DNA-loaded lipid nanoparticles (*DNA-LNPs*): A platform technology for treating common chronic diseases

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Penn Medicine

CRS Conference
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Disclosures

Companies that currently or recently funded our lab's research:

Insmed

Boehringer Ingelheim

Code Biotherapeutics

BioNTech

Companies that I have founded and have equity in (and stage):

Pelvalon (VC funded; FDA approval; acquired); medical device

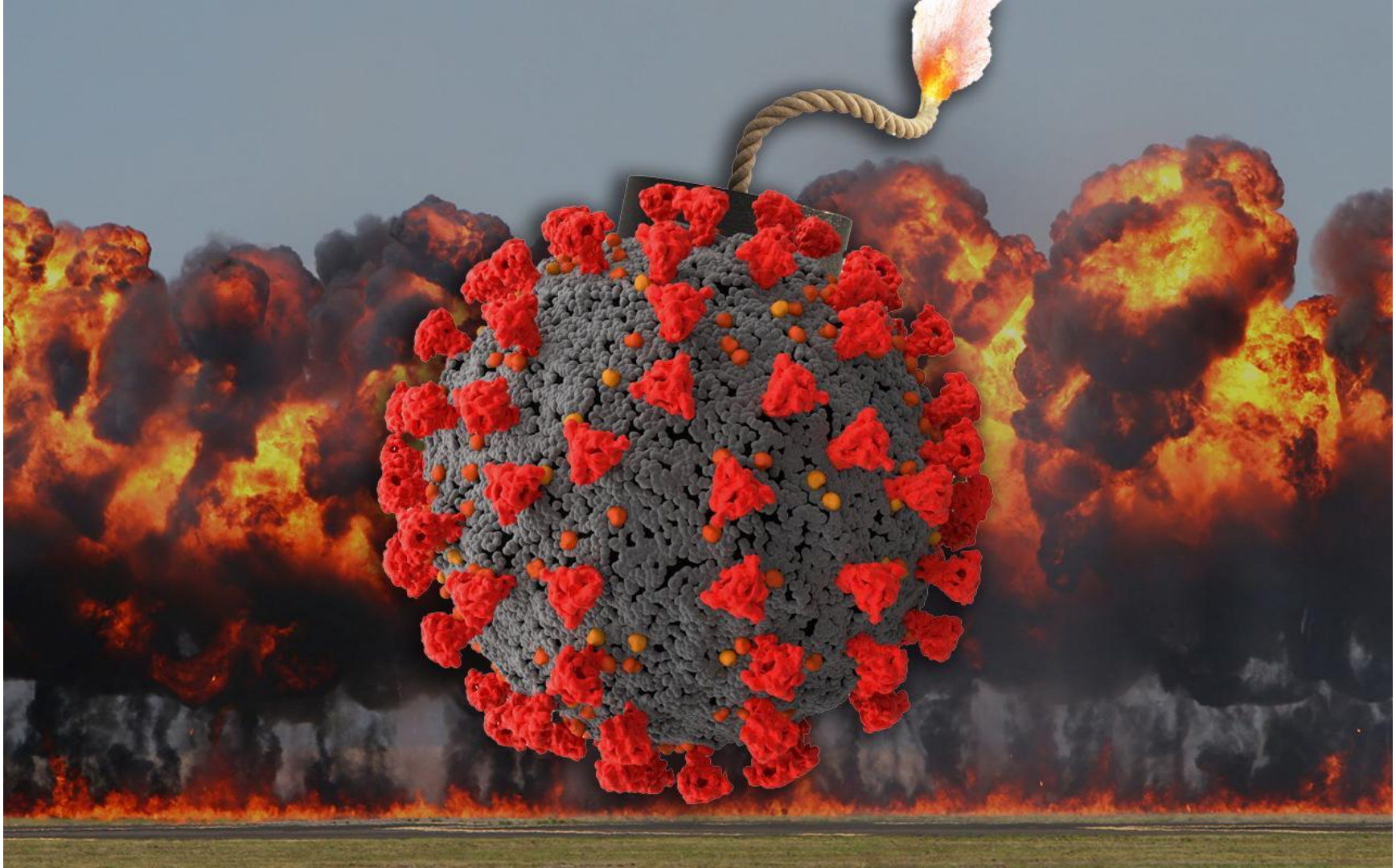
Orpheus Medical (VC funded; IP acquired); medical device

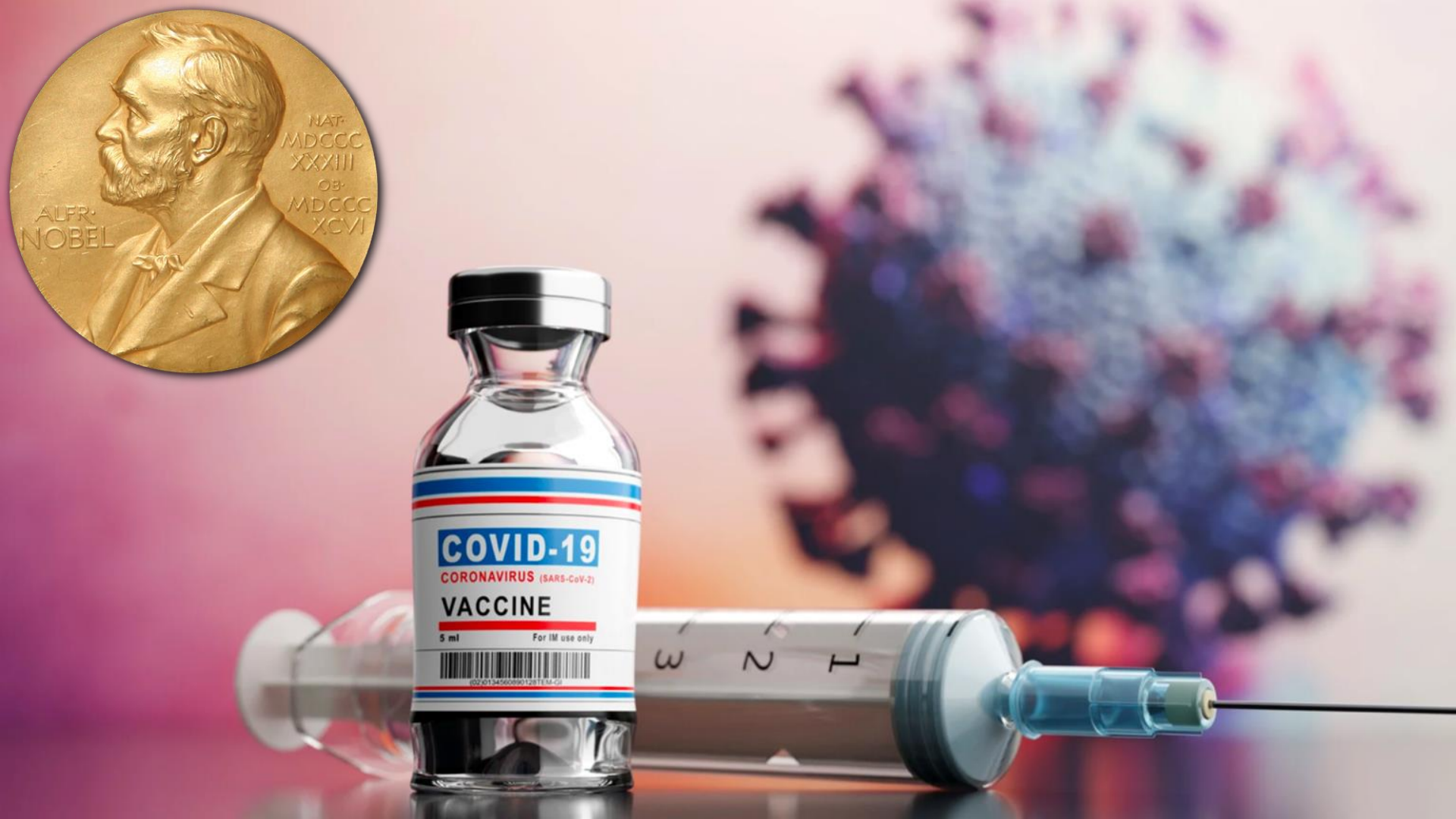
RightAir (VC funded; in clinical studies); medical device

AltruMed (NIH STTR; in clinical studies); drug-device combination

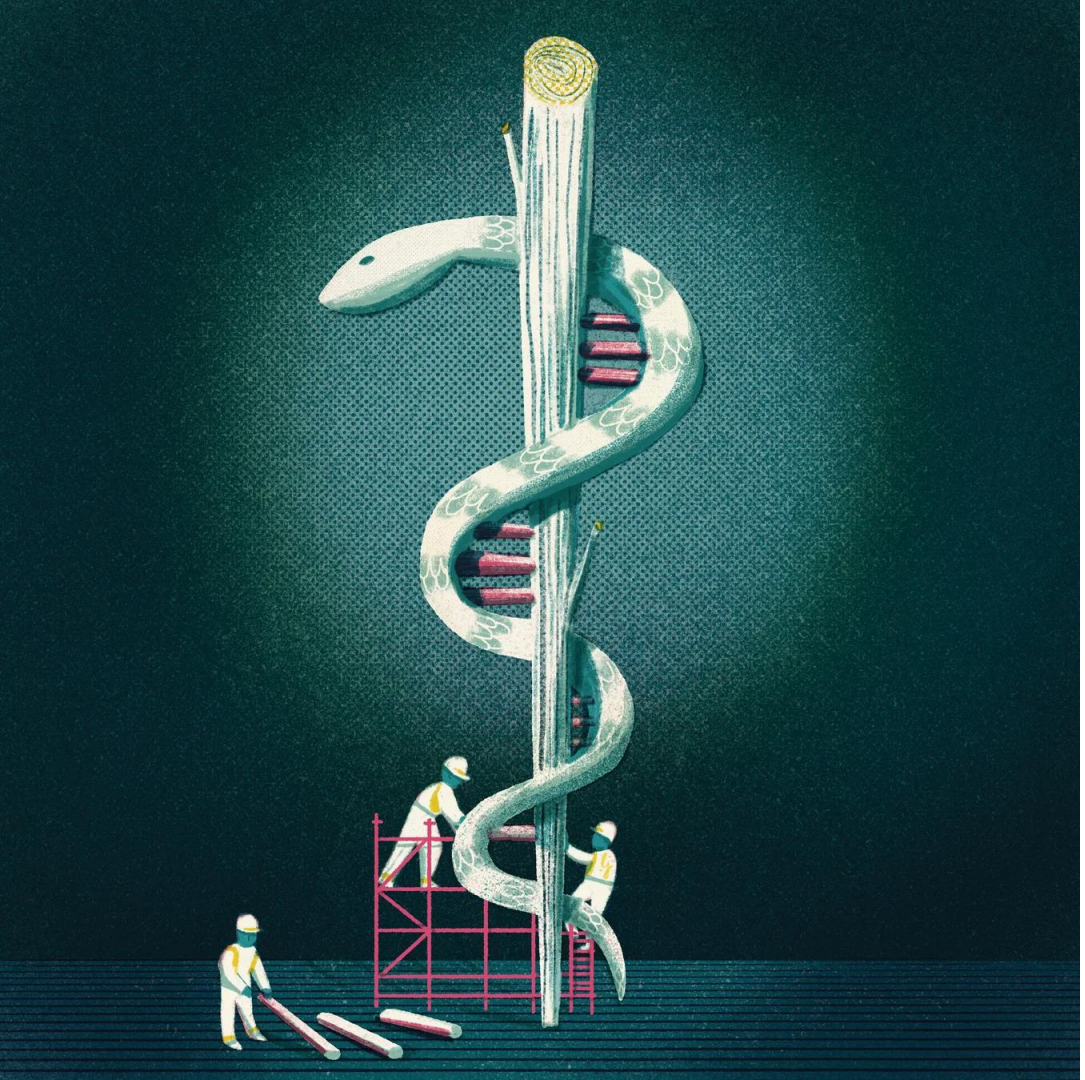
NanoMuse (NIH STTR; pre-clinical studies)

ClearXpression: pre-funded




NAT·
MDCCC
XXXIII
OB·
MDCCC
XCVI
ALFR·
NOBEL
COVID-19
CORONAVIRUS (SARS-CoV-2)
VACCINE
5 ml
For IM use only

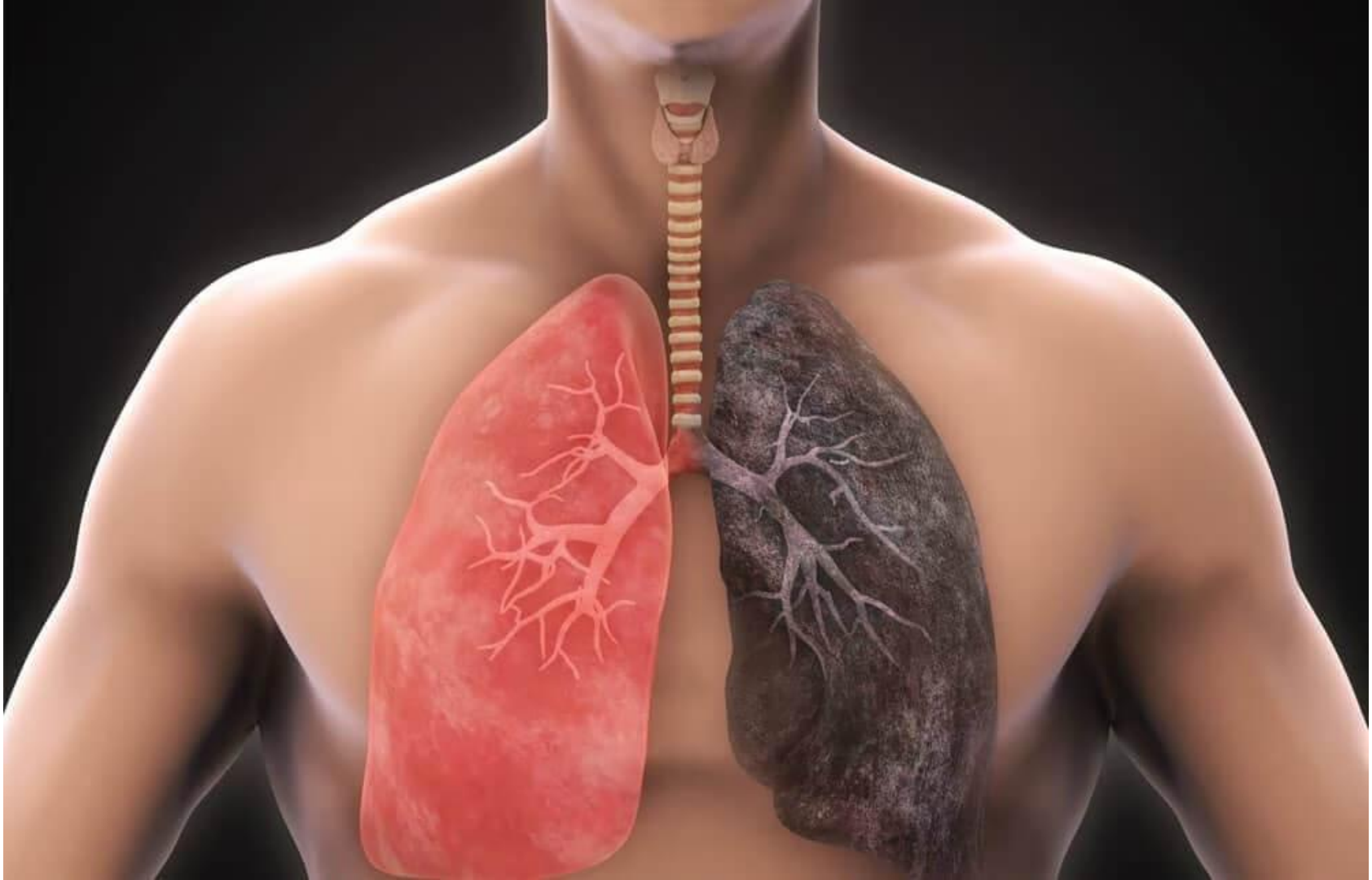

Is mRNA
the only way?

