Acuitas Therapeutics

NON-CONFIDENTIAL PRESENTATION

ACUITAS
THERAPEUTICS

Mission

- To provide our partners with the best delivery technology for mRNA therapeutics
- To continually innovate to maintain and strengthen our technological lead
- To support our partners in accelerating advancement of therapeutics to patients thereby addressing an unmet clinical need

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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 with access to additional resources at the University of British Columbia (UBC)

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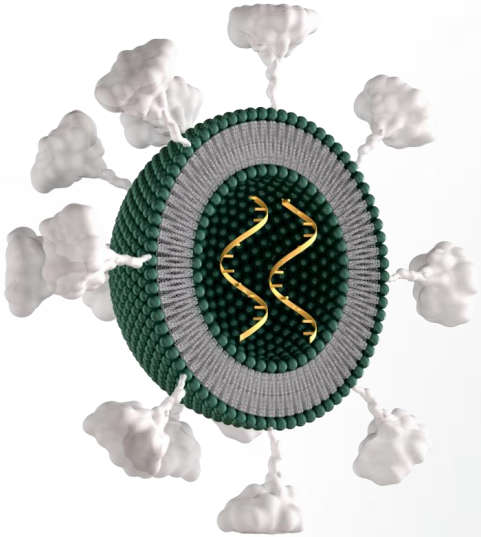
Technology Focus

- Systemic lipid nanoparticles (LNP) for intracellular delivery of molecular therapeutics – primarily nucleic acids
- Pharmaceutical applications:
  - Protein expression therapeutics (mRNA or plasmid delivery)



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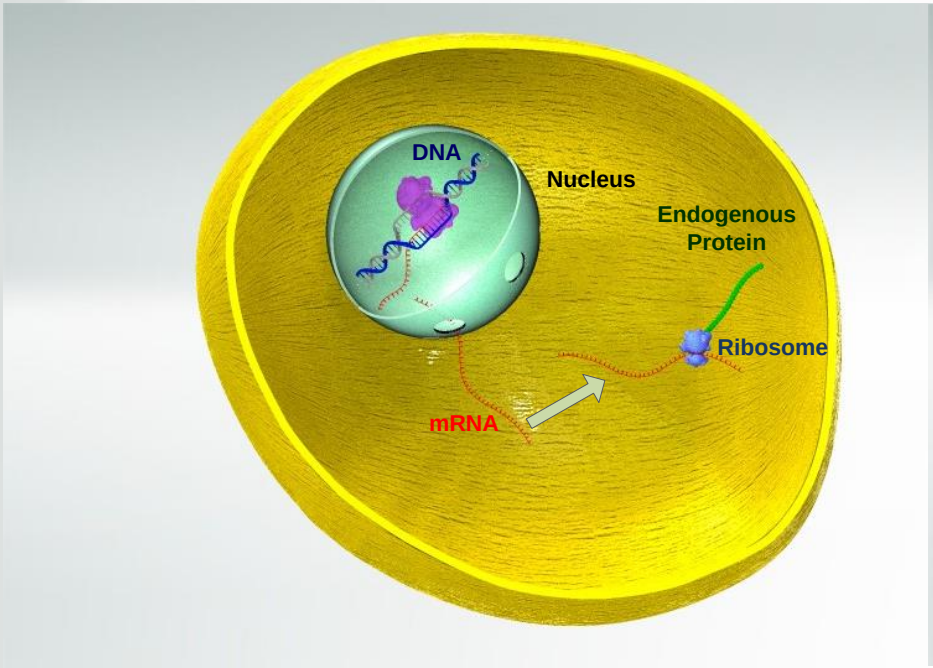
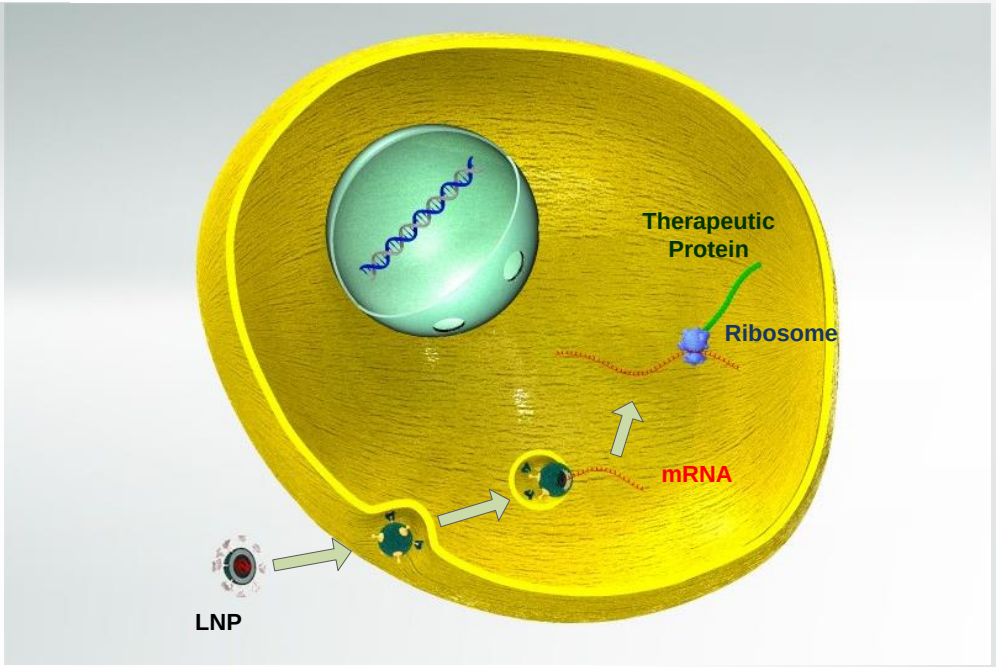
Therapeutic Opportunity: mRNA Therapy

