

ARCTURUS THERAPEUTICS

LUNAR[®]: Enabling mRNA Therapeutics and Vaccines

May 20, 2019

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 success for 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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Highlights



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

LUNAR[®] Delivery Platform Validated by Multiple Strategic Partners

Broad and Strong Intellectual Property Portfolio

- 152 Patents & Patent Applications
- LUNAR[®] Delivery Technology
- RNA Drug Substance & Drug Product Process Manufacturing



HQ: **San Diego**; Founded: **2013**; Nasdaq: **ARCT**
Outstanding Shares: **10.8 M**; Employees: **~80**;

Promising Preclinical Safety Data for LUNAR[®] Delivery and mRNA Drug Products

mRNA Medicines & Platform



Arcturus LUNAR® Delivery Platform: Enabling Genetic Medicines



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

Arcturus mRNA Medicines

LUNAR-OTC (ARCT-810) to treat Ornithine Transcarbamylase (OTC) Deficiency






LUNAR-CF to treat Cystic Fibrosis (CF); Funded by the



Arcturus Platform: Enabling Genetic Medicines



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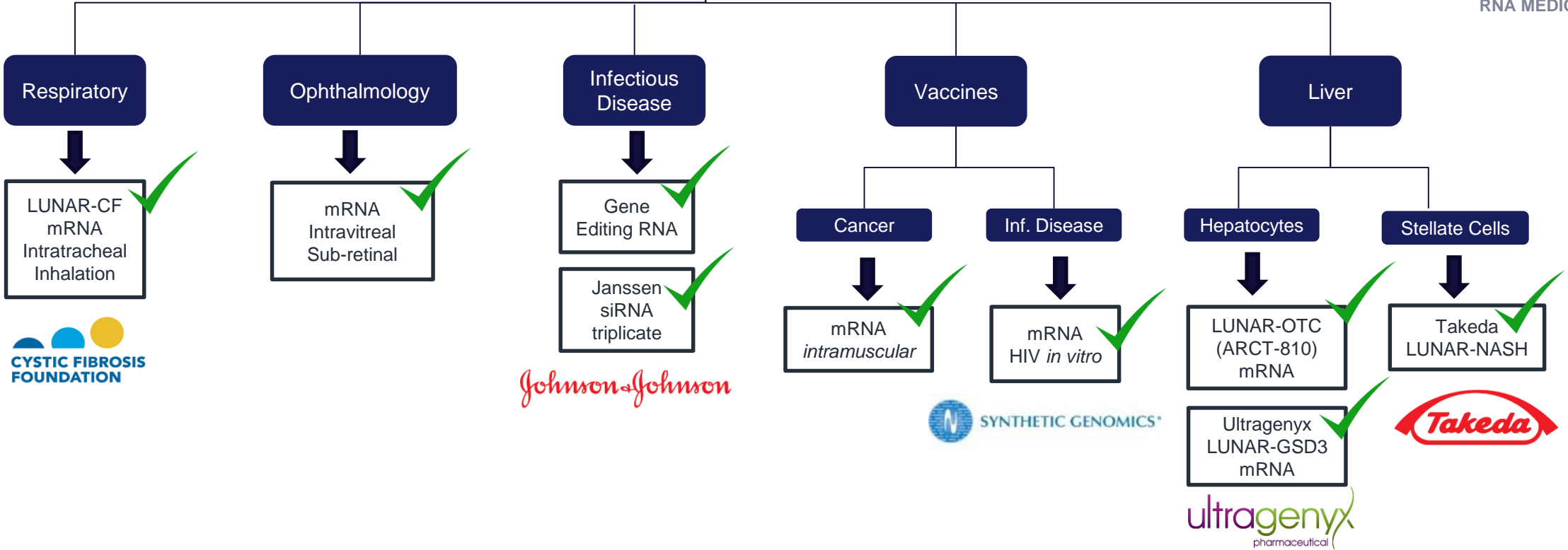
Name	Partner	Year of Initiation	Indication	Arcturus Chemistry	Arcturus Delivery	mRNA Process
LUNAR-HBV		2015	Hepatitis B	RNA	LUNAR® Hepatocytes	ARCT
LUNAR-NASH		2017	NASH	RNA	LUNAR® Stellate Cells	ARCT
LUNAR-GSD3		2016	Glycogen Storage Disease Type III	mRNA	LUNAR® Hepatocytes	ARCT
LUNAR-RARE		2016	Rare Disease	mRNA	LUNAR® Hepatocytes	ARCT
LUNAR-RPL		2017	Vaccines	SGI's Replicon RNA	LUNAR® Intramuscular	SGI

- Greater than \$1 Billion in Potential Milestones & Royalties
- Enabling Different Types of RNA – Messenger RNA, Gene Editing RNA, Replicon RNA
- Multiple Cell Types Targeted



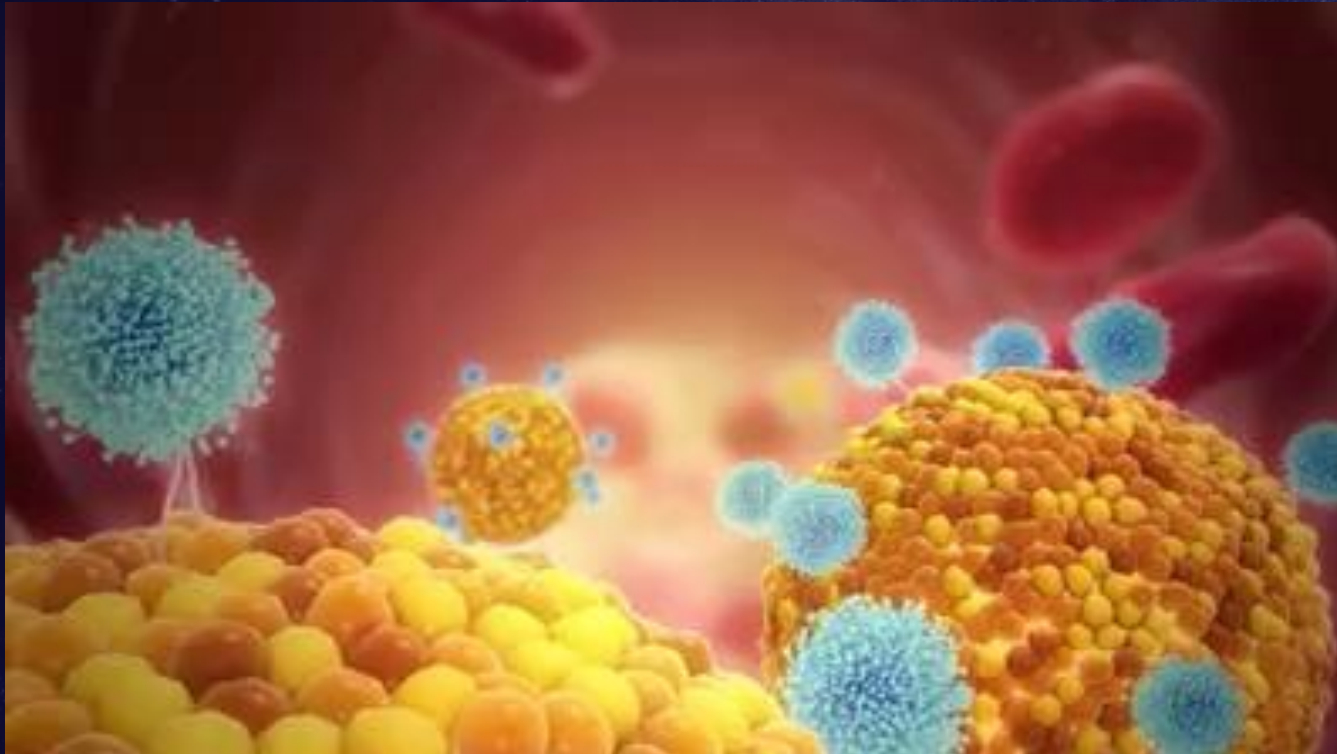
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LUNAR[®] Platform Substantial Preclinical Proof-of-Concept Demonstrated

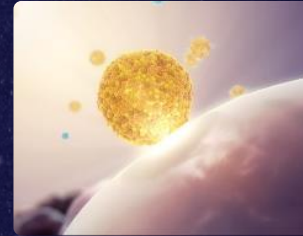


LUNAR[®] Platform Preclinical Proof-of-Concept Demonstrated in Hepatocytes, Liver Stellate Cells, Bronchial Epithelial Cells (Lung), Subretinal / intravitreal (Eye), Infectious Diseases, Cancer Vaccines

LUNAR[®] Mechanism of Delivery



LUNAR Associates
with Cell Membrane



Enters Cell
Via Endocytosis

Lipid Particle in
Endosome



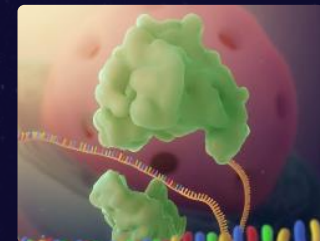
Increased Acidity as
Endosome Ages

pH-Mediated
Disruption



Rapid Biodegradation
of Vehicle

RNA
in Cytosol



RNA Processing
and Translation



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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

Diverse

Exclusive Library of over 150 Proprietary Lipids

Rational Design to Maximize Efficacy and Increase Tolerability

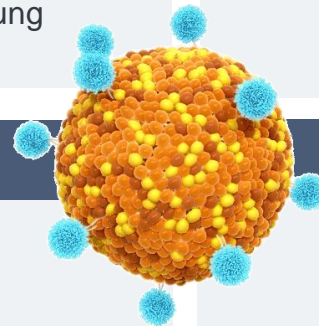
Formulation Compositions Customized for Application and Cell Type of Interest