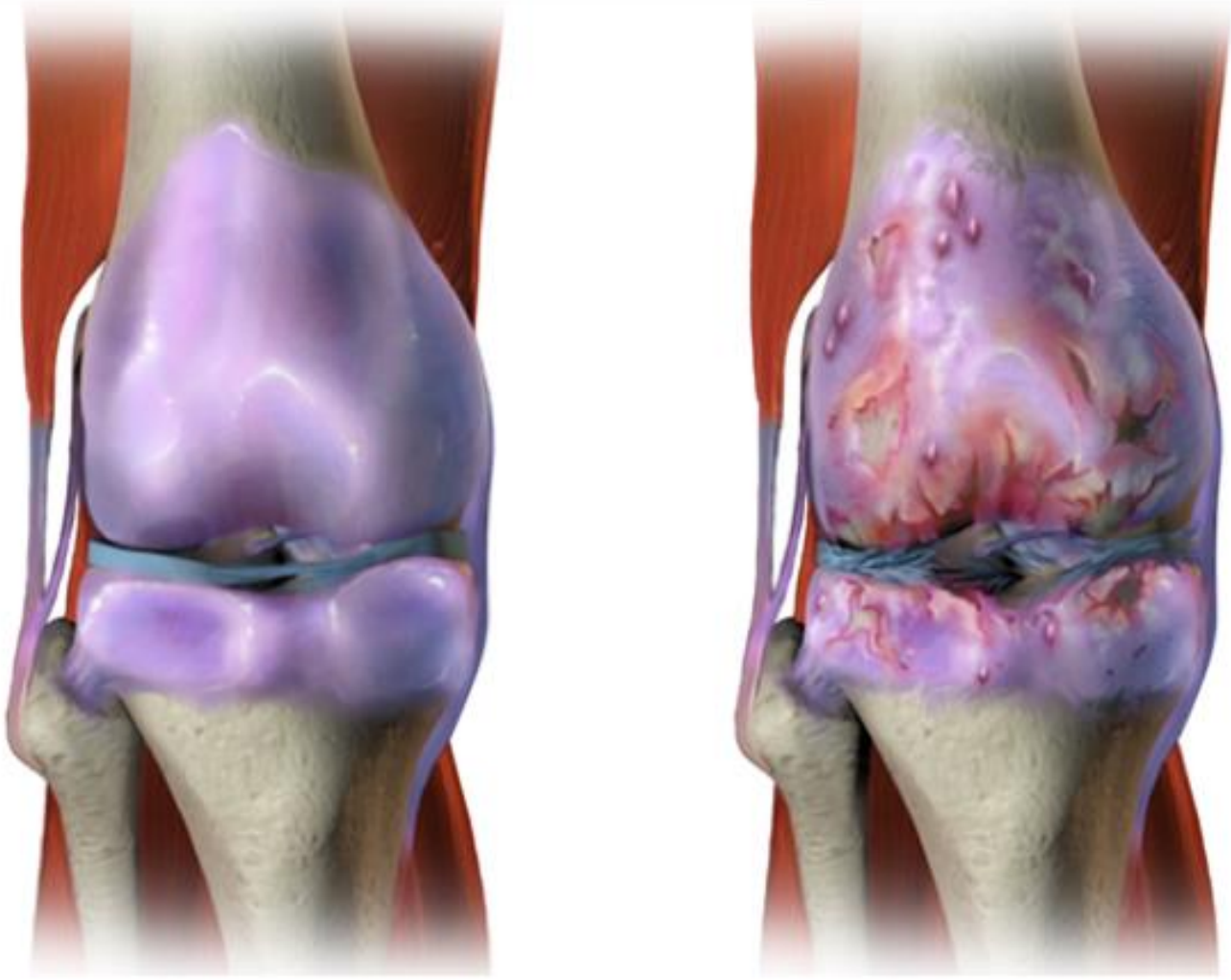


mRNA's 2 deficiencies:

- **Half-life**: just hours
- **Cell-type specificity**: difficult to genetically control

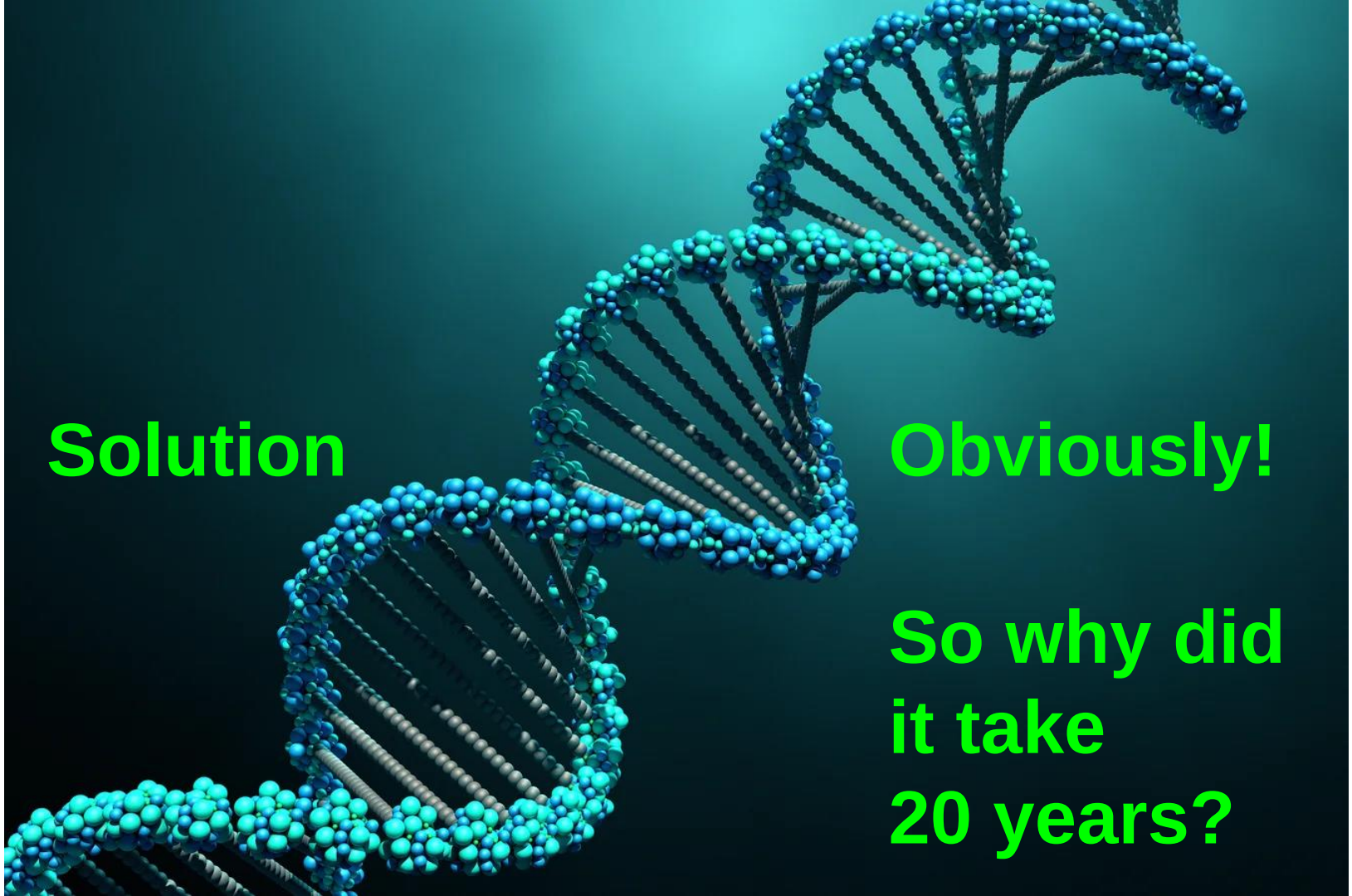

mRNA leaves behind
common
chronic
diseases

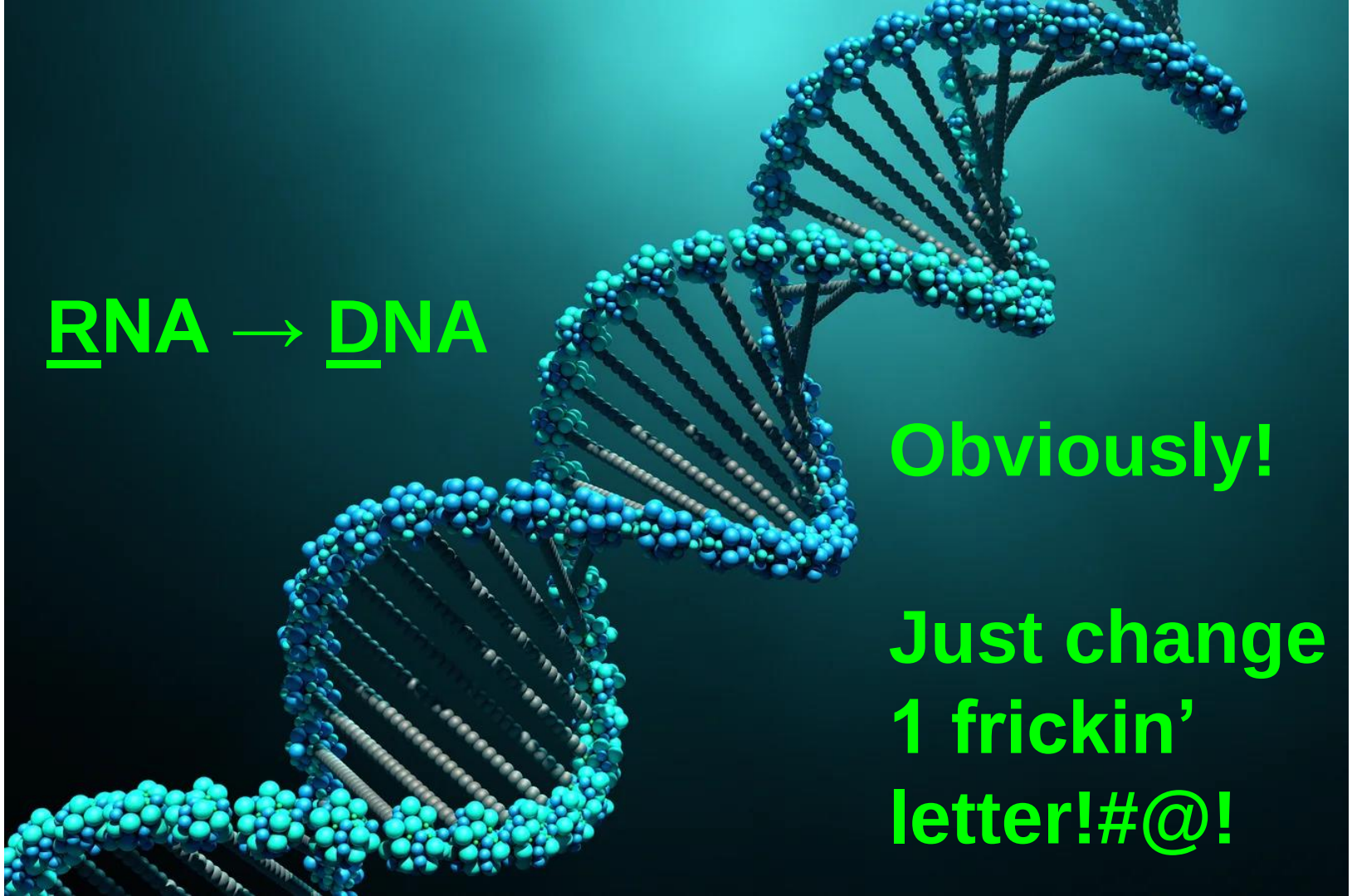




Common chronic diseases
produce the
vast majority
of morbidity and mortality
in the developed world


mRNA leaves behind
common
chronic
diseases


Solution
Obviously!
So why did it take 20 years?


RNA → DNA
Obviously!
Just change 1 frickin' letter!#@!


Your mouse will explode !!!

Outline

- The path to making the first safe & effective DNA-LNPs:
  - Making LNPs non-inflammatory (*Nature Nano* ‘25)
  - Enabling DNA loading into LNPs (*Nature Biotech* ‘25)
  - Improving DNA-LNP expression (*in revision*)
- Where DNA-LNPs fit into the genetic medicine toolbox

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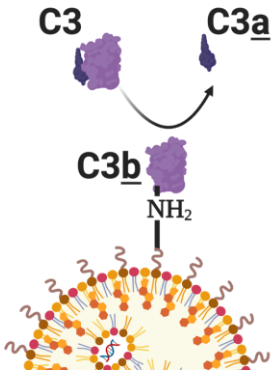
"We haven't seen any side effects with our LNPs"
optimism

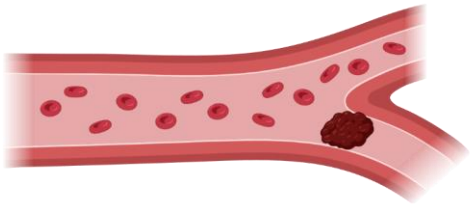
Mechanistic Engineering of Toxicology (MET) for LNPs

Complement



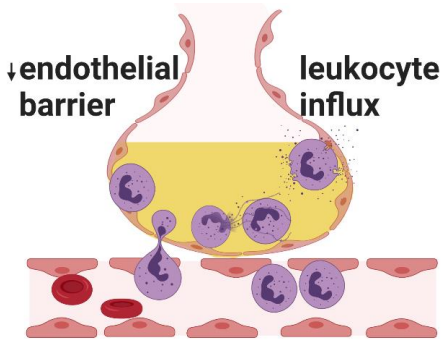
Wang, *Cell,* 2025
Zaleski, *Advanced Materials*, 2024
Wang, *Advanced Materials*, 2022

Thrombosis



Omo-Lamai, *Advanced Materials*, 2024
Zamora, *Nano Letters*, 2024

Inflammation



Patel, *Nature Biotechnology*, 2025
Omo-Lamai, *Nature Nano, 2025*
Zamora, *ACS Nano*, 2024
Parhiz, *J Controlled Release*, 2021

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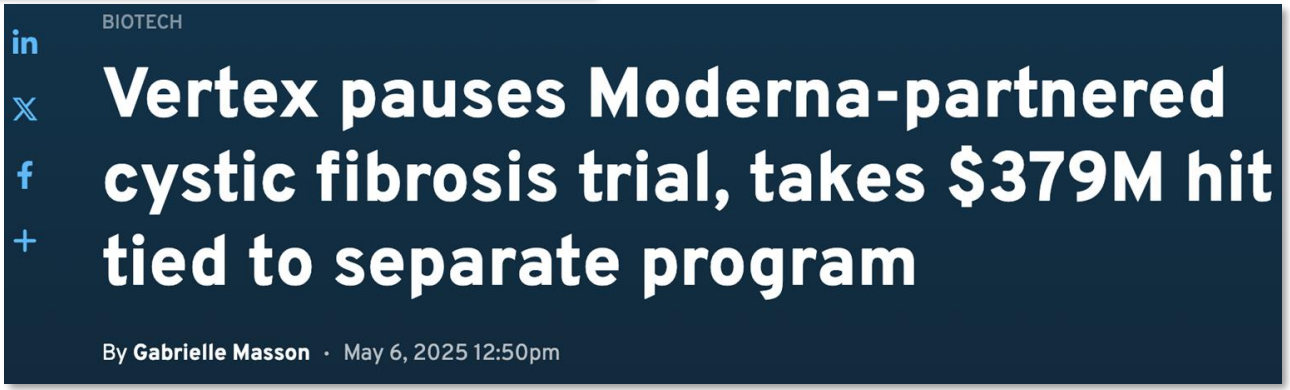
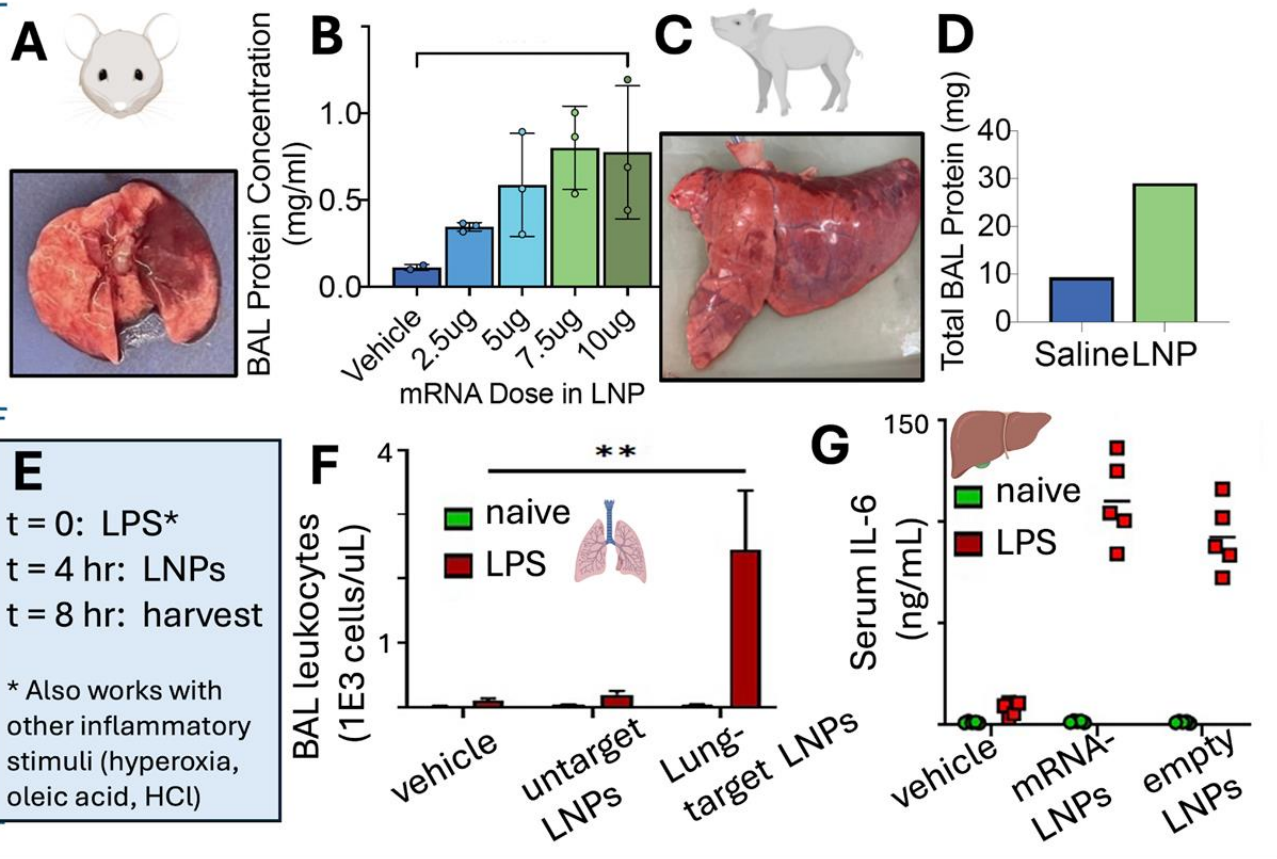
LNPs' most common toxicity
LNP-associated inflammation (**LAI**)



