

Formulation d'acides nucléiques pour les voies aériennes

Elias Fattal
Institut Galien Paris-Saclay
UMR CNRS 8612
Orsay
France

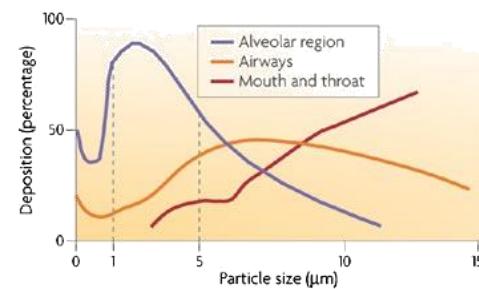
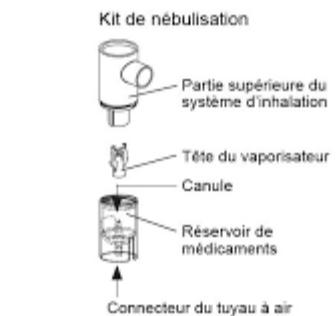
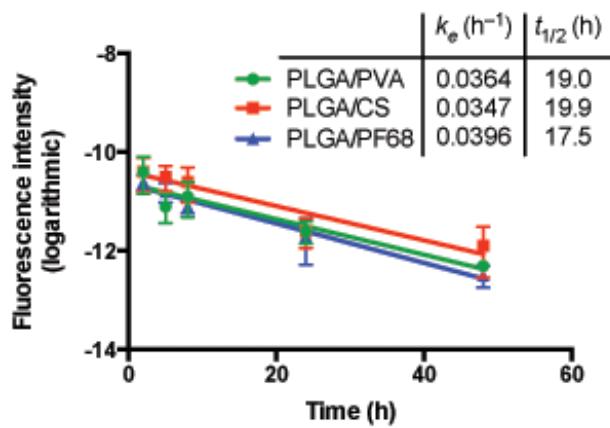


Lung diseases and nanotechnologies

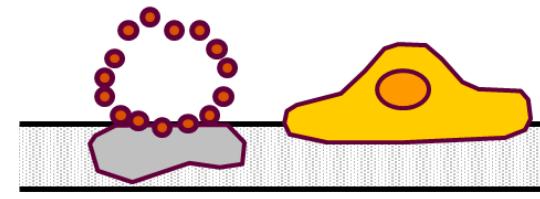
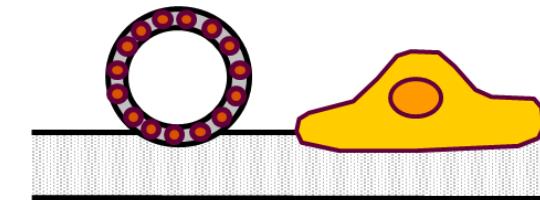
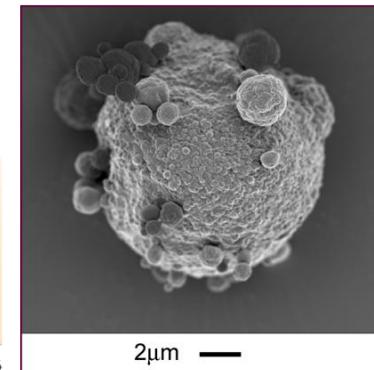
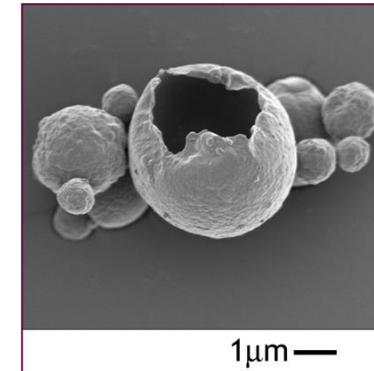
- Cystic Fibrosis (CF)
- Alpha-1-antitrypsin deficiency (ATD)
- Chronic Obstructive Pulmonary Disease (COPD)
- Emphysema
- Hyperinflammation during sepsis
- Asthma
- Idiopathic lung fibrosis
- Lung cancer
- Infectious diseases (e.g. Tuberculosis)
- Vaccines

Dosage forms for nasal/pulmonary nanoparticle delivery

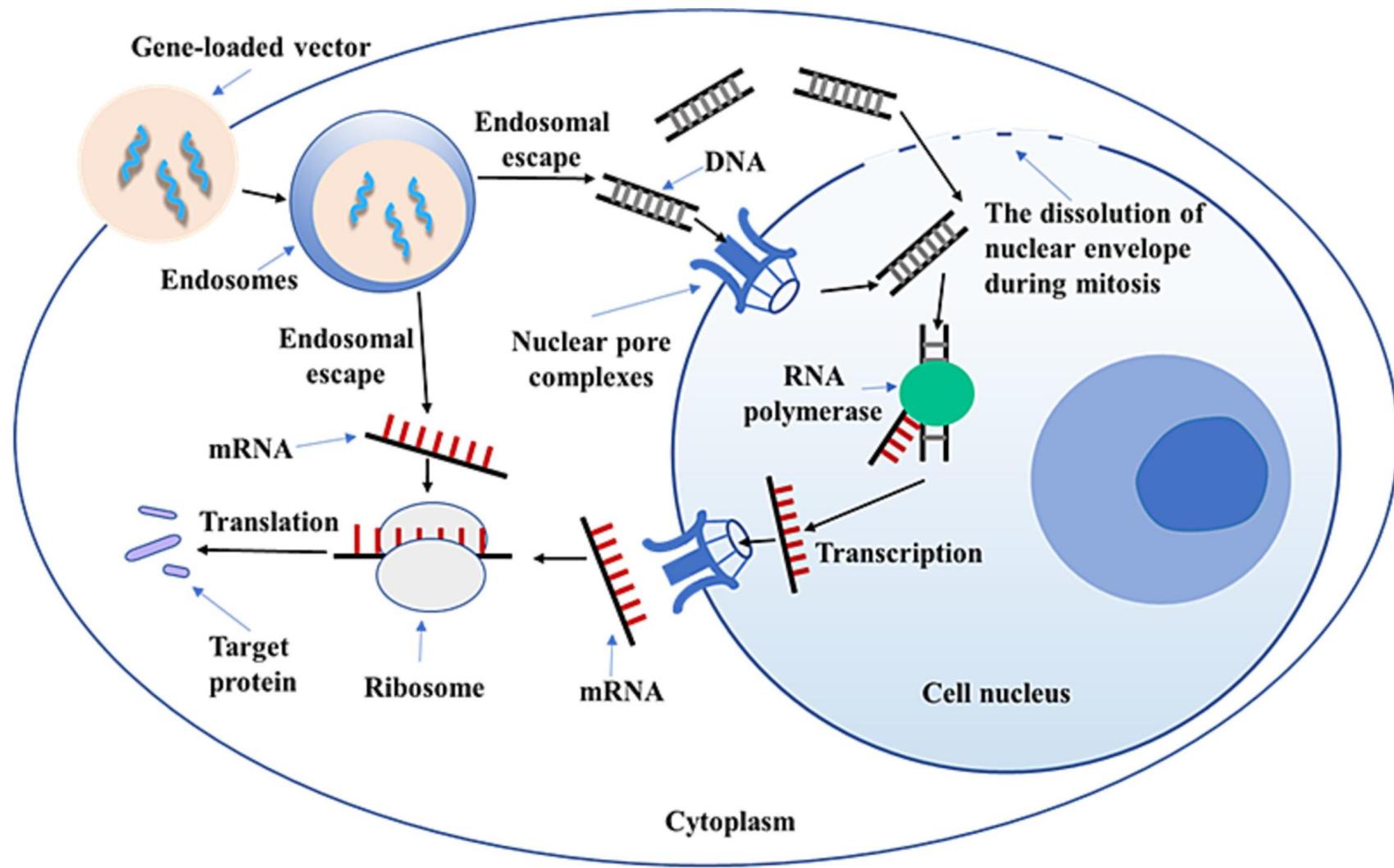
Suspension: Nebulization



Dry powders: Trojan microparticles



mRNA

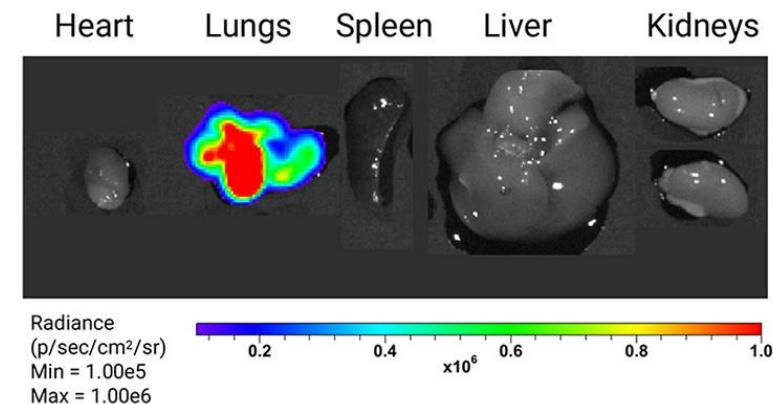


Engineering Lipid Nanoparticles for Enhanced Intracellular Delivery of mRNA through Inhalation

