Akagera Medicines

A novel mRNA TB vaccine candidate using targeted lipid nanoparticles

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7th Global Forum on TB Vaccines
Rio de Janeiro, Brazil
October 8-10, 2024

BILL & MELINDA GATES *foundation*

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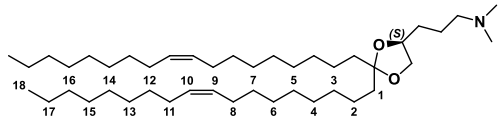
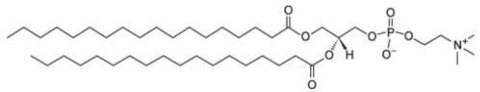
Current LNP Formulation Description

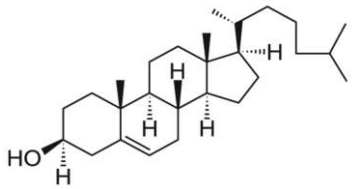
KC3-OA
ionizable lipid



DSPC

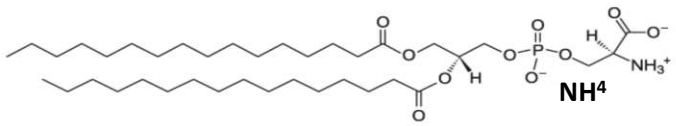


Cholesterol

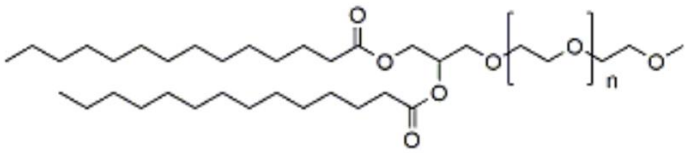


DPPS

1,2-dipalmitoyl-sn-glycero-3-phospho-L-serine (sodium salt)



PEG(2000)-DMG

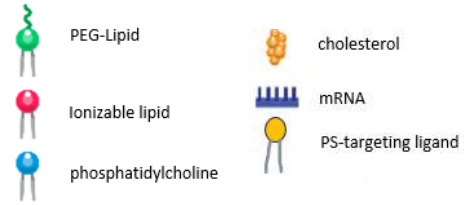


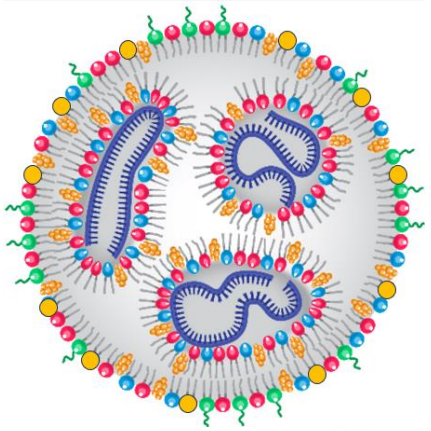
mRNA

KC3-OA/DSPC/DPPS/Chol/PEG-DMG
48/5/5/38.5/1.5 mol%
N/P = 5.25 (Lipid/mRNA)

Chaotic mixing via

Microfluidic device



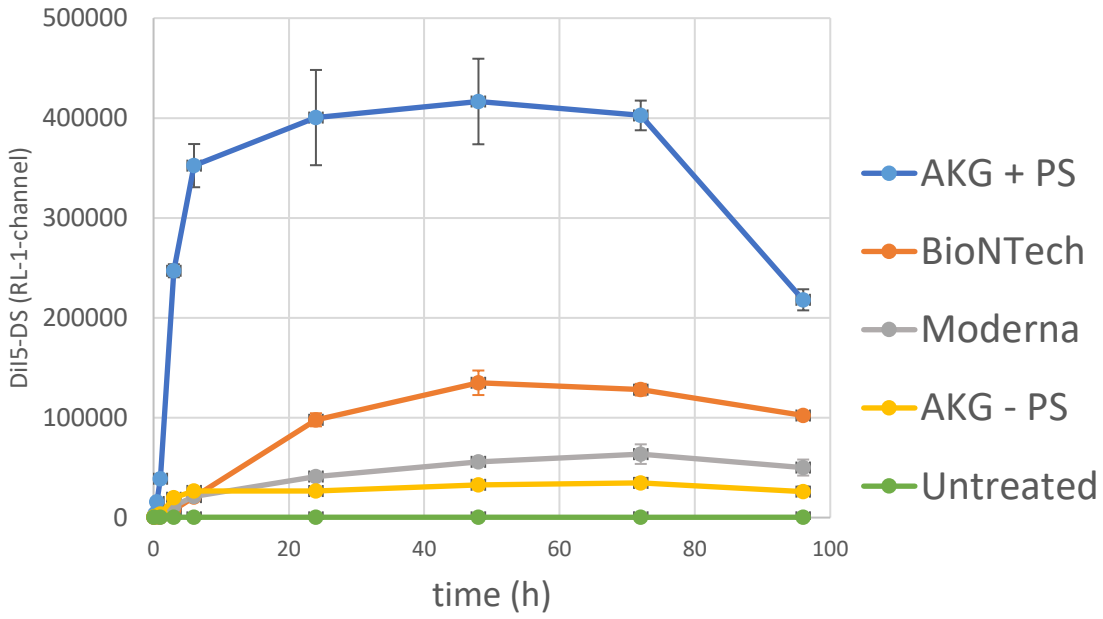


Lipid nanoparticle (LNP)
≤100 nm

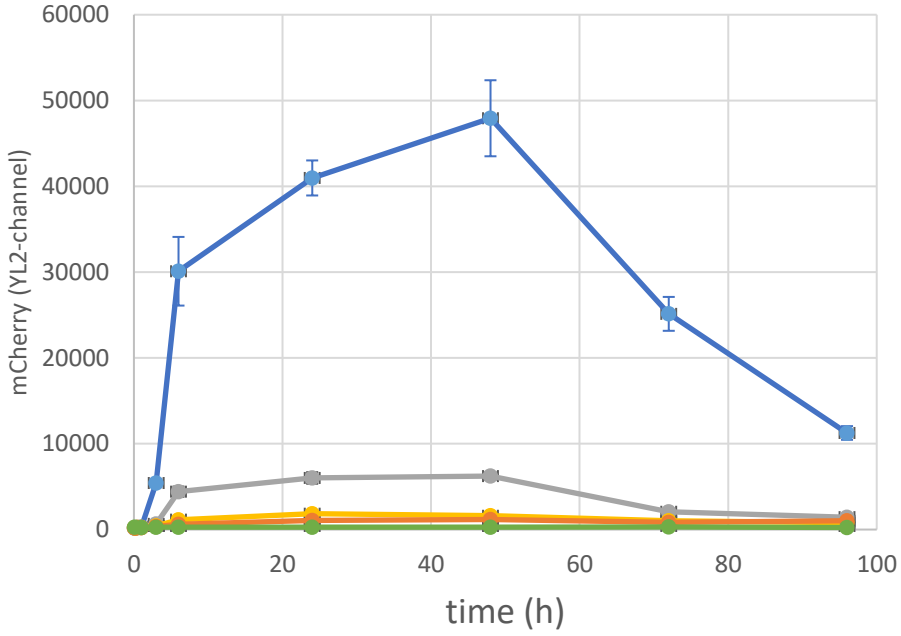
Phosphatidyl L-Serine Increases Uptake Efficiency of LNPs & Protein Expression

LNPs labeled with 0.025mol% DiI5-DS
MutuDCs, at 0.2 ug/ml mRNA

LNP cellular uptake



mCherry expression



PS targeting enhances protein expression compared to competitor formulations which lack target specificity

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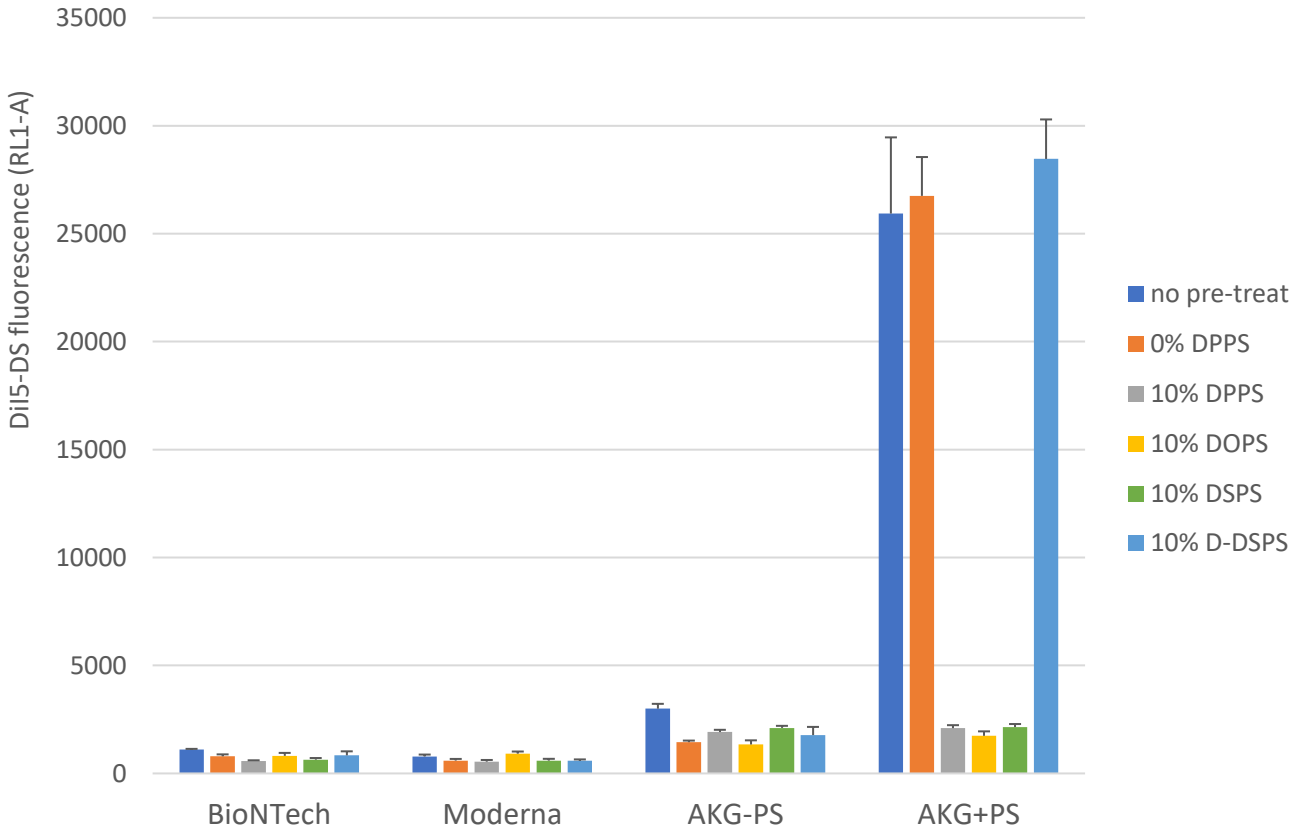
Uptake of LNPs is Isomer Specific & Can be Blocked with PS-containing Liposomes

