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mRNA vaccine delivery

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July 2022

CRS 2022 Annual Meeting & Expo

Advanced Delivery Science

July 11 – 15, 2022 | Montreal Congress Center, Montreal Canada

- Together, we chase the *miracles* of science -

The research is funded by Sanofi

Shrirang Karve is an employee of Sanofi, a company that manufactures influenza vaccines, and may hold stock in the company

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Building Sanofi's *mRNA Center of Excellence*

2 main hubs in the United States & France

Building a global team of 450+

Investment of € 400m per year

An internalized end-to-end mRNA platform

A core of research & innovation for mRNA

Building on our strengths & expertise

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Bridging Knowledge Gap on mRNA Vaccines

- Boostability in Response to Strain Change

Efficacy & Tolerability beyond pandemic stains

- Multivalent & Combination Vaccine Delivery

Appropriate level of immuno-stimulation

Thermostability & Storage

Industrialization & Manufacturing footprint

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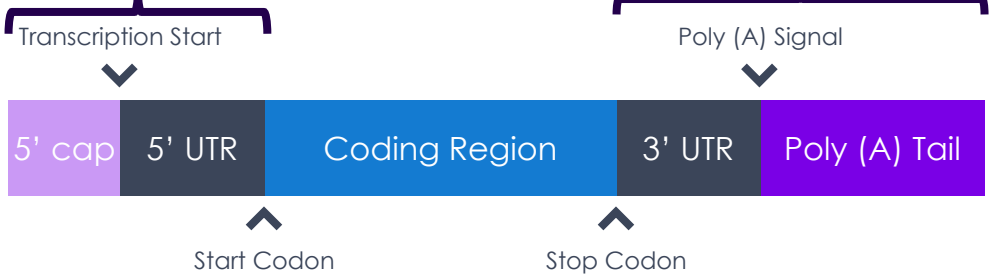
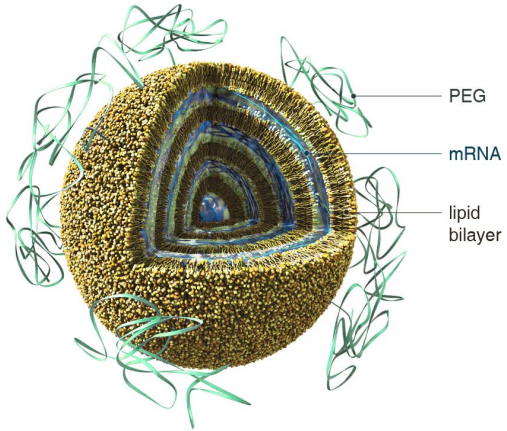
mRNA-LNP Design Attributes

Potency & stability

Stability





- Comprehensive array of platform variants
- Aimed to modulate stability, translation efficiency, and immune-stimulatory profile
- Targeting a fully integrated well-established manufacturing platform

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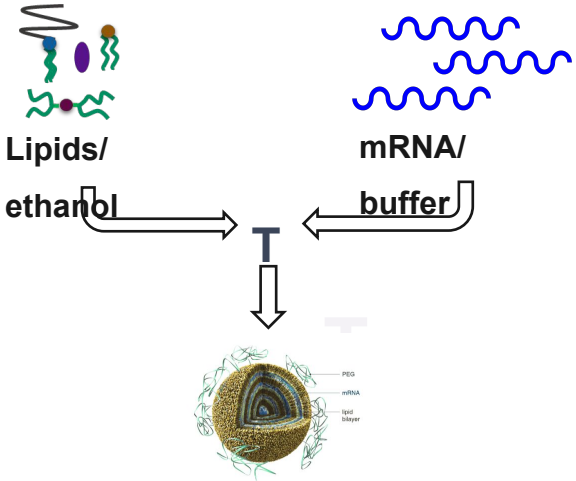
LNP formulation development

Formulation processes

Proprietary, robust, scalable LNP formulation processes

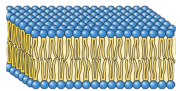


Formulation optimization

Improvements through both SAR and formulation optimization to maximize expression

How do we achieve that ?

- Composition changes
- Process changes
- New helper lipids and PEG lipids
- Excipients, buffers, antioxidants etc.



