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Phenotypic Correlates of Adoptive Cell Therapy Response in Melanoma

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I have no financial conflicts of interest

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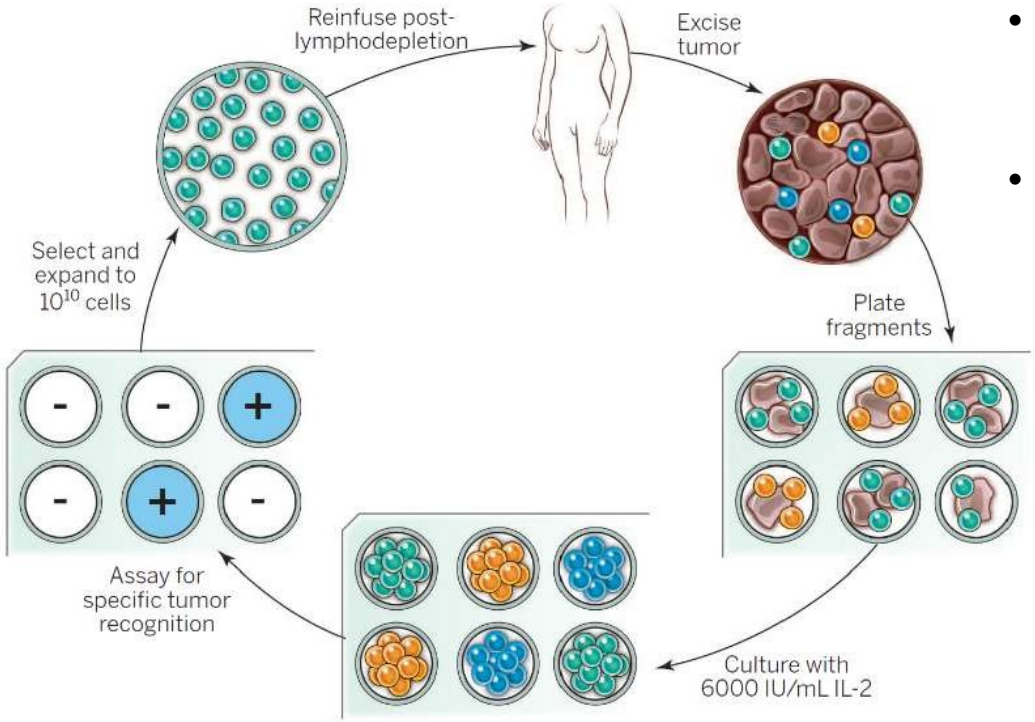
Adoptive Cell Therapy using TILs can mediate complete tumor regression in metastatic human cancers



Rosenberg SA and Restifo NP. *Science*. 2015

- ORR for TIL-ACT in ICB-naïve Melanoma ~ 55%
  (Goff SL et al, *JCO*, 2016)

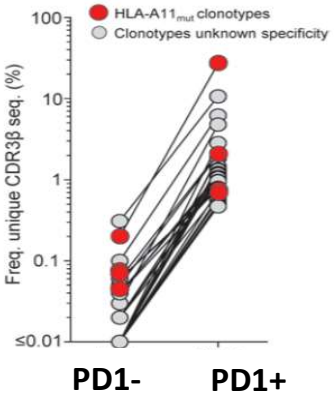
- Preliminary evidence of TIL-ACT mediating complete tumor regressions in epithelial cancers
  (Tran et al, *NEJM*, 2016, *Science*, 2014,
  Zacharakis et al, *Nature Medicine*, 2018)

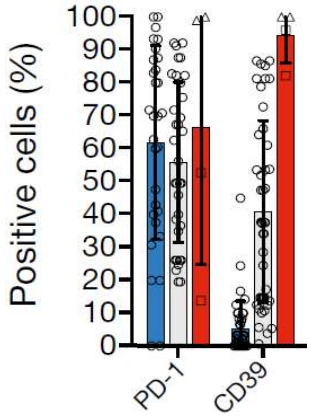
<u>Goal is to extend TIL-ACT to "immunologically tough" metastatic tumors</u>

ICB-refractory Melanoma (~20% ORR to TIL-ACT, unpublished)
Epithelial cancers in general have low immunotherapy response

Which T cell phenotypes are associated with immunotherapy response?

