The Path to Success for mRNA Vaccines

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Agenda

- Overview of unmet vaccine needs
- Potential for mRNA vaccines to address unmet needs
- History of nucleic acid vaccines
- Lessons learned from COVID-19
- Challenges/opportunities for mRNA technology
- Future outlook

Current challenges in vaccines discovery and development

- Improving suboptimal vaccines (e.g., Tb, influenza)
- Developing new vaccines for unmet medical needs (e.g., HIV, RSV, cancer)
- Responding rapidly to emerging threats (e.g., SARS, Ebola, MERS, Zika, pandemic influenza)
- Streamlining the vaccines R&D process

Vaccine technologies

Vaccine Technology	Attributes	Limitations
Live organism (e.g., oral polio, measles)	• Launches live infection • Induces broad, potent immunity (Ab, CMI)	• Potential safety risks • Not always feasible • Long R&D timelines
Inactivated organism (e.g., rabies, hepatitis A)	• Increased safety over live vaccines • Simpler R&D (attenuation not required)	• Narrow immunity (Ab) • Integrity of antigen • Not always feasible
Subunit (e.g., hepatitis B, varicella zoster)	• Increased safety (low risk of virulence) • More defined composition • Focuses immunity on key antigens	• Narrow immunity (Ab) • Requires adjuvant • Long R&D timelines

Impetus for nucleic acid vaccines:

➢ Combine positive attributes and avoid limitations of existing vaccine technologies

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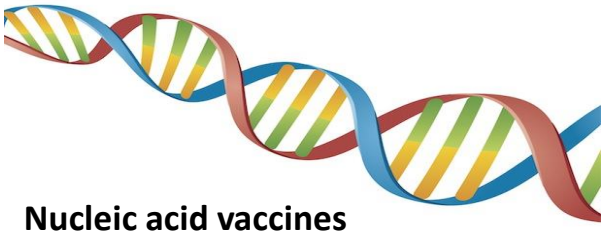

Nucleic acid vaccines

Broad utility of mRNA in animal models

Disease Target	Species	Immunogenicity	Efficacy
RSV	M, CR, GP	☑	☑
CMV	M, CR, GP, R, NHP	☑	Not tested
Rabies	M, R, NHP	☑	☑
Ebola	GP	☑	☑
Malaria	M	☑	☑
Rhinovirus	M	☑	Not tested
Flu	M, F, NHP	☑	☑
HIV/SIV	M, R, NHP	☑	Not tested
VEE	M	☑	☑
Zika	M, NHP	☑	☑
SARS-CoV-2	M, R, H	☑	☑
Yellow Fever	M	☑	Not tested
Cancer	M	☑	☑
TB, GBS, GAS	M	☑	☑

M=mouse, CR=cotton rat, R=rabbit, GP=guinea pig, F=ferret, NHP=non-human primate (Rhesus), B=bovine, H=hamster

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Circa 1918

saRNA vaccine response to 2013 H7N9 influenza outbreak

H7N9 sequences released on GISAID

Synthetic gene shipped; PCR primers ordered

DNA scale-up initiated

saRNA-H7 produced; BHK transfected with RNA

day 1 | day 2 | day 3 | day 4 | day 5 | day 6 | day 7 | day 8

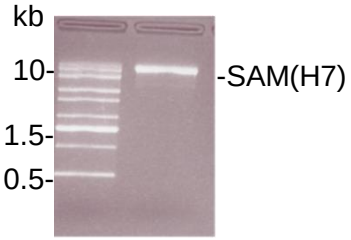
JCVI order oligos; gene synthesis begins

