Acuitas Therapeutics

NON-CONFIDENTIAL PRESENTATION

Vision

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

Mission

To provide our partners with the best LNP delivery technology fo
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

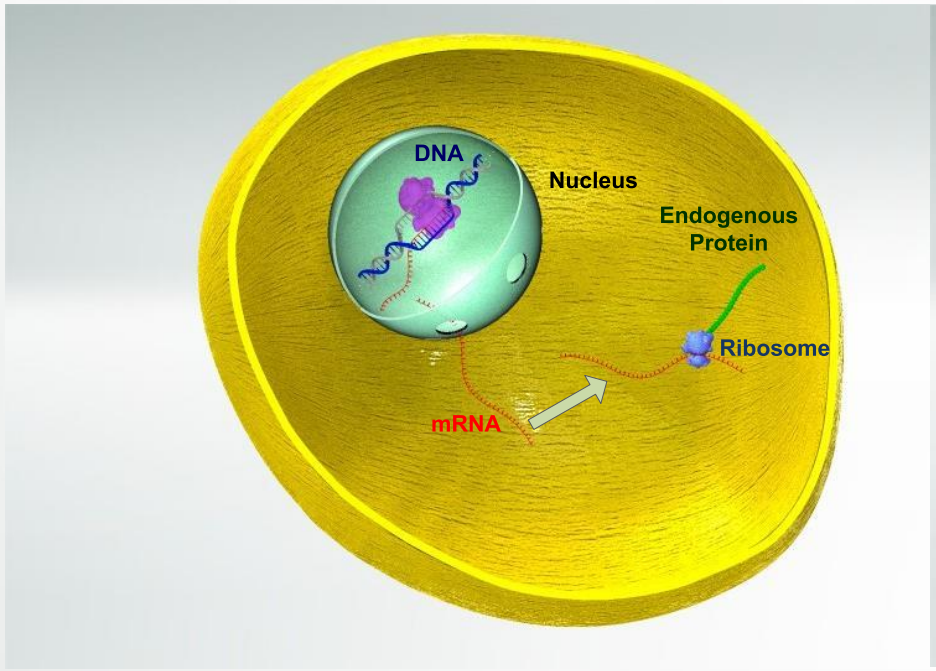
Founded February 2009; based in Vancouver, British Columbia

Highly experienced team developing lipid nanoparticle delivery systems

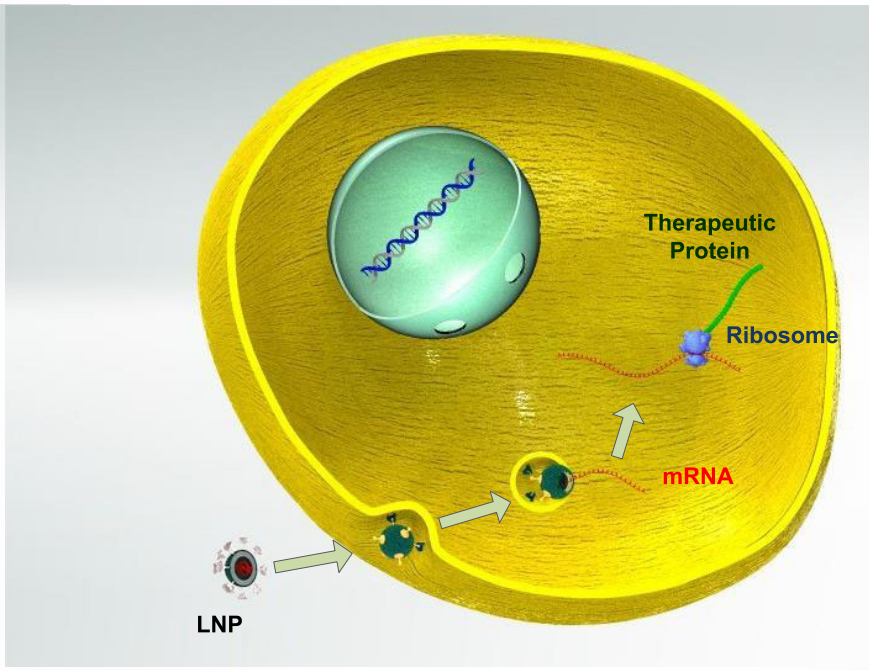
Facilities for chemistry, formulation and preclinical studies with access to additional resources at the University of British Columbia (UBC)

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 – requ
  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)
  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.

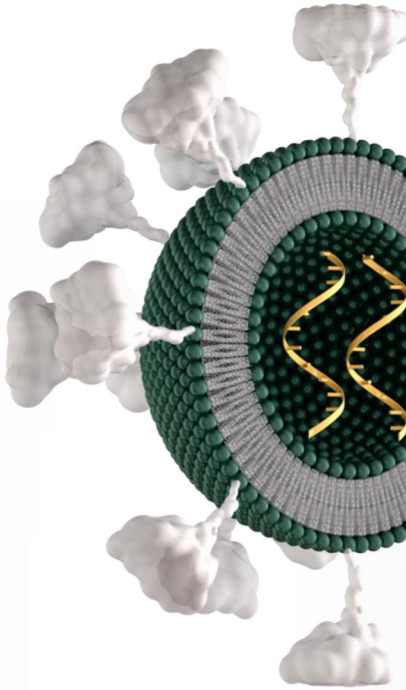
LNP Technology

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 refi 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)

