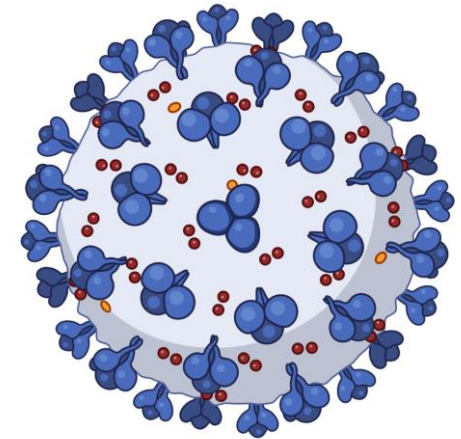


# The Future of T cell-focused vaccines

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Department of Immunology



LEIDEN  
DRUG DEVELOPMENT  
CONFERENCE

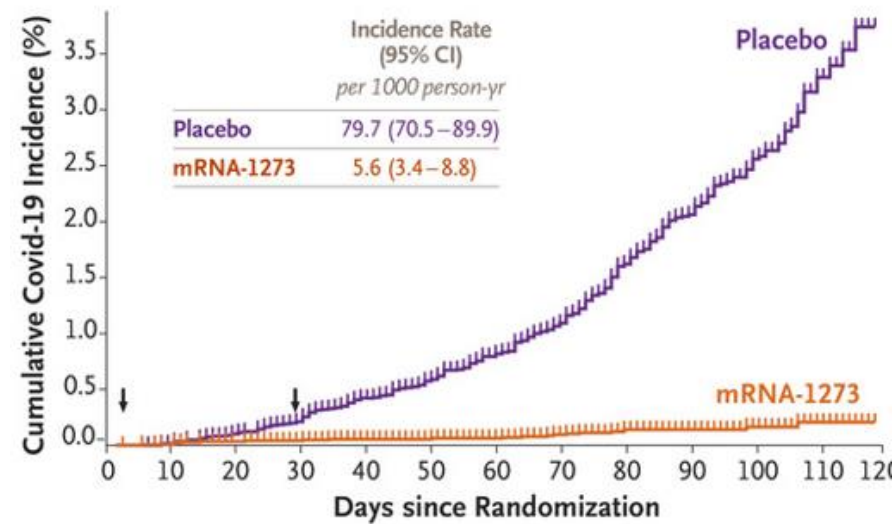
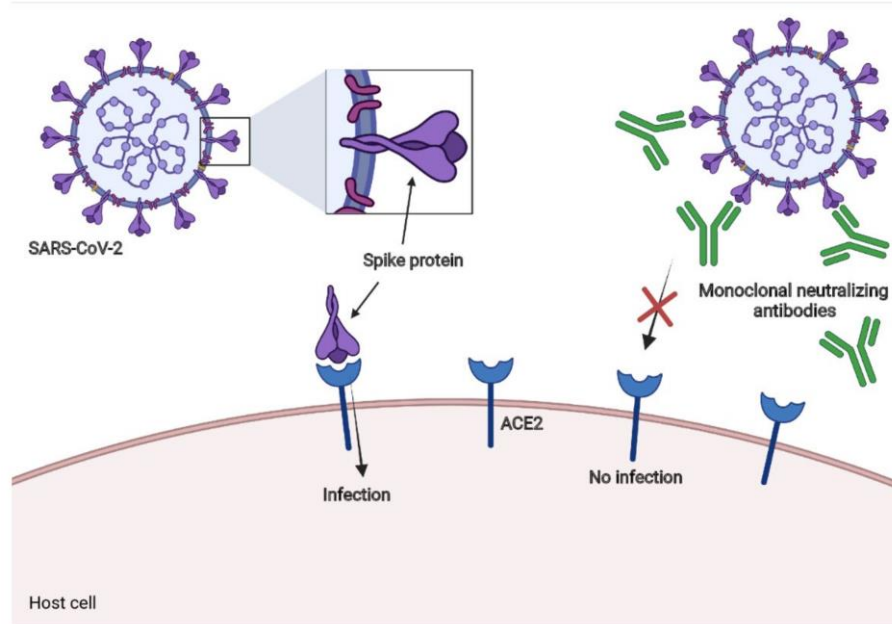
# Preventive vaccination makes use of immunological memory

Immunological Memory:

Memory B cells/ <u>Antibodies</u>	→	Correlates of protection
Memory T cells	→	Correlates of protection?

