

Acuitas Therapeutics

NON-CONFIDENTIAL PRESENTATION



ACUITAS
THERAPEUTICS

Vision

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

Mission

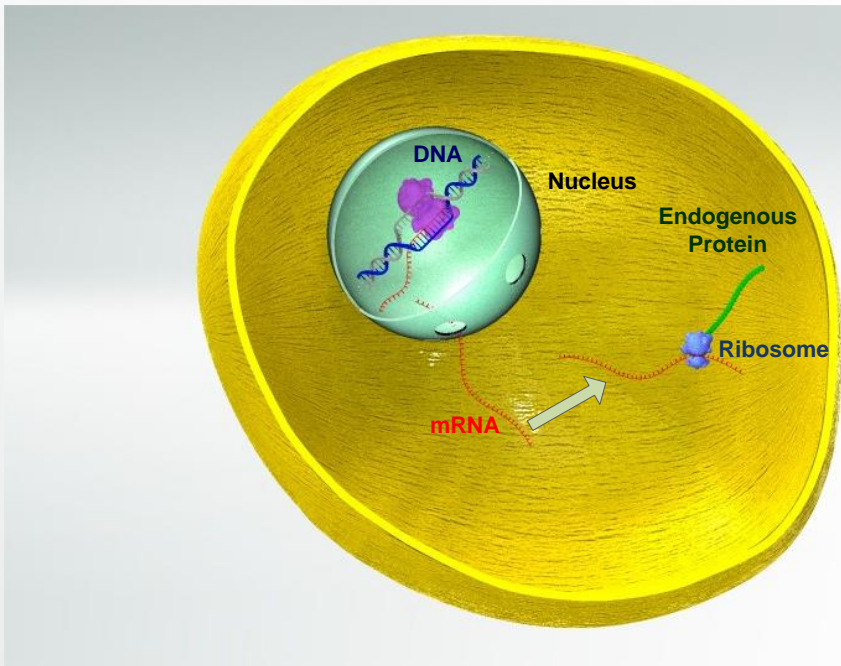
- ▶ To provide our partners with the best LNP delivery technology for nucleic acid therapeutics
- ▶ To support our partners to rapidly advance new therapeutics to address unmet medical needs
- ▶ To continually innovate to maintain and strengthen our LNP technological lead

Company Background

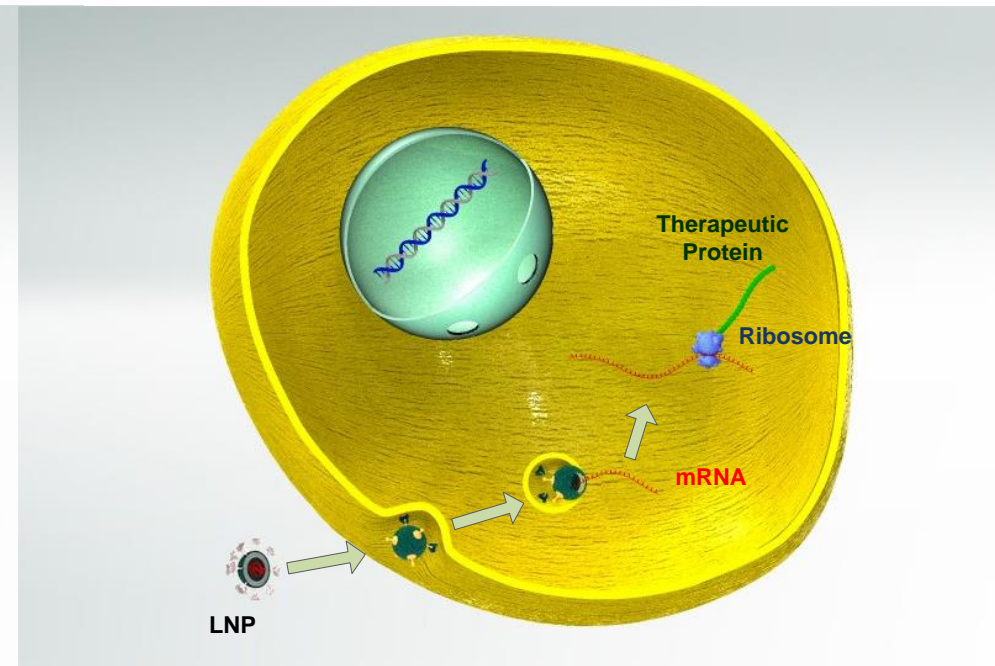
- ▶ Privately held biotechnology company
- ▶ Founded February 2009; based in Vancouver, British Columbia
- ▶ Highly experienced team developing lipid nanoparticle delivery systems
- ▶ Facilities for chemistry, formulation and preclinical studies with access to additional resources at the University of British Columbia (UBC)

Therapeutic Opportunity: mRNA Therapy

- ▶ Delivery of novel proteins to treat disease



Normal cell: Protein coded by DNA



mRNA Therapy: Protein coded by synthetic mRNA

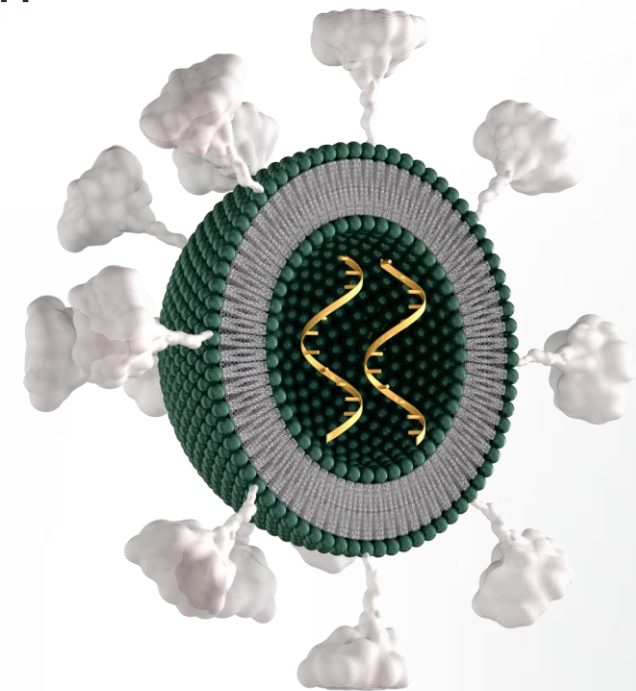
Therapeutic Opportunities

- ▶ Protein Replacement therapeutics (site specific protein expression)
 - ▶ Gaucher's disease; Pompe disease (glycogen storage disease type II); phenylketonuria – requires protein expression in liver
- ▶ Protein Replacement therapeutics (non-site specific expression)
 - ▶ Haemophilia A, B or C (lack of functional Factor VIII, IX or XI); erythropoietin (to treat anaemia), Hunter syndrome (iduronate-2-sulphatase deficiency)
 - ▶ Expression in liver with subsequent secretion
- ▶ Vaccines
 - ▶ Intracellular expression of viral or bacterial proteins providing immune response
 - ▶ Expression of tumour antigens (personalized vaccines)
- ▶ Antibodies
 - ▶ Expression of prophylactic or therapeutic antibodies to treat current and emerging diseases
- ▶ Gene Editing
 - ▶ Expression of ZFN, Cas9, TALEN, etc.

