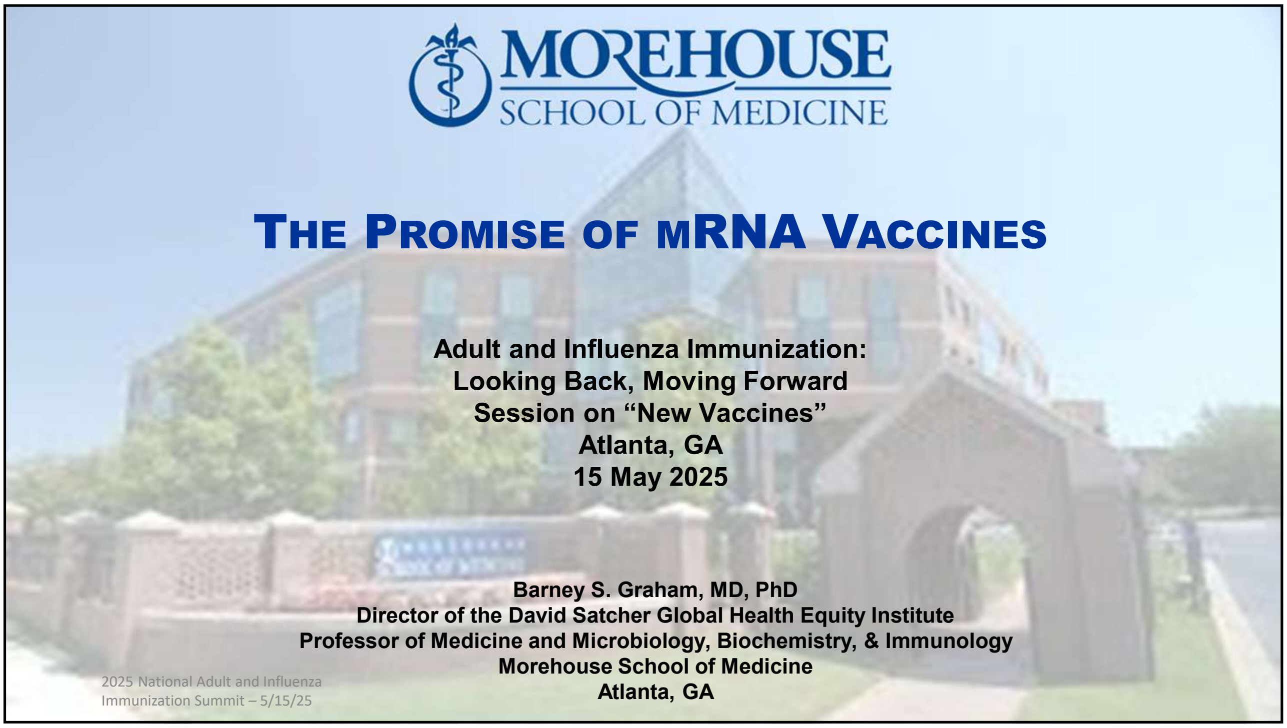


MOREHOUSE SCHOOL OF MEDICINE

THE PROMISE OF MRNA VACCINES

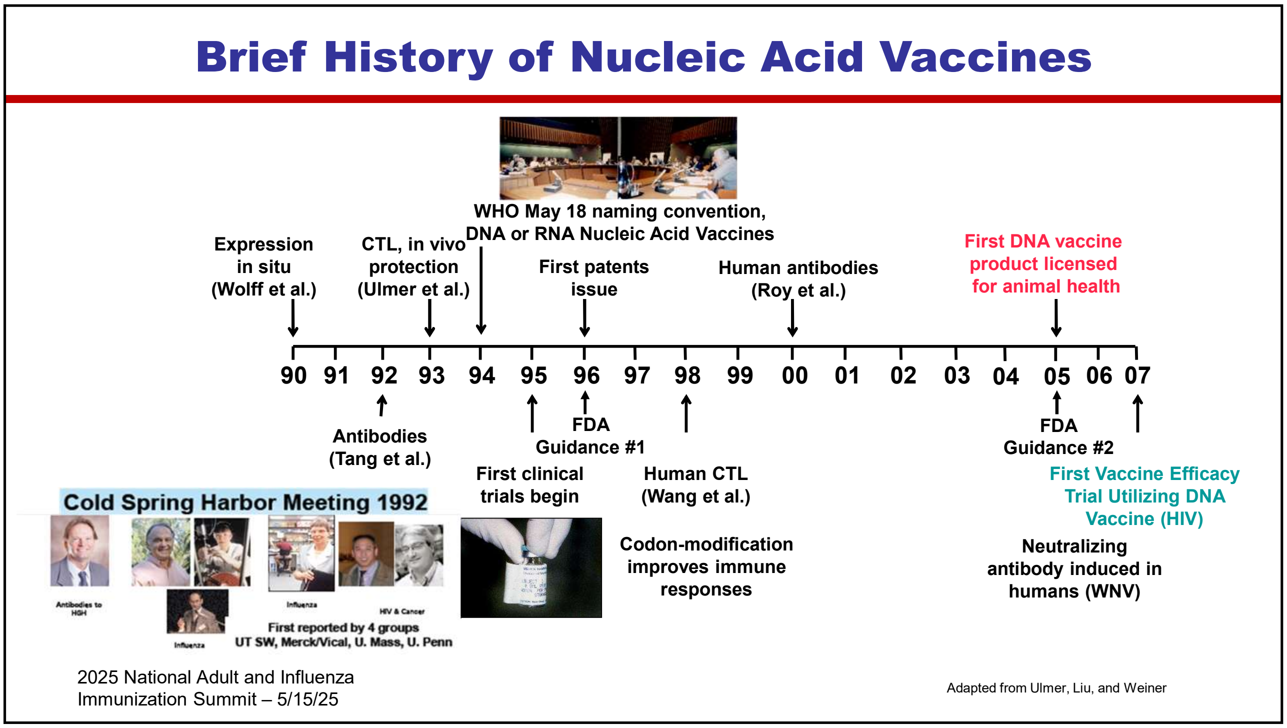
Adult and Influenza Immunization:
Looking Back, Moving Forward
Session on "New Vaccines"
Atlanta, GA
15 May 2025

Barney S. Graham, MD, PhD
Director of the David Satcher Global Health Equity Institute
Professor of Medicine and Microbiology, Biochemistry, & Immunology
Morehouse School of Medicine
Atlanta, GA

MOREHOUSE SCHOOL OF MEDICINE
I AM MSM
50 Years of Shaping the Future of Health Equity

Disclosures

- Vaccine Inventor
  - Coronaviruses
  - Respiratory syncytial virus
  - Influenza virus
  - Nipah and other paramyxoviruses
  - Zika
- Monoclonal Antibody Inventor
  - Ebola
  - SARS-CoV-2 and other coronaviruses
- Scientific Advisory Boards
  - Vaccine Company, Inc.
  - Third Rock Ventures, Foundry
  - Akagera
- Consultant
  - GSK
  - Pfizer
  - Sanofi
  - AstroZeneca
  - Exevir



Brief History of Nucleic Acid Vaccines

WHO May 18 naming convention, DNA or RNA Nucleic Acid Vaccines

Expression in situ (Wolff et al.)

CTL, in vivo protection (Ulmer et al.)

First patents issue

Human antibodies (Roy et al.)

First DNA vaccine product licensed for animal health

90 91 92 93 94 95 96 97 98 99 00 01 02 03 04 05 06 07

Antibodies (Tang et al.)