- Cellular uptake of AKG PS-targeted LNPs can be blocked by PS-containing liposomes
- Complete blocking is achieved with the natural L-isomer of PS whereas the D-isomer is ineffective
- The PS-mediated uptake of AKG LNPs is stereospecific



- LNPs labeled with 0.025mol% DiI5-DS
- Liposomes added 15 min prior to LNPs which were incubated with MutuDC cells for 1h at 37 C
- Cellular fluorescence measured by flow cytometry

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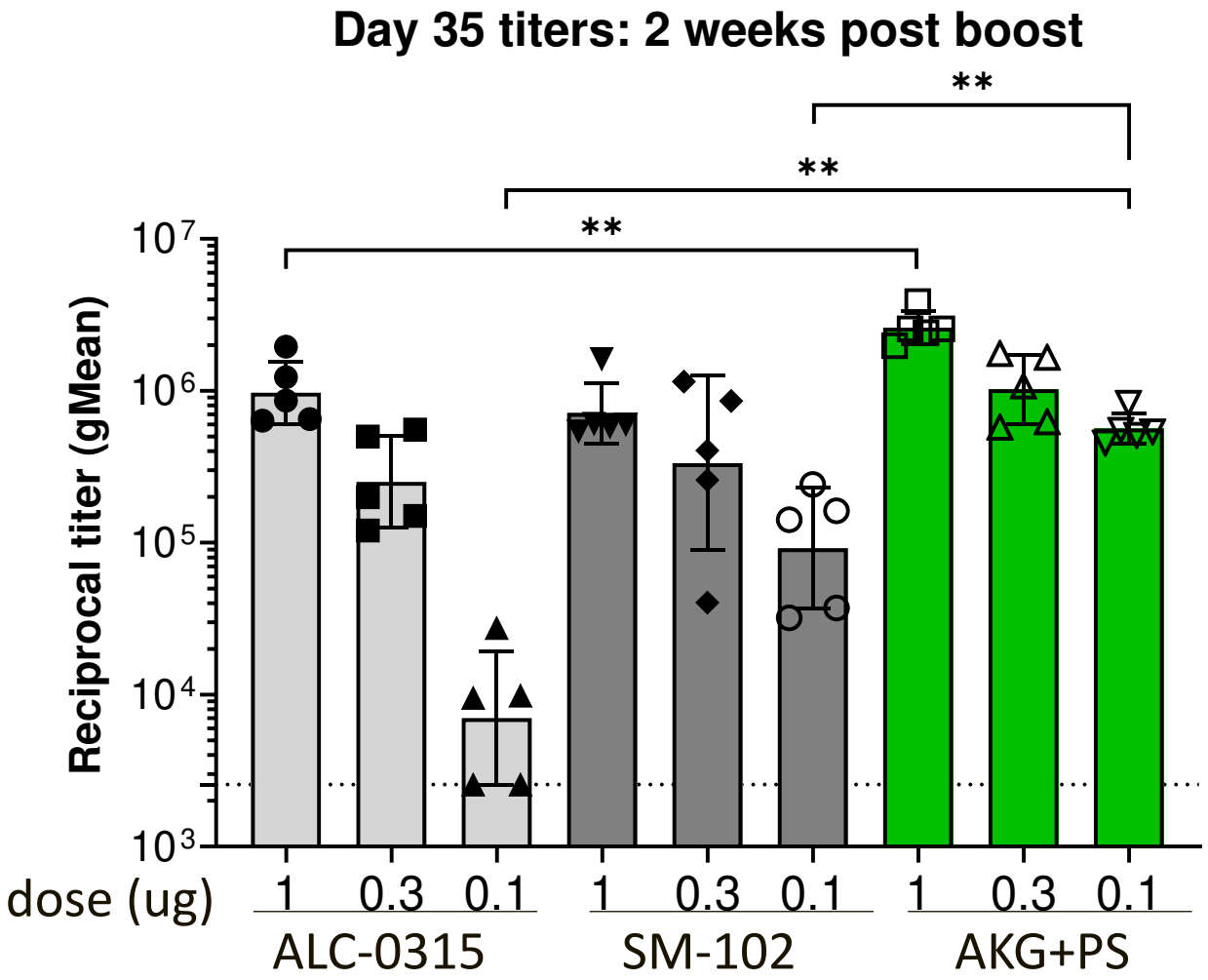
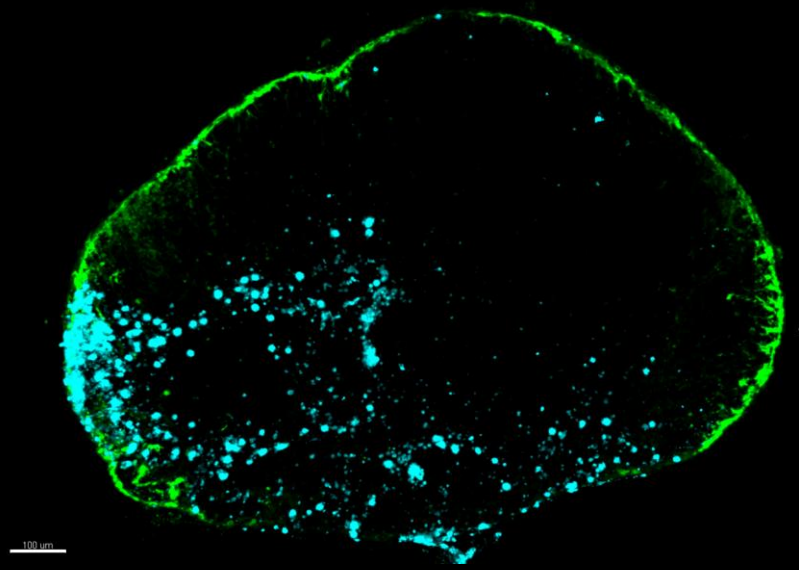
Optimization of PS-targeting for Robust Immunogenicity: Antibody responses to Spike mRNA

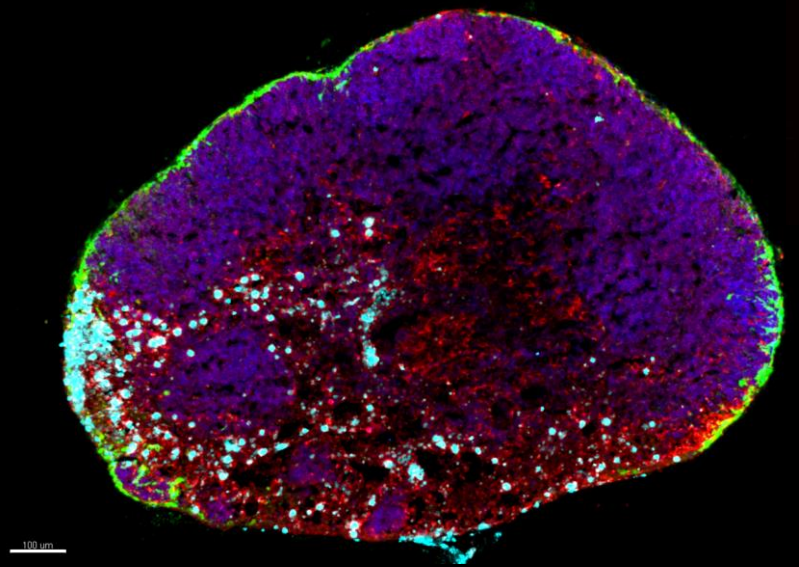


6hr LNP (1ug)

