CEPI

CEPI RNA VACCINE REGULATORY WORKSHOP

RNA Workshop Presentation Slides

Day 1

Session 1 · Technical & Regulatory Basis of RNA Vaccines

28–29 July 2026

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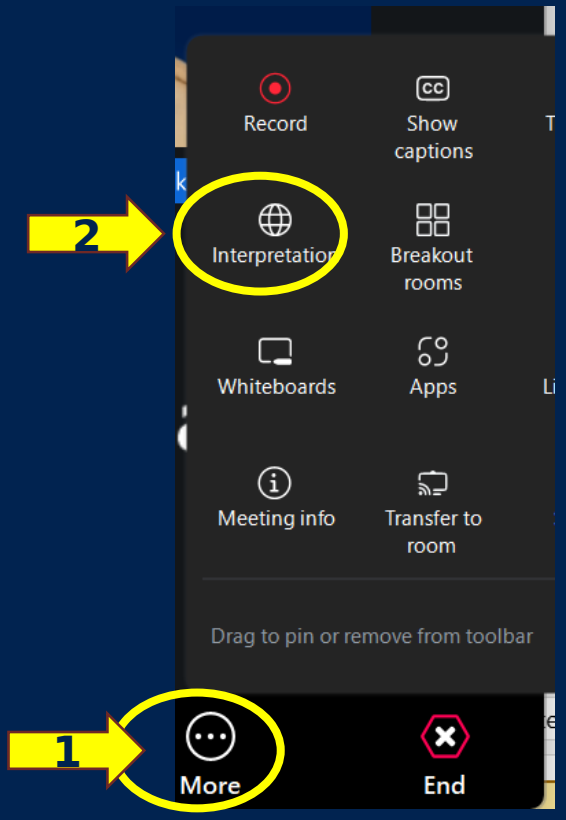
Presentation Slides — Day 1

Session 1 · Four presentations · click any item to jump

Regulatory Pathways in the Development of RNA Vaccines

28-29 July 2026

Instructions for Using Simultaneous Translation



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1. In your meeting/webinar controls, click **Interpretation** .
2. Click the language that you would like to hear.
3. (Optional) To hear the interpreted language only, click **Mute Original Audio**.

Notes:

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What is CEPI?

Vision

A world in which epidemics and pandemics are no longer a threat to humanity.

Mission

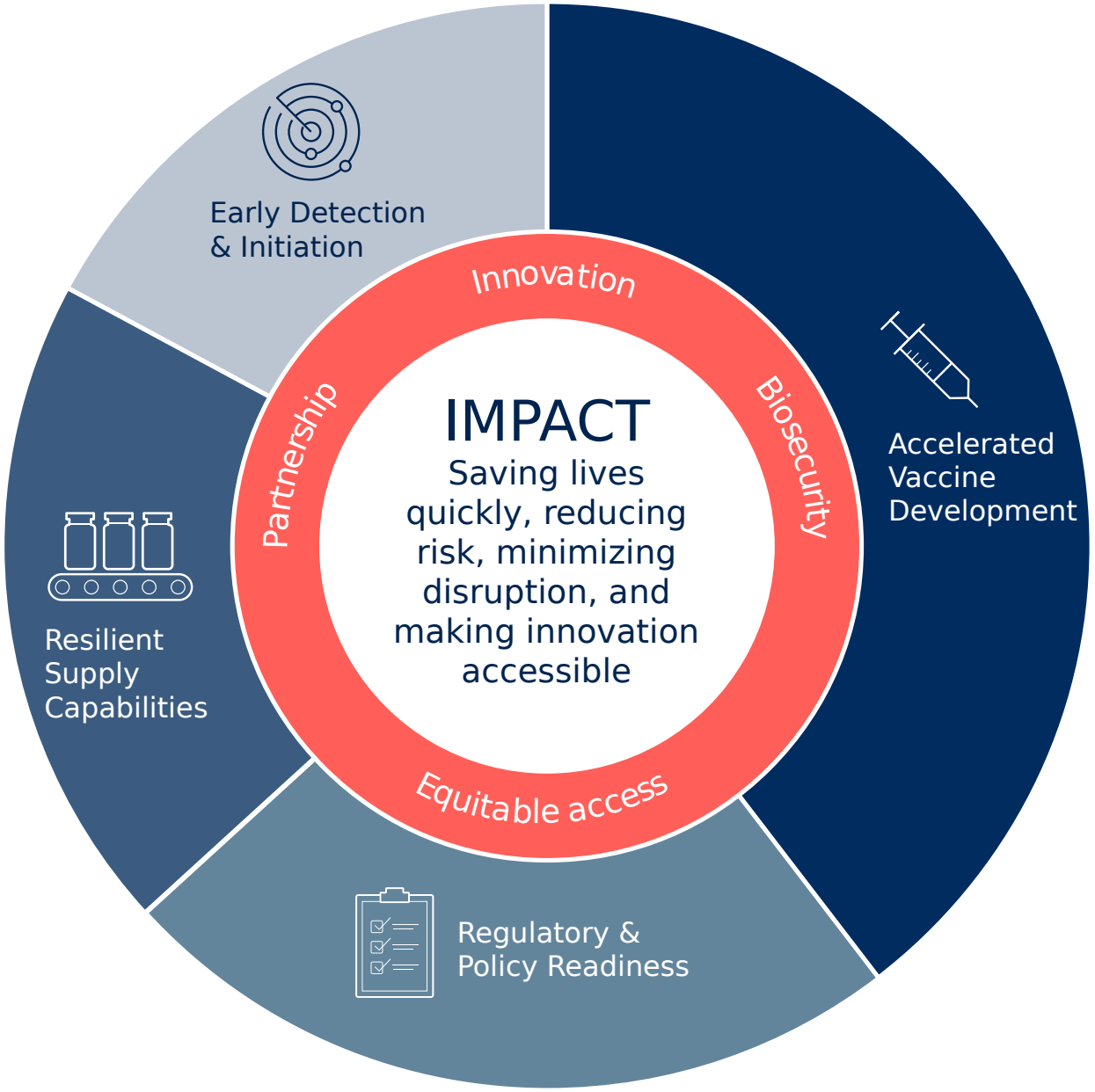
Accelerate the development of vaccines and other biological countermeasures against epidemic and pandemic threats so they can be accessible to all people in need.

Founded	2017 — Davos
Model	Public-private partnership
Mandate	Epidemic preparedness + 100 Days Mission

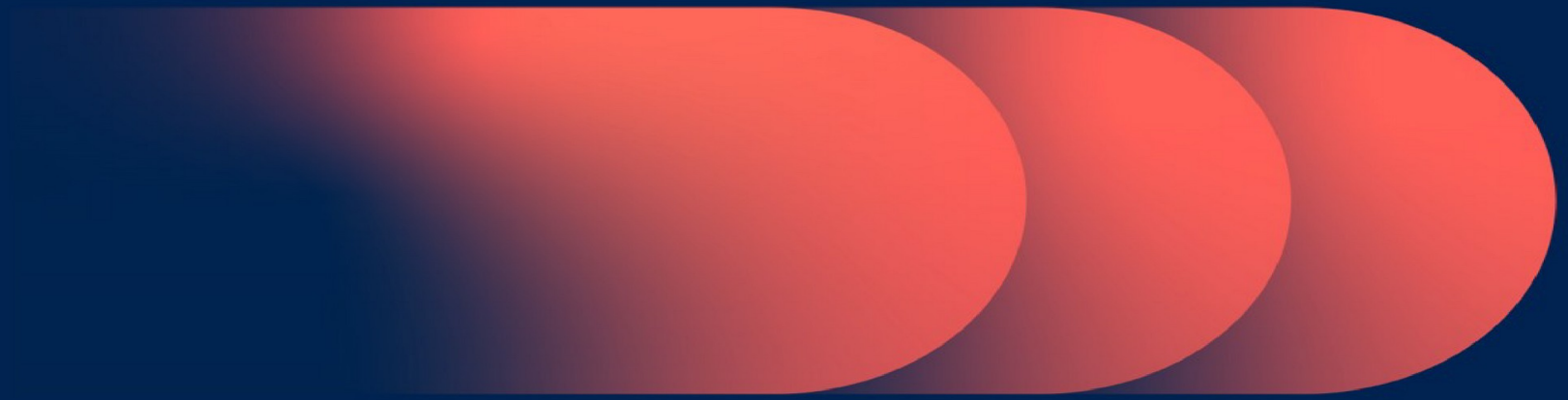
CEPI has galvanized the world to embrace the “100 Days Mission”

CEPI’s Vision:
A world in which epidemics and pandemics are no longer a threat to humanity.

CEPI’s Mission:
Accelerate the development of vaccines and other biologic countermeasures against epidemic and pandemic threats so they can be accessible to all people in need



Deep trusted collaborations enable acceleration



Gather deep insights and identify bottlenecks from collaborative networks

- Funded partners
- Academia
- Industry
- WHO
- RAG and regulators

Drive incremental innovations

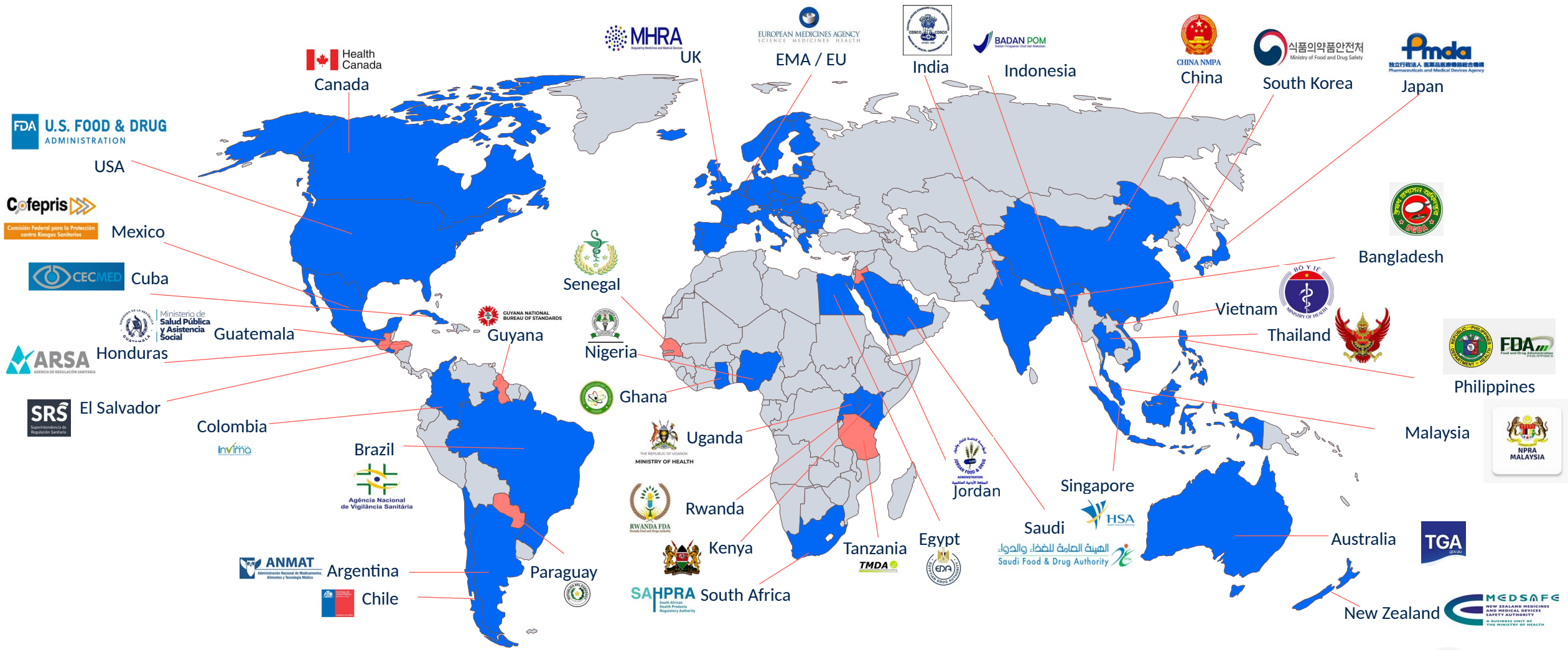
- Pre-reviewed documentation
- Lessons learnt
- Cloud based review

Drive paradigm-shifting innovations

- Maximal use of platform data
- Framework for immune correlates of protection
- Assessment of anticipated benefit-risk and RWE

CEPI Regulatory collaboration

- Regulatory Advisory Group (RAG) Deliberations
- Disease Team Meetings (Chik-V, MERS, RVF et al)
- Regulatory Readiness Dashboards and Tabletop (TTX) Exercises
- Asia, Americas and EMEA Regional Regulatory Innovation workshops



Note TTX at SCoMRA with national regulatory engagement: **South Africa, Tanzania, Uganda, Kenya, Tunisia, Nigeria, DRC, Sierra Leone, Senegal, Liberia, Congo**

SESSION 1 · MODULE 1 · 15 MINUTES

Opening & Context

Welcome, objectives, and how the two sessions fit together — plus the WHO mRNA hub in the Americas and the regional manufacturer landscape.

WELCOME

Why we are here

Strengthen regulatory capacity

Build reviewer fluency in RNA vaccine science, CMC and clinical evidence.

Promote convergence

Align around shared WHO and international frameworks rather than divergent national rules.

Prepare for the next emergency

Consolidate COVID-19 experience so the region is ready for future public-health emergencies.

A two-way dialogue

Regional regulators and international experts; manufacturers join as presenters.

Format at a glance

- Two standalone but complementary 2-hour sessions
- Delivered online — live and interactive
- Designed for NRA regulators; manufacturers present
- Interactive polling to capture the room's views
- Q&A woven throughout (~5 minutes per topic)

OBJECTIVES

By the end of both sessions, you will be able to…

1. Describe the technical basis of RNA vaccines — molecule, IVT, and why the platform is more straightforward than conventional manufacturing.
2. Discuss the platform question — is it the RNA, the LNP, or both? — and its consequences for designation, shared vs. product-specific data, and change management.
3. Apply WHO TRS 1039 and the EMA draft guideline, and recognise how they extend (and fall short) for self-amplifying and other RNA-based products.
4. Discuss regulatory considerations for developing an RNA vaccine during a public-health emergency.
5. Identify how regional resources can be leveraged and where capacity gaps remain — with live participant input.
6. Understand product-specific GMP and inspection considerations for RNA facilities.

AGENDA

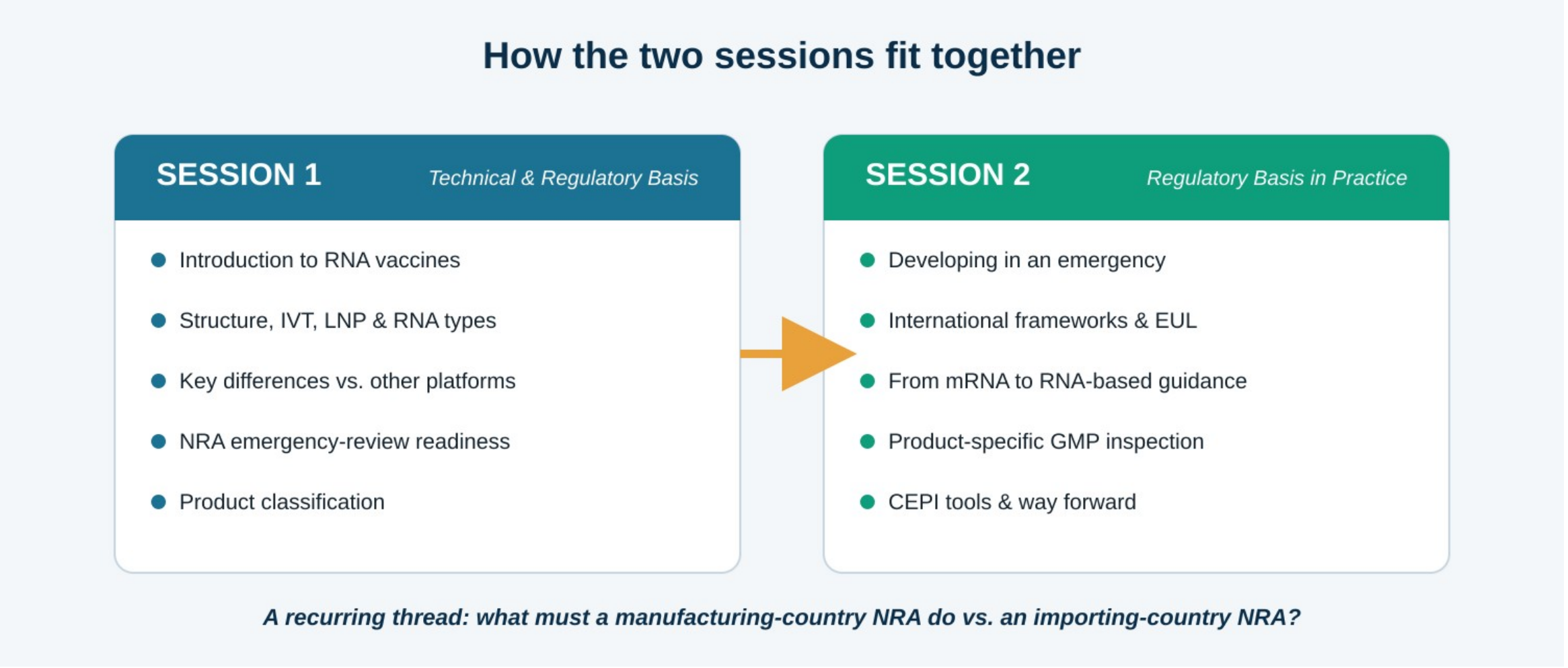
Session 1 At A Glance

Two hours · five modules · Q&A woven throughout (~5 min per topic)

15 min	**Opening & Context**	April Hernandez - CEPI
30 min	**Introduction to RNA Vaccines**	Hassan Askary - CEPI
30 min	**New Horizons in RNA Technology: Novel One-Component IAJD Delivery Platform for mRNA Vaccines & Therapeutics**	Elena N. Atochina-Vasserman, M.D., Ph.D. · Penn Institute for RNA Innovation, University of Pennsylvania
35 min	**Regulatory Considerations**	April Hernandez - CEPI
10 min	**Wrap-Up, Discussion & Bridge to Session 2**	April Hernandez - CEPI

ROADMAP

How The Two Sessions Fit Together



REGIONAL CONTEXT

The WHO mRNA Hub in the Americas

Why it matters for regulators

- The WHO mRNA technology-transfer programme seeds local manufacturing capability across low- and middle-income regions.
- Latin America hosts a designated hub, building end-to-end RNA know-how in the region.
- For NRAs this shifts the question from importing finished product to overseeing local development and manufacture.
- It raises the manufacturing-country vs. importing-country distinction we return to throughout.

Technology transfer

Shared processes and training accelerate regional readiness.

Local resilience

Reduces dependence on external supply during emergencies.

Regulatory demand

Local production means local NRAs must review RNA CMC & GMP.

LANDSCAPE

Regional RNA Developer Landscape

RNA DEVELOPERS · NORTH TO SOUTH

1 **Vaxthera**
Rionegro, Colombia · Grupo SURA vaccine developer

2 **Bio-Manguinhos / Fiocruz**
Rio de Janeiro, Brazil · WHO mRNA technology-transfer hub

3 **Instituto Butantan / Replicate**
São Paulo, Brazil · saRNA rabies programme

4 **Sinergium Biotech**
Garín, Argentina · mRNA manufacturing partner

A RECURRING THREAD

One question you will hear again and again

> ***"Does your NRA have the resources and expertise to evaluate an RNA vaccine in a public health emergency?"***

This framing recurs across both sessions. Reliance is the bridge between the two roles — a theme we develop in Module 3 and again in Session 2.

Session 1

Technical foundation and the readiness self-assessment.

Session 2

Frameworks, emergency development, GMP inspection.

Throughout

Live polling captures where your agency stands.

SESSION 1 · MODULE 2 · 30 MINUTES

Introduction to RNA Vaccines

The technical foundation, end to end — molecule and manufacturing, delivery, RNA forms, how RNA differs from other platforms, and the platform question.

A CEPI-led workshop for NRA regulators of the Americas

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CONCEPT

What is an RNA vaccine?