LNP-associated inflammation (LAI)

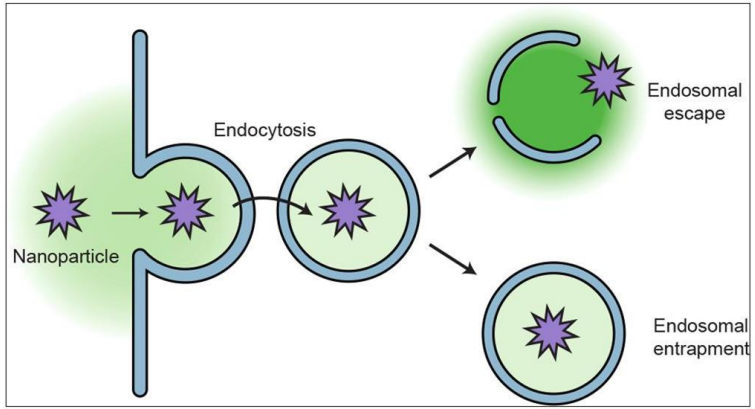
De novo inflammation in select organs (ex: inhaled into lungs)

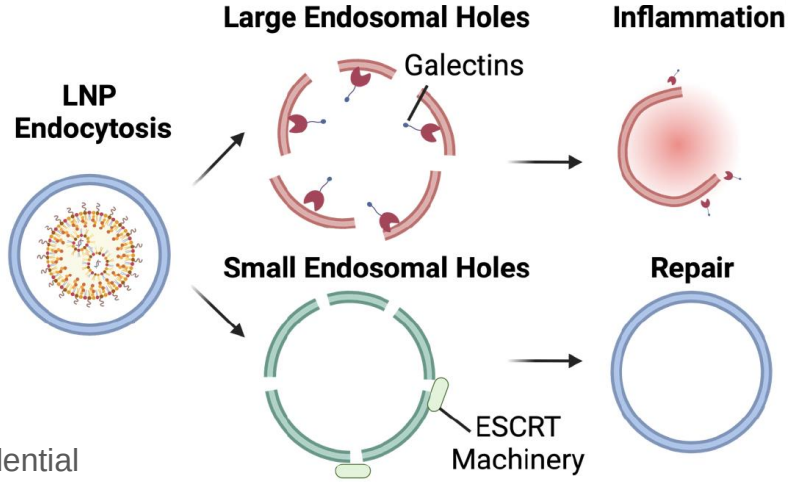
Exacerbation of pre-existing inflammation occurs in all organs tested

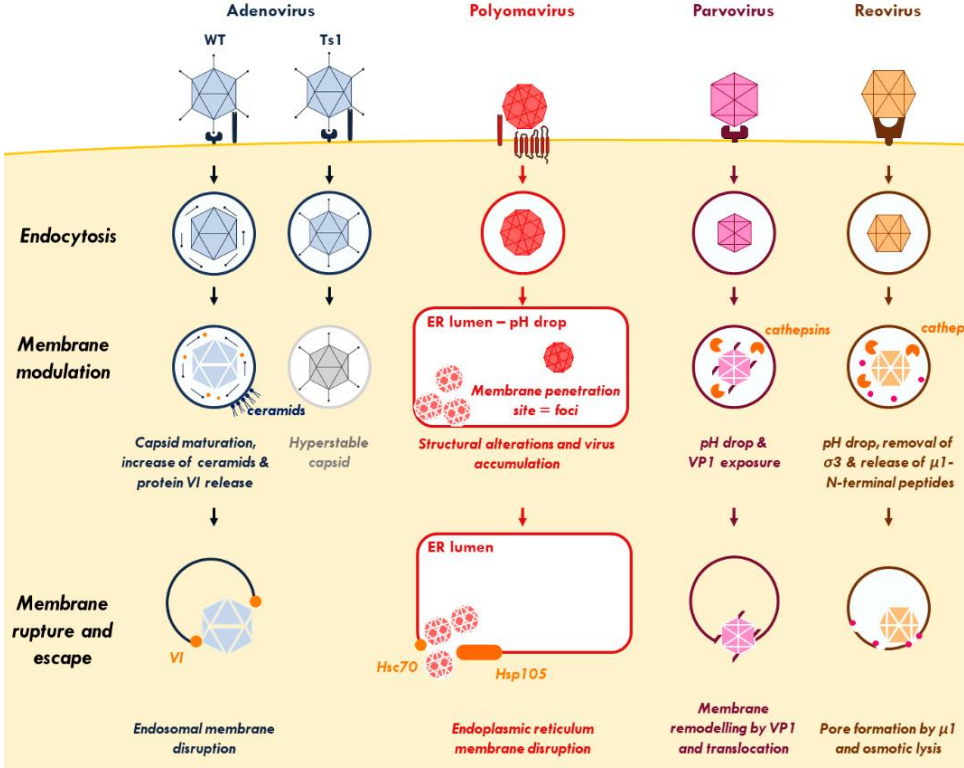


Omo-Lamai*, Wang*, Patel*, in press at *Nature Nano*

The mechanism of LAI: LNPs induce endosomal damage

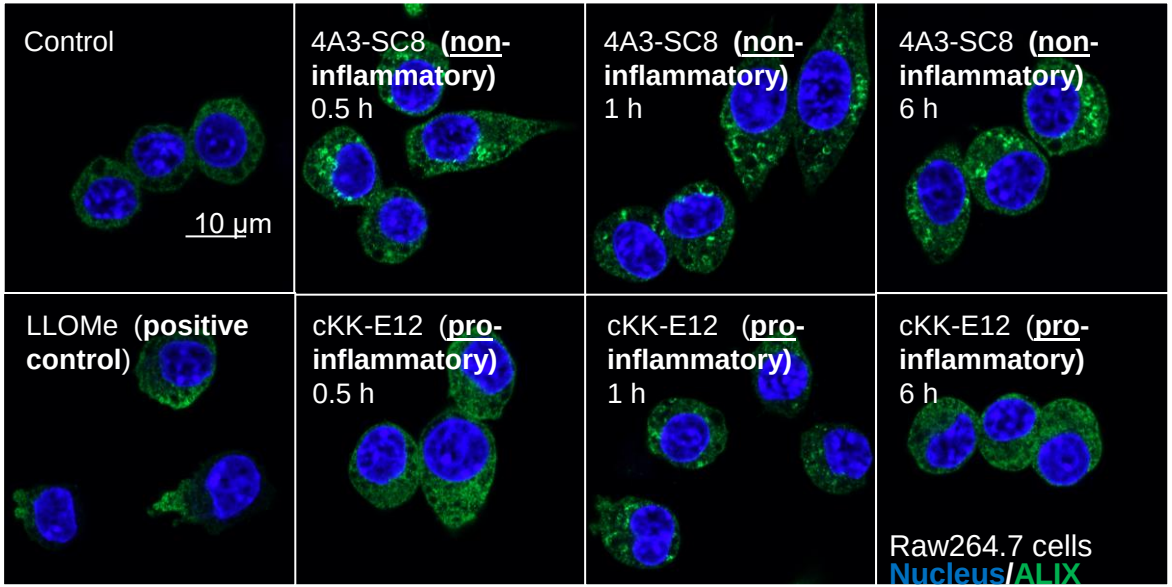


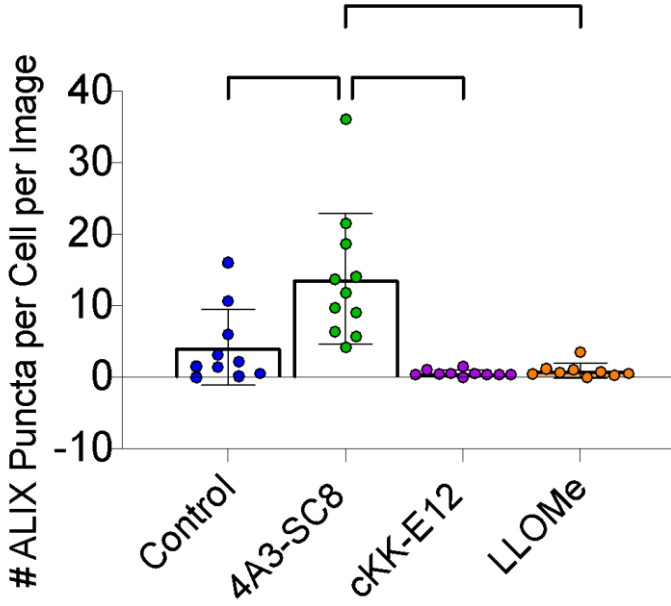




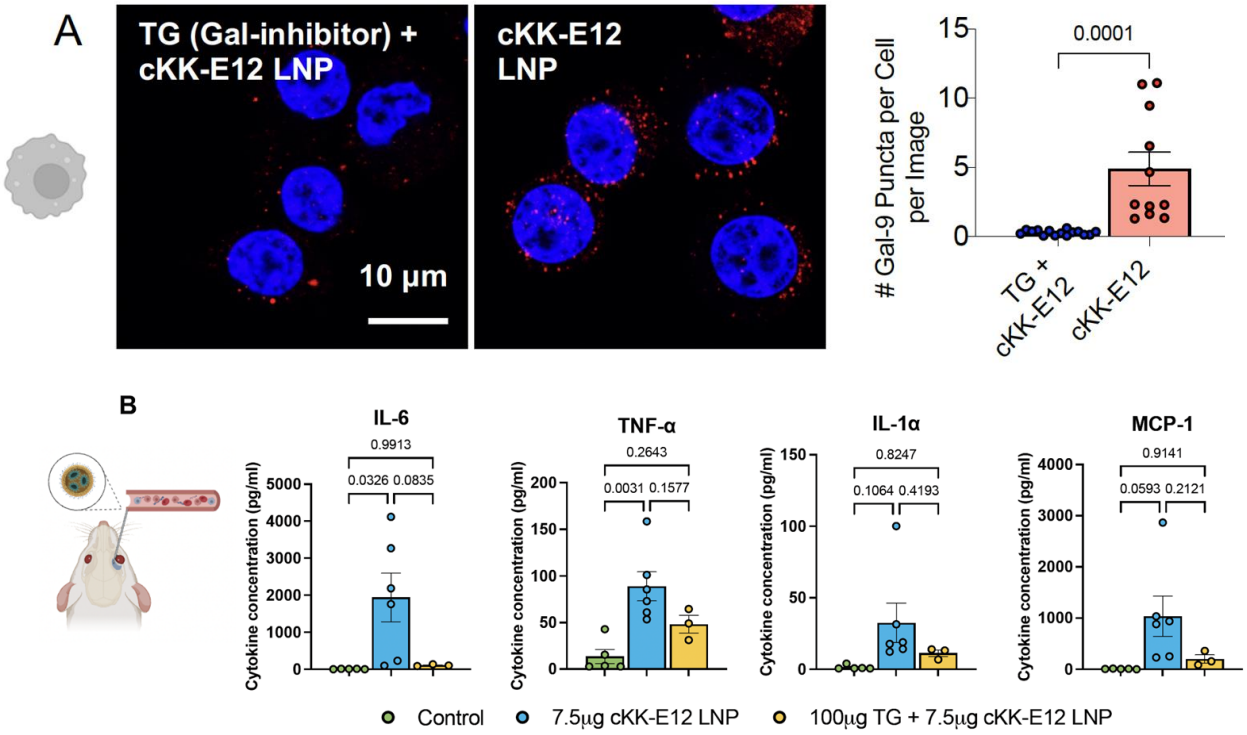
Omo-Lamai*, Wang*, Patel*, in press at *Nature Nano*

Small, reparable holes are repaired by ESCRT

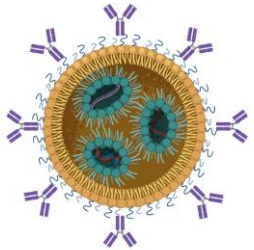




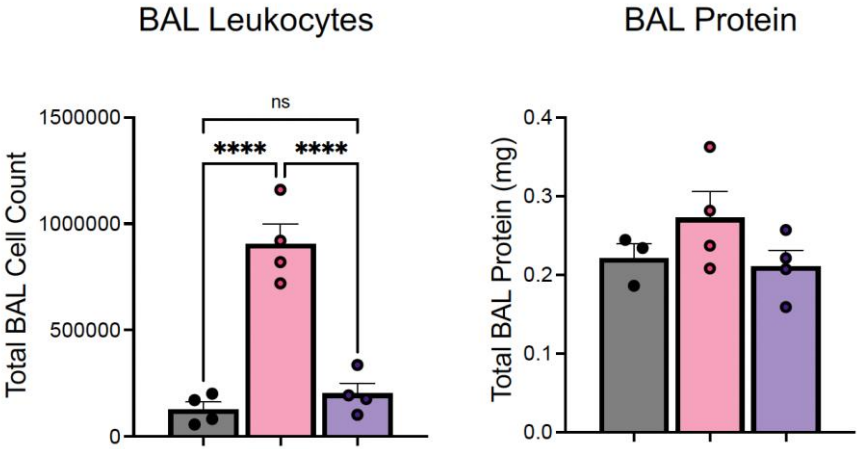
We can prevent LAI by blocking galectins, the primary sensors of endosomal damage



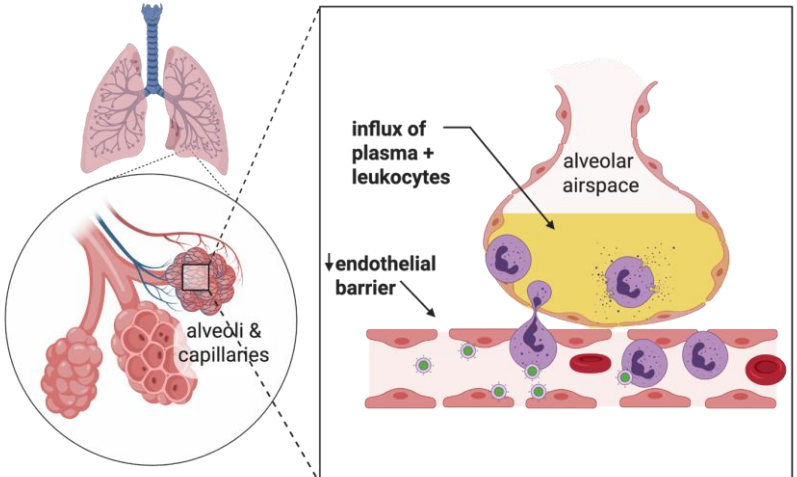
But can our new LNPs fix severe inflammation, like ARDS?