H7 gene amplified and cloned into replicon plasmid

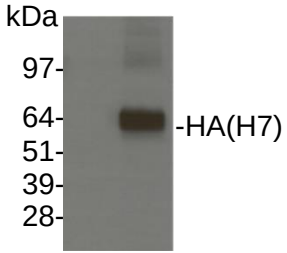
Replicon plasmid DNA template produced

RNA integrity confirmed; gene expression confirmed

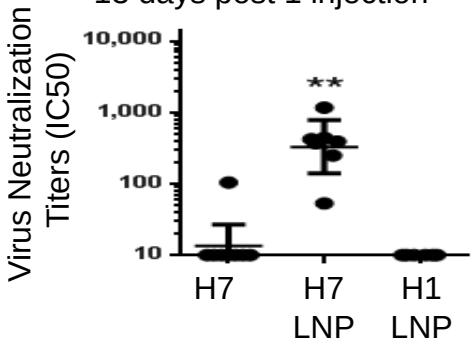
Agarose gel



Immunoblot

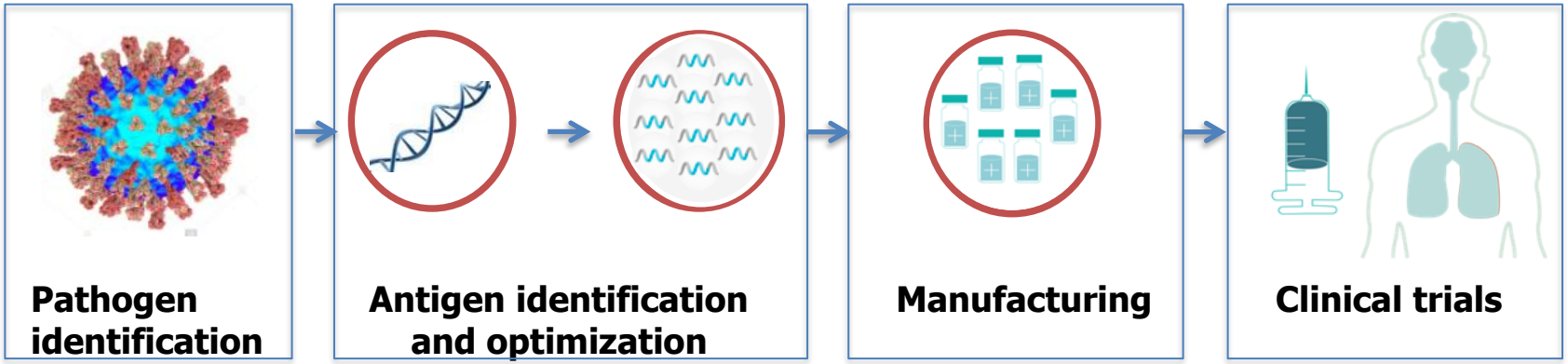


13 days post 1 injection



Hekele et al., Emerging Microbes Infect., 2013

Nucleic acid enabled rapid responses to the clinic



Zika DNA vaccine (Inovio)*

- PrM-E antigen sequence to phase I trials in ~4 months

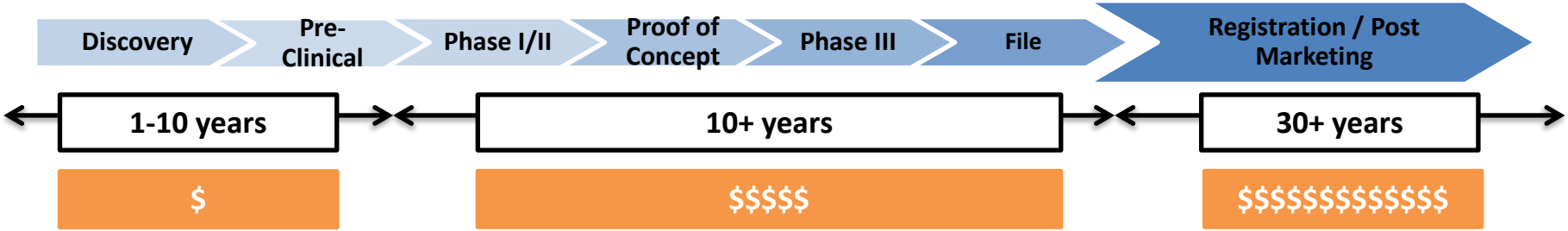
SARS CoV-2 mRNA vaccine (Moderna)**

- SARS-CoV-2 genome posted on Jan. 10, 2020
- Spike antigen clinical trial material completed within 45 days
- First phase I participants vaccinated on Mar. 16, 2020

