mRNA Technology Application

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WHO mRNA Technology Transfer Programme - Face-to-Face meeting
Cape Town, April 17-21, 2023

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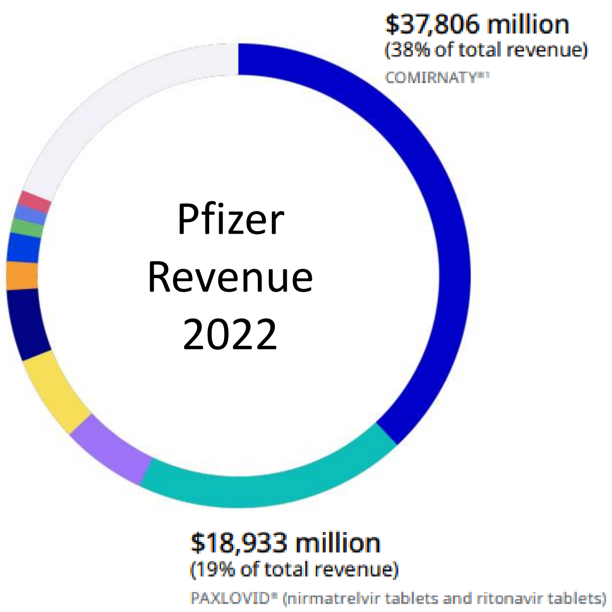
mRNA is becoming big business

Average USA SARS Cov2 mRNA vaccine price:

	monovalent	bivalent
Federal	$21	$29
commercial*		$110-$130

* Expected range



HEALTH AND SCIENCE

CNBC

What's next for Pfizer, Moderna beyond their projected $51 billion in combined Covid vaccine sales this year

PUBLISHED THU, MAR 3 2022•11:53 AM EST | UPDATED THU, MAR 3 2022•6:13 PM EST

Spencer Kimball
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NEWS

Moderna's $12 Billion in 2021 Profit Fueled by COVID Vaccine Sales

BY ERIN BRADY ON 2/24/22 AT 12:37 PM EST

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NEWS CORONAVIRUS VACCINE EARNINGS

Newsweek

Pfizer says COVID-19 vaccine will cost $110-$130 per dose

Pfizer will charge $110 to $130 for a dose of its COVID-19 vaccine once the U.S. government stops buying the shots

By TOM MURPHY AP Health Writer
October 21, 2022, 3:19 PM

abc NEWS

How The Covid-19 Vaccine Injected Billions Into Big Pharma—And Made Its Executives Very Rich

Nina Burleigh Contributor
Forbes Digital Covers Contributor Group

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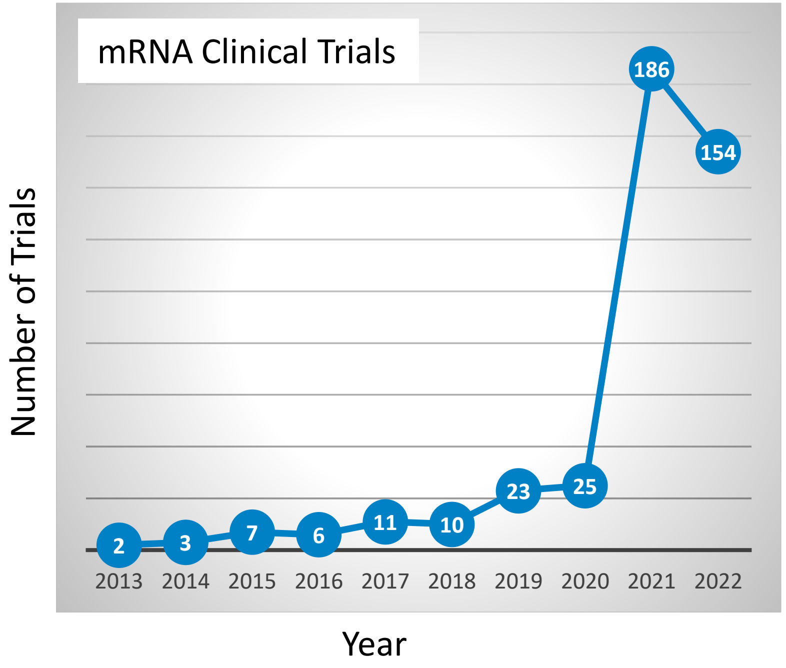
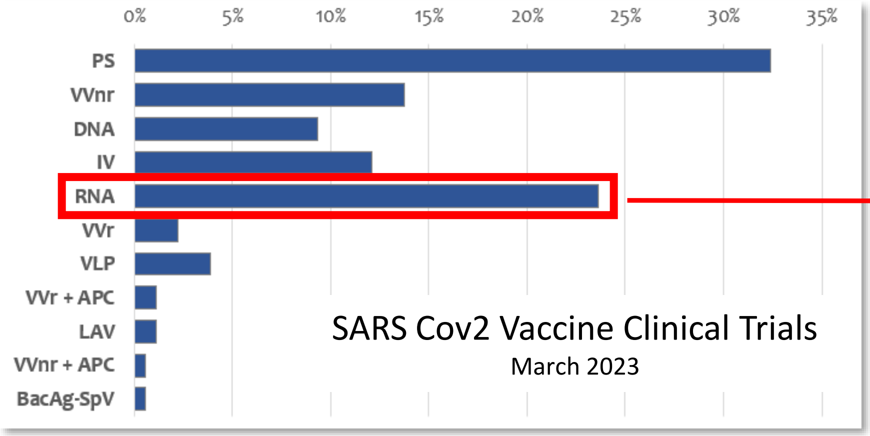
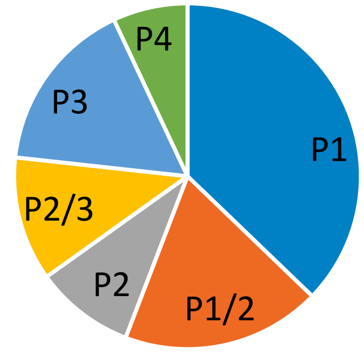
May 14, 2021, 04:30pm EDT

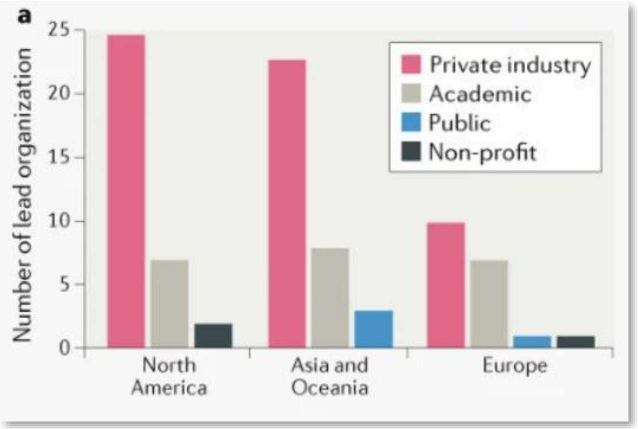
Forbes

Covid-19 pandemic catalysed global mRNA R&D









Adapted from beacon intelligence January 2023 RNA Landscape Review
[Client | Beacon Targeted Therapies (beacon-intelligence.com)]

