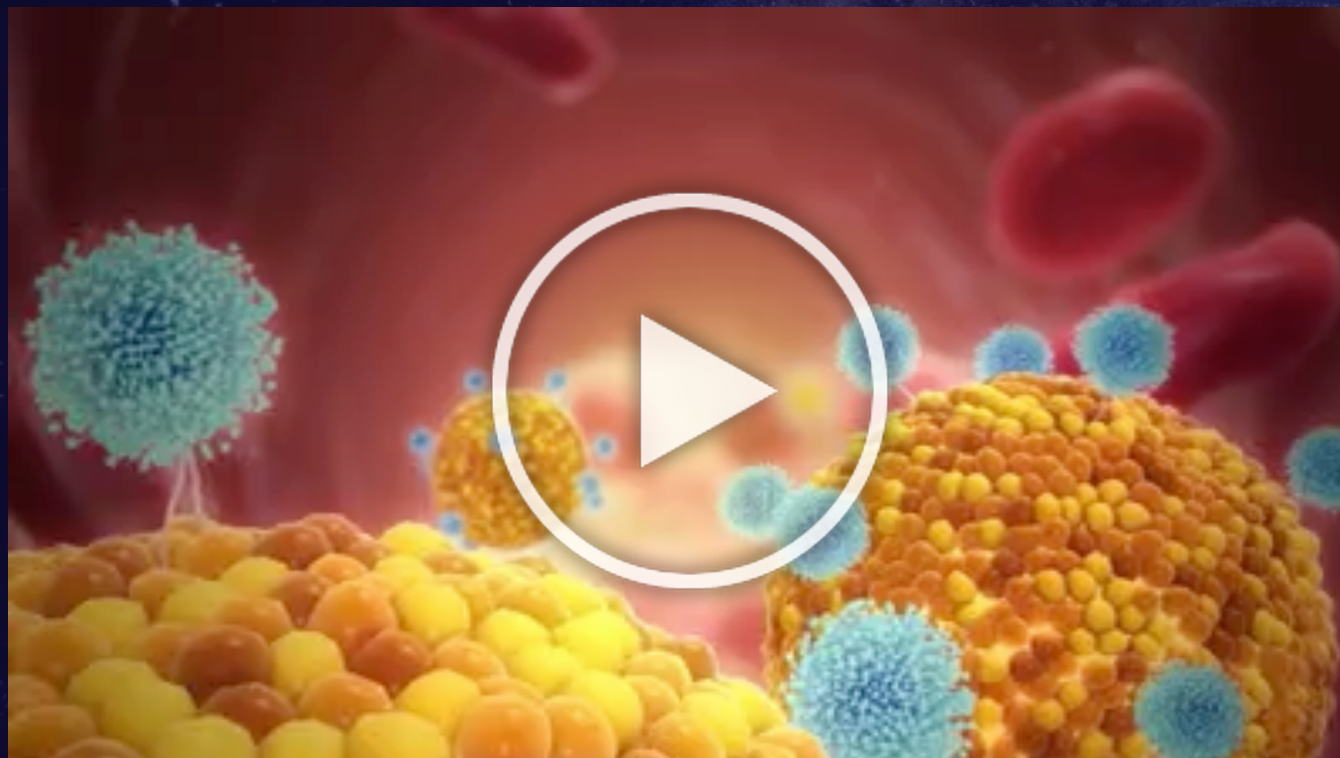
## Utilizes STARR™ mRNA

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

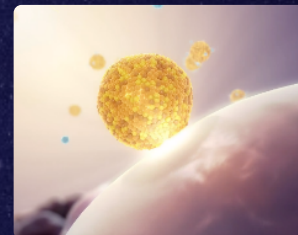
## Contains No Viruses or Viral Material

- 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

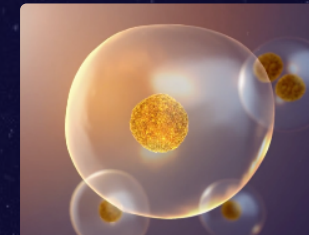


**LUNAR Associates  
with Cell Membrane**



Enters Cell  
Via Endocytosis

**Lipid Particle in  
Endosome**



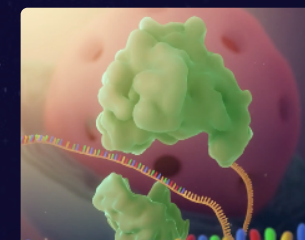
Increased Acidity as  
Endosome Ages

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

**The data generated from the Duke-NUS system gives Arcturus the ability to more efficiently select the dose and help streamline the vaccine development program, and potentially accelerate 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