LNP Technology

LIPID NANOPARTICLES FORMULATION

- ▶ Clinically validated - Acuitas developed LNP formulation used in ONPATTRO[®] (Patisiran[®])
 - ▶ Small, uniform sized particles (~80 nm)
 - ▶ Low surface charge in blood compartment
 - ▶ Lipid components manufactured under cGMP
- ▶ Improved LNP formulations exhibit substantially higher potency and therapeutic index



Expertise & Capabilities

- ▶ Synthetic chemistry
 - ▶ Design and synthesis of novel cationic lipids and PEG-lipids
 - Over 300 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
 - ▶ Lipid scale up to support GLP studies
 - ▶ Technology transfer to CMO to support clinical development

Expertise & Capabilities II

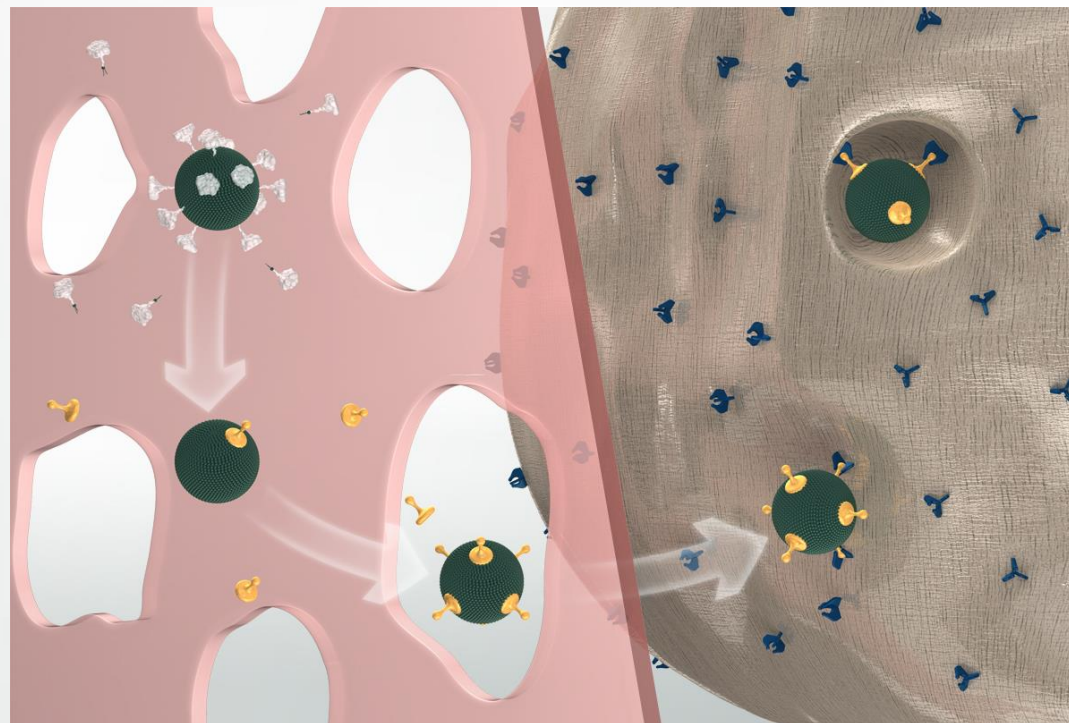
- ▶ Formulation and Analytical
 - ▶ Efficient optimization of mRNA loading and LNP biophysical parameters
 - ▶ Biophysical characterization of mRNA-LNP systems
 - ▶ Formulation scale up for GLP studies
 - ▶ Analytical development and support for GLP studies
 - LNP components
 - mRNA payload
 - ▶ Technology transfer to CMO

Expertise & Capabilities: Preclinical

- ▶ Pharmacodynamic studies for mRNA therapeutics
 - ▶ Reporter protein expression in vivo
 - ▶ Therapeutic protein expression in vivo
- ▶ Safety/Tolerability studies
 - ▶ CBC/Clin Chem/Histopathology
 - ▶ Immune characterization (cytokine/chemokine induction)
- ▶ PK/ADME
 - ▶ Nucleic acid therapeutic and LNP components