Formulation development

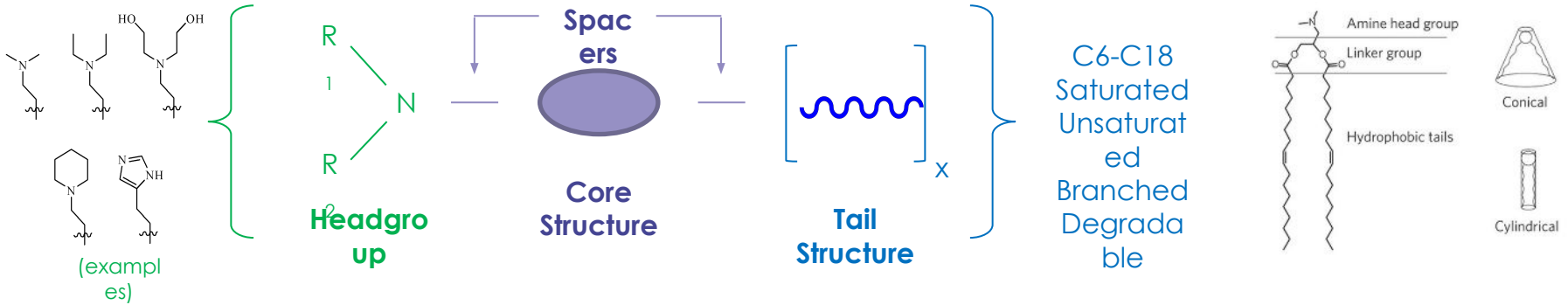
Optimizing stability profile of the 'lead' formulations for clinical development and ease of use

Development of cryo stable & lyophilized formulations for different presentations at different storage temperatures

Novel lipid design, screening, and selection

Building a suite of diverse lipids to enable current and accelerate future programs

Library Approach:



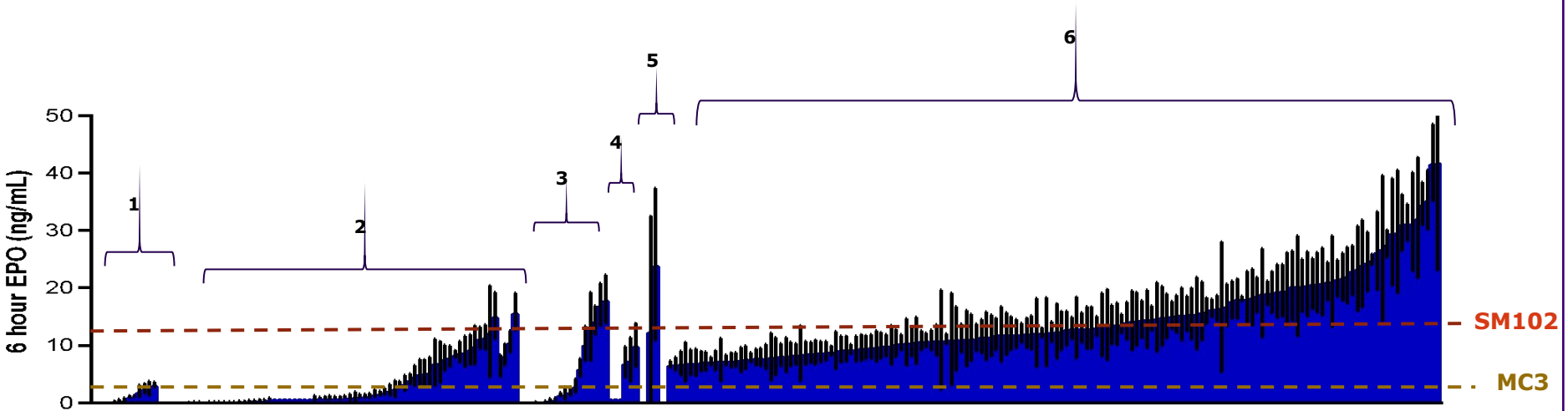
Balancing synthesis of novel tails with functional linker groups and core structures

Build on in vivo data generation to establish SAR to maximize optimization for best candidates

High-throughput LNP screenings that enable broad applicability through multiple ROAs

