



BMGF strategy to advance mRNA vaccine manufacturing

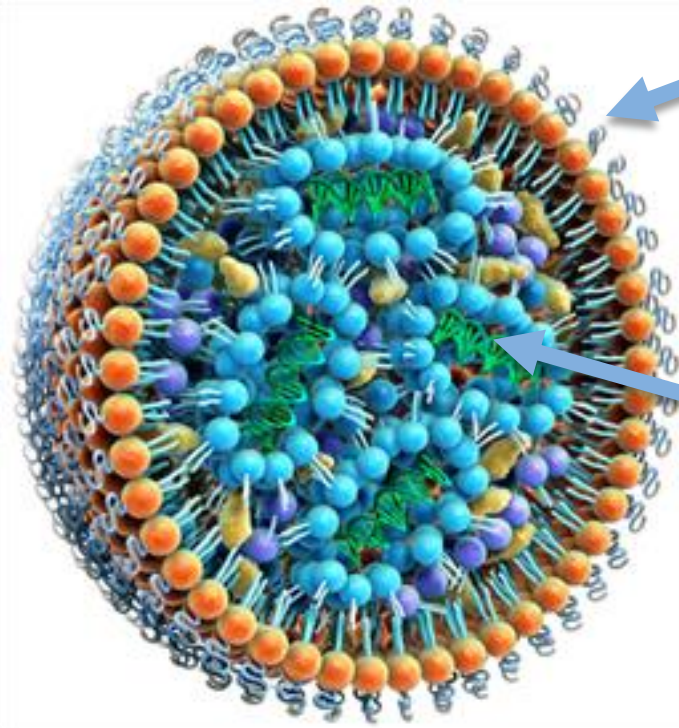
Philippe-Alexandre Gilbert

Senior Program Officer

Vaccine Development, CMC

Last Updated: October 2023

mRNA



LIPIDS

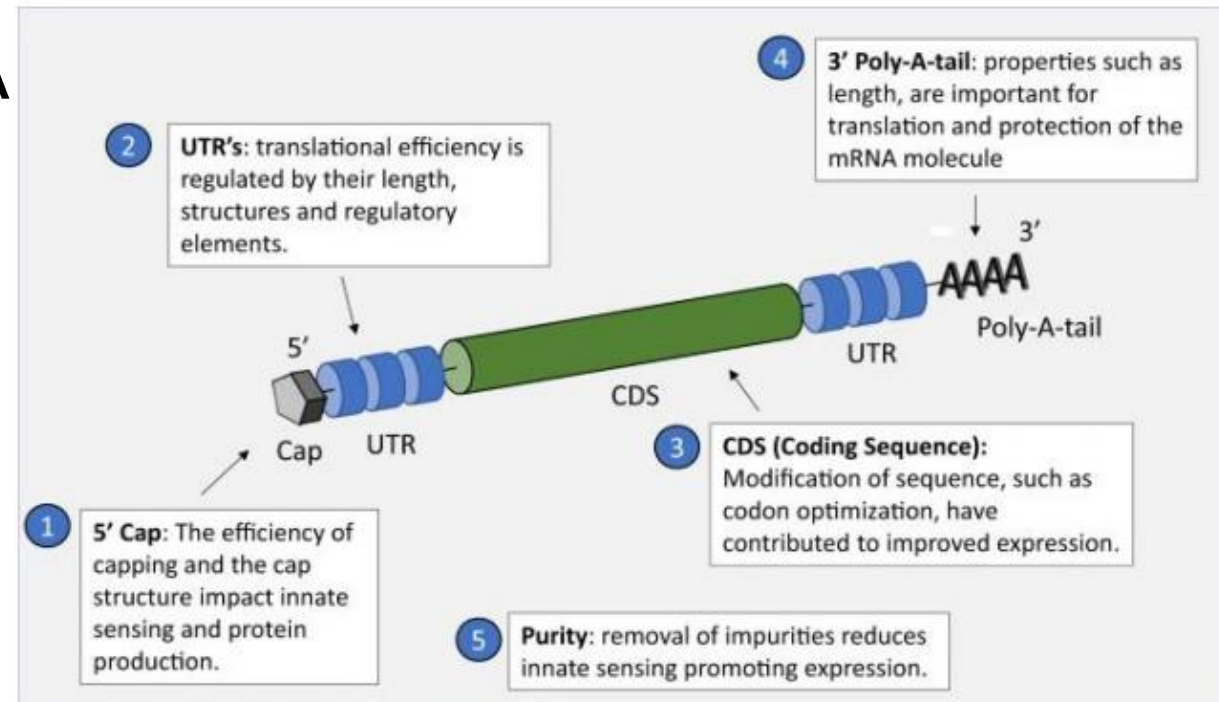
Cholesterol

Cationic lipids

Polyethylene glycol lipids

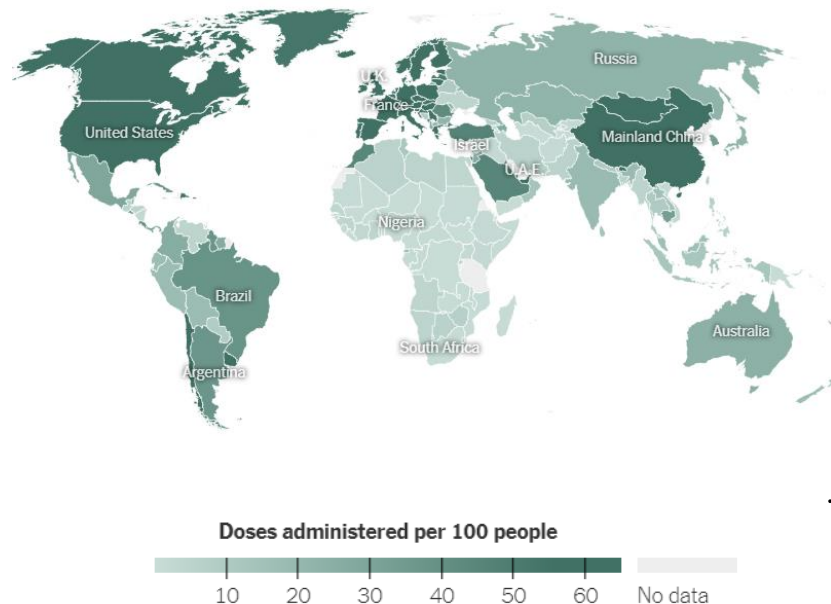
Phospholipids

mRNA

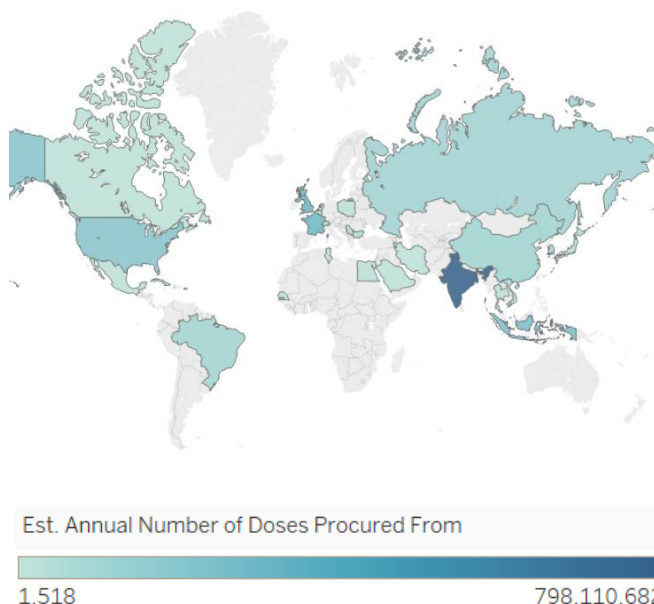


Covid-19 vaccine rollout has shown that a regional vaccine manufacturing strategy is critical component for preparedness

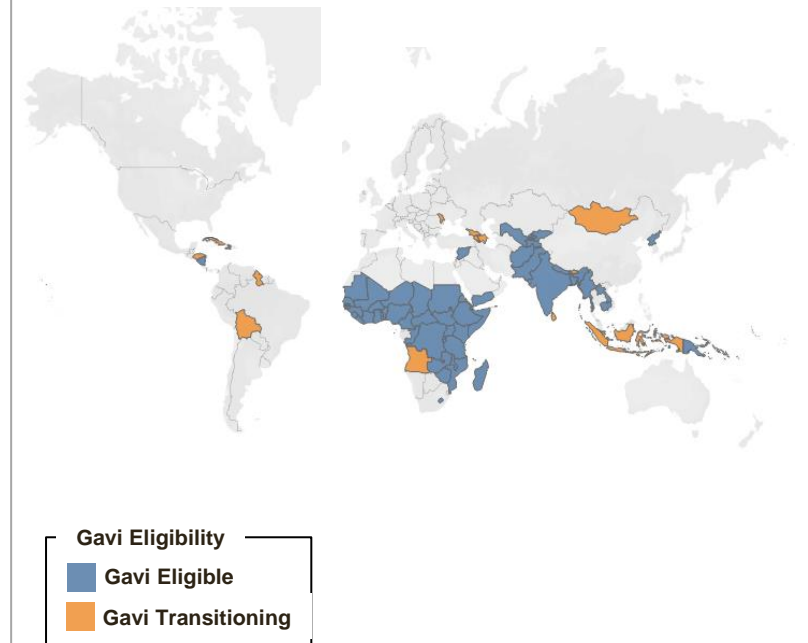
As of June 2021, vaccinations in HICs and UMICs dramatically outpace any LIC campaigns...



...countries with early rollout largely correlates with concentration of production capacity in US, EU, India and China



Lack of production capacity in Gavi-served LMICs meant that local production is not an option for COVID-19



Last updated: June 2021

MRNA TECHNICAL CHALLENGES AND OPPORTUNITIES FOR LMIC



Cost of Goods (COG)

- Access to mRNA doses to costs approaching \$1/dose or less.
- Find alternative reagent supply solution
- Use of new production methods



Thermostability

- Develop Liquid and/or Dry form Thermostable Solution
- Use of new delivery devices



Reagents and Methods Access

- Access to methods to produce mRNA
- Provide access to mRNA key critical reagents (modified nucleoside, cap enzymes, cationic lipids)
- Freedom to Operate (FTO)



Scale/Deployment

- Develop new mRNA modular technology
- Avoid scale problems
- Provide high output
- Design in consideration of deployment in LMIC

Univercells, a biotechnology Group of Affiliates on a common mission: making biologics available to all



Next-generation cell-based manufacturing technologies (scale-X™, NevoLine™)



Project Management & Operational partner for in-country bioproduction facility setup



Technology innovator focused on mRNA from sequence up to mass production (Nfinity™ platform)



Best-in-class GMP-certified CDMO specialized in the development and manufacturing of viral vectors



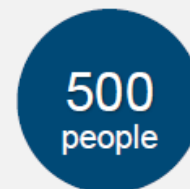
Regulatory affairs support at all stages of medicinal product development



Since 2013: **Biologics for All**
Proven track record in **scaling production and bioprocessing**

