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Towards an HIV Cure: Industry Collaboration Group

Cell and gene therapy for HIV cure: Platforms, progress and practical considerations

Session 2: Gene delivery platforms & technologies – Delivering a cure

Stay muted and with **camera off**

Webinar is being recorded and will be posted on the IAS+ platform

Share your thoughts please use the chat/Q&A

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Co-chairs

Devi SenGupta
Gilead Sciences

Roger Tatoud
Origena Consulting / IAS Consultant

Presenters

Ying Tam
Acuitas Therapeutics Inc.

Edward F Kreider
University of Pennsylvania

Paula Cevaal, The Peter Doherty Institute for Infection and Immunity

Aijun Wang
UC Davis School of Medicine

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Acuitas Therapeutics

IAS Corporate Partnership Programme Webinar Series

Cell and Gene Therapy for HIV Cure: Platforms, Progress and Practical Considerations

12 March 2026

ACUITAS
THERAPEUTICS

Overview

WHO WE ARE

Acuitas is a globally recognized biotechnology company specializing in the **development of delivery systems for nucleic acid therapeutics based on lipid nanoparticles (LNP).**

Our LNP:

- enabled three clinical firsts
- currently enable two commercial products:

onpattro® (patisiran) lipid complex injection 10 mg/5 mL

COMIRNATY® (COVID-19 Vaccine, mRNA)

Children's Hospital of Philadelphia®

WHO WE WORK WITH

We work with a variety of organizations, including:

Cutting edge **pharmaceutical & biotechnology** companies

Leading **academics in universities & institutes**

Foundations & **NGOs**

HOW WE WORK

As a technology platform provider, we exclusively work in collaboration with partners.

We do not have our own drug development programs – **we are focused on supporting our partners to bring their drug products to patients.**

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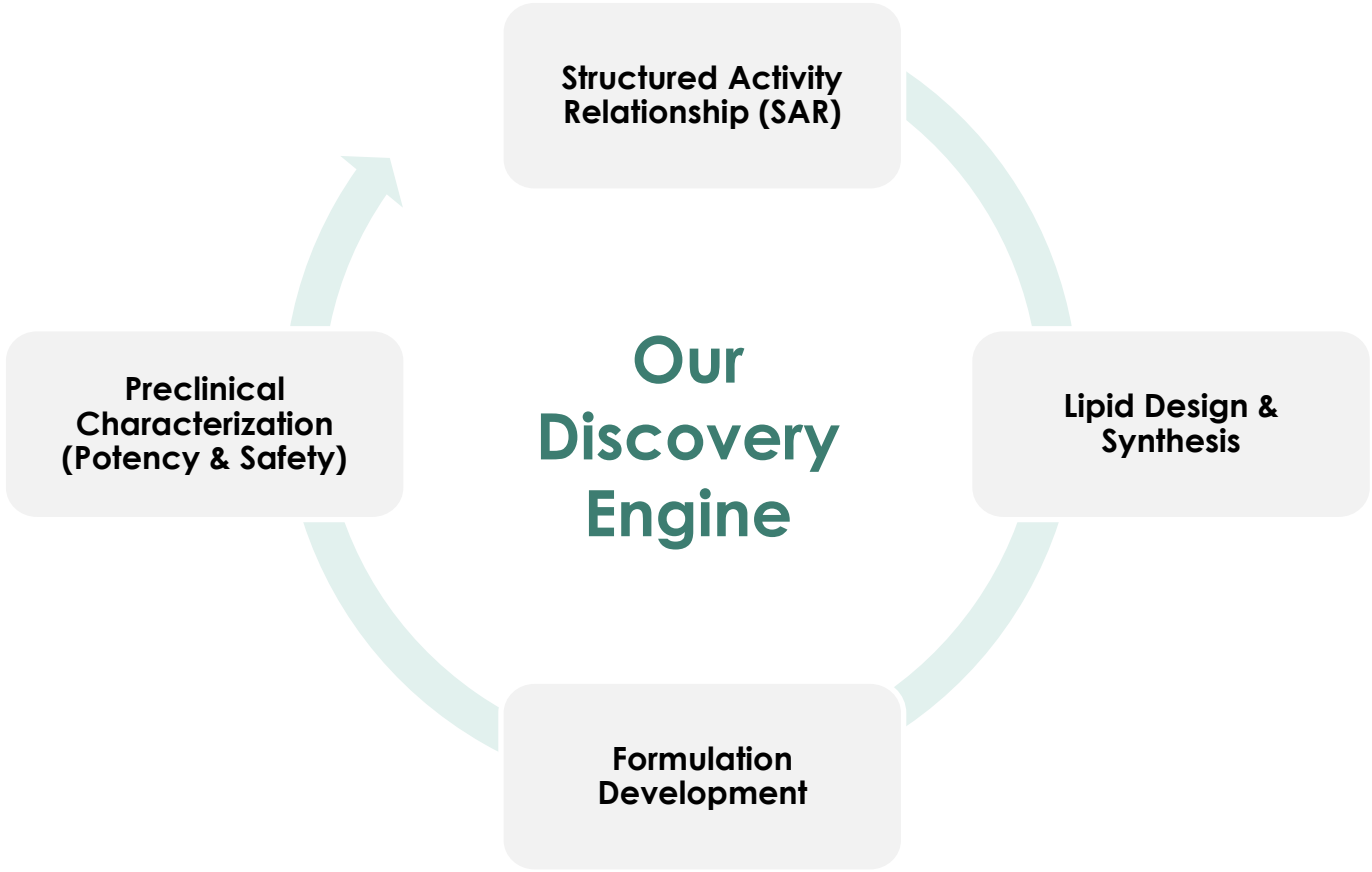
Our Approach to Innovation



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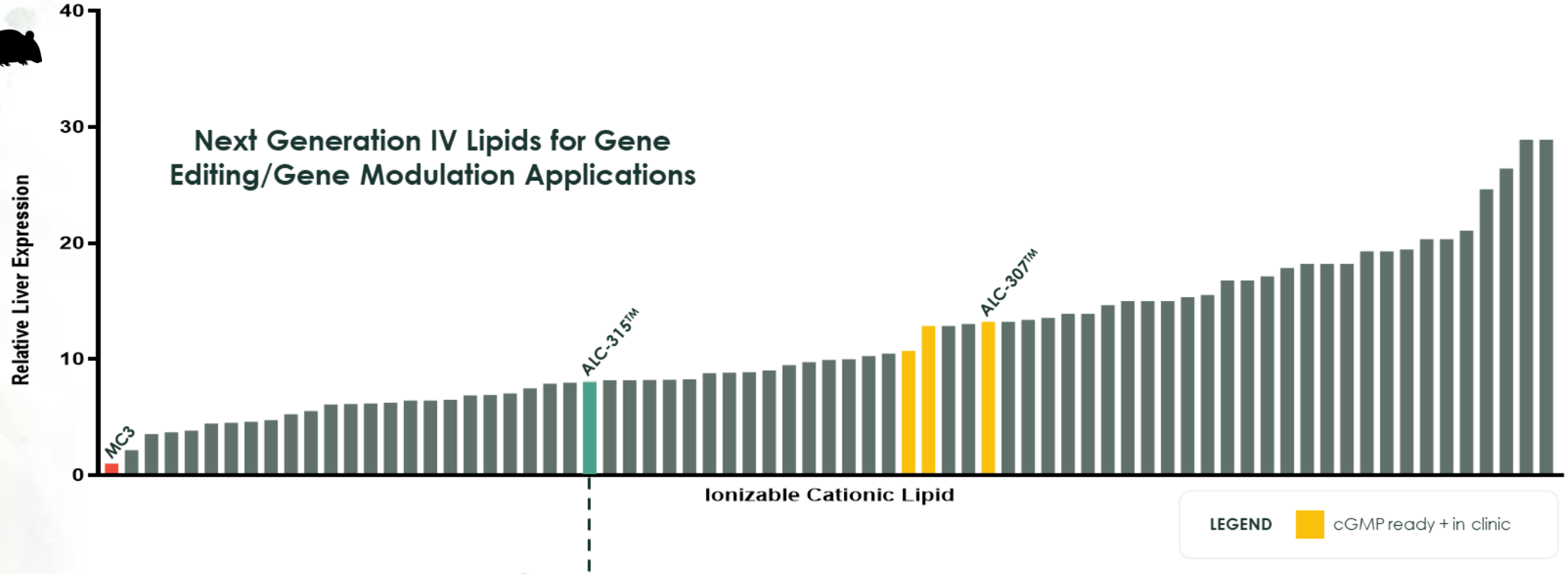
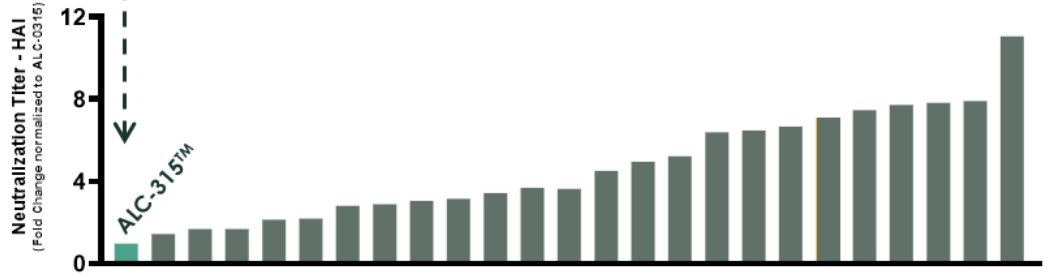
Our Approach to Innovation

Next Generation IV Lipids for Gene Editing/Gene Modulation Applications



Next Generation IM Lipids for Vaccine Applications



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Applying Our LNP Technology

Gene Editing
Expression of a **genome editing** protein to modify gene expression.

Gene Modulation
Expression of an **epigenic editor** to modify gene expression **without changing the genetic code.**

Vaccines
Expression of viral or bacterial proteins to generate a protective **immune response.**

Expression of **tumour antigens** (including personalized cancer vaccines).

Antibody and Therapeutic Protein Delivery
Expression of **proteins including prophylactic** or **therapeutic antibodies** to treat current and emerging diseases.

In Vivo CAR-T
Expression of a Chimeric Antigen Receptor for **in vivo production of CAR-T cells** to treat cancer and autoimmune disease.

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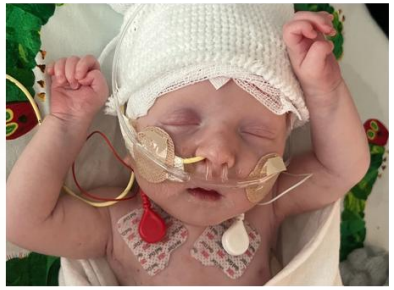
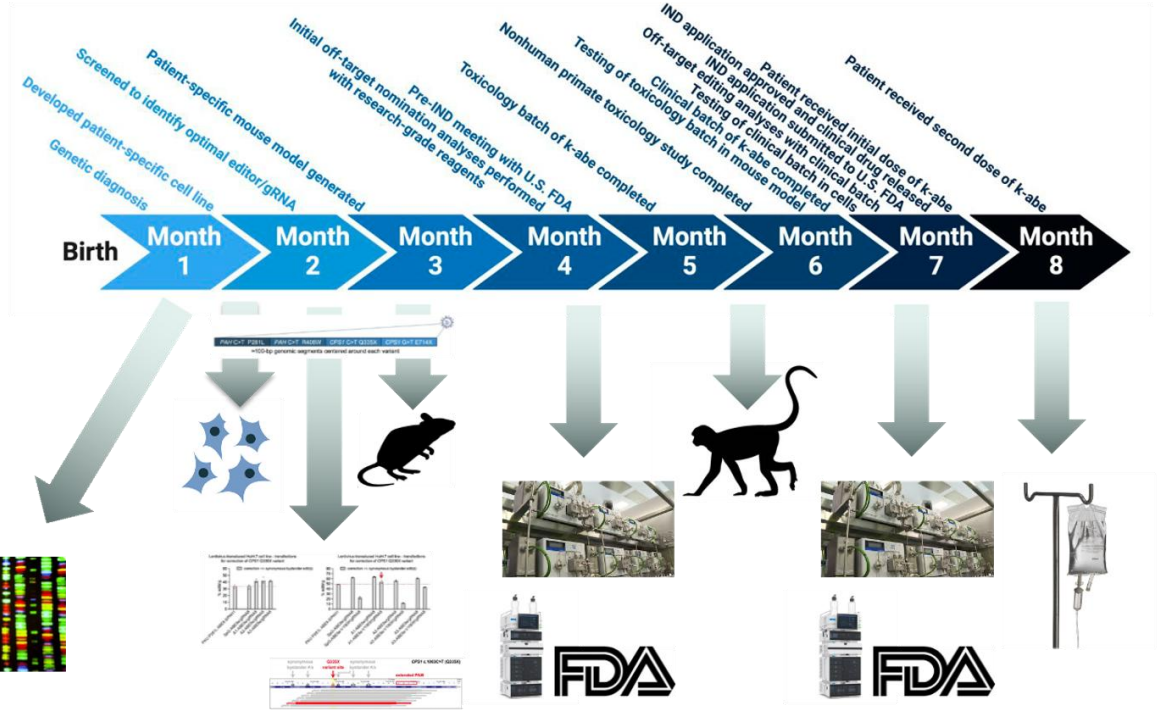
Applying Our LNP Technology

Delivery of mRNA encoding gene editing enzymes





Photos from:
https://www.chop.edu/centers-programs/genetherapy4inheritedmetabolicdisorders/future-personalized-medicine-here-kjs

Musunuru et al., NEJM 392(22), 2025

First personalized base editing therapy to treat a urea cycle disorder

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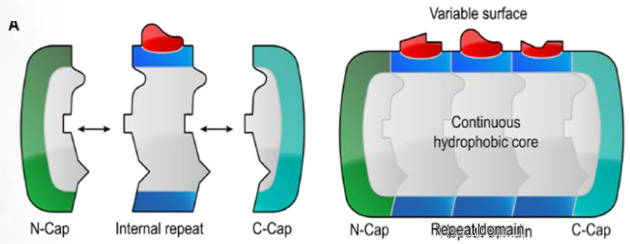
Continuous Innovation: Extrahepatic Targets

OUR APPROACH

Our extrahepatic program is focused on delivery via **cell targets that are directly accessible in the blood compartment or local administration.**

HOW WE DO IT

We use antibody mimetics called **Designed ankyrin repeat proteins (DARPins).**



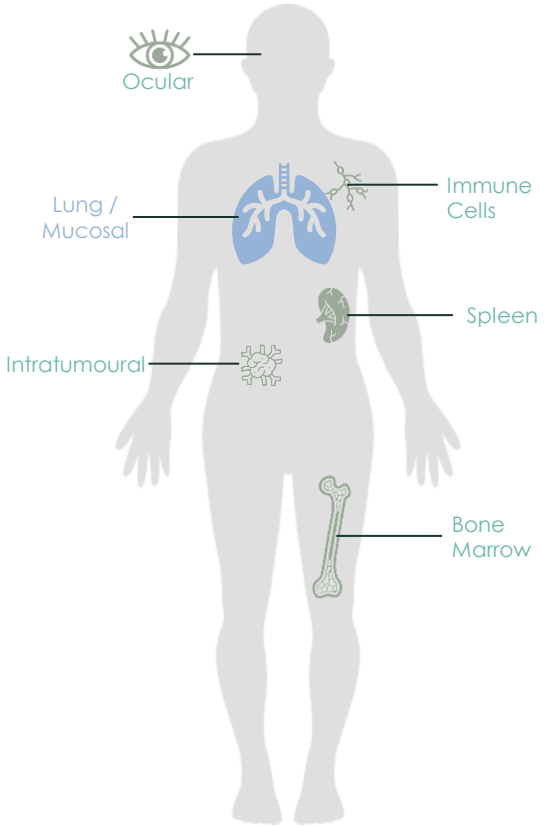
AREAS WE CAN TARGET

<u>Diseases Affecting the Lung</u>
(i.e., CF, Cancer, Infectious Disease etc.)

Mucosal (via aerosolization)

<u>Epigenetic Regulation and Gene Modification</u>

Spleen, Bone Marrow, Ocular, Intratumoural, Immune Cells



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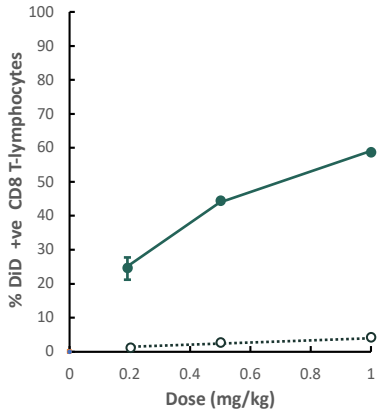
Continuous Innovation: Extrahepatic Targets

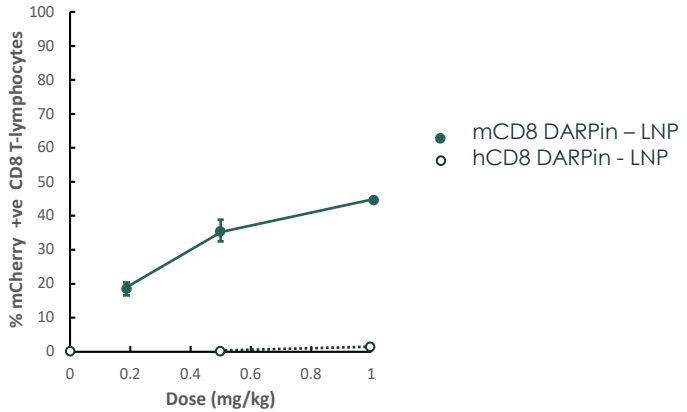
Targeted LNP for in vivo generation of CAR-T Cells

CD8 DARPin targeted mRNA LNP show **dose dependent, target specific binding / uptake and transgene expression.**

LNP Binding / Uptake



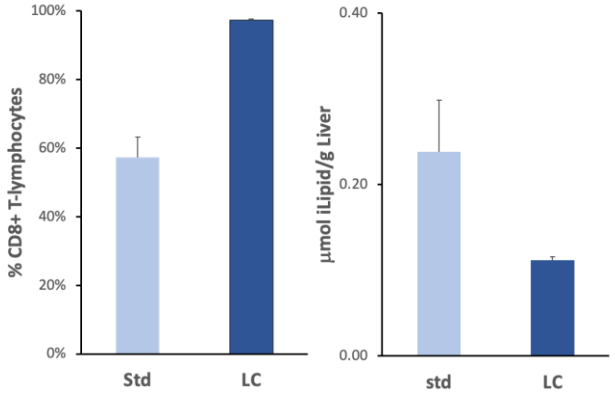
Reporter Gene Expression



Optimized long circulating (LC) LNP results in **2x increased binding / uptake and 10x increased expression.**

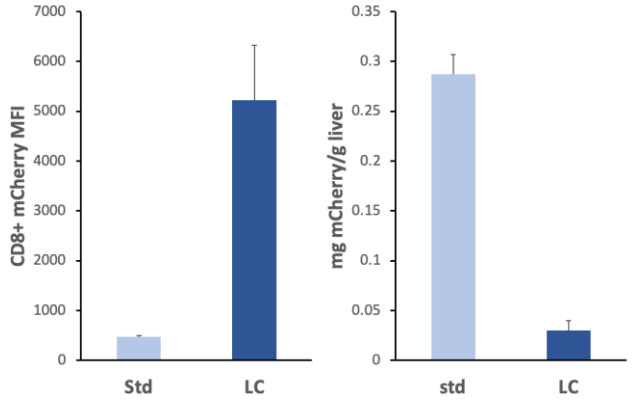
Expression in liver is ~10x lower vs. standard LNP.