The core idea

Deliver the genetic instructions for an antigen and let the recipient's own cells make the protein — triggering a protective immune response.

The vaccine carries a message, not the antigen itself.

Cell-free manufacture

Made enzymatically (IVT), not grown in cells — unlike most biologicals.

Sequence-agnostic

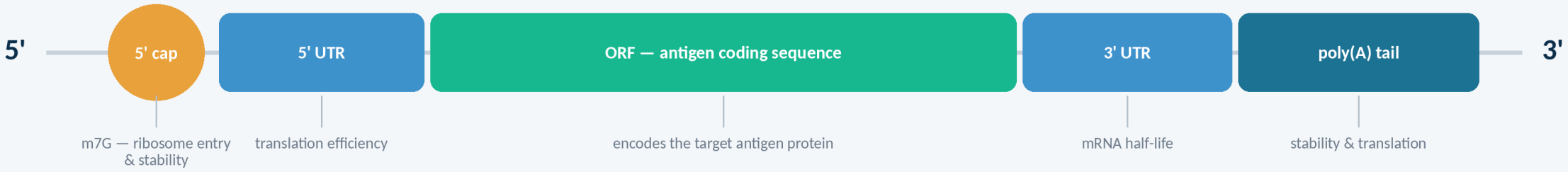
Change the coding sequence, keep the process; the basis of the platform idea.

Needs a delivery vehicle

RNA is fragile — formulated in lipid nanoparticles for stability and uptake.

Structure and function of the mRNA

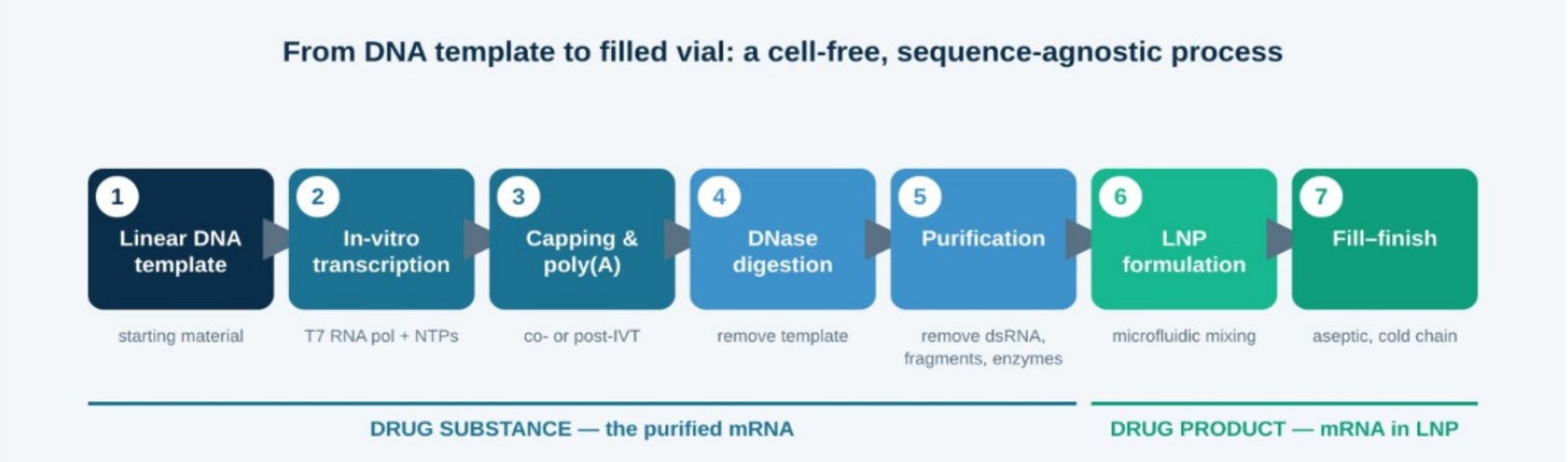
Anatomy of a non-replicating mRNA

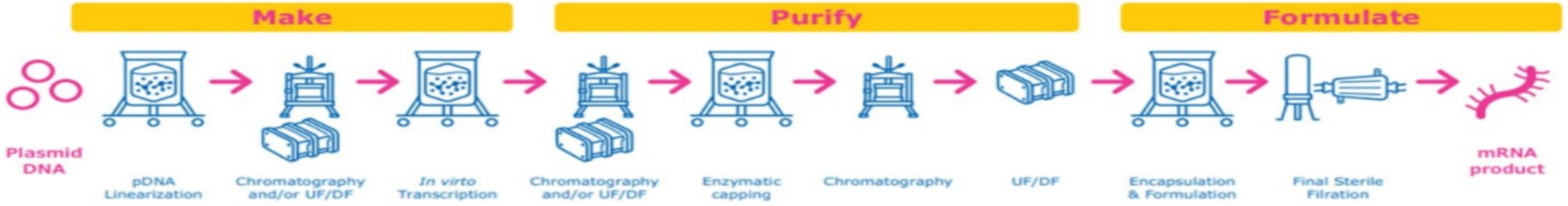


Single-stranded RNA translated in the cytoplasm into the encoded antigen.

Each element — cap, UTRs, ORF, poly(A) — must be sequence-annotated and justified in the dossier (WHO TRS 1039 §6.2; EMA draft §4.1).

How it is made: in-vitro transcription (IVT)



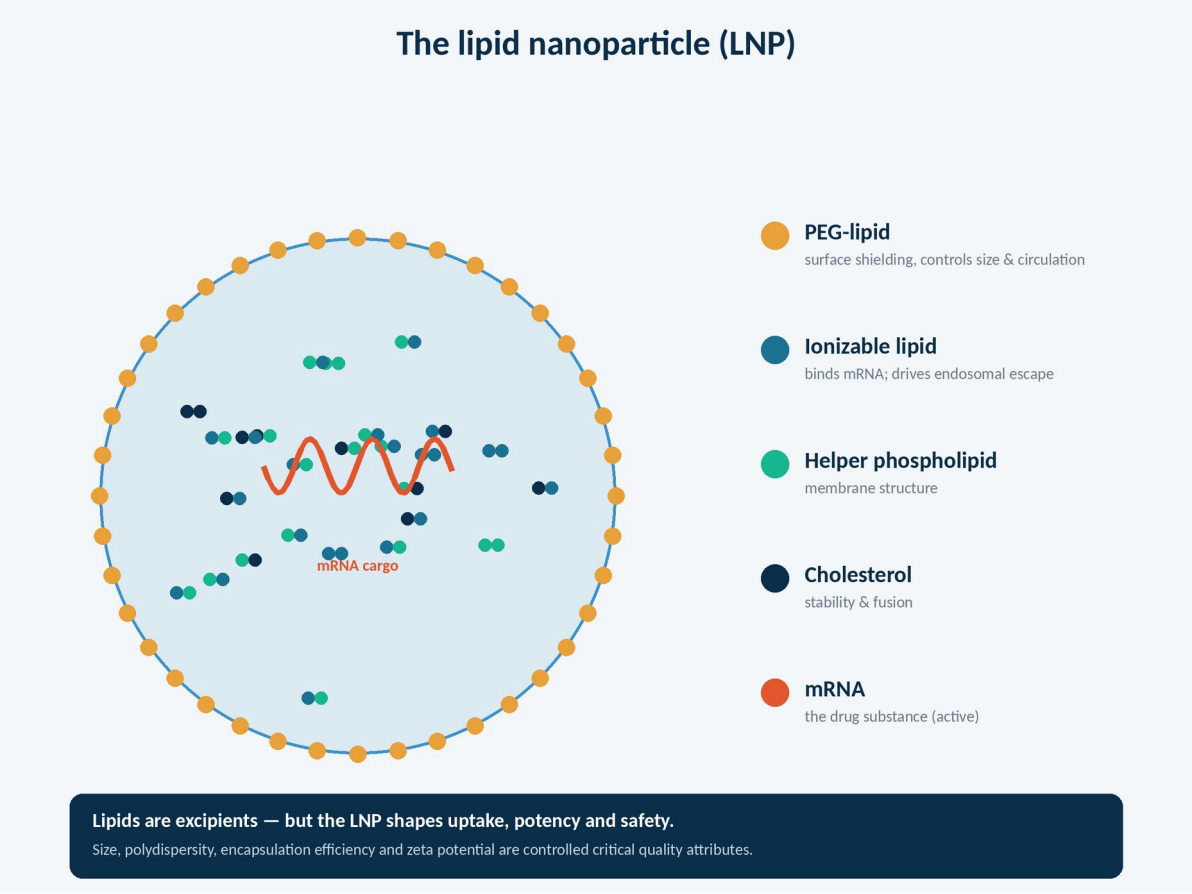


+ Fill & Finish
+ Label + Pack
Release

Image source: https://www.sigmaaldrich.com/NO/en/technical-documents/technical-article/pharmaceutical-and-biopharmaceutical-manufacturing/vaccine-manufacturing/adenovirus-vaccine-manufacturing-process

DELIVERY

The lipid nanoparticle (LNP)



Four lipids, one job: protect and deliver

- Ionizable lipid binds the mRNA and drives escape from the endosome into the cytosol.
- Helper phospholipid and cholesterol give the particle structure and stability.
- PEG-lipid shields the surface and controls particle size and circulation.
- The mRNA is the active substance; the lipids are excipients — but the LNP shapes uptake, potency and safety.
- Size, polydispersity, encapsulation efficiency and zeta potential are controlled critical quality attributes.

SPEED & ADAPTABILITY

Why the modality adapts faster than conventional vaccines

Weeks

to bring a new antigen online once the process is established

Months

the timeline for many conventional, cell-based platforms

One process, many antigens

The chemistry stays fixed; only the sequence changes.

What makes it straightforward

Cell-free, defined chemistry

No cell-culture campaigns, banks or viral clearance for the RNA itself.

Small physical footprint

Compact equipment train; easier to deploy and transfer.

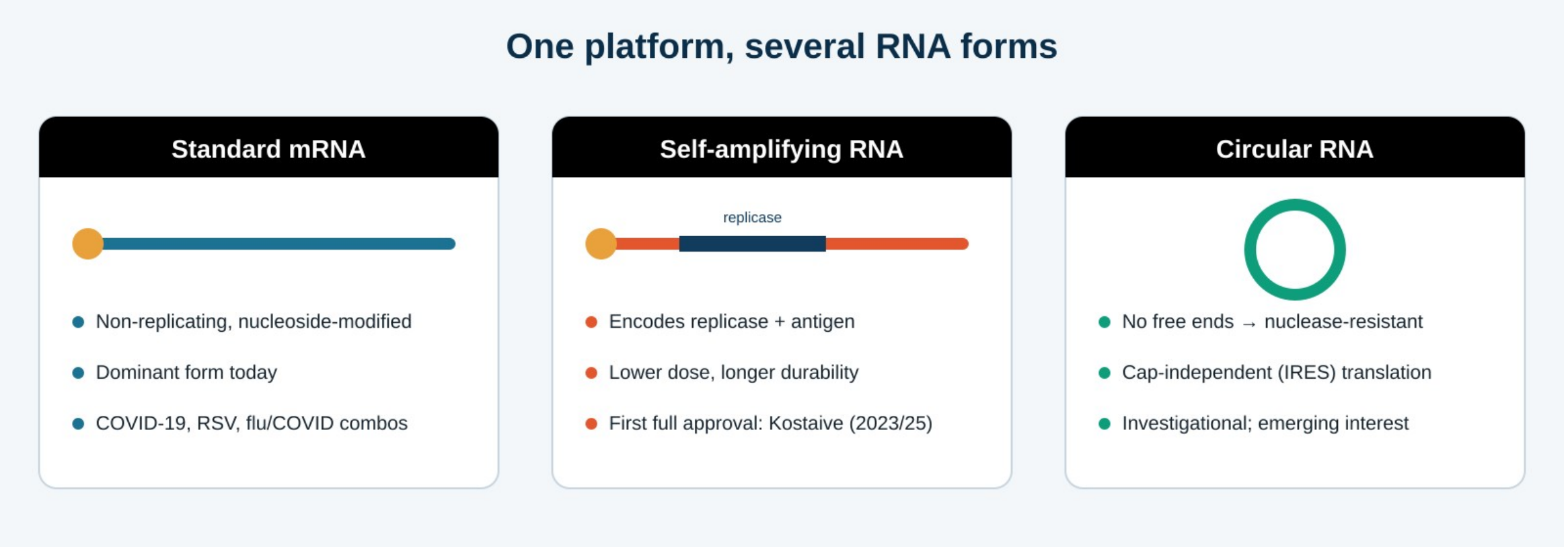
Rapid strain updates

Sequence swap without re-engineering the whole process.

Platform leverage

Prior knowledge supports faster review of the next product.

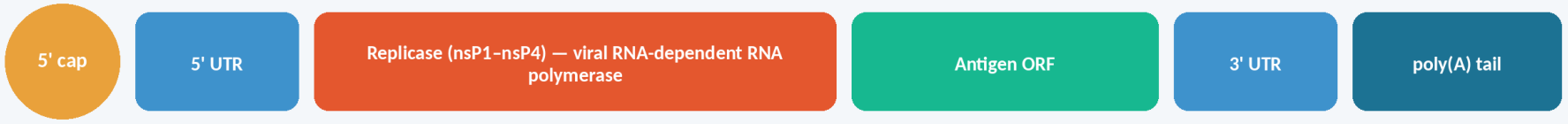
One modality, several RNA forms



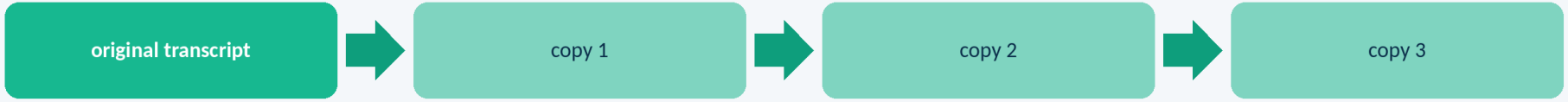
Regulators increasingly frame guidance around "RNA-based", not mRNA-only — because the toolkit is diversifying.

saRNA in focus

Self-amplifying RNA (saRNA): a larger construct that copies itself in-cell



Intracellular amplification



Result: more antigen per molecule → protective responses at substantially lower doses. Minimal CMC requirements are the same as mRNA, plus proof that the replicase drives increased antigen expression (EMA draft §6.3; WHO TRS 1039 §6.7).

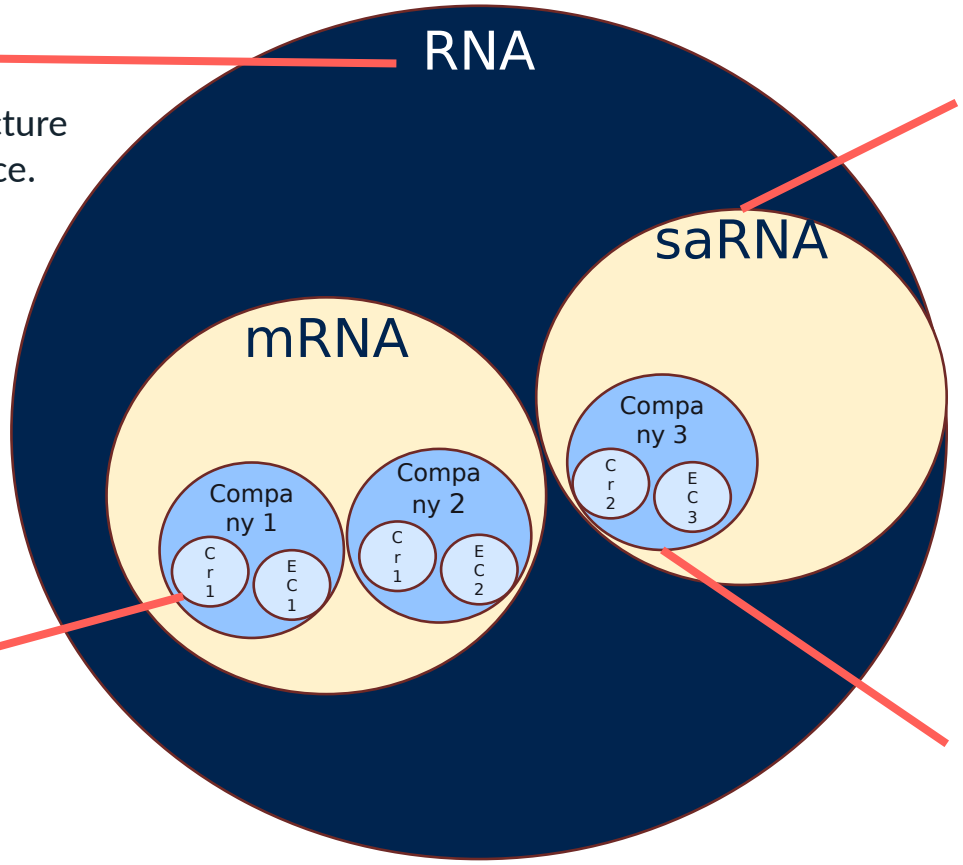
COMPARISON

Key differences from other vaccine modalities in the region

Platform	How RNA vaccines differ
Protein-based (subunit, conjugate)	No protein grown or purified — the recipient's cells make the antigen; different impurity and characterisation profile.
Inactivated whole-virus (e.g. CoronaVac)	No virus culture or inactivation; no whole-pathogen antigen mix — a single defined sequence.
Live-attenuated	No replicating pathogen; saRNA amplifies the message only, and cannot form infectious particles.
Viral-vector	No viral capsid/vector; LNP delivery avoids anti-vector immunity, easing re-dosing and updates.
Virus-like particle (HPV, HepB)	No self-assembling particle antigen; antigen is expressed transiently in vivo.
Polysaccharide / conjugate	Not a chemistry-conjugation product; protein antigen from a coded sequence, not a carrier.
DNA vaccine (closest nucleic-acid cousin)	Acts in the cytoplasm — no nuclear entry or genomic-integration concern; needs no promoter transcription in-cell.

Define Platform - Definitions used by CEPI

Modality
'Modality' refers to the structure of a product's active substance.



Common Platforms
'Common Platform' refers to the particular type of antigen vehicle within a modality.

Platform Technologies
'Platform Technologies' are antigen-agnostic methods that can be used across multiple products.

Regulatory Platforms
A 'Regulatory Platform' follows a specific, well-defined process to make products with uniform specifications and highly predictable characteristics.

Cr = Chromatography
EC = Enzyme Capping

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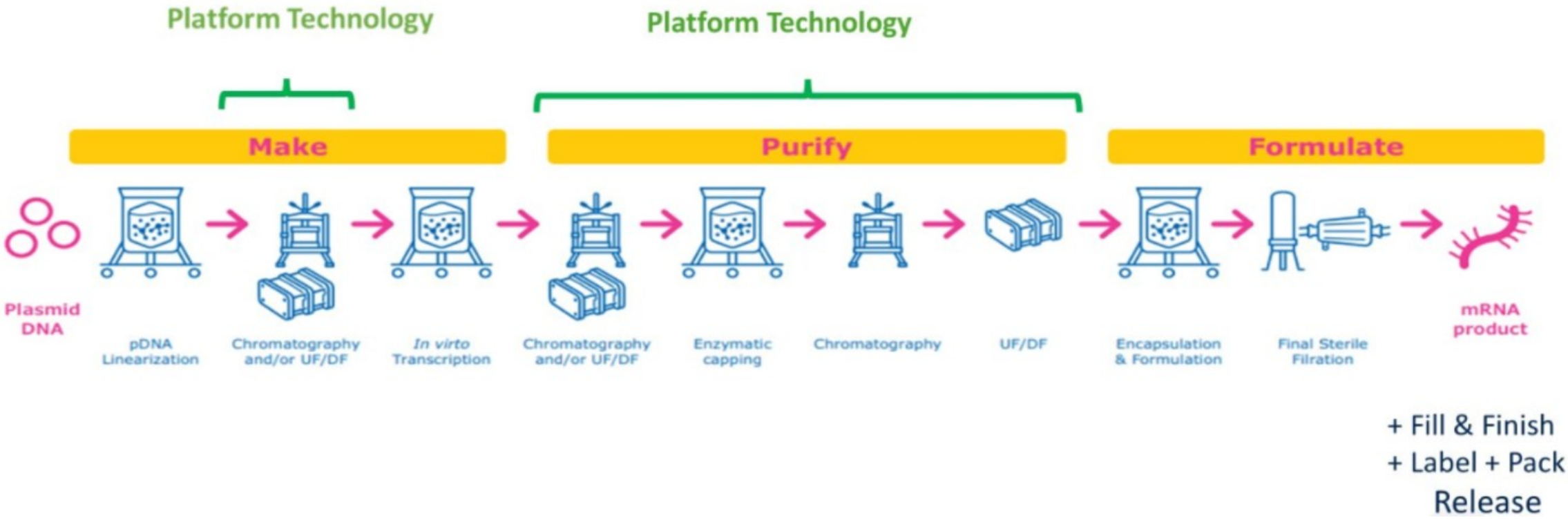
Platform Technology



Can RNA Function as a True Platform Technology?