Technology-driven affordability to support access and promote sustainability

We address the needs of the **health value chain**



From 40 nationalities



In equity & non-dilutive funding



//Adjuvant Capital

KKR

BILL & MELINDA GATES foundation

Reduction in facility size based on process intensification has multiple benefits

Culture & viral production

Compact bioreactor to concentrate vaccine production

Purification

High capacity membrane for continuous purification

Inactivation

Batch process run in staggered mode



Each unit operation can be housed in an isolator (glove box) providing increased assurance of operator safety

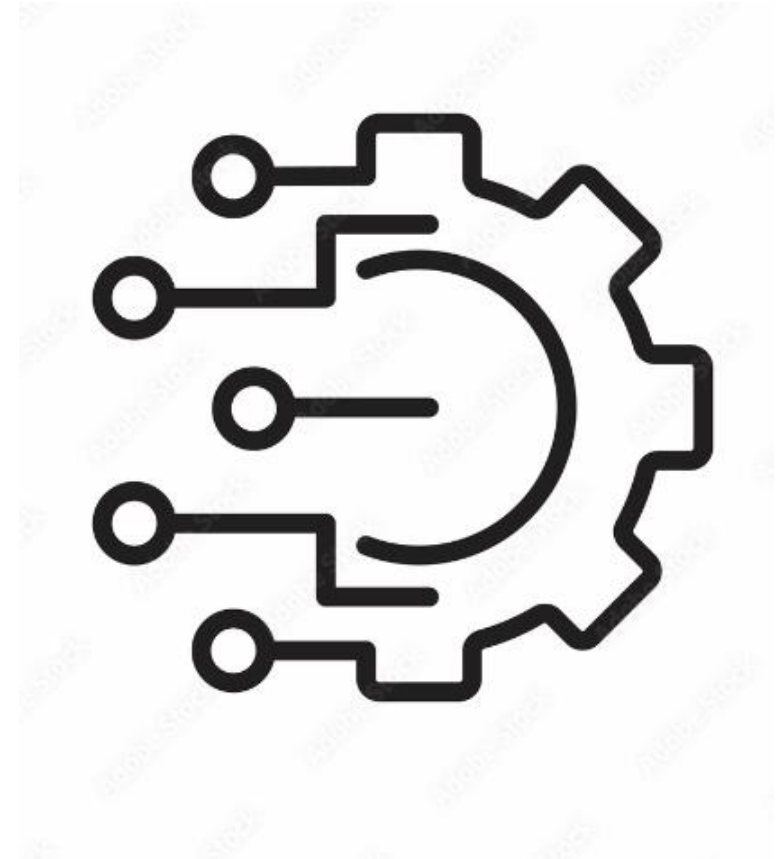
Ten-fold reduction in capital costs



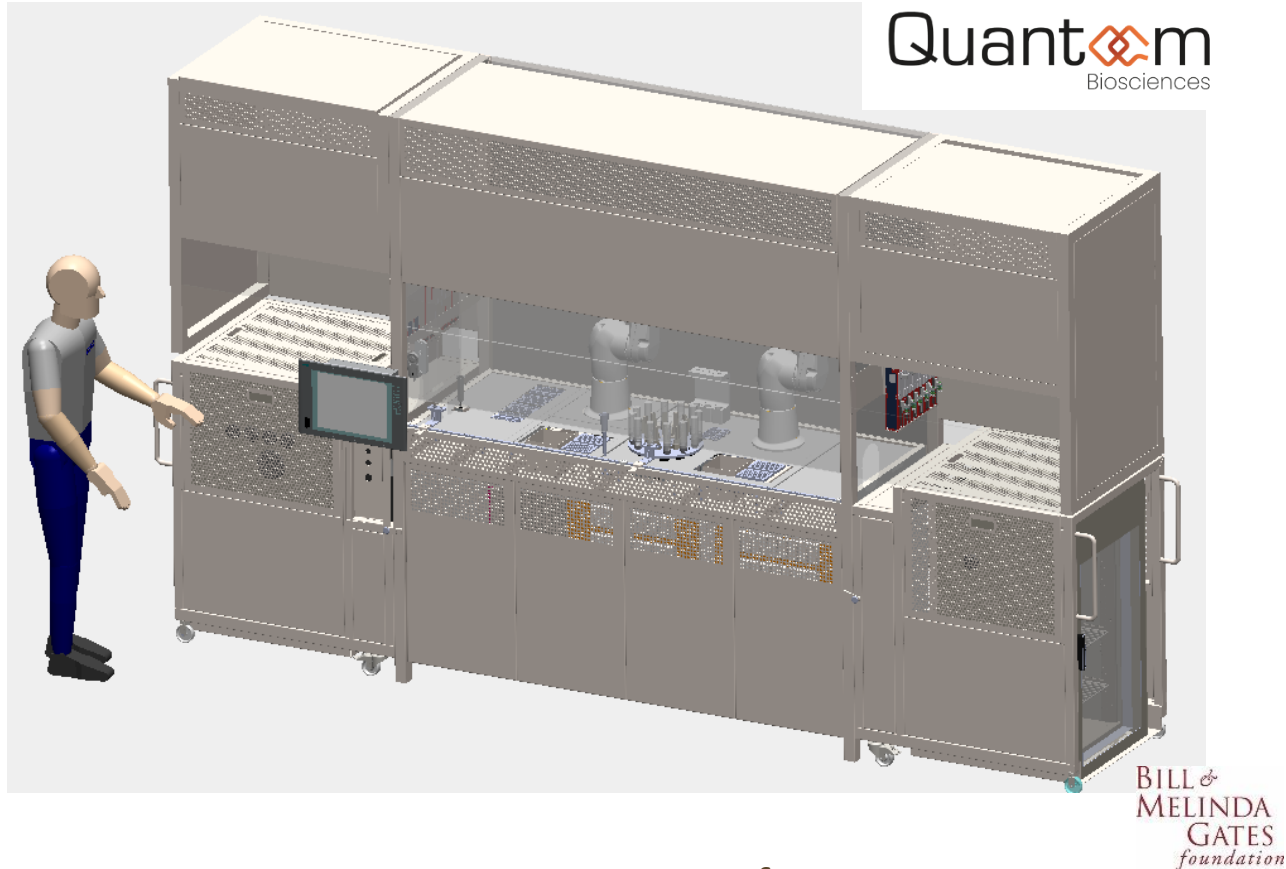
Each production train can be readily placed in a BSL3+ GAPIII compliant facility providing increased assurance of environmental safety