# Introduction

- COVID-19 pandemic caused by SARS-CoV-2 remains a global health emergency
- Vaccines eliciting neutralizing antibodies against Spike protein have shown high effectiveness



Baden et al. NEJM 2021

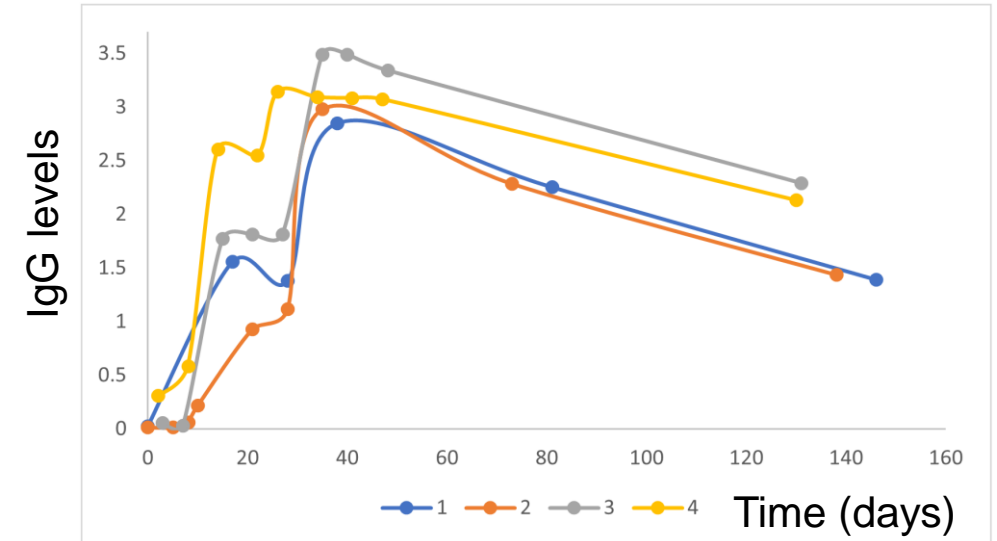
# Introduction

- The level of (neutralizing) antibodies declines after infection and vaccination

(Chia et al. Lancet Microbe 2021)

- At-risk patient groups exhibit lower humoral immunity after vaccination

(Herishanu et al. Blood 2021; Sattler et al. JCI 2021; Wadei et al. Am J. Transplant 2021)



- Mutation rate of SARS-CoV-2 is substantial → Omicron mutations in spike protein → decline in neutralizing antibody-mediated protection

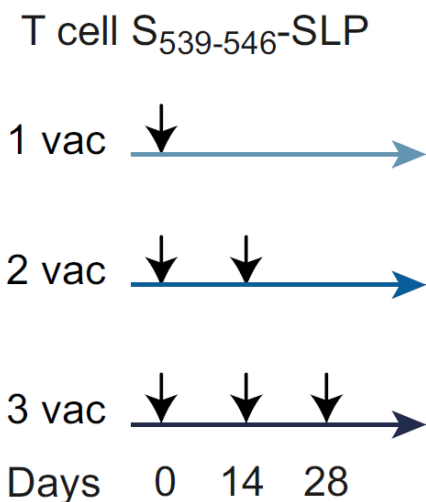
(Geurts van Kessel et al. Sci Immunol 2022)



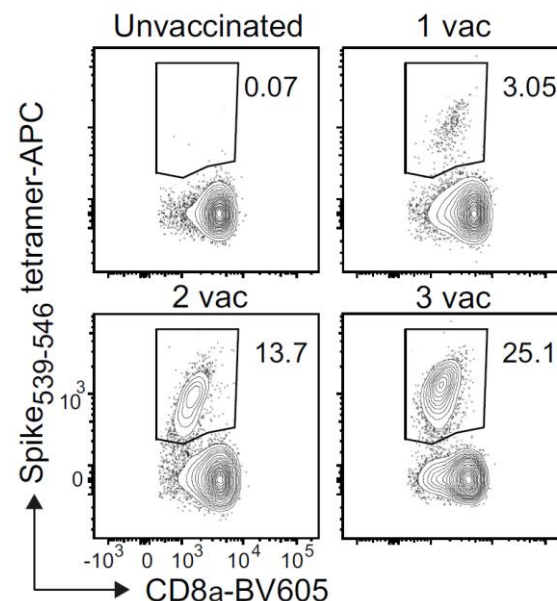
- SARS-CoV-2 specific T cell responses associate with reduced disease severity (Tan et al. Cell Rep 2021)
- T cell-focused vaccines can be directed to more conserved regions of the coronavirus → broad T cell-based cross-protection