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

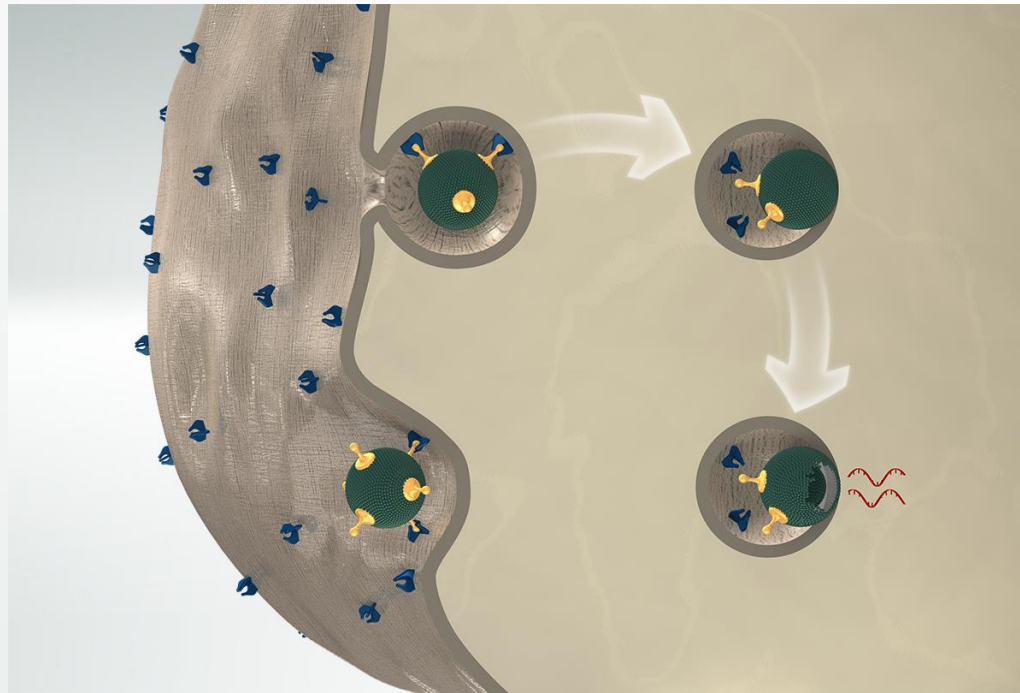


LNP with bound
ApoE

Acuitas LNP – Mechanism of Action II

► Endosomal Release

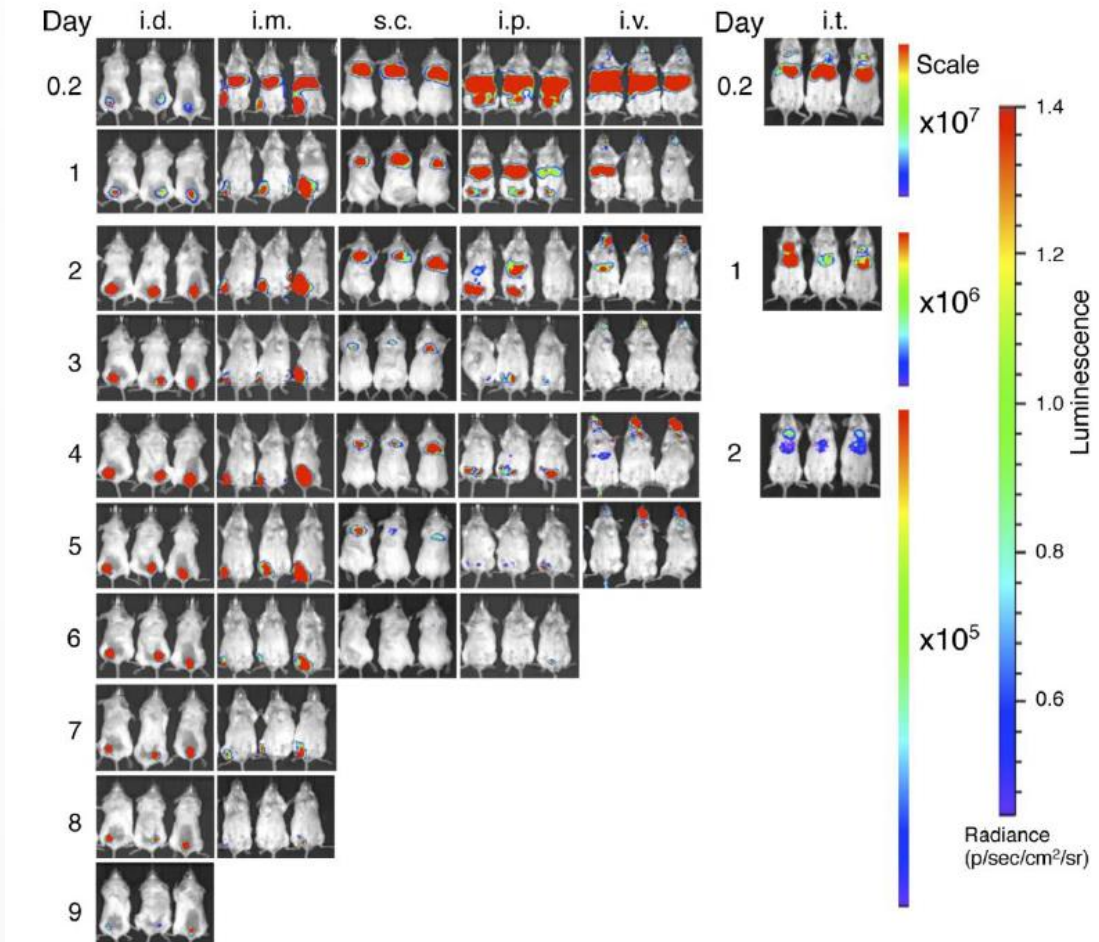
- Endosomal maturation results in drop in internal pH
- LNP cationic lipid becomes positively charged resulting in release of nucleic acid payload to cytoplasm



