

# ARCTURUS THERAPEUTICS

Building the Next Generation of RNA Medicines

D e c e m b e r 2 0 1 9

# 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; the date that an IND may be filed with the FDA; 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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# Investment Highlights



BUILDING INNOVATIVE  
RNA MEDICINES

**Arcturus is an mRNA Medicines Drug Development Company Focused on Rare Diseases**

## **LUNAR® Delivery Platform Validated by Multiple Strategic Partners**

- More than \$1 Billion in potential milestones and royalties

## **Broad and Strong Intellectual Property Portfolio**

- 177 Patents & Patent Applications
- LUNAR® Delivery Technology
- RNA Drug Substance & Drug Product Process Manufacturing



HQ: **San Diego**; Founded: **2013**; Nasdaq: **ARCT**  
Outstanding Shares: **15.1M**; Employees: **85**;  
Insider Ownership: **33%**

## **Promising Preclinical Safety Data for LUNAR® Delivery and mRNA Drug Products**

# Key Value Drivers: Platform & Pipeline



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Platform: LUNAR® Delivery, mRNA Drug Substance, and STARR (Self-Transcribing And Replicating RNA) Technology™



SYNTHETIC GENOMICS



**Strategic Partners:** More than \$1 Billion in Potential Milestones & Royalties

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## Pipeline: Arcturus mRNA Medicines

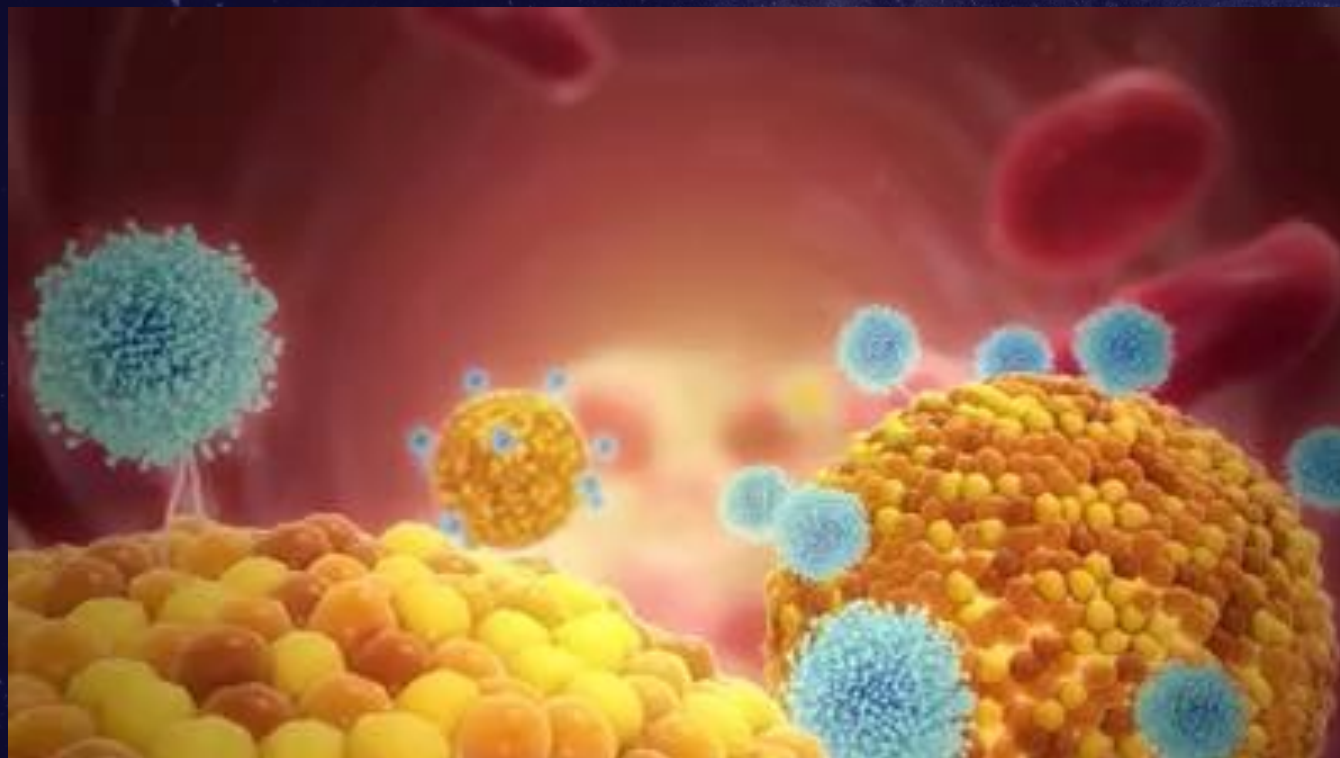
**LUNAR-OTC (ARCT-810)** to treat Ornithine Transcarbamylase (OTC) Deficiency  
OTC Deficiency market potential \$500M annual sales  
Orphan Drug Designation is received from U.S. FDA

