

Tumor-specific cytolytic CD4 T cells mediate protective immunity against human cancer



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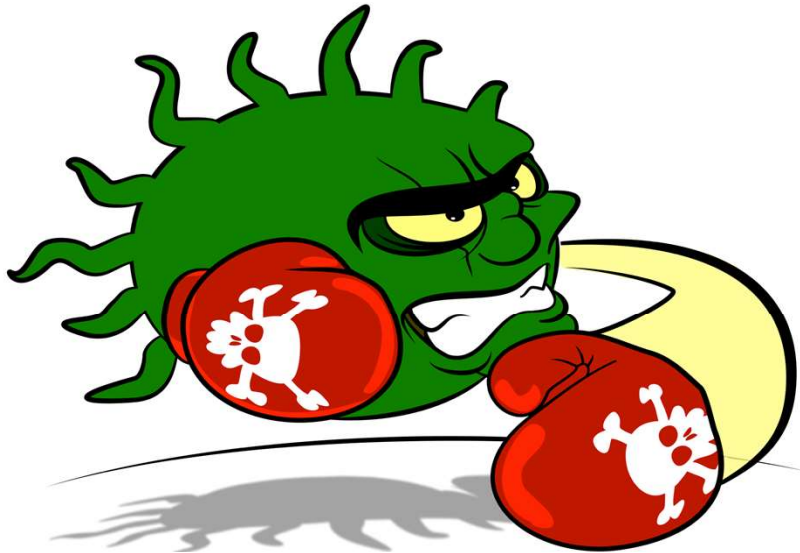
14.11.2020

Current paradigm: the main effectors in anti-tumor immunity

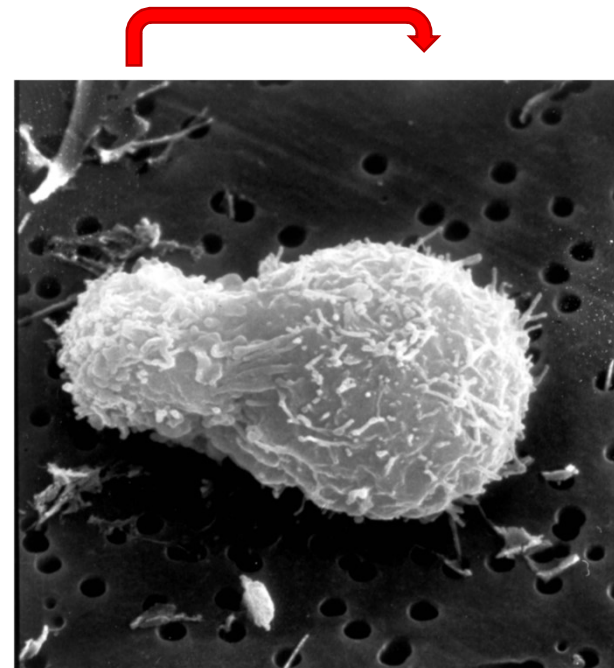
Direct Lysis (Granzymes, Perforin)