***The chemistry does not change when the antigen changes – only the coding sequence changes. Once a process is established and validated, a new antigen can be brought online in weeks rather than months. This is the scientific basis for the platform technology concept*.**

Why this platform is faster to adapt

The RNA platform comprises of a **standardised non-coding architecture** (5′/3′ UTRs, cap, poly(A)), a **standardised IVT manufacturing process**, and a **conserved LNP architecture** (ionisable lipid:cholesterol:DSPC:PEG-lipid).

Primary variability lies in the ORF, with associated impacts on construct length, codon composition, and secondary structure.

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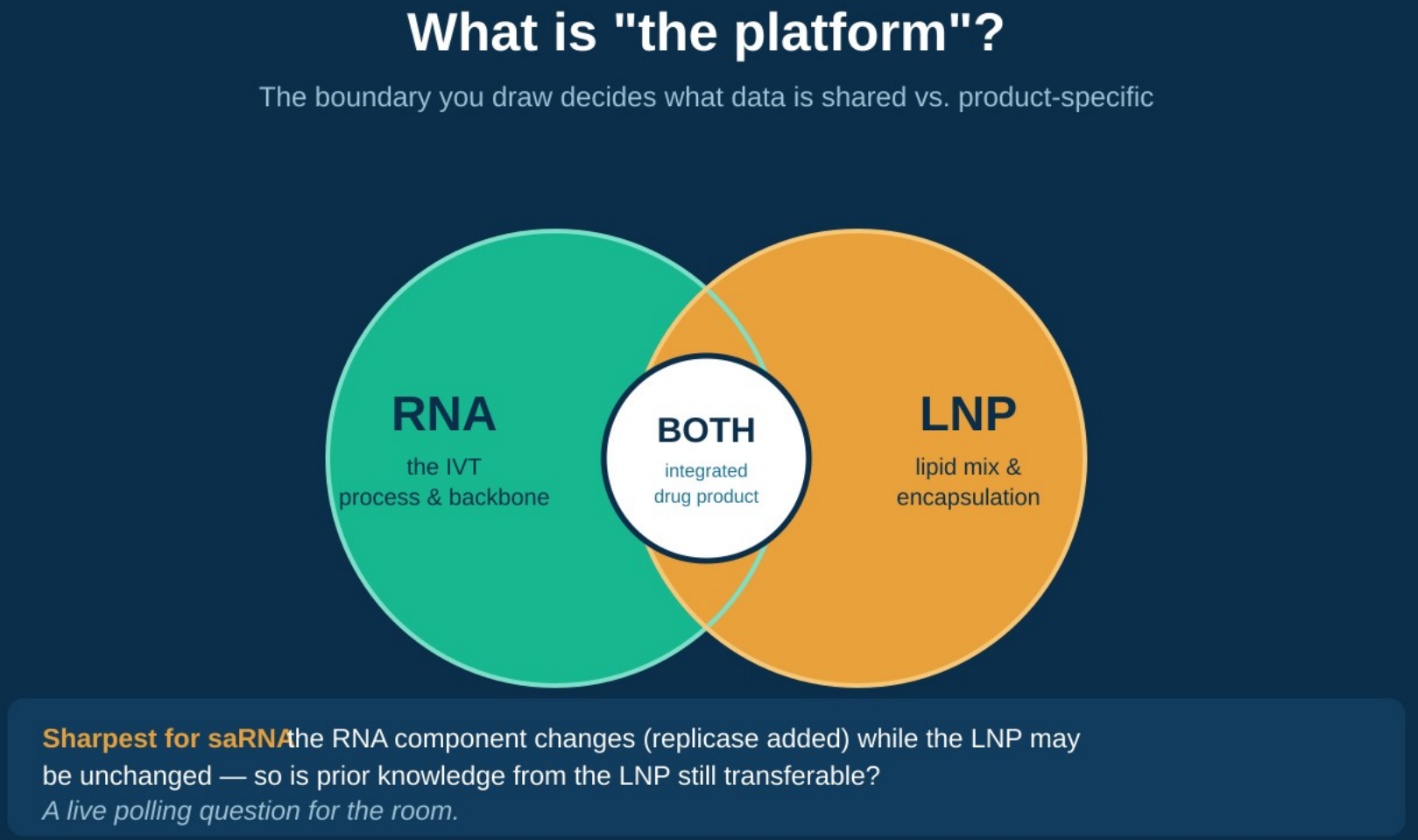
What is “the platform”? — RNA, LNP, or both



LIVE POLL

What does your agency consider to be the platform?

Choose one:

A

The RNA component

The IVT process and RNA backbone

B

The LNP component

The lipid composition and encapsulation

C

Both

The integrated RNA + LNP drug product

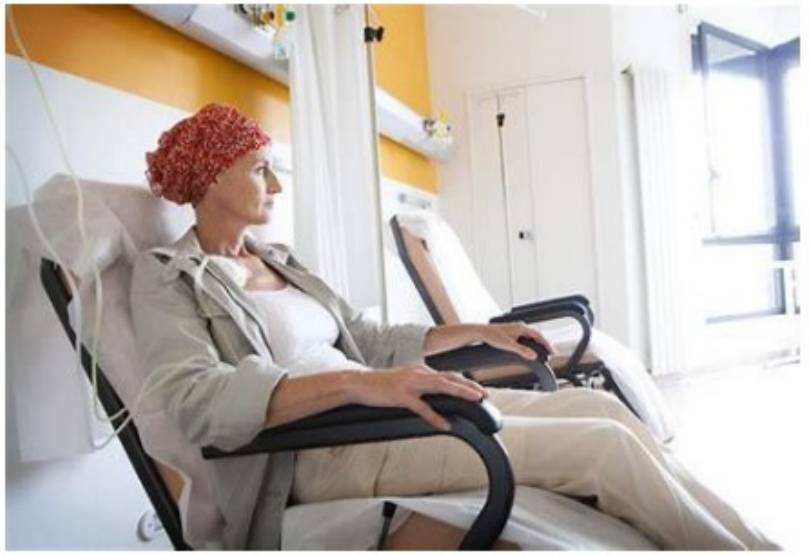
There is no single right answer — your choice shapes designation scope, data-sharing and change management. We will revisit it in Session 2.

Vaccine platform technologies can also have tremendous public health value outside a pandemic

e.g. development and regulatory review of:

- Vaccines for current (difficult to vaccinate against) and emerging deadly infectious diseases
- Vaccine-like technologies used for serious diseases – cancers, inherited genetic disorders

But **it cannot be about "cutting corners"** – developers must have evidence and regulators must be confident of safety, efficacy and quality to meet market authorisation/ licensure requirements



Guidance

Global Regulatory Perspectives on mRNA Platform Technologies

Status as of July 2026 — underlined document titles link to the source text

Agency / Body	Key position or guideline	Relevance to platform approach
US FDA Draft, May 2024 — still draft	Platform Technology Designation Program for Drug Development, implementing §506K FD&C Act (PREVENT Pandemics Act)	Defines platform technology as common manufacturing elements across products; enables leveraging of prior CMC knowledge in subsequent applications. The framework is being tested in practice.
EMA — human Draft guideline, Mar 2025; consultation closed Sep 2025	Guideline on the quality aspects of mRNA vaccines (EMA/CHMP/BWP/82416/2025)	First EU text with a dedicated section on platform technology / prior knowledge for mRNA; also covers strain changes, bi- and multivalent vaccines and saRNA. Adoption pending.
EMA — vPTMF Guideline 2022; procedural advice Rev.1, Nov 2025	vPTMF guideline EMA/CVMP/IWP/286631/2021 + procedural advice for vPTMF certification EMA/CVMP/184591/2022 Rev.1	Only PTMF certification pathway currently in force — veterinary only. Operational reference model for the proposed human PTMF (EFPIA/CEPI position paper, Mar 2023).
Ph. Eur. / EDQM Adopted Nov 2024; published Jul 2025	General chapters 5.36 mRNA vaccines for human use · 5.39 mRNA substances · 5.40 DNA templates for the preparation of mRNA substances	First harmonised quality standards for the mRNA platform and its starting materials; provides the common analytical baseline that regulators and national control laboratories worldwide can rely on.
WHO ECBS TRS No. 1039, Annex 3 (2022)	Evaluation of the quality, safety and efficacy of mRNA vaccines for the prevention of infectious diseases: regulatory considerations	Establishes mRNA quality control principles and recognises common platform elements; baseline for WHO PQ / EUL assessment and for reliance by less-resourced NRAs.
EU pharma legislation reform Compromise texts Mar 2026; application expected 2028	New Regulation and Directive replacing Directive 2001/83/EC and Regulation (EC) 726/2004	No formal EU platform authorisation pathway for human medicinal products is yet defined — the structural gap that the PTMF / DSVI framework is designed to close.

Links point to the publishing authority (FDA, EMA, EDQM, WHO). Ph. Eur. chapters 5.36 / 5.39 / 5.40 are subscription texts — the link is the EDQM adoption notice. Status of the EMA human mRNA guideline to be reconfirmed before external use. Link check: July 2026.

Novel one-component IAJD delivery platform for rapid and efficient development mRNA vaccine and therapeutics

Elena N. Atochina-Vasserman, M.D., Ph.D.
Research Assistant Professor
Infectious Diseases Department
Penn Institute for RNA Innovation
University of Pennsylvania Perelman School of Medicine

CEPI, RNA Vaccine Regulatory Workshop
July 28, 2026

The Weissman Lab
Bringing mRNA therapeutics to the world

Introduction

- COVID-19 was a landmark for mRNA vaccines as it marked the **first successful global implementation** of this technology, demonstrating its safety, efficacy, and rapid development potential.

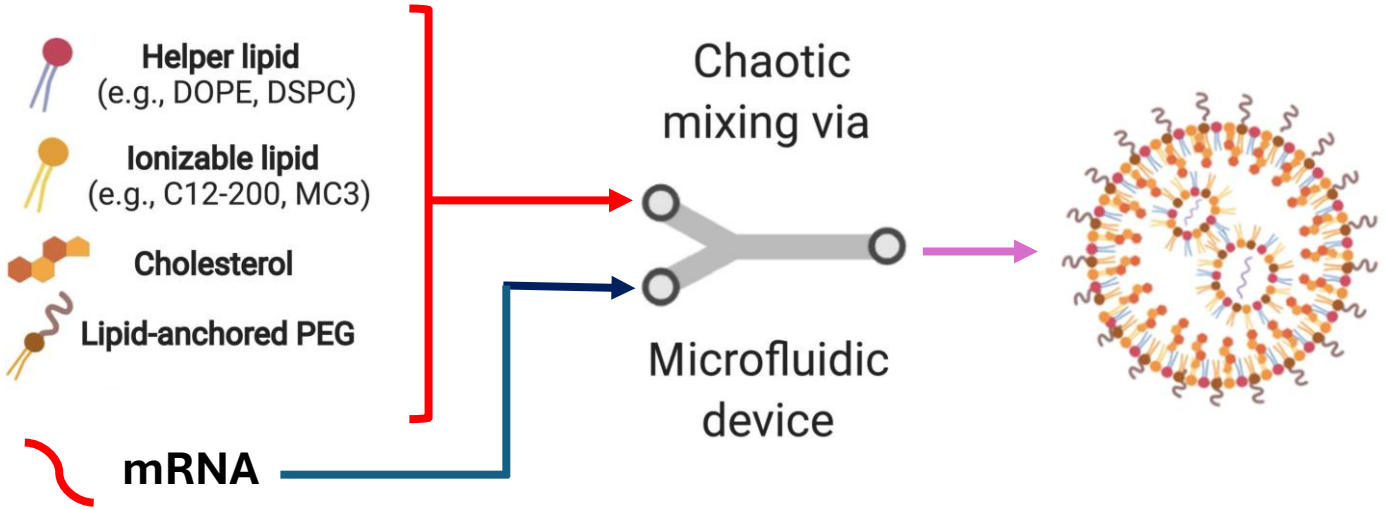
- Traditional vaccines typically take years to develop, but the Pfizer-BioNTech and Moderna mRNA vaccines were designed, tested, and authorized for emergency use **within a year**.

- A significant challenge in mRNA vaccine development remains the **delivery system**, with four-component lipid nanoparticles (LNPs) being the most advanced carriers to date.

- While mRNA-LNP vaccines have shown great promise in providing protection against infectious diseases, there are still several challenges that need to be addressed in order to **enhance their stability, efficacy, durability, and minimize side effects.**

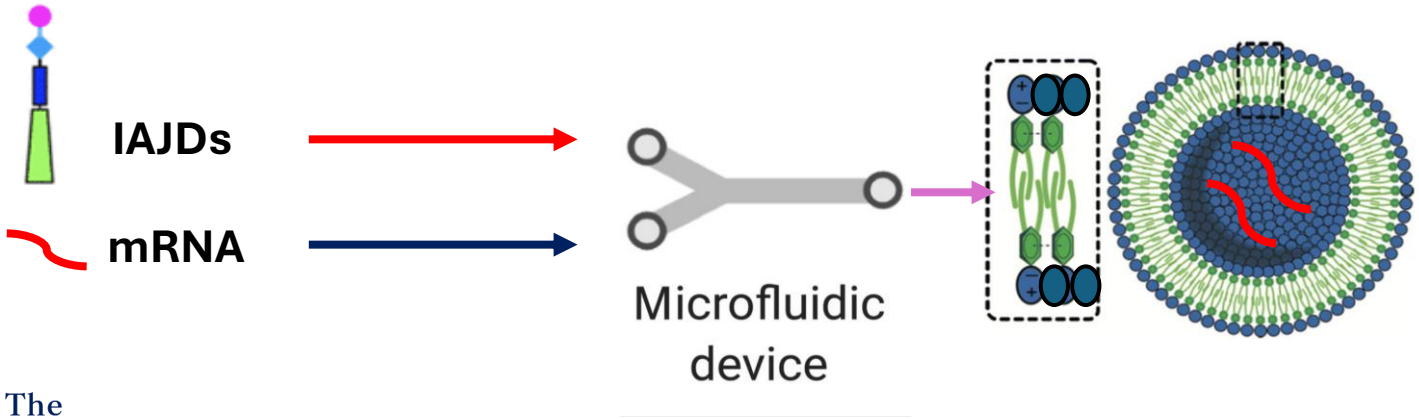
Four-component LNP vs one-component IAJD nanoparticles

Four-Component Ionizable Lipid Nanoparticles (LNP)



- Four components LNPs
- Microfluidics
- PEG adverse reaction
- Storage at -80 ℃
- 15-19 synthesis steps

One-Component Ionizable Amphiphilic Janus Dendrimers (IAJD)



- One components
- Simple mixing on vortex
- No PEG
- High EE%
- Stable at +4°C for over 6 months
- 5-7 synthesis steps
- Less cost and fast production

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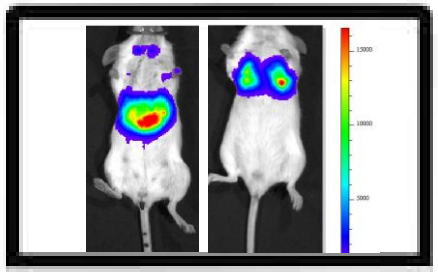
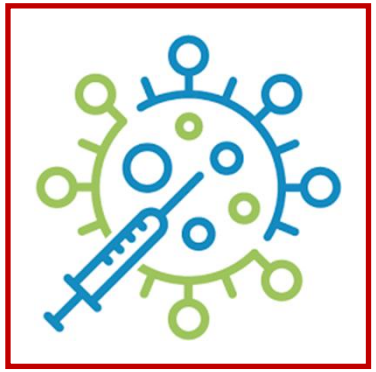
Preclinical applications of one-component IAJDs

Screening and Optimization



Immunization



Vaccines

Tissue specific delivery

Therapeutics

One-component IAJD, formulated with norovirus mRNA capsid protein, serves as a proof of concept for the potential use of one-component IAJD as a novel and efficient platform for vaccine delivery

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In this study we use norovirus mRNA capsid protein as a proof of concept for the potential use of one-component IAJD97 as a novel and efficient platform for vaccine delivery

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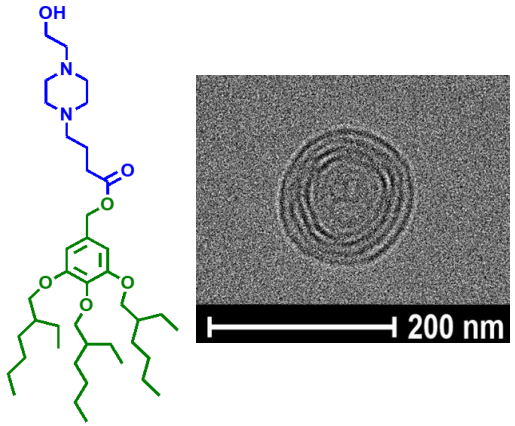
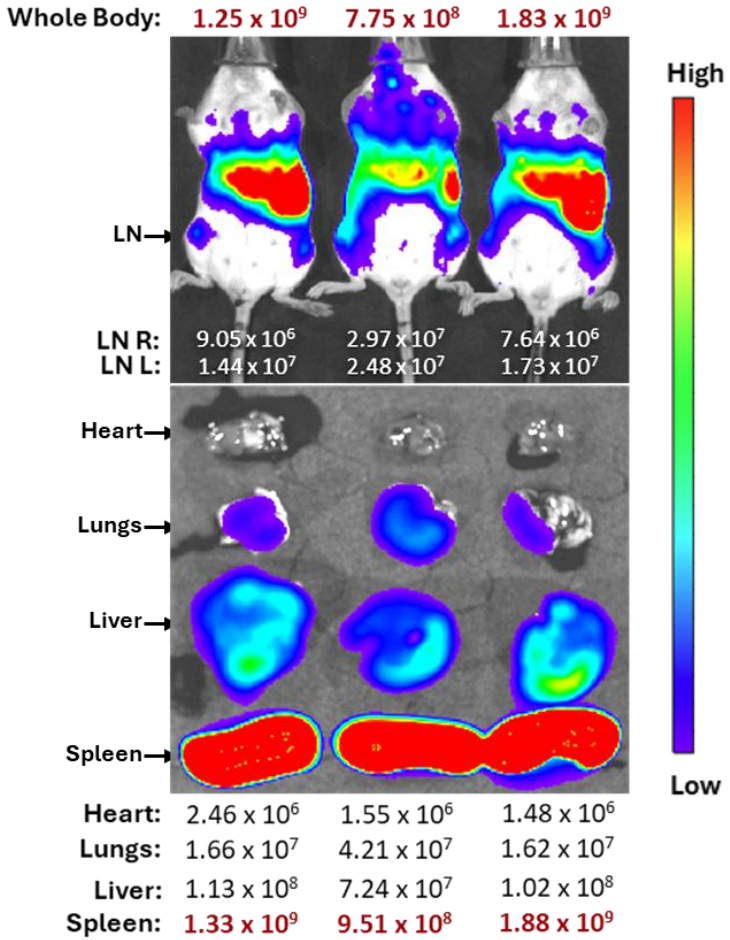
Norovirus VP1 mRNA-IAJD97 vaccine elicits potent humoral immune responses

Characteristics of IAJD97 with mLuc

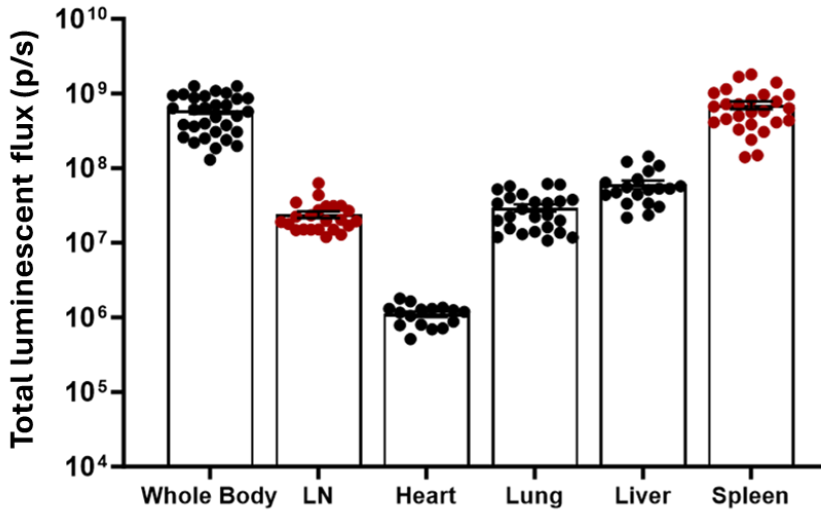


Size, nm	195 ± 7 n=23
PDI	0.130 ± 0.012 n=23
Encapsulation efficiency, %	96.7 ± 1.6 n=7
pKa	8.22 ± 0.01 n=3
Zeta potential, mV	23.0 ± 3.3 n=5

In Vivo Imaging System (IVIS)



Luciferase expression biodistribution



IVIS images of luciferase expression-whole body, organs 4 h post IV injection 5 μg of Luc mRNA-IAJD.