Biodegradable

No Accumulation of Lipids

Manufacturing Efficiency

Scalable and Reproducible Production Process

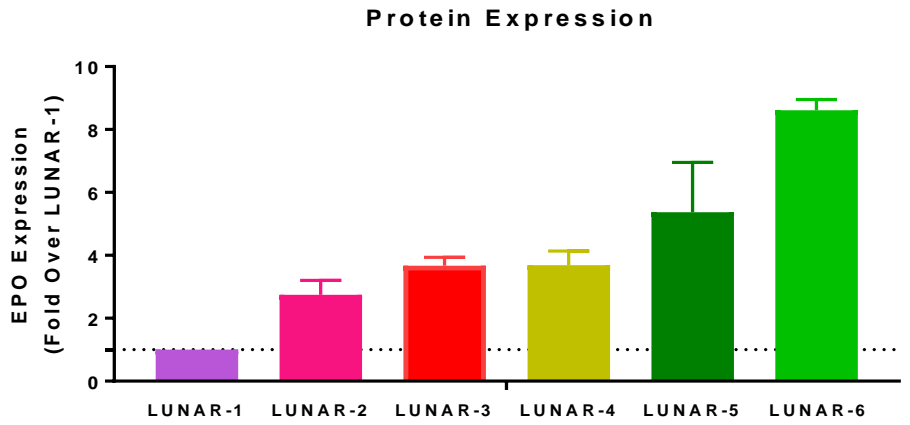
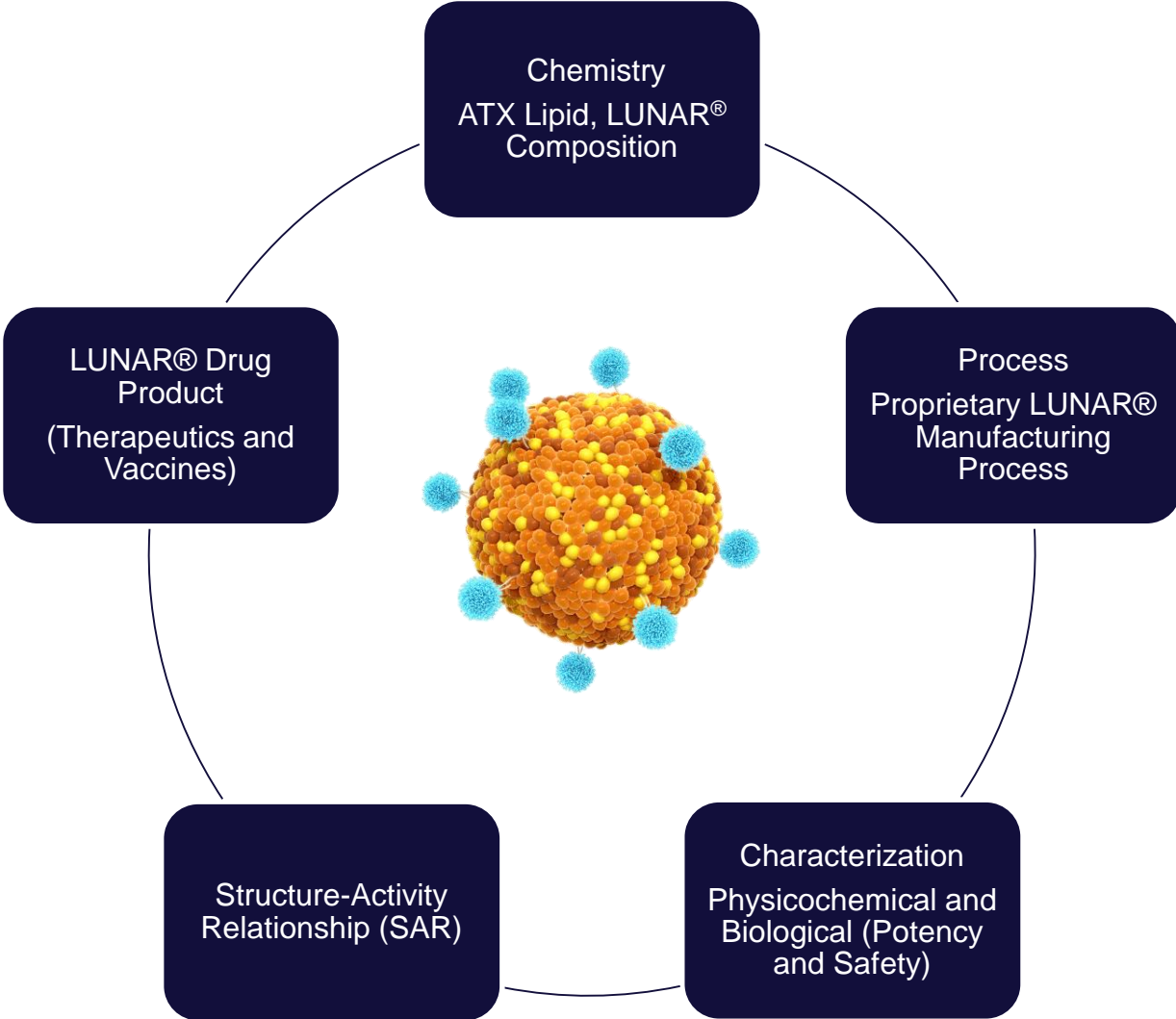


Arcturus LUNAR[®] = Next Generation of RNA Medicines

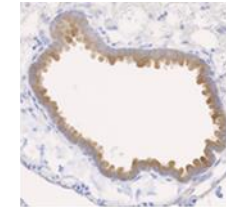
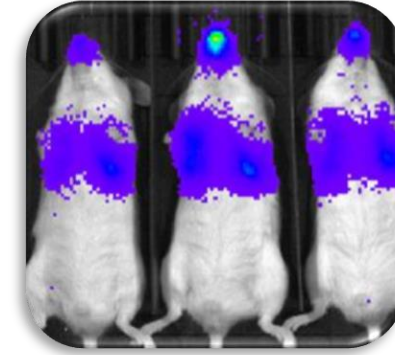
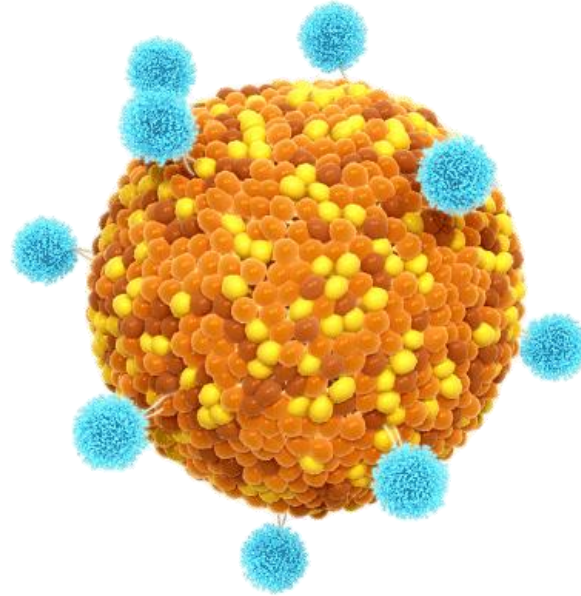
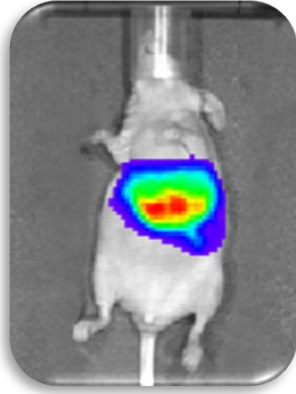
LUNAR® Platform: Rational Design and SAR Drives Next Generation



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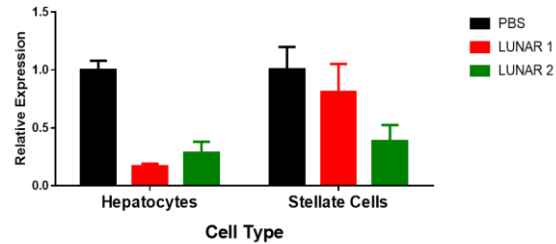


LUNAR[®]: Functional RNA Delivery to Various Cell Types



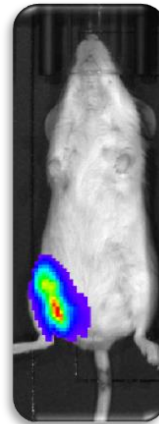
Bronchial Epithelial Cells

Target Knockdown in Liver Cell Types



LUNAR-siRNA

Liver: Hepatocytes, Stellate Cells



Muscle

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

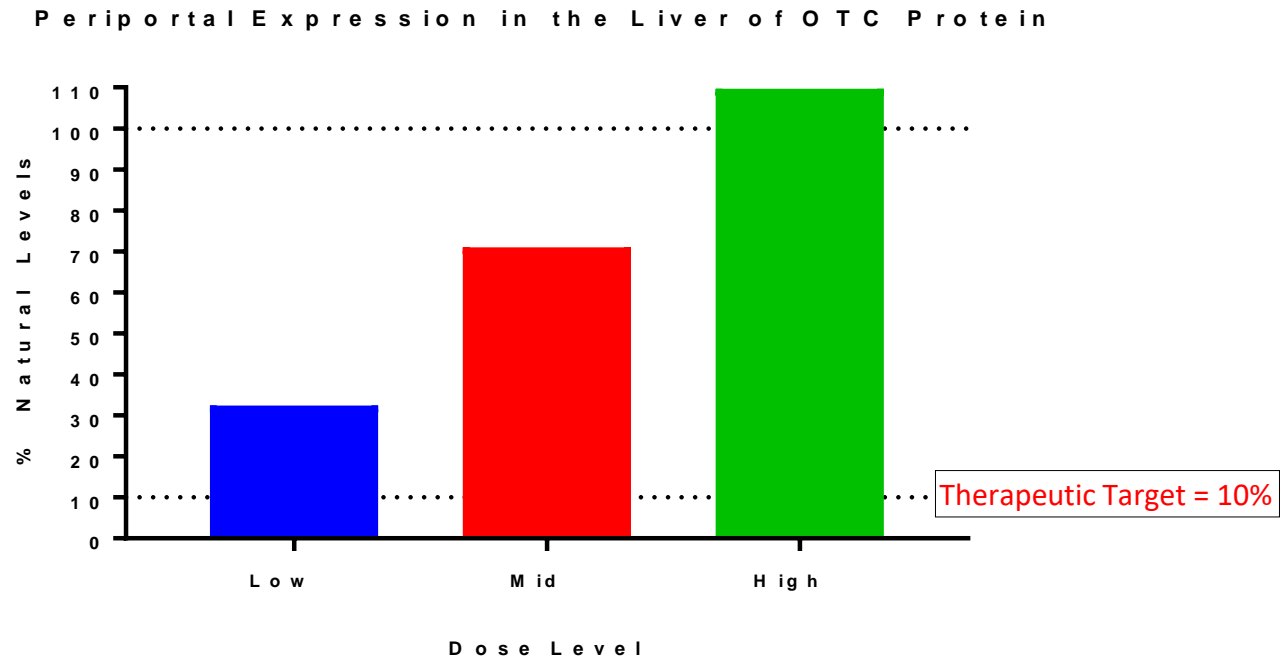
LUNAR-OTC Targets Periportal Hepatocytes



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Exceeds Therapeutic Target of 10% Protein 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



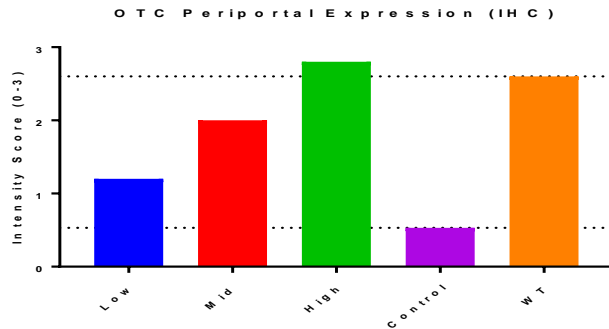
*Li, L. et al. PGC-1 α Promotes Ureagenesis in Mouse Periportal Hepatocytes through SIRT3 and SIRT5 in Response to Glucagon. Scientific Reports. 6:24156 | DOI: 10.1038/srep24156, April 2016