**LUNAR-CF** to treat Cystic Fibrosis (CF); Funded by the  
Class I CF market potential \$900M annual sales

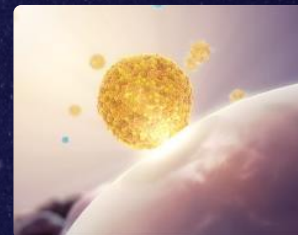




# LUNAR<sup>®</sup> Mechanism of Delivery

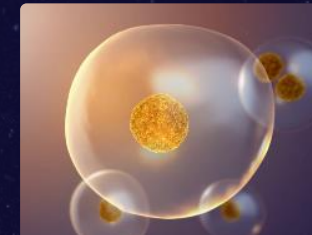


## LUNAR Associates with Cell Membrane



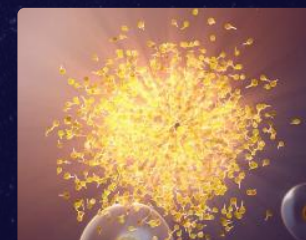
Enters Cell  
Via Endocytosis

## Lipid Particle in Endosome



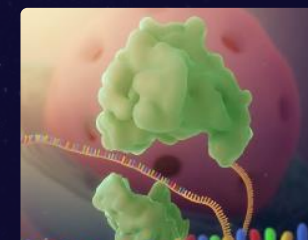
Increased Acidity as  
Endosome Ages

## pH-Mediated Disruption







Rapid Biodegradation  
of Vehicle

## RNA in Cytosol



RNA Processing  
and Translation

# Arcturus Platform: Enabling Genetic Medicines

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

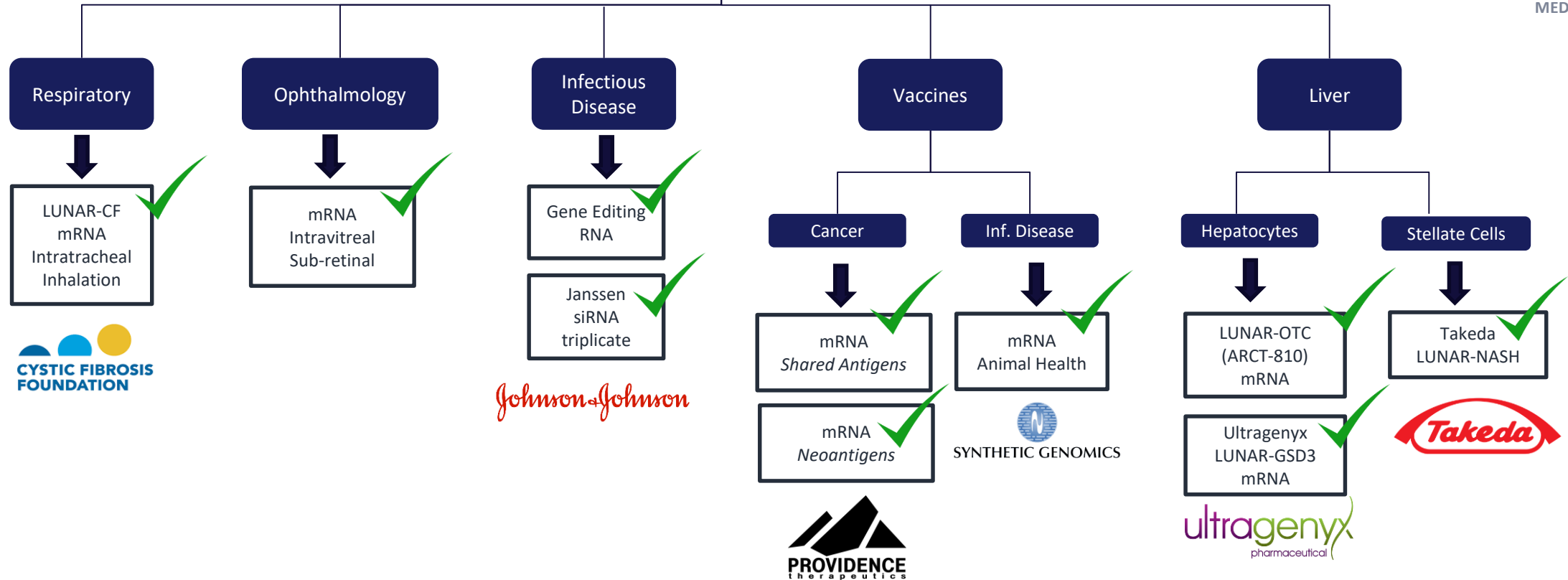
- Greater than \$1 Billion in Potential Milestones & Royalties
- Enabling Different Types of RNA – Messenger RNA, Gene Editing RNA, Replicon RNA
- Multiple Cell Types Targeted
- LUNAR-GSD3 (UX053) is a licensed program, partnered with Ultragenyx – IND Target 2020

# Arcturus Pipeline of mRNA Medicines

Name	Indication	Expected IND Date	Route of Administration	Target Organ	Target Cells	Prevalence Worldwide
<b>LUNAR-OTC (ARCT-810)</b>	Ornithine Transcarbamylase (OTC) Deficiency	Q1 2020	Intravenous (i.v.)	Liver	Hepatocytes	> 10,000
<b>LUNAR-CF</b>	Cystic Fibrosis	2021	Nebulized Aerosol to Lung	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

- Pipeline programs focus on messenger RNA (mRNA) drug products for rare diseases
- LUNAR-OTC (ARCT-810, intravenous mRNA medicine): IND Filing Target Q1 2020
- LUNAR-CF is funded by the Cystic Fibrosis (CF) Foundation: IND Filing Target 2021
- LUNAR-CV and LUNAR-MD are preclinical programs

