Simplifying Progress

LipidBrick®: An innovative lipid library for efficient and tunable mRNA-LNPs

CRS, July 2024

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Delivery of RNA and DNA is not one size fits all

- Lipid nanoparticle solutions have shifted to a mostly one size fits all format:
  - Nearly identical lipid compositions and biodistributions in vivo
  - Lack of formulations tailored to specific payload and applications

- The issues with a one size fits all approach are abundant:
  - Lack of tissue specificity and/or broad biodistribution
  - Applying complex API to the needs of the excipient
  - Lower efficacies than needed

Theranostics: Yasmin Granot-Matok et, al. pp3397 ISSN1838-7640

Unique Formulations Solve Current Challenges

1	Biodistribution	Broaden the Approach	▪ Current LNPs accumulate in the liver ▪ Need for extrahepatic delivery to broaden therapeutic applications
2	IP	Freedom to Operate	▪ The current IP landscape for LNPs is complex ▪ Components and formulations are both patented ▪ Need for secure IP to ensure translation to clinic
3	Efficacy	Uptake and Response	▪ Need for safe, non/low immunogenic delivery solutions that can be taken up abundantly ▪ Need for high transfection of cells
4	API Driven	One Size ≠ Fit All	▪ Optimization of delivery systems for specific RNA ▪ Ability to design formulations that are unique

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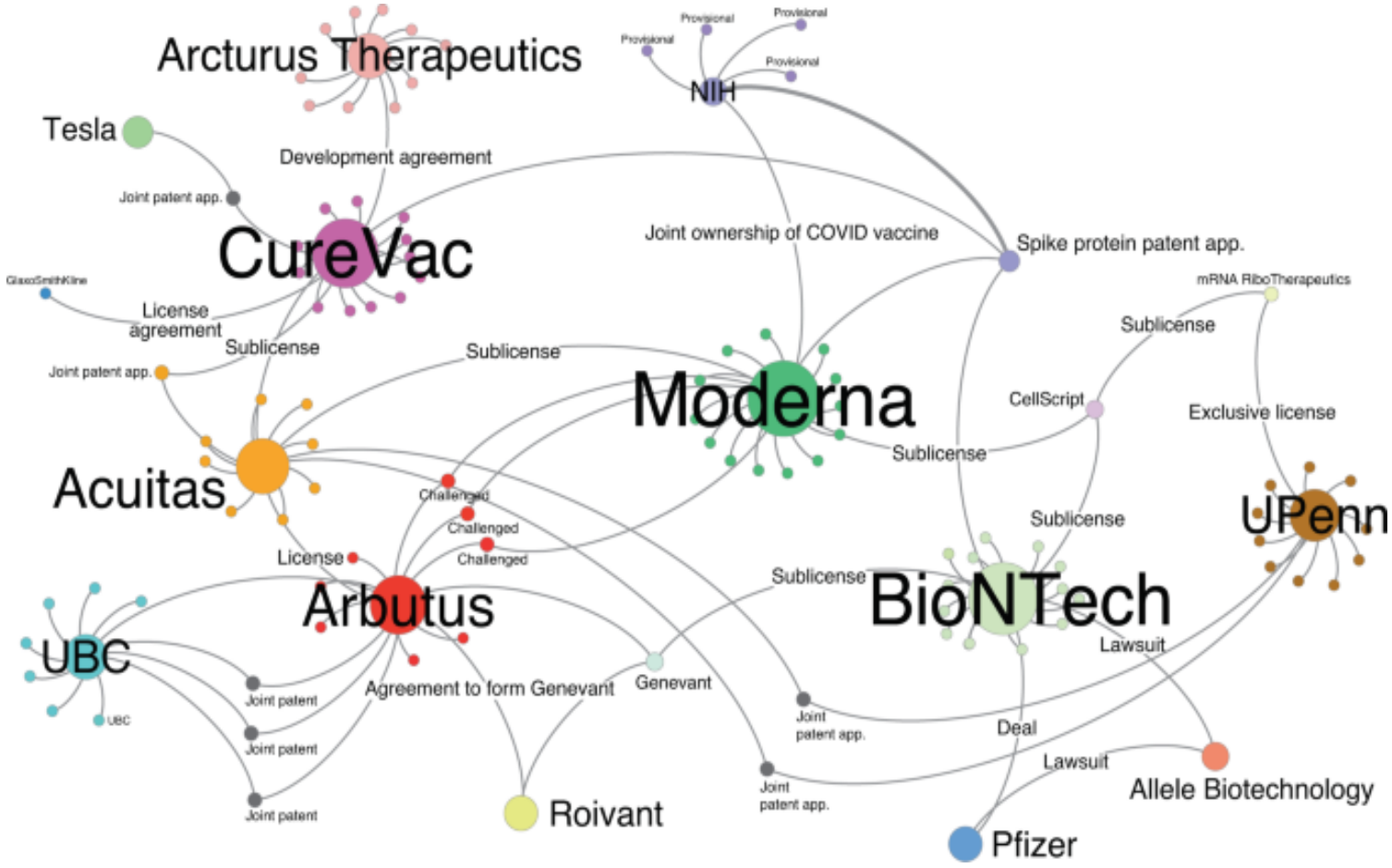
Focus on: Intellectual Property

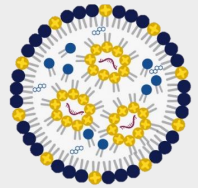
- Patents and patent infringement remain extremely relevant topics in 2024
- Majority of preclinical research is done with MC3 (Onpattro), SM-102 (Moderna), ALC-0315 (Acuitas)
- Lack of clear pathway to the clinic for several lipids



https://www.nature.com/articles/s41587-021-00912-9

Deep History in Nucleic Acid Delivery

Polyplus
Now Part of Sartorius

in vivo-jetPEI®	*in vivo*-jetPEI® GMP	*in vivo*-jetRNA®+	LipidBrick® Library
▪ Ready-to-use reagent ▪ Gold standard cationic polymer ▪ Local/Systemic administration	▪ DMF submitted to FDA & CMC documentation ▪ Several ongoing clinical trials ▪ 650+ publications	▪ Ready-to-use lipid-based nanoparticles reagent ▪ mRNA, saRNA & gRNA ▪ Utilizes IM21.7c	▪ Cationic lipids toolbox to be assembled with other lipids for LNP formulation ▪ To adapt LNP tropism
			
2001	2007	2022	2023 (IM21.7c) 2024 (Library)

Polyplus has developed multiple GMP products

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Simplifying Progress in DNA | RNA Therapeutics

Critical Raw Materials


Lipids


Transfection Reagents


pDNA


recHuman Albumin

Services


pDNA Engineering


pDNA Manufacturing


PD Services

Bioreactor Technologies


Multi-parallel Bioreactors


Scalable Stirred-Tank Bioreactors

End-to-End Solutions Supporting Scalable Nucleic Acid-based Therapeutics

Bio Analysis


At-Line HPLC


Analytical Monoliths

Data Analytics


DOE and MVDA Software

Fluid Management


Sterile Connection & Disconnection Systems


Single Use Bags


Storage & Mixers

Downstream Processing


TFF Systems & Consumables


Filters


Monoliths


SU Batch Chromatography

ATS Solutions Across the pDNA | mRNA Workflow

pDNA Design | pDNA Production | Purification | Linearisation | Purification (DSP) | mRNA Production | Purification | LNP Formulation

Reagents | Consumables Systems

CIMmultus®
CIM® plate

CIMmultus®
CIM® plate

CIMmultus®
CIM® plate

LipidBrick®
in vivo-jetRNA®+

PATfix® pDNA

CIMac™ pDNA

PATfix® mRNA

CIMac™

Services

pDNA
Engineering

pDNA
Manufacturing

Cornerstone® Development Service
(pDNA DSP, mRNA IVT & DSP)

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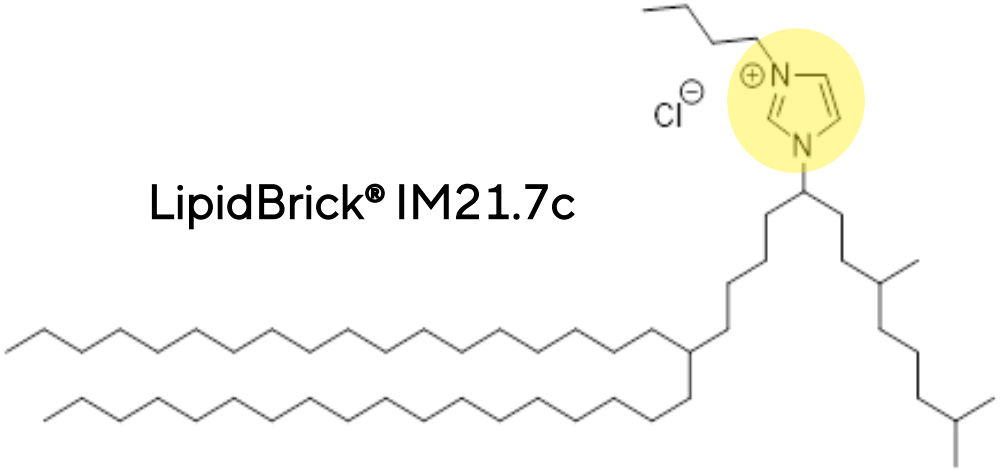
LipidBrick® library

LipidBrick® - A breakthrough technology

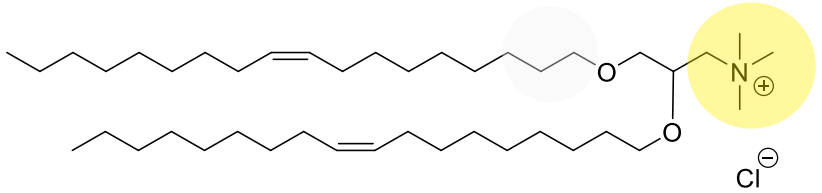
- **New generation of cationic lipids** to form LNPs
- Based on an **IMidazolium** polar head, a heterocycle, leading to **reduced toxicity** as compared to traditional cationic lipids
- IM21.7c has been **used and validated for years** in different types of formulation:
  - jetMESSENGER® (lipoplexes) → *in vitro* mRNA transfection
  - *in vivo*-jetRNA®+ (liposomes) → *in vivo* & *ex vivo* mRNA transfection
- **Sole proprietary technology of Polyplus®** (Now part of Sartorius)
  - EP18306417 (Granted in EU, China, Hong Kong, Japan. Pending or under review in the US and other countries)
  - WO2024008967A1 (Published in Jan 2024)
  - FTO analysis (US & EU patents) performed by ext. IP attorney

LipidBrick® IM21.7c

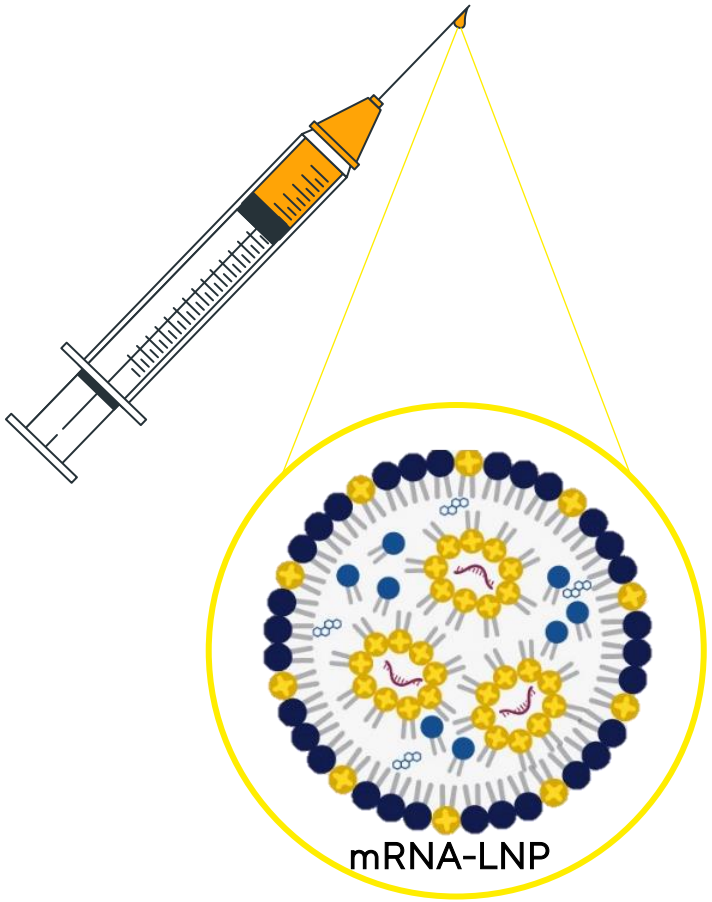


Cationic lipid
= Fixed positive charge

DOTMA - Previous generation cationic lipid



Applying LipidBrick® to Conventional LNP Design



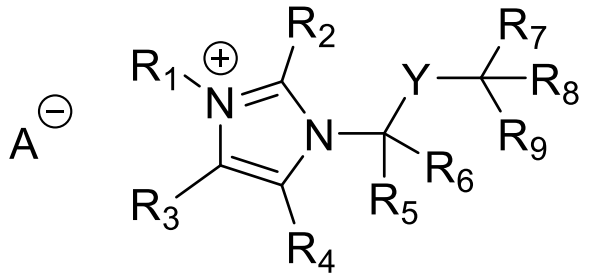
Active substance = Nucleic acids

mRNA	Carry genetic information to be translated, *in fine*, into a protein of interest

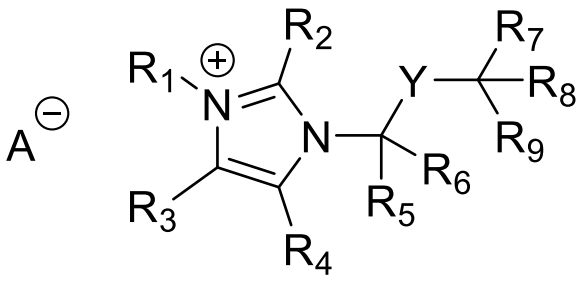
Excipient/Carrier = LNPs (lipid nanoparticles) composed of a mixture of lipids

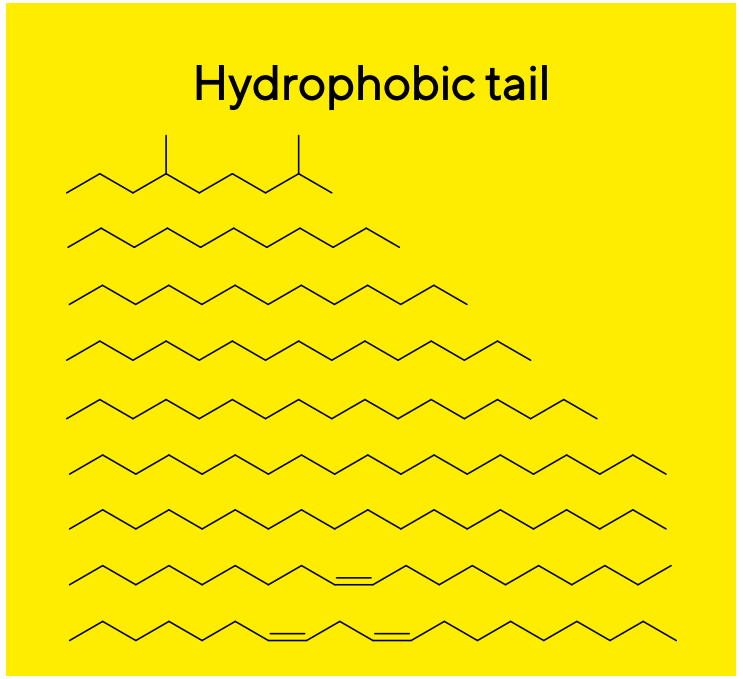
Cationic / ionizable lipid	Active positively charged lipids will interact with negatively charged nucleic acids and cell membrane (improve cell uptake)
+ LipidBrick®	
Helper lipid	Structural lipids provide LNP rigidity and stability
PEGylated lipid	Provide steric stabilization and prolong blood circulation
Cholesterol	Increase membrane fluidity and stability, promote membrane fusion