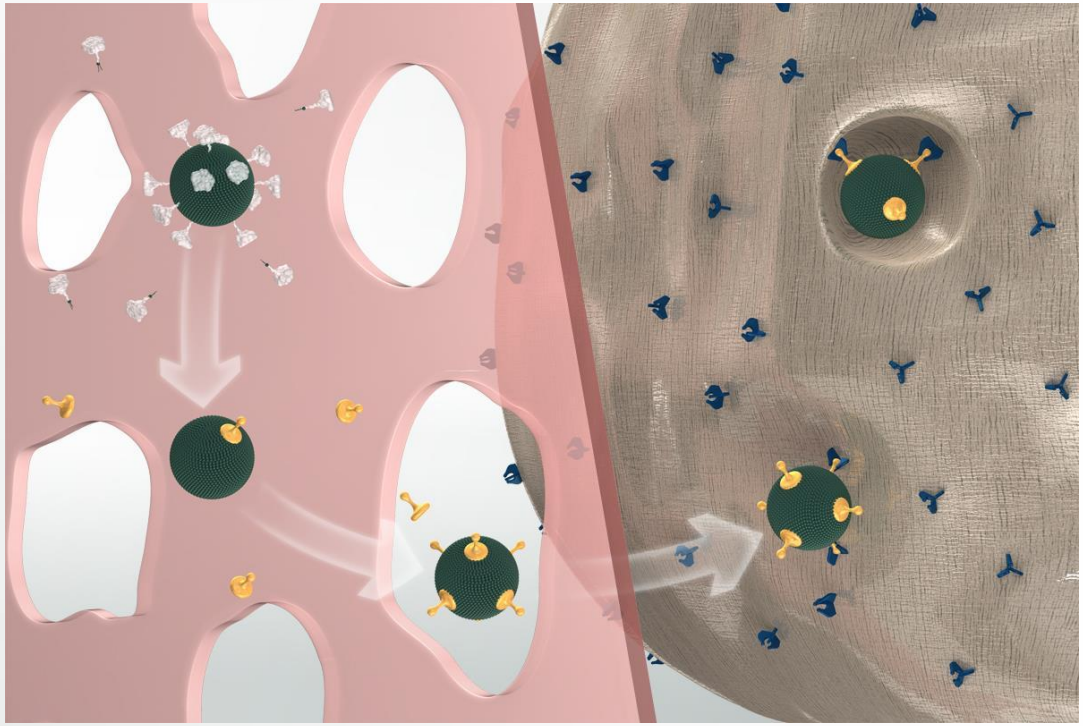
PK/ADME

- Nucleic acid therapeutic and LNP components

cuitas LNP – Mechanism of Actio

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

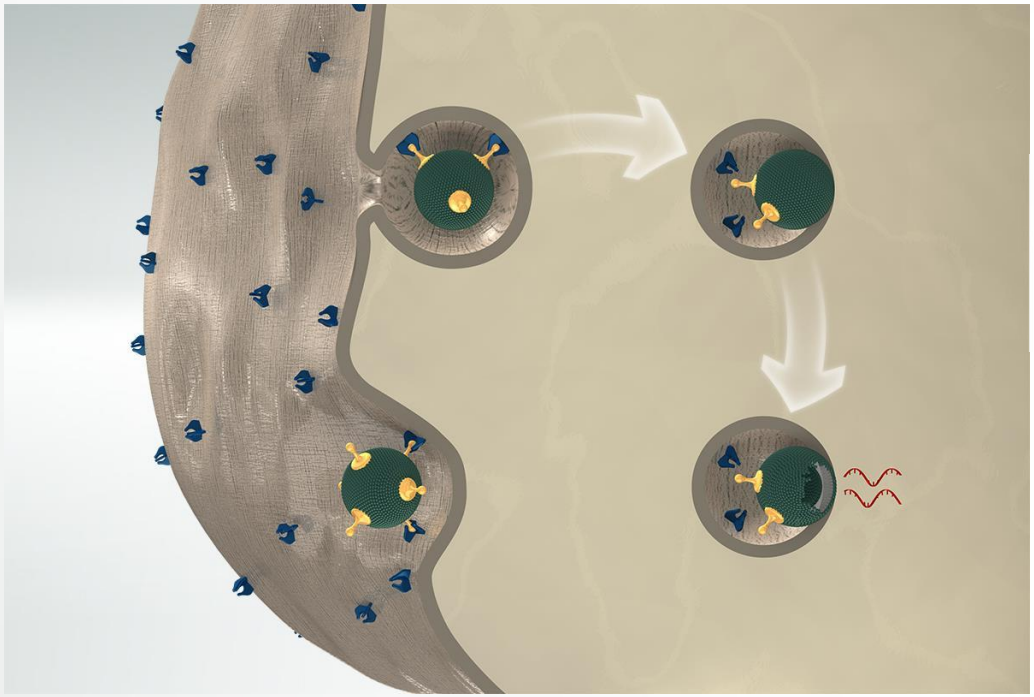
PEG-Lipid

LNP with boun
ApoE

Acuitas LNP – Mechanism of Action

Endosomal Release

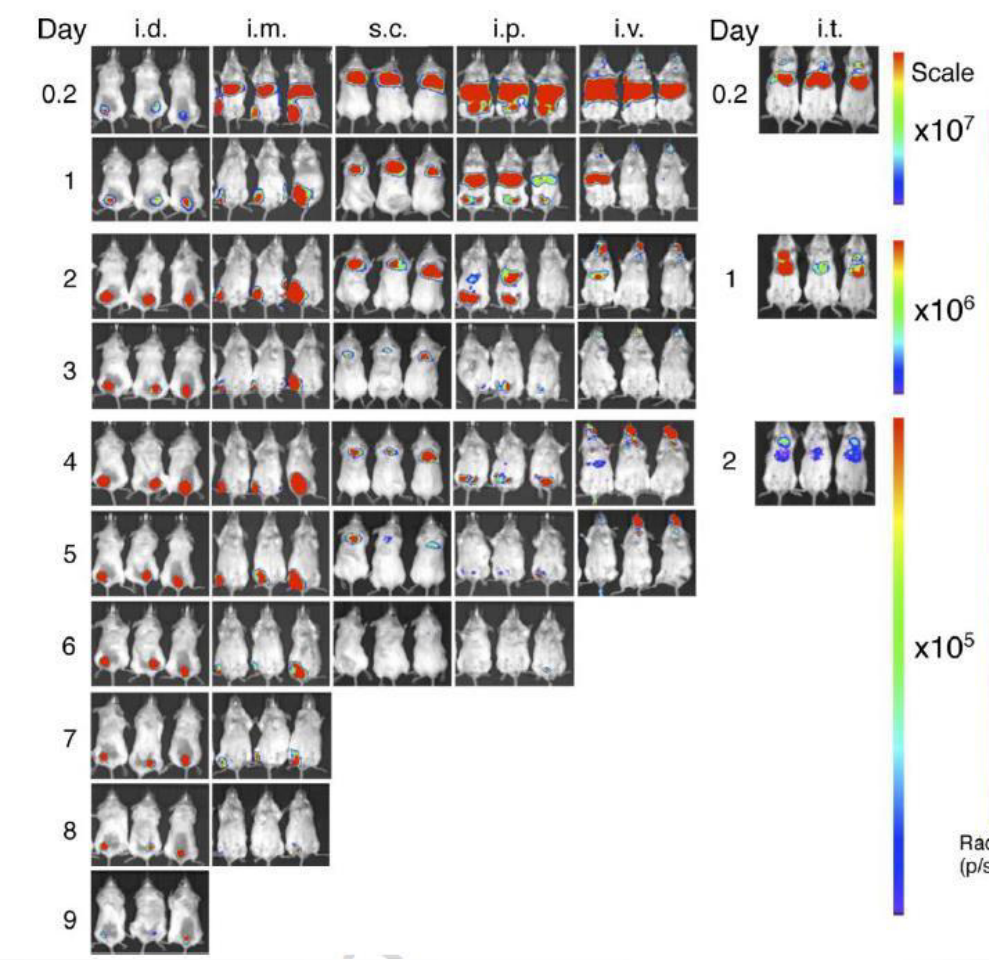
- Endosomal maturation results in drop in internal pH
- LNP cationic lipid becomes positively charged resulting in release of nuclei acid payload to cytoplasm