[COVID-19 vaccine tracker and landscape (who.int)]
[The mRNA vaccine development landscape for infectious diseases (nature.com)]
doi.org/10.1038/d41573-022-00035-z

Understanding of RNA biology continues to evolve

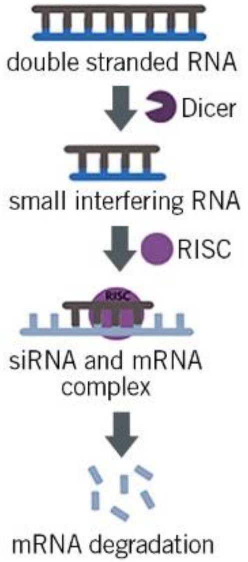
Examples of RNA types and function

Protein Synthesis	Post-transcriptional modification/DNA repair	Regulatory
Messenger RNA (mRNA) Transfer RNA (tRNA) Ribosomal RNA (rRNA)	Small nuclear RNA (snRNA) Small nucleolar RNA (snoRNA) Guide RNA (gRNA) Ribonulease P (Rnase p) Y RNA Telomerase RNA component (TERC) Spliced leader RNA (SL RNA)	Antisense RNA (asRNA) CRISPR RNA (crRNA) Long noncoding RNA (lncRNA) Micro RNA (miRNA) Piwi-interacting RNA (piRNA) Small interfering RNA (siRNA) Short hairpin RNA (shRNA)

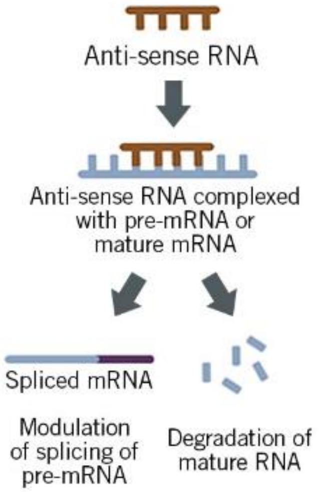
RNA Types

Some RNA applications

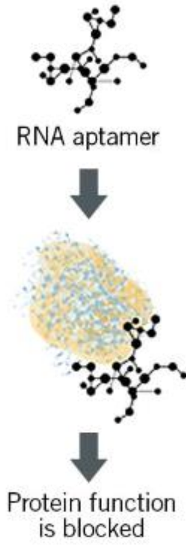
RNA Interference



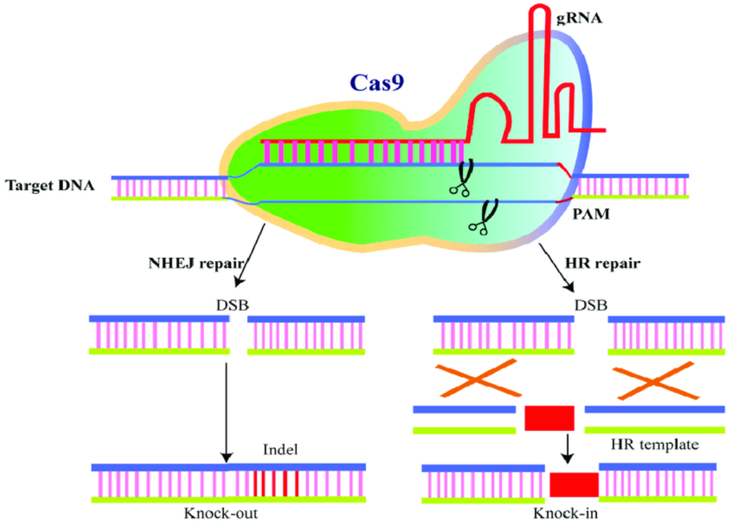
Anti-sense RNA



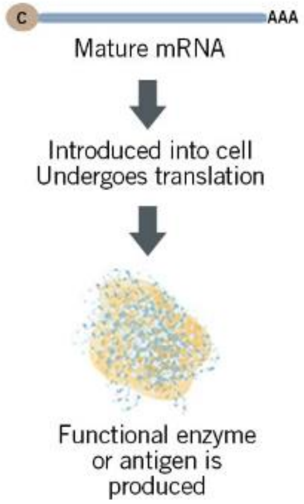
RNA Aptamers



CRISPR-based Genome Editing



mRNA Vaccines or Therapy



[RNA-based therapeutics: an overview and prospectus | Cell Death & Disease (nature.com)]

[What is the future of mRNA application? Read more (the-dna-universe.com)]

Doi: 10.1038/s41419-022-05075-2

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Applications – Crop protection

RNA interference technology in crop protection against arthropod pests, pathogens and nematodes

Moises Zotti,[a*] Ericmar Avila dos Santos,[a] Deise Cagliari,[a] Olivier Christiaens,[b] Clauvis Nji Tizi Taning[b] and Guy Smagghe[b*]

DOI 10.1002/ps.4813

Double-Stranded RNAs in Plant Protection Against Pathogenic Organisms and Viruses in Agriculture

S. Y. Morozov[1,2*], A. G. Solovyev[1,2], N. O. Kalinina[2], M. E. Taliansky[1,3]

DOI: 10.32607/20758251-2019-11-4-13-21

Colorado potato beetle

Varroa mite

Home | Greenlight Bioscience (greenlightbiosciences.com)