Nucleic acid
payload

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

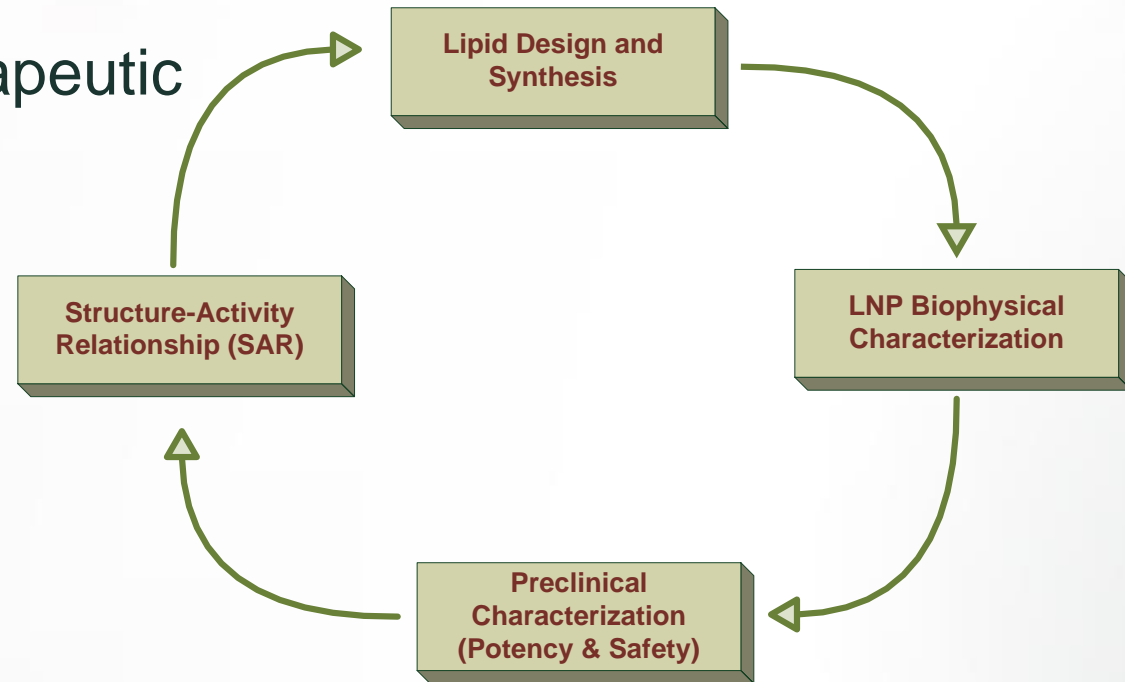


Courtesy Dr. Weissman Laboratory

mRNA-LNP Technology

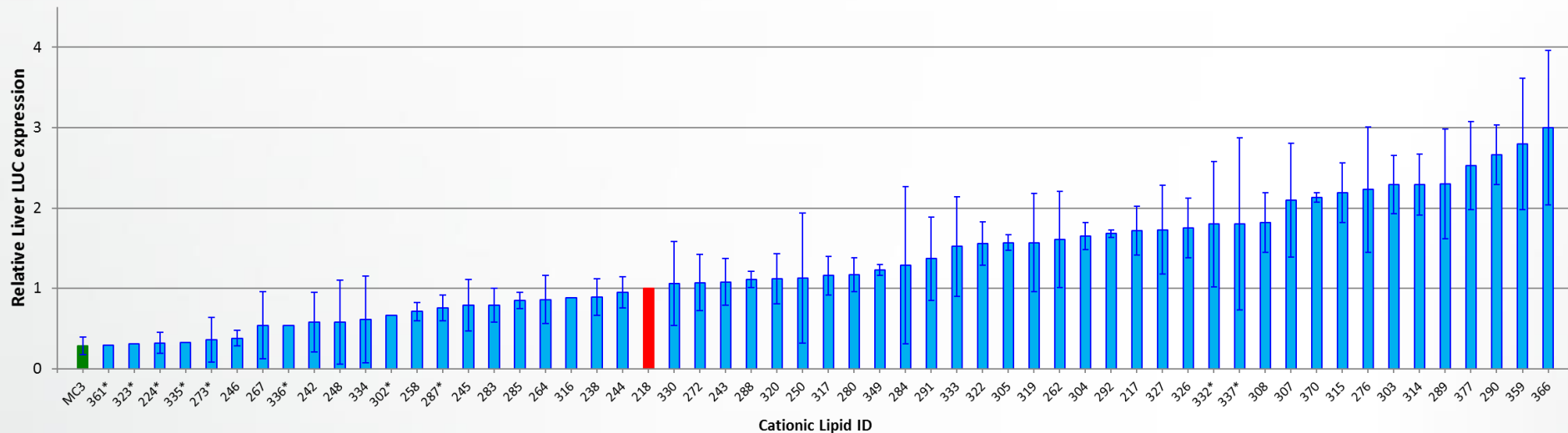
Development: Objectives & Process

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



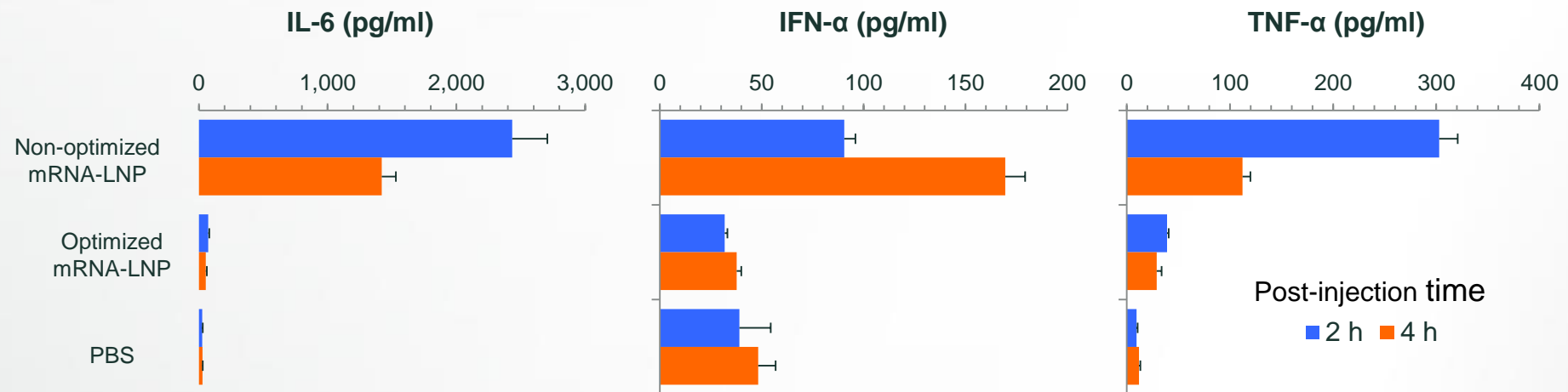
mRNA-LNP Technology : Potency Enhancement

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



mRNA-LNP Therapeutics: Safety Profile

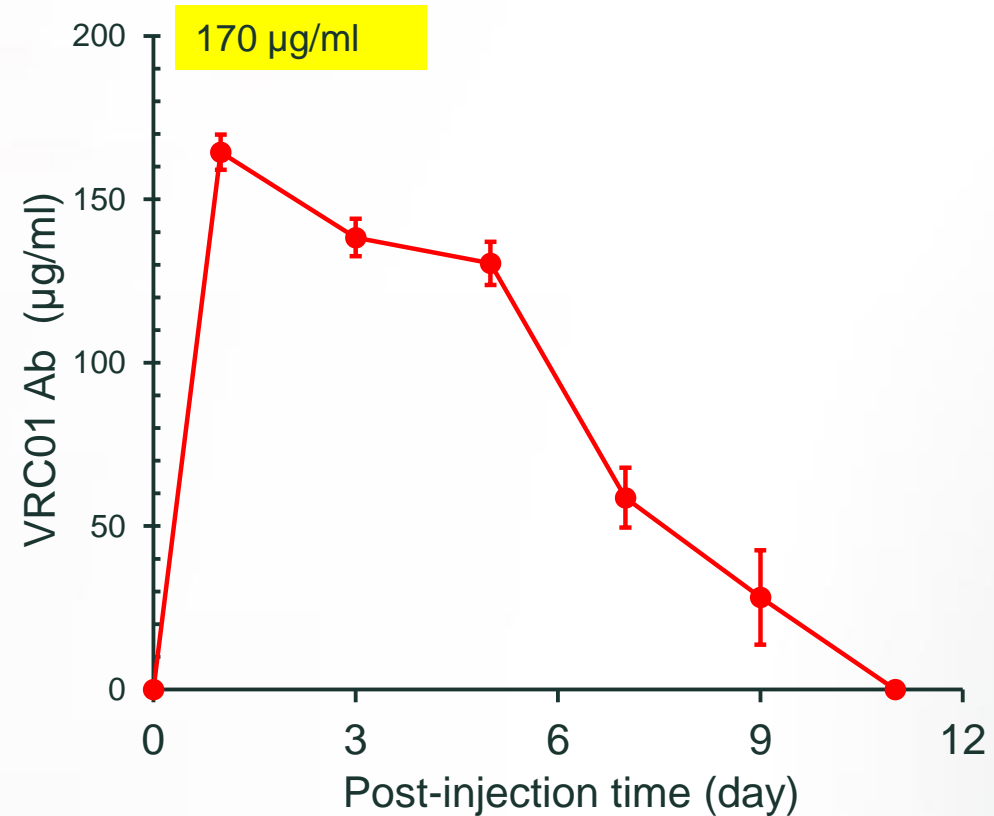
- ▶ Immune activation ameliorated by mRNA chemistry, sequence optimization and purification



Courtesy Weissman Laboratory

mRNA-LNP Therapeutics: Prophylactic 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 days