anti-PECAM
mRNA = IL-10



naive
neb-LPS + vehicle
neb-LPS + IL-10 LNPs + galectin inhibitor



Omo-Lamai*, Wang*, Patel*, in press at *Nature Nano*

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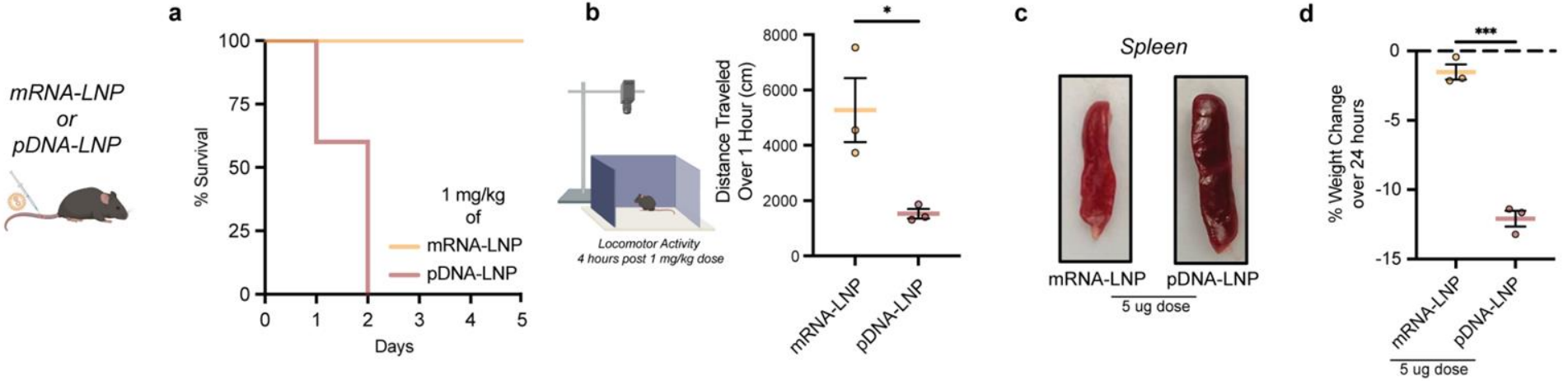
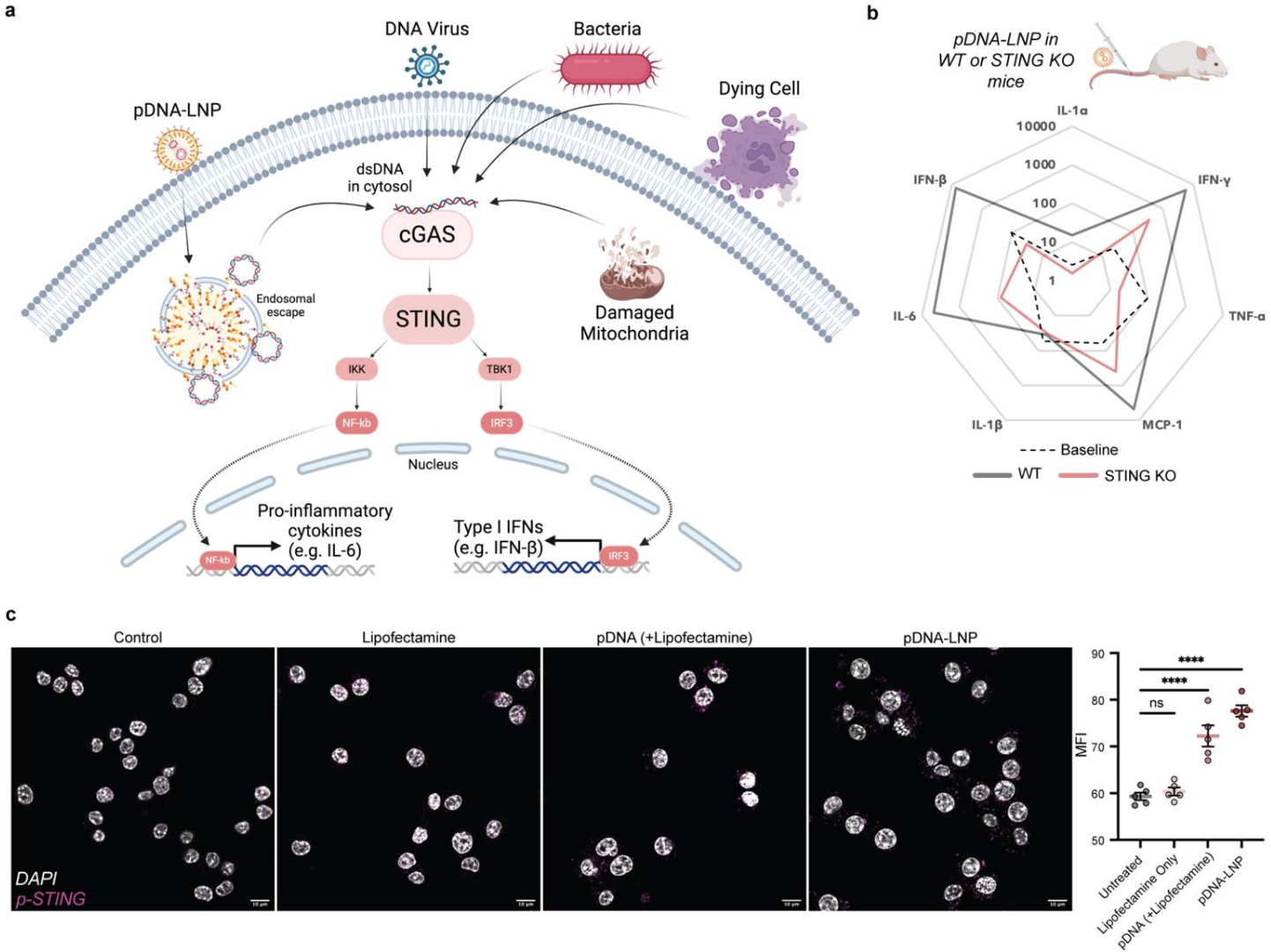
Your mouse will explode !!!

Is DNA inside an LNP really so toxic?

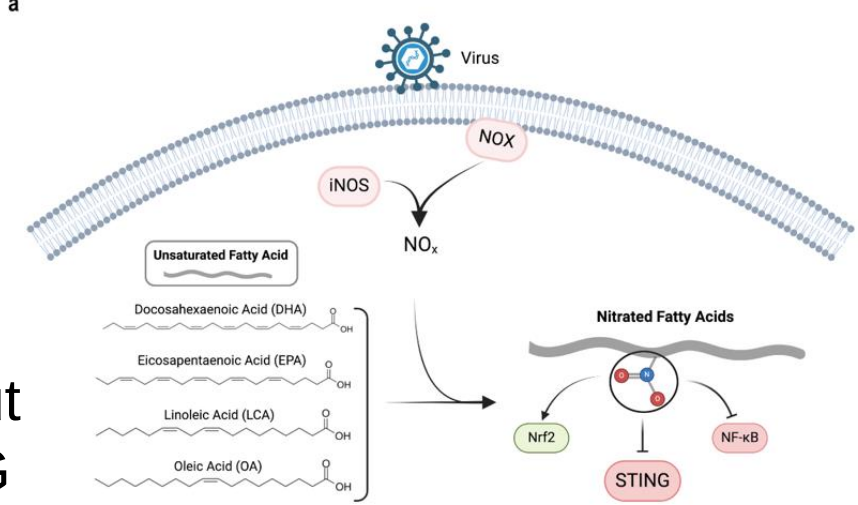


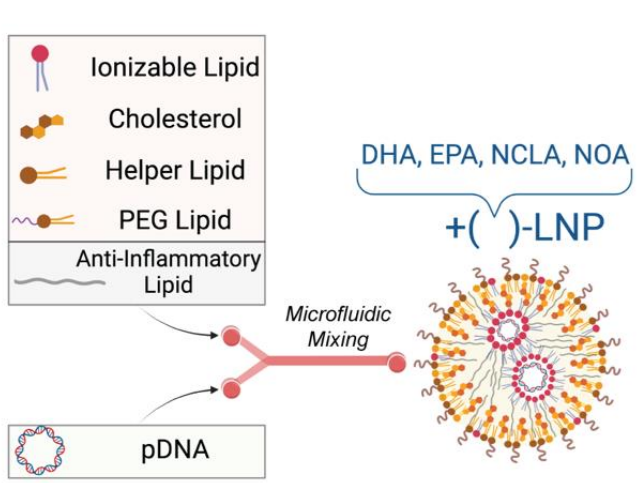
Patel & Tiwari, Nature Biotech 2025, [link]

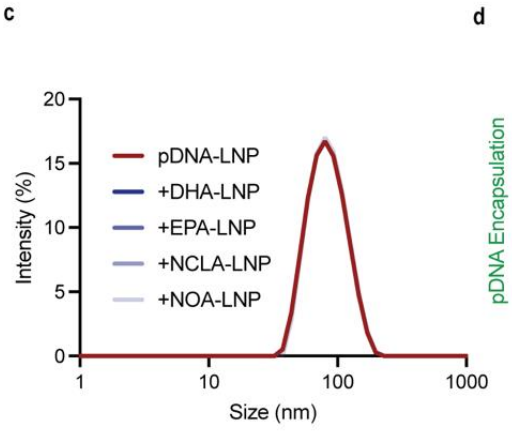
We figured out the pathway underlying this toxicity: cGAS-STING

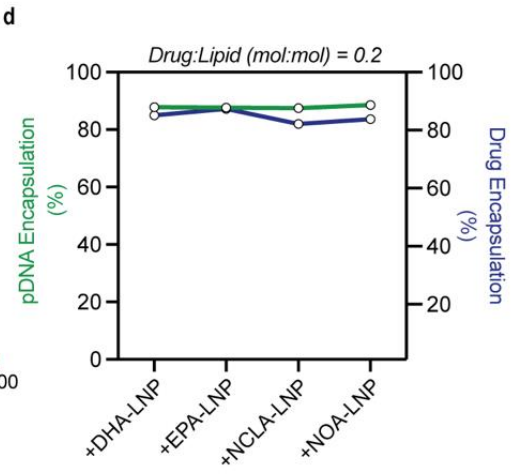


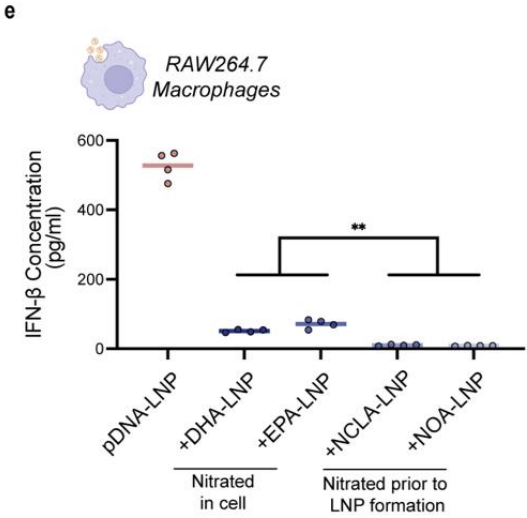
We figured out to load STING inhibitors into LNPS



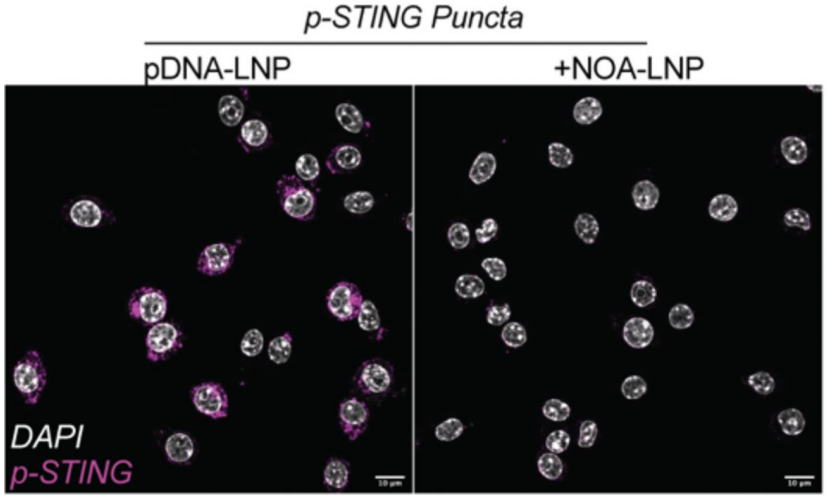


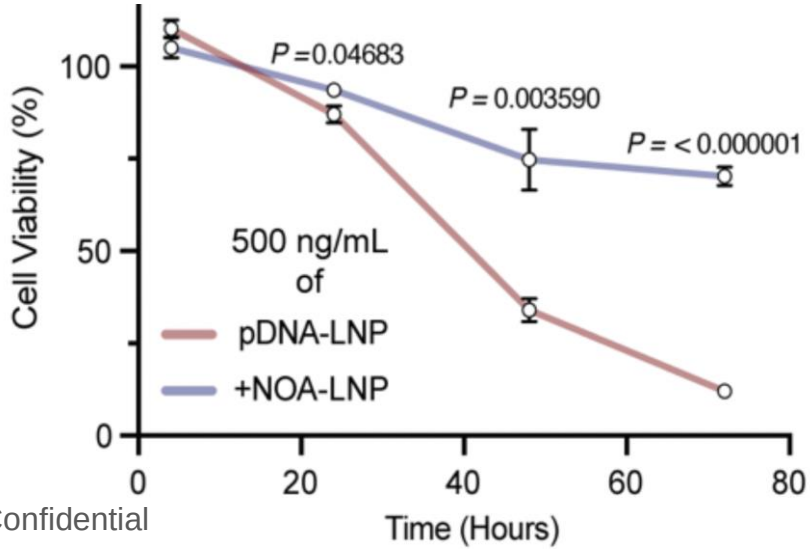


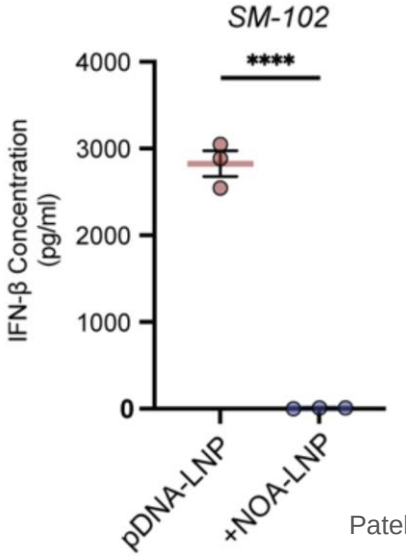




NOA-DNA-LNPs inhibit STING and improve in vitro expression

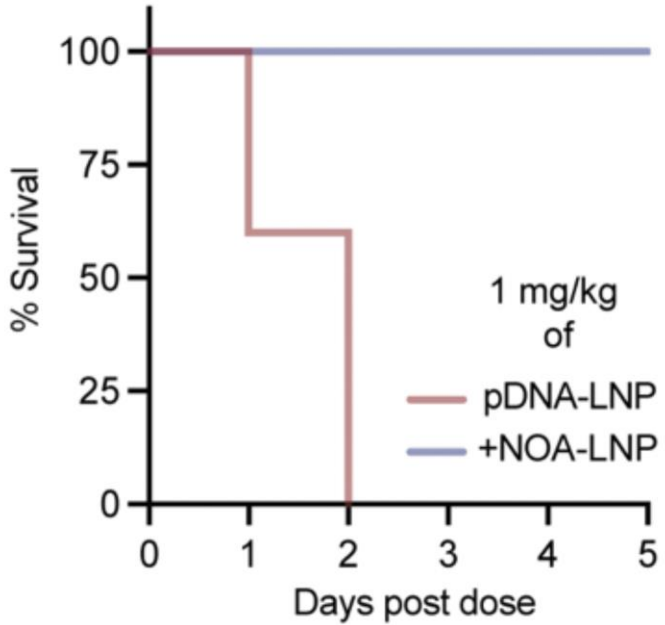






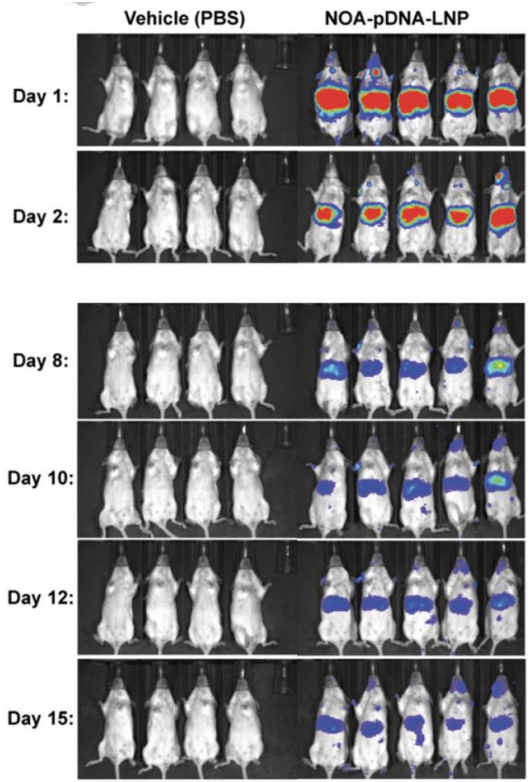
Patel & Tiwari, Nature Biotech 2025, link