- Delivery of novel proteins to treat disease



Normal cell: Protein coded by DNA



mRNA Therapy: Protein coded by synthetic mRNA

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Expertise and Capabilities

- Synthetic chemistry
  - Design and synthesis of novel cationic lipids and PEG-lipids
    - Over 250 novel compounds designed & synthesized in past 3 Years
    - Extensive SAR understanding to guide lipid design with iterative approach to refine as data set is expanded
- Product formulation, scale-up and cGMP manufacture (in partnership with Transferra Nanosciences)
- Analytical and biophysical characterization
- Preclinical characterization

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Expertise and Capabilities: Preclinical

- Pharmacodynamic studies for protein replacement therapeutics
  - Reporter protein expression in vivo by fluorescent/luminescent live imaging (luciferase, GFP, etc)
  - Therapeutic protein expression in vivo (Factor IX, EPO, etc.)
- Safety/Tolerability studies
  - CBC/Clin Chem/Histopathology
  - Immune characterization (cytokine/chemokine induction)
- PK/ADME
  - Nucleic acid therapeutic and LNP components

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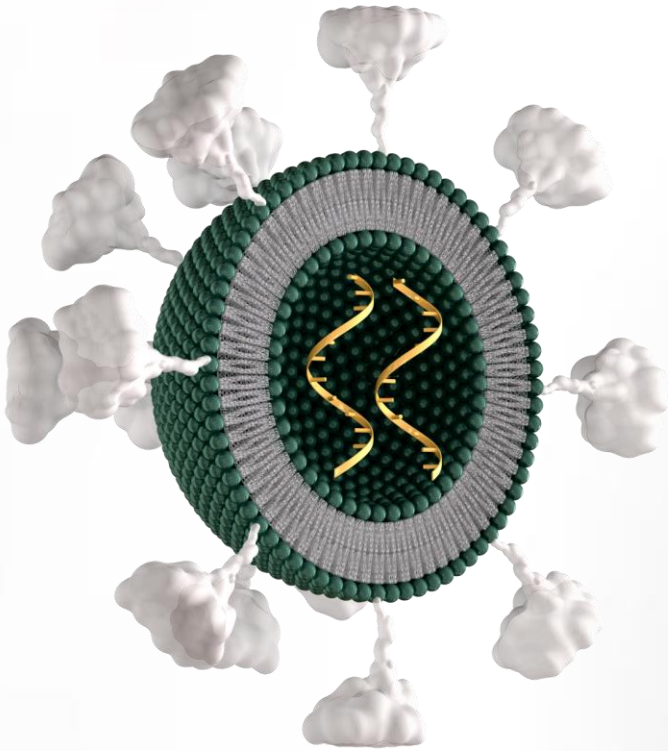
LNP Technology

LIPID NANOPARTICLES FORMULATION

- Multi-component carrier
- Small, uniform sized particles (~80 nm)
- Low surface charge in blood compartment



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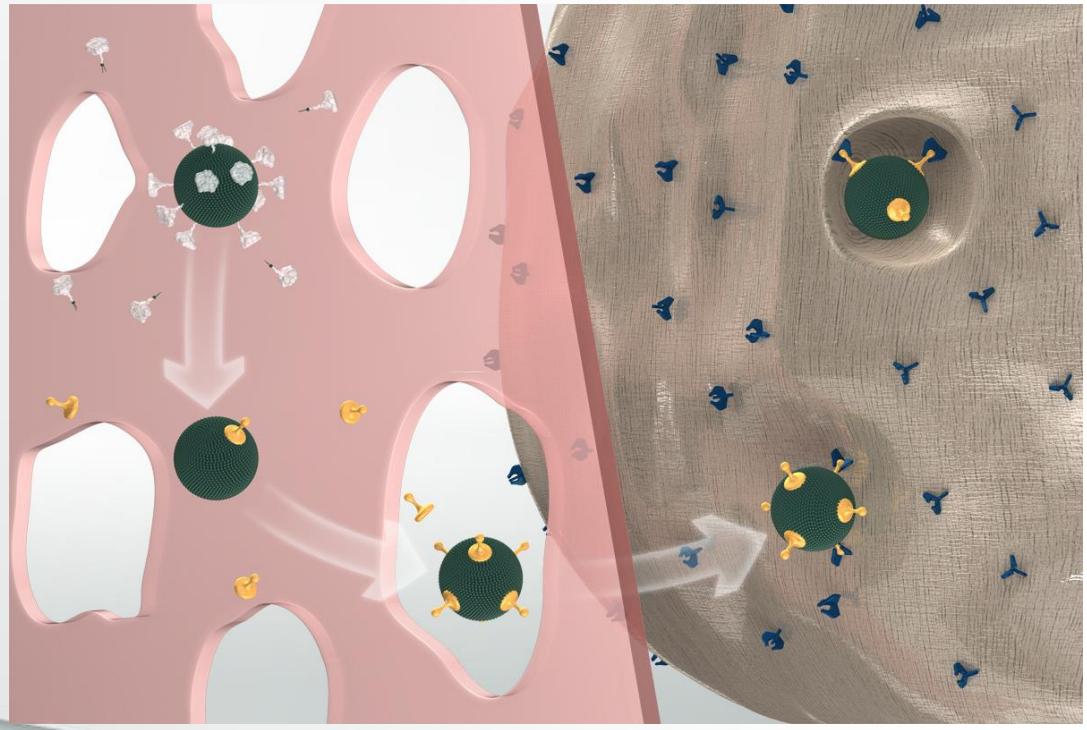
Acuitas LNP – Mechanism of Action I

