Targeted STING agonism modulates saRNA vaccine immunogenicity

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CRS 2025 ANNUAL MEETING & EXPOSITION
PHILADELPHIA, PA
JULY 13-18, 2025

NEXT-GENERATION DELIVERY INNOVATIONS

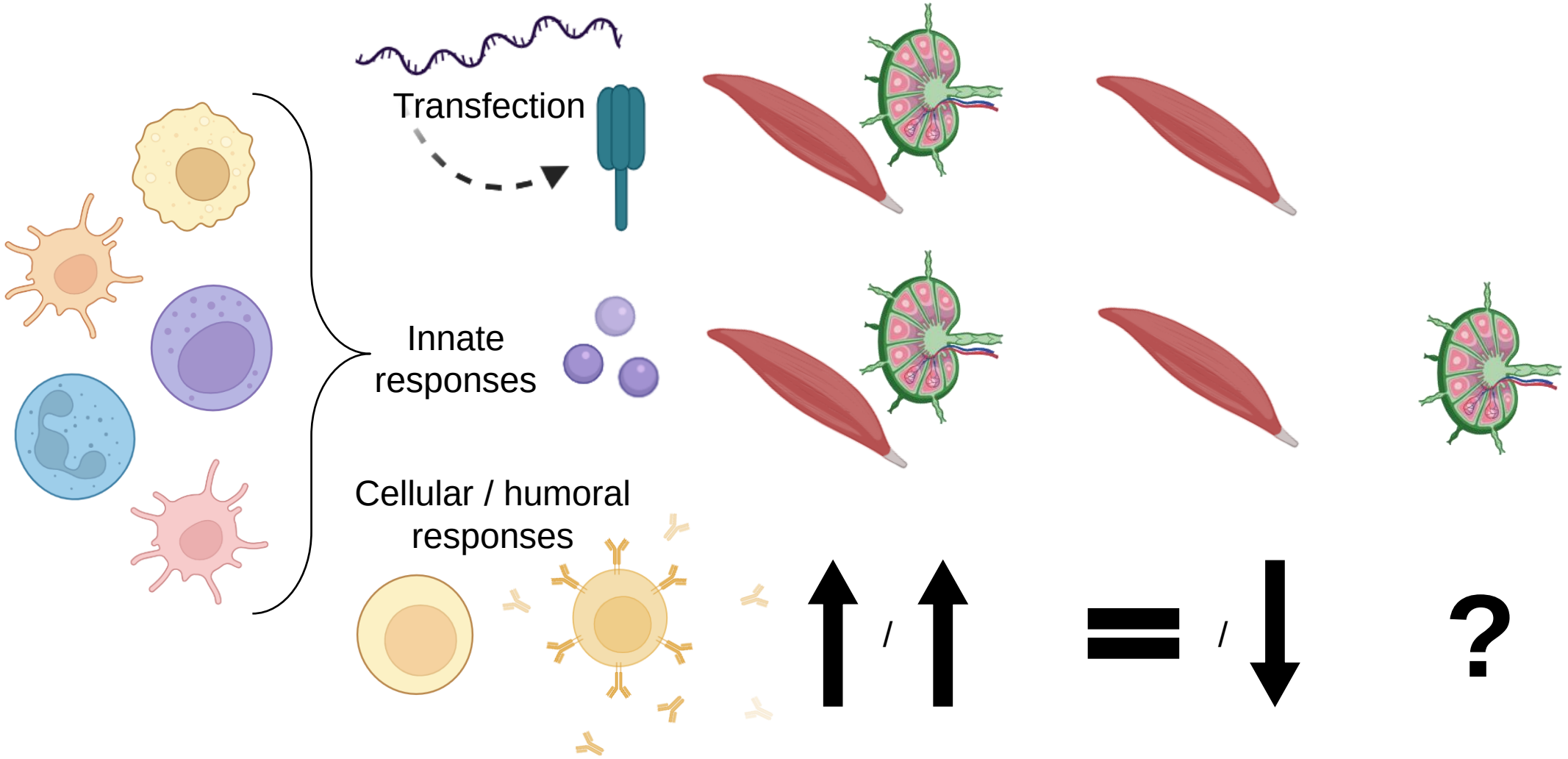
Location, Location, Inflammation

LNP

PP

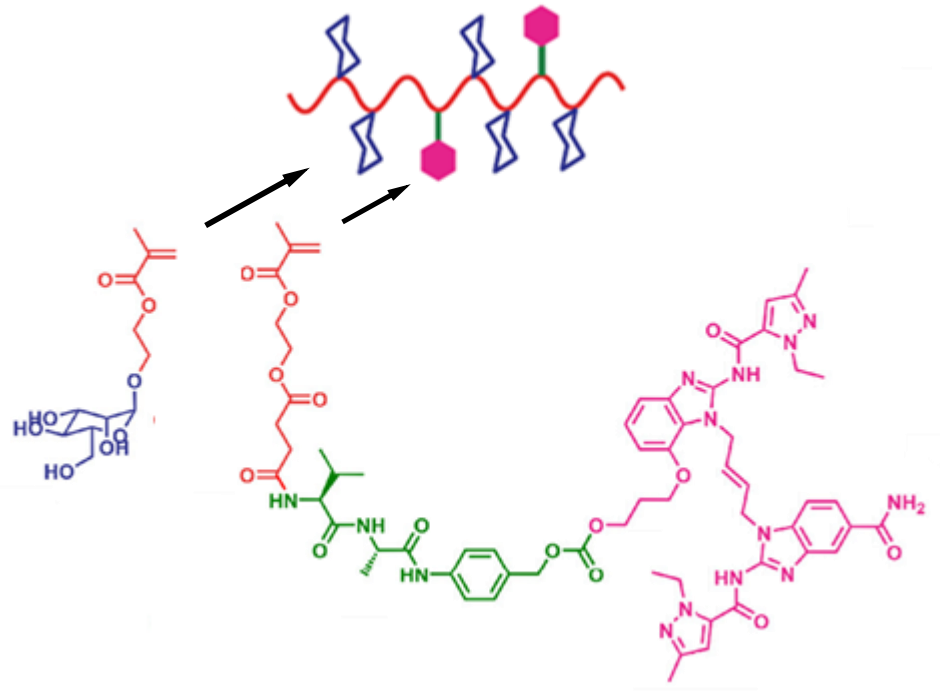
polySTING

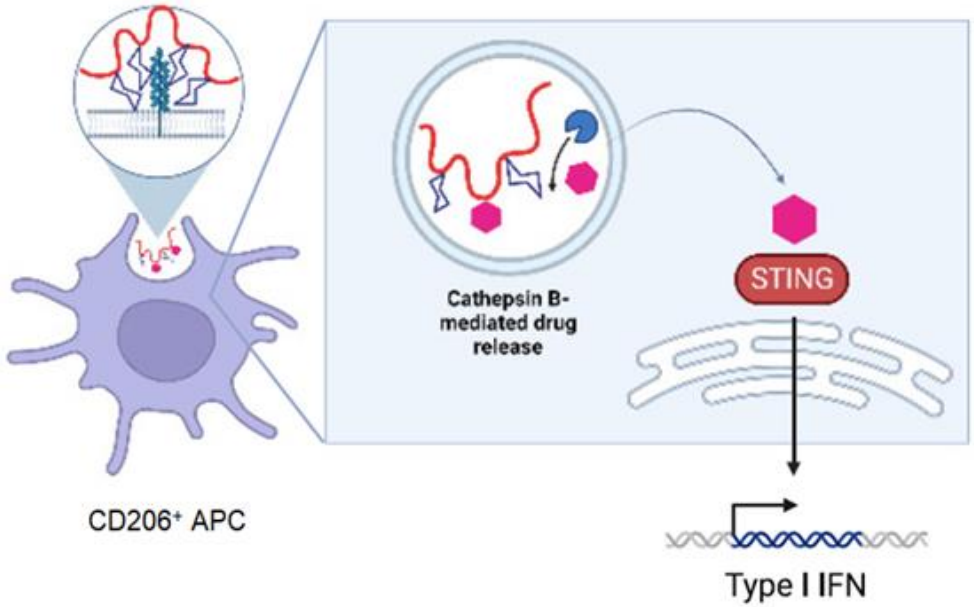
Peeler et al, unpublished



Peeler et al,
unpublished

polySTING selectively induces Type I IFN in APCs

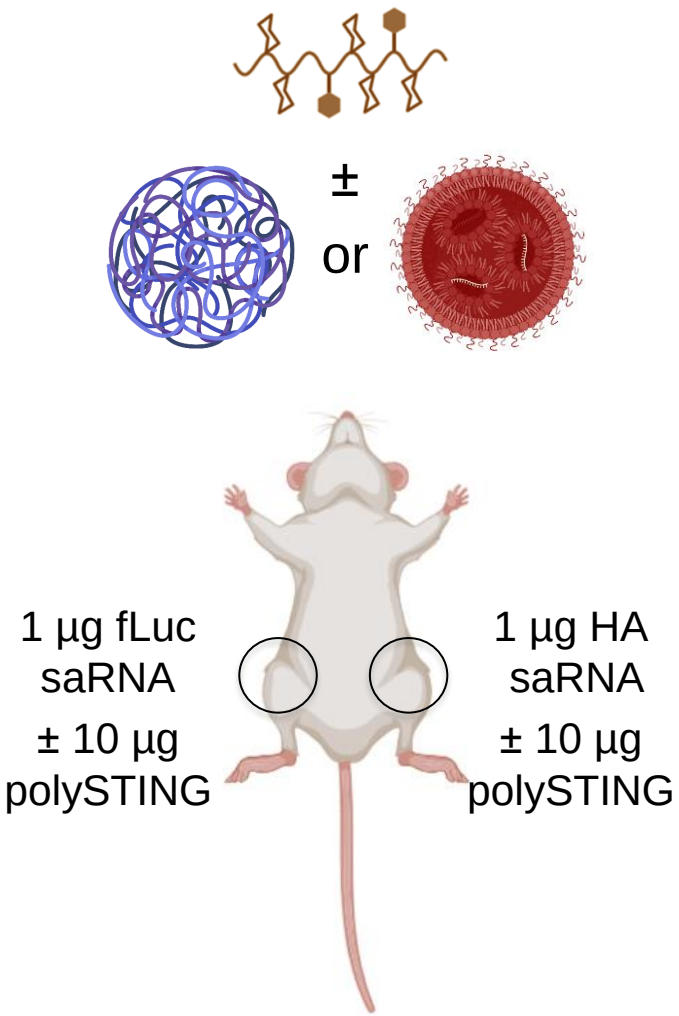