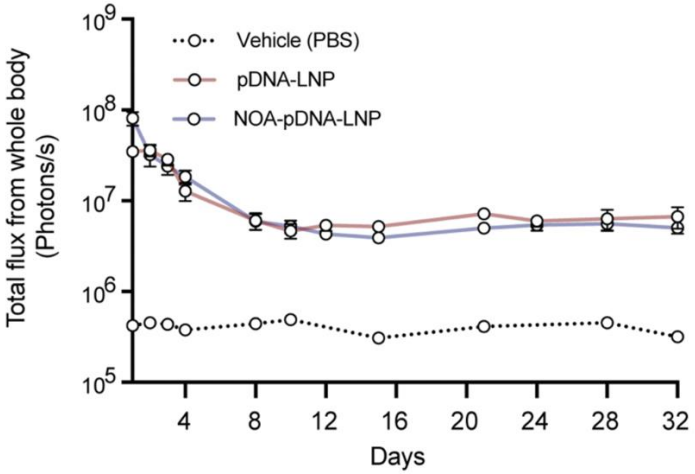
NOA completely eliminates the mortality of DNA-LNPs

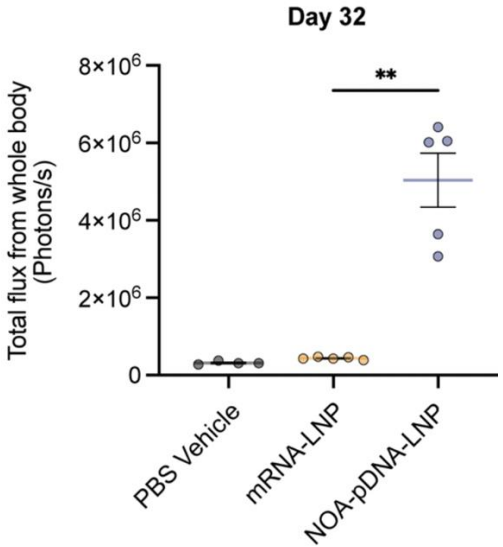


Patel & Tiwari, Nature Biotech 2025, link

NOA-DNA-LNPs express in vivo for >6 months / dose







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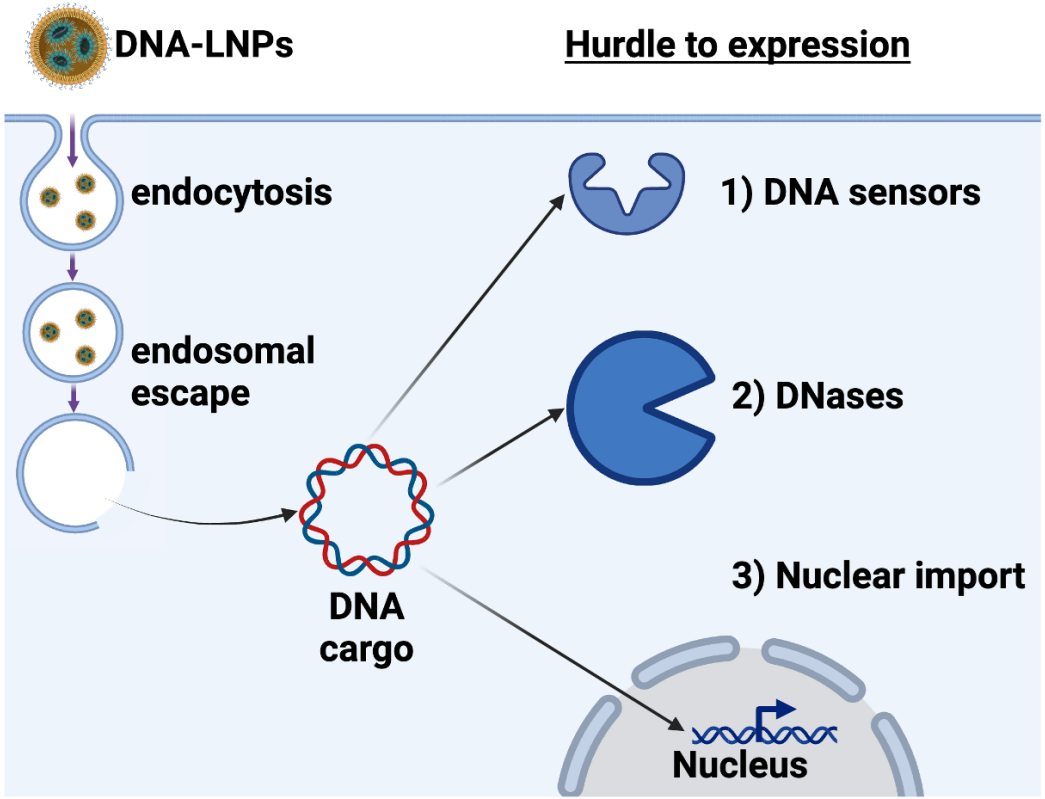
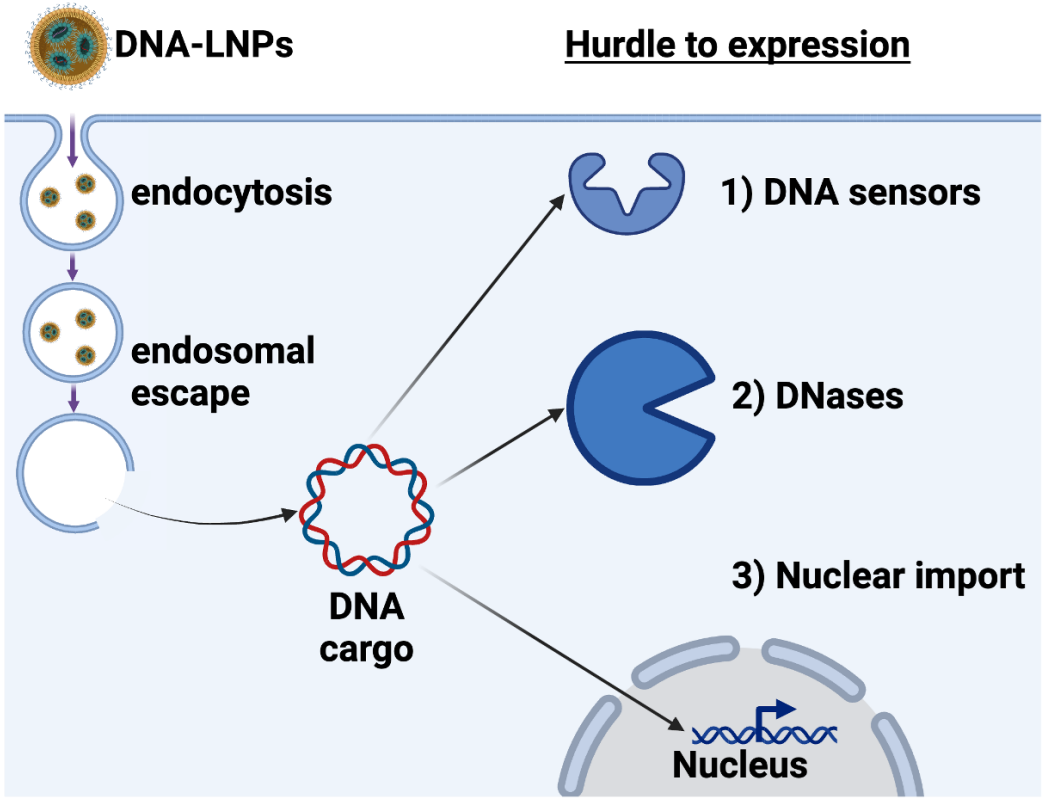
The cell's barriers to DNA-viruses, and DNA-LNPs



Nong*, Gong*, *in revision*, [bioRxiv]

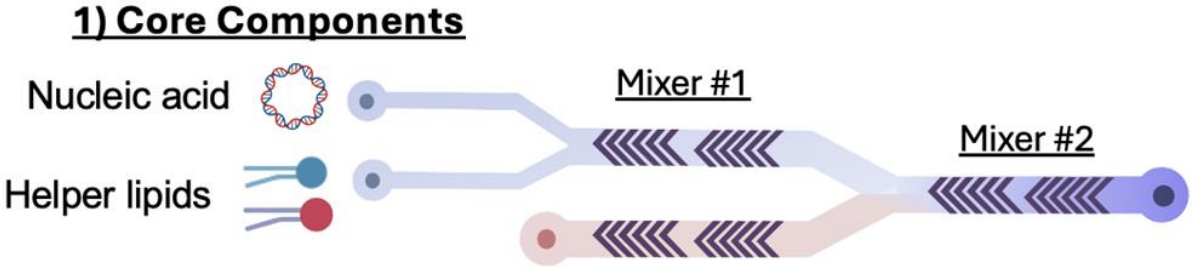
Compactify the DNA !

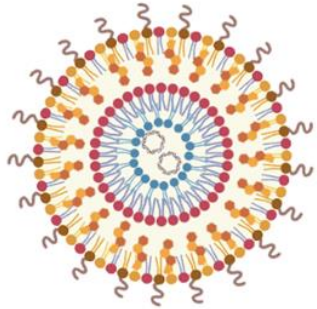
The cell's barriers to DNA-viruses, and DNA-LNPs

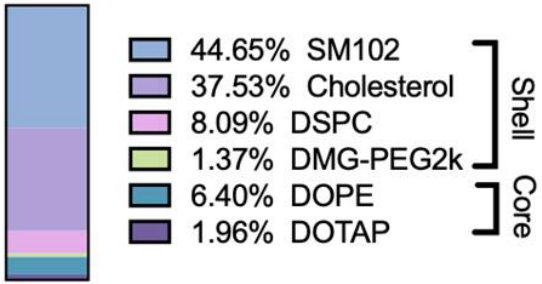


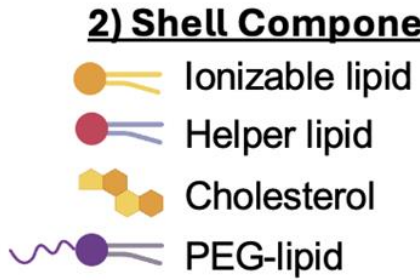
Nong*, Gong*, *in revision*, [bioRxiv]

Multi-Stage Mixing (**MSM**) microfluidics: A new paradigm to control the supramolecular arrangement of LNP components

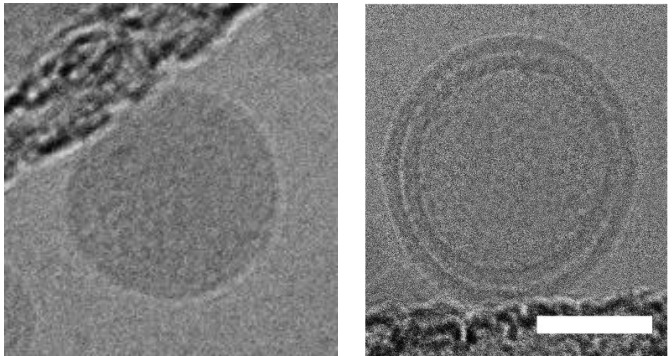






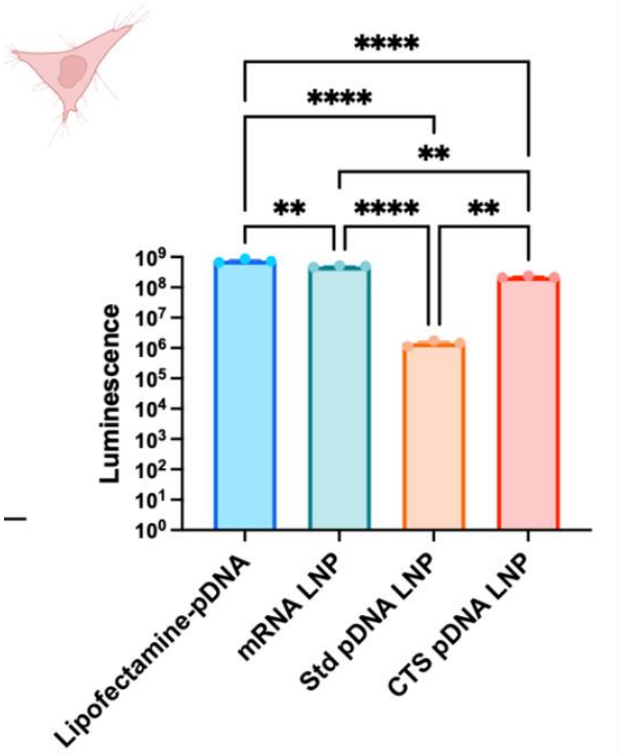


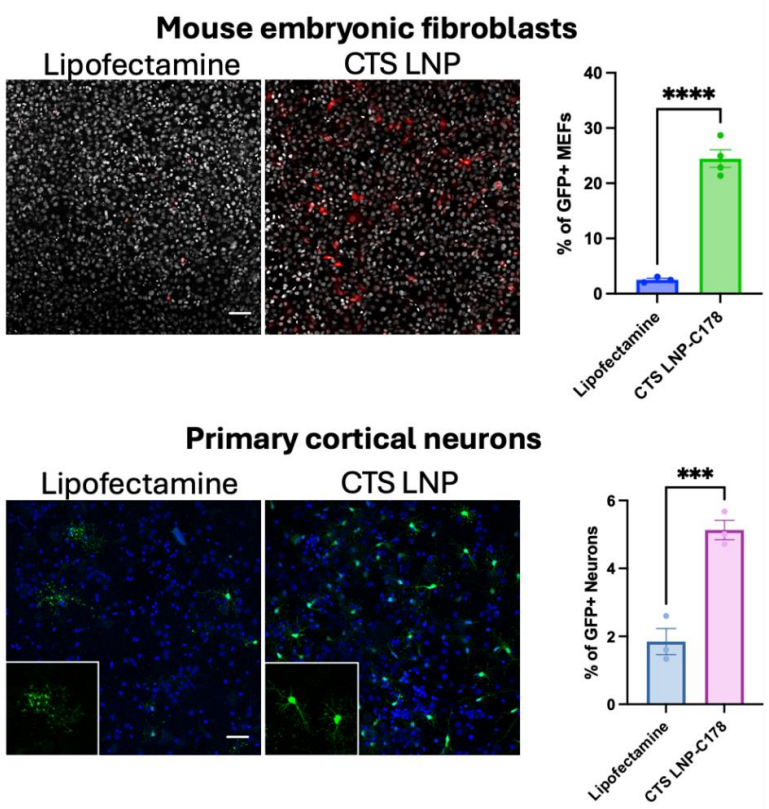
Core-Then-Shell (CTS) LNPs



Nong*, Gong*, *in revision*, [bioRxiv]

Core-then-shell (CTS) LNPs massively improve protein expression for DNA-LNPs.