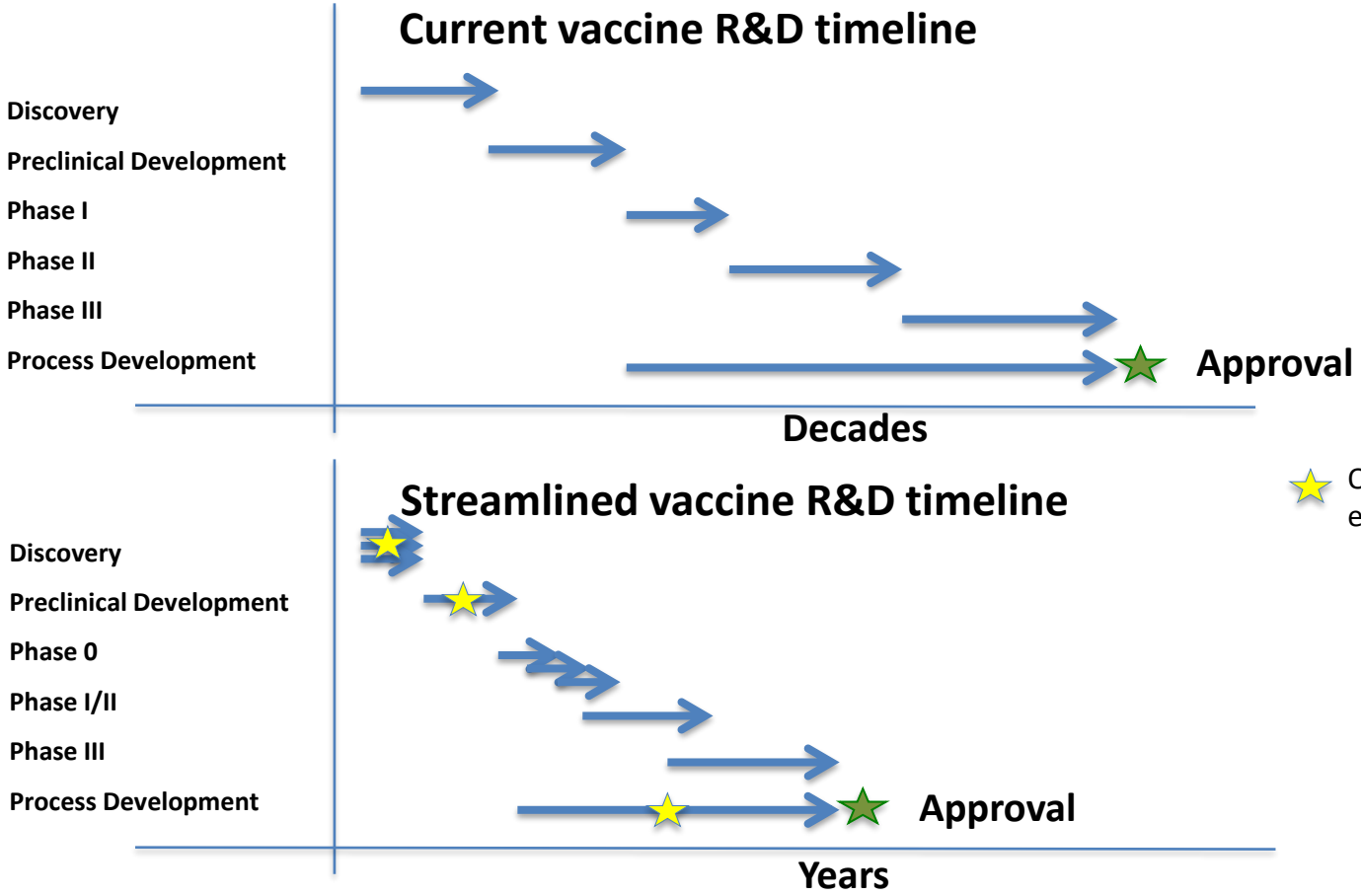
**Kudchodkar et al.,Microbes Infect. 20, 676, 2018*
***Corbett et al., Nature 586, 567, 2020.*

Current challenges in vaccines discovery and development

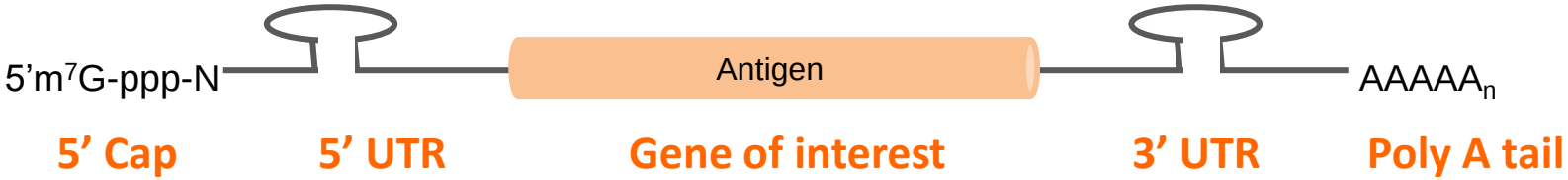
- Improving suboptimal vaccines (e.g., Tb, influenza)
- Developing new vaccines for unmet medical needs (e.g., HIV, RSV, cancer)
- Responding to rapidly emerging threats (e.g., SARS, Ebola, MERS, Zika, pandemic influenza)
- ***Streamlining the vaccines R&D process***