Intramuscular ROA

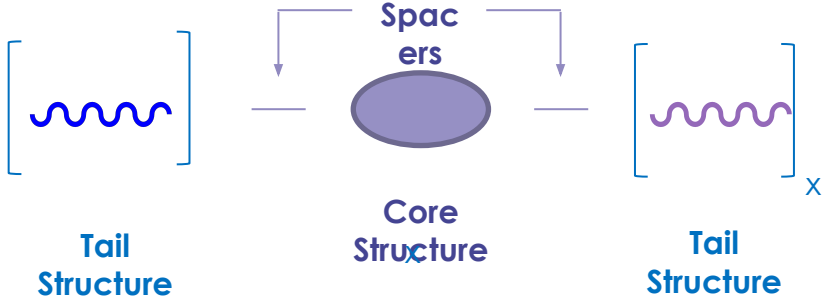
Multiple lipids families showing high EPO expression



Numbers represent different lipid families

Determining structure activity relationships (SAR) within a library matrix for selecting optimal lipid candidate

- Structure- activity relationship (SAR) approach
- Screening of alkyl chain length, linker type & length, saturation, branching etc.
- 'Heat map' identifying lipid hits and optimal designs in the family
- Deepen understanding and apply for novel designs



hEPO protein (ng/ml)												
Lipid Core X	L2-Arm A	L2-Arm B	L2-Arm C	L2-Arm D	L2-Arm E	L2-Arm F	L2-Arm G	L2-Arm H	L2-Arm I	L2-Arm J	L2-Arm K	L2-Arm L
L1-Arm A	12.2	18.1	5.7	15.3	13.1	4.2	12.3	27.8	11.2	9.9	10.6	5.8
L1-Arm B	9.8	13.9	9.4	13.0	15.6	5.3	11.2	23.4	8.6	9.7	13.6	4.8
L1-Arm C	5.6	16.6	4.3	11.4	12.3	3.2	8.5	19.2	6.6	8.8	12.6	5.1
L1-Arm D	6.7	14.6	10.0	8.9	11.1	4.1	13.1	18.3	8.4	4.7	9.7	11.0
L1-Arm E	7.3	16.7	3.7	10.4	12.1	3.6	11.0	14.8	7.1	10.5	11.2	6.7
L1-Arm F	6.1	19.8	6.4	13.6	5.9	1.1	5.7	5.5	1.1	4.2	6.6	3.4
L1-Arm G	6.2	14.0	16.0	12.2	12.0	3.7	19.5	10.9	19.3	11.4	15.5	6.0
L1-Arm H	9.4	14.7	18.2	20.7	9.4	7.5	22.2	20.5	20.8	14.3	12.1	12.6
L1-Arm I	3.1	13.7	15.5	11.7	15.1	7.3	17.9	27.0	9.0	18.5	10.9	7.2
L1-Arm J	19.8	14.4	11.8	10.1	7.0	8.7	19.2	14.9	11.0	12.4	8.9	5.1
L1-Arm K	18.7	21.7	15.5	11.3	8.0	8.0	19.6	15.4	12.1	13.8	10.6	6.8
L1-Arm L	7.5	8.4	9.9	11.4	8.1	7.4	7.9	9.4	7.1	8.0	3.5	4.3

LNP process is highly scalable

- Create small scale LNP processes that mimic our large scale process needs
- This ensures comparability from research grade to large scale GMP and beyond

Successfully completed multiple 100g scale single batch LNP drug products

	100 mg scale	5g Scale	100g Scale
Size	55-60 nm	55 nm	50 nm
PDI	<0.2	0.10	0.16
Encapsulation	80-90	90%	91%

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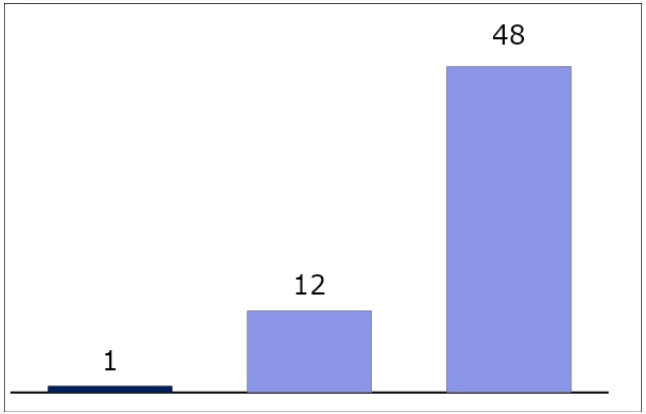
Overcoming mRNA thermostability challenges

