



# LUNAR-COV19 Vaccine

Arcturus Therapeutics: Building the Next Generation of RNA Medicines

Meeting with the EU Commission's Vaccine Team

July 2020

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# Company Highlights



**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

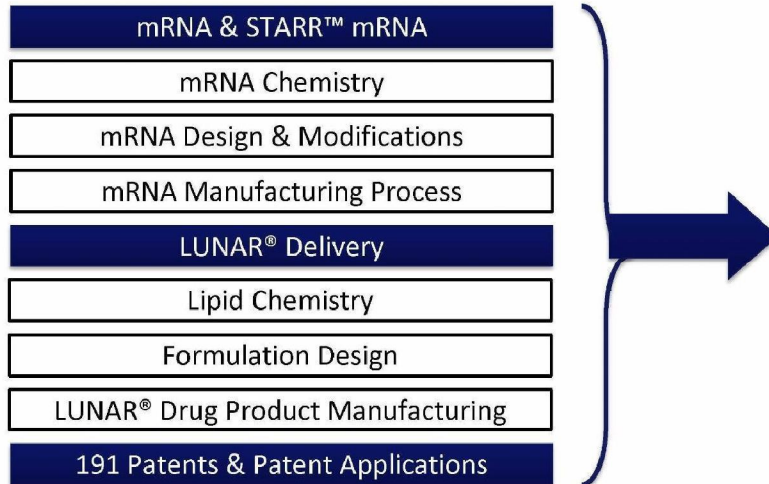


**Arcturus Technologies Validated by Multiple Strategic Partners**

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# Proprietary mRNA Technologies Driving Promising Therapeutic Programs

*Broad and Strong Intellectual Property Portfolio*







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

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## Arcturus Partnered Programs



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	SGI's Replicon RNA	LUNAR®	Preclinical
LUNAR-AH	Large Animal Health Pharma	Infectious Disease Prophylactic Vaccines	SGI's Replicon RNA	LUNAR®	Preclinical

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

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# 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

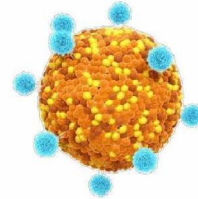
**Multiple mRNA Therapeutic Programs with Milestones in 2020**

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## Arcturus Vaccine LUNAR-COV19 is Differentiated



cap—**Replicase**—**Transgene**—polyA



### STARR™ mRNA

### &

### LUNAR® Delivery

#### Key Differences from other mRNA vaccines

Arcturus COVID-19 mRNA vaccine uses:

- Self-replicating mRNA, not conventional mRNA
- LUNAR® Nanoparticle Delivery
- Novel Manufacturing Processes for mRNA Drug Substance and Drug Product

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## Arcturus COVID-19 Vaccine has Significant Advantages

### Potential Single Shot

- Small, single intramuscular injection, devoid of adjuvants
- Simpler logistics for vaccinating large populations
- Lyophilized formulation further simplifies distribution

### Very Low Dose

- Reduced potential side effects, e.g. ISR's
- Means potentially more people vaccinated per manufactured batch

### Utilizes STARR™ mRNA (self-transcribing and self-replicating 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 mRNA vaccine
- LUNAR® Delivery Technology is Non-Viral

### Readily Manufactured

- Arcturus Proprietary Processes
- Proven; Scalable; High yields; High purities
- Capacity established in EU and US

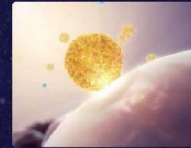


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# LUNAR<sup>®</sup> Delivery Technology

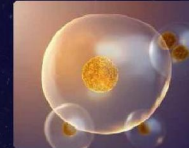


LUNAR Associates with Cell Membrane



Enters Cell Via Endocytosis

Lipid Particle in Endosome



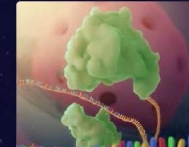
Increased Acidity as Endosome Ages

pH-Mediated Disruption



Rapid Biodegradation of Vehicle

RNA in Cytosol



RNA Processing and Translation

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# LUNAR<sup>®</sup> Delivery of mRNA; Safety in Primates