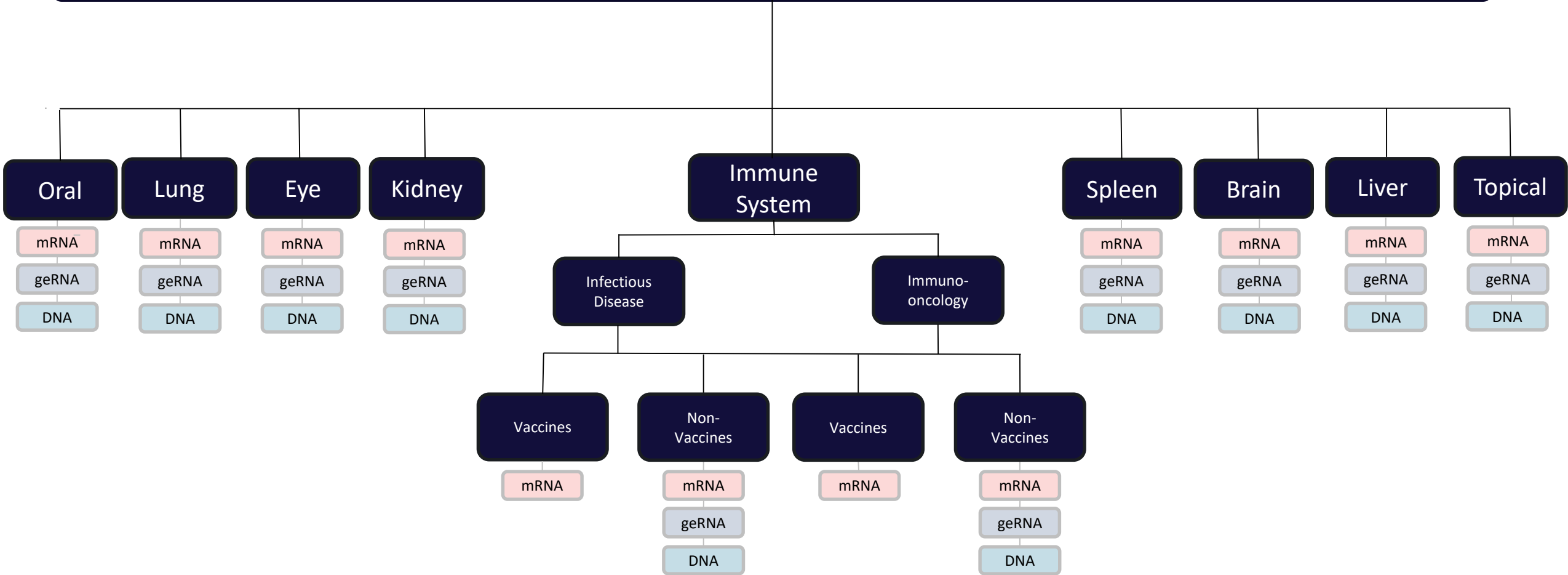
## LUNAR® Platform Substantial Preclinical Proof-of-Concept Demonstrated



LUNAR® Platform Preclinical Proof-of-Concept Demonstrated in Hepatocytes, Liver Stellate Cells, Bronchial Epithelial Cells (Lung), Photoreceptors (Eye), Infectious Diseases, Cancer Vaccines



Target Opportunities for LUNAR<sup>®</sup> Delivery Platform Exceed \$100 Billion in Potential Value



# 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 spikes of ammonia.
- OTC Deficiency patients are typically referred for liver transplant.