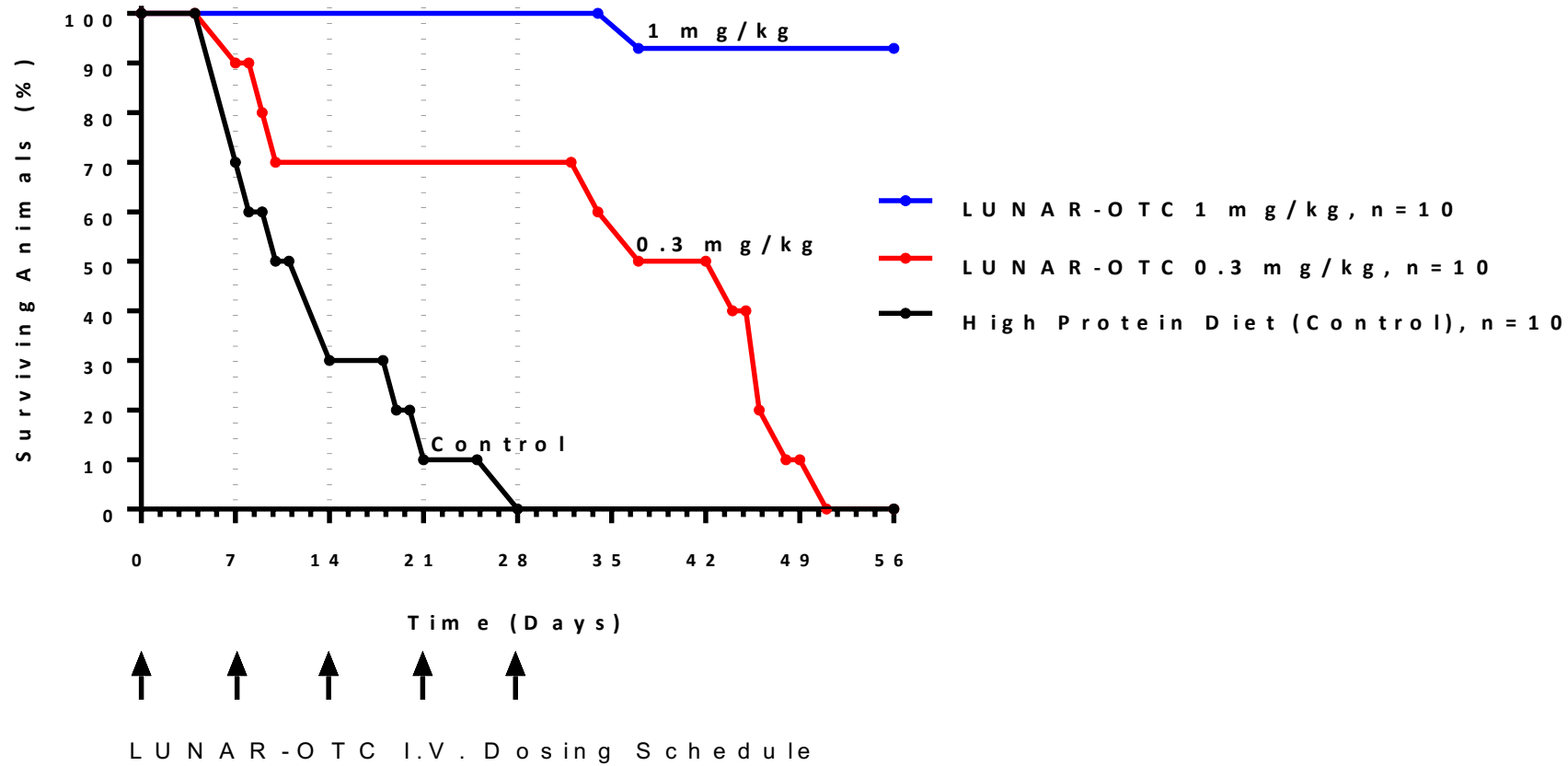
# LUNAR<sup>®</sup>-OTC

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

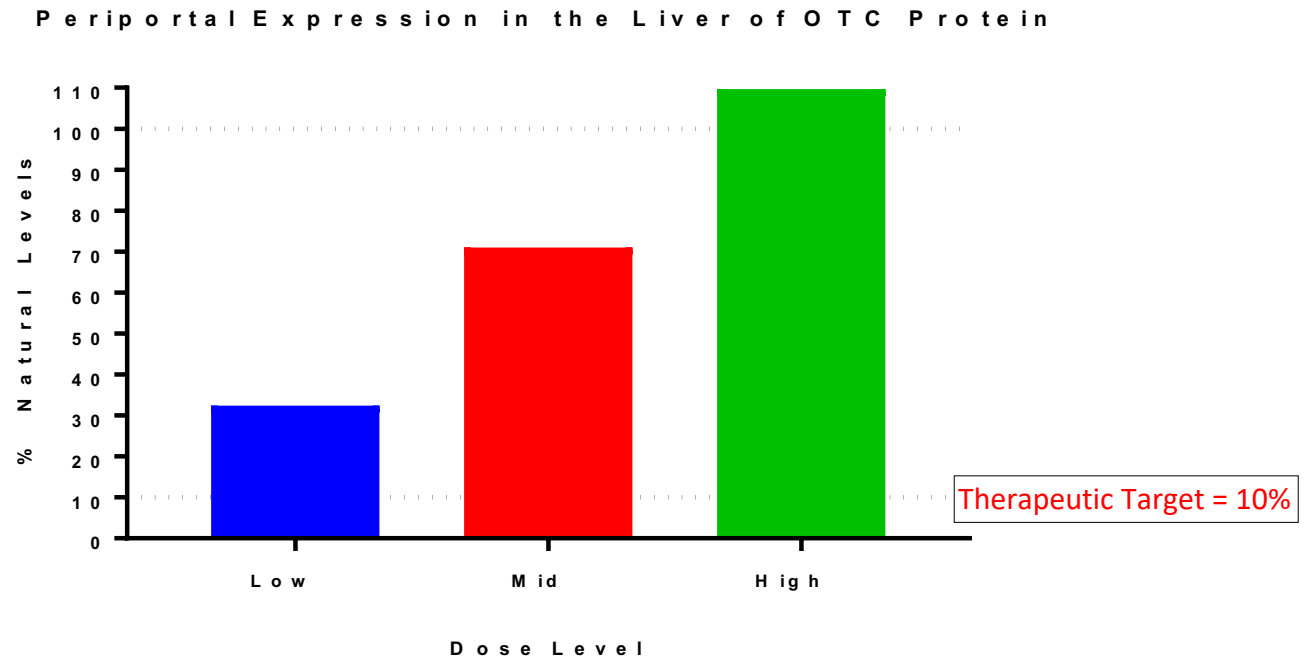


# LUNAR-OTC



## 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