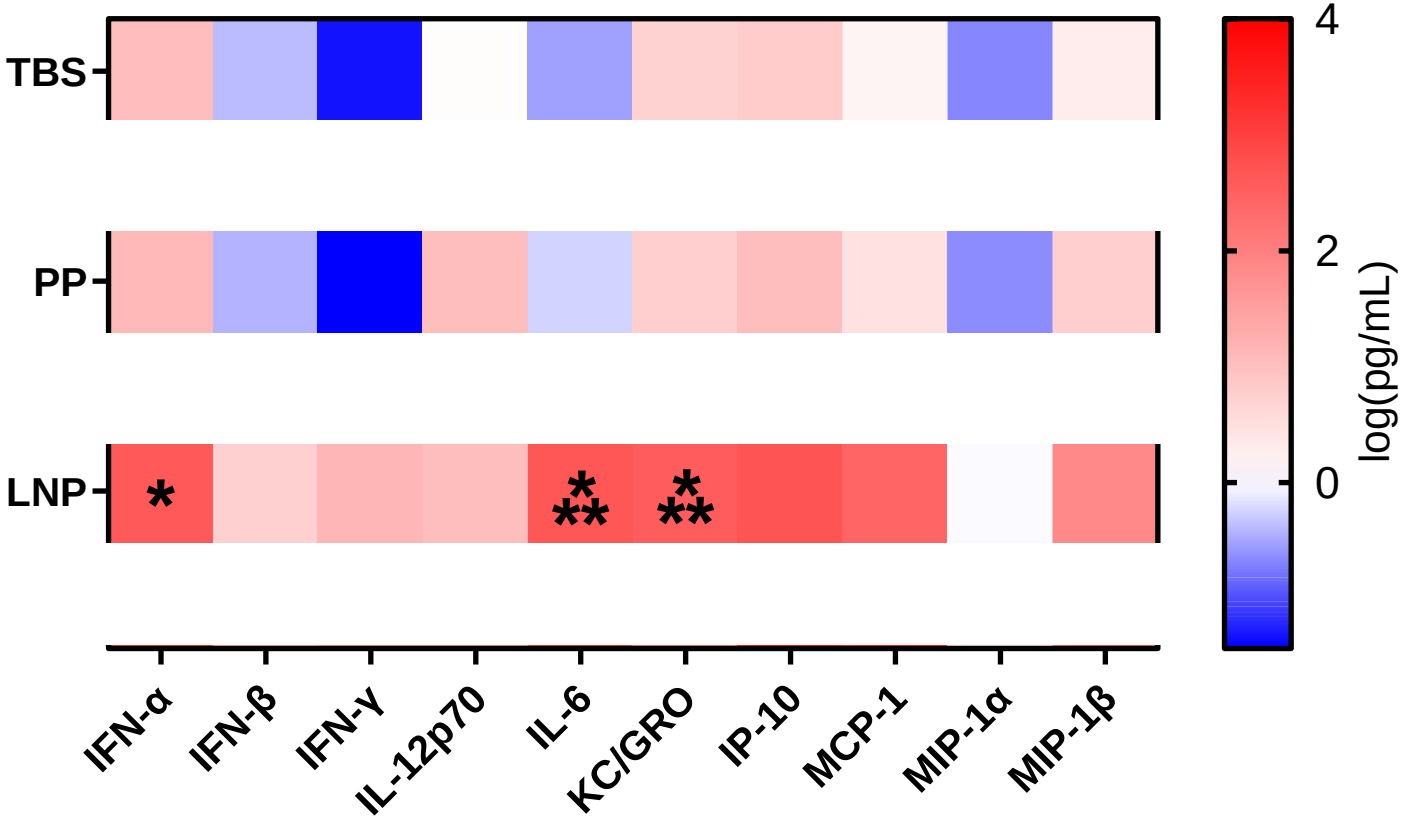


Nguyen, Song, Pun, Stayton, et al, *ACS Central Sci* 2024

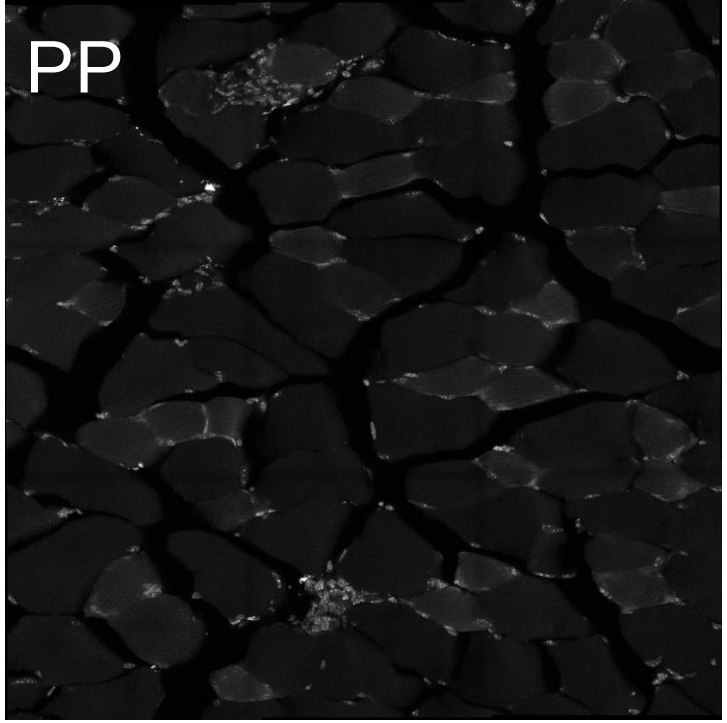
Peeler et al,
unpublished

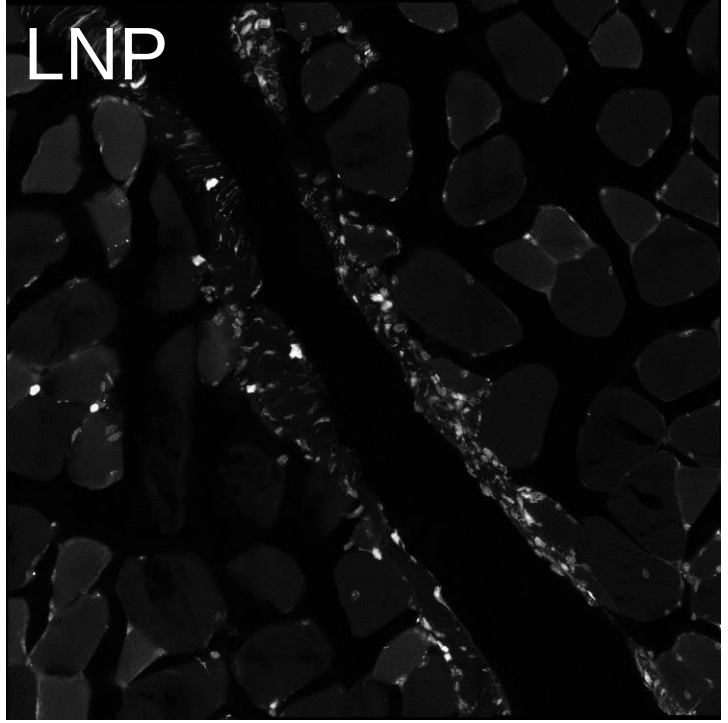
polySTING safely compliments saRNA inflammation

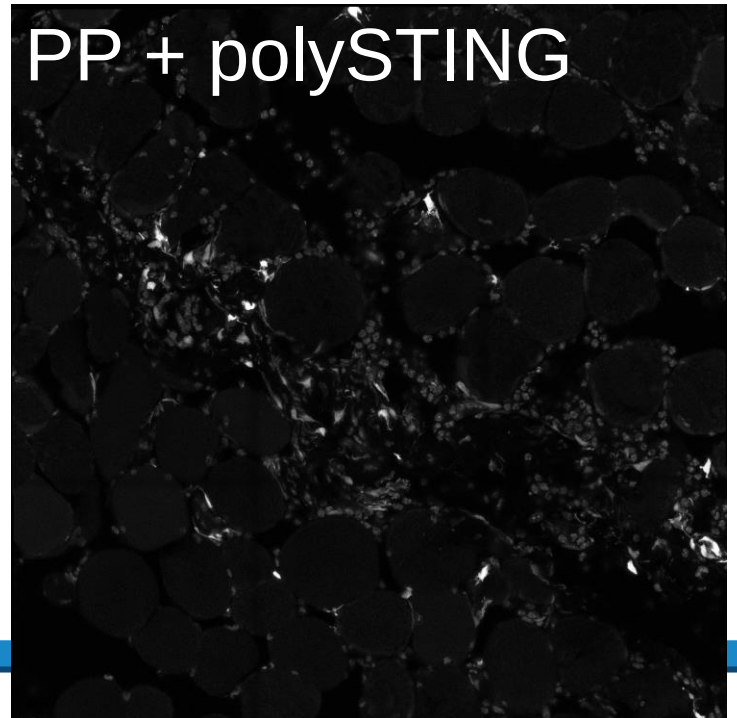


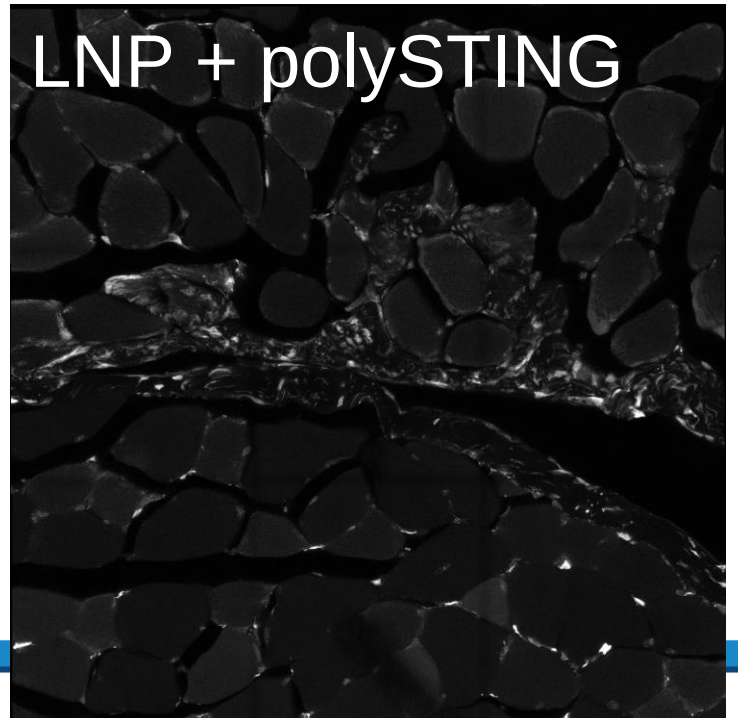


Median shown (N=3-5). Significance via one-way ANOVA with Tukey's post-hoc multiple comparison test (* = p < 0.05; ** = p < 0.01; *** = p < 0.001; **** = p < 0.0001).