Nucleic acid payload

Expression: Influence of site of mRN administration

IVIS images of BALB/c mice following administration of luciferase mRNA-LNP (0.2 mg/kg) by the indicated route



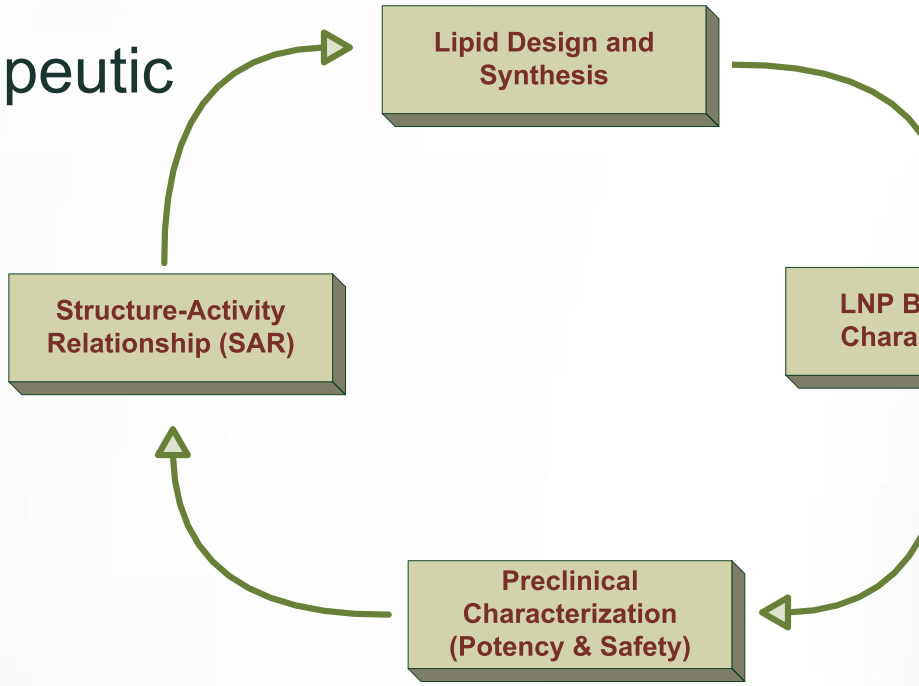
Courtesy Dr. Weissman Laboratory

mRNA-LNP Technology Development: Objectives & Process

Enhance potency and safety profile for LNP carriers

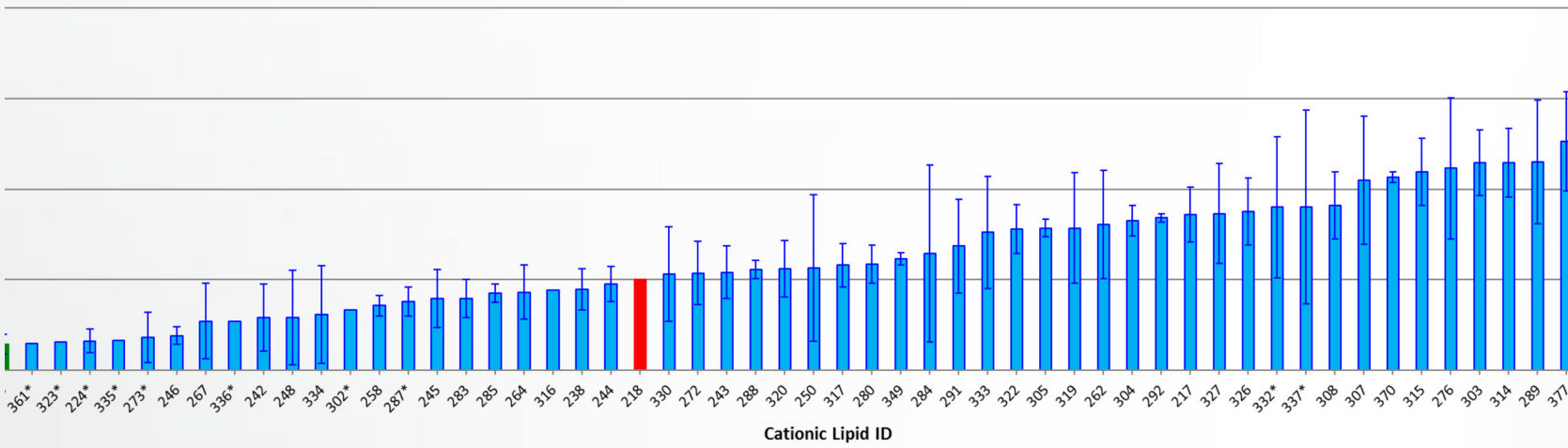
Enable broad range of mRNA therapeutic applications

Iterative approach to identify improved LNP compositions



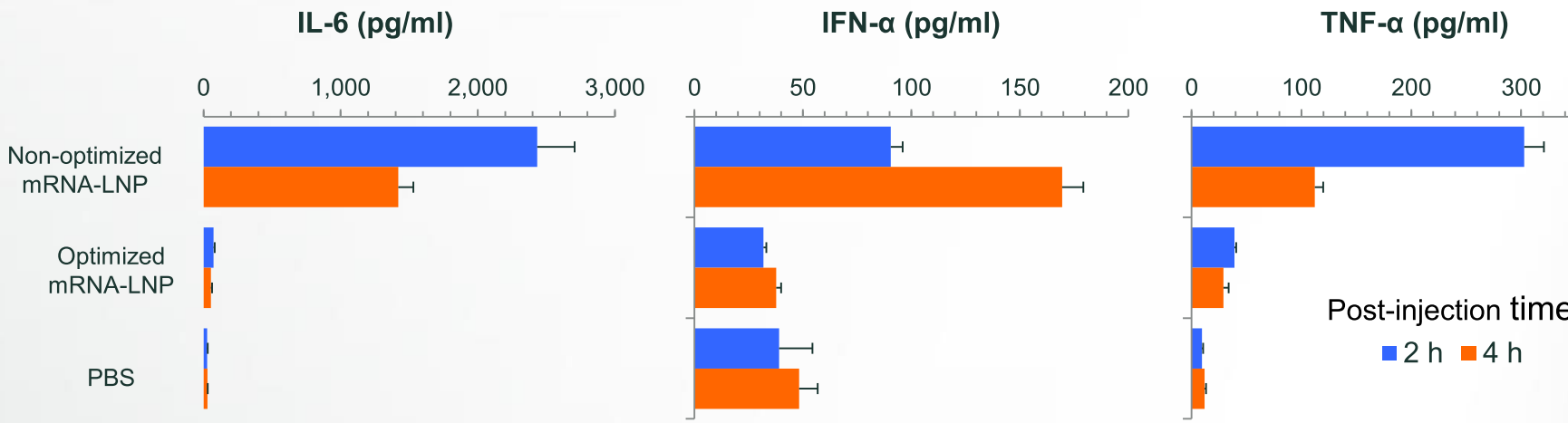
mRNA-LNP Technology : Potency Enhancement