LNP Binding / Uptake



CD8+ T-cells *Liver*

Reporter Gene Expression



CD8+ T-cells *Liver*

Delivery of mRNA to CD8+ T-lymphocytes by DARPin targeted LNP

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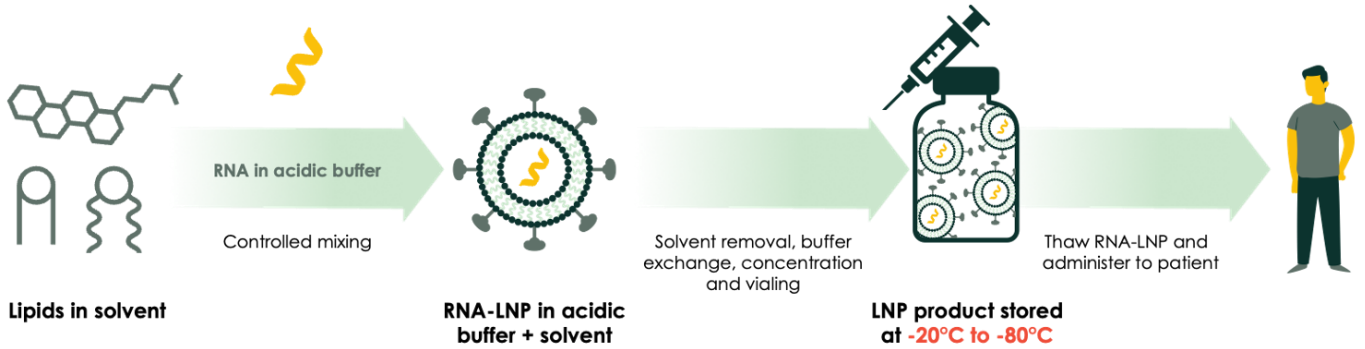
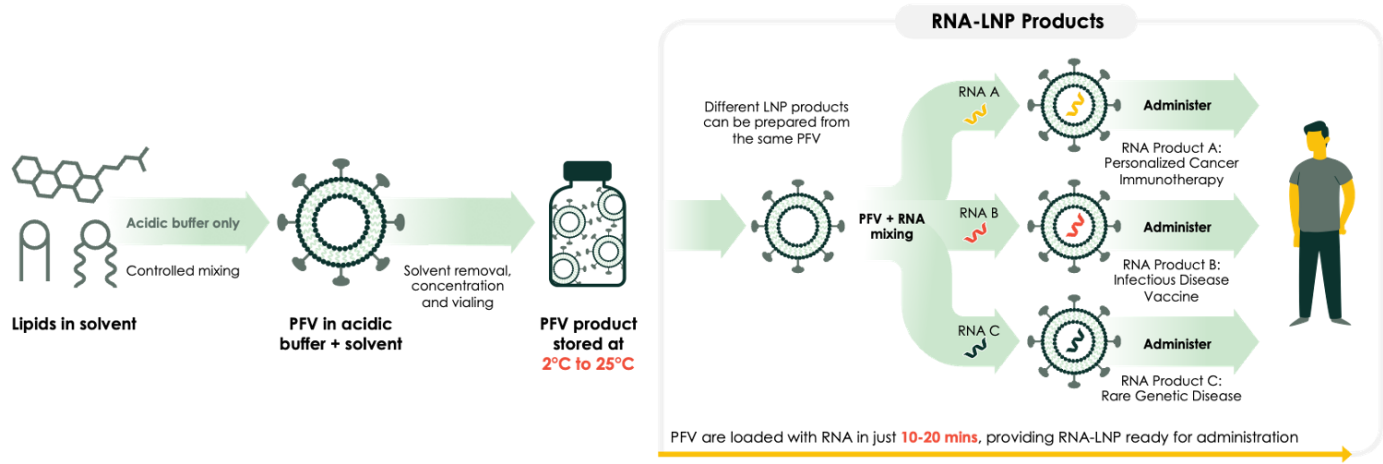
Continuous Innovation: Pre-Formed Vesicles (PFV)

Conventional Method



PFV Method



Alternative mRNA LNP Manufacturing by Pre-formed Vesicles (PFV)

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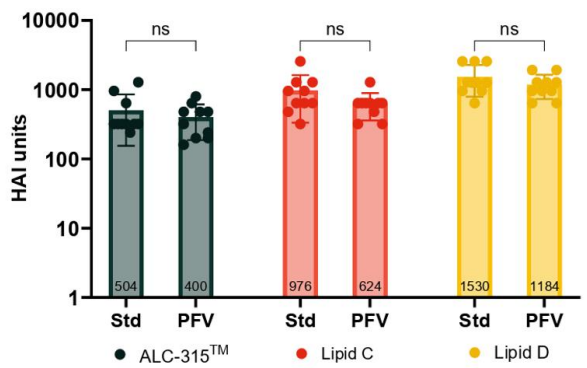
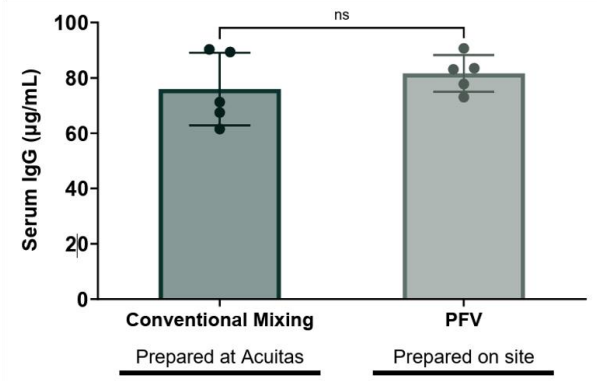
Continuous Innovation: Pre-Formed Vesicles (PFV)

IM: Day 28 HAI Titres (0.2 μg)



IV: Day 1 Plasma IgG (0.5 mg/kg)



- Conventional and PFV methods exhibit equivalent *in vivo* vaccine performance across lead LNP formulations
- PFV formulation prepared at point of use has IV potency equivalent to conventional formulation of IgG mRNA

PFV and conventionally manufactured mRNA LNP have equivalent activity

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Continuous Innovation: Pre-Formed Vesicles (PFV)

Refrigerated (2-8°C) (and potential for room temperature) long term **storage & distribution**

Flexible, small-scale manufacturing capability

Infectious Disease Vaccine

Improve **accessibility and distribution**

Regional-specific vaccine formulation

On-demand variant selection

Personalized Cancer Vaccine

Adaptable **neoantigen modification**

Rare Genetic Disease Therapeutics

Fast and cost-effective

Modular, flexible, platform approach

PFV provide enhanced accessibility to mRNA LNP medicines

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Summary

- Continual development of progressively more active and better tolerated LNP
- Enable a broad range of therapeutic modalities, including in the gene editing and gene modulation space as well as in vivo CAR-T cell generation
- Developing strategies to delivery payloads to extrahepatic cell targets
- Pre-formed vesicles (PFVs) - simple, highly flexible, point-of-care mRNA-LNP manufacturing option that maintains particle characteristics, stability and potency vs conventional methods
  - Significant benefits for cost, storage, distribution and formulating small batches for personalized medicines

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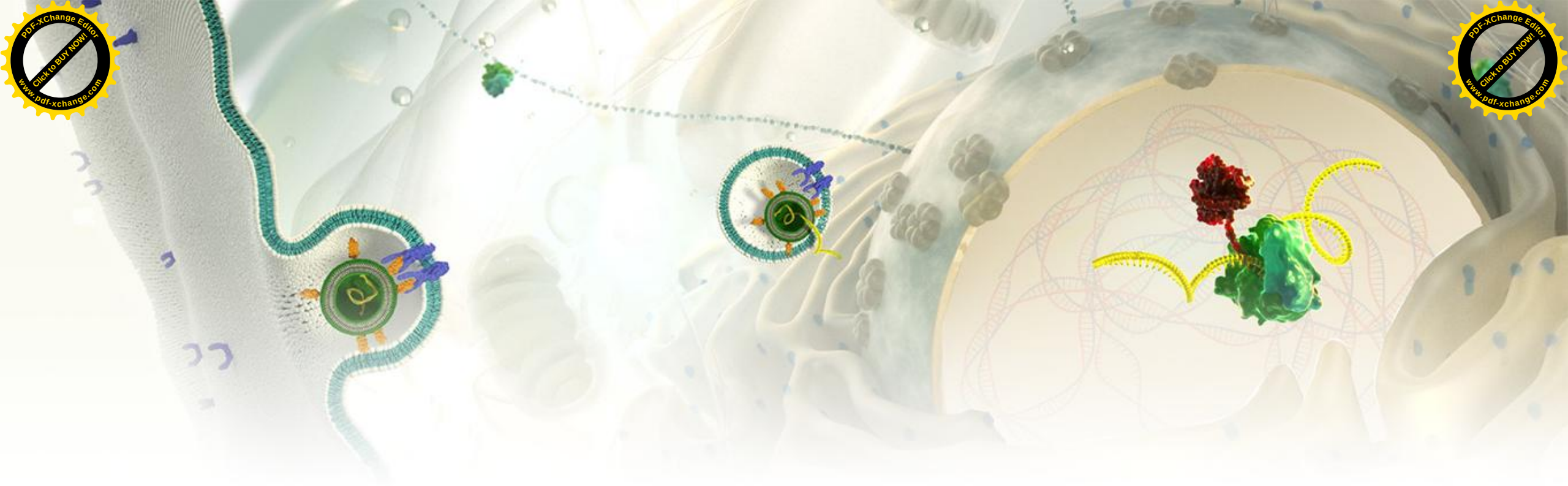

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https://acuitastx.com/

ACUITAS
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From Vaccines to Gene Therapy: Tailoring mRNA-LNP interventions for HIV Cure

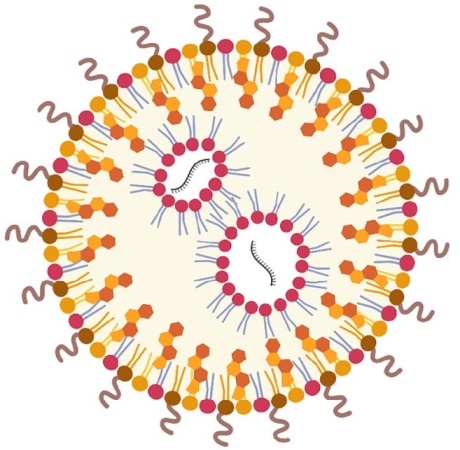
Edward (Ted) Kreider, MD, PhD
Assistant Professor
Division of Infectious Diseases, Department of Medicine
Penn Institute for RNA Innovation
University of Pennsylvania

Penn
University of Pennsylvania

Institute for RNA Innovation

The mRNA-LNP platform is a powerful tool for basic, translational, and clinical investigation

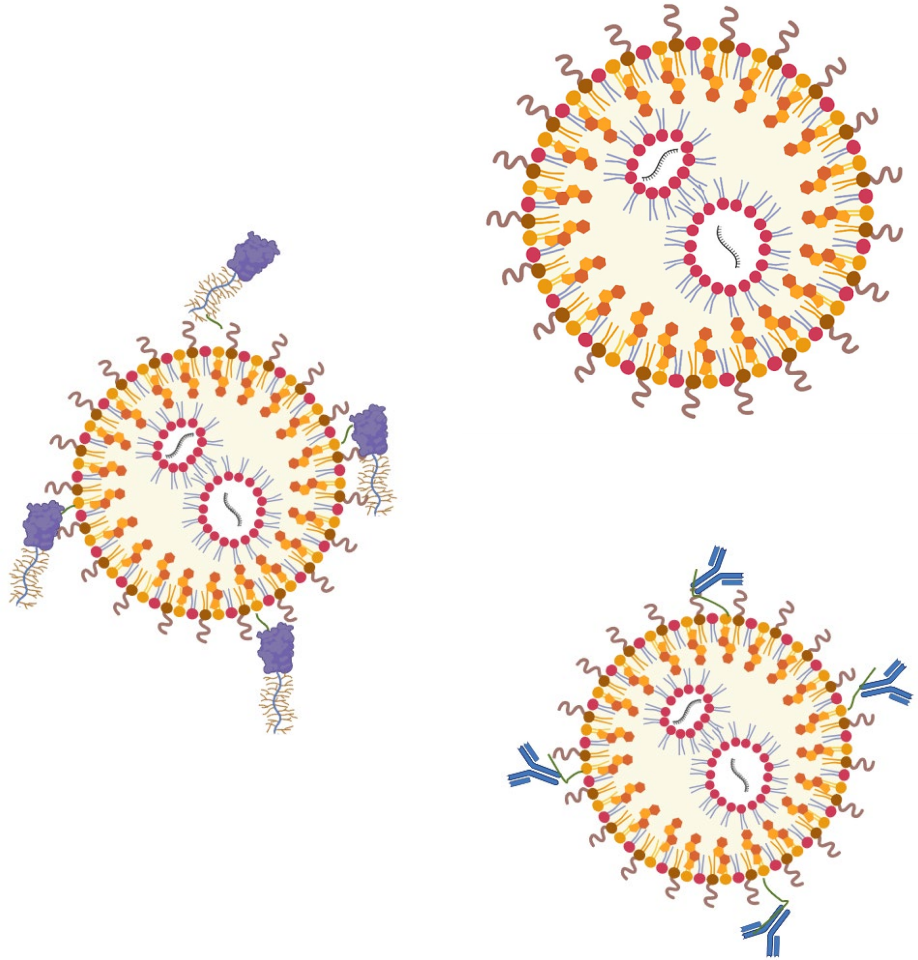
- No insertional mutagenesis, prescreening
- FDA approved
  - RNAi
  - Vaccines
  - Gene therapy
- Rapid to produce using cell-free methods
  - Catalyze discovery
  - Accelerate translation
- Inexpensive at scale



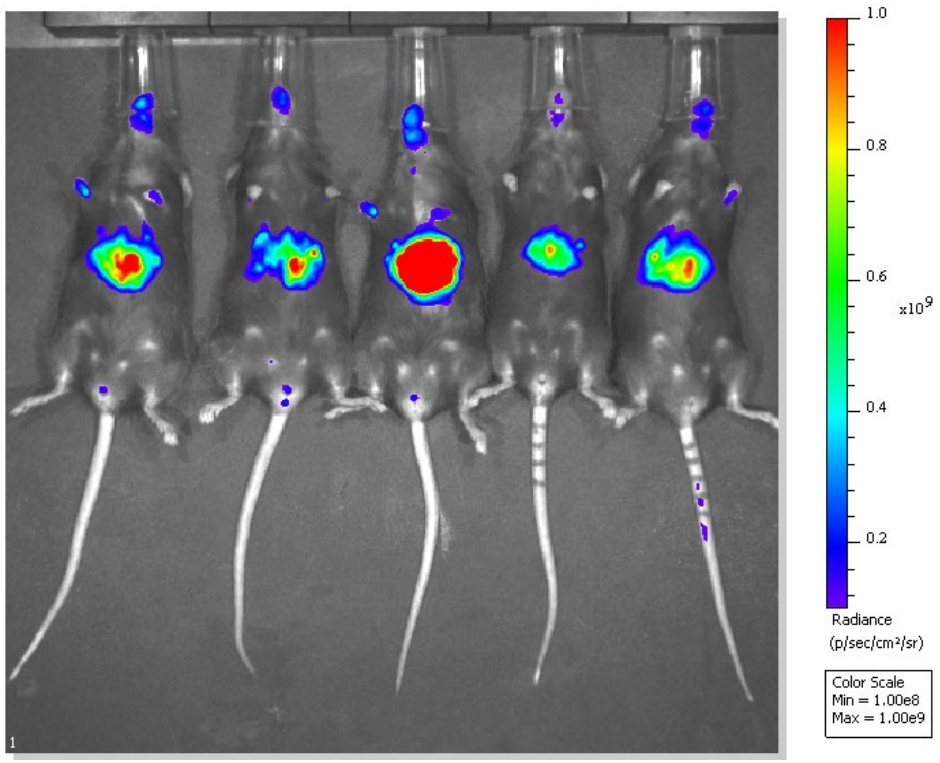
- **Timed, tissue- and cell type-directed, transient expression of a protein of interest**
  - **Work of others**
  - **Work at Institute for RNA Innovation**

The mRNA-LNP platform is modular in nature and can be used to build customized interventions

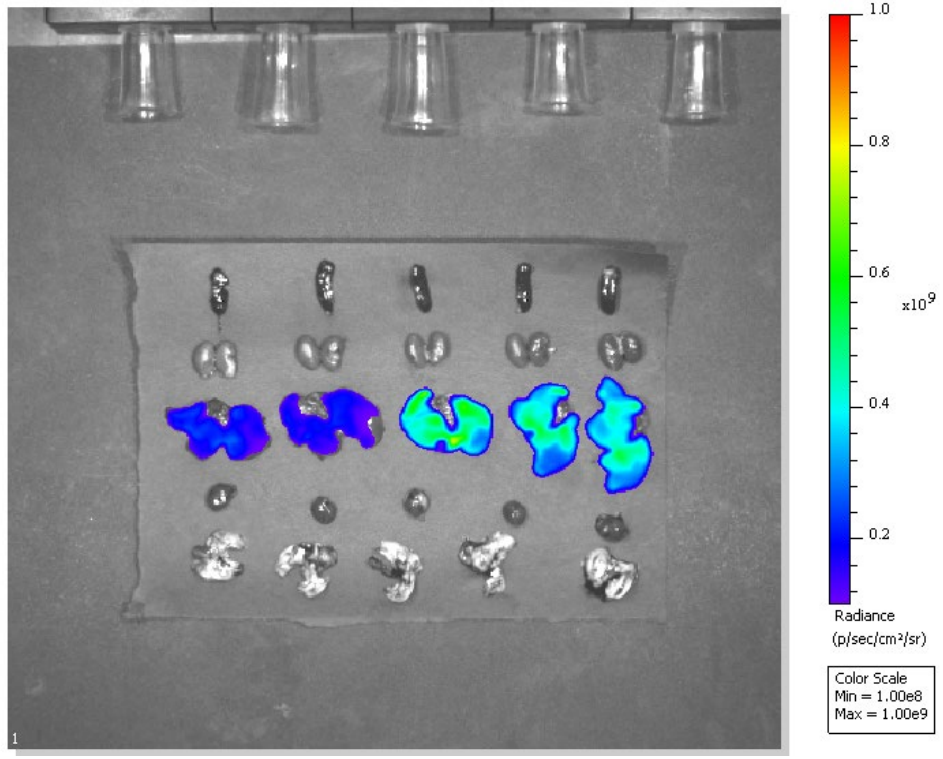
- Cargo – nucleic acid
  - Nucleoside-mod mRNA, siRNA, etc.
- Carrier - lipid nanoparticles (**LNPs**)
  - mRNA → cytosol → protein
  - Adjuvant activity
  - Targeting
    - Route
    - Composition
    - Moieties



Intravenous administration of many mRNA-LNPs results in efficient mRNA delivery to the liver

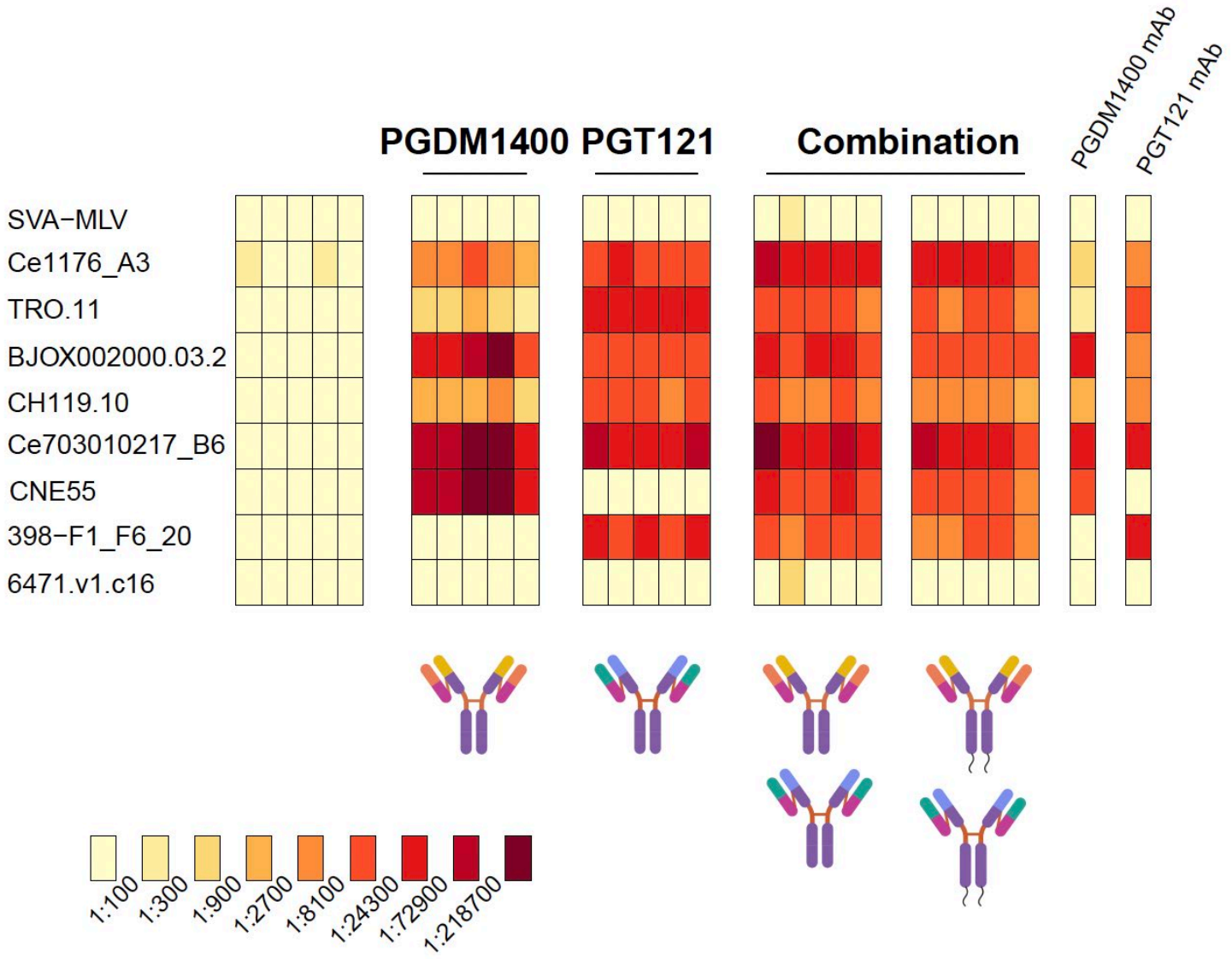


Liver



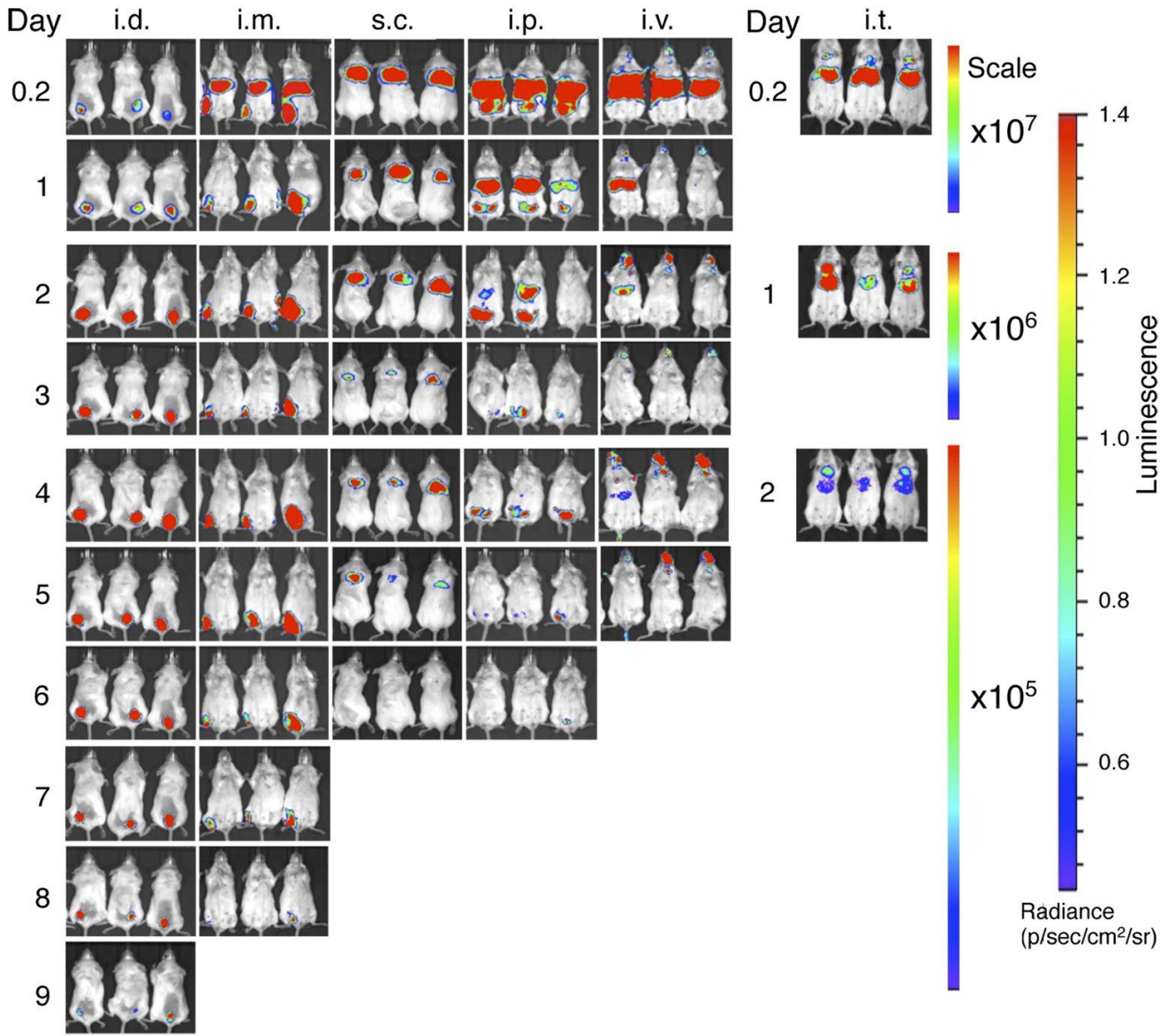
30ug of *luc* mRNA-LNP injected IV retroorbitally, light flux measured 8 hrs later

