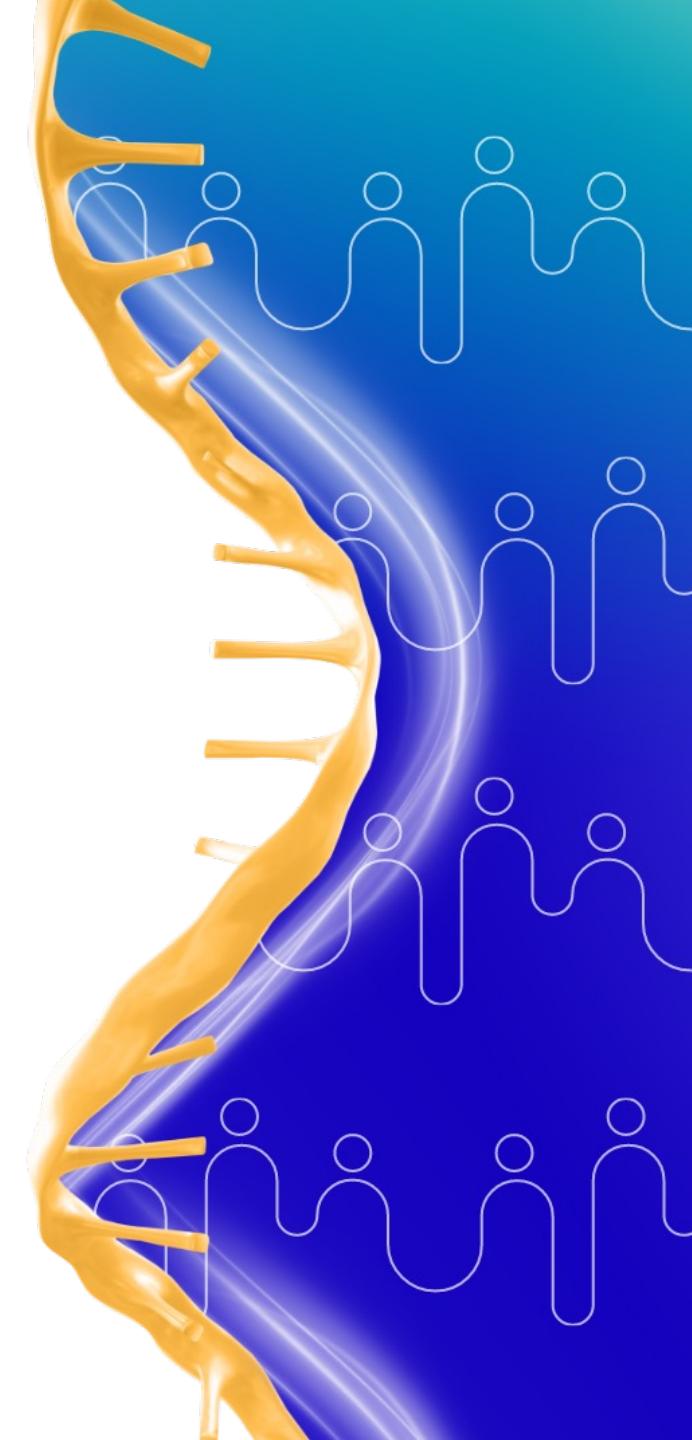


# REPLICATE

## Novel Self-Replicating RNA Vectors Broaden Therapeutic Window and Expand Use Outside of Vaccines

— May 2024



# Our vision is to address key limitations of RNA technologies and open broader applications for RNA-based treatments

## Linear mRNA: a breakthrough for vaccines but known limitations

- **Narrow therapeutic window<sup>1,2</sup>** limit use cases in vaccines (seasonal / pandemic / personalized)
- **Low durability<sup>3</sup> and total protein expression** have precluded use as “protein factories”

## Current self-replicating RNA (srRNA) outperforms mRNA

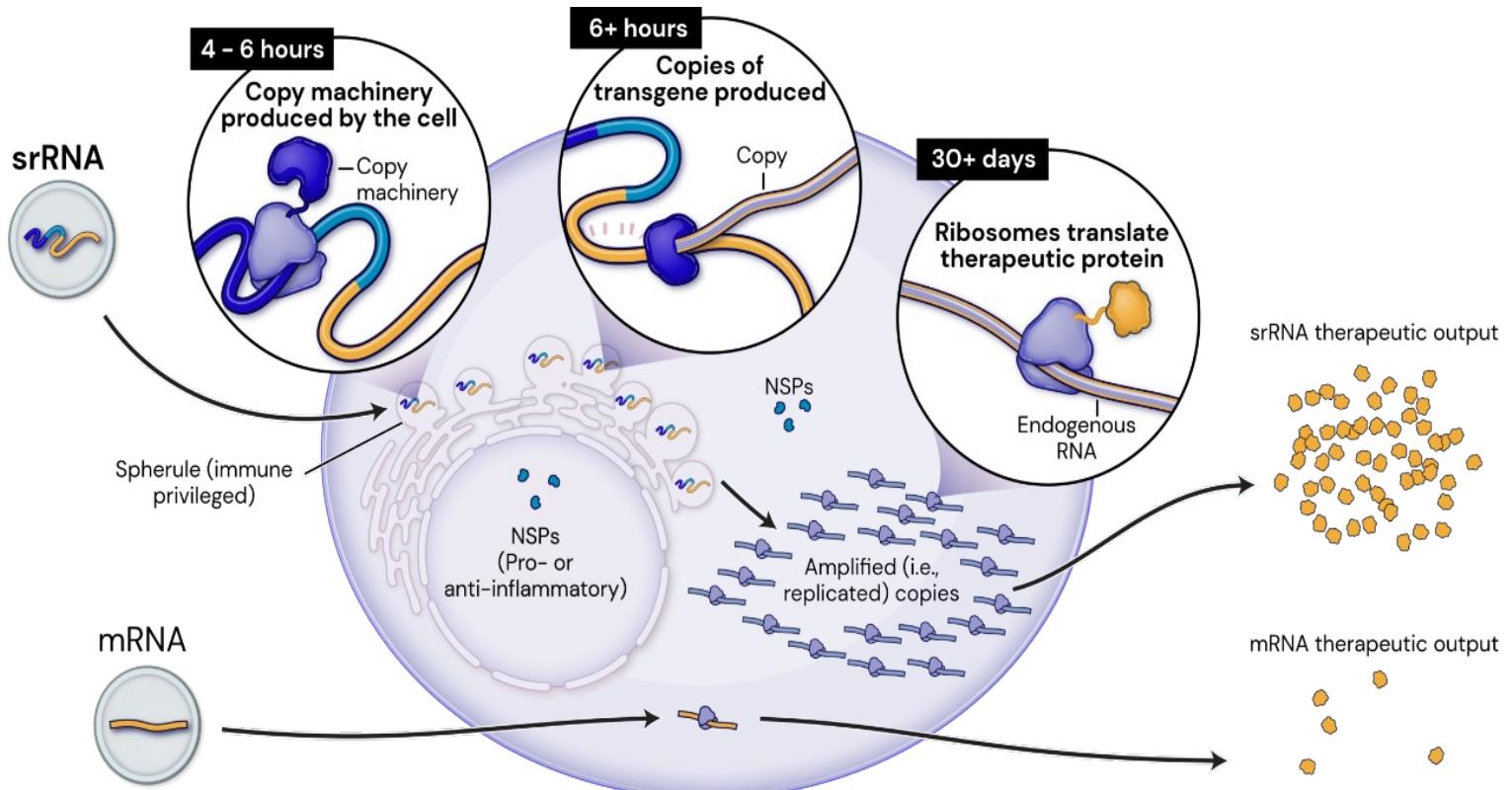
- *~10x lower doses clinically than mRNA<sup>4</sup>*
- *No improvement in therapeutic index<sup>4</sup>*

