

# 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; our efforts to develop a vaccine against COVID-19, the safety, efficacy or reliability of a our COVID-19 vaccine candidate; 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 Vaccines and Medicines Company**

## Publicly Traded (Nasdaq: ARCT)

- Headquarters: San Diego, CA
- Number of Employees: 97
- Founded: 2013

## Promising Therapeutic Candidates

- LUNAR-COV19 (COVID-19 Vaccine)
- LUNAR-OTC (Ornithine Transcarbamylase Deficiency)
- LUNAR-CF (Cystic Fibrosis)
- Additional Earlier Stage Programs



**Arcturus Technologies Validated by Multiple Strategic Partners**

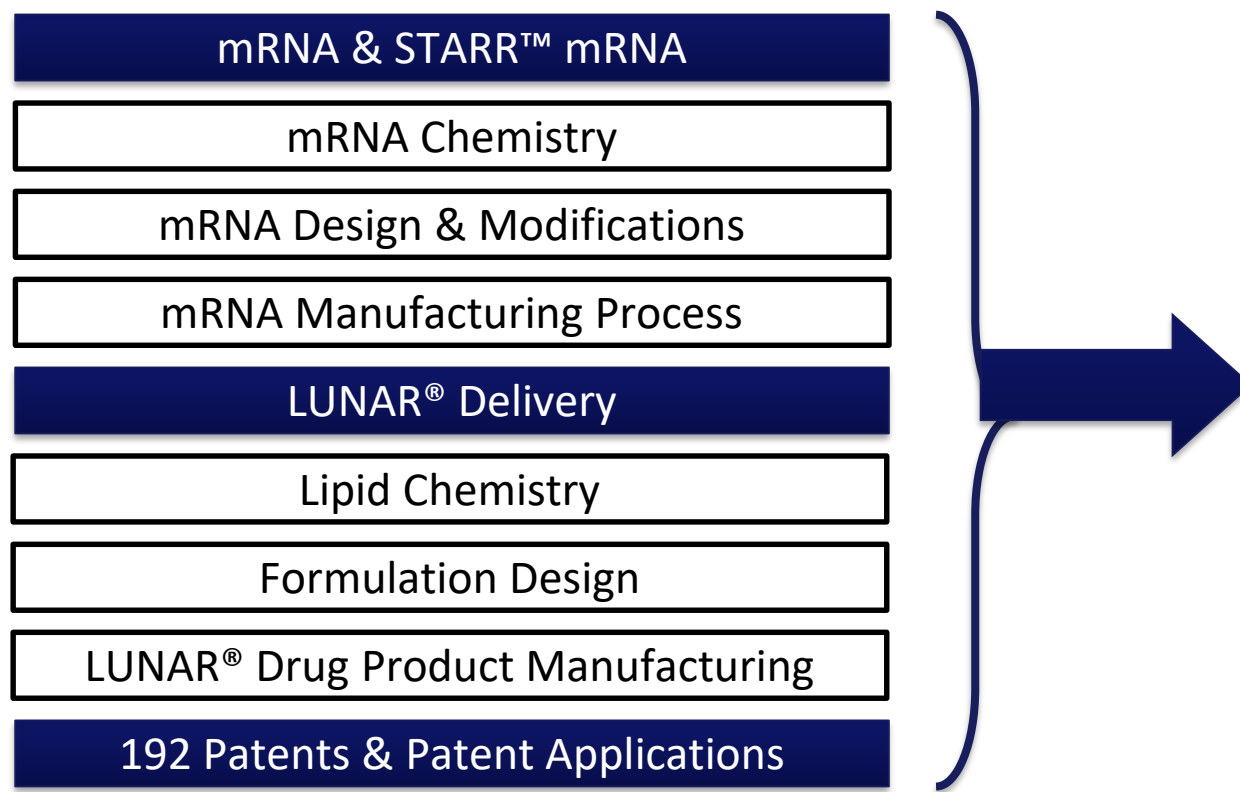


# Proprietary mRNA Technologies Driving Promising Therapeutic Programs

*Broad and Strong Intellectual Property Portfolio*



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| Program                           | Indication                                     |
|-----------------------------------|--|
| LUNAR-COV19<br>(ARCT-021)         | COVID-19 Vaccine                               |
| LUNAR-OTC<br>(ARCT-810)           | Ornithine Transcarbamylase<br>(OTC) Deficiency |
| LUNAR-CF                          | Cystic Fibrosis                                |
| LUNAR-CV                          | Rare Cardiovascular Disease                    |
| LUNAR-MD                          | Rare Metabolic Disease                         |
| ADDITIONAL EARLIER STAGE PROGRAMS |  |









# Arcturus Pipeline of mRNA Medicines

| Name                          | Indication                                  | Route of Administration | Target Organ (Cell Type)           | Prevalence Worldwide | Anticipated Milestones                |
|-------------------------------|---|-------------------------|------------------------------------|----------------------|---------------------------------------|
| <b>LUNAR-COV19 (ARCT-021)</b> | COVID-19 Vaccine                            | Intramuscular (i.m.)    | Muscle (Myocytes, Dendritic Cells) | Global               | Phase 1/2 Initiate Dosing Summer 2020 |
| <b>LUNAR-OTC (ARCT-810)</b>   | Ornithine Transcarbamylase (OTC) Deficiency | Intravenous (i.v.)      | Liver (Hepatocytes)                | > 10,000             | Phase 1 Data Q4 2020                  |
| <b>LUNAR-CF</b>               | Cystic Fibrosis                             | Inhaled Aerosol         | Lung (Bronchial Epithelial Cells)  | > 70,000             | DC Selection 2020 IND 2021            |
| <b>LUNAR-CV</b>               | Rare Cardiovascular Disease                 | Intravenous (i.v.)      | Liver (Hepatocytes)                | Undisclosed          | IND 2021                              |
| <b>LUNAR-MD</b>               | Rare Metabolic Disease                      | Intravenous (i.v.)      | Liver (Hepatocytes)                | Undisclosed          | IND 2022                              |

**Multiple mRNA Therapeutic Programs with Milestones in 2020**

# Partnerships Maximize Platform

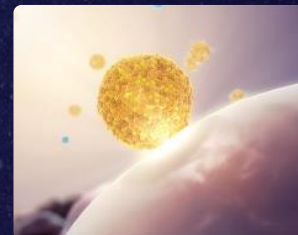
| Program    | Partner  | Indication                          |
|------------|--|-------------------------------------|
| LUNAR-HBV  |  | Hepatitis B Virus (HBV)             |
| LUNAR-NASH |  | Nonalcoholic Steatohepatitis (NASH) |
| LUNAR-GSD3 |  | Glycogen Storage Disease Type III   |
| LUNAR-RARE |  | Undisclosed Rare Disease            |
| LUNAR-RPL  | Undisclosed<br>Large Pharma  | Vaccines                            |
| LUNAR-AH   | Undisclosed<br>Animal Health Pharma  | Vaccines                            |