## Arcturus LUNAR<sup>®</sup> Delivery of mRNA in Primates at High Doses

- No adverse events observed at multiple i.v. doses of 1000 ug of LUNAR<sup>®</sup>-formulated mRNA

## Arcturus LUNAR-OTC Program Illustrates Safety of LUNAR Delivery of mRNA

- Anticipated dosing for LUNAR-OTC is 20,000 ug, monthly; i.v.
- IND accepted in US; CTA approved in New Zealand

## Arcturus COVID19 Vaccine Dose is Considerably Lower

- Anticipated dose is low (1-10 ug; intramuscular, i.m.)

**Because dose of COVID-19 vaccine is low, and delivered with LUNAR<sup>®</sup>, safety profile is promising**

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## Arcturus Developing COVID-19 Vaccine with **DukeNUS** Medical School



### Arcturus Duke-NUS Partnership Initiated March 4, 2020

- Duke-NUS Medical School: an academic world leader in coronaviruses and infectious diseases
- 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 streamline the vaccine development program**



**STARR™ RNA Technology**

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# STARR™ Technology

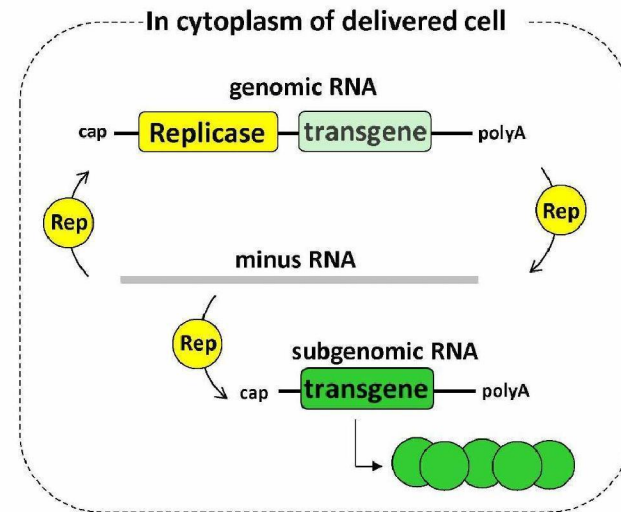
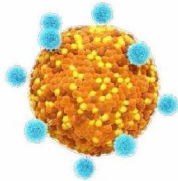


Cargo: Synthetic IVT

Self-Transcribing and Replicating RNA (STARR)



Delivery Vehicle: LUNAR®



STARR™ technology can be used to generate a protective immune response or drive therapeutic protein expression