Anti-tumor TILs are generally defined by expression of exhaustion markers PD1, CD39….





Gros et al, JCO, 2014

(Neoantigen-specific in **red**) Simoni et al, Nature, 2018
(HPV-specific) Krishna et al, Cancer Research 2018
(Neoantigen) Scheper et al, Nature Medicine, 2019
(Tumor) Duhen et al, Cancer Immunology Research 2018

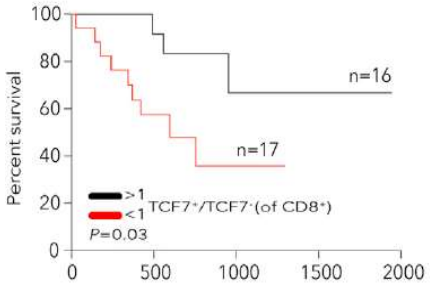
CD39- TILs are thought to be “bystander” T cells (**blue**)

.. Memory T cell phenotypes have been suggested in immunotherapy response in both ICB and ACT

In ACT, CD27+ T cells in infusion product and TIL-persistence

Rosenberg SA et al, Clinical Cancer Research, 2011

In ICB, CD39- TIM3- TCF7^{high} melanoma TILs by scRNA



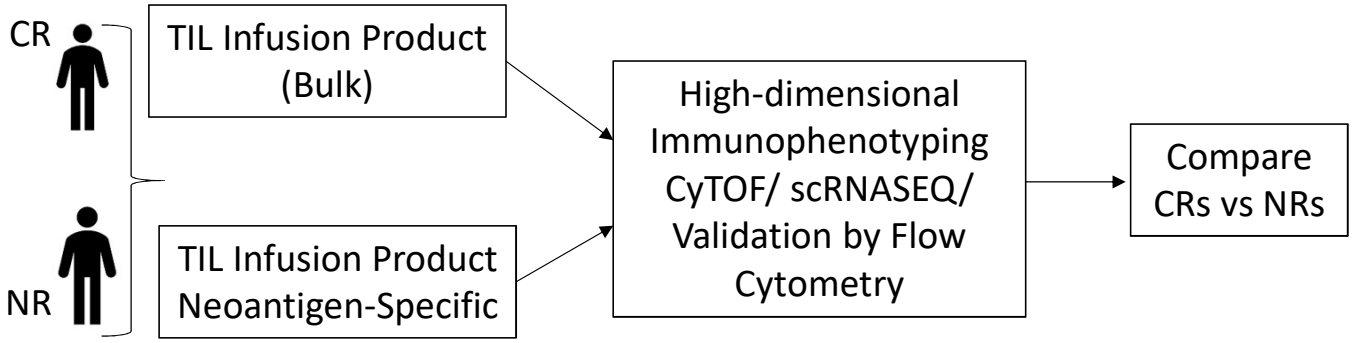
Feldman et al, Cell, 2019

“Progenitor”-exhausted TILs in murine models

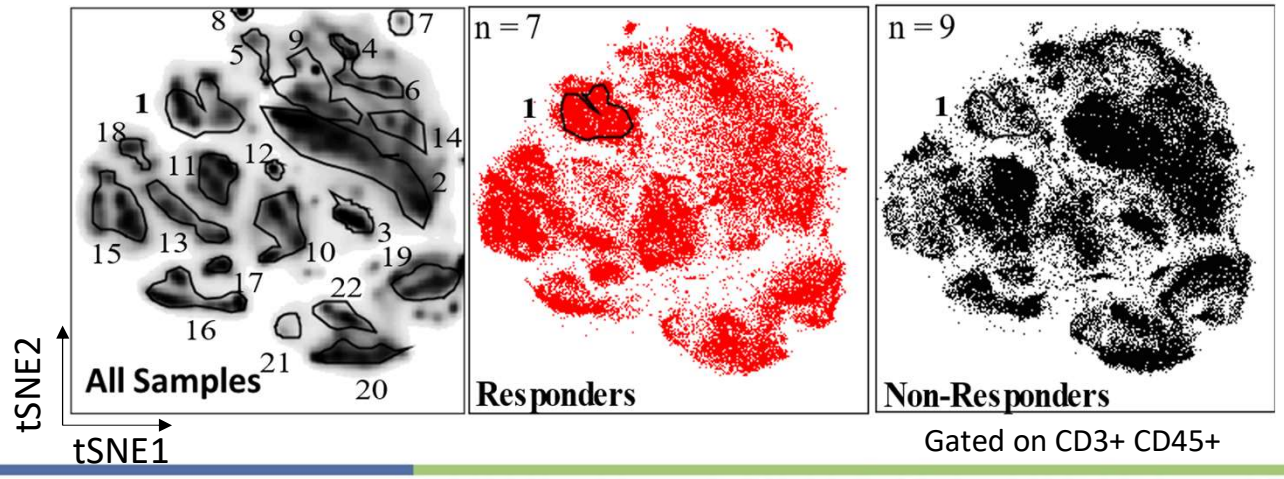
Miller BC et al, Nature Immunology, 2019
Siddiqui et al, Kurtulus et al, Immunity, 2019

Which T cell phenotypes in bulk and anti-tumor TIL infusion products are associated with TIL ACT-response in melanoma?

- Non-genetically engineered TIL
- Restrict focus to αPD-1-naïve patients
- Exclude PRs, SDs (to eliminate tumor-intrinsic resistance mechanisms)



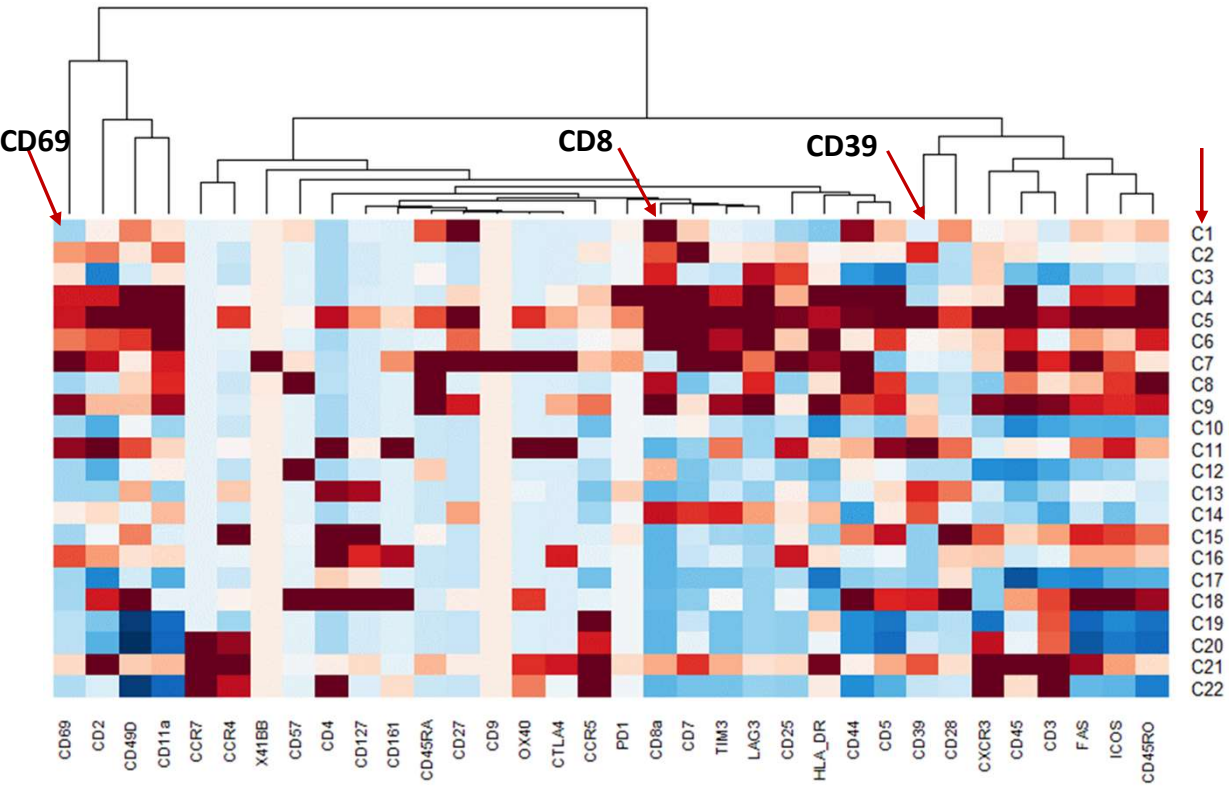
Mass Cytometry analysis of 38 cell surface proteins