## Novel, optimized srRNA platform achieve superior performance

- Superior therapeutic index\* (>30-fold) in vaccines
  - Clinical biological activity / protection at
    - Doses 300-1000x lower than linear mRNA
    - Doses 50x lower than approved srRNA
    - Single doses
  - Clinically safer profile
  - Preclinical data shows superior T cells
- Protein Factories: Preclinical head-to head data vs. mRNA and circular RNA
  - Higher, more durable protein expression
  - Ability to screen vector library for desired PK profile

# srRNA are an instruction manual for your body's own cells to create fully natural mRNA

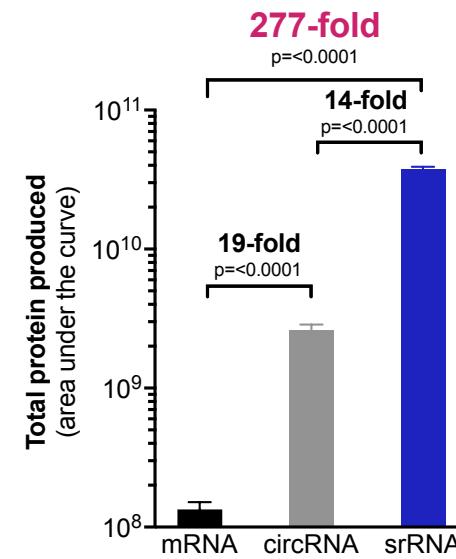
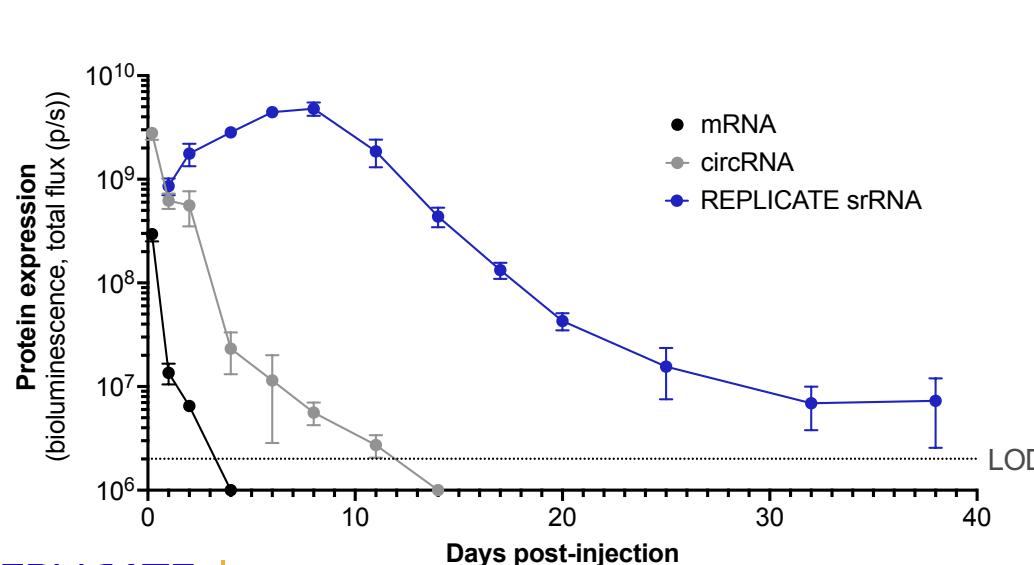
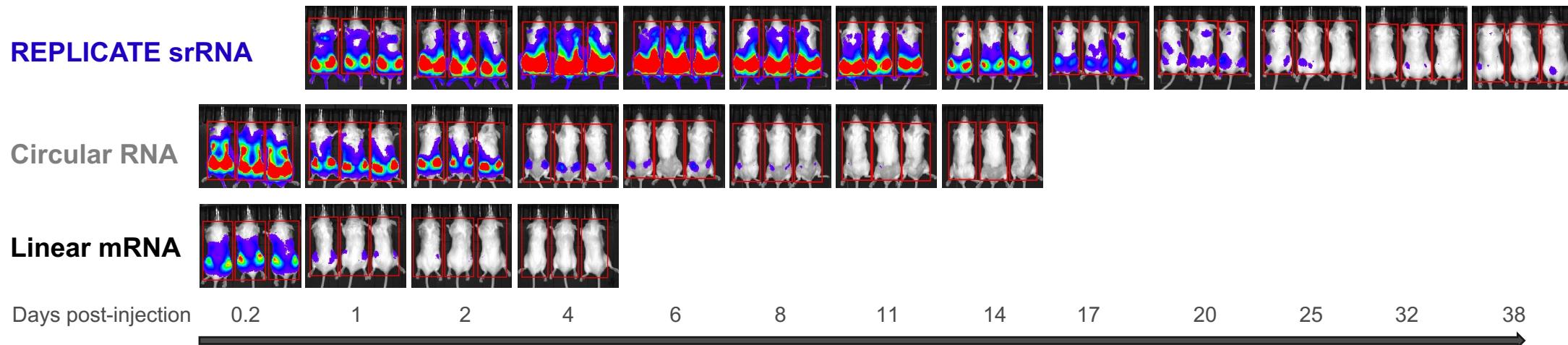
## Mechanism for protein expression



Replication machinery is only created the first few hours; mRNA production is a self-limiting process