Combinations of bnAbs can be passively delivered following intravenous antibody mRNA-LNP injection



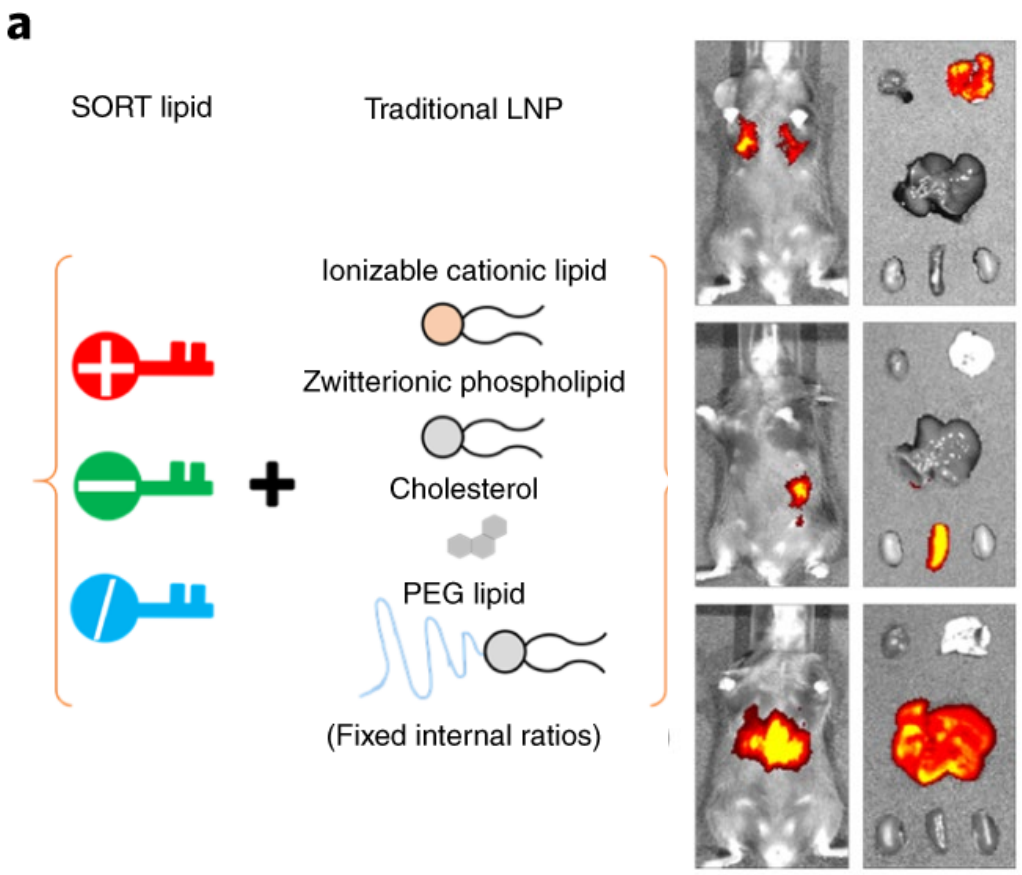
(Su, et al., in preparation)

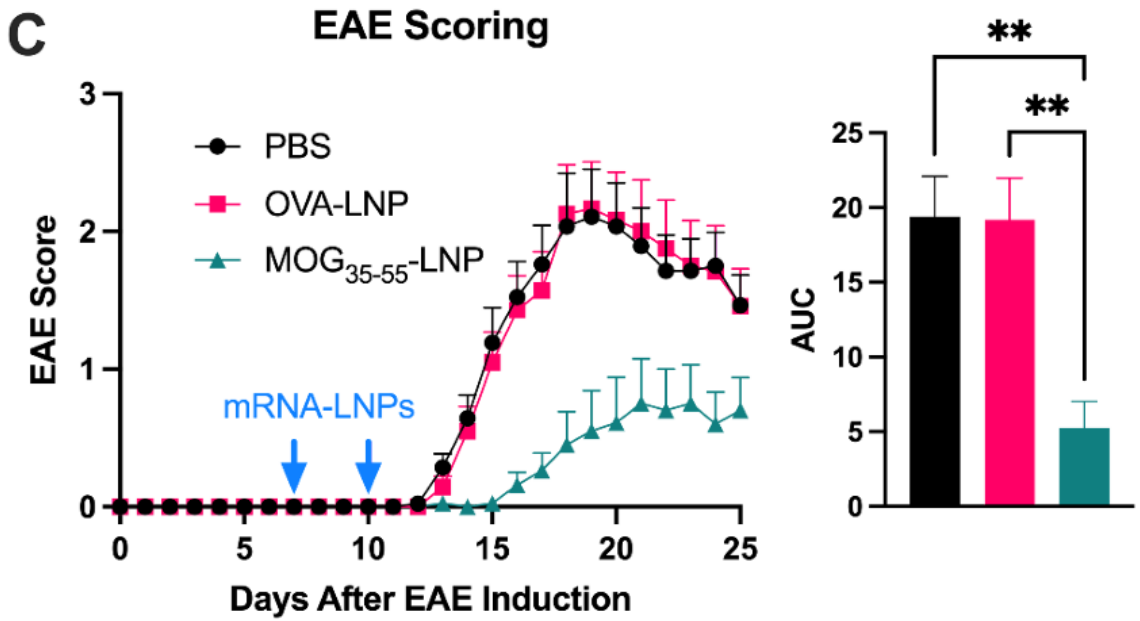
Route of administration can alter mRNA biodistribution



(Pardi, et al., 2015)

Inclusion of charged lipids can alter mRNA biodistribution and adjuvant activity

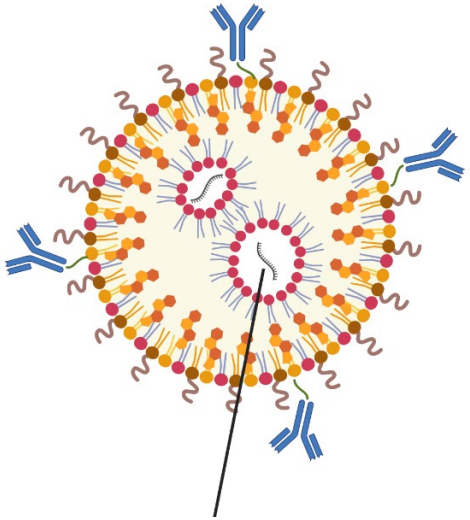




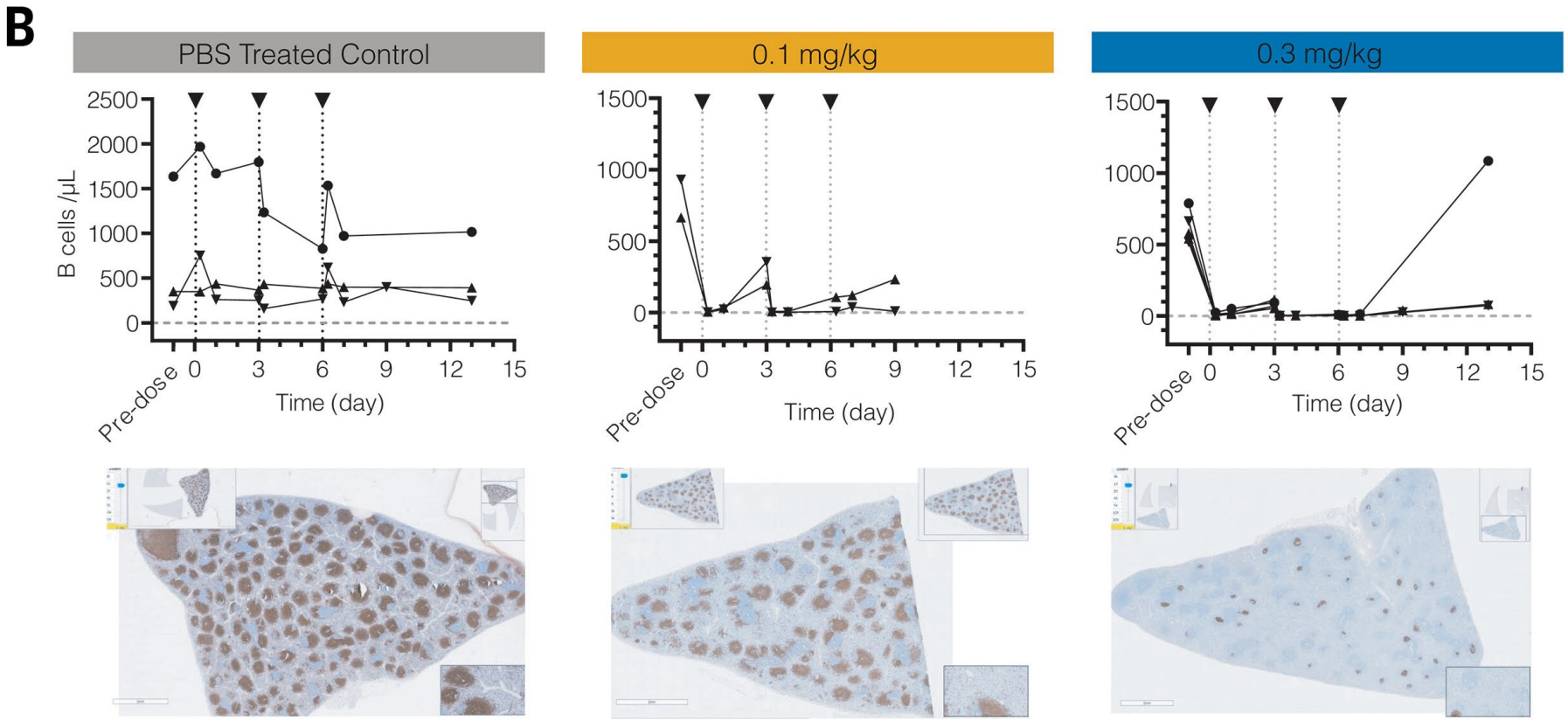
(Cheng, et al., 2020; Melamed, et al., bioarxiv)

Three low doses of aCD8-targeted B Cell CAR mRNA-LNPs results in peripheral B cell depletion

Anti-CD8 mAb

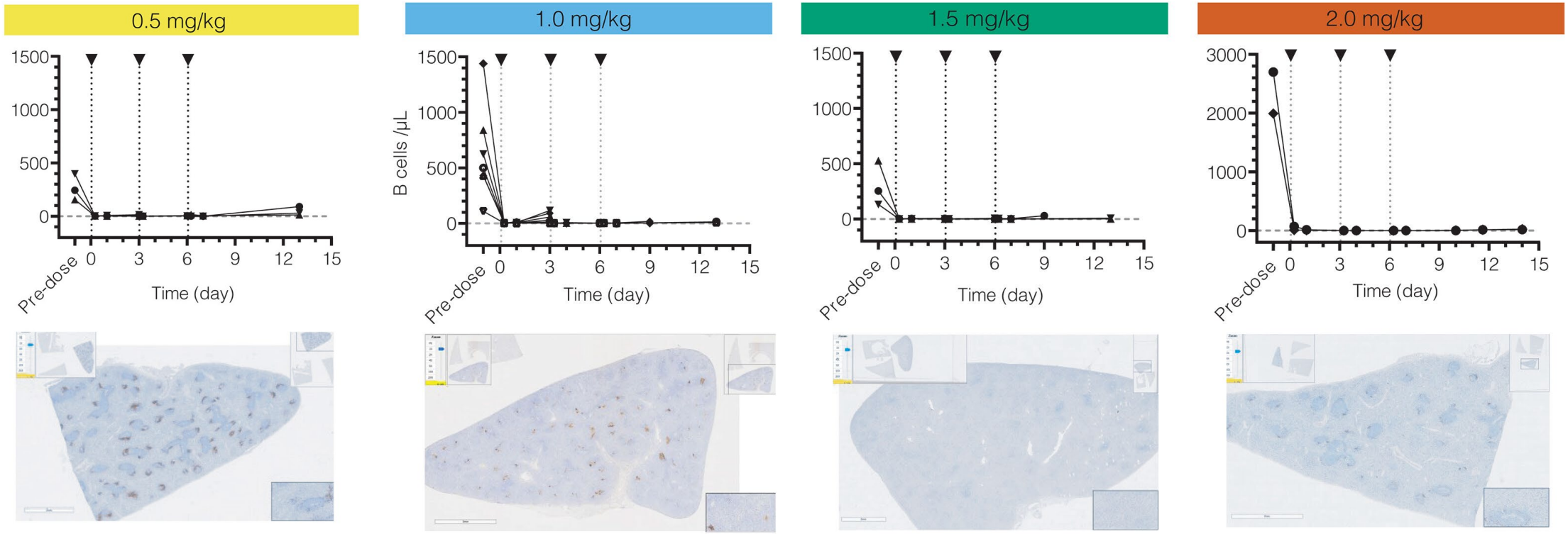


Anti-B cell CAR



(Hunter, et al., 2025)

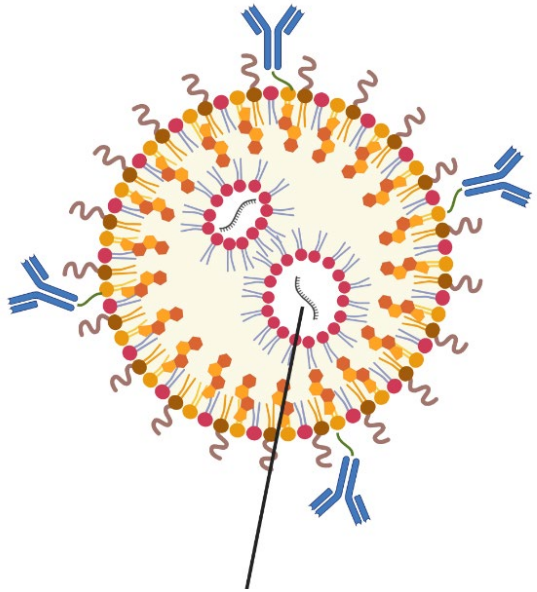
Three high doses of aCD8-targeted B Cell CAR mRNA-LNPs results in profound peripheral and SLT B cell depletion



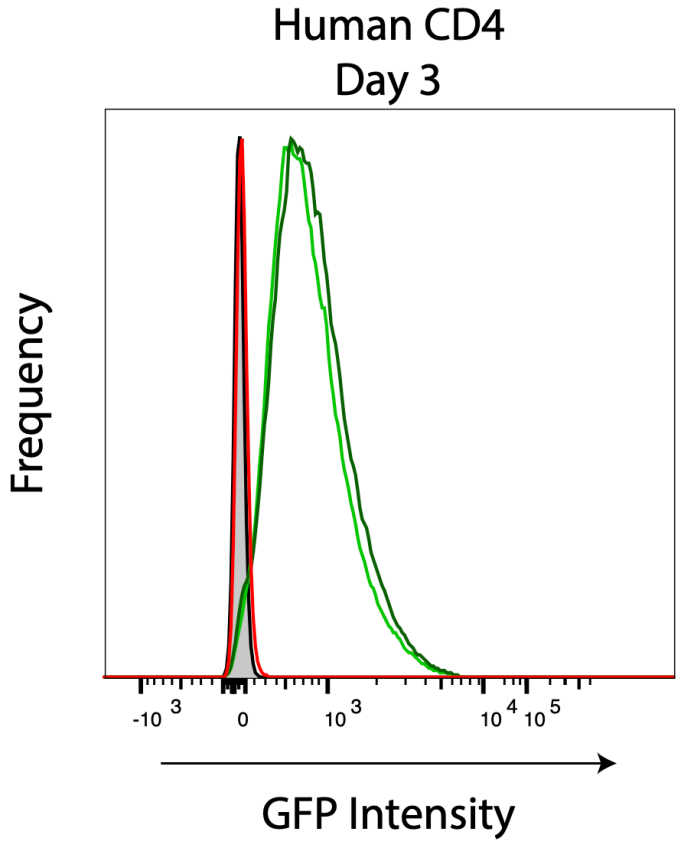
(Hunter, et al., 2025)

balizumab-targeted mRNA-LNPs efficiently deliver to resting CD4+ T cells

Anti-CD4 mAb



mRNA (reporter, Tat)



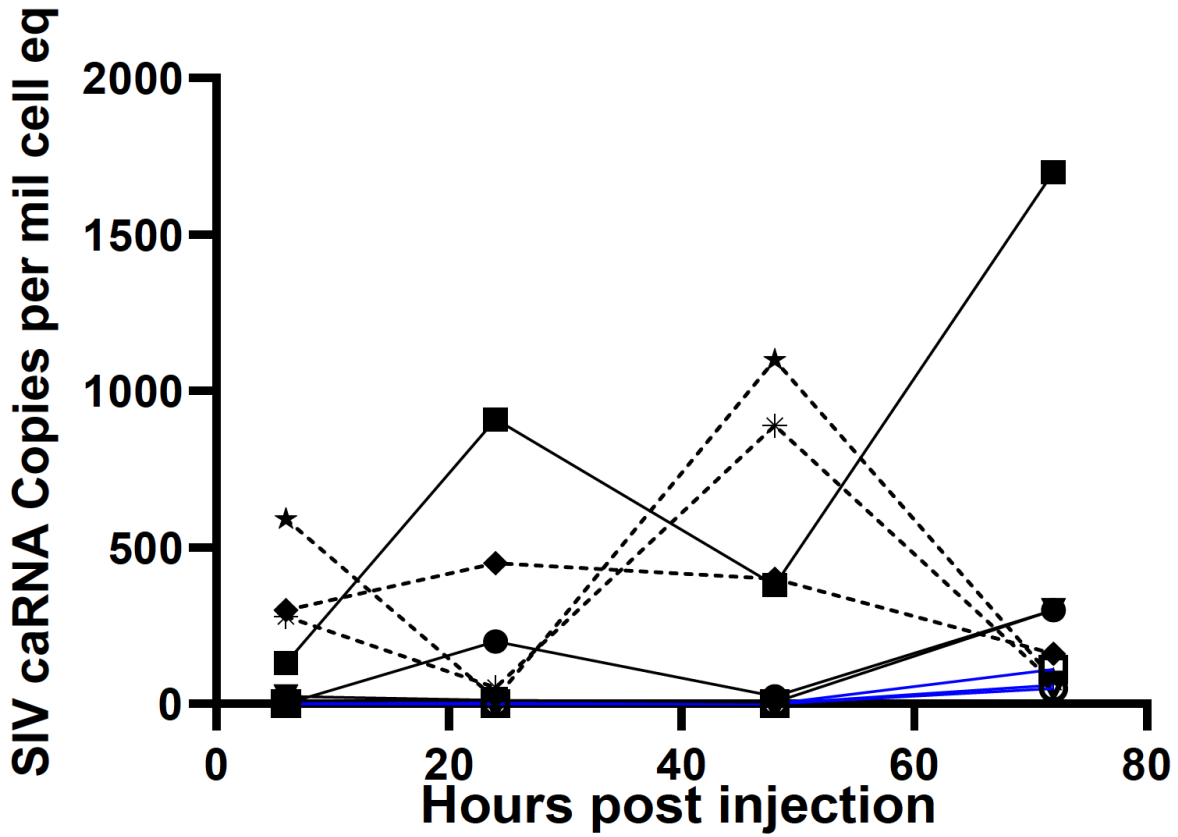
No treatment (grey fill)
Ib-GFP 1ug/million cells
Ib-GFP 2ug/million cells

Ib-luciferase 1ug/million cells

- Ibalizumab:
  - Binds D2 of CD4
  - Rapidly internalized

(Kreider, et al., in preparation)

Ibalizumab-targeted LNPs deliver a latency reversing agent to the lentiviral reservoir for reactivation