FasL

IFN γ , TNF α

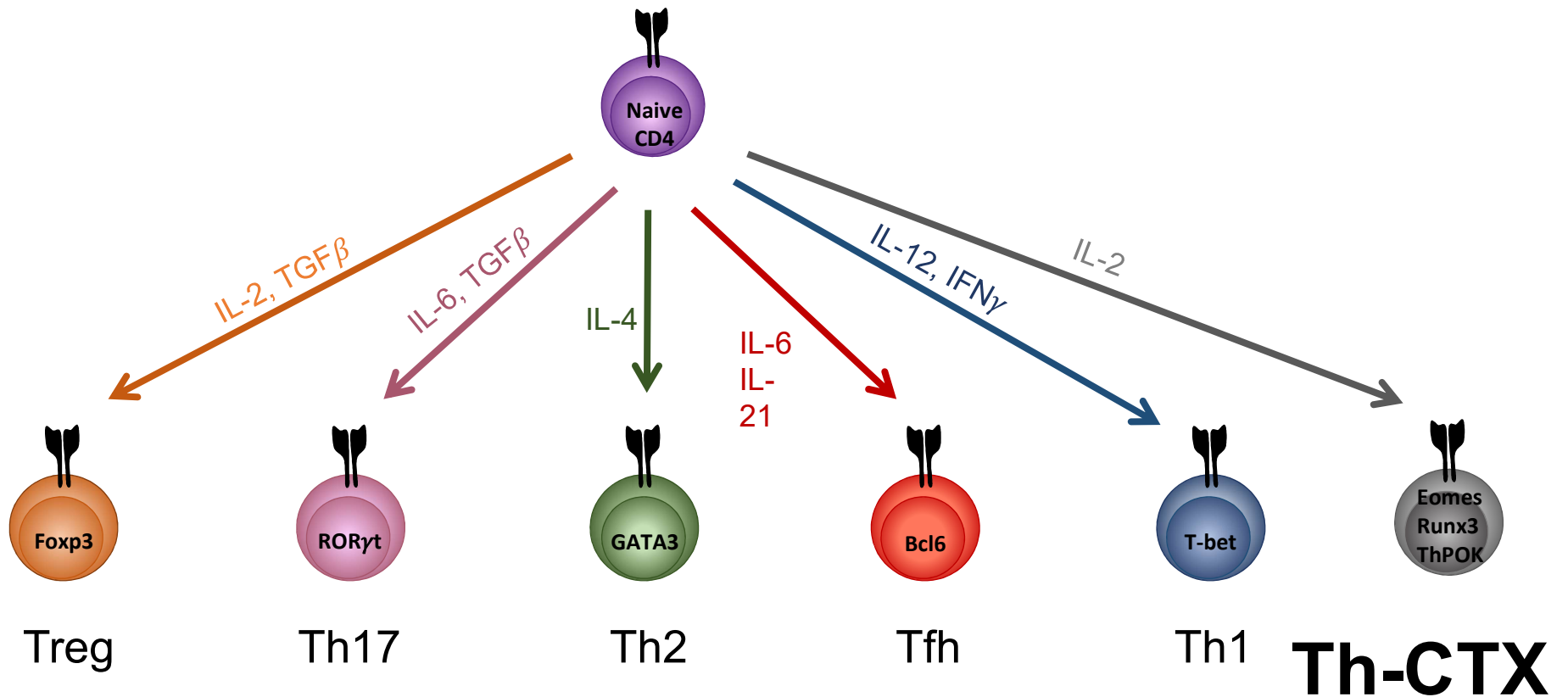


Cytotoxic CD8 T cells



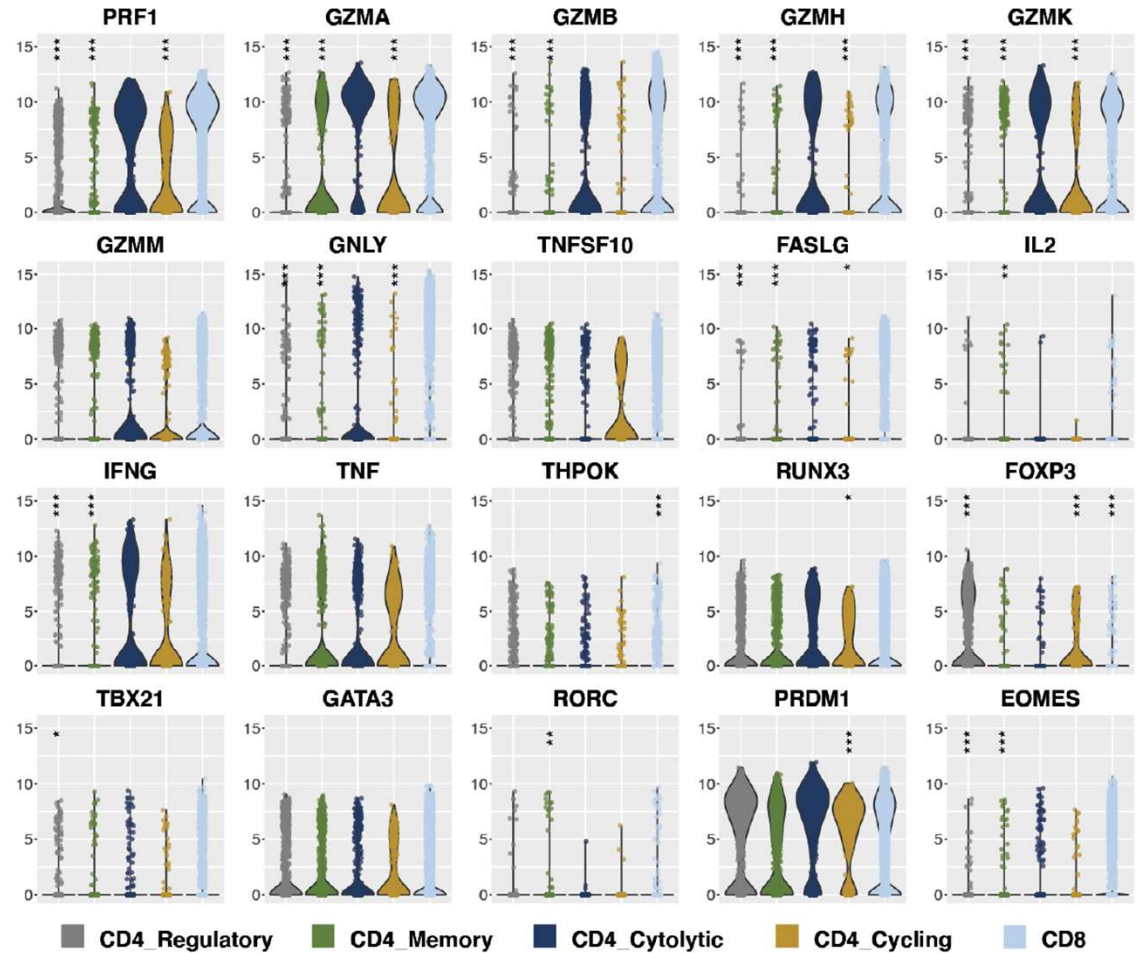
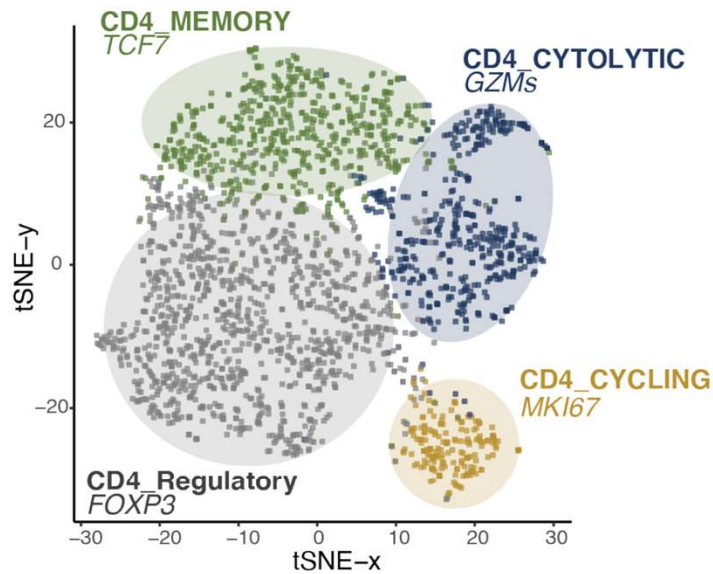
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Helper and cytotoxic CD4 T cell subsets



What about Th-CTX in cancer patients?

