Arbutus BIOPHARMA

LNP:
Delivering mRNA Therapeutics to the Clinic

Live Webinar | September 12, 2017 @1pm ET / 10am PT

NASDAQ: ABUS www.arbutusbio.com

Today's Speakers

Adam Cutler

Vice President, Corporate Affairs

MODERATOR

Dr. Adam Judge

Nucleic Acid-Based Drug Expert

- +15 years experience in discovery and development of nucleic acid-based drugs with Arbutus/Tekmira/Protiva
- Author of +35 peer-reviewed publications and +8500 journal citations
- PhD in Cellular Immunology from The University of Birmingham Medical School, UK.

Dr. James Heyes

Vice President, Drug Delivery

- +16 years experience as a lipid chemist discovering and developing technologies like Arbutus Biopharma's novel LNP platform
- PhD in Medicinal and Pharmaceutical Chemistry from The University of London, UK.

Dr. Peter Lutwyche

Chief Technical Operations Officer

- +20 years of experience in the pharmaceutical development of nucleic acid-containing LNP products
- Formerly, Director of Pharmaceutical Development for Arbutus and QLT Inc.
- PhD in Chemistry from The University of British Columbia, Canada.

Agenda

1. mRNA therapeutics & current challenges of delivery
2. Arbutus' LNP drug delivery technology
3. Recent technological advancements in the LNP platform
4. LNP technology enables mRNA product development
5. Intellectual property & pharmaceutical development for clinical use of mRNA therapeutics
6. Q&A

Arbutus BIOPHARMA

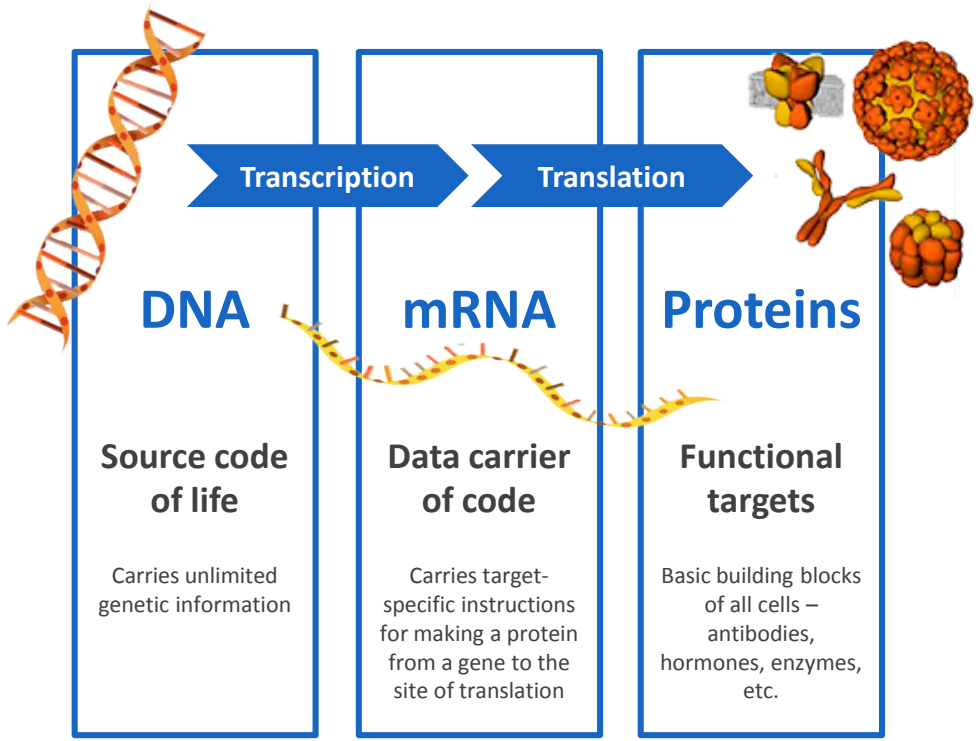
Curing Chronic Hepatitis B

mRNA Therapeutics

mRNA: An Exciting New Therapeutic Modality

Exploiting a fundamental mechanism in biology

- Template for any natural or engineered protein



- High level protein production within target tissues
  - Secreted, intracellular or membrane-bound

Table: Wide array of therapeutic applications

mRNA encoded proteins	Example
• Intracellular proteins • Secreted therapeutic proteins	• Rare genetic disease e.g. OTC Deficiency • Antibodies for cancer immunotherapy
• Gene editing enzymes (e.g CRISPR, ZFN, meganucleases)	• Gene disruption for TTR amyloidosis • Gene correction for inborn errors of metabolism
• Pathogen-derived antigens	• Vaccines for emerging viruses
• Tumor-derived antigens	• Personalized cancer vaccines

Effective delivery systems will be transformative for mRNA-based drug development

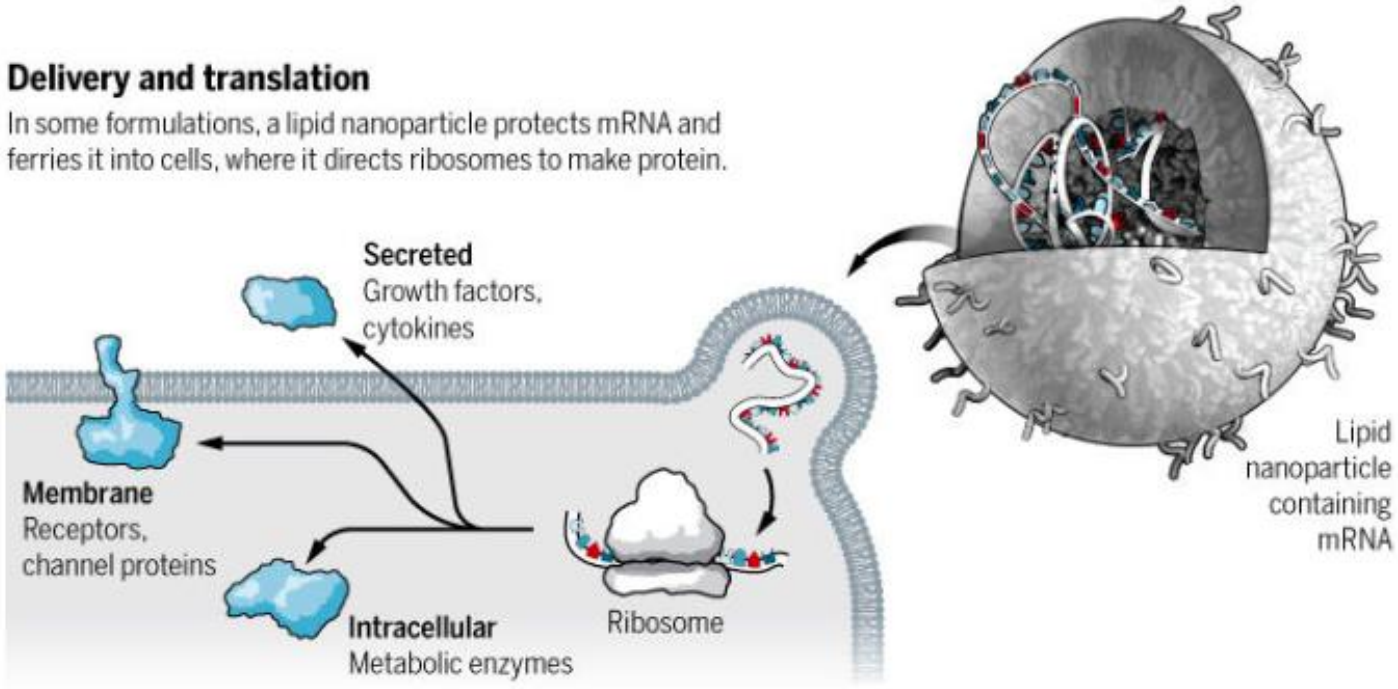
mRNA Therapeutics: The Delivery Challenge

- mRNA requires intracellular delivery
- Prone to rapid degradation and excretion
- Very large macromolecule does not pass freely through cell membranes

mRNA delivery has distinct challenges

- Oligonucleotide chemistries that confer drug-like properties are not tolerated
- Ligand-conjugate delivery platforms (e.g. GalNAc-oligonucleotides) are not suitable

Pharmaceutical development of mRNA will require specialised delivery systems for most applications