- Receptor-mediated uptake in hepatocytes
  - Loss of PEG-lipid from the LNP surface allows binding of ApoE
  - Bound ApoE facilitates receptor binding and endocytosis



ApoE

PEG-Lipid

LNP with bound ApoE

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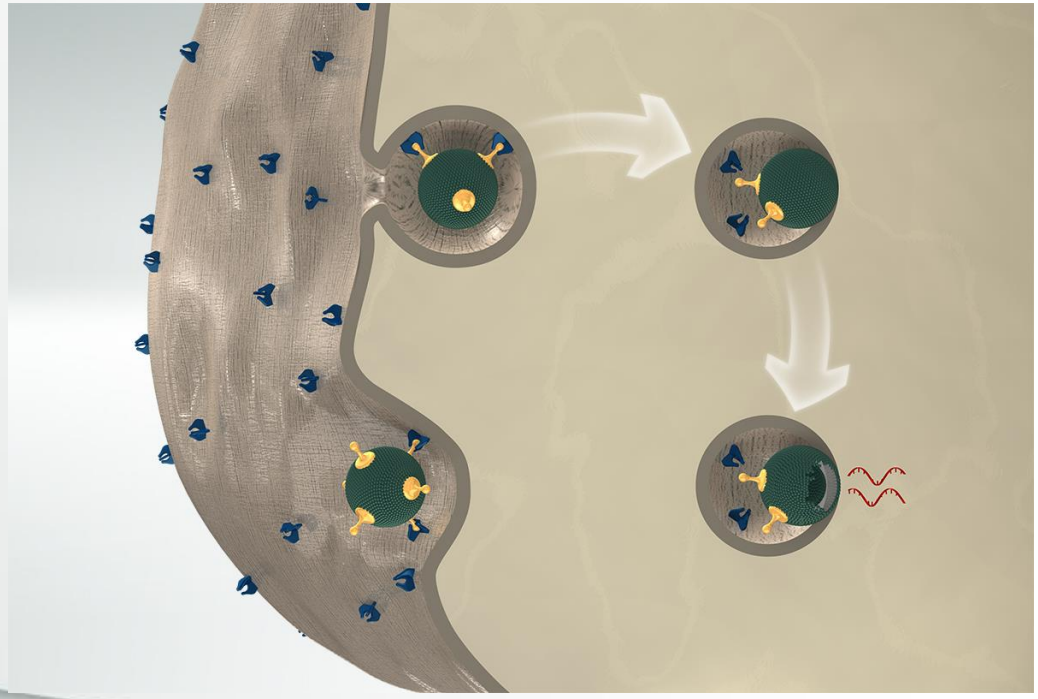
Acuitas LNP – Mechanism of Action II

- 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



Nucleic acid payload

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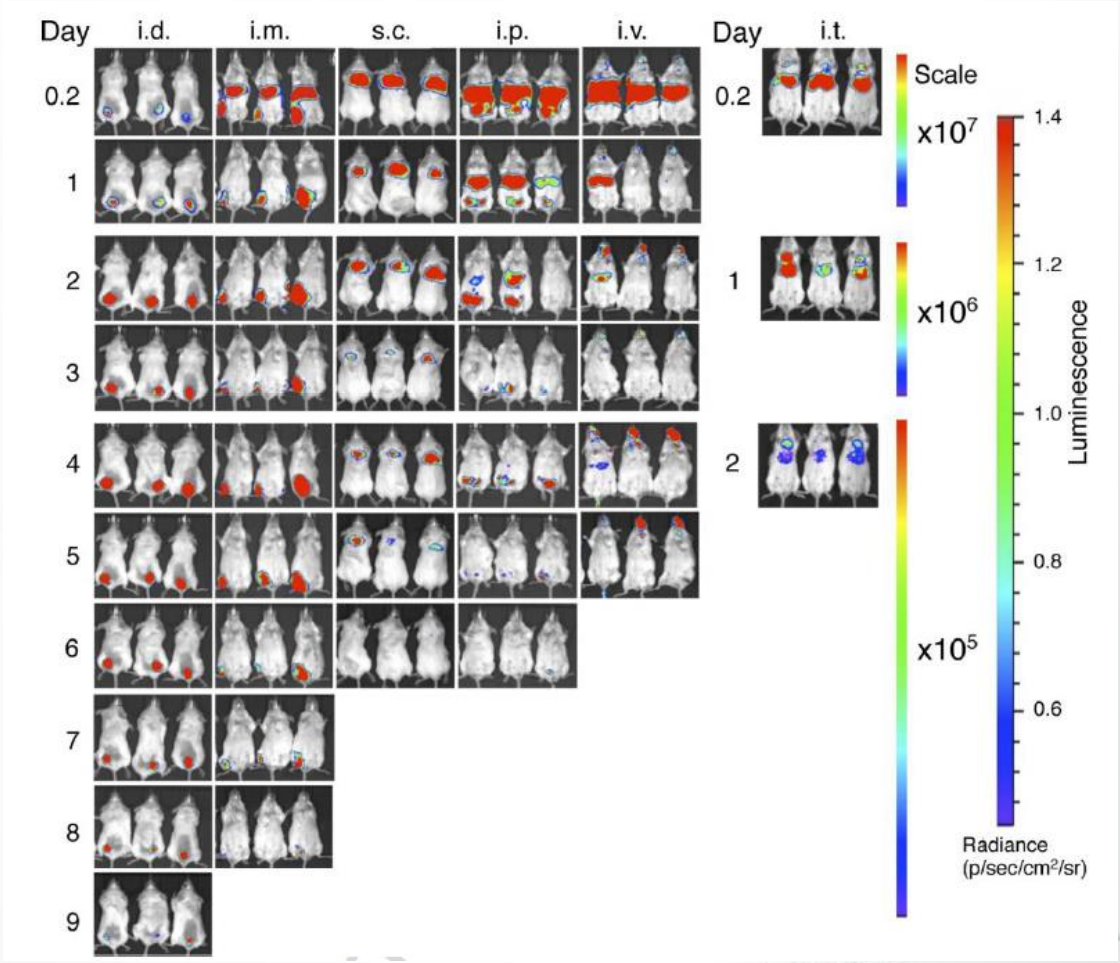
Protein Expression: Influence of site of mRNA-LNP administration