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

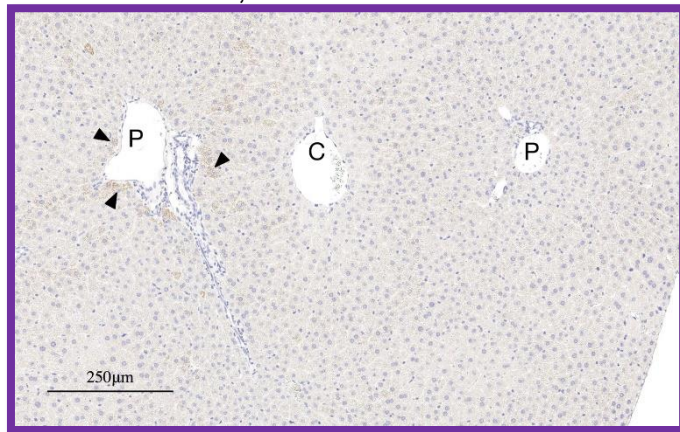
Ornithine Transcarbamylase Expression in OTC spf-ash Mice



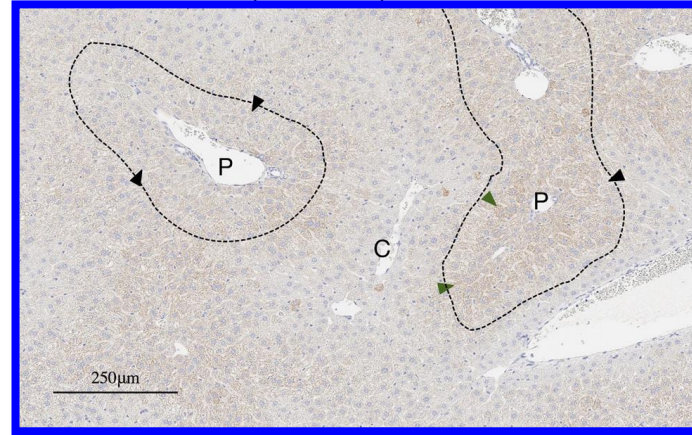
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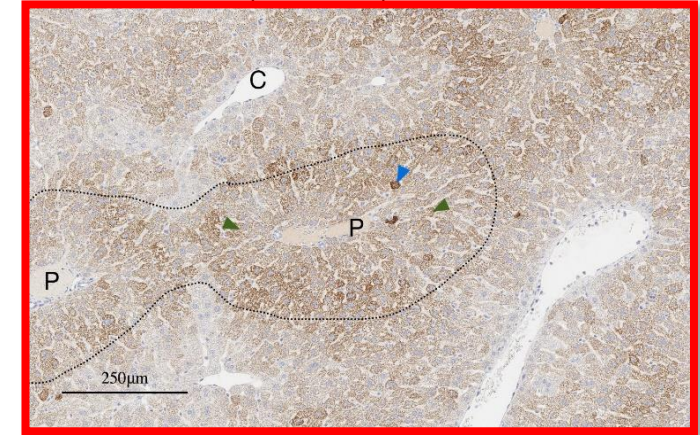
Control, IHC Score = 0.5



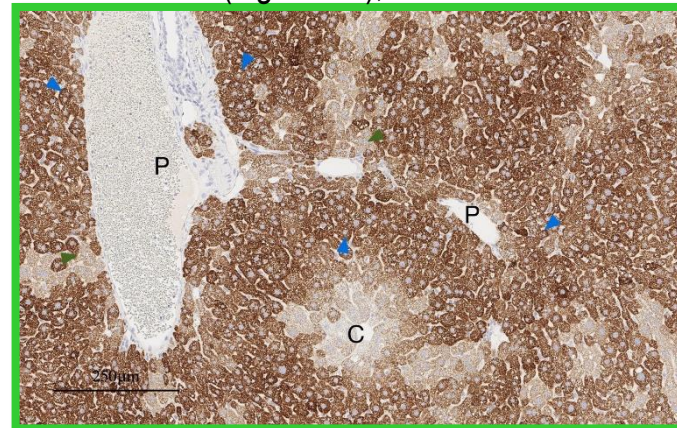
LUNAR-OTC (low dose), IHC Score = 1.2



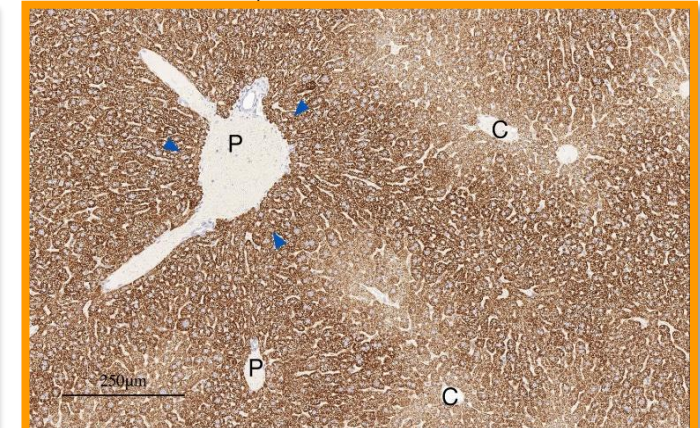
LUNAR-OTC (mid dose), IHC Score = 2.0



LUNAR-OTC (high dose), IHC Score = 2.8



WT, IHC Score = 2.6



METHODS

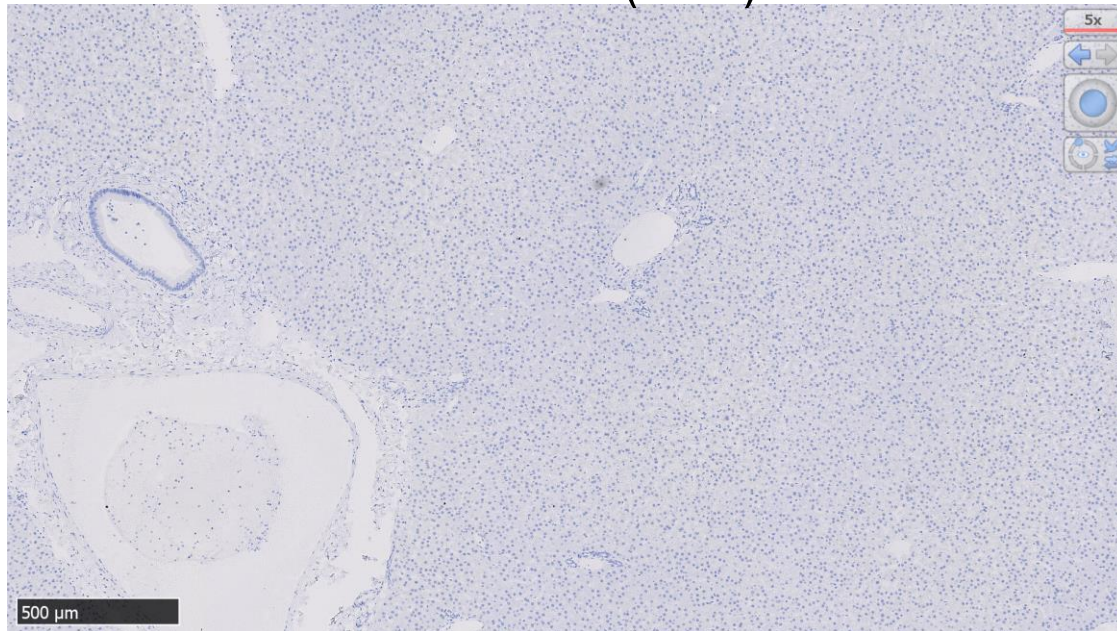
- Slides were evaluated by a board-certified veterinary pathologist using light microscopy.
- OTC immunolabeling in portal hepatocytes was scored 0-3, where 0=immunolabeling absent; 1=weak immunolabeling; 2=moderate immunolabeling; 3=intense immunolabeling.
- An intensity score was recorded for fifteen random portal areas (five per tissue piece) per sample and averaged to obtain a mean immunolabeling score for each animal.

A mixture of weak (black arrowheads), moderate (green arrowheads) and intense OTC immunolabeling (blue arrowheads) is visible surrounding portal tracts (P; immunolabeling score 2). Immunolabeling of hepatocytes surrounding central veins (C) is weak to absent.

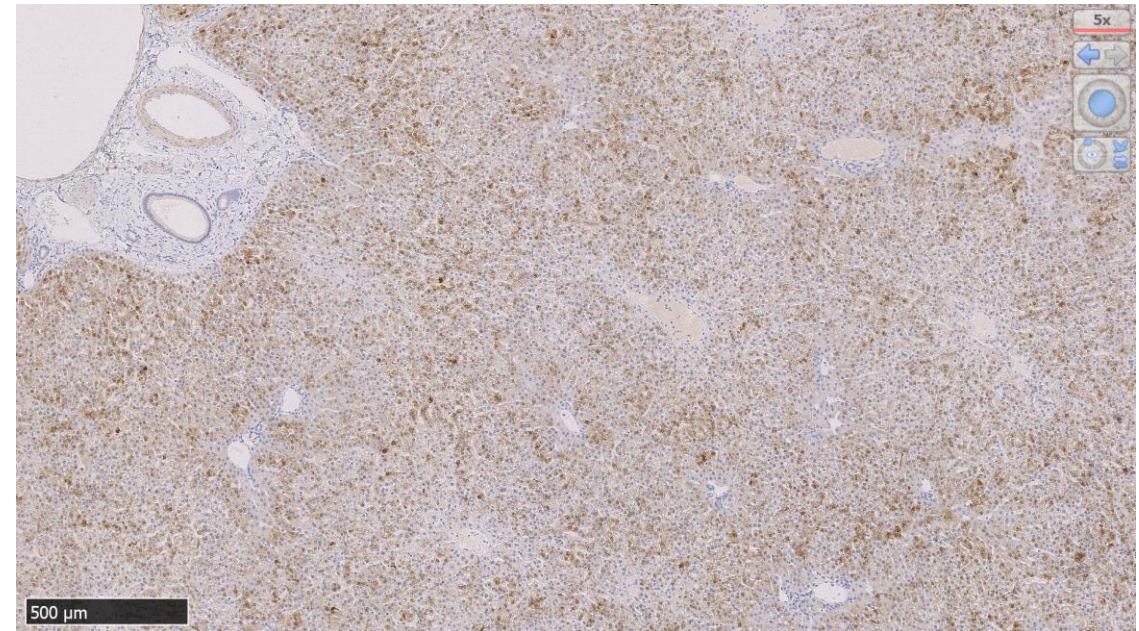
LUNAR-OTC treatment increases OTC expression in periportal hepatocytes, main site of ureagenesis
(ammonia detoxification)

LUNAR[®] Delivery of mRNA encoding Intracellular Protein to NHP Liver

Control (PBS)