Adapted from Science: doi:10.1126/science.aal0686

mRNA Therapeutics: The Immunology Challenge

- mRNA can activate inflammatory responses including cytokine and Interferon release
- Poses unique challenges to mRNA-based drug safety and efficacy in the clinic
- Exacerbated by mRNA quality and inappropriate delivery systems
  - Chemical modification of mRNA is not a universal solution

Overcoming this challenge requires a multi-factorial approach:

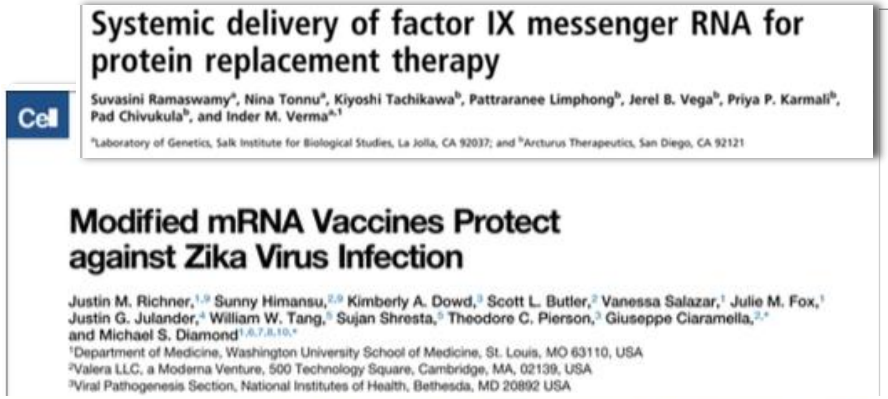
mRNA Sequence Design	mRNA Purification & Quality Control	Delivery Vehicle Design & Control of Final Drug Product	Testing in Appropriate Human & Animal Models that Reflect Clinical Risk

Recent Progress in mRNA Drug Development

Advances towards and into the clinic

- Potent mRNA vaccine platforms have advanced into the clinic
  - Development speed ideal for emerging threats
  - Personalised cancer vaccines
- Successful mRNA delivery in large animal models
  - Therapeutic protein expression at clinically feasible dose
- First demonstrations of in vivo gene editing and repair

Many of these advancements are enabled by Arbutus' LNP delivery platform


Systemic delivery of factor IX messenger RNA for protein replacement therapy

Suvasini Ramaswamy[a], Nina Tonnu[a], Kiyoshi Tachikawa[b], Pattraranee Limphong[b], Jerel B. Vega[b], Priya P. Karmali[b], Pad Chivukula[b], and Inder M. Verma[a,1]

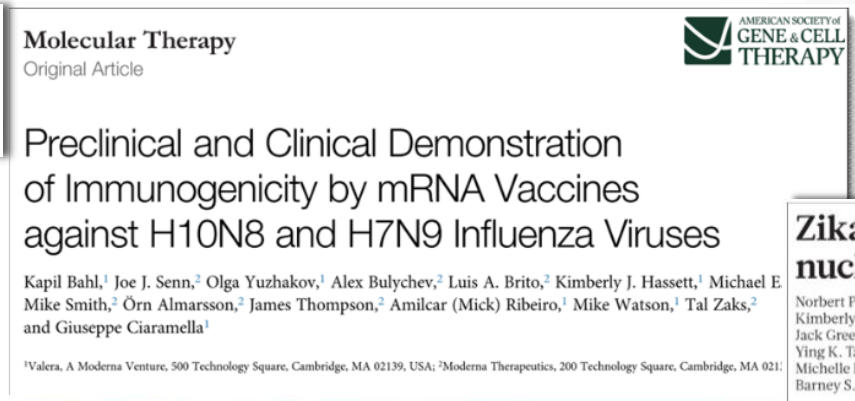
[a]Laboratory of Genetics, Salk Institute for Biological Studies, La Jolla, CA 92037; and [b]Arcturus Therapeutics, San Diego, CA 92121

Cell

Modified mRNA Vaccines Protect against Zika Virus Infection

Justin M. Richner,[1,9] Sunny Himansu,[2,9] Kimberly A. Dowd,[3] Scott L. Butler,[2] Vanessa Salazar,[1] Julie M. Fox,[1] Justin G. Julander,[4] William W. Tang,[5] Sujan Shresta,[5] Theodore C. Pierson,[3] Giuseppe Ciaramella,[2,*] and Michael S. Diamond[1,6,7,8,10,*]

[1]Department of Medicine, Washington University School of Medicine, St. Louis, MO 63110, USA
[2]Valera LLC, a Moderna Venture, 500 Technology Square, Cambridge, MA, 02139, USA
[3]Viral Pathogenesis Section, National Institutes of Health, Bethesda, MD 20892 USA


Molecular Therapy

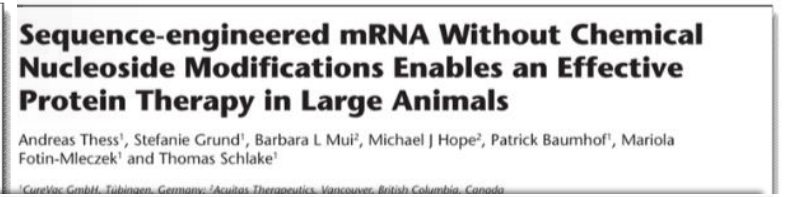
Original Article

AMERICAN SOCIETY of GENE & CELL THERAPY

Preclinical and Clinical Demonstration of Immunogenicity by mRNA Vaccines against H10N8 and H7N9 Influenza Viruses

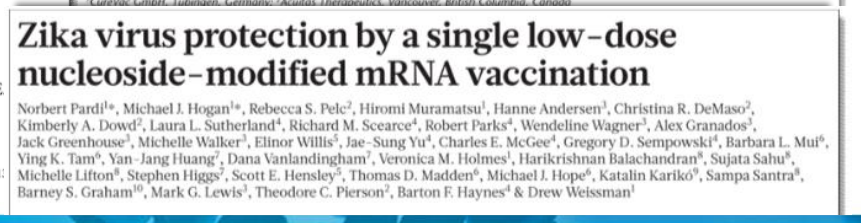
Kapil Bahl,[1] Joe J. Senn,[2] Olga Yuzhakov,[1] Alex Bulychev,[2] Luis A. Brito,[2] Kimberly J. Hassett,[1] Michael E Mike Smith,[2] Örn Almarsson,[2] James Thompson,[2] Amilcar (Mick) Ribeiro,[1] Mike Watson,[1] Tal Zaks,[2] and Giuseppe Ciaramella[1]

[1]Valera, A Moderna Venture, 500 Technology Square, Cambridge, MA 02139, USA; [2]Moderna Therapeutics, 200 Technology Square, Cambridge, MA 021


Sequence-engineered mRNA Without Chemical Nucleoside Modifications Enables an Effective Protein Therapy in Large Animals

Andreas Thess[1], Stefanie Grund[1], Barbara L Mui[2], Michael J Hope[2], Patrick Baumhof[1], Mariola Fotin-Mleczek[1] and Thomas Schlake[1]

[1]CureVac GmbH, Tübingen, Germany; [2]Acuitas Therapeutics, Vancouver, British Columbia, Canada


Zika virus protection by a single low-dose nucleoside-modified mRNA vaccination

Norbert Pardi[1]*, Michael J. Hogan[1]*, Rebecca S. Pelc[2], Hiromi Muramatsu[1], Hanne Andersen[1], Christina R. DeMaso[2], Kimberly A. Dowd[2], Laura L. Sutherland[4], Richard M. Scearce[4], Robert Parks[4], Wendeline Wagner[3], Alex Granados[3], Jack Greenhouse[3], Michelle Walker[3], Elinor Willis[3], Jae-Sung Yu[4], Charles E. McGee[4], Gregory D. Sempowski[4], Barbara L. Mui[6], Ying K. Tam[6], Yan-Jang Huang[7], Dana Vanlandingham[7], Veronica M. Holmes[1], Harikrishnan Balachandran[8], Sujata Sahu[8], Michelle Lifton[8], Stephen Higgs[7], Scott E. Hensley[5], Thomas D. Madden[6], Michael J. Hope[6], Katalin Karikó[9], Sampa Santra[8], Barney S. Graham[10], Mark G. Lewis[3], Theodore C. Pierson[2], Barton F. Haynes[4] & Drew Weissman[1]