Varroa destructor (Adult Male) (5048079279) - Varroa destructor - Wikipedia

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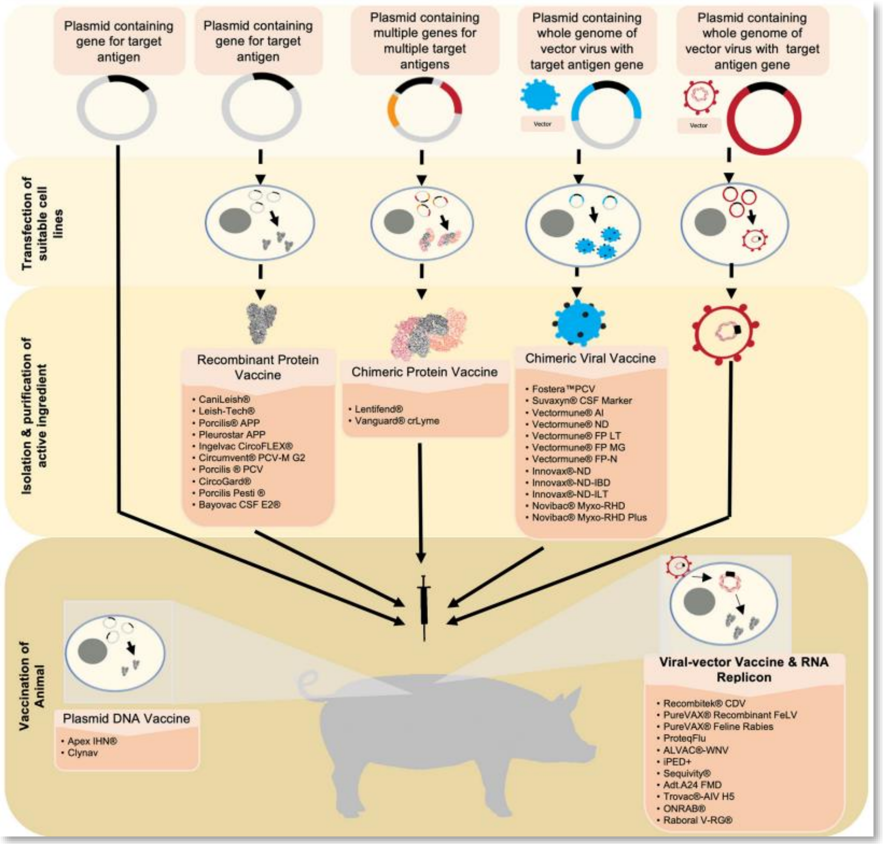
Applications – Veterinary health



Viral vector and RNA based vaccines

Species	Vaccine	Manufacturer	Pathogen	Technology (viral-vector)
Canine	Recombitek® CDV	Boehringer Ingelheim	Canine Distemper Virus	Viral-Vector (canarypox)
Feline	PureVAX® Recombinant FeLV	Boehringer Ingelheim	Feline Leukemia Virus	Viral-Vector (canarypox)
	PureVAX® Feline Rabies	Boehringer Ingelheim	Rabies	Viral-Vector (canarypox)
Equine	ProteqFlu	Boehringer Ingelheim	Equine Influenza	Viral-Vector (canarypox)
	ALVAC®-WNV	Pfizer	West Nile Virus	Viral-Vector (canarypox)
Swine	Fostera™PCV	Zoetis	Porcine Circovirus Type 2	Chimeric Viral-vector (PCV-1)
	Suvaxyn® CSF Marker	Zoetis	Classical Swine Fever virus	Chimeric Viral-vector (BVDV)
	iPED+	Merck Animal Health	Porcine Endemic Diarrhea virus	RNA Replicon (VEEV)
	Sequivity®	Merck Animal Health	Swine influenza A virus	RNA Replicon (VEEV)
Bovine	Adt.A24 FMD	GenVec	Foot and Mouth Disease	Viral-vector (adenovirus)
Avian	Trovac®-AIV H5	Boehringer Ingelheim	Avian Influenza	Viral-vector (fowlpox)
	Vectormune® AI	CEVA Biomune	Avian Influenza	Chimeric Viral-vector (HVT/MD)
	Vectormune® ND	CEVA Biomune	Newcastle Disease	Chimeric Viral-vector (HVT/MD)
	Vectormune® FP LT	CEVA Biomune	Infectious Laryngotracheitis virus	Chimeric Viral-vector (fowlpox)
	Vectormune® FP MG	CEVA Biomune	Mycoplasma Gallisepticum	Chimeric Viral-vector (fowlpox)
	Vectormune® FP-N	CEVA Biomune	Newcastle Disease	Chimeric Viral-vector (fowlpox)
	Innovax®-ND	Merck Animal Health	Newcastle Disease	Chimeric Viral-vector (HVT/MD)
	Innovax®-ND-IBD	Merck Animal Health	Newcastle disease and Infectious bursal disease	Chimeric Viral-vector (HVT/MD)
	Innovax®-ND-ILT	Merck Animal Health	Newcastle disease and infectious laryngotracheitis	Chimeric Viral-vector (HVT/MD)
Wildlife	ORNAB®	Artemis Technologies, Inc.,	Rabies	Viral-vector (human adenovirus type 5)
	Raboral V-RG®	Boehringer Ingelheim	Rabies	Viral-vector (vaccinia virus)
Rabbits	Novibac® Myxo-RHD	Merck Animal Health	Rabbit Hemorrhagic Disease	Chimeric Viral-vector (myxoma virus)
	Novibac® Myxo-RHD Plus	Merck Animal Health	Rabbit Hemorrhagic Disease	Chimeric Viral-vector (myxoma virus)

vaccines for animals 2020 review.pdf

doi.org/10.3389/fvets.2021.654289

Applications – human health

Cancer, vaccines, gene therapy...

Adapted from: Beacon Targeted Therapies RNA Digest: January 2023

MAR 02, 2023

Intellia Therapeutics Announces FDA Clearance of Investigational New Drug (IND) Application for NTLA-2002, an In Vivo CRISPR-Based Investigational Therapy for the Treatment of Hereditary Angioedema (HAE)

mRNA cancer vaccine an 'exciting' advance in reducing risk of melanoma relapse, trial shows

NBC News

Story by Linda Carroll and Reynolds Lewis • Yesterday 10:02 AM

NEWS | 15 February 2023

mRNA vaccine effective against RSV respiratory disease

nature medicine

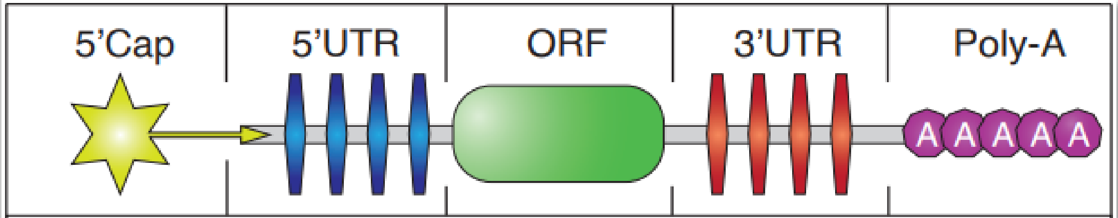
mRNA vaccine effective against RSV respiratory disease (nature.com)

Press Releases - Intellia Therapeutics (intelliatx.com)

mRNA cancer vaccine an 'exciting' advance in reducing risk of melanoma relapse, trial shows (msn.com)

mRNA technology will continue to improve

- Balance innate/adaptive immune response
- Translation efficiency - potency
- Multi-valency
- Stability
- Manufacturing quality & cost



Biological Relevance

Cap	5' UTR	ORF	3'UTR	Poly A
-Eukaryotic modification -Important for translation initiation, mRNA stability, nuclear export. -When suboptimal, recognized as PAMPs by the innate immunity. -RNA Close-Loop.	-Recognition by translation machinery. -Recognized and scanned by ribosomes. -Important for mRNA translation and stability. -RNA Close-Loop.	-Sequence encoding the gene of interest (GOI), in mRNA vaccine encodes the antigen.	-Important for translation initiation and mRNA stability.	-Important for mRNA stability. -Recognition by Poly-A Binding Proteins (PABP) and recruitment of translation factors. -Important for translation initiation (RNA-Looping).