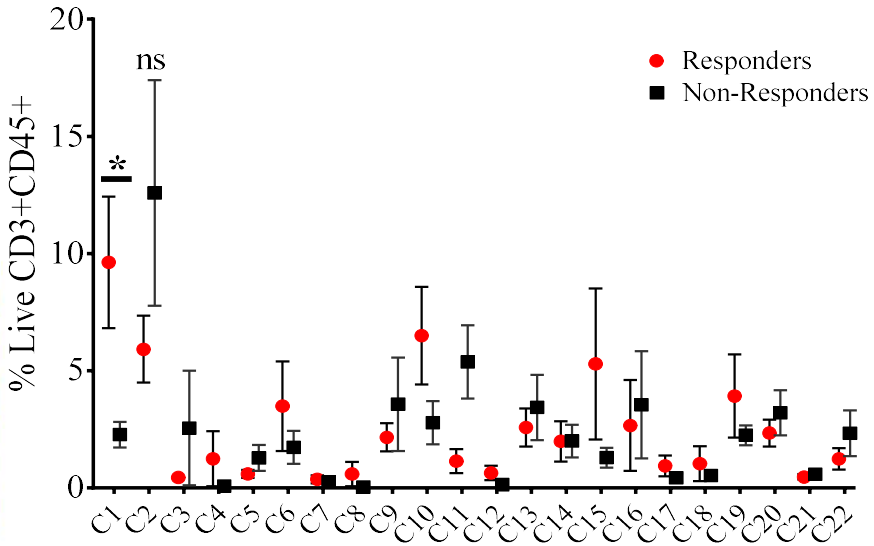


Gregoire Altan-Bonnet, NCI

Gated on CD3+ CD45+

TIL infusion product phenotyping reveals differences between melanoma CRs and NRs