**Can T cells protect against SARS-CoV-2 in the absence of neutralizing antibodies?**

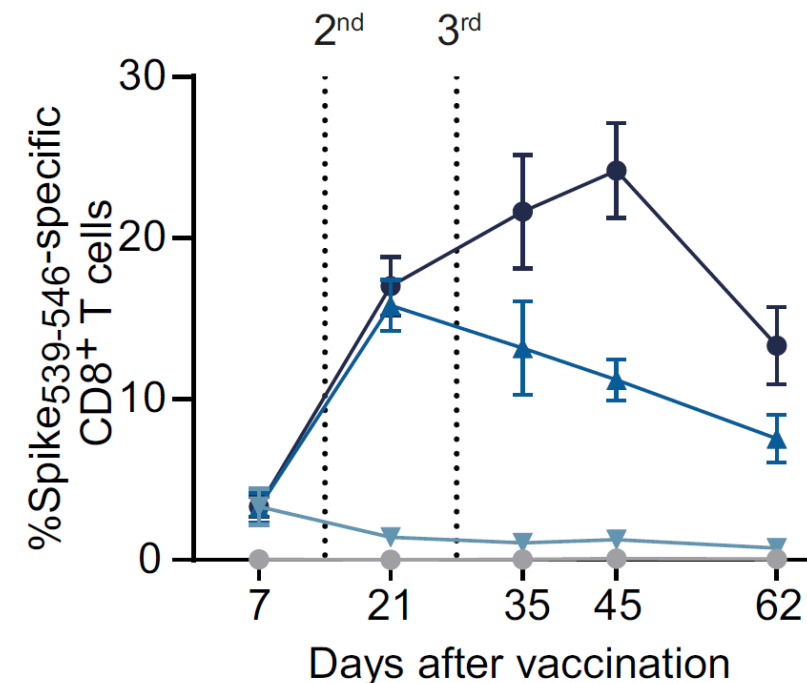
# Development of a vaccine eliciting an exclusive and protective CD8<sup>+</sup> T cell response against SARS-CoV-2



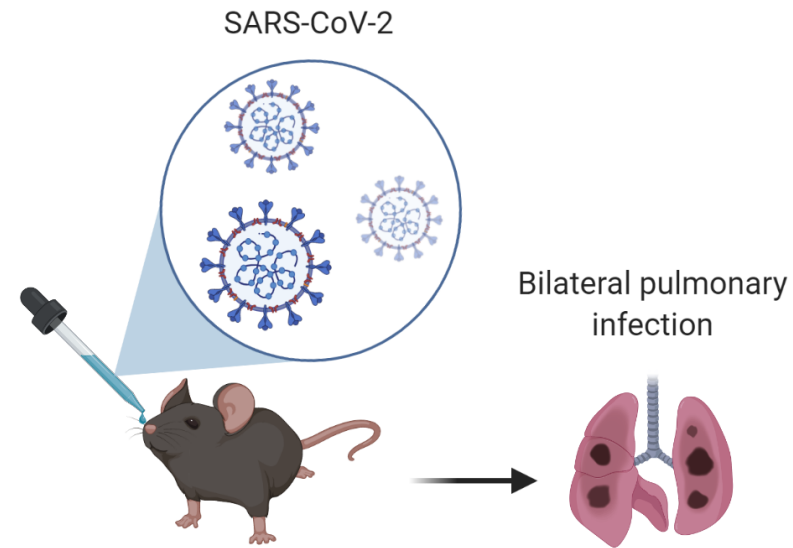
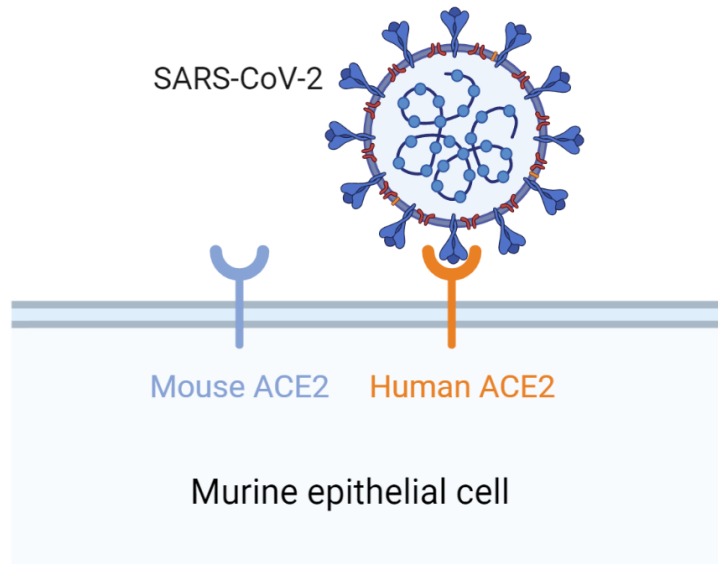
S.C., 100 ug SLP, 20 ug CpG  
IKNQCVN**FNF**NGLTGTGVLTESNK