# REPLICATE srRNA outperforms circRNA and linear mRNA

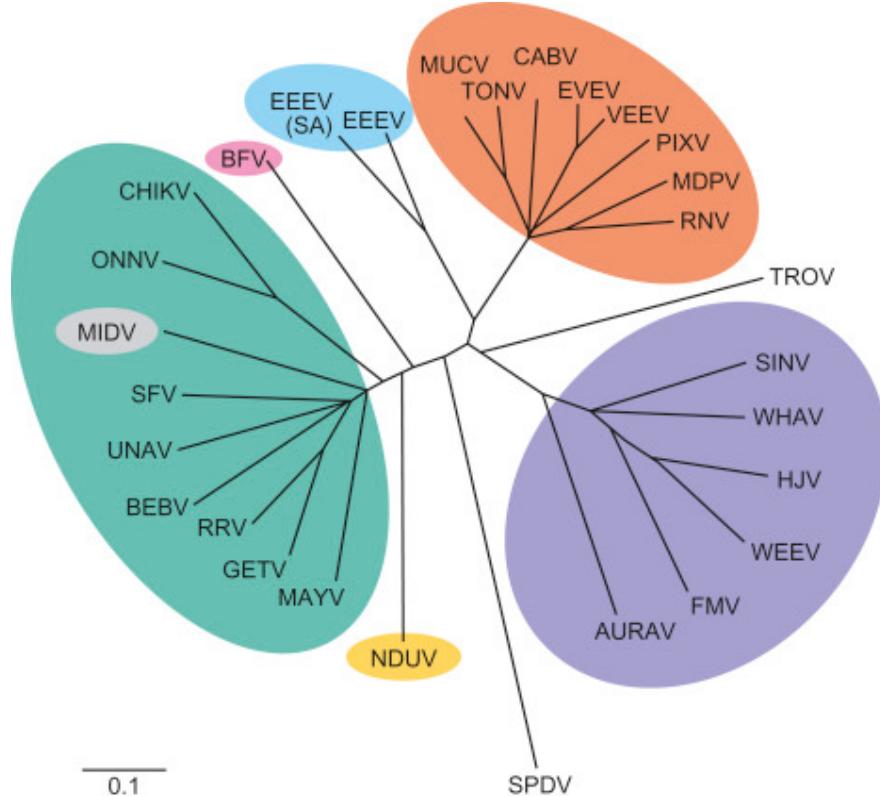
## Luciferase expression (bioluminescence)



**Higher, more durable protein expression unlocks:**

- Lower doses (better safety, pediatric applications)
- Complex vaccines
  - Multiplex infectious disease
  - Multi-target cancer vaccines
- Protein replacement applications

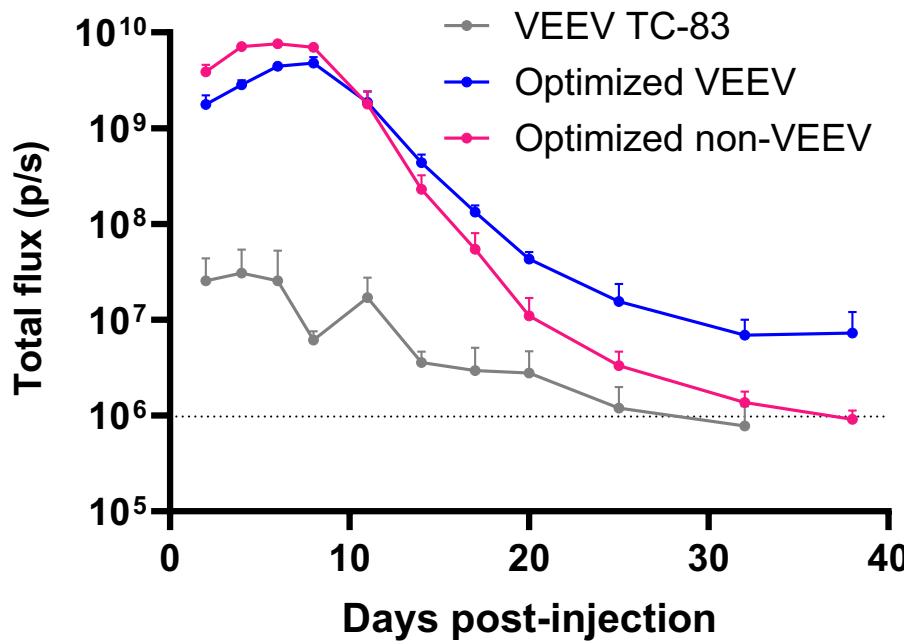
# Replicate vectorizes new members of the alphaviral family



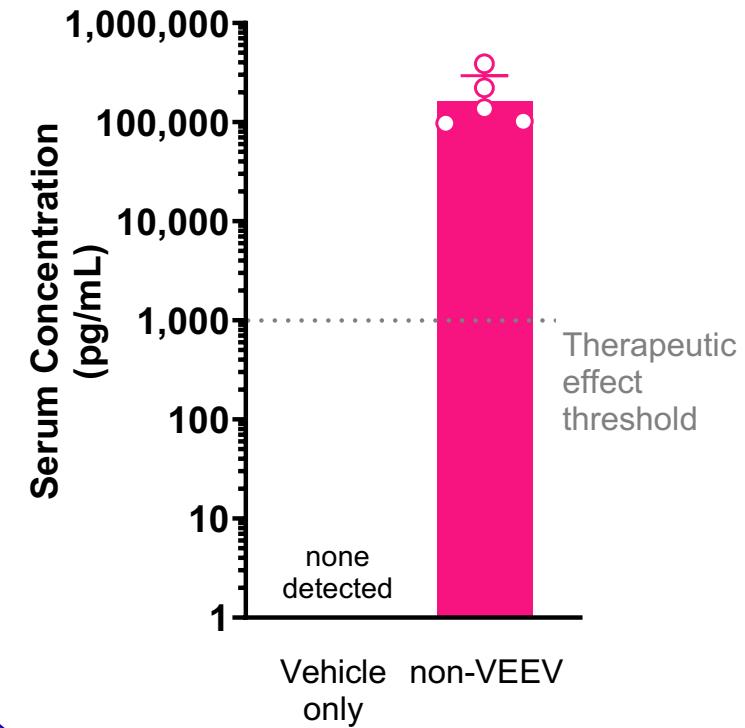
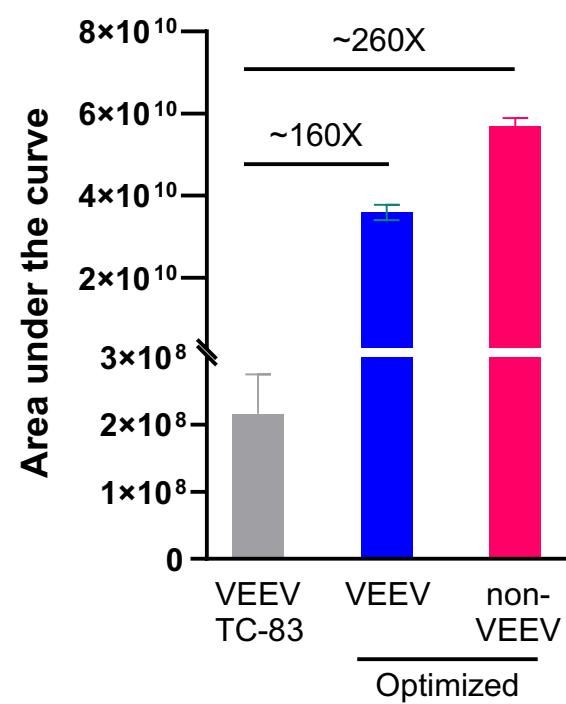
- Only VEEV-based vectors have been used in synthetic products
- Mining additional non-VEEV alphavirus family members allows to explore diverse biology
- A bigger toolbox of vectors allows for “fit for purpose”, customized drug development