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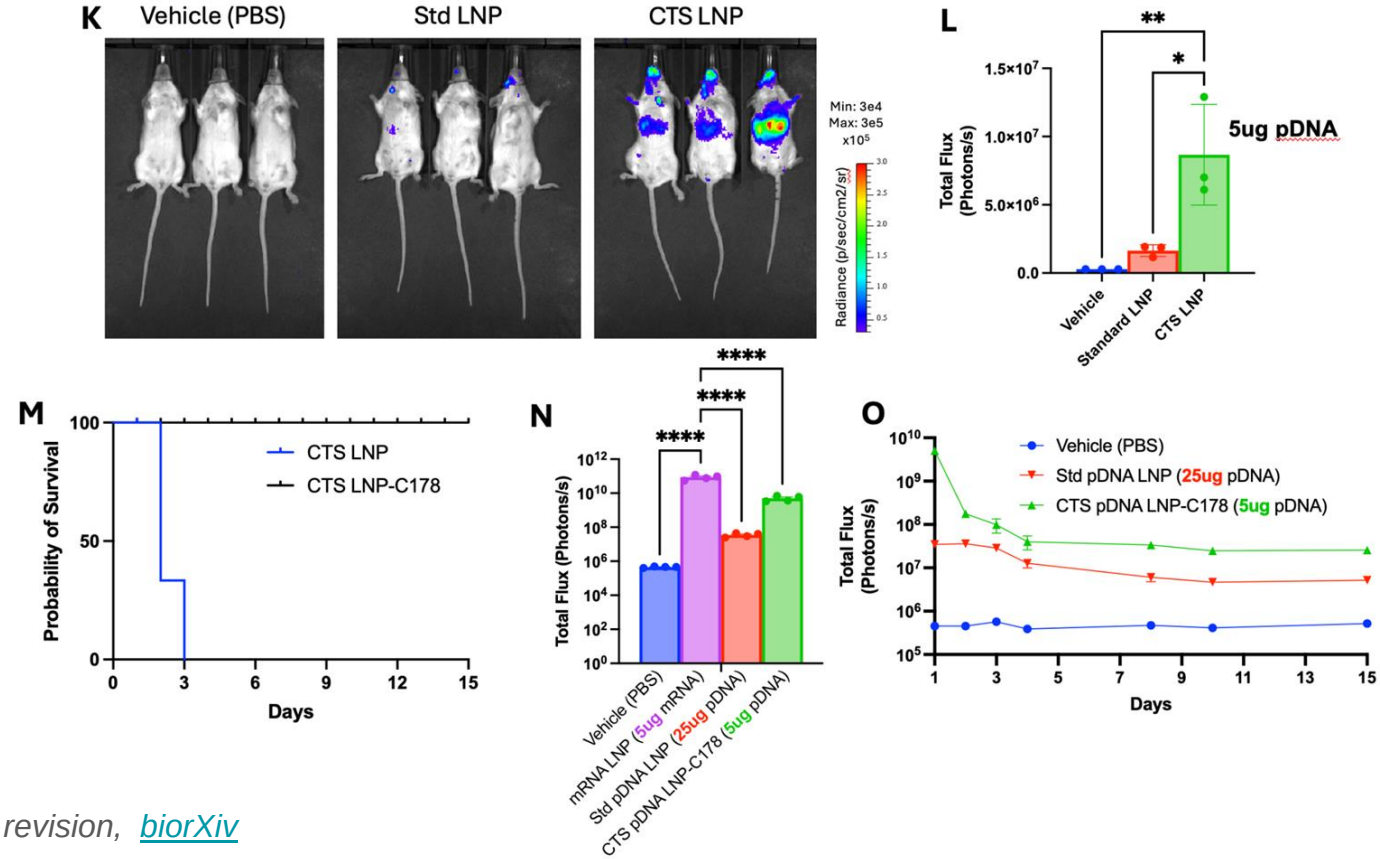
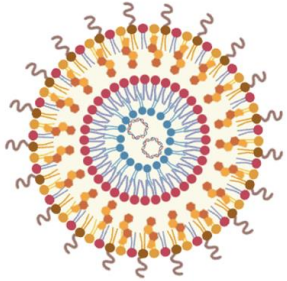
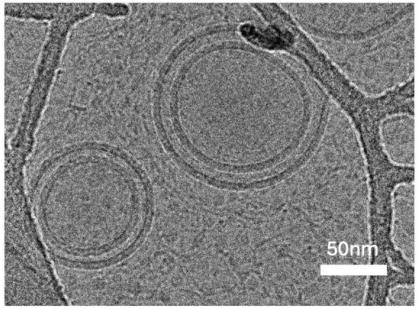


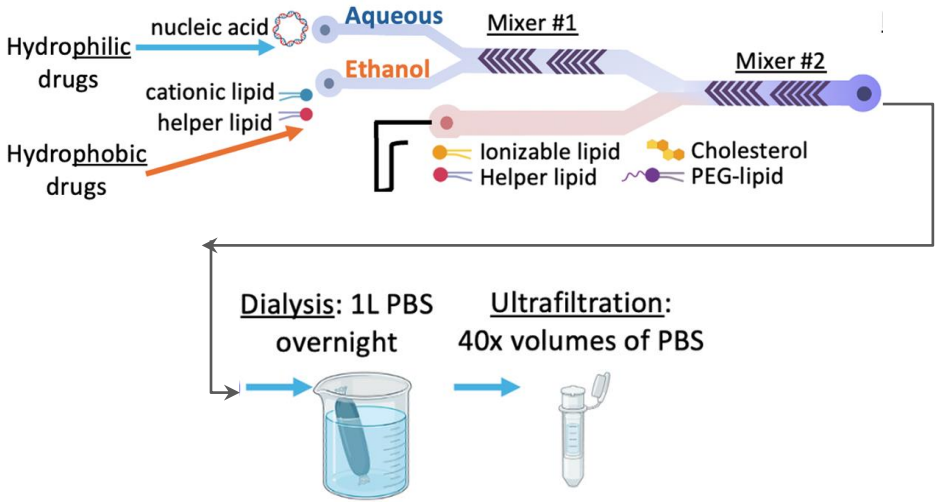
Nong*, Gong*, *in revision*, [*bioRxiv*]

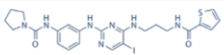
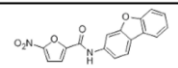
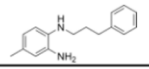
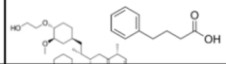
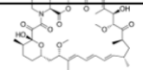
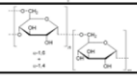
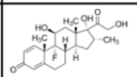
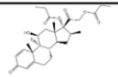
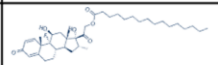
Core-then-shell (CTS) LNPs can load diverse drugs

Core-Then-Shell (CTS) LNP



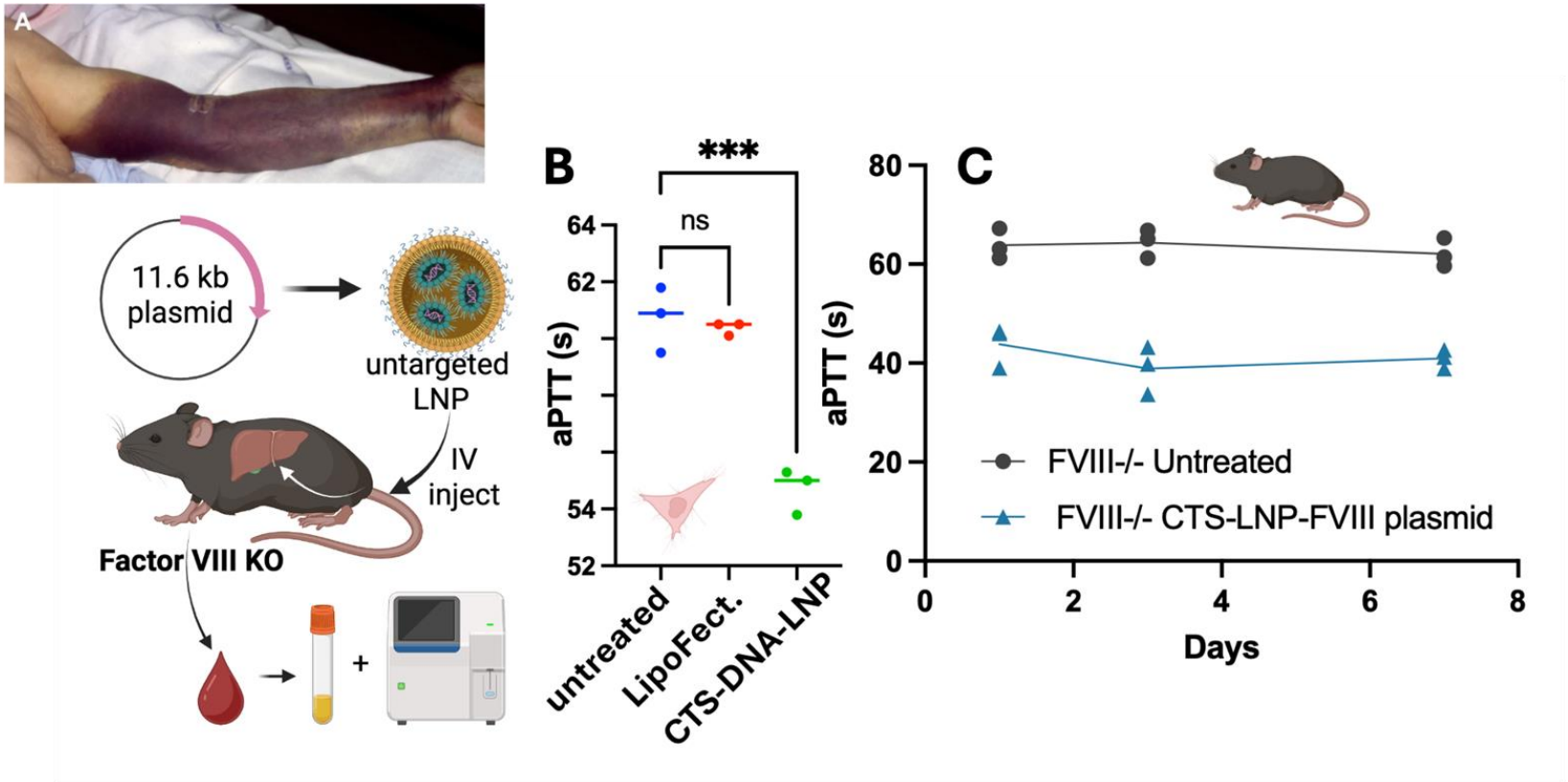




Drug	Structure	Loading Eff. % (D/L)
BX-795		**27.3%** (0.013)
C-178		**97.5%** (0.021)
JSH-23		**9.5%** (0.0025
4-PBA		**48.5%** (0.73)
everolimus		**59.1%** (0.024)
FITC-dextran (70kDa)		**22.1%** (0.0001
dexamethasone-21P (LogP = 1)		**43.4%** (0.086)
dexamethasone (Log P = 1.7)		**29.6%** (0.059)
betamethasone diprop. (LogP = 4)		**59.1%** (0.118)
dexamethasone-palmitate (LogP 8.6)		**29.6%** (0.164)

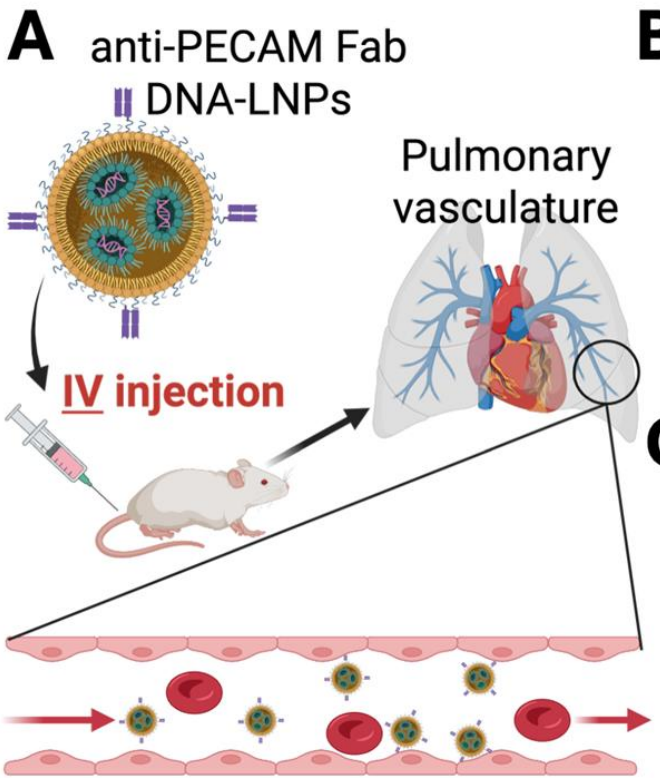
Nong*, Gong*, *in revision*, [bioRxiv]

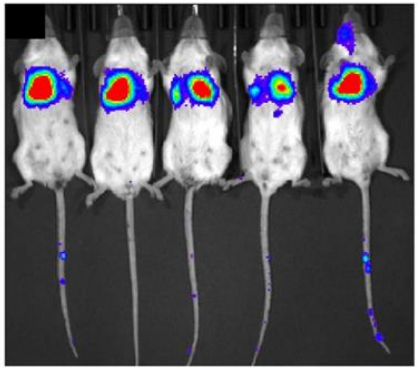
Core-then-shell (CTS) DNA-LNPs can ameliorate disease

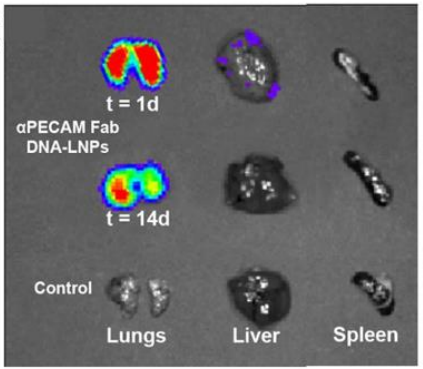


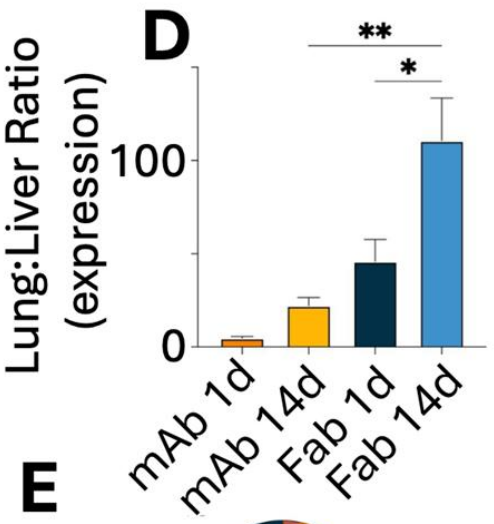
Nong*, Gong*, *in revision*, [bioRxiv]

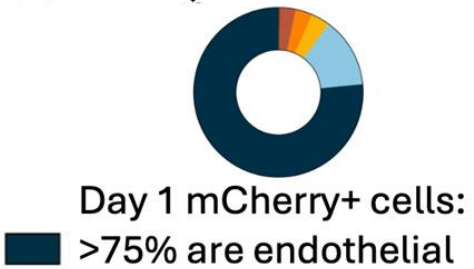
Targeted DNA-LNPs show better cell-type-specificity than mRNA-LNPs, even before adding cell-specific promoters











Marzolini & Brysgel, *under review*

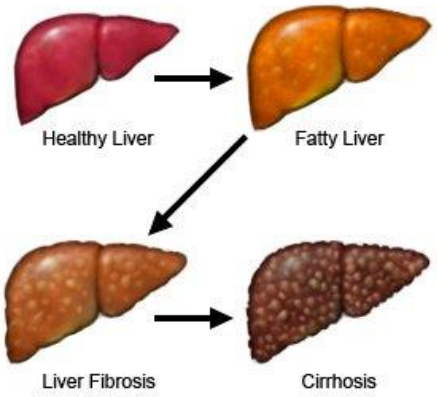
Outline

- The path to making the first safe & effective DNA-LNPs:
  - Making LNPs non-inflammatory (*Nature Nano* ‘25)
  - Enabling DNA loading into LNPs (*Nature Biotech* ‘25)
  - Improving DNA-LNP expression (*in revision*)
- Where DNA-LNPs fit into the genetic medicine toolbox

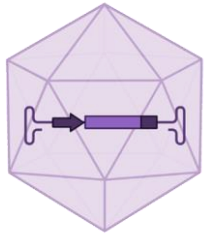
The niche for DNA-LNPs: Common chronic diseases

- Common chronic diseases constitute the vast majority of morbidity and mortality in the developed world:
  - atherosclerosis, obesity, fibrosis, cancer...