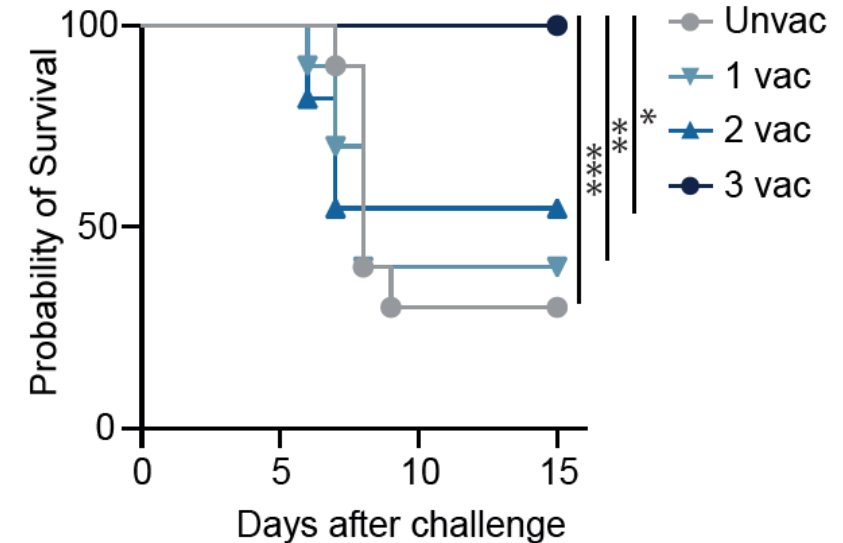
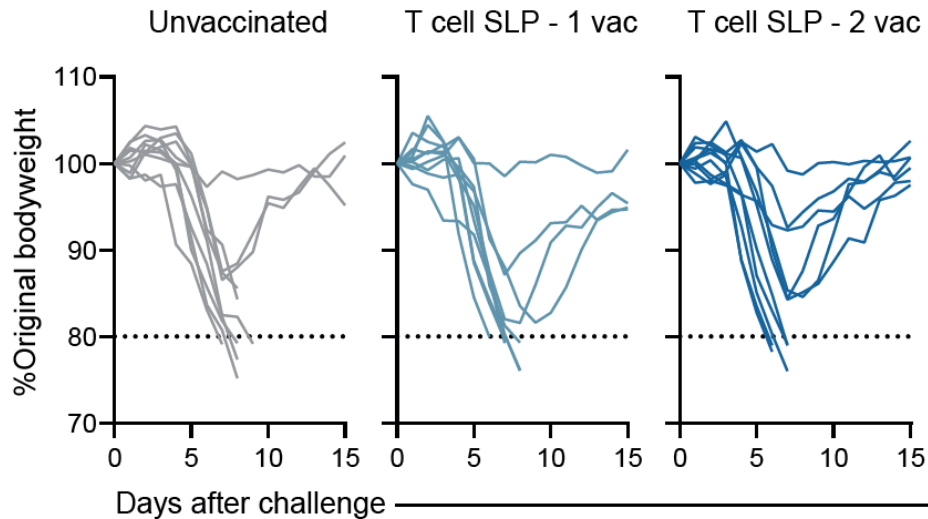
No induction of spike-specific antibodies  
or CD4<sup>+</sup> T cell responses