36826
36827
36848
BO24
DG56
DI48
CX51
CX55
DG59

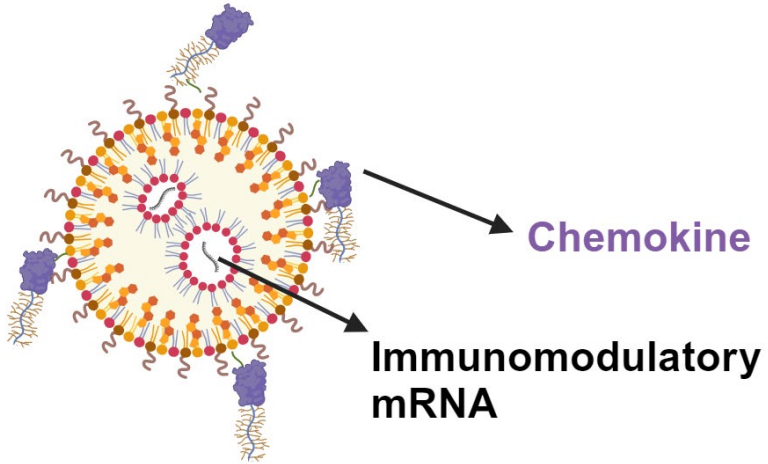
Ib-eLNP

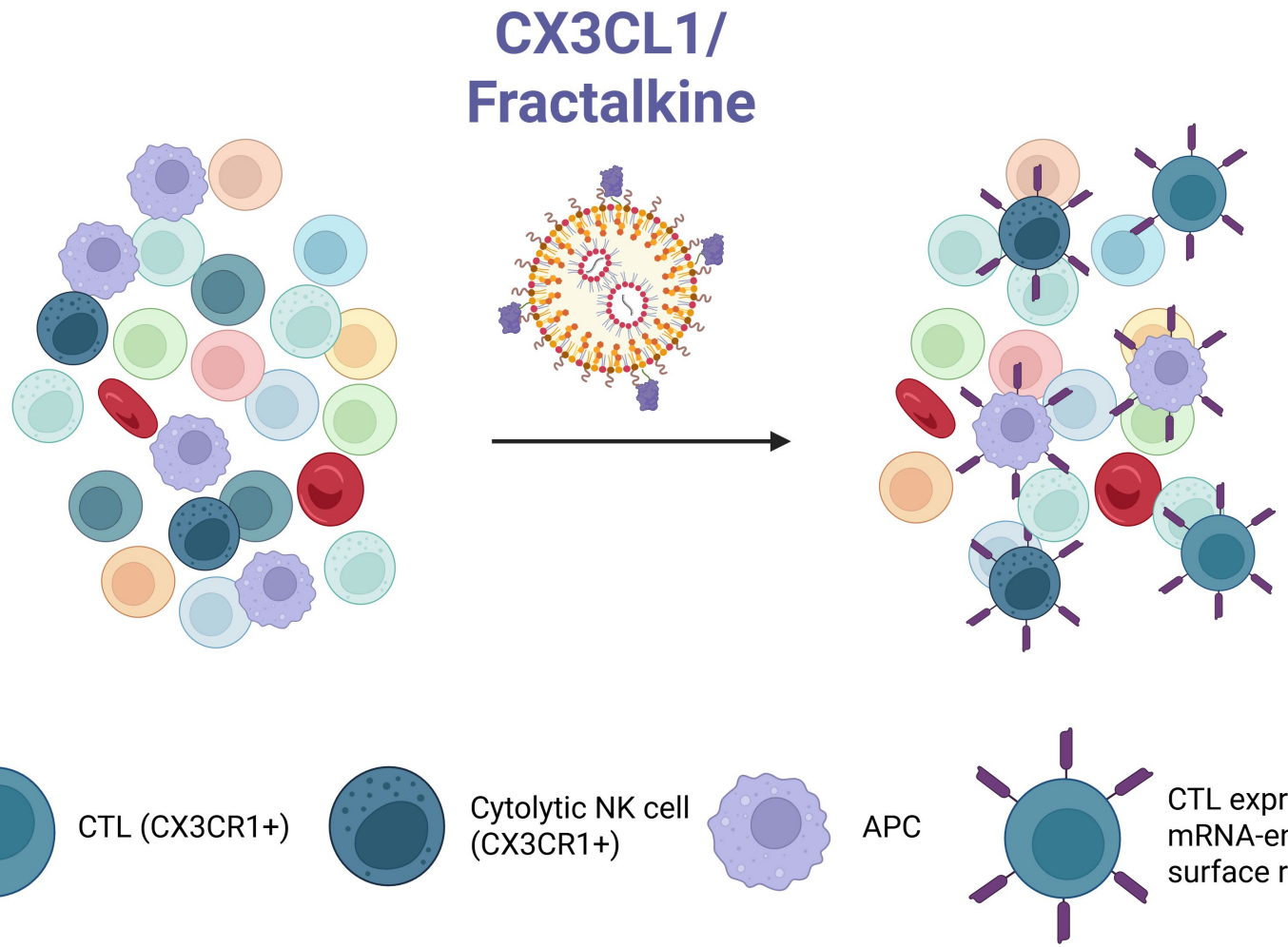
Ib-targeted Tat mRNA-LNPs (LRA)

(GF, AA, CB, RR, MS, WW, YT, JL, DW, EFK; CROI 2026)

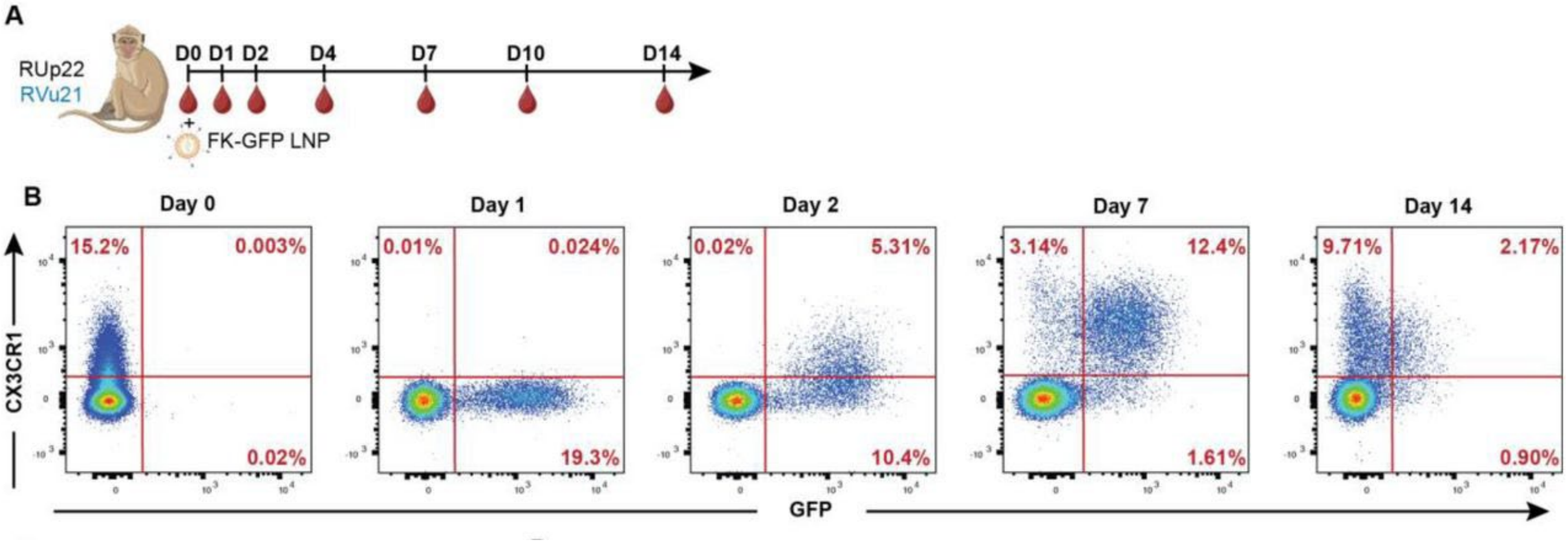
(Kreider, et al., in preparation)

Fractalkine targeting could permit mRNA delivery to subset of PBMCs that express the cognate receptor, cytolytic effectors



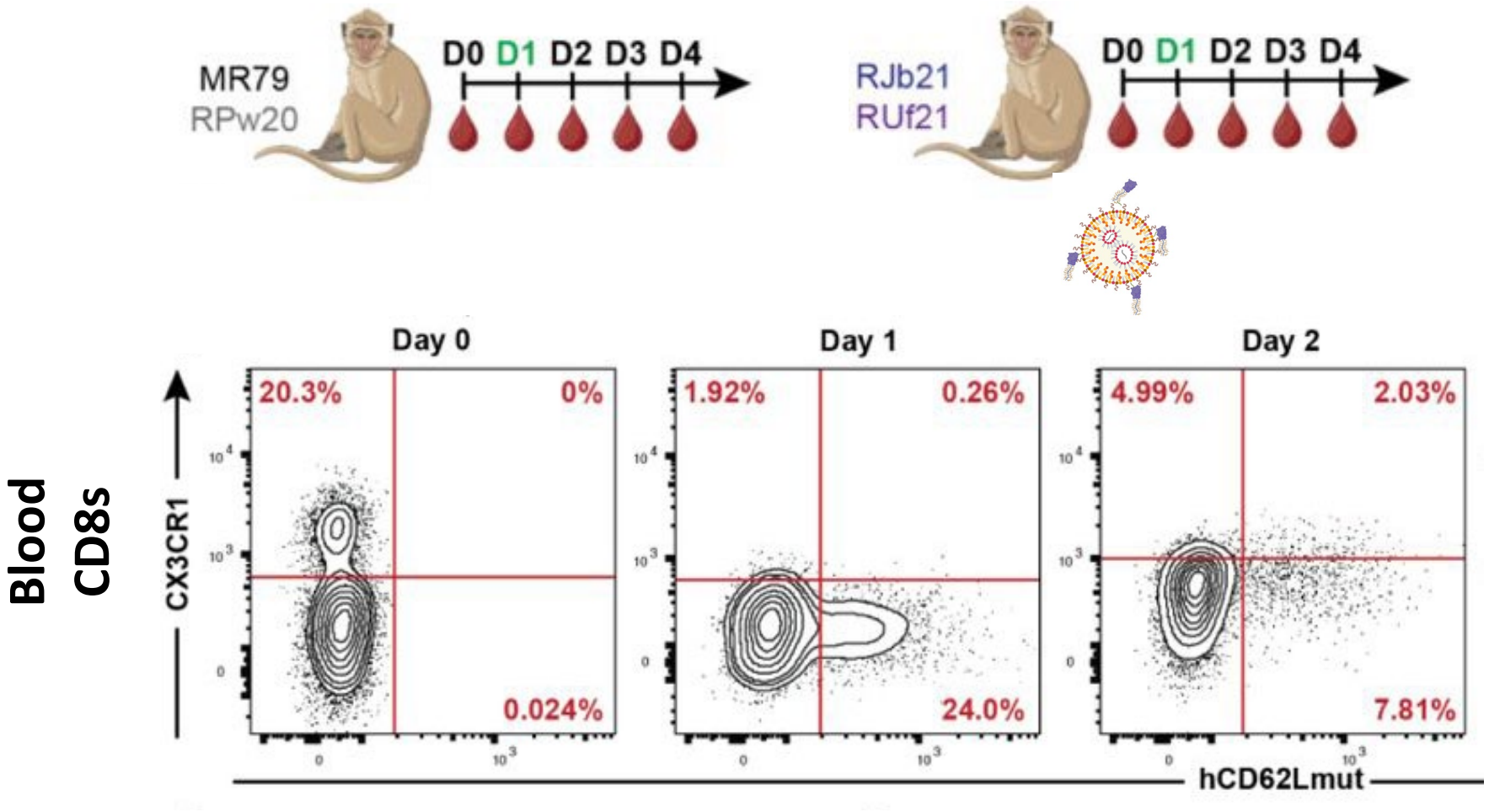


Fractalkine-targeted mRNA-LNPs efficiently deliver mRNA to cells that express the fractalkine receptor, CX3CR1



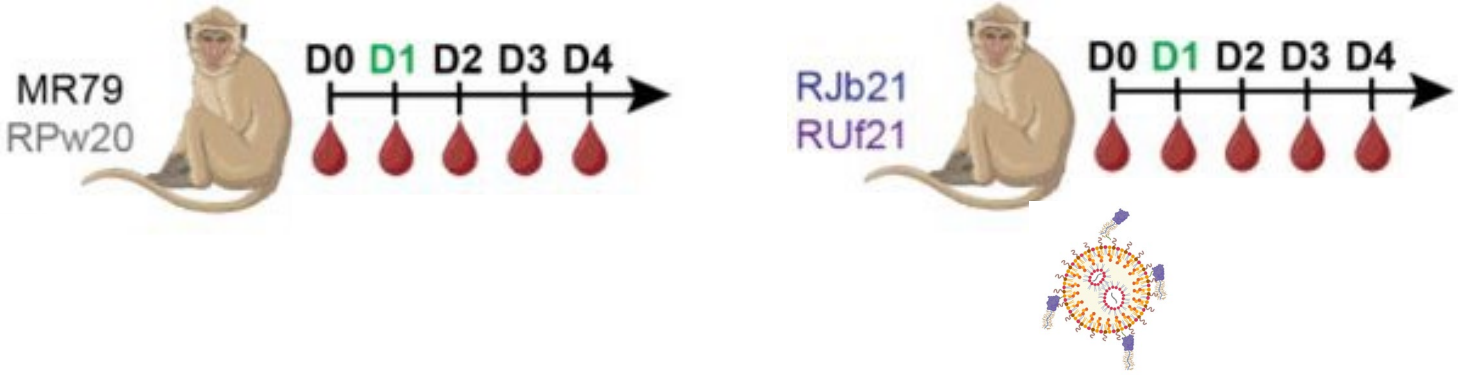
(Corrigan, et al., bioarxiv, 2025)

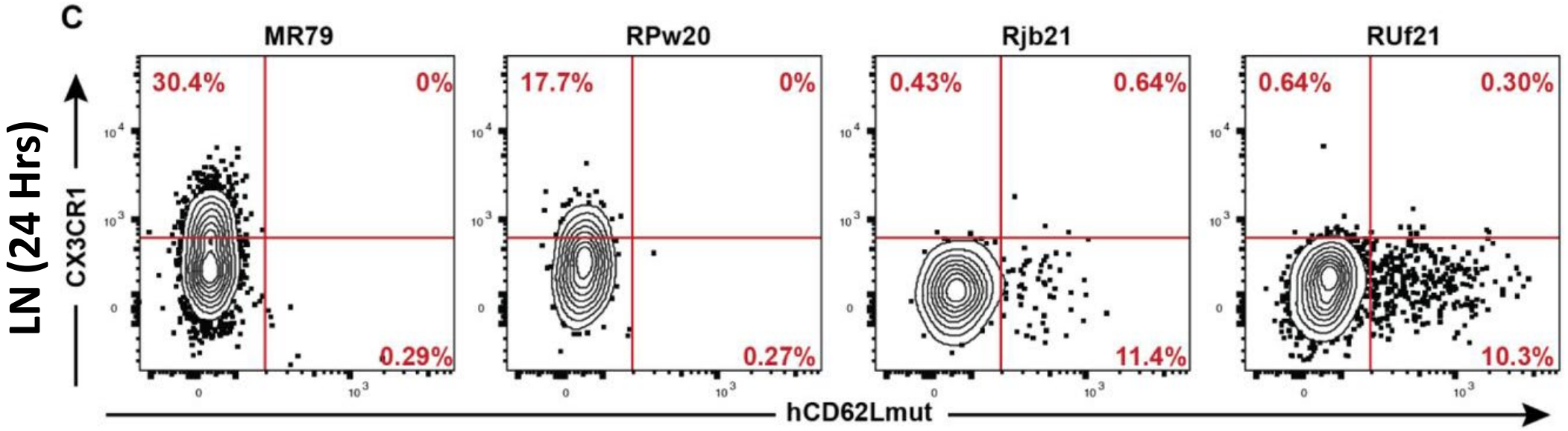
CX3CR1+ PBMCs were reprogrammed to express a LN trafficking receptor CD62L using fractalkine-targeted mRNA-LNPs



(Corrigan, et al., bioarxiv, 2025)

Human CD62L-expressing cells were isolated from the LN at 24hrs, consistent with trafficking into lymphoid tissue





(Corrigan, et al., bioarxiv, 2025)

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Conclusions

- The mRNA-LNP platform is a powerful research tool with translational potential beyond vaccines
  - Timed, transient expression of any protein of interest
  - Tailored to HIV Cure
- Cell and organ delivery is determined by
  - Route of administration
  - Lipid composition
  - Targeting moieties
- Many applications
  - Vaccine development
  - Gene therapy

Acknowledgements

Kreider Lab
Amie Albertus
Obinna Uzosike
Justin Su

Weissman Lab
Jenna Muscat-Rivera
Houping Ni
Jilian Melamed
Drew Weissman

Betts Lab
Angela Corrigan
Bettina Pampena
Jayme Nordin
Danica Fulmer
Michael Betts

Wu Lab
Vincent Wu

Acuitas
Raj Ramalingam
Molly Sung
Paulo Lin
Ying Tam

Lifson Lab
Jeff Lifson

Haynes Lab
Barton Haynes

BioQual

Kumar Lab
Hongil Kim
Priti Kumar

Ferrari Lab
Cindy Bowman
Guido Ferrari

Williams Lab
Wilton Williams

Paiardini Lab
Maura Statzu
Justin Harper
Mirko Paiardini

Finzi lab
Jonathan Richard
Mehdi Benlarbi
Andres Finzi

Claiborne lab
Francesco Pennino
Federica Severi
Tyler Yang
Daniel Claiborne

Montaner lab
Matthew Fair
Richard Khumoekae
Emery Register
Paridhima Sharma
Ian Tietjen
Zhe (Roger) Yuan
Luis Montaner

NIH National Institute of Allergy and Infectious Diseases

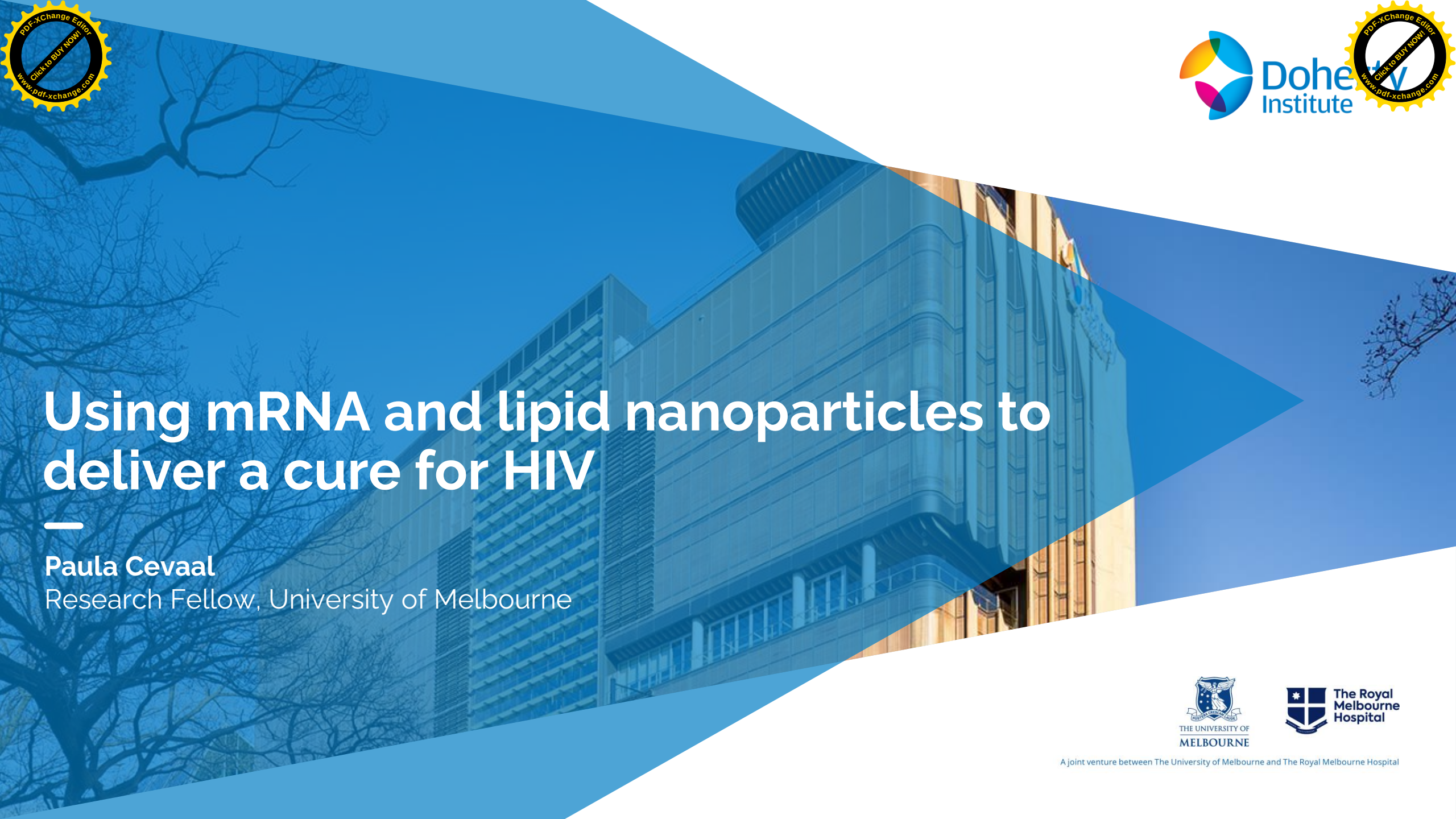
ERASE HIV

BEAT-HIV DELANEY COLLABORATORY

CIAVCR Consortium for Innovative HIV/AIDS Vaccine and Cure Research

DP2 (DP2AI184637), CIAVCR (UM1AI169633), ERASE HIV (UM1AI164662), BEAT-HIV (UM1AI191272)
Combined Adult and Pediatric Infectious Disease T32, Penn Measey Scholars in Molecular Medicine
Figures throughout generated with Prism, Biorender, and Adobe Illustrator

Doherty Institute



Using mRNA and lipid nanoparticles to deliver a cure for HIV

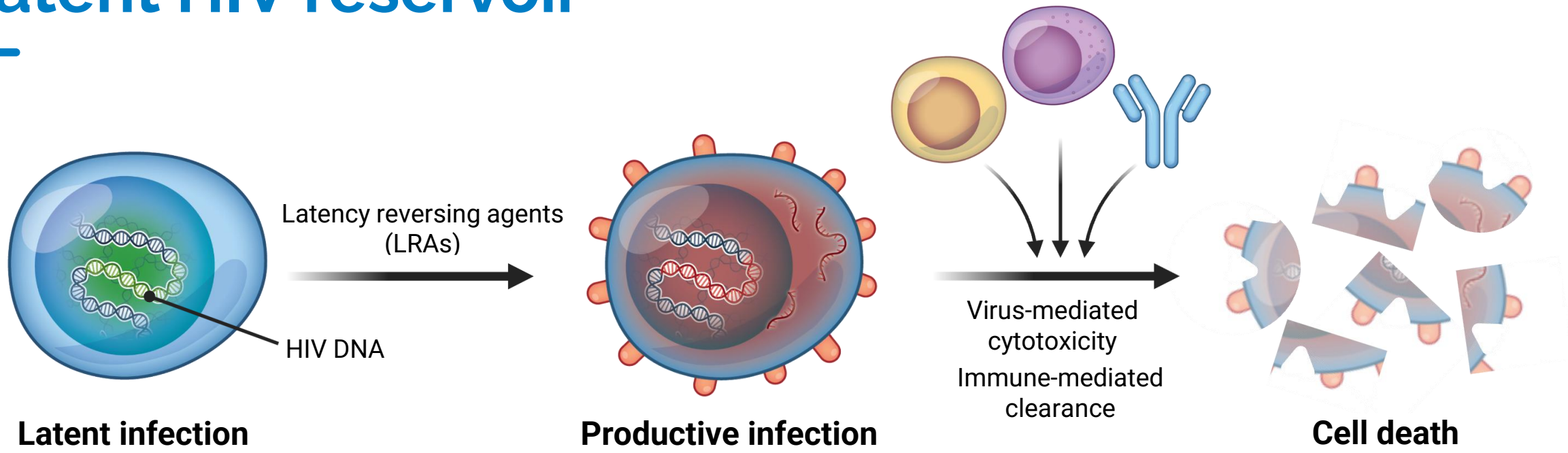
Paula Cevaal
Research Fellow, University of Melbourne

THE UNIVERSITY OF MELBOURNE

The Royal Melbourne Hospital

A joint venture between The University of Melbourne and The Royal Melbourne Hospital

‘Shock and kill’ as a strategy to deplete the latent HIV reservoir



LRAs alone have thus far **failed to reduce the size of the latent reservoir** in clinical trials