**Greater than \$1 Billion in Potential Milestones & Royalties**

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

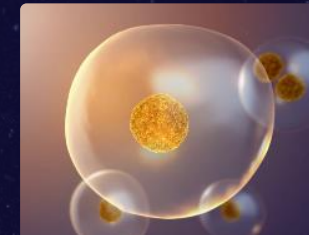


**LUNAR Associates  
with Cell Membrane**



Enters Cell  
Via Endocytosis

**Lipid Particle in  
Endosome**



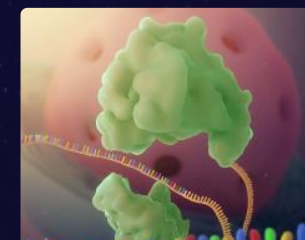
Increased Acidity as  
Endosome Ages

**pH-Mediated  
Disruption**



Rapid Biodegradation  
of Vehicle

**RNA  
in Cytosol**

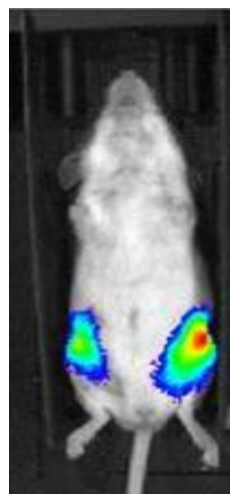


RNA Processing  
and Translation

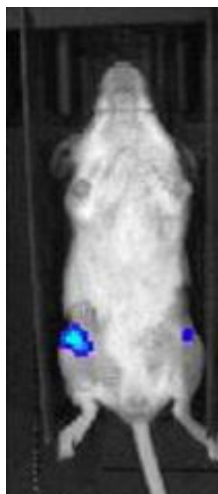
# STARR™ mRNA Superior to Conventional mRNA

*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**



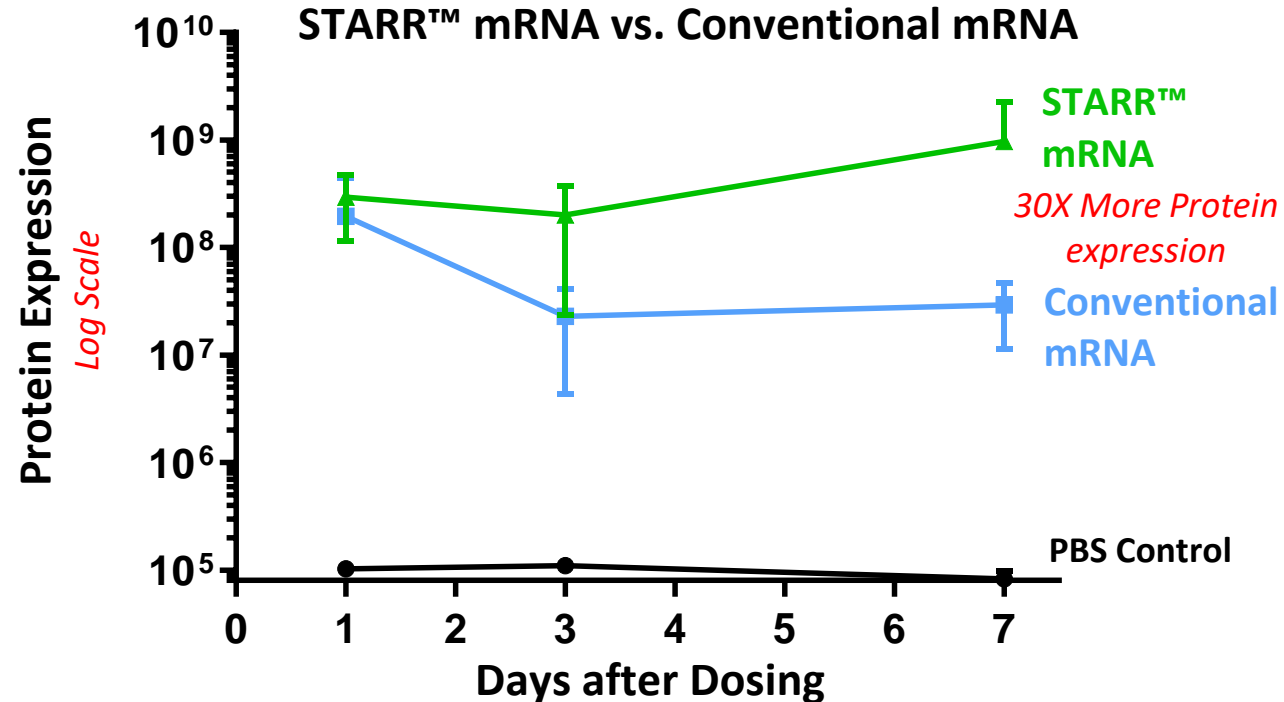
**Conventional  
mRNA**



**PBS  
Control**

## Protein Expression Over 7 days

### STARR™ mRNA vs. Conventional mRNA



**STARR™ mRNA technology together with LUNAR® delivery may enable single vaccine administration at very low dose**



# **LUNAR-COV19 (ARCT-021)**

## **COVID-19 Vaccine Candidate**

# Arcturus COVID-19 Vaccine Candidate has Significant Advantages



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- Duke-NUS Partnership **DukeNUS**  
Medical School
- mRNA Vaccine: Simple, No Adjuvants, No Viruses
- STARR™ mRNA: Produces 30X more Protein than Conventional mRNA
- LUNAR® Technology: non-viral Delivery System 
- Promising Preclinical Data: Neutralizing Antibodies & Cell-mediated Immunity
- Potential Single-Shot: Simpler Logistics for Vaccinating Large Populations
- Very Low Dose: Enables Rapid Global Scale-up
- Readily Manufactured: Arcturus Processes + Strategic Partnership **Catalent**

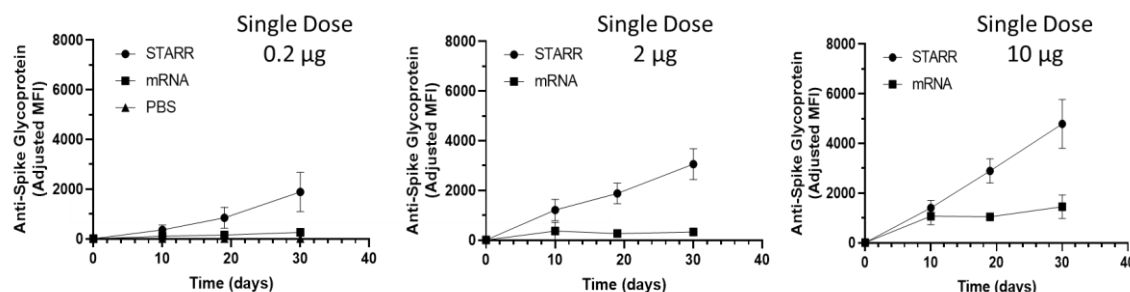
# Preclinical Data: Broad and Robust Immune Response



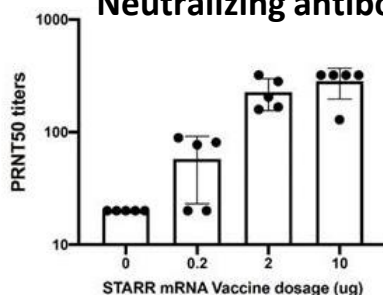
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## Humoral Immunity

**STARR™ induces more robust titers compared to conventional mRNA**



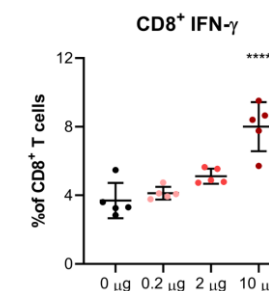
**Neutralizing antibody titers and high seroconversion at low doses**



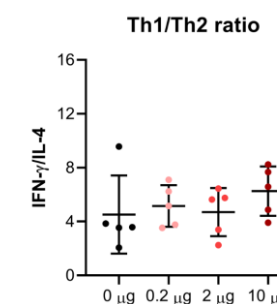
| Single Dose (µg) | Seroconversion | Neutralizing Antibody Titers (Geometric Mean) |
|------------------|----------------|---|
| 0.2              | 80 %           | 58  |
| 2                | 100 %          | 218   |
| 10               | 100 %          | ≥ 320   |