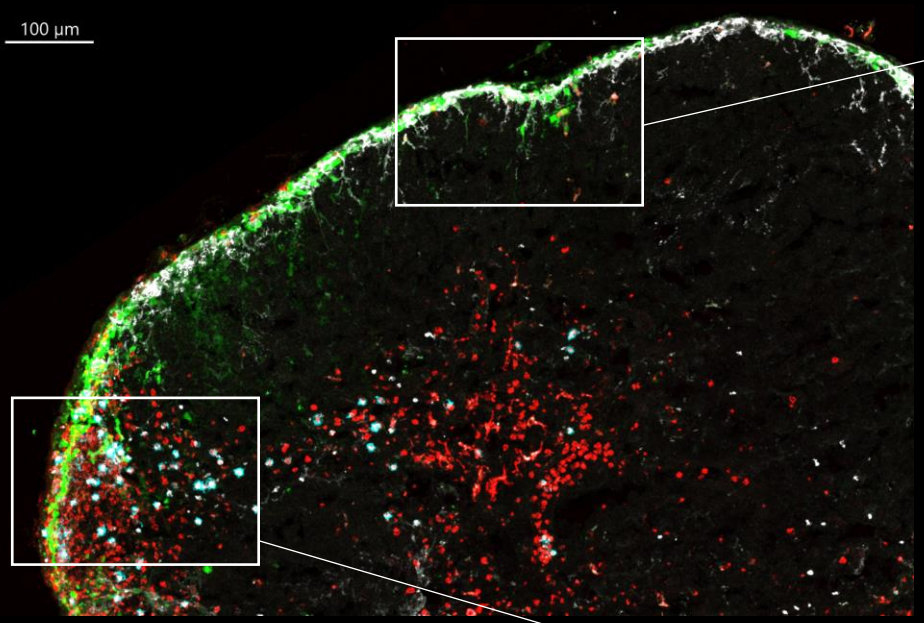
Michael Gerner, Ph.D.
Ada de la Cruz
University of Washington



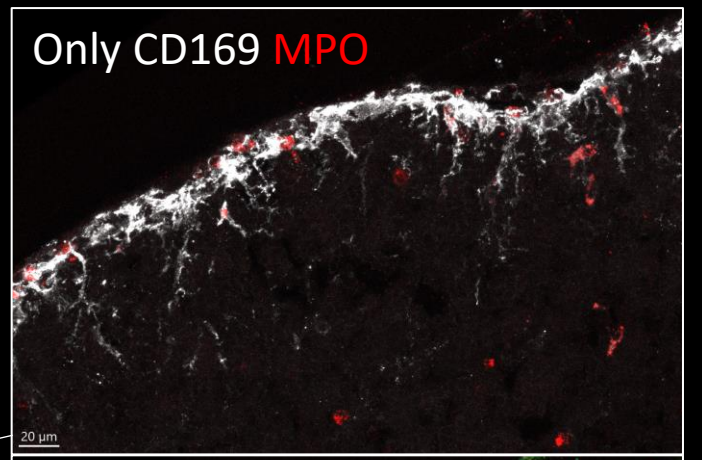
LNP ZsGreen

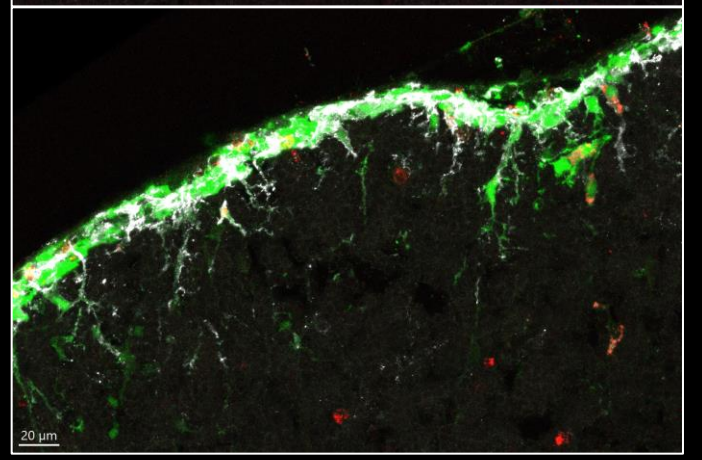


B220 (B cells) MHC-II LNP ZsGreen

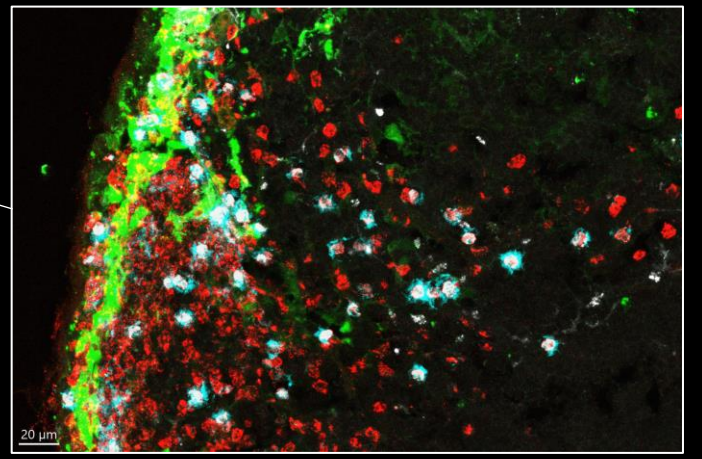


CD169 MPO LNP ZsGreen





CD169 MPO LNP ZsGreen



MPO, myeloperoxidase
(enriched in neutrophils)

24hr post immunization – Zsgreen mRNA

ALC-0315 / BioNTech

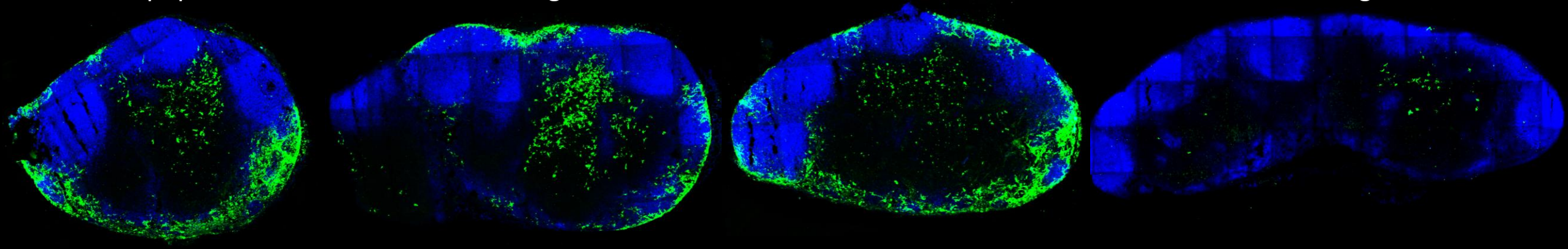
12R popLN

12R ingLN

AKG LNP

17L popLN

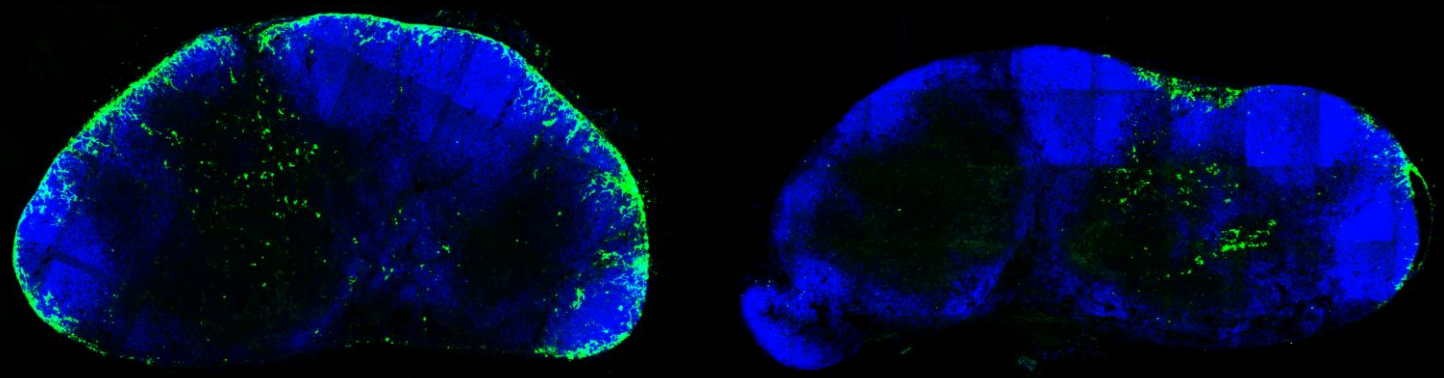
17L ingLN



AKG PtdSer-LNP

18L popLN

18L ingLN



popLN: popliteal LN, most proximal to site of injection

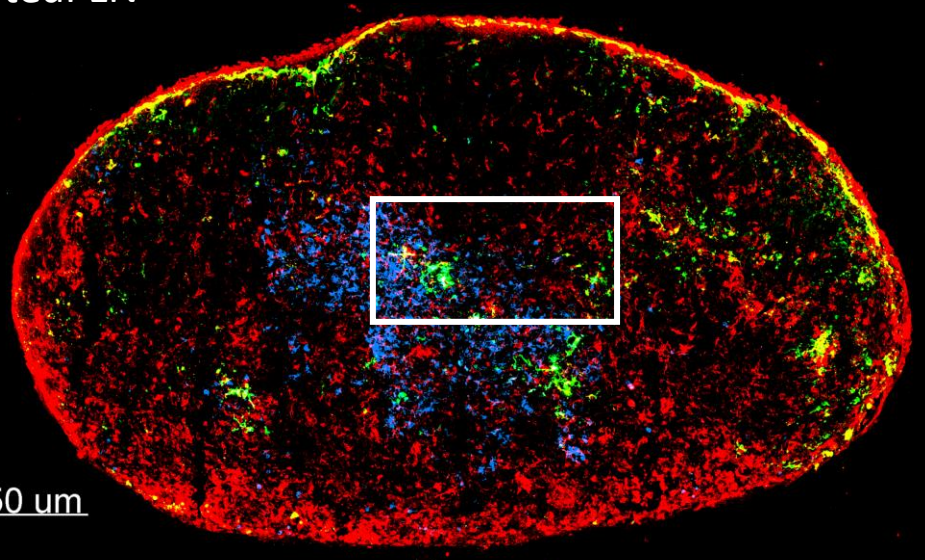
ingLN: inguinal LN, further downstream from the popLN