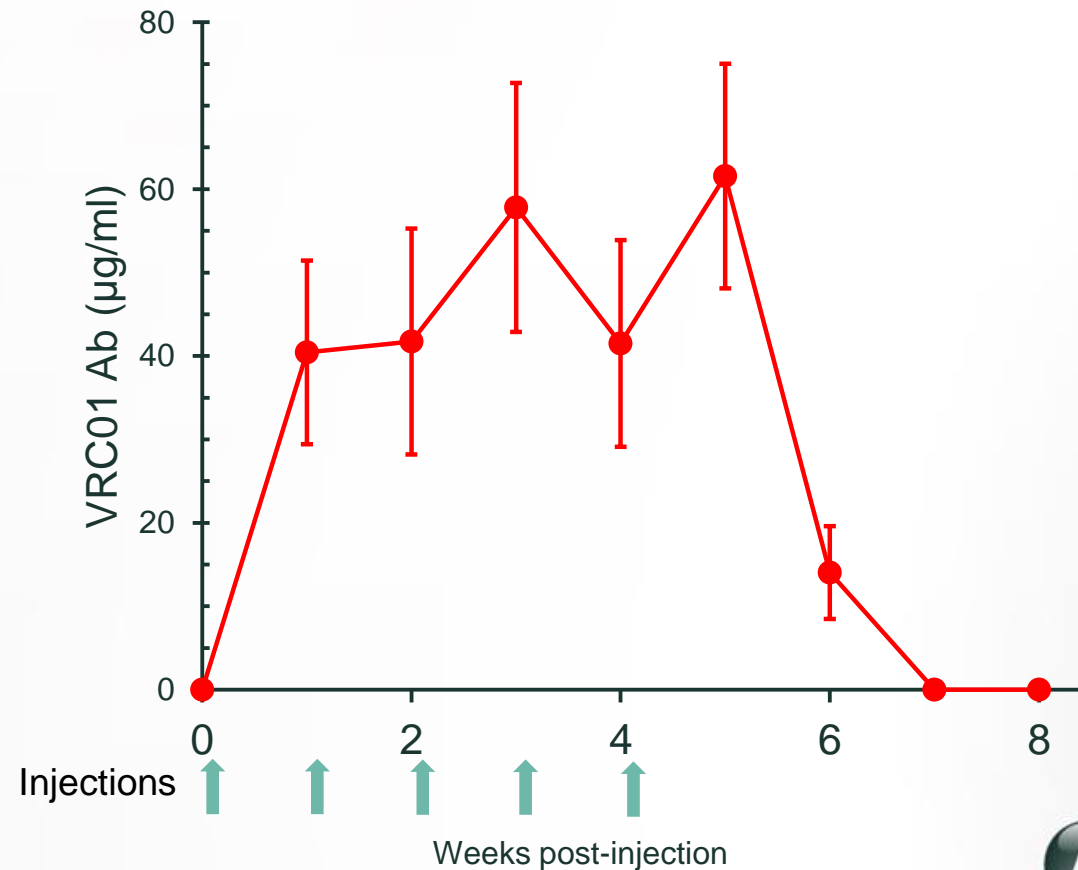
Courtesy Weissman Laboratory

Pardi et al. Nature Commun. 2017



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).