## Cellular Immunity

**Adaptive Cellular  
(CD8+ cells)**



**Balanced (Th1/Th2)  
immune response**



- Single administration with a very low dose of Arcturus COVID vaccine results in potent immune reaction
- STARR™ mRNA generates neutralizing antibodies (anti-SARS-CoV-2 Spike Glycoprotein IgG) and a cellular T-cell mediated immune response at a much lower dose level compared to conventional mRNA

# Clinical Development Plan to Rapidly Advance LUNAR-COV19



- **Initiate Phase 1/2 dosing this summer 2020**
- **Enroll up to 108 healthy volunteer adults, including the elderly, to evaluate safety and immune response**
- **Trial design allows us to potentially rapidly select dose to take forward to large registrational studies**
- **Based on anticipated single, low dose vaccine and Catalent partnership, Arcturus could potentially manufacture hundreds of millions of doses in 2021**
- **Arcturus retains global rights to LUNAR-COV19**



# **LUNAR-OTC (ARCT-810)**

## **Ornithine Transcarbamylase (OTC) Deficiency**

# 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

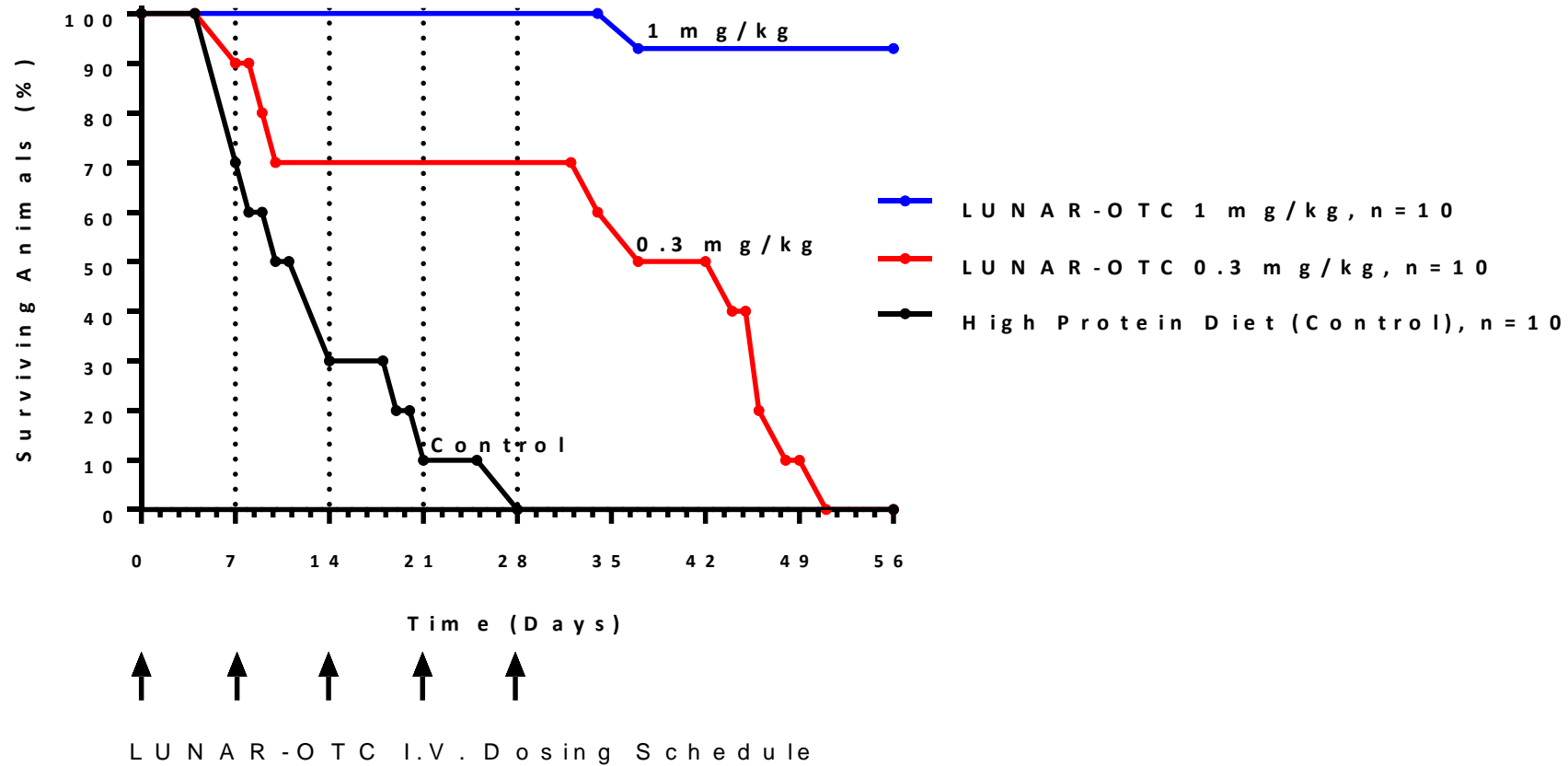
# LUNAR-OTC

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

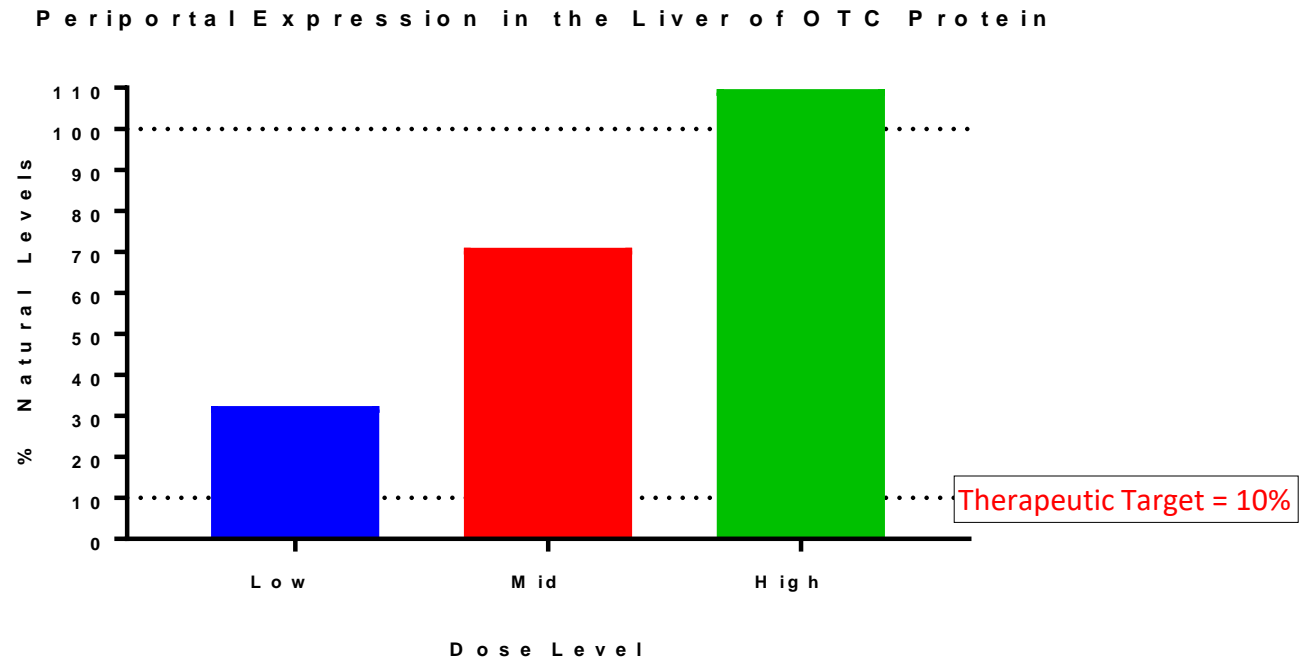


# LUNAR-OTC



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)**



# ARCT-810 Phase 1/1b Study Ongoing

## Two Single Dose Studies

- New Zealand Phase 1 clinical trial underway, up to 30 healthy volunteers – Clinical Trial Application (CTA) approved
- U.S. Phase 1b clinical trial in up to 12 stable OTC-deficient patients – IND allowed to proceed