## **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

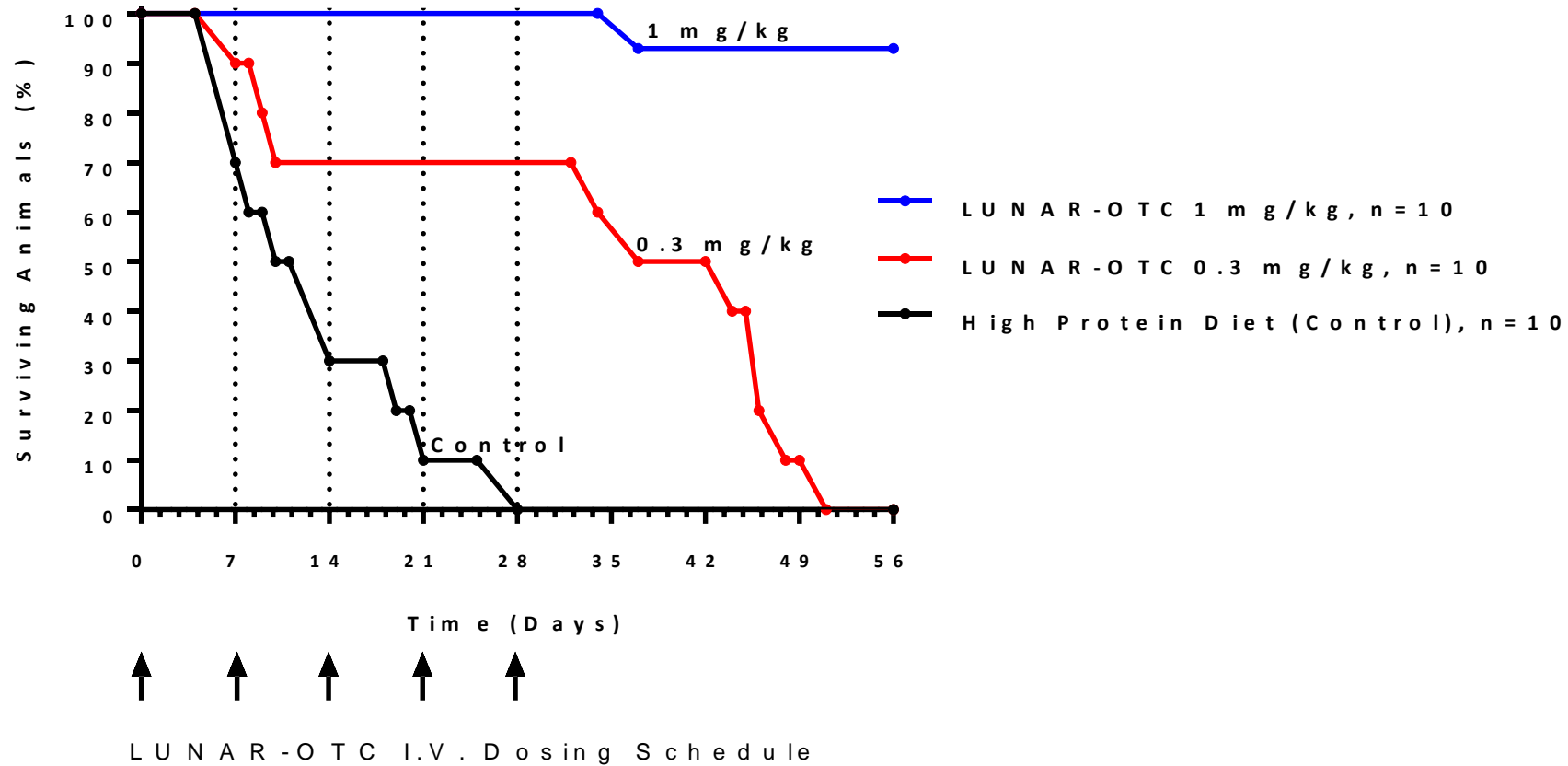
# LUNAR<sup>®</sup>-OTC

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

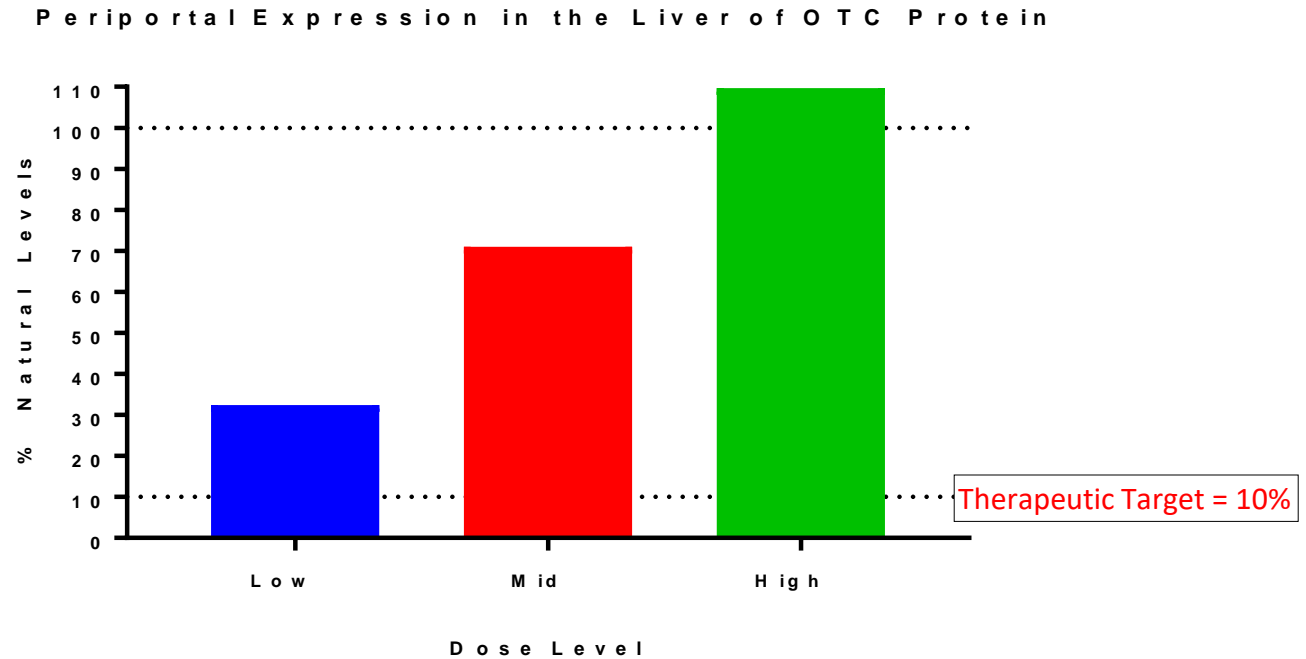


# LUNAR-OTC



## 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

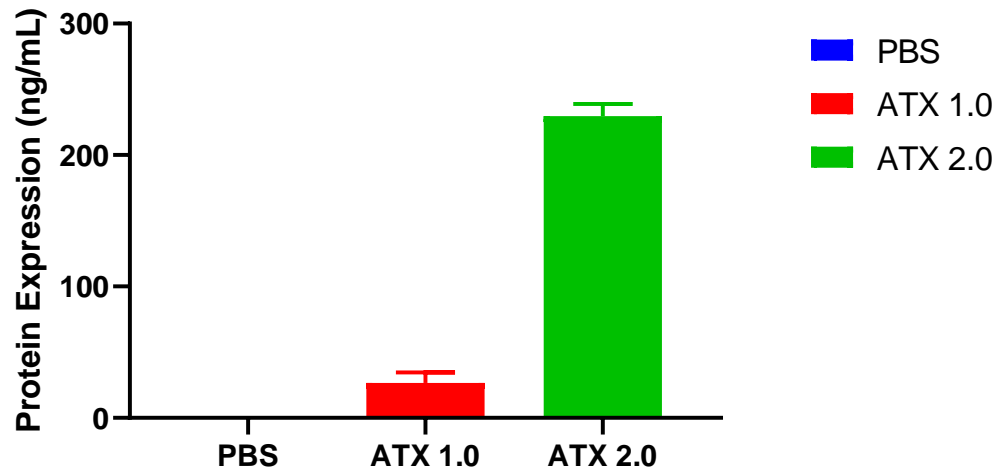
\*Lamers, W.H., Hakvoort, T.B.M., and Köhler, E.S. 'Molecular Pathology of Liver Diseases' in Monga S.P.S. (ed.), *MOLECULAR PATHOLOGY LIBRARY SERIES*, Springer Publishing, New York, pp. 125-132 | DOI: 10.1007/978-1-4419-7107-4

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

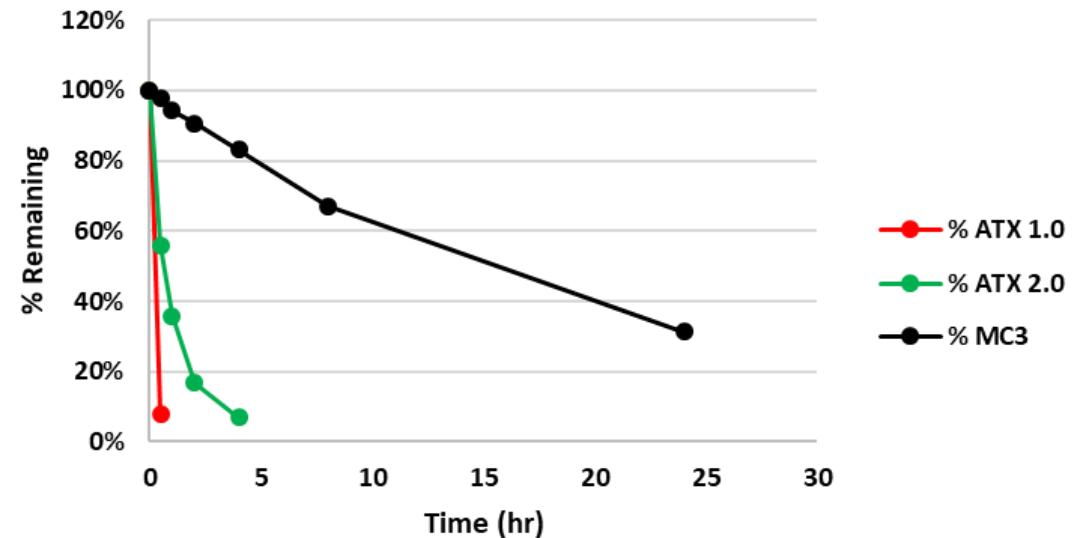
# ATX Lipids are Effective and Degrade Rapidly