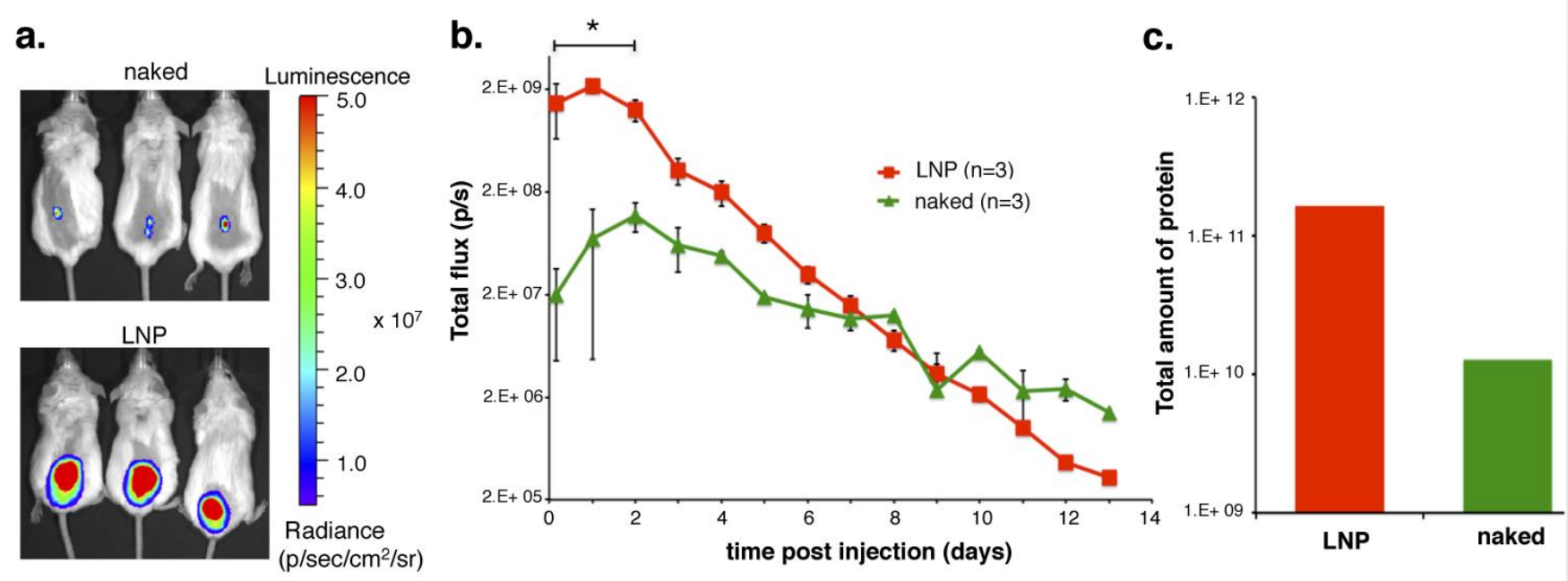
- IVIS images of BALB/c mice following administration of luciferase mRNA-LNP (0.2 mg/kg) by the indicated route
- Is mRNA-LNP uptake in non-liver cells receptor-mediated?



Courtesy Dr. Weissman Laboratory

Local Protein Expression: Naked mRNA vs mRNA-LNP

- Intradermal administration of naked mRNA or mRNA-LNP.