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



NA-LNP Therapeutics: Safety Pro

Immune activation ameliorated by mRNA chemistry, sequence optim
and purification

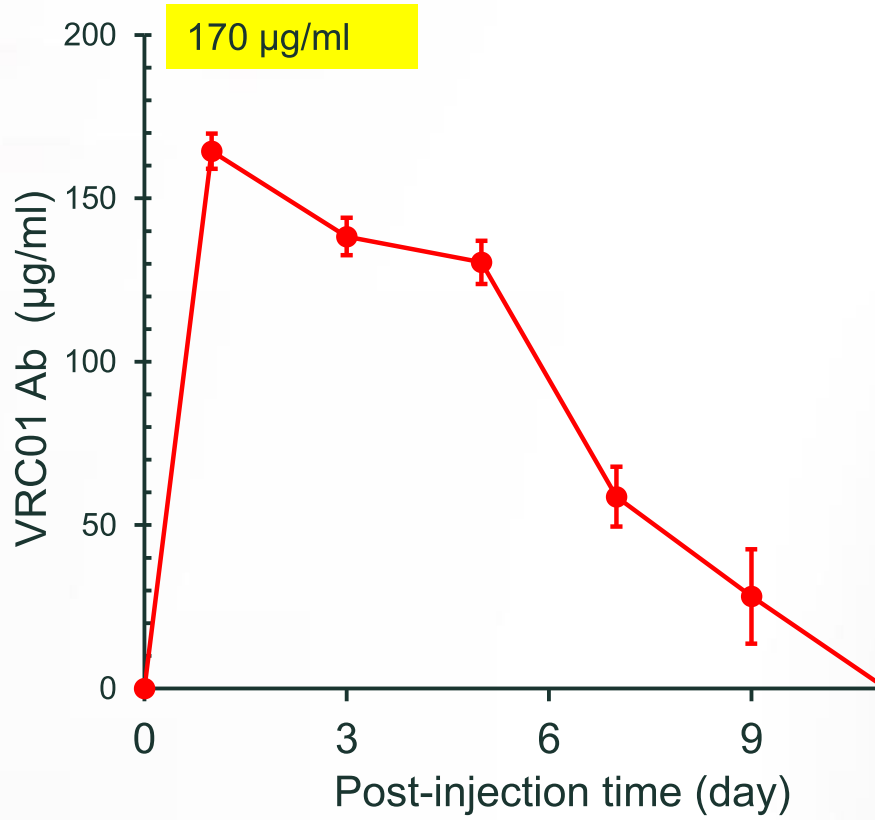


Courtesy Weissman Laboratory

A-LNP Therapeutics: Prophylatic Ant
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



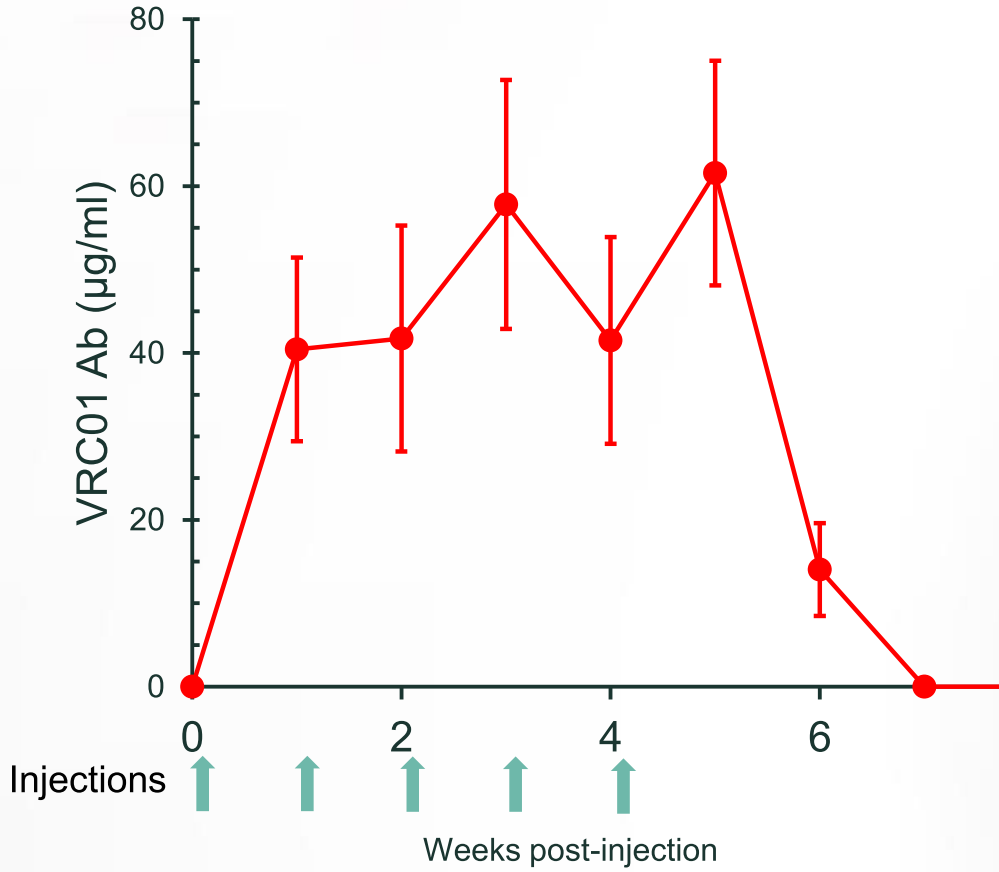
Courtesy Weissman Laboratory

Pardi et al. Nature Commun. 2017

A-LNP Therapeutics: Prophylactic An 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).