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### Protein Expression (*in vivo*)



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

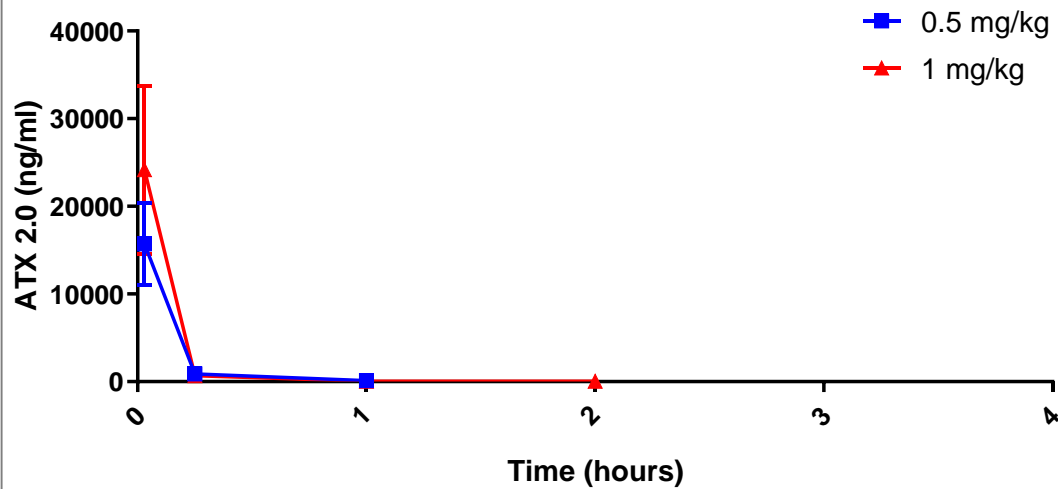


Next Generation ATX Lipids Retain Degradability & Improve Delivery Efficiency

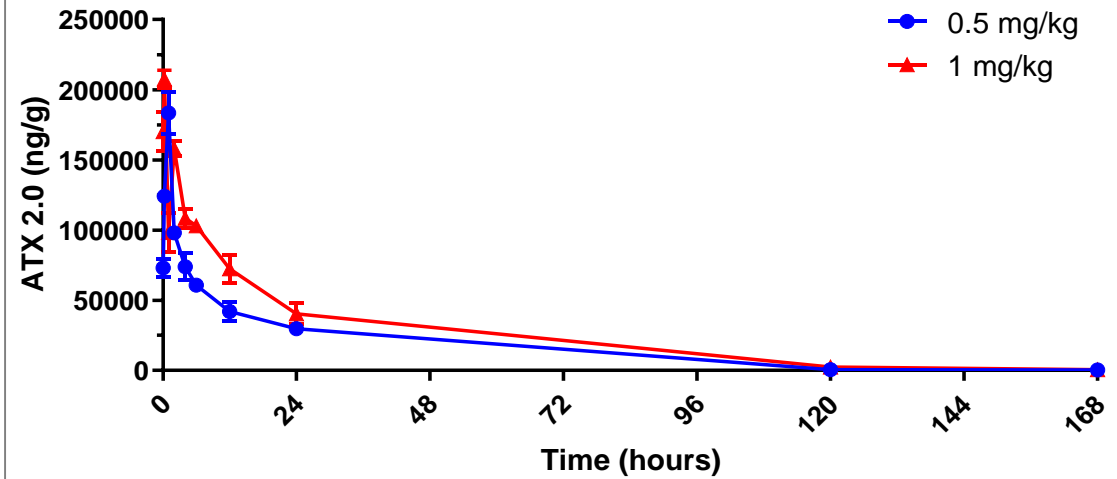


# ATX 2.0 Lipid Rapidly Clears *in vivo*

## 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® 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)

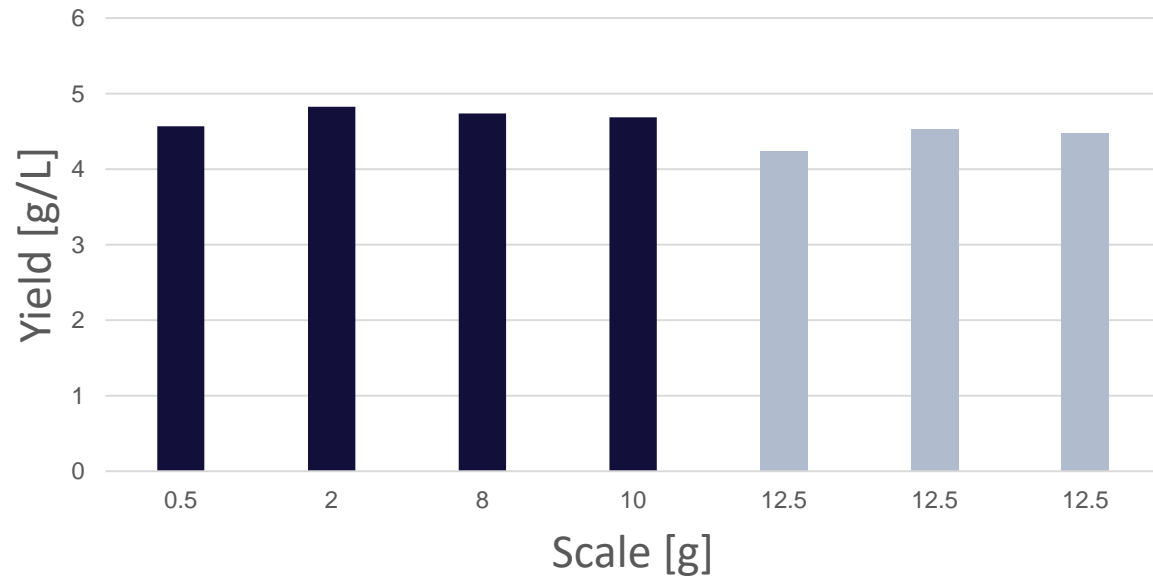
## Arcturus mRNA chemistry shows promising efficacy and tolerability data