Acceleration of vaccine R&D

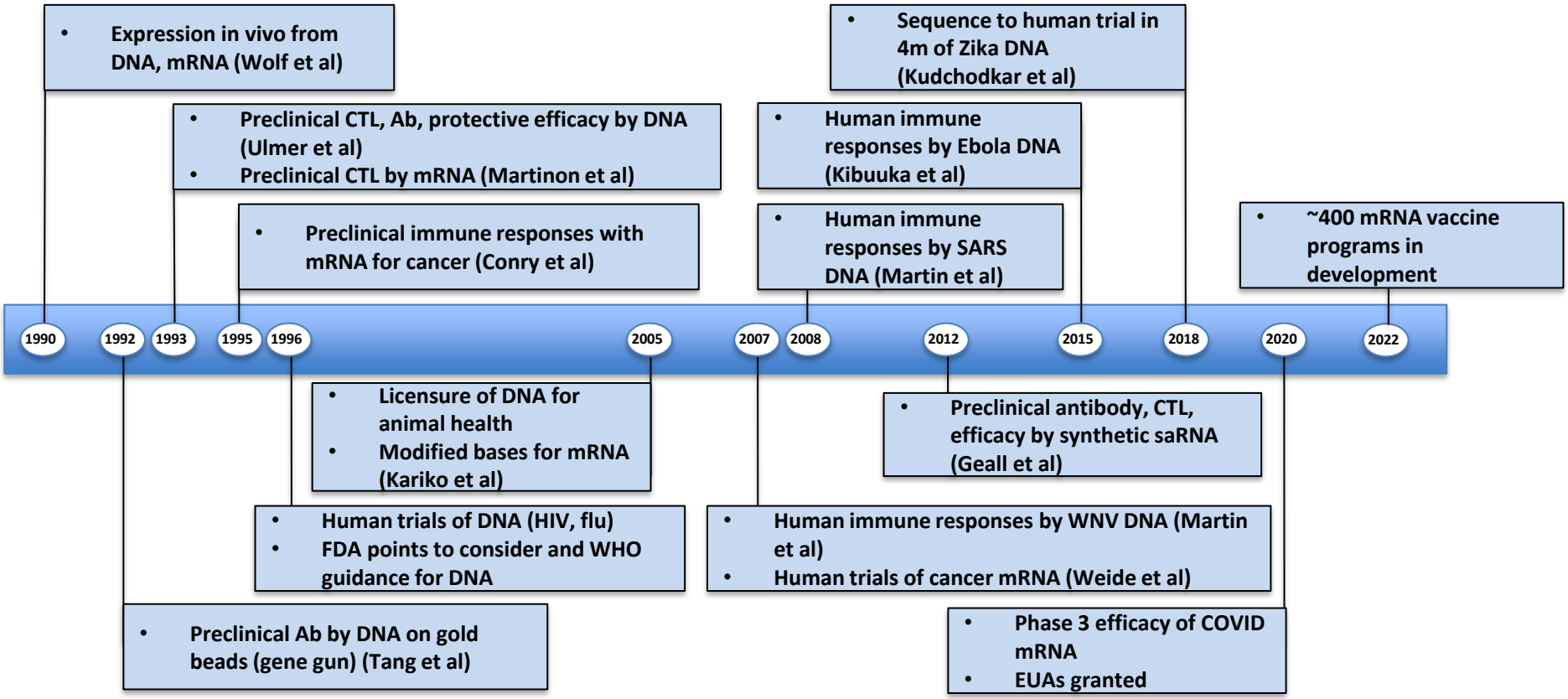


mRNA vaccines

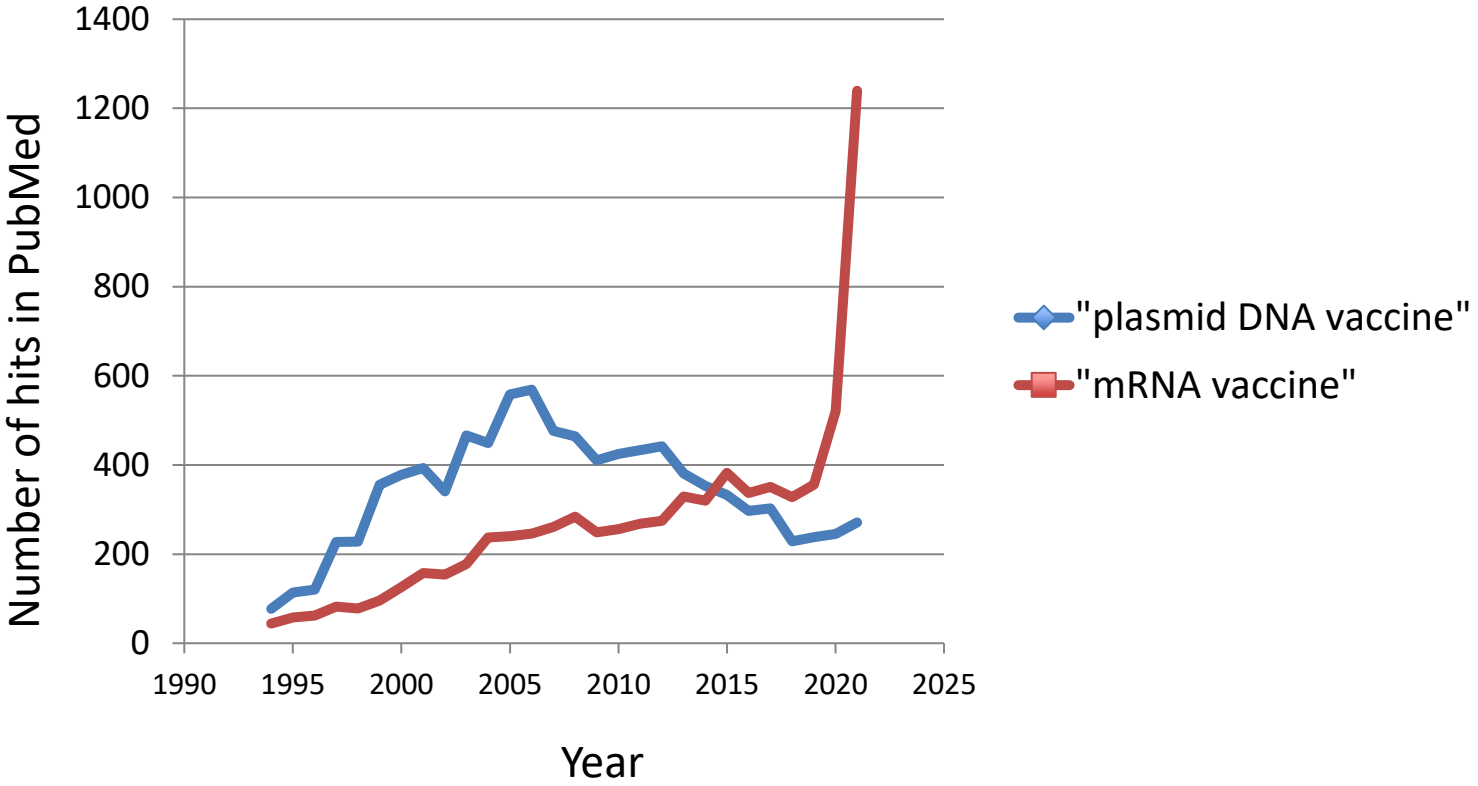


- Broad utility in animal models
- Rapidly growing scientific literature
- >90% efficacy in phase 3 clinical trials for SARS CoV-2
- Emergency Use Authorization for SARS CoV-2
- Billions of doses of vaccine administered

Pathway to success of mRNA vaccines



Scientific publications on DNA and mRNA vaccines

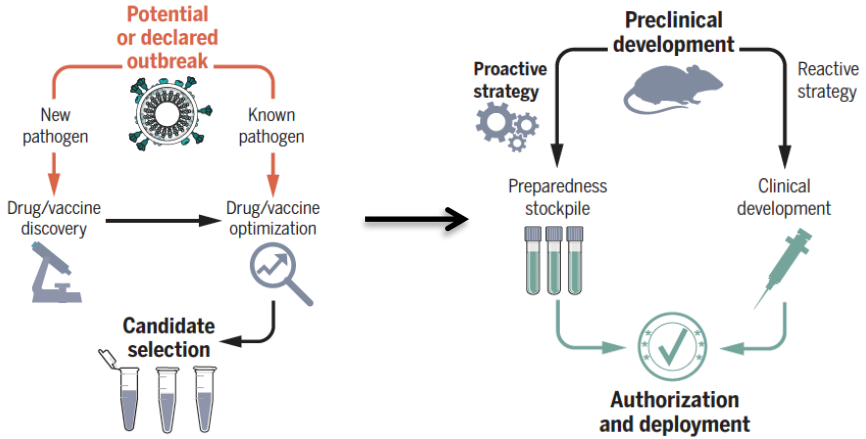


Foundational knowledge on nucleic acid vaccines paved the way to success

- Mechanism of action:
  - Location, kinetics of antigen expression in situ
  - Role of innate immune stimulation in adaptive immune response
- Safety:
  - Low risk of immunologic tolerance or autoimmunity
- Breadth of utility:
  - PoC for immunogenicity in animal models and humans
  - Licensure of nucleic acid products for animal health
  - Potential application to non-infectious diseases
  - Use of nucleic acid vaccines to facilitate screening and selection of antigens
- Technology readiness:
  - Established guidelines for Regulatory issues by WHO and National Regulatory Authorities
  - Established supporting industries for manufacture, raw materials and assessment of nucleic acid products