Region Optimization

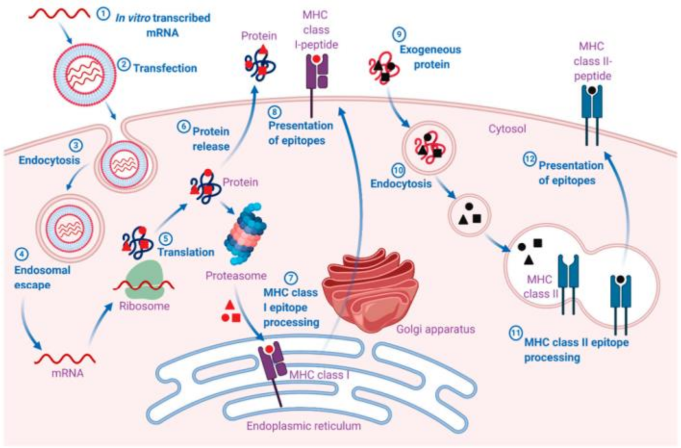
Cap	5' UTR	ORF	3'UTR	Poly A
-Natural Cap-1 to avoid PRRs recognition and enhance translation. -Enzymatic capping for higher capping efficiency.	-Inclusion of Kozak Sequence. -No strong secondary structures. -No other start codon. -Polysome profiling to count the ribosome loading in sequences *in-silico*.	-Codon optimization increases translation. -Low optimal codons may be important for an adequate folding.	-Optimal sequences derived from high stable mRNA (β-Globin). -2x copies in tandem -RNA Close-Loop	-Poly-A sequences of 120 units. -Adding a Poly-U sequence, providing a dsRNA in the poly-A, increase adjuvant effect.

Whole Molecule Optimization

-Avoiding binding sites of miRNAs present in the target cells.
-Uridine depletion to avoid recognition by innate immunity.
-Production at high temperature (50ºC) using a thermostable polymerase and/or low Mg^{2+} concentration, to decrease dsRNA levels.
-mRNA purification using HPLC to decrease dsRNA amount.
-Avoidance of highly stable and long secondary structures that could activate PRRs.

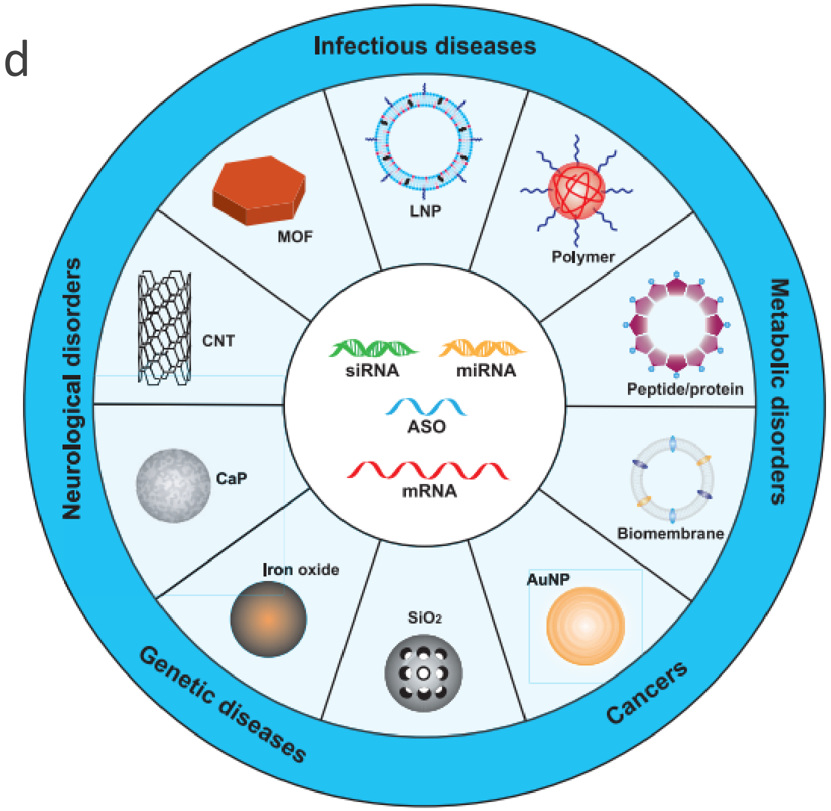
Doi:10.1016/j.molmed.2019.10.002

mRNA formulation/delivery will continue to improve



doi.org/10.3390/pharmaceutics12020102

- Temperature stability and shelf-life
- Potency
- Immune modulation
- Needleless delivery
- Cost