Design of innovative lipids

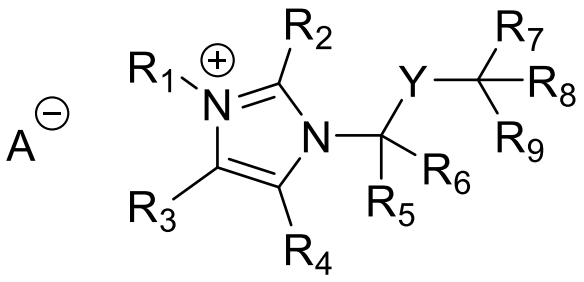


Design of innovative lipids

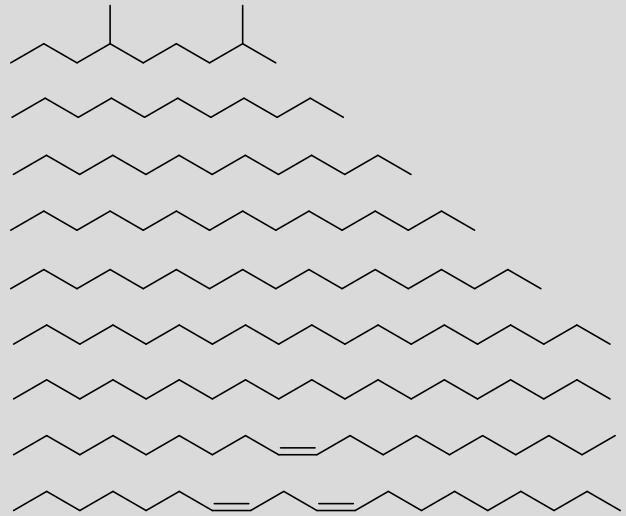




Design of innovative lipids



Hydrophobic tail



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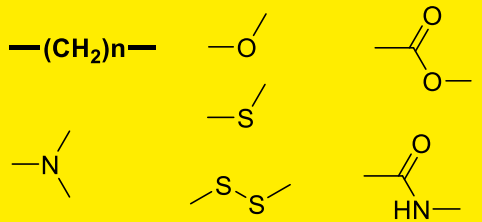

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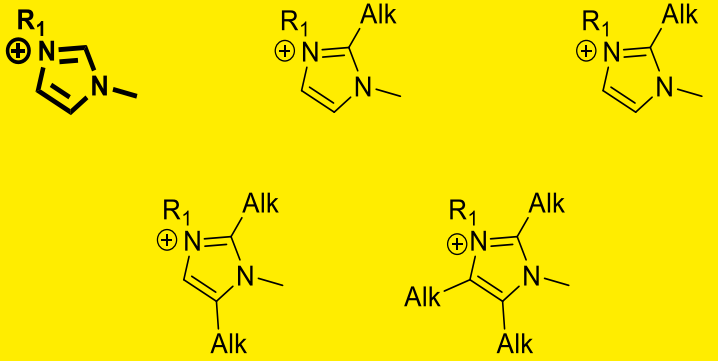
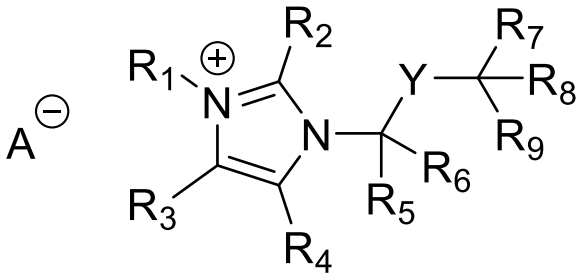
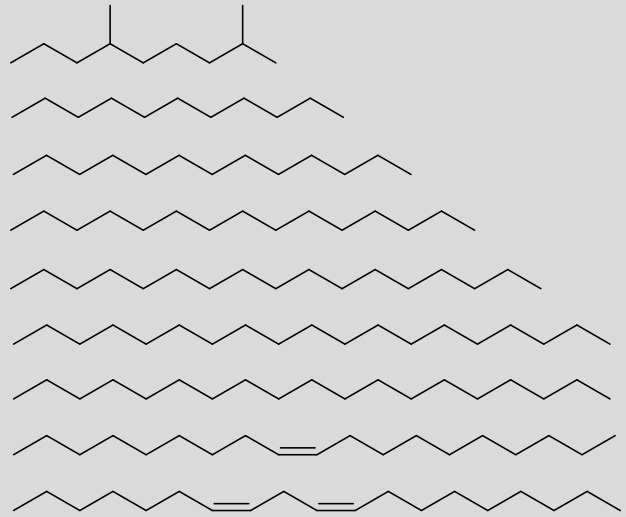
Design of innovative lipids

Polar head





Hydrophobic tail



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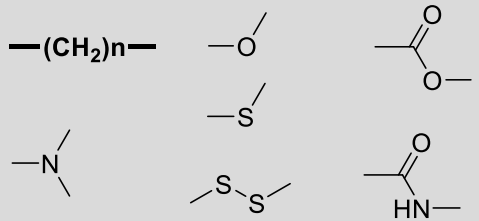

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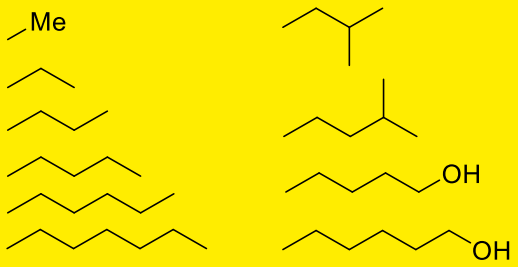
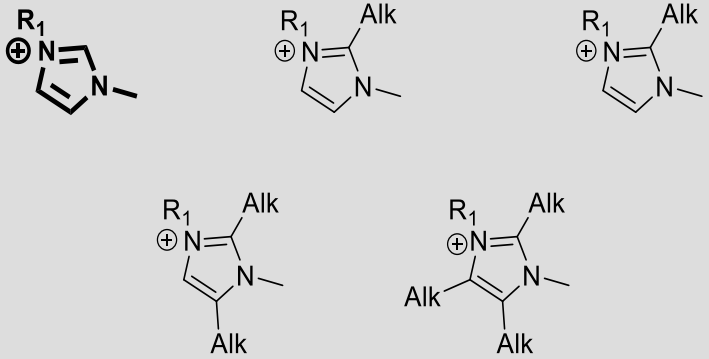
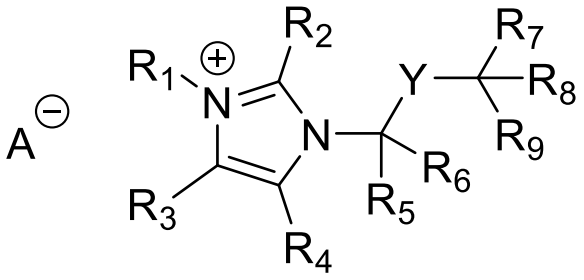
Design of innovative lipids

Functional group



Polar head





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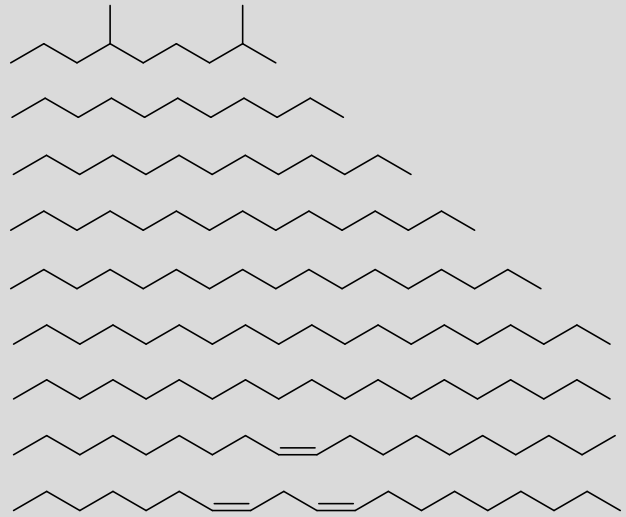

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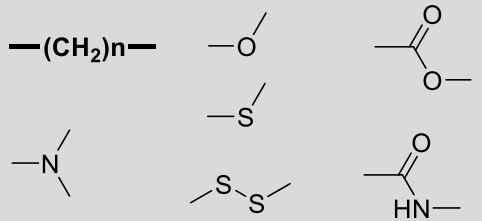

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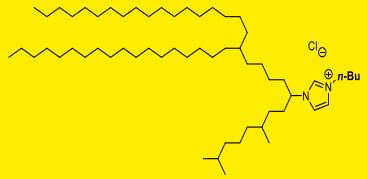
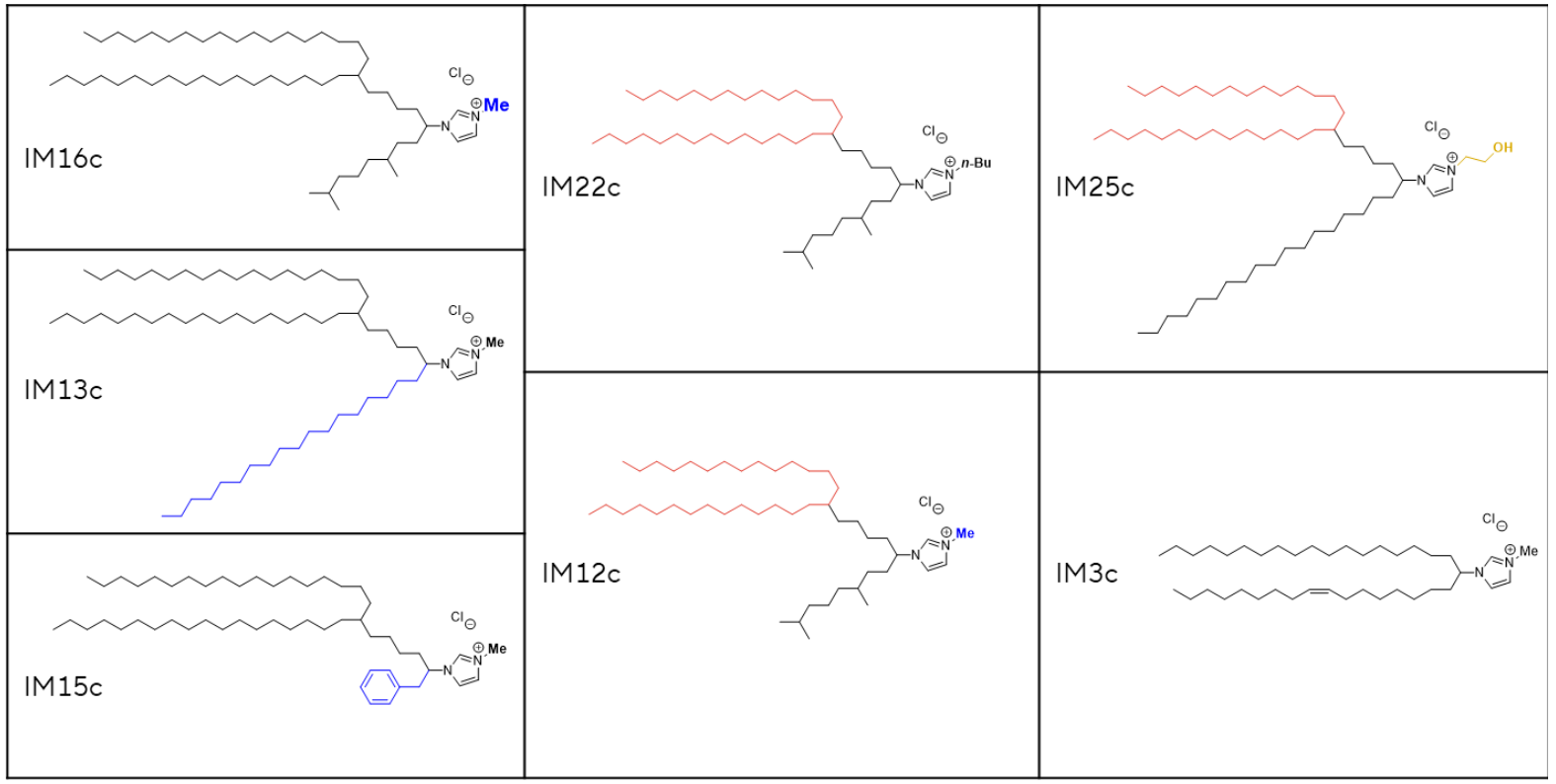
LipidBrick® - A Full Library Offering Plenty of New Options

IM21.7c
CAS n°: 2416939-42-7





Proof of Concept: LipidBrick®-based LNPs

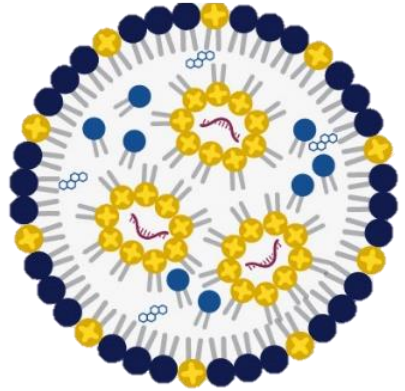
LipidBrick® are versatile

- **LipidBrick® IM21.7c has been shown to be suitable with:**

  - Different compositions:
    - As **complete substitution of ionizable lipid** → 4-lipid LNP
    - In **addition to ionizable lipid** → 5-lipid LNP

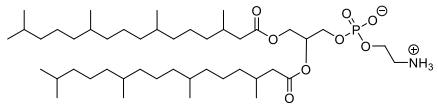
  - **Many different lipids**:
    - Phospholipids (DOPE, DPyPE, DSPC, DPPC, DOPC, PLPE)
    - PEGylated lipids (DMG-PEG2k, DSG-PEG2k, ALC-0159, DSPE-PEG2k, DSPE-PEG5k)
    - Sterol lipids (Cholesterol, β-sitosterol)
    - Ionizable lipids (DODMA, Dlin-MC3-DMA, SM-102, ALC-0315)

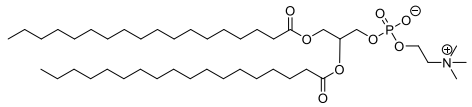
  - **Different nucleic acids**:
    - mRNA, saRNA, gRNA, pDNA, etc.

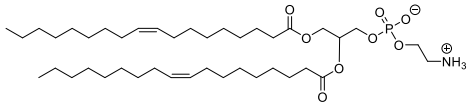


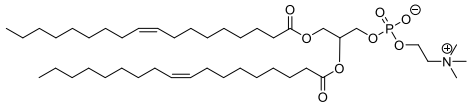
IM21.7c is suitable with Different Phospholipids for LNP formulation

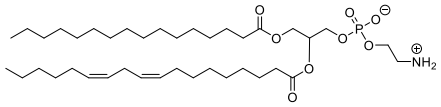
IM21.7c (mM)	DODMA (mM)	Helper Lipid (mM)		Cholesterol (mM)	DSG-PEG$_{2k}$ (mM)	Size	PDI	Zeta	EE%
IM21.7c 4	DODMA 3	DPyPE	1	1.85	0.15	54±1	0.085	+16	100
		PLPE	1			52±9	0.197	+14	100
		DOPE	1			60±5	0.155	+13	100
		DOPC	1			50±10	0.163	+17	100
		DPPC	1			59±8	0.134	+17	100
		DSPC	1			43±3	0.162	+15	100