FDA Guidance #1

First clinical trials begin

Human CTL (Wang et al.)

Codon-modification improves immune responses

FDA Guidance #2

First Vaccine Efficacy Trial Utilizing DNA Vaccine (HIV)

Neutralizing antibody induced in humans (WNV)

Cold Spring Harbor Meeting 1992

First reported by 4 groups
UT SW, Merck/Vical, U. Mass, U. Penn

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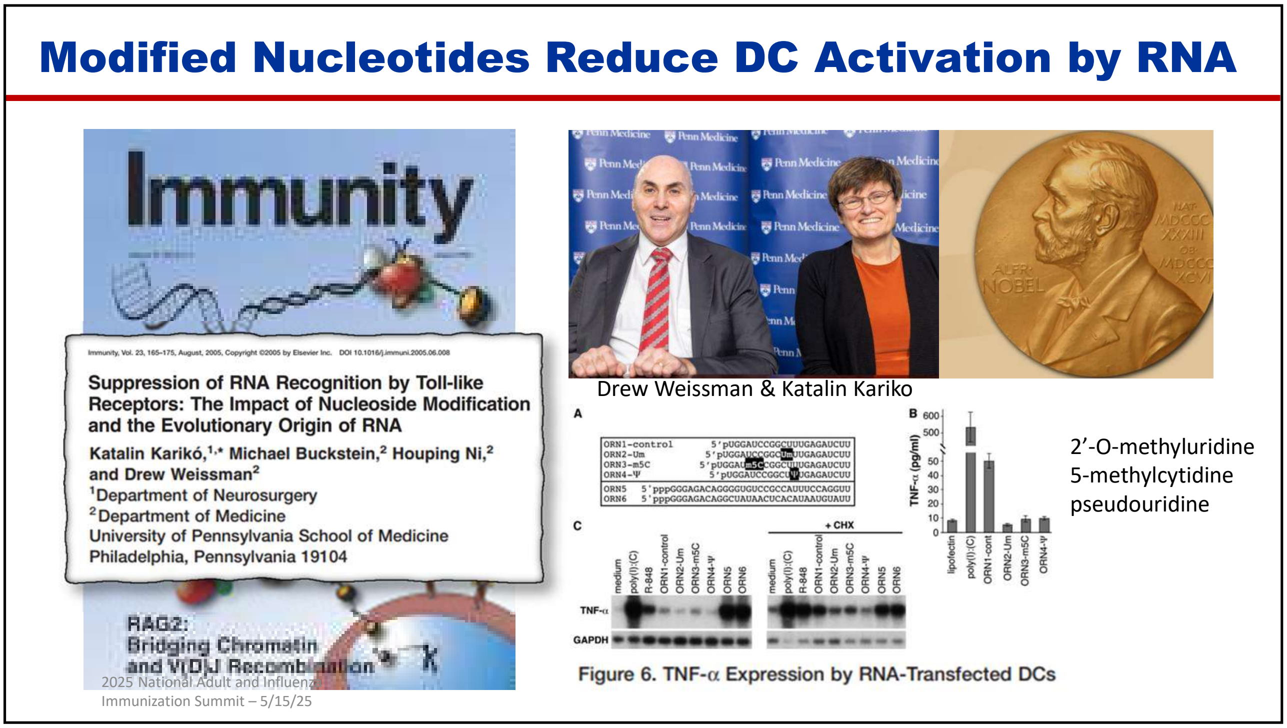
Immunization Summit – 5/15/25

Adapted from Ulmer, Liu, and Weiner



Modified Nucleotides Reduce DC Activation by RNA

Immunity, Vol. 23, 165–175, August, 2005, Copyright ©2005 by Elsevier Inc. DOI 10.1016/j.immuni.2005.06.008

Suppression of RNA Recognition by Toll-like Receptors: The Impact of Nucleoside Modification and the Evolutionary Origin of RNA

Katalin Karikó,[1,*] Michael Buckstein,[2] Houping Ni,[2] and Drew Weissman[2]
[1]Department of Neurosurgery
[2]Department of Medicine
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania 19104

Drew Weissman & Katalin Kariko

Figure 6. TNF-α Expression by RNA-Transfected DCs

2'-O-methyluridine
5-methylcytidine
pseudouridine

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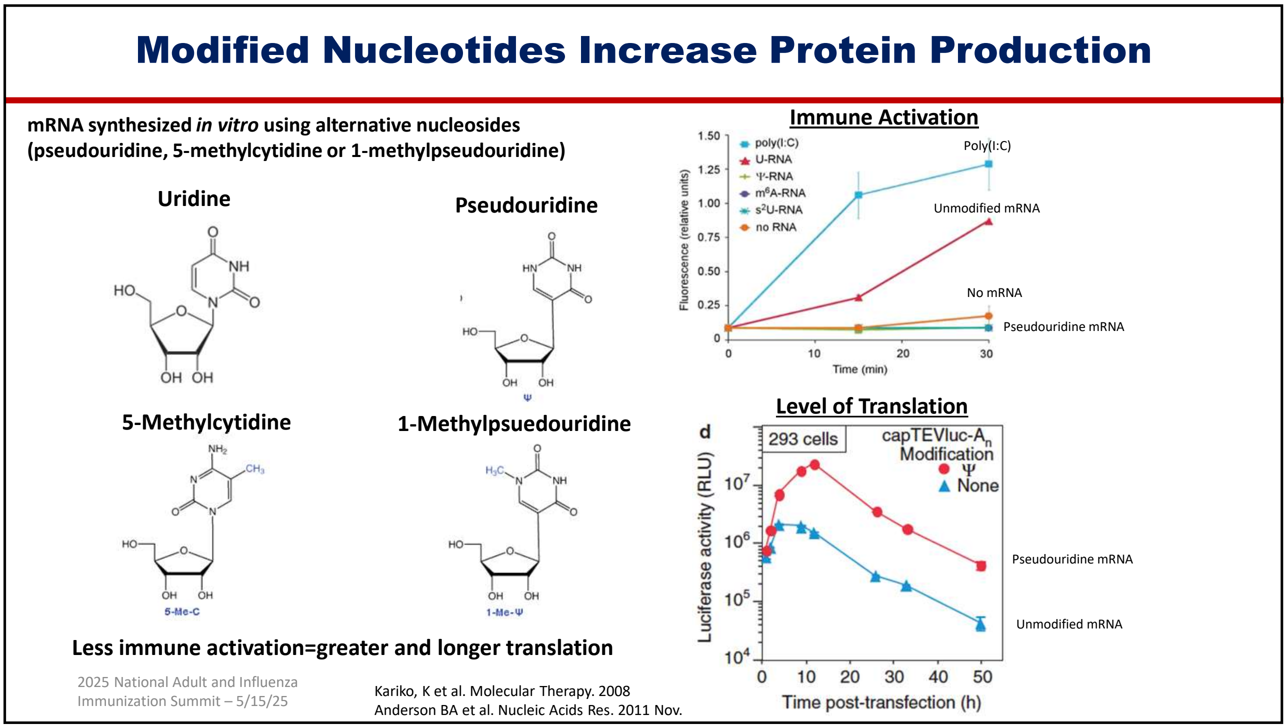


Modified Nucleotides Increase Protein Production

mRNA synthesized *in vitro* using alternative nucleosides (pseudouridine, 5-methylcytidine or 1-methylpseudouridine)