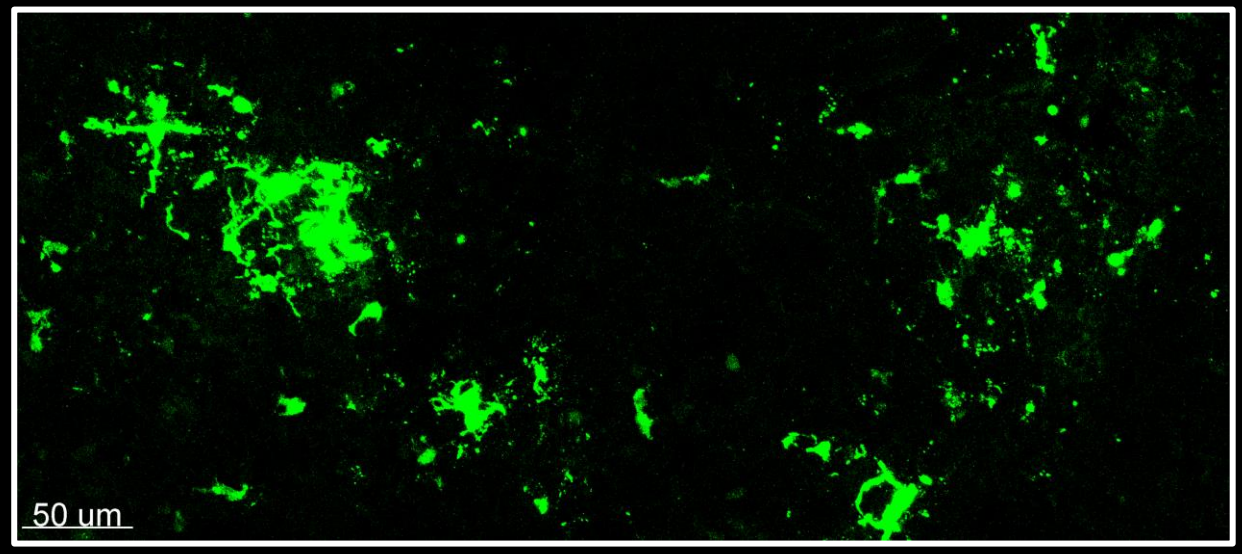
B220^{+} B cells ZsGreen

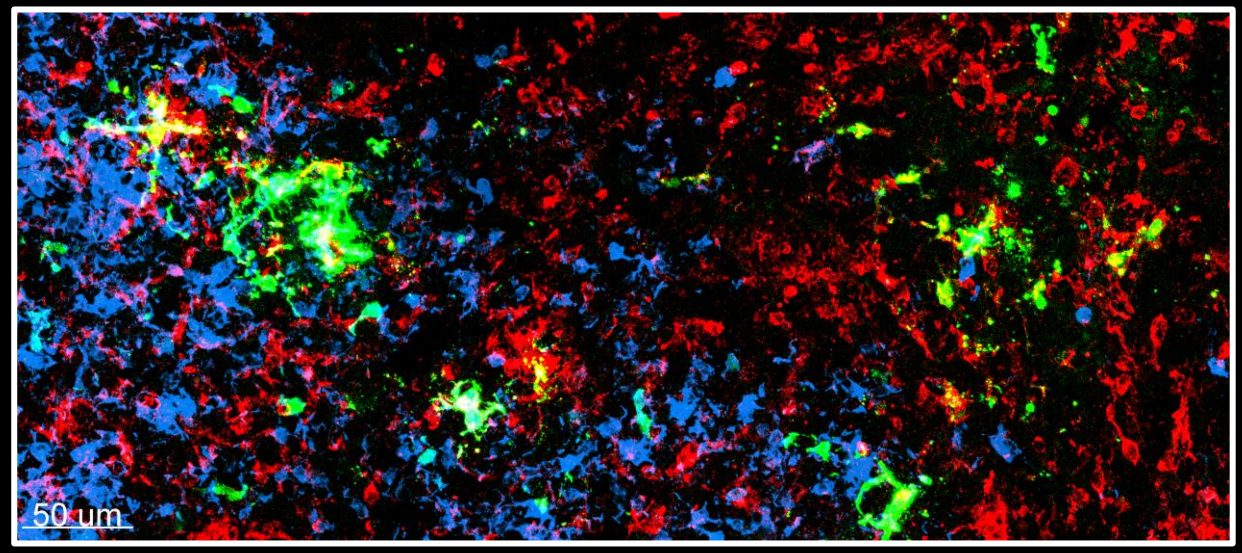
72hr post immunization

38L popliteal LN

AKG PtdSer-LNP





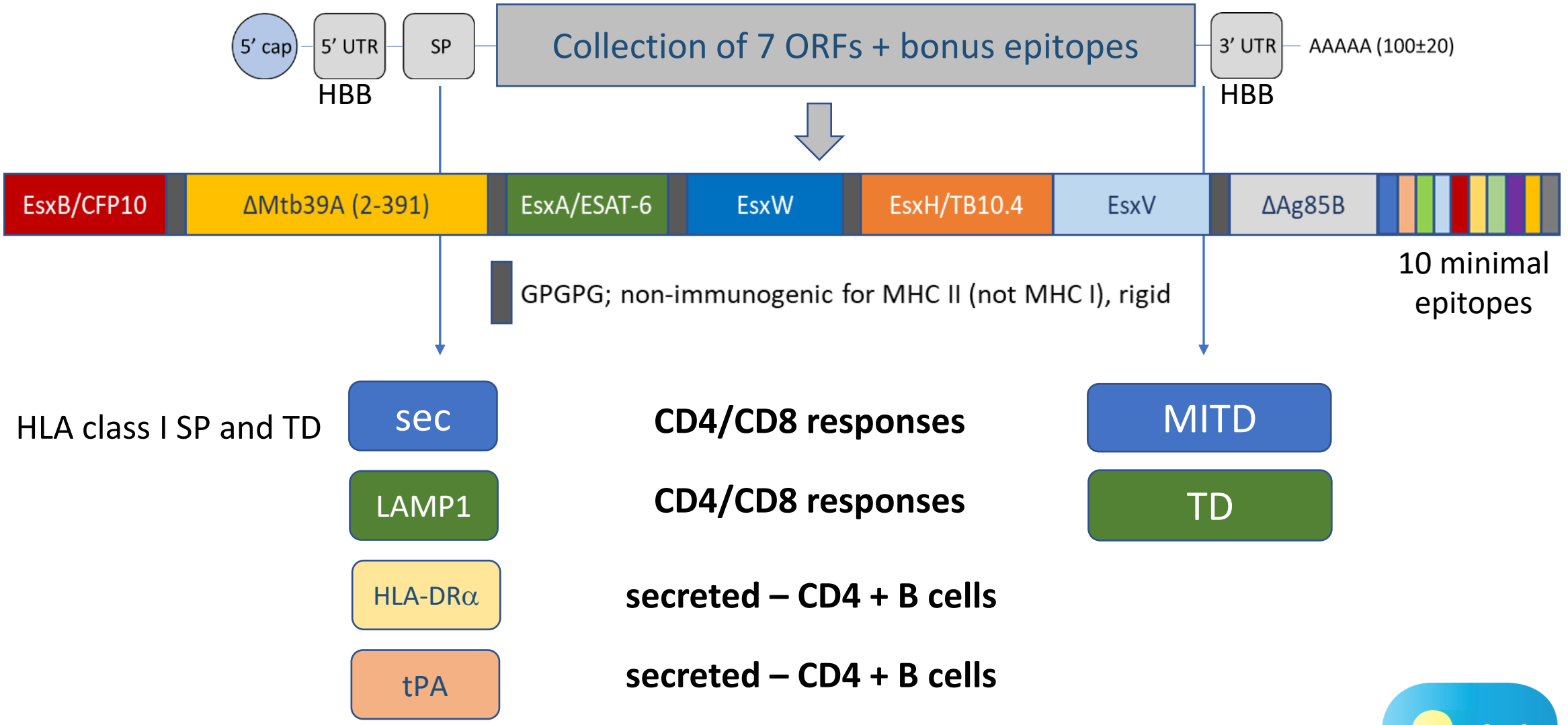


CD11c Fascin-1 ZsGreen

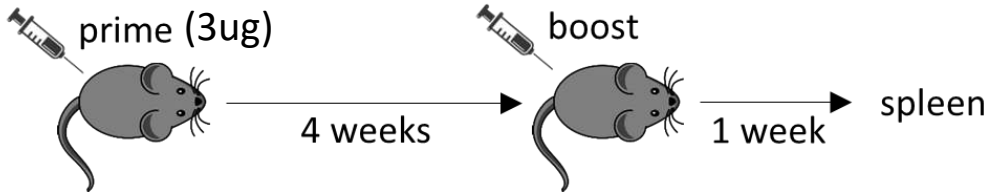
72hr – popliteal LN, AKG-PtdSer targeted LNP