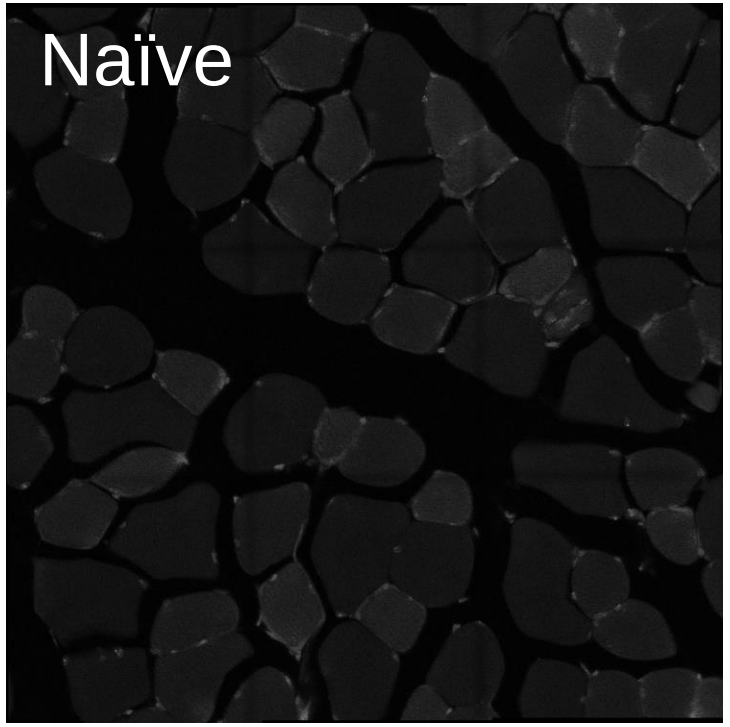




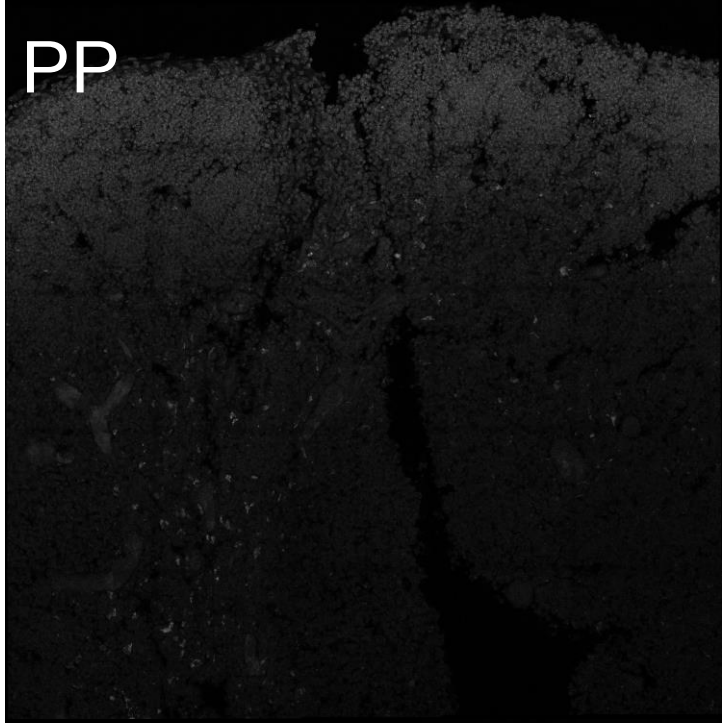


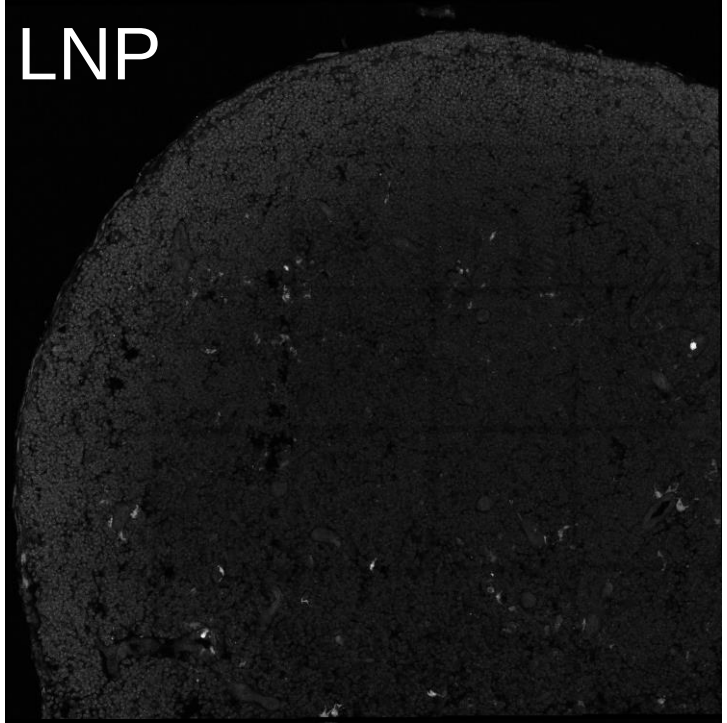


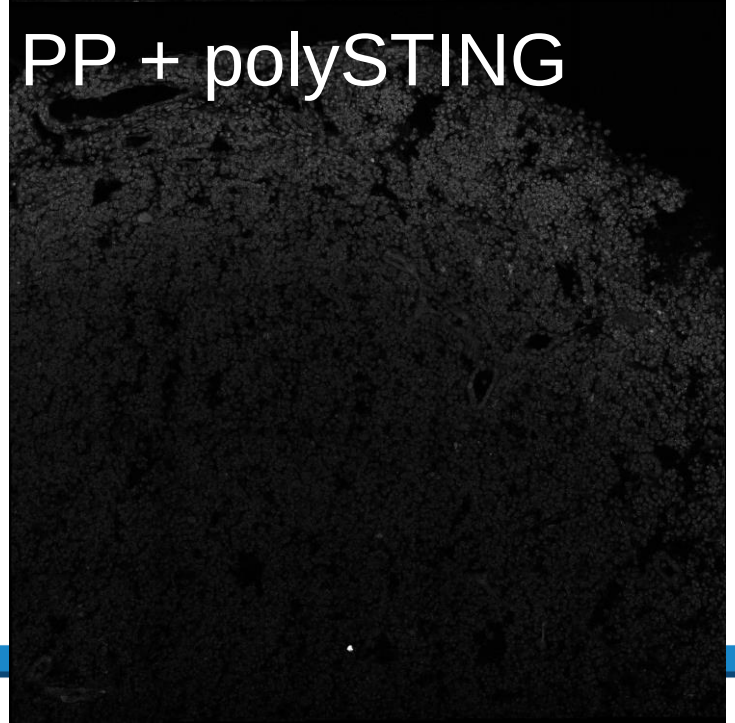
Muscle

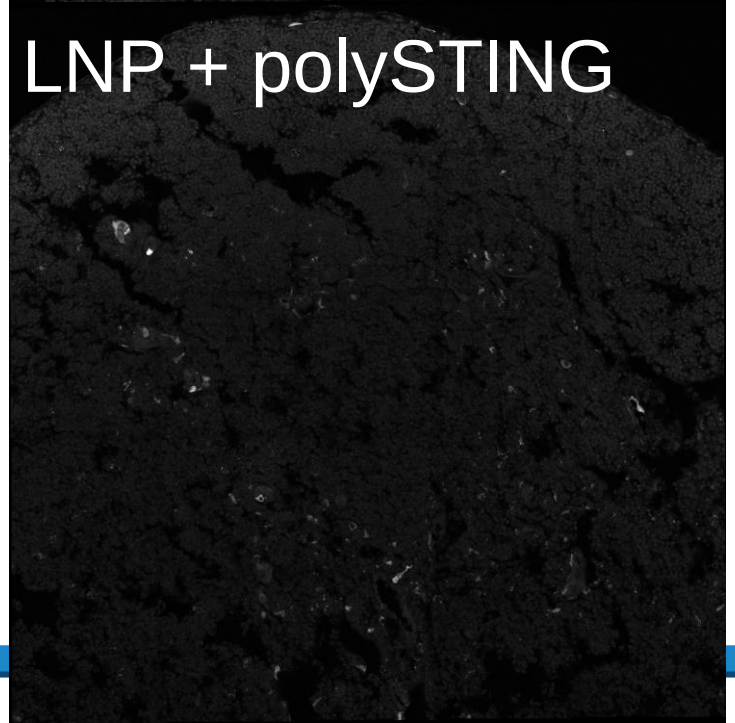


tdTomato

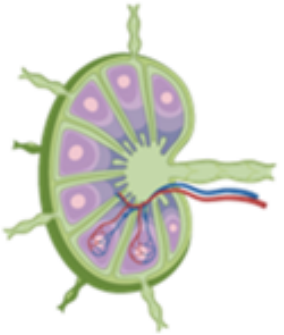


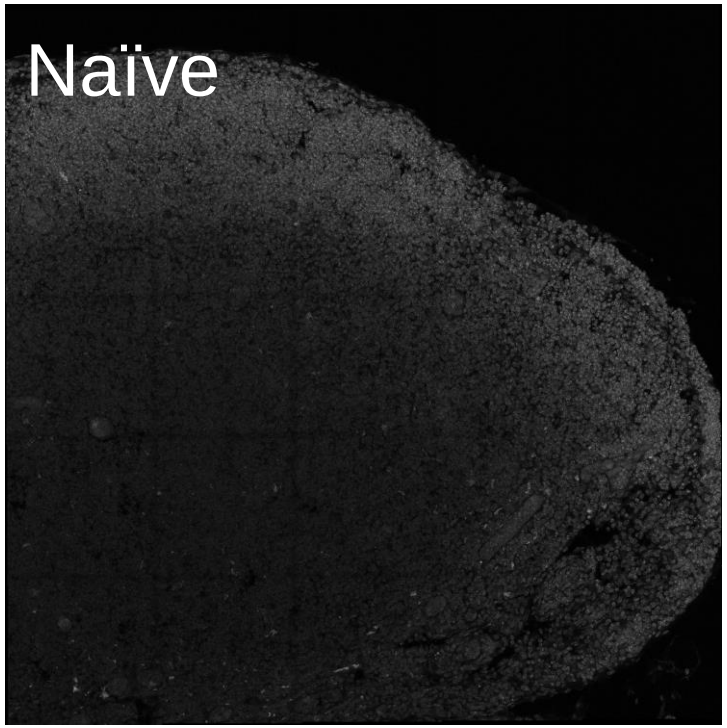






Lymph node





tdTomato

Peeler et al,
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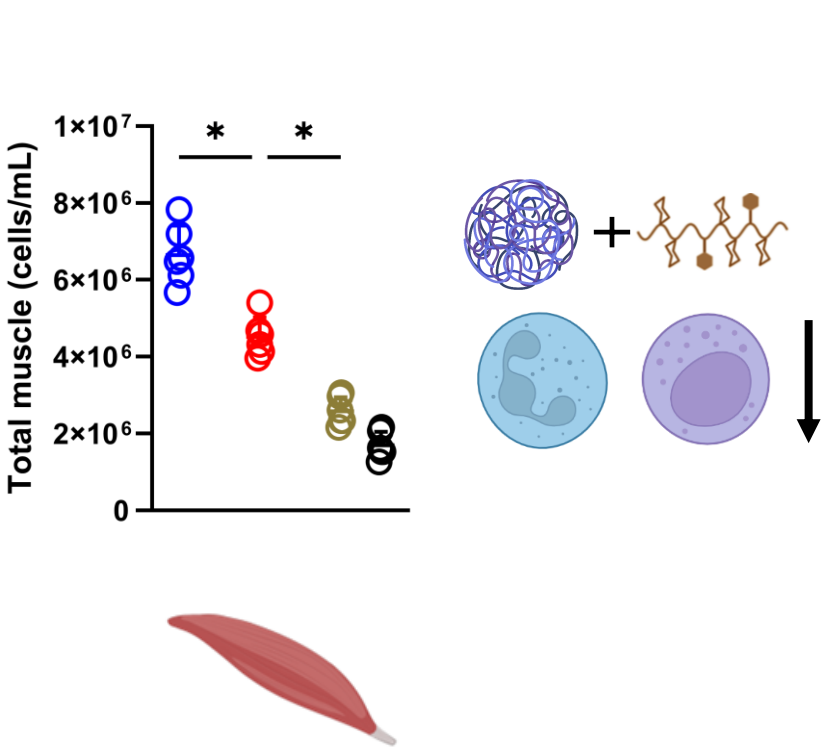
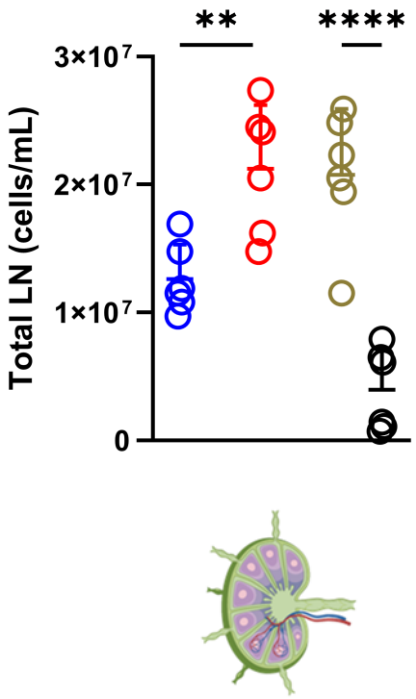
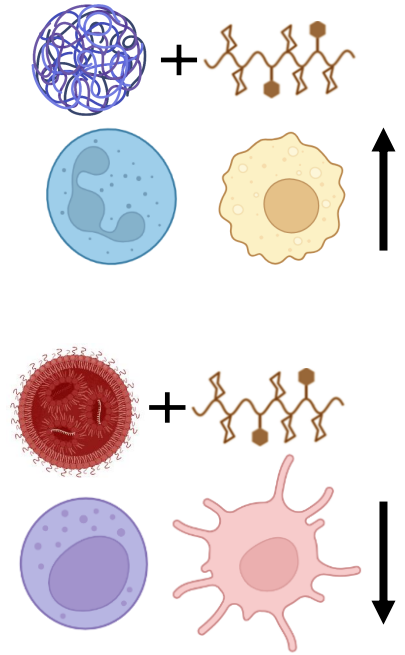
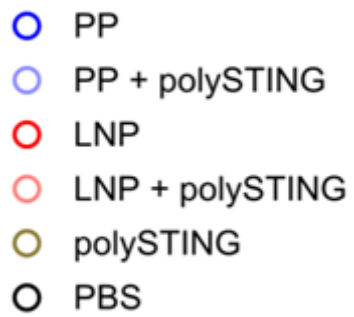
Inflammatory crosstalk alters innate cell recruitment and trafficking