Uridine

Pseudouridine

5-Methylcytidine

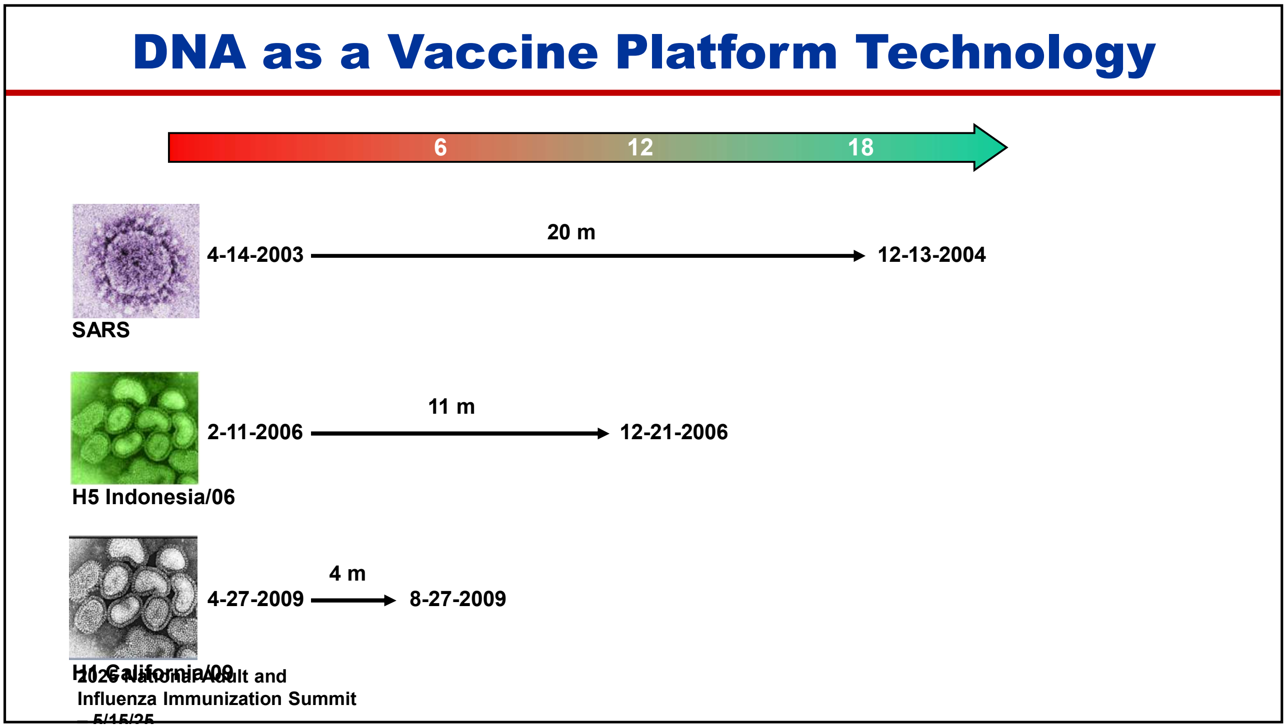
1-Methylpsuedouridine

Less immune activation=greater and longer translation

Immune Activation

Level of Translation

Kariko, K et al. Molecular Therapy. 2008
Anderson BA et al. Nucleic Acids Res. 2011 Nov.