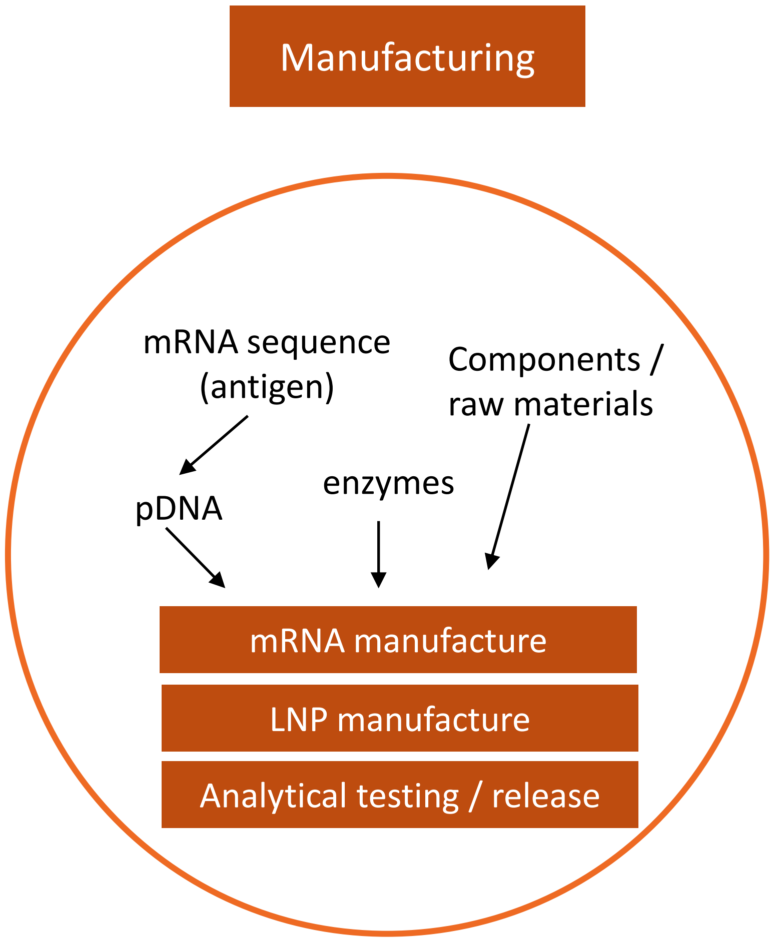


Representative nanomaterials include lipid nanoparticle (LNP), polymer, peptide/protein, biomembrane, gold nanoparticle (AuNP), silica (SiO_2), iron oxide, calcium phosphate (CaP), carbon nanotube (CNT), and metal-organic framework (MOF).

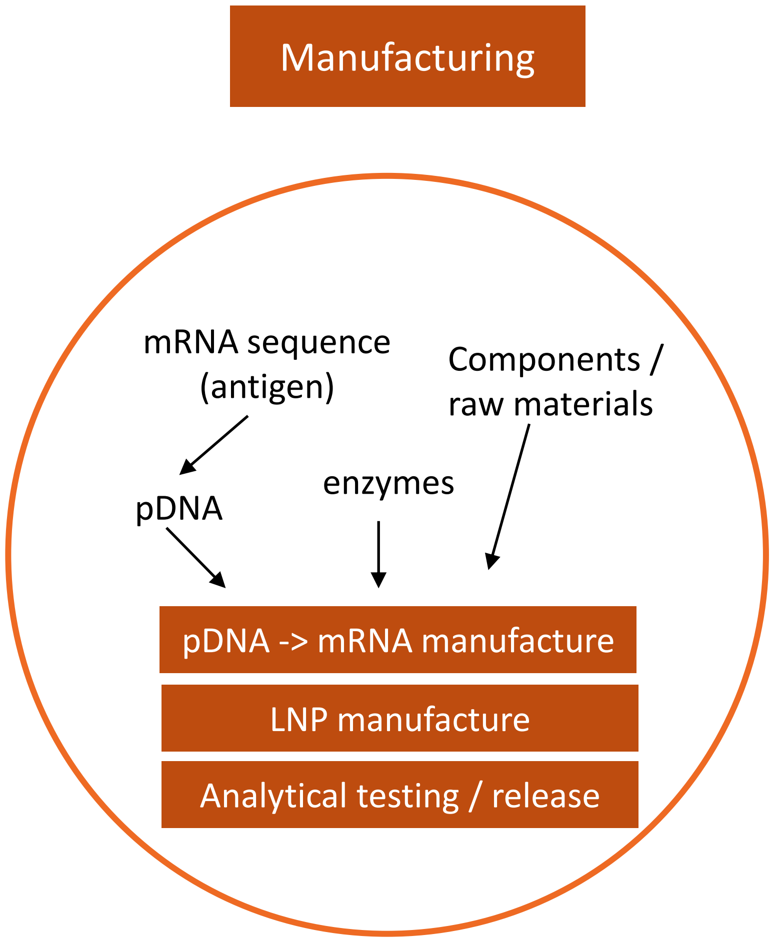
doi.org/10.1016/j.matt.2020.09.020

mRNA reduces barriers to entry for vaccines

- Less capital intensive infrastructure vs. other vaccine platforms
  - Smaller footprint/scale vs cell-culture or fermentation
  - Multi-product facilities for drug substance/product manufacture
- Cell-free manufacturing processes
  - Greater worker safety (e.g. no live viruses used)
  - Shorter manufacturing cycle times
- Platform manufacturing process
  - Standardized manufacturing process (less changes for different antigens)
  - Shorter lead times to clinical development
  - Rapid iteration in exploratory medicine trials
  - Standardized release testing methods
  - Easier switching of products
  - Easier to produce multi-valent products



Manufacturing alone insufficient for sustainability



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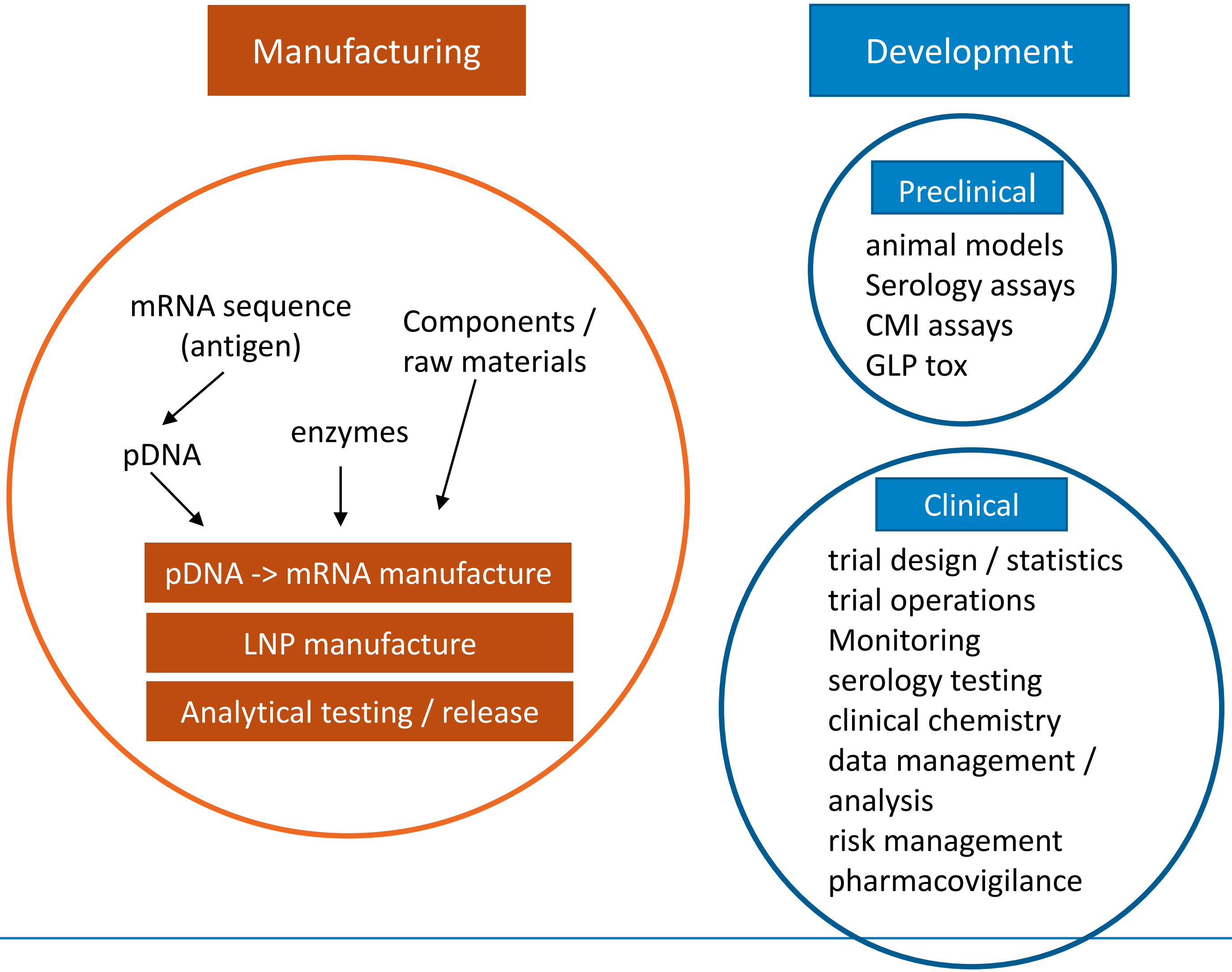