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# mRNA vs Replicon RNA

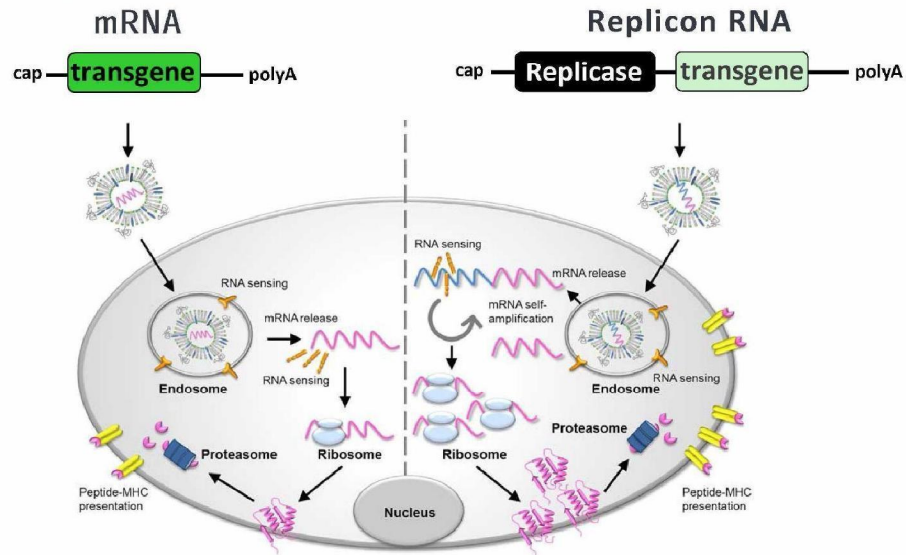


Figure modified from Maruggi, et al. (2019) [iGEM](#). Therapy 27:757

Different profiles of transgene expressions

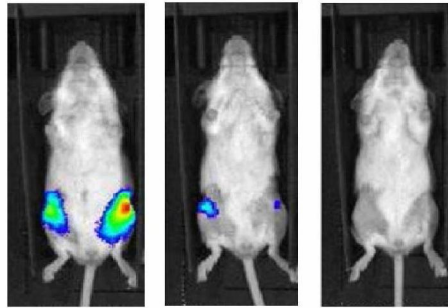
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# STARR™ mRNA Superior to Conventional mRNA

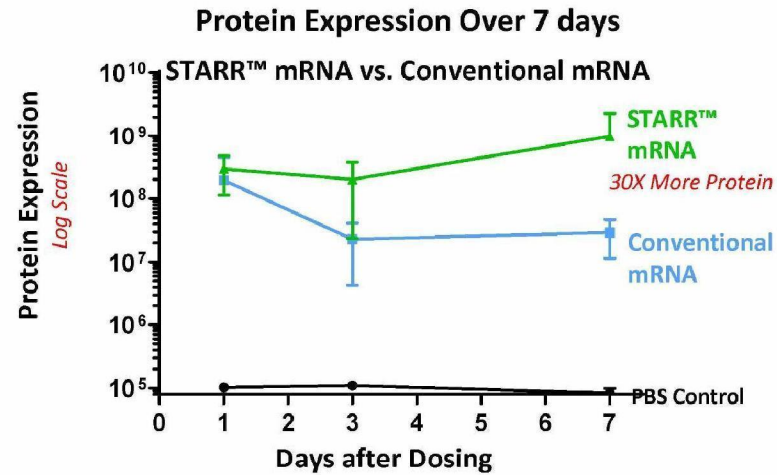
*Self-Transcribing and Replicating mRNA (STARR™) delivered with LUNAR® provides higher protein expression and potentially longer-lasting duration of protein expression in mouse*



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



STARR™ Technology      Conventional mRNA      PBS Control



- BALB/c mice were administered a 2 mg dose of either STARR™ RNA or mRNA expressing luciferase in a 50 mL injection volume.
- Protein expression was measured on days 1, 3 and 7 after administration.

**STARR™ protein expression increased ~10 fold whereas mRNA decreased ~100 fold over 7-day period**



**STARR™ mRNA SARS-CoV-2 Vaccine**

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# Immunogenicity Study Design



Type of Construct	Antigen	Dose ( $\mu\text{g}$ )	Dosing Schedule	Bleed Dates (Day)	# of mice/group	Assays
STARR™	Full Length Spike (1278 AA)	0.2, 2.0, 10.0	Day 0 Day 28 <sup>c</sup>	10, 20, 30, 40, 50, 60	5	Neutralizing Ab Titer <sup>a</sup> Total Anti-S IgM <sup>b</sup> Total Anti-S IgG <sup>b</sup>
mRNA	Full Length Spike (1278 AA)	0.2, 2.0, 10.0	Day 0 Day 28 <sup>c</sup>	10, 20, 30, 40, 50, 60	5	Neutralizing Ab Titer <sup>a</sup> Total Anti-S IgM <sup>b</sup> Total Anti-S IgG <sup>b</sup>
Negative Control	PBS		Day 0 Day 28 <sup>c</sup>	10, 20, 30, 40, 50, 60	5	Neutralizing Ab Titer <sup>a</sup> Total Anti-S IgM <sup>b</sup> Total Anti-S IgG <sup>b</sup>

<sup>a</sup>Neutralization assay conducted on Vero-E6 cells with a SARS-CoV-2 Singapore Clinical Isolate.