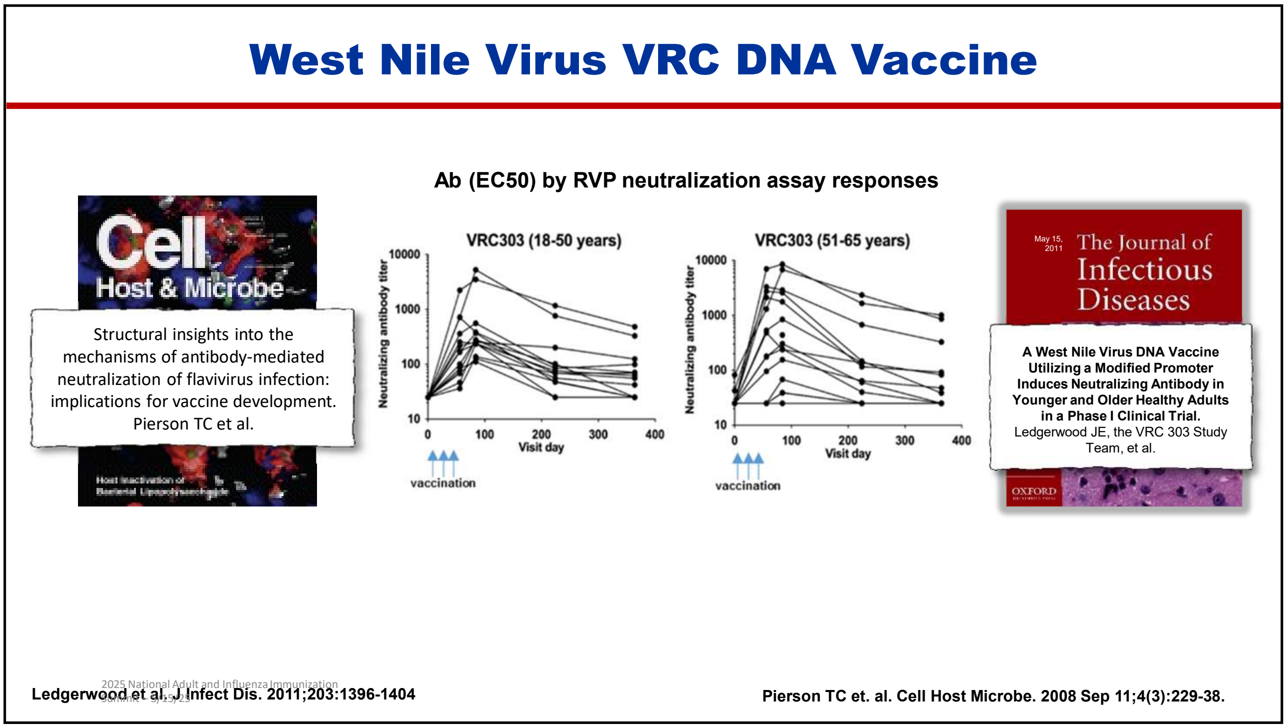


DNA as a Vaccine Platform Technology

SARS: 4-14-2003 → 20 m → 12-13-2004

H5 Indonesia/06: 2-11-2006 → 11 m → 12-21-2006

H1 California/09: 4-27-2009 → 4 m → 8-27-2009



West Nile Virus VRC DNA Vaccine

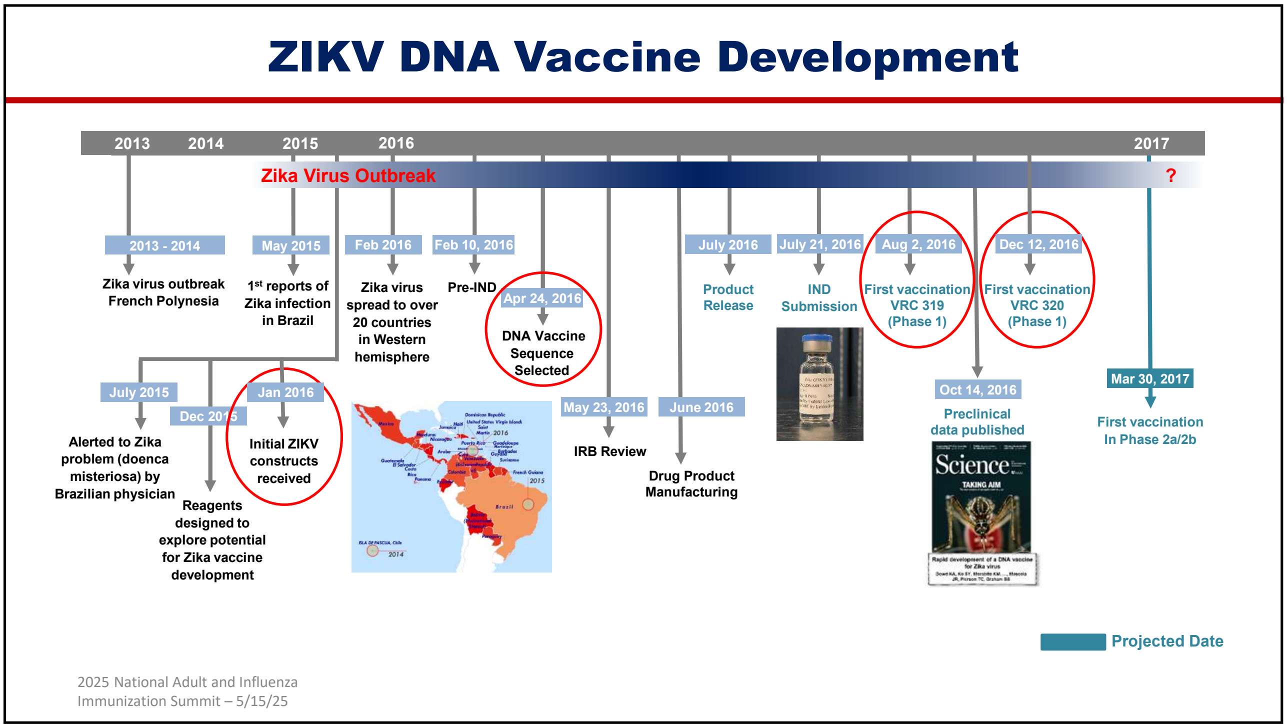
Ab (EC50) by RVP neutralization assay responses

Structural insights into the mechanisms of antibody-mediated neutralization of flavivirus infection: implications for vaccine development.
Pierson TC et al.

A West Nile Virus DNA Vaccine Utilizing a Modified Promoter Induces Neutralizing Antibody in Younger and Older Healthy Adults in a Phase I Clinical Trial.
Ledgerwood JE, the VRC 303 Study Team, et al.

Ledgerwood et al. J Infect Dis. 2011;203:1396-1404

Pierson TC et. al. Cell Host Microbe. 2008 Sep 11;4(3):229-38.



ZIKV DNA Vaccine Development

2013 - 2014
Zika virus outbreak French Polynesia

May 2015
1st reports of Zika infection in Brazil

July 2015
Alerted to Zika problem (doenca misteriosa) by Brazilian physician

Dec 2015
Reagents designed to explore potential for Zika vaccine development

Jan 2016
Initial ZIKV constructs received

Feb 2016
Zika virus spread to over 20 countries in Western hemisphere

Feb 10, 2016
Pre-IND

Apr 24, 2016
DNA Vaccine Sequence Selected

May 23, 2016
IRB Review

June 2016
Drug Product Manufacturing

July 2016
Product Release

July 21, 2016
IND Submission

Aug 2, 2016
First vaccination VRC 319 (Phase 1)

Oct 14, 2016
Preclinical data published

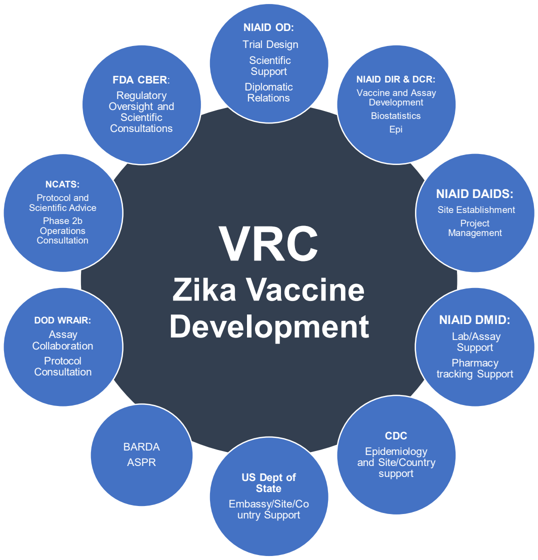
Rapid development of a DNA vaccine for Zika virus
Dowd KA, Ko SY, Morabito KM, ..., Mascola JR, Pierson TC, Graham BB

Dec 12, 2016
First vaccination VRC 320 (Phase 1)

Mar 30, 2017
First vaccination In Phase 2a/2b

🟦 Projected Date

VRC Zika Vaccine USG Collaboration



VRC
Zika Vaccine Development

NIAID OD:
Trial Design
Scientific Support
Diplomatic Relations

NIAID DIR & DCR:
Vaccine and Assay Development
Biostatistics
Epi

NIAID DAIDS:
Site Establishment
Project Management

NIAID DMID:
Lab/Assay Support
Pharmacy tracking Support

CDC
Epidemiology and Site/Country support

US Dept of State
Embassy/Site/Country Support

BARDA
ASPR

DOD WRAIR:
Assay Collaboration
Protocol Consultation

NCATS:
Protocol and Scientific Advice
Phase 2b Operations Consultation

FDA CBER:
Regulatory Oversight and Scientific Consultations

Decision to support DNA vs. Whole-inactivated

- Both likely to work based on animal model data or historical precedent
- Both difficult to scale-up
- Both have willing Pharma partners
- Both have unknowns: Epitope authenticity; durability, final cost

- Inactivated whole virus is a licensed technology in clinical use
- Inactivated whole virus has more antigens and is a more native particle
- Inactivated whole virus is given by traditional needle and syringe

- DNA is farther advanced in clinical development
- DNA induces antibody responses and CD8 T cell responses
- DNA may facilitate mRNA advancement

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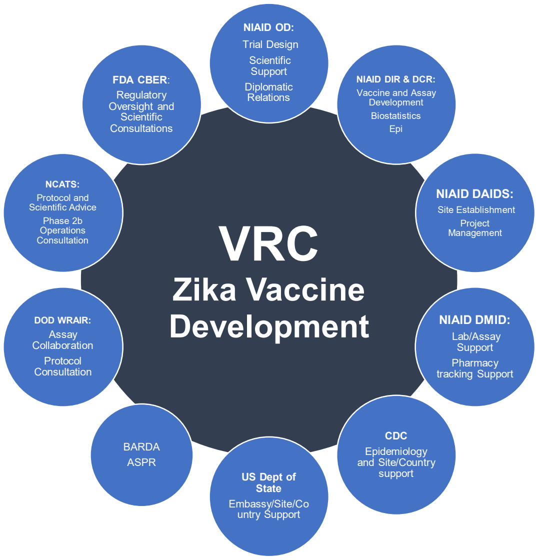