**Primary Goal:** Identify safest doses to take forward into multiple dose clinical trials

**Primary Endpoints:** Safety and tolerability

**Exploratory Endpoints:** Biomarkers ureagenesis, plasma ammonia levels and OTC enzyme activity, urine orotic acid levels

## Dosing

- Single ascending dose (SAD) studies; randomized, placebo controlled and blinded
- Healthy volunteer study – up to 5 dose levels; Patient study – up to 3 dose levels
- All doses are within the anticipated range for therapeutic biological effect

## Timing of Human Data

- Phase 1 healthy volunteer study has initiated; targeted to complete in Q4 2020
- Phase 1b patient study initiation dependent on COVID19 status

# **LUNAR-CF**

## **Cystic Fibrosis**

# 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



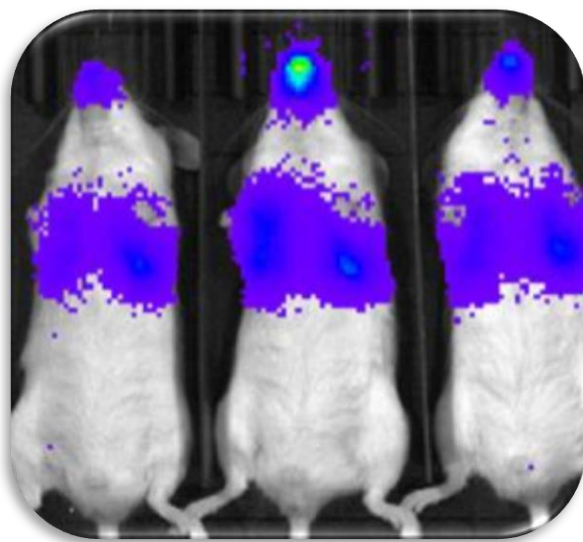
## **LUNAR-CF Aims to Restore CFTR Function**

- 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

# Delivery of LUNAR<sup>®</sup>-mRNA to Rodent Airways

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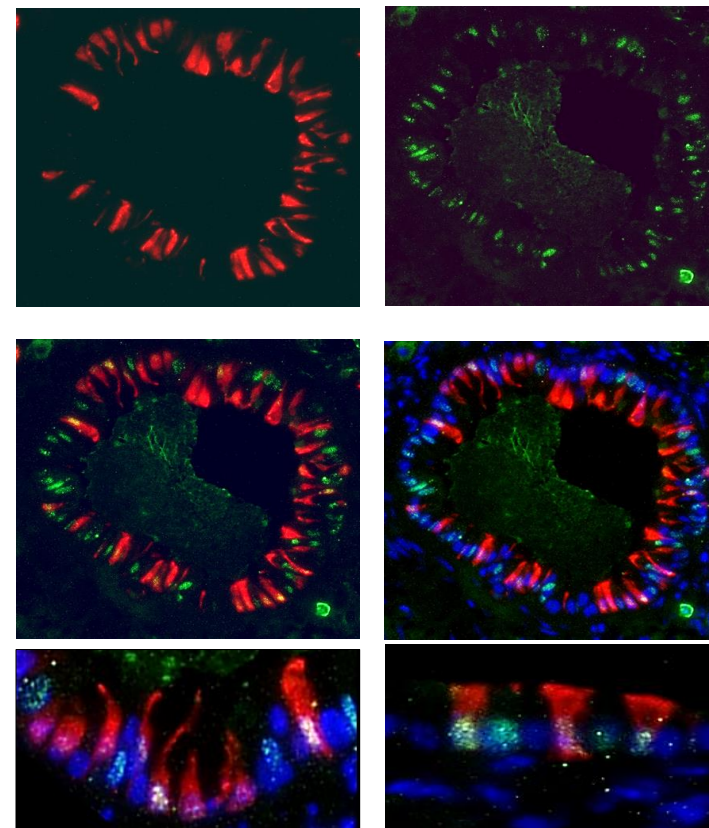
Nebulization: Upper/Lower Airways



LUNAR<sup>®</sup> + Luciferase mRNA

LUNAR<sup>®</sup> Targets Mice Epithelial Airways (**TdTomato**),  
Including Ciliated Cells (**TdTomato**/**FoxJ1**)

**TdTomato** / **FoxJ1** / Dapi

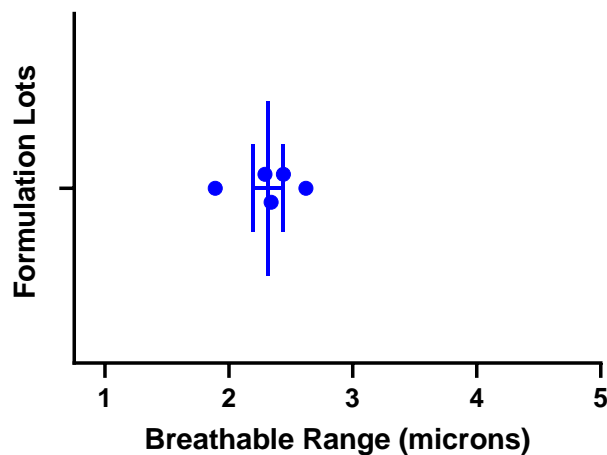


Efficient delivery of LUNAR<sup>®</sup>-mRNA formulations in rodent airways



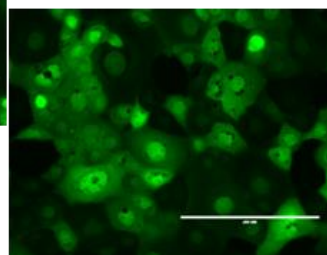
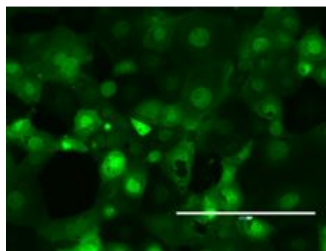
# LUNAR<sup>®</sup>, an aerosolized delivery platform for lung

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



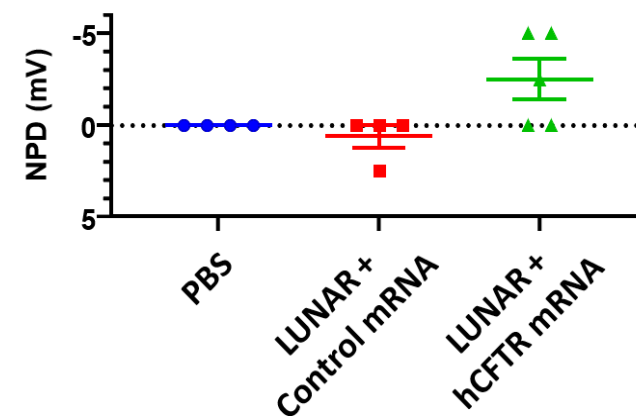
Aerosolized LUNAR<sup>®</sup>-mRNA (EGFP)  
maintains activity

Pre-Nebulization



Post-Nebulization

LUNAR<sup>®</sup>-mRNA (hCFTR) is biologically  
active *in vivo* (NPD, Mouse)



Aerosolized LUNAR<sup>®</sup> droplets are in the optimal breathable range (1-5 microns)