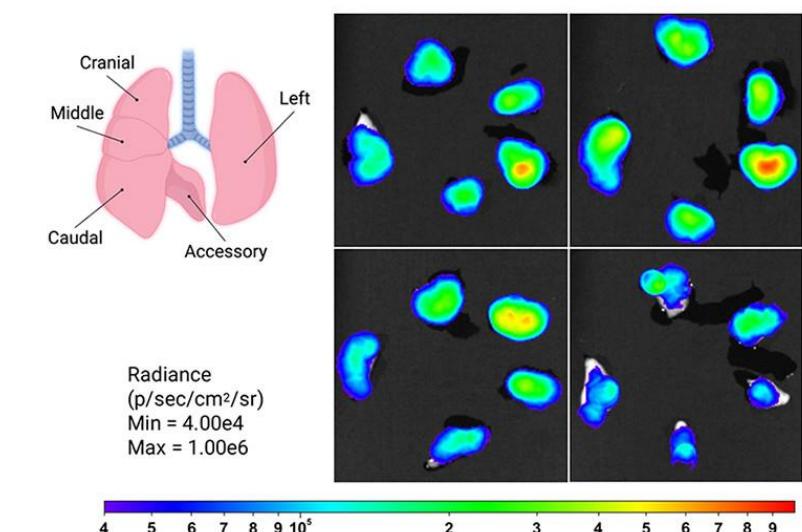
Site-specific versus systemic delivery

- Improved biodistribution
- Allows controlling the tissue concentration
- Specific cell targeting
- Reduces side effects
- Improve compliance

a



b

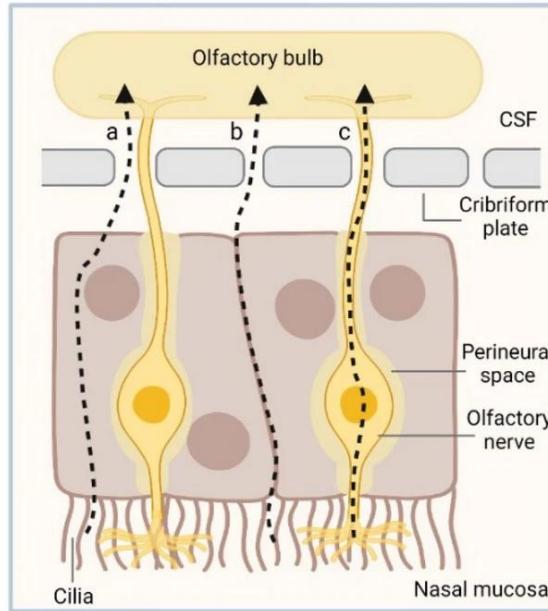


ACS Nano 2022, 16, 9, 14792–14806

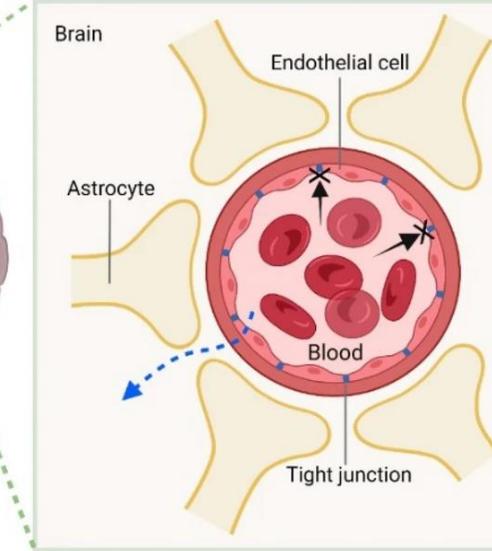
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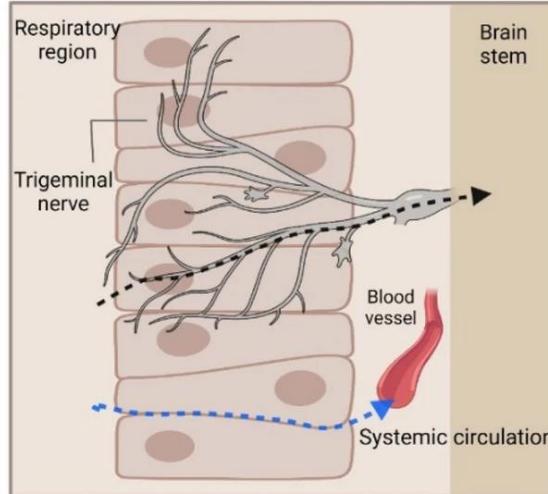
A. Olfactory pathway