- Multiple studies showed modest increase in unspliced RNA, only in some cases multiply spliced RNA
- No change in frequency infected cells or time to viral rebound

Reviewed in: Zerbato, Curr Op Virol, 2019; Kim, Cell Host Microbe, 2018

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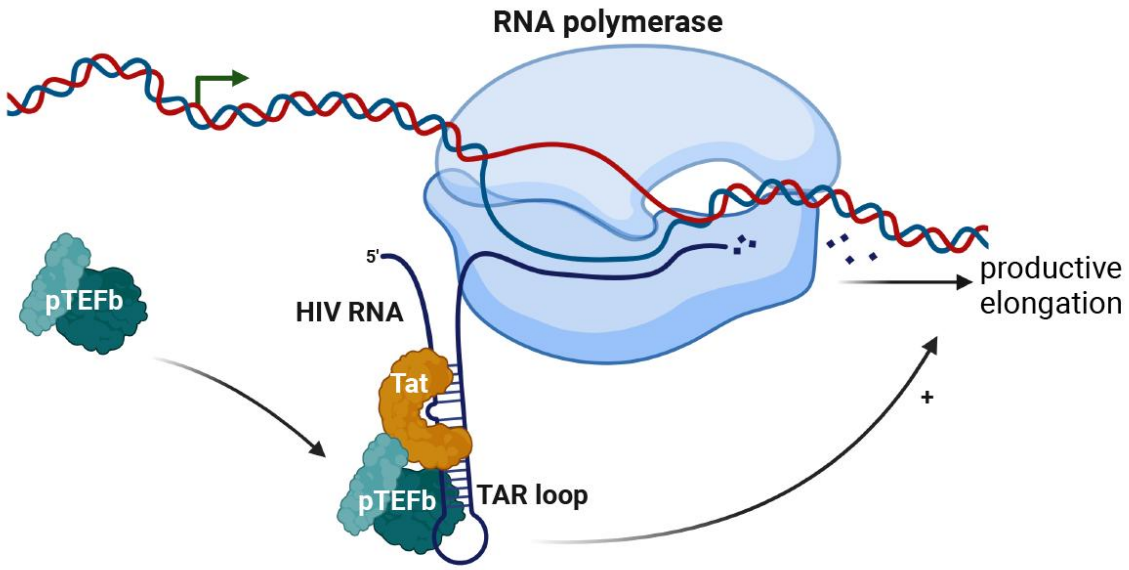
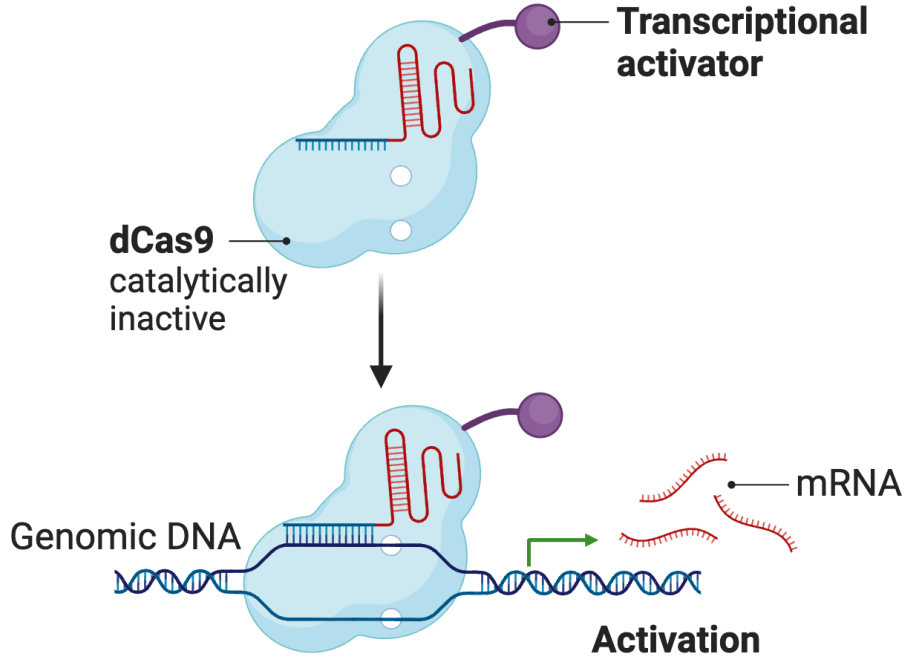
Can we harness the power of mRNA as a novel **therapeutic entity**, to design or enable a **new generation of LRAs?**

Two promising new latency-reversing agents

HIV's own protein Tat



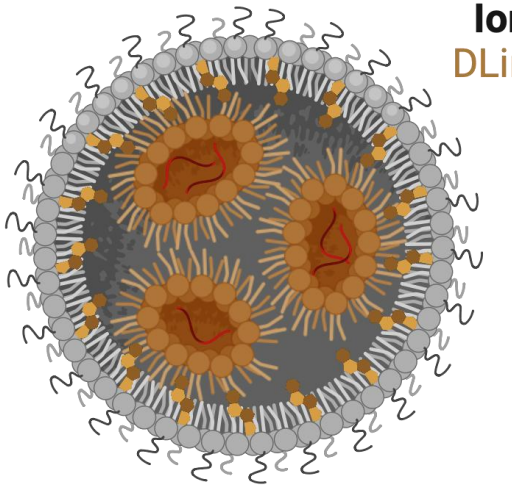
CRISPR activation



Both approaches are **highly HIV-specific**
Main **challenge** is their **delivery** to resting T cells

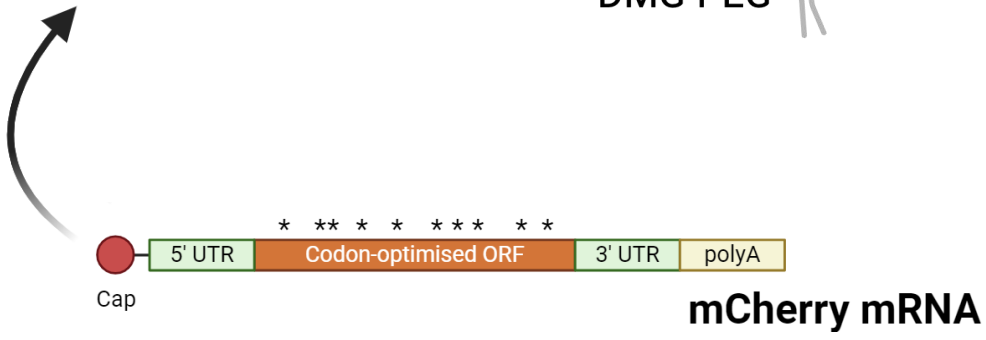
[1] Konermann, Nature (2015) [2] Zhang, Sci Rep (2015) [3] Bialek, PloS One (2016) [4] Limsirichai, Mol Ther (2016) [5] Ji, Mol Ther (2016) [6] Saayman, Mol Ther (2016) [7] Klinnert, J Gen Virol (2022) [8] Ahlenstiel, Curr Op HIV AIDS (2019) [9] Das, Curr Op Virol (2019) [10] Van Gulck et al., Antimicrob Agents Chemother (2023) [11] Tang et al., JCI Insight (2018) [12] Pardons,et al., Nat Commun (2023)

Novel LNP X can transfect non-stimulated CD4+ T-cells with high efficiency

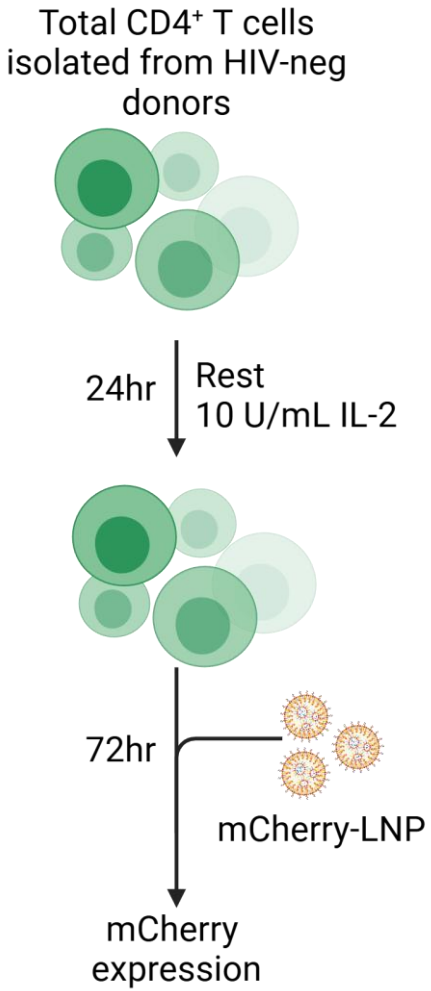


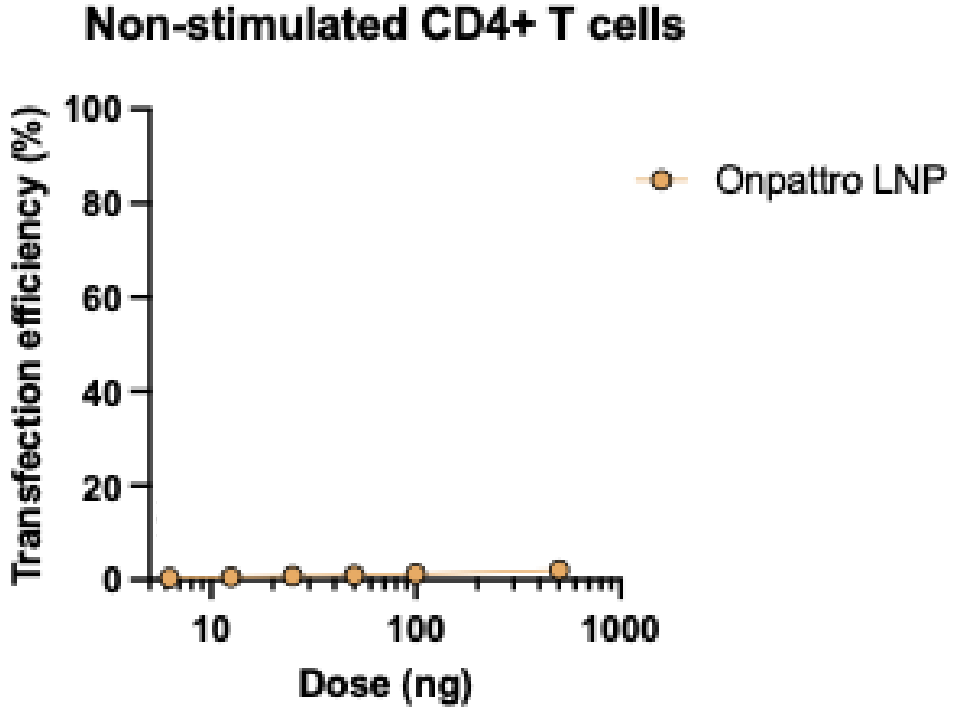
Onpattro LNP

	mol %
Ionizable lipid DLin-MC3-DMA	50
Helper lipid DSPC	10
Sterol Cholesterol	38.5
PEG-lipid DMG-PEG	1.5



mCherry mRNA





Cevaal, Kan, Fisher, Moso et al., *Nat Commun* 2025

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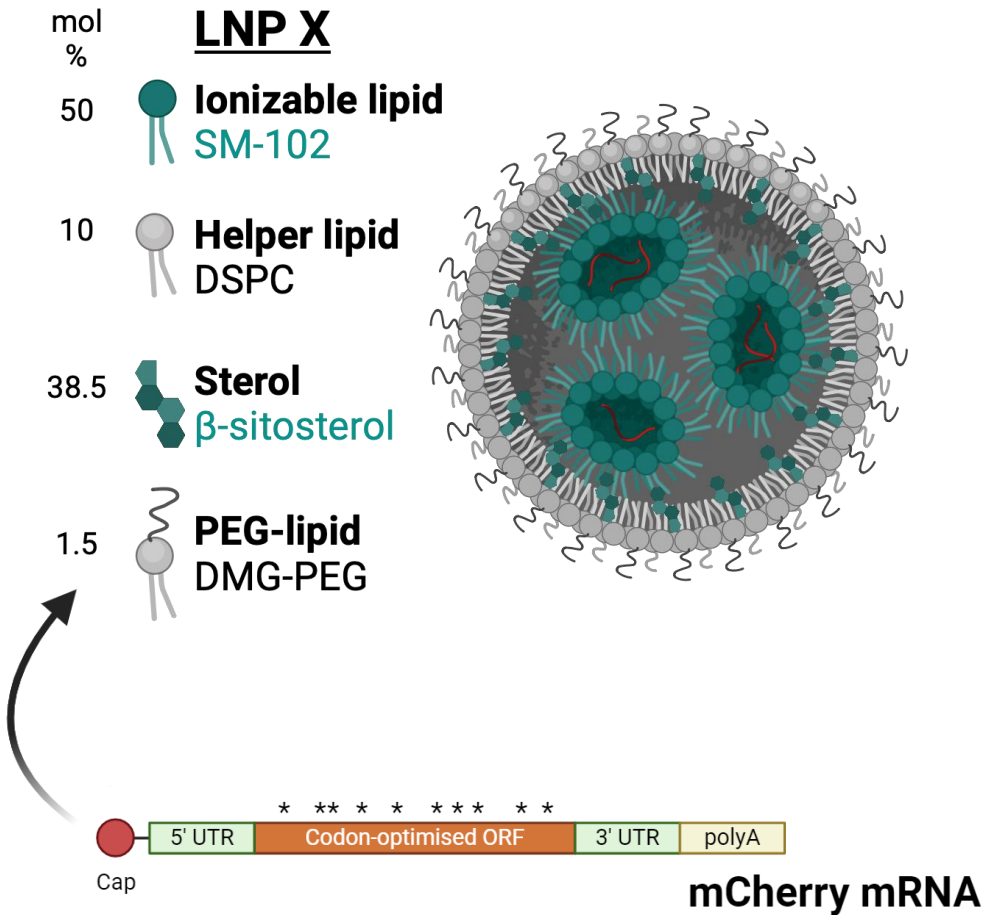
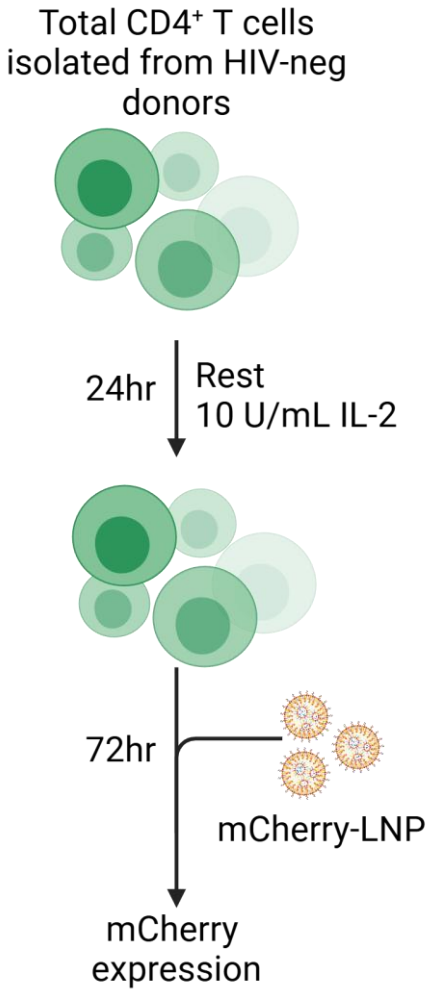
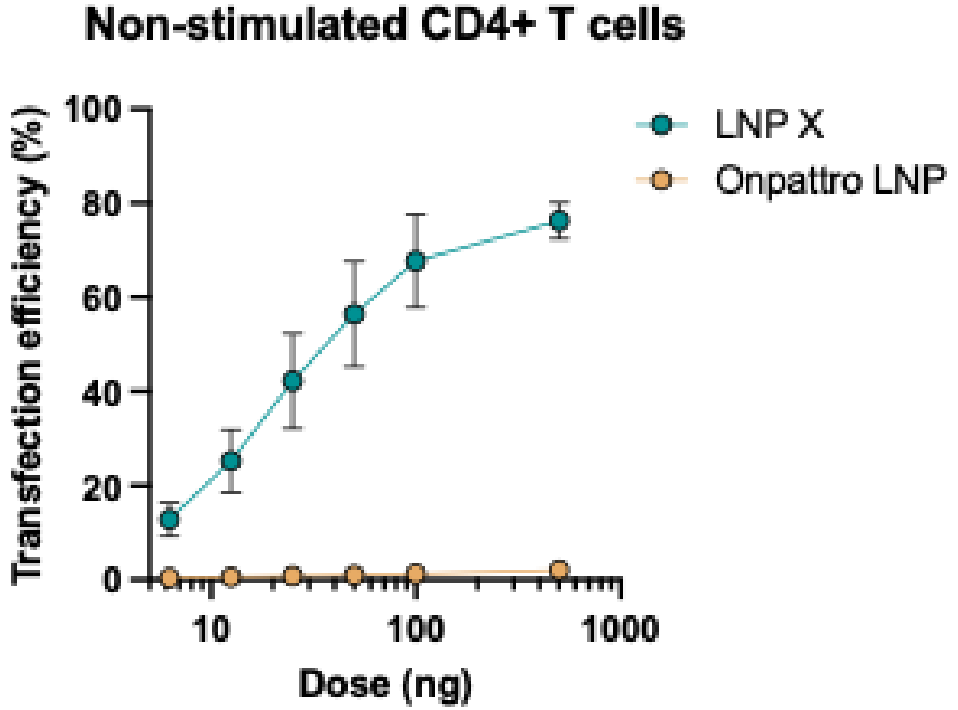
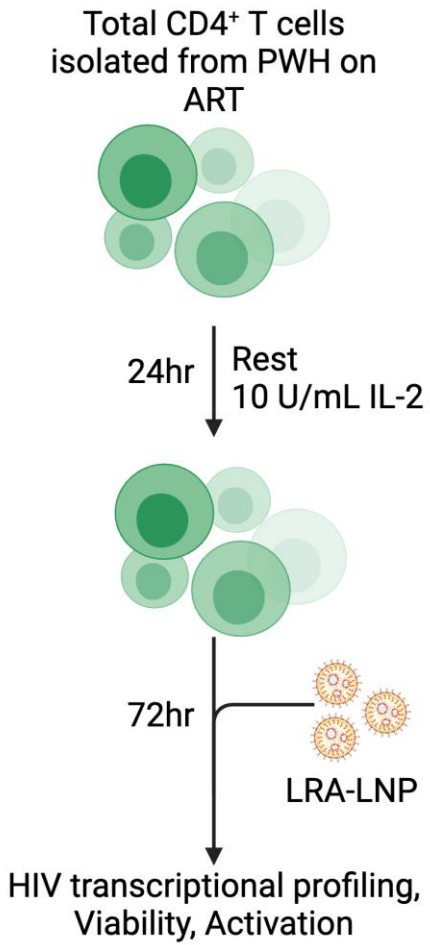


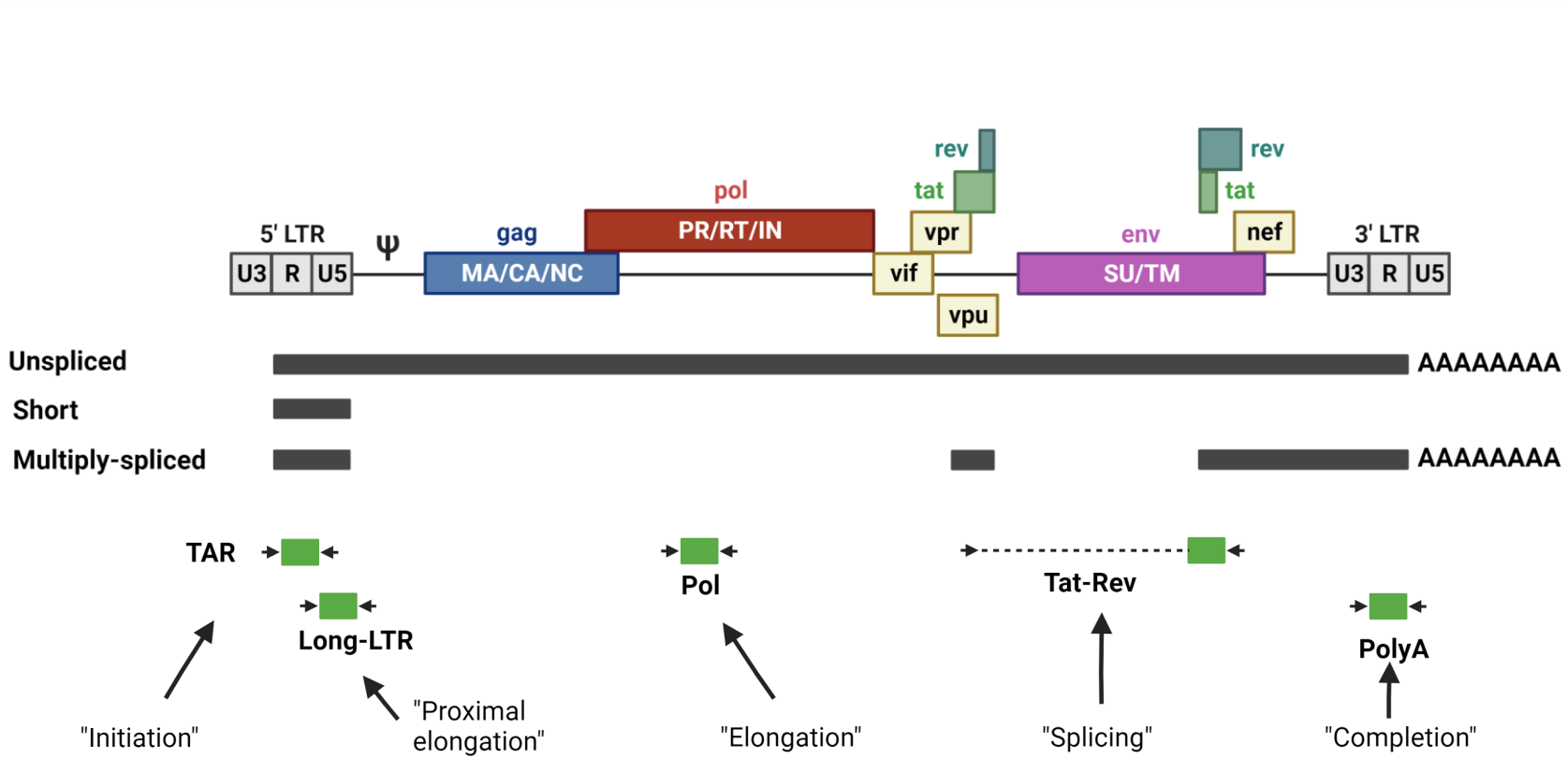




Cevaal, Kan, Fisher, Moso et al., *Nat Commun* 2025

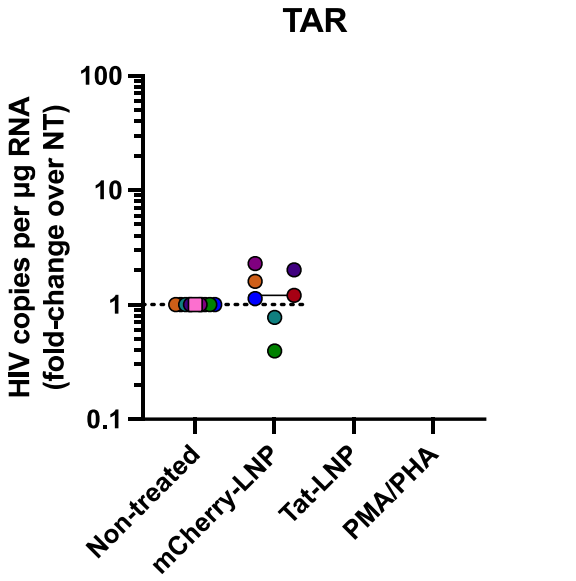
Assessed impact on transcription using digital PCR for multiple viral transcripts