Lessons learned from SARS-CoV-2

- mRNA vaccines are safe and effective in humans
- Success was built on the foundation of decades of R&D on coronaviruses and nucleic acid vaccine technologies
- mRNA technology exemplified a “vaccines on demand” capability



Edwards et al., Science., 2022

Remaining challenges for mRNA vaccines

Challenges:

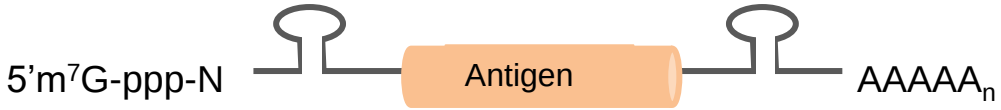
- Increasing thermostability
- Decreasing mRNA dose
- Decreasing reactogenicity
- Increasing potency/breadth of immunity
- Understanding mechanism of action

Key Enablers:

- mRNA engineering
- mRNA delivery
- Antigen design
- High quality manufacturing

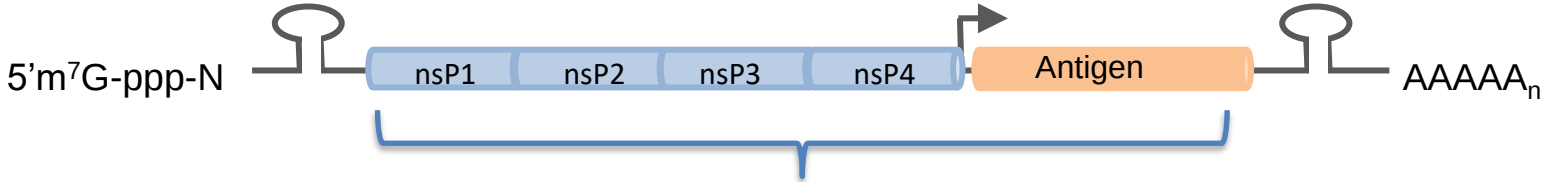
Opportunity: mRNA vaccine engineering

Conventional mRNA Vaccines



- Natural bases
- Modified bases

Self-Amplifying mRNA Vaccines (saRNA)



- Replicase and antigen genes on same mRNA
- Replicase and antigen genes on separate mRNAs