Courtesy Dr. Weissman Laboratory

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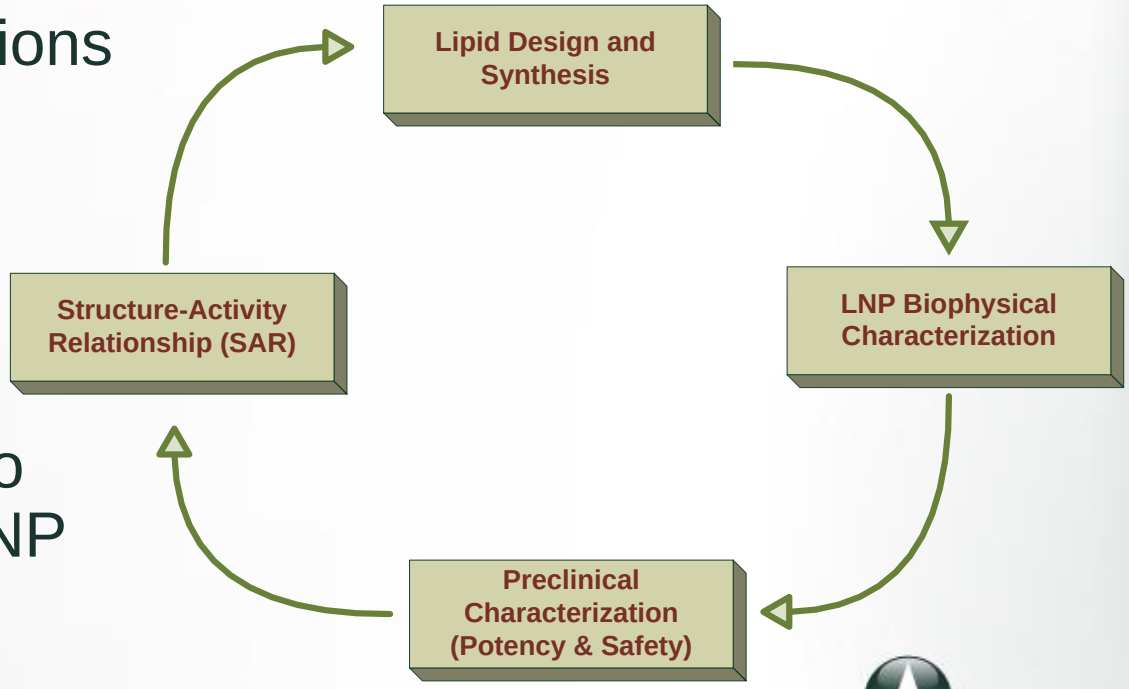
mRNA-LNP Technology Development: Objectives & Process

- 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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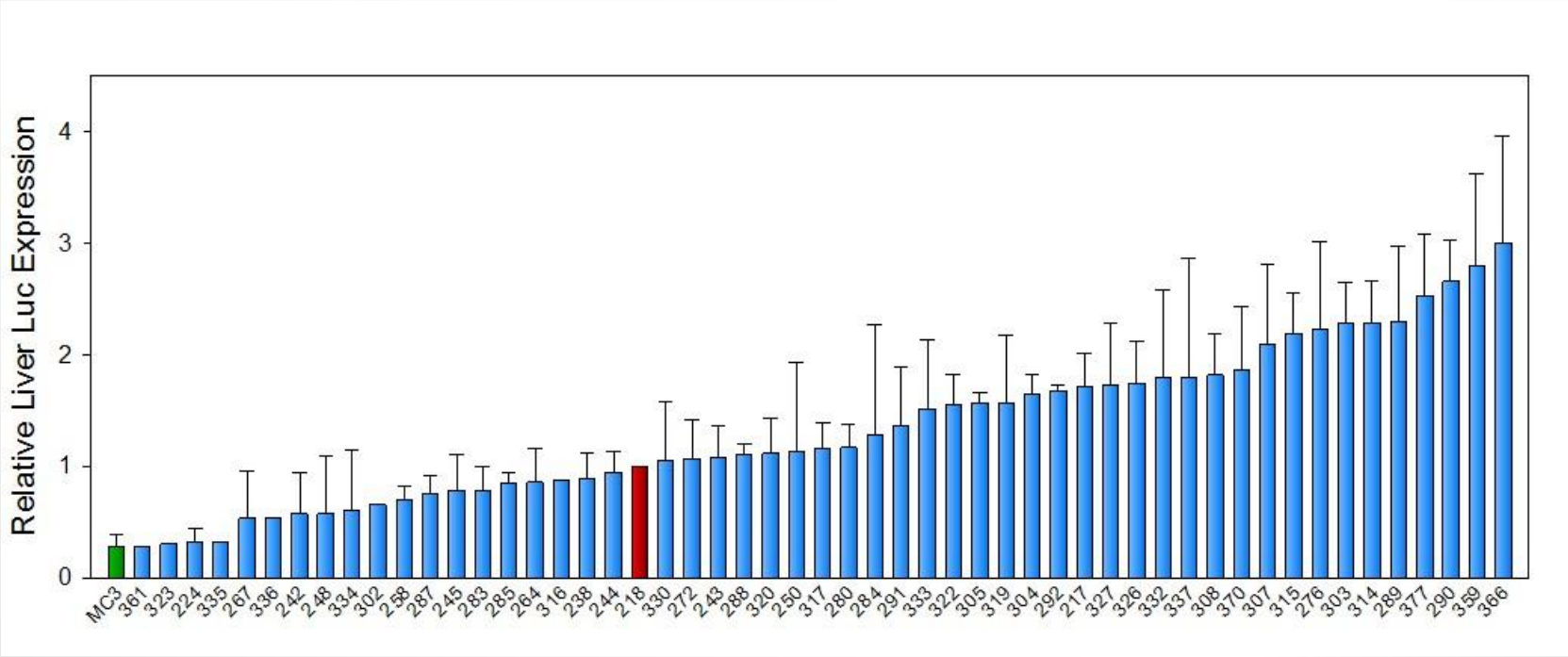
mRNA-LNP Technology : Potency Enhancement

- Screening program combined with key SAR relationship analysis results in substantial improvement in LNP potency.