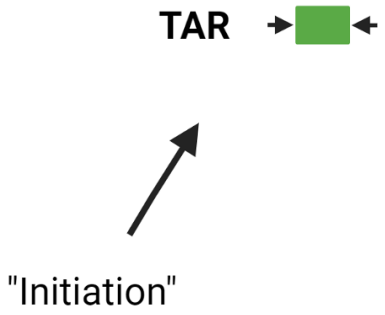




Yukl et al., Sci Trans Med (2018), Tumpach et al., Viruses (2023)

Tat-LNPs overcome transcriptional blocks to potently reverse HIV latency *ex vivo*





n=8; lines represent median, one-tailed Wilcoxon signed-rank test

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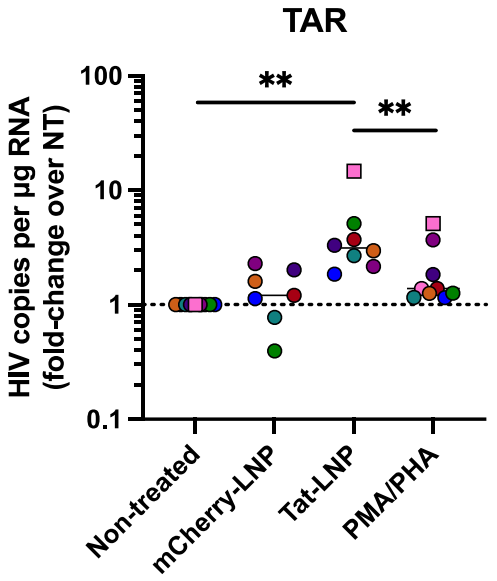

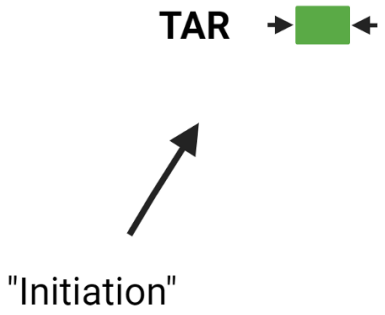

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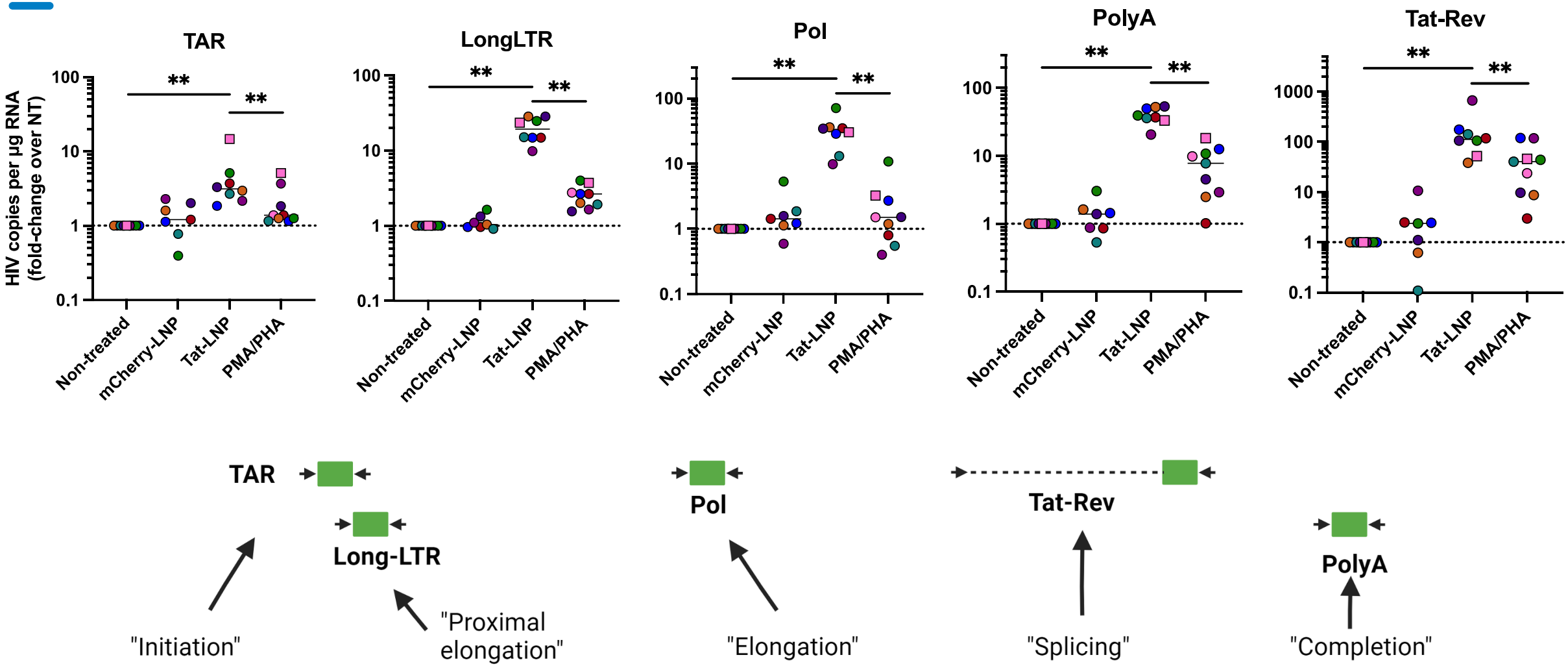

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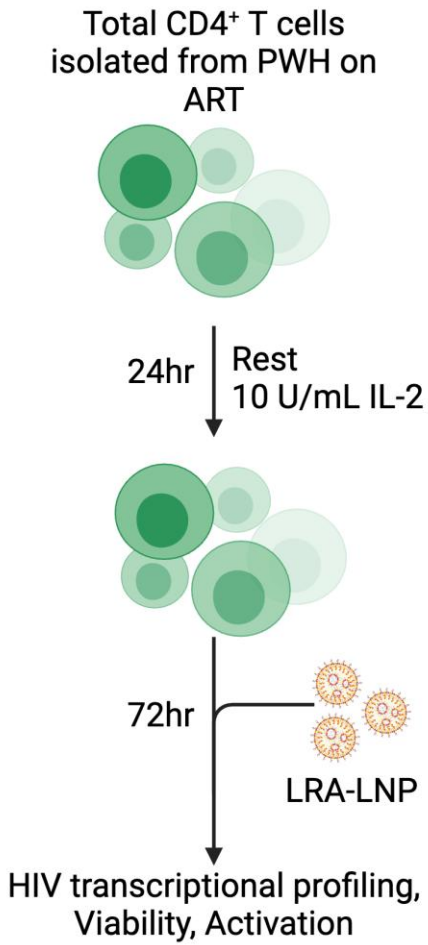
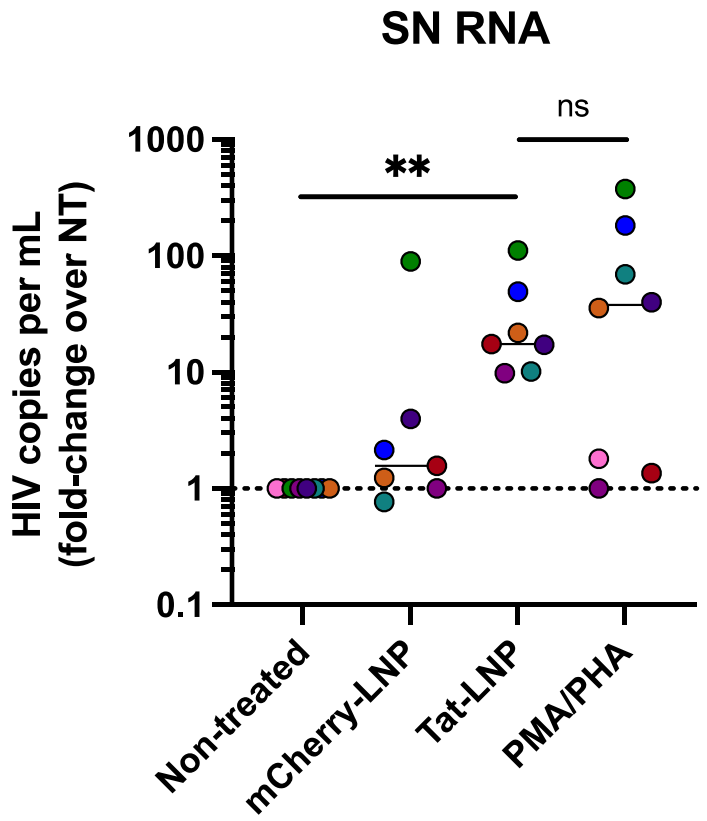
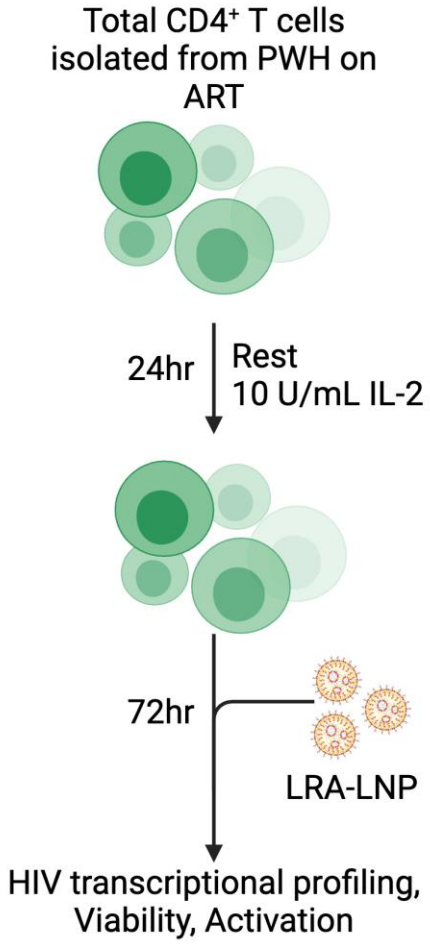
Tat-LNPs overcome transcriptional blocks to potently reverse HIV latency *ex vivo*

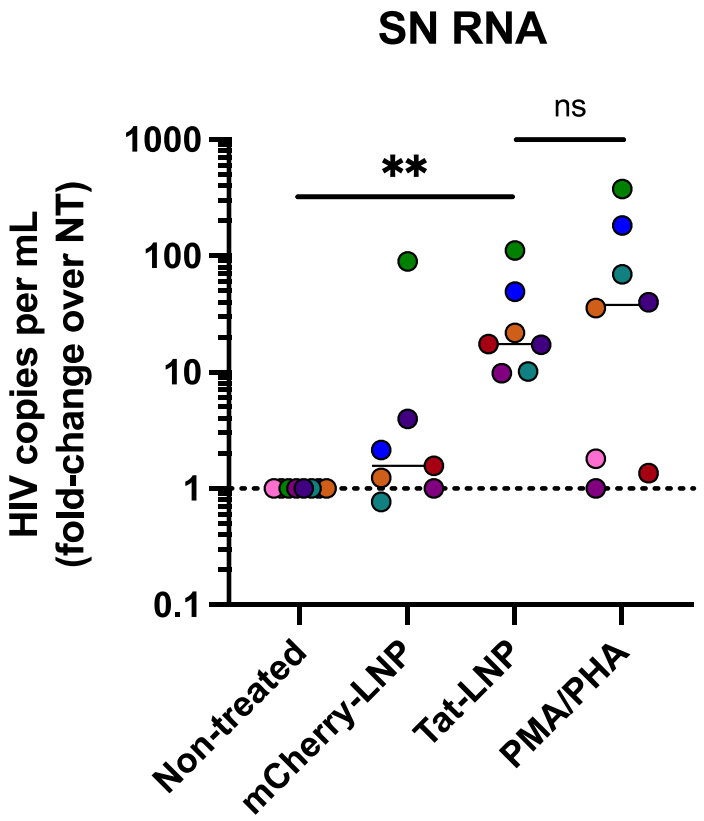


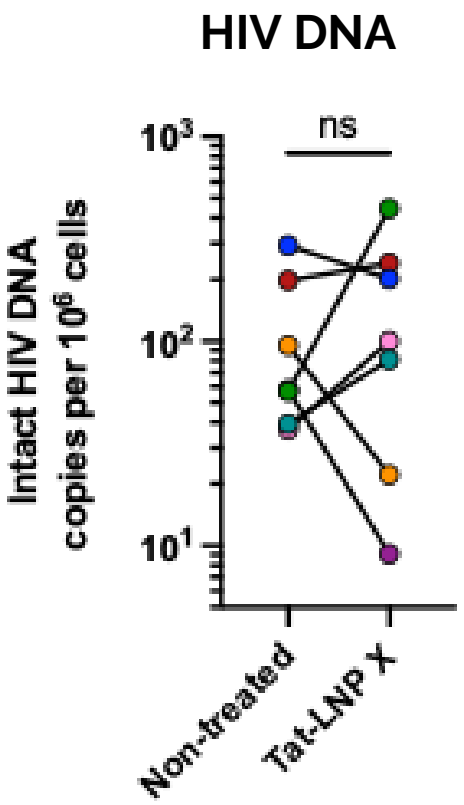


Cevaal, Kan, Fisher, Moso et al., *Nat Commun* 2025

No decrease in HIV reservoir size despite potent latency reversal



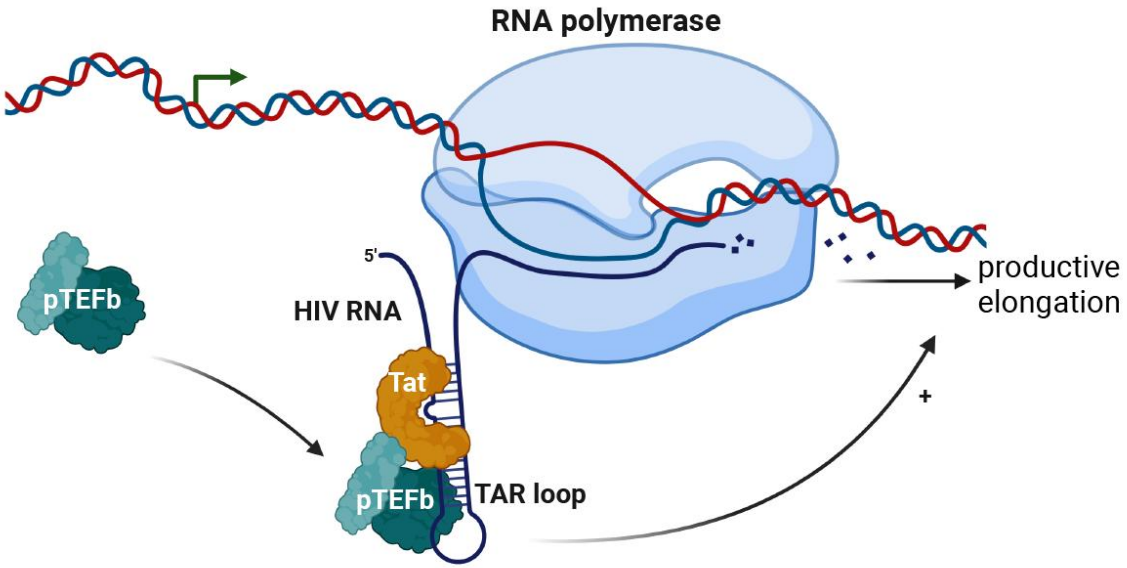




Cevaal, Kan, Fisher, Moso et al., *Nat Commun* 2025

Two promising new latency-reversing agents

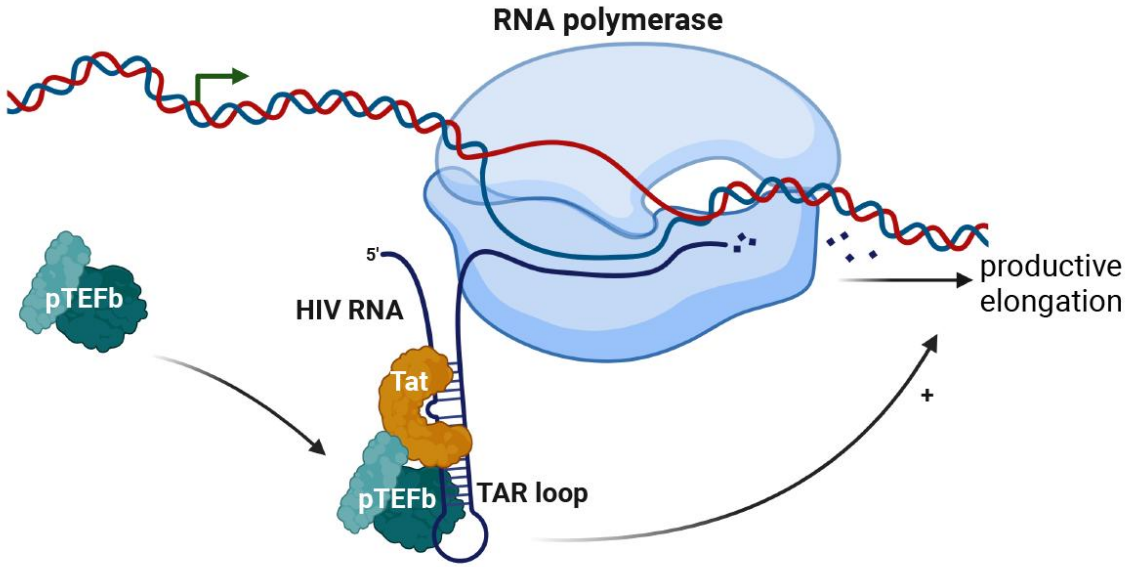
HIV's own protein Tat



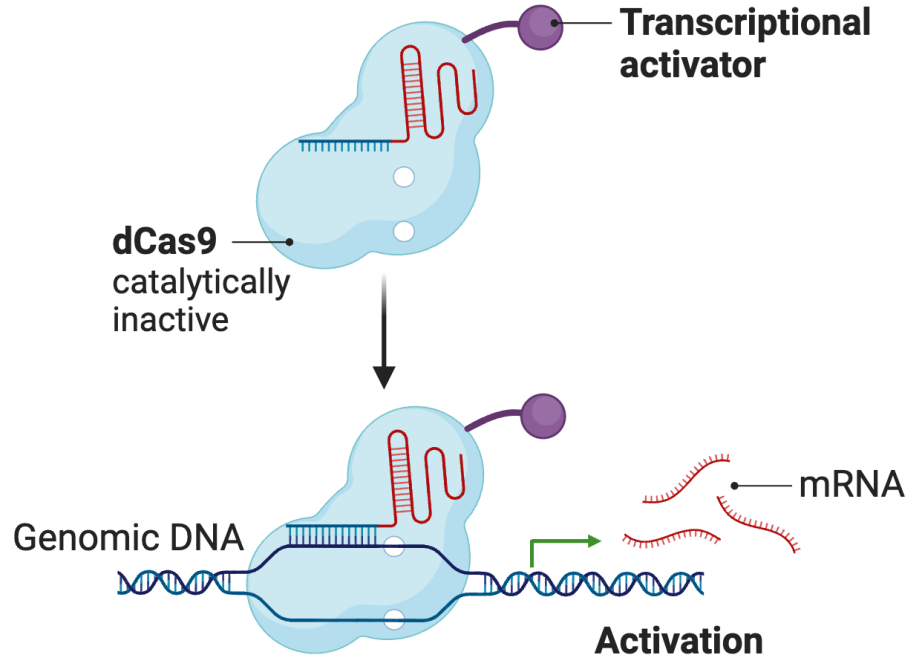
- Does Tat's **potency** translate to **in vivo** settings?
- **Immune effector cells** or **pro-apoptotic compounds** required for reservoir elimination?
  - bNAbs
  - Checkpoint blockade
  - Venetoclax
- Can Tat reveal **deeply latent provirus** that express minimal to no TAR transcripts?