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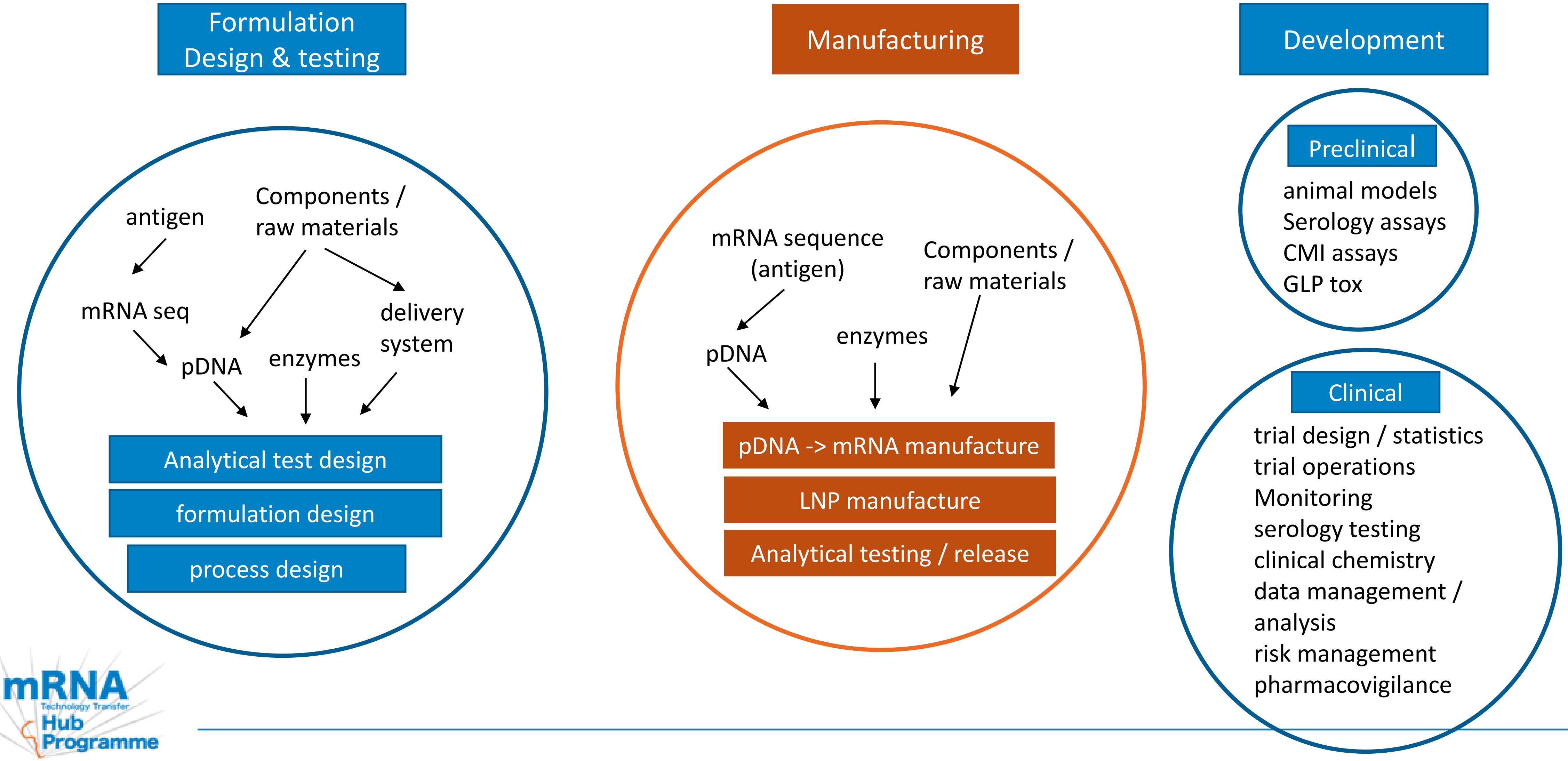
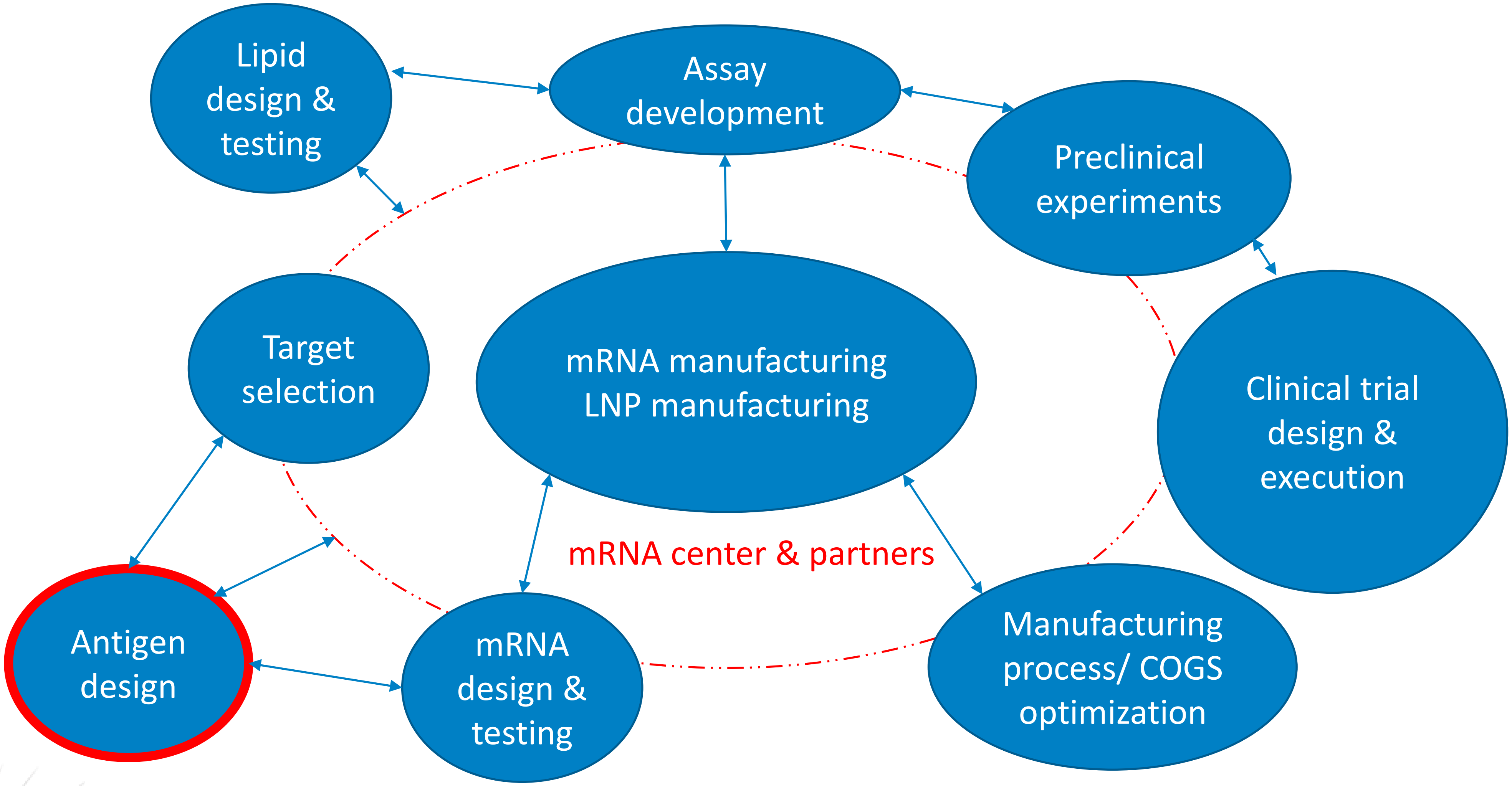