\*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

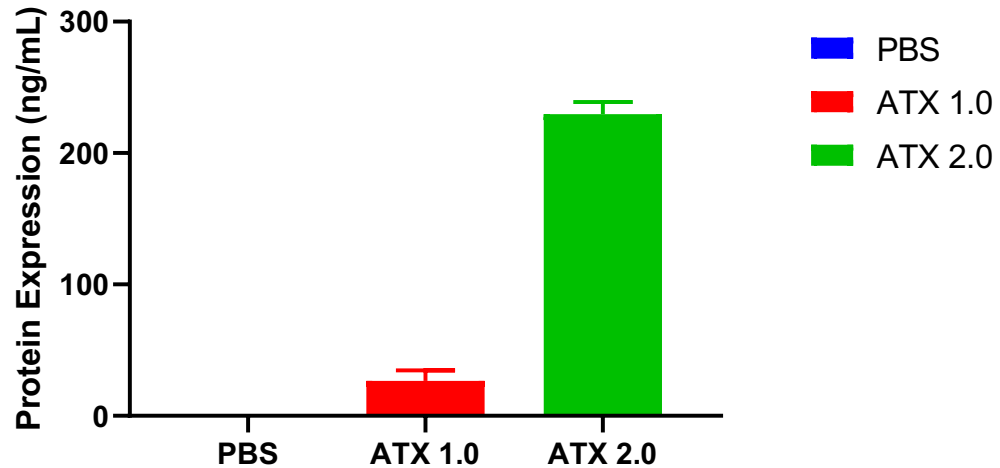
**LUNAR-OTC treatment increases OTC expression in mouse periportal hepatocytes (main site of ureagenesis)**