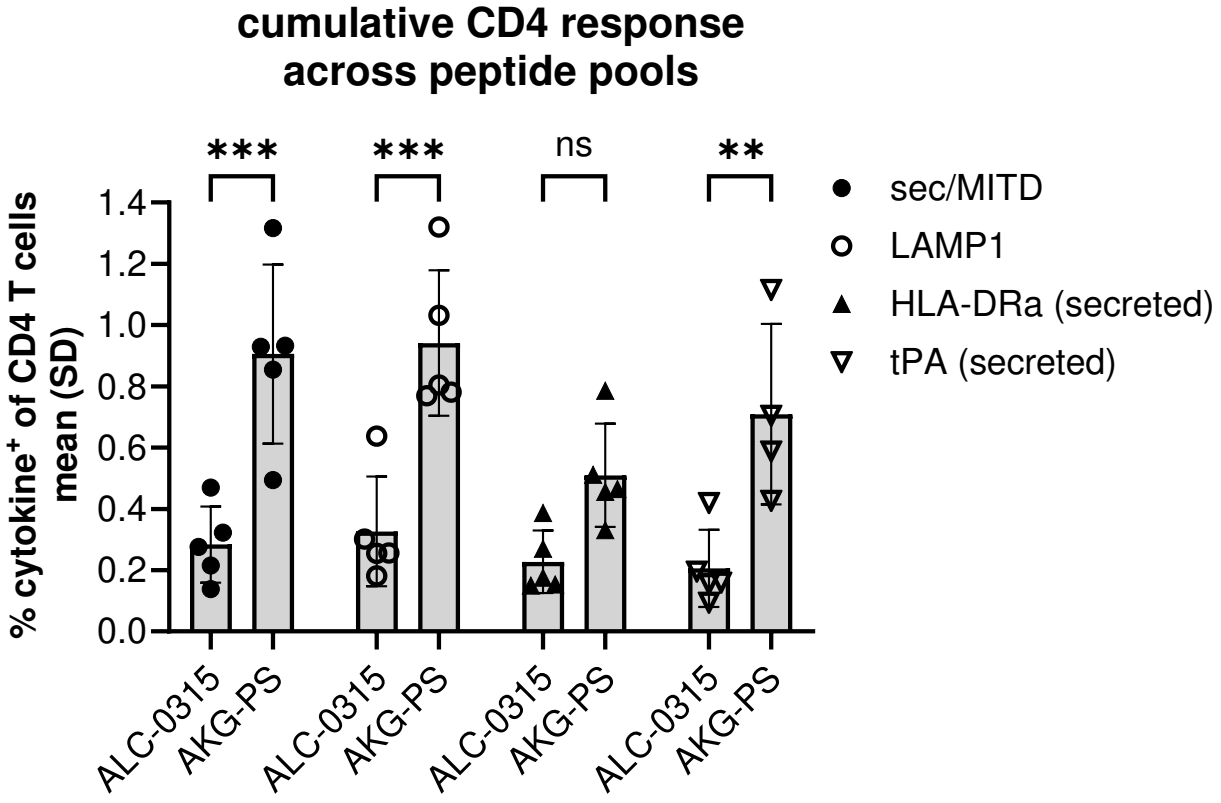
Antigen is dominant in the SCS macrophages; some in the T cell zone. Within the T cell zone, antigen located within either Fascin-1^{HI} migratory DCs or CD11c^{HI} LN-resident DCs.

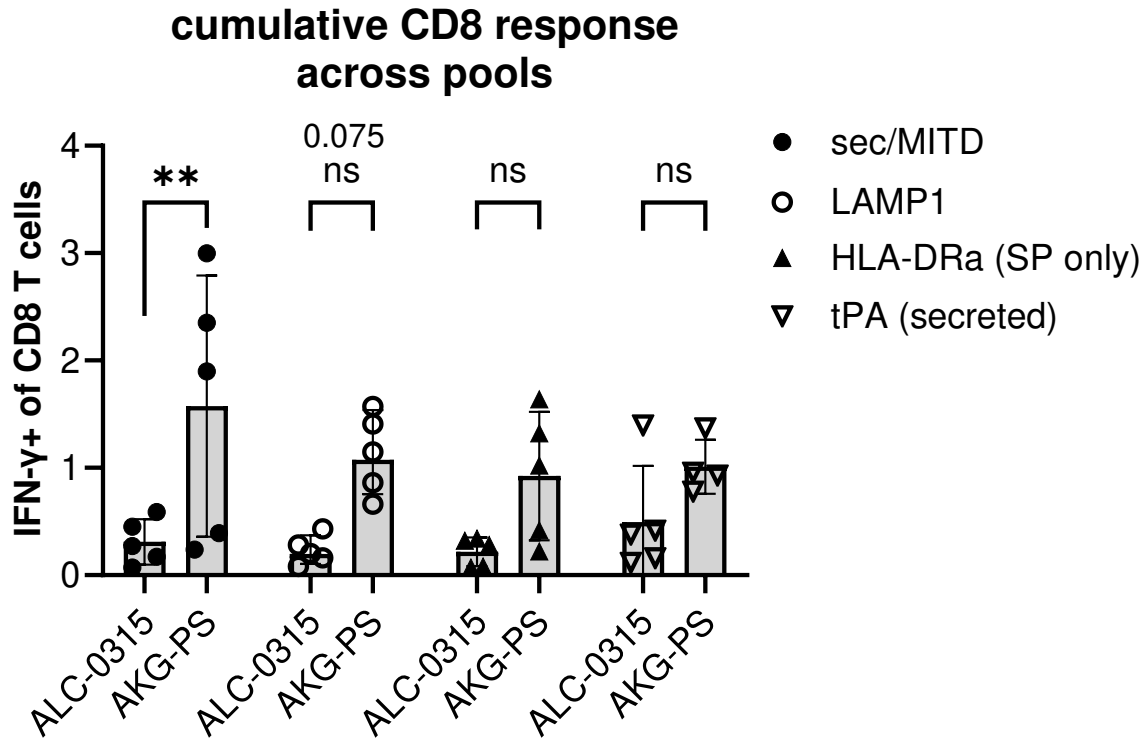
Antigen selection and mRNA design – 1st generation mRNA



Mtb-specific T cell responses—1st gen mRNAs







Akagera's lead LNP formulation generates a larger 2°effector memory CD4 T cell response with a greater *per cell* capacity to produce IFN-γ than the ALC-0315 formulation.

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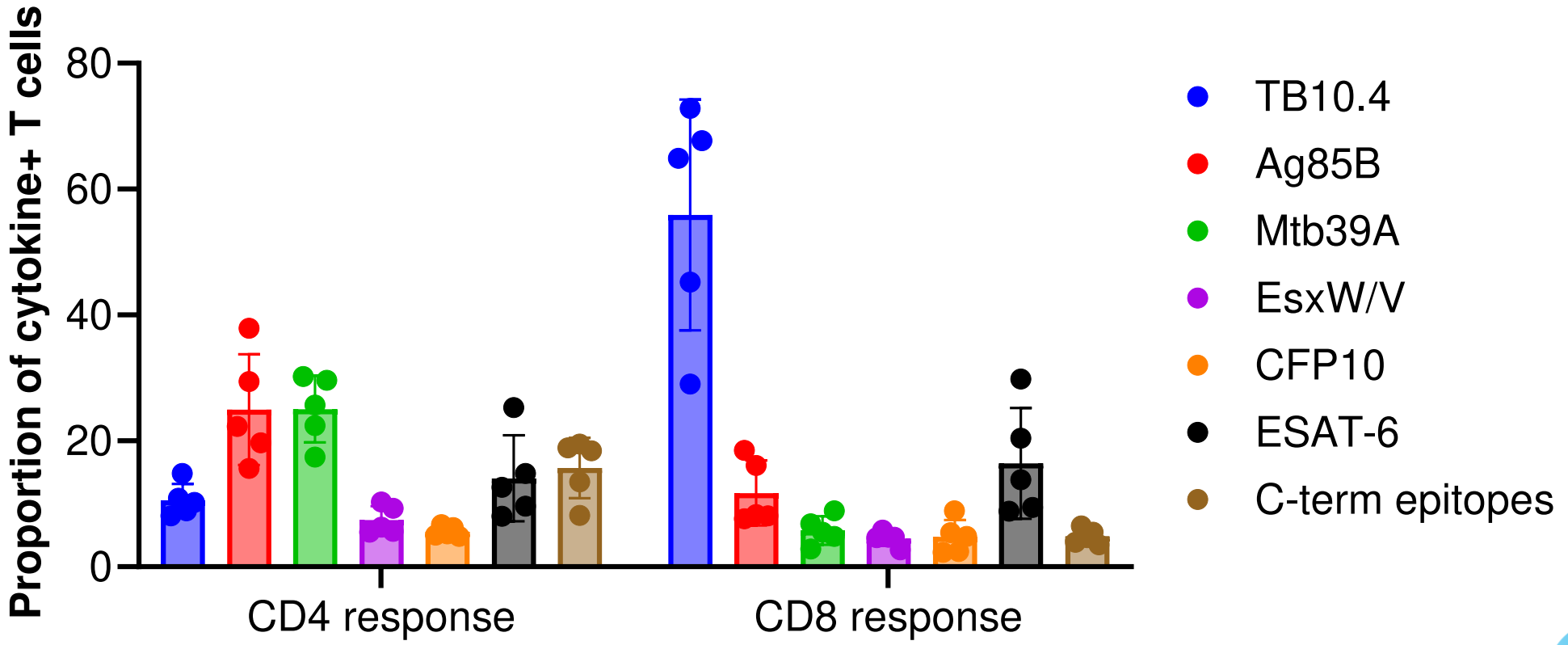
Breadth of Mtb-specific T cell responses in CB6F1 mice