LUNAR-RFP

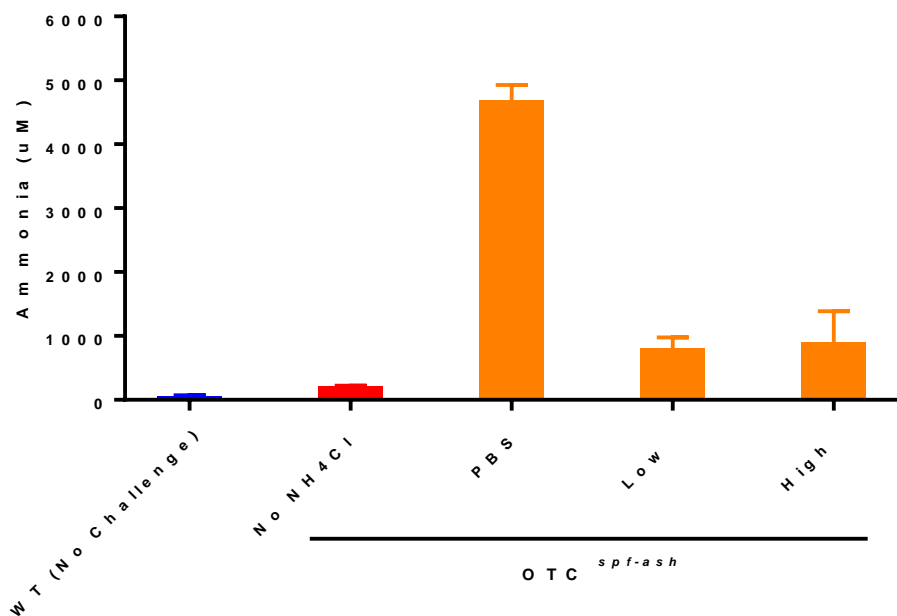


LUNAR Demonstrates Functional Delivery of mRNA encoding RFP (Red Fluorescent Protein) to NHP Liver

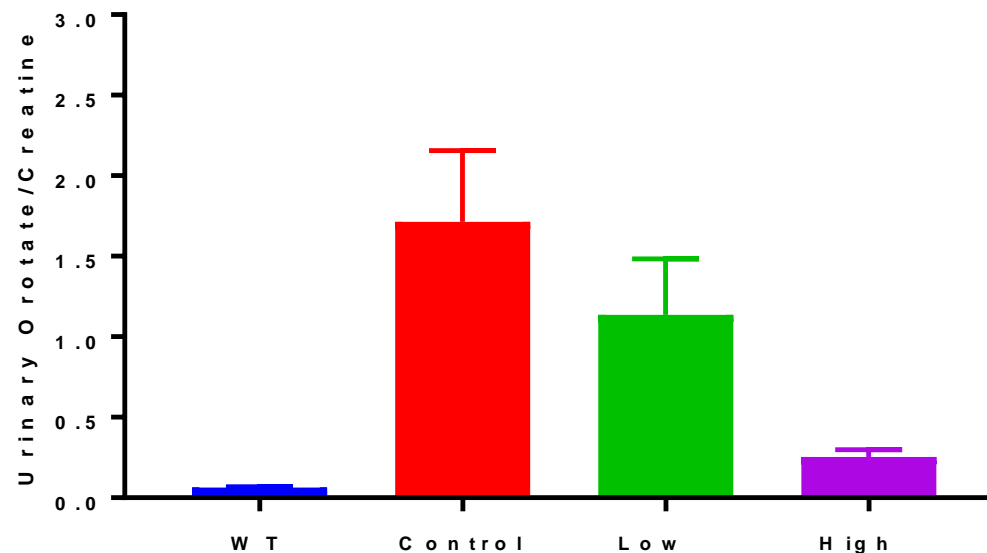


Functional Efficacy: Ammonia Reduction and Urinary Orotate

Ammonium Chloride Challenge in OTC *spf-ash* Mice
Day 7 Post Single-Dose



Urinary Orotate / Creatinine Ratio
Day 14 Post Single-Dose

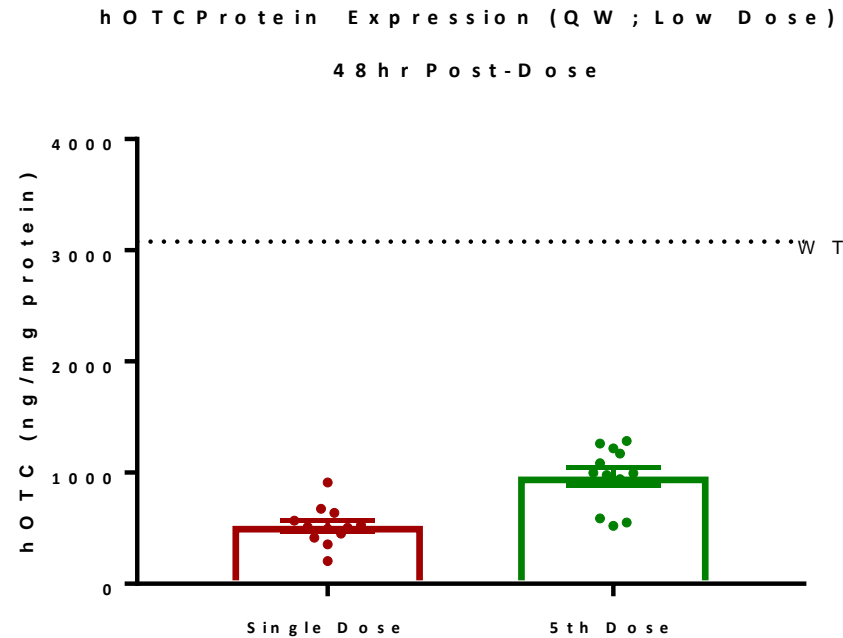


80% NH₄ Reduction and Restoration of Ureagenesis a Single Dose of LUNAR-OTC in OTC *spf-ash* Model

LUNAR-OTC Protein Expression & Accumulation in Mice

LUNAR-OTC Dosed Weekly X5

Livers processed for hOTC 48 hours post 1st and 5th dose

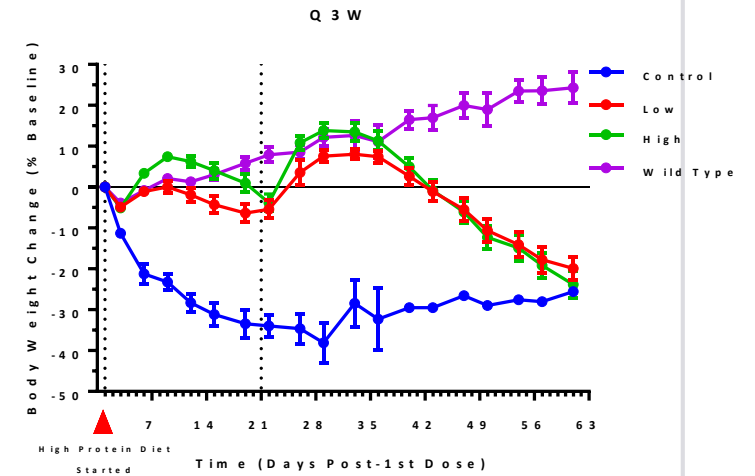
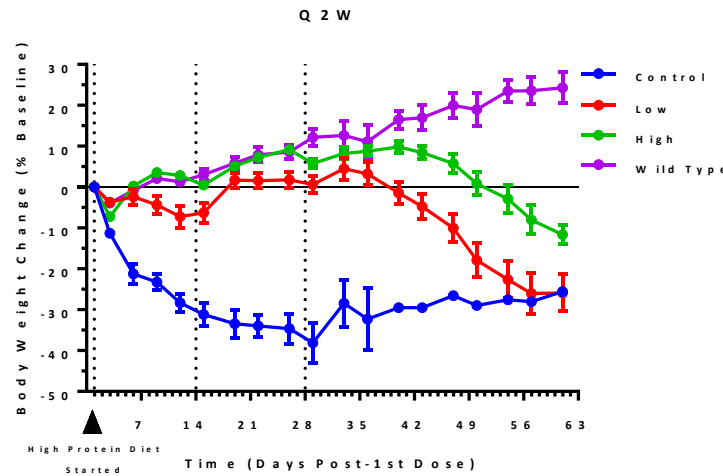
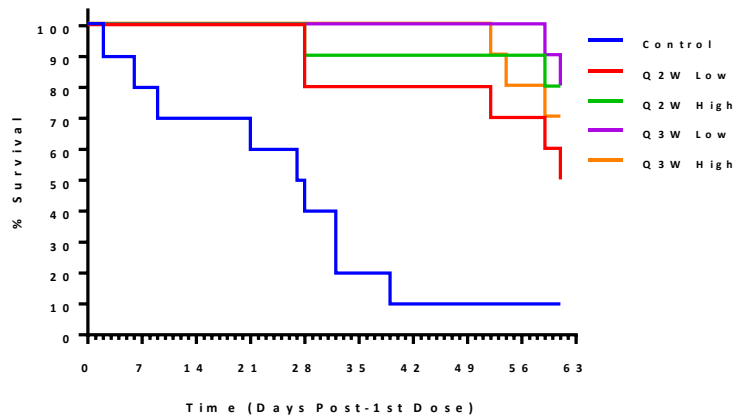


hOTC Accumulates with Weekly Dosing Indicating a Dosing Frequency of > 1 week

Q2W & Q3W Dosing Efficacy in a High Protein Diet Induced Hyperammonemia Model in OTC^{spf-ash} Mice