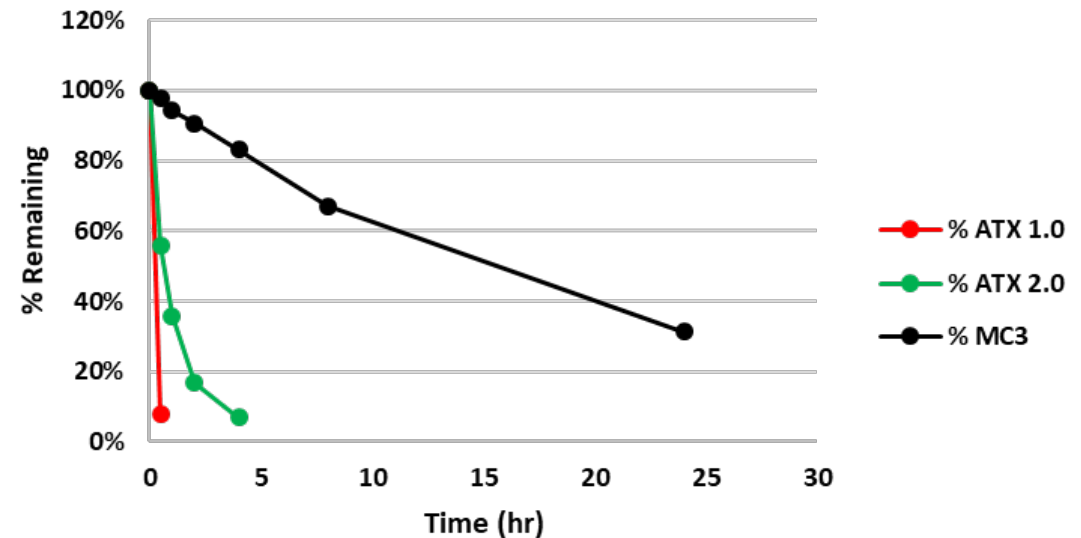
# ATX Lipids are Effective and Degrade Rapidly

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### Protein Expression (*in vivo*)



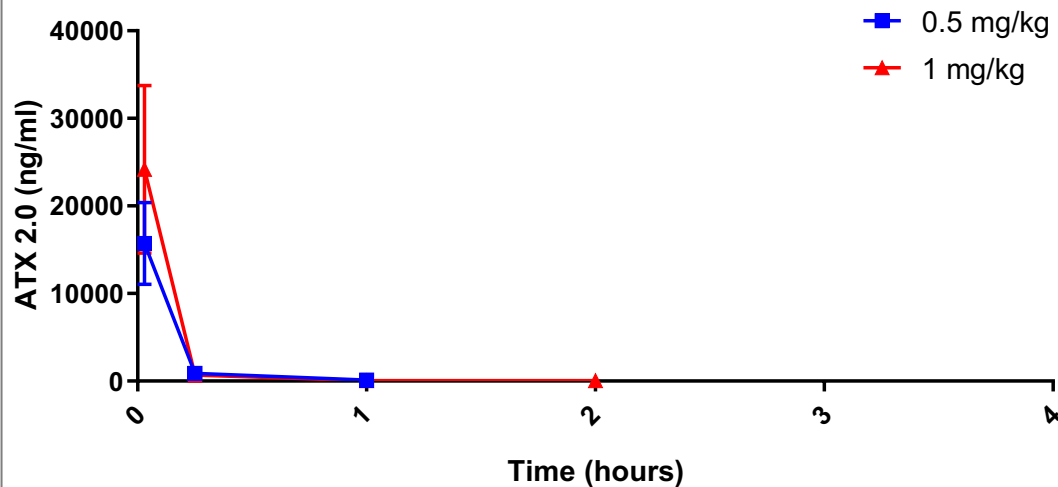
### Esterase Catalyzed Degradation (*in vitro*)



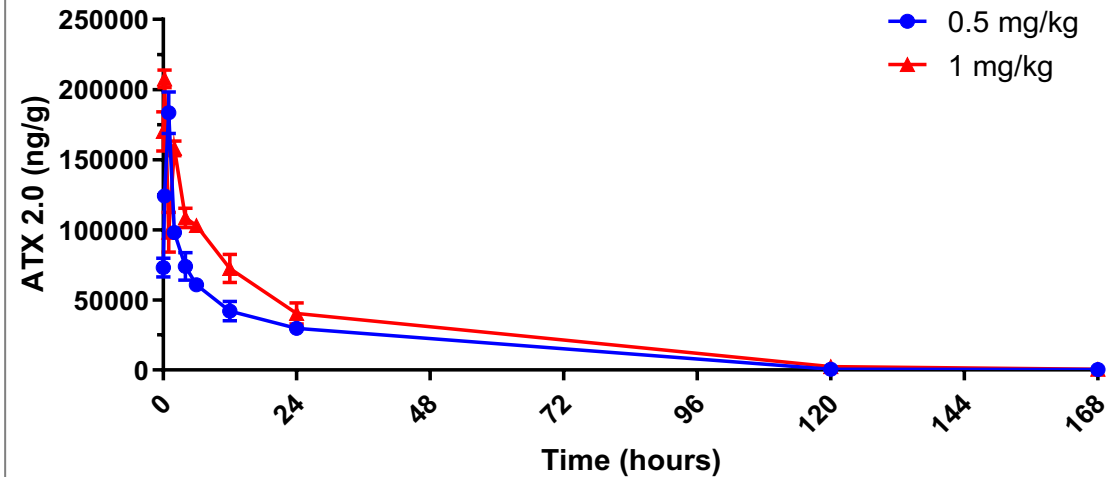
Next Generation ATX Lipids Retain Degradability & Improve Delivery Efficiency

