Acuitas Therapeutics

NON-CONFIDENTIAL PRESENTATION

ACUITAS
THERAPEUTICS

Vision

Acuitas is the premier LNP technology provider globally, enabling our partners to advance new therapeutics to address unmet clinical needs

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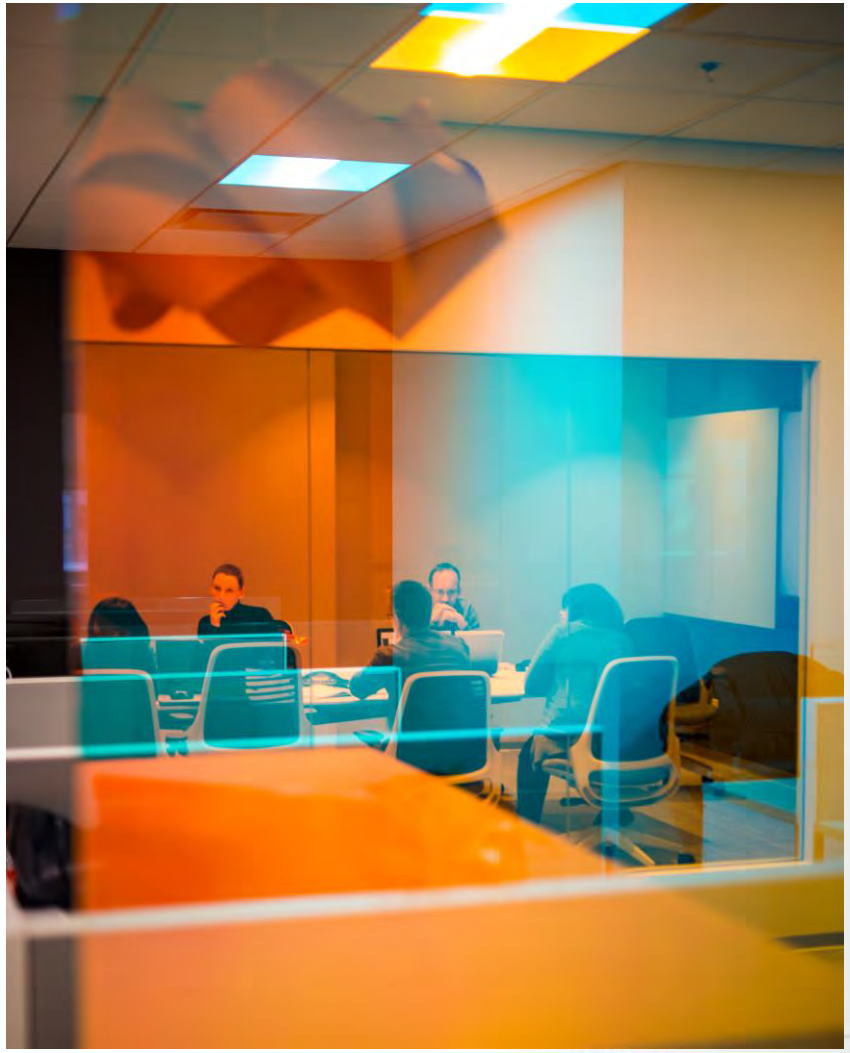
Mission

- To provide our partners with the best LNP delivery technology for nucleic acid therapeutics
- To support our partners to rapidly advance new therapeutics to address unmet medical needs
- To continually innovate to maintain and strengthen our LNP technological lead



Company Background

- Privately held biotechnology company
- Founded February 2009; based in Vancouver, British Columbia
- Highly experienced team developing lipid nanoparticle delivery systems
- Facilities for chemistry, formulation and preclinical studies

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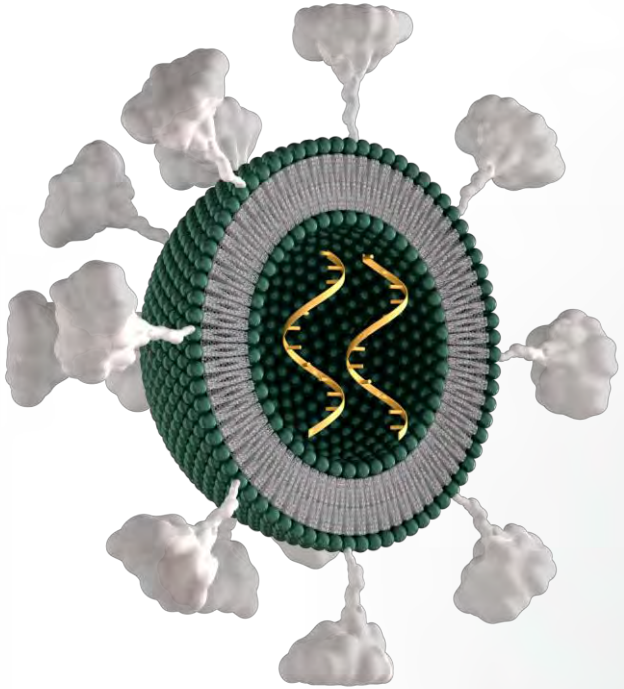
LNP Technology

LIPID NANOPARTICLES FORMULATION

- Clinically validated - Acuitas developed LNP formulation used in ONPATTRO® (Patisiran®)
  - First Approved RNAi product
  - Approved in US, Europe, Japan & elsewhere
- Improved LNP formulations exhibit substantially higher potency and therapeutic index