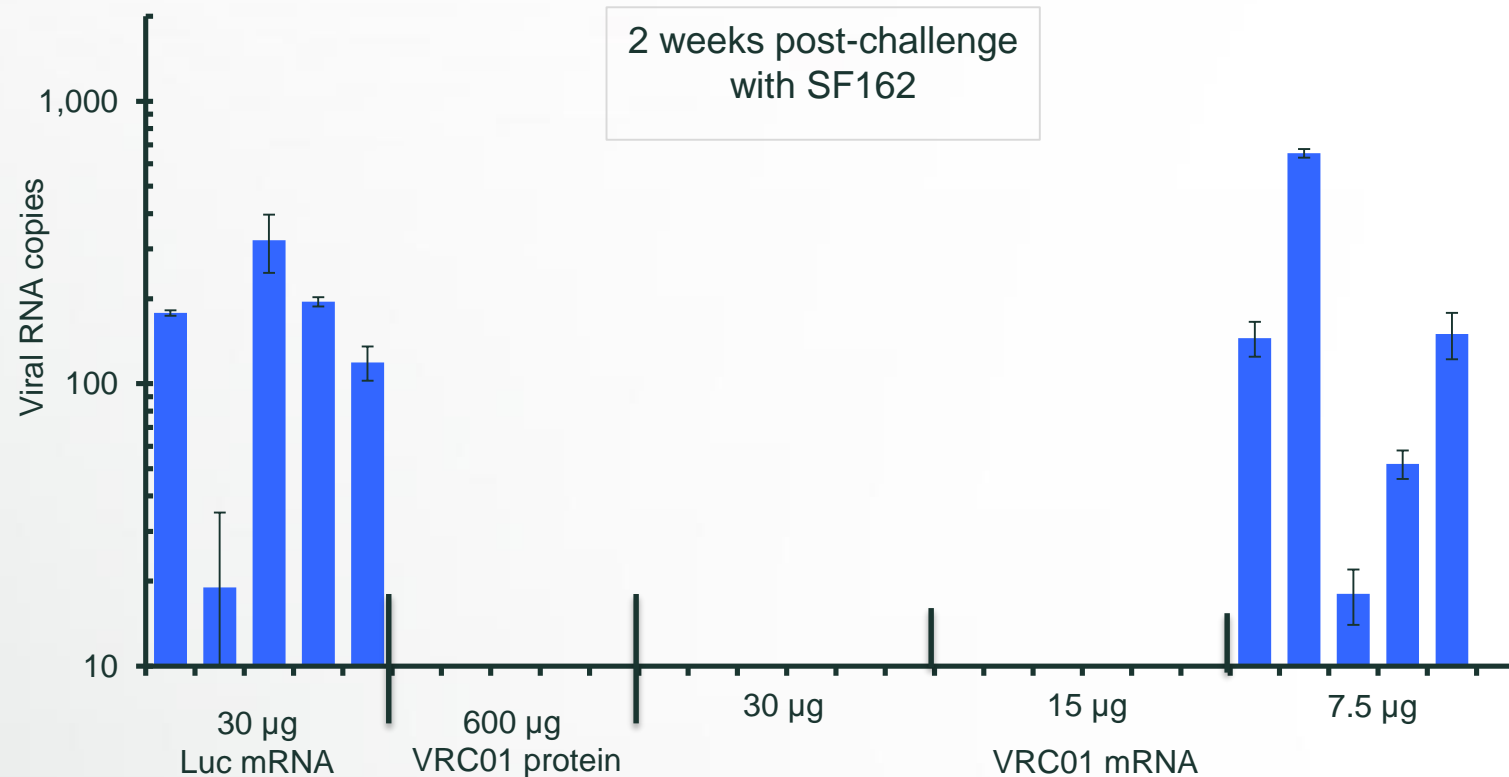
Courtesy Weissman Laboratory

Pardi et al. Nature Commun. 2017



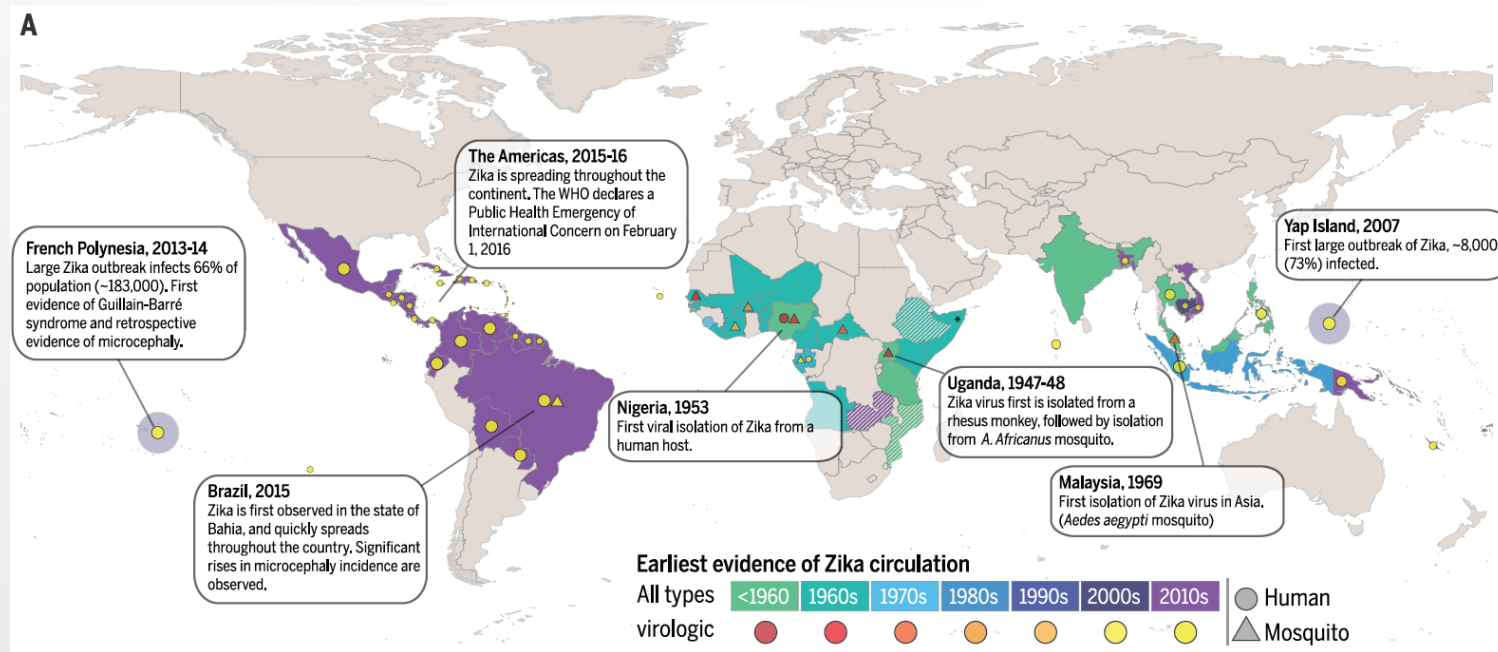
mRNA-LNP Therapeutics: Prophylactic Antibody Expression

- ▶ Administration of VRC01 mRNA-LNP provides dose-dependent protection from HIV strain SF 162



Global Spread of Zika Virus

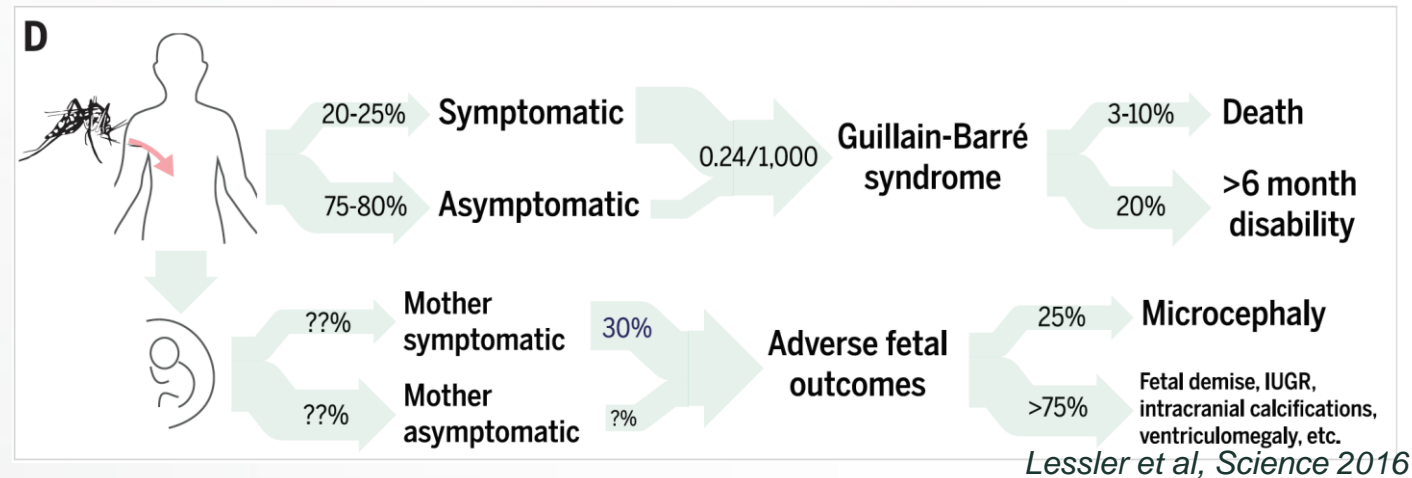
- ▶ 1950 – 2014: ZIKV infection not linked to severe disease.
- ▶ 2015 – 2016: ZIKV spread rapidly through Brazil and Americas: 168,000 confirmed and >500,000 suspected cases of ZIKV infection



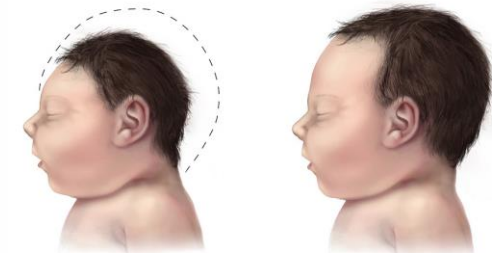
Lessler et al, Science 2016

Zika-Associated Disease

► Natural history of Zika virus infection:



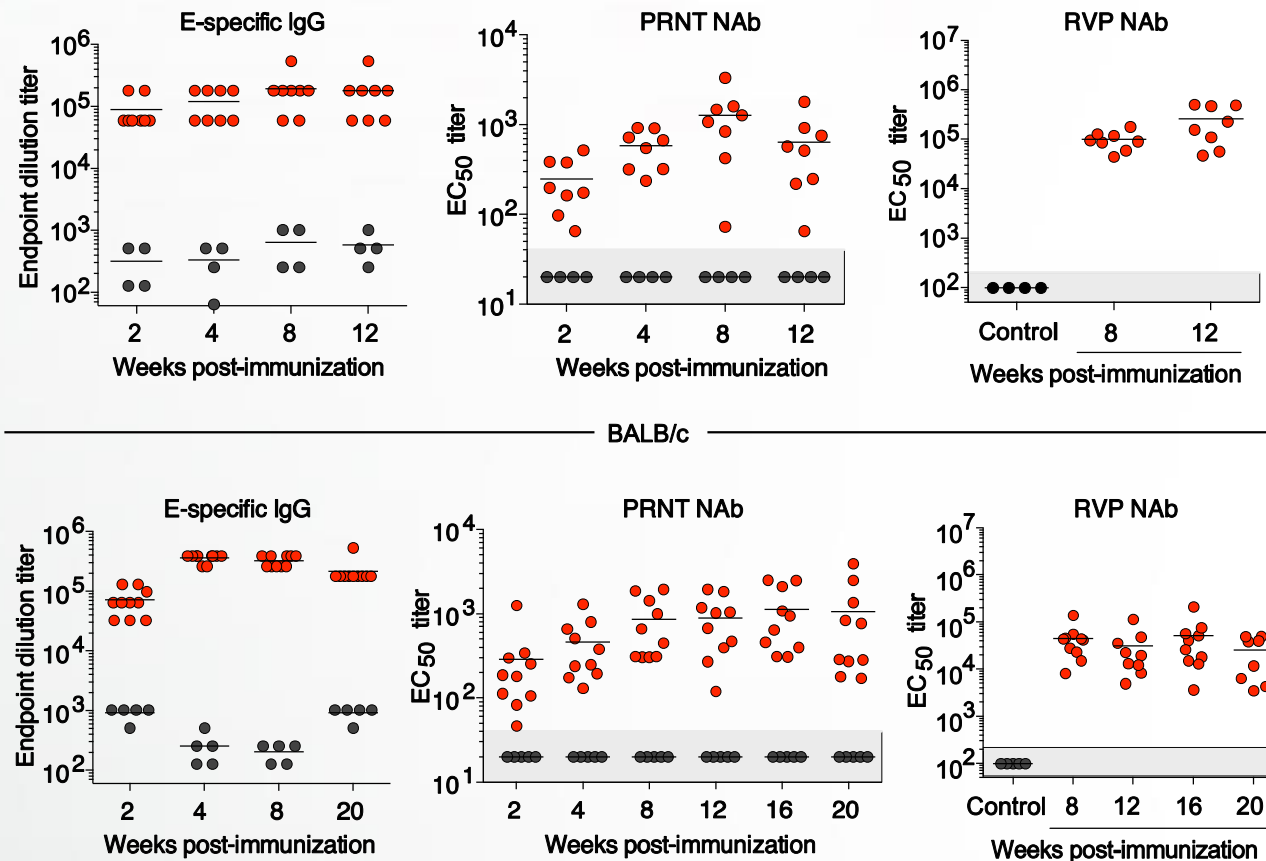
- Microcephaly (small head size) associated with numerous disabilities
- 2,079 cases of microcephaly in Brazil to date
- Evidence for causal relationship:
 - Virus isolated from amniotic fluid and fetal brain
 - ZIKV infects neural progenitor cells in mice