Serum diluted 1:10 and neutralization criteria was no CPE after 4-day incubation at 37°C

<sup>b</sup>Spike specific IgM and IgG responses will be assayed by Luminex Binding Assay

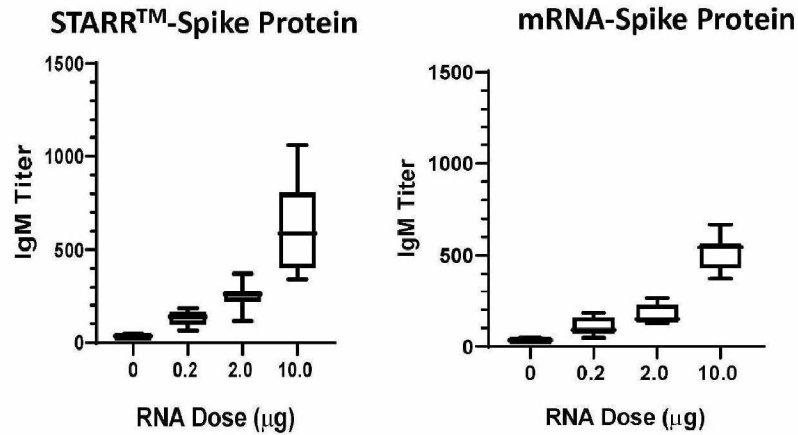
<sup>c</sup>Boost at day 28 as was not given due to steadily increasing Ab levels

Dr. Eng Eong Ooi's Lab at Duke-National University of Singapore (DUKE-NUS) independently conducted all immunogenicity Assays

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# Anti-Spike Glycoprotein IgM Immune Response

## 10 Days Post Vaccination



### Summary of Anti-Spike Protein IgM Titer Results

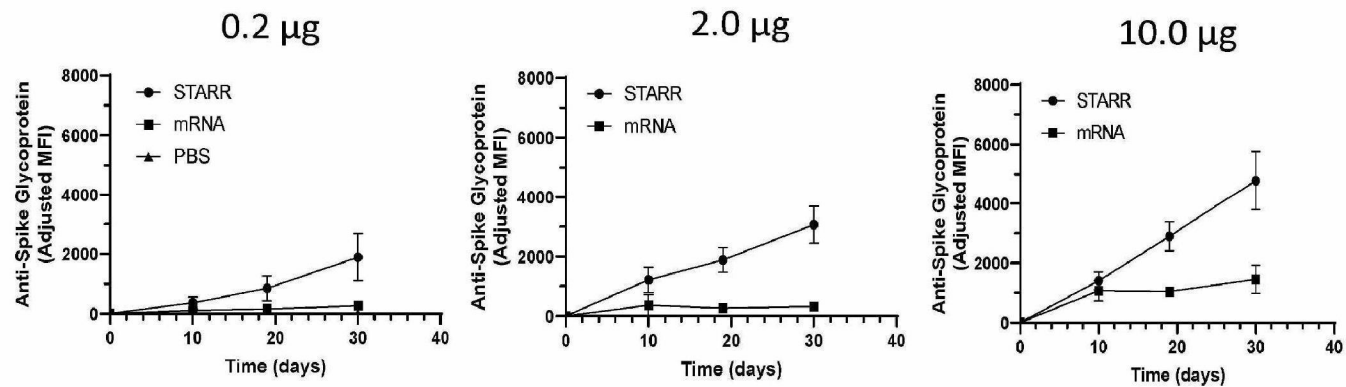
- Increase in IgM titers with increasing RNA dose for both STARR™ and mRNA Spike protein post immunization
- Higher IgM titers observed for STARR™-Spike compared to mRNA-Spike at equivalent RNA doses

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# Anti-Spike Glycoprotein IgG Antibody Titers



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RNA MEDICINES



## Summary of Results

- Anti-spike glycoprotein IgG titers increases from Day 0 to Day 30 with STARR™
- Higher anti-SARS-CoV-2 Spike Glycoprotein IgG elicited by STARR™ compared to mRNA
- IgG continues to increase produced with STARR™ whereas a plateau is reached with mRNA
- Dose dependent increase in IgG titers

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## Viral Neutralization Assay Results