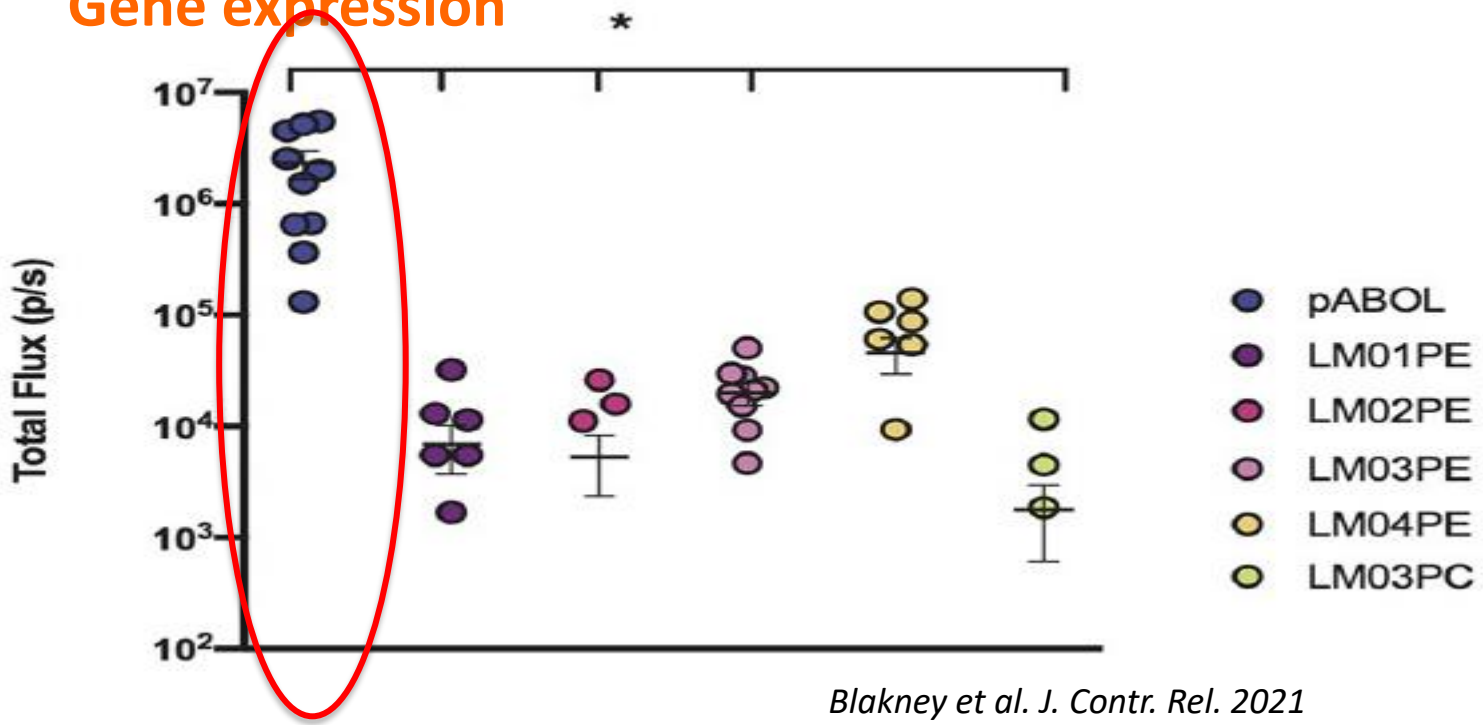
Attributes of mRNA versus saRNA

	Conventional mRNA	saRNA
Advantages	Simplicity	Substantial amplification of RNA
	Relatively small size	Longer duration of transgene expression
	Functional with modified bases	Potency at low mRNA doses
	Enhanced stability vs saRNA	More amenable to co-expressing multiple ORFs
		Enhanced T cell responses relative to conventional mRNA
Limitations	Short-term expression of transgene	Complexity
	Lower magnitude of T cell responses relative to saRNA	Reduced stability
		Relatively large size: difficult to manufacture
		Susceptible to interference by innate anti-viral responses