- Common, chronic diseases are perfectly suited to DNA-LNPs' attributes:
  - 6 months expression / dose. Redosable.
  - Expression or knockdown (by expressing shRNA) of any protein.
  - No cargo size limitation
  - DNA-LNPs' *promoter regions* enable truly cell-type-specific expression and titration of dose via doxycycline pills

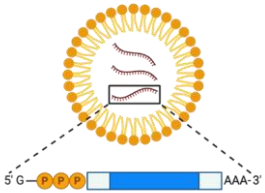


Advantages of DNA-LNPs for common chronic diseases

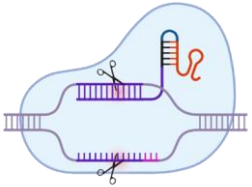


- Integration: DNA-LNPs do not integrate into the genome like AAV
- Cargo size: DNA-LNPs enable cargo >10 kb, c.t. 4.4 kb for AAV
- Immunogenicity: DNA-LNPs << AAV, and can be redosed
- Promoters: DNA-LNPs can have cell-type-specific promoters

- Cargo: DNA-LNPs can encode shRNA which is ~siRNA
- Promoters: DNA-LNPs can have cell-type-specific promoters



- Duration: mRNA ~ hours, DNA-LNPs ~ 6 months
- Promoters: DNA-LNPs can have cell-type-specific promoters



- Duration: For non-monogenic diseases, permanence is risky
- Targets: Common chronic diseases don’t have knockout targets
- Genomic instability risk: High with CRISPR, very low w DNA-LNPs
- Every mutation is a new drug: DNA-LNPs replace whole gene

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- Eno Essien, MD
- **Zhicheng Wang, PhD**
- Yufei Wang, PhD
- **Jia Nong, PhD**
- Sach Tiwari, PhD
- Jichuan Wu, MD, PhD
- Liam Chase
- Aparajeeta Majumder

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- **Jacob Myerson, PhD**
- **Oscar Marcos Contreras, PhD**
- Norbi Pardi, PhD
- Jeremy Katzen, MD

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- R41-NS130812 (NanoMuse)
- Code Bio SRA
- BioNTech SRA

BRENNER BIOENGINEERING LAB


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SCIENCE
BENEFITS
EVERYONE
STANDING
UP FOR SCIENCE
IS STANDING UP FOR
PEOPLE WITH
CANCER
STROKE
ALZHEIMER
TBI
HEART DISEASE
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MAKES
US
STRONGER

Questions?

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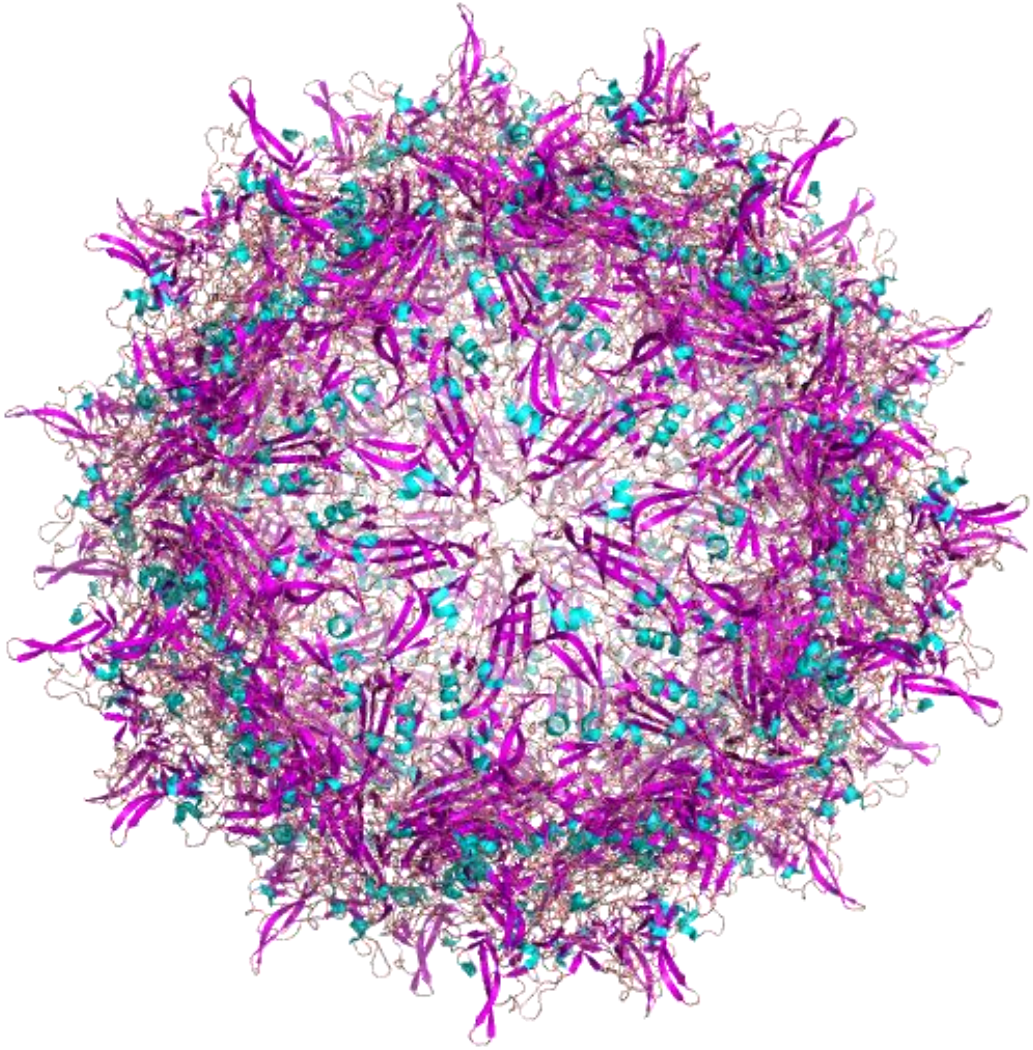
APPENDIX



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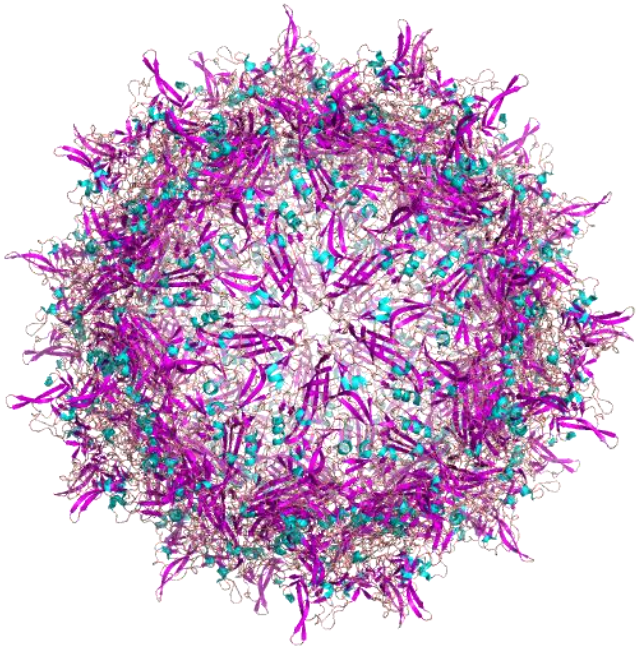

AAV: New problems emerged with new uses

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- Genomic integration far higher than thought
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- Senescence
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- Death

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Cell Reports Medicine

CellPress
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Article

Senescence and inflammation are unintended adverse consequences of CRISPR-Cas9/AAV6-mediated gene editing in hematopoietic stem cells

Anastasia Conti,[1] Kety Giannetti,[1] Federico Midena,[1,2] Stefano Beretta,[1] Nicolò Gualandi,[1] Rosaria De Marco,[1,2] Edoardo Carsana,[1] Angelica Varesi,[3] Teresa Tavella,[1] Laura Alessandrini,[1,2] Parinaz Zarghamian,[4,5] Alessandra Weber,[1] Samuele Ferrari,[1] Chiara Brombin,[6] Diego Gilioli,[1,2] Lucrezia della Volpe,[1,2] Stephanie Z. Xie,[3] Ivan Merelli,[1,7] Toni Cathomen,[4,8] Luigi Naldini,[1,2] and Raffaella Di Micco[1,9,10,*]

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Ectopic clotting factor VIII expression and misfolding in hepatocytes as a cause for hepatocellular carcinoma

Audrey Kapelanski-Lamoureux,[2,13] Zhouji Chen,[1,13] Zu-Hua Gao,[3,4,11] Ruishu Deng,[1] Anthoula Lazaris,[4] Cynthia Lebeaupin,[1,8] Lisa Giles,[5] Jyoti Malhotra,[5,12] Jing Yong,[1] Chenhui Zou,[7] Ype P. de Jong,[7] Peter Metrakos,[6] Roland W. Herzog,[9] and Randal J. Kaufman[1,5,8,10]

PHARMA

Sarepta tries to quell concerns over DMD gene therapy Elevidys as patients delay treatment after death report

By **Angus Liu** · May 7, 2025 8:03am

BIOTECH

ASGCT: Neurogene details new safety measures after young patient's death in AAV gene therapy trial

By **Darren Incorvaia** · May 16, 2025 3:00pm

BIOTECH

Rocket crashes as gene therapy patient dies, FDA imposes hold

By **Nick Paul Taylor** · May 27, 2025 9:49am

Cell & Gene Therapy | gene therapy | FDA | Rocket Pharmaceuticals

Goal: A platform technology for gene therapy of hematological diseases

Design Specifications

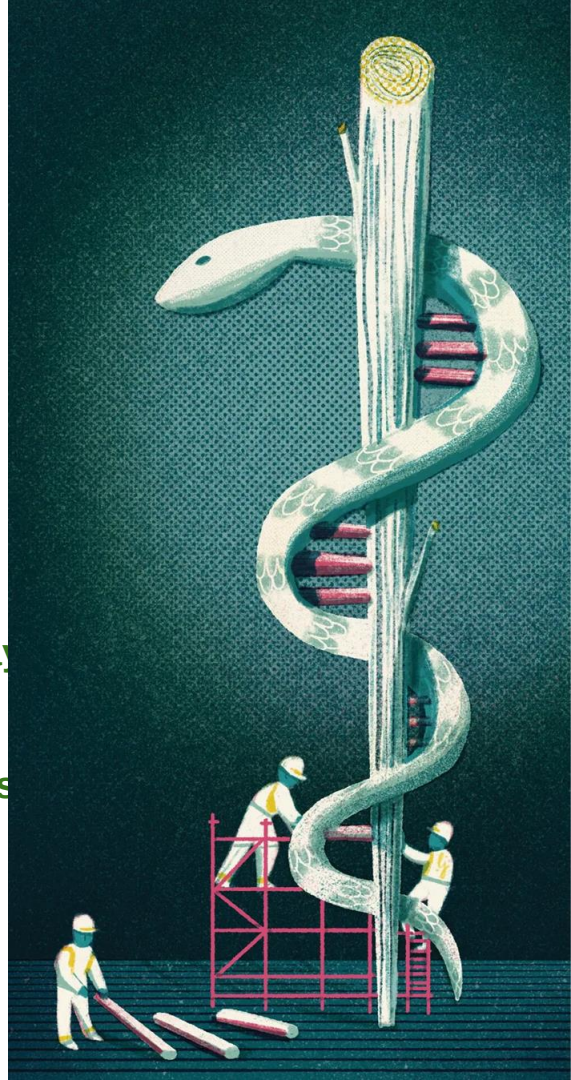
- Safe:

AAV?

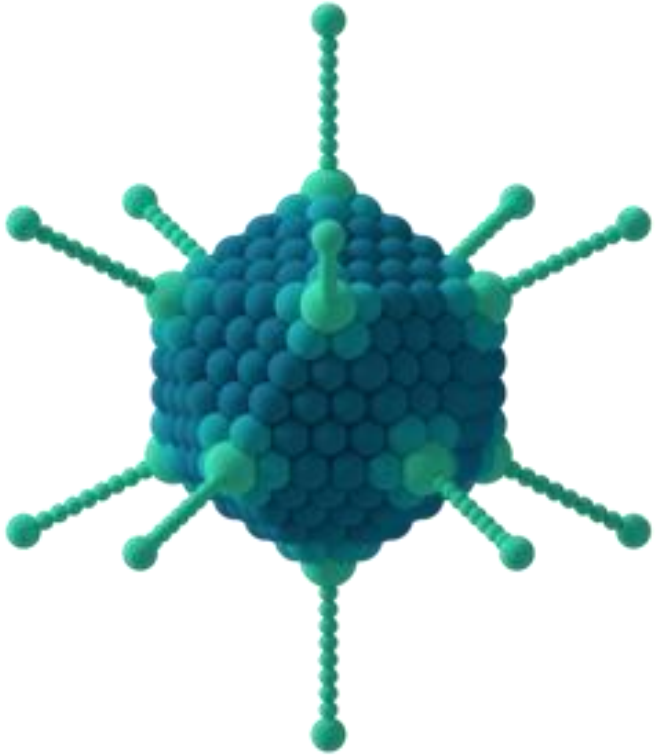
  - Minimal acute side effects
  - Non-immunogenic (no adaptive immunity) — **No**
  - No off-target DNA-damage
- Effective
  - Disease remission that is durable
  - Efficacy similar to non-gene therapy alternatives — **May**
- Dosing:
  - Repeat dosing is safe & effective
  - Dosing must be infrequent and convenient — **Yes**
- **Engineerable**
  - Modular components
  - Well-understood mechanisms
  - Any size gene

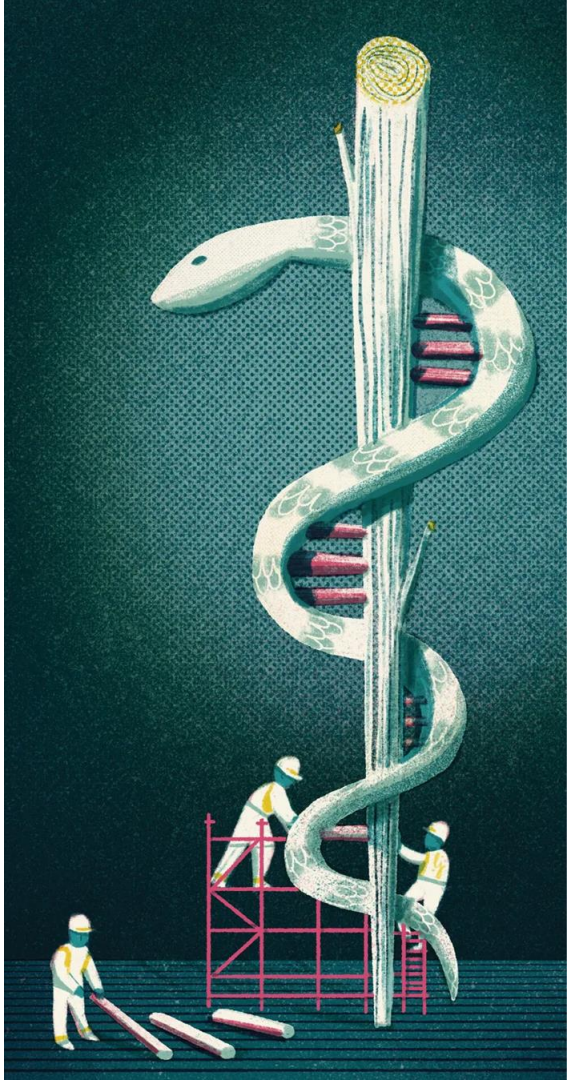
No

  - Express only in desired cell type
  - Reversible



Think outside the capsid (box)





Outline

- Goal: A platform technology for gene therapy of hematological diseases
- Unmet need in gene therapy: problems with current approaches
- The path to making the first safe & effective DNA-LNPs:
  - Making LNPs non-inflammatory
  - Enabling DNA loading into LNPs
  - Improving DNA-LNP expression
- Summary of DNA-LNPs' benefits & applications
- Proposed CSL Project, with Pilot Data
- Expanding beyond rare hematological diseases, within CSL's portfolio