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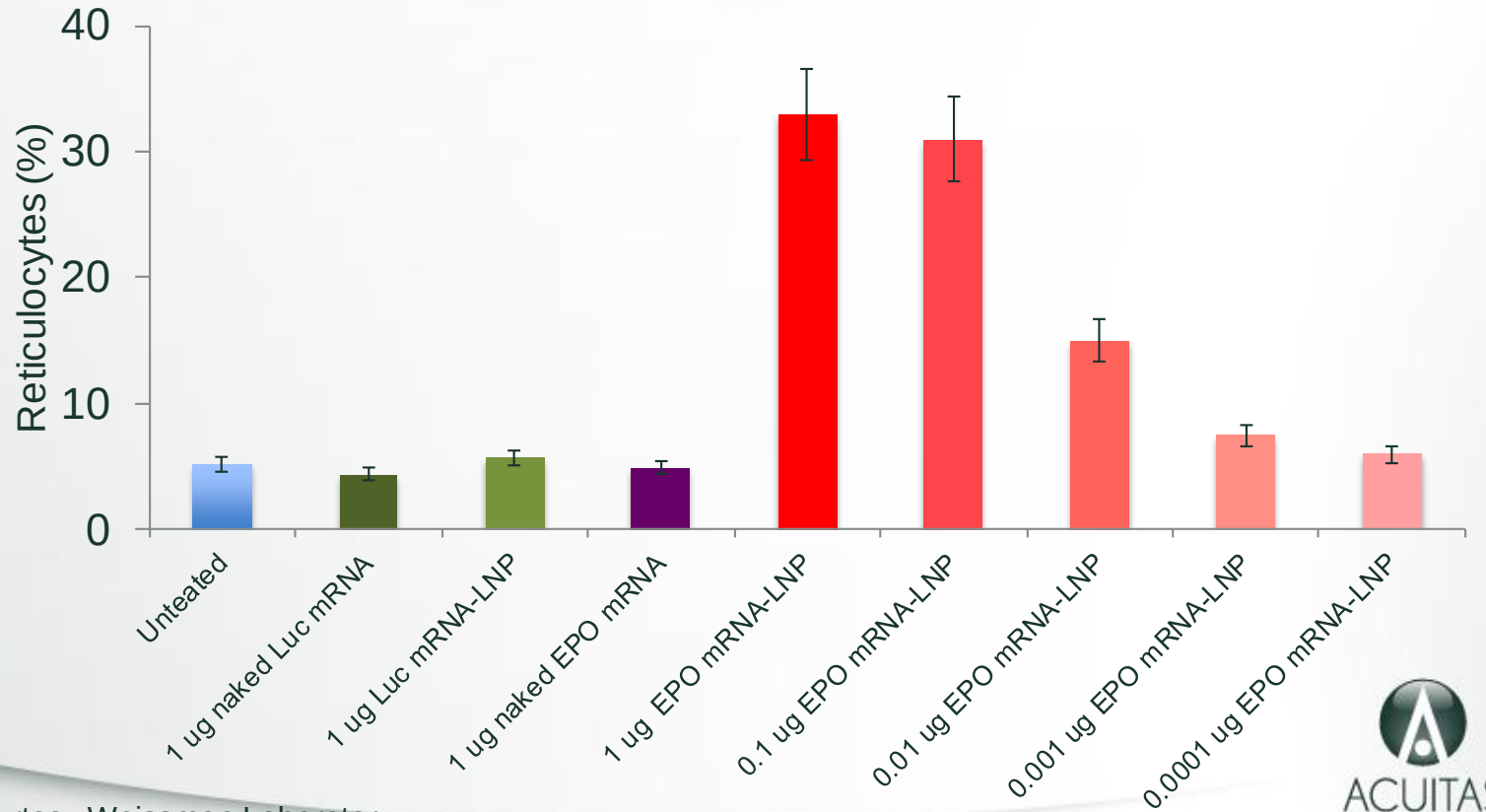
mRNA-LNP Therapeutics: Erythropoeitin expression

- Single injection (i.v.) of EPO mRNA-LNP increases reticulocyte counts 4 days later in a dose dependent manner



mRNA-LNP Therapeutics: Influenza A vaccine

- Mouse adapted PR8 hemagglutinin was codon-optimized and cloned into an mRNA production vector. 1-Me-pseudouridine modified mRNA was made, HPLC-purified, and administered as the naked mRNA or in LNP.
- Naïve mice were immunized once with 10 or 30 µg of mRNA-LNPs or naked mRNA intradermally. Mice were bled and analyzed over time.

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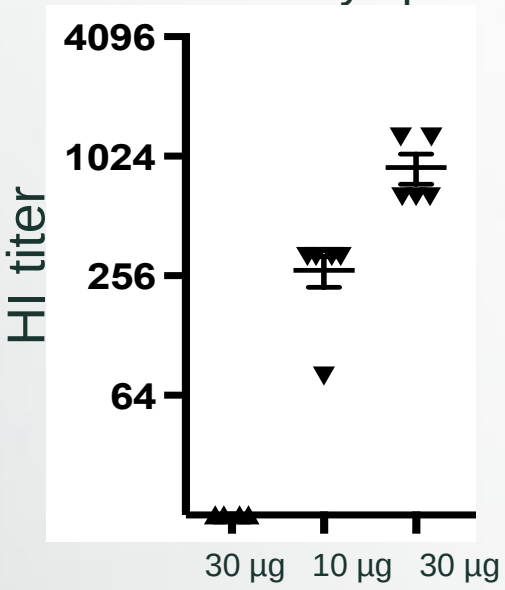
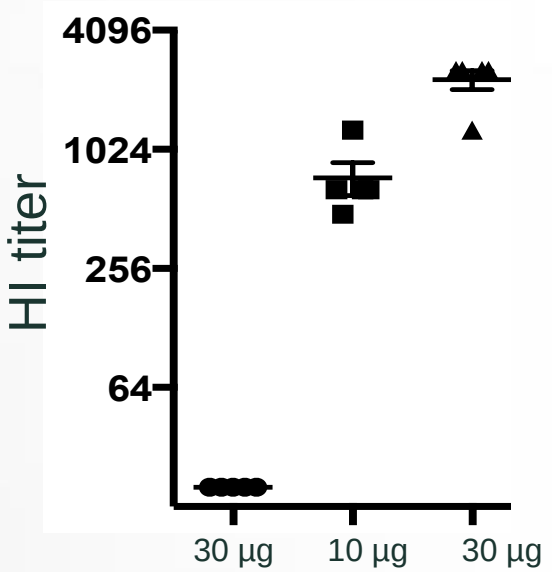
mRNA-LNP Therapeutics: Influenza A Vaccine