Arbutus BIOPHARMA

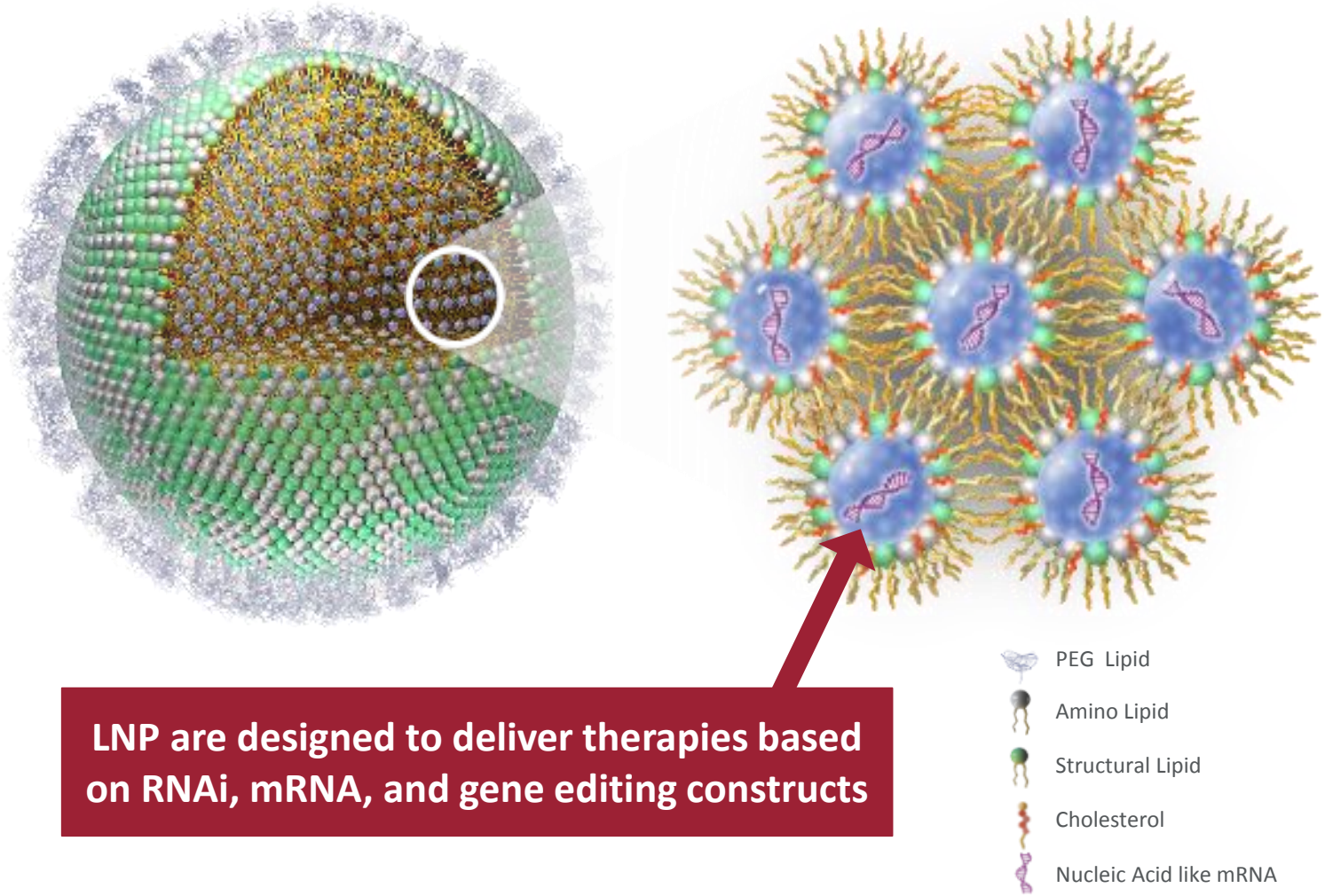
Curing Chronic Hepatitis B

Lipid Nanoparticle (LNP) Technology

Arbutus is the Leader in LNP Technology

LNP technology is Clinically Validated and Ideal for mRNA

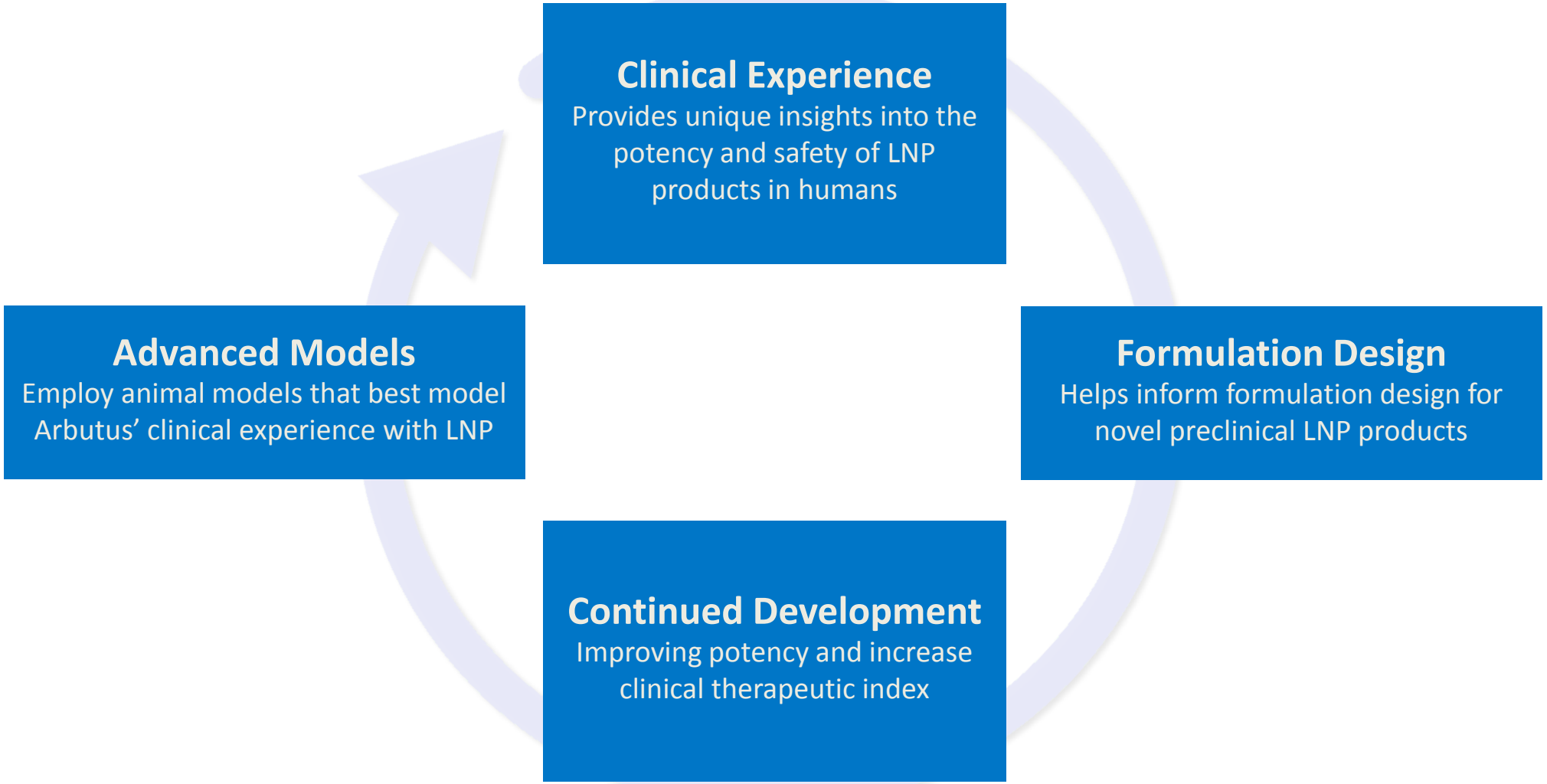
- LNP are highly tuned mixtures of lipids.
- Protect nucleic acids in the blood, and provide access to the target cells.
- Validated in multiple clinical trials (over 400 patients).
- Arbutus has considerable expertise advancing LNP programs rapidly into the clinic.