Ona N. et al., ...Atochina-Vasserman EN, (2026) Science Advances.

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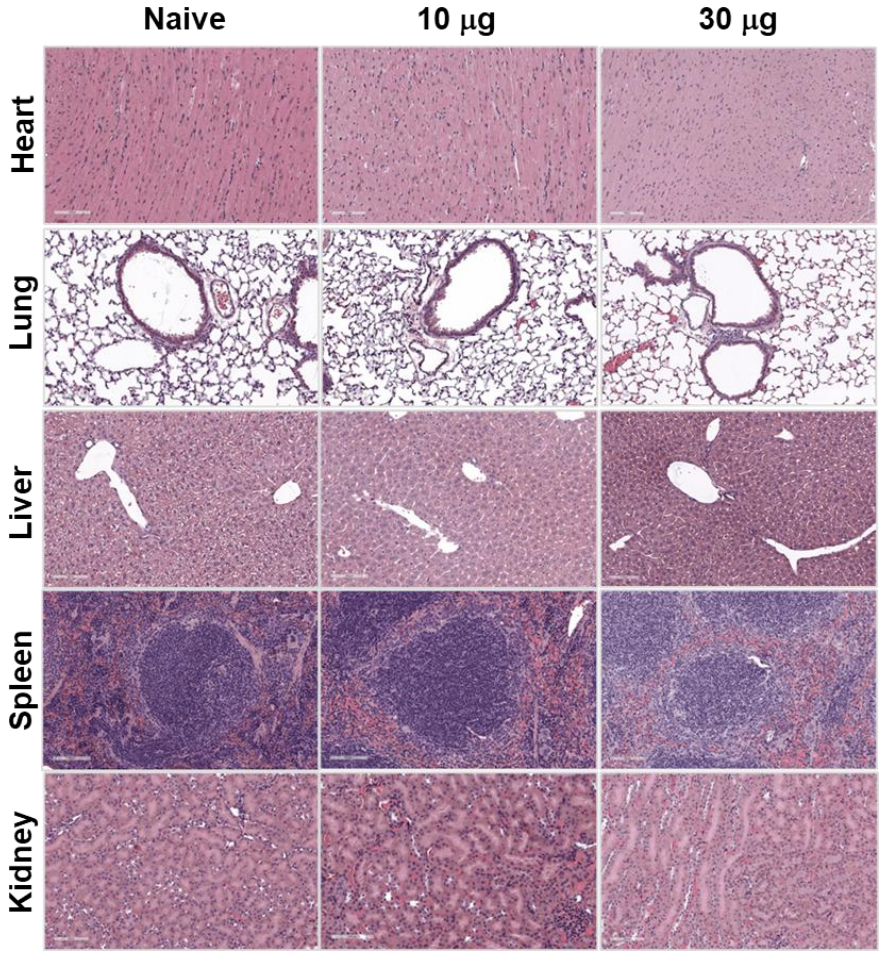
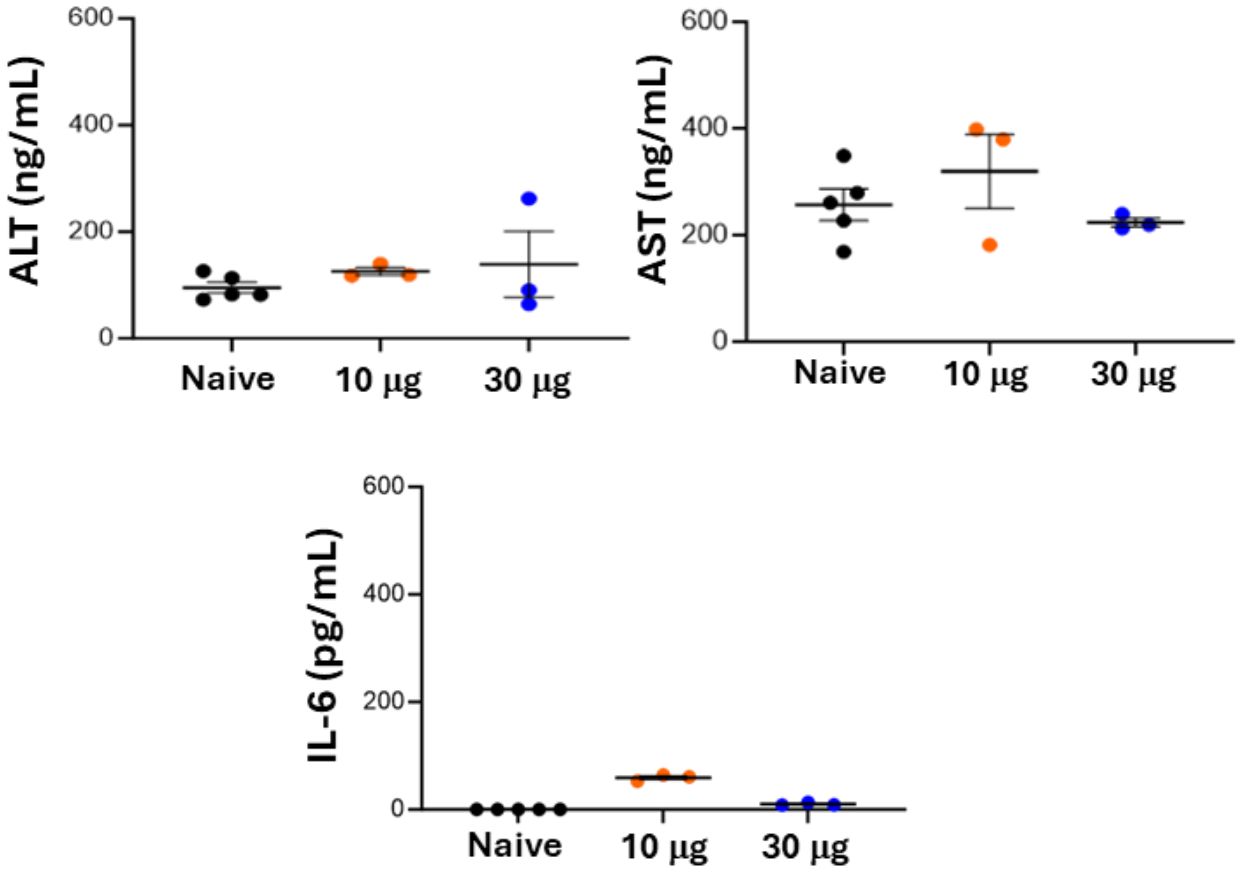
Lack of toxicity with Luc mRNA-IAJD97 delivery





Mice injected with 10, 30 µg of Luc mRNA-IAJD97 with no pathology in organs at either dose

Liver health at 24 hours post-injection- no significant increases in IL-6, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) observed compared to naïve mice

Ona N. et al., ...Atochina-Vasserman EN, (2026) Science Advances.

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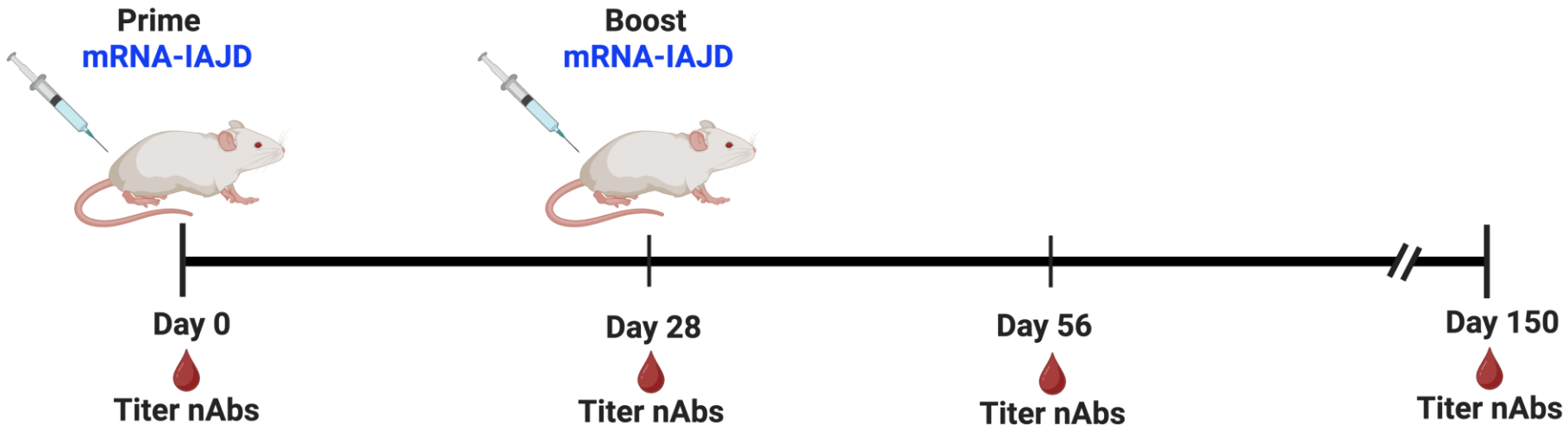
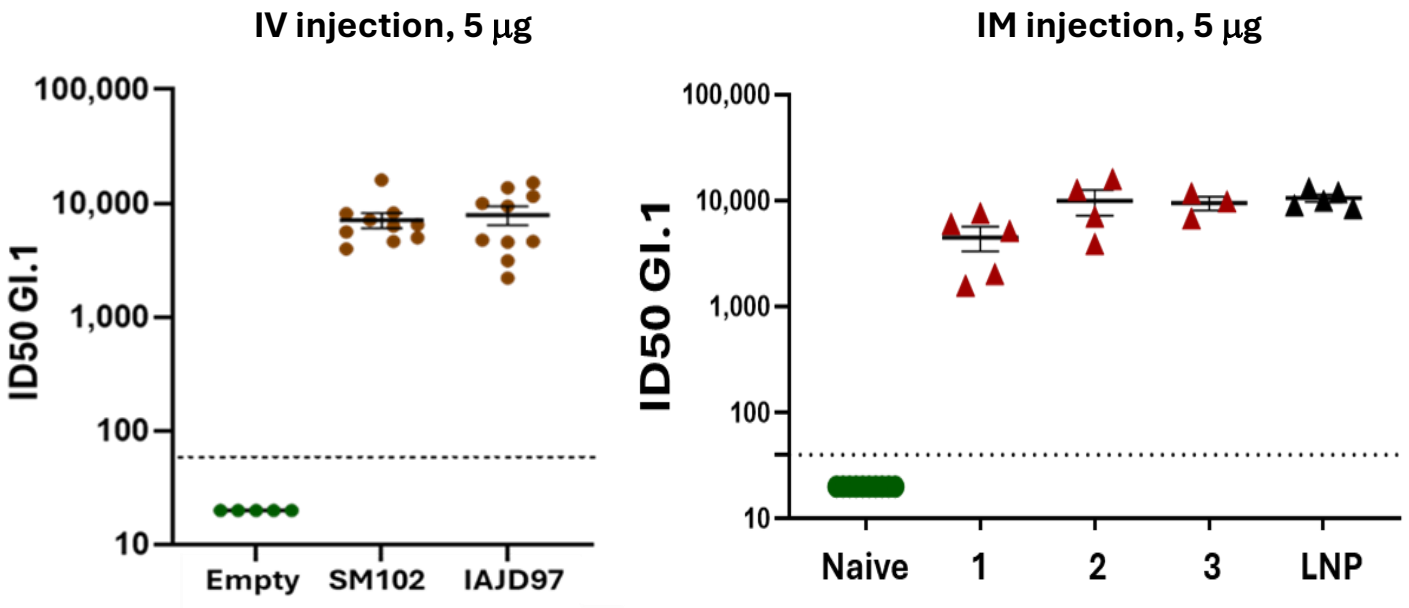
Schematic presentation of the vaccination schedule



- Immunized Day 0 and 28, IM or IV, mRNA Norwalk GI.1 IAJD97
- Day 0, 28, 56 and 150 serum analyzed for VLP-binding ligand blocking in a neutralization assay.
- Inguinal and popliteal lymph nodes were collected Day 7, Tfh- and GC B cells measured by flow cytometry.
- Day 42 Spleens measured via single cell suspensions to determine CD4+ and CD8 T cell responses to peptide stimulation

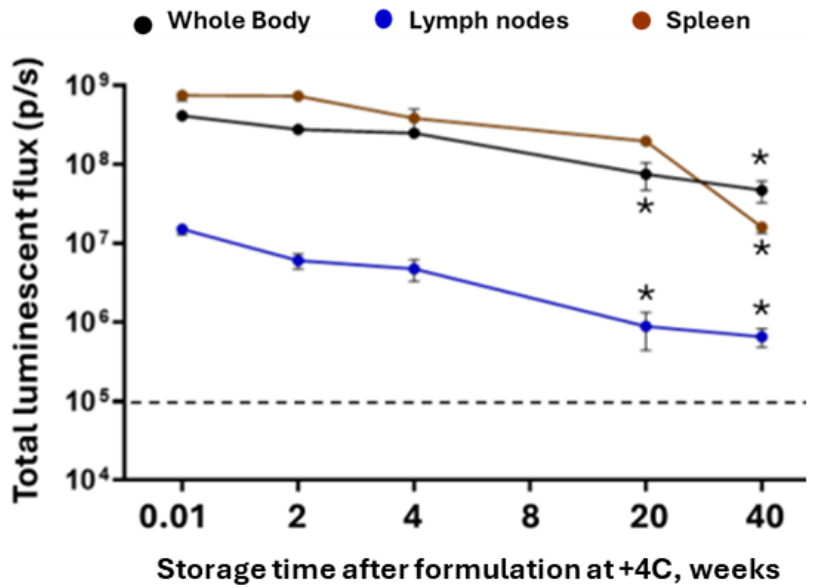
Norovirus VP1 mRNA-IAJD97 vaccine elicits potent humoral immune responses

Neutralization Abs titer, Day 60



Immunization day 0, 28 by IV or IM, mRNA Norwalk GI.1 IAJD97.
Sera collected on day 60, analyzed for neutralizing antibody titers.

Formulation stability at +4°C



Luc mRNA-IAJD(A) formulation remains stable at +4C for at least 26 weeks.

Ona N. et al., ...Atochina-Vasserman EN, (2026) Science Advances.

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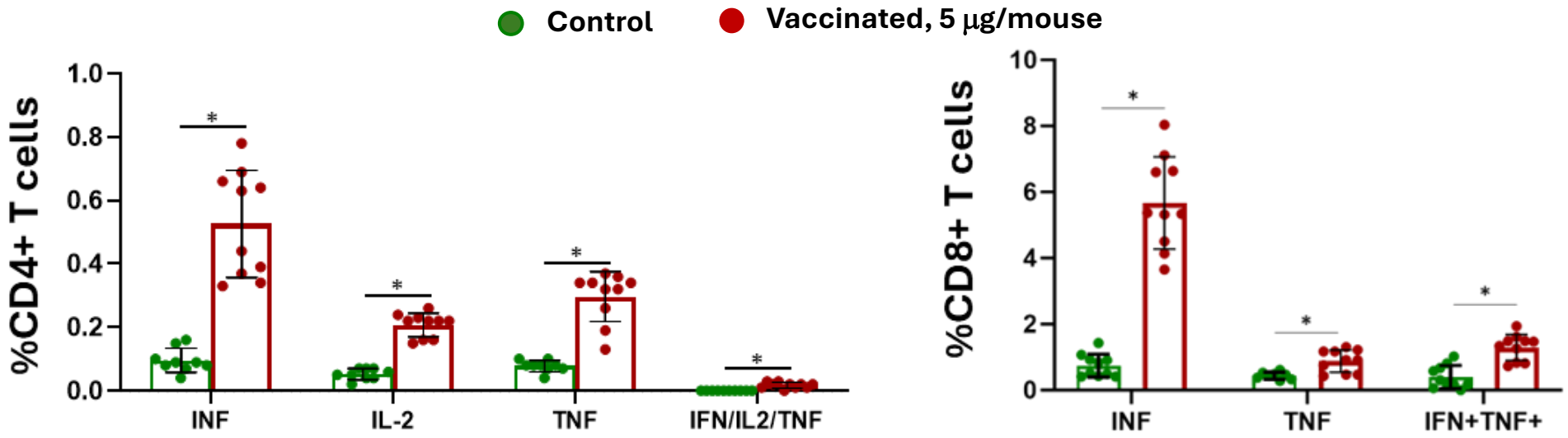
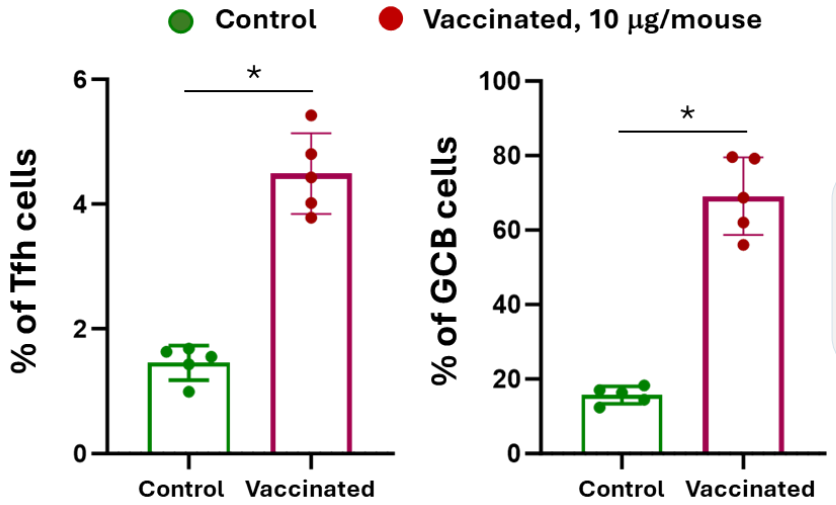
Norovirus VP1 mRNA-IAJD97 vaccine elicits strong cellular immune responses



BALB/c mice immunized IV with 5 μg norovirus-GII.4 mRNA-IAJD, days 0 and 28.
Cytokine production by CD4 and CD8 T cells that expressed IFNγ, IL-2, and TNFα were determined by flow cytometry.
Day 42 (14 days post boost) splenocyte single-cell suspension stimulated with GII.4 capsid protein peptide pool



Tfh- and GCB cells in LNs at day 7 mice immunized IM 10 μg of norovirus GII.4 mRNA-IAJD

Ona N. et al., ... Atochina-Vasserman EN, (2026) Science Advances.