RNA Dose/ Construct	% Seroconversion					
	0.2 µg		2.0 µg		10.0 µg	
	D10	D19	D10	D19	D10	D19
STARR™	40%	60%	80%	100%	100%	100%
mRNA	20%	20%	20%	0%	40%	80%

### Seroconversion Criteria

No observed CPE 4 days after coincubation  
of Vero cells with virus and 1/10 dilution of serum

STARR™ expressed spike protein gene yielded superior inhibition of SARS-CoV-2 infection compared to spike protein gene expressed by mRNA at all RNA vaccination doses

# LUNAR-COV19 Positive Preclinical Data

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



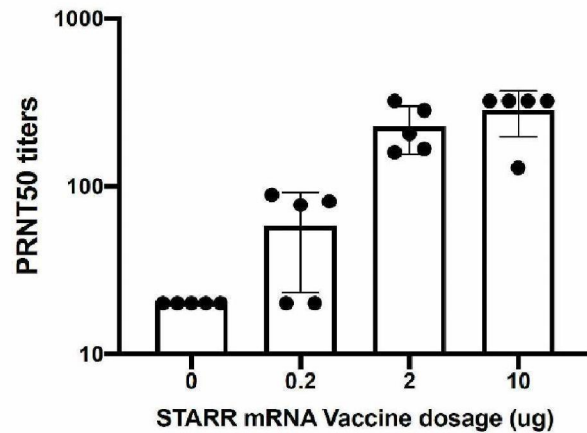
## Seroconversion Rate (% of Animals) – STARR™ mRNA vs. Conventional mRNA

Single 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 animals seroconverted by day 19 at a single low dose (2 µg)**

## Day 30 Mouse Neutralizing Antibody Titters

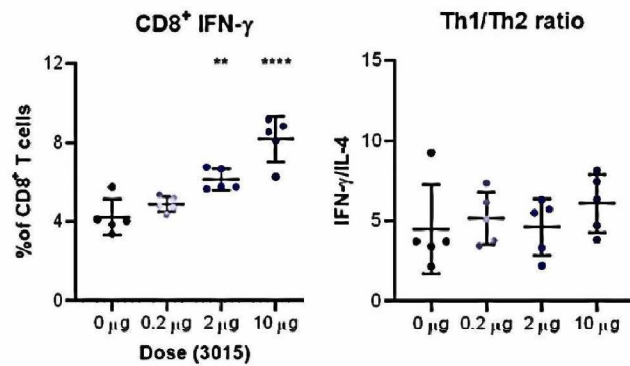


RNA Dose (μg)	% Seroconversion	Neutralizing Antibody Titters (Geometric Mean)
0.2	80%	57.7±2.0
2.0	100 %	217.9±1.4
10.0	100 %	≥ 320

### Neutralizing Antibody Titer Results Summary

- 80% of mice vaccinated with a single dose of 0.2 μg had neutralizing antibody titers at ≥ 20
- 100% of mice vaccinated with 2 μg and 10 μg had neutralizing antibody titers ≥ 217

# Arcturus Vaccine elicits a Balanced Cell Mediated Immune Response



RNA Dose (µg)	% IFN-g + CD8 <sup>+</sup> T Cells	CD4 <sup>+</sup> 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

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## 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 response increase in IFN-g positive CD8<sup>+</sup> T-cells
- Potential single shot simplifies vaccination campaigns
- Safety: balanced cellular immune response – low probability of 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 most promising COVID-19 vaccine**



**Drug Substance / Drug Product  
CMC**

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INTERNAL RNA DEVELOPMENT PLATFORMS

# Drug Substance: mRNA Design



## Arcturus' proprietary mRNA optimization platform

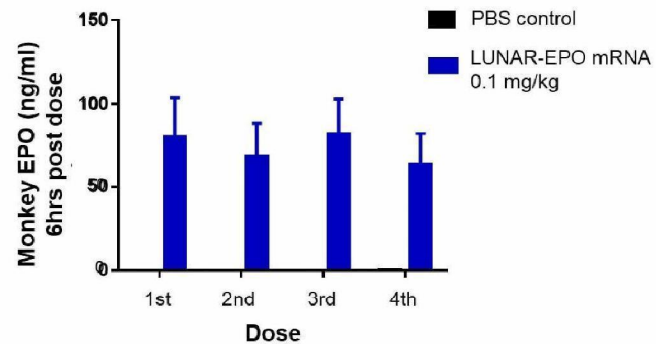
### Optimized conditions

- mRNA sequence
  - Chemistry
  - Process optimization
- ➔
- Improved protein expression and duration
  - Improved functional activity