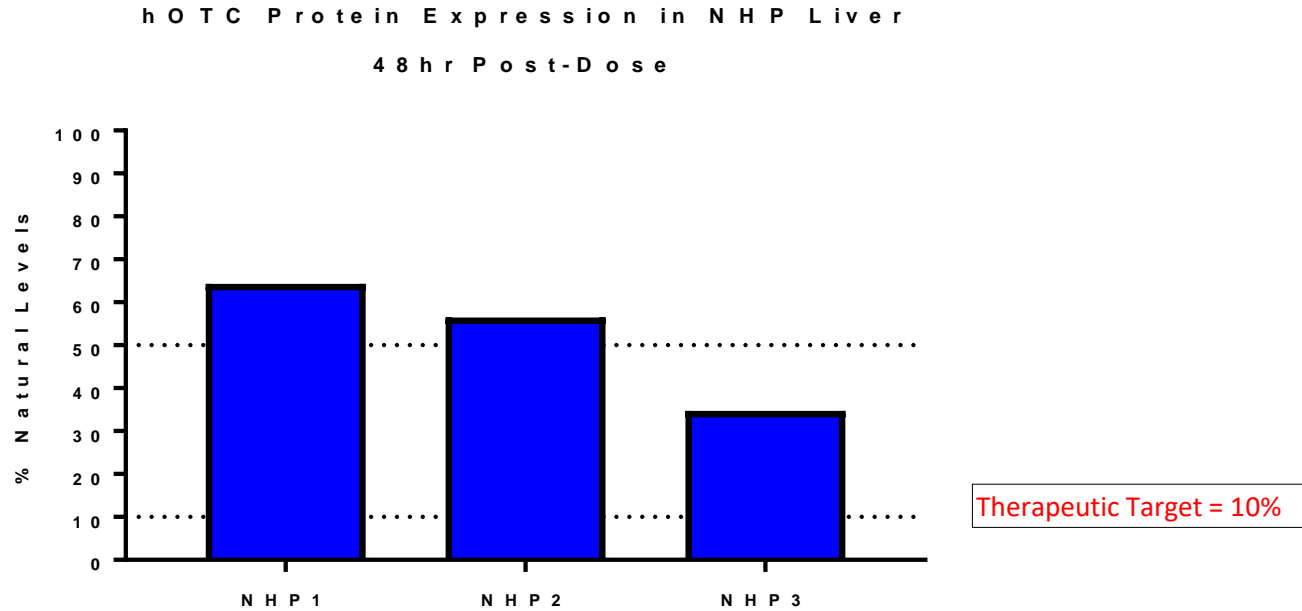


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Q3W Dosing Provides Prolonged Efficacy in High Protein Diet Induced Hyperammonemia in OTC^{spf/ash} Mice

hOTC Protein Expression in Non-Human Primates



Single Dose of LUNAR-OTC Provides up to 50% of WT 48 hours Post Dose

mRNA structure and optimization



- Nucleotide Optimization
 - Nucleotide chemical optimization is gene dependent
- 5' UTR Optimization 3' UTR Optimization
 - Arcturus has proprietary UTR library used to optimize protein expression and mRNA stability
- 5' CAP structure
 - Arcturus has optimized capping scheme
- Poly-A structure
 - Arcturus has identified optimal poly A tail length
- Codon Optimization
 - Arcturus has proprietary codon optimization algorithms for the open reading frame (ORF)



Arcturus mRNA Manufacturing



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

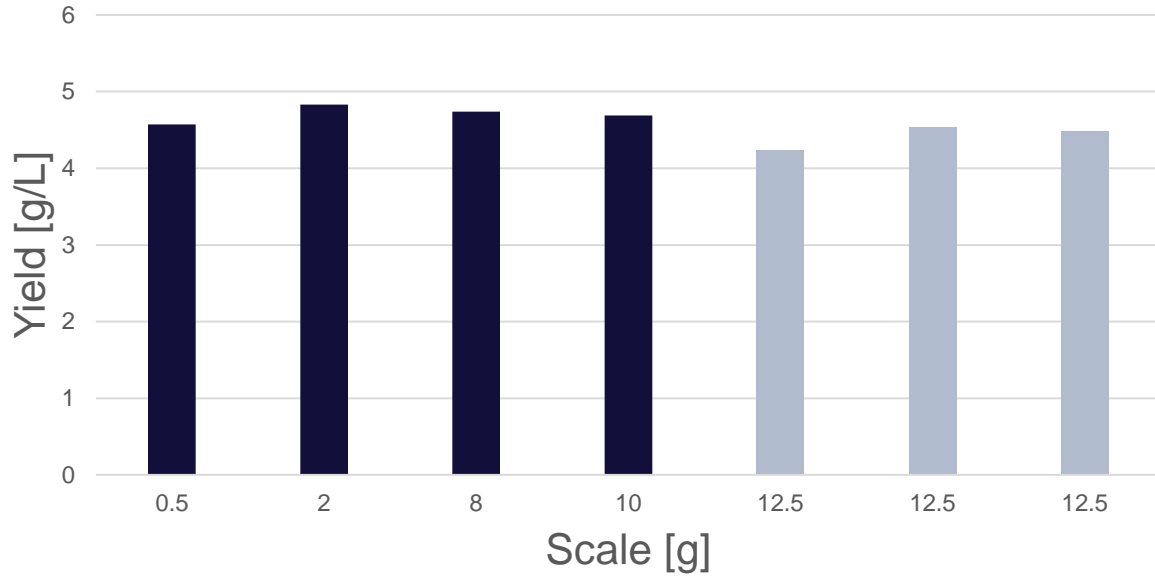
Arcturus' Internal mRNA Production: Up to 30 g in Less Than One Week

Key manufacturing advantages

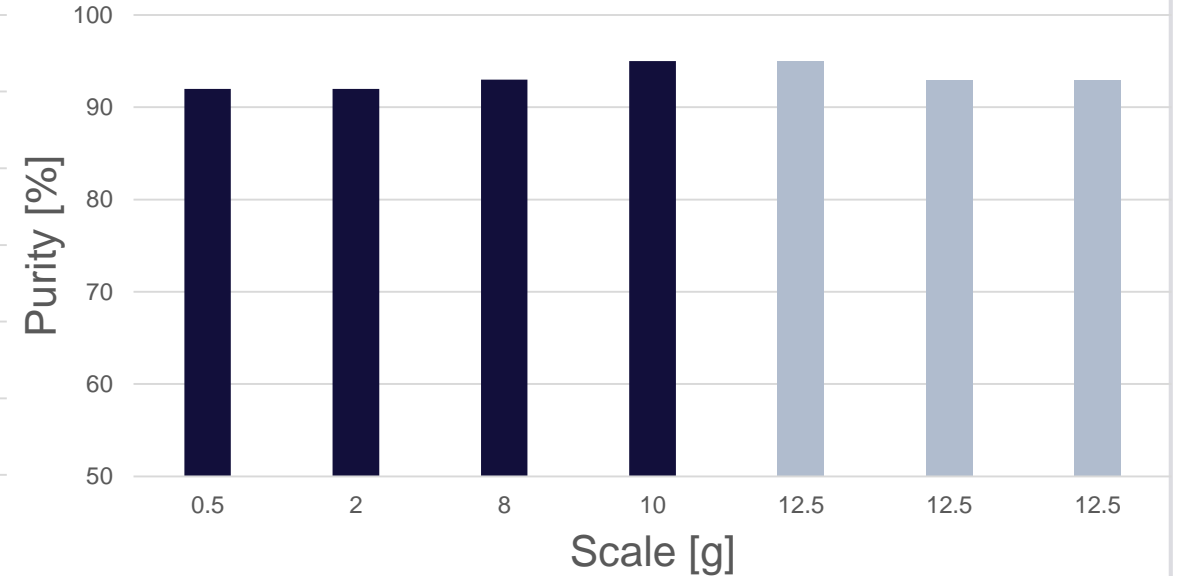
- High mRNA purity
 - Minimal “Shortmers” (abortive and degradation products) – greater than 90% purity
 - Low dsRNA, an immunogenic impurity
 - High capping efficacy – greater than 95% cap 1 mRNA
 - Low residual DNA – less than 100 ppb
 - Low residual protein – non detected
- Process efficiency
 - Low cost of goods – 70% recovery over the purification process
 - Short plant time – 3-5 days in plant
 - Process robustness – low batch to batch variability
 - Scalable and flexible process
 - Scalable to greater than 1 kg
 - Process adaptable to multiple chemistries

Process Scalability & Reproducibility

RNA Yield



RNA Purity



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

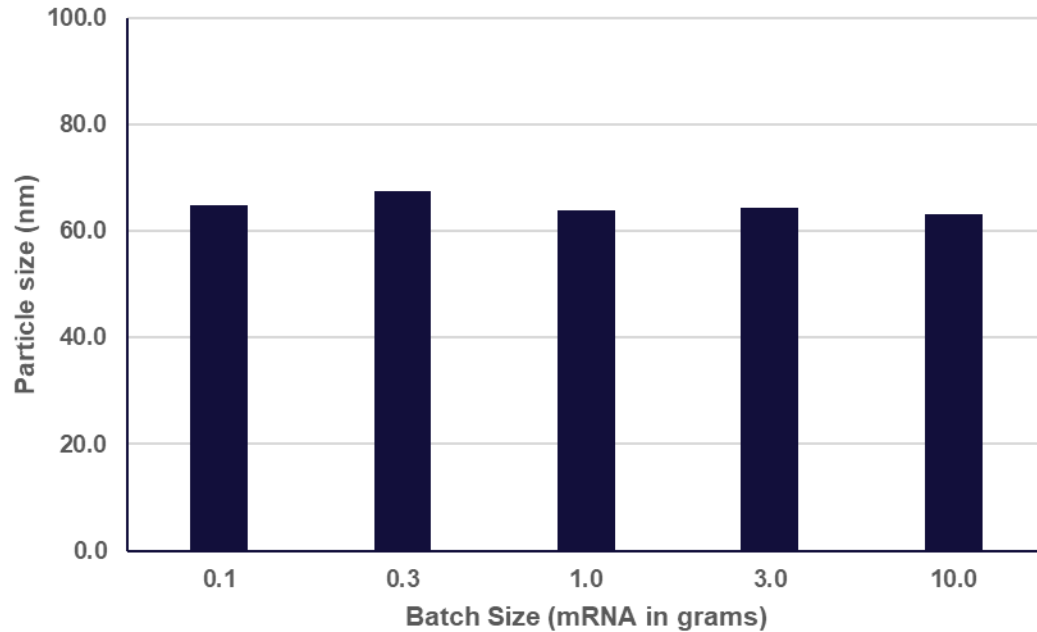
Three 12.5 g lots produced in recent campaign are of equivalent quality and yield