Aerosolized LUNAR<sup>®</sup> maintains activity as measured by EGFP protein expression & Nasal Potential Difference (NPD)

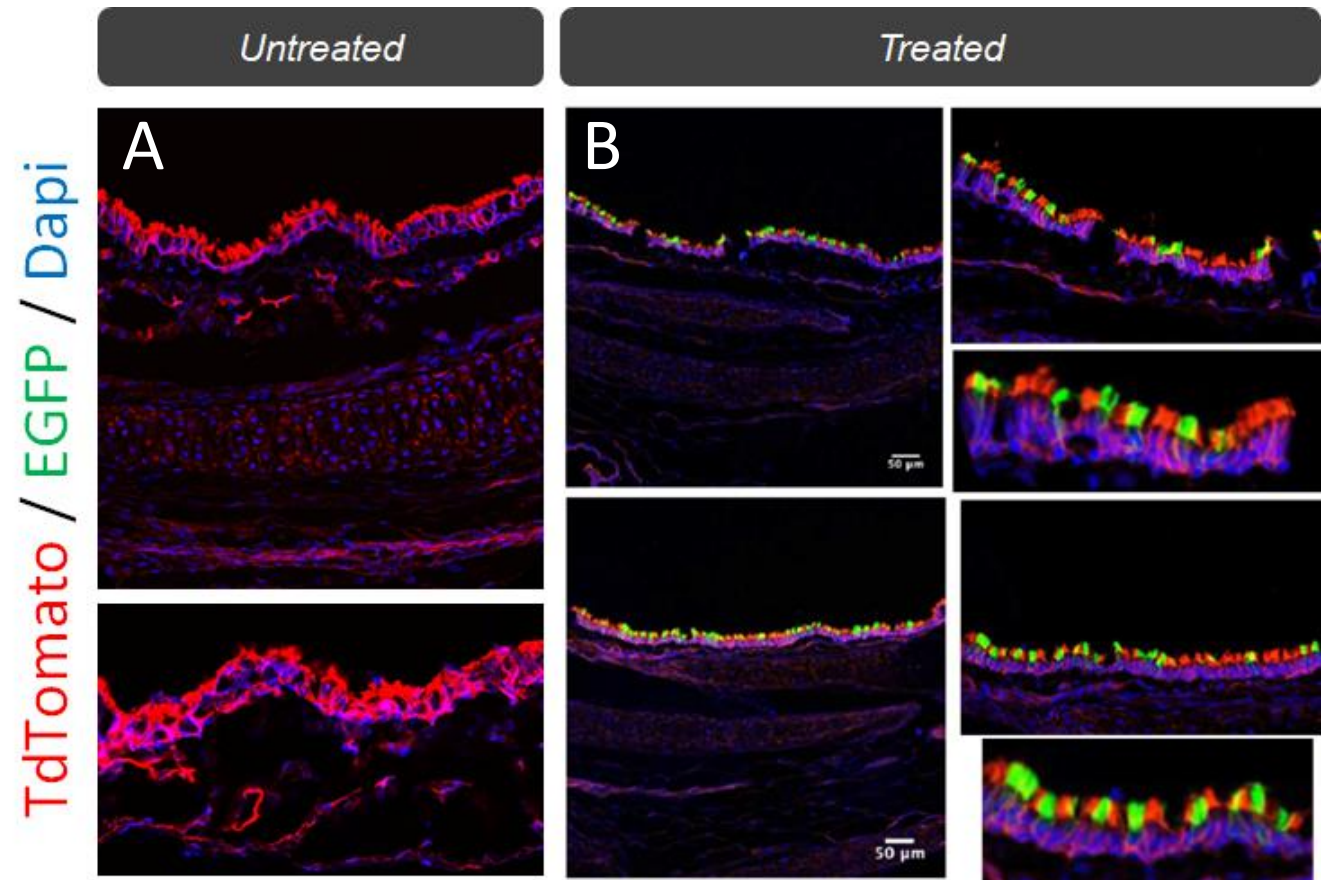
# Delivery of LUNAR<sup>®</sup>-mRNA into Epithelial Airways in Ferret

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



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- Ferrets are an excellent species for modeling certain human lung diseases\*
- Novel LUNAR<sup>®</sup> formulations of CRE mRNA were tested in a transgenic ROSA26TG ferret model
- Activation of EGFP expression indicates that LUNAR<sup>®</sup> targets epithelial airways
- Anticipated next steps: Development Candidate Nomination 2020, IND Filing 2021



In collaboration with John Engelhardt

**LUNAR<sup>®</sup> effectively delivered mRNA to the tracheal epithelial airways in a Ferret model**

# Moving Forward

# Anticipated Milestones and Cash Position

## LUNAR-COV19 (ARCT-021)

|                       |             |
|-----------------------|-------------|
| Phase 1/2 Initiation  | Summer 2020 |
| Initial Clinical Data | Q3/Q4 2020  |

## LUNAR-OTC (ARCT-810)

|              |         |
|--------------|---------|
| Phase 1 Data | Q4 2020 |
|--------------|---------|

## LUNAR-CF

|                                 |      |
|---------------------------------|------|
| Development Candidate Selection | 2020 |
| IND Application Filing          | 2021 |