mRNA PRODUCTION SYSTEM - DESIGN PRIME DIRECTIVES

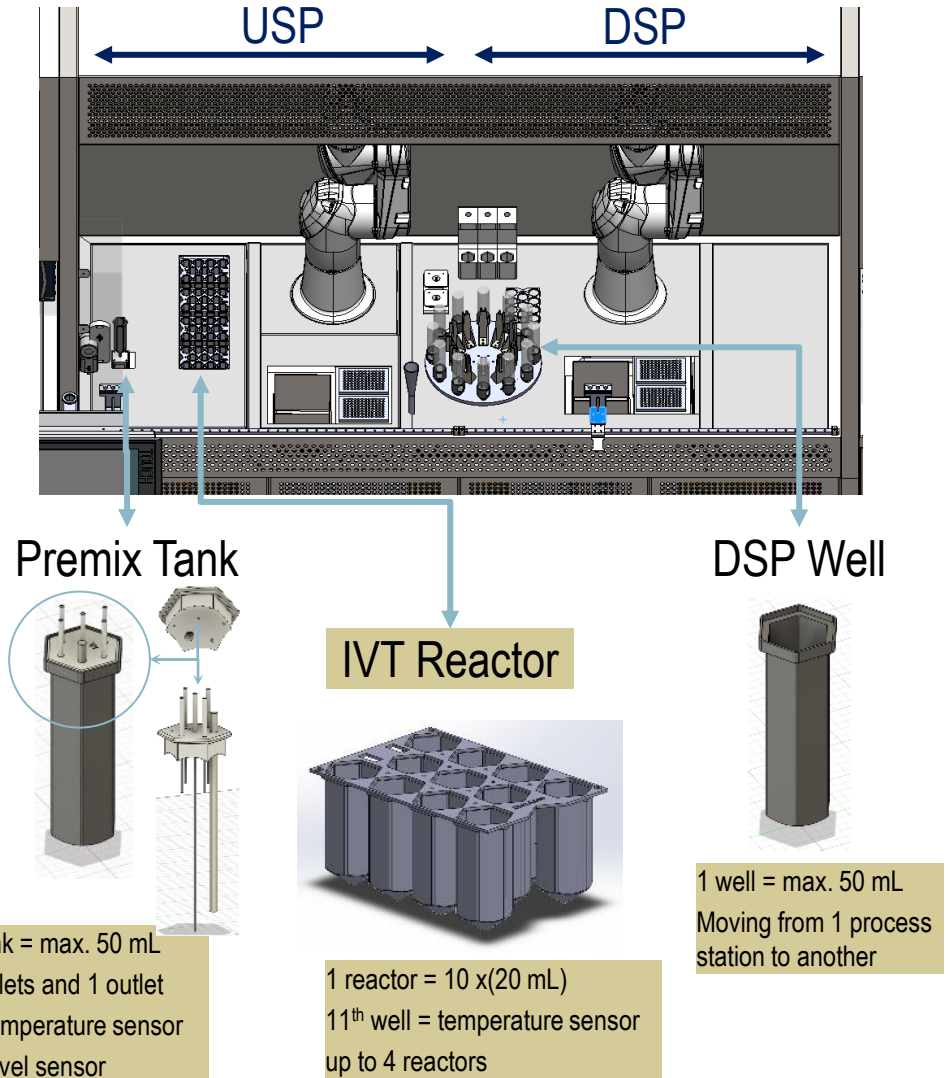
- Use known mRNA and LNP reagents
- Maintain low cost of good operation
- Scale out - not scale up
- Fully automated – better control
- New purification methods (avoid complex system such as tangential flow filtration)
- Wide range of output with the same machine
- R&D operation and GMP operation with the same machine