- PR8 mRNA-LNP vaccination results in higher levels of neutralizing antibodies compared to acute PR8 infection

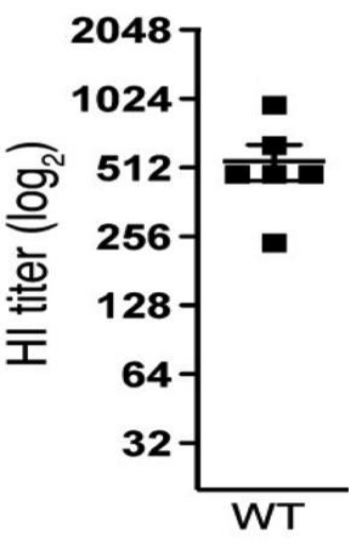
14 days p.i.



28 days p.i.



Acute PR8 infection



Wolf, A.I., et. al. J Clin Invest. 2011 121:3954-3964

Courtesy Dr. Weissman Laboratory

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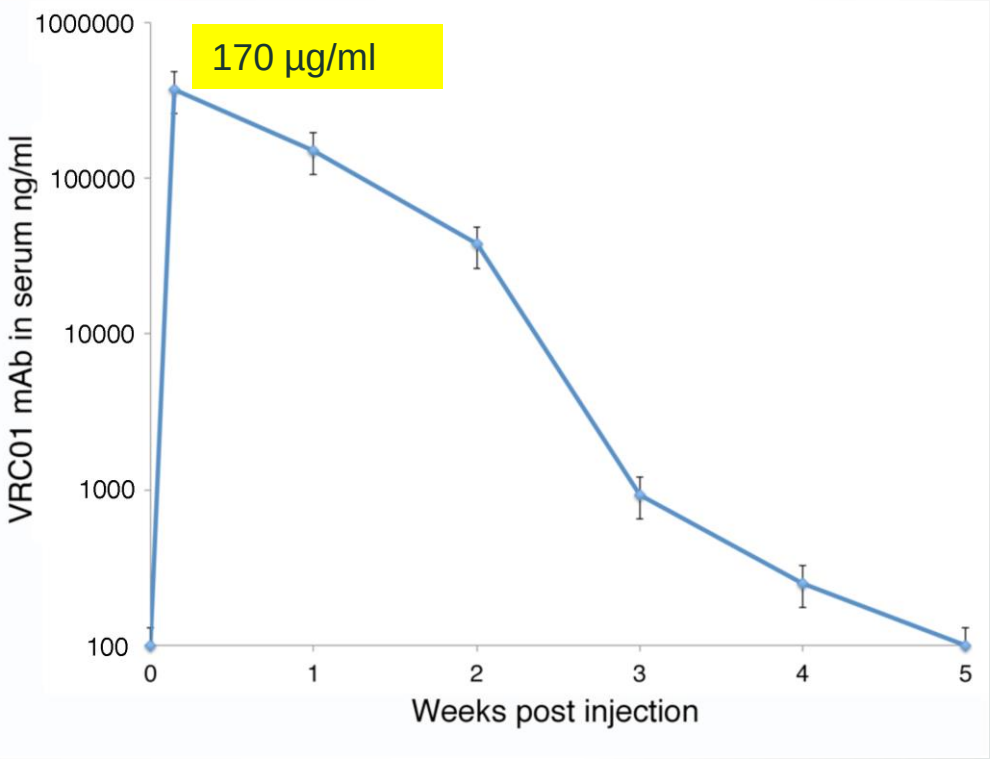
mRNA-LNP Therapeutics: Prophylatic Antibody Expression

- Broadly neutralizing HIV monoclonal antibody (VRC01) treatment of humanized mice
- Single dose (1 mg/kg mRNA-LNP) provides high levels of circulating antibody for several weeks