# 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



## External Validation

- Multiple strategic partnerships over many years confirms the positive safety profile of Arcturus LUNAR<sup>®</sup> 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<sup>®</sup> 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**

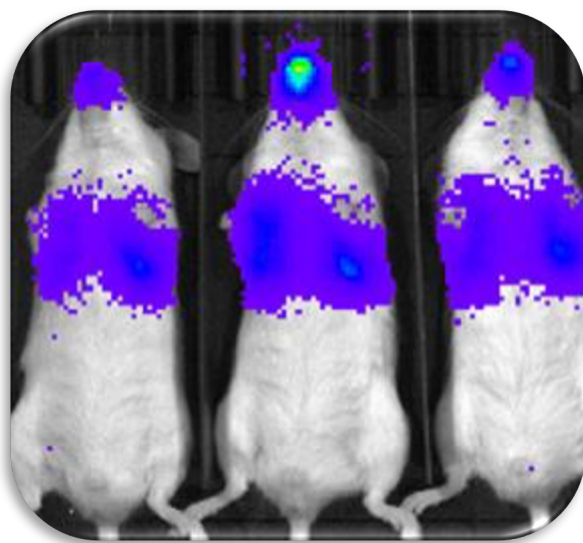
- An mRNA replacement therapy has the potential to deliver a new copy of CFTR into the lungs of CF patients, independent of any genotype
- A functional CFTR protein can restore chloride channel efflux in the airways, reducing mucus accumulation, tissue scarring and minimizing the progressive respiratory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



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

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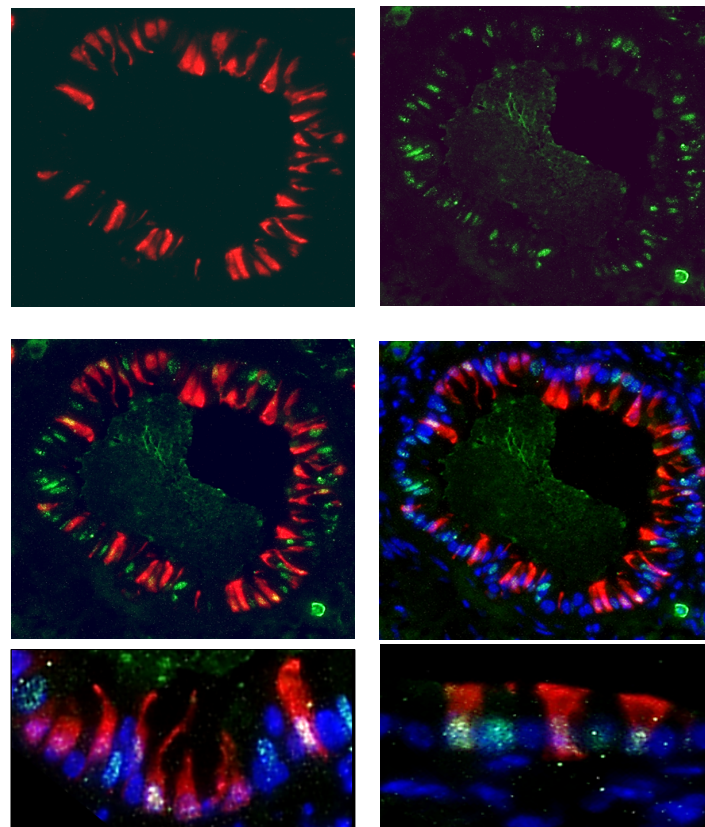
## Nebulization



LUNAR<sup>®</sup> + Luciferase mRNA

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

TdTomato / FoxJ1 / Dapi

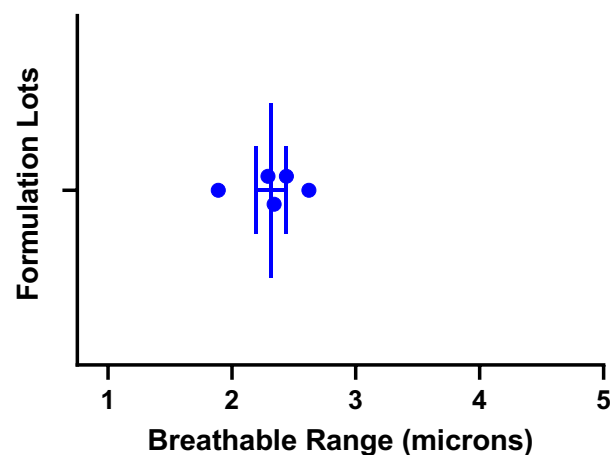


Functional Nebulized Delivery of LUNAR<sup>®</sup>+ mRNA into Lung Epithelial Cells