# K18-hACE2 transgenic mouse model for SARS-CoV-2 infection



# K18-hACE2 Tg mice are protected against SARS-CoV-2 by a 3<sup>rd</sup> T cell SLP vaccination

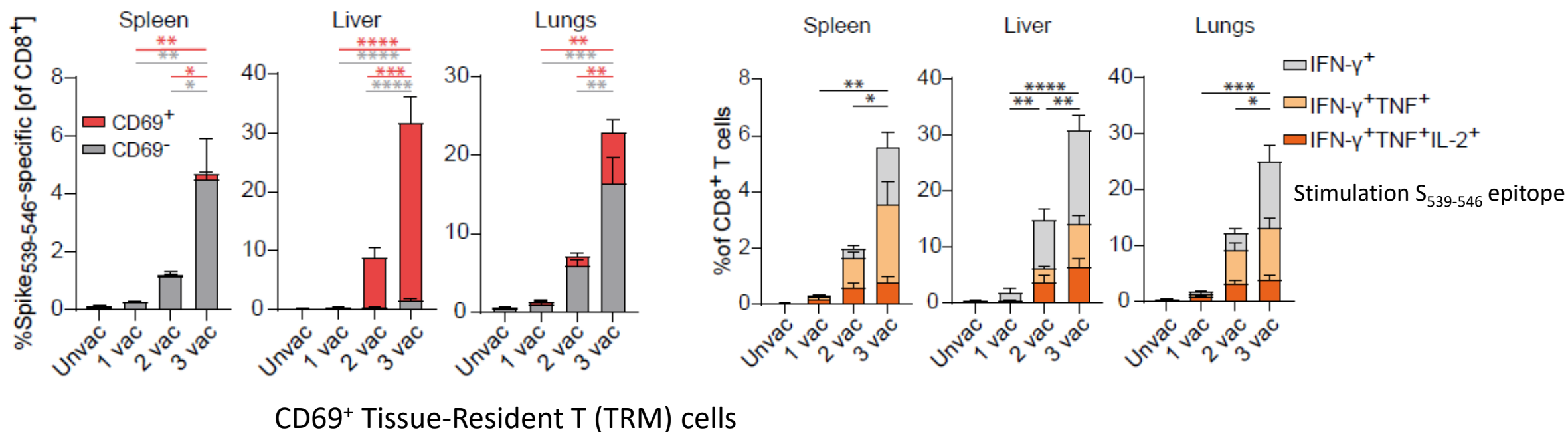


**What are the characteristics of this CD8<sup>+</sup> T cell mediated protection?**

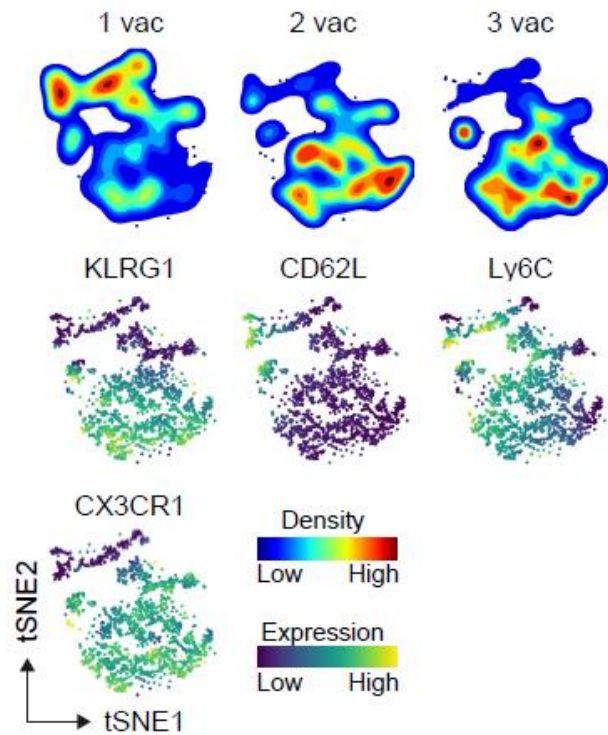
→ phenotypical & functional profiling of the antigen-specific CD8<sup>+</sup> T cells system-wide



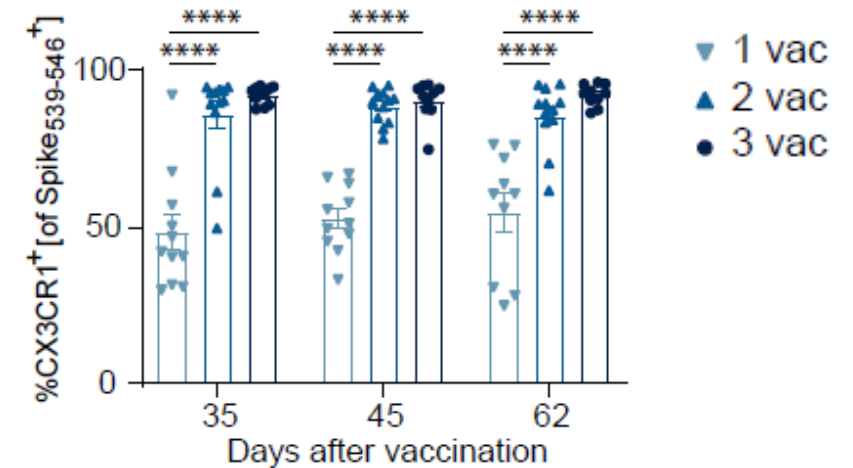
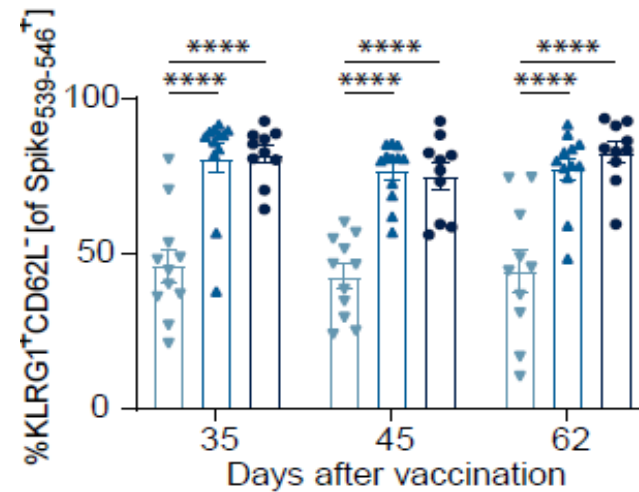
# Booster SLP vaccinations increase the magnitude of functional CD8<sup>+</sup> circulating and TRM cells