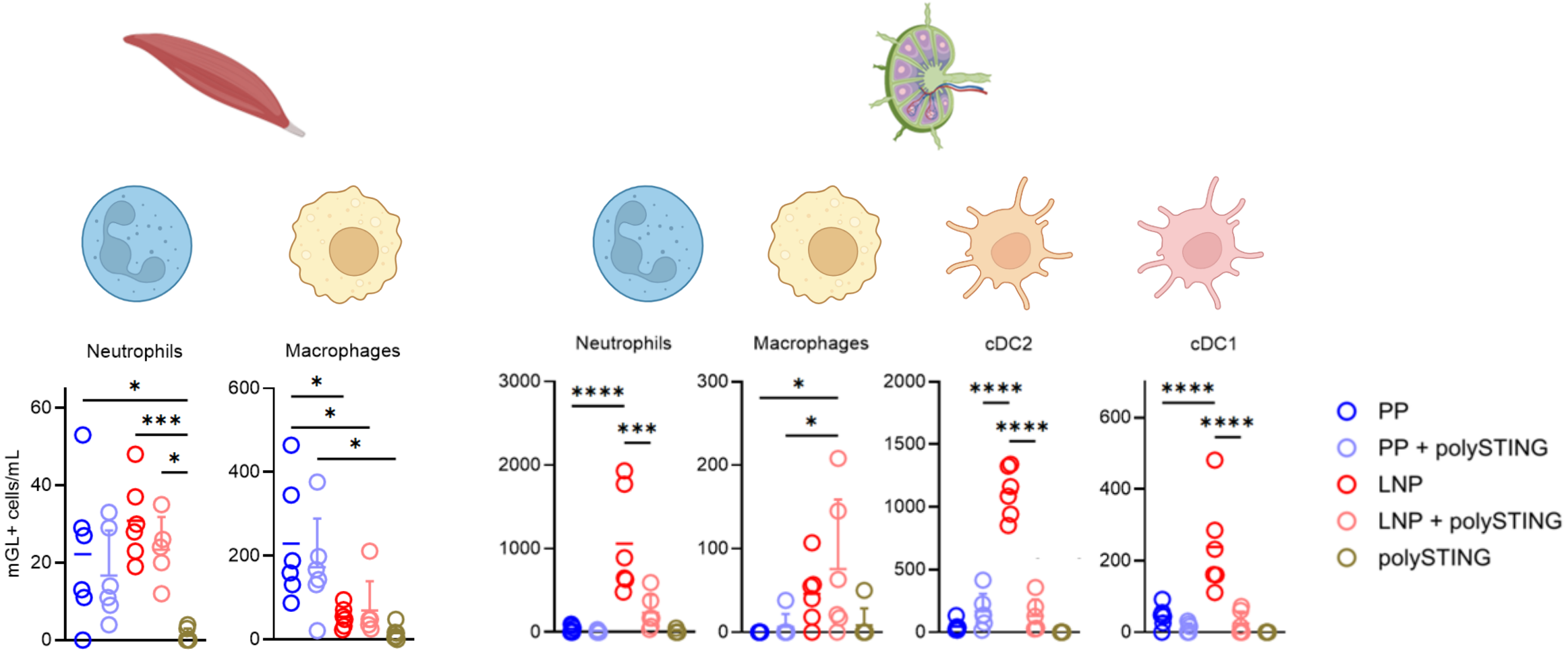




Mean +/- SD shown. Significance via one-way ANOVA with Tukey's post-hoc multiple comparison test (* = p < 0.05; ** = p < 0.01; *** = p < 0.001; **** = p < 0.0001; N =6).

Peeler et al,
unpublished

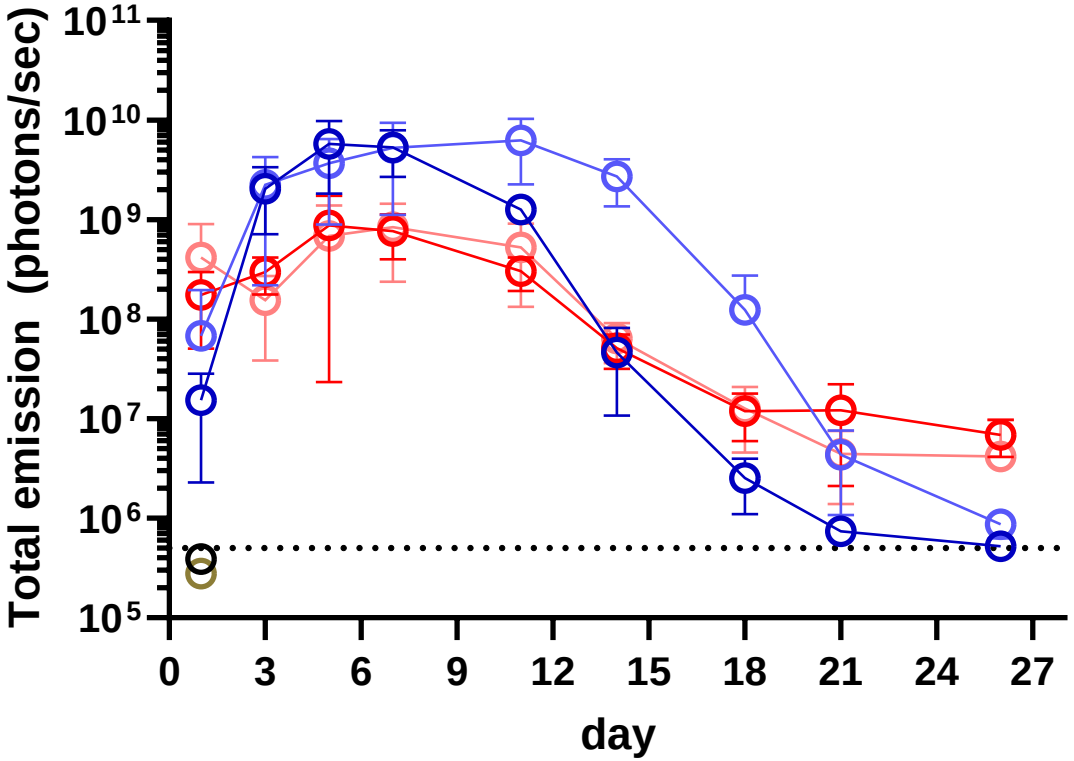
PP and LNP transfect different APCs

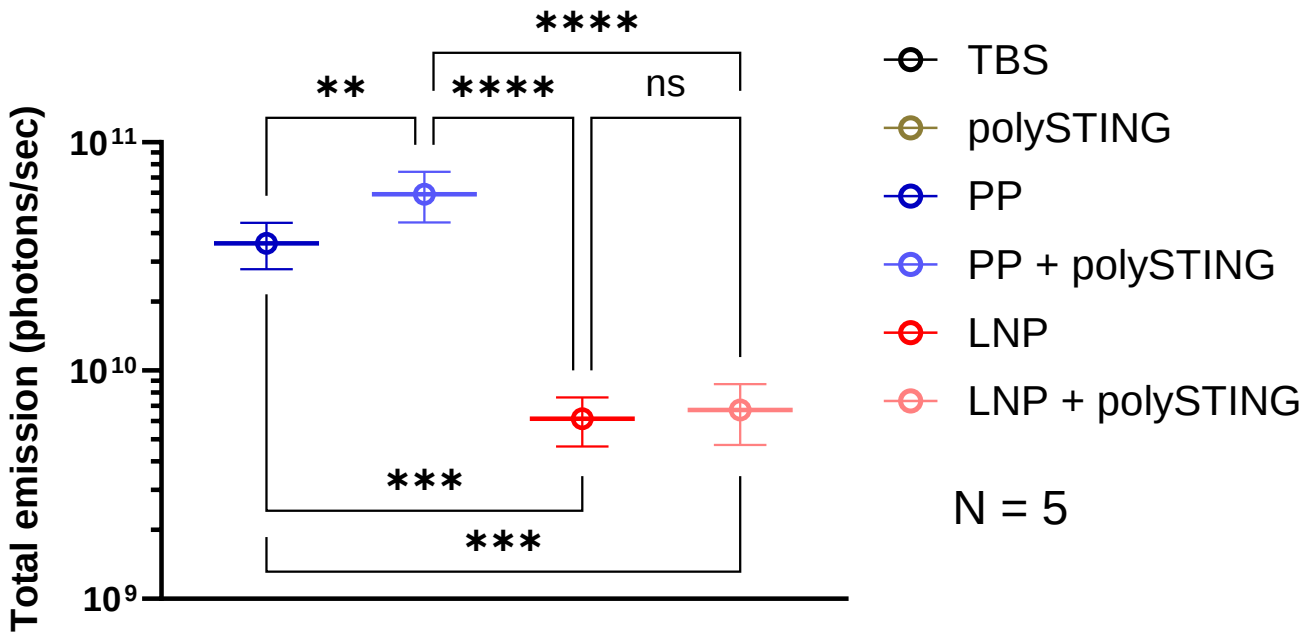


Mean +/- SD shown. Significance via one-way ANOVA with Tukey's post-hoc multiple comparison test (* = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$; **** = $p < 0.0001$; N =6).

Peeler et al,
unpublished

Co-administered polySTING prolongs polyplex saRNA expression





Mean +/- SD shown. Significance via one-way ANOVA with Tukey's post-hoc multiple comparison test (** = p < 0.01; *** = p < 0.001; **** = p < 0.0001).