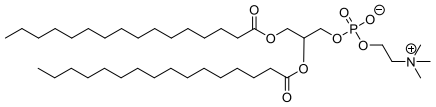
DPyPE 

DSPC 

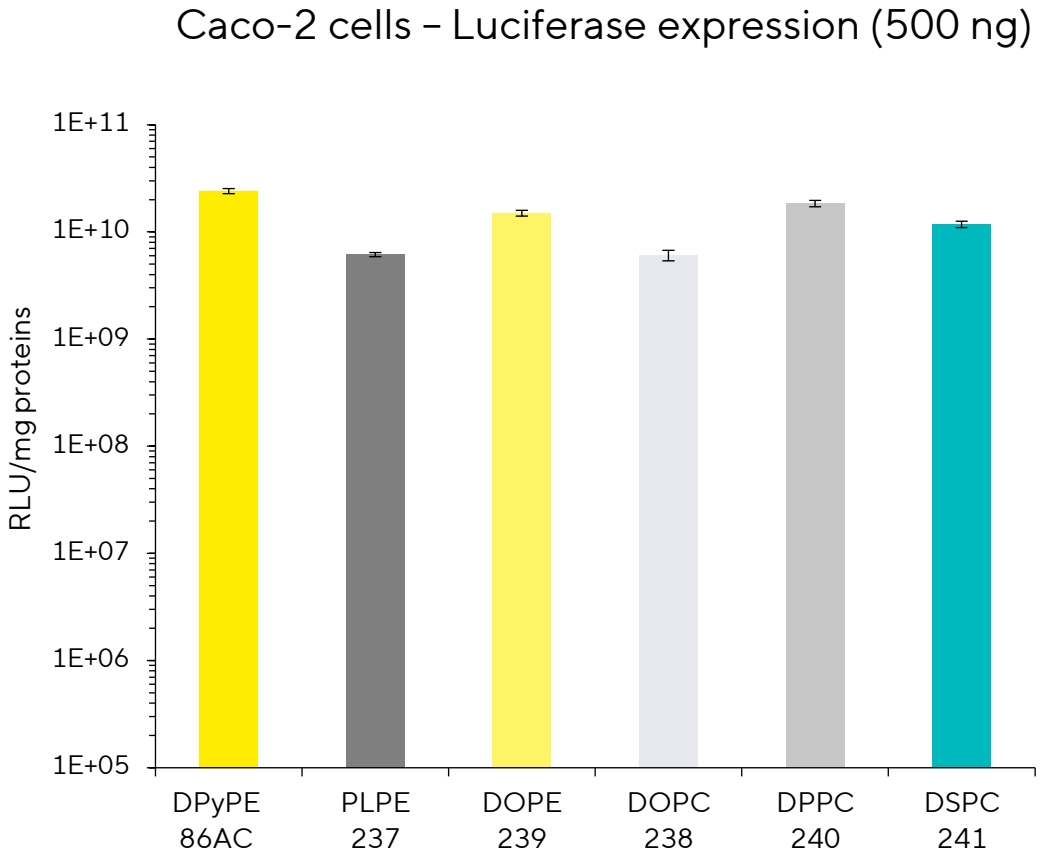
DOPE 

DOPC 

PLPE 

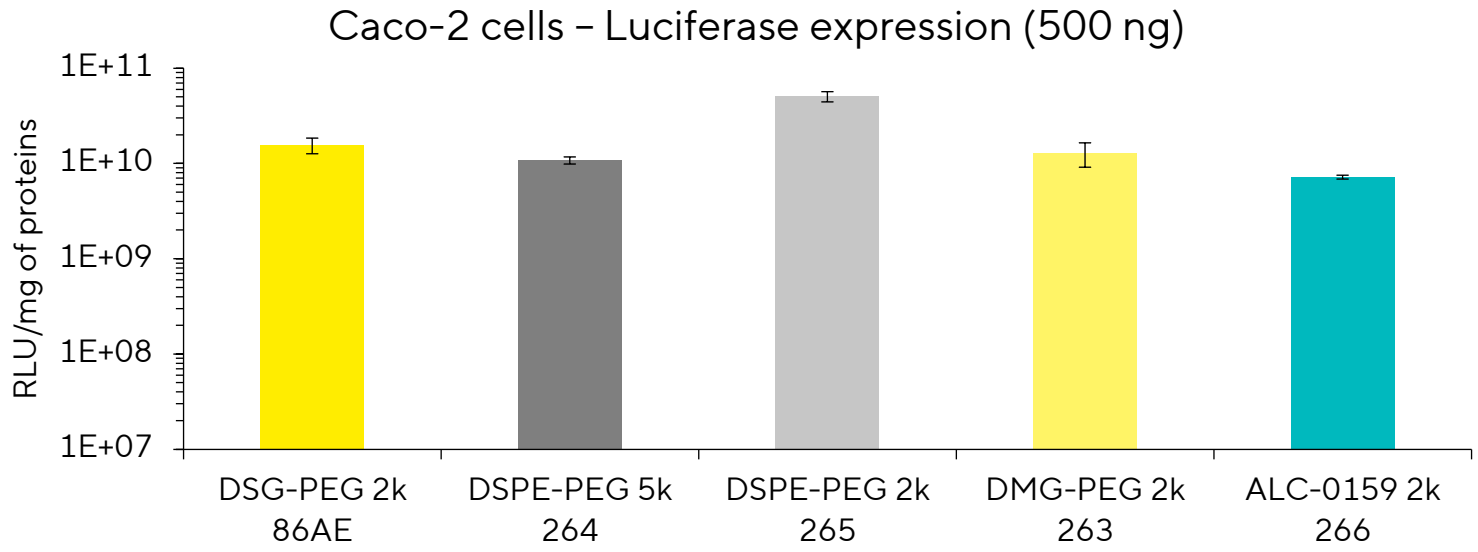
DPPC 

5-lipid LNP formulation



IM21.7c is suitable with Different PEGylated Lipids for LNP formulation

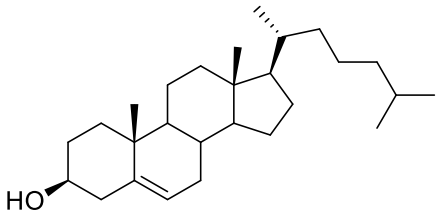
Cationic lipid (mM)	Ionizable lipid (mM)	Helper Lipid (mM)	Cholesterol (mM)	PEG-lipid (mM)		Size	PDI	Zeta	EE%
IM21.7c 4	DODMA 3	DPyPE 1	1.85	DSG-PEG$_{2k}$	0.15	75±5	0.050	+11	100
				DSPE-PEG$_{5k}$	0.15	61±4	0.082	+2	100
				DSPE-PEG$_{2k}$	0.15	85±3	0.056	+24	100
				DMG-PEG$_{2k}$	0.15	40±3	0.198	+18	100
				ALC-0159	0.15	36±6	0.216	+18	100



5-lipid LNP formulation

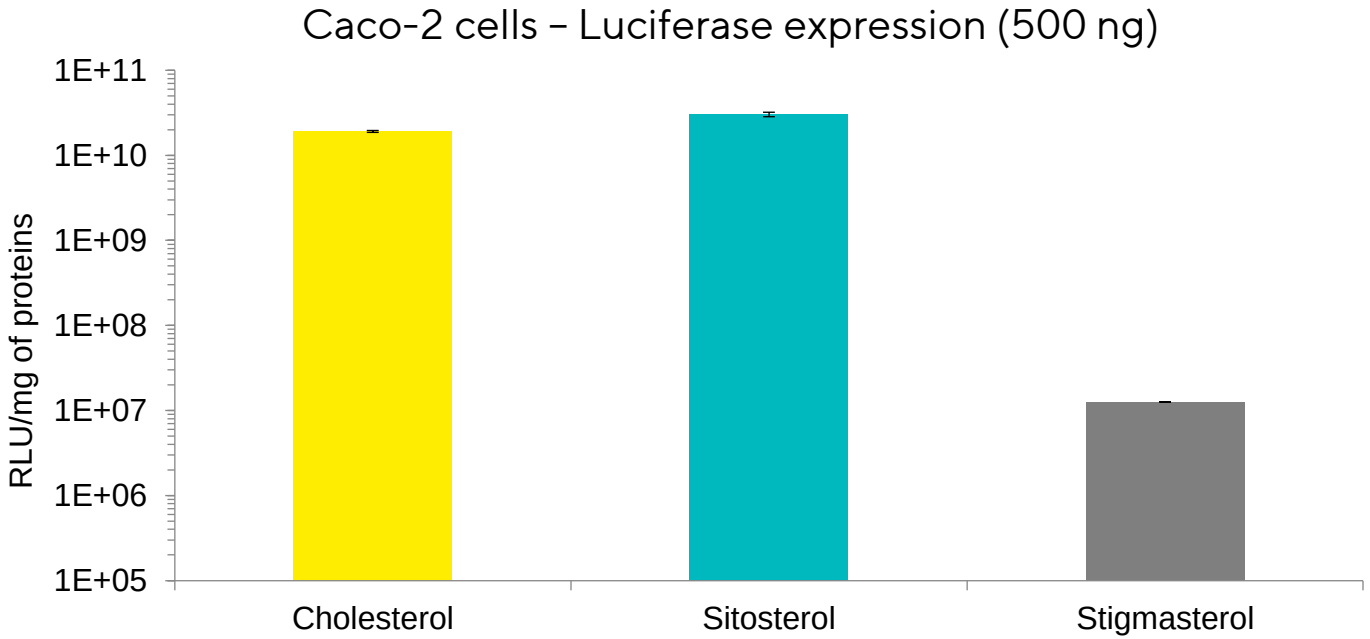
IM21.7c is suitable with different Sterols for LNP formulation

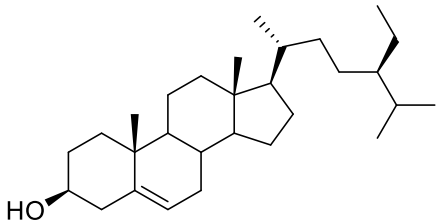
Cationic Lipid (mM)	Ionizable Lipid (mM)	Helper Lipid (mM)	Sterol (mM)		DSG-PEG$_{2k}$ (mM)	Size	PDI	Zeta	EE%
IM21.7c 4	DODMA 3	DPyPE 1	Cholesterol	1.85	0.15	55±3	0.152	+14	100
			β-sitosterol	1.85		77±9	0.163	+14	100
			Stigmasterol	1.85		**127±11**	0.177	+7	100



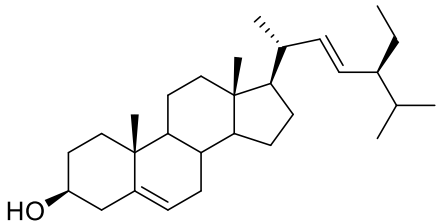
Cholesterol

5-lipid LNP formulation





β-sitosterol



Stigmasterol

Screening mRNA-LNP formulations

Table 1: Summary of CQAs for mRNA product development and manufacture (continued)

Attribute quality	CQA*	Justification of importance	Stage tested	Stage of manufacture (DS/DP)	Is CQA unique for RNA products?	Regulatory precedence?	Release and stability assay methods
Product characterization and quality	Encapsulation efficiency	Encapsulation protects the mRNA from degradation and stabilizes it, it is needed for delivery and efficacy, and is an important measure of quality	Stability/Release	DP	No	Yes	RP-LC-Fluorescence detection
	Surface charge	Surface charge affects the distribution of nanoparticles and affects performance and process consistency	Characterization	DP	No	Yes	ELS iCIEF TNS binding assay
	LNP size	Affects distribution and uptake of nanoparticles and impacts safety and efficacy	Stability/Release	DP	No	Yes	DLS (SR-DLS or RT-MALS in/online option) NTA
	LNP polydispersity	Polydispersity is a measure of the homogeneity and impacts safety and efficacy	Stability/Release	DP	No	Yes	DLS (SR-DLS or RT-MALS in/online option)

https://www.biophorum.com/news/an-industry-standard-for-mrna-lnp-analytics/

Screening mRNA-LNP formulations

Table 1: Summary of CQAs for mRNA product development and manufacture (continued)

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	Surface charge	Surface charge affects the distribution of nanoparticles and affects performance and process consistency	Characterization	DP	No	Yes	ELS iCIEF TNS binding assay
	LNP size	Affects distribution and uptake of nanoparticles and impacts safety and efficacy	Stability/Release	DP	No	Yes	DLS (SR-DLS or RT-MALS in/online option) NTA
	LNP polydispersity	Polydispersity is a measure of the homogeneity and impacts safety and efficacy	Stability/Release	DP	No	Yes	DLS (SR-DLS or RT-MALS in/online option)

EE%: > 95%

Zeta potential: 5-20 mV

Size: 25-100 nm

PDI: < 0.2

https://www.biophorum.com/news/an-industry-standard-for-mrna-lnp-analytics/

LipidBrick® library: mRNA-LNP characterization

Cationic / Ionizable lipid (mM)		Helper Lipid (mM)		Cholesterol (mM)	DSG-PEG (mM)
IMXX.Xc/DODMA	4/3	DPyPE	1	1.85	0.15

	IM21.7c	IM16c	IM13c	IM15c	IM22c	IM12c	IM25c	IM3c
Size (nm)	45 ± 2	56 ± 3	74 ± 4	66 ± 6	40 ± 2	29 ± 1	86 ± 2	41 ± 2
Zeta (mV)	+10	+13	+11	+9	+14	+12	+10	+16
PDI	0.158	0.132	0.090	0.113	0.140	0.120	0.053	0.104
EE (%)	99	99	99	99	99	99	99	99

Results confirmed in 4-lipid LNP formulation.

Screening mRNA-LNP formulations

Table 1: Summary of CQAs for mRNA product development and manufacture (continued)

Attribute quality	CQA*	Justification of importance	Stage tested	Stage of manufacture (DS/DP)	Is CQA unique for RNA products?	Regulatory precedence?	Release and stability assay methods
Product characterization and quality	Encapsulation efficiency	Encapsulation protects the mRNA from degradation and stabilizes it, it is needed for delivery and efficacy, and is an important measure of quality	Stability/Release	DP	No	Yes	RP-LC-Fluorescence detection
	Surface charge	Surface charge affects the distribution of nanoparticles and affects performance and process consistency	Characterization	DP	No	Yes	ELS iCIEF TNS binding assay
	LNP size	Affects distribution and uptake of nanoparticles and impacts safety and efficacy	Stability/Release	DP	No	Yes	DLS (SR-DLS or RT-MALS in/online option) NTA
	LNP polydispersity	Polydispersity is a measure of the homogeneity and impacts safety and efficacy	Stability/Release	DP	No	Yes	DLS (SR-DLS or RT-MALS in/online option)
	Lipid content	Lipid content impacts function of the DP	Stability/Release	DP	No	Yes	LC-CAD LC-ELSD

Quantification by BIA experts

https://www.biophorum.com/news/an-industry-standard-for-mrna-lnp-analytics/

Lipid quantification (preliminary results)

	Theoretical mass%	Measured mass%	Starting mass	Mass yield
IM21.7c	63.0%	66.5%	1.802 mg	1.515 mg
Cholesterol	21.1%	18.2%	0.603 mg	0.418 mg
DOPE	10.5%	11.0%	0.301 mg	0.257 mg
PEG-DMG 2K	5.3%	4.3%	0.152 mg	0.099 mg

Data generated by Sartorius BIA Separations.

Analysis was done on a PATfix™ system with an ELSD detector, using a monolithic CIMac™ C4 HLD-0.1 Analytical Column (2 µm).

Mass yield is 84%, not a lot of lipids are lost.

Ratio are slightly different in favour of the cationic lipid and the DOPE.