CDC

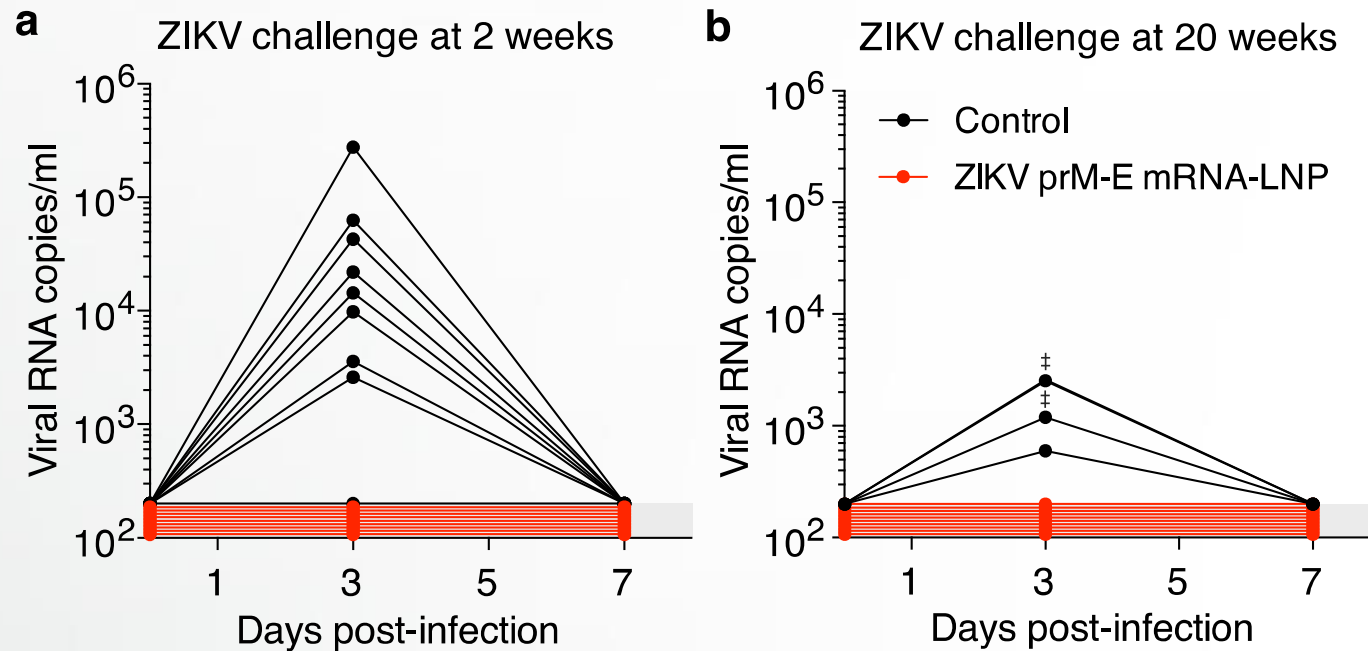
Zika mRNA-LNP: Murine Immune Response

► IgG anti-Zika E protein levels after a single immunization.



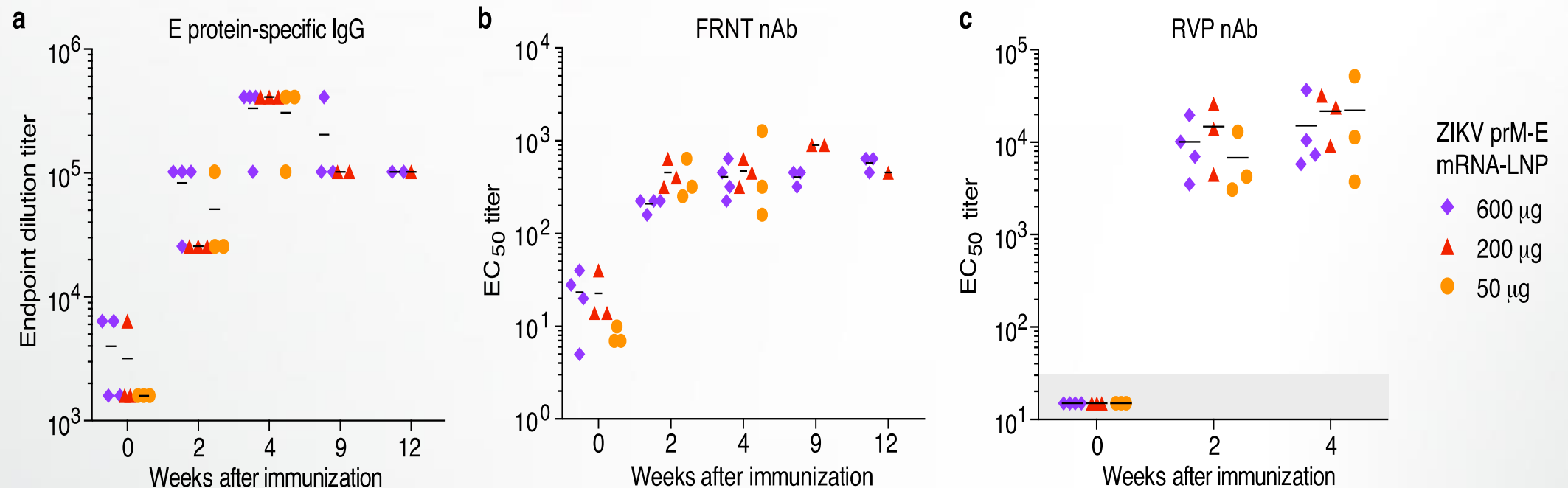
Zika mRNA-LNP: Protection from Viral Challenge in Mouse

- ▶ Mice immunized 2 weeks or 5 months before challenge with Zika prM-E mRNA-LNPs were completely protected.