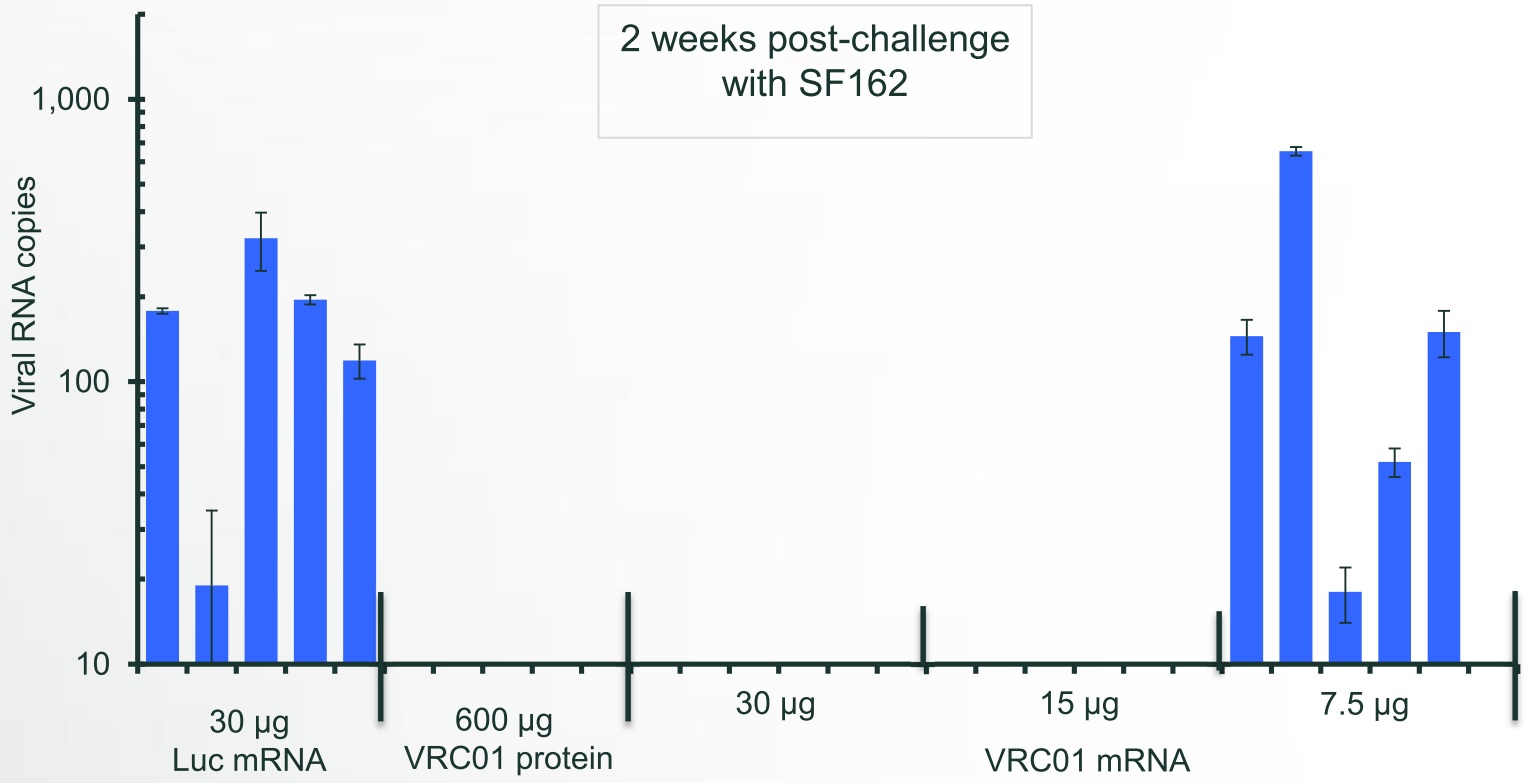


Courtesy Weissman Laboratory

Pardi et al. Nature Commun. 2017

A-LNP Therapeutics: Prophylactic An Expression

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

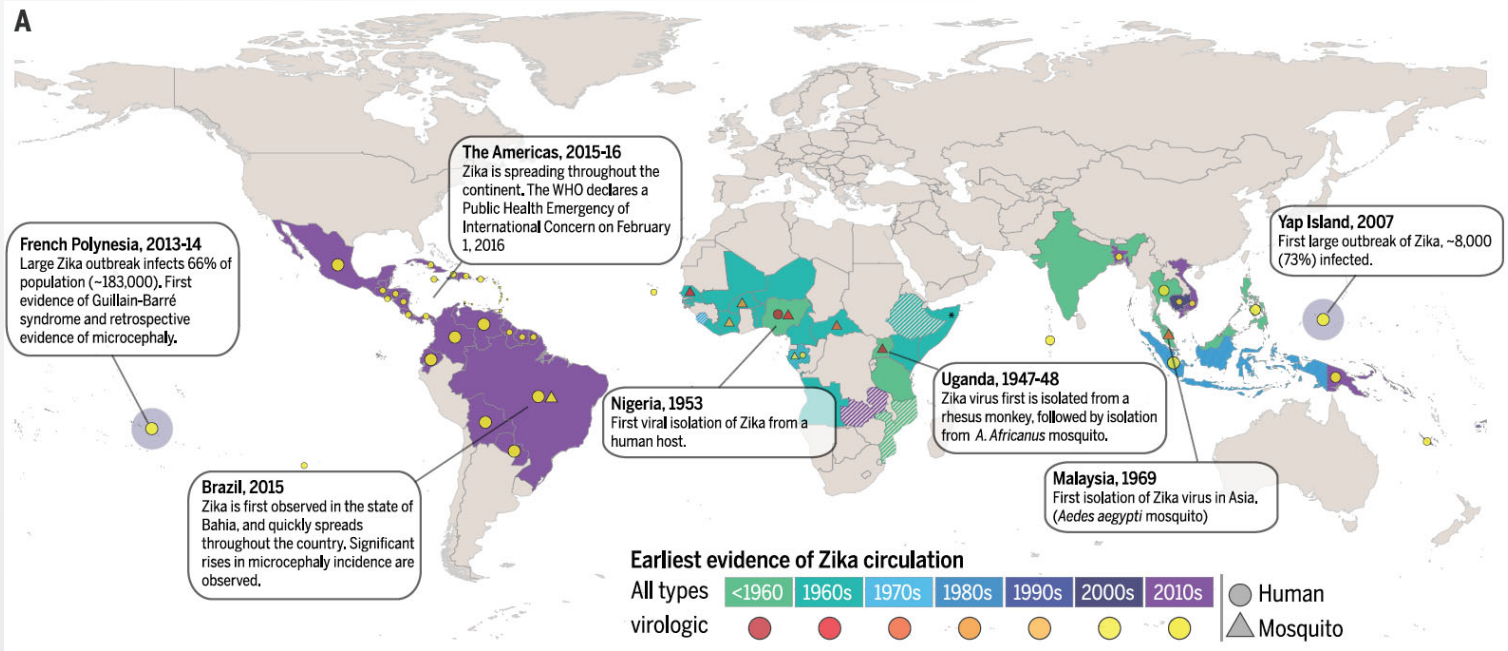


Courtesy Weissman Laboratory

Pardi et al. Nature Commun. 2017

Global Spread of Zika Virus

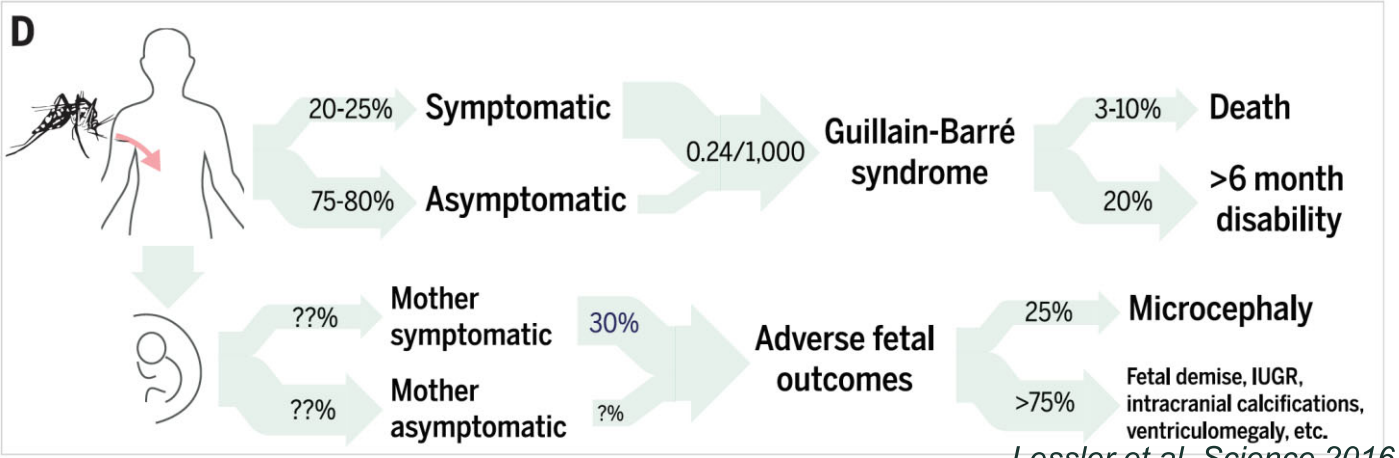
- *1950 – 2014*: ZIKV infection not linked to severe disease.
- *2015 – 2016*: ZIKV spread rapidly through Brazil and Americas: 168,000 confirmed and >500,000 suspected cases of ZIKV infection