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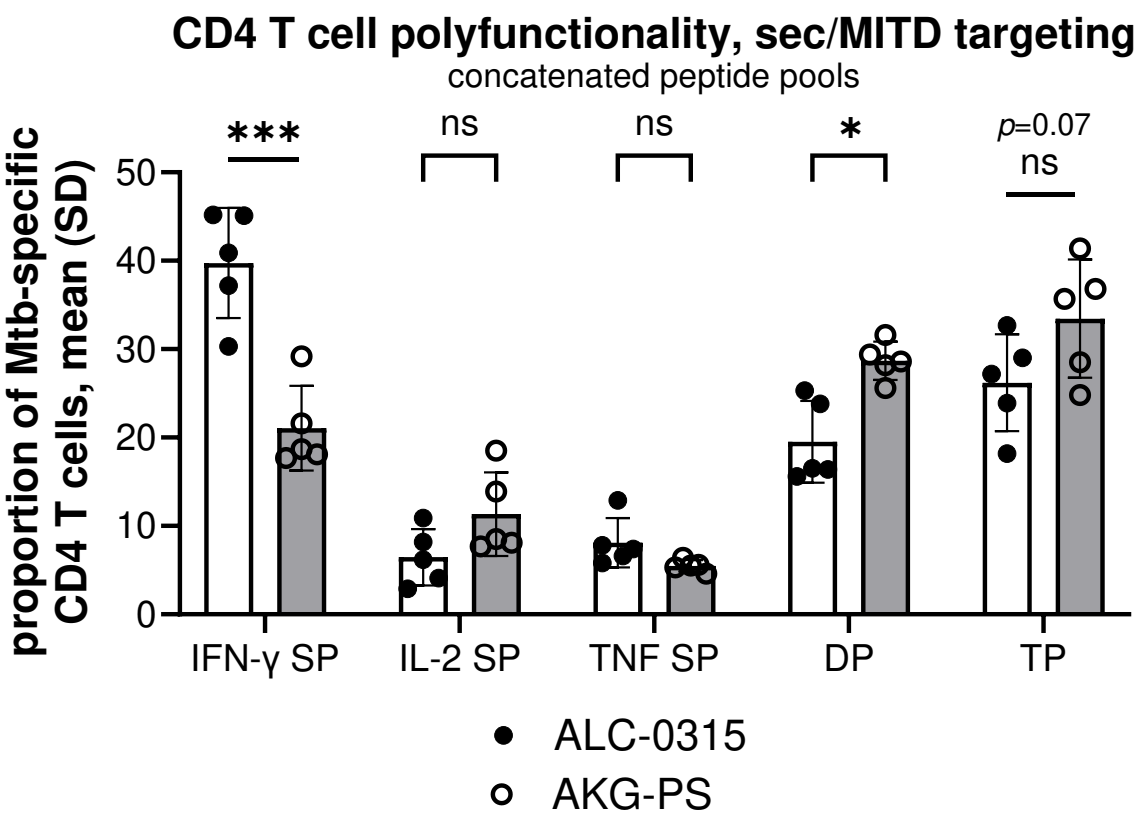
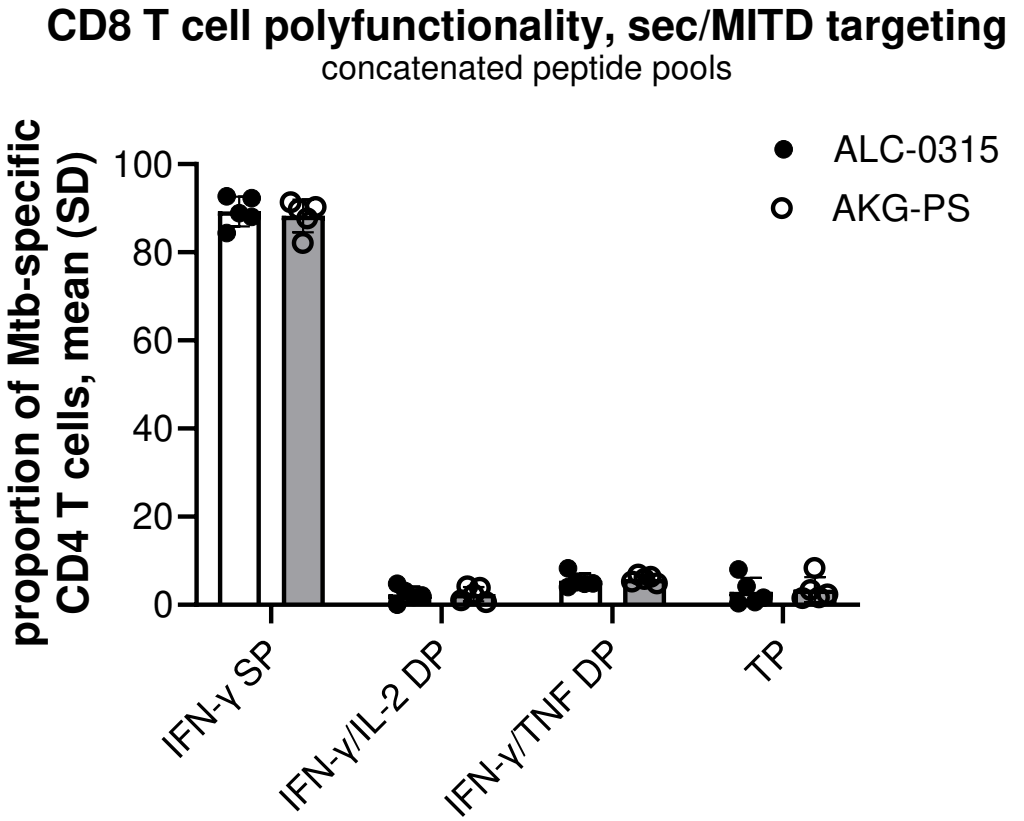
Polyfunctionality for sec/MITD mRNA





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Antigen selection and mRNA design

1st gen construct

immunodominant CD8 epitope

10 minimal epitopes

GPGPG; non-immunogenic for MHC II (not MHC I), rigid

10 weeks for mRNA production and mRNA-LNP formulation

2nd gen construct

immunodominant CD8 epitope

linker

replaces TB10.4

PPE "AANR" motif epitopes

3rd gen construct and "Add-on" construct

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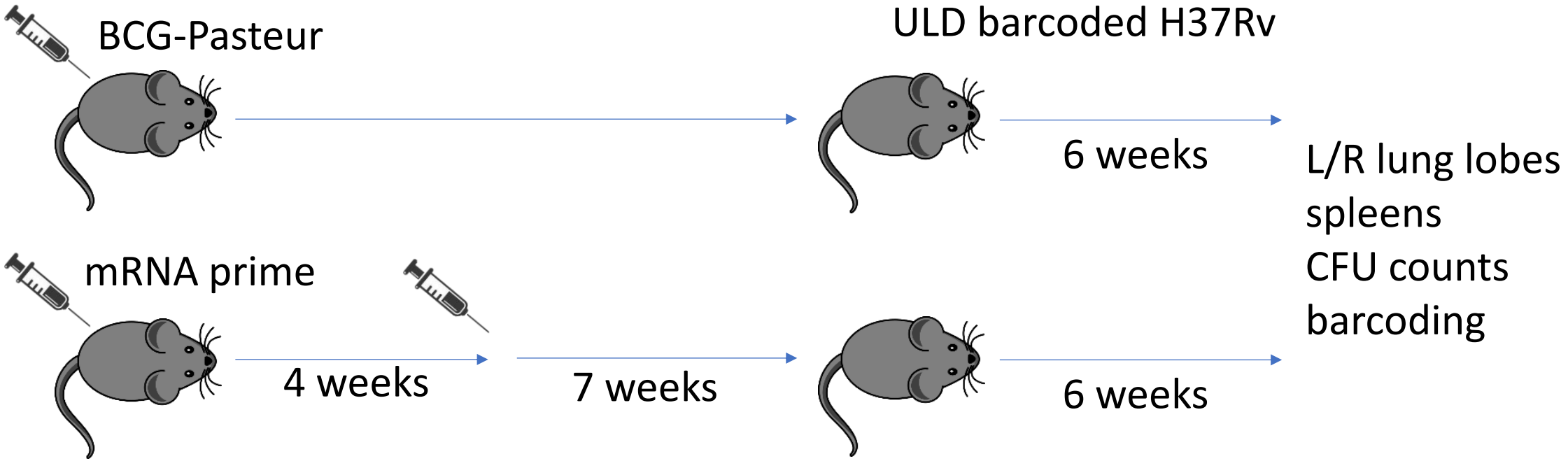
Prophylactic efficacy study using the ULD model in CB6F1 mice