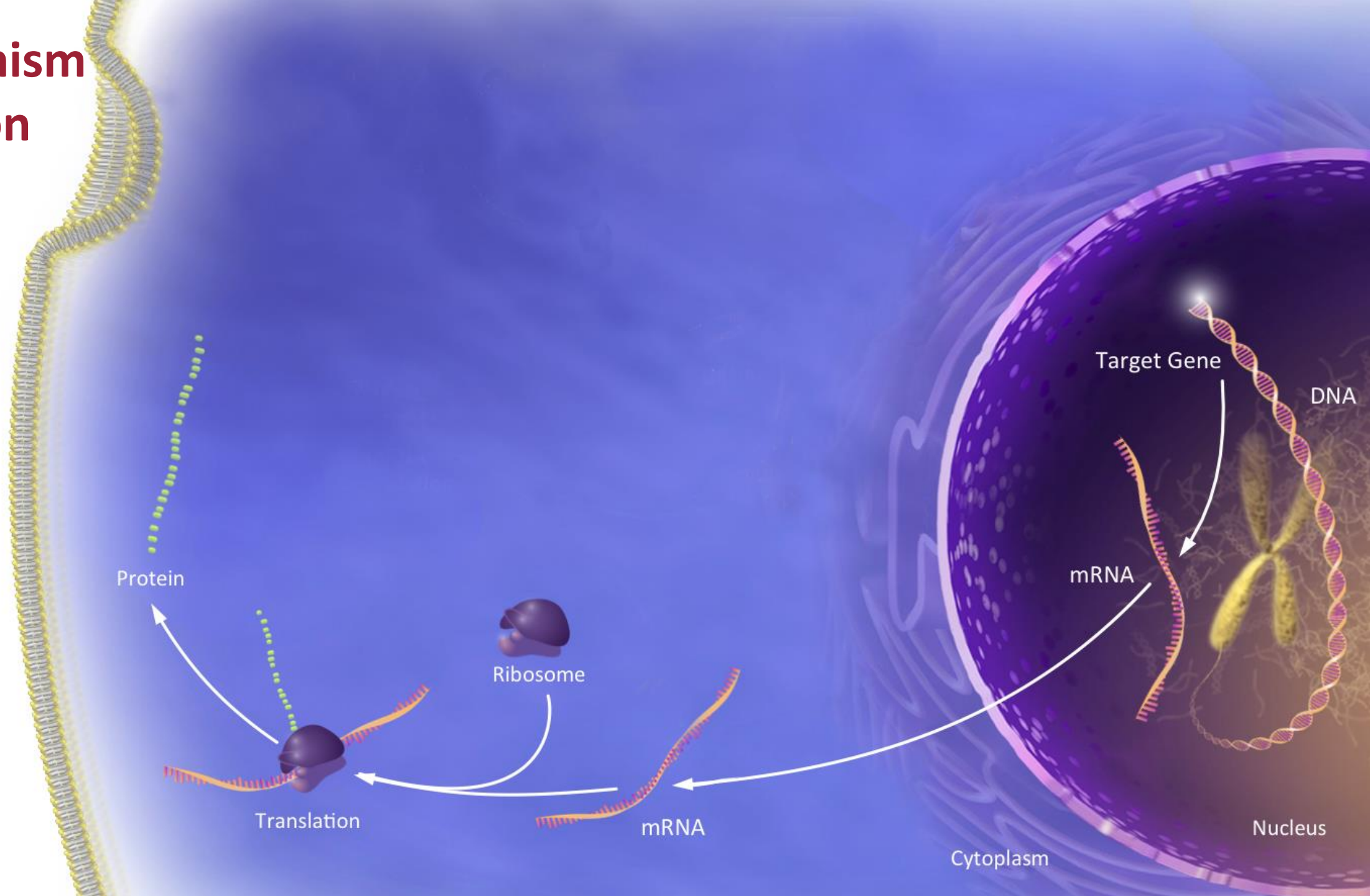
LNP are designed to deliver therapies based on RNAi, mRNA, and gene editing constructs

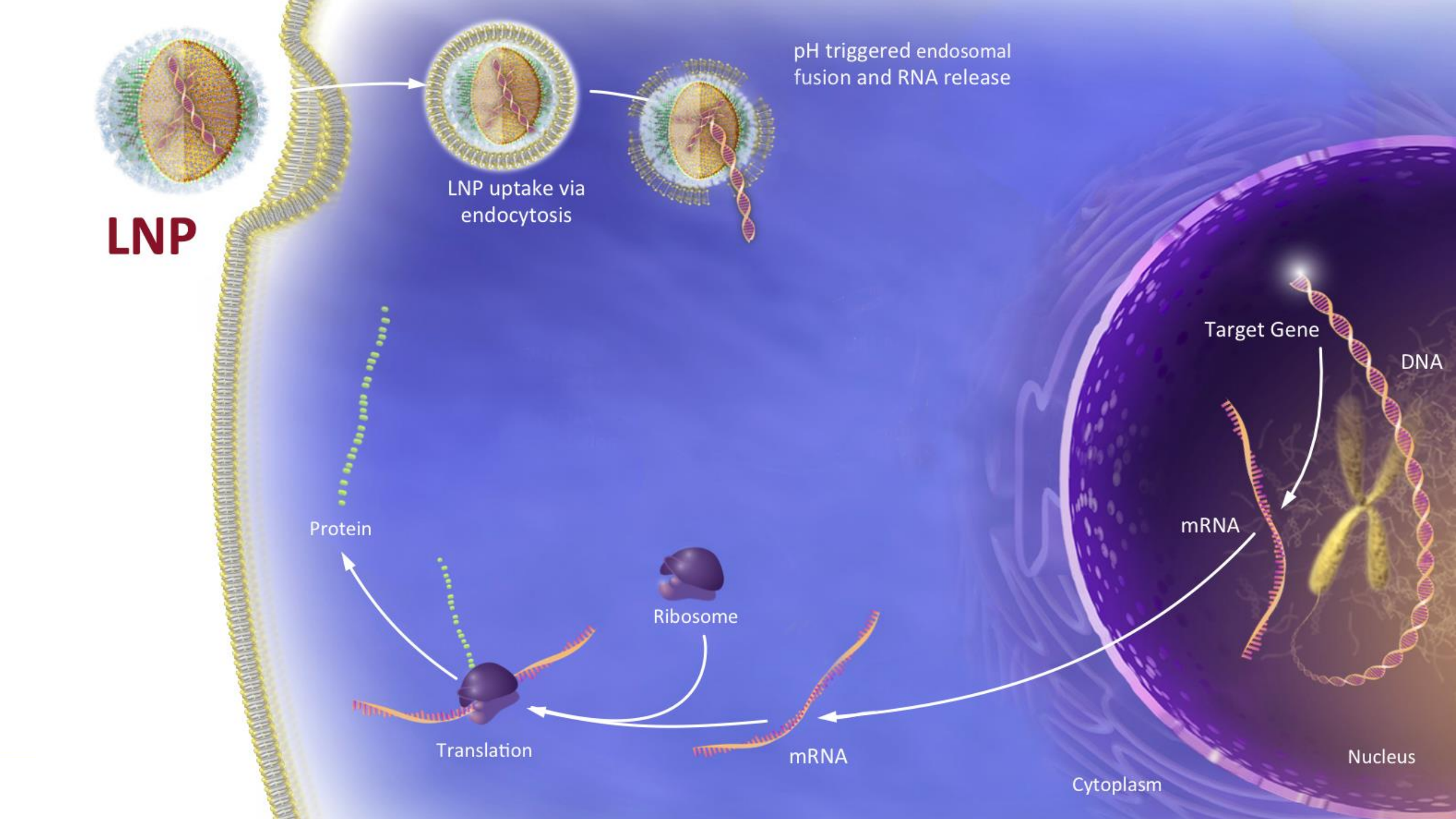
Clinical Experience Drives LNP Platform Development