VRC Zika Vaccine USG Collaboration

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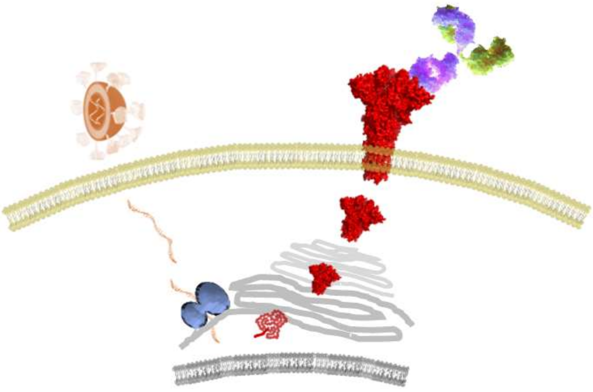
Immunization Summit – 5/15/25

mRNA immunization strategy

Protein expression affected by mRNA chemistry and manufacturing process



- Authentic antigen presentation
- Induction of both antibody and CD8 T cells
- Th1-biased CD4 T cells
- Vaccine components rapidly degraded
- Only requires entry into cytoplasm
- No anti-vector immunity
- Rapid platform manufacturing
- Chemical synthesis, no bioreactor requirement
- Scalable

Flavivirus Nucleic Acid Vaccines

A West Nile Virus DNA Vaccine Induces Neutralizing Antibody in Healthy Adults during a Phase 1 Clinical Trial

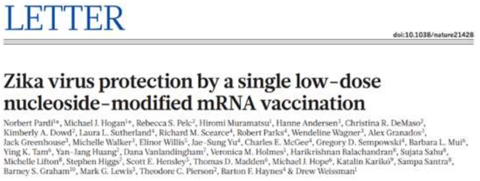
WNV 2007

Rapid development of a DNA vaccine for Zika virus
Dowd KA, Ko SY, Morabito KM, ..., Mascola JR, Pierson TC, Graham BS

Zika 2016

DNA → mRNA

2017



LETTER

doi:10.1038/nature21428

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[3], 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[5], 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]

2020

SCIENCE ADVANCES | RESEARCH ARTICLE

VIROLOGY

Development of a potent Zika virus vaccine using self-amplifying messenger RNA

Kate Luisi[1*], Kaitlyn M. Morabito[2*], Katherine E. Burgomaster[3*], Mayuri Sharma[1†], Wing-Pui Kong[2], Bryant M. Foreman[3], Sonal Patel[1], Brian Fisher[2], Maya A. Aleshnick[3‡], Jason Laliberte[1], Madison Wallace[1], Tracy J. Ruckwardt[2], David N. Gordon[3], Christine Linton[1§], Nicole Ruggiero[1||], Jessica L. Cohen[1], Russell Johnson[1], Kunal Aggarwal[1], Sung-Youl Ko[2], Eun Sung Yang[2], Rebecca S. Pelc[3¶], Kimberly A. Dowd[3], Derek O'Hagan[1], Jeffrey Ulmer[1], Sally Mossman[1], Anna Sambor[1], Edith Lepine[1#], John R. Mascola[2], Theodore C. Pierson[3**], Barney S. Graham[2**], Dong Yu[1**]

2023

npj | vaccines

www.nature.com/npjvaccines

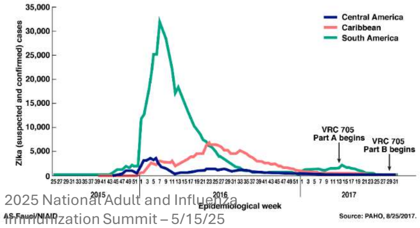
ARTICLE OPEN

Check for updates

An optimized messenger RNA vaccine candidate protects non-human primates from Zika virus infection

Brooke Bollman[1,12], Naveen Nunna[1], Kapil Bahl[1], Chiaowen Joyce Hsiao[1], Hamilton Bennett[1], Scott Butler[2], Bryant Foreman[3], Katherine E. Burgomaster[3], Maya Aleshnick[3], Wing-Pui Kong[4], Brian E. Fisher[4], Tracy J. Ruckwardt[4], Kaitlyn M. Morabito[4], Barney S. Graham[4], Kimberly A. Dowd[3], Theodore C. Pierson[3] and Andrea Carfi[1]

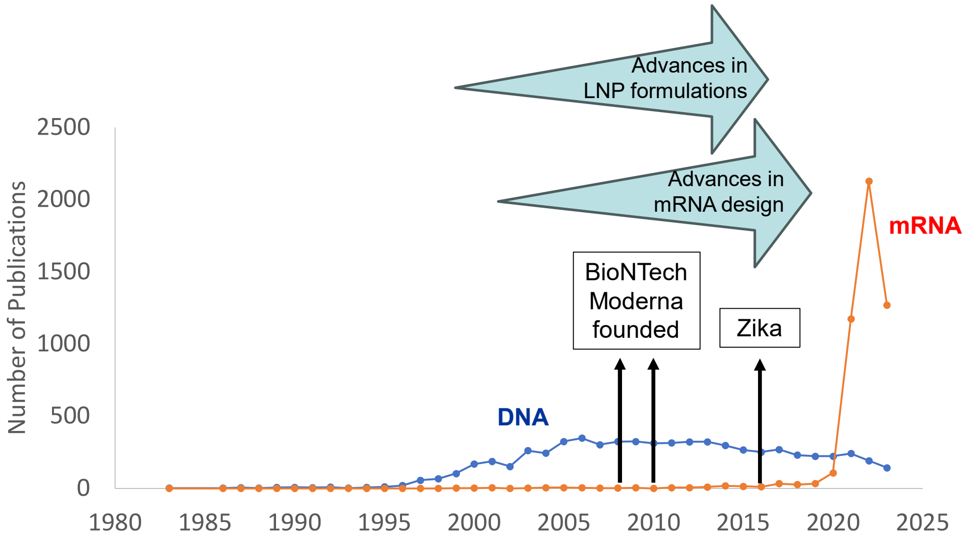
Suspected and Confirmed Zika Cases in the Americas, 2015-2017



AS Fauci/NIAID

Source: PAHO, 8/25/2017.

Publications on Nucleic Acid Vaccines



Pandemic Preparedness

Threats & Outbreaks

2001	**Nipah**
2001	**Smallpox**
2002	**SARS-CoV-1**
2002	**WNV**
2005	**H5N1 influenza**
2008	**Marburg**
2009	**H1N1 influenza**
2011	**Chikungunya**
2012	**MERS-CoV**
2014	**Ebola**
2014	**EV-D68**
2016	**Zika**

Generalizable and Precise Antigen Design


nature
immunology

REVIEW ARTICLE

nature
immunology

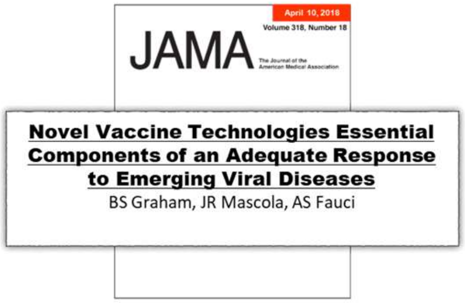
Emerging viral diseases from a vaccinology perspective: preparing for the next pandemic

Barney S. Graham* and Nancy J. Sullivan*

Distinct human pDC populations
Regulating macrophage phagocytosis
Controlling the tumor microenvironment