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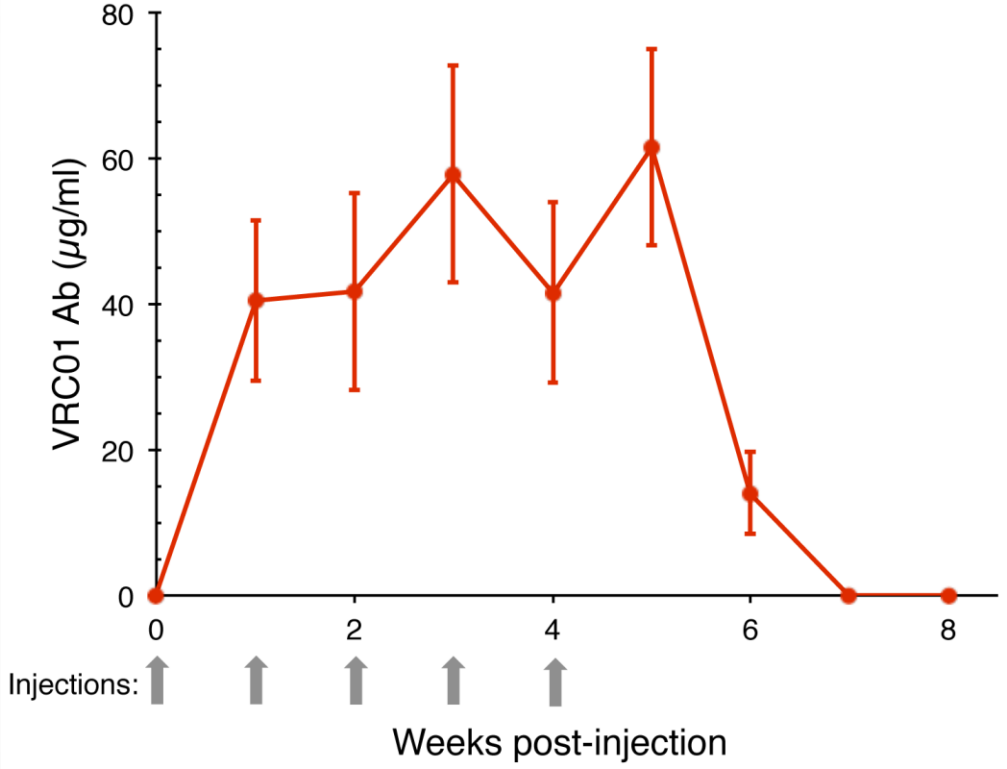
mRNA-LNP Therapeutics: Prophylactic Antibody Expression

- Repeat administration of VRC01 mRNA-LNP results in sustained antibody levels
- Plasma antibody levels measured immediately prior to next injection (7 days post-injection).



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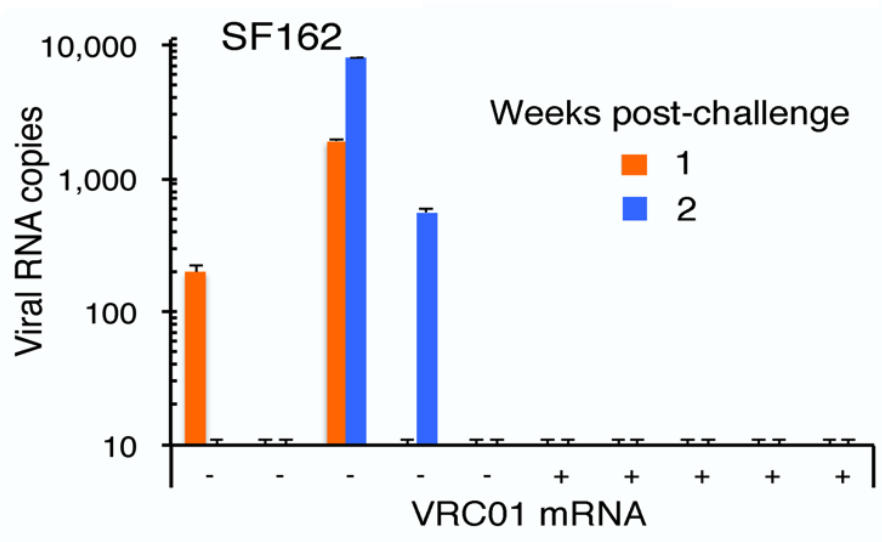
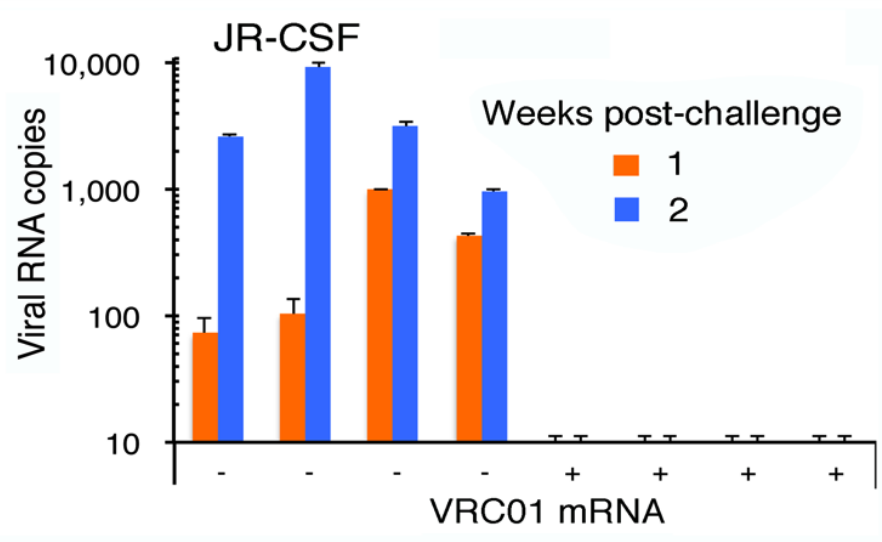
mRNA-LNP Therapeutics: Prophylactic Antibody Expression

- Administration of VRC01 mRNA-LNP completely protects humanized mice from HIV challenge





Courtesy Weissman Laboratory

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What makes Acuitas Unique?

- Highest potency LNP carriers for mRNA therapeutics
- Broad partnership experience in mRNA therapeutics field
- Proven ability to support rapid advancement of clinical candidates
- Strong academic collaborations with Key Opinion Leaders
  - Optimization of mRNA constructs to enhance protein expression levels in vivo
  - Expanding clinical opportunities for mRNA therapeutics

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