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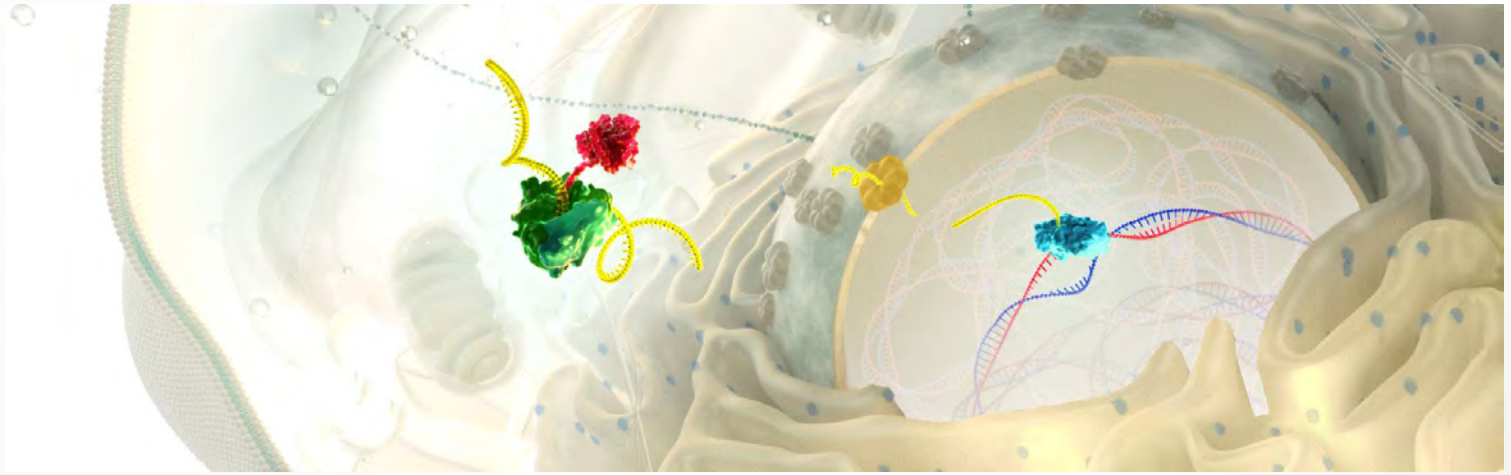
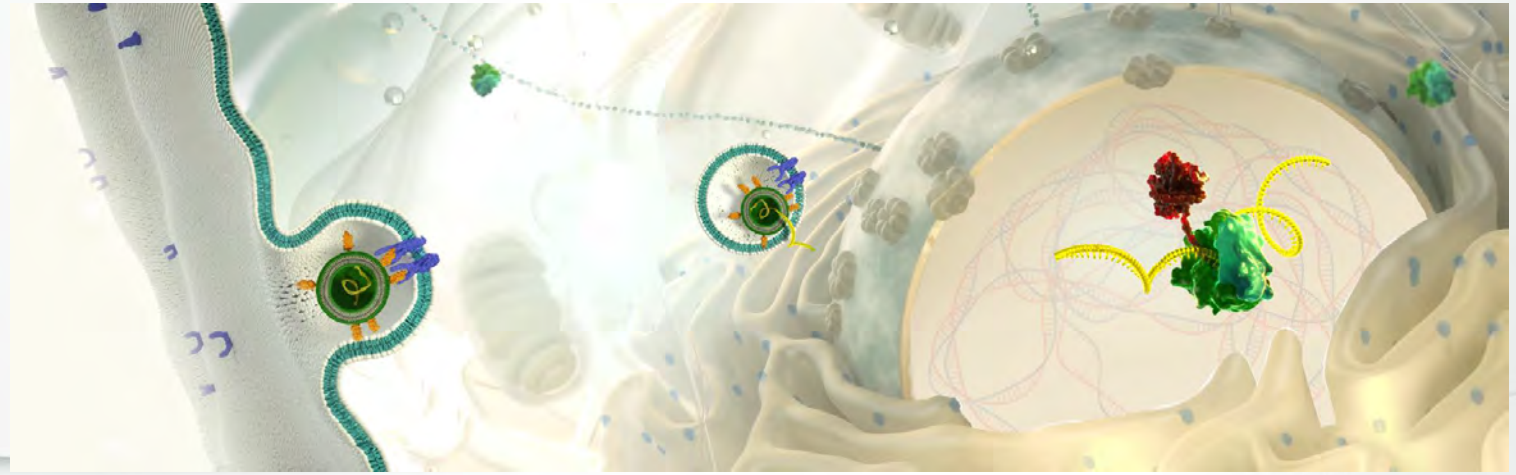
Therapeutic Opportunity: mRNA Therapy

- Delivery of novel proteins to treat disease

Normal cell: Genomic DNA transcribed to mRNA



mRNA Therapy: Synthetic mRNA delivered in LNP



Therapeutic Opportunities

- Vaccines
  - Intracellular expression of viral or bacterial proteins generating protective immune response
  - Expression of tumour antigens (personalized vaccines)
- Antibodies
  - Expression of prophylactic or therapeutic antibodies to treat current and emerging diseases
- Protein Replacement therapeutics
  - Expressing a human protein to address genetic disorders such as haemophilia & cystic fibrosis
- Genome Editing/Base Editing
  - Expressing a genome editing or base editing protein to modify human gene expression

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Acuitas Capabilities

CMC

- Chemistry
- LNP Formulation & Characterization

Preclinical

- Pharmacodynamic studies
- Safety studies
- PK/ADME

Clinical & Regulatory

- Clinical translation
- Regulatory support
- Clinical support

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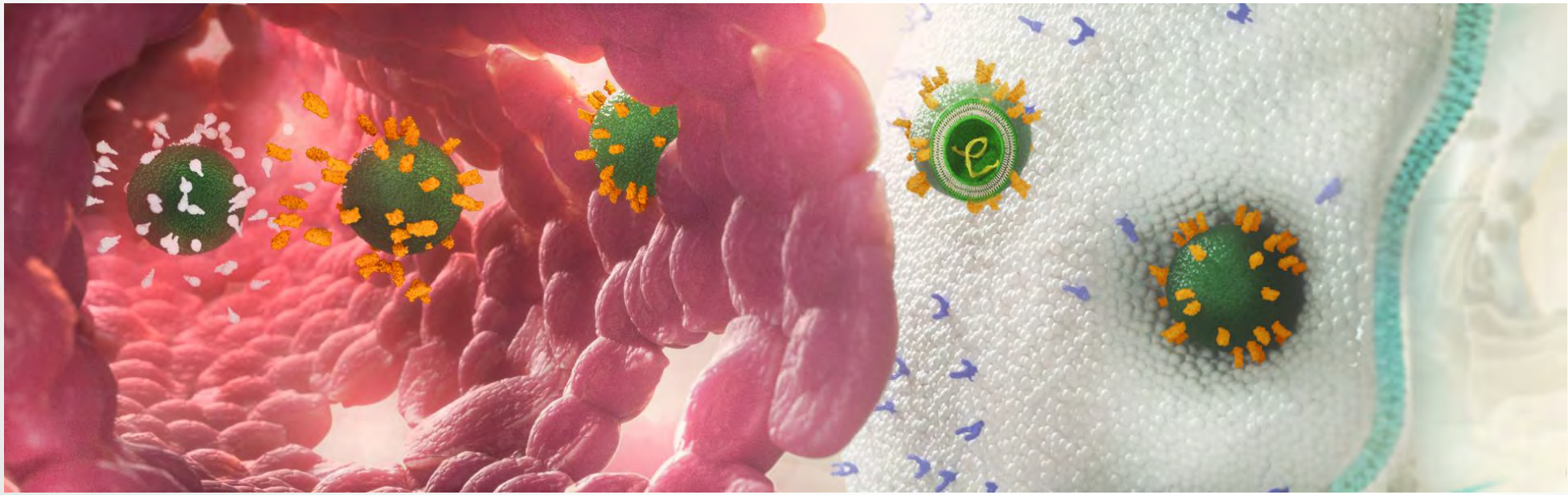
Acuitas LNP: Mechanism of Action

- Receptor-mediated uptake into hepatocytes
  - Loss of PEG-lipid from the LNP surface allows binding of ApoE
  - Extravasation from fenestrated capillaries allows direct access to interstitial space
  - Bound ApoE facilitates receptor binding and endocytosis