1. Unvaccinated
2. BCG-Pasteur
3. 1st gen sec/MITD
4. 1st gen LAMP-1
5. 2nd gen sec/MITD

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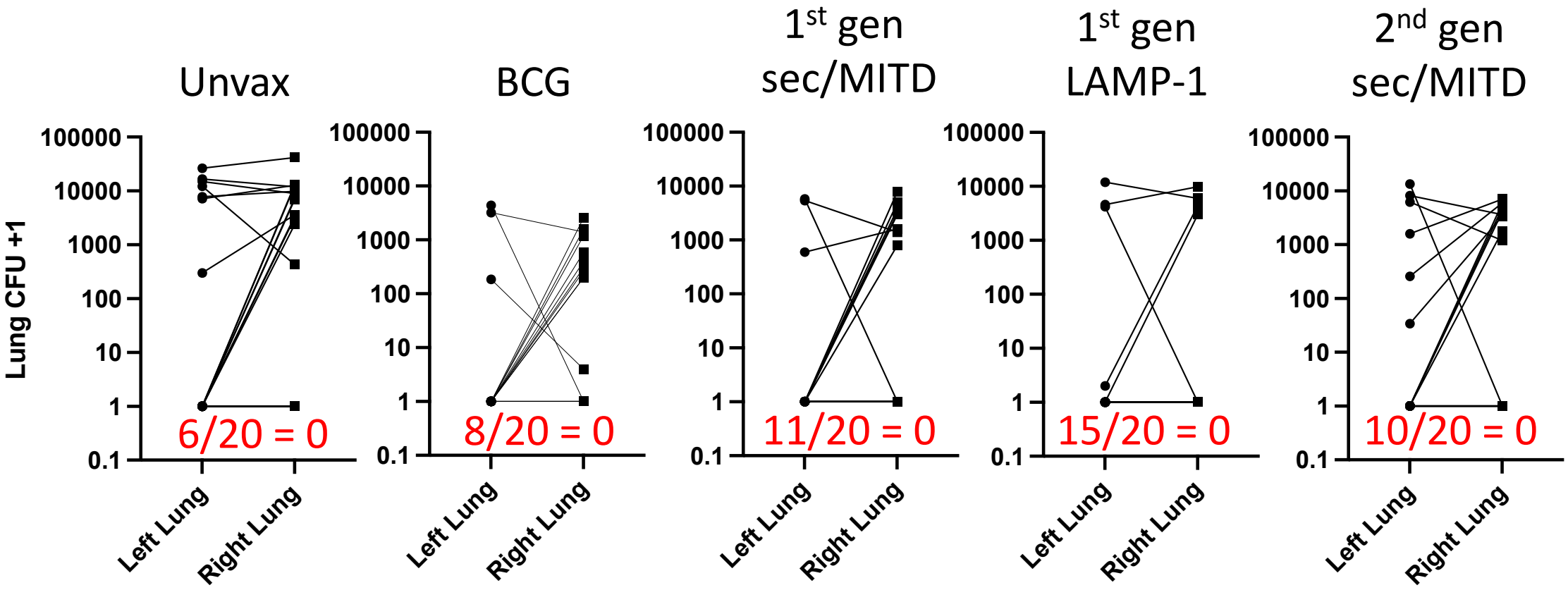
Prophylactic efficacy study using the ULD model in CB6F1 mice



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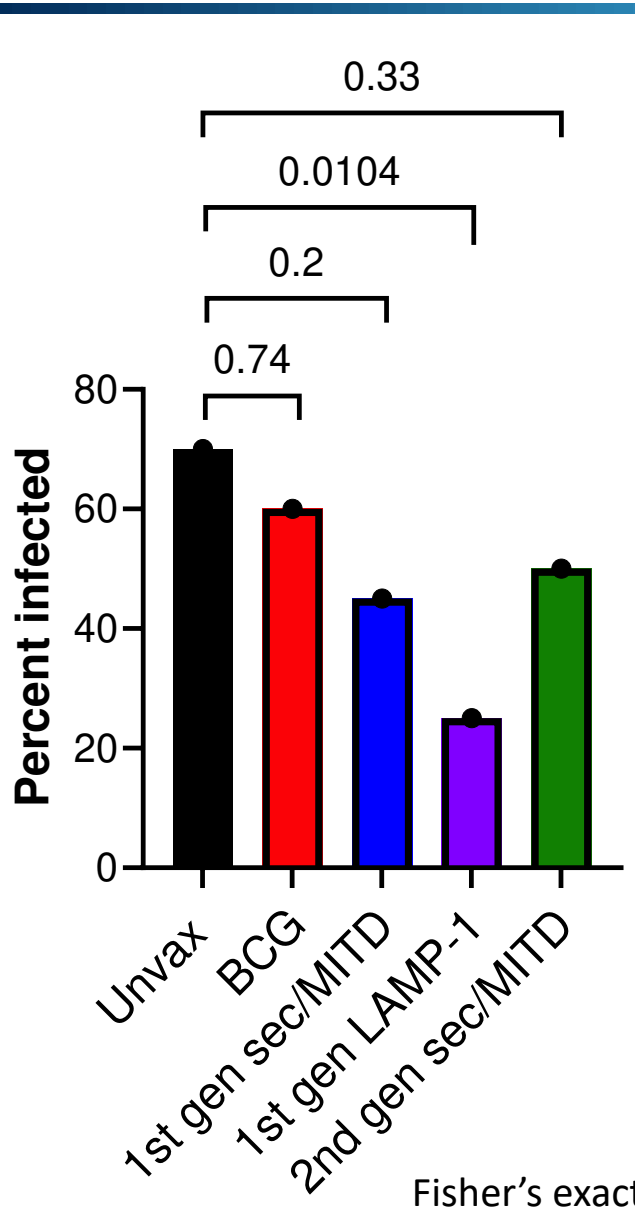

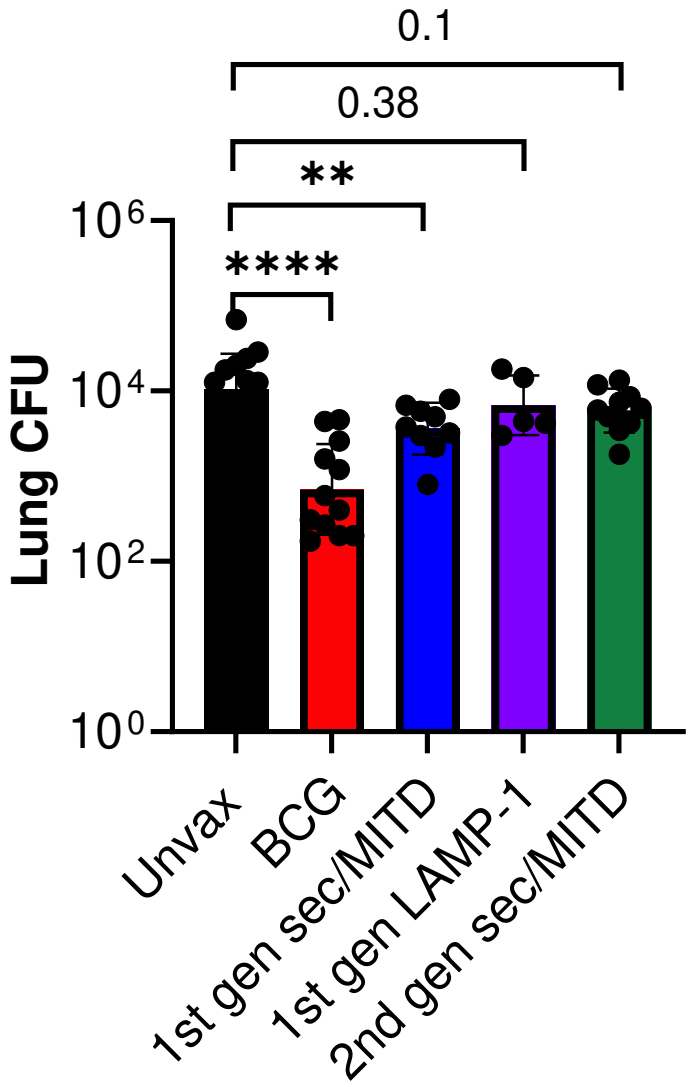

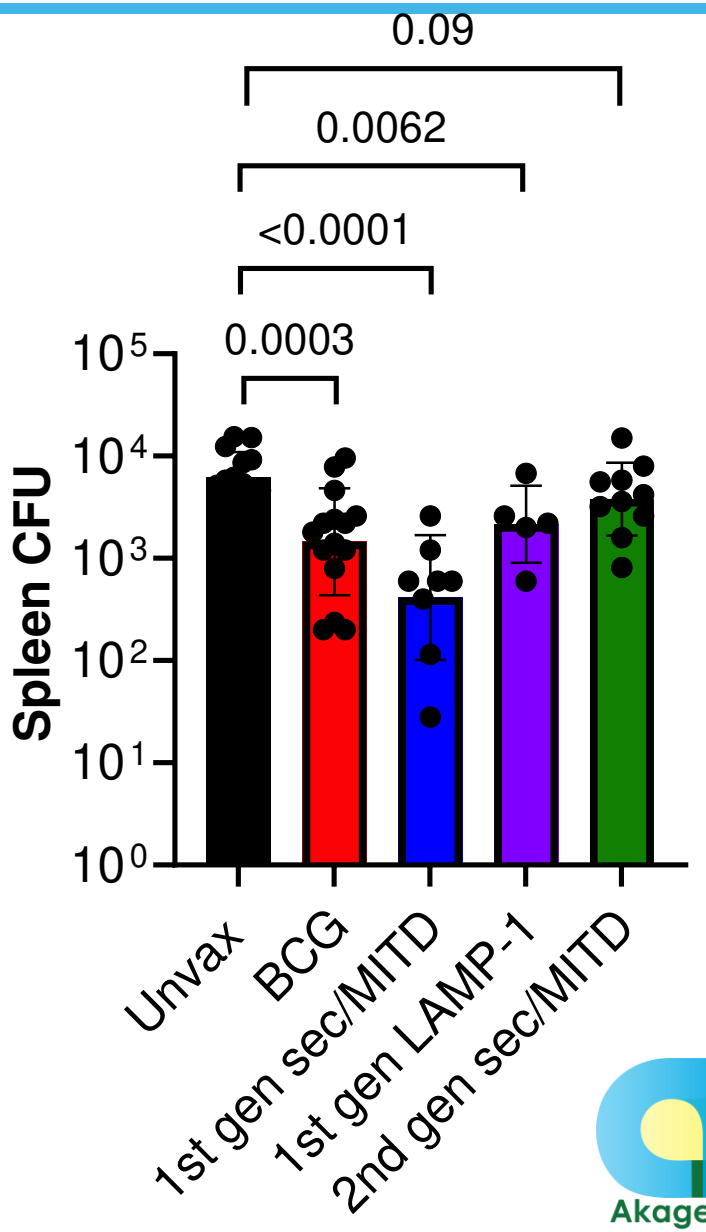

Fisher's exact test

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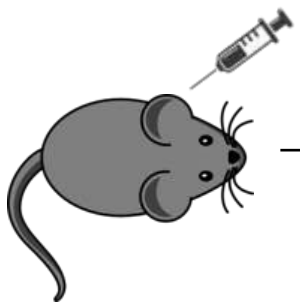
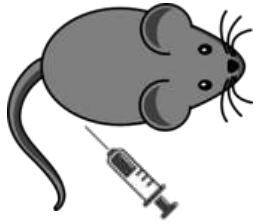
Therapeutic vaccination in a chronic CoMtb infection model

high dose *Mtb*, i.d.