## Sustained hEPO activity in NHPs upon repeat dosing

### Weekly Dosing in Non-Human Primates



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

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# Drug Substance (mRNA) Manufacturing

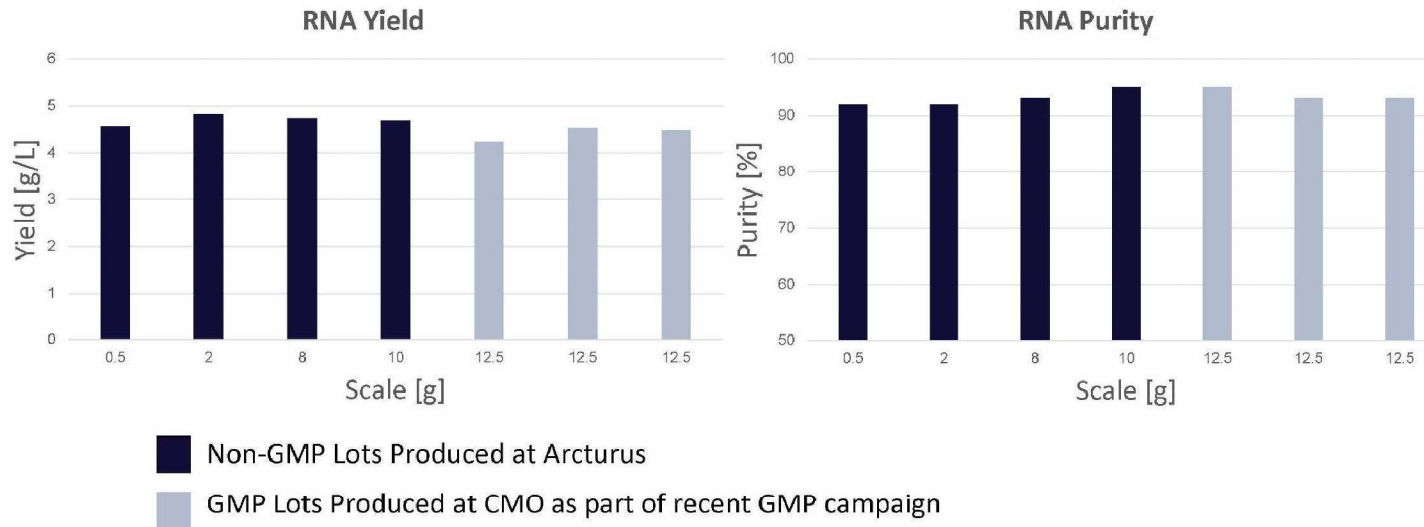


Features	Benefits
<b>Optimized IVT Method</b>	Reduced Cost; Higher Purity
<b>Improved Capping Reaction</b>	Reduced Cost of Goods
<b>Proprietary Purification Process</b>	Higher Purity in a Shorter Time
<b>Efficient</b>	Entire Process Less Than One Week
<b>Scalable to &gt; 1Kg</b>	Access Large Patient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