# Novel, optimized srRNA vectors show superior protein expression

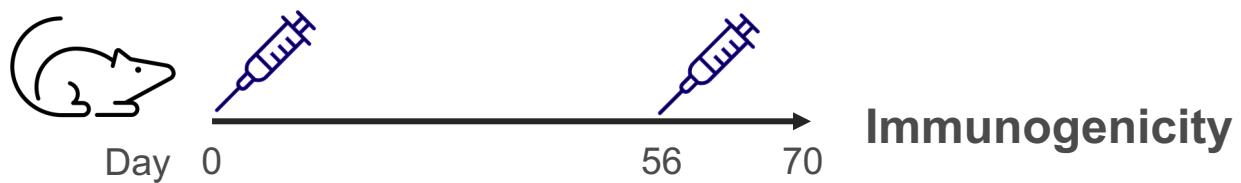
Bioactivity measured as luciferase enzymatic activity by *in vivo* imaging



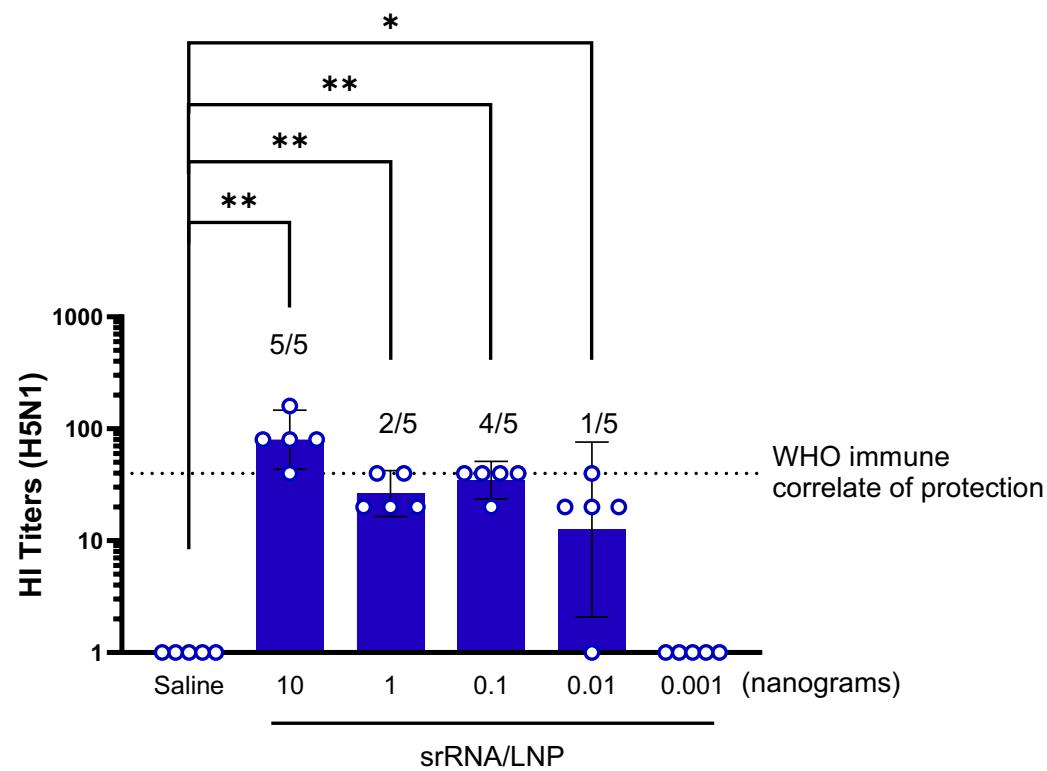
Bioactivity measured as protein production in serum



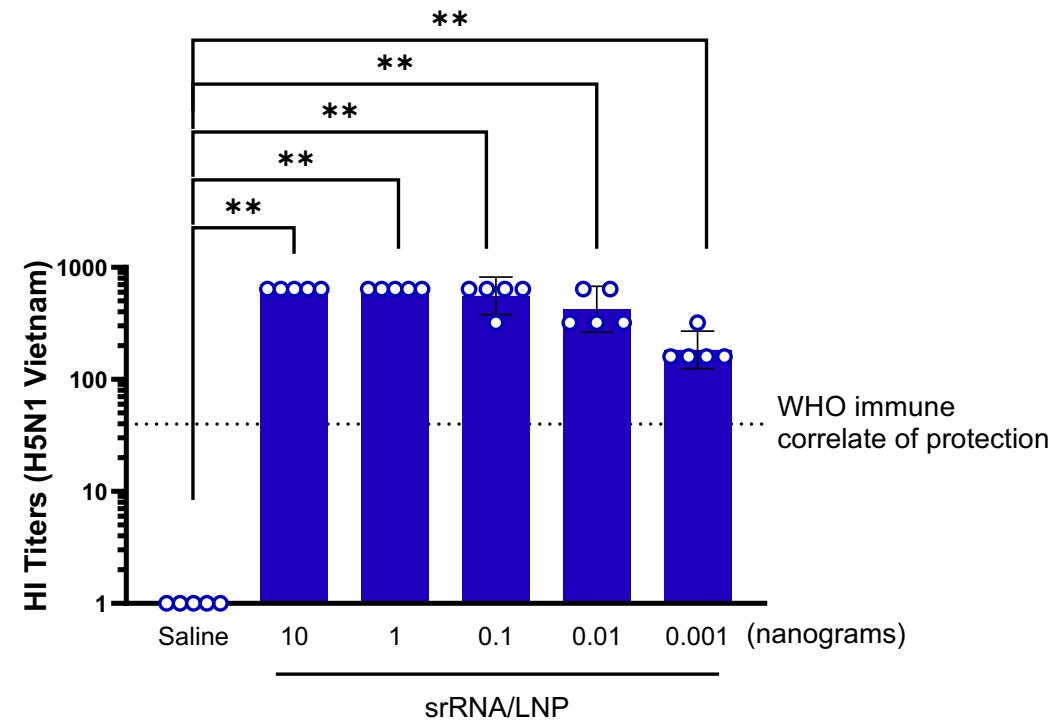
# Preclinical flu vaccine shows protection at 1 picogram dose



Neutralizing antibodies (HI) –  
One dose (Day 21)