The transcriptomic signature of Th-CTX in cancer patients

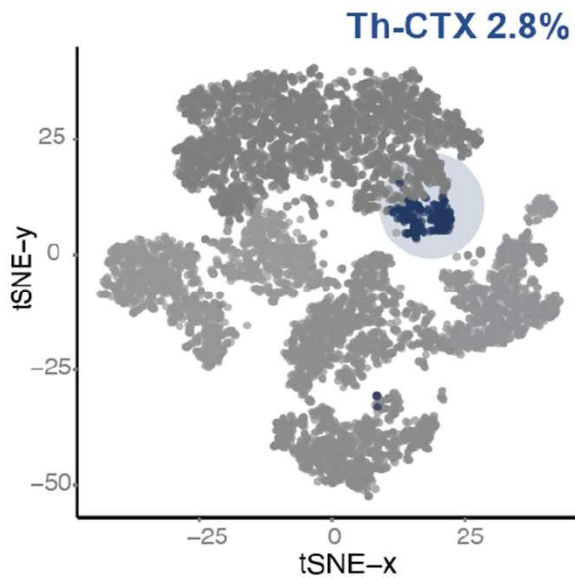


Cachot et al, under revision

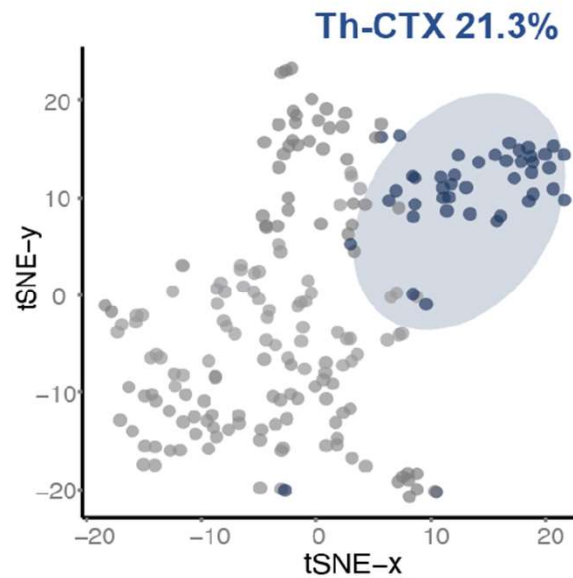
Melanoma patients

The transcriptomic signature of Th-CTX in cancer patients

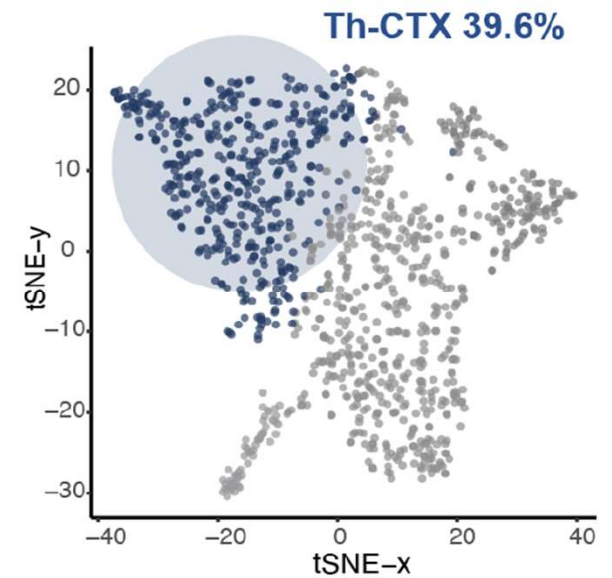