## Cash Position

\$59.5 million as of March 31, 2020

\$75.5 million added in Q2 2020 from Secondary Offering

\$9.6 million added in Q2 2020 for Ultragenyx Option

\$4.9 million added from COVID-19 vaccine contract

**Sufficient to support operations for more than two years**



## Management Team



**Joseph E. Payne, MSc**  
President & CEO



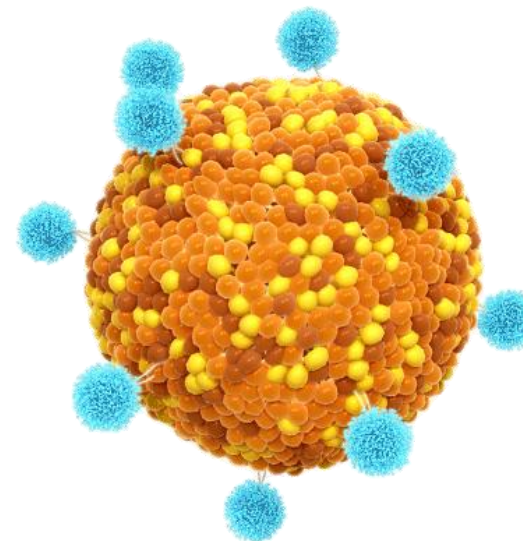
**Pad Chivukula, Ph.D.**  
CSO & COO



**Andrew Sassine, MBA**  
CFO



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



## Board of Directors



**Peter Farrell, Ph.D.**  
Chairman of the Board



**Karah Parschauer, JD**  
Director of the Board



**Edward W. Holmes, M.D.**  
Director of the Board



**James Barlow, MA**  
Director of the Board



**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

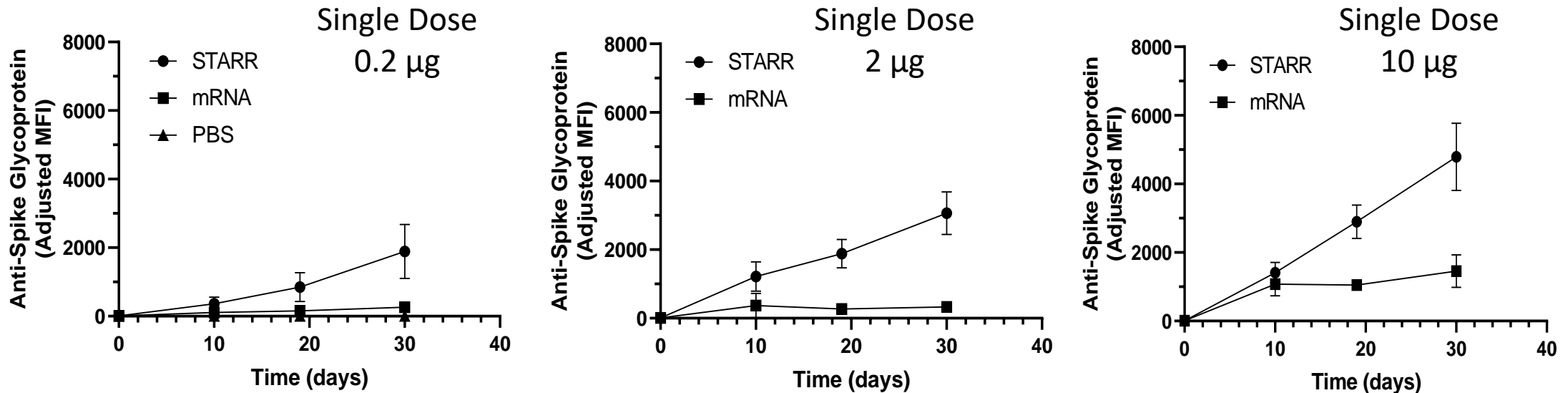






# Appendix

# Higher and More Robust Antibody Titters



- **Higher titers** (anti-SARS-CoV-2 Spike Glycoprotein IgG) elicited by STARR™ mRNA
- **Titers continue to increase** with STARR™ mRNA; plateau is reached with conventional mRNA
- Dose dependent increase in IgG titers

# LUNAR-COV19 Positive Preclinical Data

*Arcturus COVID-19 vaccine to begin human dosing this Summer*



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## Seroconversion Rate (% of Animals) – STARR™ mRNA vs. Conventional mRNA

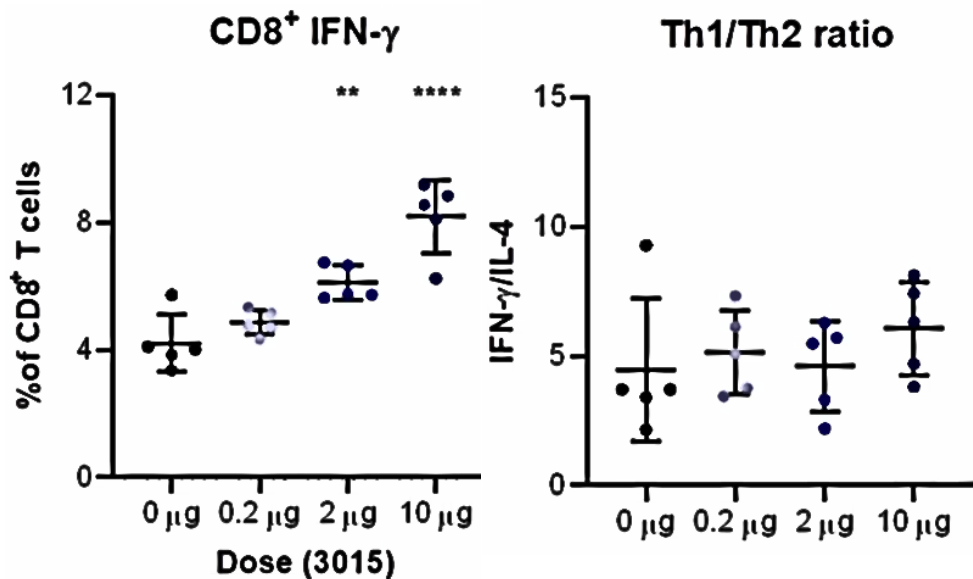
| Single<br>Dose (µg)* | LUNAR® Delivery |            |                       |        |
|----------------------|-----------------|------------|-----------------------|--------|
|                      | STARR™ mRNA (%) |            | Conventional mRNA (%) |        |
|                      | Day 10          | Day 19     | Day 10                | Day 19 |
| 0.2                  | 40              | 60         | 20                    | 20     |
| <b>2</b>             | 80              | <b>100</b> | 20                    | 0      |
| 10                   | 100             | 100        | 40                    | 80     |

\*One microgram (µg) is 1 billionth of a kilogram (i.e. 1 Kg STARR™ mRNA contains 500 million doses at 2 µg /dose)

**100% of mouse seroconverted by day 19 at a single low dose (2 µg)**



# Arcturus Vaccine elicits a Balanced Cell Mediated Immune Response



| RNA Dose (μg) | % IFN-g + CD8 <sup>+</sup> T Cells | CD4+ Th1/Th2 (IFN-g/IL4) |
|---------------|------------------------------------|--------------------------|
| 0.0           | 4.0                                | 4.6                      |
| 0.2           | 4.5                                | 5.3                      |
| 2.0           | 6.0                                | 5.0                      |
| 10.0          | 8.0                                | 6.0                      |

## Results Summary

- RNA dose dependent increase in IFN-g positive CD8<sup>+</sup> T-cells
- Th1 biased CD4<sup>+</sup> response and lack of change in Th1/Th2 ratio with increased RNA dose indicate balanced cell mediated immune response

# LUNAR-COV19 Data Summary

- Very low dose: Strong neutralizing antibody response with just a single dose of 0.2 – 10 µg STARR™ RNA
- Strong humoral response continuous increase in neutralizing antibodies beyond Day 30
- Strong T-cell response: dose responsive increase in IFN-g positive CD8<sup>+</sup> T-cells
- Potential single shot simplifies vaccination campaigns
- Safety: balanced cellular immune response – favorable profile to mitigate against immune pathology and Vaccine Induced Enhancement
- Superior immunogenic profile of STARR™ compared to conventional mRNA
- Adjuvant-free, Preservative-free, Antibiotic-free reduces public concerns

**Arcturus LUNAR-COV19 is a promising COVID-19 vaccine**

# Arcturus Safety Profile

## External Validation

- Multiple strategic partnerships over many years confirms the positive potential 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)

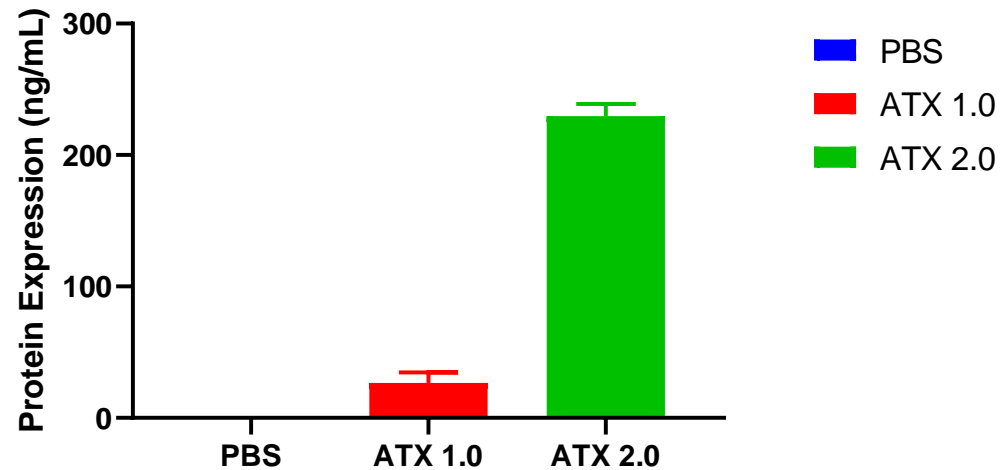
## Arcturus mRNA chemistry shows promising efficacy and tolerability data