DENSIFICATION: RNA IN VITRO TRANSLATION UNIT



- Lower footprint
- Bioburden controlled cabinet
- Lower CAPEX



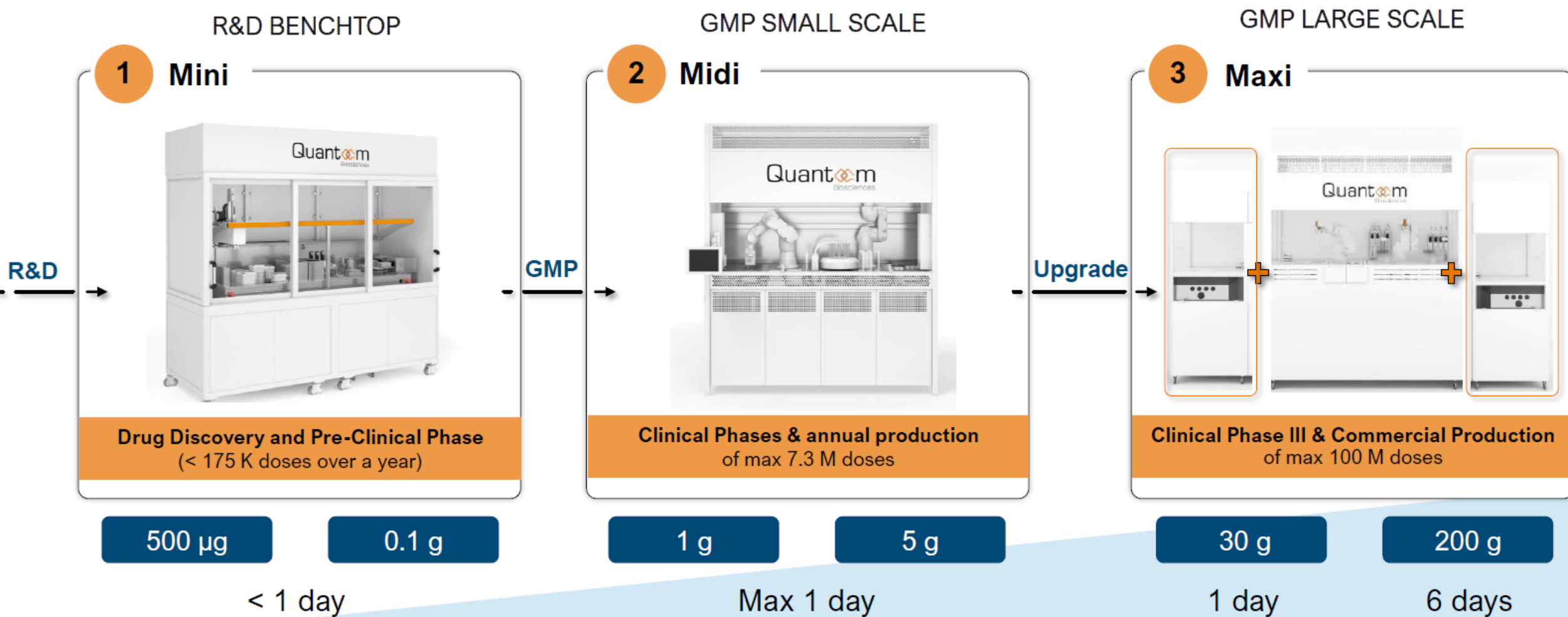


WP3 – RNA Production Equipment Development & Prototype

Machine installed (qualification ongoing) in the mobile lab @Quantoom



Ntensify™ – 3 models designed for increasing RNA capacity requirements



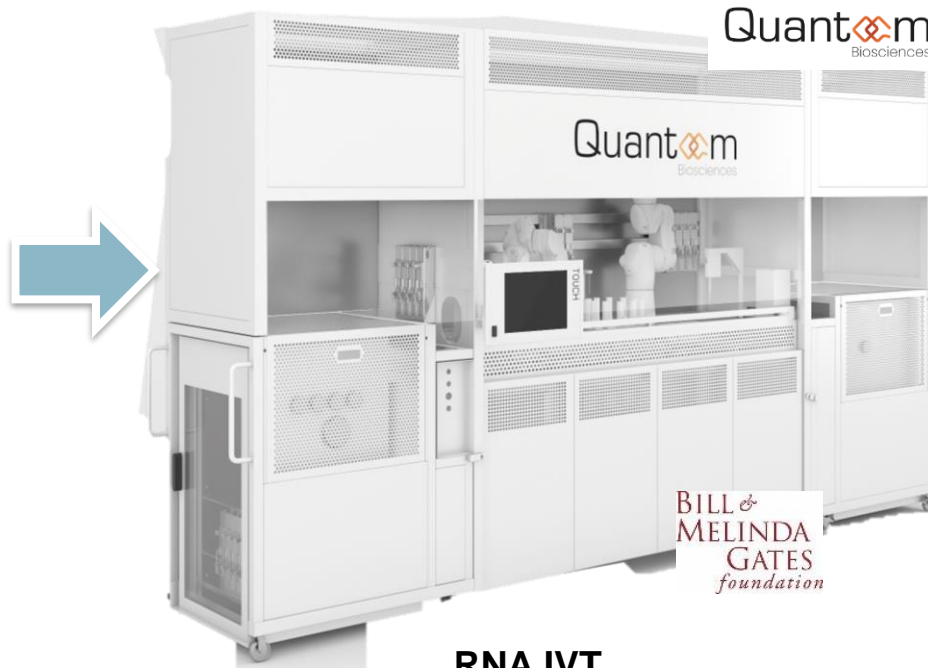
Capacity (drug substance) /batch

Note: 1 dose assumed to be 50 μ g

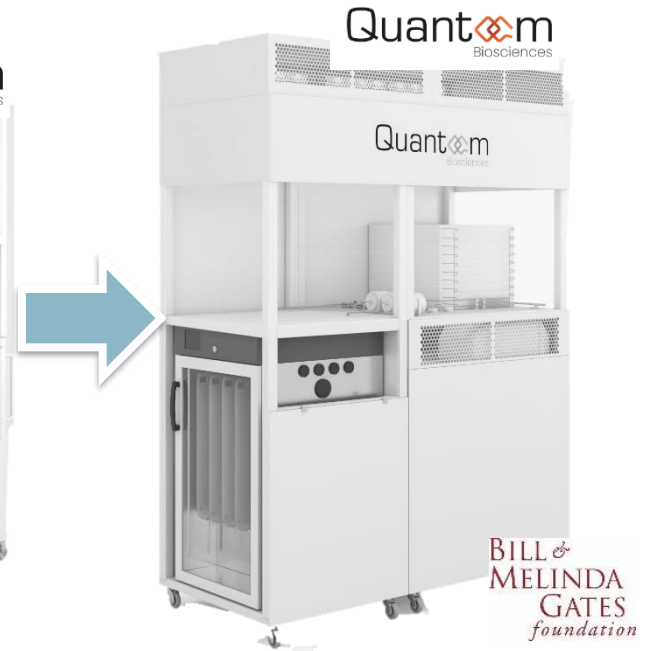
CHAINING: DNA TO RNA TO LNP



Synthetic Linear DNA



RNA IVT



LNP Formulation

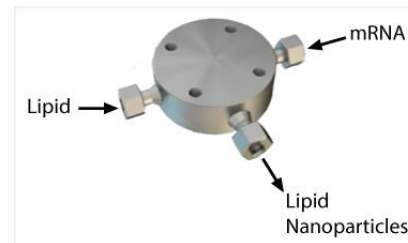