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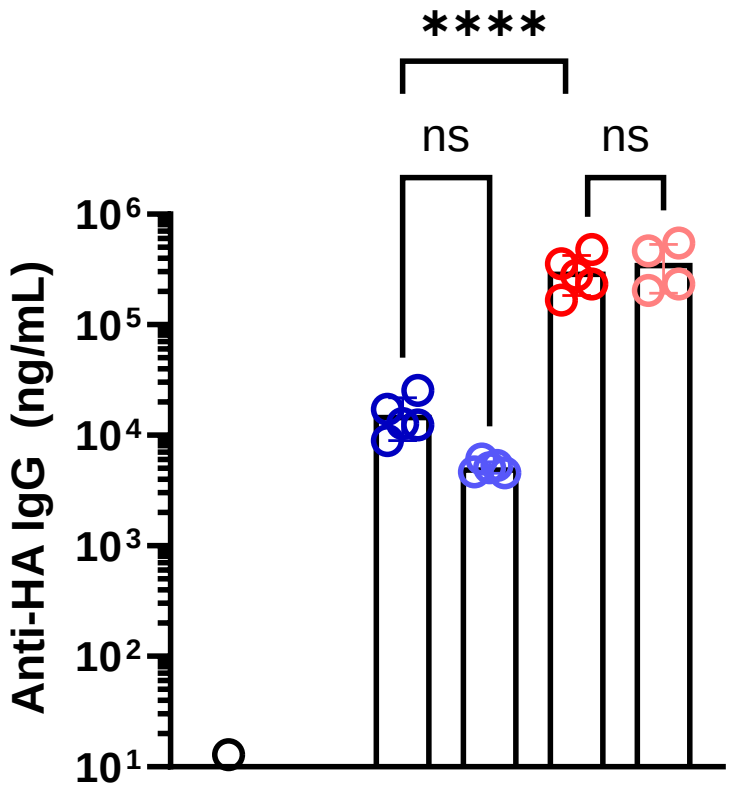
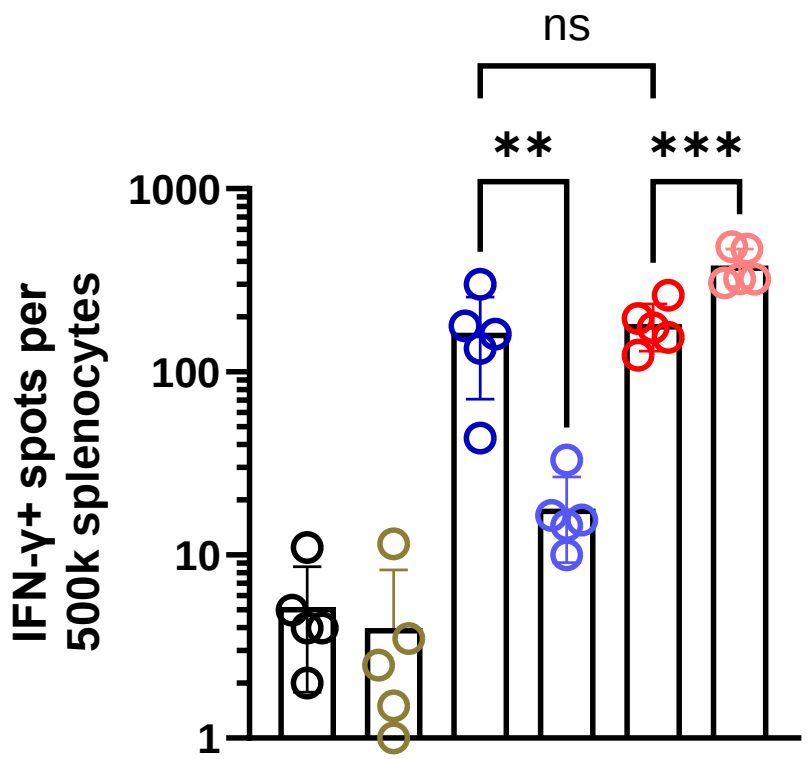
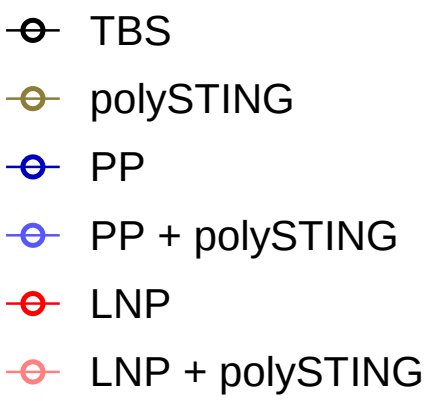
polySTING blunts PP-induced adaptive responses but enhances LNP cellular response







N = 5

Boost @ week 6
Analysis @ week 8

Mean +/- SD shown. Significance via one-way ANOVA with Tukey's post-hoc multiple comparison test (** = p < 0.01; *** = p < 0.001; **** = p < 0.0001).

Summary

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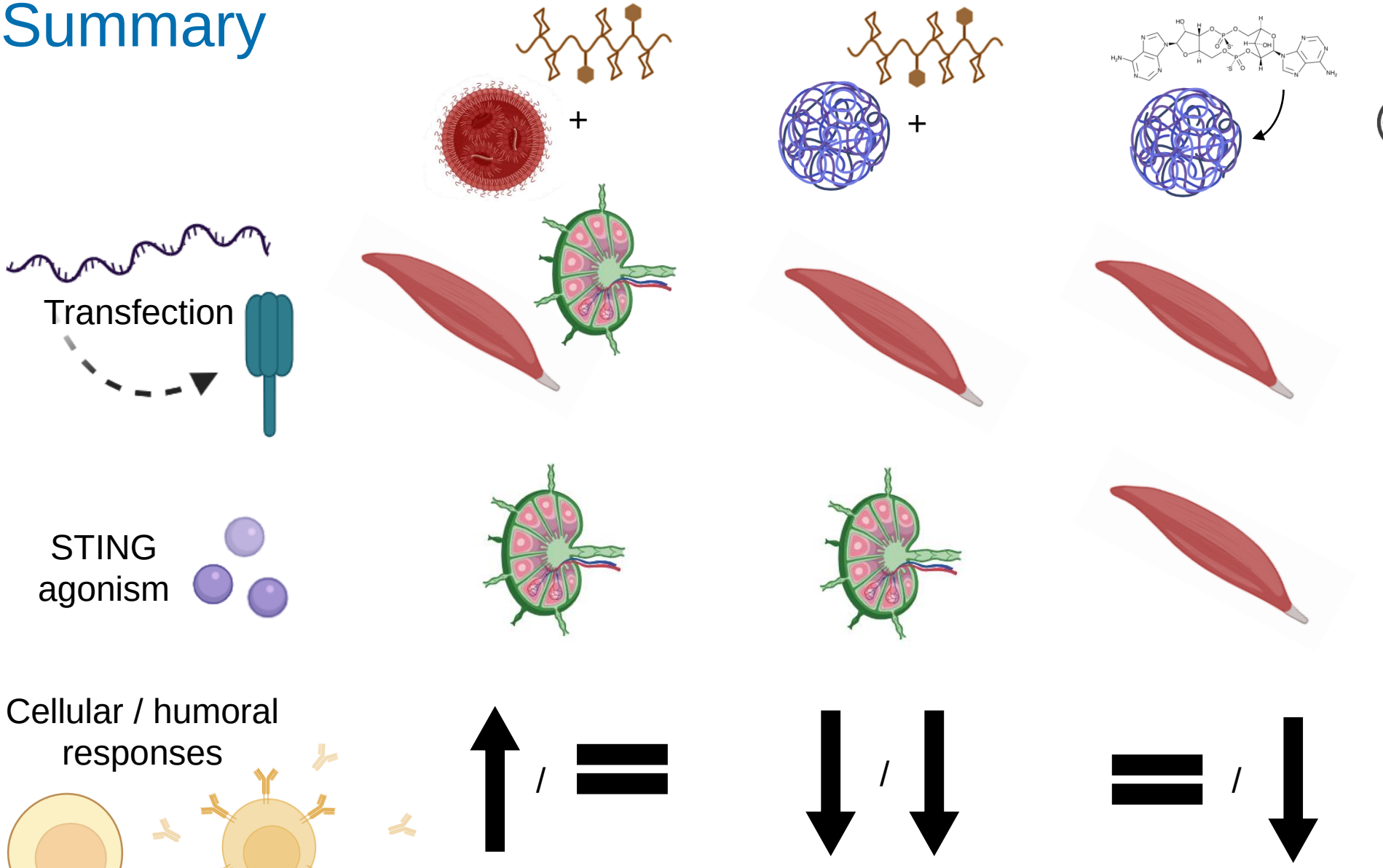

Timing/dose/location of LN STING agonism

Length/location of antigen expression

Secreted vs. transmembrane antigens

LNP/RNA chemistry

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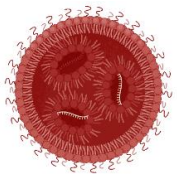
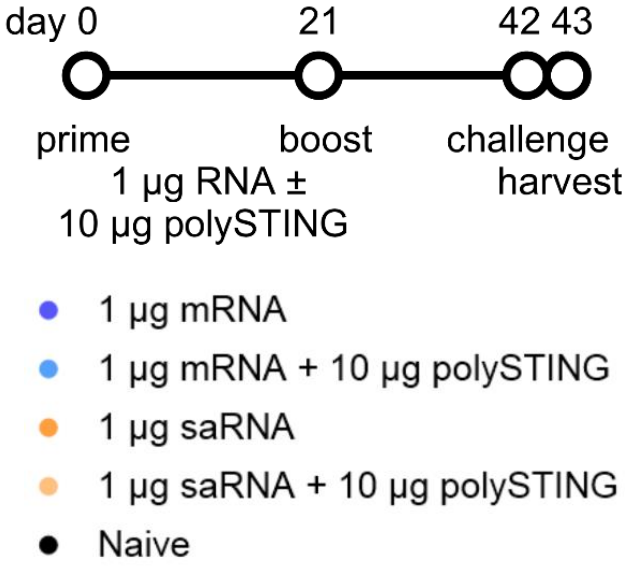
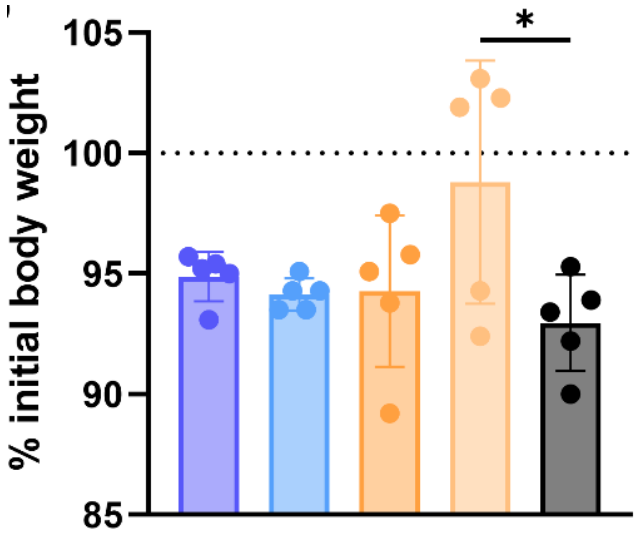
unpublished

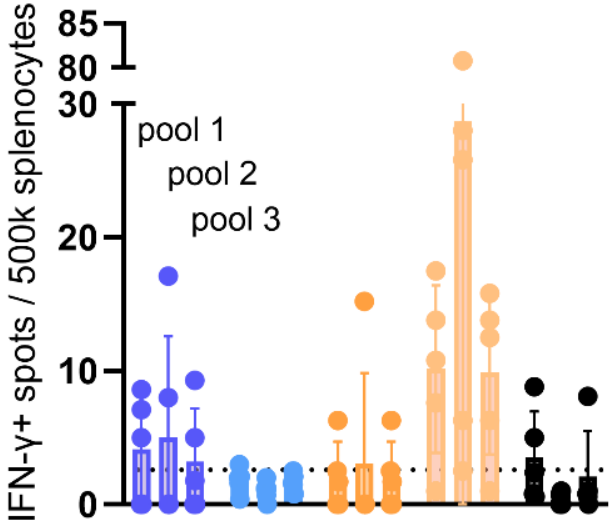
PolySTING boosts/skews T_H1 response to LNP OXA23 saRNA but not mRNA



Acinetobacter baumanii







Mean +/- SD shown (N =5). Significance via one-way ANOVA with Tukey's post-hoc multiple comparison test (* = $p < 0.05$; ** = $p < 0.01$).