# Spike-specific CD8<sup>+</sup> T cells in blood acquire an effector memory phenotype after booster vaccinations

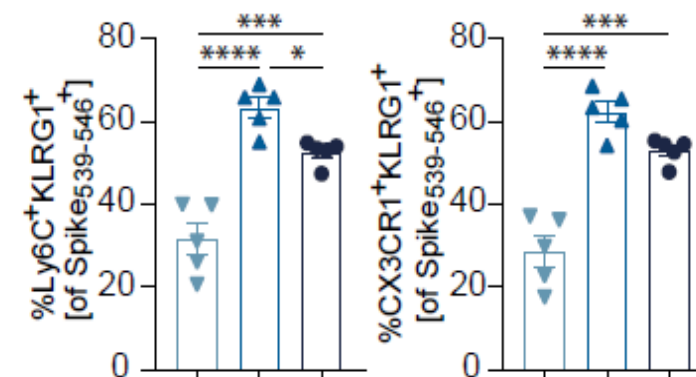
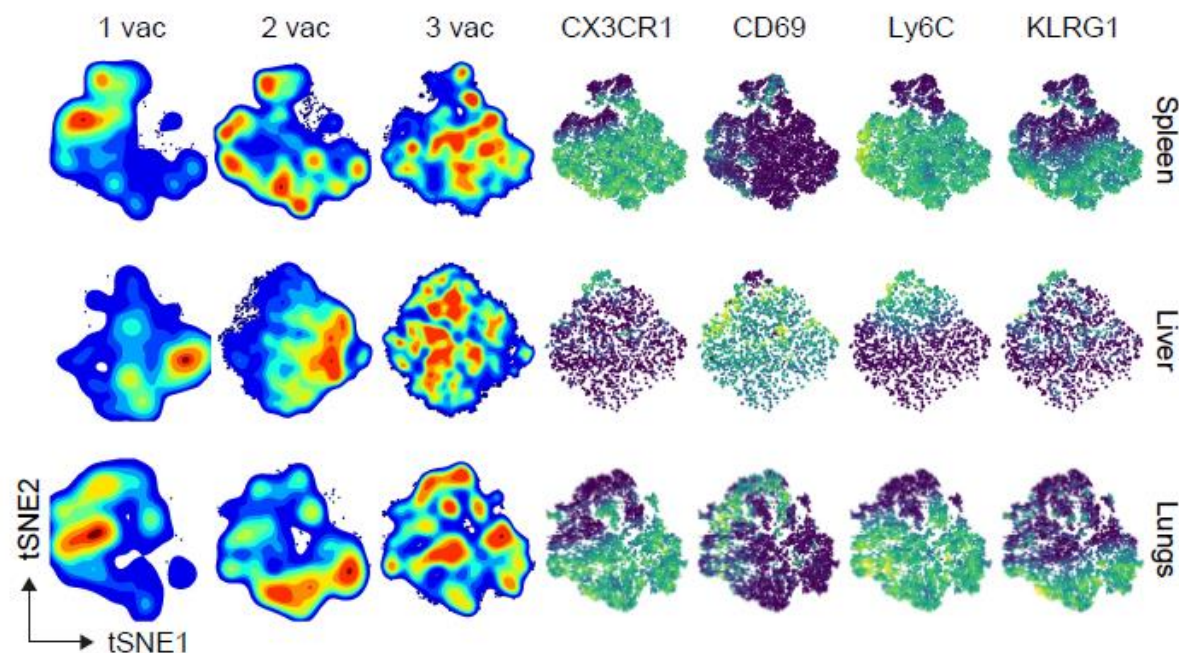