Breast cancer, n=3



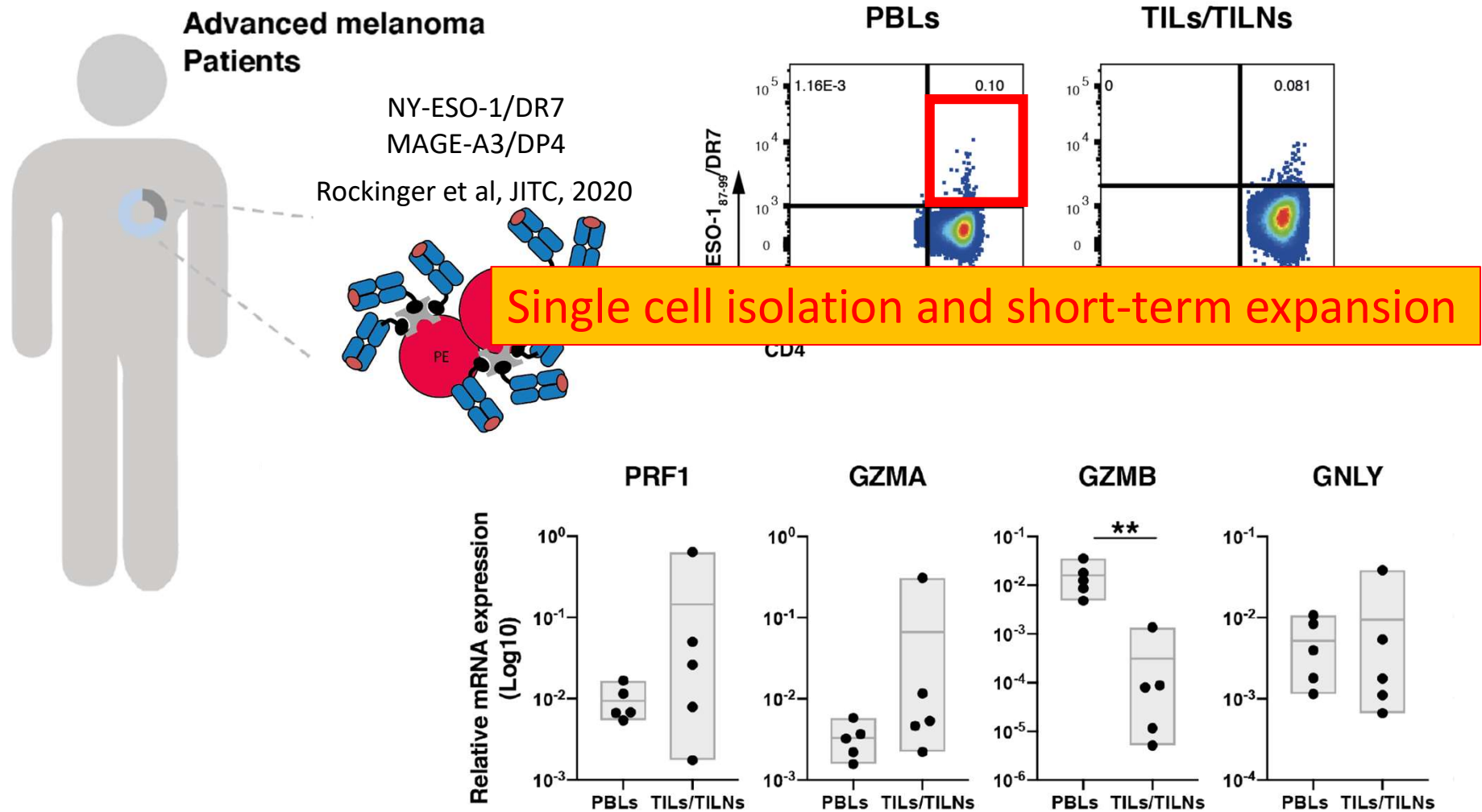
Head and Neck cancer, n=18



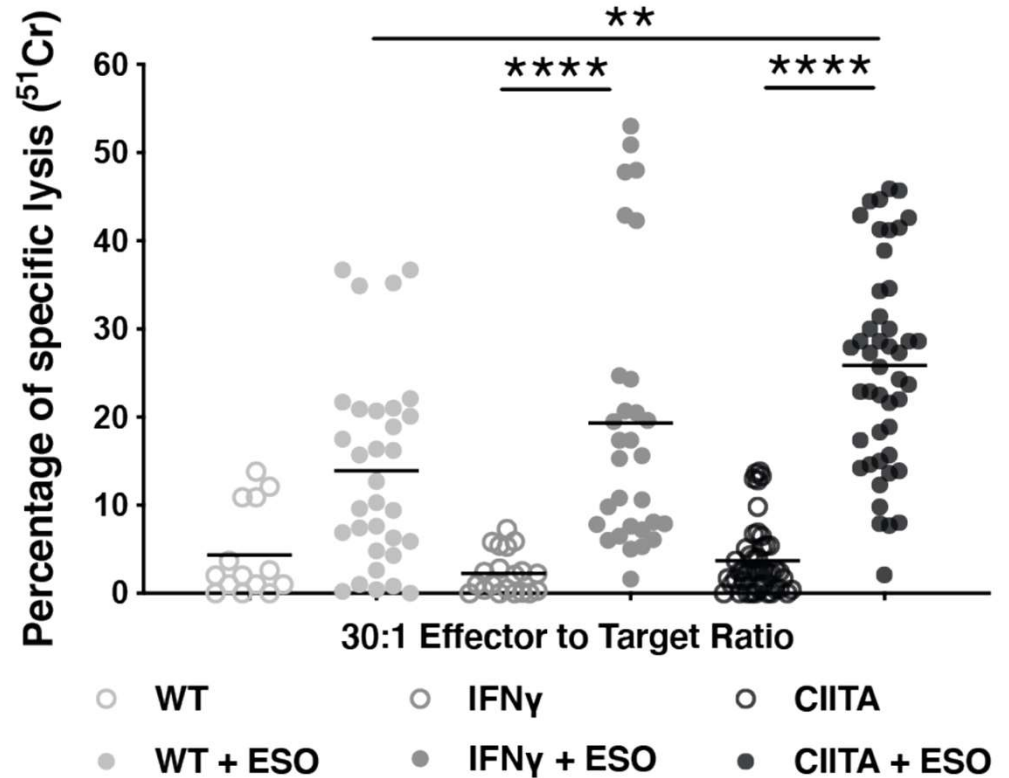
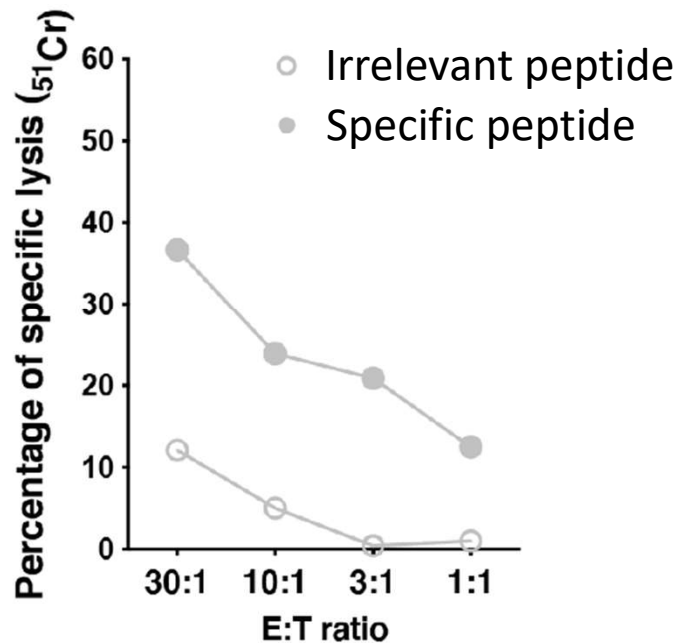
Liver cancer, n=6



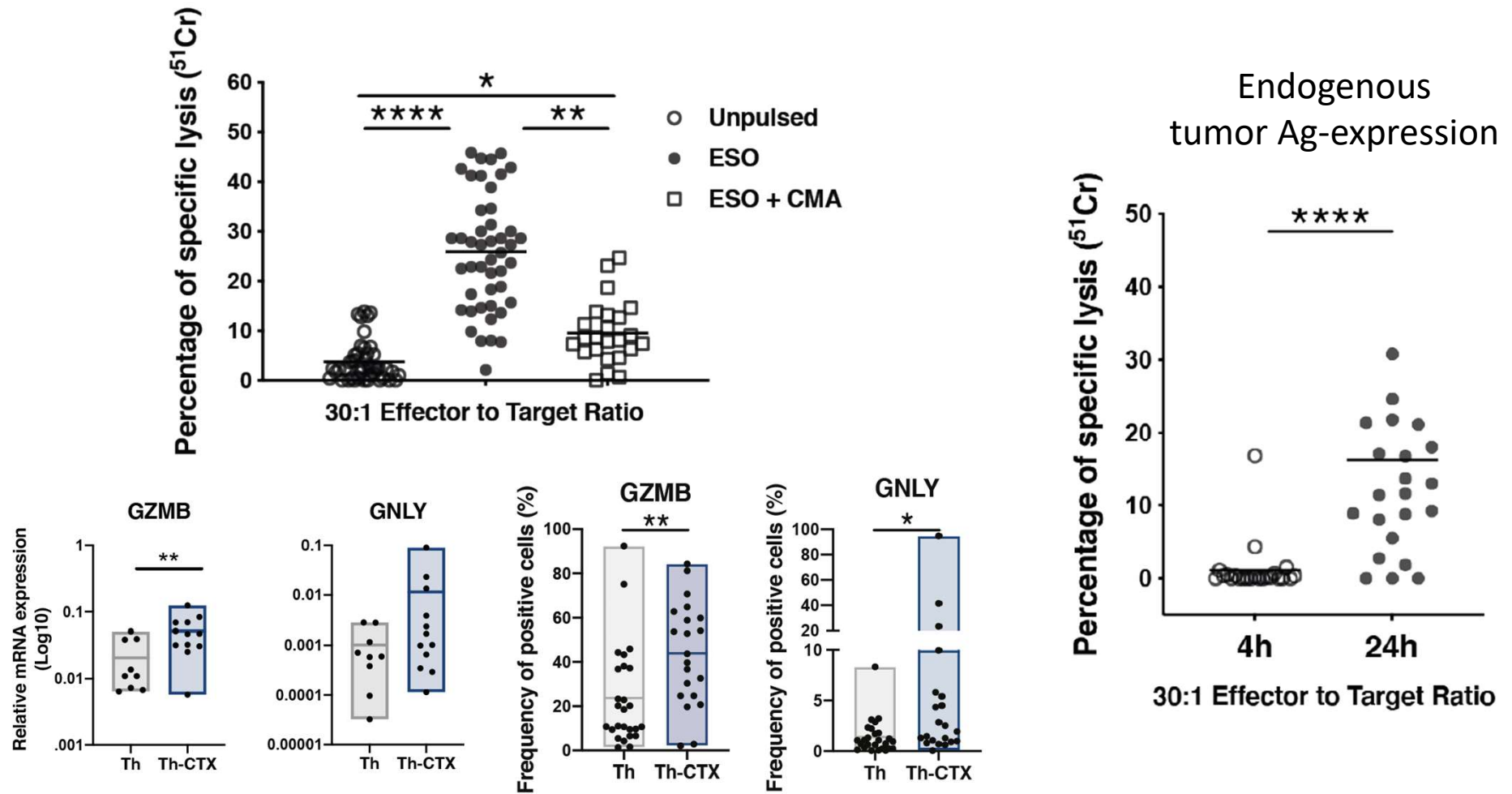
Ex-vivo tumor-specific Th-CTX in cancer patients