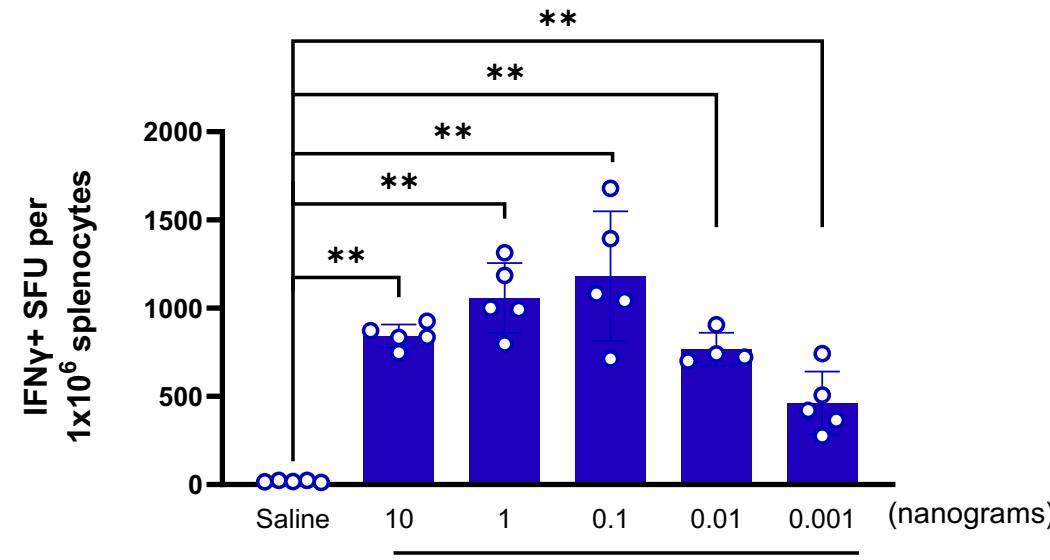


Neutralizing antibodies (HI) –  
Two doses (Day 70)

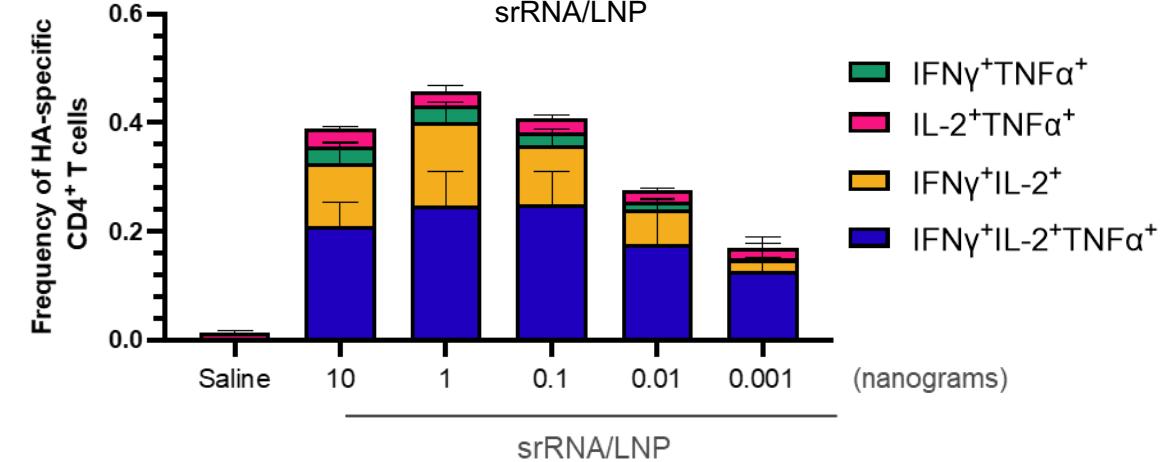
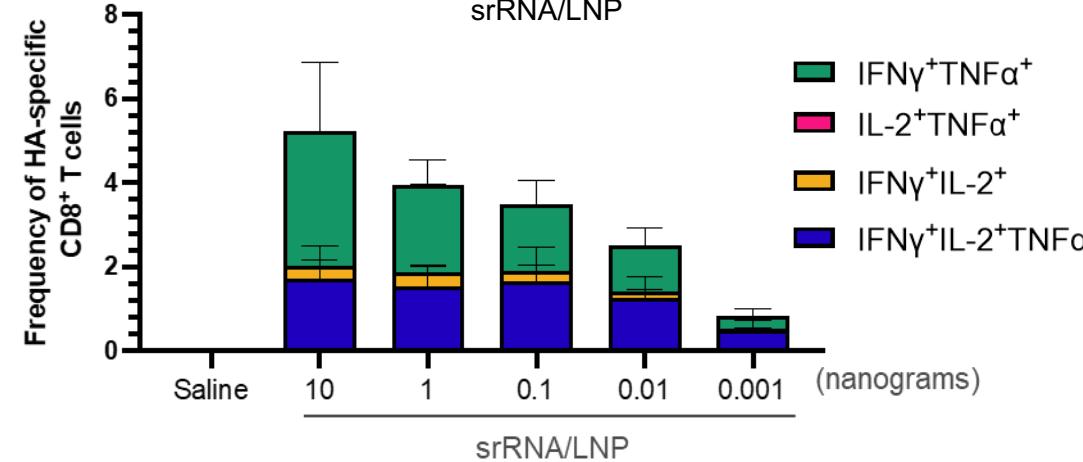
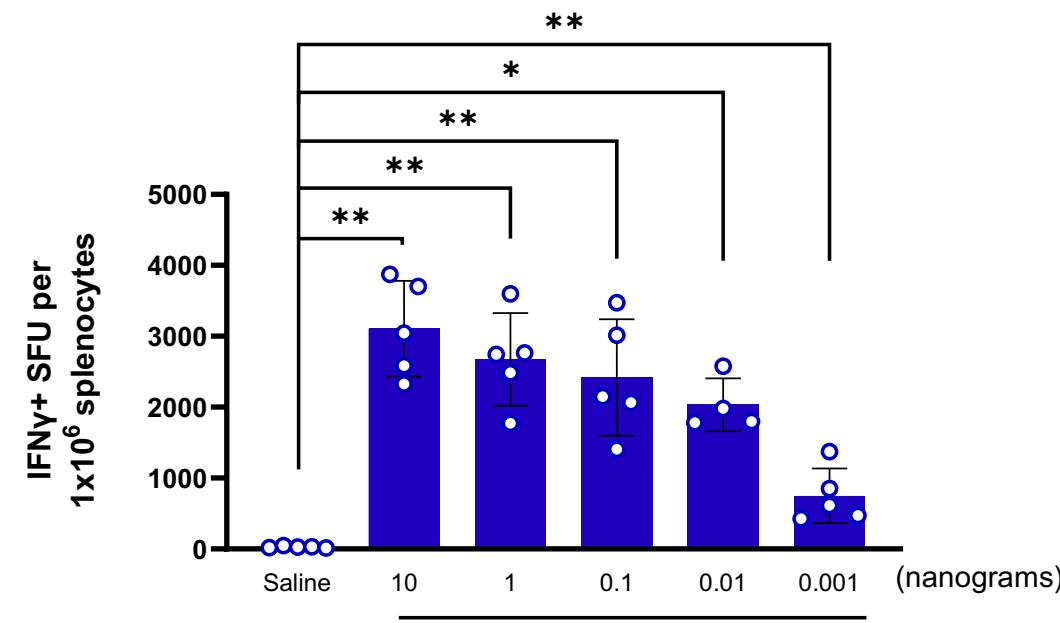