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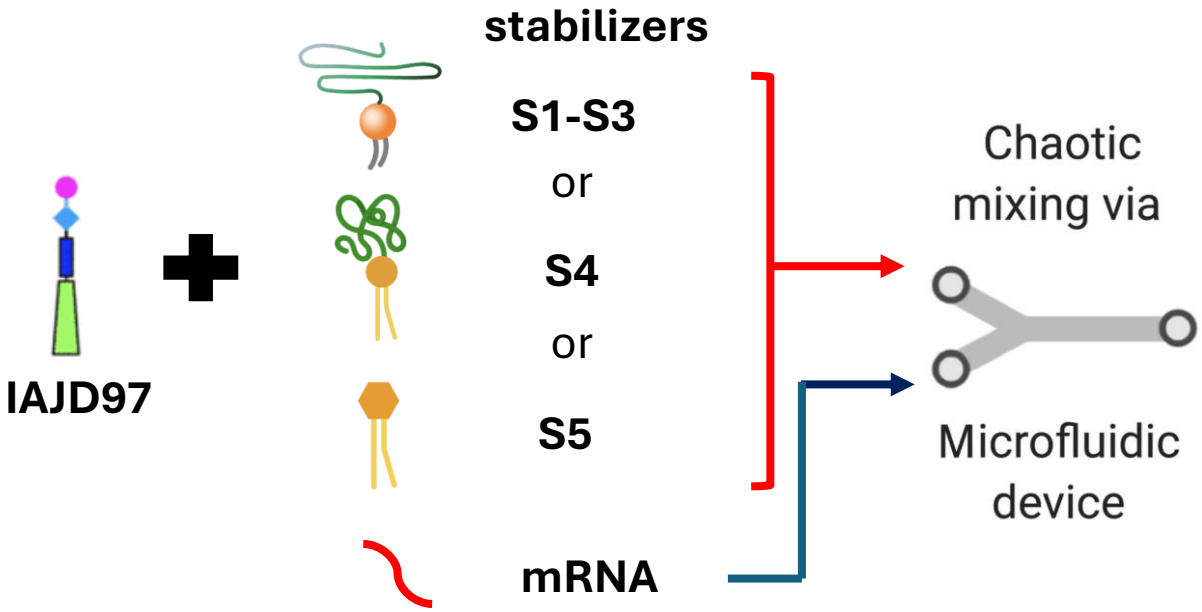
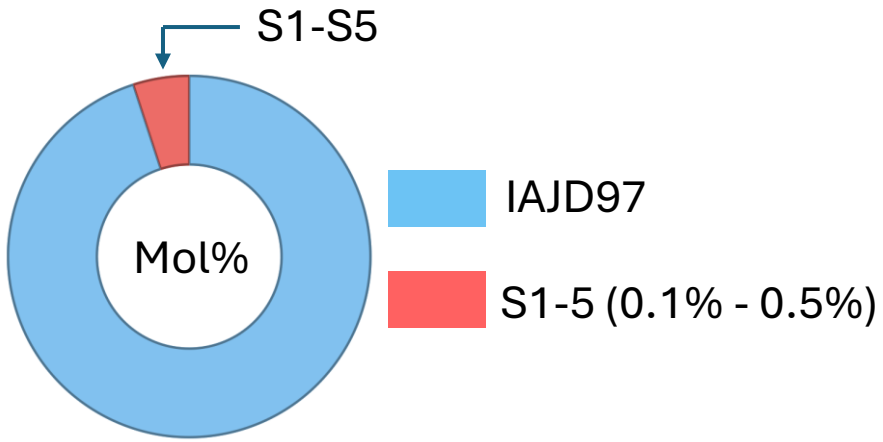
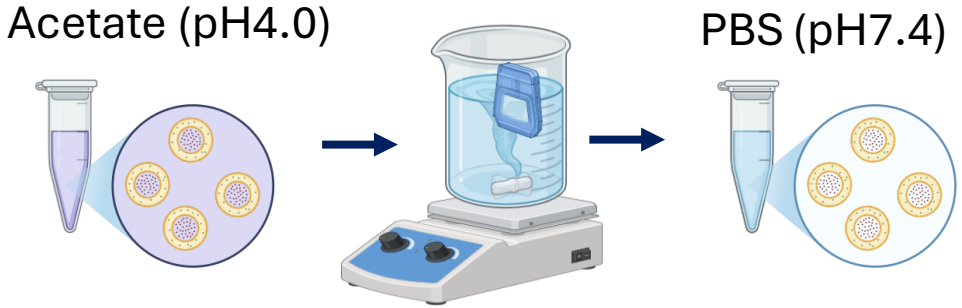
Optimization of IAJD97–mRNA formulations with stabilizers



1. **IAJD97 with Stabilizers**
   - Mol%
   - N/P ratio
2. **Microfluidic mixing**
3. **Dialysis against PBS (pH7.4)**





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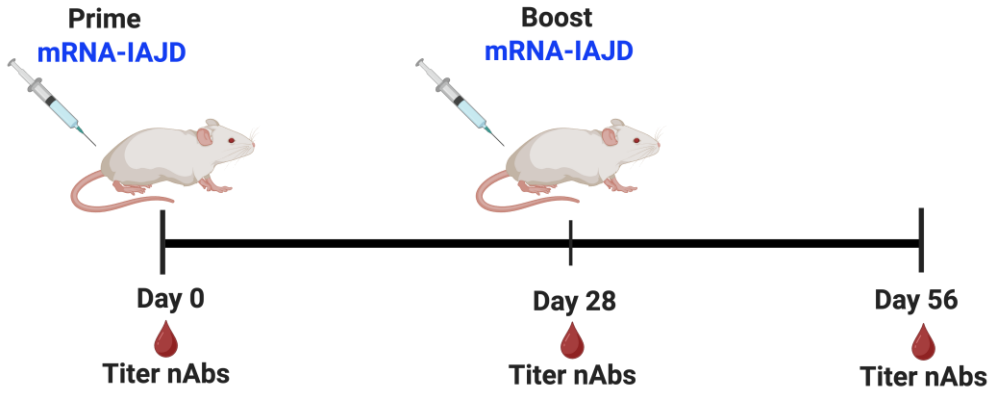
Novel platform for efficient mRNA vaccine delivery using one-component IAJD

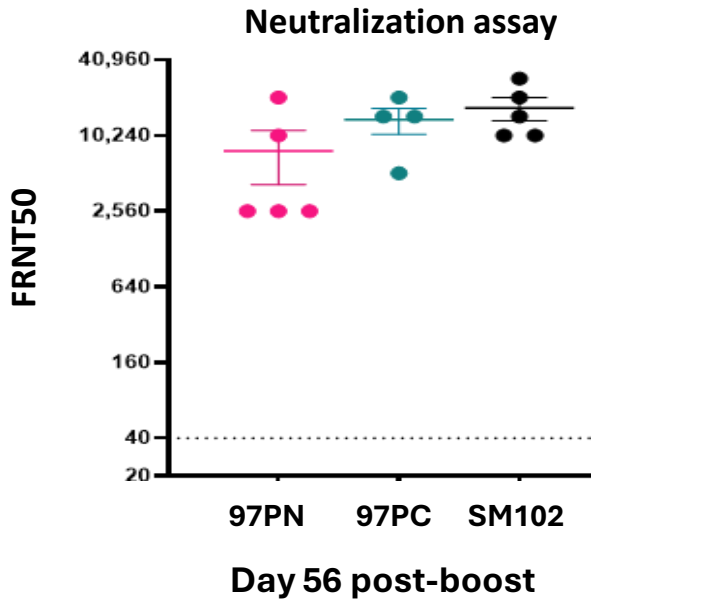
Proof of principle of IAJD vaccines

- Influenza
- HIV

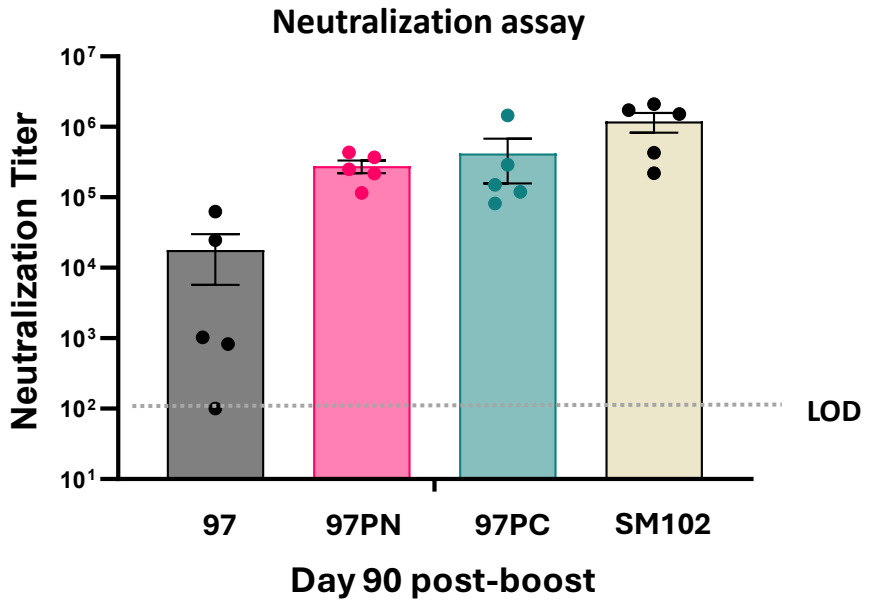
1 µg per mouse, IM injection



Influenza (PR8)



HIV Env (11MUTB)



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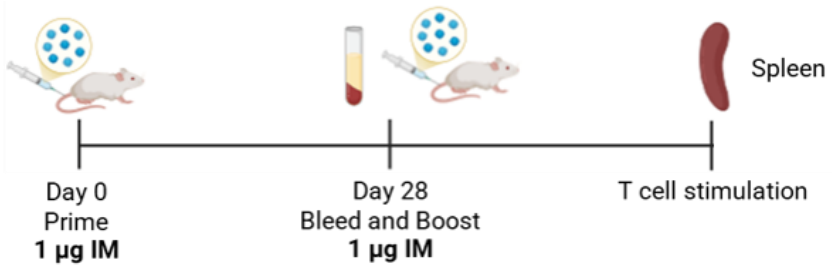
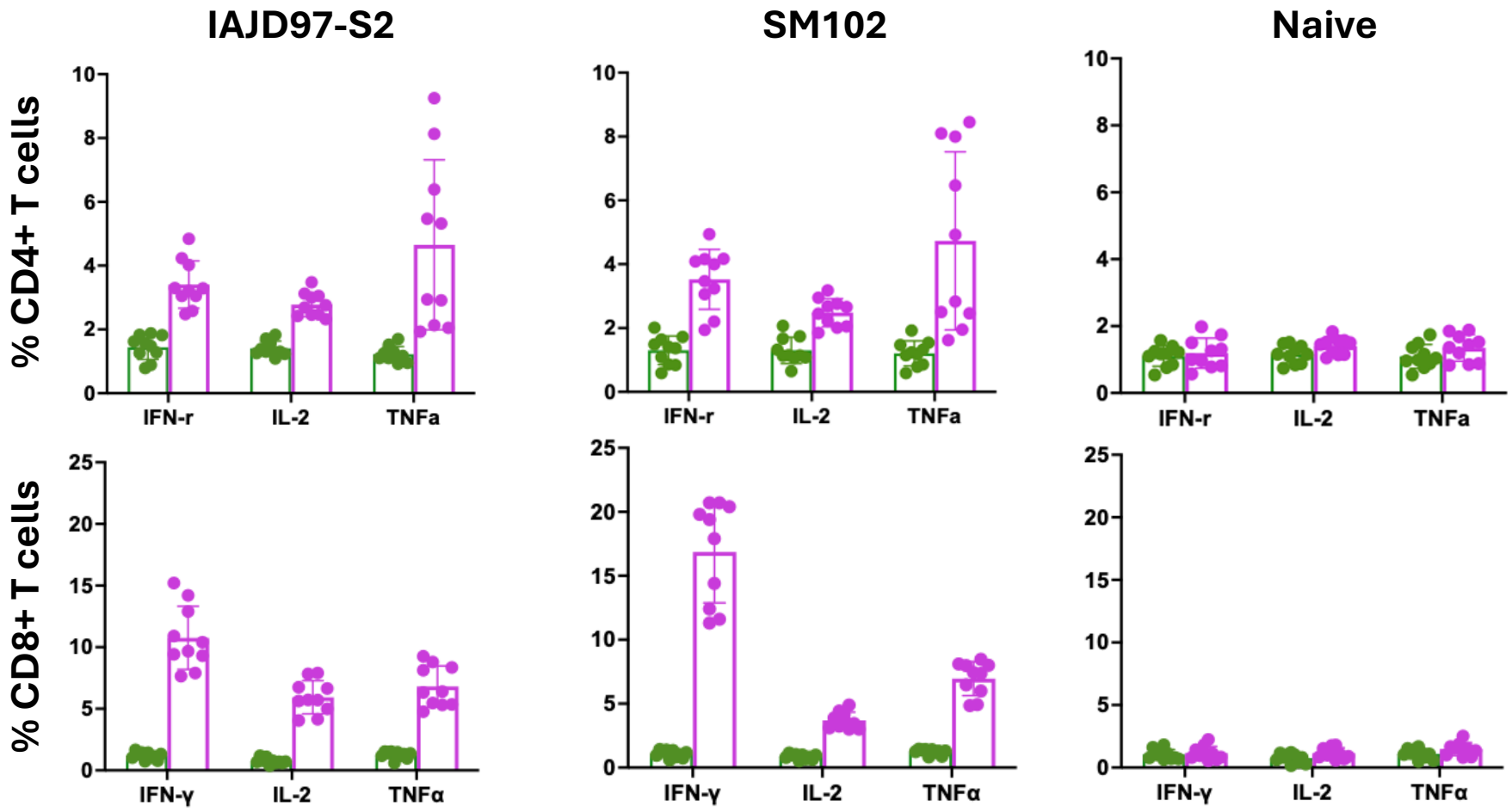
One-component IAJD97 vaccine induces strong antigen-specific T cell response



1 ug HIV (11MUTB) per mouse, IM injection

10 days after boost



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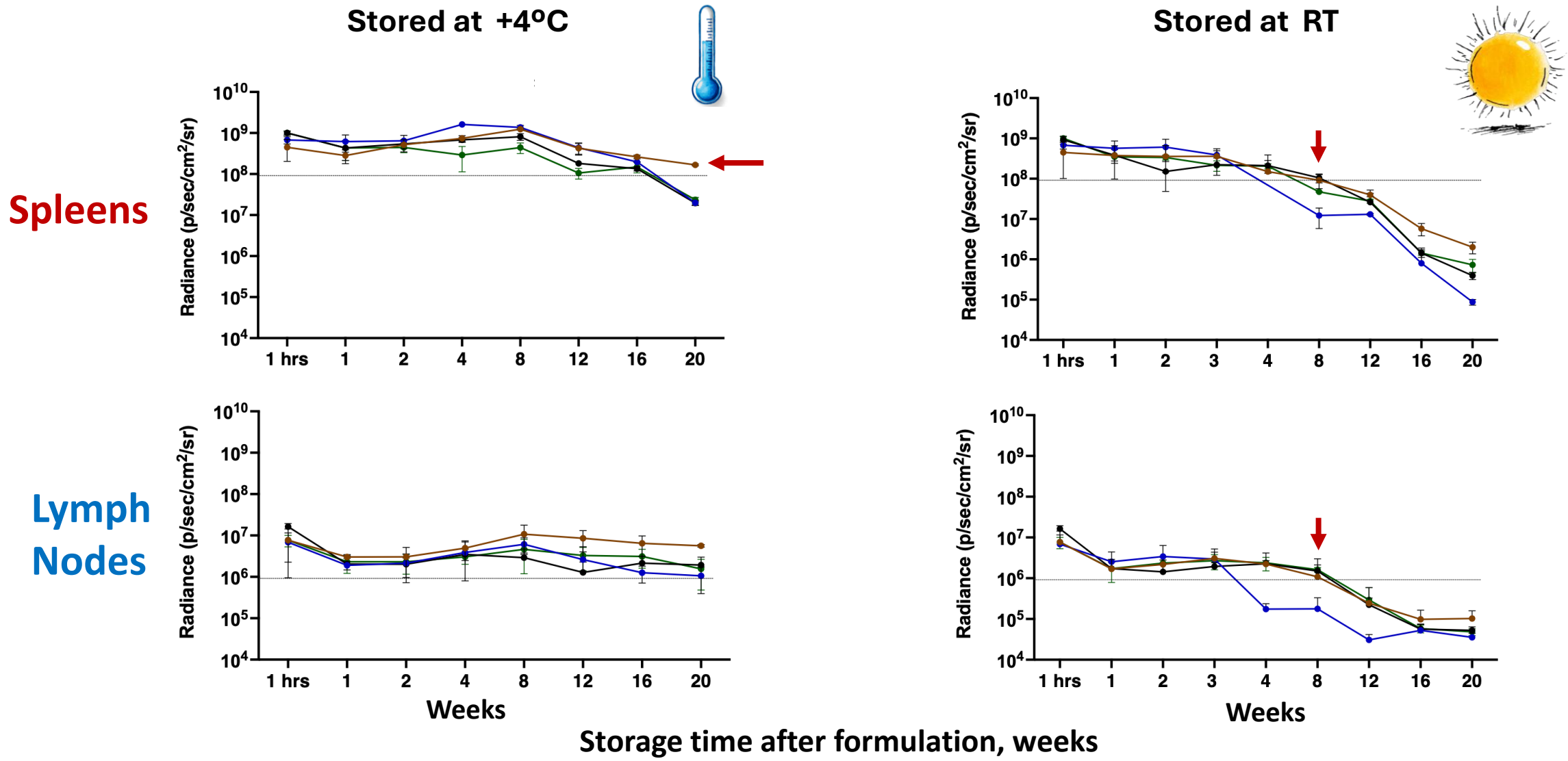
Stability of Luc mRNA–IAJD97 various formulations at +4 °C and room temperature (RT)



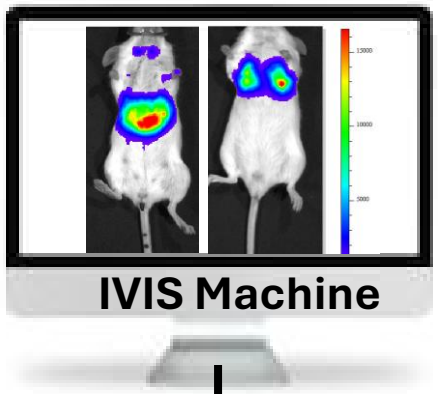
Luc mRNA IAJD97 formulations with stabilizers were injected either 1 hour after preparation (fresh) or after storage at 4°C or room temperature (RT) at points for 1-20 weeks. At each storage time point, formulations were i.m. injected at 5 µg per mouse, and luciferase signal was measured by IVIS four hours post-injection.