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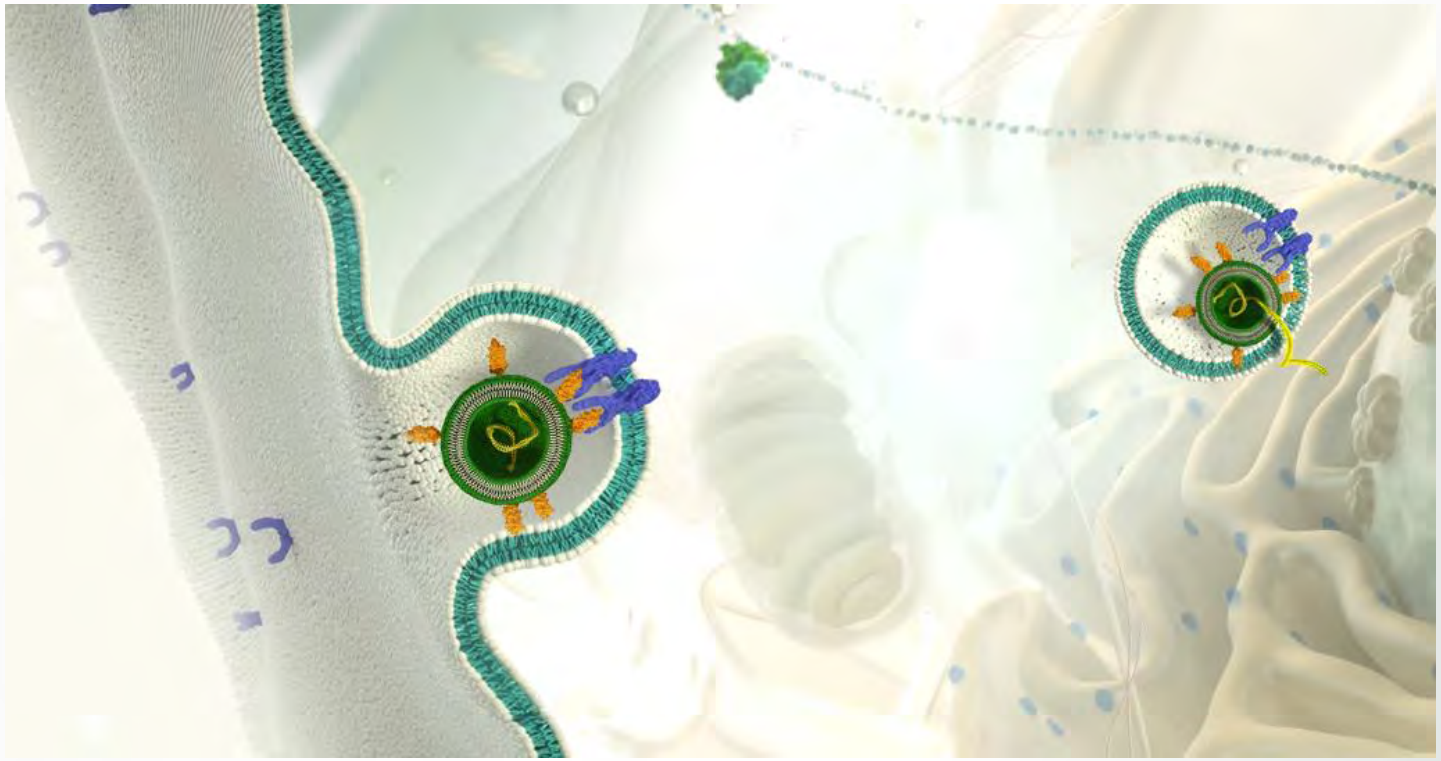
Acuitas LNP: Mechanism of Action

- Endosomal Release
  - Endosomal maturation results in drop in internal pH
  - LNP cationic lipid becomes positively charged resulting in release of nucleic acid payload to cytoplasm



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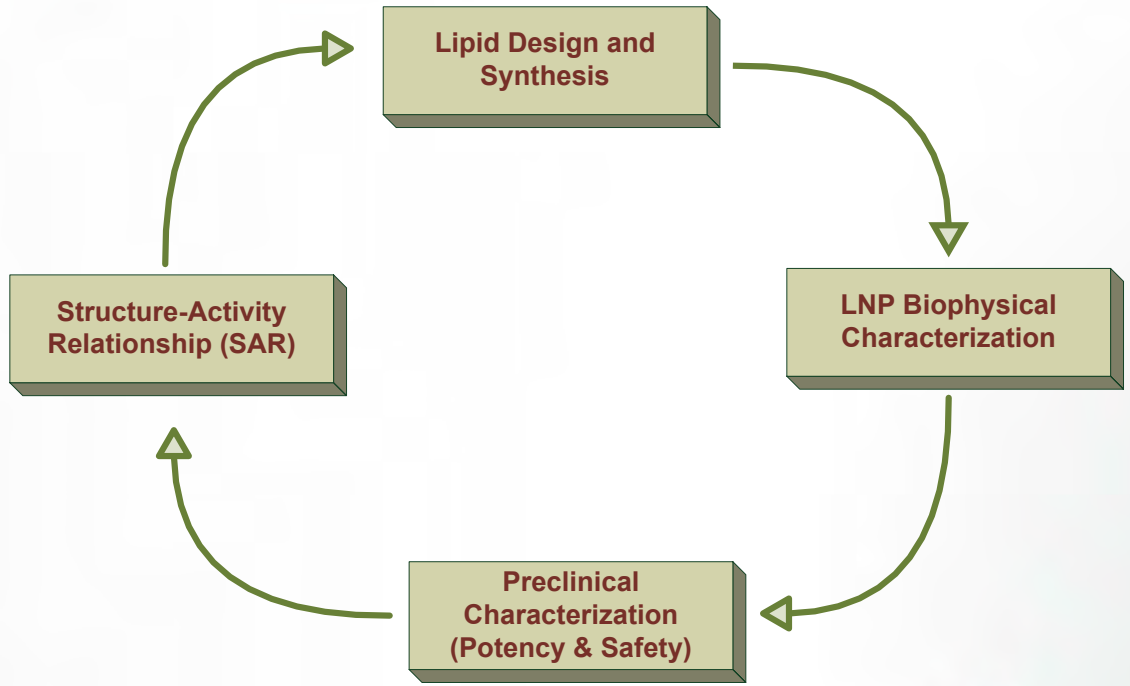
mRNA-LNP Technology Development: Objectives & Process

- Enhance potency and safety profile for LNP carriers
- Enable broad range of mRNA therapeutic applications
- Iterative approach to identify improved LNP compositions



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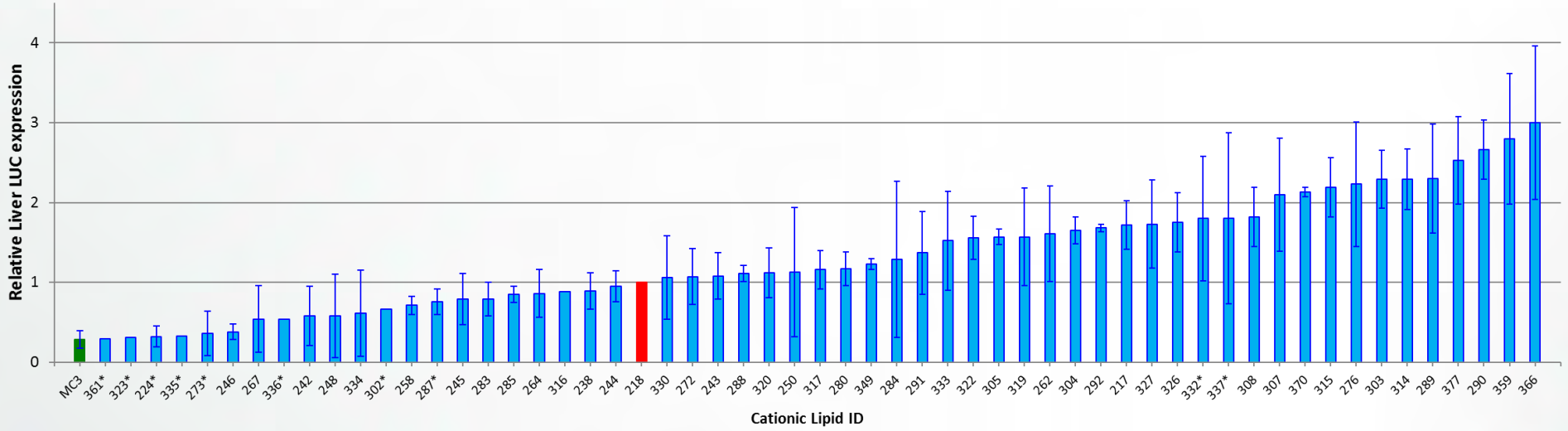
mRNA-LNP Technology: Potency Enhancement