- Efficacy of OTC mRNA in mouse model @ 0.1 – 1 mg/kg
- Well tolerated in mouse @ 7 mg/kg single dose

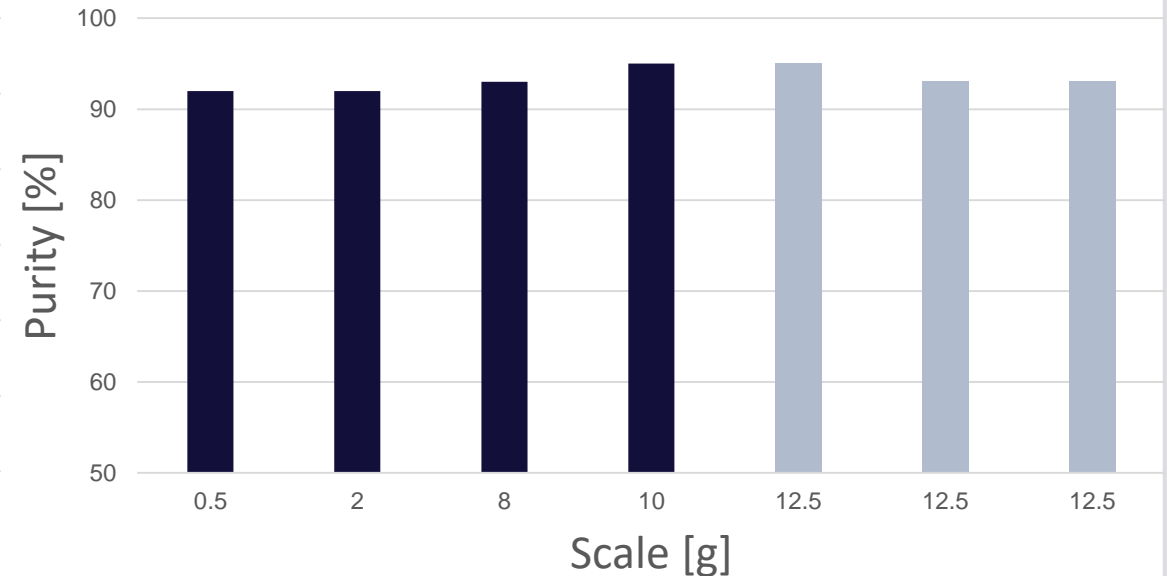
# mRNA Drug Substance



RNA Yield



RNA Purity



- Lots produced at Arcturus
- Lots produced at CMO as part of recent GMP campaign

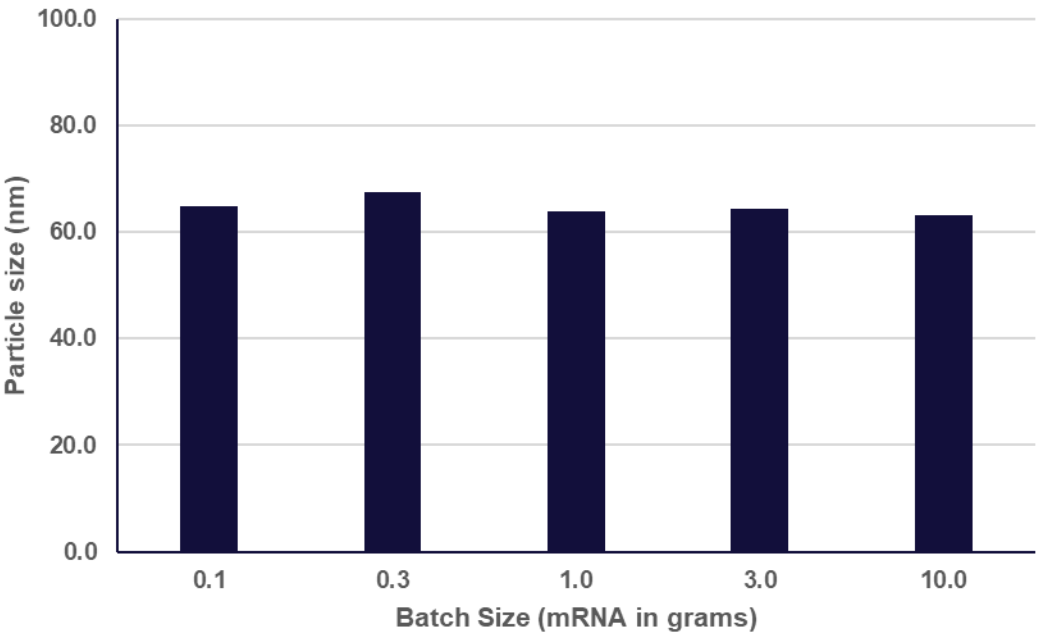
**Three 12.5 g lots produced in recent campaign are of equivalent quality and yield**