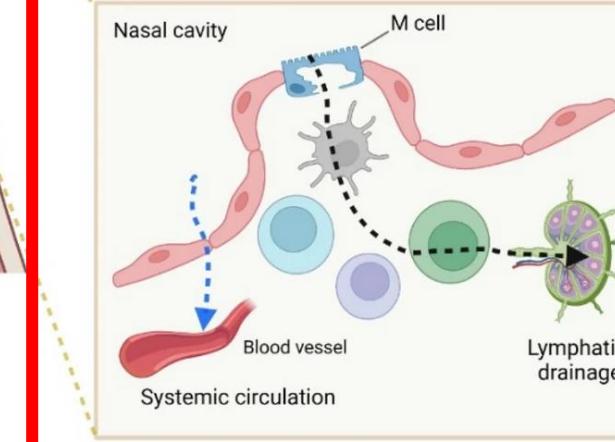
C. Systemic pathway via BBB

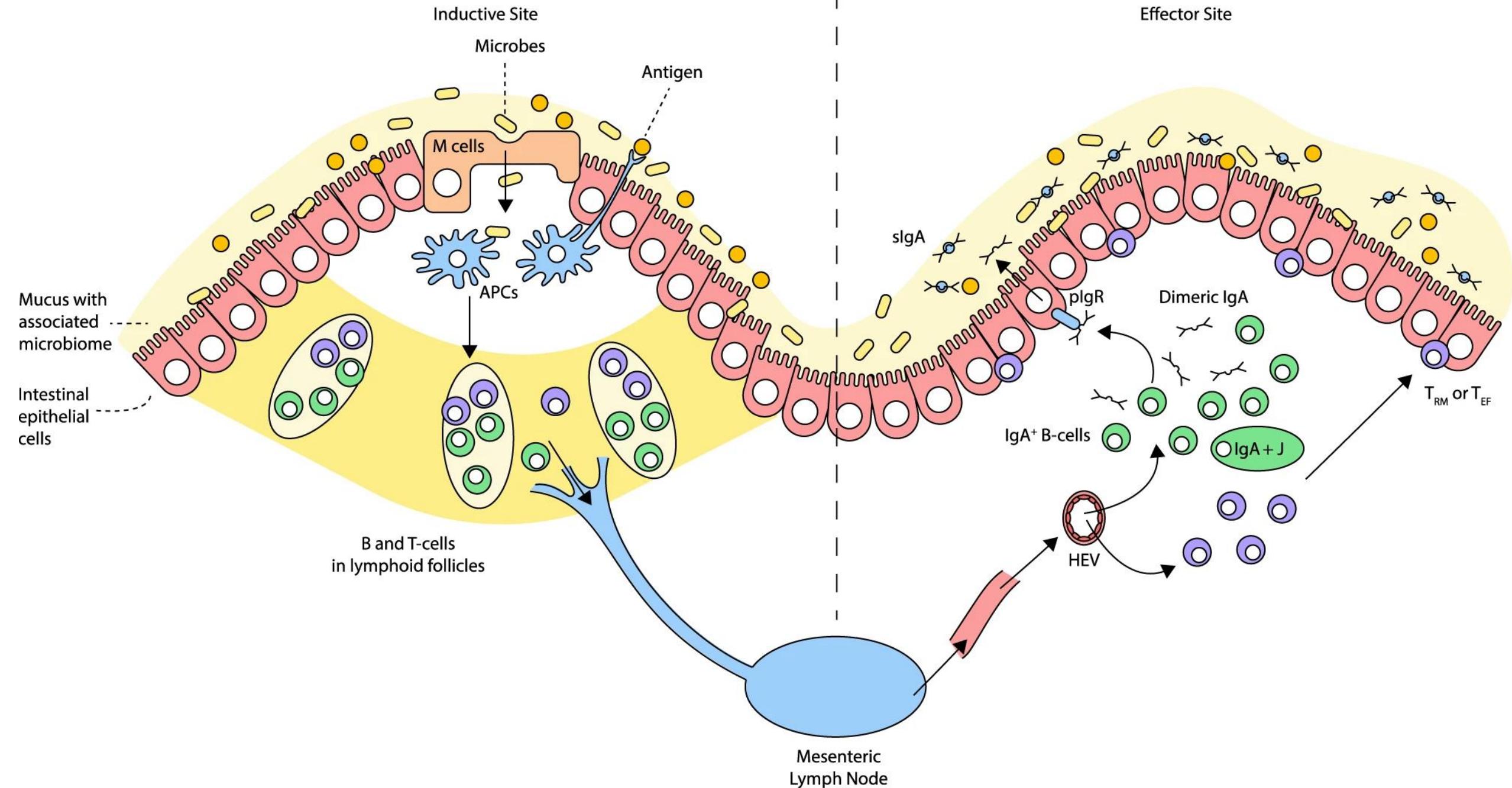


B. Respiratory pathway



D. NALT





Different types of intranasal vaccines for COVID-19



Virus-vectored vaccines

Vectors: adenovirus*, influenza virus, PIV, lentivirus, RSV, NDV



Protein subunit vaccines

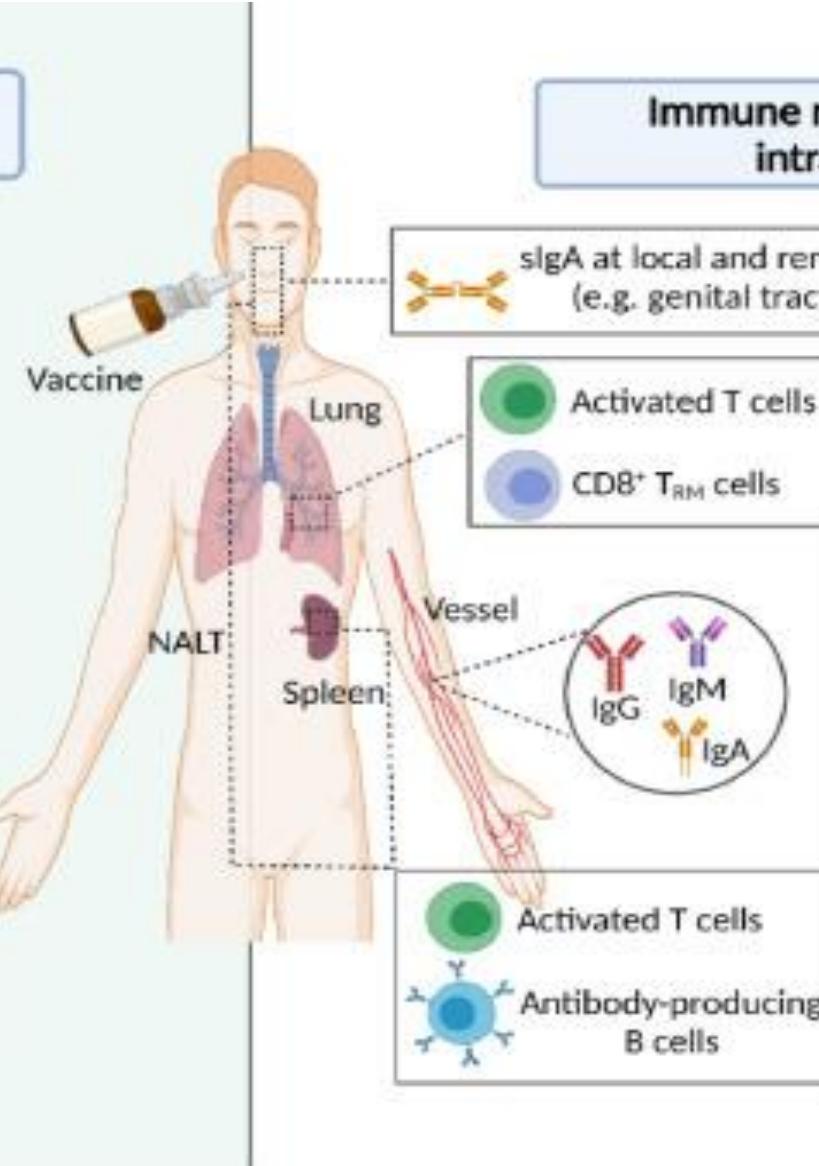
Addition of adjuvants is necessary to enhance the immunogenicity



Other nasal vaccines in development

Live-attenuated vaccines
Bacterium-vectored vaccines
DNA vaccines (require further study)

Immune responses induced by intranasal vaccines



Results

Prevent lung inflammation and pathology

Clear infectious virus in vital organs

Undetectable viral RNA in upper and lower respiratory tracts

Provide long-term immunity (up to 9 months)

Prevent viral shedding and transmission

bioRxiv posts many COVID19-related papers. A reminder: they have not been formally peer-reviewed and should not guide health-related behavior or be reported in the press as conclusive.

New Results

 Follow this preprint

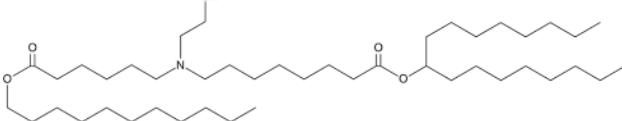
Intranasal mRNA-LNP vaccination protects hamsters from SARS-CoV-2 infection

Gabriela Baldeon Vaca,  Michelle Meyer, Ana Cadete, Chiaowen Joyce Hsiao, Anne Golding, Albert Jeon, Eric Jacquinet, Emily Azcue, Chenxia Monica Guan, Xavier Sanchez-Felix, Colette A. Pietzsch, Matthew A. Hyde, Margaret E. Comeaux, Julie M. Williams, Jean C. Sung, Andrea Carfi, Darii  Alexander Bukreyev,  Kapil Bahl

doi: <https://doi.org/10.1101/2023.01.11.523616>

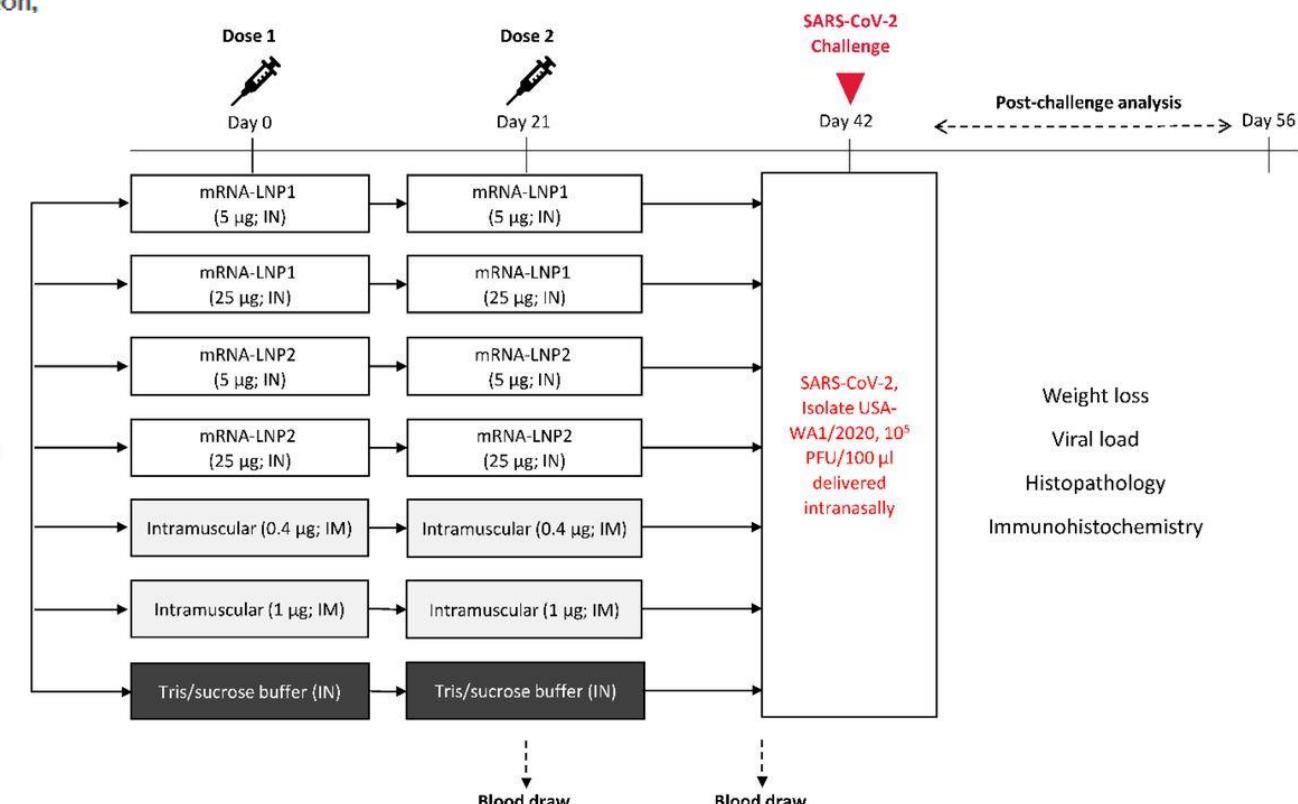
This article is a preprint and has not been certified by peer review [what does this mean?].

- LNP1: mRNA-1273 uses SM102 as ionizable lipid

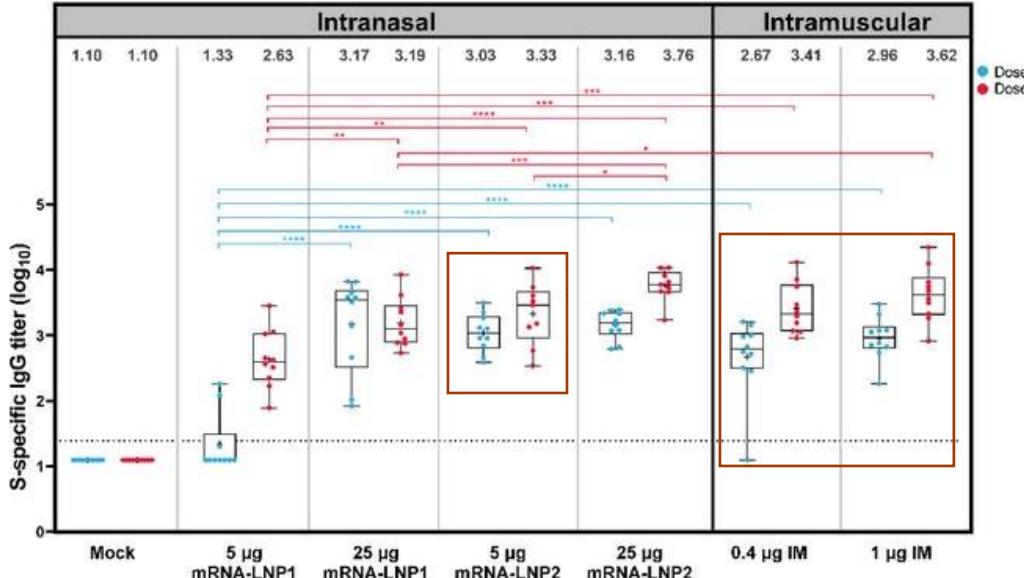


- LNP2: undisclosed formulation of i.n. delivery “LNP is modified to improve vaccine delivery to respiratory tissue”