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

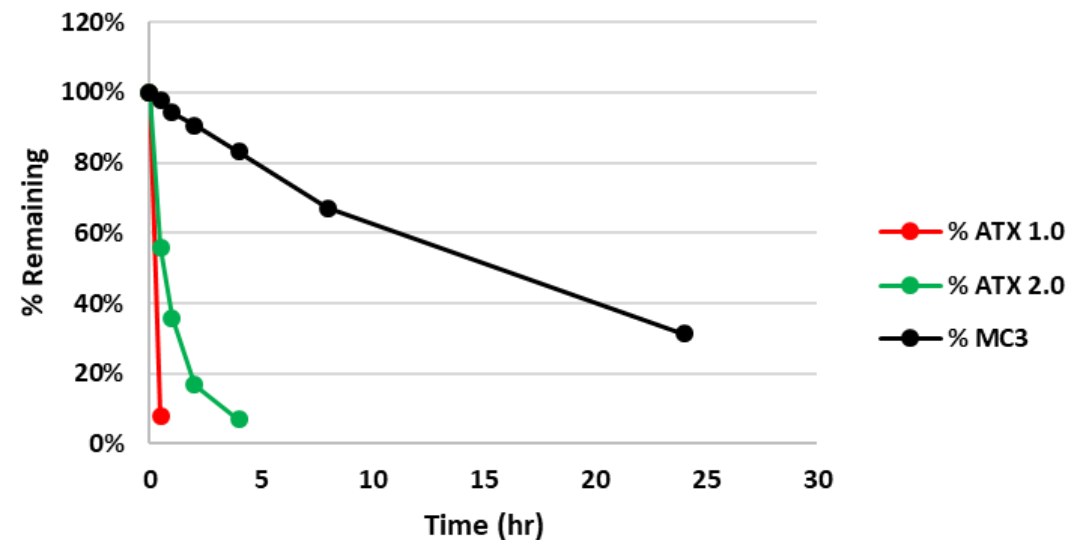
# ATX Lipids are Effective and Biodegradable

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## Protein Expression (*in vivo*)



## Esterase Catalyzed Degradation (*in vitro*)

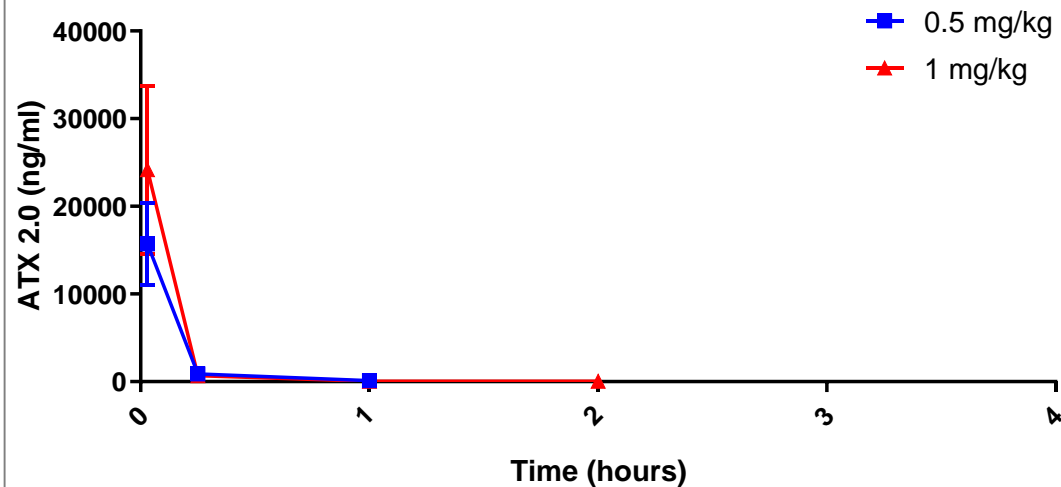


Next Generation ATX Lipids Retain Degradability & Improve Delivery Efficiency

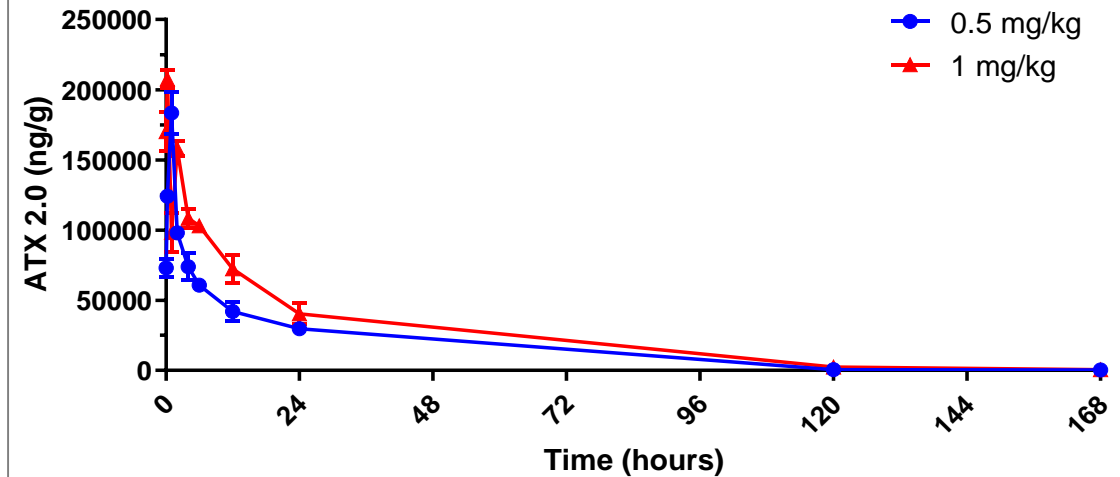
# ATX 2.0 Lipid is Biodegradable and Clears *in vivo*



## Plasma



## Liver



- ATX Lipid (the major component in LUNAR® technology) is degraded *in vivo*
- ATX 2.0 Lipid Half-Life in the Liver is Approximately 20 hours

# Drug Substance: mRNA Design

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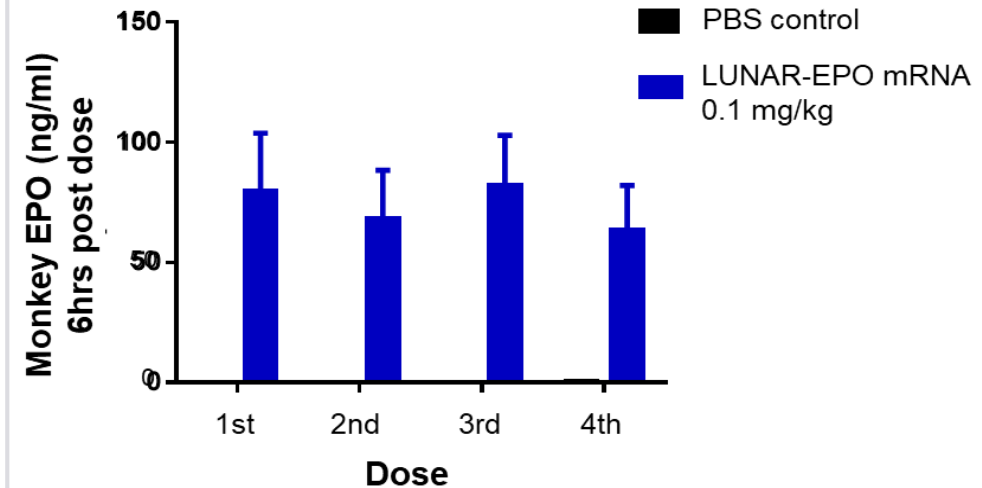
Optimize  
mRNA sequence  
Chemistry  
Process