Lessler et al, Science 2016

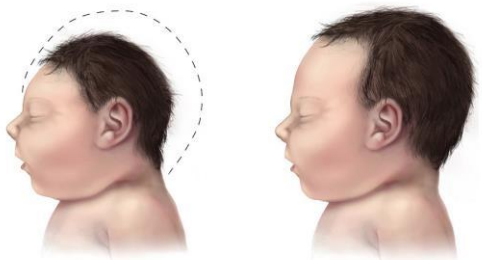
Zika-Associated Disease

- Natural history of Zika virus infection:



Lessler et al, Science 2016

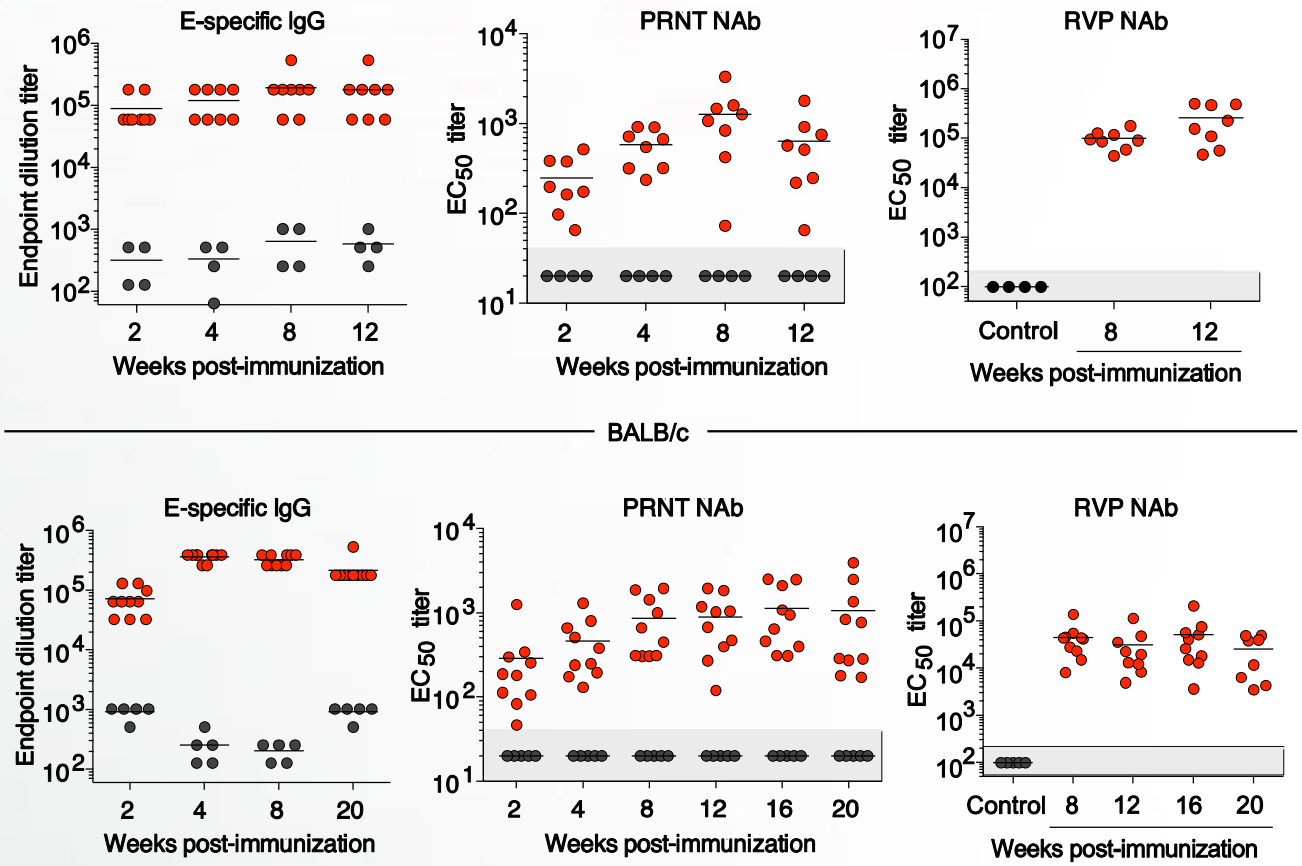
- Microcephaly (small head size) associated with numerous disabilities
- 2,079 cases of microcephaly in Brazil to date
- Evidence for causal relationship:
  - Virus isolated from amniotic fluid and fetal brain
  - ZIKV infects neural progenitor cells in mice