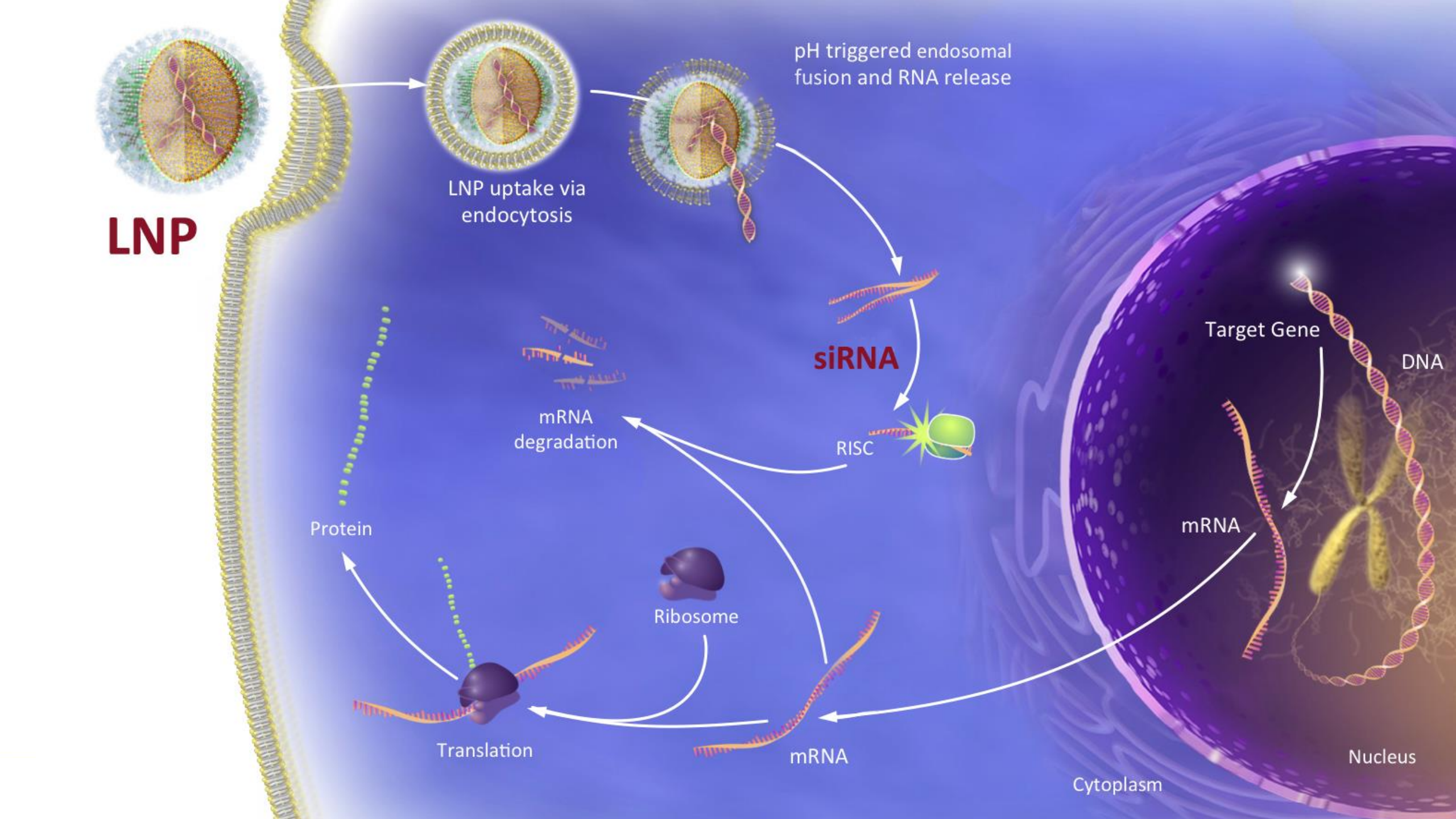
Arbutus's next generation LNP formulations



Mechanism of Action




LNP
LNP uptake via endocytosis
pH triggered endosomal fusion and RNA release
Target Gene
DNA
mRNA
Protein
Ribosome
Translation
mRNA
Nucleus
Cytoplasm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Ribosome
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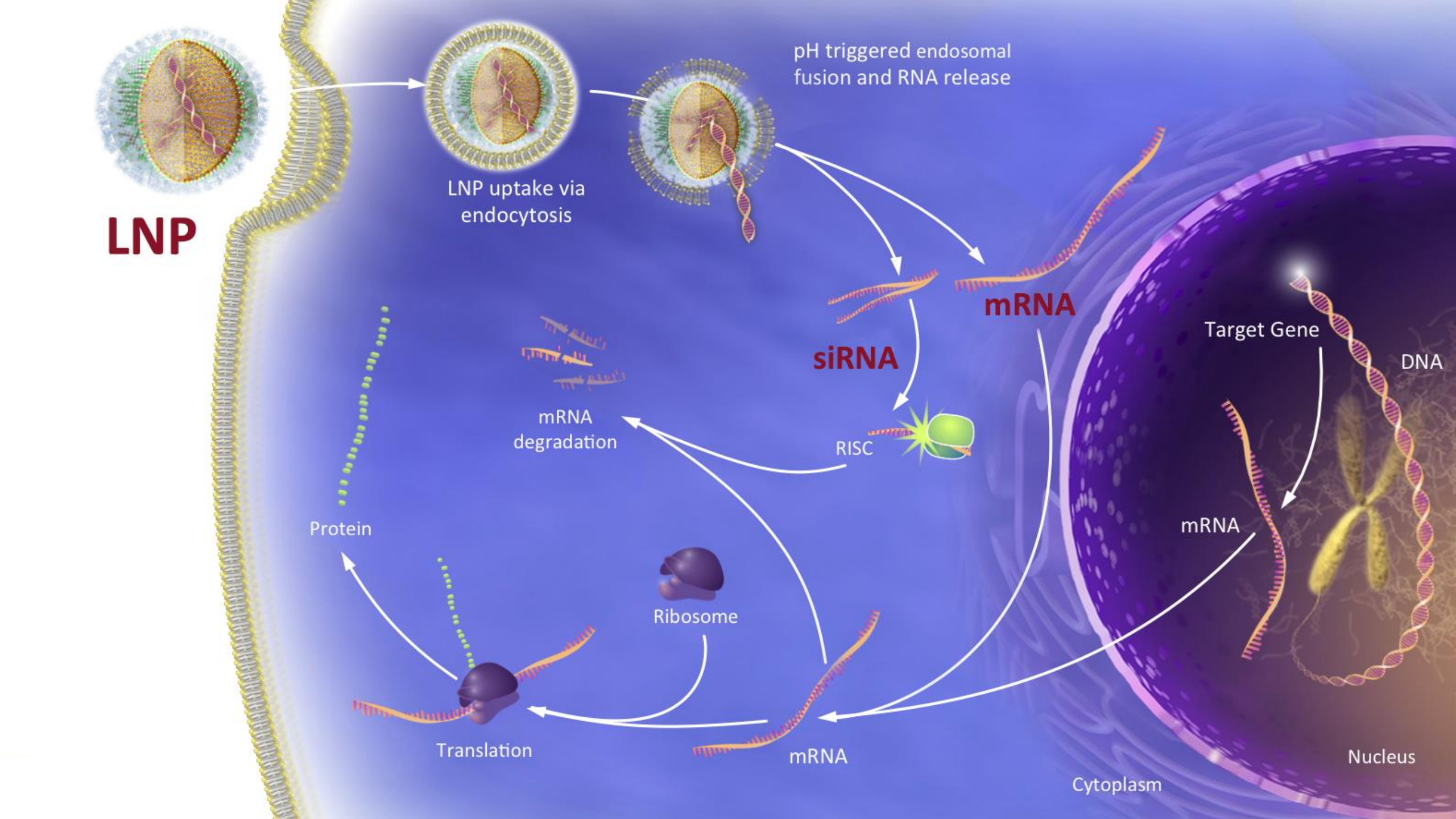
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Target Gene
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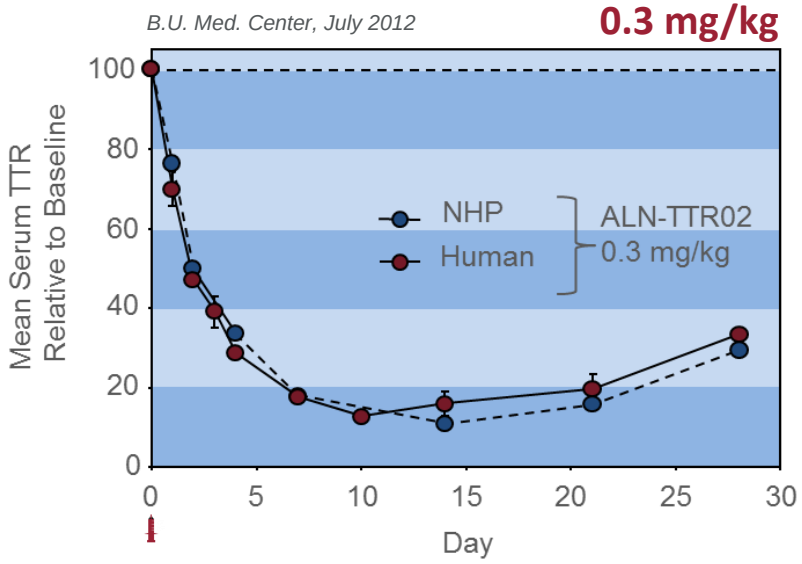
Cytoplasm