# Preclinical flu vaccine elicits polyfunctional T cell responses

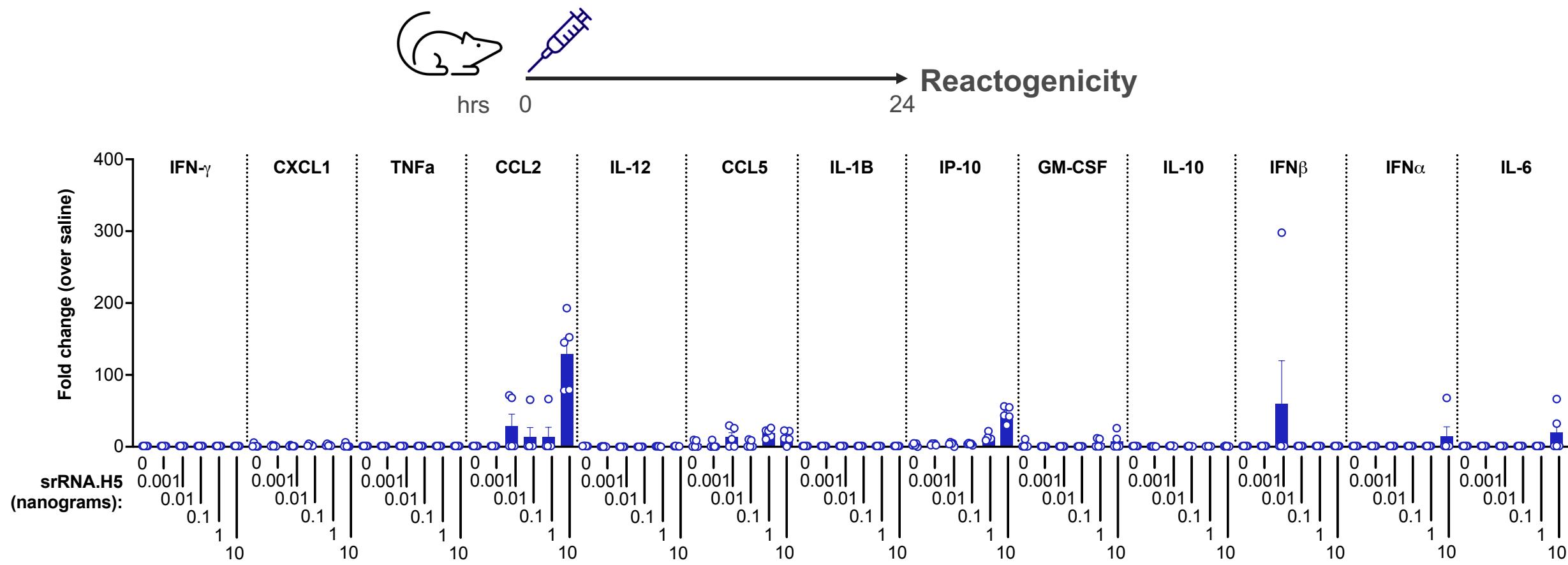
**CD8+ T cells**



**CD4+ T cells**

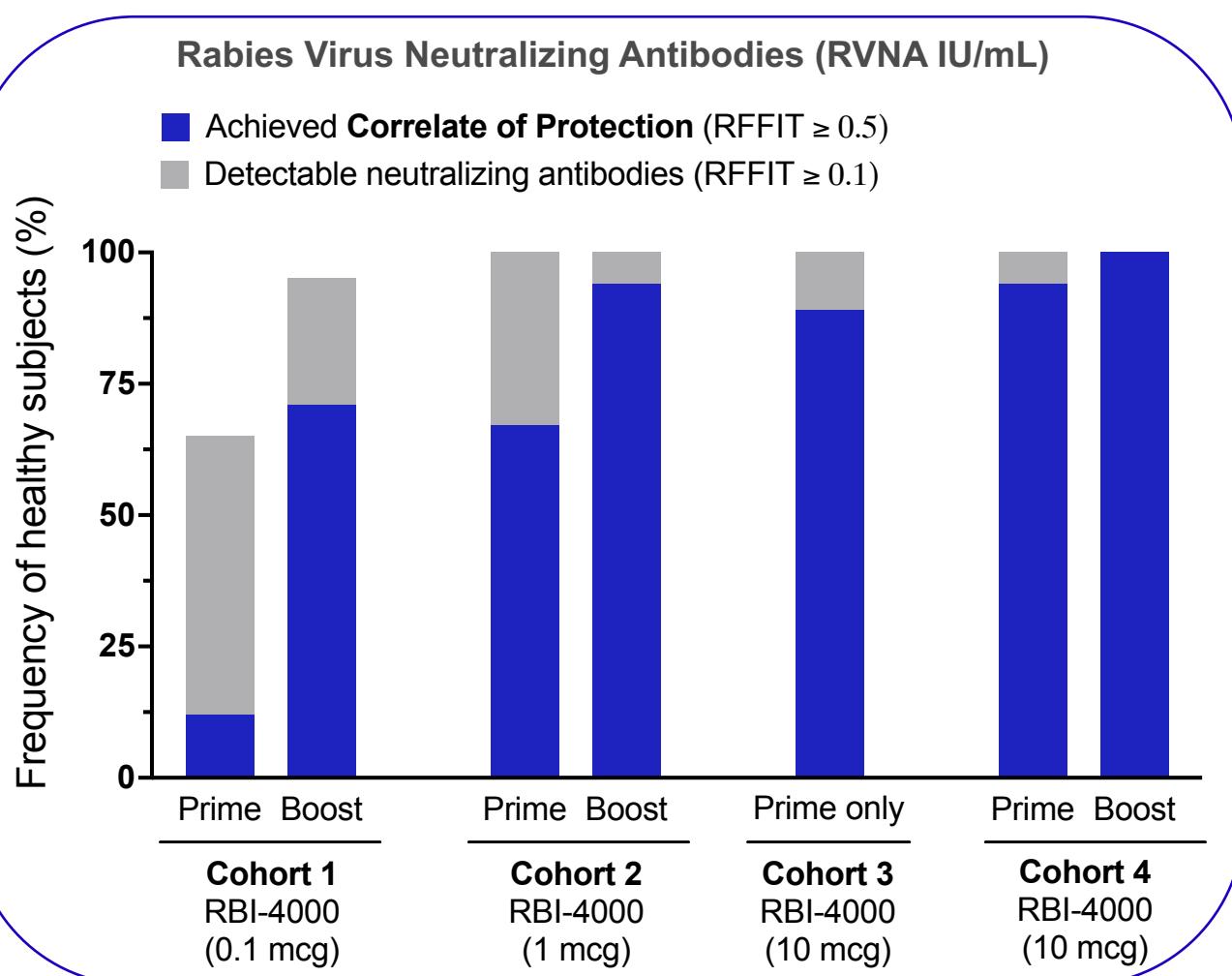


# Sub nanogram doses levels elicit minimal reactogenicity mediators



# Clinical validation of optimized srRNA platform

Expansion of therapeutic index observed with novel srRNA vectors



- ✓ Lowest clinical dose reported for xRNA modality with clinical bioactivity at 0.1 micrograms
- ✓ No dose-limiting toxicities observed at highest dose tested of 10 micrograms