Opportunity: mRNA delivery

pABOL polymer versus LNP

Gene expression



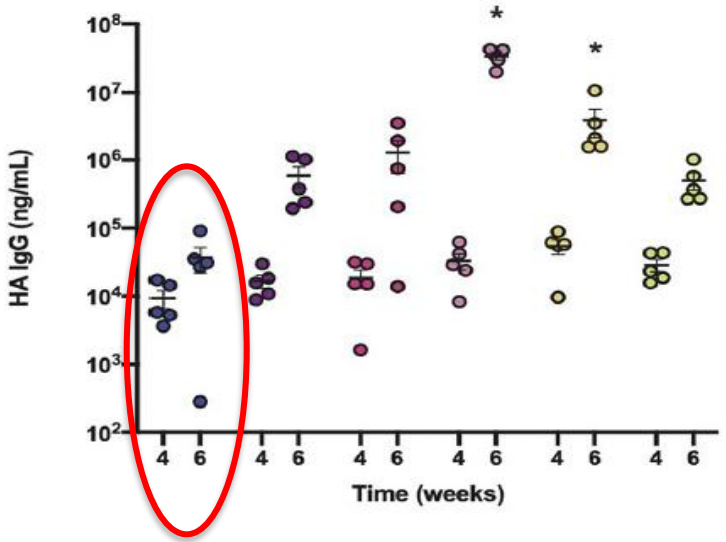
Blakney et al. J. Contr. Rel. 2021

Opportunity: mRNA delivery

pABOL polymer versus LNP

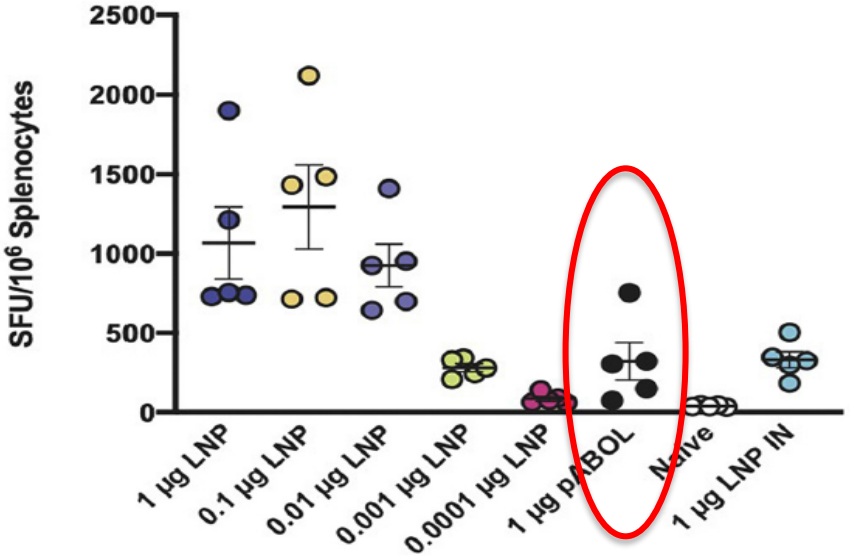
Immunogenicity

Influenza HA Ab

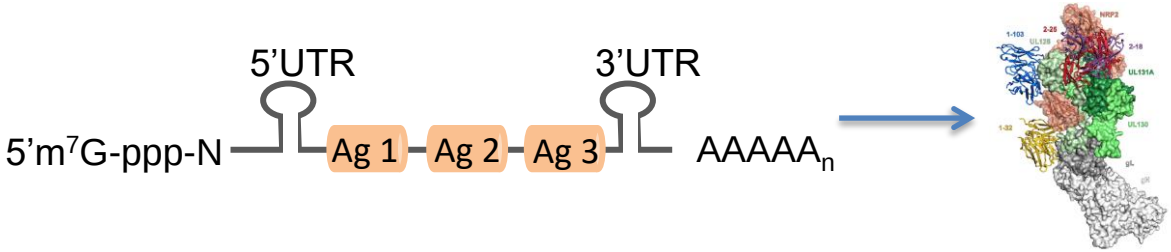


Blakney et al. J. Contr. Rel. 2021

SARS-CoV-2 spike T cells

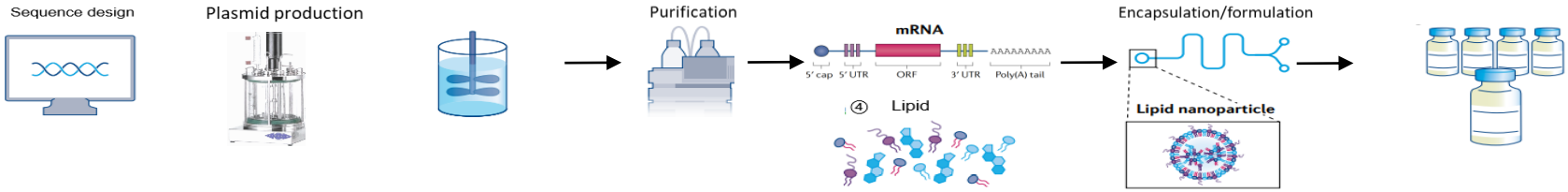


Optimization through antigen design



Issue	Solutions
Antigen conformation	Preservation of native conformation Co-expression of quaternary complexes
Antigen stability	Introduction of stabilizing mutations
Antigen composition	Identification of protective antigens (B/T cell) Co-expression of multiple antigens/epitopes

Opportunity: End to end high quality manufacturing



Process parameters:

Sequence design	DNA plasmid	IVT	Purification	Lipid	Encapsulation
UTRs	Fermentation	High yield	Process/product-related impurities	Novelty	RNA protection
Poly-A tail	Linearization	Integrity		Efficacy	mRNA purity
Nucleotides	Purification	Enzymes	High recovery	Safety	Lipid purity
GOI optimization		High Capping		Stability	Thermostability
Cap structure				Manufacturability	Safety
					Delivery efficiency
					Cell targeting
					Route administration

mRNA vaccines have potential to:

- Address unmet medical needs by induction of potent, broad immune responses
- Streamline vaccines R&D timelines and facilitate the rapid production of vaccines
  - Elimination of biologics in production
  - Generic methods to produce, purify and characterize product
  - Rapid response to newly emerging pathogens
  - Enable personalized medicines
- Disruptive innovation with potential for broad utility
  - Vaccines (preventive and therapeutic)
  - Cancer immunotherapy
  - Gene and cell therapy
  - Gene editing

Outlook for mRNA vaccines

- Copy and paste approaches to other disease targets may have limited utility
- Broad application of the mRNA technology will require innovation:
  - mRNA engineering
  - Novel delivery systems
  - Antigen design
  - High quality manufacturing
- Strong driving forces for success:
  - Large resource and intellectual capital being applied
  - Broad design space available
  - Potential for large return on investment
  - Major human health benefits