# Aerosolized LUNAR<sup>®</sup>

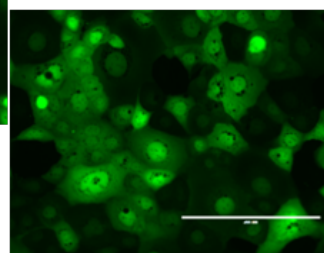
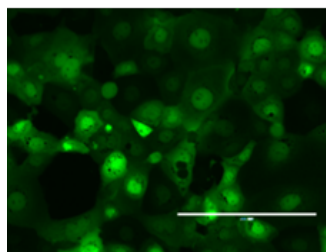
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Aerosolized LUNAR<sup>®</sup>  
Particles are Breathable



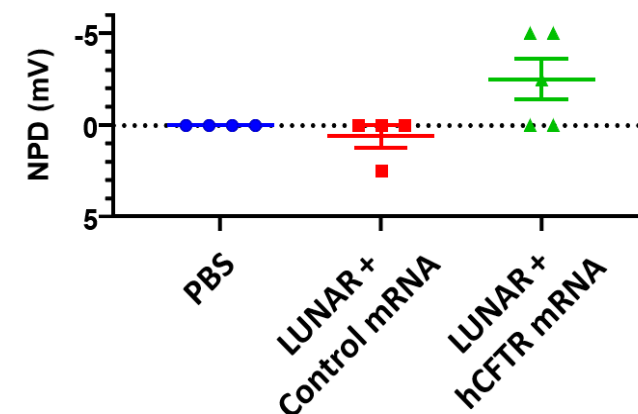
Aerosolized LUNAR<sup>®</sup>-mRNA (GFP)  
maintains activity

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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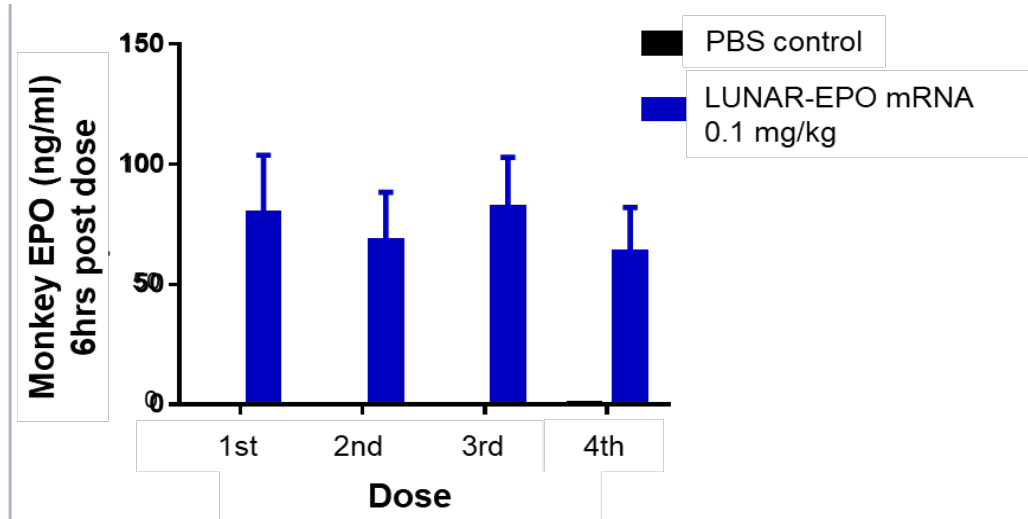
Optimize  
mRNA sequence  
Chemistry  
Process