CDC

nRNA-LNP: Murine Immune Resp

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

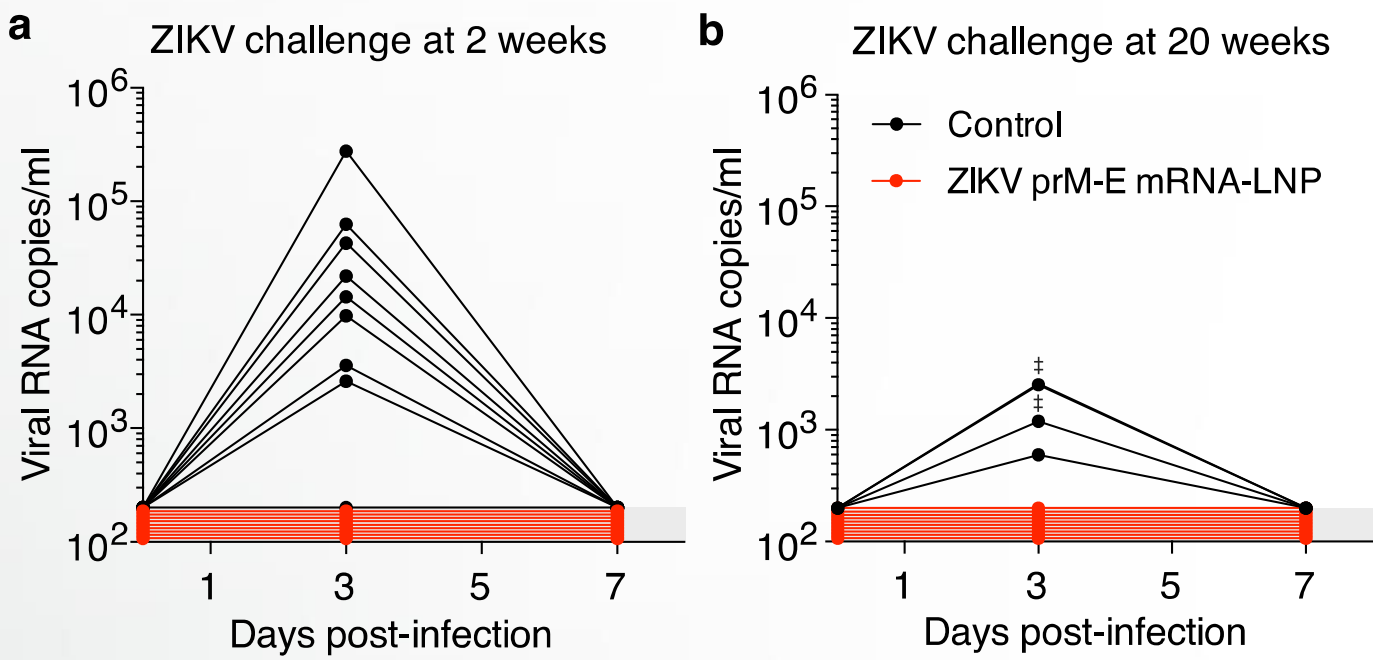


Courtesy Weissman Laboratory

Pardi et al., Nature 2017

RNA-LNP: Protection from Viral Chall
Mouse

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

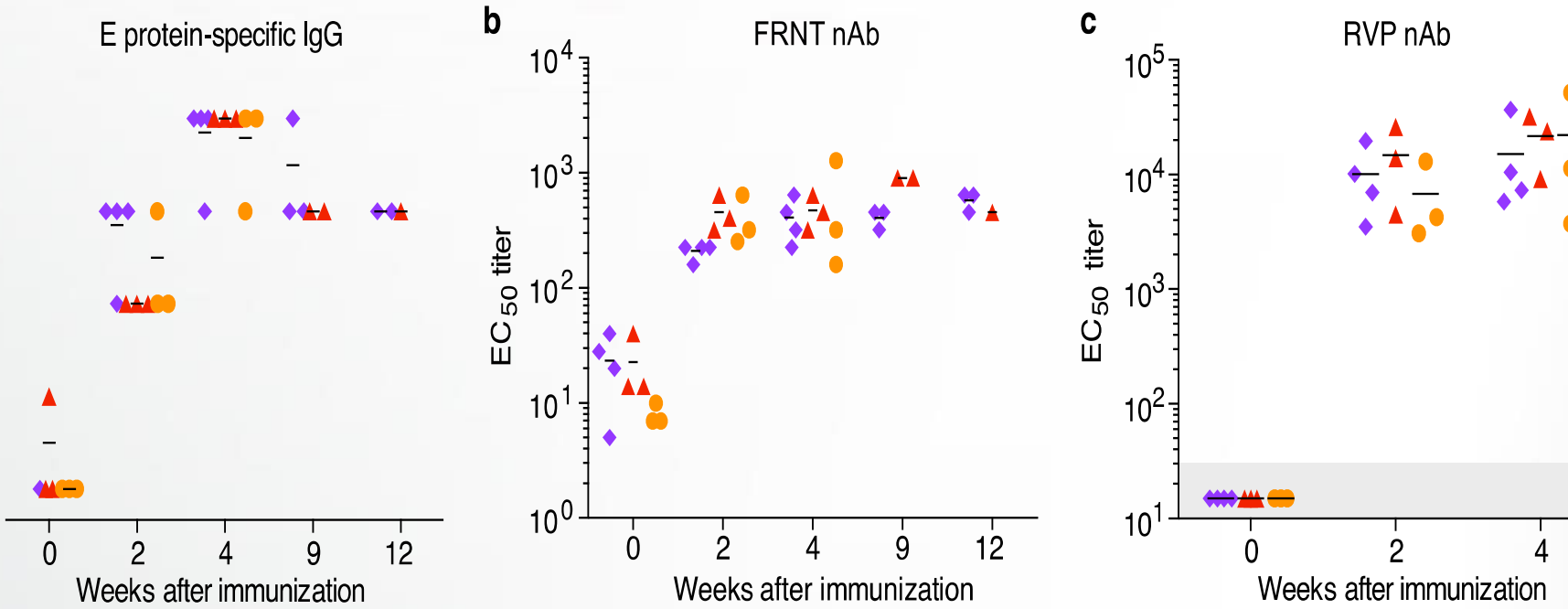


Courtesy Weissman Laboratory

Pardi et al., Nature 2017

RNA-LNP: Protection from Viral Chall
Macaques

- Zika modified mRNA-LNP vaccine in macaques

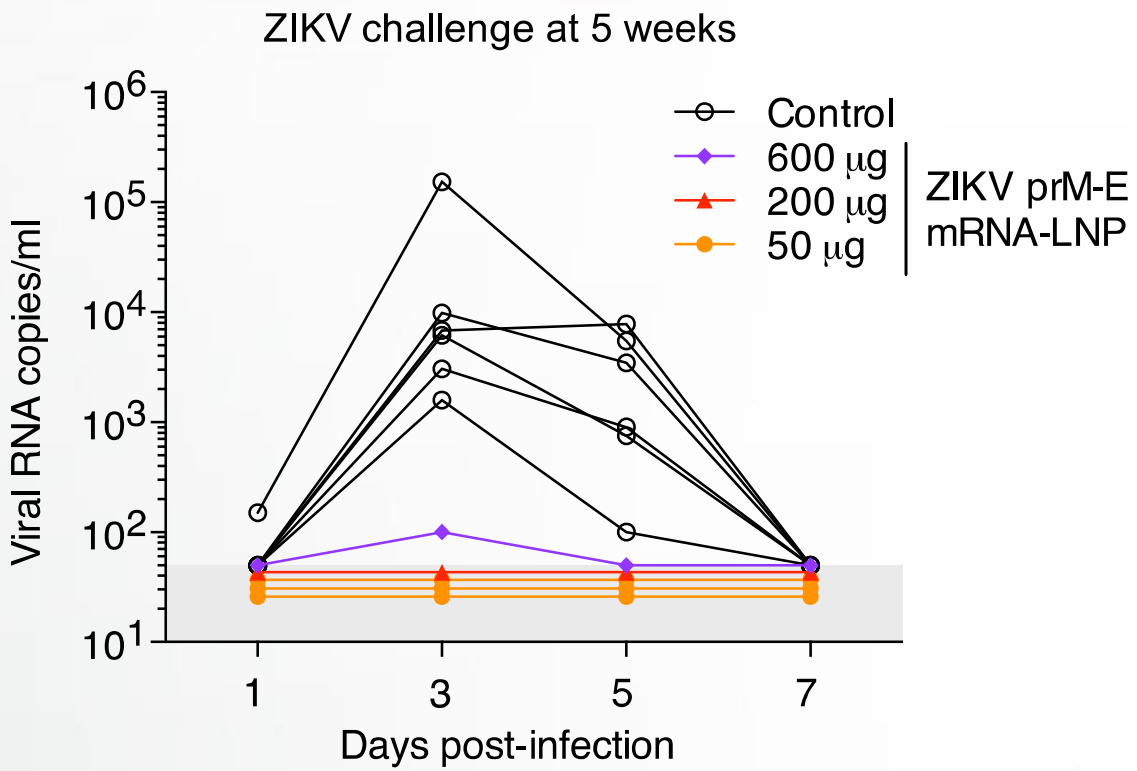


Courtesy Weissman Laboratory

Pardi et al., Nature 2017