Prototype Pathogens

Speed

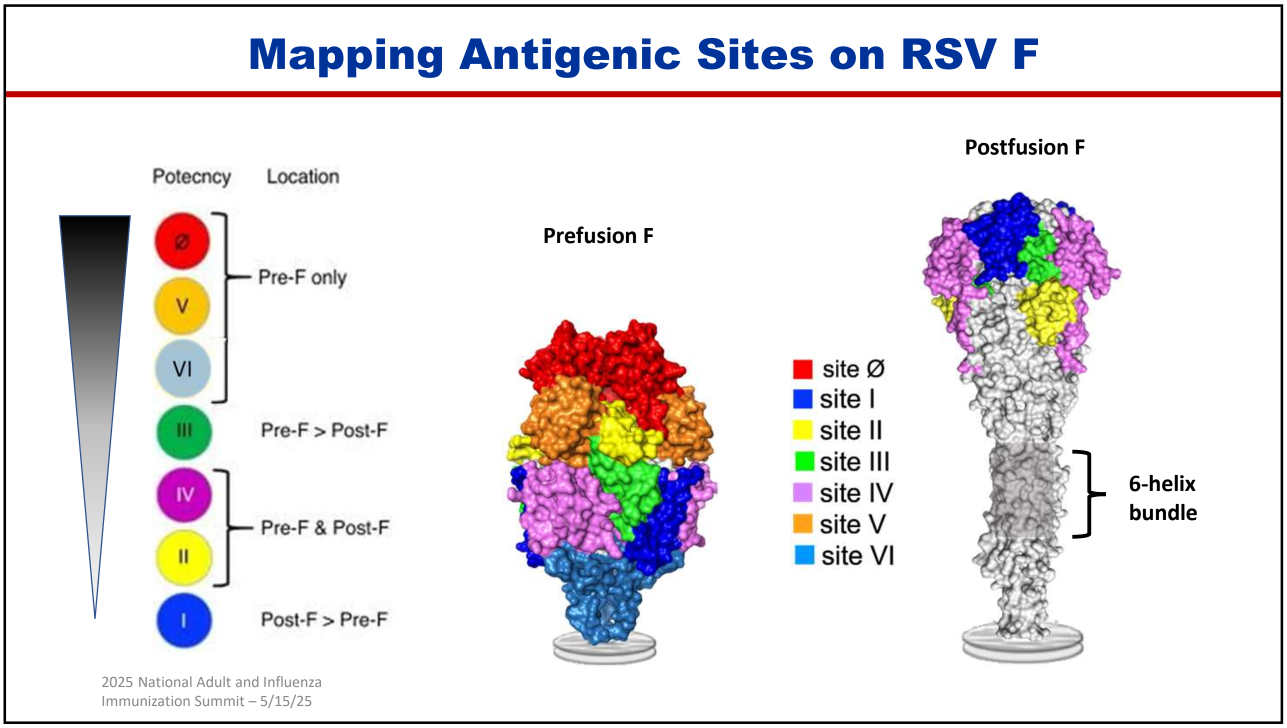

April 10, 2018
Volume 318, Number 18

JAMA
The Journal of the
American Medical Association

Novel Vaccine Technologies Essential Components of an Adequate Response to Emerging Viral Diseases

BS Graham, JR Mascola, AS Fauci

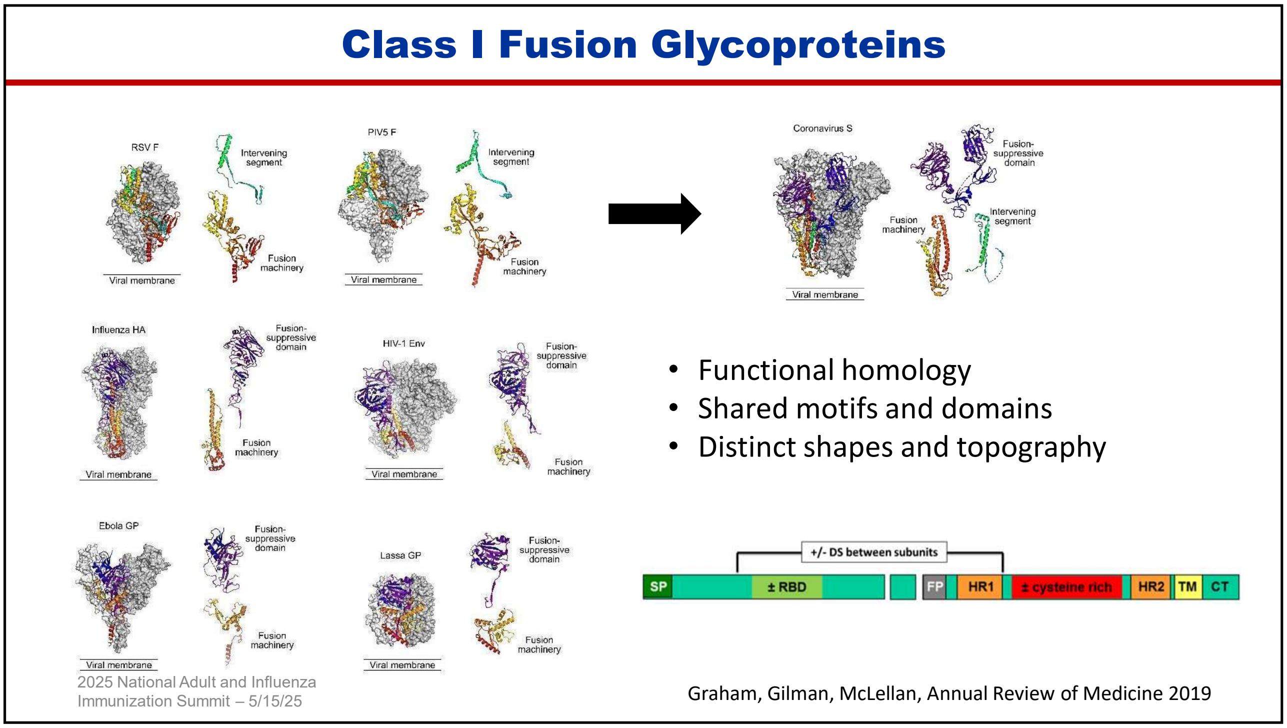
Platform Manufacturing



Mapping Antigenic Sites on RSV F

- 🟥 site Ø
- 🟦 site I
- 🟨 site II
- 🟩 site III
- 🟪 site IV
- 🟧 site V
- 🟦 site VI