- Screening program combined with key SAR relationship analysis results in substantial improvement in LNP potency.
- Relative activities of LNP with different cationic lipids



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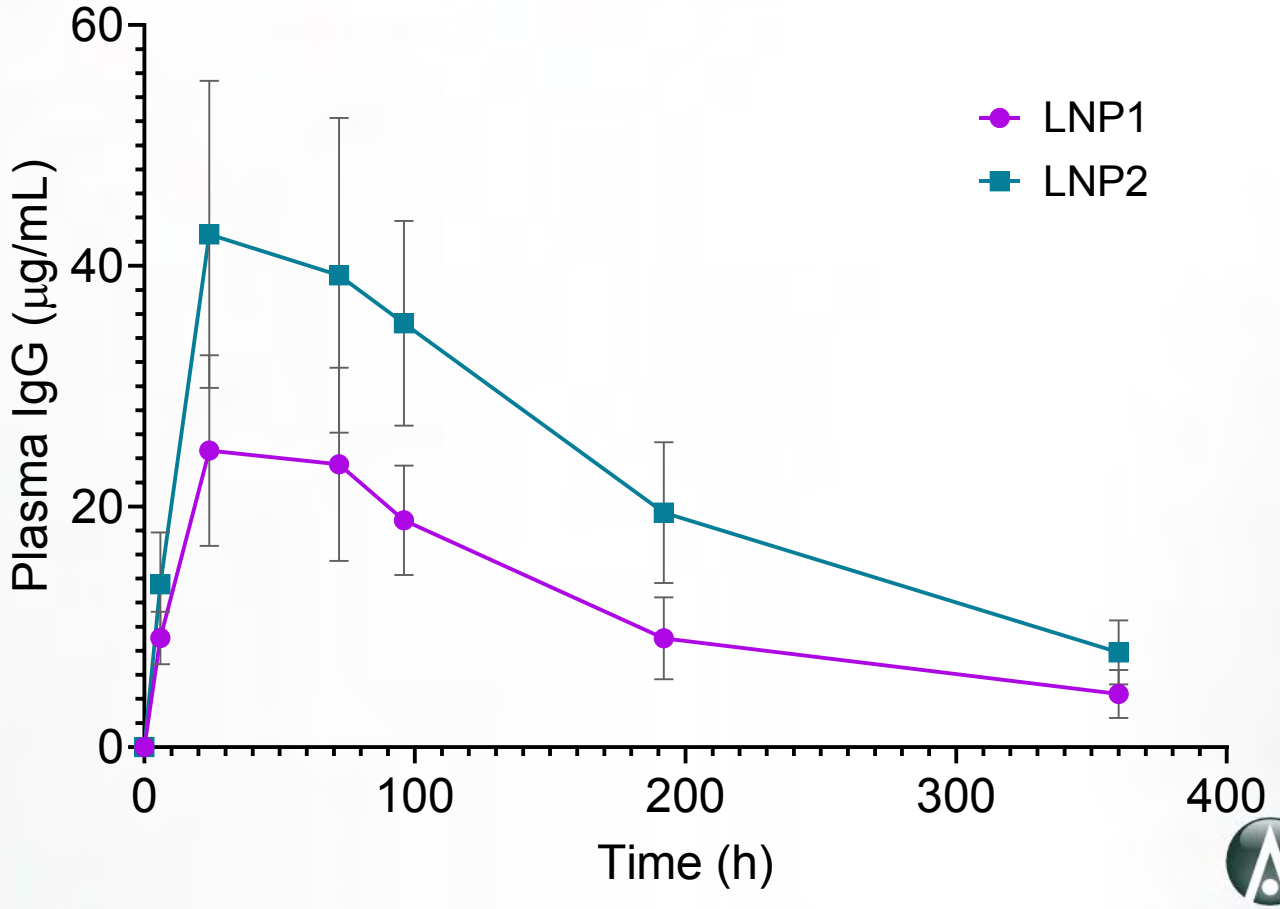
mRNA LNP Technology: NHP Potency Studies

- High level Antibody expression after iv administration of mRNA LNP
- mRNA LNP Design improvements can substantially improve pharmacodynamics (protein expression)



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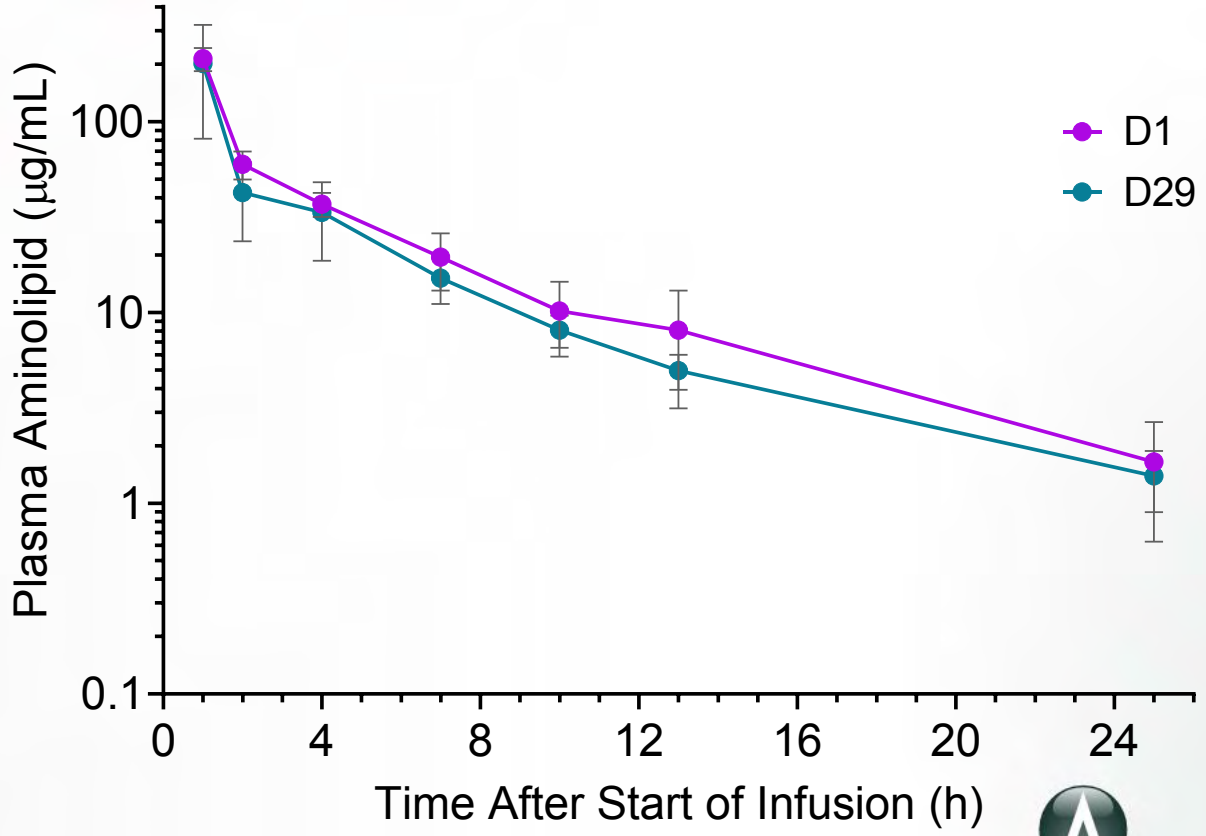
mRNA LNP Technology: NHP PK Studies