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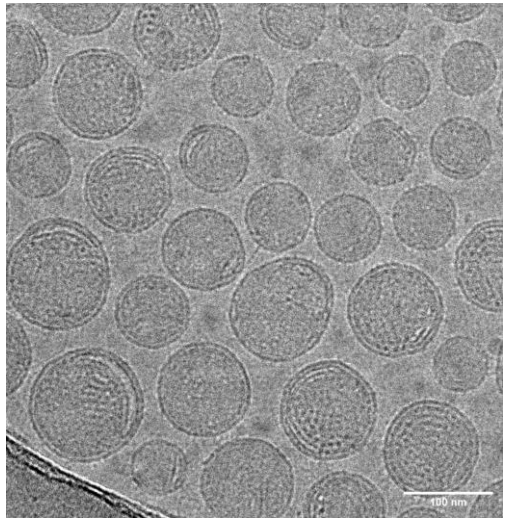
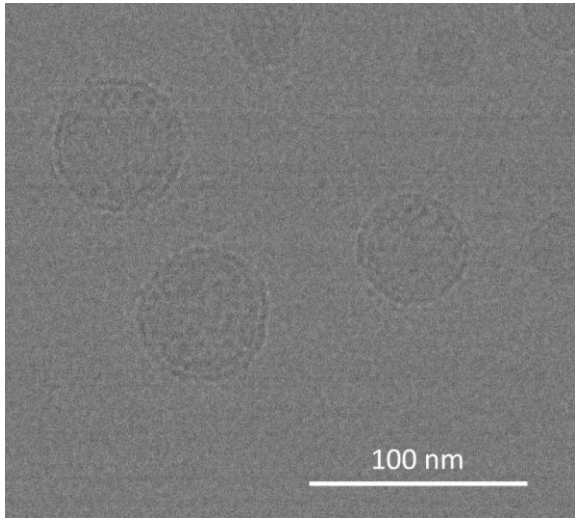
LipidBrick® enables to formulate mRNA-LNPs

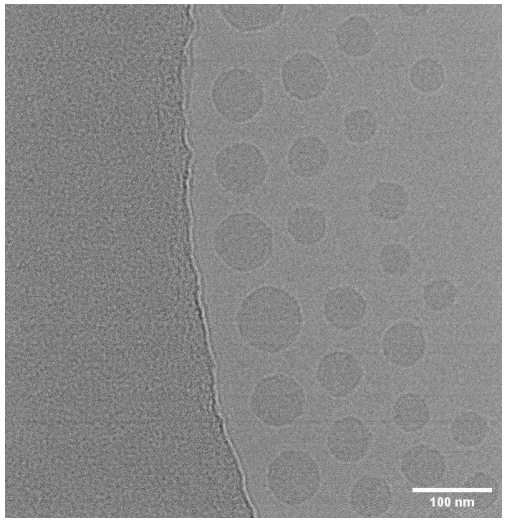
4-lipids LNP IM21.7c



5-lipids LNP IM21.7c



SM-102 LNP (Moderna)

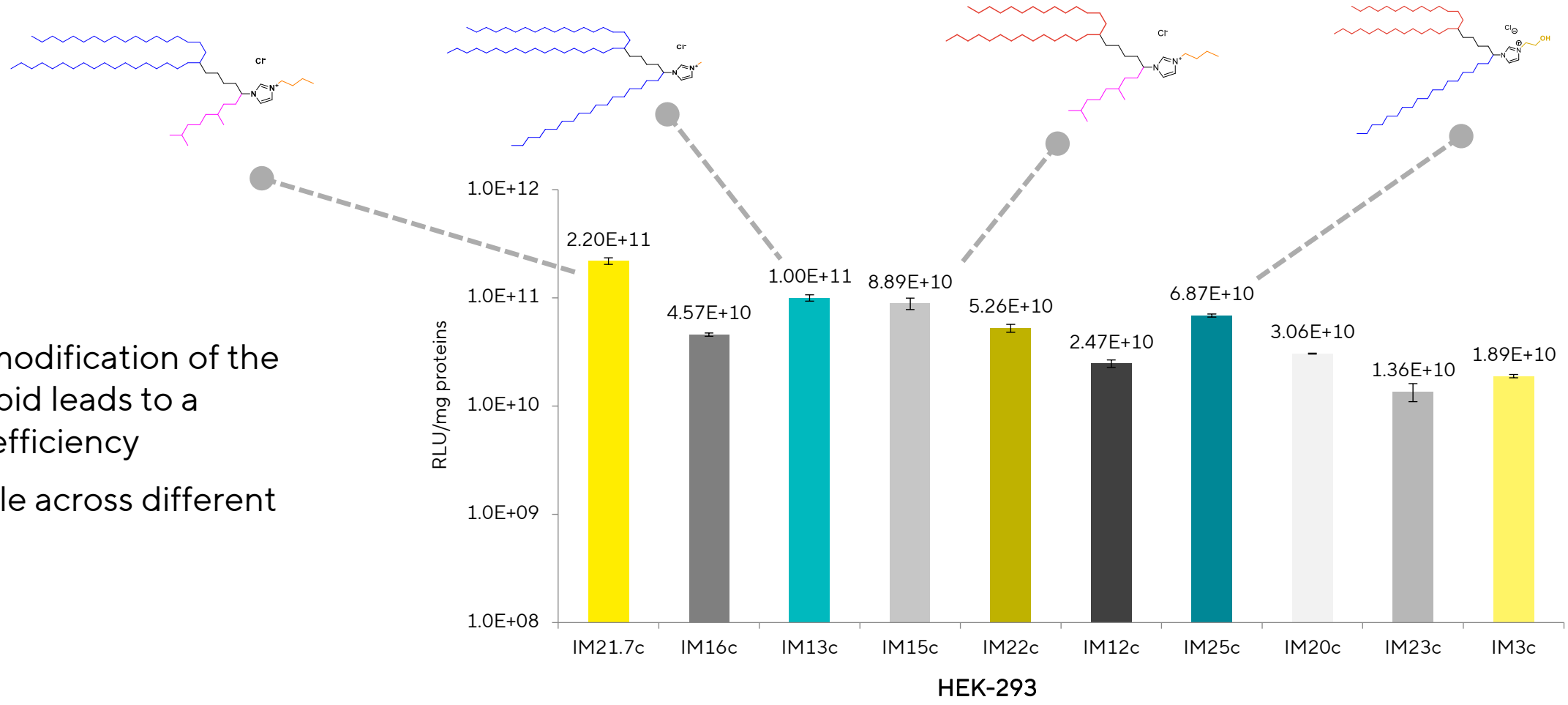


CryoTEM images

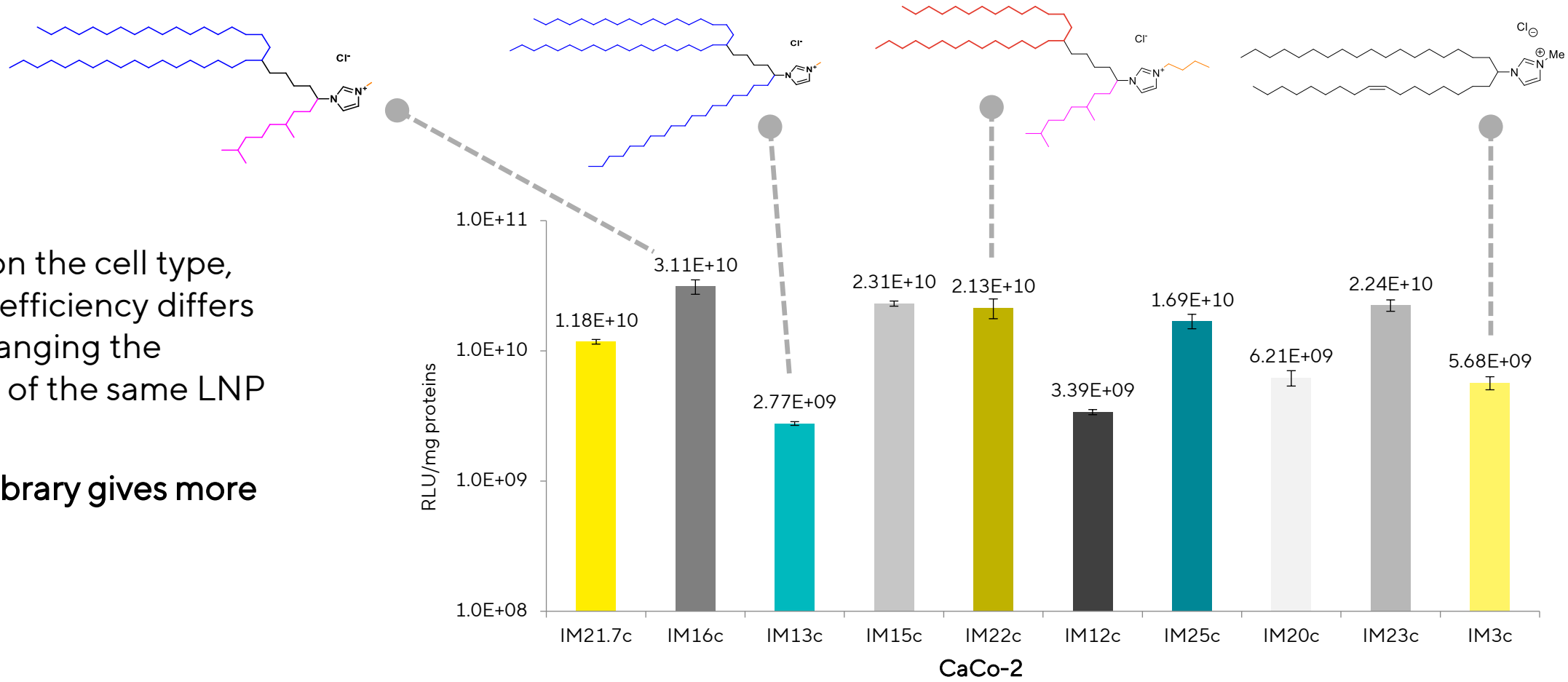
Get Beyond the Liver with LipidBrick®

LipidBrick® Library Offers Consistent Efficiency & Flexibility

- The sole modification of the cationic lipid leads to a different efficiency
- Repeatable across different cell lines



LipidBrick® Library Offers Consistent Efficiency & Flexibility



- Depending on the cell type, transfection efficiency differs simply by changing the cationic lipid of the same LNP formulation
- **LipidBrick® library gives more options**

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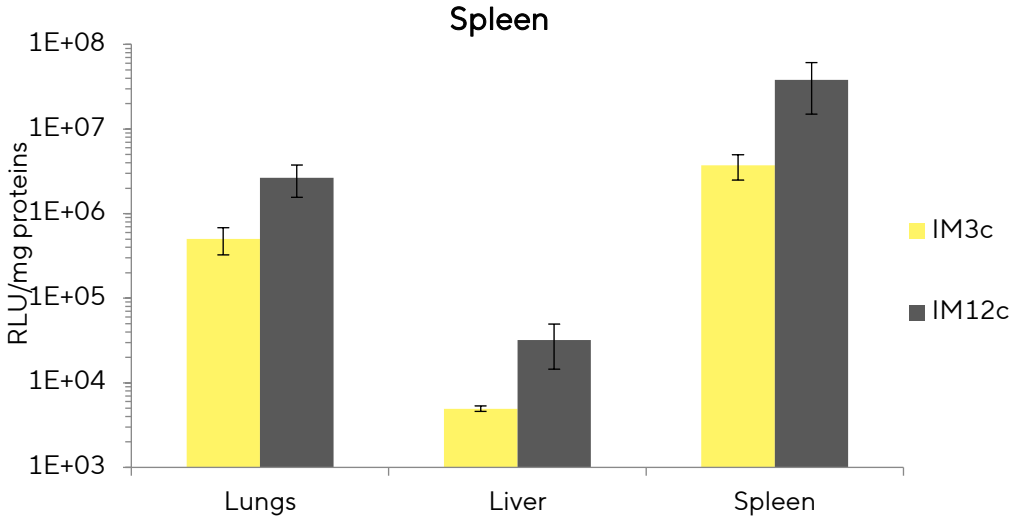
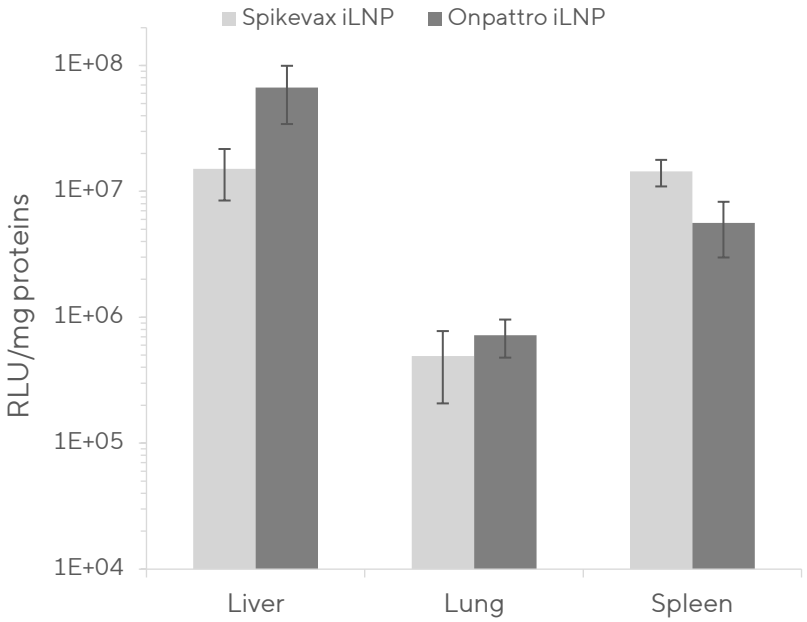
Adapt LNP Tropism to Your Specific Application with LipidBrick® Library

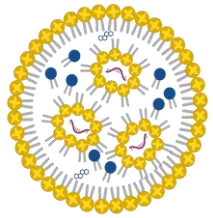


- Deliver RNA to different organs while **bypassing liver**
- Enhance the efficacy of LNPs by **fine-tuning formulations** around a specific LipidBrick® (here IM21.7c)
- **LipidBrick® Library provides new delivery options for RNA-based therapeutics & vaccines**

Get Beyond the Liver with LipidBrick® (in 4- or 5-lipid LNP conformation)

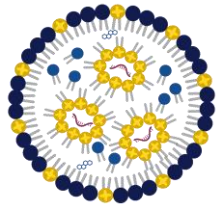


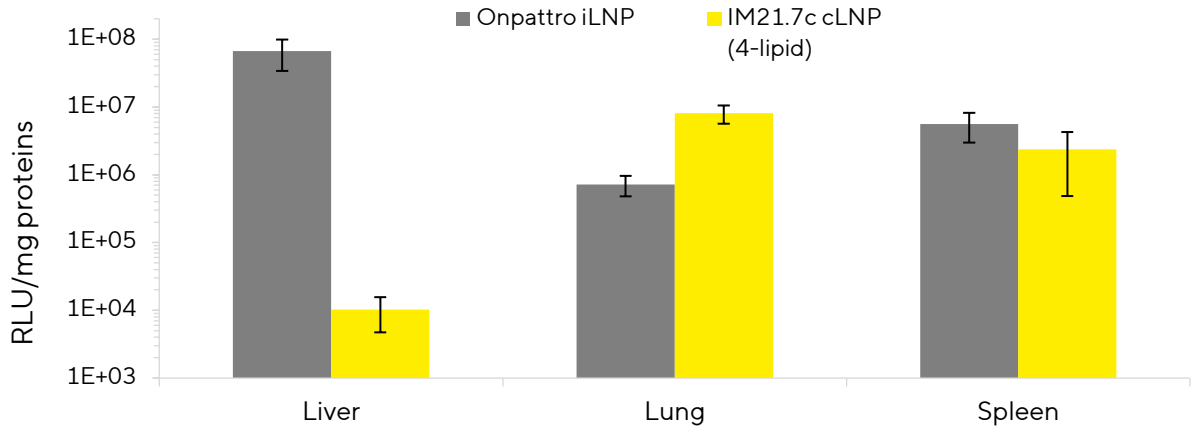
After IV injection with 10 µg FLuc mRNA LNPs