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

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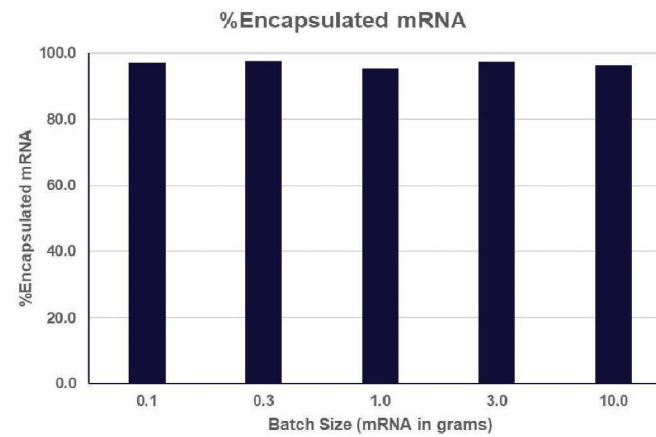
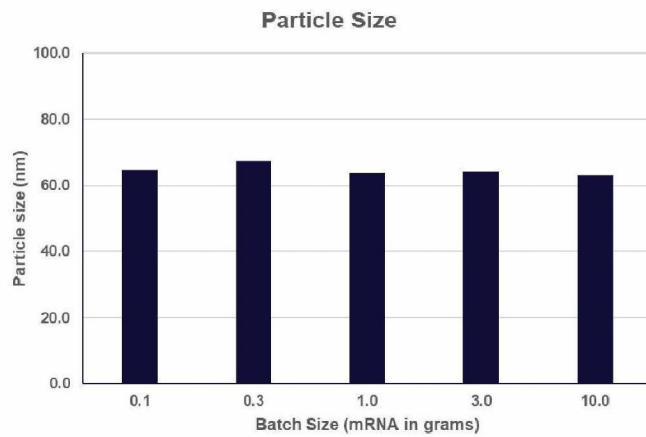
# Drug Substance (mRNA) Manufacturing



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

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



- 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

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## cGMP Manufacturing LUNAR-COV19 Summary



- We plan to manufacture 30g of LUNAR-COV19 drug product this year
- The anticipated vaccine human dose is between 1  $\mu$ g - 10  $\mu$ g of RNA
- Bulk drug product and fill/finish to be completed in Austria and Germany. Drug mRNA substance manufactured in the U.S. at Catalent
- Additional manufacturing capacity ex-US not yet announced
- Our Phase 2/3 and commercial product will be a lyophilized vaccine packaged in vials
- We are committed to producing tens of millions of doses in 2020 and hundreds of millions of doses in 2021 and beyond

**Hundreds of millions of dose capacity in 2021 and beyond**



# LUNAR-COV19 Clinical Plans

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# LUNAR-COV19 Clinical Plan



Phase 1/2 Clinical Trial to begin in Summer 2020

## Shipment of GMP Manufactured LUNAR-COV19 Vaccine

### Human Dosing to Initiate this Summer

- Phase 1/2 clinical trial at single site: Duke-NUS Medical School in Singapore

**Primary Goal:** Identify optimal dose

**Primary Endpoints:** Safety and tolerability

**Secondary Endpoints:** Measures of immunogenicity and virus neutralization

Also evaluating T-cell responses (CD8+ and TH1/TH2 and epitope mapping)

### Study Design:

- 108 healthy volunteer adults
- 3 dose levels
- Elderly as well as younger adults

Trial design allows us to potentially rapidly select dose to take forward to large registrational studies

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# LUNAR-OTC (ARCT-810) Clinical Plan

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Phase 1 Clinical Trial to begin based on COVID-19 restrictions being lifted

## Two Single Dose Studies to Initiate in 2020

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

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

**Primary Endpoints:** Safety and tolerability

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

## Study Design\*

- 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

\* Doses are > thousand-fold higher than anticipated effective LUNAR-COV19 vaccine dose (1 to 10 µg)

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## Arcturus COVID-19 Vaccine Opportunity Overview



### Vaccines are Needed ASAP

- The pandemic has impacted the global economy
- Significant health risks when removing COVID-19 'stay-at-home' restrictions

### Availability of Vaccines is Limited

- Extraordinarily high demand, > 5 billion people
- Manufacturing large amounts is very difficult
- Countries are now securing rights and access for their citizens
- First batches of vaccines are already accounted for, eliminating initial access to supply (i.e. U.S. (BARDA) aligned with Moderna, J&J; UK with AstraZeneca, etc.)

### Secure Rights and Access to Vaccine(s)

- Singapore has secured rights to the first batch of doses of Arcturus COVID-19 vaccine
- Ongoing discussions with governments globally
- Rights to Arcturus COVID-19 vaccine is secured upon execution of an agreement