# LUNAR<sup>®</sup>-mRNA Drug Product

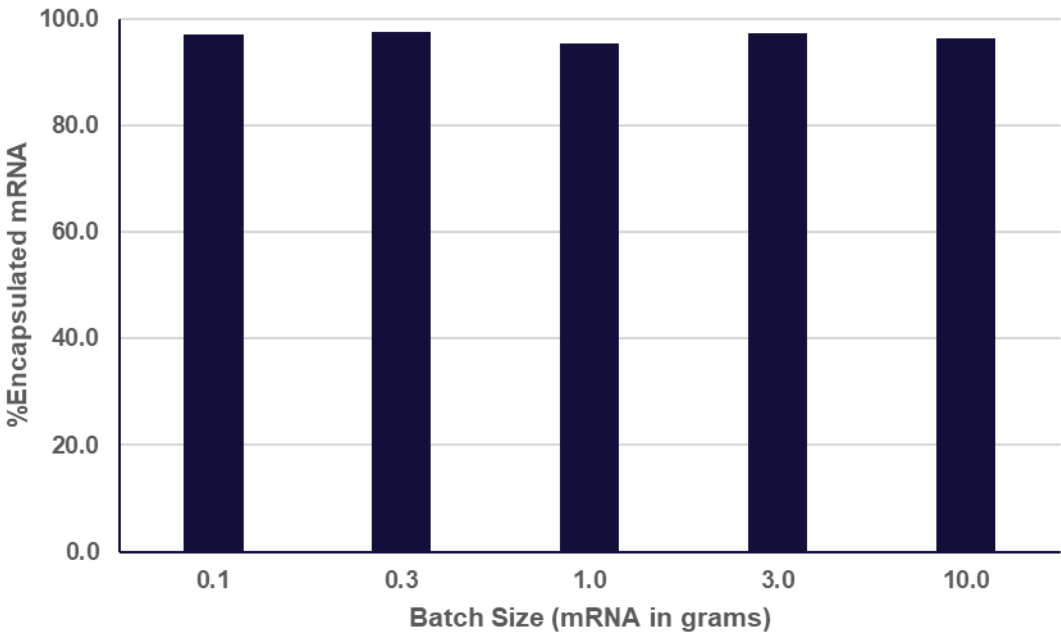


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Particle Size



%Encapsulated mRNA



- Scalability of Drug Product demonstrated from milligram to multigram scale with yields  $\geq 85\%$
- Multiple batches (10g) of LUNAR<sup>®</sup>-OTC mRNA manufactured

# 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**

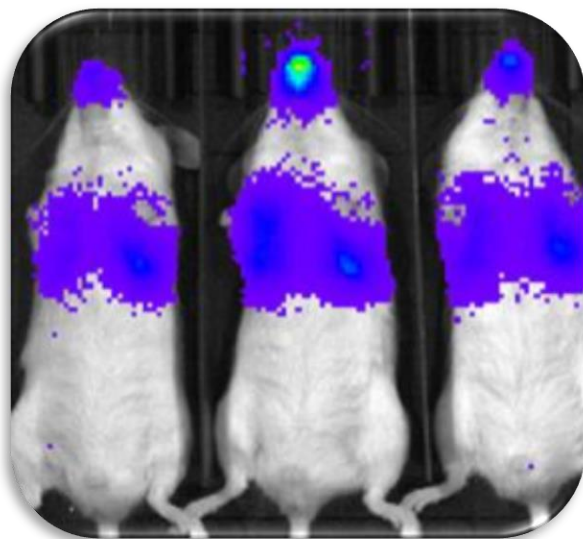
- An mRNA replacement therapy has the potential to deliver a new copy of CFTR into the lungs of CF-patients, independent of any genotype
- A functional CFTR protein can restore chloride channel efflux in the airways, reducing mucus accumulation, tissue scarring and minimizing the progressive respiratory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



# LUNAR<sup>®</sup> Targeting Lung

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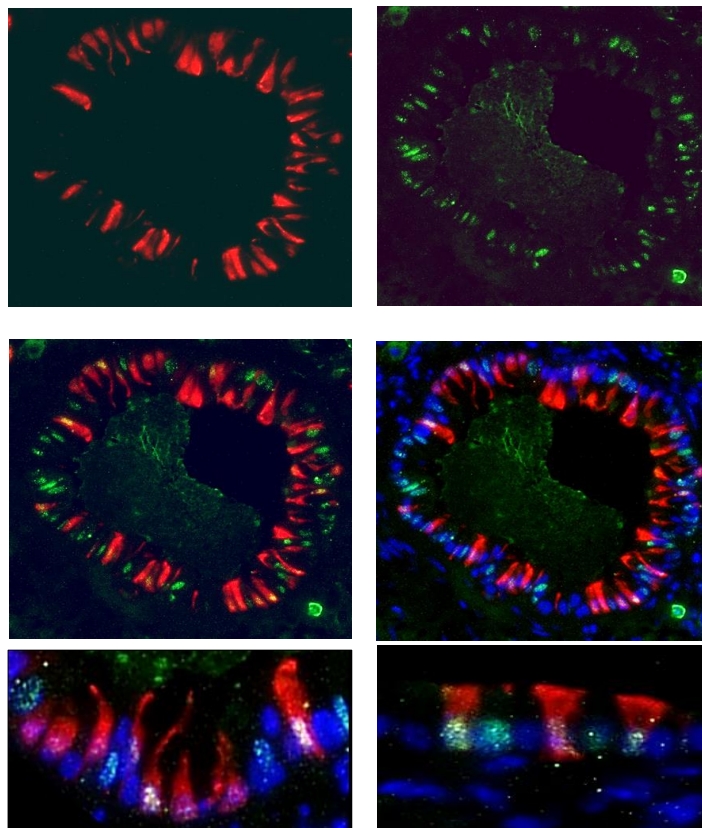
## Nebulization