Summary

One-component IAJD97, formulated with mRNAs encoding immunogens for norovirus, influenza and HIV, serves as a proof of concept for the potential use of one-component IAJD as a novel and efficient platform for vaccine delivery

Preclinical applications of one-component IAJDs

Screening and Optimization



Immunization

Vaccines

Tissue specific delivery

Therapeutics

One-component IAJD, formulated with norovirus mRNA capsid protein, serves as a proof of concept for the potential use of one-component IAJD as a novel and efficient platform for vaccine delivery

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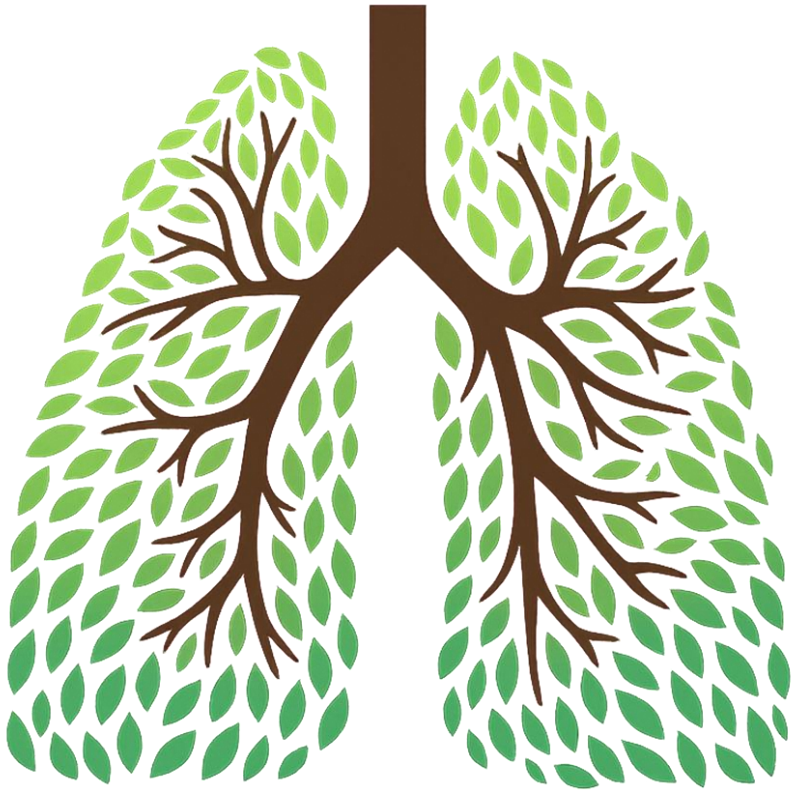
Lung structure



In the human lung, the airway branches about **23 times** from the trachea to the alveolar sacs

Fun facts about lungs

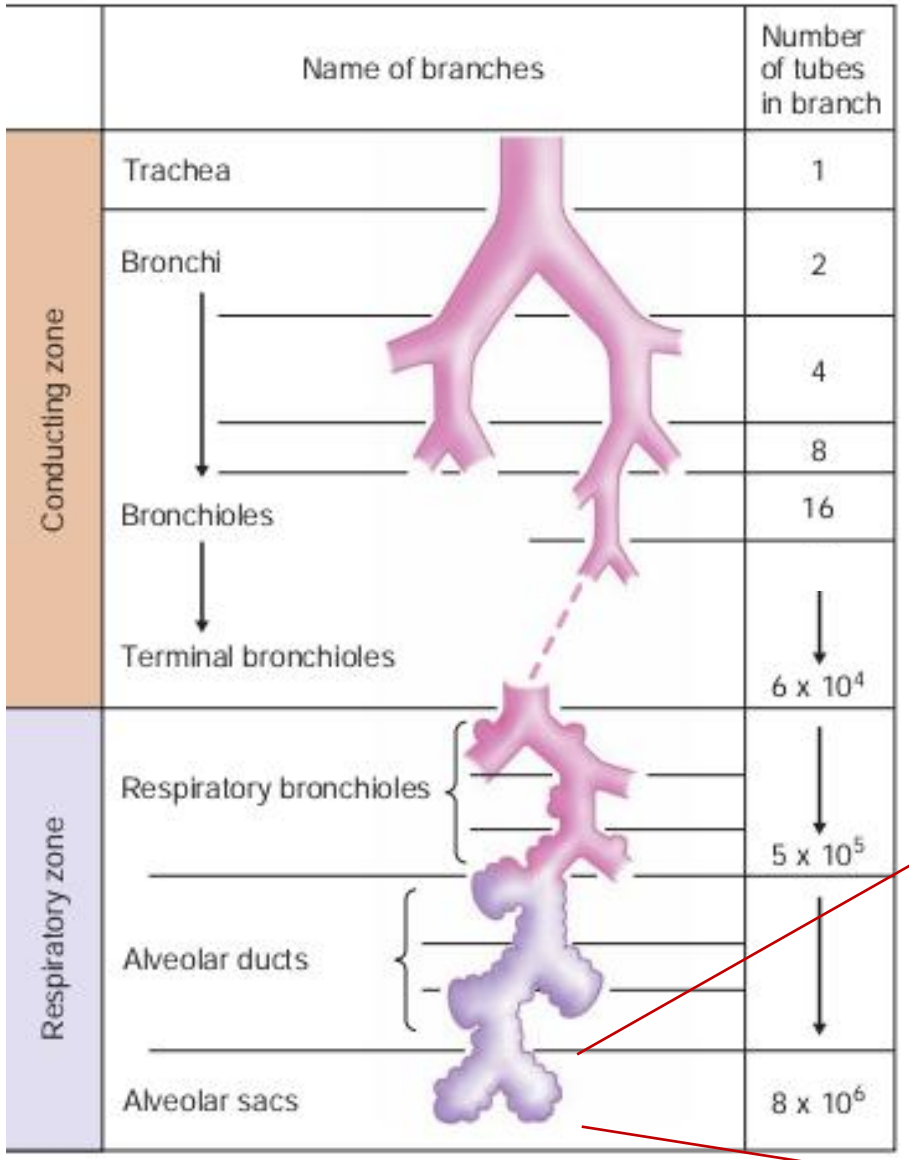
The entire blood volume of the human body passes through the lungs in the resting state - **5 liters per minute**

The total surface area of the lung is about **80 meters square**, equivalent to the size of a badminton court

The lungs contain approximately **1,500 miles** of airways and 300 to 500 million alveoli

Total lung weight is about **300-400 grams**

Clinical need to target the respiratory airways



- The **first 16 generations** are the **conducting airways** (from trachea to terminal bronchioles), which do not participate in gas exchange
- The **last 7 generations** are the **respiratory zone**, including respiratory bronchioles, alveolar ducts, and finally **alveolar sacs**, where gas exchange occurs.
- The main function of the lungs is (rapid) gas exchange
- Gas exchange occurs in the alveolus where the thin laminar blood flow and inspired air are separated only by a thin tissue layer

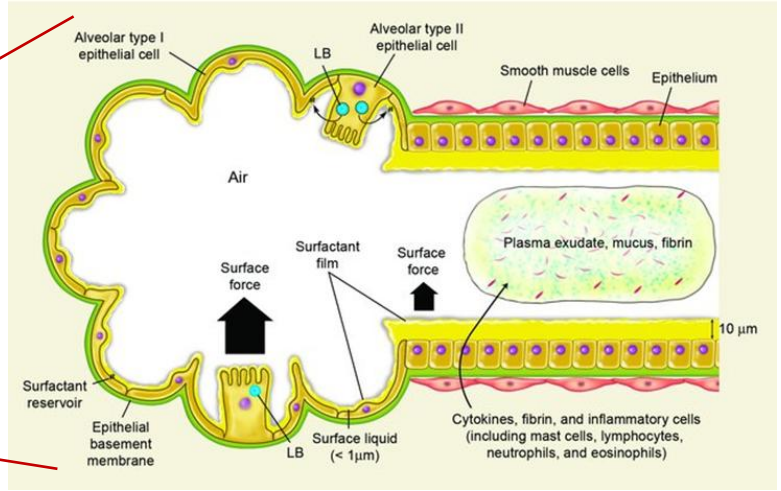
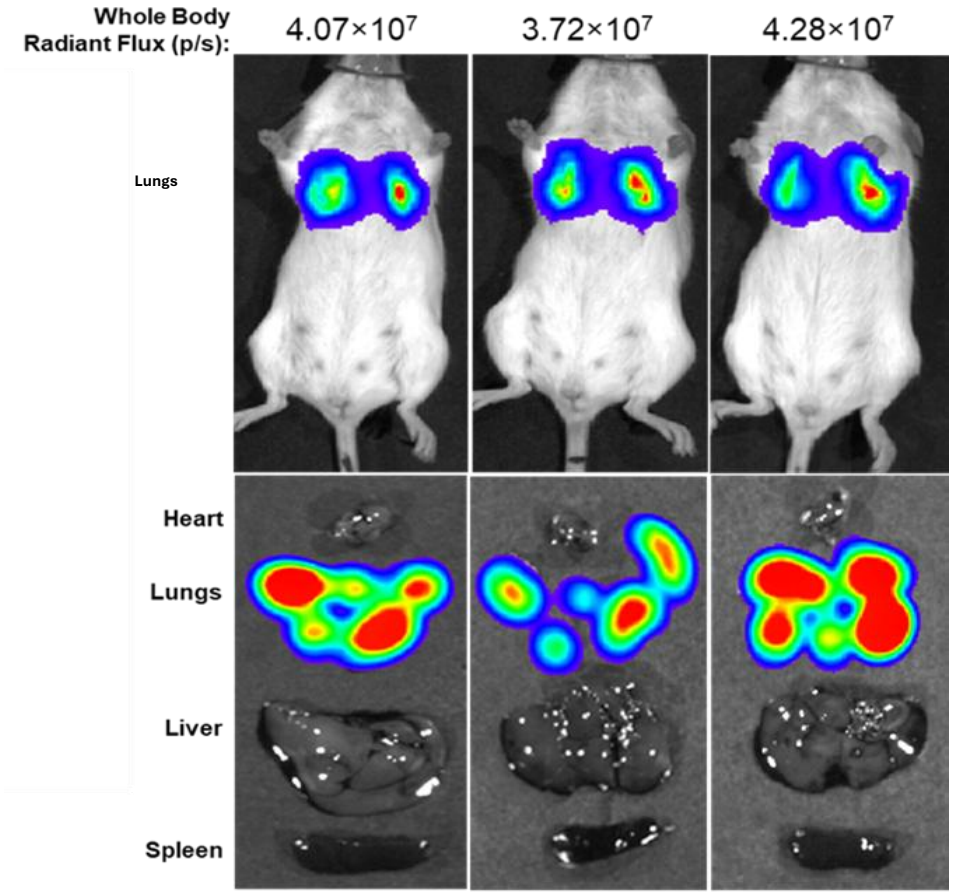


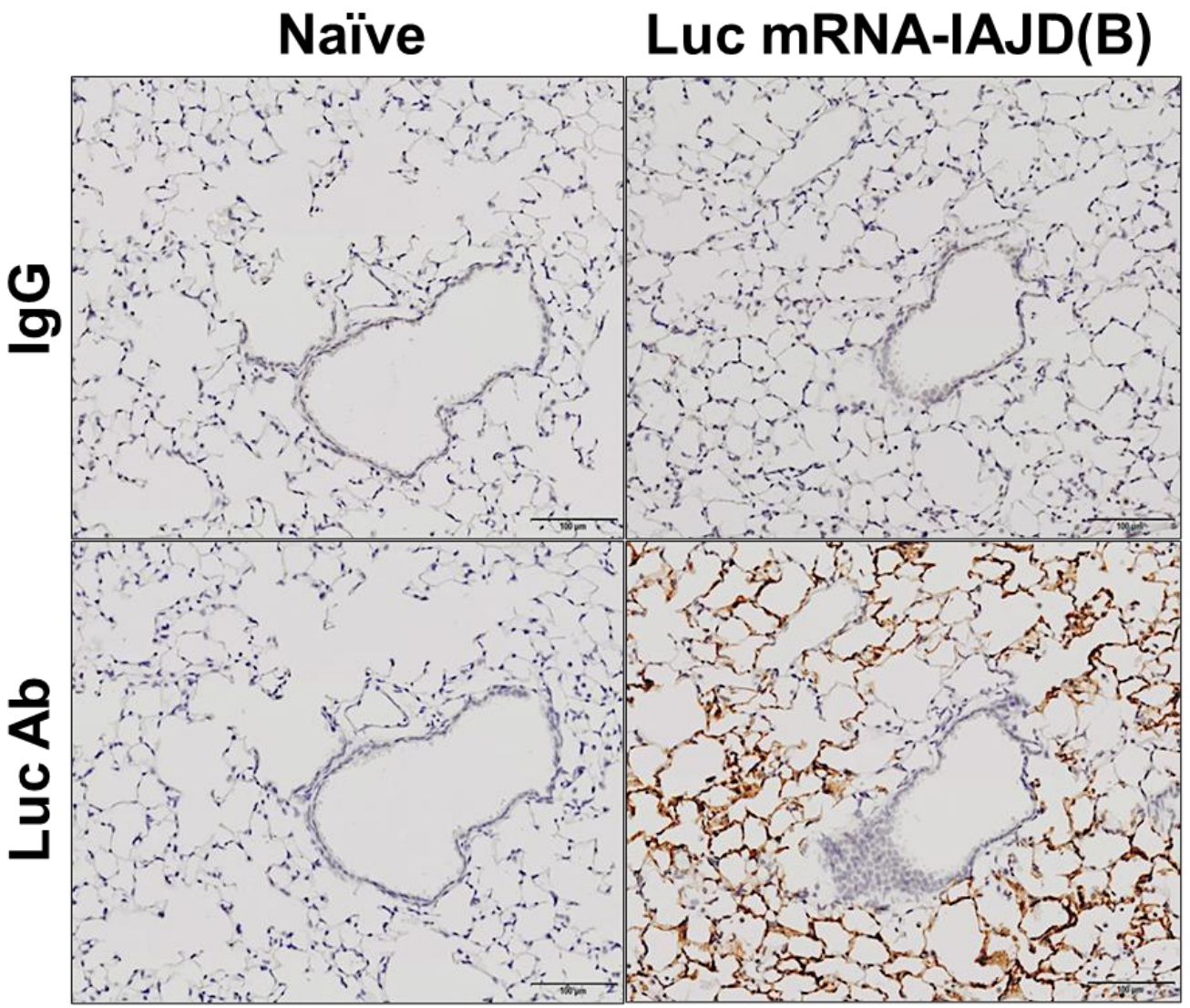
Image adapted from: https://doi.org/10.1016/B978-0-323-44887-1.00006-7

Specificity of IAJD34 for targeted mRNA delivery to the lower regions of the lung

10 µg Luc/mouse
4 hrs post iv injection



Heart Flux (p/s):	5.20×10^{4}	5.08×10^{4}	1.36×10^{4}
Lungs Flux (p/s):	**3.72×10^{8}**	**2.44×10^{8}**	**4.20×10^{8}**
Liver Flux (p/s):	1.51×10^{5}	2.49×10^{6}	2.30×10^{6}
Spleen Flux (p/s):	6.49×10^{4}	1.43×10^{5}	3.81×10^{5}



Meshanni, M., ... Atochina-Vasserman EN, *Nature Communication*, 16:1806, 2025

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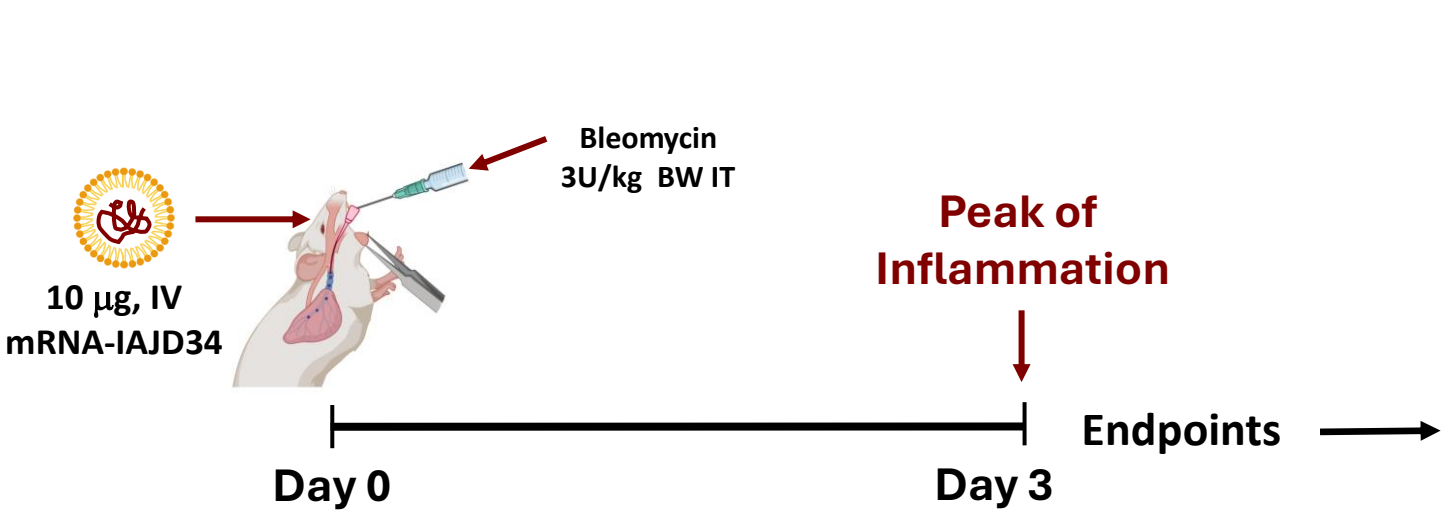
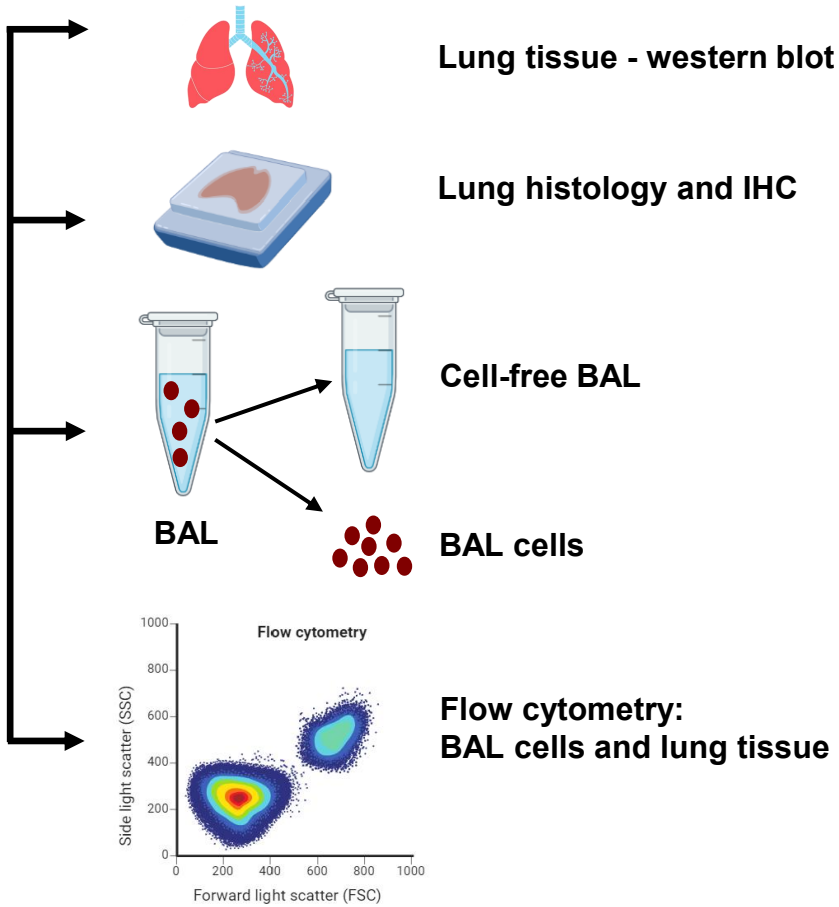
Using TGF-β mRNA-IAJD34 to treat acute lung injury

Evaluate the effects of TGF-β mRNA-IAJD34 on bleomycin-induced injury





RO injection 10 µg of TGF-β mRNA or empty IAJD34 administered to anesthetized mice, then 50 µL PBS or bleomycin (3U/kg BW) intratracheally. Endpoints measured at 3 days post bleomycin.