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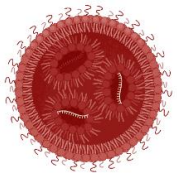
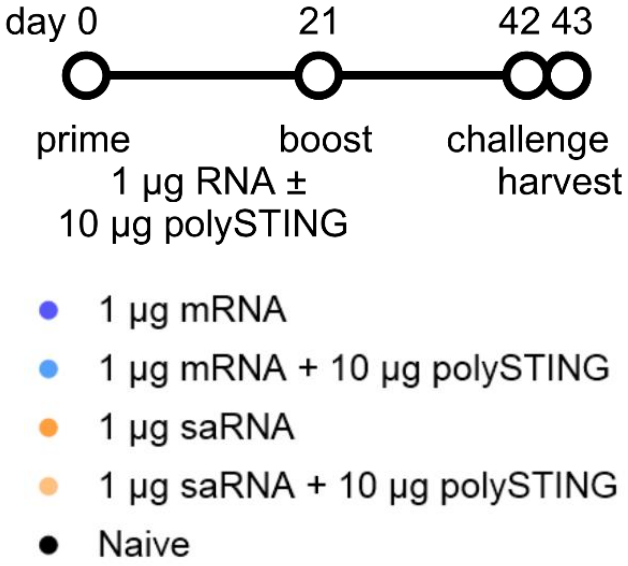
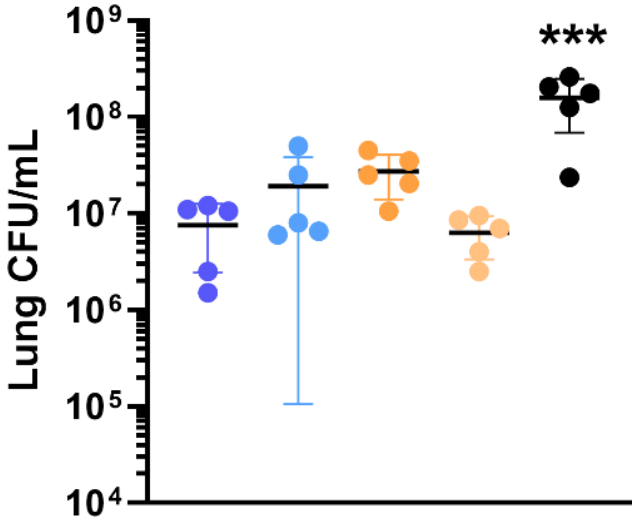
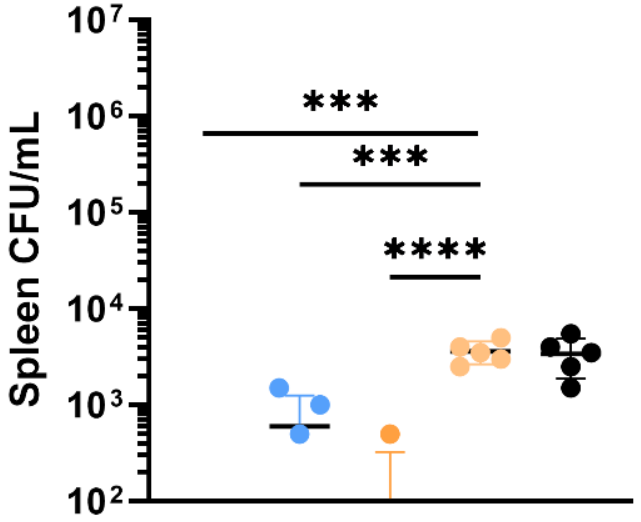
PolySTING shifts OXA23 saRNA-mediated protection from spleen to lung



Acinetobacter baumanii





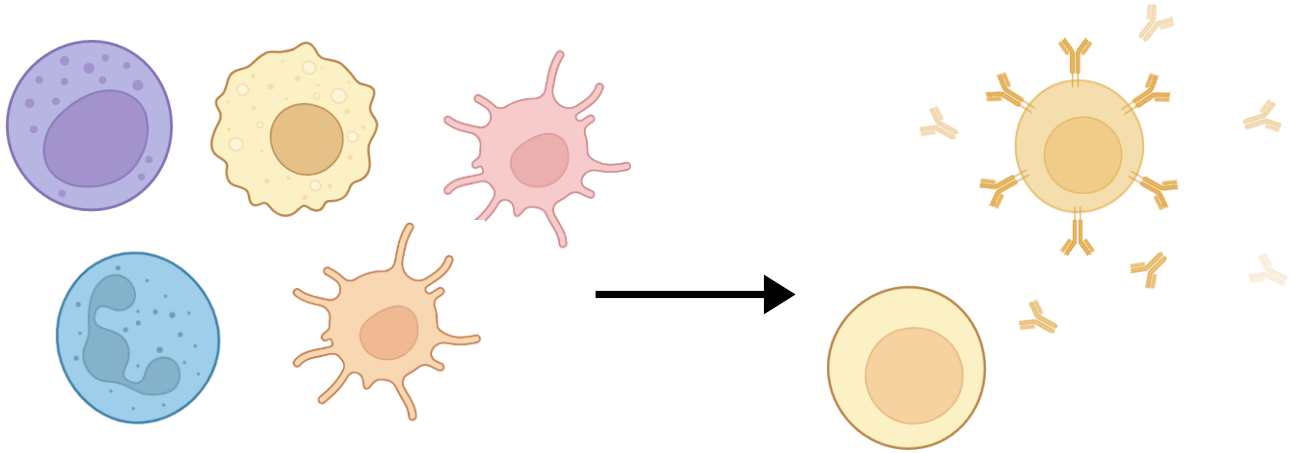


Mean +/- SD shown (N =5). Significance via one-way ANOVA with Tukey's post-hoc multiple comparison test (* = $p < 0.05$; ** = $p < 0.01$).

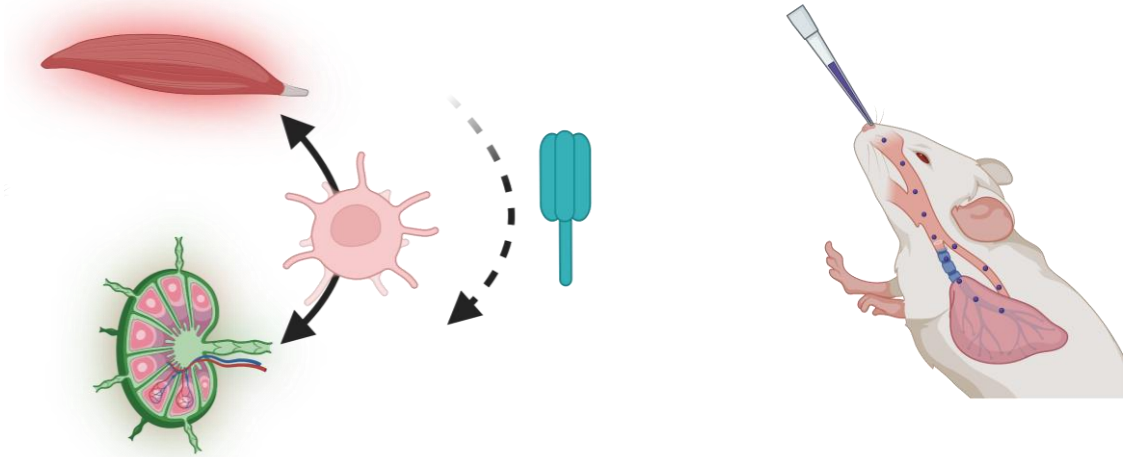
Peeler et al,
unpublished

Implications for future work

- Understanding innate-adaptive crosstalk:
  - Why did T cells decrease?
  - How to boost B cells?
  - T_H1 helping neutrophils?



- Engineering vaccine delivery
  - Secreted antigen constructs
  - Mucosal co-delivery vehicles



Thank you

Imperial College London

KAVLI INSTITUTE FOR NANOSCIENCE DISCOVERY

UNIVERSITY OF OXFORD

<u>John Tregoning</u>
Ziyin Wang
Chubicka Thomas
Livia Spiga

<u>Patrick Stayton</u>
Simba Jokonya
Ben Nguyen

<u>Robin Shattock</u>
Paul McKay
Marco Briones Orta

<u>Molly Stevens</u>
Lijun Hu

MARIE CURIE ACTIONS

BactiVac network

UKRI Medical Research Council

@djpeeler.bsky.social dpeeler@uoregon.edu davidpeeler.com

The Biomaterial Research for Immunomodulation, Drug delivery, and Genetic Engineering (BRIDGE) lab

Recruiting postdocs and PhD students to start in 2026!

UNIVERSITY OF OREGON

Phil and Penny Knight Campus for Accelerating Scientific Impact

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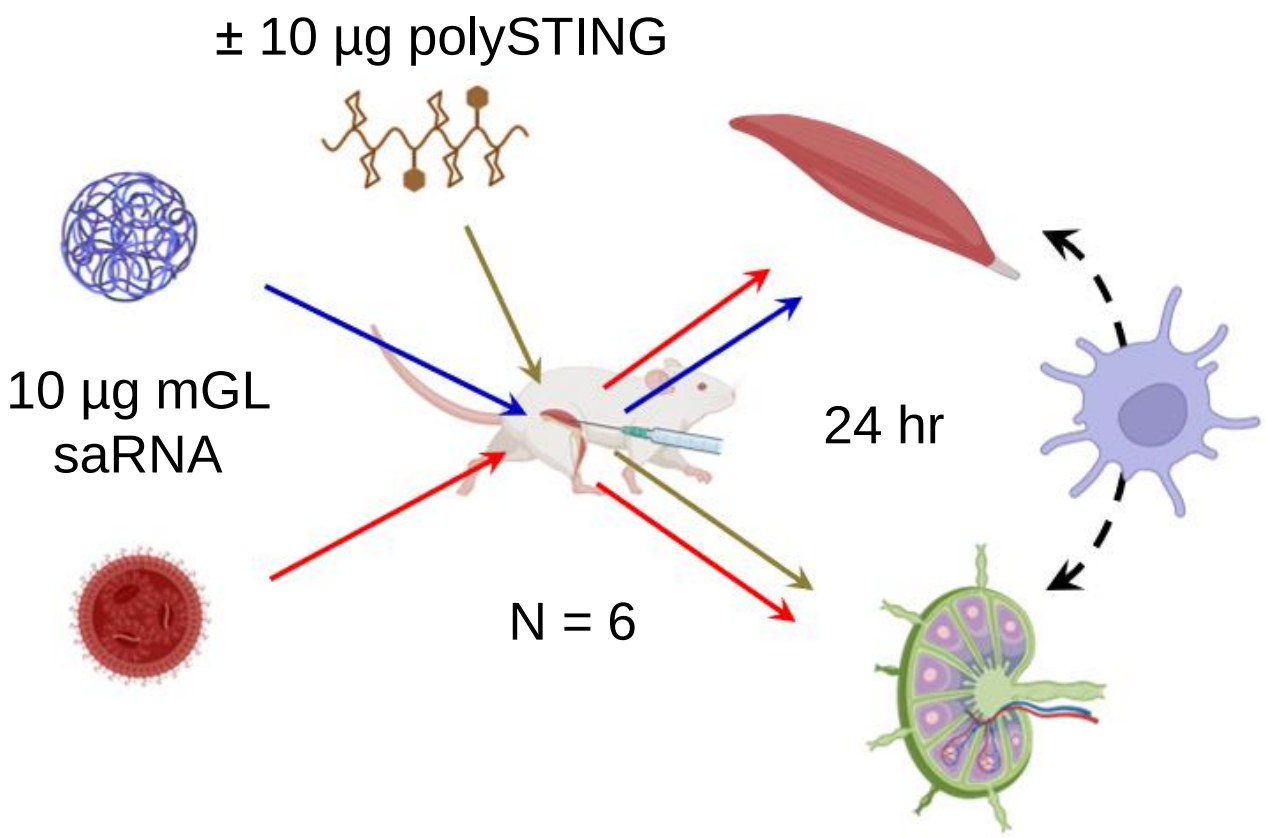
Which innate cell types are transfected/take up polySTING?