Tumor-specific Th-CTX cells are cytotoxic in cancer patients

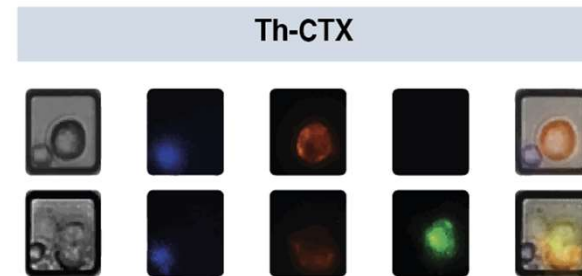
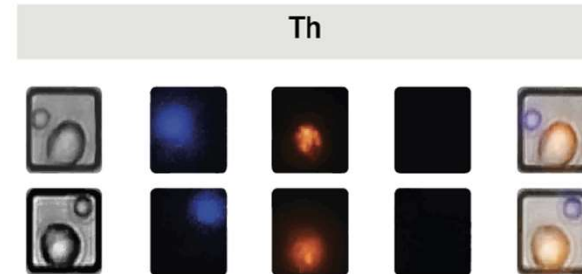
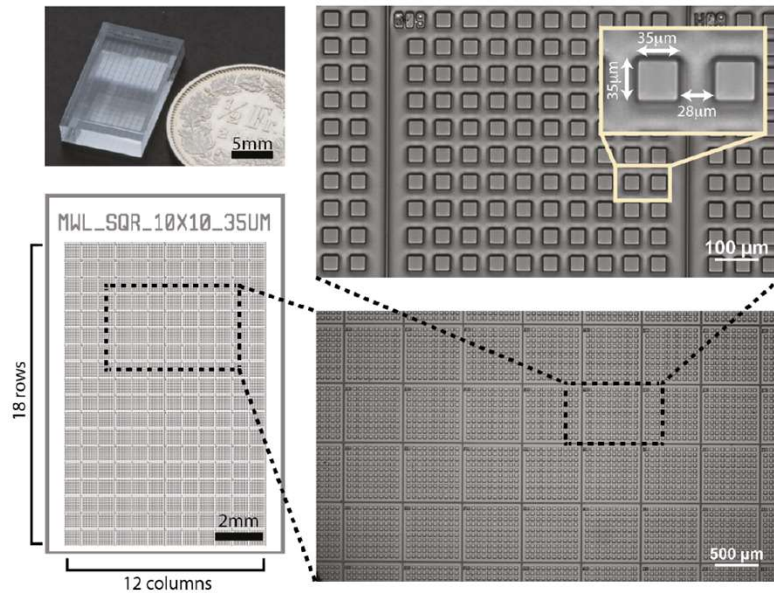


Tumor-specific Th-CTX cells are cytotoxic in cancer patients



CMA : Concanamycin A

Zoom-in : Single cell cytotoxicity



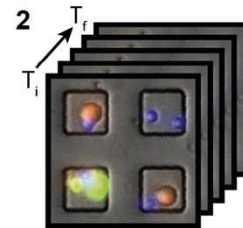
■ = T cell
■ = Tumor cell
■ = Dying cell

1 Network training

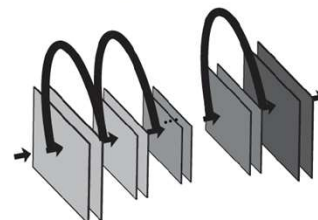
Extract frames to label

Train DNN

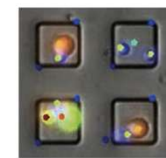
Deconvolutional layers



Input:
Time-lapse images



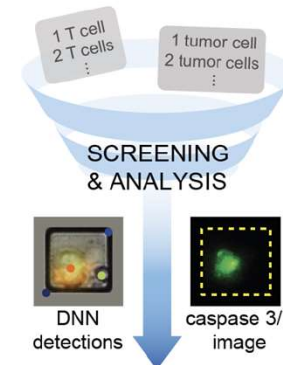
Deep Neural Network
(DeepLabCut 2.2)