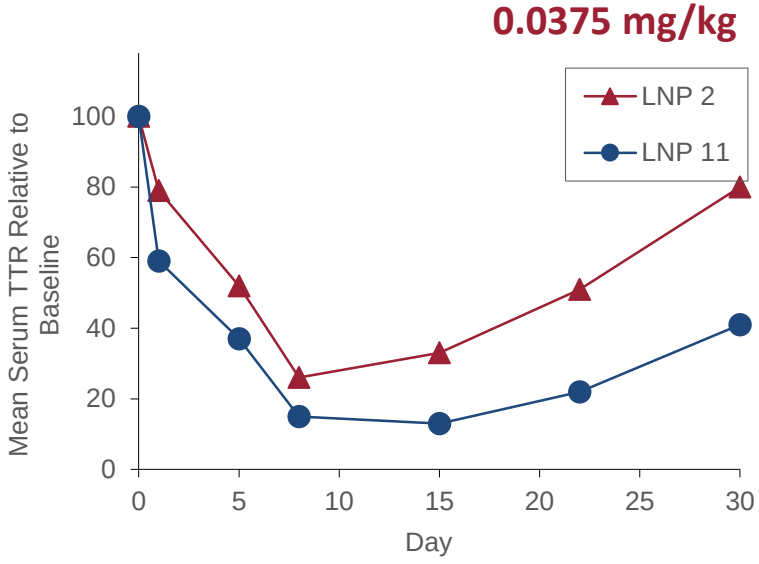
Recent Advances in the Arbutus LNP Platform

Improved Therapeutic Index in Non-Human Primates

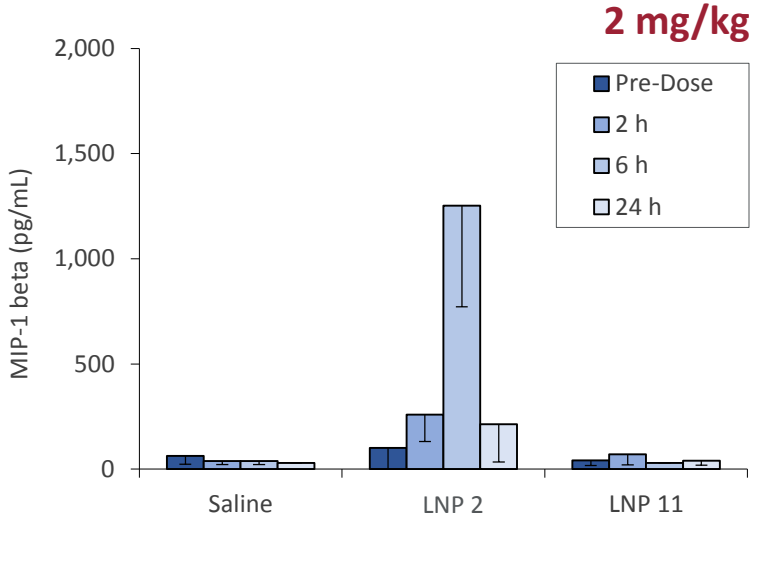
Historical Alnylam Data with patisiran



Novel LNP Potency in NHP



Novel LNP – Representative Cytokine



- LNP screening conducted with the same TTR siRNA sequence as patisiran
- Improved potency 8-fold over patisiran formulation
- Additionally, markedly reduced immune stimulation at higher doses predicts increased TI
- These composition improvements translate readily to mRNA payloads

Arbutus BIOPHARMA

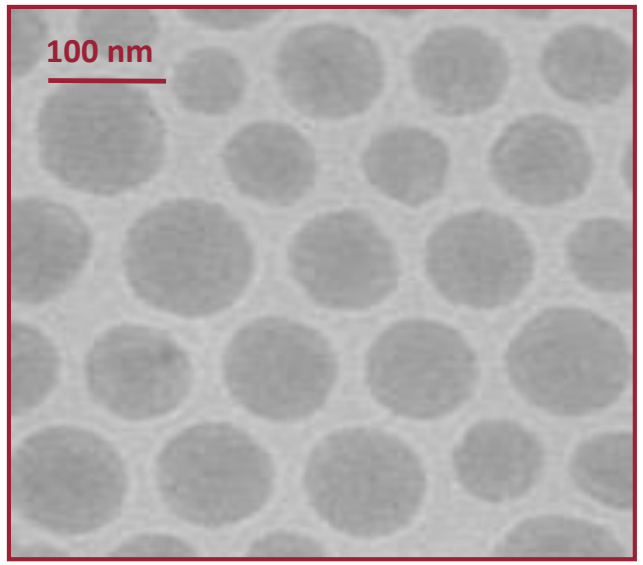
Curing Chronic Hepatitis B

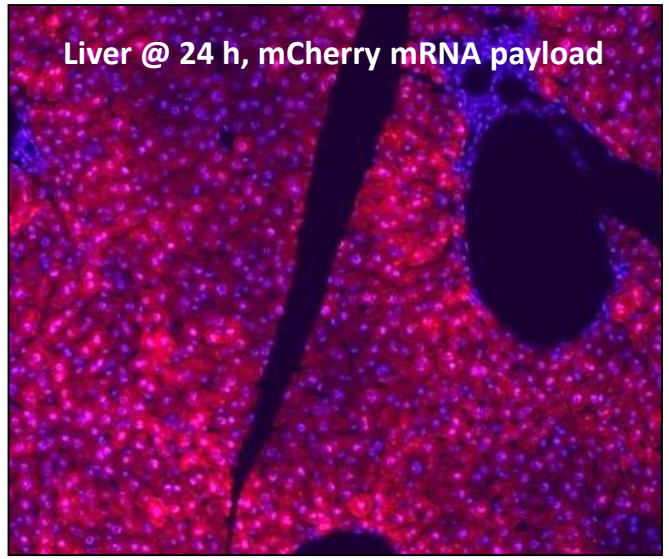
Leaders in LNP-mediated mRNA Delivery

Arbutus LNP Enable mRNA Product Development

Integrating the Latest LNP Technology

- Arbutus LNP technology is broadly applicable to Nucleic Acids, including mRNA
  - Very high encapsulation efficiency (>90%), high yields
- mRNA-LNP possess non-lamellar, electron dense particle morphology
- mRNA-LNP is delivered to all hepatocytes, with homogenous expression profile throughout the liver