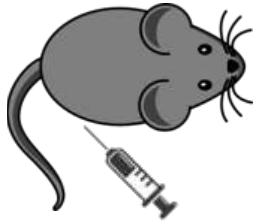
8-10 weeks

CB6F1



3 ug mRNA-LNP

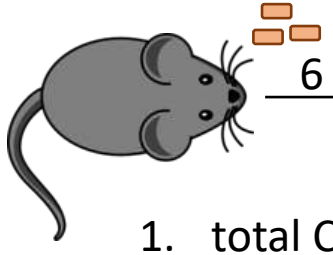
4 weeks



3 ug mRNA-LNP

6-8 weeks

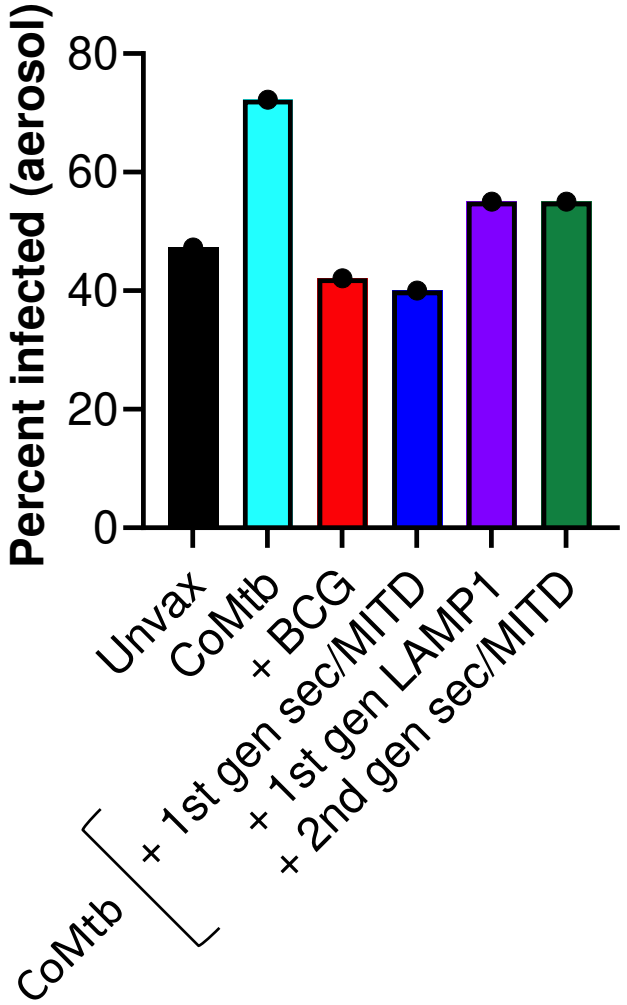
virulent *Mtb* challenge (1-3 CFU of a distinct strain)

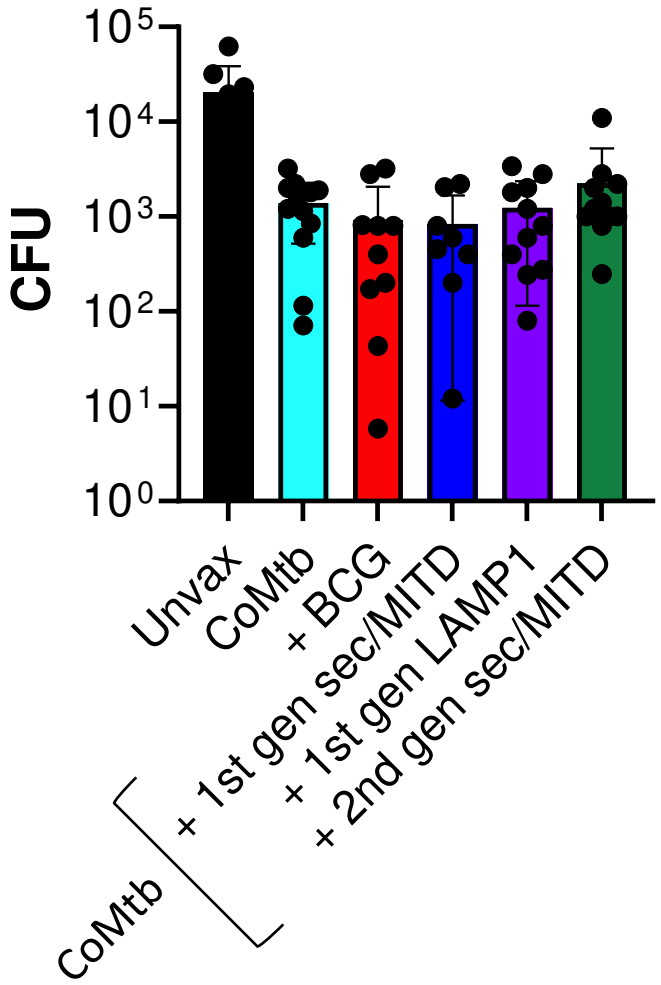


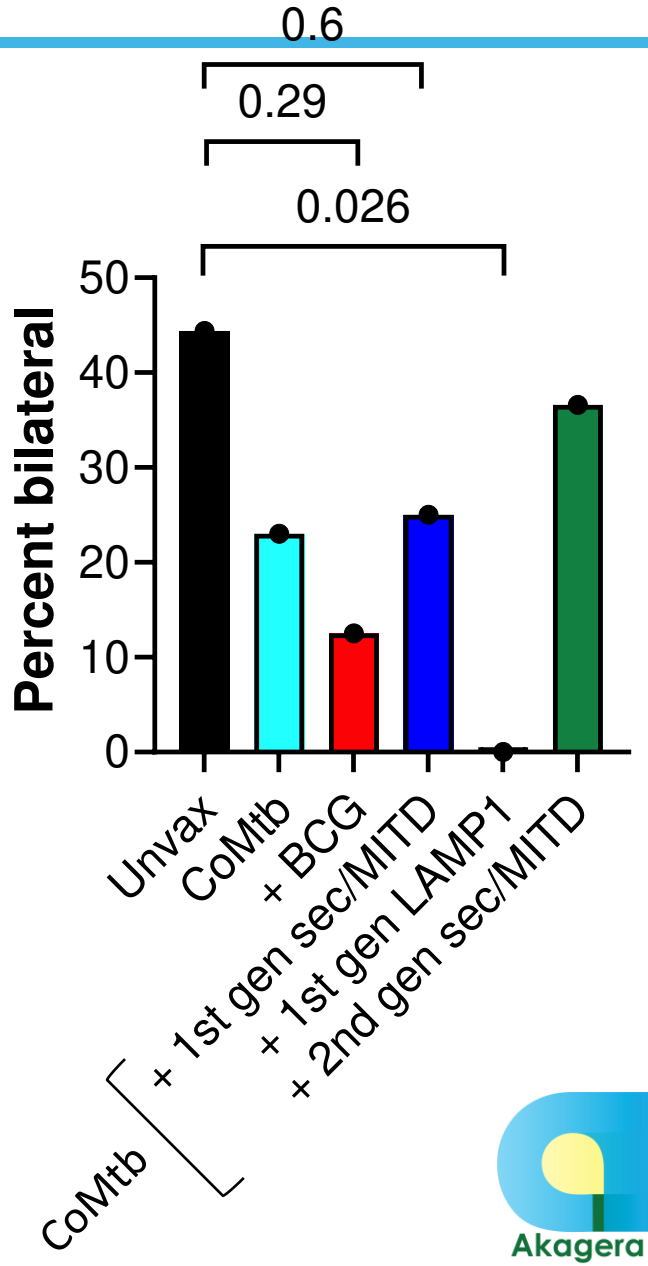
6 weeks

1. total CFU burden in lungs
2. bacterial dissemination between lung lobes
3. prevention of 2° infection
4. CFU in draining LNs

Therapeutic vaccination in a chronic CoMtb infection model







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- Mark Hayes
- Alex Koshkaryev
- Milton Quintanilla

Kevin Urdahl

- Courtney Plumlee
- Sara Cohen

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HOSPITAL · RESEARCH · FOUNDATION

Michael Gerner

- Ada de la Cruz

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