2025 National Adult and Influenza
Immunization Summit – 5/15/25

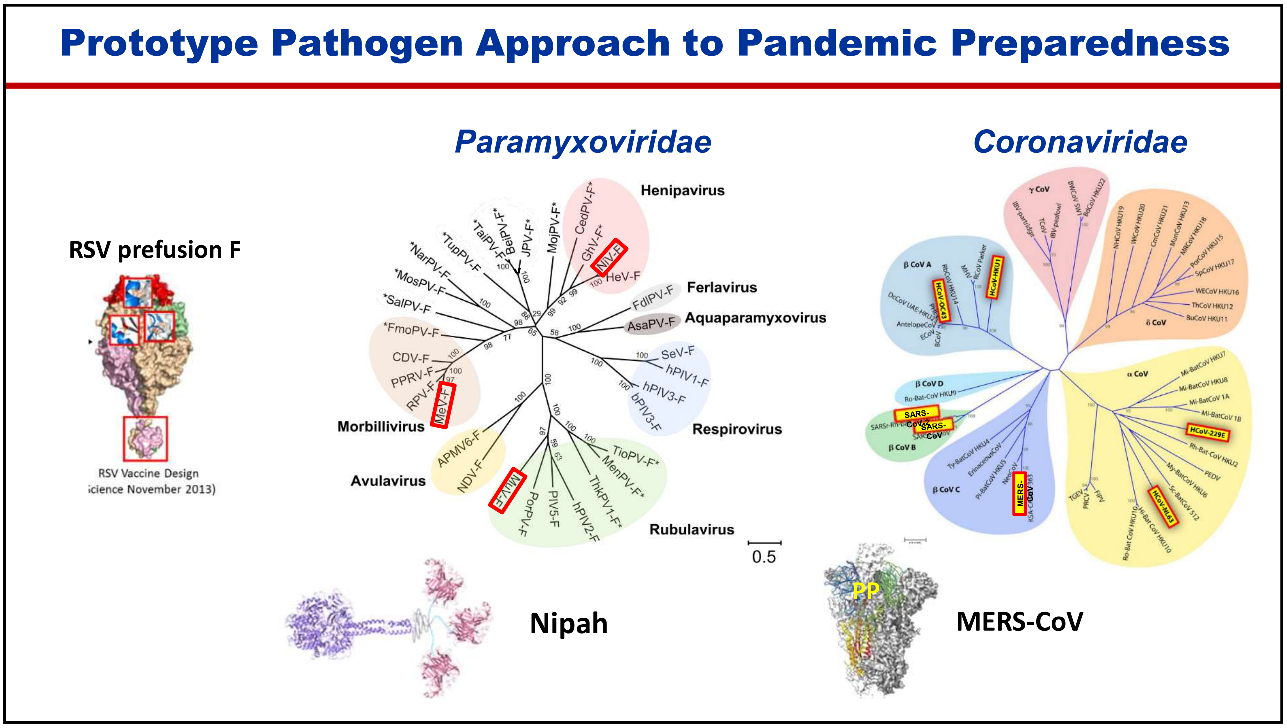


Class I Fusion Glycoproteins

- Functional homology
- Shared motifs and domains
- Distinct shapes and topography

2025 National Adult and Influenza
Immunization Summit – 5/15/25

Graham, Gilman, McLellan, Annual Review of Medicine 2019



Prototype Pathogen Approach to Pandemic Preparedness

Paramyxoviridae

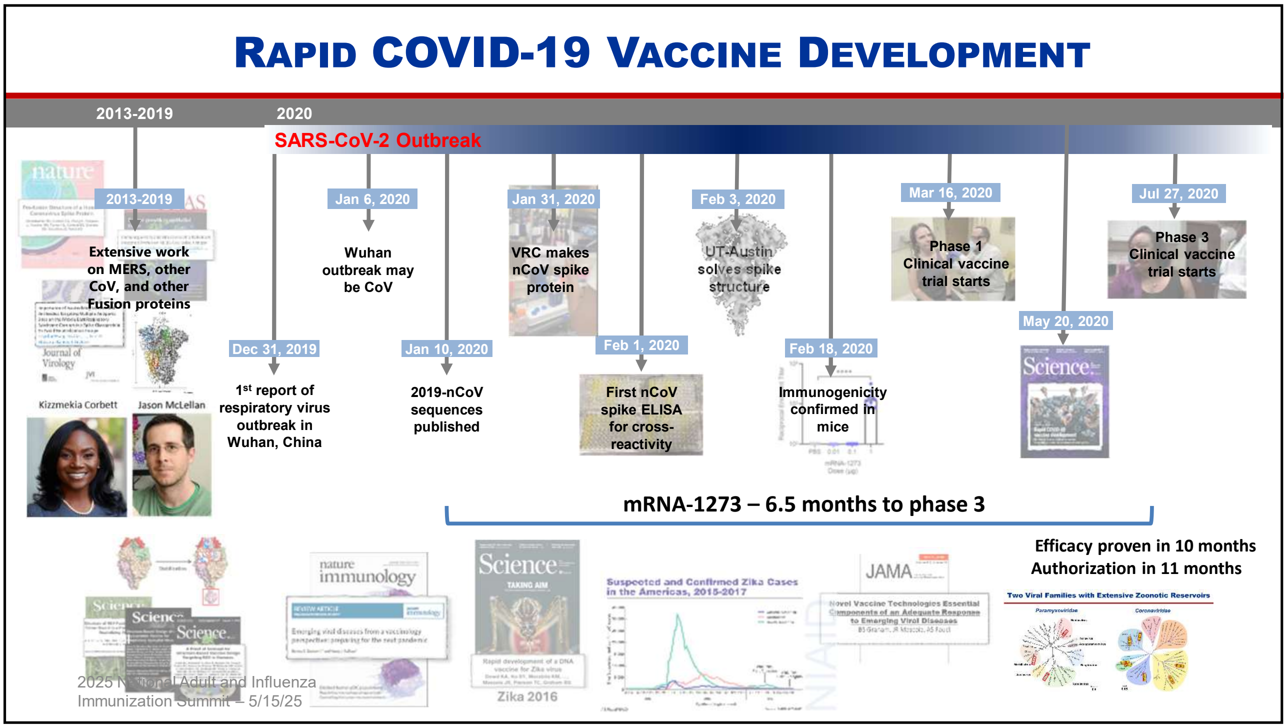
Coronaviridae

RSV prefusion F

RSV Vaccine Design
Science November 2013)

Nipah

MERS-CoV



RAPID COVID-19 VACCINE DEVELOPMENT

2013-2019

2020

SARS-CoV-2 Outbreak

2013-2019 Extensive work on MERS, other CoV, and other Fusion proteins

Kizzmekia Corbett

Jason McLellan

Dec 31, 2019 1st report of respiratory virus outbreak in Wuhan, China

Jan 6, 2020 Wuhan outbreak may be CoV

Jan 10, 2020 2019-nCoV sequences published

Jan 31, 2020 VRC makes nCoV spike protein

Feb 1, 2020 First nCoV spike ELISA for cross-reactivity

Feb 3, 2020 UT-Austin solves spike structure

Feb 18, 2020 Immunogenicity confirmed in mice

Mar 16, 2020 Phase 1 Clinical vaccine trial starts

May 20, 2020

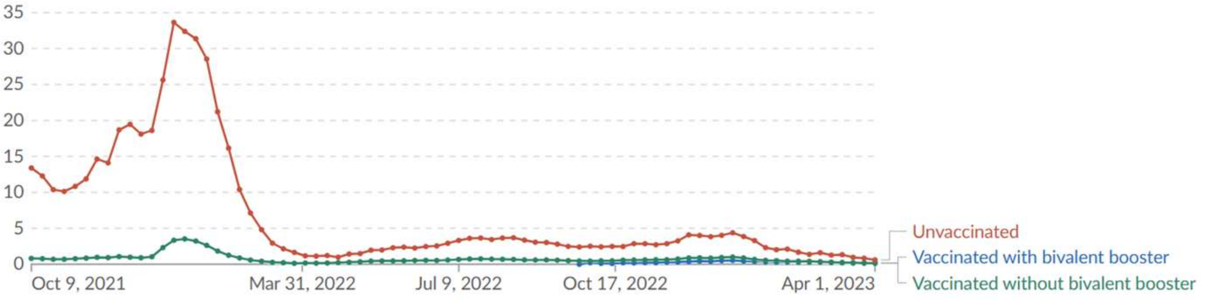
Jul 27, 2020 Phase 3 Clinical vaccine trial starts

mRNA-1273 – 6.5 months to phase 3

Efficacy proven in 10 months
Authorization in 11 months

United States: COVID-19 weekly death rate by vaccination status, All ages

Death rates are calculated as the number of deaths in each group, divided by the total number of people in this group. This is given per 100,000 people.