LUNAR + Luciferase mRNA

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

TdTomato / FoxJ1 / Dapi



Functional Nebulized Delivery of LUNAR + mRNA into Lung Epithelial Cells

# Drug Substance: mRNA Design

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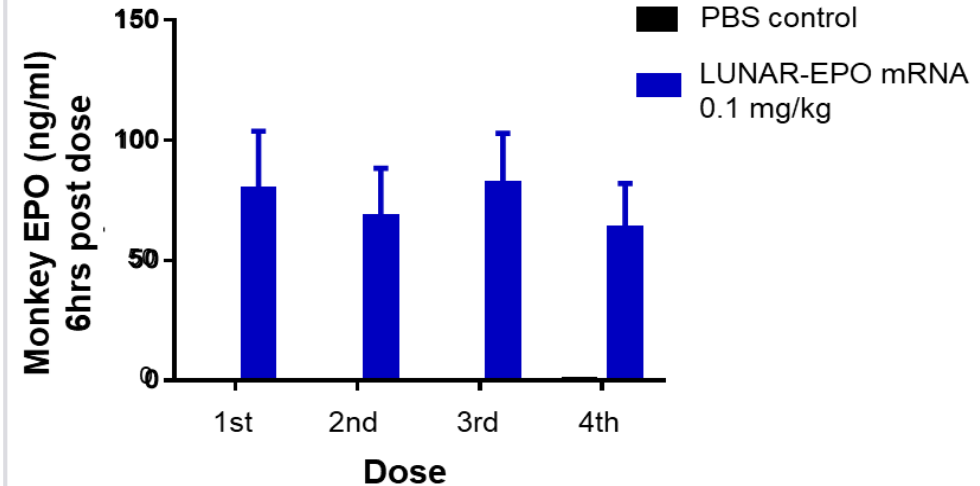
Optimize  
mRNA sequence  
Chemistry  
Process



Improve  
Protein Expression  
Duration  
Functional Activity



## Weekly Dosing in Non-Human Primates

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

# Arcturus mRNA Manufacturing



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RNA MEDICINES



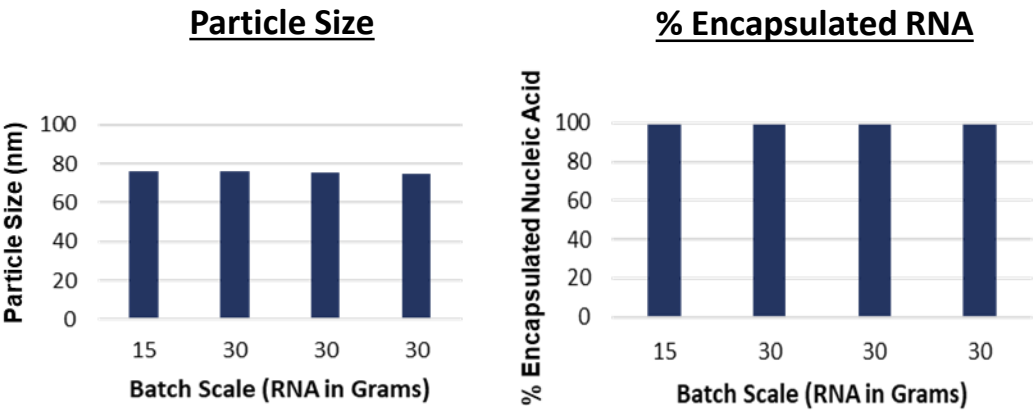
Features	Benefits
Optimized IVT Method	Reduced Cost; Higher Purity
Improved Capping Reaction	Reduced Cost of Goods
Proprietary Purification Process	Higher Purity in a Shorter Time
Efficient	Entire Process Less Than One Week
Scalable to > 1Kg	Access Large Patient Populations
Adaptable	Can Utilize a Variety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

**Arcturus' Internal mRNA Production: Up to 30 g in Less Than One Week**

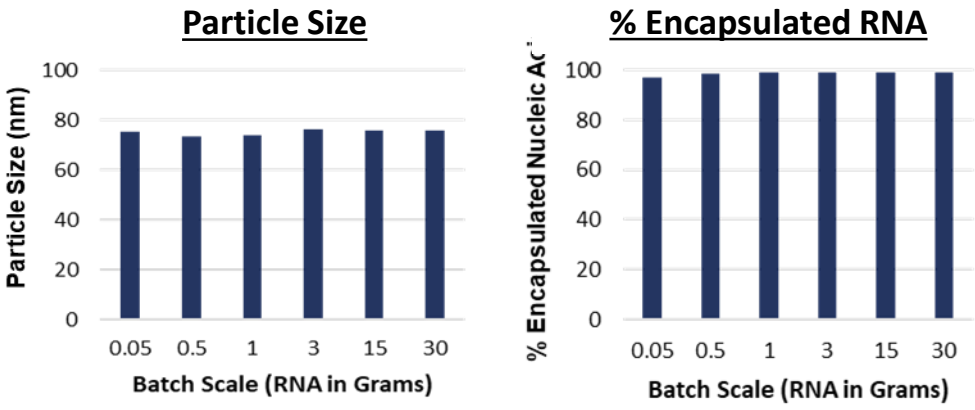
# Drug Product: LUNAR<sup>®</sup> Formulation & Production



## LUNAR<sup>®</sup> Reproducibility



## LUNAR<sup>®</sup> Scalability



- Proprietary, Reproducible & Scalable Drug Product Production Process
- LUNAR-Formulated mRNA Successfully Scaled From Milligram to Multigram Batch Sizes

# Board of Directors



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*Chairman of the Board*



**Founder & Chairman  
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**Karah Parschauer, JD**  
*Director of the Board*



**General Counsel  
of Ultragenyx**



**Dr. Edward W. Holmes**  
*Director of the Board*



**President & CEO  
of Sanford Consortium**



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



**Former CAO  
of Allergan**



**Dr. Magda Marquet**  
*Director of the Board*



**Chairman & Co-Founder  
of Althea**



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



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



**Former Portfolio Manager  
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**Dr. Emil D. Kakkis**  
*Board Advisor*



**President & CEO  
of Ultragenyx**



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# Management Team



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*Founder, President & CEO*



**Dr. Pad Chivukula**  
*Founder, CSO & COO*



**Andrew Sassine, MBA**  
*CFO*



**Kevin Skol, MBA**  
*Sr. VP of Business  
Development & Alliance  
Management*



**Dr. Suezanne Parker**  
*VP of Translational Biology*