- LNP plasma profiles and exposure unchanged after repeated bi-weekly dosing



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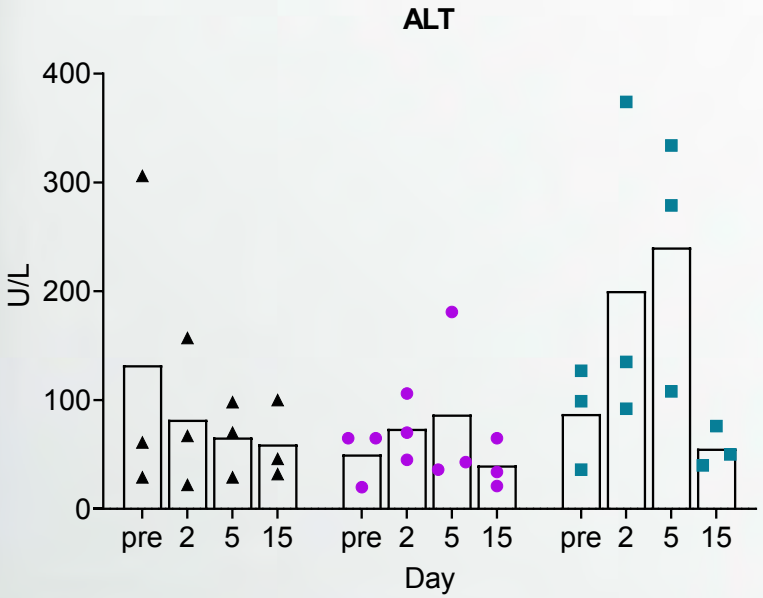
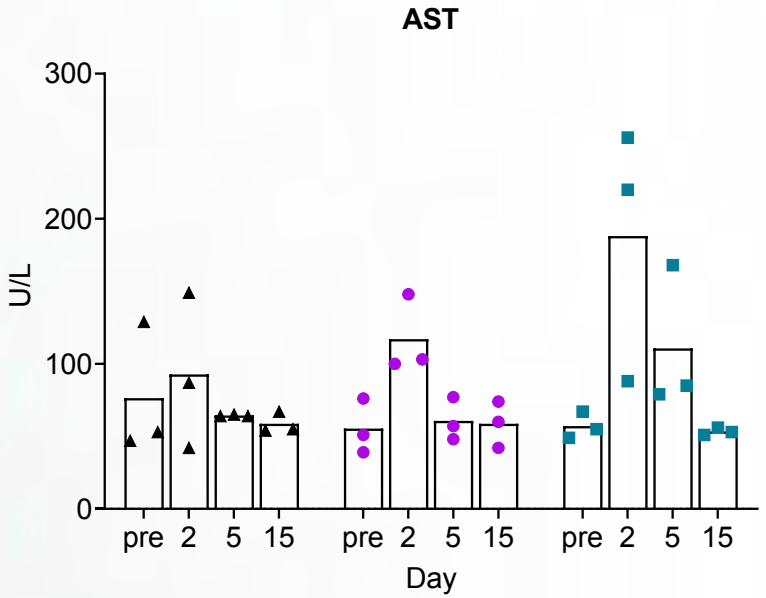
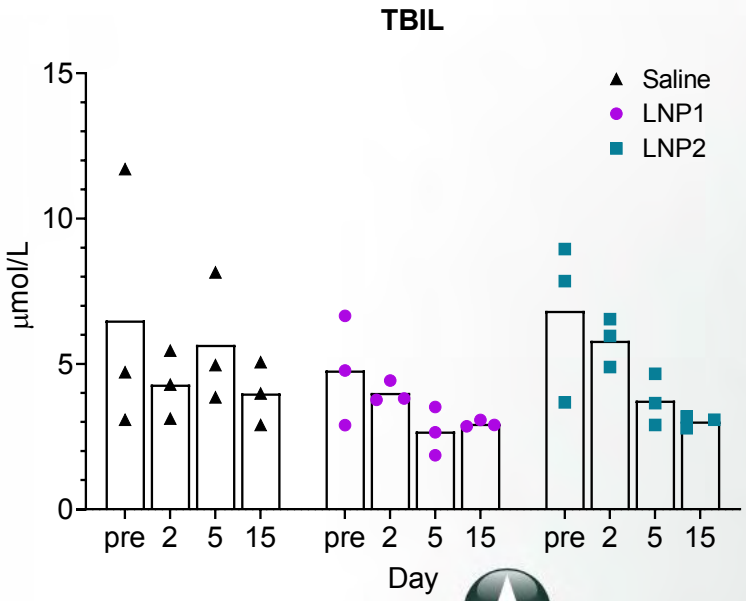
mRNA LNP Technology: NHP Safety Studies

- Transient increases in ALT/AST above control levels on Days 2 and 5
- No other mRNA LNP-related changes in clinical chemistry or hematology







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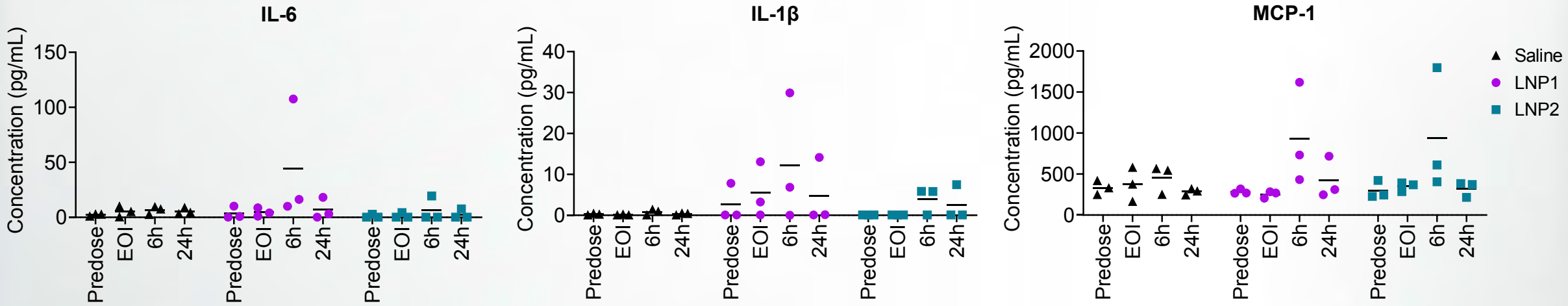
mRNA LNP Technology: NHP Safety Studies