Storage at 4°C is needed for vaccines outside pandemic

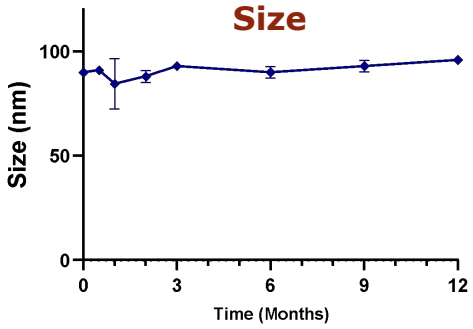


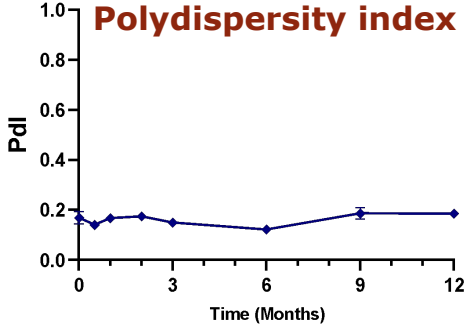
Stability of lyophilized mRNA drug product achieved

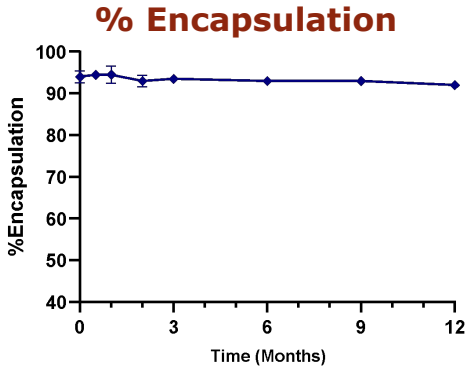
Development of fully liquid formulation underway

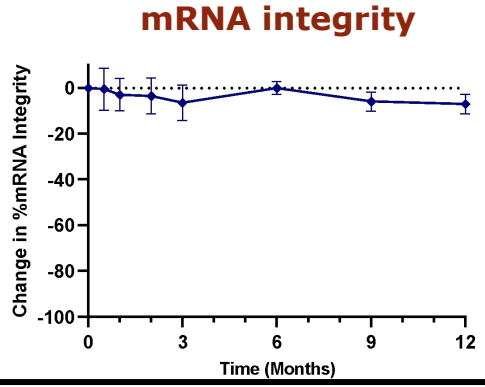
Evaluation of dry powder as novel delivery system