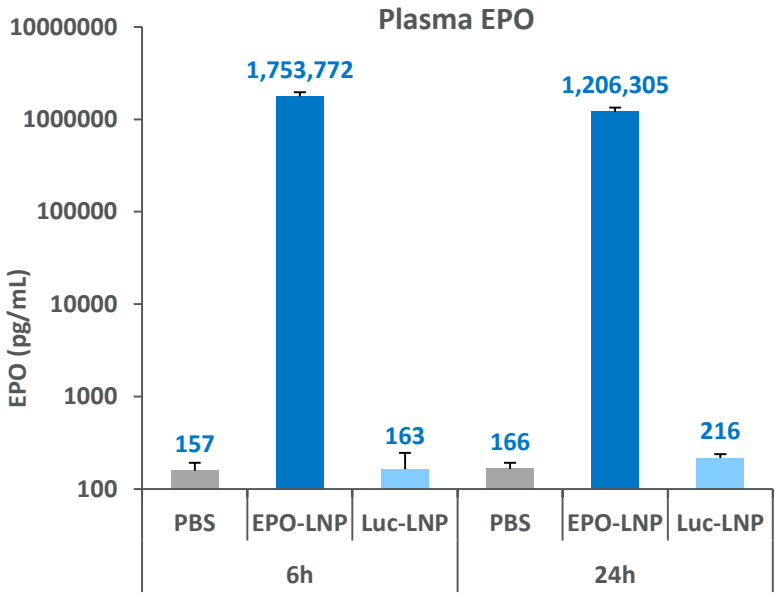


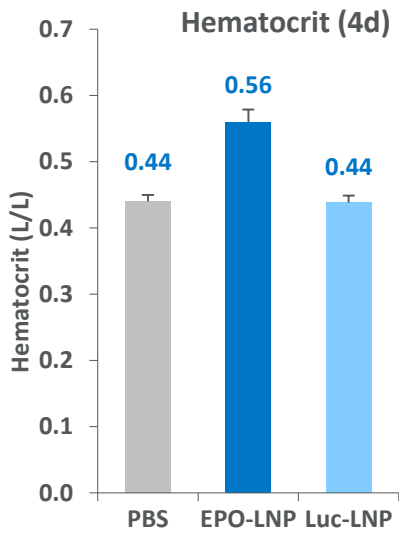


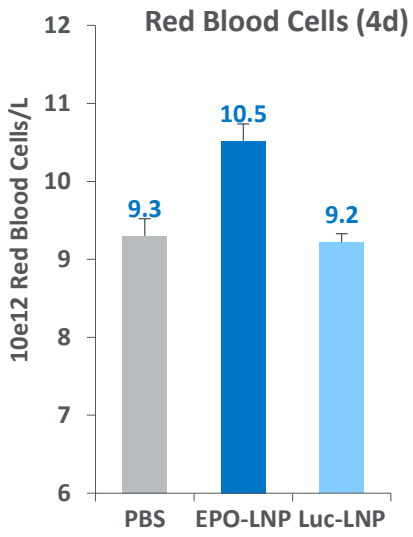
mRNA Encoding Therapeutic Proteins

LNP-mediated mRNA delivery yields pronounced pharmacodynamic effects

LNP Bearing mRNA Payloads Administered i.v. (0.05 mg/kg) to Balb/C Mice (n = 5)





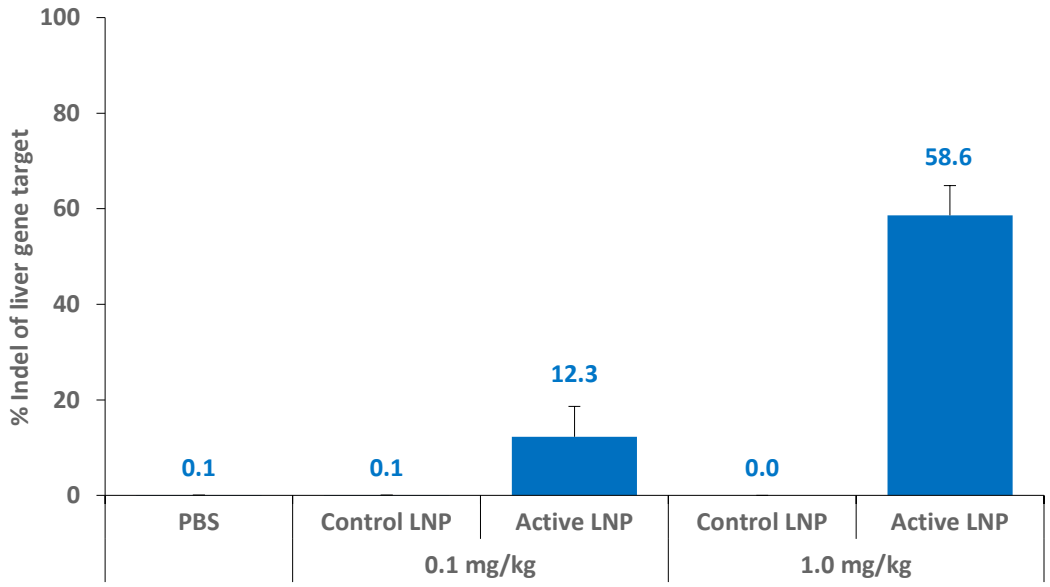


- LNP bearing an EPO mRNA payload are used to rapidly generate large quantities of protein in the blood
- Concomitant increase in RBC and hematocrit at clinically relevant doses

mRNA Encoding Gene Editing Nucleases

LNP delivery enables exciting new approach to human therapeutics

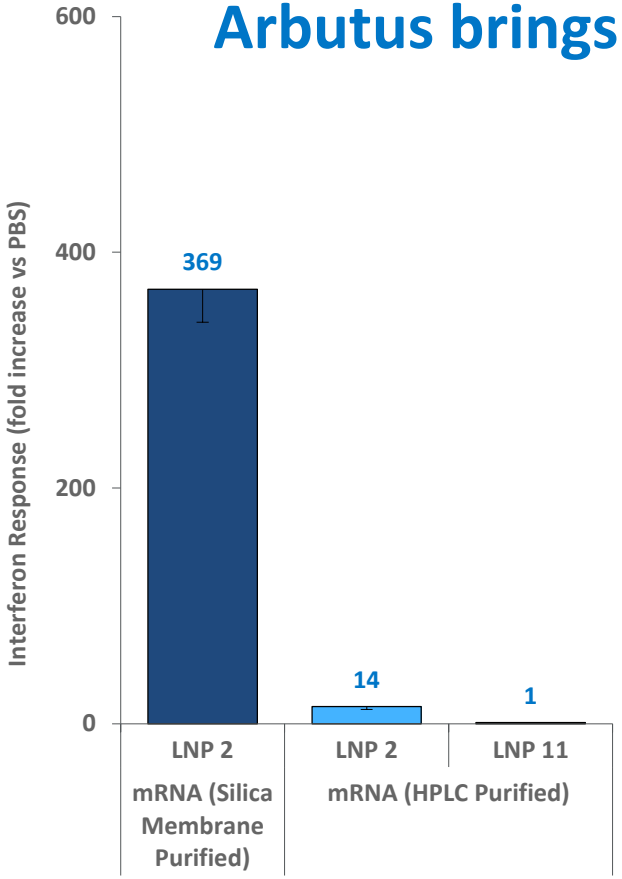
Deep Sequencing Analysis of DNA from livers of mice treated with LNP (Day 7, n=5)



- Gene editing is a new approach enabling the deletion or repair of specific target genes
- Requires delivery of RNA encoding the gene editing nucleases
- These include CRISPR/Cas9, Meganucleases, TALENs and Zinc Finger Nucleases
- Arbutus LNP has successfully worked with all of them, observing meaningful gene editing with a single clinically relevant dose
- Effects of gene editing are very long lived, so expect a cumulative effect on repeat dosing

Improvements in the mRNA-LNP Platform

Optimization of mRNA payload and LNP design



Arbutus brings critical expertise in appropriate nucleic acid payload selection

- Unpurified mRNA is considerably more inflammatory than siRNA of a similar quality in LNP
- Issue ***not*** resolved by widely used mRNA chemical modification strategies
- HPLC-purification of mRNA in LNP reduces the inflammatory response significantly.
- The response is completely abrogated in combination with novel LNP formulations (e.g. LNP 11)

0.5 mg/kg IV mRNA-LNP administration, n=5, t=4 h

LNP Mediated mRNA Delivery

HIGHLIGHTS

- Safe and successful delivery of mRNA demands appropriate attention.
- LNP technology readily adapted to use with mRNA.
- Arbutus' clinical experience provides a unique understanding of the most salient hurdles.
- mRNA payloads are more likely to provoke inflammatory responses than smaller oligonucleotides.
- Potency and tolerability of the LNP platform continue to increase.
- Demonstrated potential in a wide array of mRNA-based applications, including;
  - Therapeutic Proteins
  - Vaccines
  - Gene Editing