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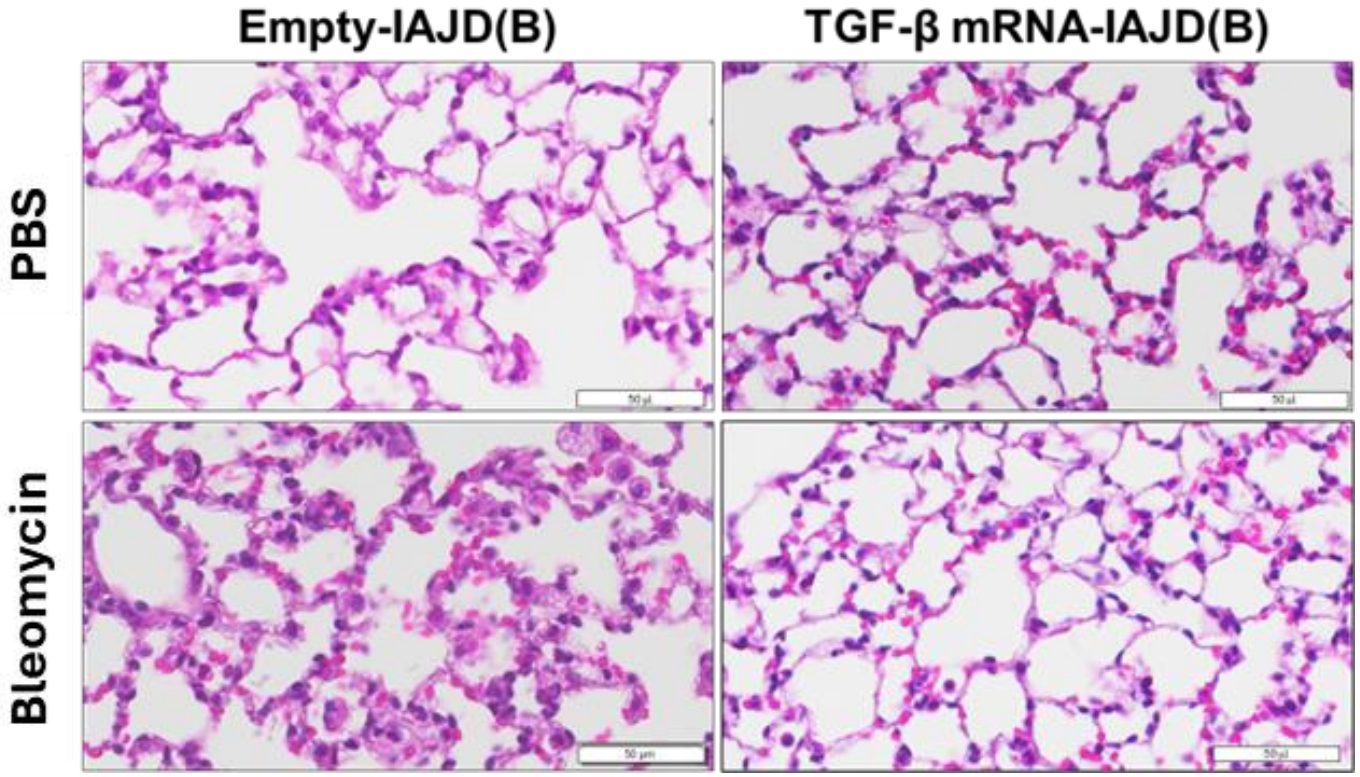
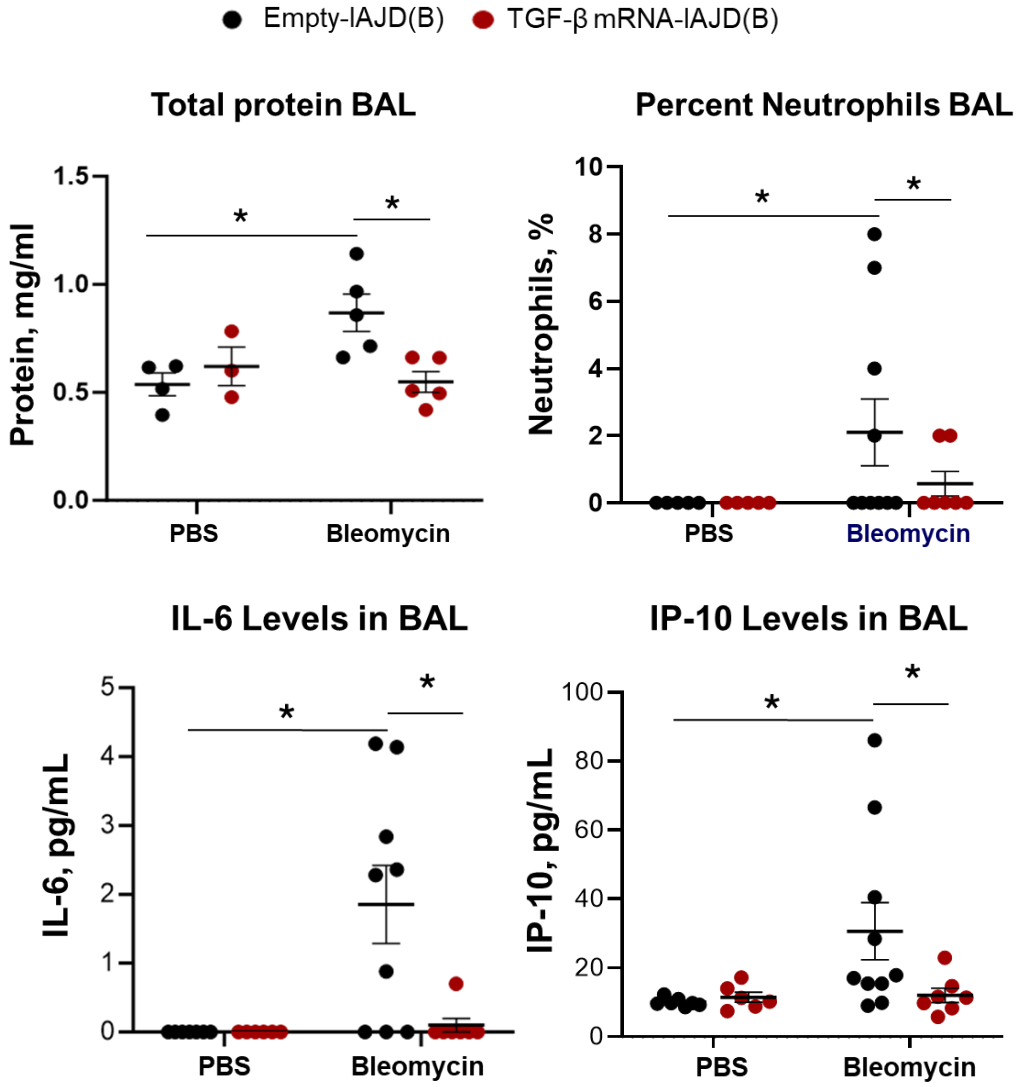
Effects of TGF-β mRNA-lAJD treatment on bleomycin-induced lung injury





BALB/c mice +/- bleomycin (3U/kg BW) and empty or 10 µg TGF-β mRNA-IAJD34. Lung tissue was collected 3 days post exposure and injection.

Meshanni, M., ... Atochina-Vasserman EN, *Nature Communication*, 16:1806, 2025

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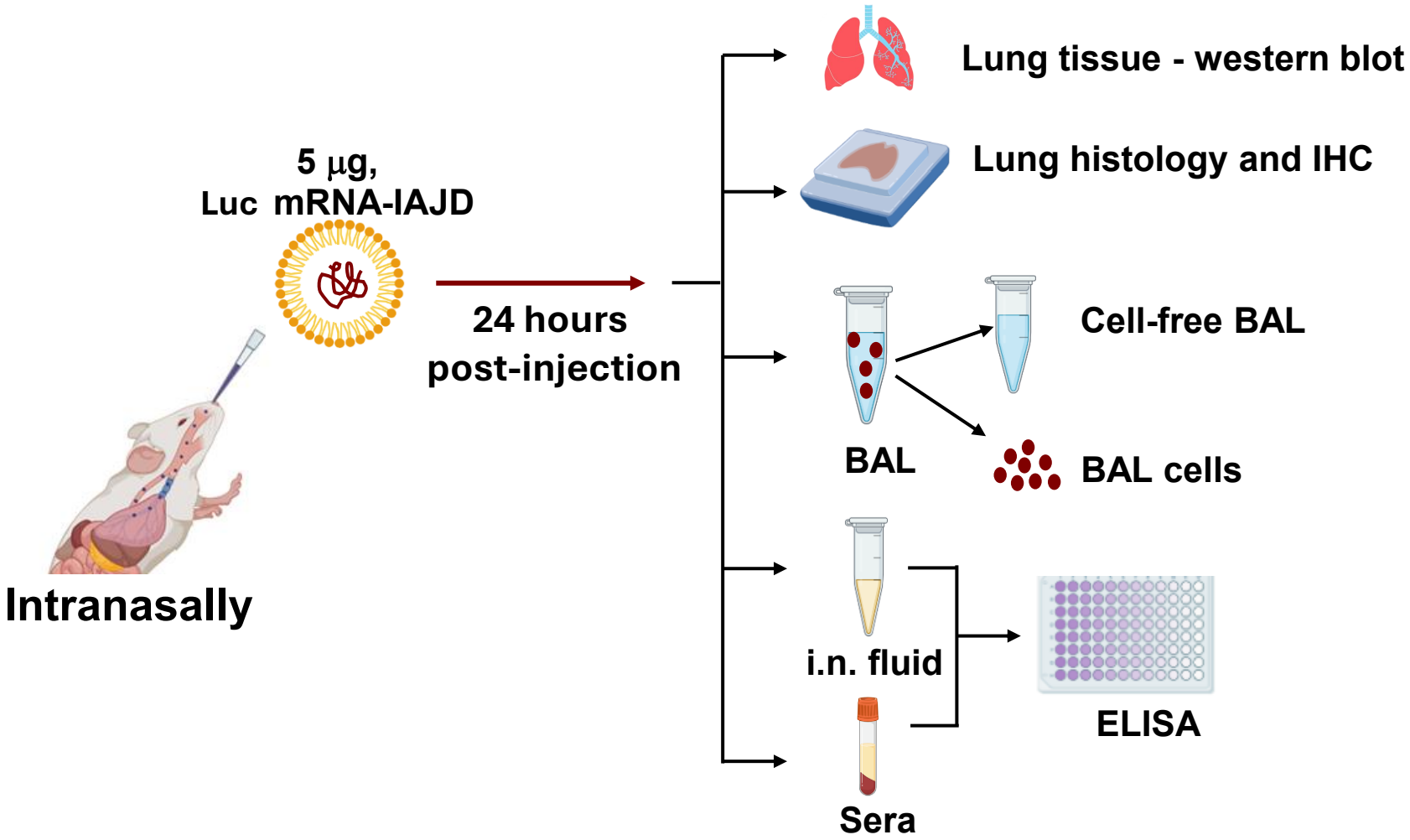
Intranasal delivery of Luc mRNA-IAJD and endpoints



Intranasal instillation of PBS or 5 μg of Luc mRNA-IAJD administered to anesthetized mice, tissue & sera analysis at 24 post.

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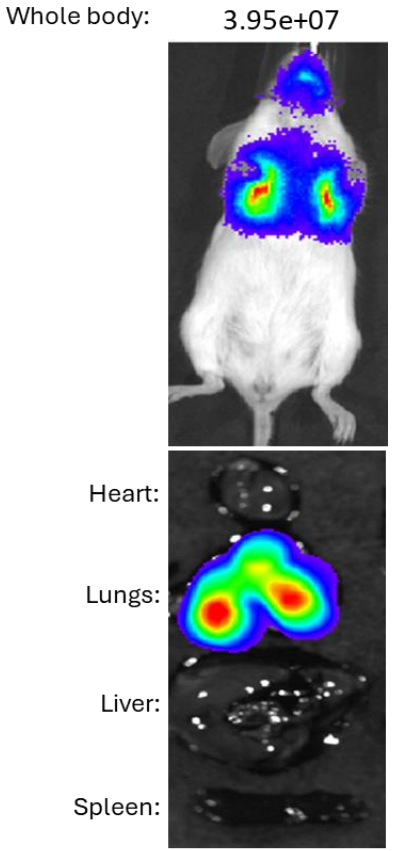
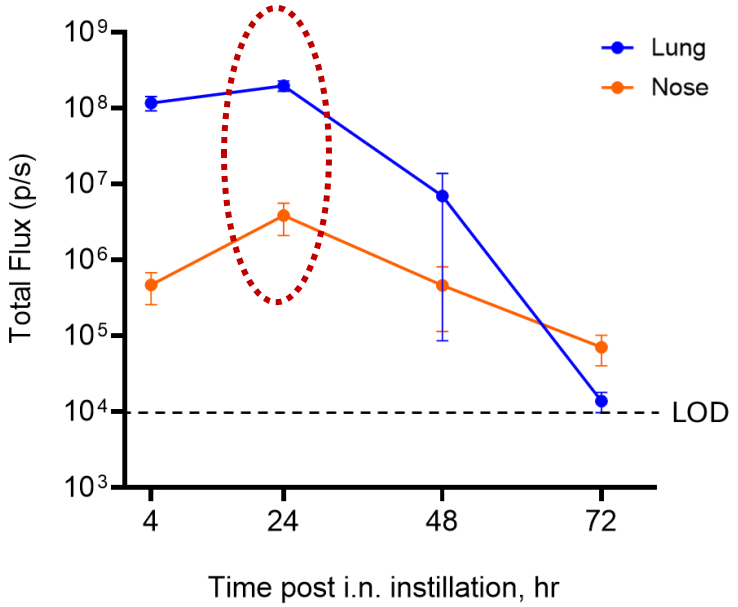
Specificity of IAJD97pII for targeted mRNA delivery to the upper-airway epithelial cells

IVIS

4 hrs post IN injection

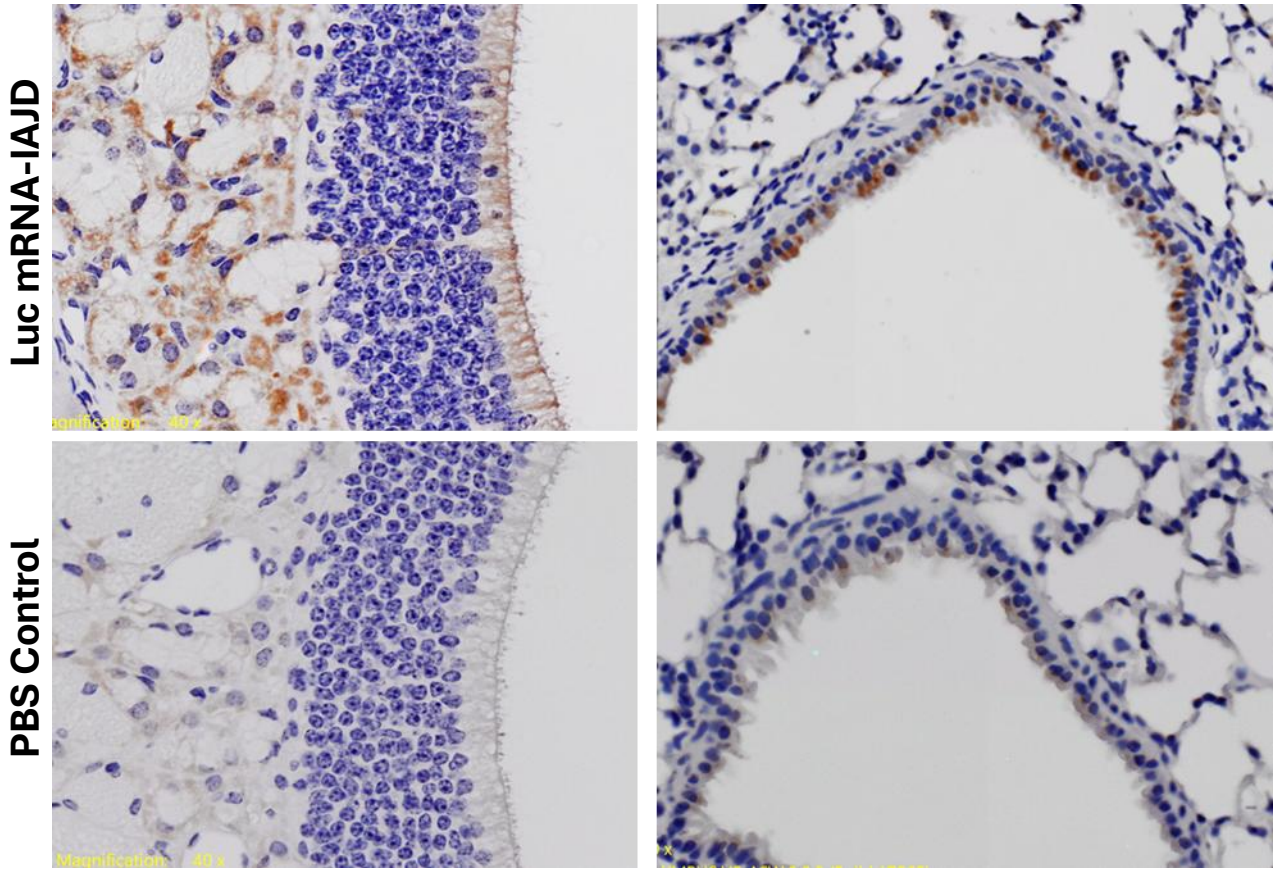




Intranasal administration of Luc mRNA-IAJD (5 µg) and luciferase activity via IVIS measured at 4, 24, 48, and 72 h.
Max activity at 24 h, post injection, identifying IHC (40 x) timepoint.

Nasal Turbinates

Lungs



5 µg/mouse, 24 hrs post IN administration

Significant staining was observed in nasal ciliated columnar epithelial cells and lung bronchoalveolar epithelial cells, indicating extensive mRNA delivery to nasal and upper-airway epithelial cells.

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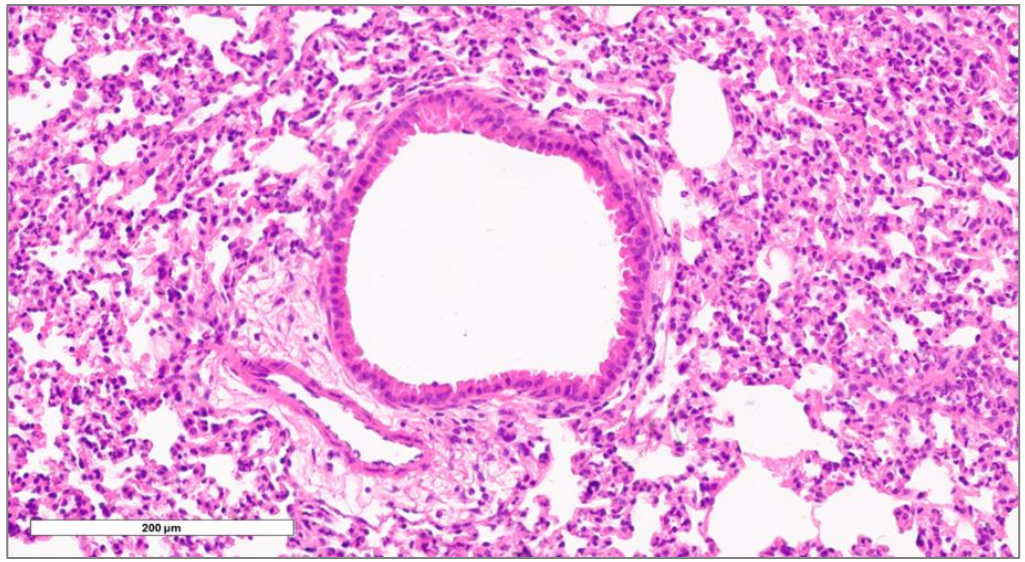
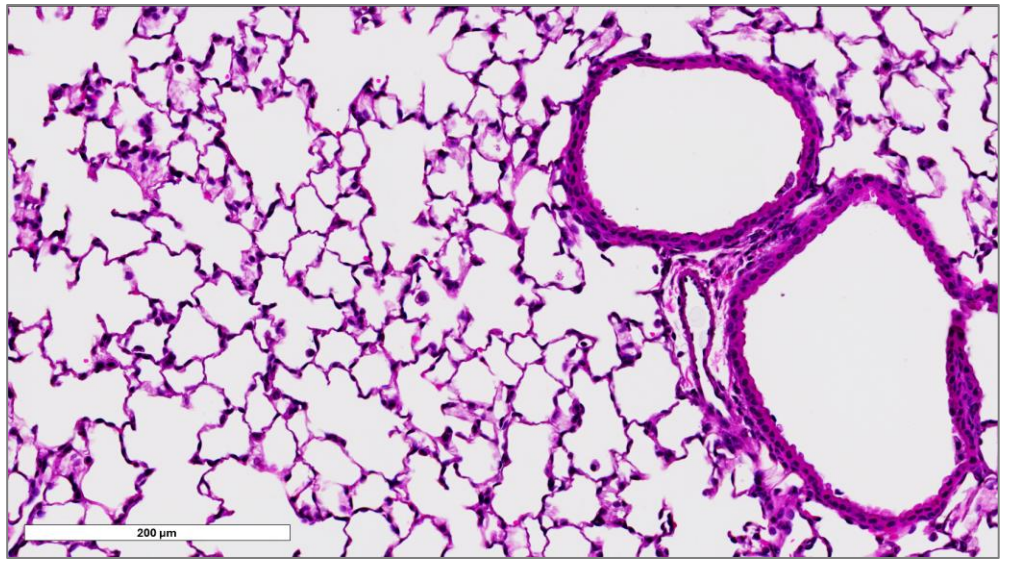
Novel one-component IAJD platform for intranasal mRNA Influenza vaccine delivery

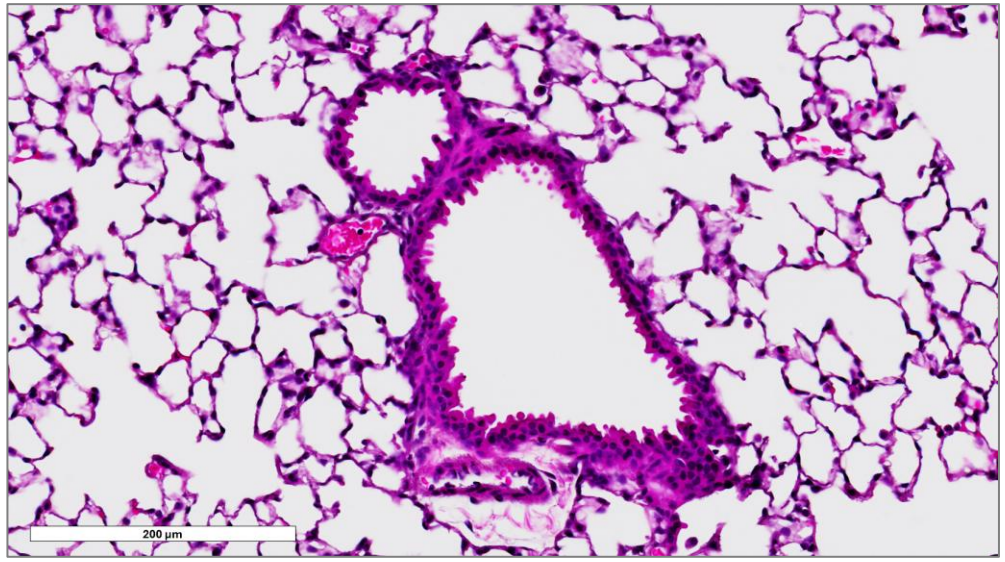
H5N1 mRNA-LNP



H5N1 mRNA-IAJD



Naive



BALB/c mice were injected intranasally with 5 µg of mRNA formulated with LNP or IAJD. 24 hours post-administration, the lungs were collected and analyzed for inflammation.