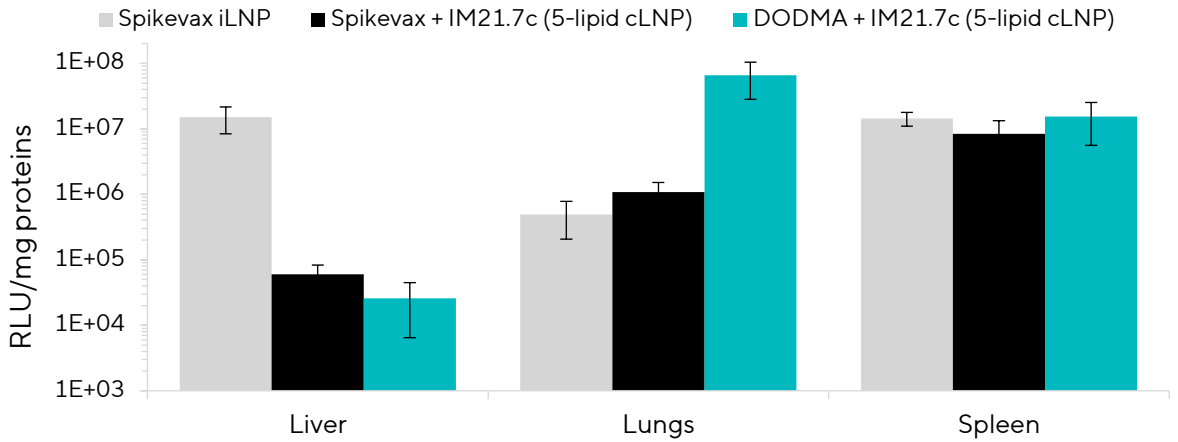


Replace ionizable lipid by LipidBrick®

Add LipidBrick® as 5th lipid

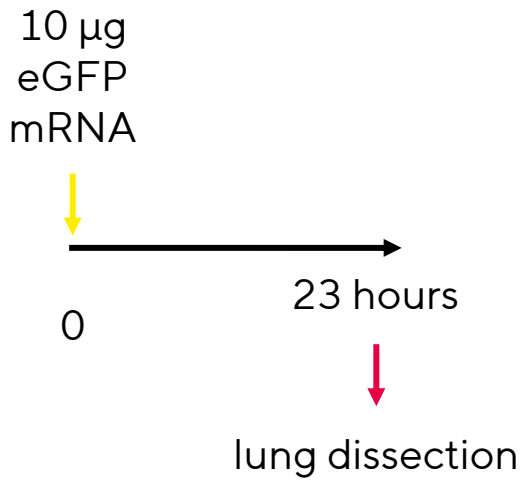




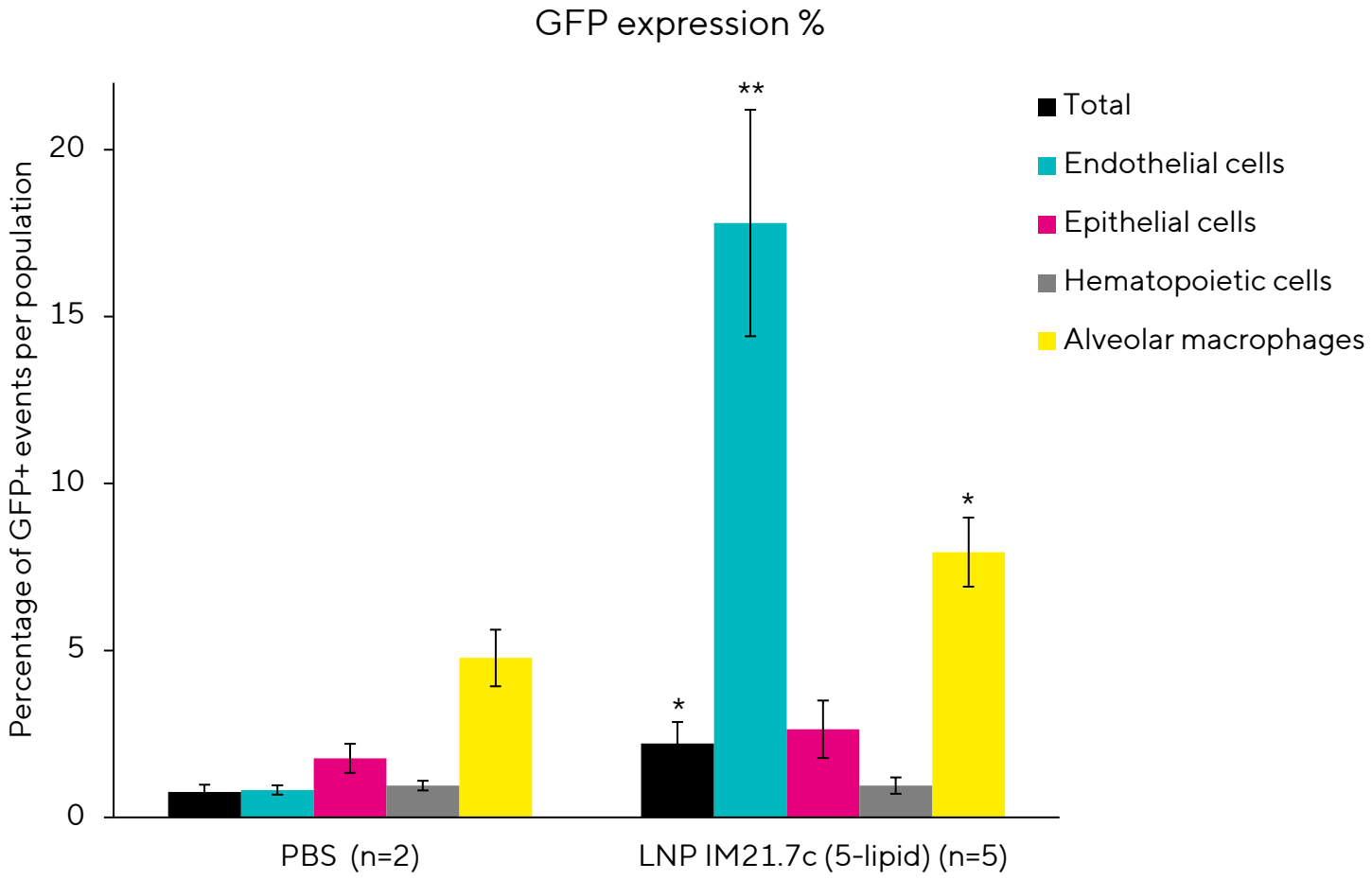


IM21.7c-LNPs mainly targets endothelial cells and alveolar macrophages

Retro-orbital injection



- Interesting for treatments for lung respiratory diseases

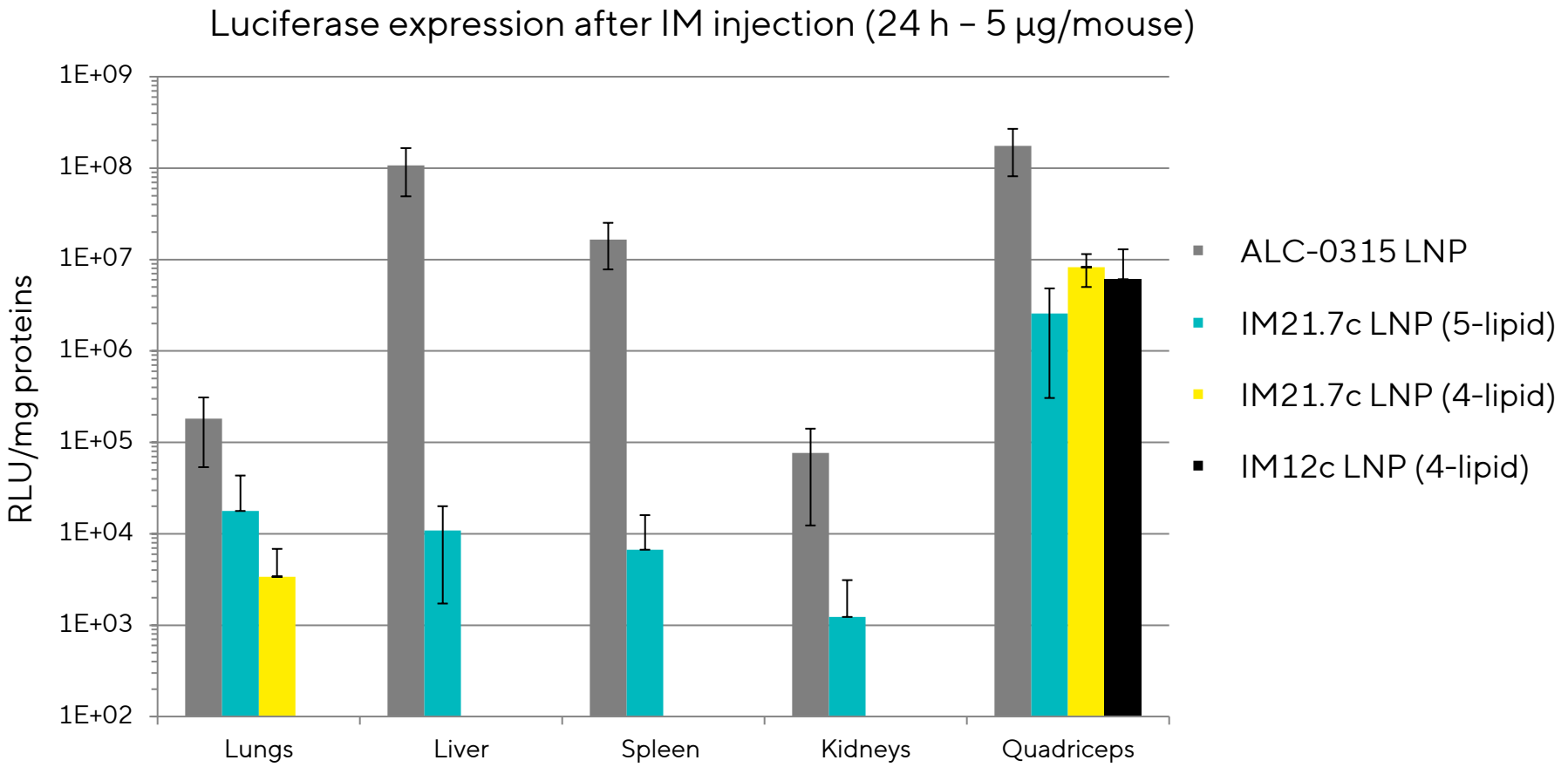


Unpaired t test *p<0.5 and **p<0.01

Reduce Liver Off-Target Effects with LipidBrick®

Intramuscular injection

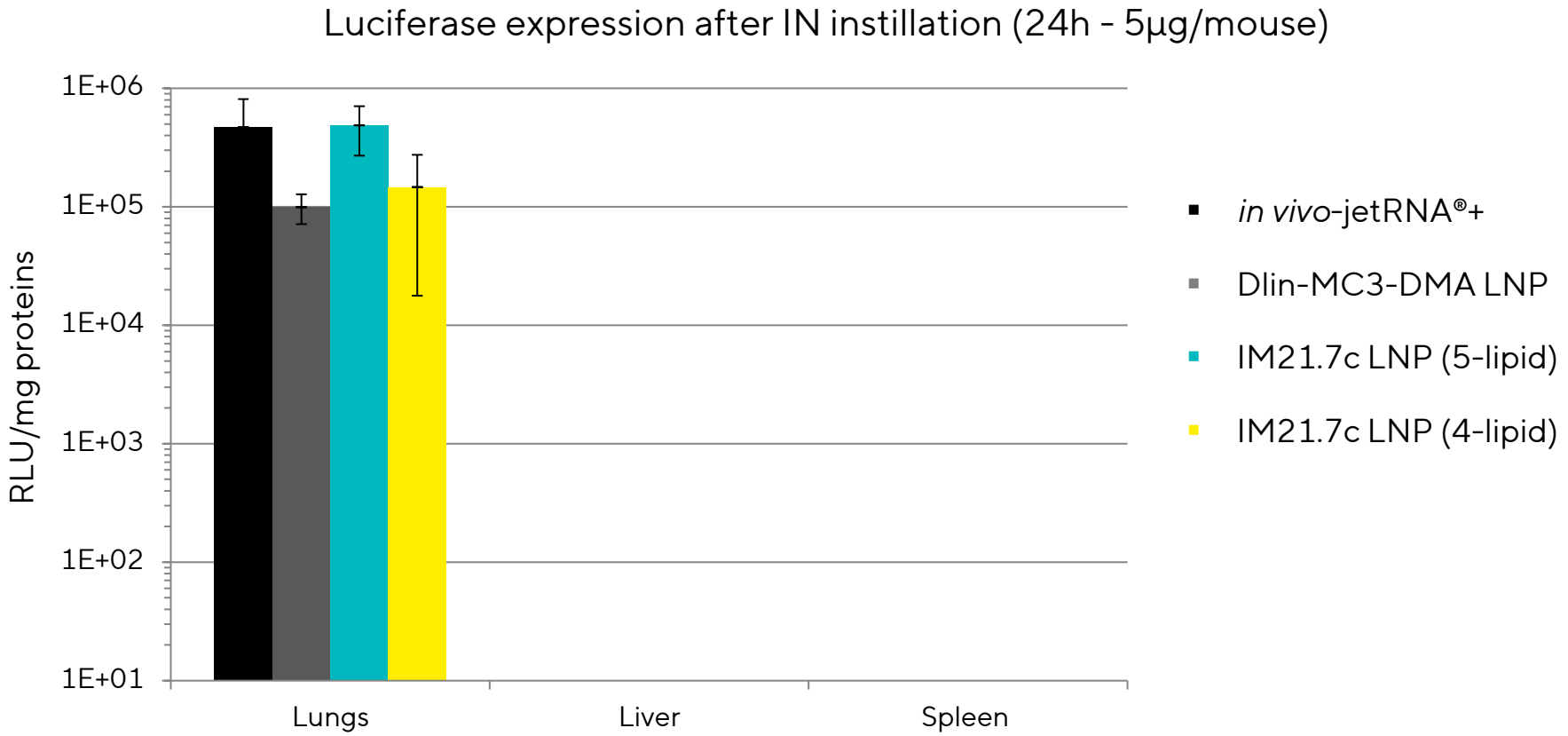
- Precise local targeting
- Reduced Side Effects
- Immune Resp. Management
- Interesting for oncology, vaccination, local gene editing or protein replacement, tissue regeneration



Transfect the Lungs Efficiently using LipidBrick® via Intranasal Instillation

Intranasal instillation

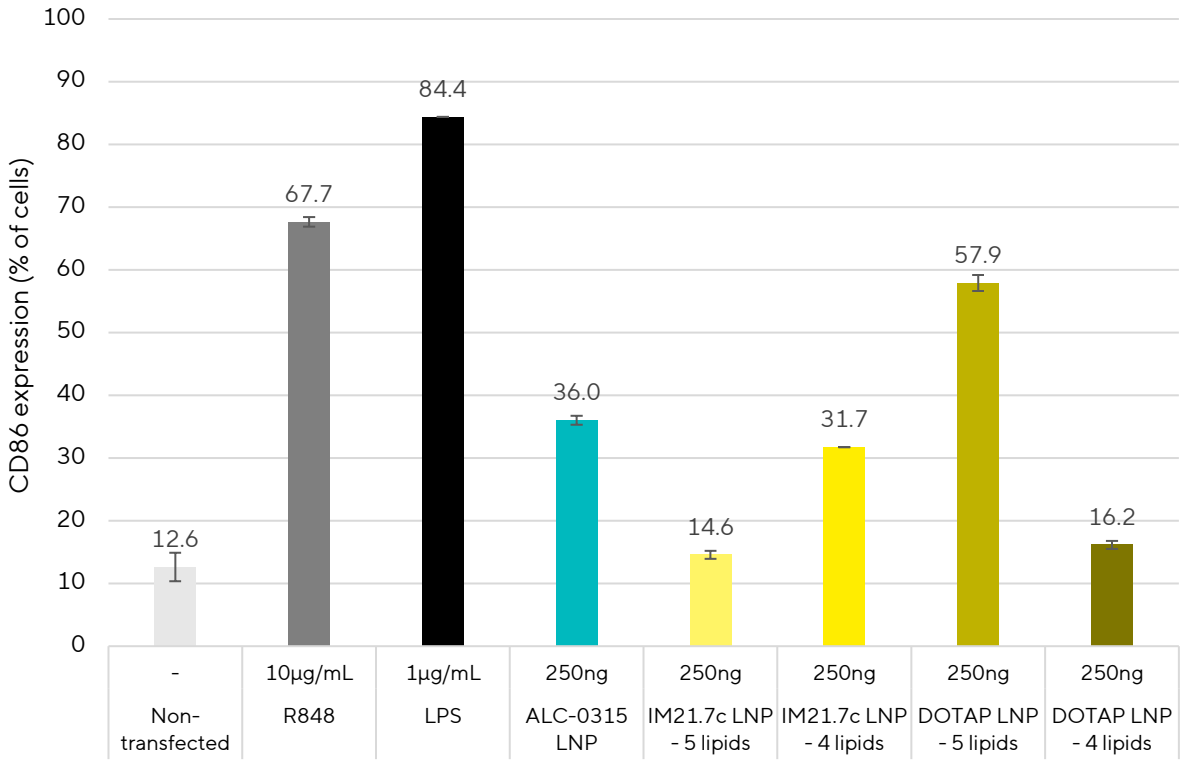
- Interesting for treatments for cystic fibrosis



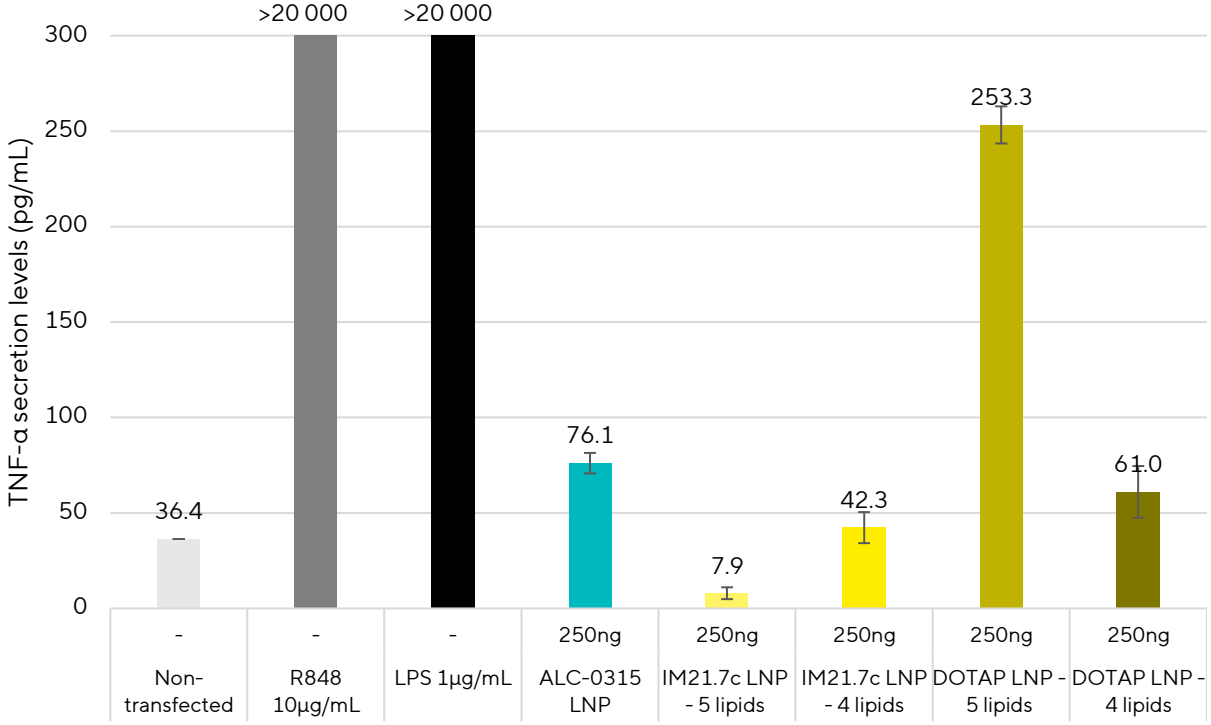
LipidBrick®-LNPs are safe & weakly immunogenic