Two promising new latency-reversing agents

HIV's own protein Tat

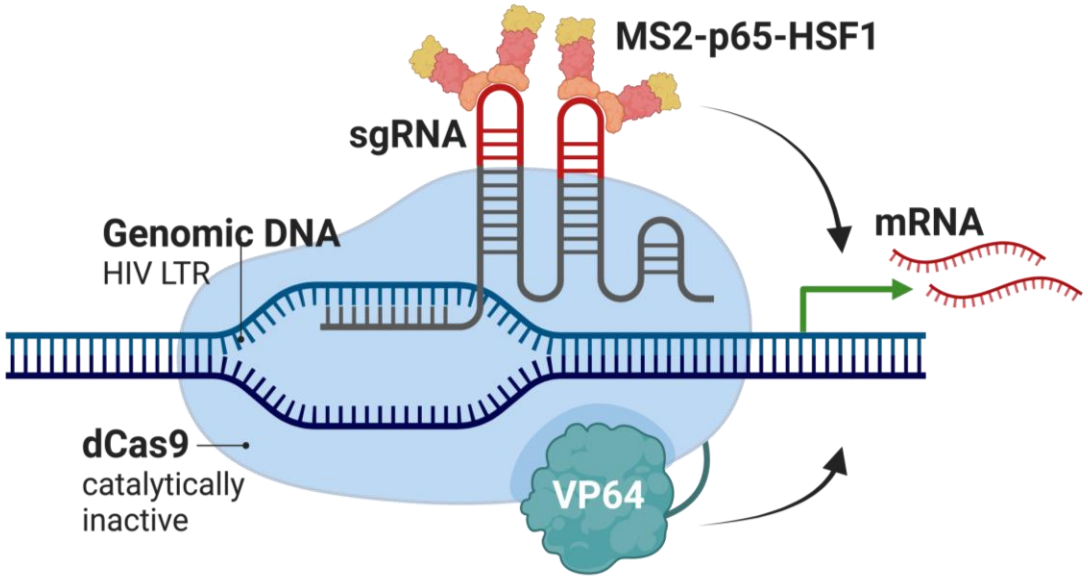


CRISPR activation

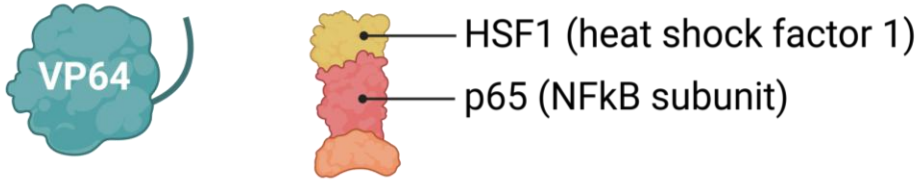


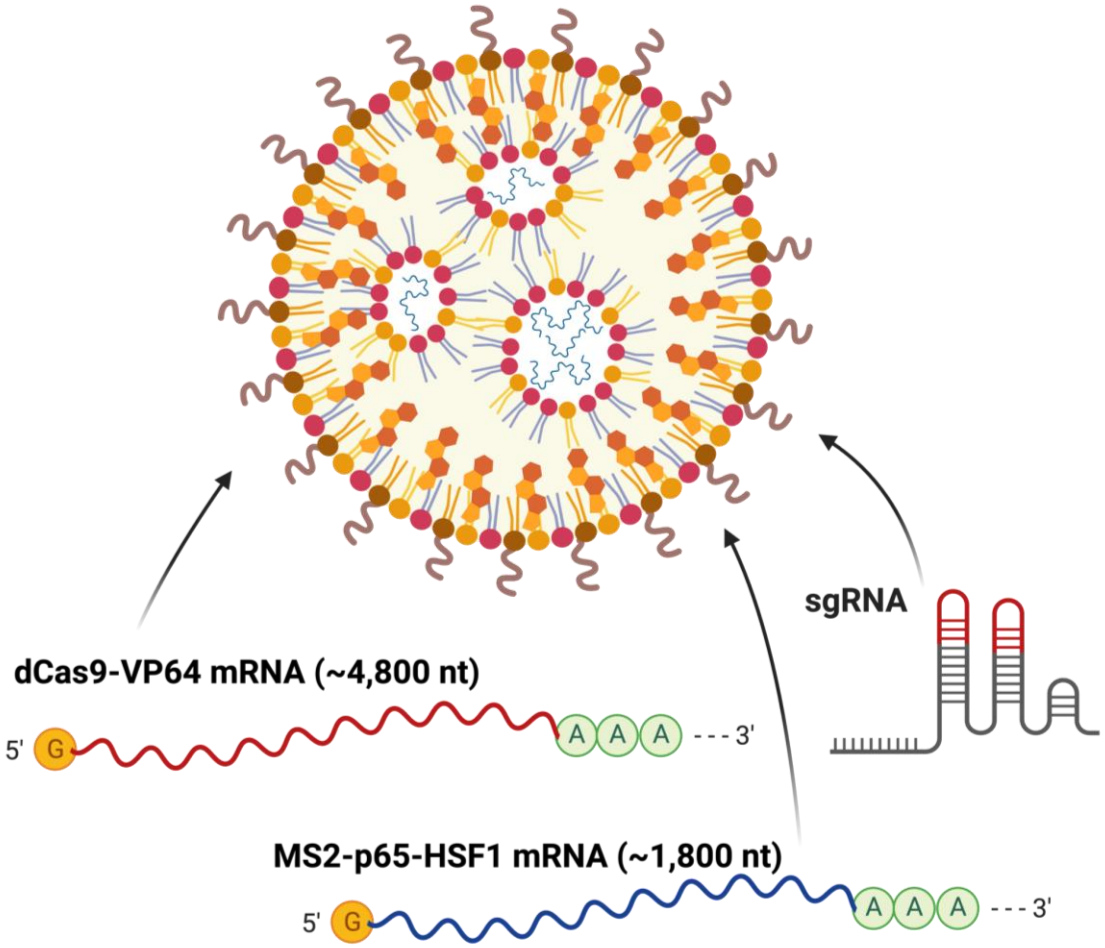
Could CRISPRa **overcome potential limitations** of Tat,
either alone or **in combination**?

Encapsulating three-component CRISPR activation system into one LNP

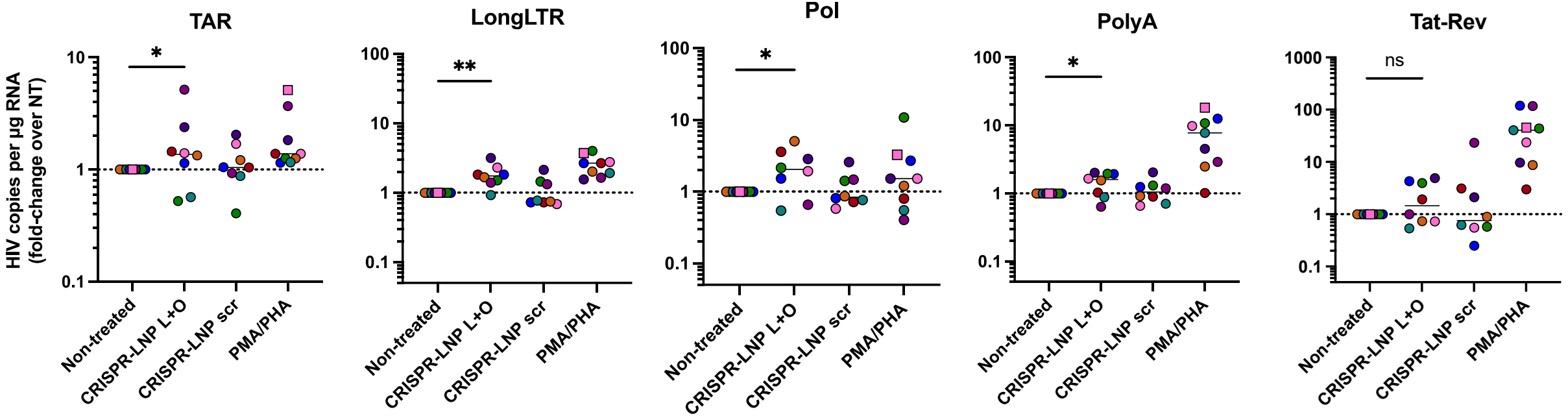


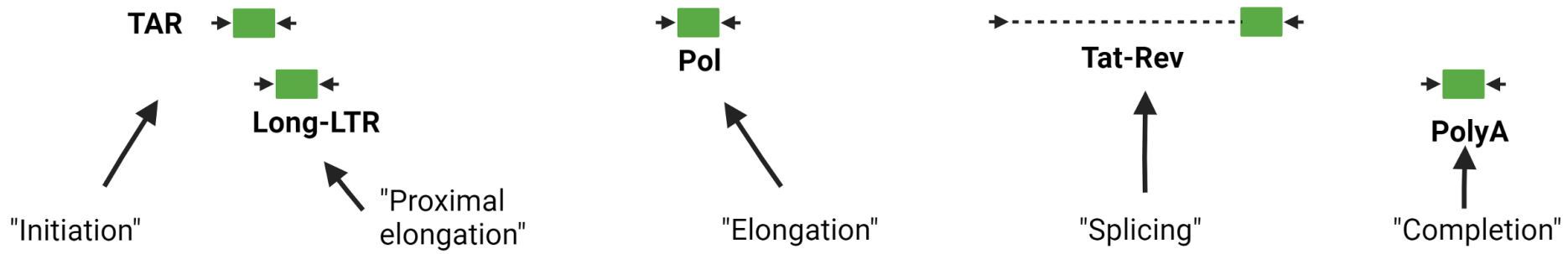
Transcriptional activation domains





CRISPRa-LNPs overcome some barriers to HIV transcription *ex vivo*, but effect size is modest





n=8; lines represent median, one-tailed Wilcoxon signed-rank test

Cevaal, Kan, Fisher, Moso et al., *Nat Commun* 2025

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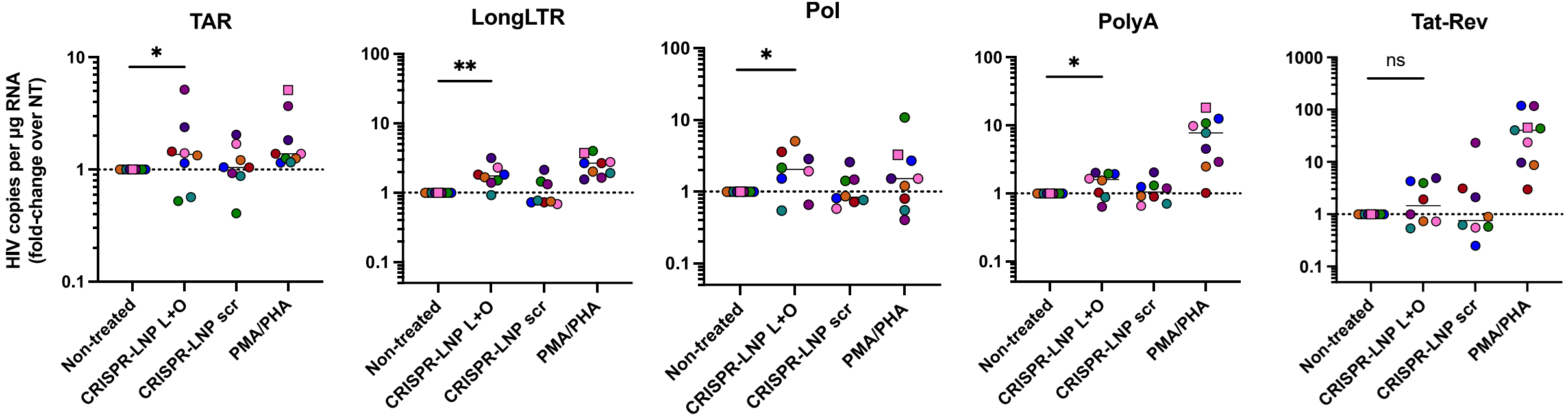


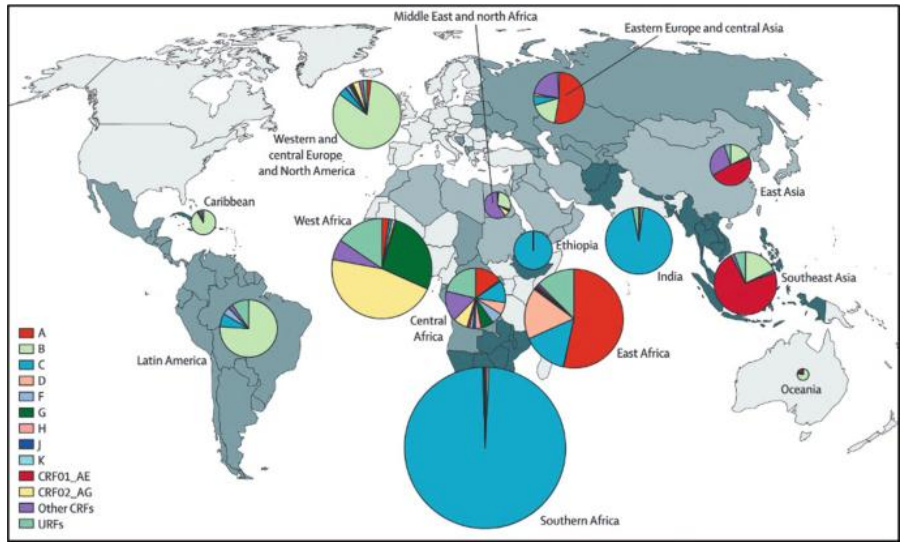
Bottleneck in potency is the **efficiency of delivery** –
much reduced for large mRNAs such as CRISPR-Cas9

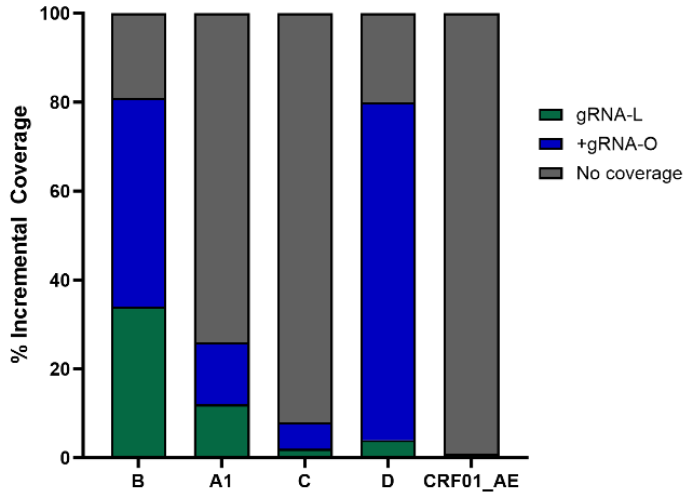
n=8; lines represent median, one-tailed Wilcoxon signed-rank test

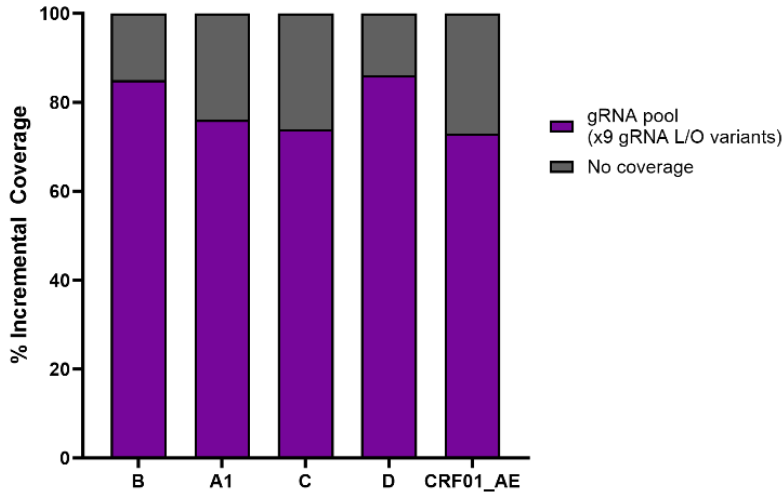
Cevaal, Kan, Fisher, Moso et al., *Nat Commun* 2025

CRISPR-based cure strategies: expanding beyond HIV subtype B

HIV subtype B represents <12% of global infections







Approach 1: subtype-specific gRNAs

\+

Companion diagnostic for HIV subtyping

Approach 2: cross-clade gRNA pool

Compromise on potency?

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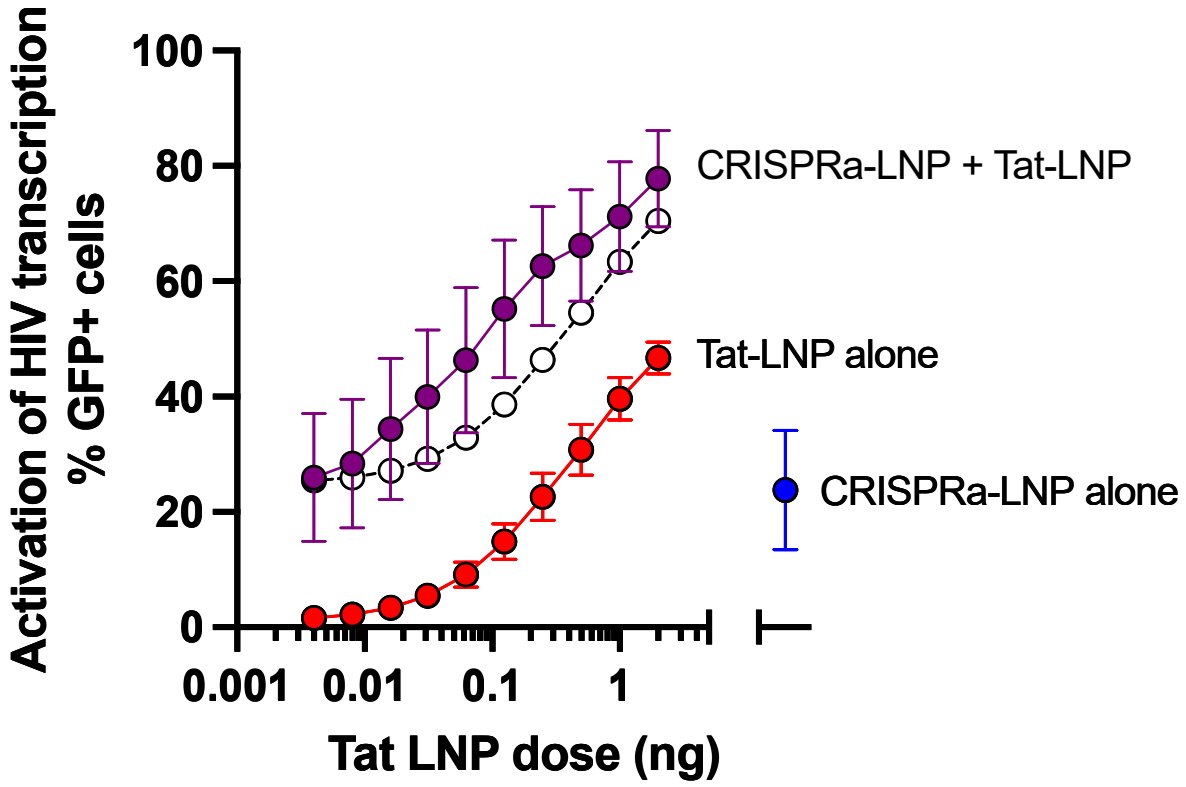
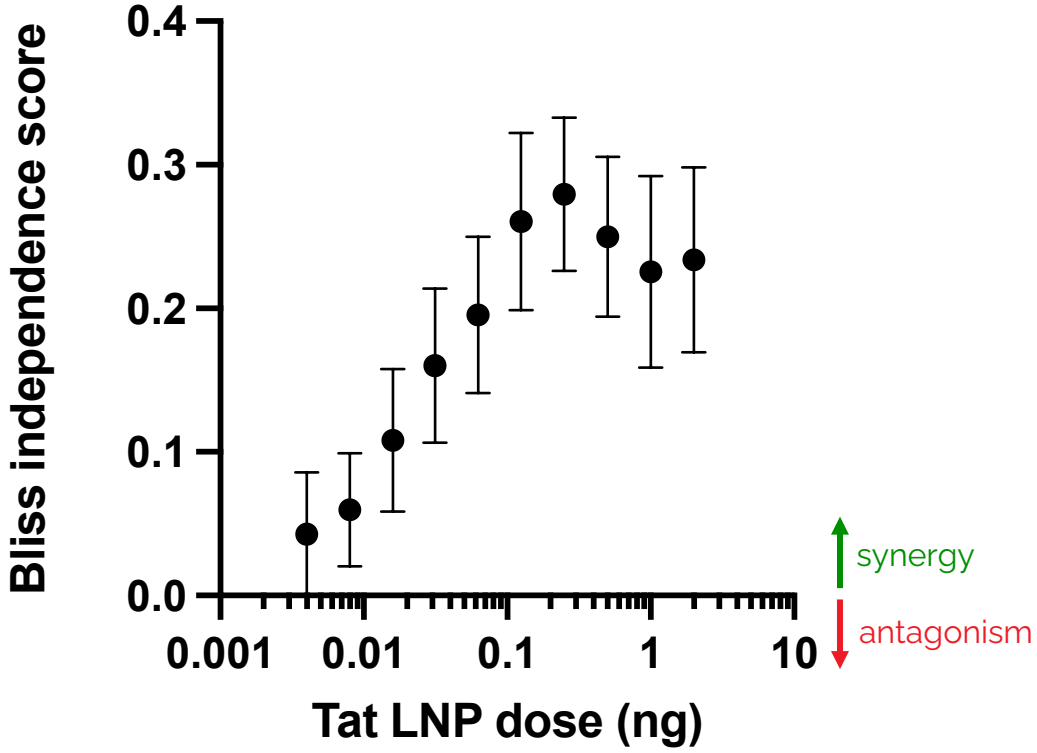
MAKING AIDS HISTORY

Synergistic reactivation with CRISPRa-LNPs and Tat-LNPs in cell line model



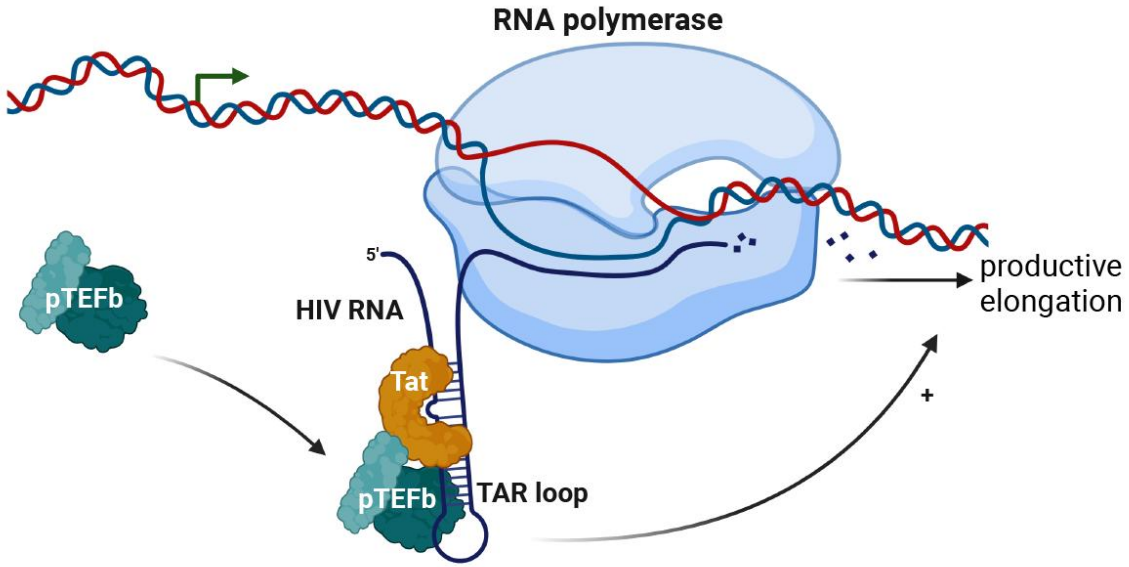


Synergy potentially allows for using **one hundredth the dose** of Tat mRNA previously used