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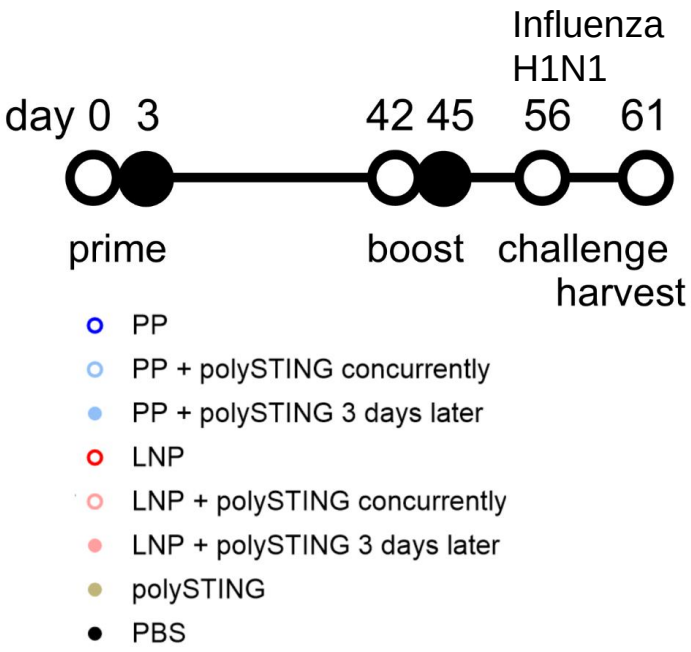
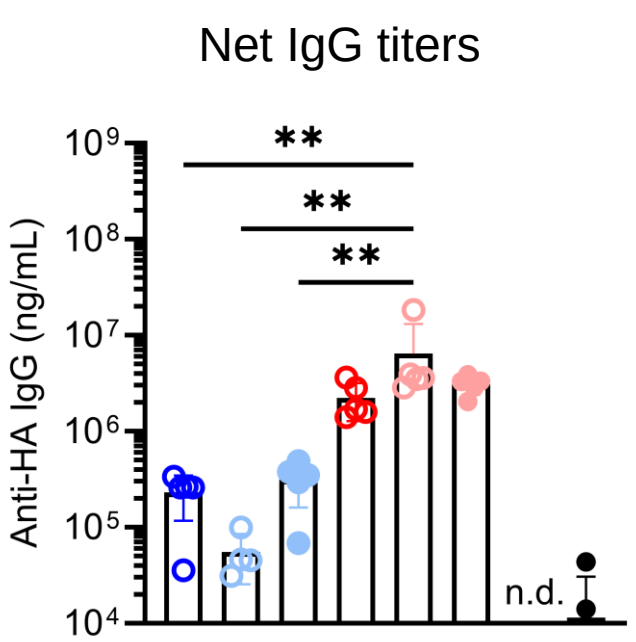
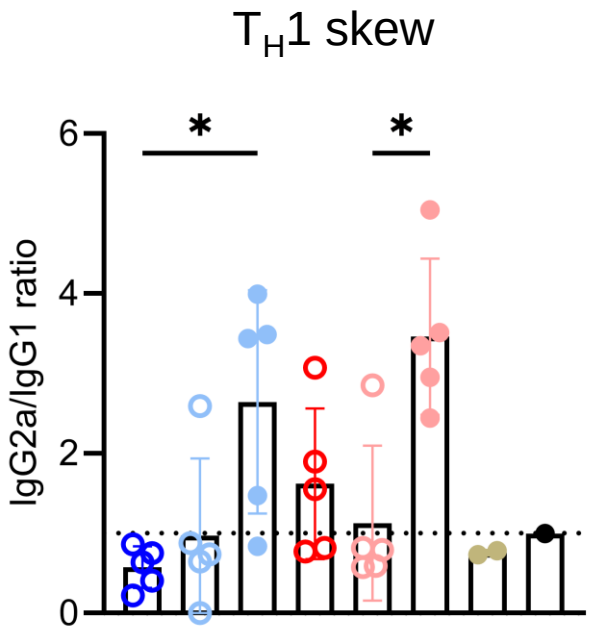
Delayed polySTING delivery skews towards T_H1-associated antibodies for both PP & LNP



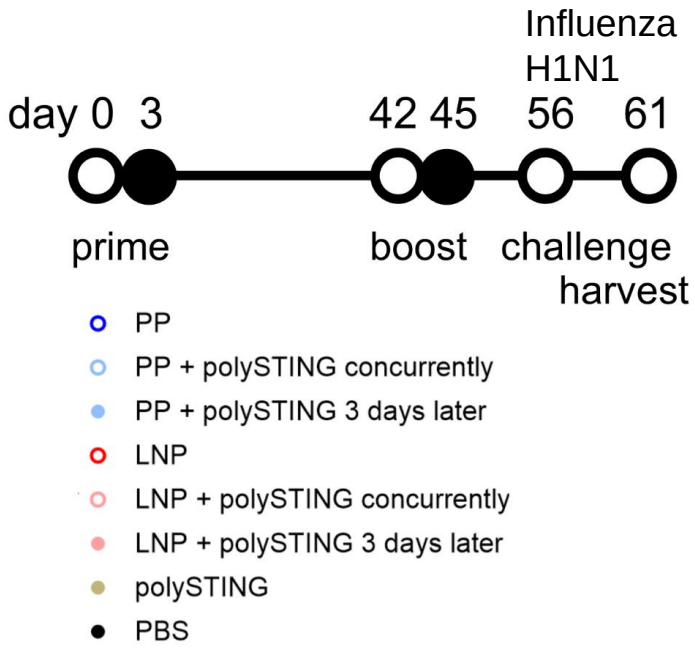


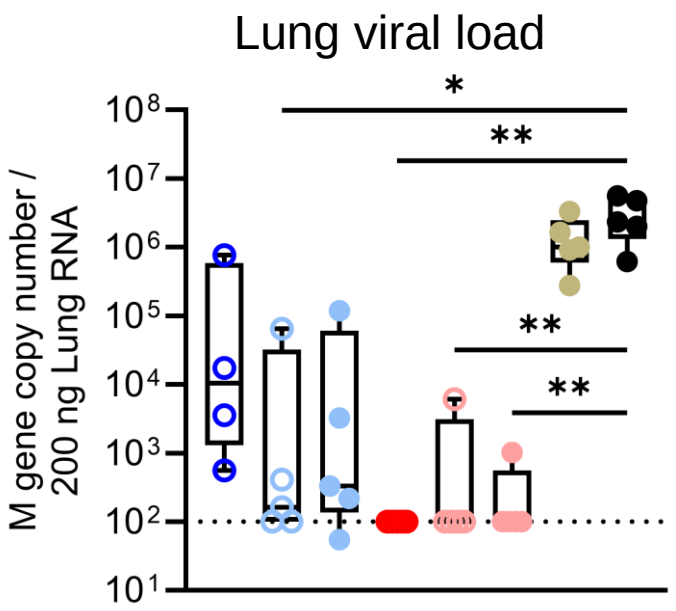


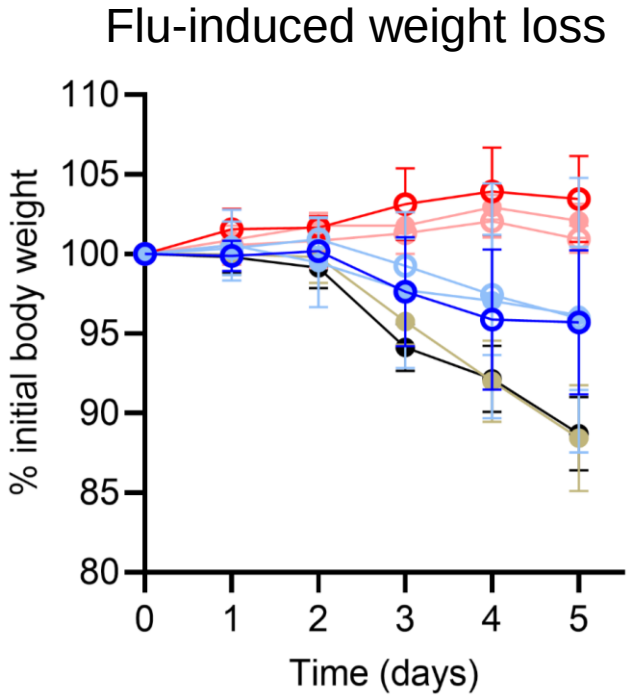
Mean +/- SD shown (N =5). Significance via one-way ANOVA with Tukey's post-hoc multiple comparison test (* = p < 0.05; ** = p < 0.01; *** = p < 0.001; **** = p < 0.0001).

Peeler et al,
unpublished

PolySTING does not significantly improve PP-saRNA vaccine protection from flu infection







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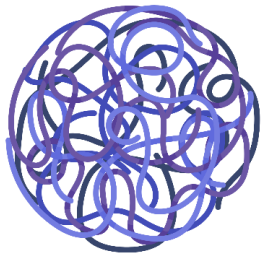
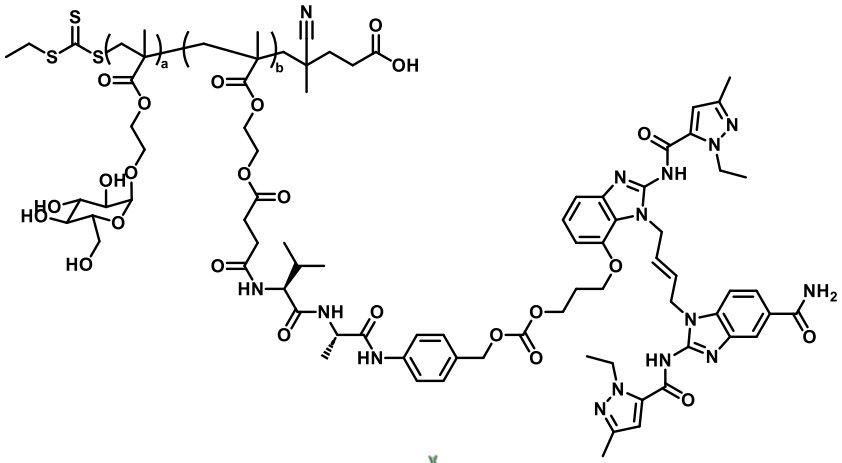
Peeler et al,
unpublished

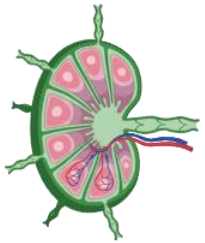
What if we change the location of STING agonism?