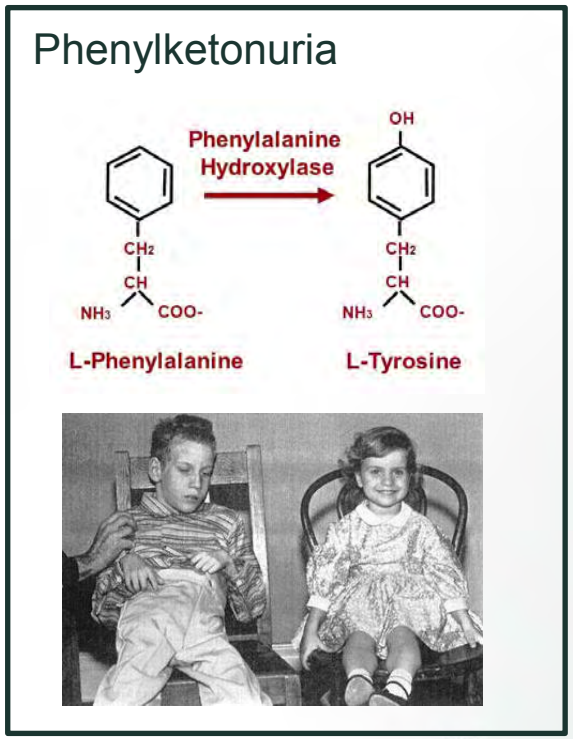
- Small, transient increases in some cytokines/chemokines at 6 hours post-infusion; return to baseline by 24 hours



mRNA LNP Therapeutics: Gene Editing to Address Genetic Disorder

Phenylketonuria – Hepatic *PAH* deficiency causes CNS damage

- *PAH* deficiency in hepatocytes leads to an increase in phenylalanine and a decrease in methionine and tyrosine
- In the brain this causes a deficiency of the neurotransmitter dopamine, reduced protein synthesis, and demyelination
- A mouse model for Phenylketonuria (PAH^{enu2}) with a T>C mutation exists



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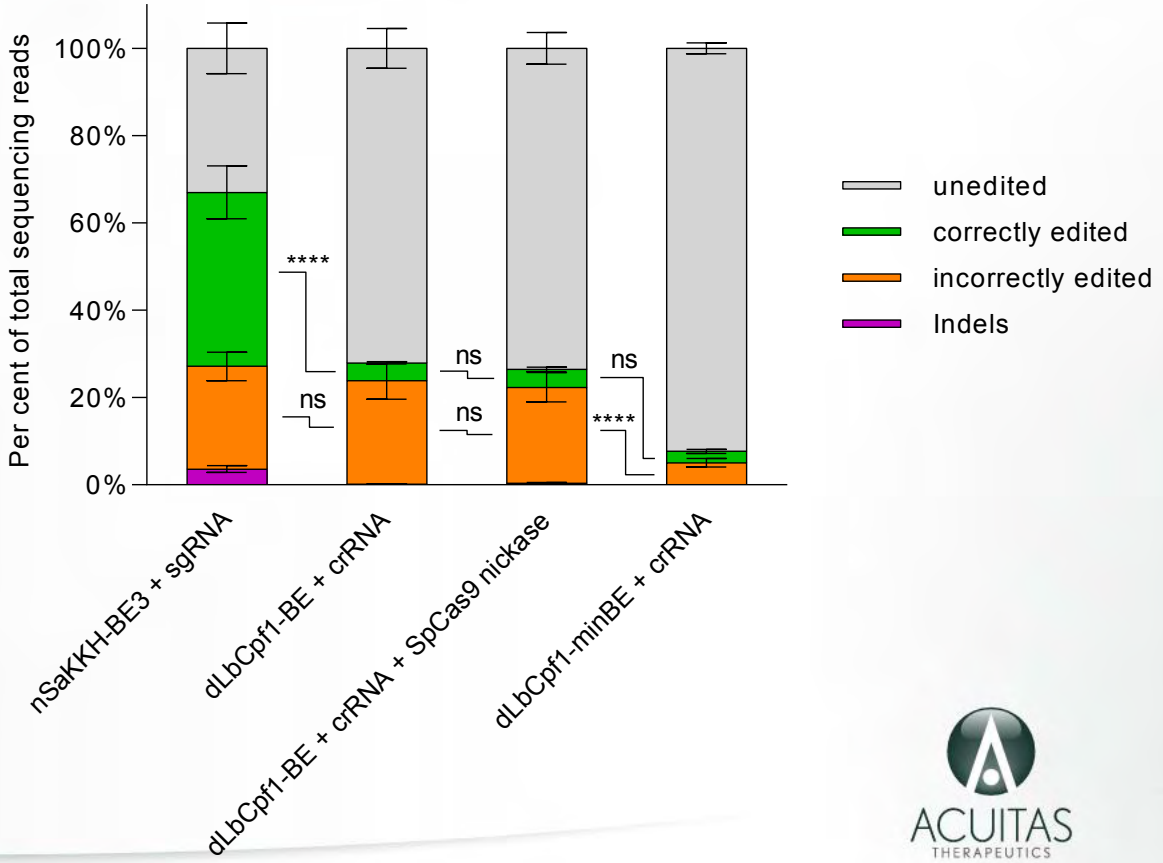
mRNA LNP Therapeutics: Gene Editing to Treat Genetic Disease

Establishment of a base editor for the *PAH*^{enu2} locus

- The APOBEC *Sa*Cas9-KHH base editor efficiently corrects the *PAH*^{enu2} locus



Courtesy of Schwank laboratory

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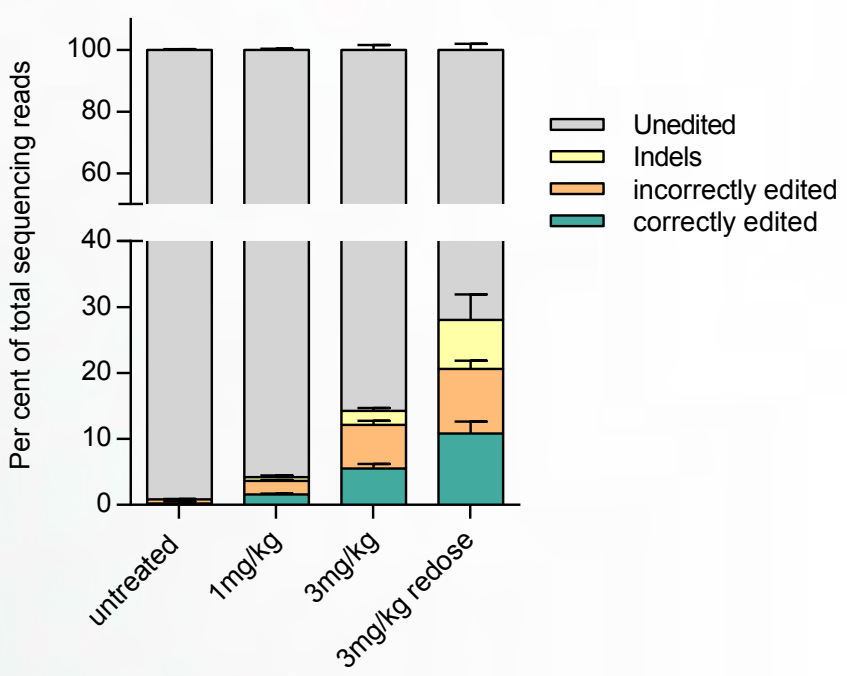
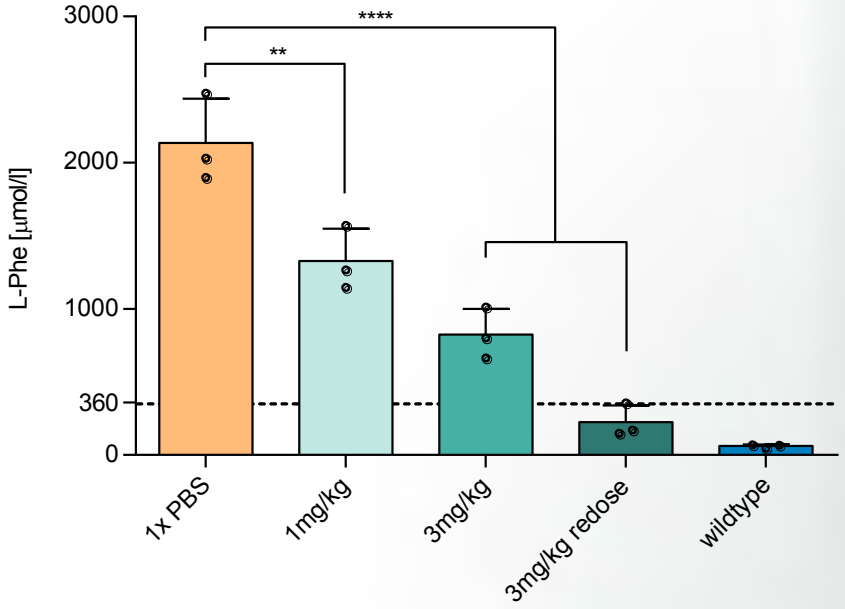
mRNA LNP Therapeutics: Gene Editing to Treat Genetic Disease