Output:
feature coordinates

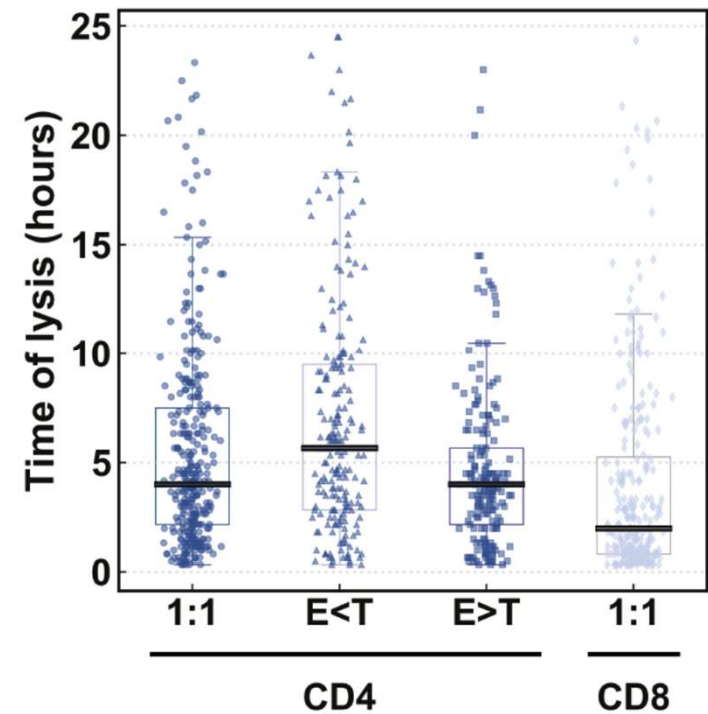
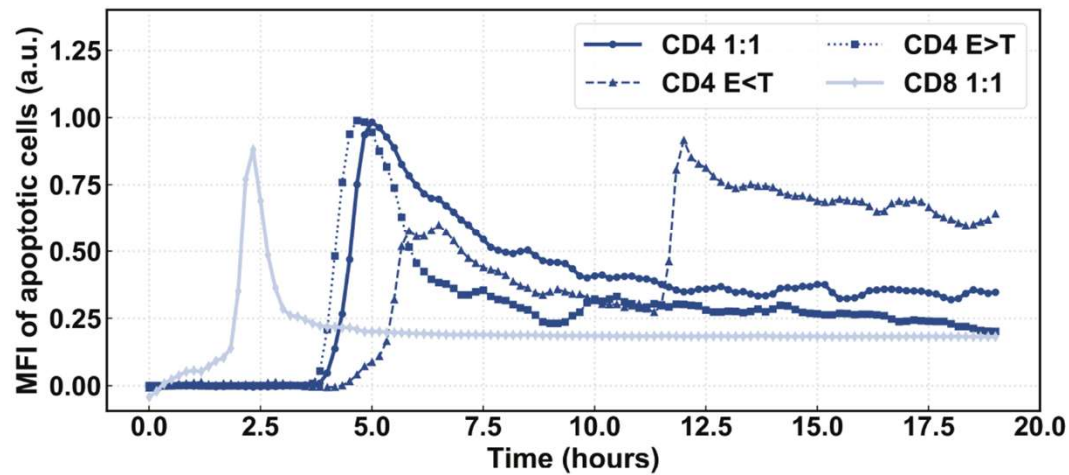
- Lower left corner
- Upper right corner
- Alive tumor cell
- Alive T cell
- Lysed tumor cell
- Lysed T cell