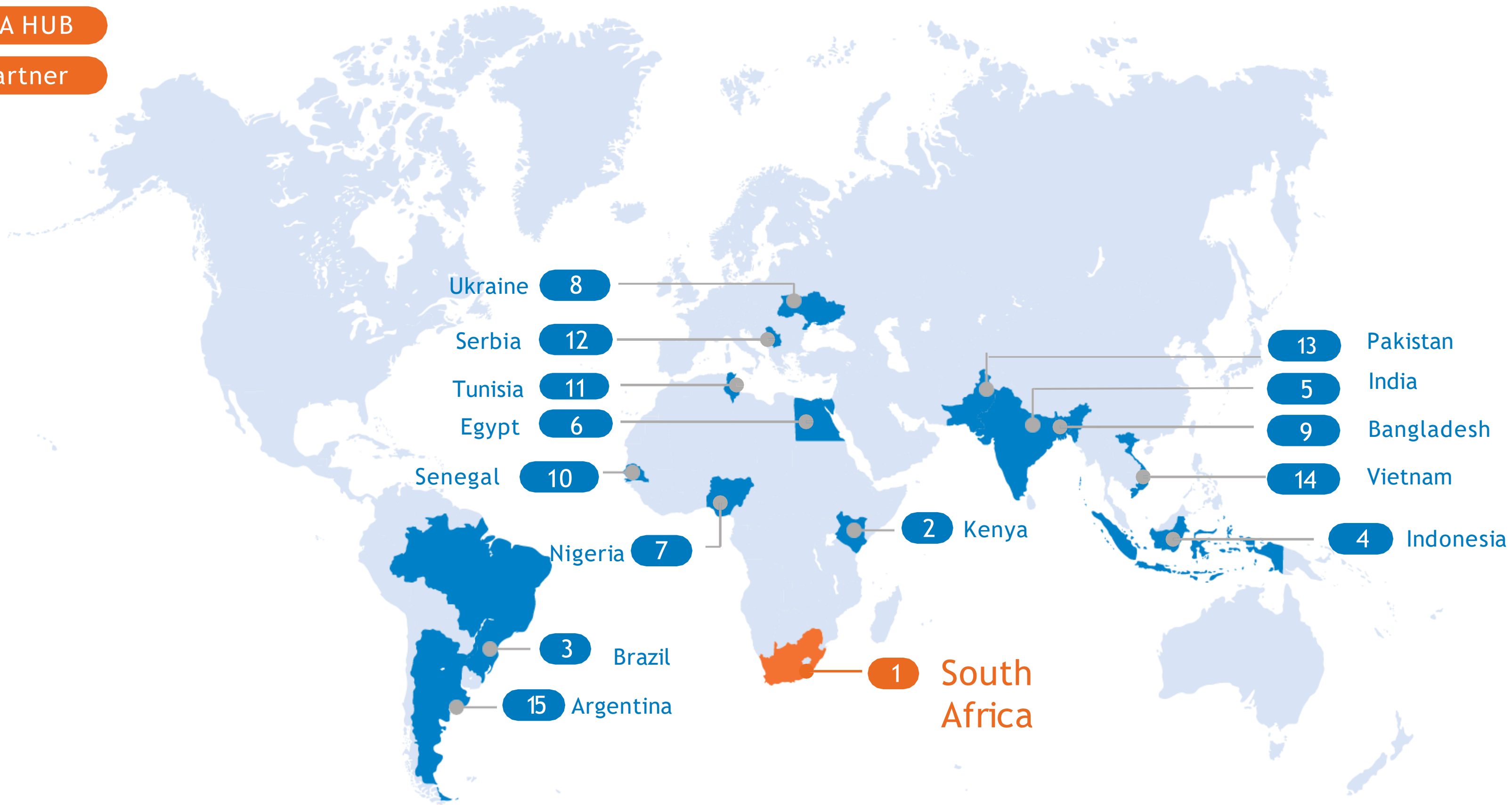
Sustainability - We must build a mRNA R&D ecosystem



mRNA manufacturing technology ecosystem: connecting 15 LMIC's across 4 continents