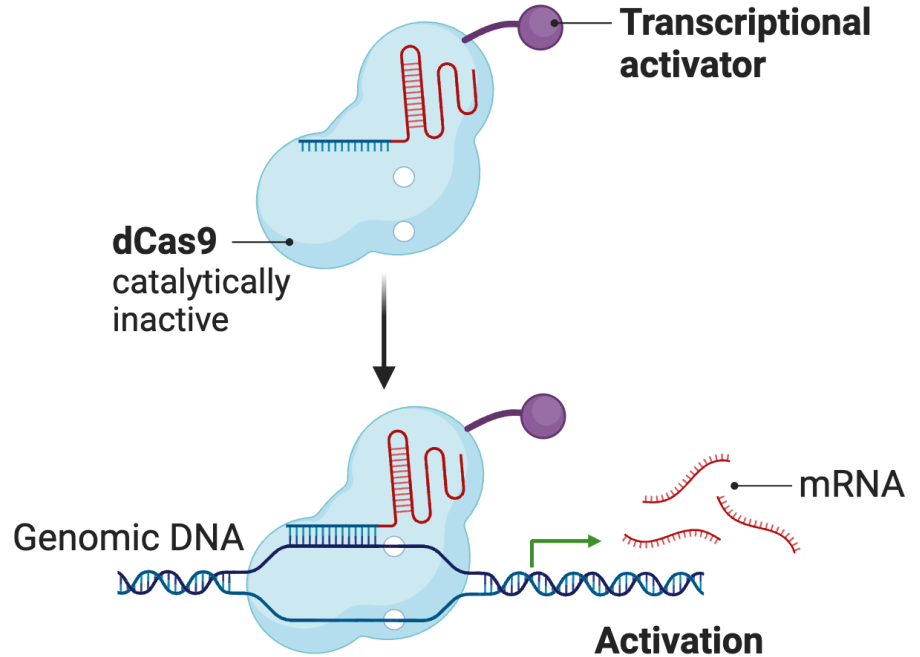
Two promising new latency-reversing agents

Explored separately or in combination

HIV's own protein Tat

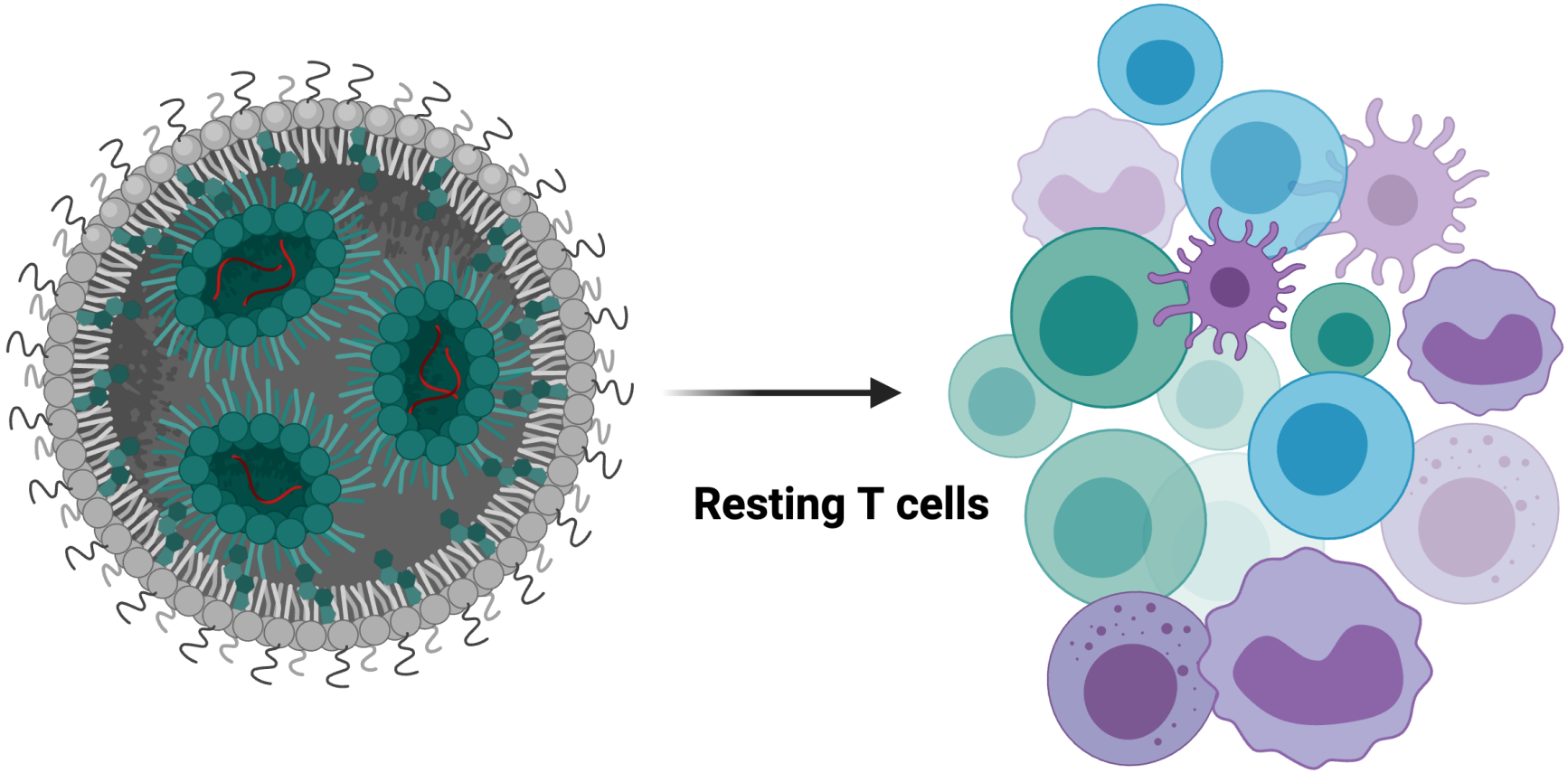


CRISPR activation



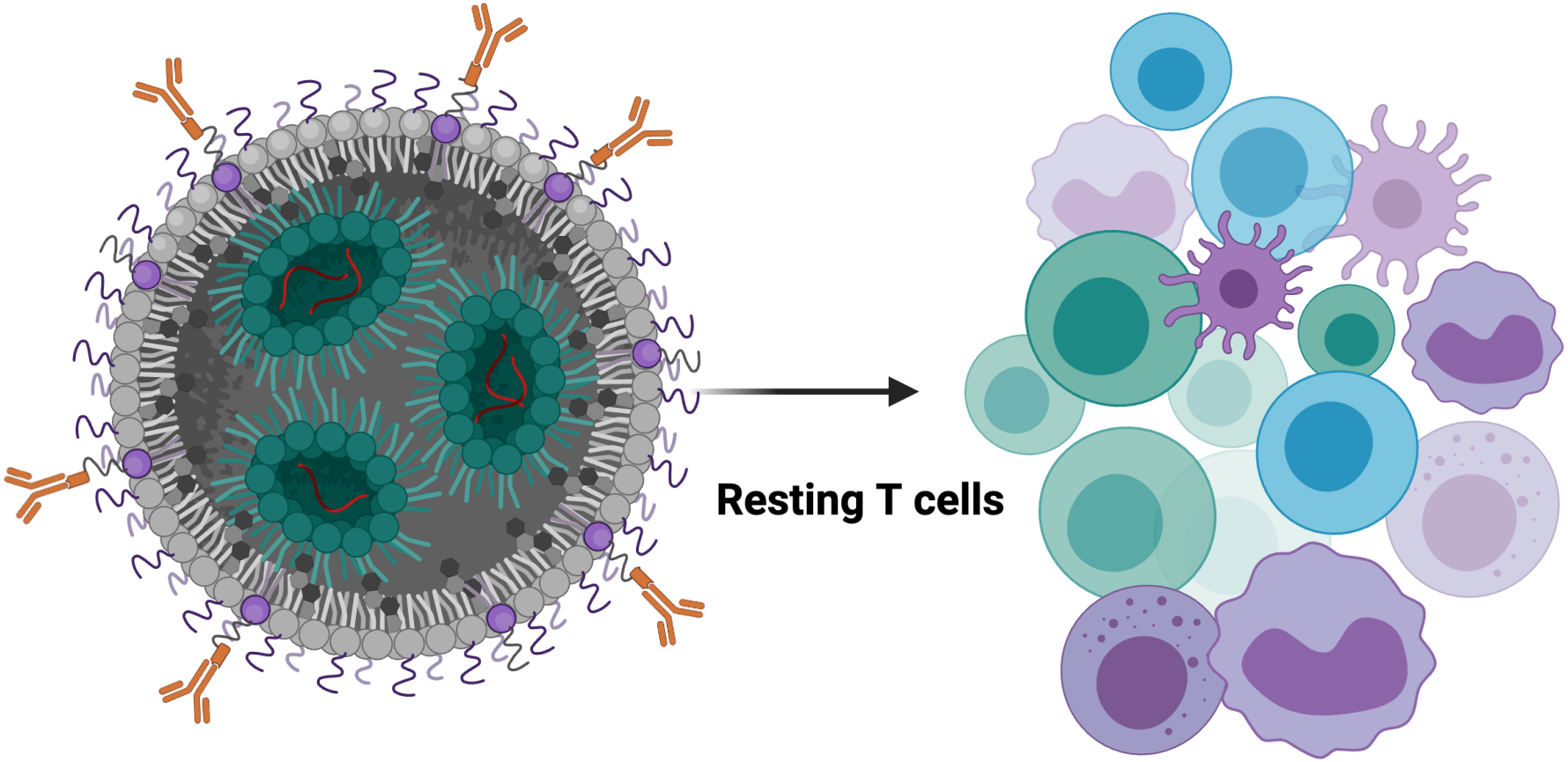
What about **in vivo** delivery and efficacy?

LNP X potently transfects isolated CD4+ T cells, but what about *in vivo* delivery?



T cells are surrounded by phagocytes that **scavenge nanoparticles**, **limiting the nanoparticle dose** that reaches T cells *in vivo*

LNP X potently transfects isolated CD4+ T cells, but what about *in vivo* delivery?

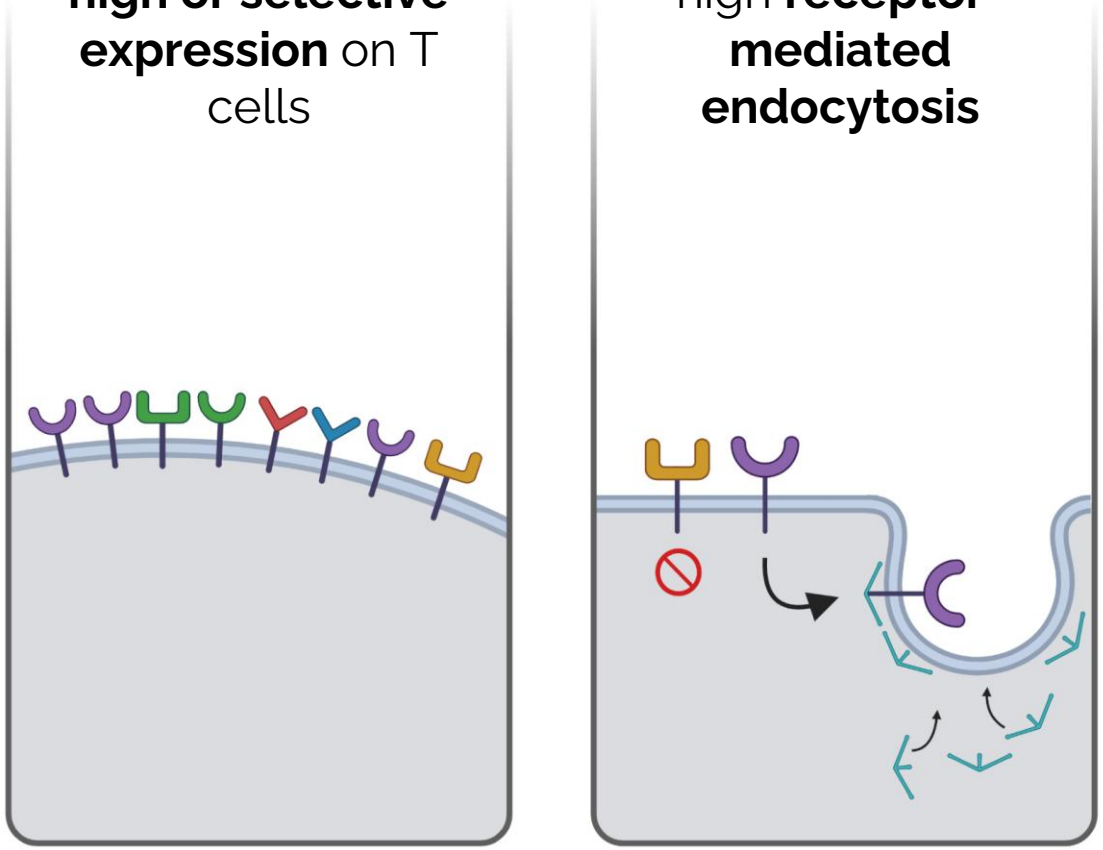


T cells are surrounded by phagocytes that **scavenge nanoparticles**, **limiting the nanoparticle dose** that reaches T cells *in vivo*

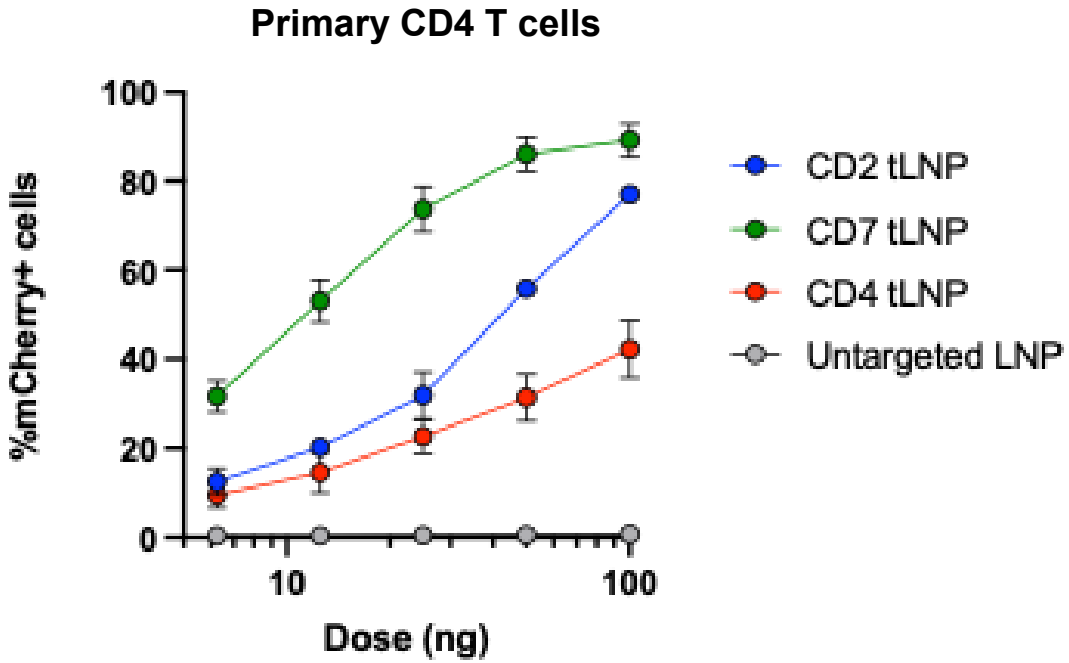
New paradigm in cell-specific targeting: focus on receptor internalization

Receptors with **high or selective expression** on T cells

Receptors exhibiting high **receptor-mediated endocytosis**

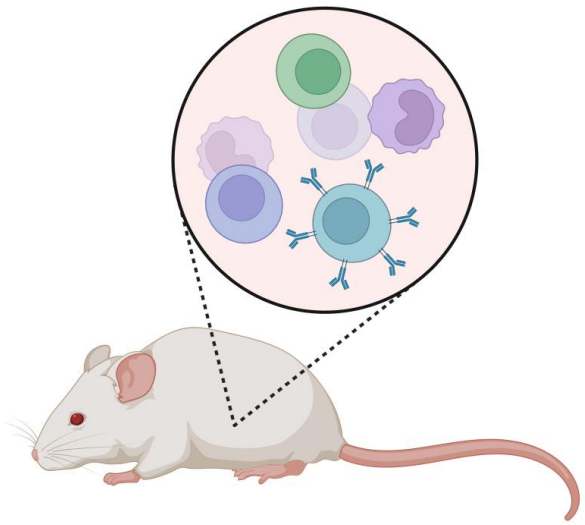


- **Library screening** of potential target receptors
- Target **validation** using different nanoparticle platforms

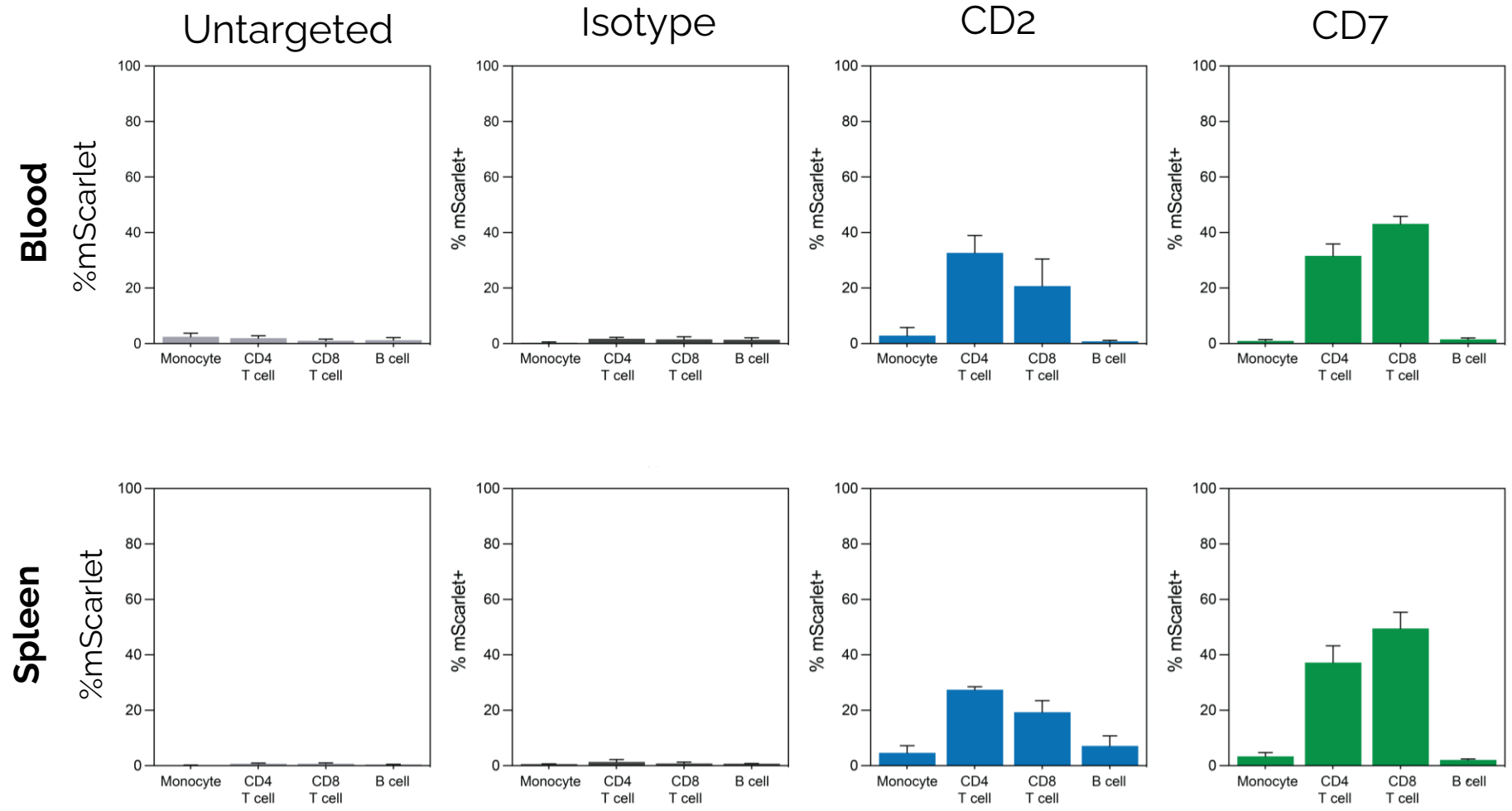


Enhanced mRNA expression in hu T cells from HIS mice *in vivo* in blood and spleen

Human immune system mice



i.v. administration
16 hr treatment
0.5 mg/kg



n=3-4 mice per group

Project summary

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- Need for more potent, **HIV-specific LRAs** → mRNA lipid nanoparticle technology
- Novel LNP formulation X is able to **transfect CD4+ T cells in the absence of pre-stimulation**
- **Tat-LNP X** induces multiply-spliced RNA **by >100-fold**, outperforming PMA/PHA *ex vivo*, but does not induce reservoir clearance in isolated CD4+ T cells
- **CRISPRa** may pose an **alternative or complementary strategy** to Tat, but further optimisation of large mRNA delivery is required
- Targeting **rapidly cycling receptors** enables efficient mRNA delivery to T cells ***in vivo***

Acknowledgements

Peter Doherty Institute, Melbourne, Australia
Sharon Lewin
Michael Roche
Bridget Fisher
Michael Moso
Abigail Tan
Abdalla Ali
Stan Kan
Rory Shepherd
Wei Zhao
Youry Kim
Jesslyn Ong
Sushama Telwatte
Damian Purcell
Marvin Holz

Alfred Hospital, Melbourne, Australia
James McMahon

Utrecht University (The Netherlands)
Jori Symons

University of Melbourne, Australia
Frank Caruso
Christina Cortez-Jugo
Denzil Furtado
Rob de Rose

Monash University, Melbourne, Australia
Colin Pouton
Angus Johnston
Thomas Payne
Moore Chen
Haiyin Liu
Serena Tao

Johns Hopkins (USA)
Andrew Redd
Natalie Howard

Rakai Health Services (Uganda)
Edward Kankaka

Peter MacCallum Cancer Centre, Melbourne, Australia
Joe Trapani
Mohamed Fareh

WEHI, Melbourne, Australia
Marcel Doerflinger
Marc Pellegrini
Jan Schäfer
Le Wang

UCSF (USA)
Steven Deeks
Becky Ho

AHRI (South Africa)
Thumbi Ndung'u

People living with HIV

Harold and Cora Brennen Benevolent Trust

ACH2 Australian Centre for HIV and Hepatitis Virology Research

mRNA VSC

Australian Government
National Health and Medical Research Council

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