IM21.7c-LNPs triggers low activations of primary human moDCs *in vitro*

CD86 expression 24h after *in vitro* stimulation of moDCs

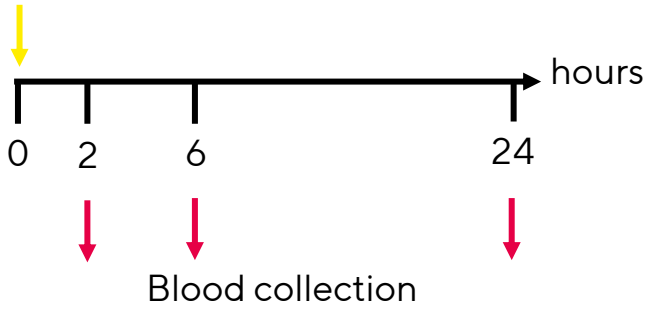


TNFα secretion 24h after *in vitro* stimulation of moDCs



LipidBrick®-LNPs triggers the same low cytokine profile as ALC-0315 LNPs

IV injection
CleanCap® Fluc mRNA (5moU); 10µg



Cationic/Ionizable lipid (mM)		*Helper lipid (mM)*		*Cholesterol (mM)*	*PEG lipid (mM)*	
*LNP **LipidBrick®** 5-lipid **(IMXXc/DODMA)***	*4/3*	*DPyPE*	*1*	*1.85*	*DSG-PEG_{2k}*	*0.15*

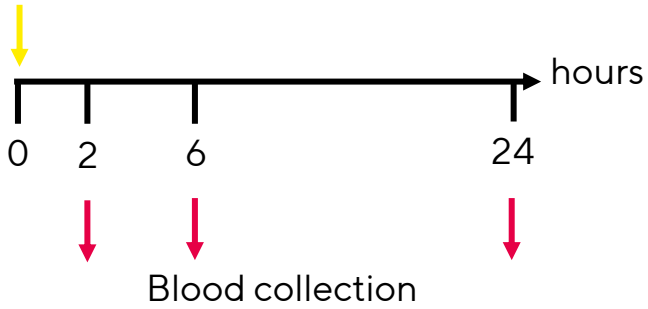
Average (N=6 mice)			PBS			LPS			LNP BNT			LNP with LipidBrick® IM21.7c			LNP with LipidBrick® IM12		
Function	Method	Cytokine	2 h	6 h	24 h	2 h	6 h	24 h	2 h	6 h	24 h	2 h	6 h	24 h	2 h	6 h	24 h
Pro-inflammation Innate & Adaptative immunity Anti-viral and anti-tumoral activities Cytokine release	MACSPlex	**IFN-γ**															
Pro-inflammation Cytokine release Cell proliferation Cell Proliferation & Apoptosis Anti-viral and anti-tumoral activities	MACSPlex	**TNF-α**															
Pro-inflammation Macrophage activation Increase neutophil & monocyte function	MACSPlex	**GM-CSF**															
Pro-inflammation	ELISA	**IL-1α**															
Pro-inflammation Cell Proliferation & Apoptosis	ELISA	**IL-1β**															
Regulate T-cell proliferation and differentiation	MACSPlex	**IL-2**															
Anti-inflammation T-cell & B-cell proliferation & differentiation	MACSPlex	**IL-4**															
Pro-inflammation B-cell differentiation Eosinophil activation	MACSPlex	**IL-5**															
Pro-inflammation Differentiation Cytokine release	ELISA	**IL-6**															
Anti-inflammation Inhibition of pro-inflammatory cytokines Immunoregulation	MACSPlex	**IL-10**															
Pro-inflammation Cell differentation Activates NK cells Regulates T-cell & B-cell cooperation	MACSPlex	**IL-12**															
Pro-inflammation	MACSPlex	**IL-17A**															
Pro-inflammation	MACSPlex	**IL-23**															

Legend in pg/mL
> 10^4
10^3 - 10^4
201-1000
51-200
0-50

LipidBrick®-LNPs triggers the same low cytokine profile as ALC-0315 LNPs

Intramuscular injection

CleanCap® Fluc
mRNA (5moU); 5 µg



Cationic/Ionizable lipid (mM)		*Helper lipid (mM)*		*Cholesterol (mM)*	*PEG lipid (mM)*	
*LNP **LipidBrick®** 4-lipid*	*5*	*DOPE*	*1*	*1.85*	*$DMG\text{-}PEG_{2k}$*	*0.15*

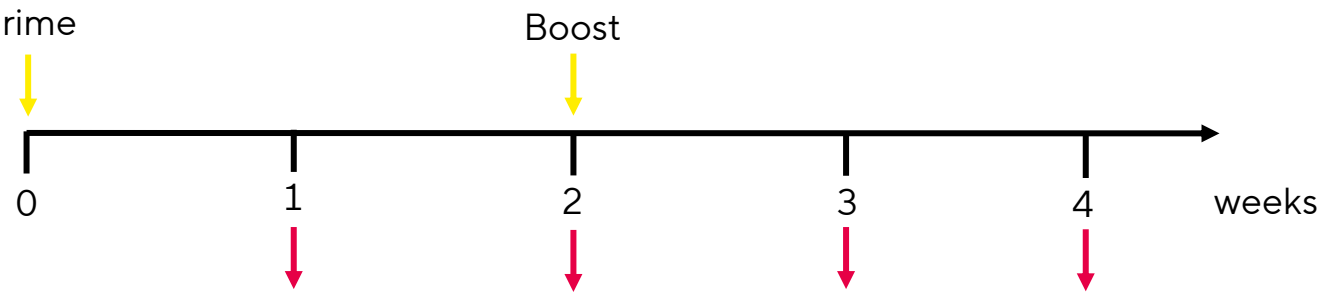
Average (N=6)			LNP BioNTech ALC-0315			LNP LipidBrick® IM21.7c 5-lipid			LNP LipidBrick® IM21.7c 4-lipid			LNP LipidBrick® IM12c 5-lipid		
Function	Method	Cytokine	2h	6h	24h	2h	6h	24h	2h	6h	24h	2h	6h	24h
Pro-inflammation Innate & Adaptative immunity Anti-viral and anti-tumoral activities Cytokine release	MACSPlex	**IFN-γ**												
Pro-inflammation Cytokine release Cell proliferation Cell Proliferation & Apoptosis Anti-viral and anti-tumoral activities	MACSPlex	**TNF-α**												
Pro-inflammation Macrophage activation Increase neutophil & monocyte function	MACSPlex	**GM-CSF**												
Pro-inflammation	ELISA	**IL-1α**												
Pro-inflammation Cell Proliferation & Apoptosis	ELISA	**IL-1β**												
Regulate T-cell proliferation and differentiation	MACSPlex	**IL-2**												
Anti-inflammation T-cell & B-cell proliferation & differentiation	MACSPlex	**IL-4**												
Pro-inflammation B-cell differentiation Eosinophil activation	MACSPlex	**IL-5**												
Pro-inflammation Differentiation Cytokine release	ELISA	**IL-6**												
Anti-inflammation Inhibition of pro-inflammatory cytokines Immunoregulation	MACSPlex	**IL-10**												
Pro-inflammation Cell differentation Activates NK cells Regulates T-cell & B-cell cooperation	MACSPlex	**IL-12**												
Pro-inflammation	MACSPlex	**IL-17A**												
Pro-inflammation	MACSPlex	**IL-23**												

Legend in pg/ml

- $> 10^4$
- 10^3 - 10^4
- 201-1000
- 51-200
- 0-50

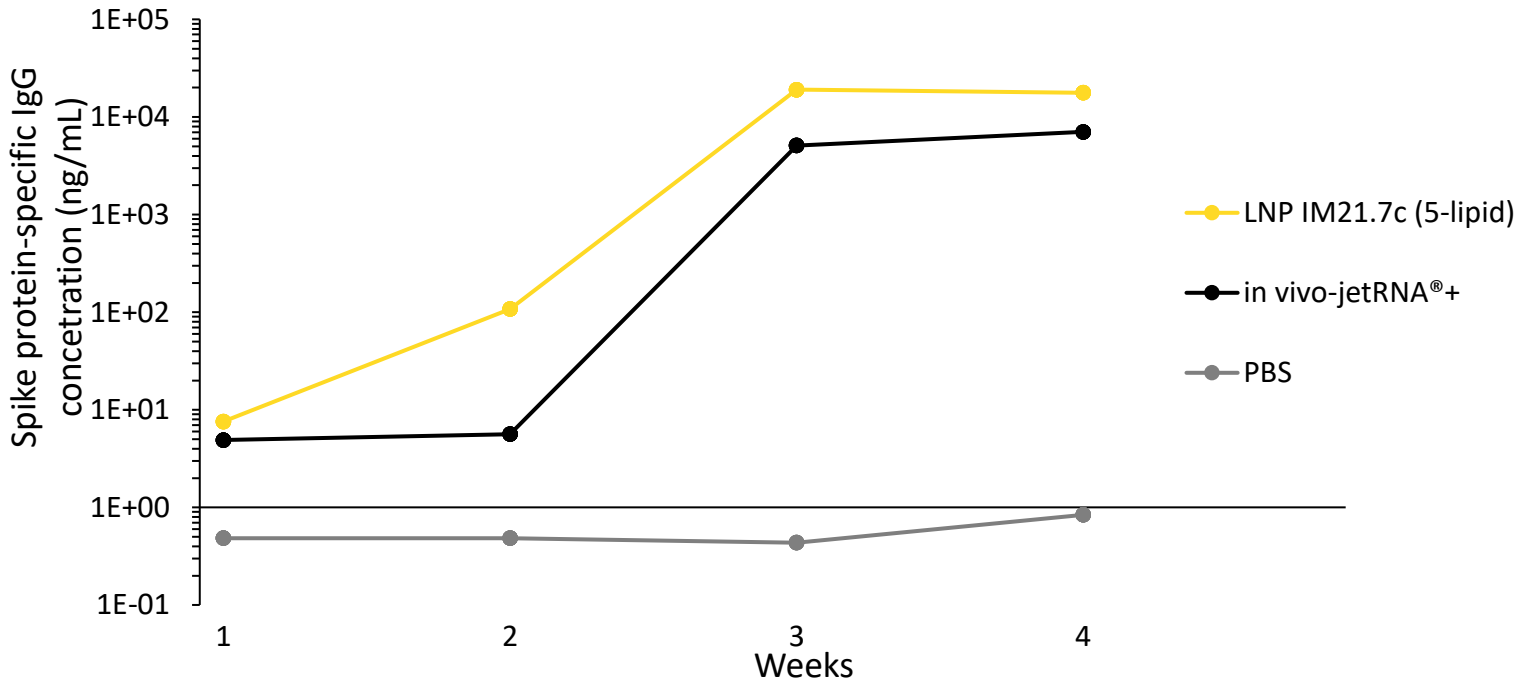
LipidBrick® for Vaccination & Immunisation

IM21.7c-based LNPs lead to strong humoral immune response



IM injection
SARS-CoV-2 mRNA (5 µg)

Bleed



Cationic/Ionizable lipid (mM)		*Helper lipid (mM)*		*Cholesterol (mM)*	*PEG lipid (mM)*	
*LNP **LipidBrick®** 5-lipid **(IM21.7c/DODMA)***	*4/3*	*DPyPE*	*1*	*1.85*	*DSG-PEG_{2k}*	*0.15*

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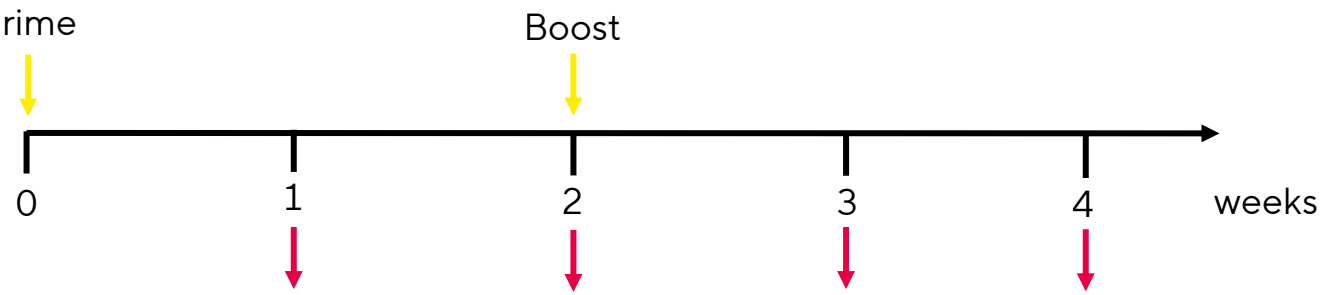
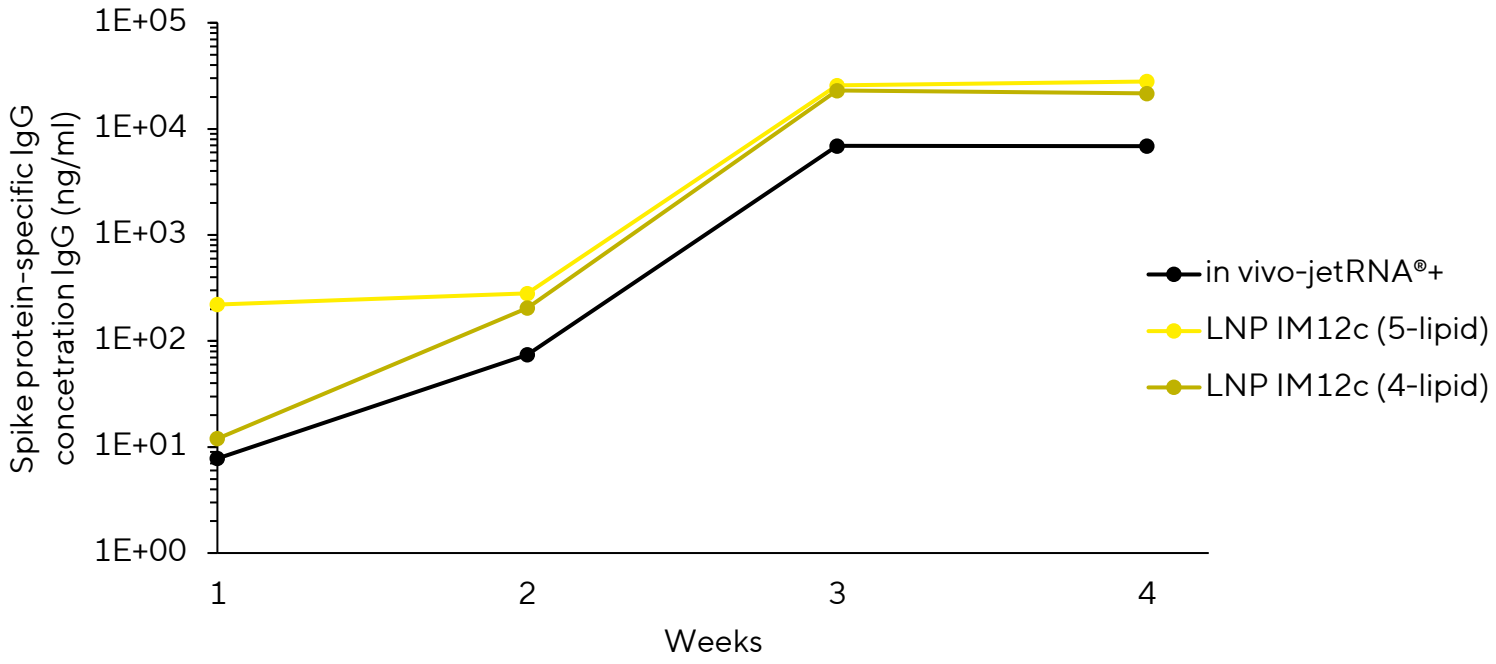
IM12c-based LNPs lead to strong humoral immune response