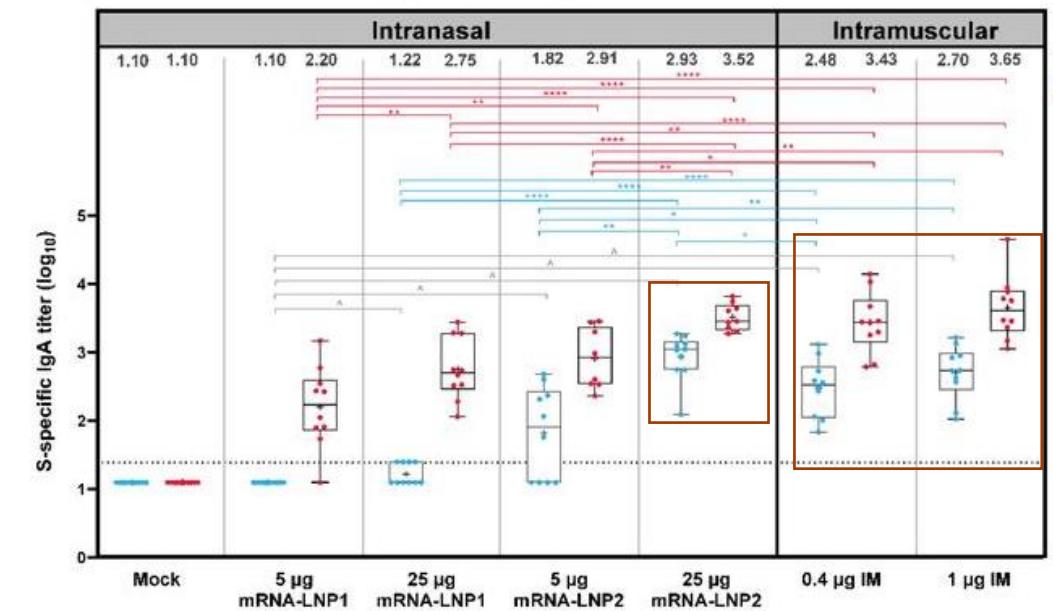
N=10
hamsters/group



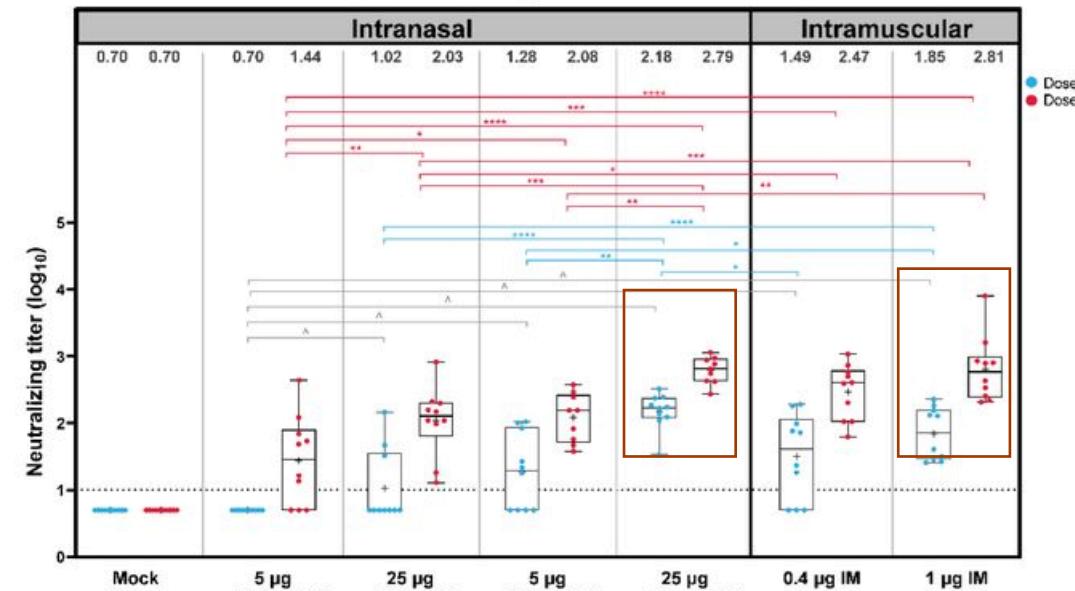
IgG Binding Antibodies



IgA Binding Antibodies



Neutralizing Antibodies

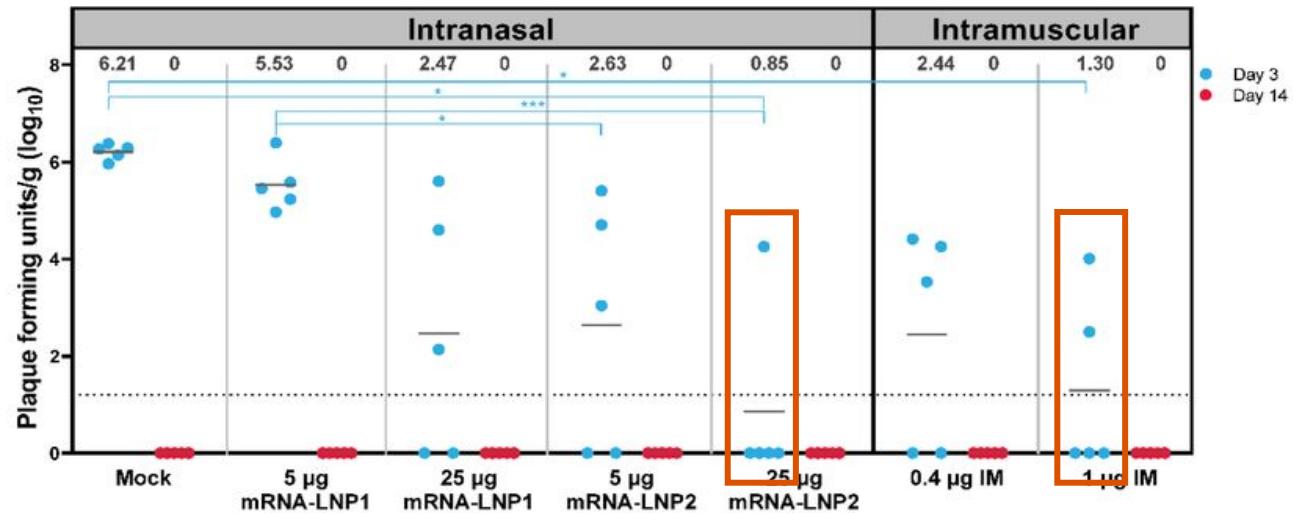


25 μg mRNA-LNP2 i.n. ~ 1μg I.M.

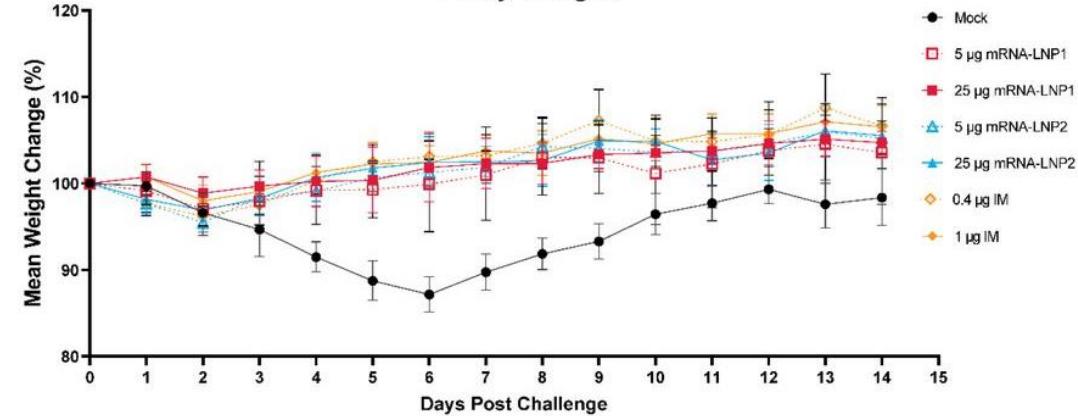
Intranasally administered mRNA-LNP vaccines, especially when the LNP is modified to improve vaccine delivery to respiratory tissue, can induce comparable binding IgA and IgG and neutralizing antibody levels against the SARS-CoV-2 spike protein as intramuscular vaccine