- Chaining reduces the safety issues and batch-to-batch variations associated with physical handling
- Because the processes are essentially closed, there is also less likelihood of contamination. “Chaining reduces the safety issues and batch-to-batch variations associated with physical handling,”

LNP FORMULATION SYSTEM - DESIGN PRIME DIRECTIVES

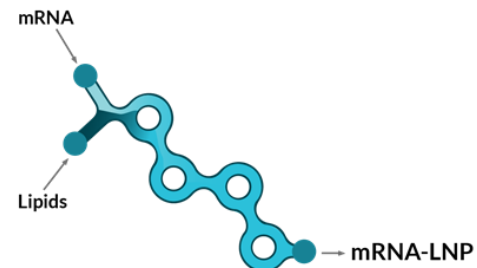
T-mixer



Impingement jet mixer

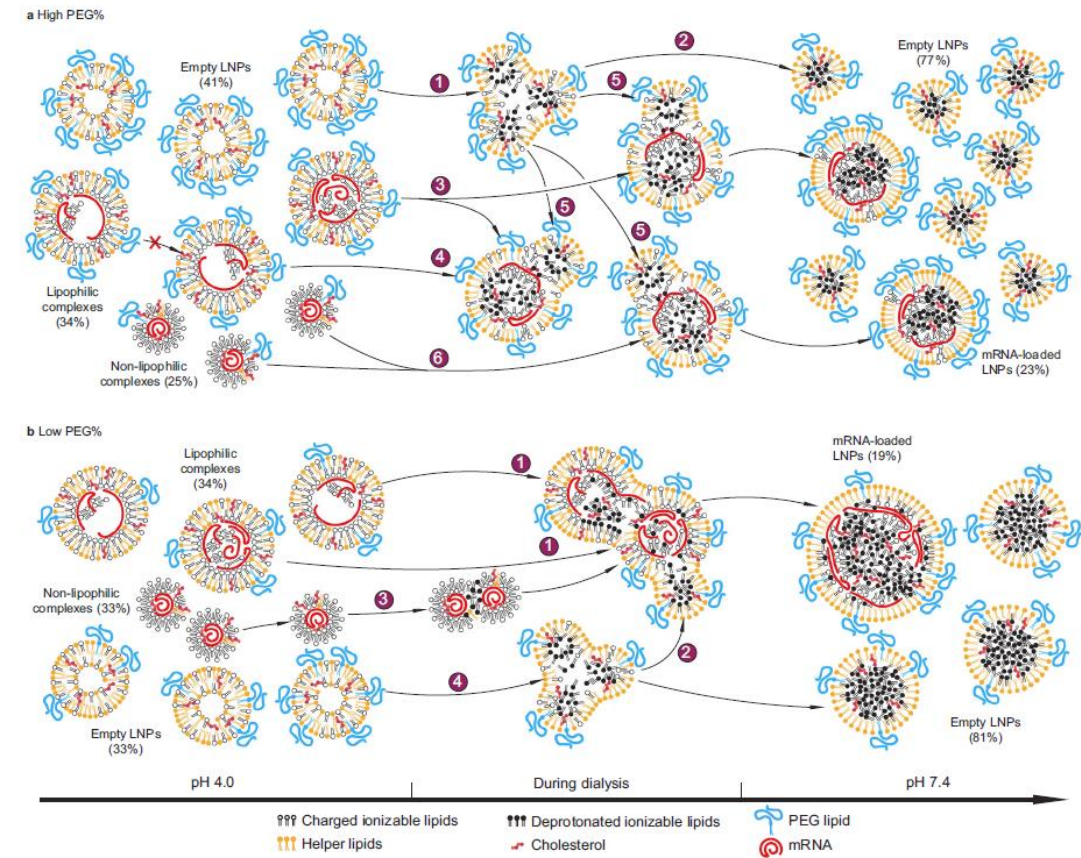


Microfluidics



Article

<https://doi.org/10.1038/s41467-022-33157-4>



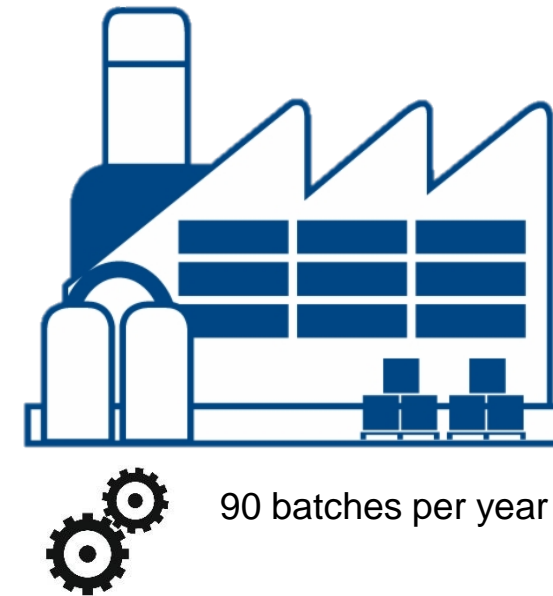
RNA: GAME CHANGER PLATFORM FOR LMIC

COST OF GOODS (COG)