LUNAR[®]-mRNA Drug Product Process Scalability

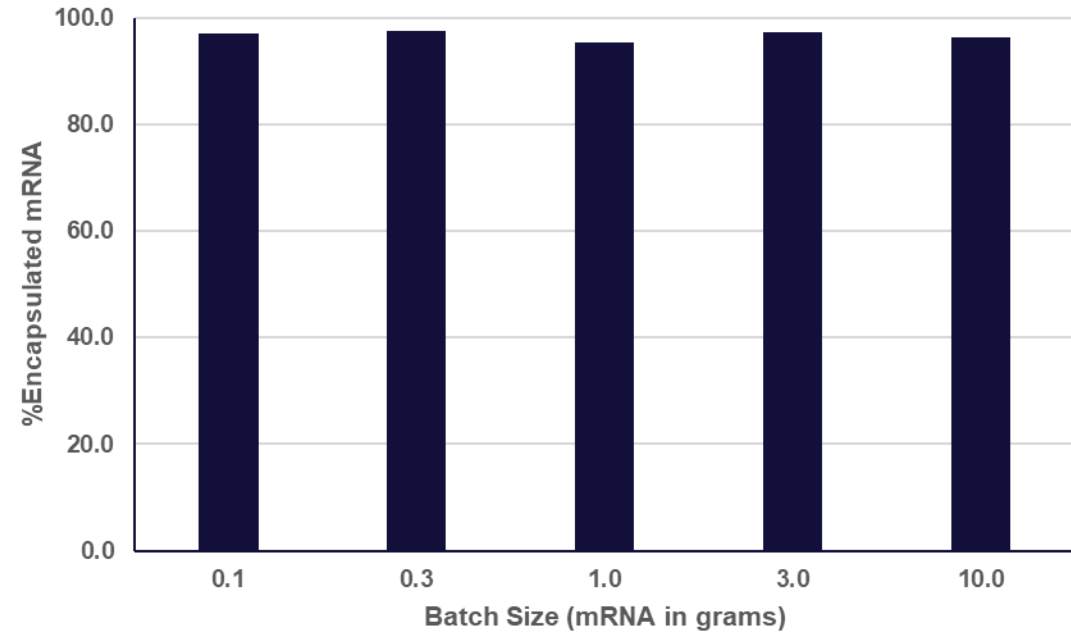


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Particle Size



%Encapsulated mRNA



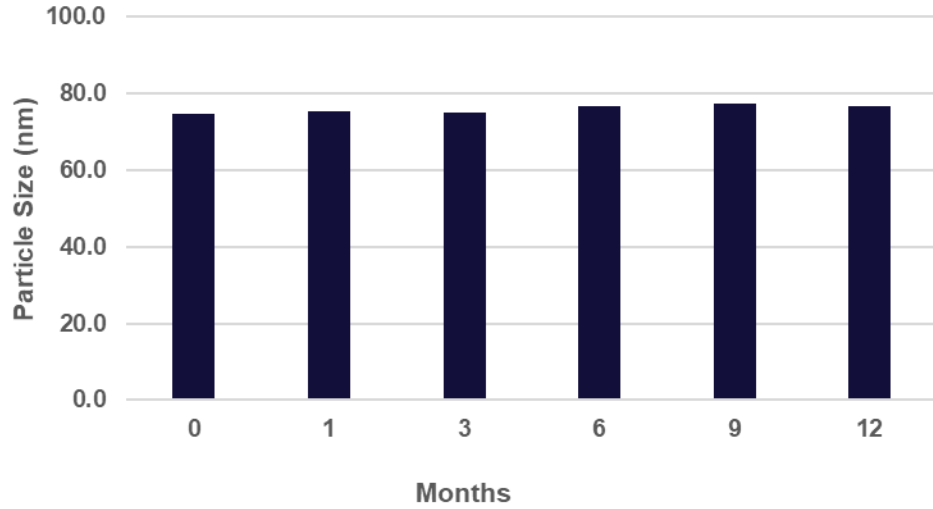
- Scalability of Drug Product demonstrated from milligram to multigram scale with yields $\geq 85\%$
- Multiple batches (10g) of LUNAR[®]-OTC mRNA manufactured
- Current inventory is sufficient to support IND-enabling studies and early clinical development

LUNAR[®] Demonstrates Robust Frozen Stability

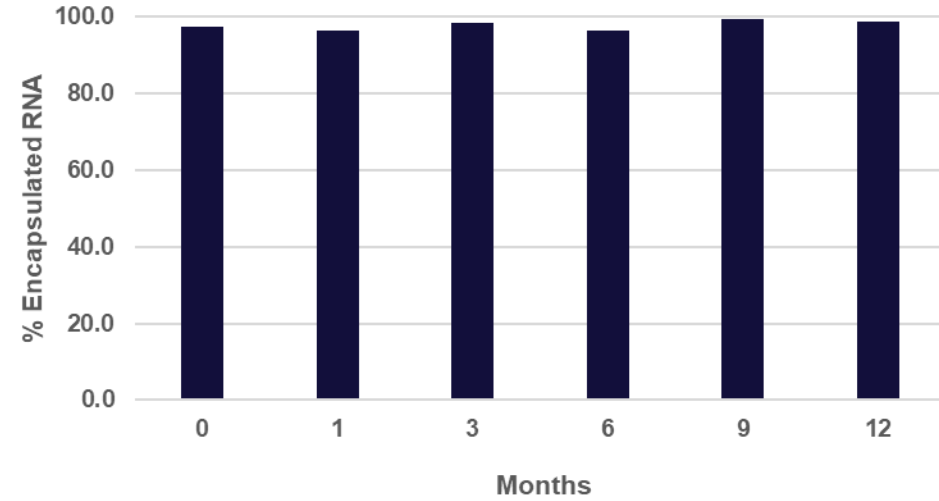


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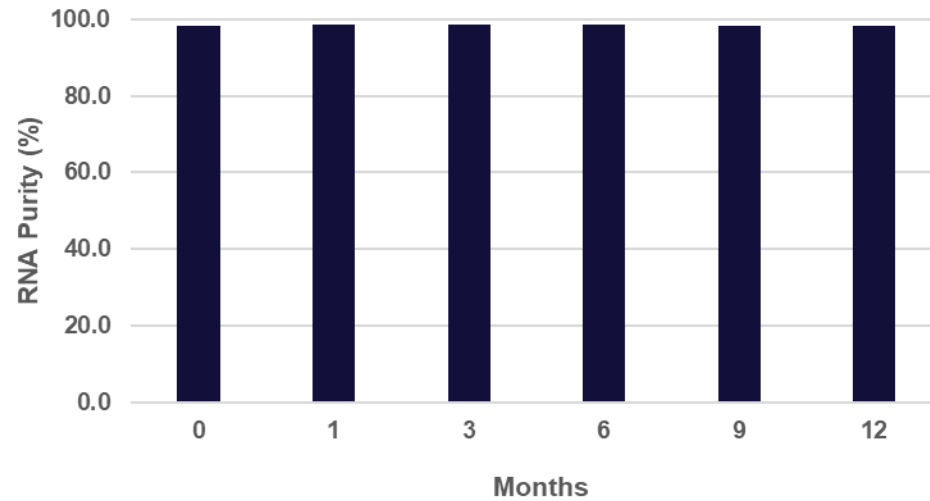
Particle Size



% Encapsulated RNA



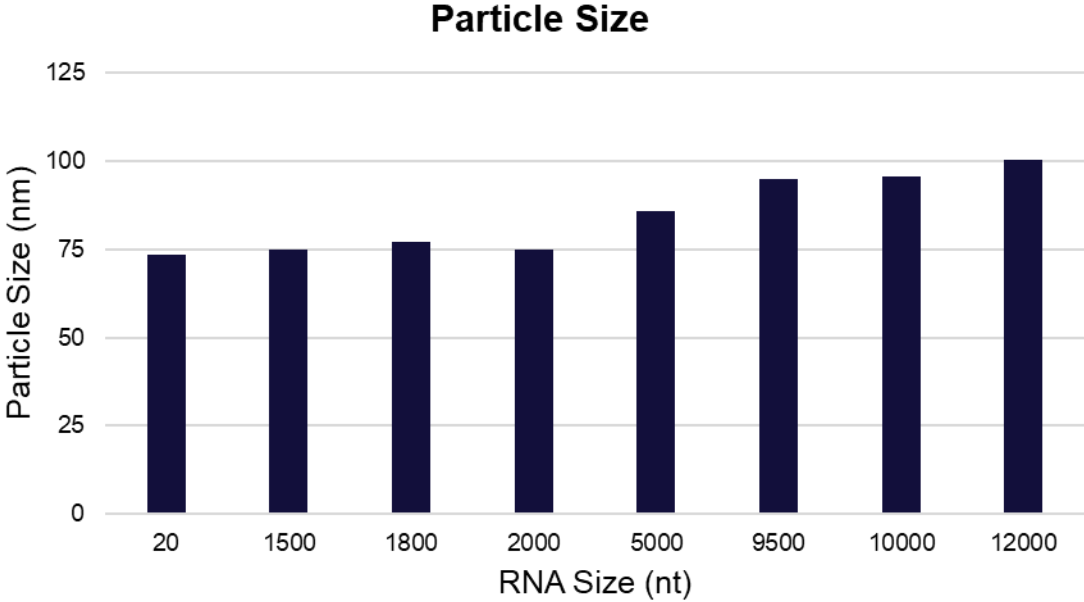
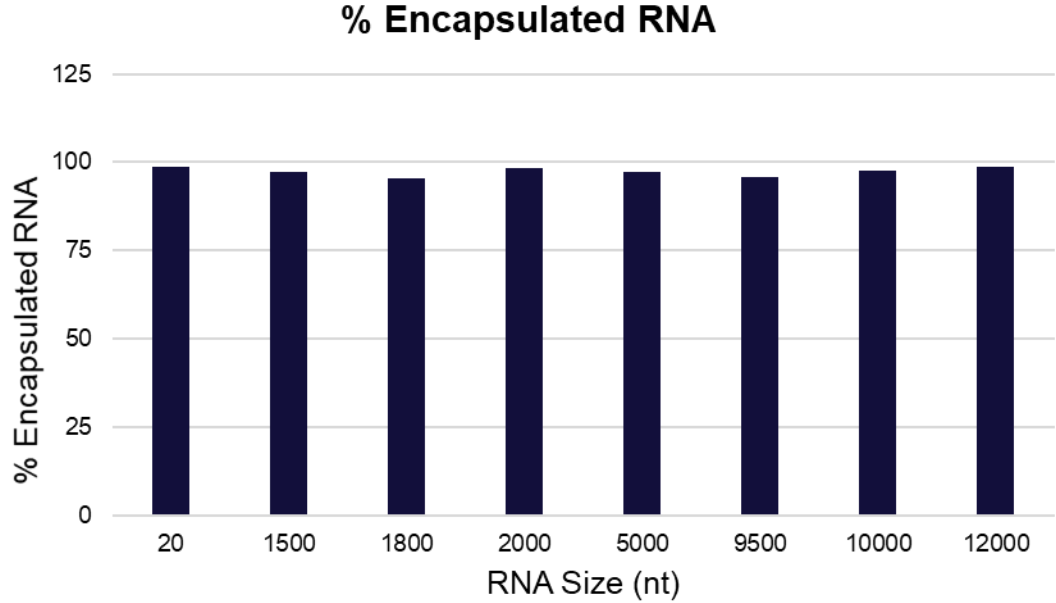
RNA Purity



LUNAR[®]: Compatible Across RNA Platforms



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LUNAR Nanoparticles are designed to effectively encapsulate and deliver small to large RNAs