IM injection
SARS-CoV-2 mRNA (5 µg)

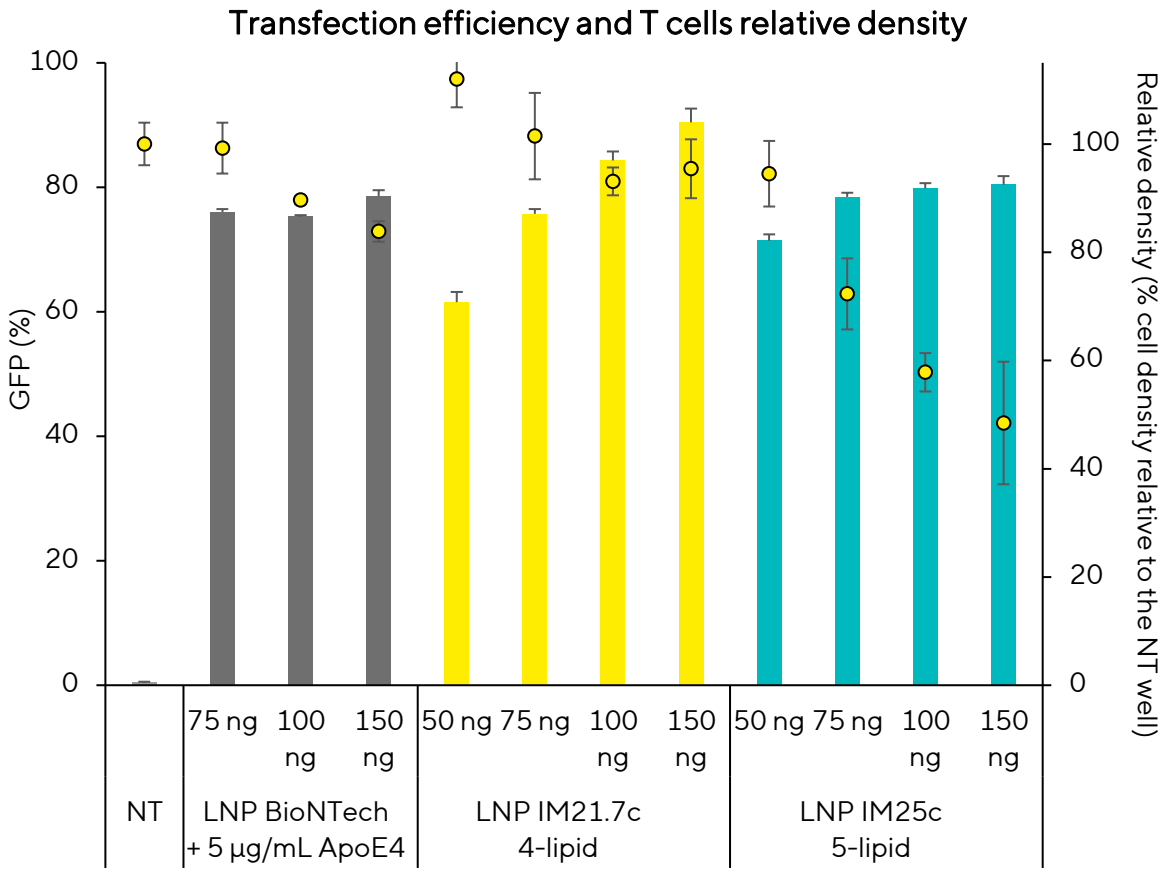
Bleed

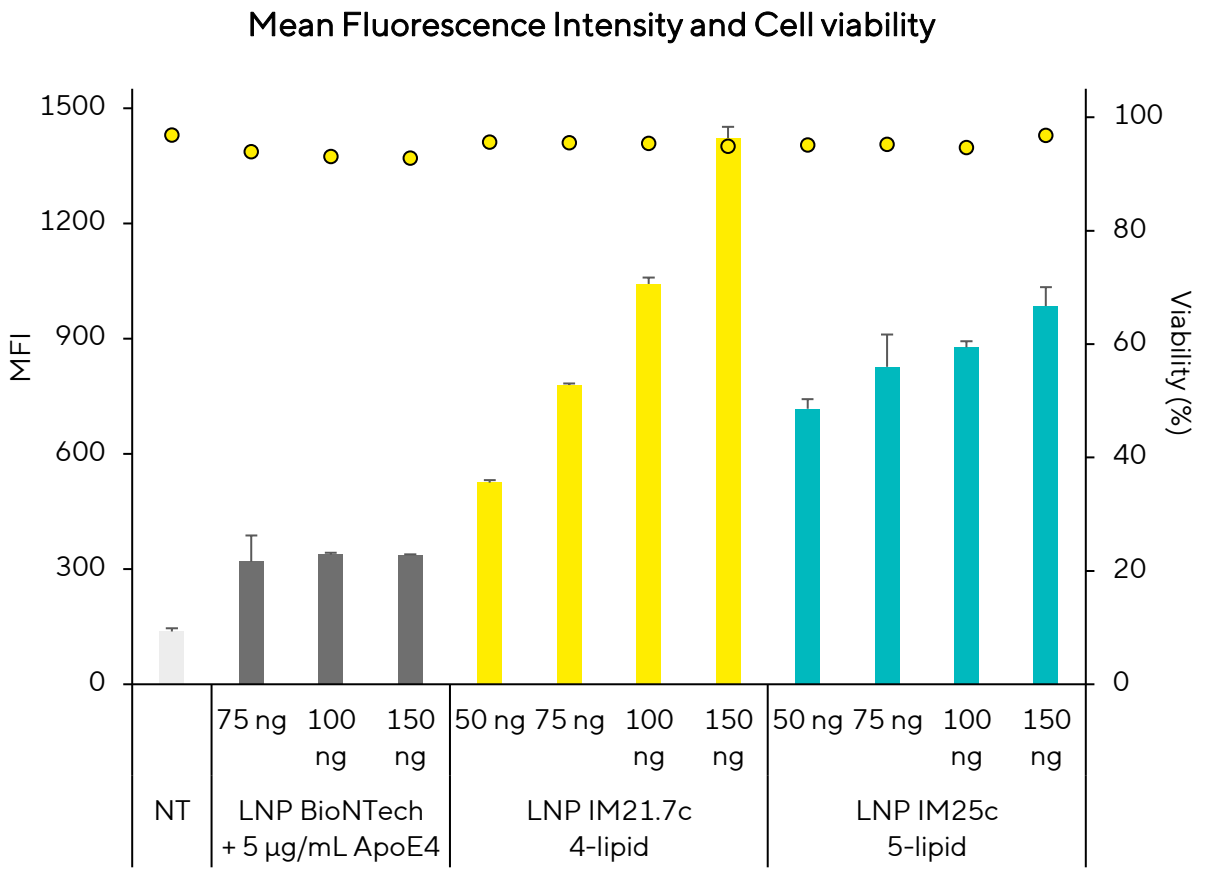
Cationic/Ionizable lipid (mM)		*Helper lipid (mM)*		*Cholesterol (mM)*	*PEG lipid (mM)*	
*LNP **LipidBrick®** 5-lipid **(IM12c/DODMA)***	*4/3*	*DPyPE*	*1*	*1.85*	*DSG-PEG_{2k}*	*0.15*
*LNP **LipidBrick®** 4-lipid **(IM12c)***	*5*	*DOPE*	*1*	*3.85*	*DMG-PEG_{2k}*	*0.15*



LipidBrick® for *Ex Vivo* Cell Therapy

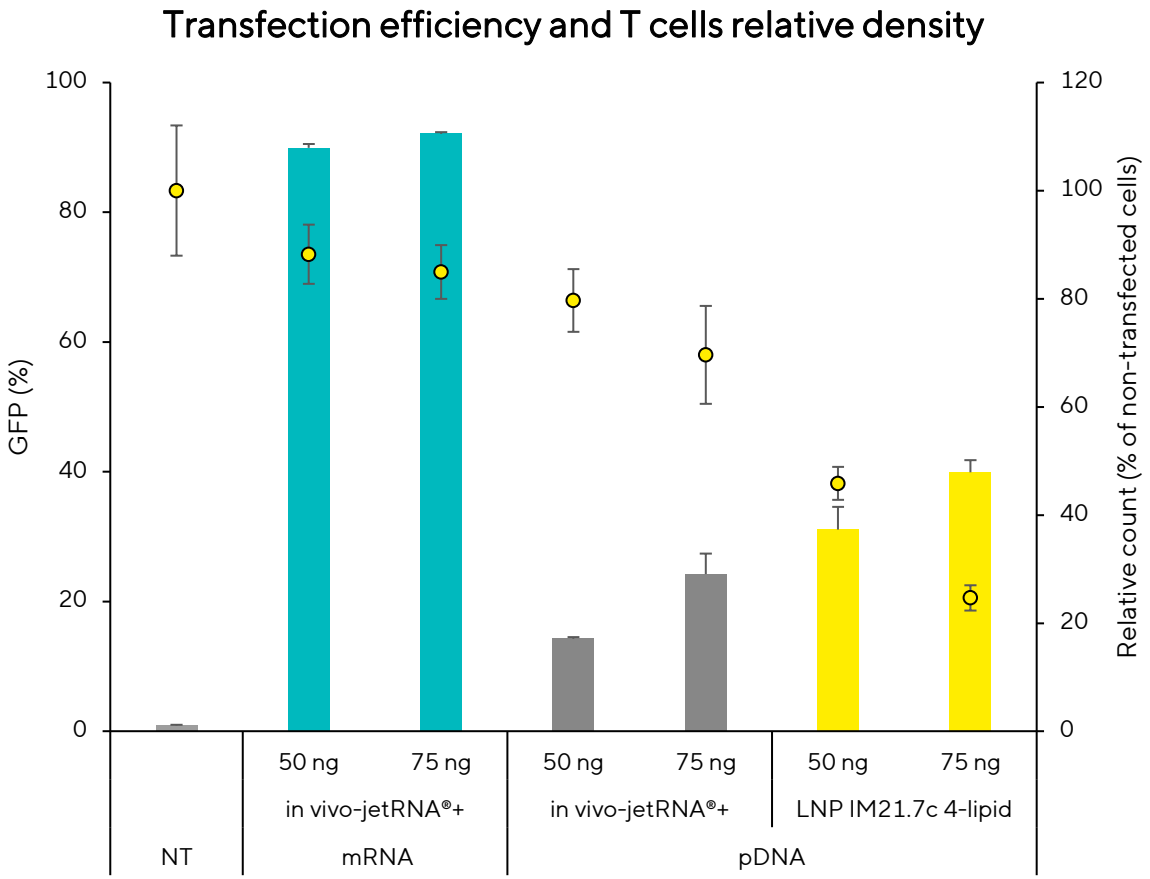
Reach High Ex Vivo Delivery Efficacy & Viability with IM21.7c & IM25c-LNPs on Human Primary T cells

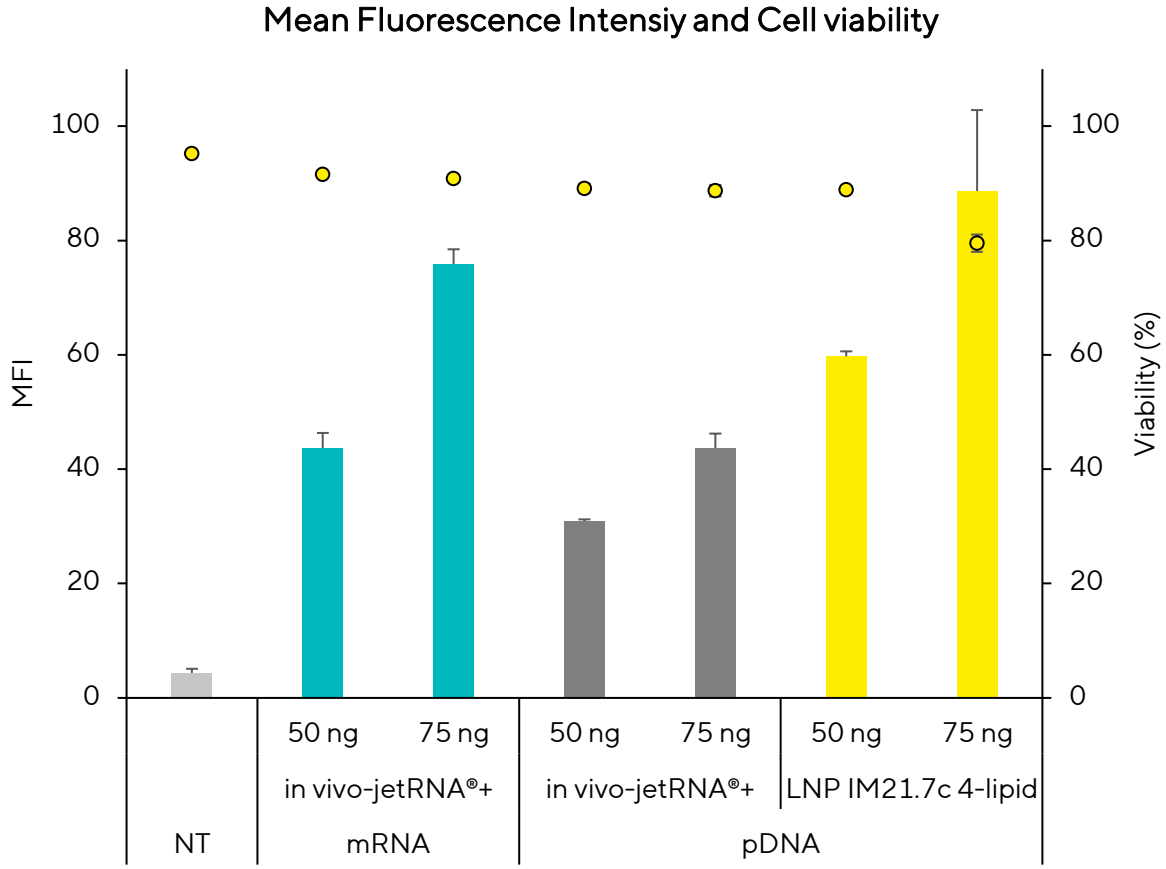




Results obtained after 48 hours; LipidBrick-LNPs do not require ApoE supplementation
Dedicated 4-lipid LNP formulation + Optimized Ex vivo T cells protocol available

IM21.7c-LNPs lead to Efficient DNA Transfection of Primary T cells





Results obtained after 48 hours; LipidBrick-LNPs do not require ApoE supplementation

Dedicated 4-lipid LNP formulation + Optimized Ex vivo T cells protocol

Cationic/Ionizable lipid (mM)		*Helper Lipid (mM)*		*Cholesterol (mM)*	*PEG lipid (mM)*	
*LNP **IM21.7c** 4-lipid*	*2*	*DOPE*	*3*	*4.85*	*$DMG\text{-}PEG_{2k}$*	*0.15*