a

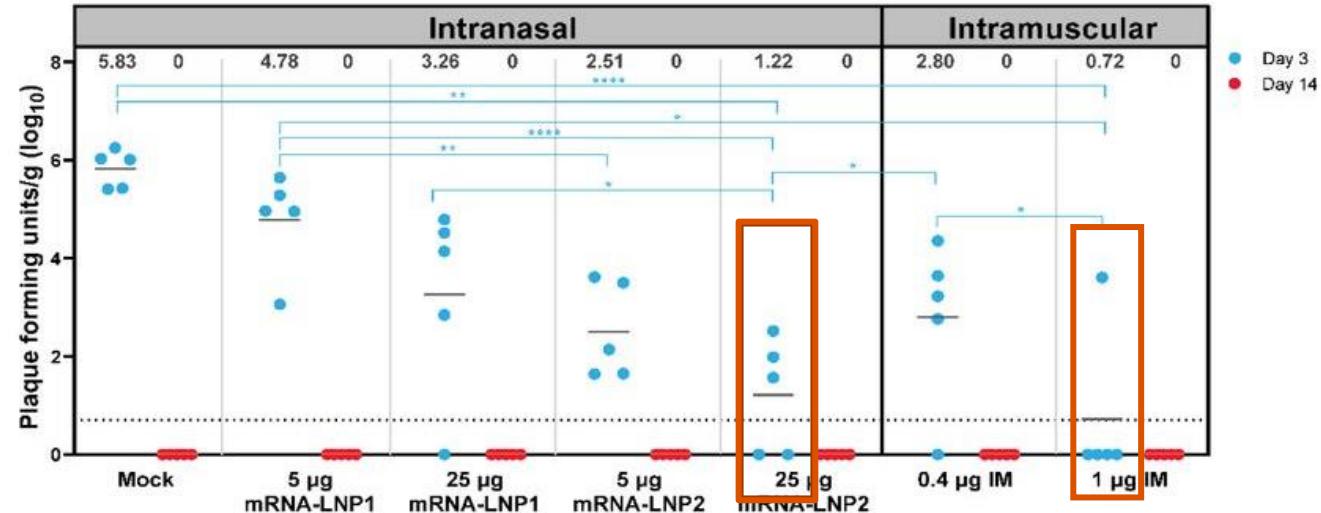
Lung Viral Load

**c**

Body Weight

**b**

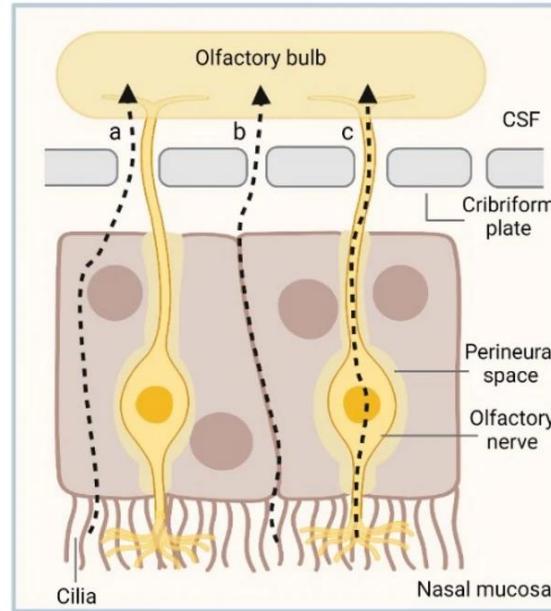
Nasal Turbinete Viral Load



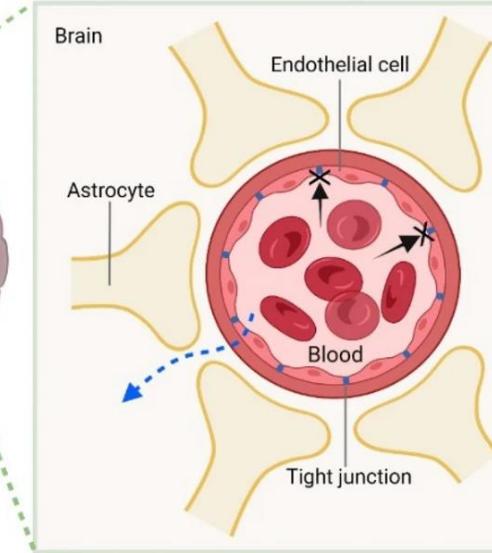
25 µg mRNA-LNP2 i.n. ~ 1µg I.M.

The viral loads in the nasal turbinates and lungs of the hamsters in the vaccination groups were significantly lower three days after the viral challenge. In the mRNA-LNP2 vaccinated group, the viral loads were below detection levels in four hamsters.

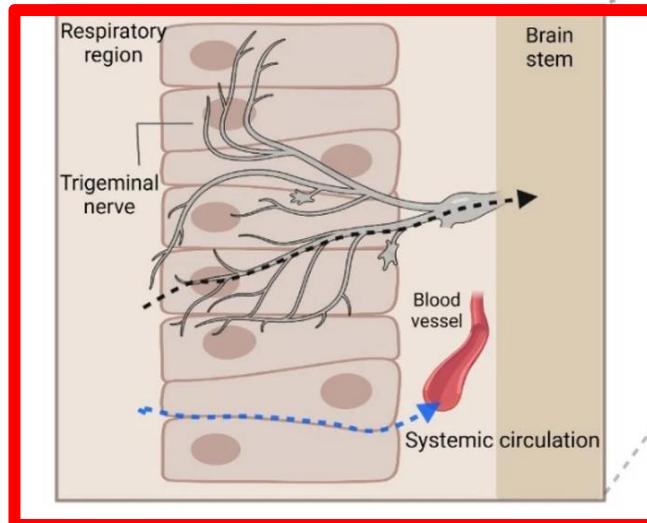
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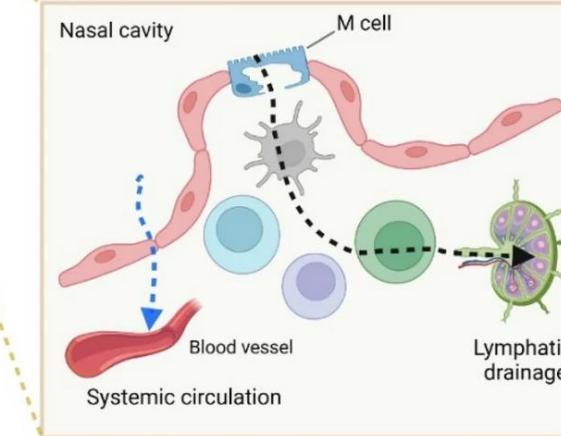
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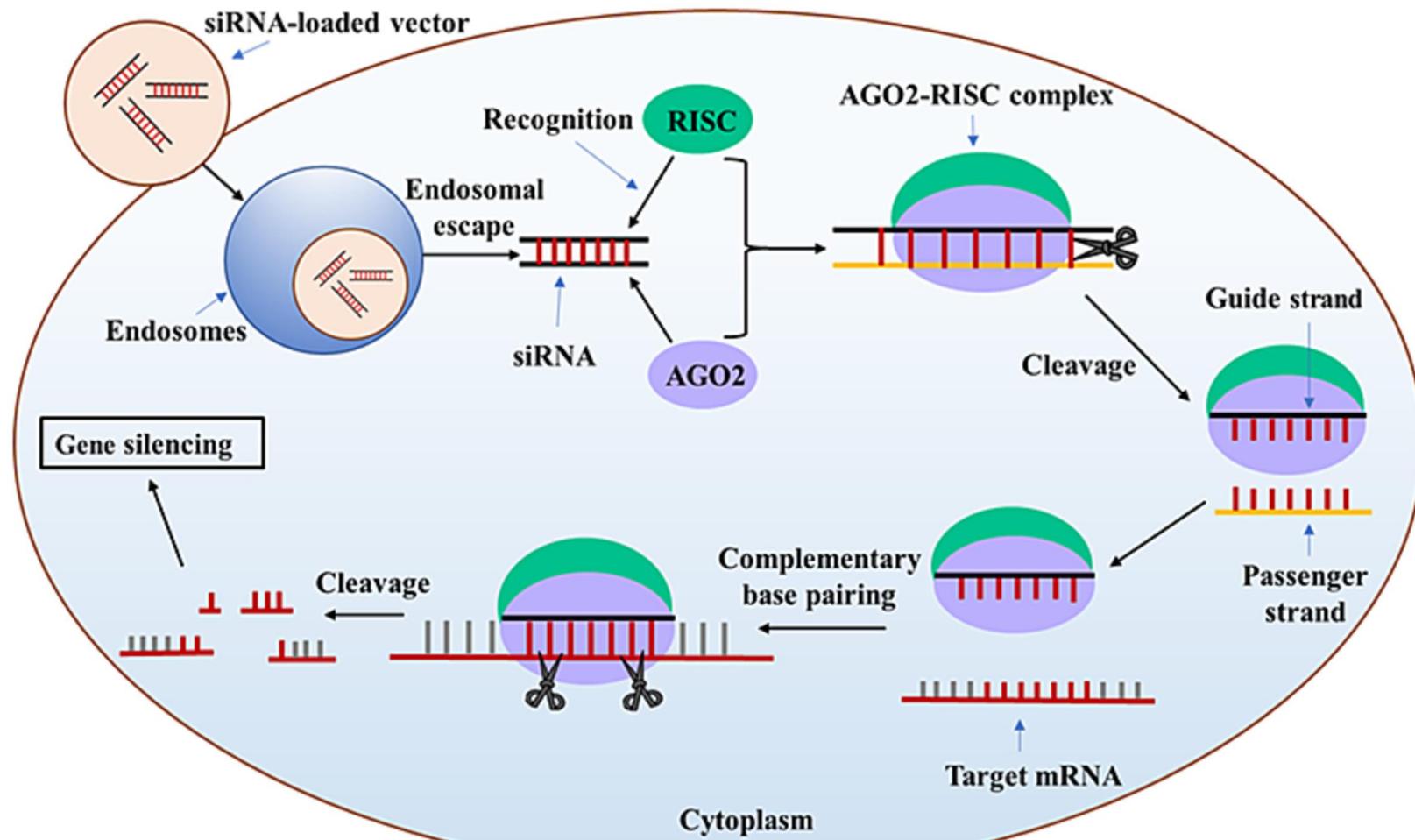
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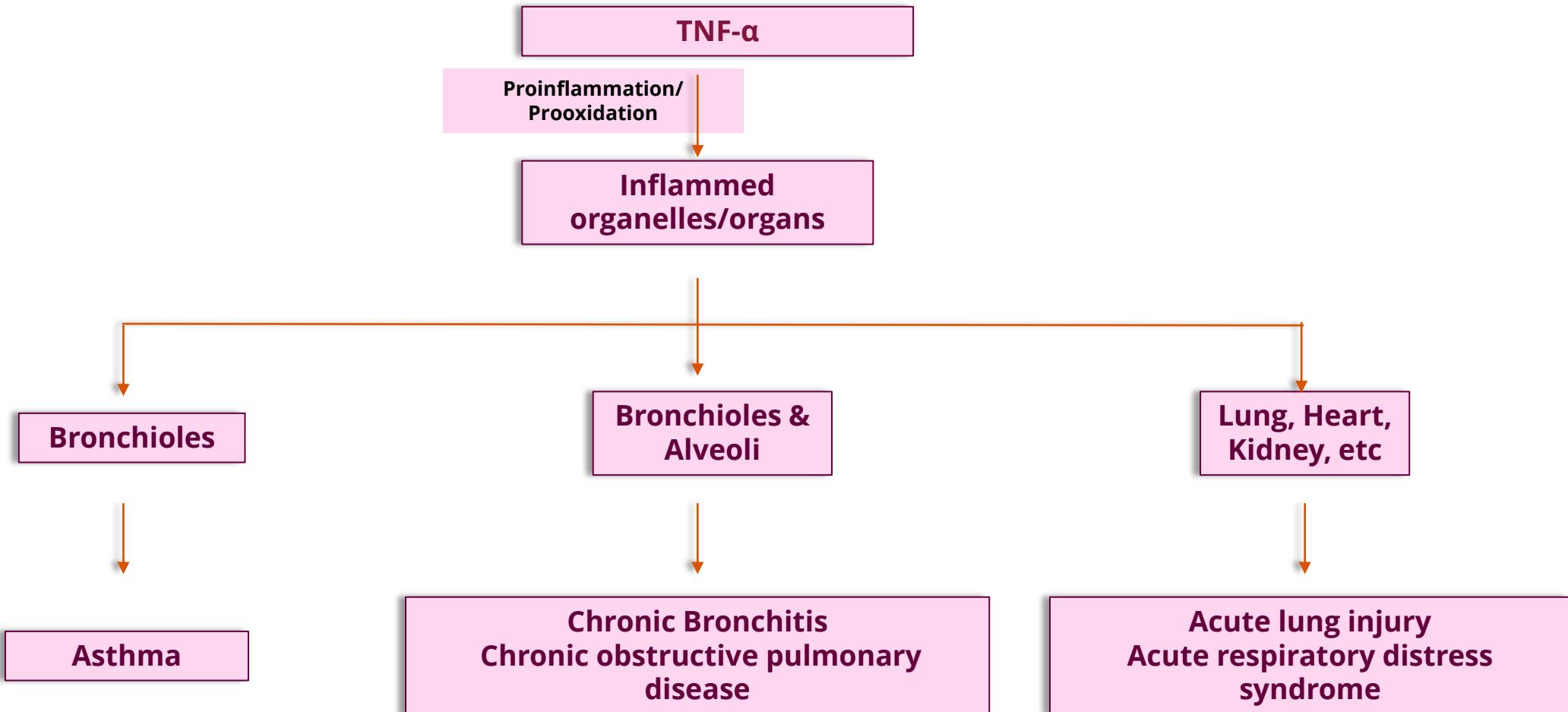
D. NALT