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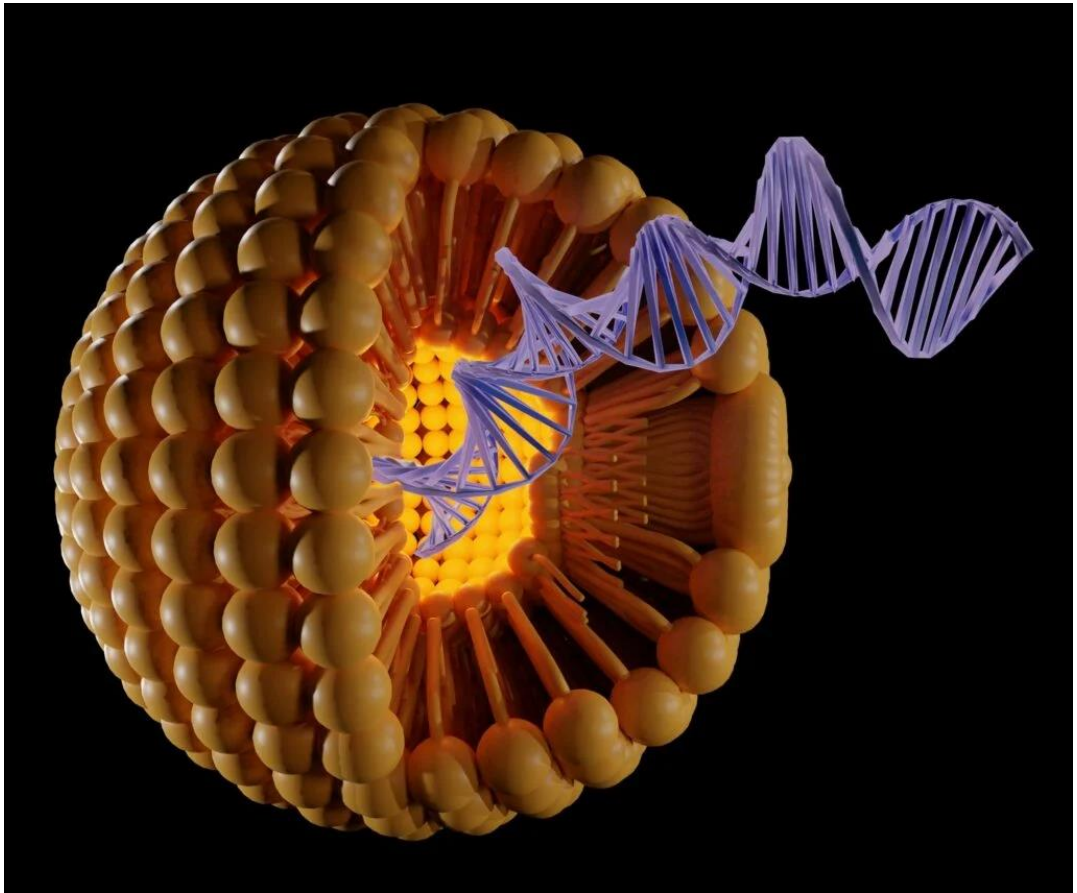

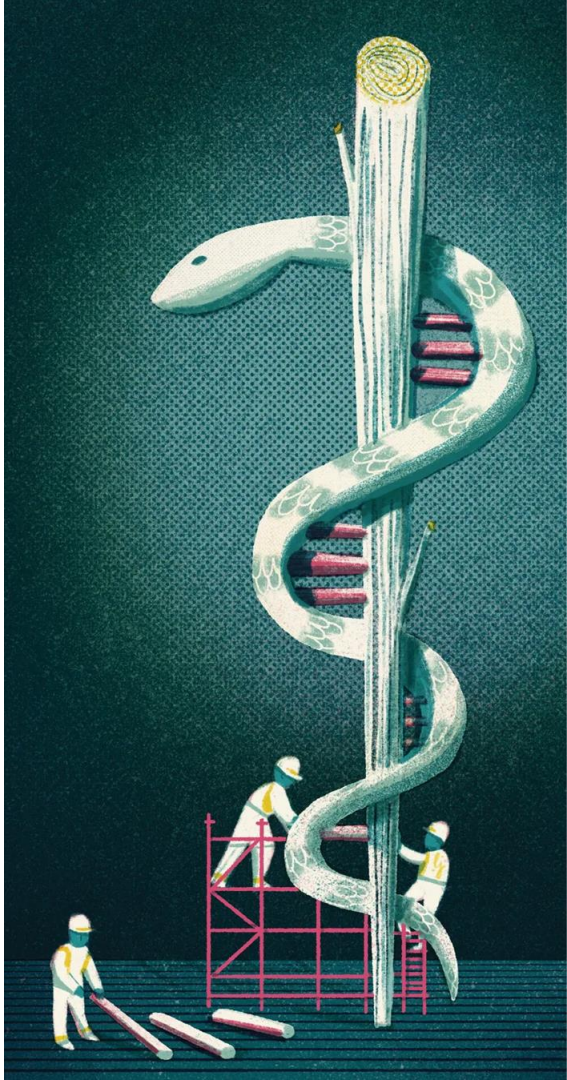

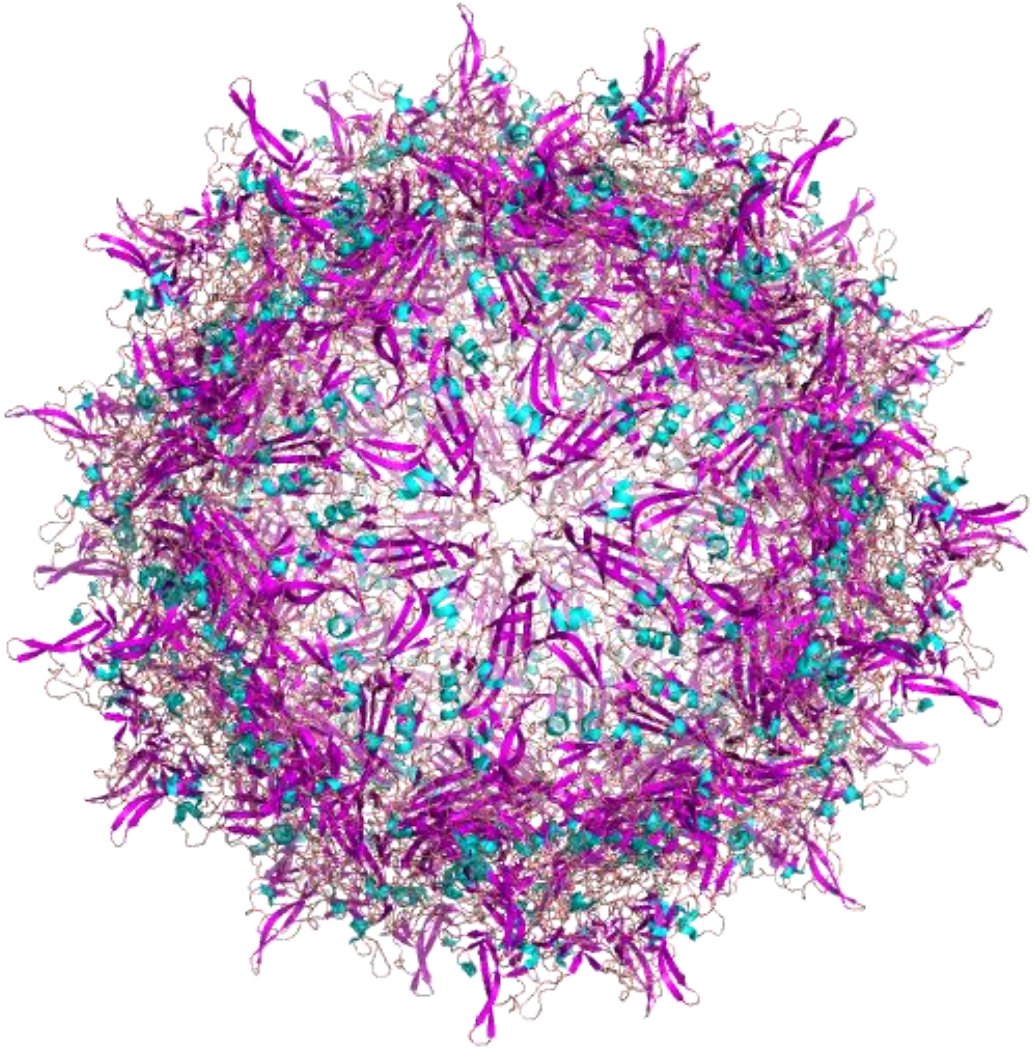

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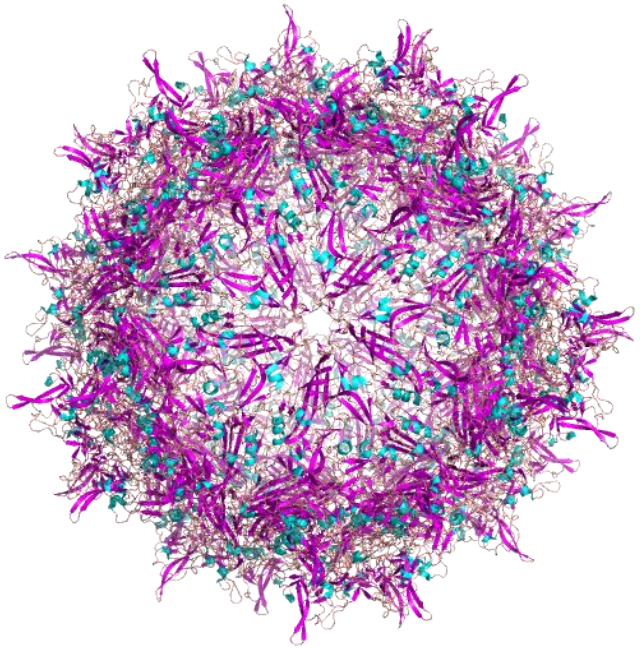

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Article

Senescence and inflammation are unintended adverse consequences of CRISPR-Cas9/AAV6-mediated gene editing in hematopoietic stem cells

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AAV: New problems emerged with new uses

“Newer problems”

- Endothelial injury
- Genomic integration far higher than thought
- DNA damage
- Senescence
- Cancer risk
- Death

Molecular Therapy
Original Article

Ectopic clotting factor VIII expression and misfolding in hepatocytes as a cause for hepatocellular carcinoma

Audrey Kapelanski-Lamoureux,[2,13] Zhouji Chen,[1,13] Zu-Hua Gao,[3,4,11] Ruishu Deng,[1] Anthoula Lazaris,[4] Cynthia Lebeaupin,[1,8] Lisa Giles,[5] Jyoti Malhotra,[5,12] Jing Yong,[1] Chenhui Zou,[7] Ype P. de Jong,[7] Peter Metrakos,[6] Roland W. Herzog,[9] and Randal J. Kaufman[1,5,8,10]

PHARMA

Sarepta tries to quell concerns over DMD gene therapy Elevidys as patients delay treatment after death report

By **Angus Liu** · May 7, 2025 8:03am

BIOTECH

ASGCT: Neurogene details new safety measures after young patient's death in AAV gene therapy trial

By **Darren Incorvaia** · May 16, 2025 3:00pm

BIOTECH

Rocket crashes as gene therapy patient dies, FDA imposes hold

By **Nick Paul Taylor** · May 27, 2025 9:49am

Cell & Gene Therapy | gene therapy | FDA | Rocket Pharmaceuticals

Goal: A platform technology for gene therapy of hematological diseases

Design Specifications

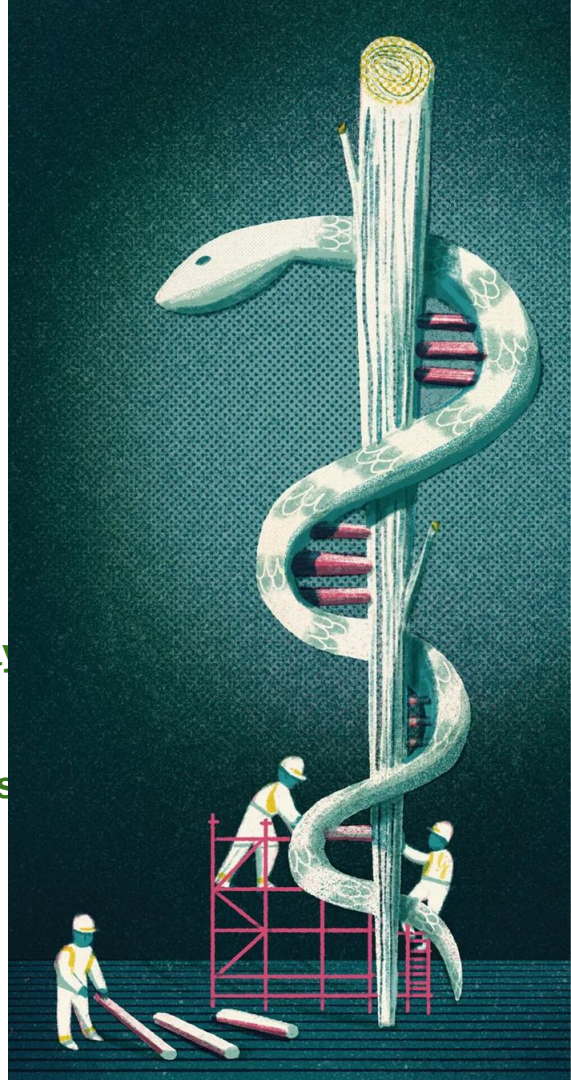
- Safe:

AAV?

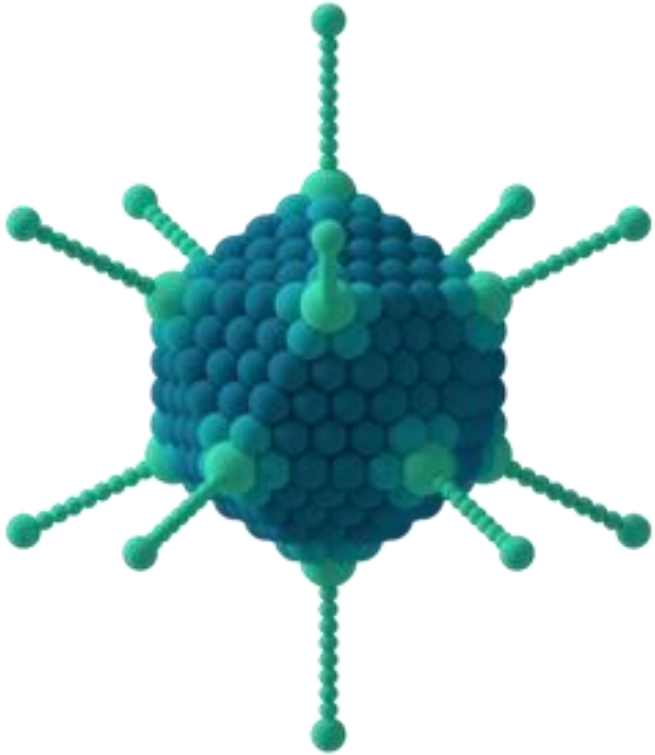
  - Minimal acute side effects
  - Non-immunogenic (no adaptive immunity) — **No**
  - No off-target DNA-damage
- Effective
  - Disease remission that is durable
  - Efficacy similar to non-gene therapy alternatives — **May**
- Dosing:
  - Repeat dosing is safe & effective
  - Dosing must be infrequent and convenient — **Yes**
- **Engineerable**
  - Modular components
  - Well-understood mechanisms
  - Any size gene

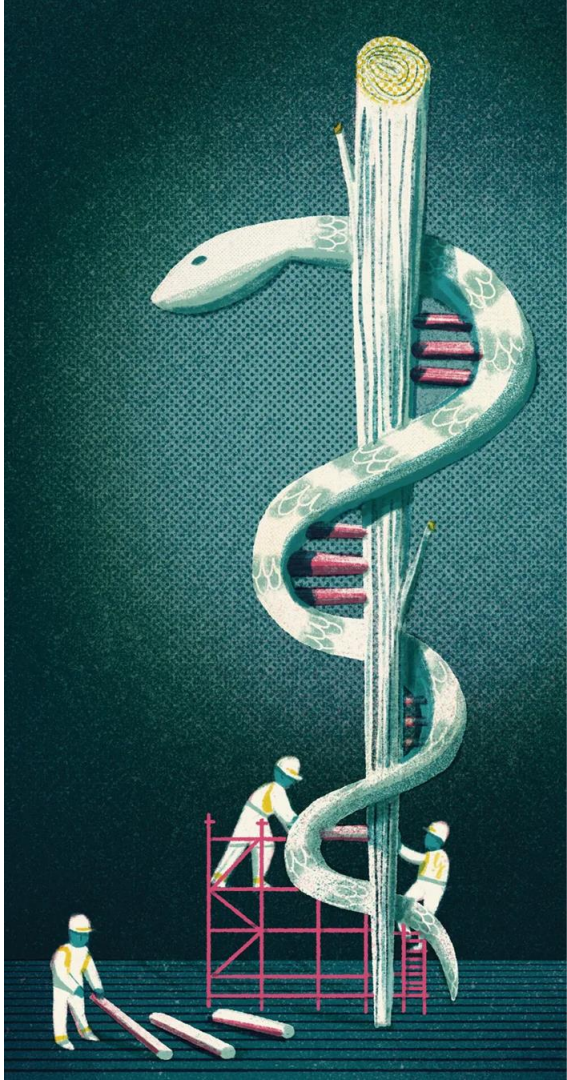
No

  - Express only in desired cell type
  - Reversible



Think outside the capsid (box)





Outline

- Goal: A platform technology for gene therapy of hematological diseases
- Unmet need in gene therapy: problems with current approaches
- The path to making the first safe & effective DNA-LNPs:
  - Making LNPs non-inflammatory
  - Enabling DNA loading into LNPs
  - Improving DNA-LNP expression
- Summary of DNA-LNPs' benefits & applications
- Proposed CSL Project, with Pilot Data
- Expanding beyond rare hematological diseases, within CSL's portfolio

Think outside the capsid (box)