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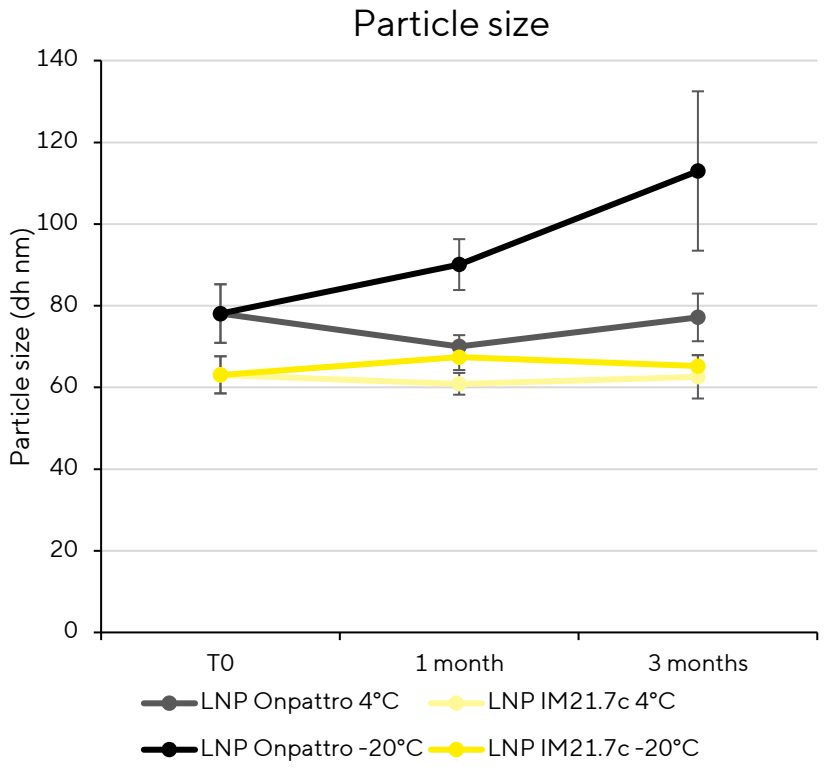
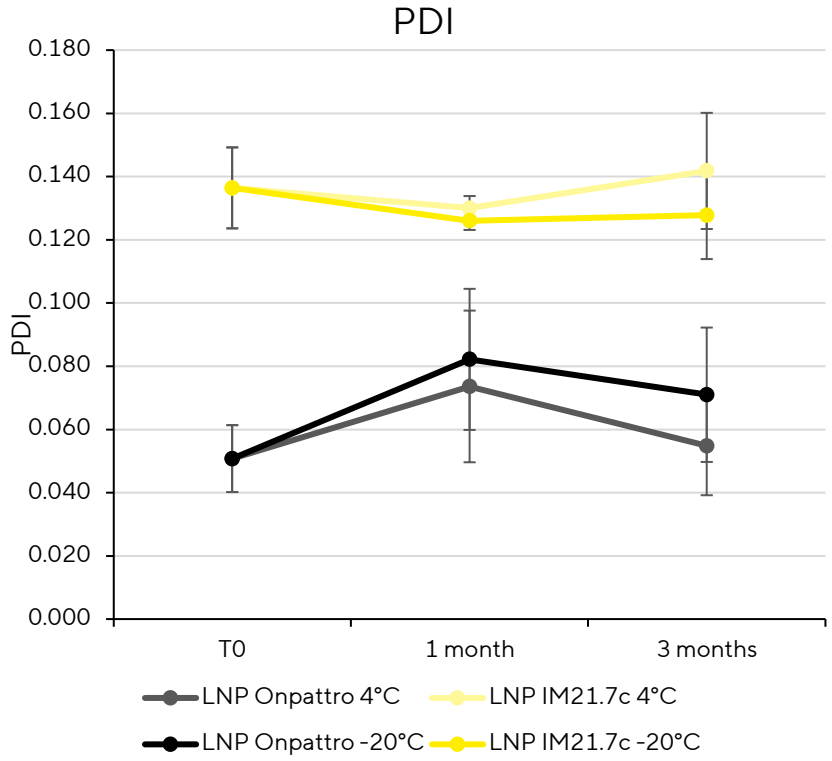
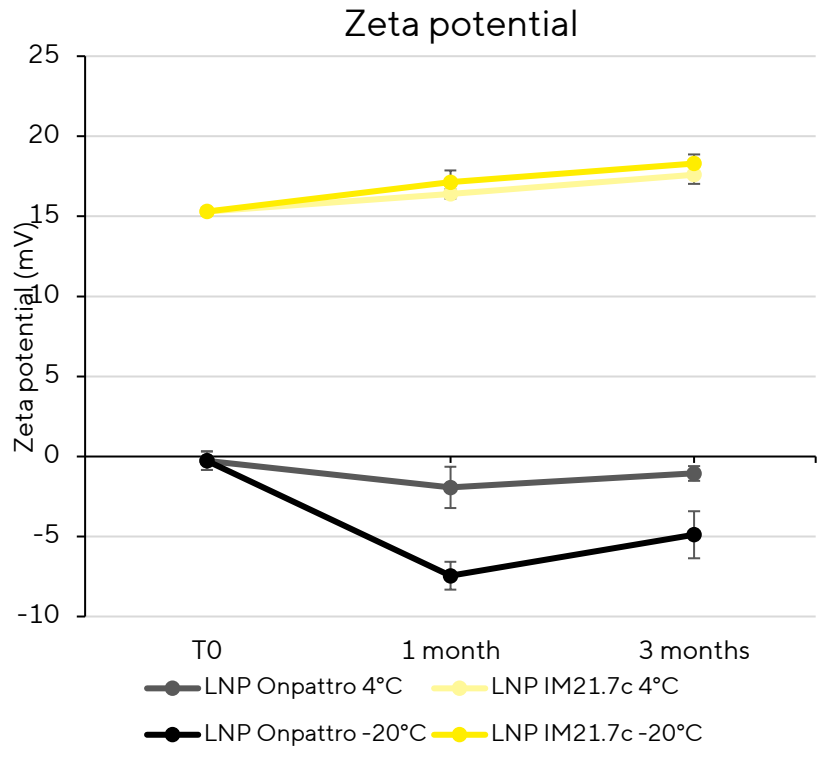
IM21.7c-LNPs are Stable

IM21.7c-LNPs maintain Size, PDI & zeta potential stable for ≥3 months at 4°C & -20°C







4-lipid LNP formulation

Buffer containing sucrose

Cationic/Ionizable lipid (mM)		*Helper Lipid (mM)*		*Cholesterol (mM)*	*PEG lipid (mM)*	
LNP Onpatto (Dlin-MC3)	*5*	*DSPC*	*1*	*3.85*	*DMG-PEG$_{2k}$*	*0.15*
*LNP **LipidBrick® IM21.7c***	*5*	*DOPE*	*1*	*3.85*	*DMG-PEG$_{2k}$*	*0.15*

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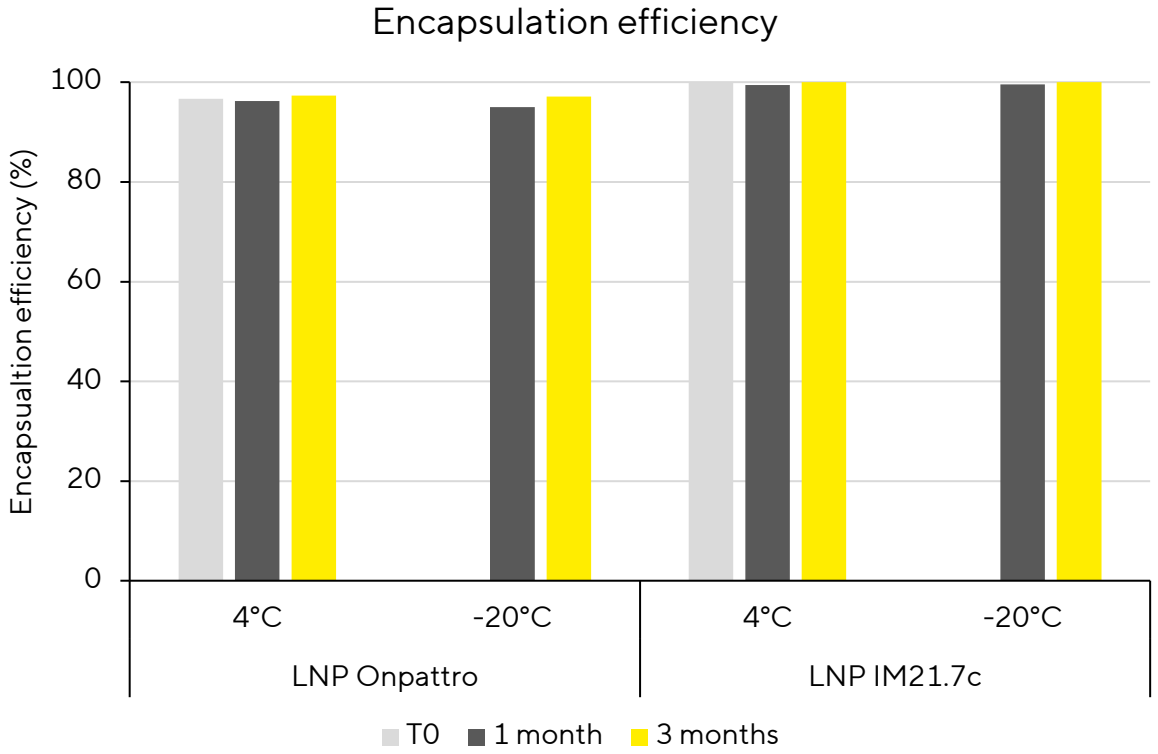
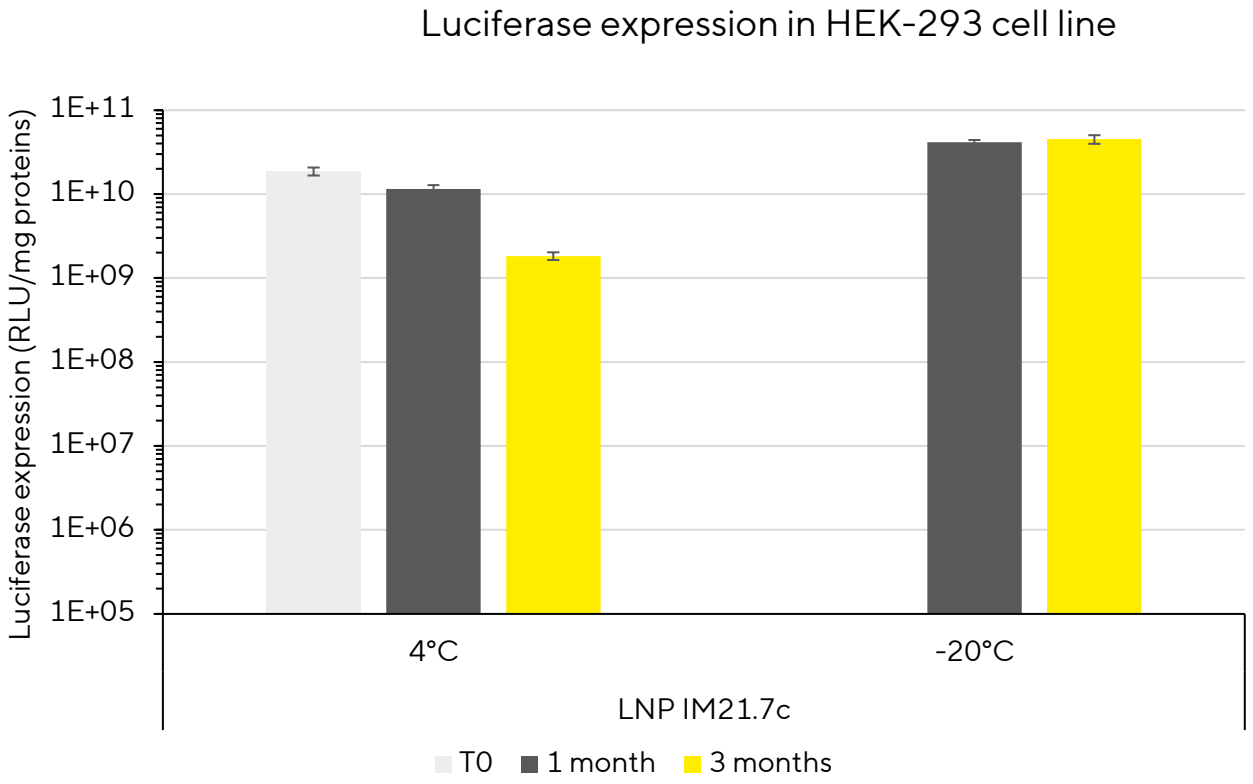
IM21.7c-LNPs Maintain a stable EE% & Transfection Efficiency for ≥3 months at -20°C





Cationic/Ionizable lipid (mM)		*Helper Lipid (mM)*		*Cholesterol (mM)*	*PEG lipid (mM)*	
LNP Onpatto (Dlin-MC3)	*5*	*DSPC*	*1*	*3.85*	*DMG-PEG$_{2k}$*	*0.15*
*LNP **LipidBrick® IM21.7c***	*5*	*DOPE*	*1*	*3.85*	*DMG-PEG$_{2k}$*	*0.15*

4-lipid LNP formulation

Buffer containing sucrose

Summary

LipidBrick® advantages

- **Efficient**: Modulate LNP properties to adapt the biodistribution depending on the therapeutic purpose
  - LipidBrick® shows a great potential by adapting and enlarging the biodistribution of LNPs

- **Secure**: Use a unique lipid structure protected by an independent patent owned by Polyplus®
  - Independent IP covering the use of LipidBrick® library with nucleic acid in LNP formulation

- **Support**: *in vitro* and *in vivo* proof of concept have been successfully performed
  - In addition to our extensive PoC data, our Scientific Support team is here to help you optimize and accelerate the development of your LNPs.

- **Flexible**: Versatile Library allowing to select the Best Suited LipidBrick® for each application
  - Consistent Efficiency & Flexibility to Fine-Tune your LNP formulations on your specific therapeutic purposes

LipidBrick® Library kit (8 x 50mg) is now available

- **Flexibility**: Select from 8 unique, IP-protected LipidBrick® structures for complete application coverage
- **Consistency :** All shown to be efficient in LNP formulations for *in vitro* & *in vivo* applications
- **Optimization**: Find your ideal LipidBrick® fast for each of your therapeutic application
- **Perfect trial size**: Accessible, convenient, and ideal for 1st screening rounds

Item	Description	Type	Quality Grade	Pack size	Order number
LipidBrick® Library Kit	50 mg of each of 8 different LipidBrick® lipids	Cationic lipids (powder and oil)	Research Grade*	8 lipids x 50 mg	101000241

*GMP grade development of specific lipid(s) upon request

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Accessibility Leads to Accelerated Therapeutics

- Earlier access to lipids that can be clinically translated allows for accelerated development of therapeutics
- Sartorius is committed to flexible purchase & use agreements
  - Use under standard purchase and supply agreements
  - Flexible licensing agreements
  - Flexible Development Options for library lipids
- Removing the financial barrier to LNP formulation development

Product	Part number	Pack size
LipidBrick® IM21.7c	101000232	50 mg - NEW
	101000172	250 mg
	101000173	1 g
LipidBrick® Library Kit	101000241	8 lipids x 50 mg - NEW

Removing the Barrier to Entry- Formulation Support Built In

- **Expert Scientific & Regulatory Support teams**
  - Expertise in LNP Formulation, High-Throughput Screening (HTS), Design of Experiments (DoE) & Transfection
  - Access to a Dedicated Team of Field Application Specialists for Specific On-Site Support
  - Scientific, Quality and Regulatory assistance (>15 years of GMP Expertise in Excipients & Raw Materials)
- **Optimized LNP Formulations Guidance**
  - Recommended 'starting points' LNP formulations for enhanced performance in various applications (*in vivo*, *ex vivo*, etc.)
  - Backed by a wealth of internal Proof of Concept data
- **Protocols & Methodologies**
  - Detailed protocols for LNP Formulation and Characterization (DLS)
  - Step-by-step Transfection Guidelines for *in vitro*, *in vivo*, and *ex vivo* applications
- **In-Lab Formulation Tools**
  - Access to our LNP formulation spreadsheet to Ease the Generation of new LNP formulations (and associated calculations)

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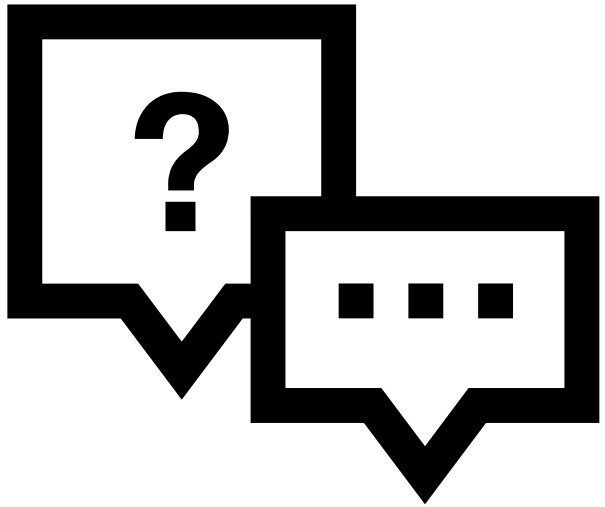
Any questions?



Quentin Huaulmé, PhD
Chemistry Research Scientist
Polyplus, now part of Sartorius
Quentin.huaulme@sartorius.com

Claire Guéguen, PhD
R&D Life Sciences Manager
Polyplus, now part of Sartorius
Claire.gueguen@sartorius.com

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