3

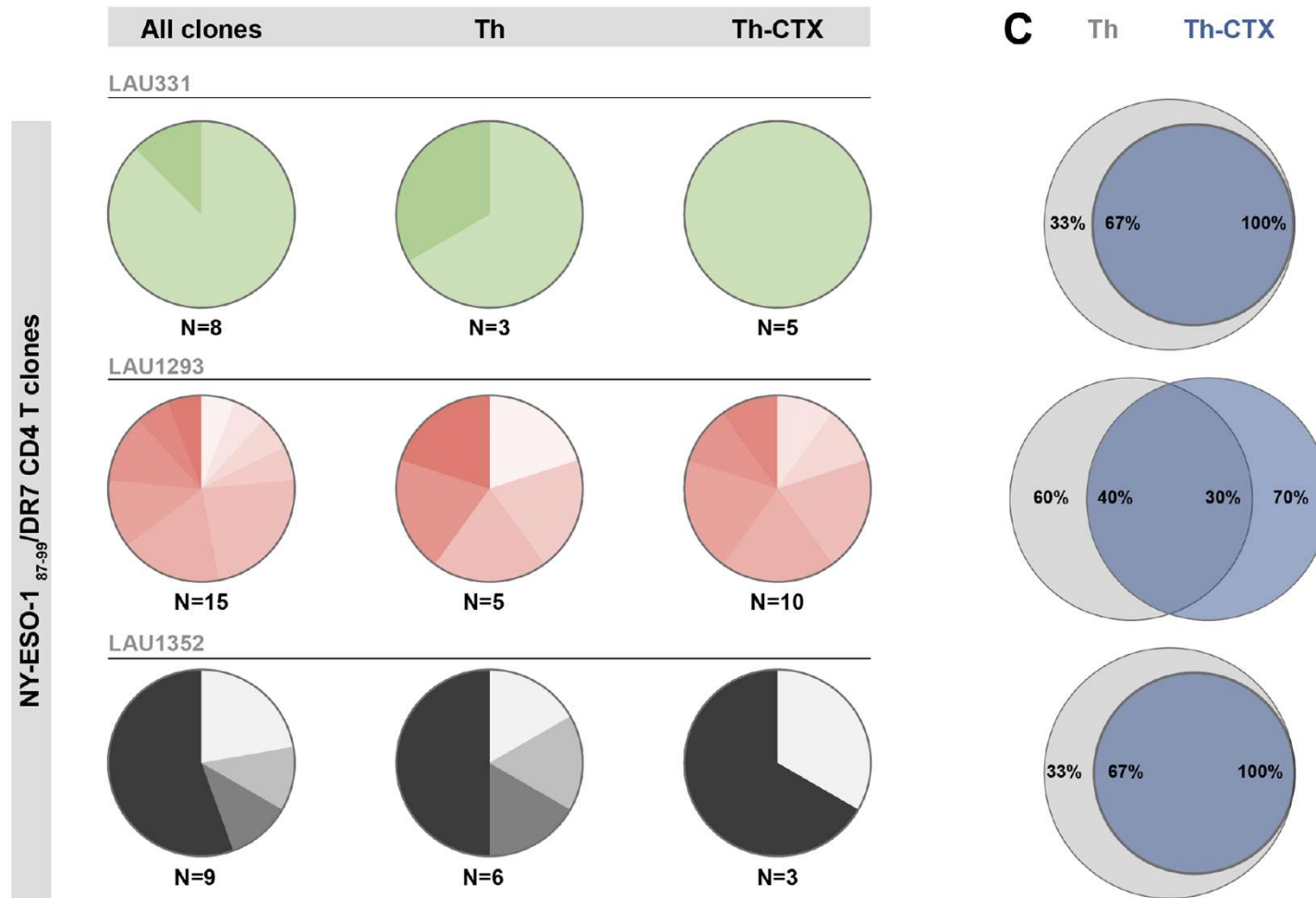


- ✓ Lysis kinetics
- ✓ Percentage of lysis
- ✓ Time of lysis

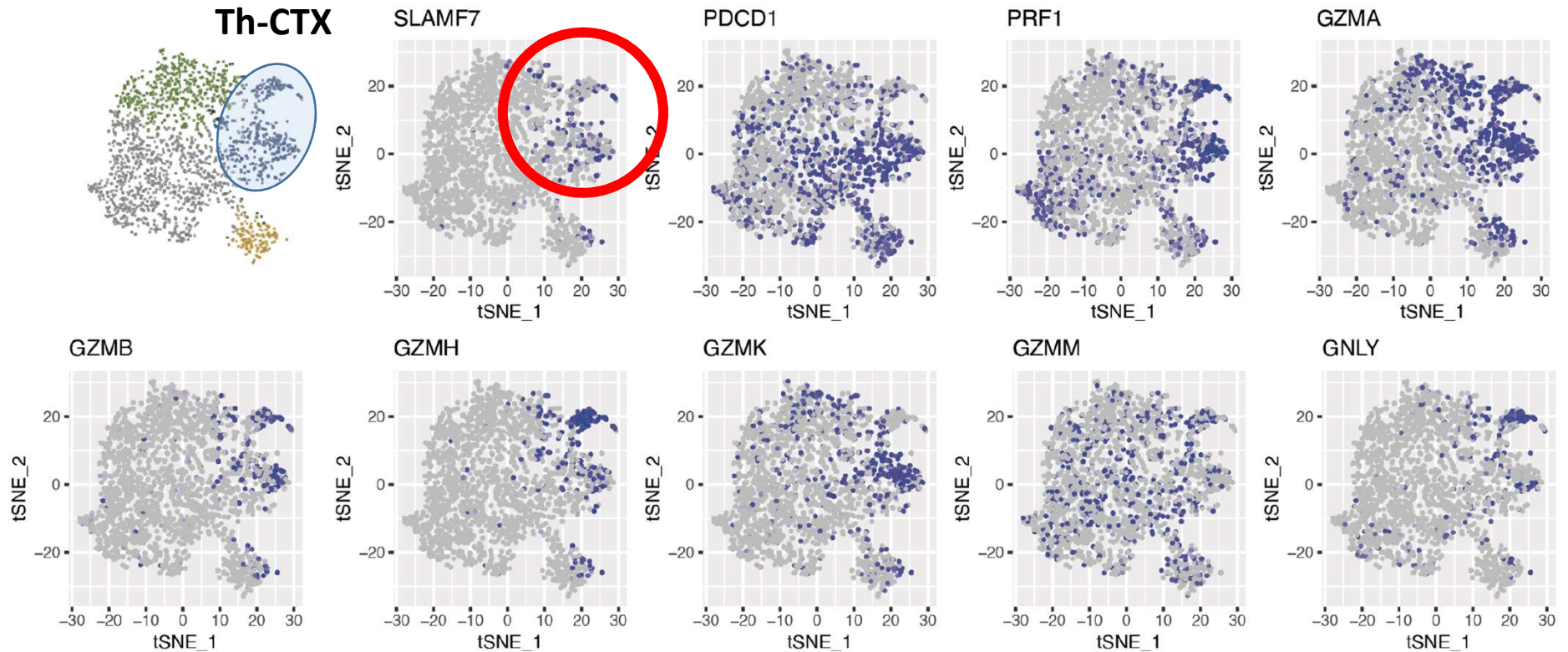
Tumor-specific CD4 T cells kill with delayed kinetics



Key attributes of cytotoxic tumor-specific CD4 T cells: TCR?



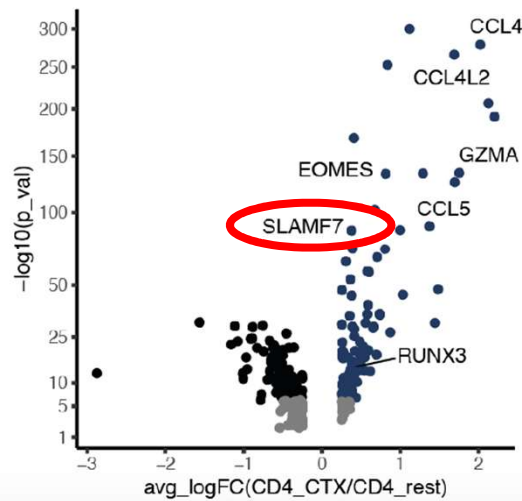
Key attributes of cytotoxic tumor-specific CD4 T cells: SLAMF7



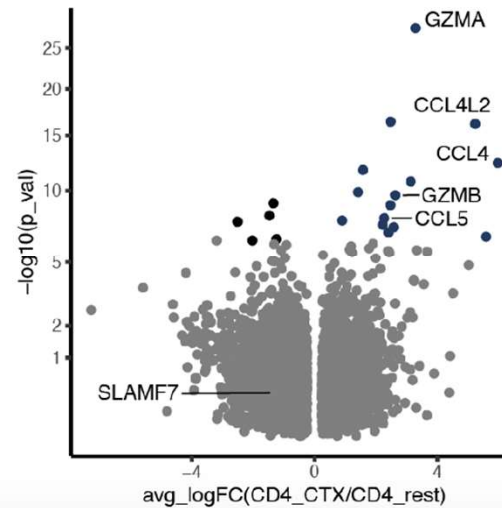
Melanoma patients

Key attributes of cytotoxic tumor-specific CD4 T cells: SLAMF7

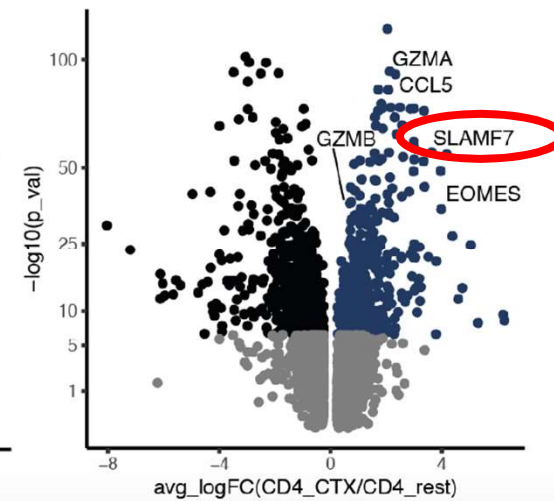
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Head and Neck cancer, n=18