Blood – day 62



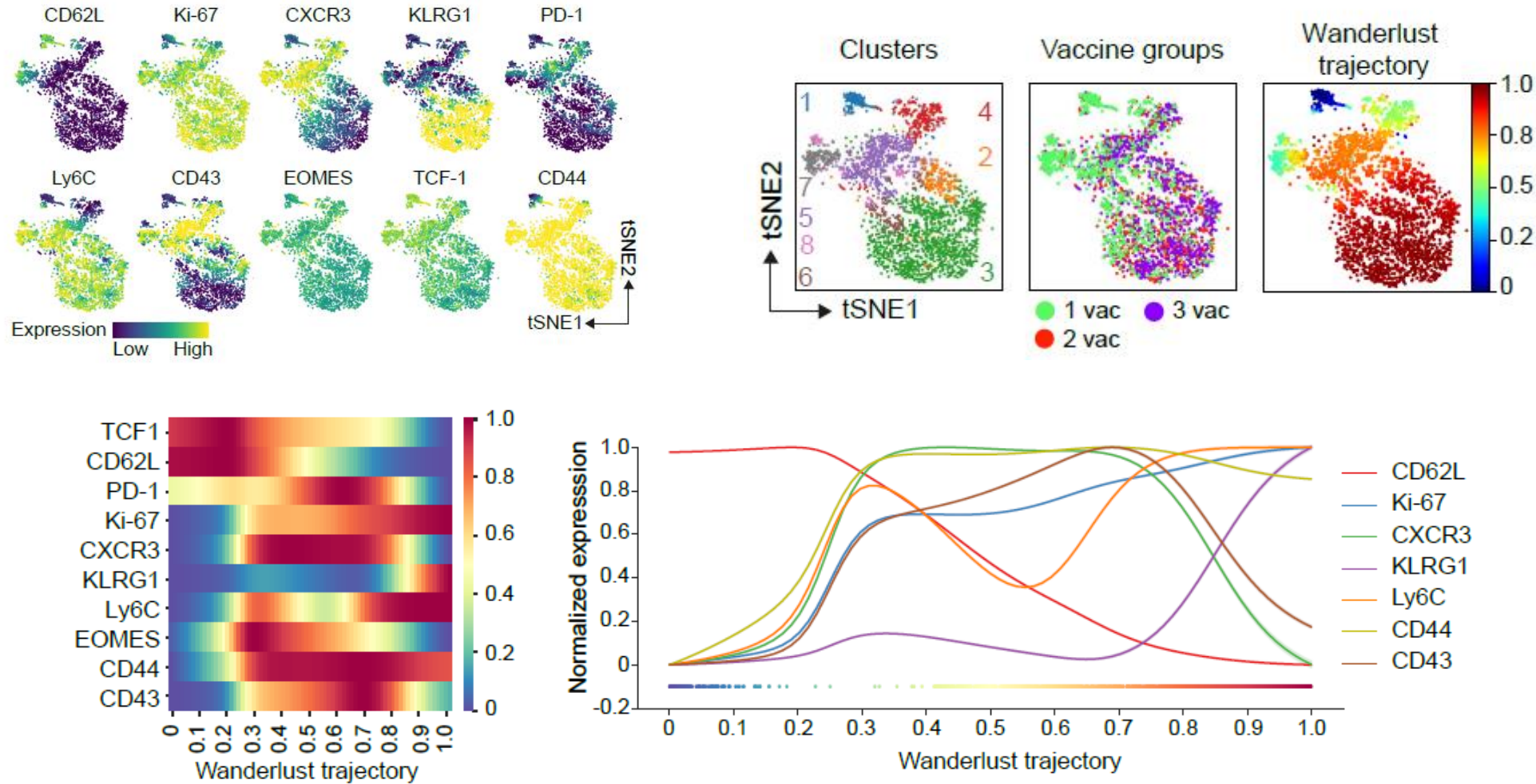
Blood – kinetics

# Spike-specific CD8<sup>+</sup> T cells in tissues acquire an effector memory phenotype after booster vaccinations



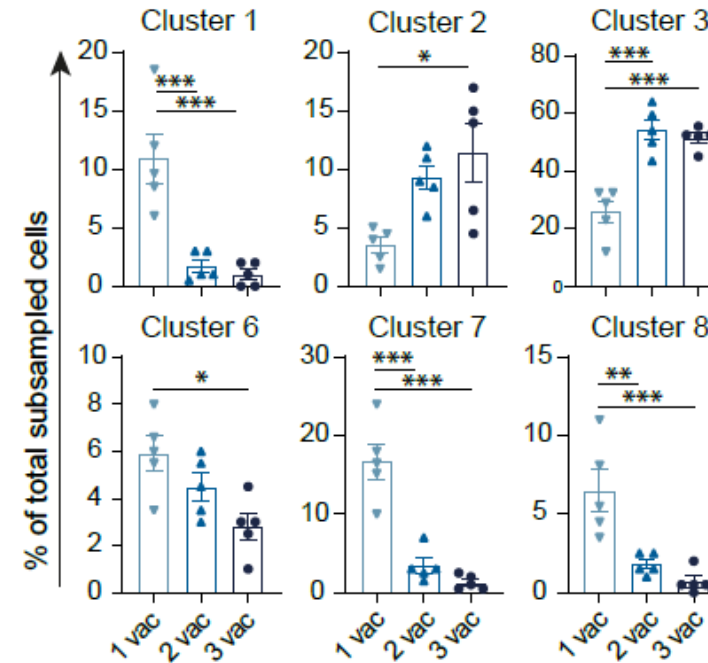
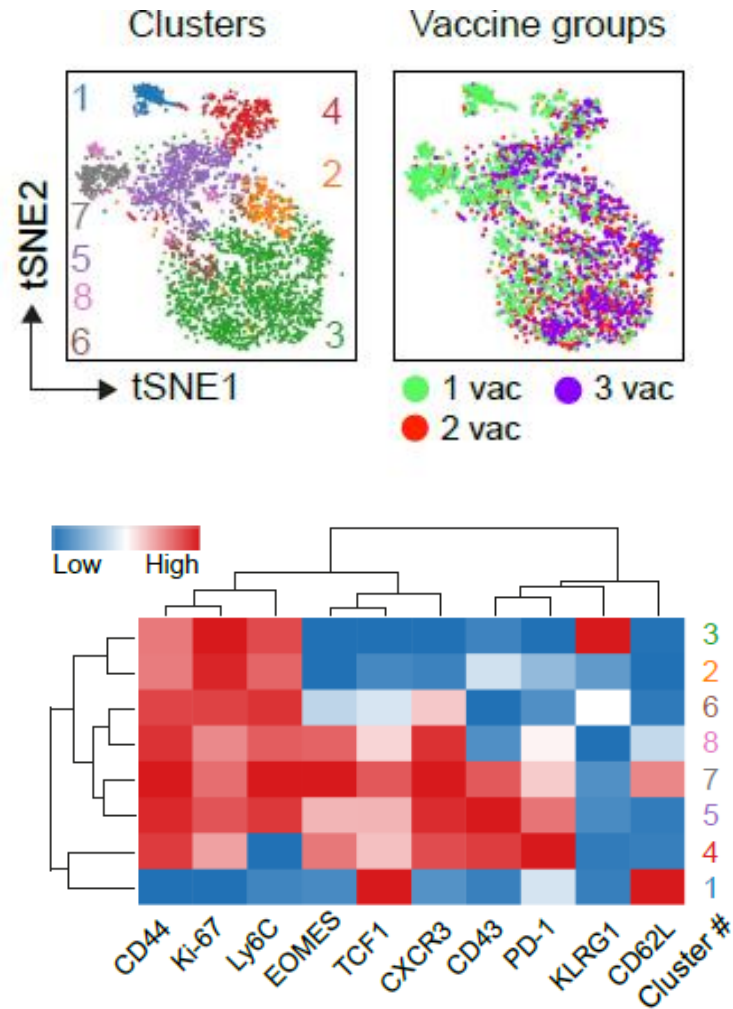