“Single and Low Dose Self-Replicating RNA Vaccine Provides Effective Immune Protection Against Rabies in Healthy Volunteers”

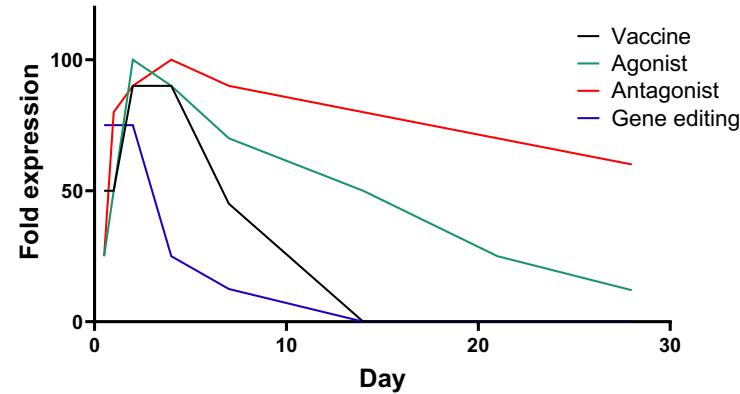
**Session Date:** Saturday May 11, 2024

**Room:** Room 314–317

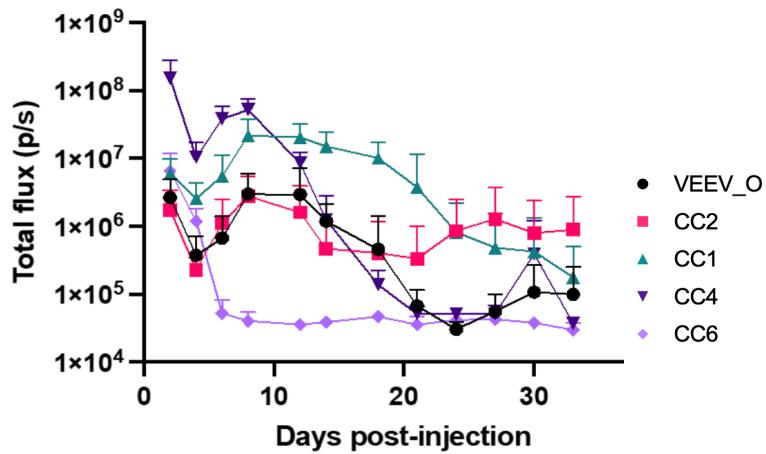
**Presentation Time:** 10:15am – 10:30am

# Novel srRNA vectors have different protein expression profiles

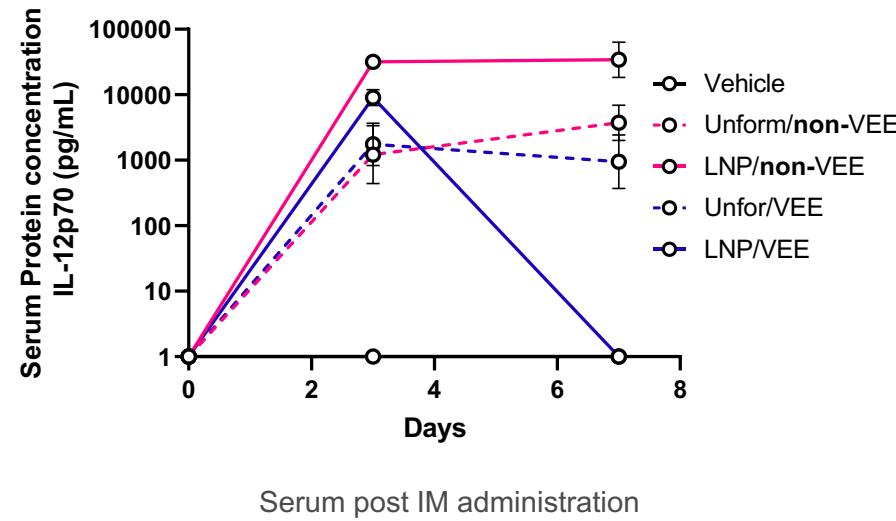
Desired protein expression profile



Protein expression profiles from novel srRNA vectors  
Data from Anna Blakney (UBC)