Manufacturing Step	Key Materials	\$/dose*			
		Vaccine 1		Vaccine 2	
mRNA production		Buy	Make	Buy	Make
	pDNA	0.39	0.14	0.10	0.04
	2' O-methyl transferase	0.06	0.03	-	-
	Guanylyl transferase	0.14	0.05	-	-
	T7 RNA polymerase	0.02	0.01	0.00	0.00
	CleanCap®	-	-	0.25	0.13
LNP production	Cationic lipid	4.16	0.04	1.72	0.01
	DSPE	0.01	0.00	0.16	0.00
	Cholesterol	0.47	0.00	0.19	0.00
	DMG-PEG	0.00	0.00	0.08	0.00
Total		5.25	0.27	2.50	0.18

In-house raw material production
0.25 cents/dose

MODELING 50-250M DOSES OUTPUT



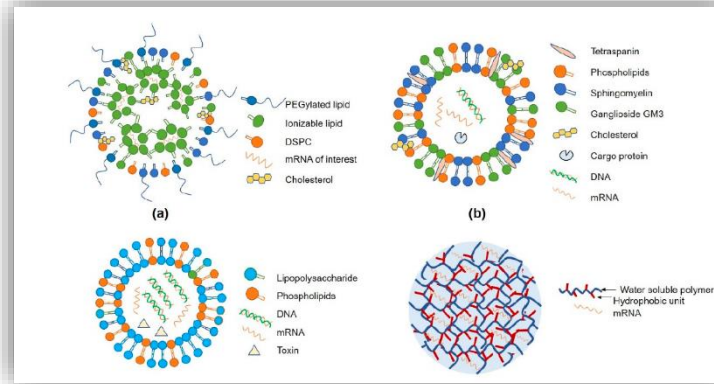
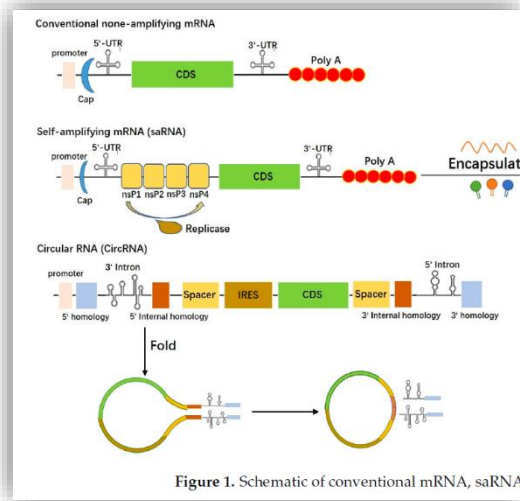
50-250M doses/year

Lower footprint (10 fold)
Lower CAPEX (5 fold)

MODULAR FACILITIES

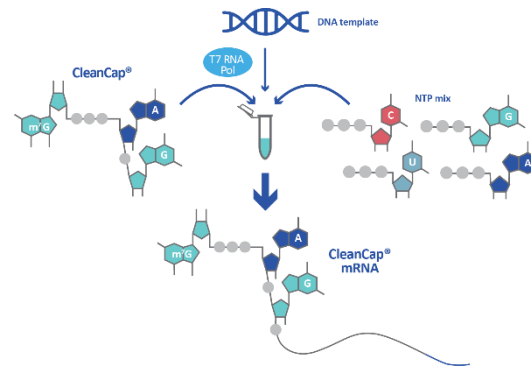


What is next?

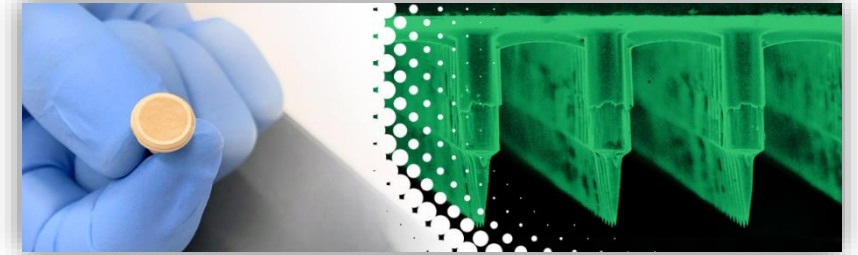


-New LNP (Ionizable lipids, Adjuvant)

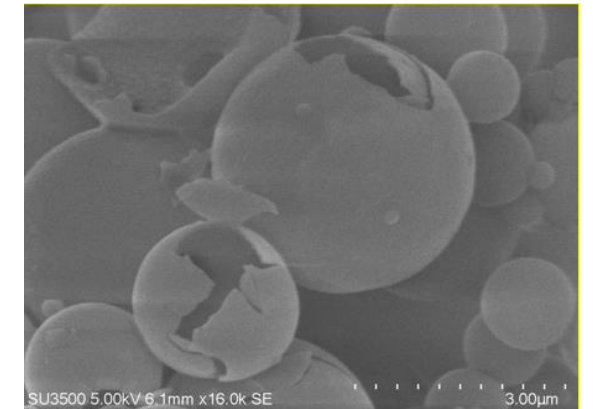
-saRNA
-circRNA
-xRNA



-Advanced reagents (enzymes)



-Microneedle



-Advanced Lyophilization



-Advanced potency assays

Gates Foundation to Accelerate mRNA Vaccine Innovation and Manufacturing in Africa and Globally