Optimized lyophilized formulation for 2-8C storage









Promising 1 year stability at 2-8 C storage

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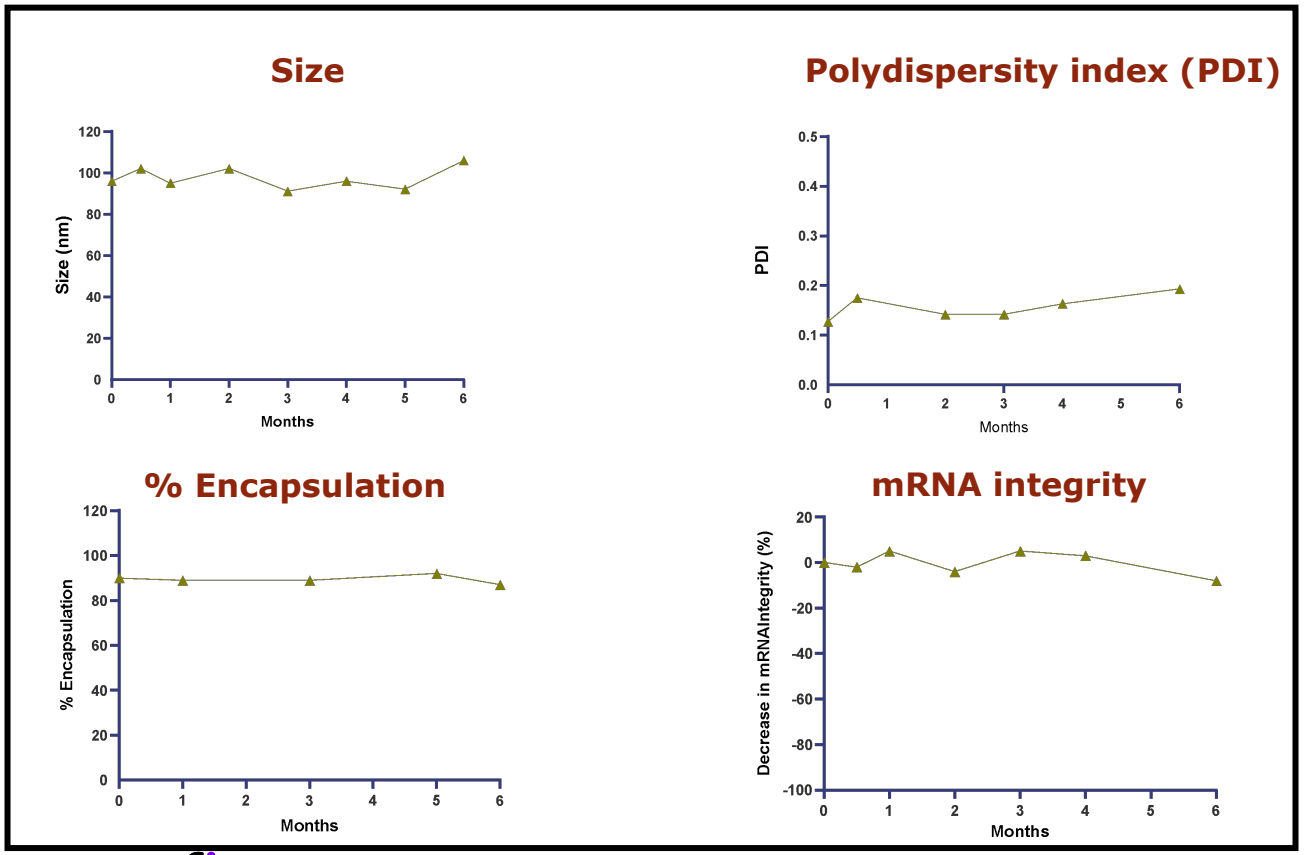
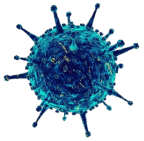
Dry powder formulation for 2-8C storage



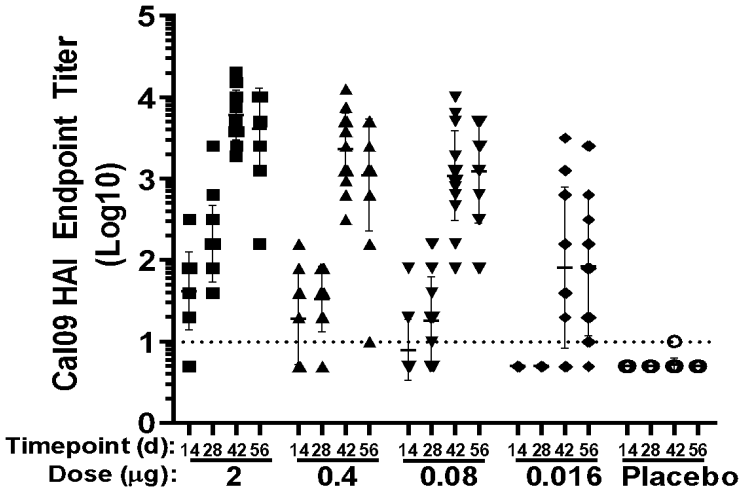
Exploring dry powder formulation for expanding mRNA applications and improvement in thermostability

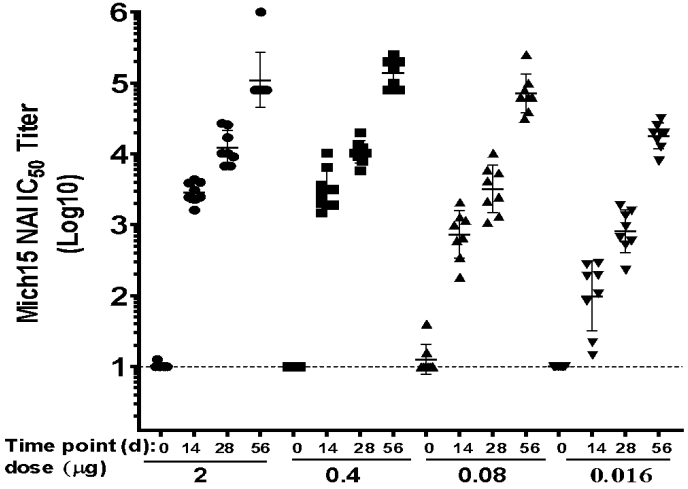
Dose response of influenza (HA & NA) vaccines in mice