Polyplex saRNA (PP)

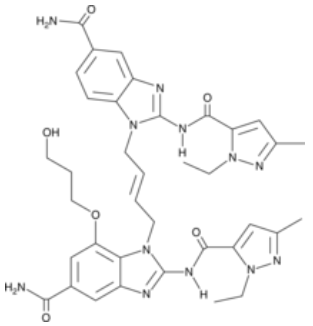


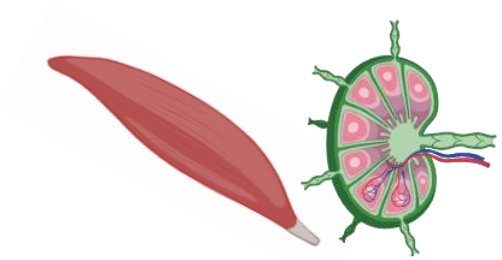
polySTING



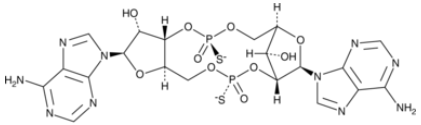


diABZI





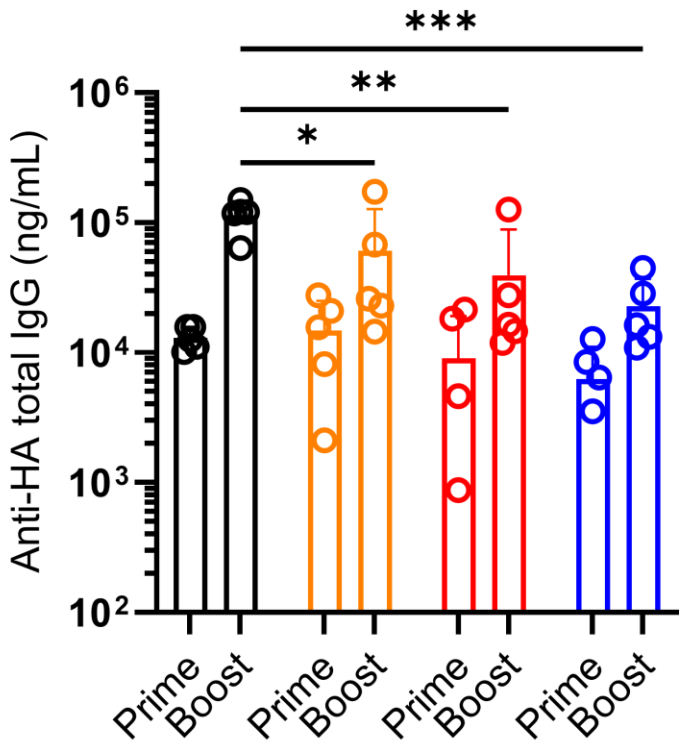
Cyclic dinucleotide (CDN)

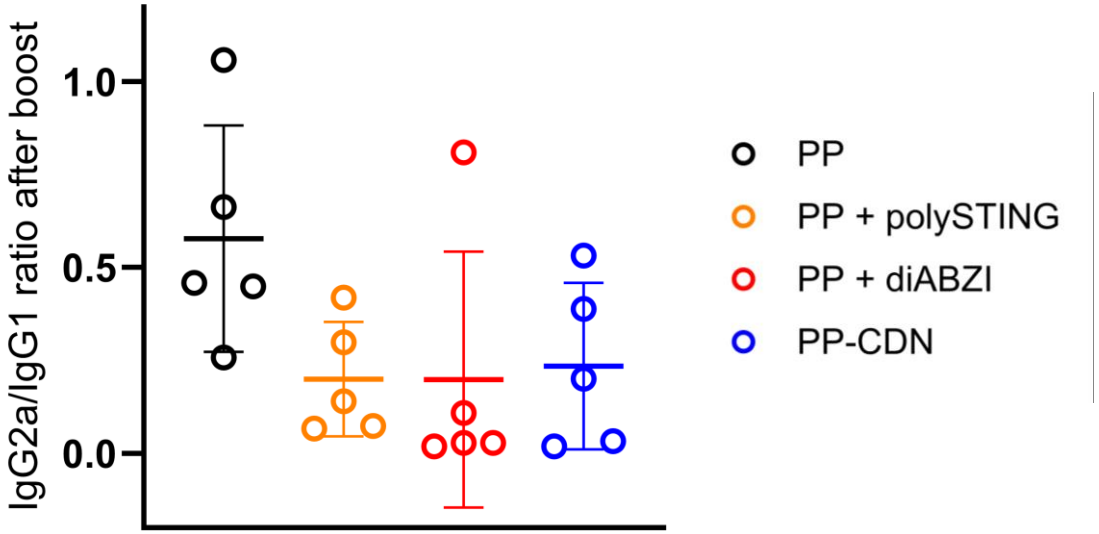


Peeler et al,
unpublished

Concurrent STING agonism decreases PP-saRNA IgG2a antibody responses

1 µg saRNA
5 µg STING agonist
Boost @ week 6
Analysis @ week 8





Mean +/- SD shown (N =5). Significance via two-way ANOVA with Tukey's post-hoc multiple comparison test (* = p < 0.05; ** = p < 0.01; *** = p < 0.001).

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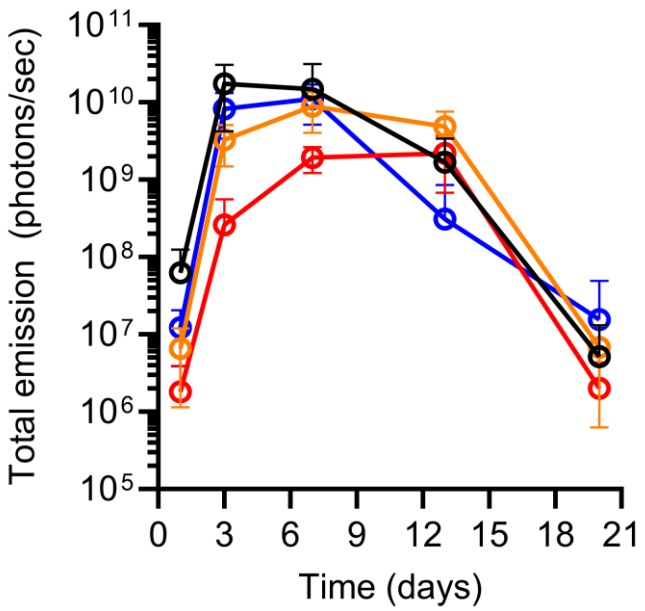
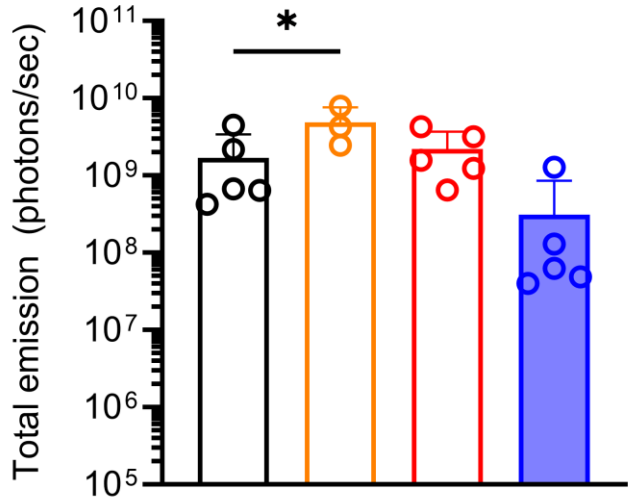
Only LN STING agonism decreases PP-saRNA T cell responses

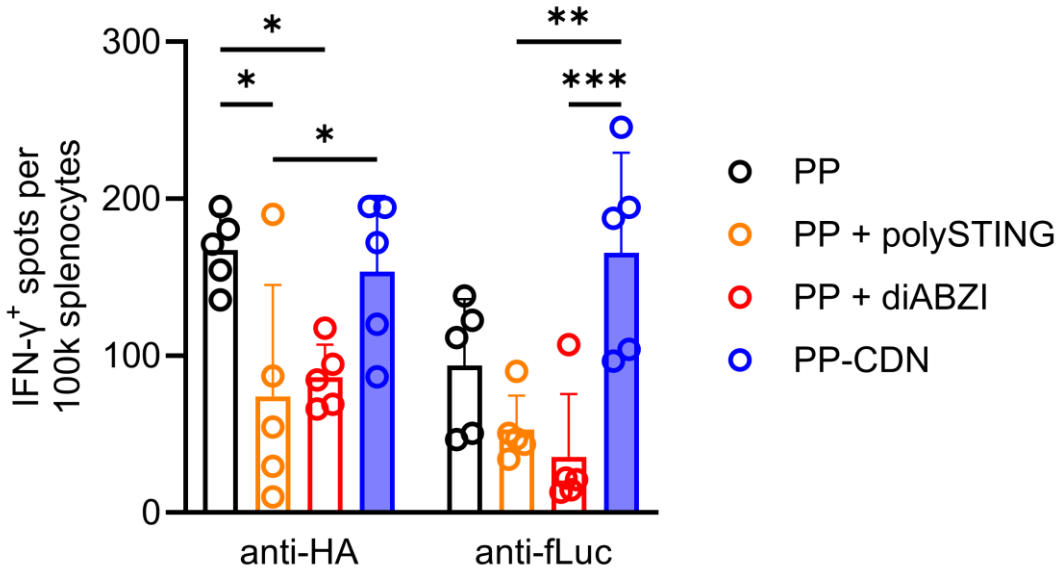
Transfection time course



Transfection at day 13

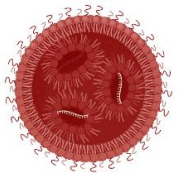


Splenocyte ELISpot

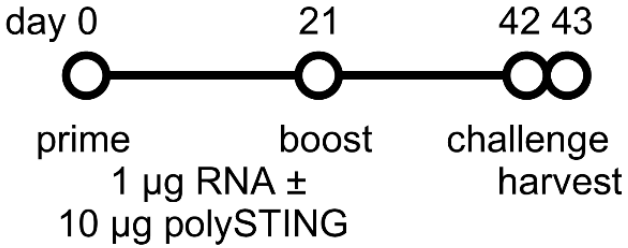


Mean +/- SD shown (N =5). Significance via one-way ANOVA with Tukey's post-hoc multiple comparison test (* = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$).

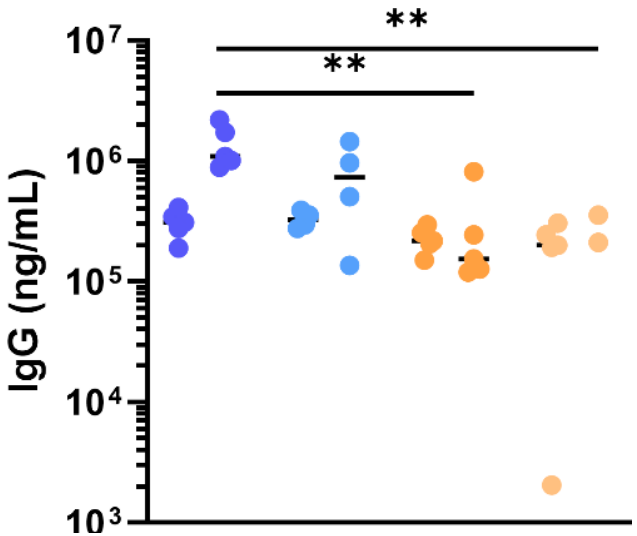
IgG2a/IgG1 ratio boosted, but overall titers lower → cellular T_H1 responses responsible for protection?

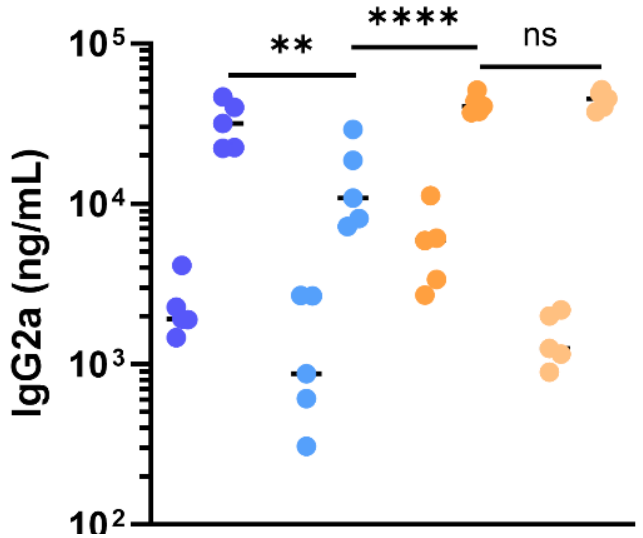


Acinetobacter baumanii



- 1 µg mRNA
- 1 µg mRNA + 10 µg polySTING
- 1 µg saRNA
- 1 µg saRNA + 10 µg polySTING
- Naive





Mean +/- SD shown (N =5). Significance via one-way ANOVA with Tukey's post-hoc multiple comparison test (* = $p < 0.05$; ** = $p < 0.01$).