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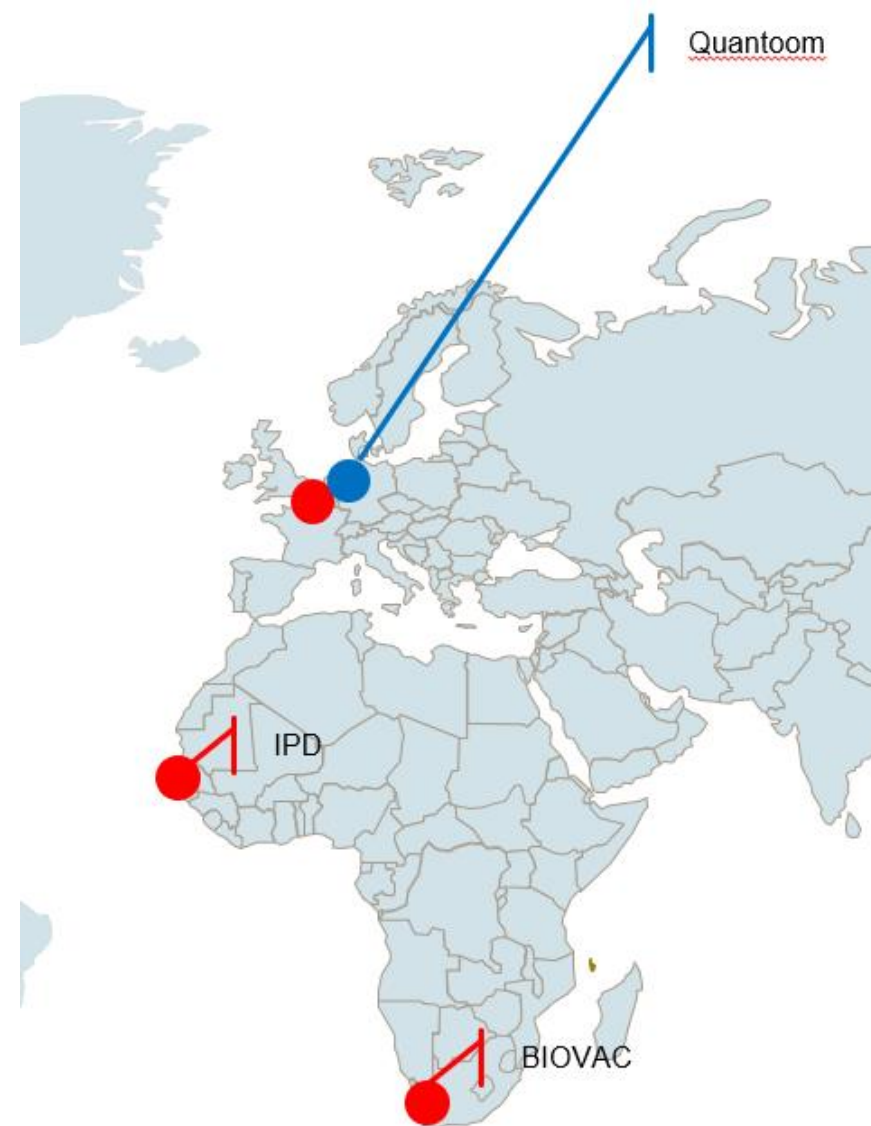


DAKAR (October 9, 2023) – Today at the 2023 Grand Challenges Annual Meeting, Bill Gates, Co-chair of the Bill & Melinda Gates Foundation, announced new investments to advance access to mRNA research and vaccine manufacturing technology that will support low- and middle-income countries' (LMICs) capacity to develop high-quality, lifesaving vaccines at scale.

The move builds on lessons the foundation has learned from more than 20 years of working with vaccine manufacturers in LMICs and the opportunity to leverage recent scientific advances to develop low-cost, high-quality health tools that reach more people around the world. mRNA technology is considered a potential game-changer for a range of infectious diseases, including

RNA ACCESS 2023 GRANTS

GRANT NUMBER	YEAR	LOCATION	TITLE	AMOUNT	DESCRIPTION
INV-064834	2023	Belgium	Quantoom Sustainability	\$20M	<ul style="list-style-type: none"> LNP Formulation Unit LNP FTO In Silico Design unit Critical Reagents Internalization
INV-064835	2023	West Africa	DCVM IPD mRNA Enabling	\$5M	<ul style="list-style-type: none"> Establish a R&D mRNA laboratory and pilot scale Training on R&D capabilities and first production at IPD
INV-064836	2023	South Africa	DCVM BIOVAC mRNA Enabling	\$5M	<ul style="list-style-type: none"> Intensify Midi and Ncapsulate Training at Quantoom
INV-XXXXX	2024	TBD	DCVM XXXXX mRNA Enabling	\$10M	TBD



Based on this new mRNA access mission and our desired impact, the Foundation is now focusing on four new strategy pillars

	Access to mRNA R&D and GMP manufacturing equipment at <u>commercial scale</u>	Access to mRNA <u>supportive technologies</u> and methods	Access to critical raw materials	Access to mRNA candidate design services
Pillar objective	Enable DCVMs to acquire R&D and <u>commercial</u> Quantoom units for mRNA development and manufacturing	Enable DCVMs to access supportive technologies such as <u>thermostability</u> , <u>potency</u> , <u>delivery</u>	Enable DCVMs to access critical raw materials, with appropriate freedom-to-operate, and specific focus on LNPs	Enable DCVMs to develop their own mRNA vaccine portfolio Provide DCVMs with latest mRNA candidate design & bioinformatics capabilities
Desired timing for impact	<i>Next 3-5 years</i>	<i>Next 2-3 years</i>	<i>Next 1-2 years</i>	<i>Next 3-5 years</i>

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