LUNAR AND mRNA PLATFORMS ARE DRIVING DEVELOPMENT PIPELINE

Cystic Fibrosis



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

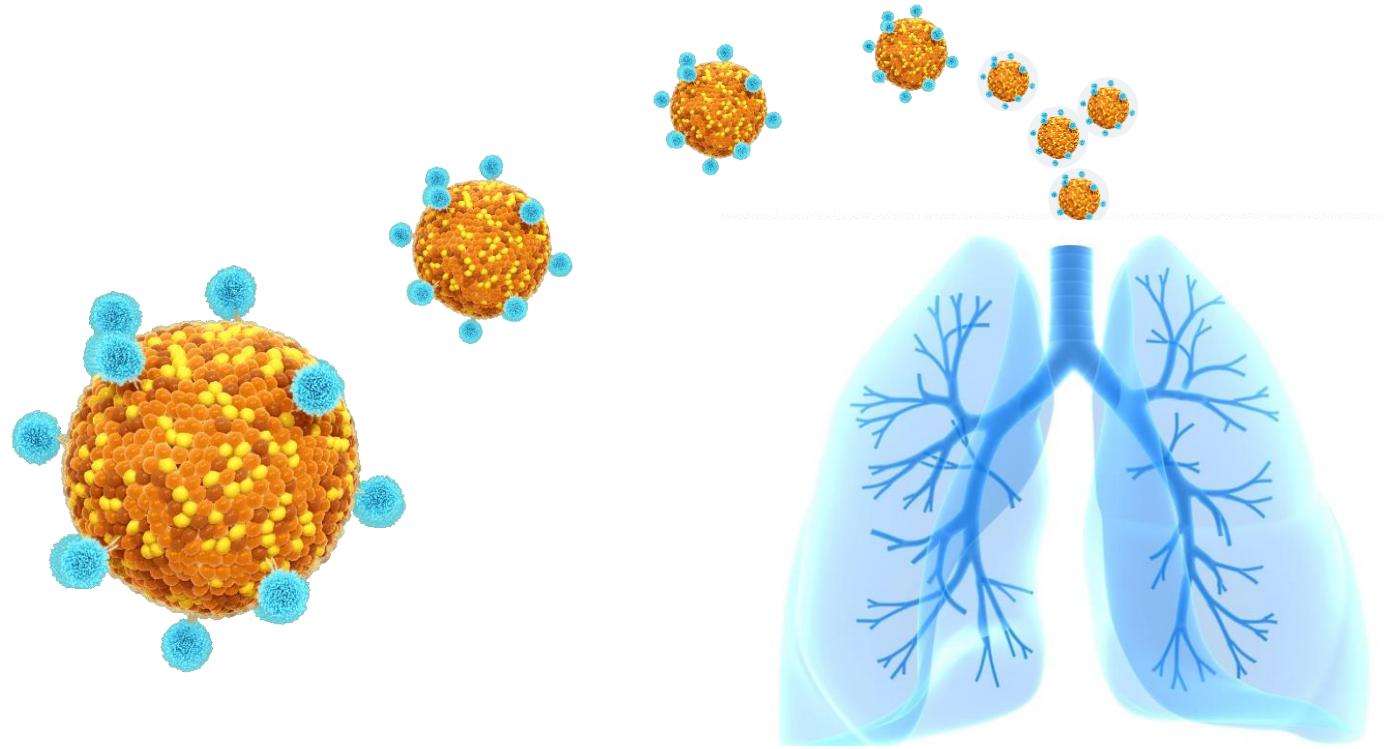
- An mRNA replacement therapy has the potential to deliver a new copy of CFTR into the lungs of CF-patients, independent of any genotype
- A functional CFTR protein can restore chloride channel efflux in the airways, reducing mucus accumulation, tissue scarring and minimizing the progressive respiratory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

mRNA Replacement Therapy

LUNAR[®]-CF Drug



Cargo: mRNA



Delivery vehicle: LUNAR[®]

Delivery format: Aerosol

Targeted Patient Population

Class I patients with Cystic Fibrosis (potential to expand to all classes)

LUNAR[®]-CF

Arcturus' proprietary mRNA optimization platform

Optimized conditions

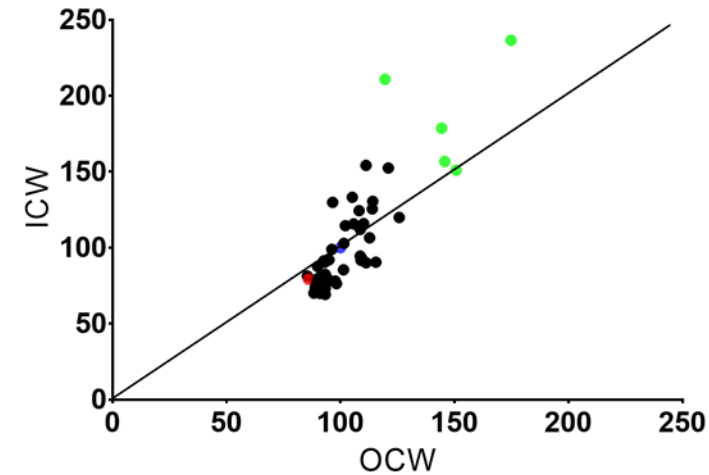
- mRNA sequence
- Chemistry
- Process optimization



- Improved protein expression and duration
- Improved functional activity



CFTR (native) expression

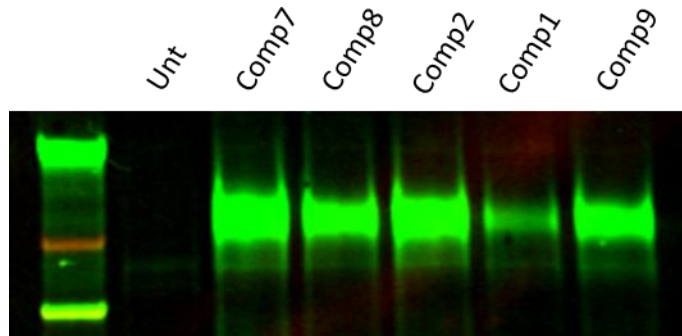


- Codon optimized sequences were generated and screened in CFBE cells in vitro
- Expression levels are several folds higher than the natural sequence (blue dot)

Protein expression is improved with codon optimized leads

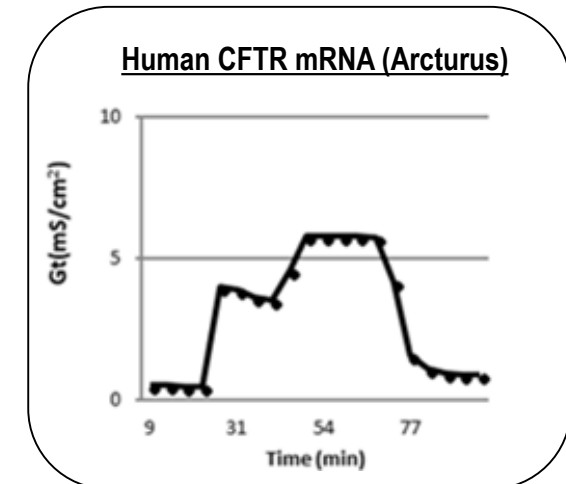
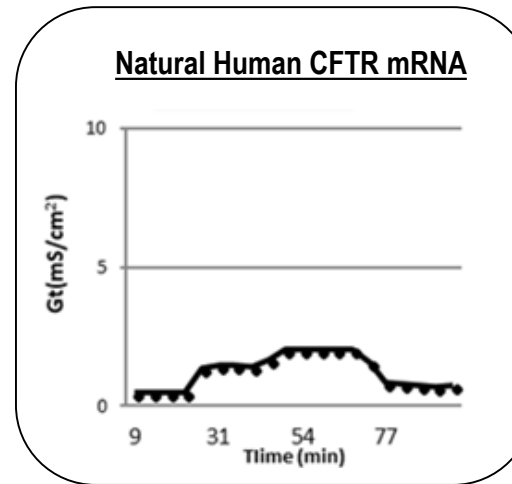
LUNAR[®]-CF

CFTR (denature) expression



- CFTR optimized-mRNAs transfected in CFBE cells
- Arcturus' codon optimized mRNAs (Comps 2, 7, 8, 9) express higher levels of mature protein (C-band) than the natural sequence (Comp1)

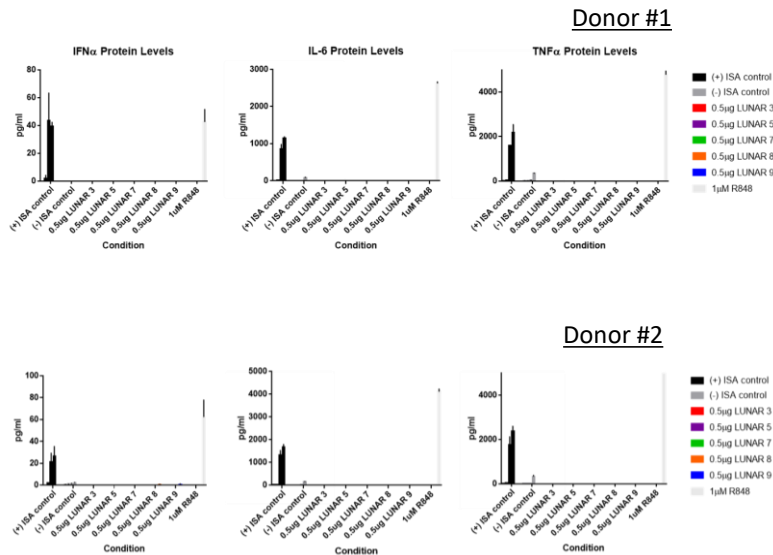
Functional Assay: Transepithelial Conductance in an epithelial cell model (FRT)



- Arcturus' codon optimized mRNAs are several fold more active than the natural sequence

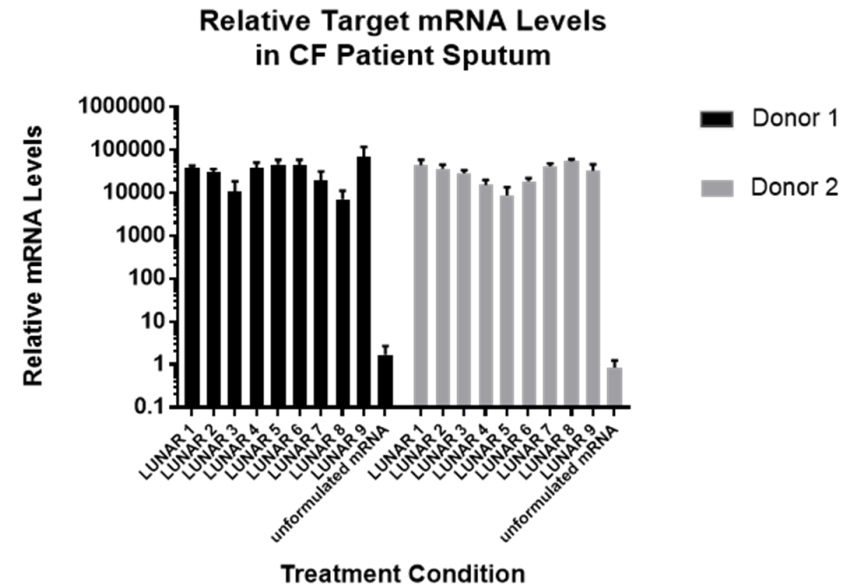
Lead CFTR mRNAs are higher expressers and more functionally active than natural sequence