Strengthen the ecosystem through R&D collaborations

1	Afrigen	mRNA HUB
	Biovac	1st partner
2	Biovax Kenya	
3	Bio-Manguinhos	
4	Biofarma	
5	BiologicalE	
6	BioGeneric Pharma	
7	Biovaccines Nigeria	
8	Darnitsa	
9	Incepta Vaccine	
10	Institut Pasteur de Dakar	
11	Institut Pasteur de Tunis	
12	Institut Torlak	
13	National Institute of Health	
14	Polyvac	
15	Sinergium Biotech	



Developing a portfolio - assessment process

- Incorporation of analysis by the Partnership for African Vaccine Manufacturing (PAVM)
  - Framework for Action (4/2021, 3/2022)
  - Market Design and Demand Intelligence Workshop (6/2022)
- Review of CEPI, GAVI, BMGF and WHO priority diseases
- Input from key opinion leaders and experts
- Initial assessment of potential for mRNA/LNP application and technical feasibility
- Preliminary, high-level assessment of needs
- Engage with partners and supporters to pressure test, elaborate

Assessing mRNA utility and development feasibility

Targets in

mRNA/LNP Suitability & Testing

- What is the degree of antigen complexity?
- Is the antigen design space well understood?
- How many antigens should be included
- Are there adequate preclinical models of immunity or protection
- Is mRNA likely to induce protective immune response?
- Are research tools and assays accessible

Clinical & Regulatory Development Path

- Does correlate of protection exist?
- What are the access/safety risks for the target population?
- Are clinical endpoints established?
- Is there an established regulatory path for approval?
- What is the degree of complexity of the clinical studies?

Additional Criteria

- What is the burden of disease
- Are the antigens available?
- How important is genetic diversity of the pathogen?
- What is the complexity of the formulation?
- Are existing vaccines adequate and accessible?
- Are clinical study participants accessible?
- What is the market potential?
- Is funding available?

Priorities out

mRNA Technology Transfer Hub Programme

Initial assessment

Archetype	Disease	Pathogen	GAVI	WHO	CEPI	PAVM	mRNA app	difficulty
Legacy	Measles							
	Tuberculosis	**						
	Whooping Cough							
	Tetanus							
	Diphtheria							
	Hepatitis B							
	Yellow Fever	*						
	Typhoid							
	Cholera							
Expanding	Rotavirus							
	Pnemococcal	**						
	Papilloma Virus	#						
	HIV/AIDS							
	Malaria	*						
	SARS-Cov-2							
Outbreak	Chikungunya	*						
	Lassa Fever							
	Rift Valley Fever	*						
	Ebola							
Next Horizon	Varicella							
	Hepatitis A							
	Influenza							
	Syphilis	#						
	Genital herpes	#						
	Otitis	**						
	Gonorrhea	**/#						
	Chlamydia	#						
Other	RSV							
	Strep A	**						
	Group B Strep	**						
	Rabies							

*	mosquito vector
	eukaryotic parasite
**	antibiotic resistance
#	STI

	RNA virus
	DNA virus
	Gram +ve bacteria
	Gram -ve bacteria

Initial assessment

- A good fraction of the targets are likely tractable using mRNA technology for vaccines
- Many targets for existing childhood bacterial vaccines may be suitable for an mRNA approach, but antigens may not be easily available, and/or mRNA delivery may result in poor immunogenicity due to glycosylation of the expressed antigens
- Some bacterial targets are unsuitable for mRNA as the antigens require a polysaccharide component (glycoconjugates)
- Initial focus should be on prophylactic vaccines. Therapeutic vaccines present a much greater hurdle, and may require a heterologous prime/boost vaccination or combination with therapeutics
- Further analysis is needed with some of the "additional criteria" category, especially disease burden/medical need and market potential in LMICs

*	mosquito vector
	eukaryotic parasite
**	antibiotic resistance
#	STI

	RNA virus
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	Gram +ve bacteria
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	Yellow Fever	*						
	Typhoid							
	Cholera							
Expanding	Rotavirus							
	Pnemococcal	**						
	Papilloma Virus	#						
	HIV/AIDS							
	Malaria	*						
	SARS-Cov-2							
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	Syphilis	#						
	Genital herpes	#						
	Otitis	**						
	Gonorrhea	**/#						
	Chlamydia	#						
Other	RSV							
	Strep A	**						
	Group B Strep	**						
	Rabies							

Initial potential targets

- ❑ Address critical unmet needs
- ❑ Establish the foundation for next generation vaccines
- ❑ Address important mosquito-borne diseases
- ❑ Build vaccines R&D capability & capacity

- ❑ Gonorrhea
- ❑ Hep B
- ❑ HPV
- ❑ HSV
- ❑ Measles
- ❑ Rabies
- ❑ Rift valley fever
- ❑ RSV
- ❑ Varicella
- ❑ Yellow fever

Prioritization is pending

Initial potential targets

- Address critical unmet needs
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- Gonorrhea
- Hep B
- HPV
- HSV
- Measles
- Rabies
- Rift valley fever
- RSV
- Varicella
- Yellow fever

Prioritization is pending

From Partner discussions & presentations of this week

- Dengue
- HIV
- HPV
- Hep B
- Influenza
- Lassa fever
- Leishmaniasis
- Nipah virus
- Rabies
- Rift valley fever
- Rota
- RSV
- TB
- TBE
- West nile virus
- Yellow fever
- Zika virus

RSV vaccine plan: Dr. Mani Margolin's presentation 16:00 Hr on 20/4

mRNA Technology Transfer Hub Programme

Closing thoughts

- Lower barriers to entry for mRNA technology provides an opportunity for LMIC's to become self-sufficient for many vaccines in terms of manufacturing of drug substance and drug product
- Manufacturing alone is insufficient for sustainability
- The mRNA/LNP platform continues to improve for potency, quality and cost
- We must develop the know-how, capability and capacity for vaccines from concept, design, testing/optimization, manufacture and clinical development/registration
- This can be achieved by selection of target candidates along with building an ecosystem which provides technology/know-how access and teaching
- Success will come more easily through genuine partnership and mutual support through an mRNA/LNP R&D and manufacturing ecosystem
- RNA has applications beyond vaccines – in human, veterinary and agricultural applications…

Acknowledgements

Afrigen
Biologics & Vaccines

World Health Organization

medicines patent pool

mRNA Technology Transfer Hub Programme

mRNA Technology Transfer Hub Programme

ACTaccelerator ACCESS TO COVID-19 TOOLS

medicines patent pool

World Health Organization

THANK YOU