Zika mRNA-LNP: Protection from Viral Challenge in Macaques

► Zika modified mRNA-LNP vaccine in macaques



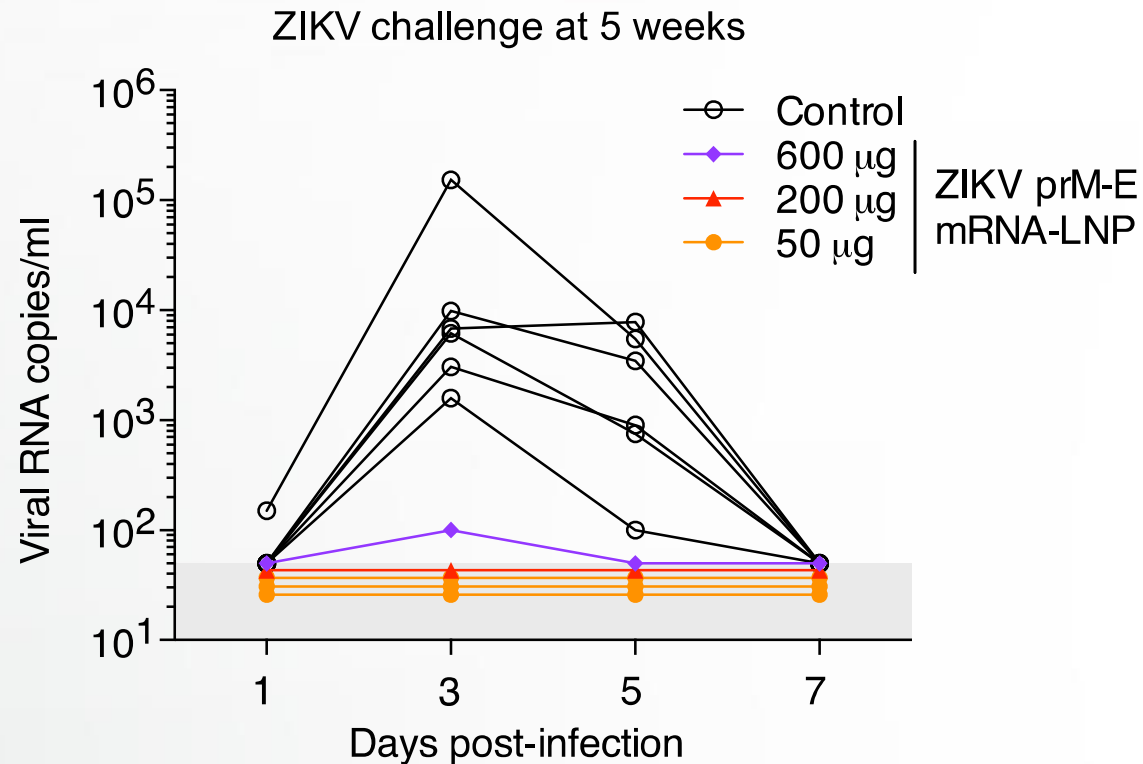
Courtesy Weissman Laboratory

Pardi et al., Nature 2017



Zika mRNA-LNP: Protection from Viral Challenge in Macaques

- ▶ Macaques immunized once with 50 μg Zika prM-E mRNA-LNPs are completely protected from infection

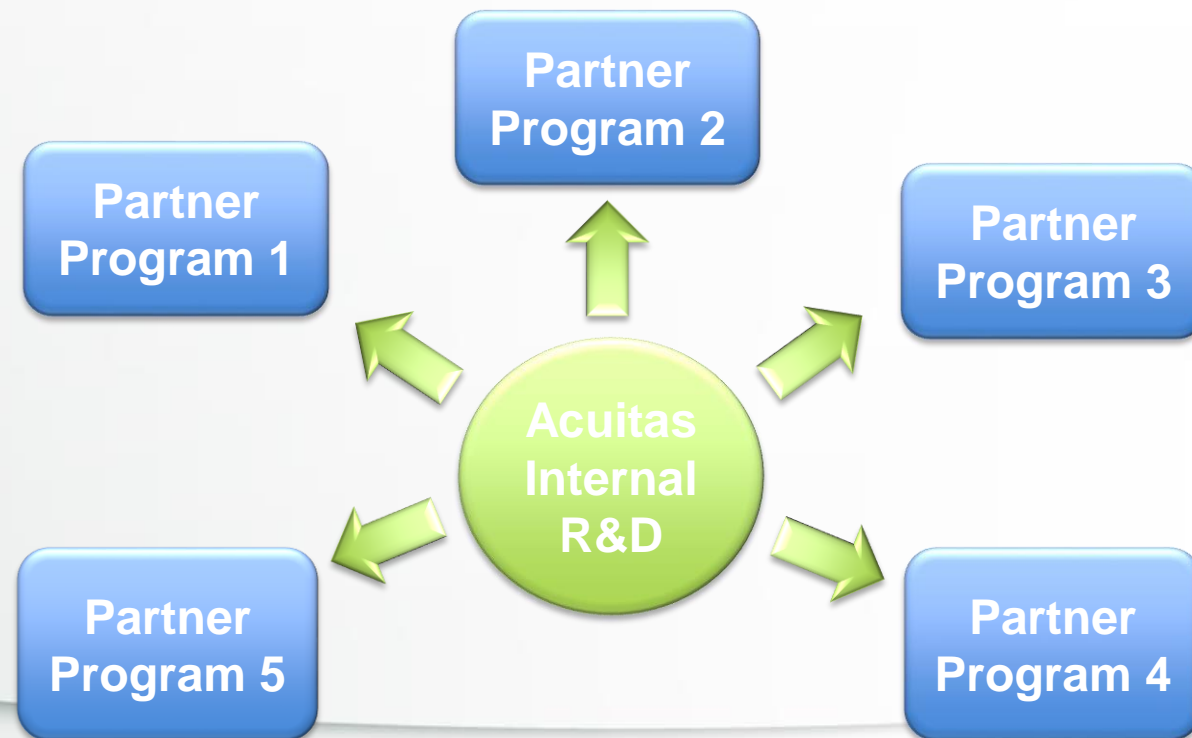


What makes Acuitas Unique?

- ▶ Highest potency LNP carriers for mRNA therapeutics
- ▶ Broad IP portfolio providing commercial rights for mRNA-LNP therapeutics
- ▶ Broad partnership experience in mRNA therapeutics field
- ▶ Strong academic collaborations with KOLs
 - ▶ Optimization of mRNA constructs to enhance protein expression levels in vivo
 - ▶ Expanding clinical opportunities for mRNA therapeutics

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



Contact Information

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