RNA-LNP: Protection from Viral Chall
Macaques

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



Courtesy Weissman Laboratory

Pardi et al., Nature 2017

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 viv
  - Expanding clinical opportunities for mRNA therapeutics

BioNTech-Pfizer Exhibit 1248
BioNTech SE and Pfizer Inc. v. ModernaTX, Inc. IPR2023-01359
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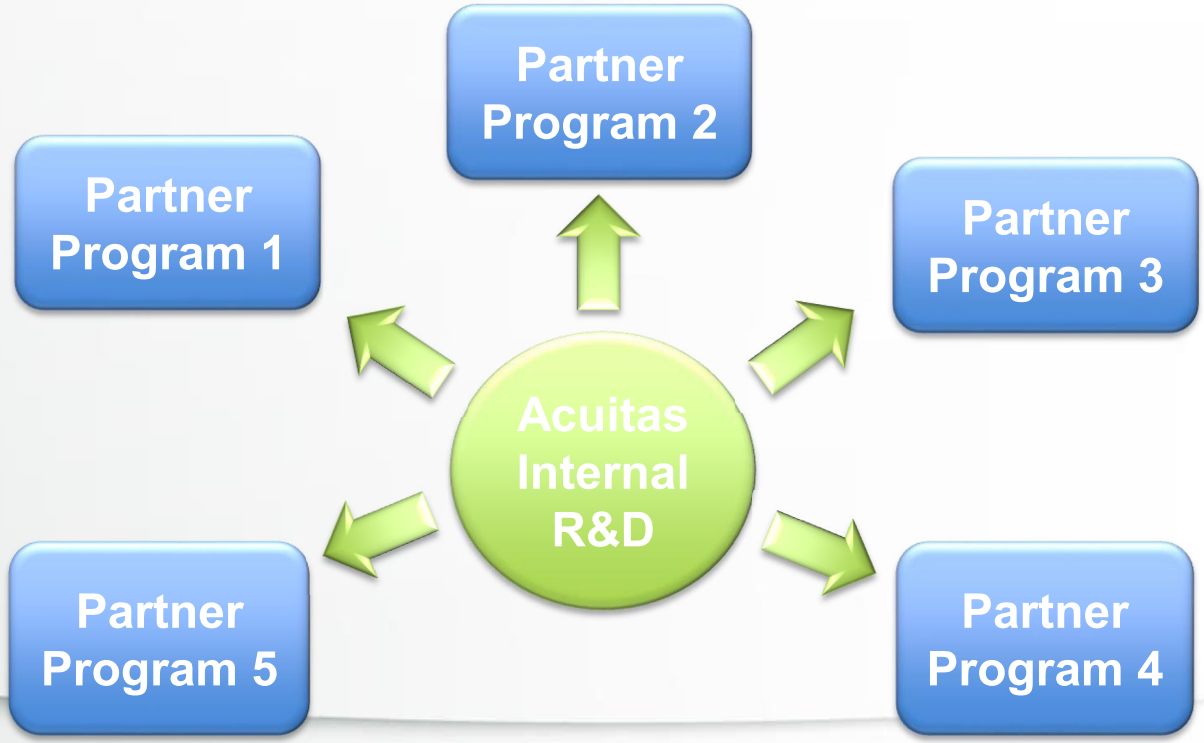
Acuitas Business Model

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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