In vivo correction of *Pah*^{enu2} mouse

- IV Administered mRNA-LNP delivering base editor corrects gene and restores function





Courtesy of Schwank laboratory

mRNA LNP Therapeutics: COVID Vaccines

- SARS-CoV-2 emerged as global pandemic in early 2020
- High transmissibility and high rate of morbidity and mortality; >9 million confirmed infections as of July 2020
- Evaluated saRNA-LNP vaccine expressing SARS-CoV-2 spike protein in mouse model
  - Full-length, pre-fusion stabilized spike protein
  - Two IM injection (of 0.01-10 µg saRNA)
  - Antibody (total IgG and neutralizing) titres
  - Cellular responses

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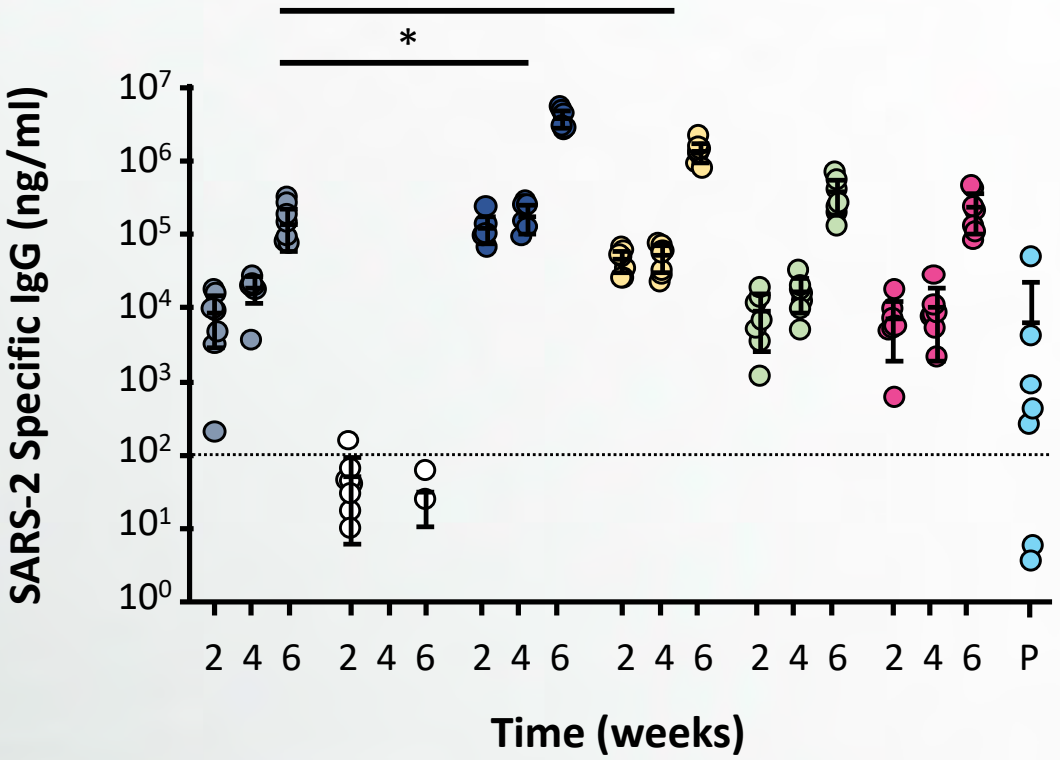
mRNA LNP Therapeutics: COVID Vaccine

SARS-CoV2- specific Antibody (IgG) Responses



- Electroporated +ve pDNA Control
- RABV Control
- 10 μg mRNA LNP
- 1 μg mRNA LNP
- 0.1 μg mRNA LNP
- 0.01 μg mRNA LNP
- Recovered COVID-19 patients

- i.m. immunization with saRNA-LNP induces high plasma levels of virus-specific IgG

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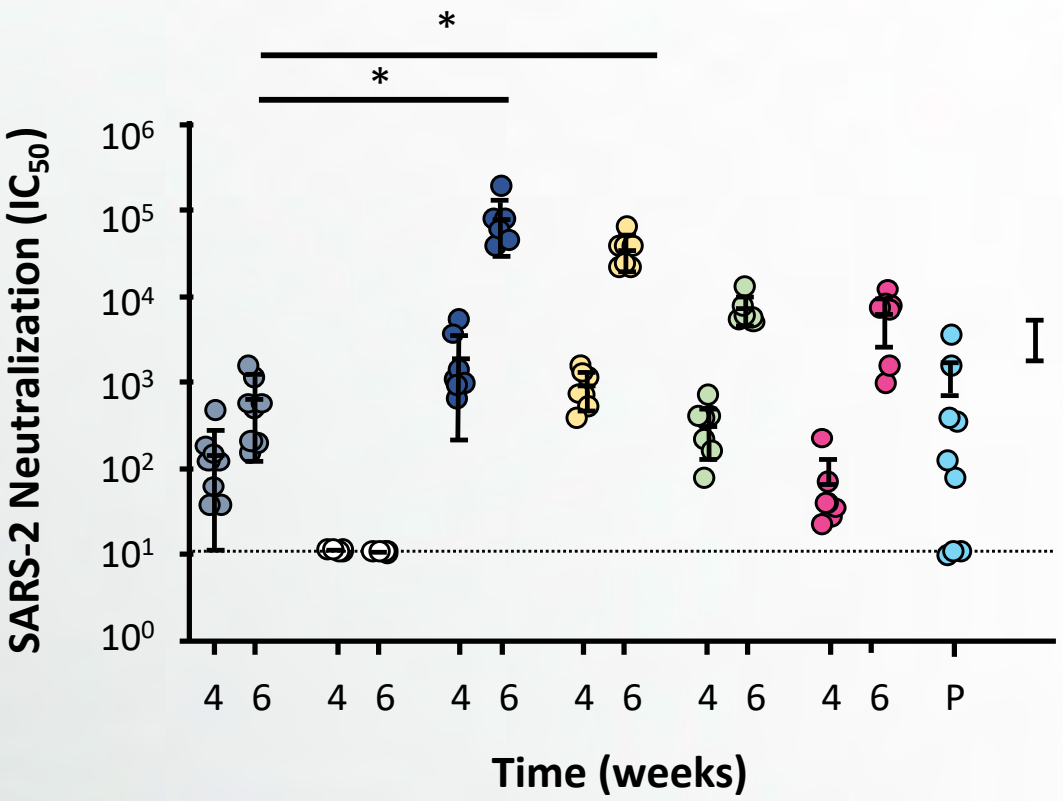
mRNA LNP Therapeutics: COVID Vaccine