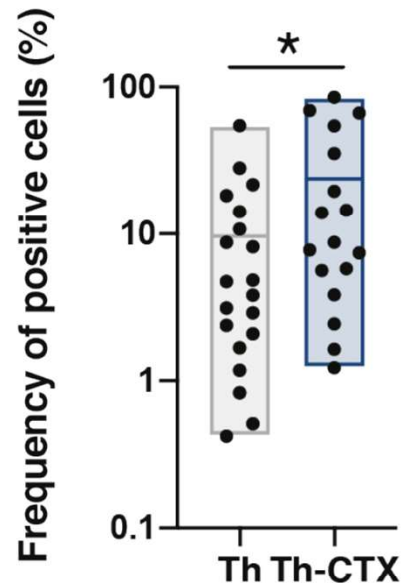
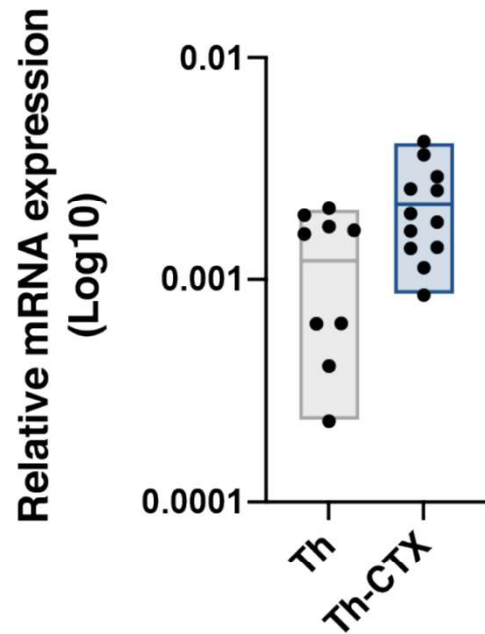


Liver cancer, n=6

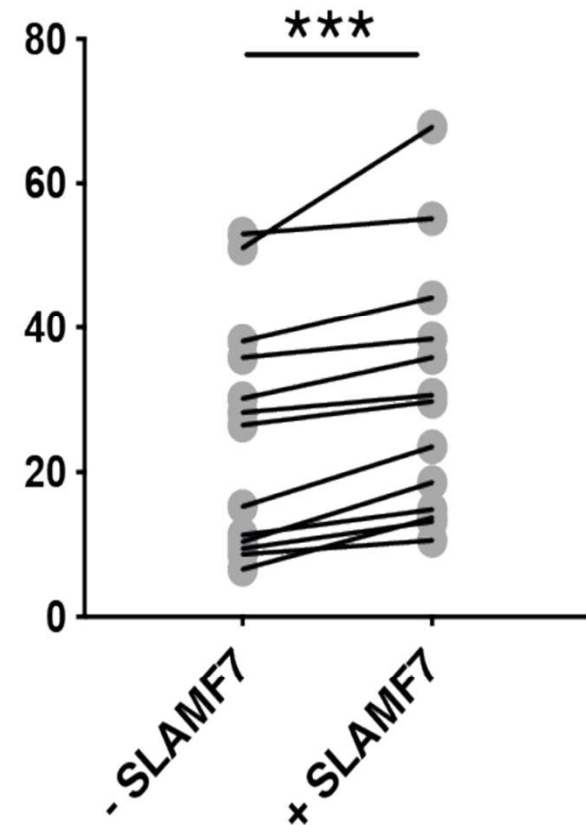


Agonistic triggering of SLAMF7 unleashes cytotoxic functions

SLAMF7 in tumor-specific CD4 T cells

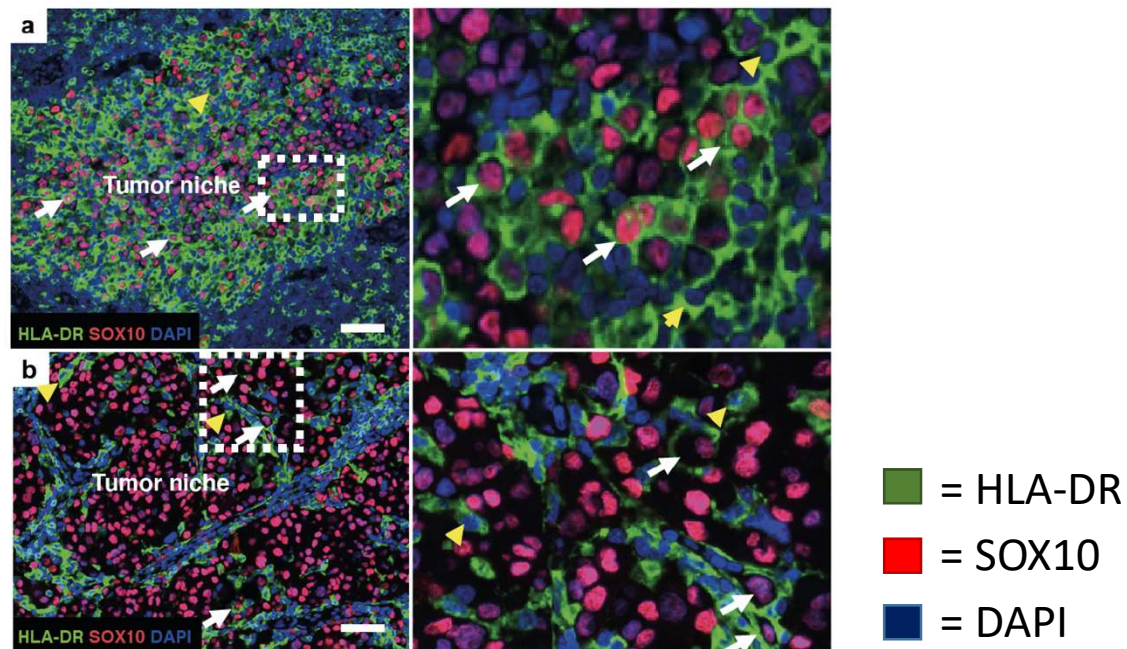


mAb SLAMF7



Conclusions

- Frequent existence of fully active tumor-specific cytotoxic CD4 T cells in cancer patients
- SLAMF7 as a therapeutically targetable molecule directly regulating CD4 T cell cytotoxicity
- Potential of targeting Th-CTX in cancer immunotherapy



Acknowledgments

Targeting of Cytokine Secreting Lymphocyte (TCSL) Group



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HELMUT HORTEN STIFTUNG

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