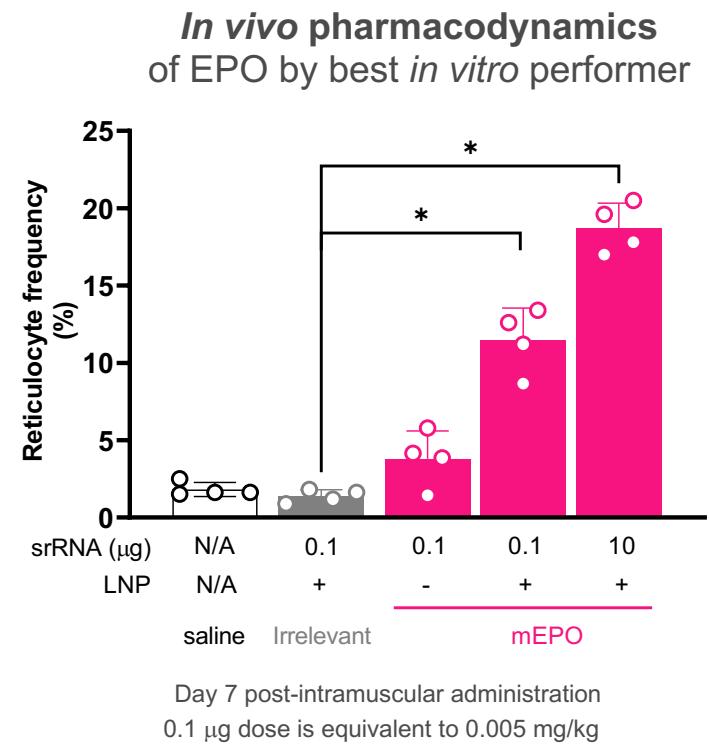
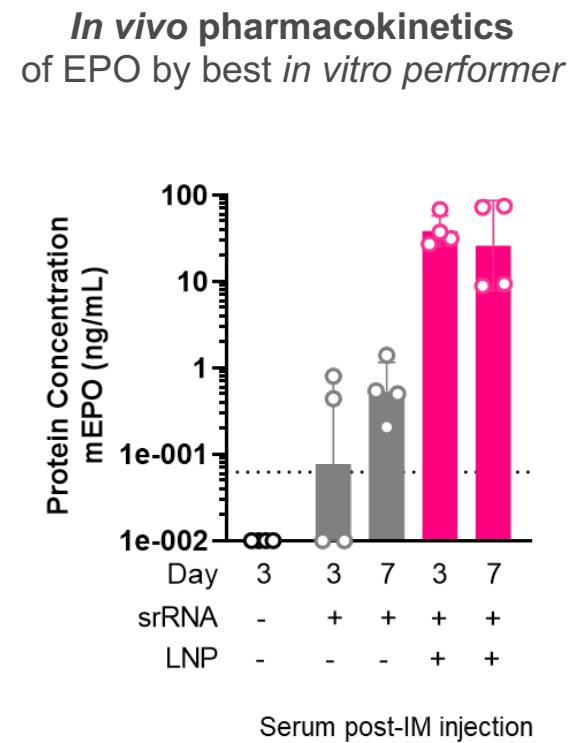
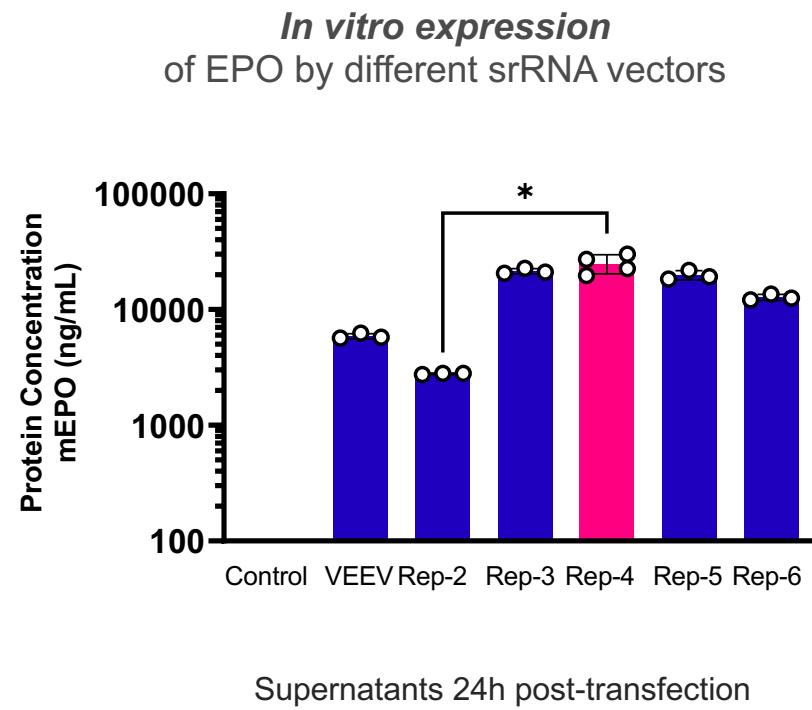


Delivery formulation can affect protein expression



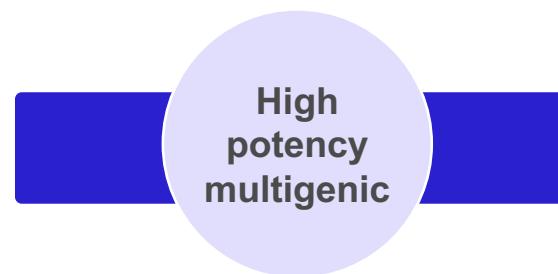
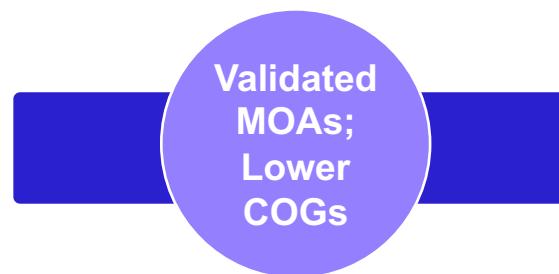
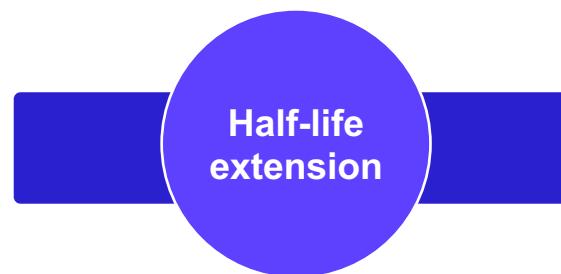
Serum post IM administration

# Novel srRNA vectors express protein at biotherapeutic levels



# Why RNA instead of biologics in protein drug replacement?

srRNA has the potential to improve existing biologics and enable new ones



srRNA drives faster and simpler development and for complex and high cost-of-goods biologics

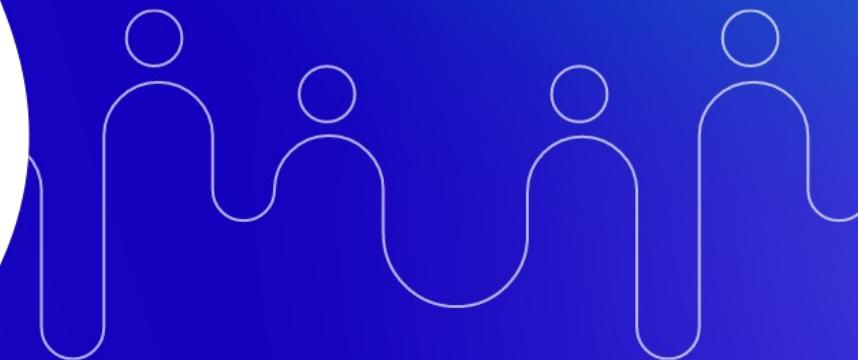
# Thank you

Drs. Darina Spasova, Shigeki Miyake-Stoner, Christian Maine and extended Replicate team

Dr. Anna Blakney and Credo Casmil (UBC)

Scientific Advisors: Dr. Phil Santangelo (Emory), Dr. Kim Lyerly (Duke), Dr. Zachary Hartman (Duke), Dr. Jeff Ulmer, and Dr. Mike Ehlers

ASGCT organizing committee



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