Arbutus BIOPHARMA

Curing Chronic Hepatitis B

Intellectual Property & Pharmaceutical Development

Arbutus has Dominating Intellectual Property

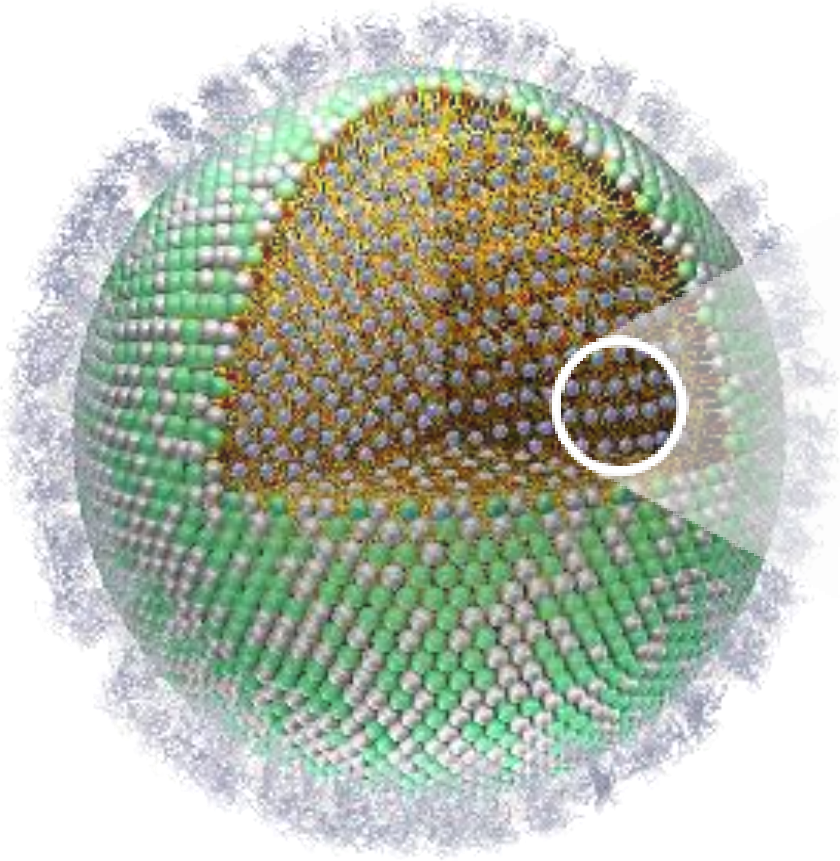
IP Covers All Critical Aspects of LNP

Structures of Individual Lipid Components

Cationic and PEG-Lipids

Lipid Formulations

Captures all commonly used, most active ranges of lipid ratios



LNP containing any mRNA Payload

Broad patent claims directed to any mRNA-LNP

Particle Morphology (Internal Form/Structure)

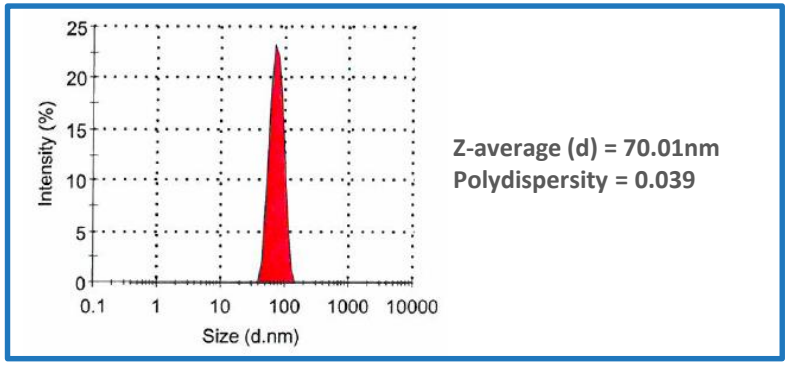
Covers all LNP with ‘electron dense’ core

Manufacturing Process

Robust, scalable LNP formulating process

Robust, Scalable LNP Manufacturing Process

- Elegant Controlled Mixing Process
- Applicable broadly for nucleic acid encapsulation
- Easily scalable and reproducible
- Efficient (high encapsulation)
- Easily Transferable
- GMP compliant
- Protected by IP



Z-average (d) = 70.01nm
Polydispersity = 0.039

Stable Nucleic Acid-LNP Products

- Arbutus's LNP products are usually provided in liquid, "ready-to-use" format, Stable for 2y+ at 5 °C
- Arbutus has developed siRNA and mRNA lyophilized products stable at ambient temperatures and higher

Arbutus LNP Pharmaceutical Development

HIGHLIGHTS

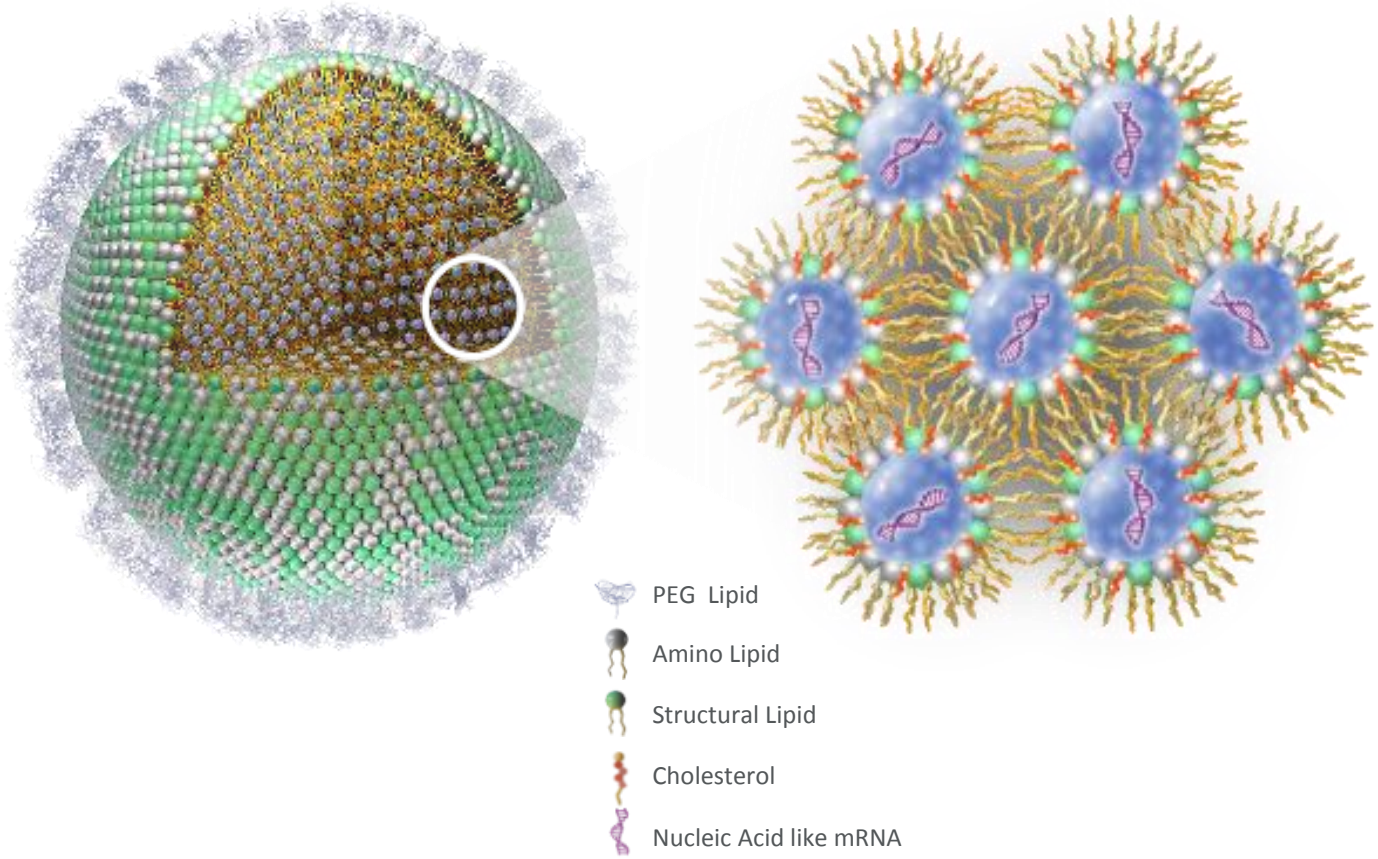
- Over a decade of pharmaceutical development experience for nucleic acid products
- Global regulatory experience (Europe, North America and Asia) resulting in approvals for clinical trials with multiple LNP-based products
- LNPs are a Platform Technology – “plug and play” Pharmaceutical Development for expedited development
- Manufacturing process is scaled
  - Ready for large scale GMP production and validation
  - Manufacturing process technology transferred to commercial scale CMOs
- Cost Efficiencies
  - High encapsulation manufacturing process and low cost of lipid excipients
  - High potency of LNP reduces amount of nucleic acid required
- Stable products – liquid or lyophilized

Arbutus LNP Enables mRNA Therapeutics

The ONLY clinic-ready LNP technology

Arbutus' clinical experience and LNP capabilities add value to mRNA partners through:

- Access to potent, clinic-ready LNP formulations designed to maximize activity and safety
- A robust, scalable GMP manufacturing process and regulatory expertise
- Rapid advancement of preclinical candidates into the clinic (~12 months to IND)
- Freedom to operate through access to dominant IP LNP portfolio



Q&A

Further questions, email: IR@arbutusbio.com