Influenza (HA/NA)

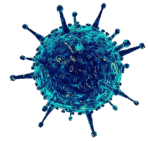
- Mice given 1 or 2 doses (d0, d28) of hemagluttinin (HA) or neuraminidase (NA) (0.016 - 2ug)





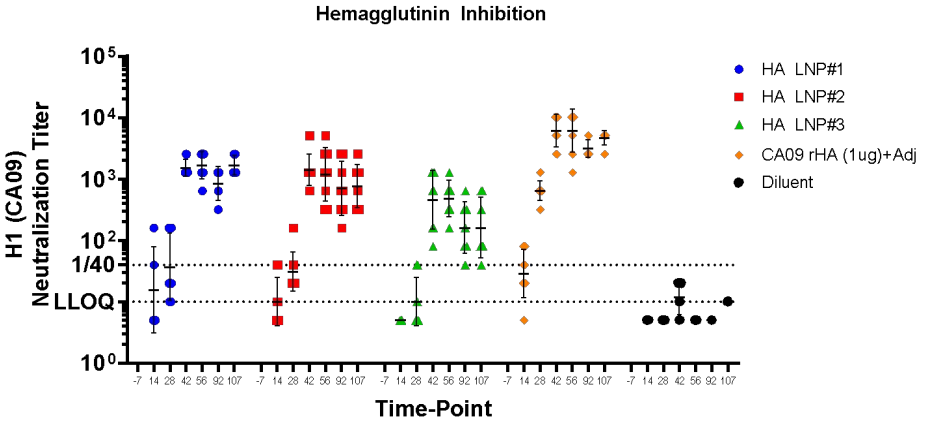
Clear dose response observed from 0.016 – 2ug for both HA & NA LNP vaccines

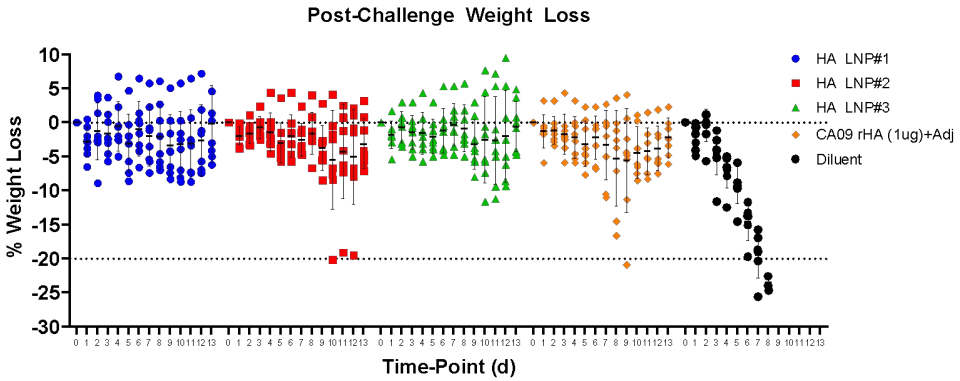
HA Challenge Study in Mice: *Protection from lethal challenge observed with multiple LNPs*



Influenza (HA)

- Mice challenged with Belgium09 influenza (day 93 post-dose) and monitored for weight loss/survival
- 3 different LNPs (0.4 ug) tested against rHA subunit controls





Protection with all three LNPs after 0.4 ug dose

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Breaking Barriers to Go Beyond

	mRNA 1.0	mRNA 2.0	mRNA 3.0
Immunogenicity	High	High	High
Reactogenicity	Moderate to high	Tolerability profile in line with established vaccines	Tolerability profile in line with established vaccines
Thermostability	~1 month shelf life (2-8°C)	Lyophilized or 9 – 12 months fully liquid	Lyophilized or 9 – 12 months fully liquid
Duration of expression	1 – 3 days	1 – 3 days	Extended halflife
Next Gen features	-	Multivalent and combination delivery without interference	Efficient cell & organ specificity
	Applicable to pandemic market	**Required profile for vaccines beyond pandemic**	**Optimal profile for therapeutics**