Immunostimulatory Activity In Vivo



- LUNAR[®]-mRNAs show minimal immunostimulatory activity

CF Sputum Stability

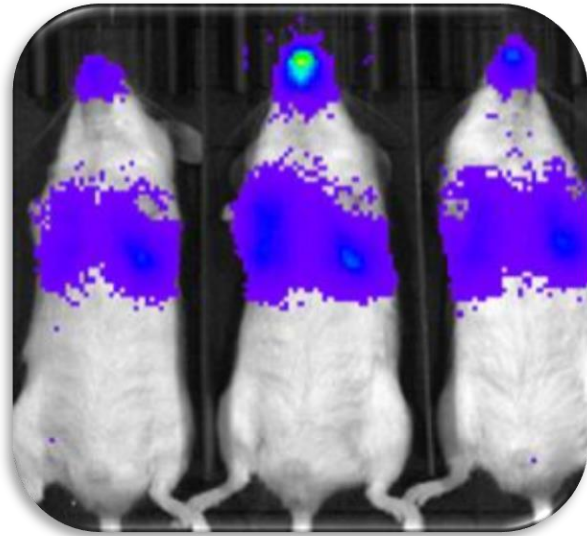


- LUNAR[®] protects the mRNA from degradation in CF patient sputums

LUNAR[®]-mRNA formulations are stable in CF mucus with low immunostimulatory activity

LUNAR[®] Targeting Lung

Nebulization: LUNAR[®]-Luc mRNA

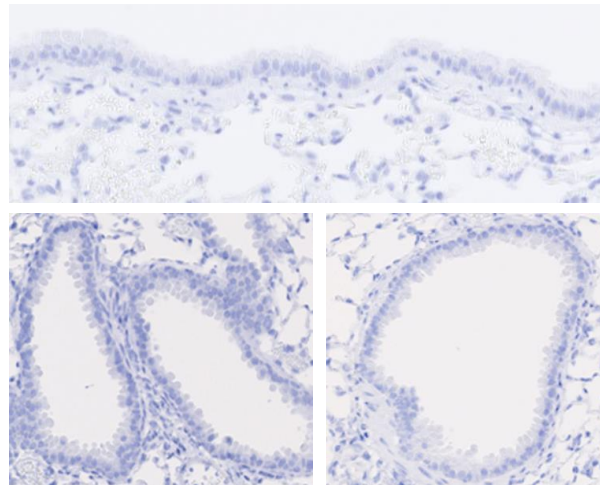


LUNAR-Luc mRNA

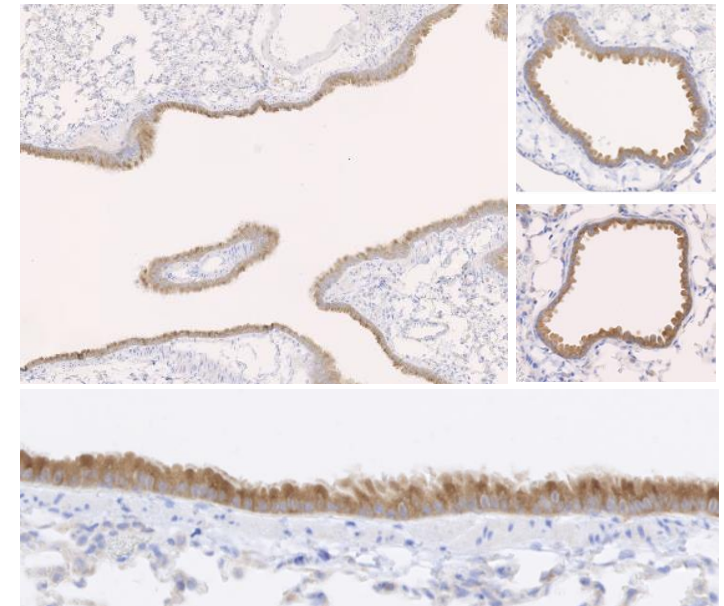
- Aerosolized (nose-only) LUNAR[®]-mRNA targets the upper/lower respiratory tracts

LUNAR[®] delivery (IT) into lung epithelial airways

Control PBS



LUNAR-eGFP mRNA



- Aerosolized (IT) LUNAR[®]-eGFP mRNA is delivered to epithelial airways as observed by the presence of eGFP protein

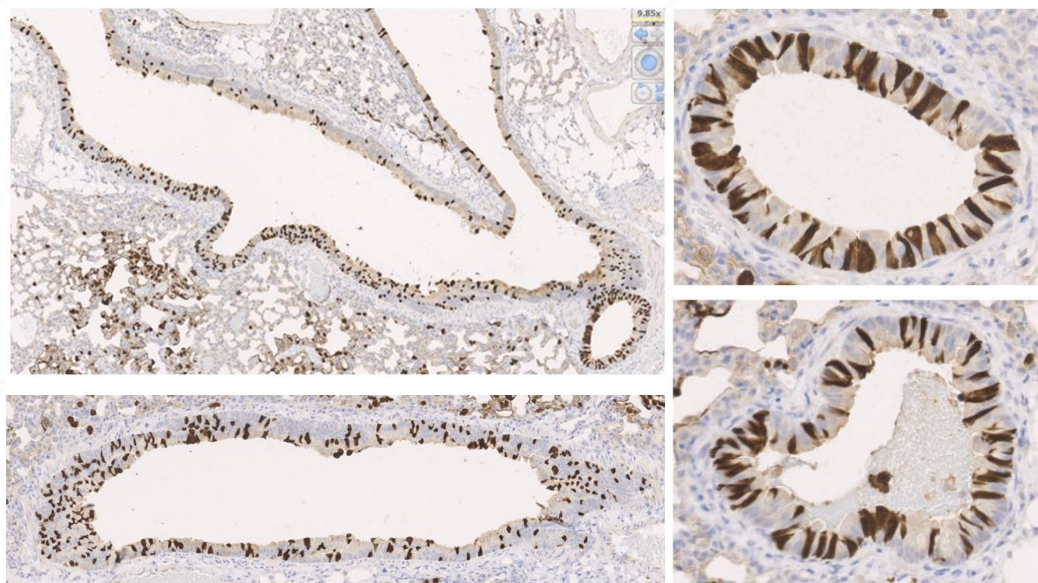
LUNAR[®] is compatible with an aerosolized format and efficiently targets the epithelial airways

LUNAR[®] Targeting Lung



BUILDING INNOVATIVE
RNA MEDICINES

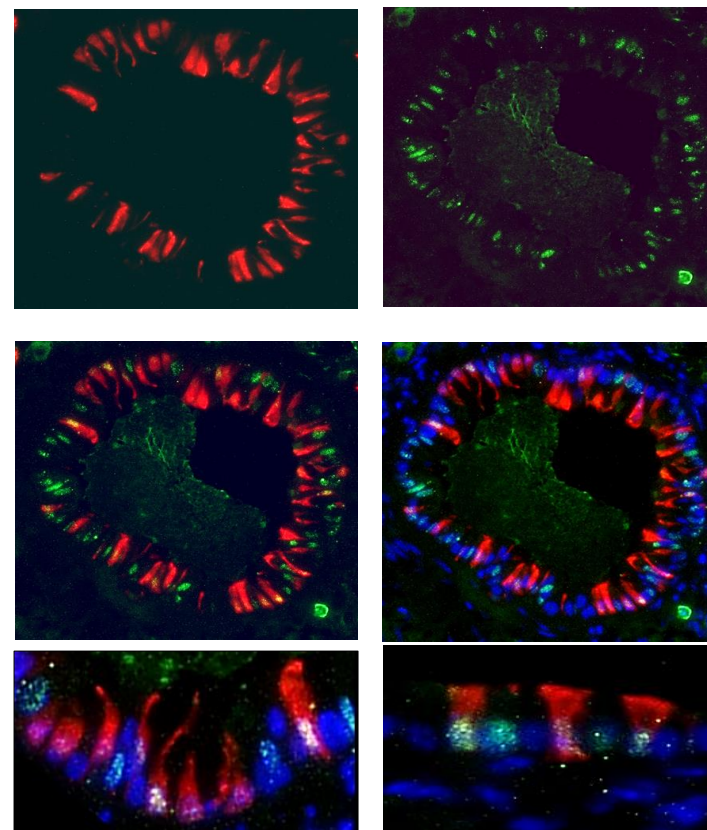
LUNAR[®] Delivery (IT) in Epithelial Airways



- LUNAR[®]-Cre mRNA is delivered (IT) into epithelial airways in the Floxed-TdTomato transgenic mice
- TdTomato protein is detected in the airways

LUNAR[®] targets lung ciliated epithelial cells (FoxJ1)

TdTomato/FoxJ1/Dapi

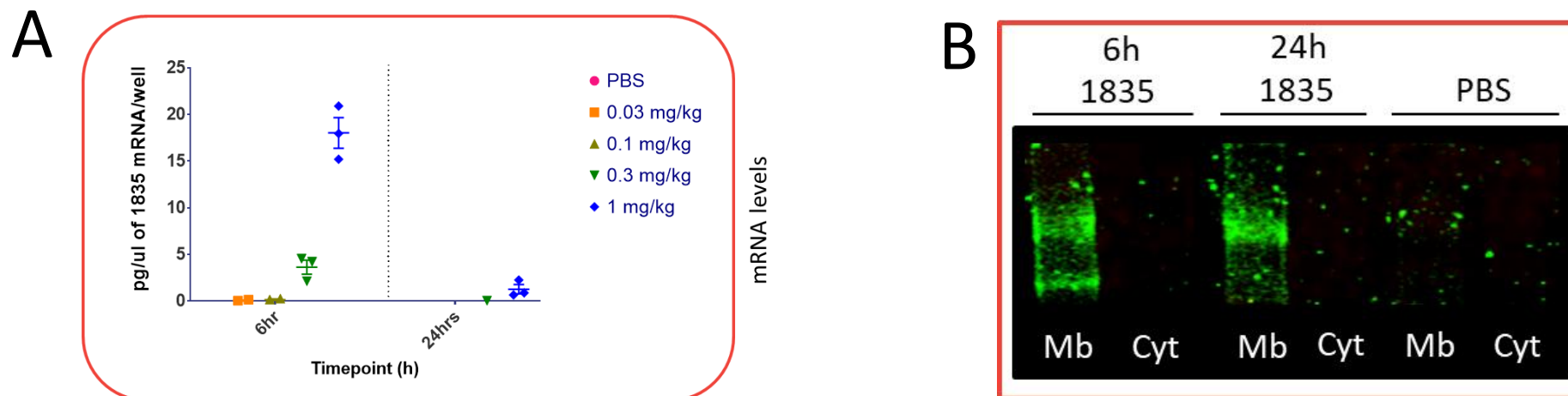


POC of selective delivery into lung epithelial cells in the mouse airways

LUNAR[®] Targeting Lung



Detection of CFTR in mouse lungs



- Efficacious delivery of hCFTR mRNA in the lungs of CFTR KO mice (A)
- hCFTR protein detected in WT mice (B)

CFTR mRNA and protein detected in WT and CFTR KO mice

Summary



BUILDING INNOVATIVE
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- LUNAR[®] delivery platform enables all RNA medicines
 - ❖ Functional delivery of multiple RNA modalities enabled across cell types and routes of administration
 - ❖ Rational design and SAR drive continuous platform and product improvement
- In vivo proof of concept achieved for multiple programs (OTC, CFTR)
- Arcturus proprietary manufacturing processes for mRNA and DP poised to drive programs into development