Data source: Centers for Disease Control and Prevention (2023)

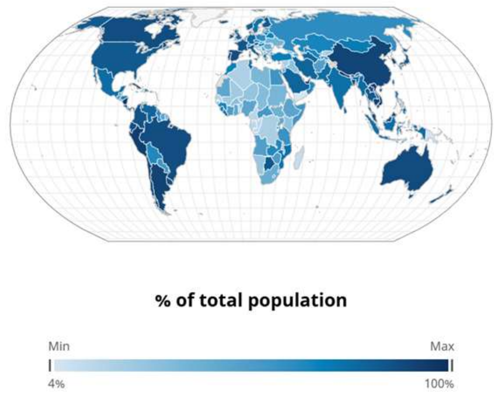
OurWorldinData.org/coronavirus | CC BY

Note: The mortality rate for the 'All ages' group is age-standardized to account for the different vaccination rates of older and younger people.

Safety and Effectiveness of mRNA Vaccines

Percentage of total population vaccinated with at least one dose of a COVID-19 vaccine

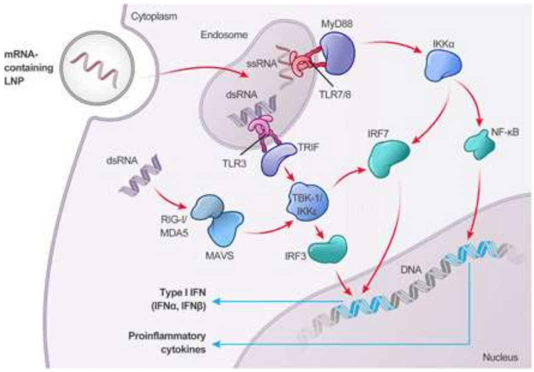
World, 31 December 2023



- ~13.7 billion COVID-19 vaccine doses given
- ~50% were mRNA
- Adverse events
  - local reactions
  - systemic reactions
  - ~2 per 100,000 myocarditis
  - No documented long-term disability
  - No evidence of vaccine-associated mortality
- In 2021 >14 million deaths averted based on mortality attributed to COVID-19, and >19 million deaths averted based on excess mortality
- ~3 million deaths averted in U.S.

mRNA immunization strategy

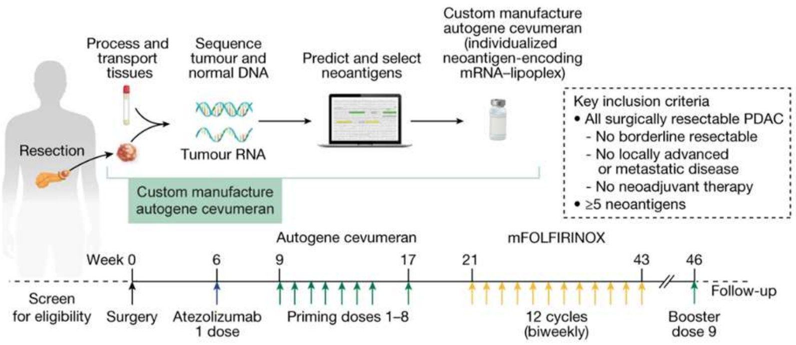
Protein expression affected by mRNA chemistry and manufacturing process



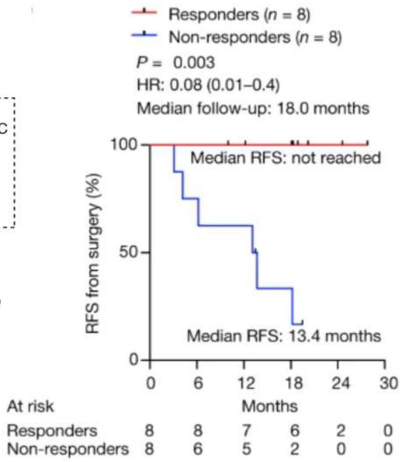
Nelson et al. Sci Adv 2020

- COVID-19 data indicate mRNA is safe and efficacious
- Stability and supply chain is improving
- Small footprint, small batch manufacturing is well suited for LMICs and rapid iterative design cycles
- mRNA is not magic – antigen design is critical
- Need to minimize mRNA side effects and reduce cost

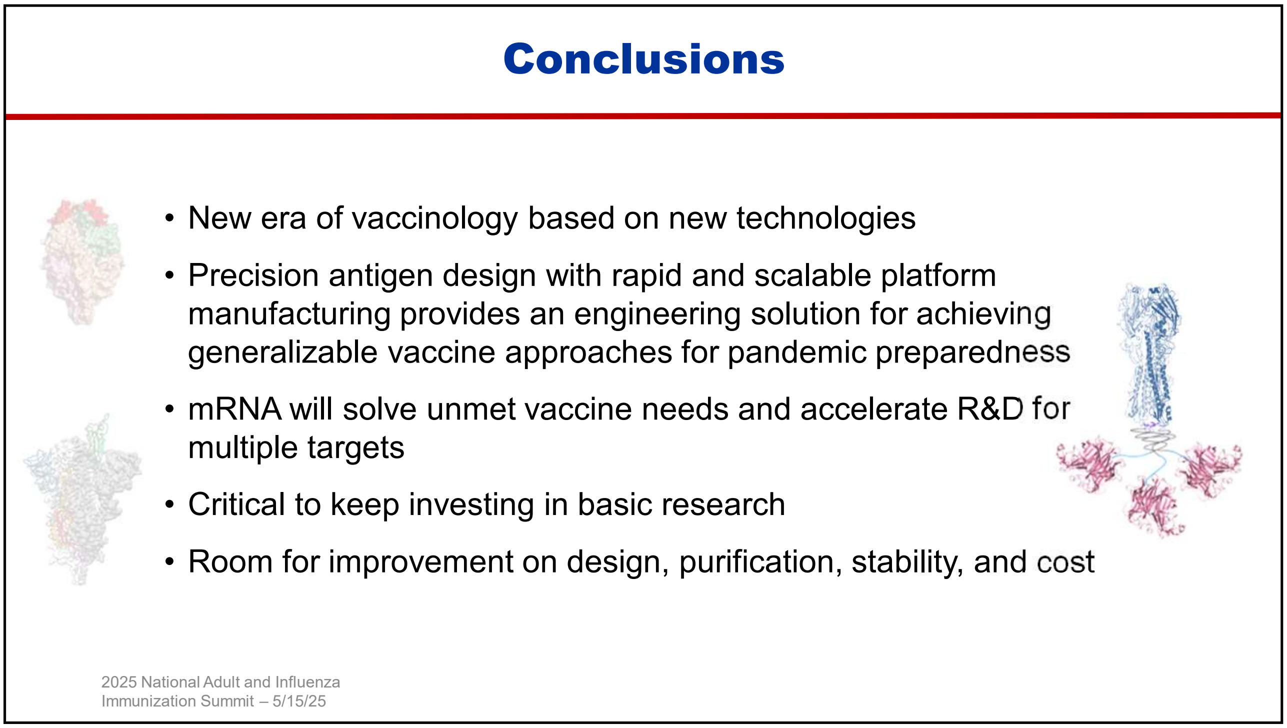
mRNA Vaccine for Pancreatic Cancer



Anti-PD-L1 mRNA vaccine Modified chemoRx



Sethna Z, et al. RNA neoantigen vaccines prime long-lived CD8+ T cells in pancreatic cancer. Nature. 2025 Mar;639(8056):1042-1051.



Conclusions

- New era of vaccinology based on new technologies
- Precision antigen design with rapid and scalable platform manufacturing provides an engineering solution for achieving generalizable vaccine approaches for pandemic preparedness
- mRNA will solve unmet vaccine needs and accelerate R&D for multiple targets
- Critical to keep investing in basic research
- Room for improvement on design, purification, stability, and cost