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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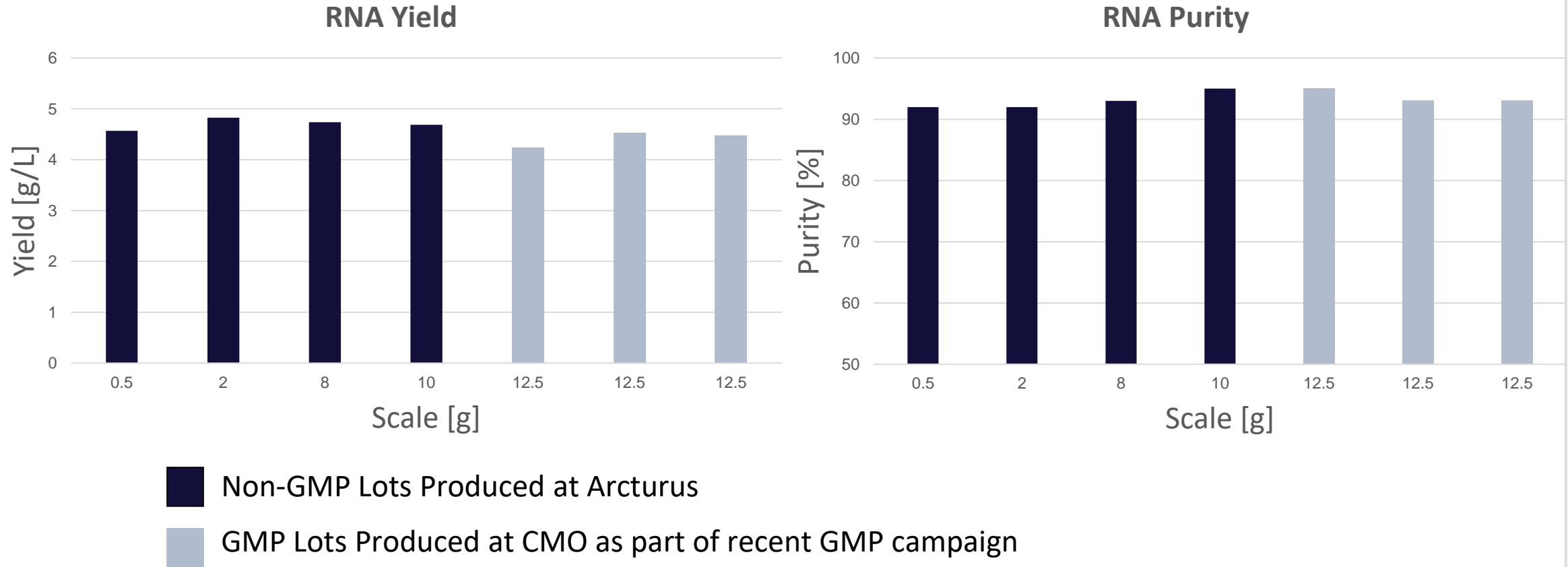
| Features                         | Benefits                               |
|----------------------------------|--|
| Optimized IVT Method             | Reduced Cost; Higher Purity            |
| Improved Capping Reaction        | Reduced Cost of Goods                  |
| Proprietary Purification 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



BUILDING INNOVATIVE  
RNA MEDICINES



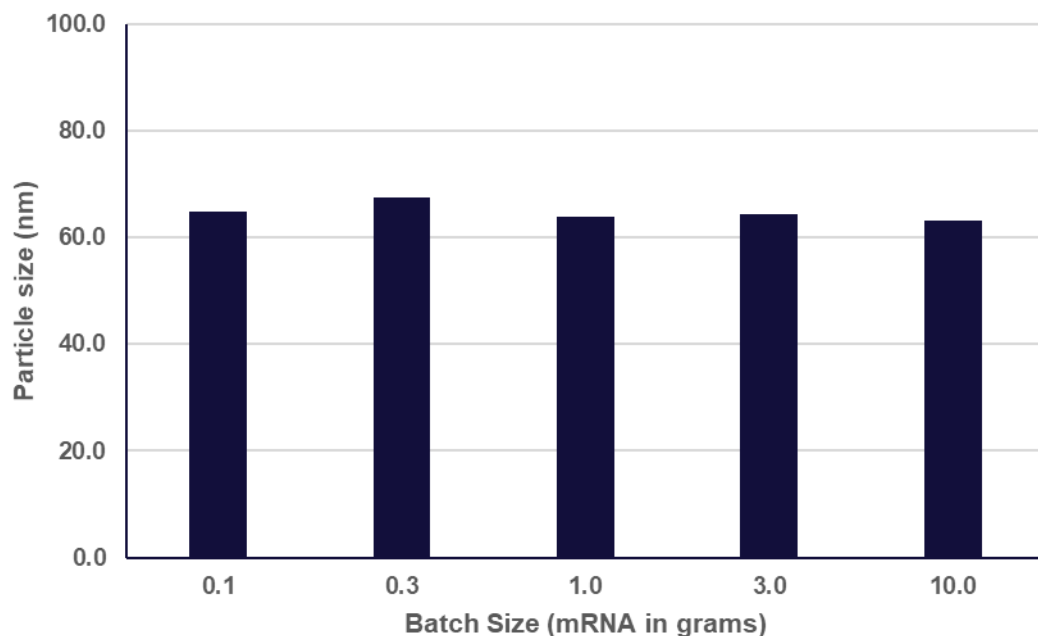
**Three 12.5 g lots produced in recent GMP campaign are of equivalent quality and yield**

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

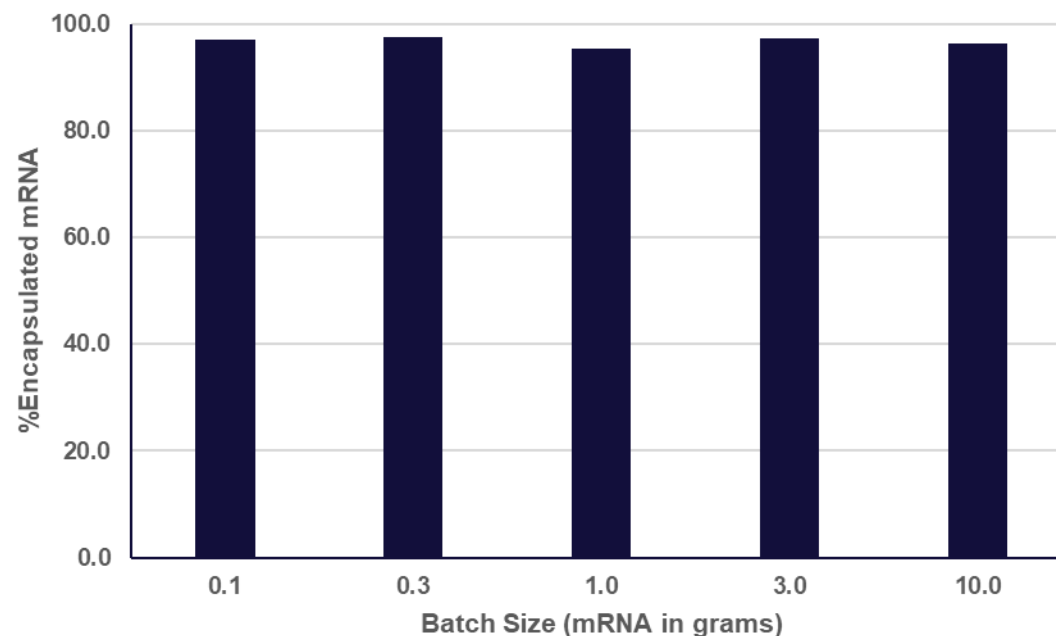


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Particle Size



%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