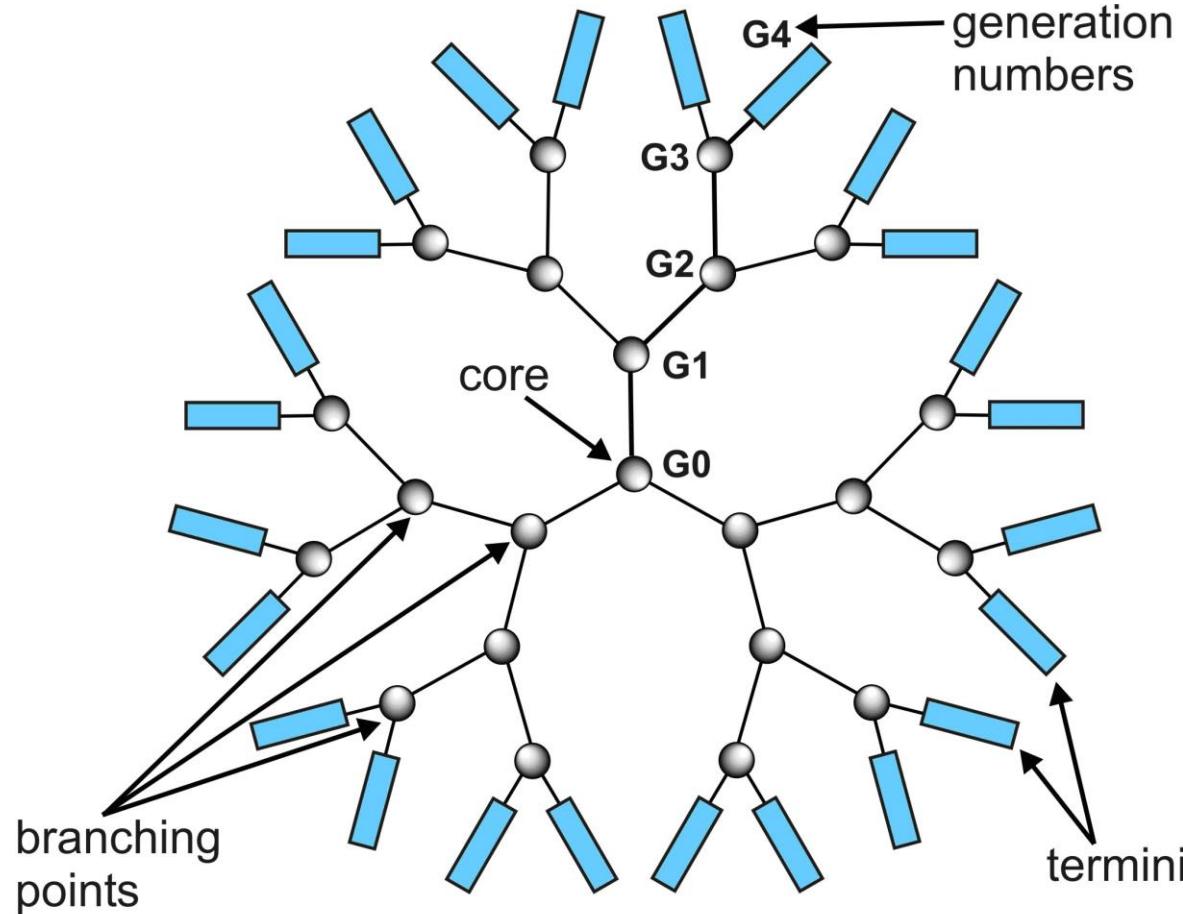
siRNA



Role of TNF α in pulmonary pathophysiology



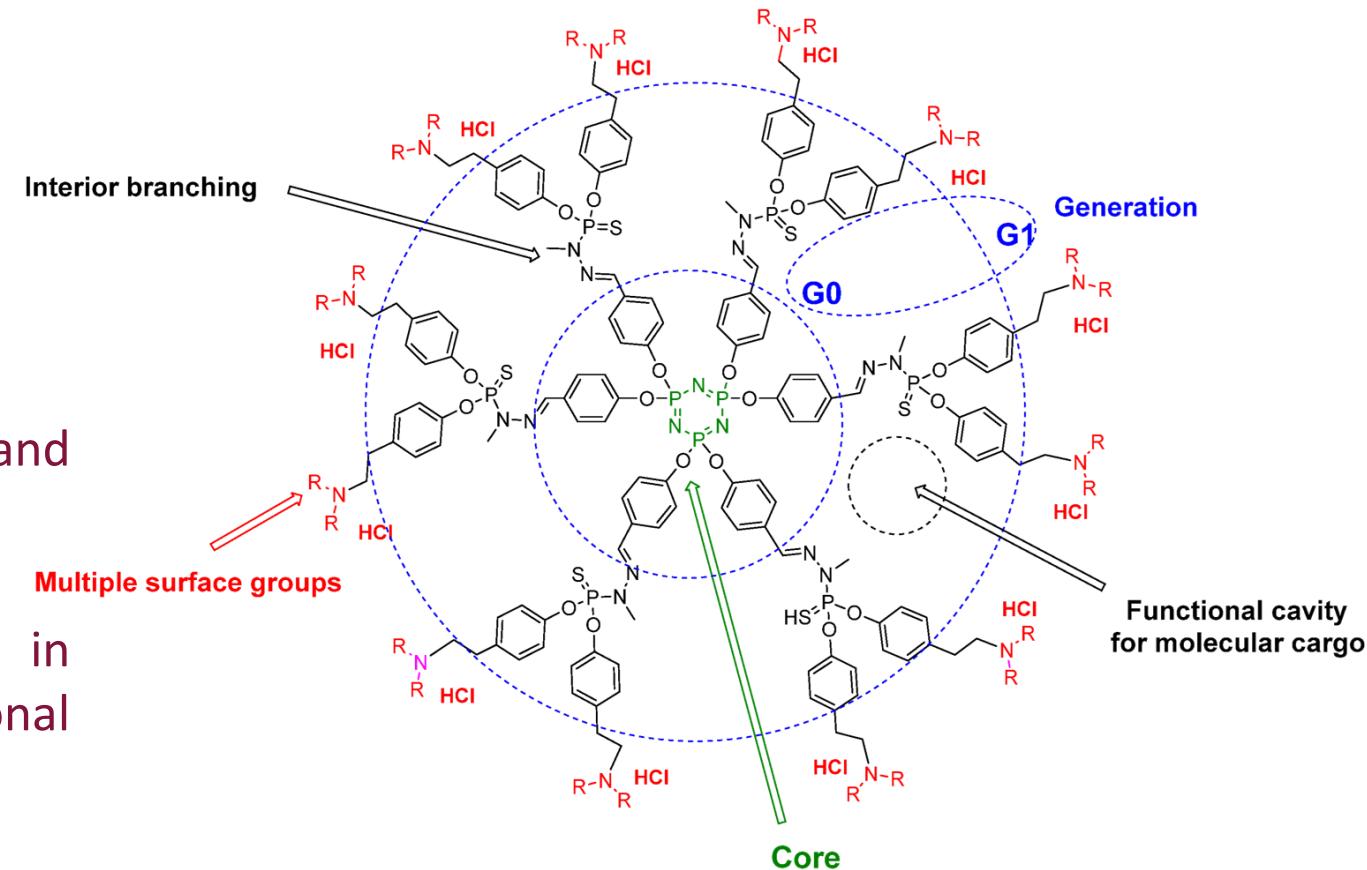
Dendrimers for siRNA delivery



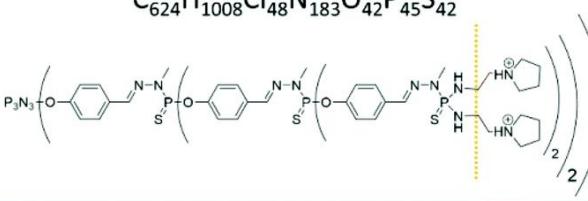
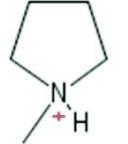
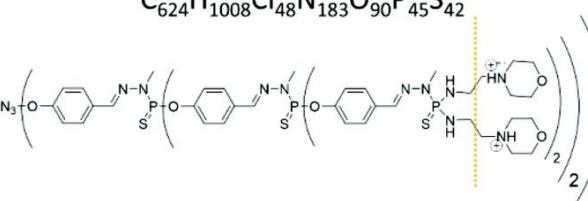
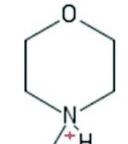
DENDRIMER