# Progressive differentiation of vaccine-specific CD8<sup>+</sup> T cells after booster vaccination





# Progressive differentiation of vaccine-specific CD8<sup>+</sup> T cells after booster vaccination



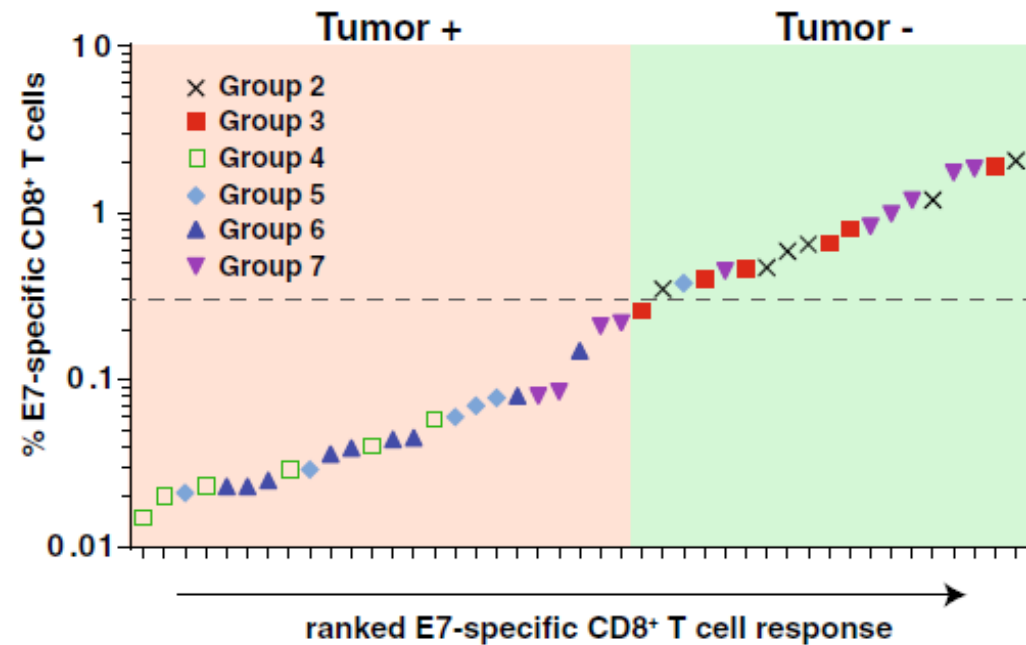
# Booster vaccinations eliciting CD8<sup>+</sup> T cell responses are a promising strategy against coronavirus-mediated disease independent of neutralizing antibodies

A third vaccination with a single CD8<sup>+</sup> T cell epitope protects against SARS-CoV-2 infection in the absence of neutralizing antibodies

- First booster (2nd vaccination): Differentiation of virus-specific CD8<sup>+</sup> T cells (effector-memory)
- Second booster (3rd vaccination):
  - Slightly altered differentiation > Induction of ex-T<sub>RM</sub> cells
  - Additional increase of functional virus-specific CD8<sup>+</sup> circulating and tissue-resident memory T (T<sub>RM</sub>) cells in blood, spleen, lungs and liver > Threshold for CD8<sup>+</sup> T cell-mediated protection?

# Defined thresholds of vaccine-specific CD8<sup>+</sup> T cell responses correlate to tumor protection

Viral vectors eliciting differential E7-specific CD8<sup>+</sup> T cell responses > differential tumor protection



Beyranvand Nejad et al. Journal for Immunotherapy of Cancer 2019

- Development of T cell-focused vaccines:  
as an addition to current vaccine platforms or addition of CD8 T cell epitopes to current vaccine platforms?
- What is the contribution of CD8<sup>+</sup> T cell responses in presence of neutralizing antibodies?



# Acknowledgments

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# SLP vaccination with a single epitope solely induces a CD8 T cell response

- No spike-specific antibodies found in serum
- No cytokine-producing CD4<sup>+</sup> T cells upon peptide stimulation of splenocytes