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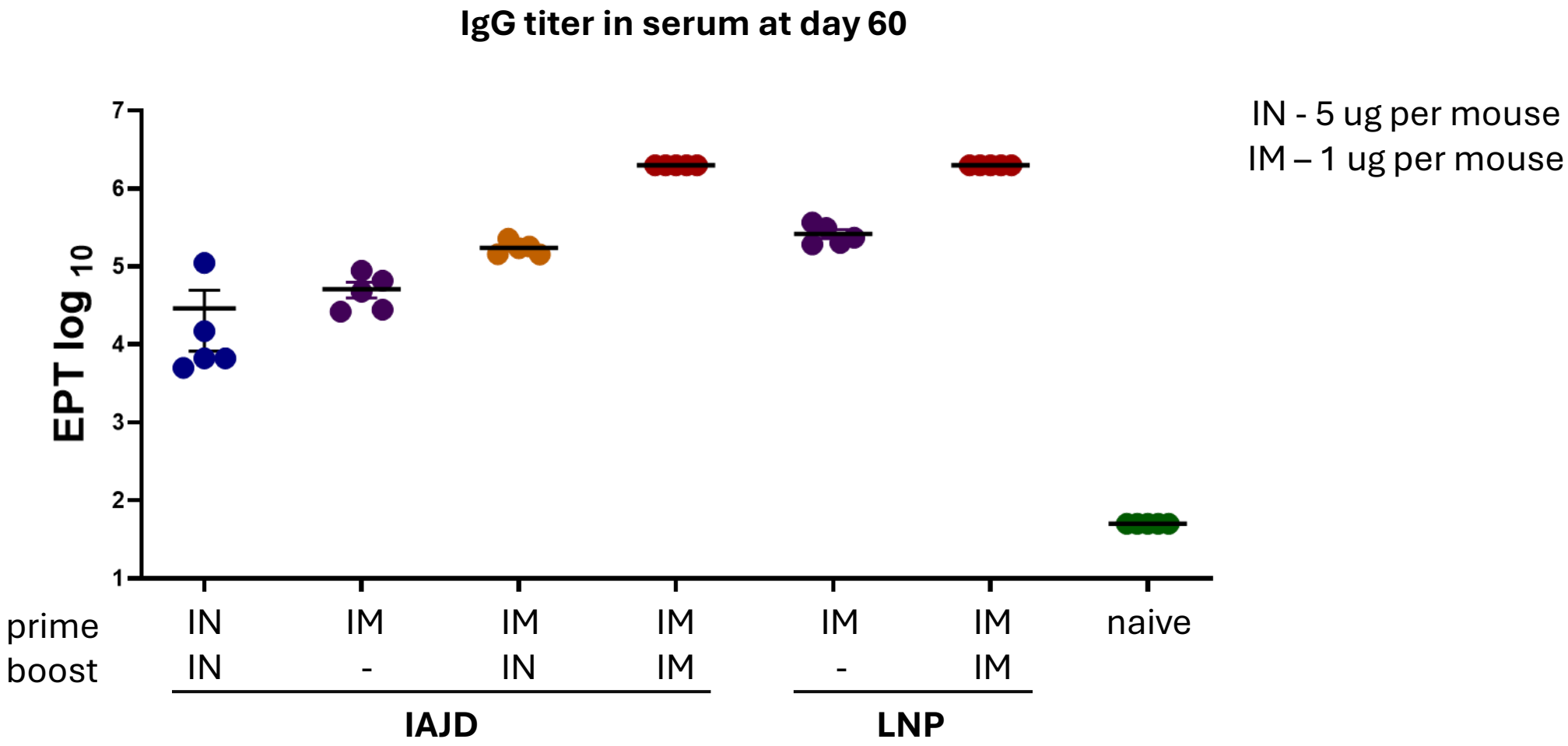
Novel one-component IAJD platform for efficient mRNA Influenza vaccine delivery



Mice were immunized on days 0 and 28 by IN or IM administration of mRNA H5N1 formulated with IAJD97-S2 or LNP. Sera were collected on Day 60 and analyzed for total IgG titers.
The study is still ongoing. Bronchoalveolar lavage samples were collected and will also be analyzed for IgG and IgA responses.

Acknowledgments

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Regulatory Considerations

35 minutes • Three orientation topics

Regulatory Pathways in the Development of RNA Vaccines

CEPI

What we'll cover in the next 35 minutes

Three linked topics that frame how NRAs prepare to review RNA vaccines.

- **1. NRA emergency review capacity —** a self-assessment framework covering review and inspection readiness: where does your NRA stand today, and what needs strengthening?
- **2. Product classification considerations —** how novel RNA products (particularly saRNA) get categorised: vaccine, biological, or gene therapy? — with implications for review pathway, dossier expectations, and the inspectorate involved
- **3. Manufacturing-country vs. importing-country NRA roles —** the recurring framing question of the workshop — different responsibilities, reliance pathways, and reference-NRA decisions across the region

CEPI

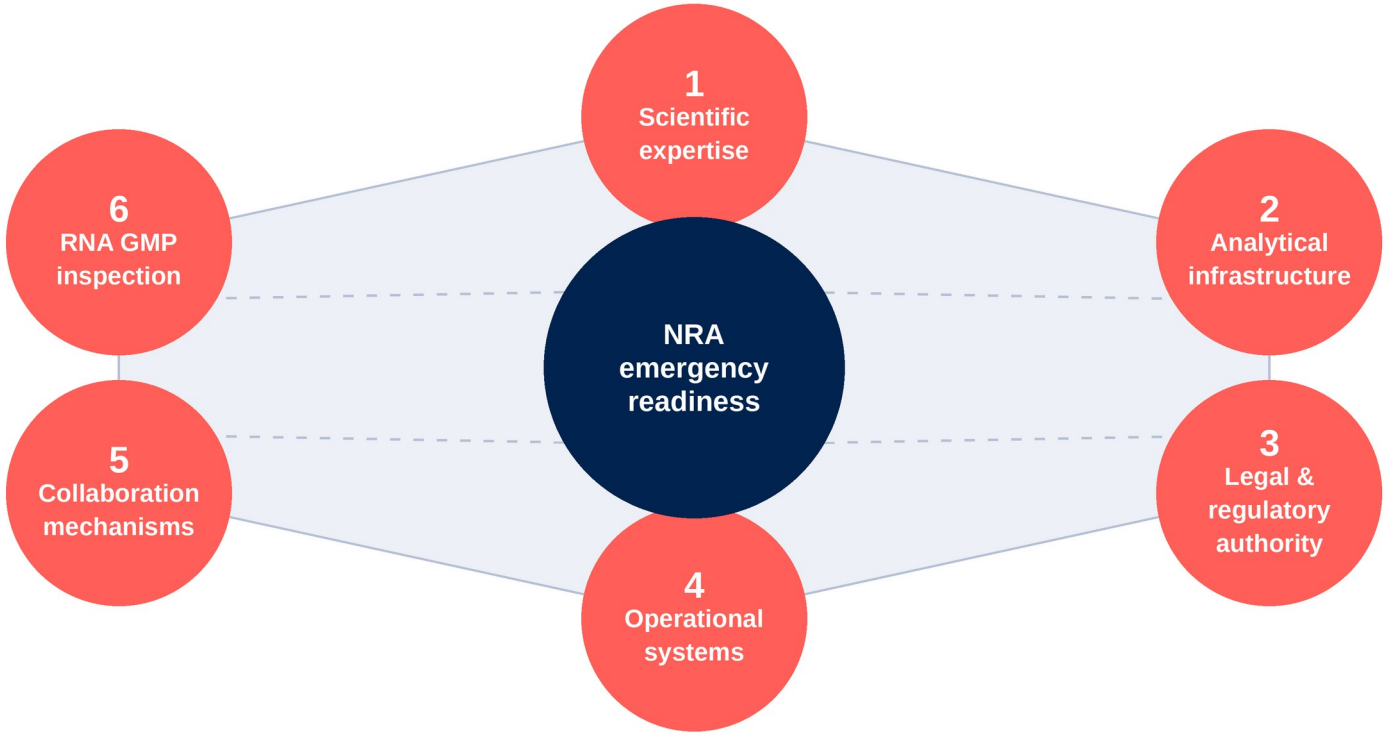
TOPIC 1 • ~15 MIN

NRA Emergency Review Capacity

A structured self-assessment — from score to gap to remediation.

The Readiness Framework

A structured way for an NRA to evaluate its readiness to review — and to inspect, or rely on inspection of — RNA vaccines under emergency tempo, and to identify where investment is needed.



Score → Gap → Remediation as the deliverable: not a critique, but an actionable output each NRA takes home.

Domain 1: Scientific Expertise

What good looks like — and common gaps.

- **What proficiency looks like:** at least one reviewer per functional area (CMC, nonclinical, clinical) who has actively reviewed an RNA product or completed structured training
- **Specific competencies:** RNA sequence identity, capping and poly(A) analytics, LNP characterisation (DLS/NTA, encapsulation), immunology of endogenous expression, biodistribution and shedding evaluation
- **Common gaps:** single points of expertise (one reviewer who knows RNA), limited succession planning, few reviewers with active LNP experience
- **Remediation options:** structured training (WHO, ICDRA, CEPI-supported), secondments to reference NRAs, joint review with regional partners, and participation in tabletop exercises

Domain 2: Analytical Infrastructure

In-house capability, third-party access, or oversight only — pick a model and know it.

- **Three viable models:** in-house testing (labs at the NRA itself), designated third-party labs (contracted or through OMCL-style networks), or oversight-only (NRA relies on manufacturer or reference-NRA release data)
- **Analytical methods to have access to:** identity (RT-PCR / sequencing), integrity (capillary electrophoresis), capping (LC-MS), residual DNA (qPCR), LNP size (DLS / NTA), encapsulation (RiboGreen or similar), potency (cell-based expression assay)
- **Common gaps:** LC-MS and cell-based potency assays are the most frequently missing capabilities
- **Remediation options:** OMCL-style regional labs, reliance on reference-NRA release, formal agreements with academic labs, WHO EQAS participation

Domain 3: Legal And Regulatory Authority

The powers the NRA needs — and where legal frameworks come under strain.

- **What proficiency looks like:** a clear legal basis for emergency authorisation, explicit authority to accept reliance and reference-NRA decisions, defined lot-release powers, and post-market surveillance mandates that hold up under emergency tempo
- **Specific competencies:** domestic emergency authorisation pathway (EUA / EUL-equivalent), reliance and Collaborative Registration Procedure (CRP) mechanisms, authority to grant conditional or time-limited approvals, ability to modify or withdraw authorisations rapidly
- **Common gaps:** legal ambiguity about what the NRA can accept from reference authorities; emergency authorisation pathway requires legislative change; post-market surveillance authority lags behind product deployment
- **Remediation options:** interim regulations or emergency guidance to bridge legislative gaps; formal reliance agreements (WHO CRP participation);

Domain 4: Operational Systems

The workflows and infrastructure that let the NRA move at emergency tempo.

- **What proficiency looks like:** rolling review capability with documented triggers and stopping rules; defined timelines with escalation paths; case-tracking infrastructure that holds up under load; delegated decision authority that avoids single-point bottlenecks
- **Specific competencies:** acceptance of partial and rolling submissions, tiered decision-making with clear escalation, case-management systems (even lightweight) that maintain traceability, ability to redeploy reviewers rapidly across product areas
- **Common gaps:** paper-based tracking that doesn't scale under emergency volume; single-thread review workflows that can't parallelise; limited decision authority below senior leadership; unclear governance for expedited decisions
- **Remediation options:** SOPs for rolling review; case-management systems (WHO templates or lightweight custom tools); documented delegated

Domain 5: Collaboration Mechanisms

How the NRA connects with reference authorities, regional partners, and international bodies.

- **What proficiency looks like:** formal reliance agreements with reference NRAs, active participation in regional and global regulator forums, WHO listed authority status where applicable, and standing information-sharing channels that don't rely on ad-hoc contact
- **Specific competencies:** reliance and CRP use in routine as well as emergency contexts; PAHO NRAr work-sharing participation; bilateral MOUs with reference NRAs (FDA, Health Canada, EMA); membership in ICDRA / ICMRA and similar forums
- **Common gaps:** collaboration is ad-hoc rather than formalised; reliance is used only in emergencies rather than as a routine efficiency tool; information-sharing lags because channels aren't standing
- **Remediation options:** formalise existing informal relationships into standing MOUs; join WHO CRP; participate actively in PAHO NRAr and joint assessment exercises; assign named liaison staff for each reference NRA relationship

Domain 6: RNA GMP Inspection Readiness

Can the NRA inspect — or credibly rely on inspection of — RNA manufacturing sites?

- **What proficiency looks like:** the NRA can inspect, or credibly rely on inspection of, the RNA drug substance and the LNP drug product against RNA-specific GMP criteria; an inspector has observed an RNA / LNP site; and findings feed the review and lot-release decisions
- **Specific competencies:** assessing RNase control and segregation; qualifying microfluidic LNP encapsulation (mixing, in-line particle sizing); ultra-cold-chain and excursion monitoring; and oversight of RNA analytics (integrity, capping, sizing, potency)
- **Common gaps:** conventional checklists omit RNA / LNP specifics; few inspectors have seen an RNA facility; over-reliance on desk assessment; and an unclear split of inspection duties across NRAs
- **Remediation options:** RNA-specific inspection aide-memoire; joint or observed inspections with reference NRAs; PIC/S participation; inspector training (WHO, PIC/S, CEPI); and reliance on reference-NRA inspection reports
- **The score-to-gap-to-remediation deliverable:** across all six domains, each NRA scores itself, identifies its top three gaps, and commits to a concrete remediation action

CEPI

TOPIC 2 • ~10 MIN

Product Classification Considerations

Vaccine, biological, or gene therapy? — and why it matters.

Why Classification Matters

The category a product falls into determines the review pathway, the dossier expectations, and the inspectorate involved.

- **Vaccine pathway:** biological product for the prevention of infectious disease; typically reviewed by the vaccines division with standard nonclinical and clinical requirements for prophylactic biologicals
- **Advanced therapy / gene therapy pathway:** product that alters or acts on the host's genetic material; requires additional considerations (biodistribution, persistence, shedding, insertional risks) and often a different inspectorate
- **The classification decision is not always obvious:** novel modalities (saRNA, taRNA, circRNA) sit at the boundary. Different jurisdictions have taken different views
- **Regulator consequences:** the classification decision determines which regulation and guidance applies, which committee reviews, and which inspectorate handles GMP

The Butantan / Replicate Bioscience saRNA rabies vaccine

A regional example that puts the classification question on the table for Latin American NRAs.

- **The product:** RBI-4000 — a self-amplifying RNA rabies vaccine being developed by Instituto Butantan (Brazil) in collaboration with Replicate Bioscience (USA)
- **The classification question:** saRNA encodes a viral replicase that amplifies the RNA in the cell — some jurisdictions consider this a gene therapy characteristic; others treat it as a vaccine with novel modality considerations
- **Implications for the review pathway:** biodistribution and shedding studies may be expected at levels not required for conventional vaccines; the CMC package will include replicase-specific attributes
- **For ANVISA and other regional NRAs:** the classification decision here will influence how similar saRNA products from other developers are handled — an important precedent moment for the region

How to Approach the Decision

- **Look to precedent:** how have reference NRAs (FDA, EMA, Health Canada) classified similar novel RNA products?
- **Consider intended use and mechanism:** prophylaxis against an infectious disease supports vaccine classification; therapeutic intent or genome-modifying mechanism supports gene therapy classification
- **Engage early:** novel-modality products benefit from early scientific advice — before pivotal studies — to lock in the classification and pathway
- **Document the reasoning:** the classification decision should be recorded with rationale; downstream questions (dossier expectations, GMP inspectorate, post-market obligations) all reference it

CEPI

TOPIC 3 • ~10 MIN

Manufacturing-country vs. Importing-country NRA roles

The recurring framing question — and how reliance pathways distribute the review burden.

Two Different Reviewer Perspectives

Reliance pathways distribute the review burden between manufacturing-country and importing-country NRAs.

MANUFACTURING-COUNTRY NRA

Primary reviewer role

- Full CMC + nonclinical + clinical review
- GMP inspection of the manufacturing site
- Lot release for domestic market
- Post-market surveillance for domestic use
- **Regional examples:**
  ANVISA (Bio-Manguinhos products),
  ANMAT (Sinergium products)

RELIANCE

reports, decisions, inspection findings

IMPORTING-COUNTRY NRA

Reliance / oversight role

- Relies on manufacturing-country + reference NRA
- GMP inspection may be waived under reliance
- Local labelling & patient information review
- Post-market surveillance for local use
- **Regional examples:**
  many Caribbean and Central American NRAs receiving imported products

Reliance Pathways and Reference-NRA Decisions Across The Americas

- **WHO Collaborative Registration Procedure (CRP):** reliance framework for products with WHO Emergency Use Listing or prequalification
- **PAHO NRAr work-sharing:** regional network coordinating NRA authorities across Latin America and the Caribbean
- **Bilateral MOUs:** e.g., ANVISA–FDA information-sharing arrangements; other bilateral relationships that support faster review
- **Reference-NRA decisions:** FDA, EMA, Health Canada, and other WHO-listed authorities produce authorisation and inspection reports that reliance-based NRAs can use to accelerate their own reviews

The Framing Question That Recurs Across The Workshop

"What must a manufacturing-country NRA do versus an importing-country NRA?"

- **In Session 2:** the Emergency Development and GMP Inspections modules touch on this question repeatedly — who inspects, who releases, who accepts reliance
- **In the Closing:** the question returns explicitly as one of the workshop's takeaways
- **In your own NRA planning:** on the score-to-gap-to-remediation self-assessment, this framing shapes the answers — the two roles need different capabilities and different investments

UP NEXT — 10 MIN

Wrap-Up & Bridge to Session 2

Synthesis of the technical foundation and a preview of the regulatory basis session tomorrow.