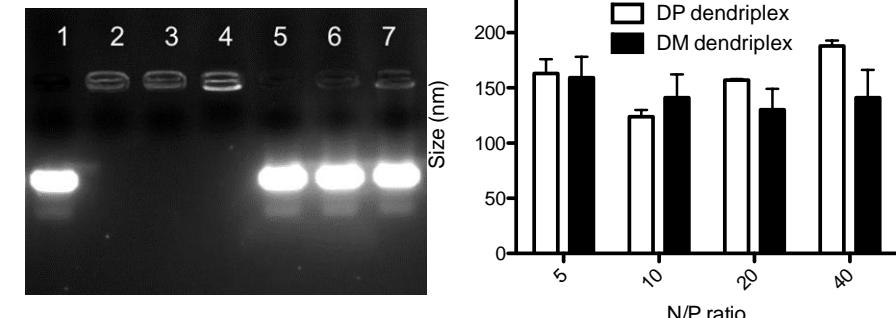
Advantages of Phosphorous Dendrimers

- Few synthesis steps and high yields
 - High solubility in water
 - High chemical stability
 - Perfect reproducibility of the syntheses
 - Large quantities under GMP conditions
 - Easy modification of the chemical nature and number of end groups
 - Inexpensive starting materials
 - Have *per se* anti-inflammatory effects in Experimental Arthritis (Science Translational Medicine, 2011, vol 3, 81ra35)

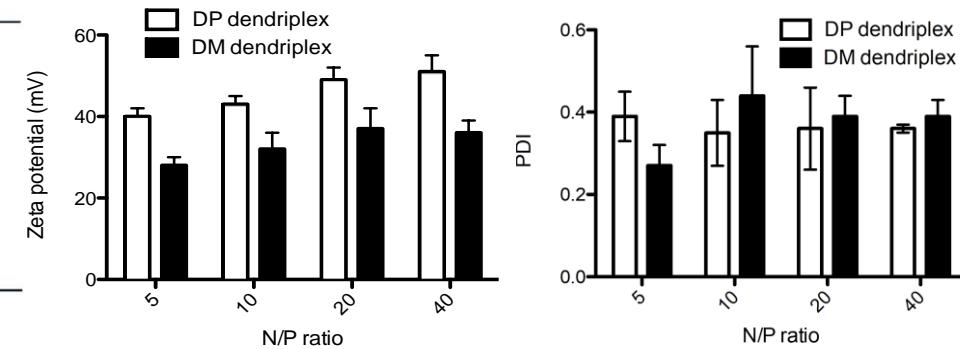


SiRNA binding properties of phosphorus dendriplexes

Name	Formula and Structure	Terminal	Gen	MW (Da)	Solubility
DP	$C_{624}H_{1008}Cl_{48}N_{183}O_{42}P_{45}S_{42}$ 	pyrrolidinium 	3	16173	Water HEPES buffer
DM	$C_{624}H_{1008}Cl_{48}N_{183}O_{90}P_{45}S_{42}$ 	morpholinium 	3	16845	Water HEPES buffer

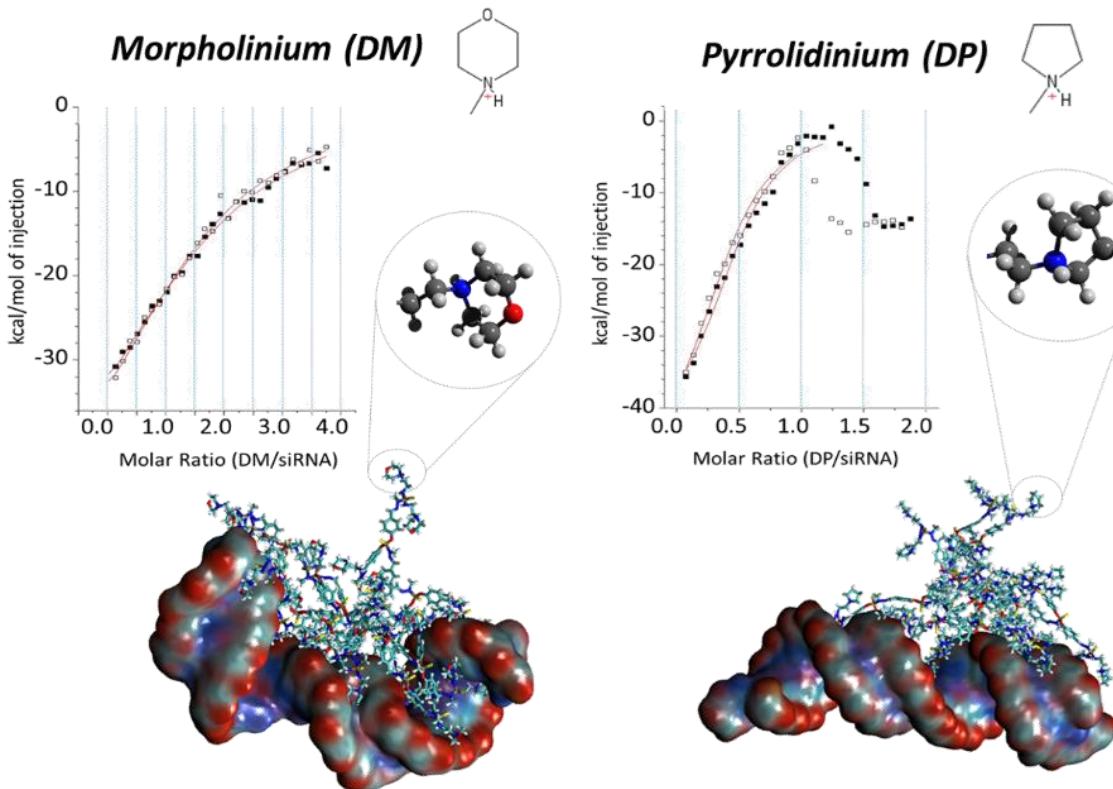


DP dendriplexes DM dendriplexes



Pyrrolidinium end-groups display better binding properties than the morpholinium

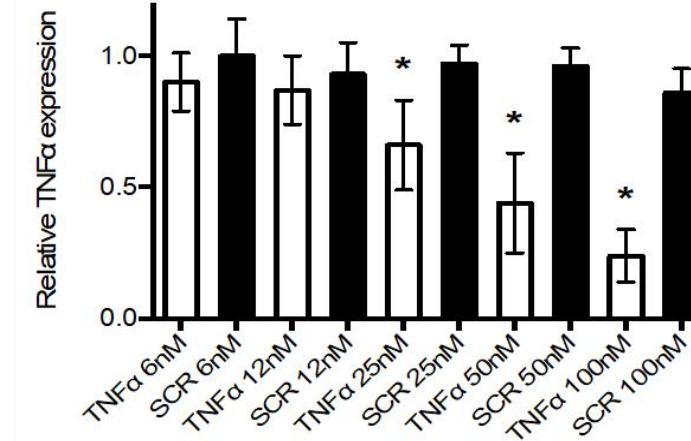
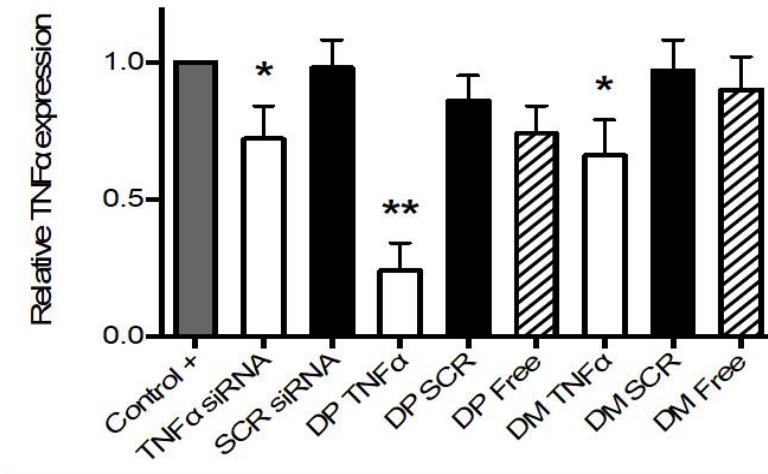
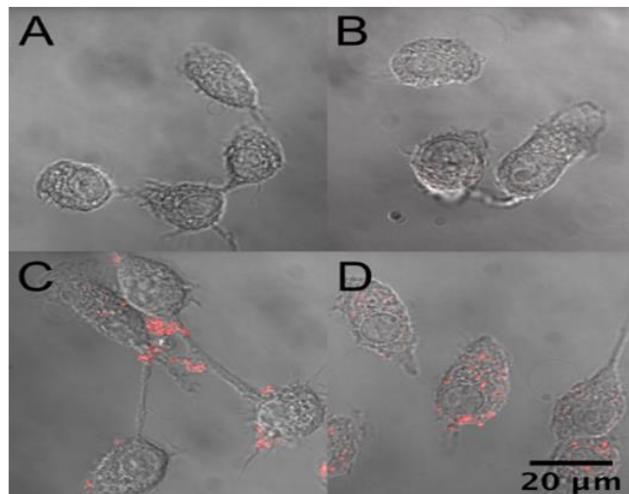
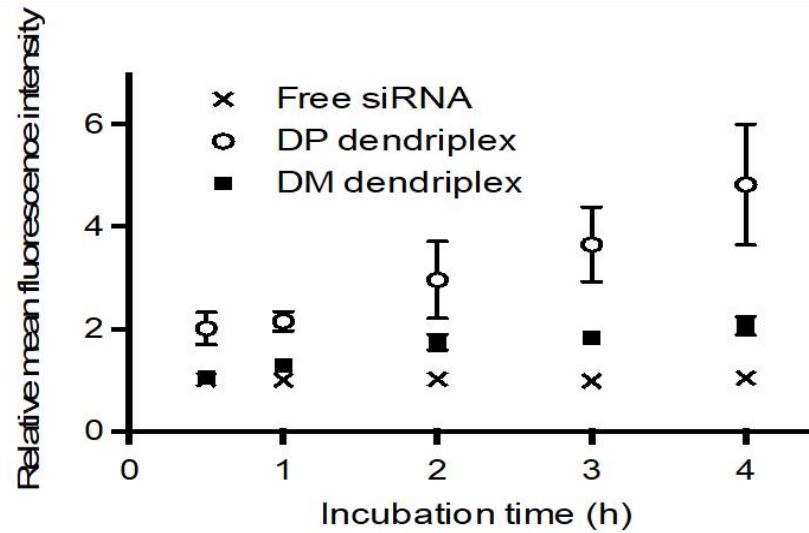
Interaction Mechanisms of Phosphorus Cationic Dendrimers with siRNA