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 |

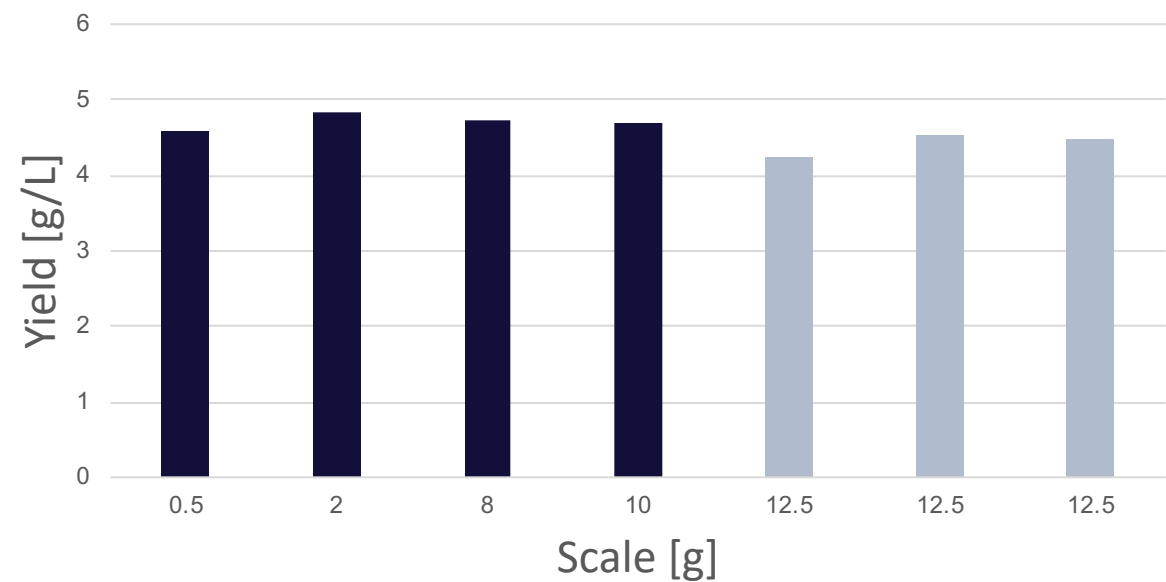
Arcturus Internal non-GMP mRNA Production Capabilities: Up to 30 g in Less Than One Week