SARS-CoV2- Neutralizing Ab Responses



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- 10 μg mRNA LNP
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- 0.01 μg mRNA LNP
- Recovered COVID-19 patients

- i.m. immunization with saRNA-LNP induces antibodies that mediate highly efficient viral neutralization in a linear dose-dependent manner

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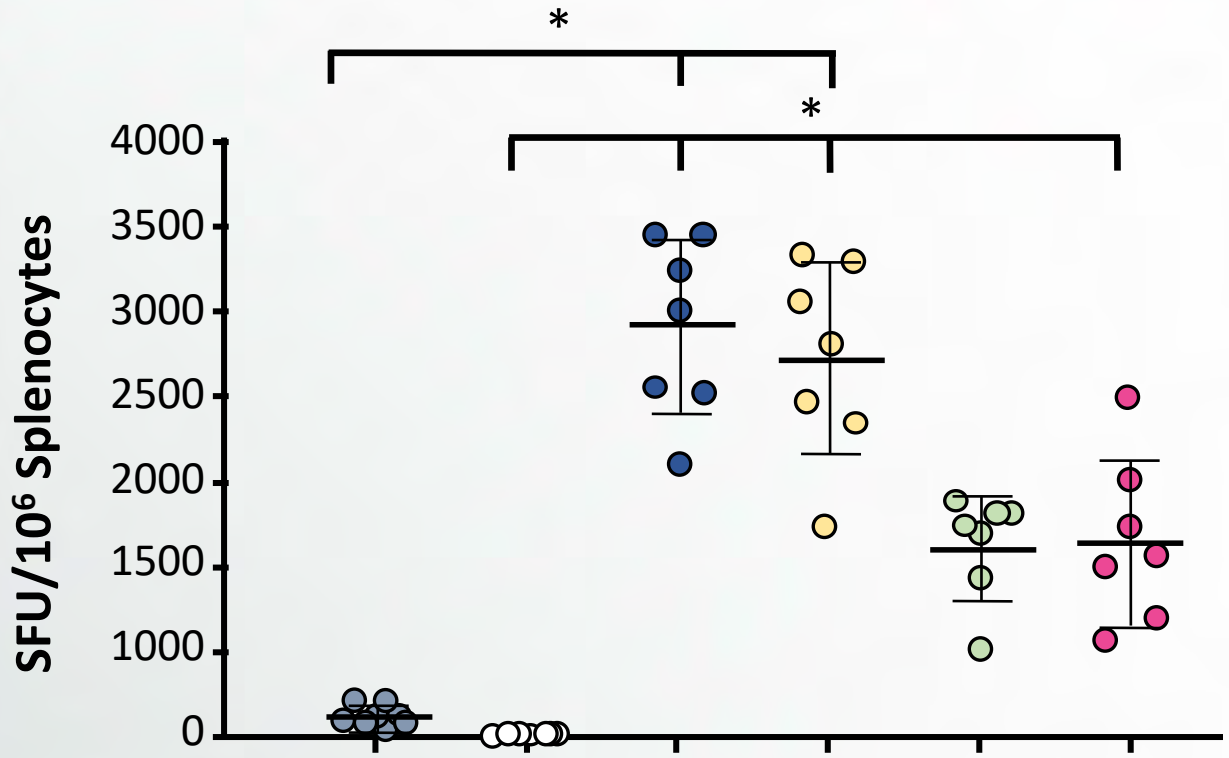
mRNA LNP Therapeutics: COVID Vaccine

SARS-CoV2- Cellular Responses



- Electroporated +ve pDNA Control
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- 10 μg mRNA LNP
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- 0.1 μg mRNA LNP
- 0.01 μg mRNA LNP

- i.m. immunization with saRNA-LNP induces robust Ag-specific, Th1-biased cellular responses

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What makes Acuitas the Leader?

- Highest potency LNP carriers for mRNA therapeutics
- Broad IP portfolio providing commercial rights for mRNA-LNP therapeutics
- Broad partnership experience in mRNA therapeutics field
  - Multiple partnered products in clinical development
- Strong academic collaborations with KOLs
  - Expanding clinical opportunities for mRNA therapeutics

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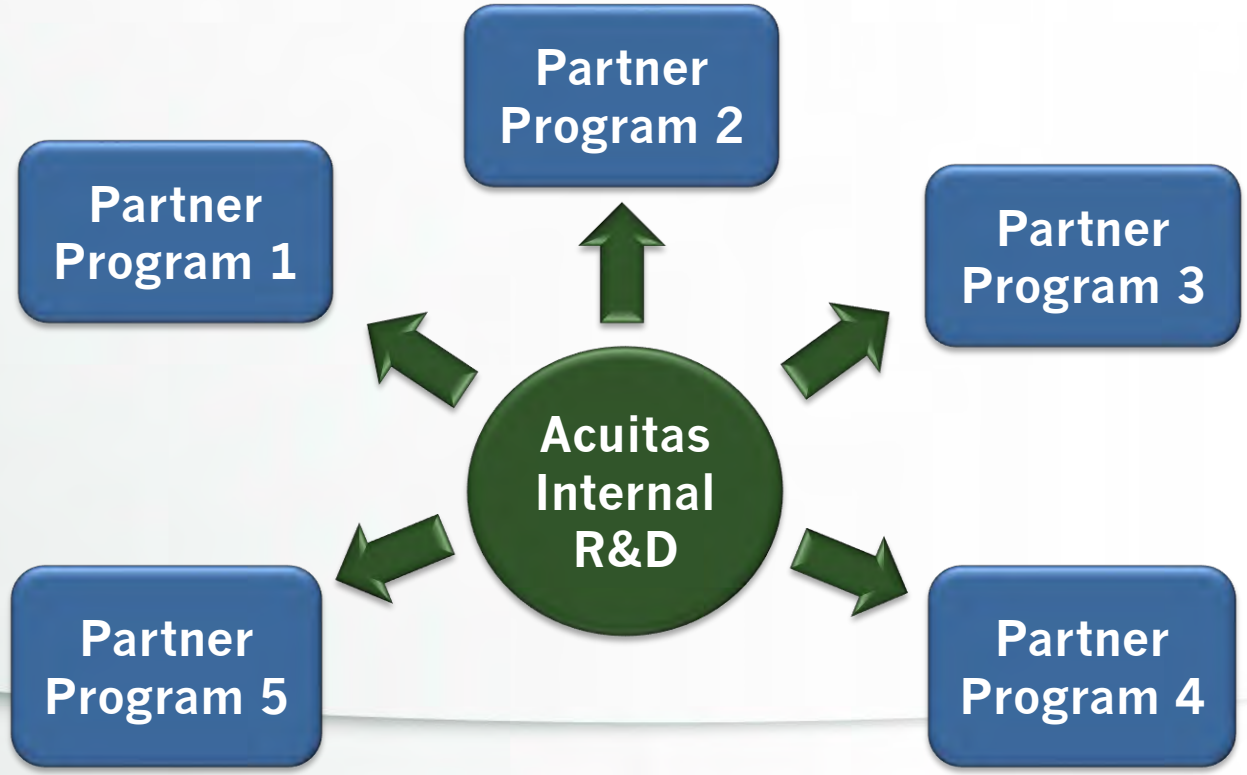
Acuitas Business Model

- Partner with multiple pharmaceutical/biotechnology companies to advance mRNA-LNP therapeutics
- Maintain leadership position in LNP Technology while supporting partner development programs



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