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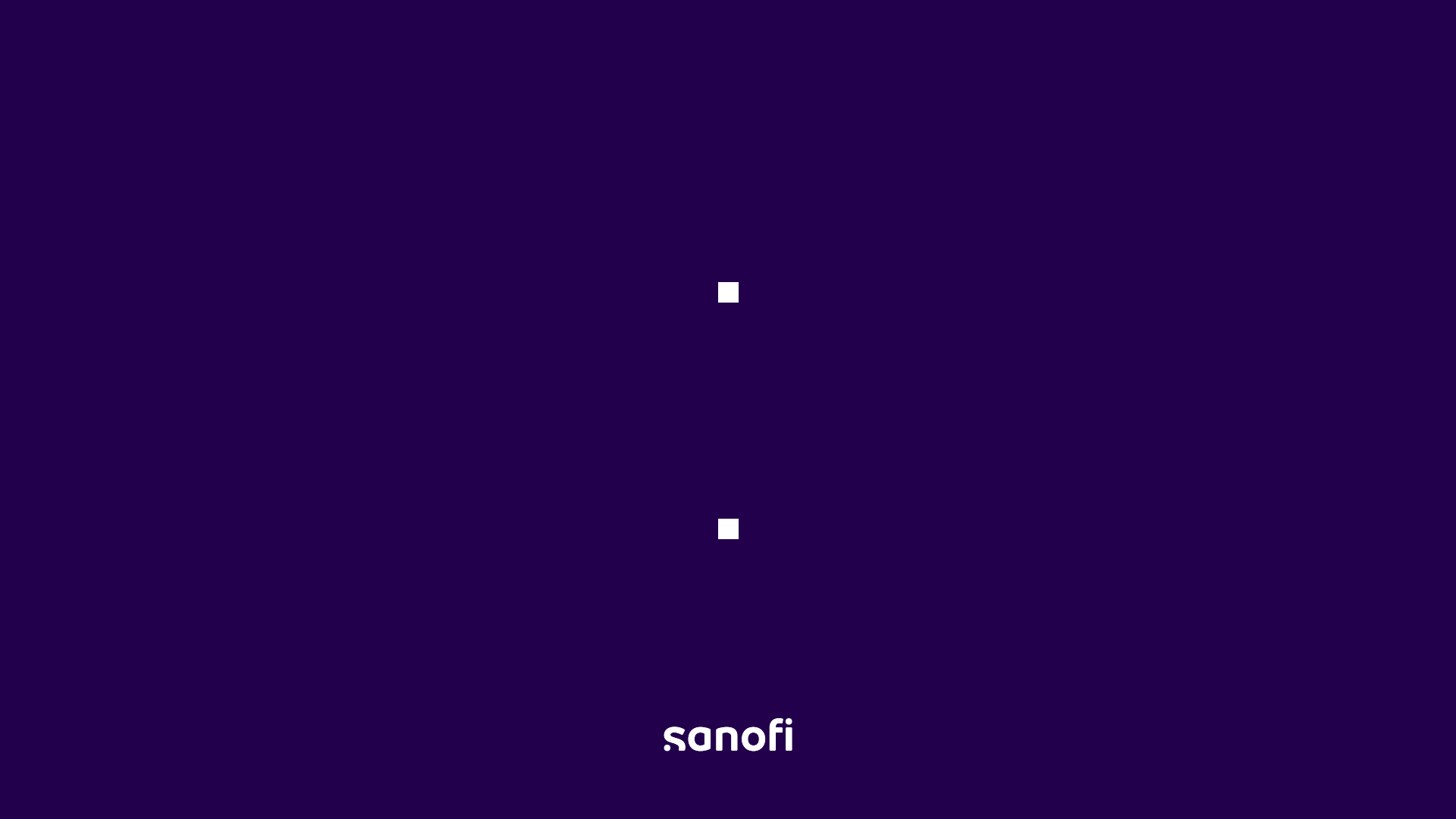
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