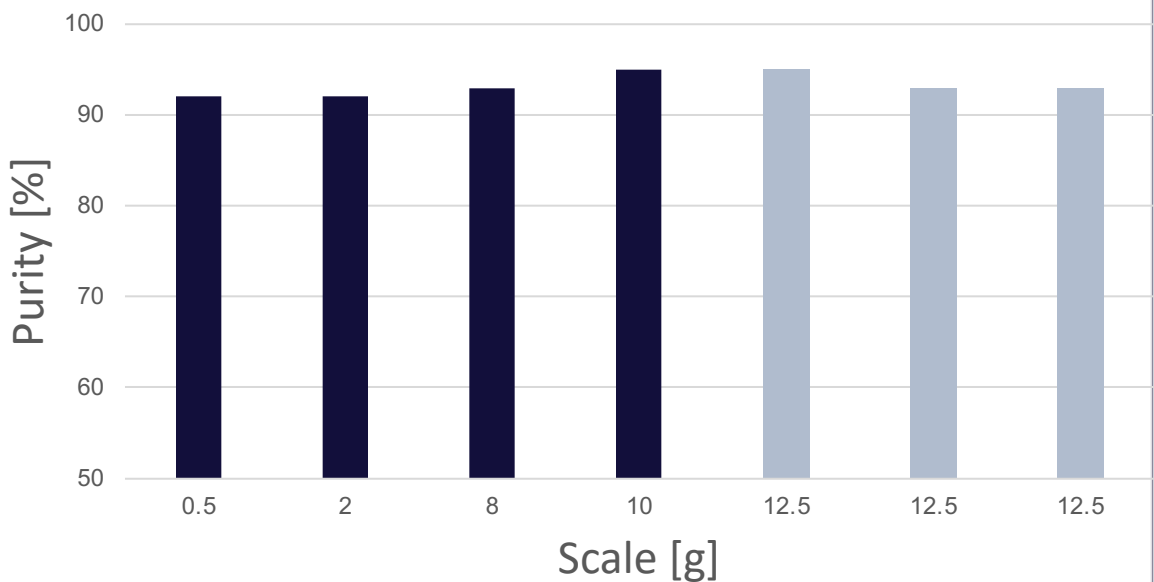
# Drug Substance (mRNA) Manufacturing



RNA Yield



RNA Purity



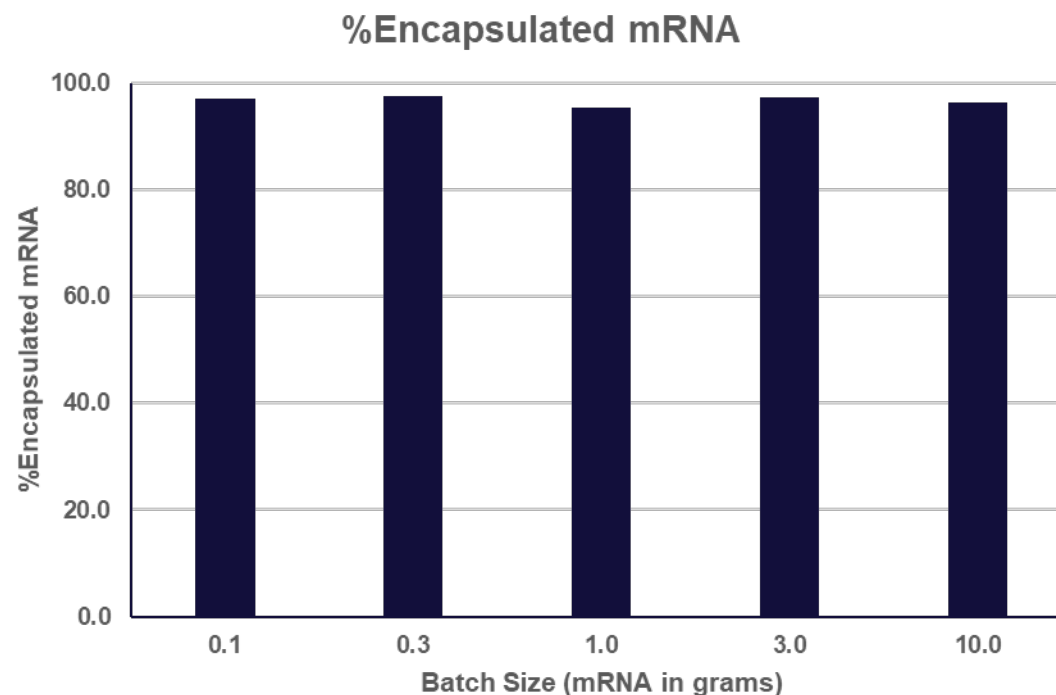
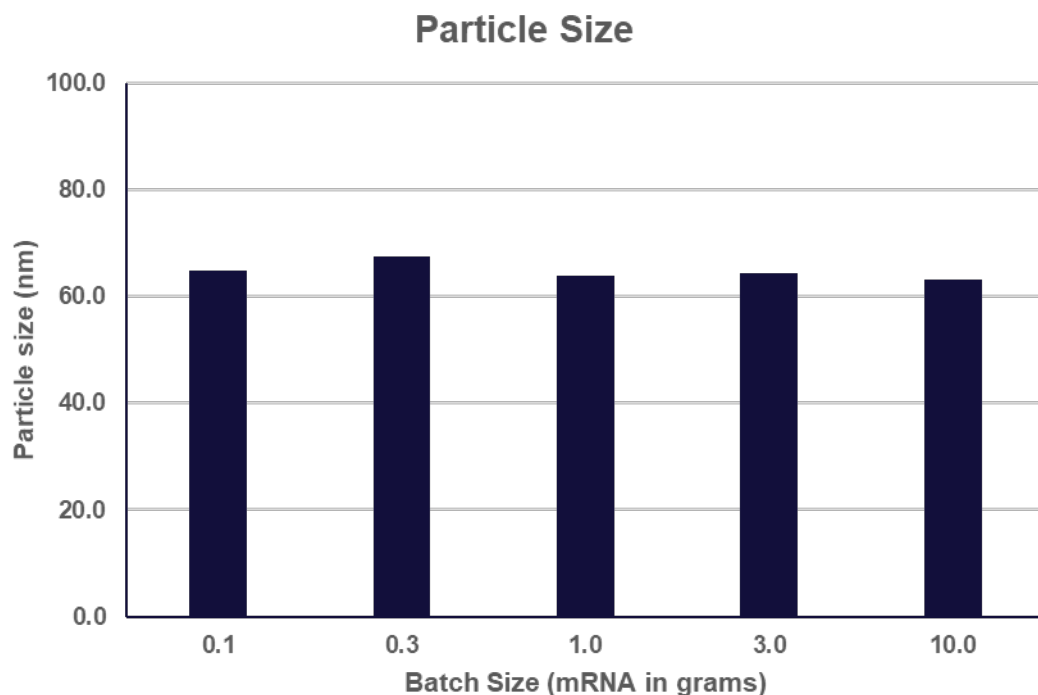
- Non-GMP Lots Produced at Arcturus
- GMP Lots Produced at CMO as part of recent GMP campaign

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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- 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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**Magda Marquet, Ph.D.**  
*Director of the Board*



**Joseph E. Payne, MSc**  
*Director of the Board,  
President & CEO*



**Andrew Sassine, MBA**  
*Director of the Board,  
CFO*



**Emil D. Kakkis, M.D., Ph.D.**  
*Board Advisor*



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*President & CEO*



**Pad Chivukula, Ph.D.**  
*CSO & COO*



**Andrew Sassine, MBA**  
*CFO*



**Steve Hughes, M.D.**  
*Chief Development Officer*