Property	Unit	DP	DM	DP/DM
$N_{\text{siRNA/dendrimer}}$	#	2.25 ± 0.03	0.60 ± 0.03	3.75 ± 0.53
k_d	μM	5.60 ± 0.85	21.49 ± 2.11	4.02 ± 1.06
ΔH	kcal/mol	-47.00 ± 2.83	-53.25 ± 0.21	0.88 ± 0.06
$T\Delta S$	kcal/mol	-39.65 ± 2.95	-46.96 ± 0.21	0.84 ± 0.07
ΔG	kcal/mol	-7.35 ± 0.12	-6.29 ± 0.00	1.17 ± 0.02

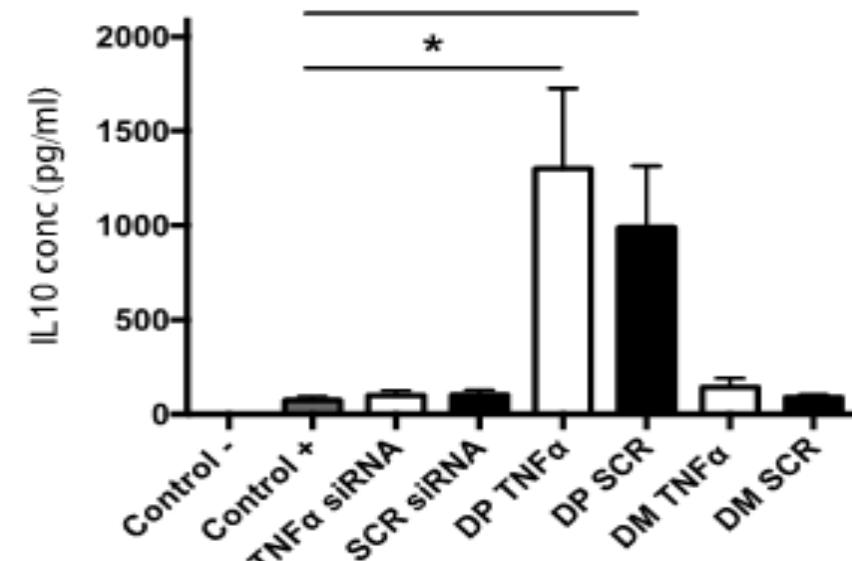
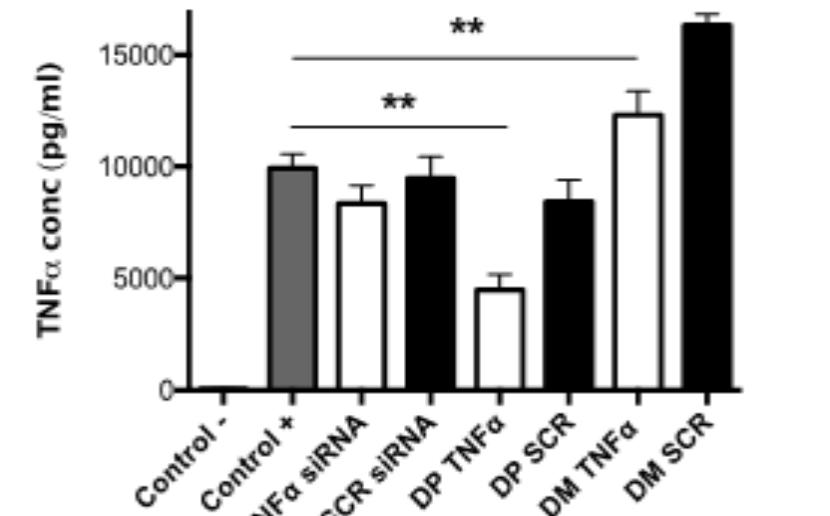
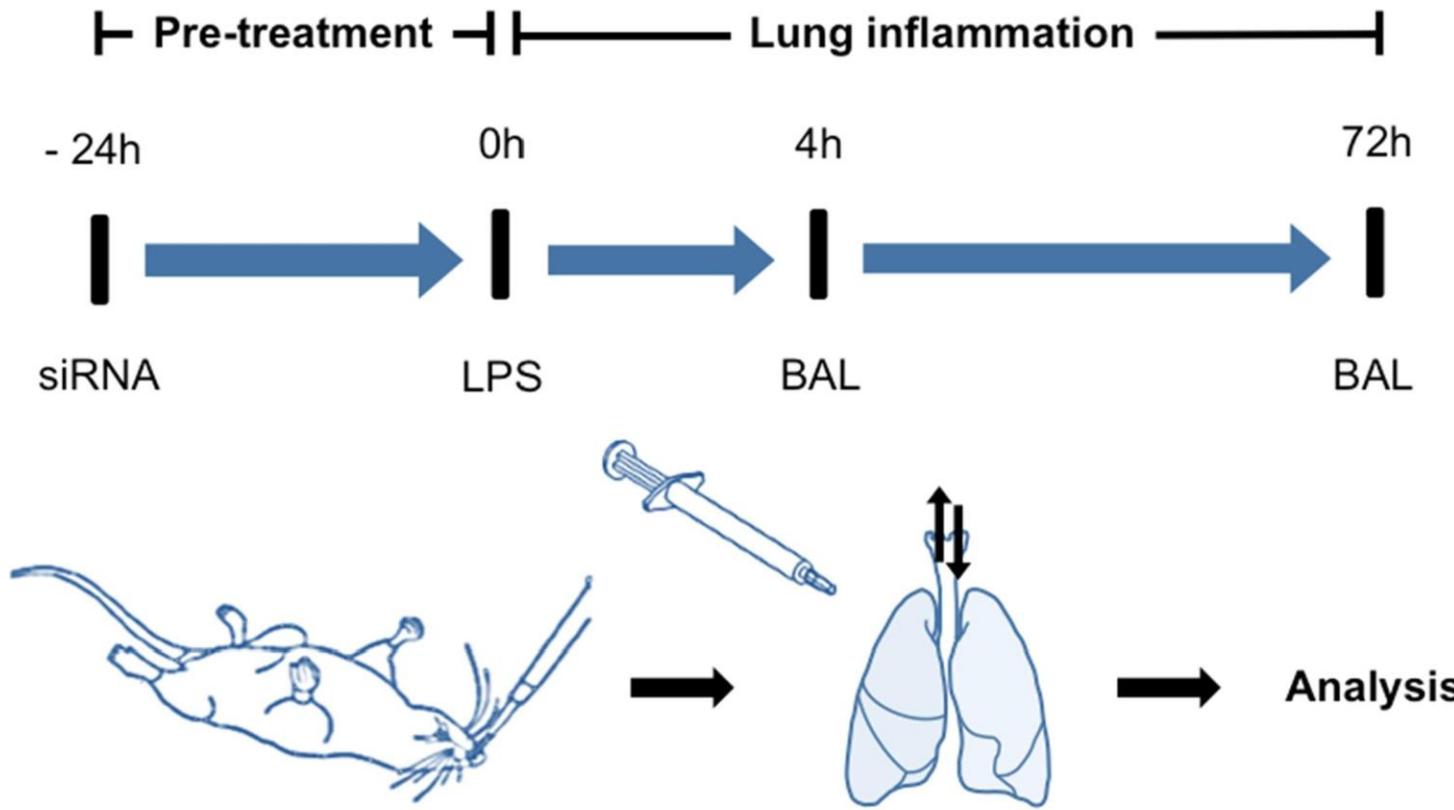
- DP requires a lower number of terminal groups to directly bind the siRNA while leaving a large part of it free to eventually catch another siRNA molecule.
- Higher affinity for DP than DM

Dendriplexes/RAW 264.7 cells activated by LPS interaction and antiTNF α effect



Dendriplexes with pyrrolidinium end groups allow better siRNA cell penetration and dose dependent TNF α inhibition

In vivo TNF α inhibition after incubation with RAW 264.7 LPS-activated cells and intranasal administration in mice of siRNA-loaded dendriplexes



Conclusions

- ✓ Nasal and Pulmonary routes are both suitable for the delivery of coding and non-coding RNA
 - ✓ Vaccine delivery
 - ✓ SiRNA delivery targeting inflammatory diseases such as acute lung injury
 - ✓ LNPs are major breakthrough in the delivery

Acknowledgements

Institut Galien Paris-Saclay

Kamila Bohne Japiassu
Qinglin Wang
Adam Bohr
Christian Ruge
Alessandro Marengo

François Fay
Nicolas Tsapis
Juliette Vergnaud

Stephanie Denis (Cell Culture)
Catherine Cailleau (Animal experiments)

Ingénierie et Plateformes au Service de l'Innovation Thérapeutique

Valérie Nicolas (Imaging)
Claudine Deloménie (Transcriptomics)

LCC CNRS Toulouse
Jean Pierre Majoral

University of Goias,Brasil
Eliana Lima



ARROW-NANO