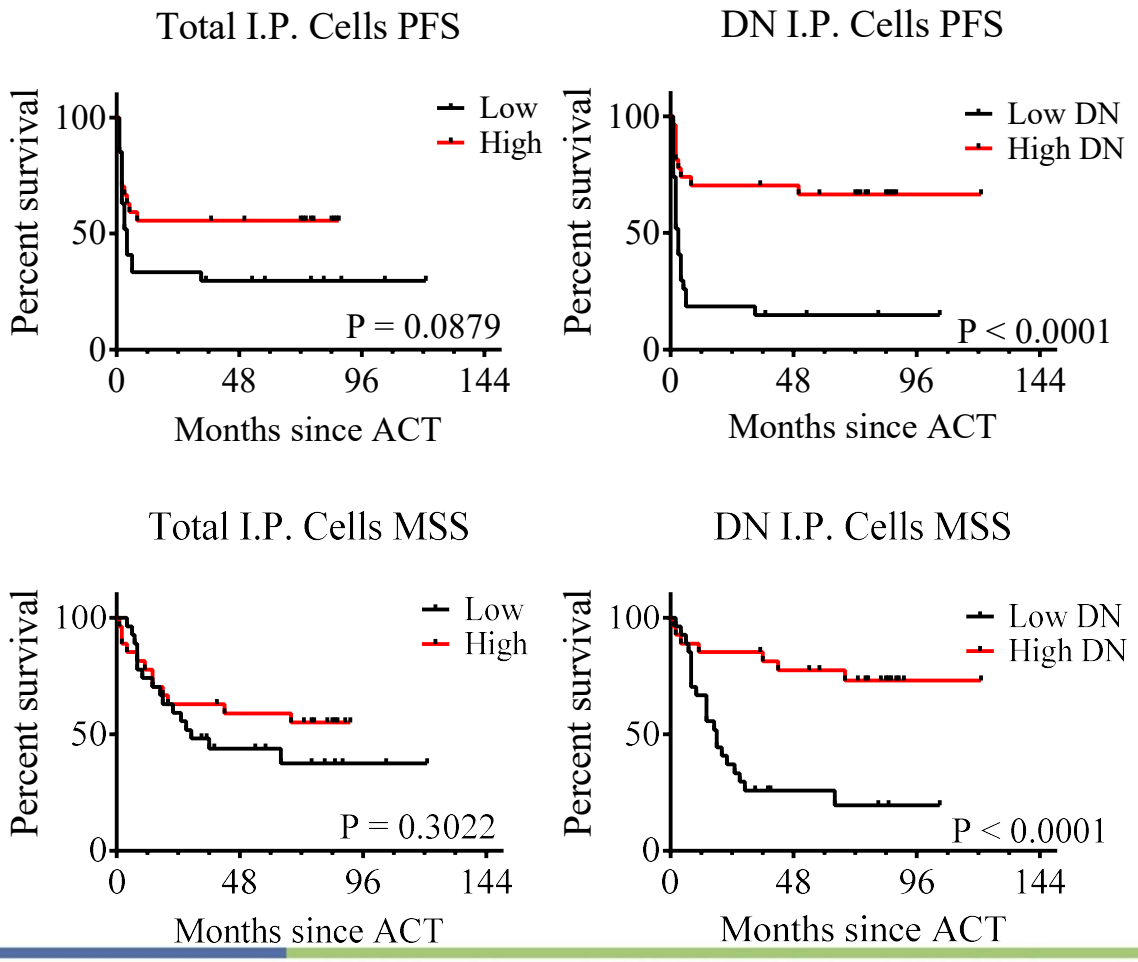




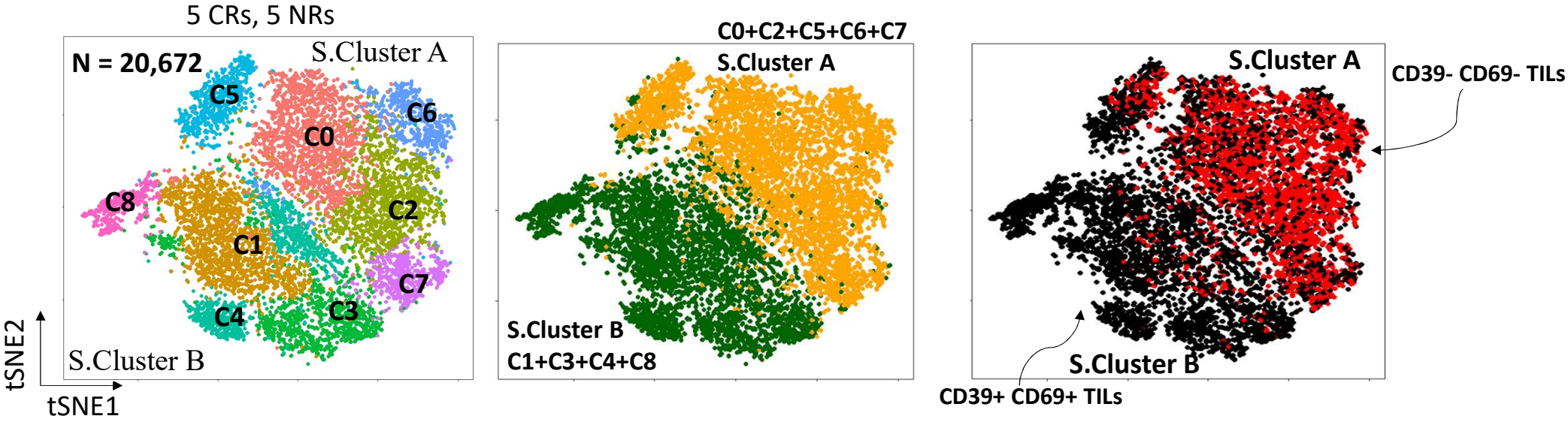
Wilcoxon Rank-Sum Test adjusted by multiple corrections

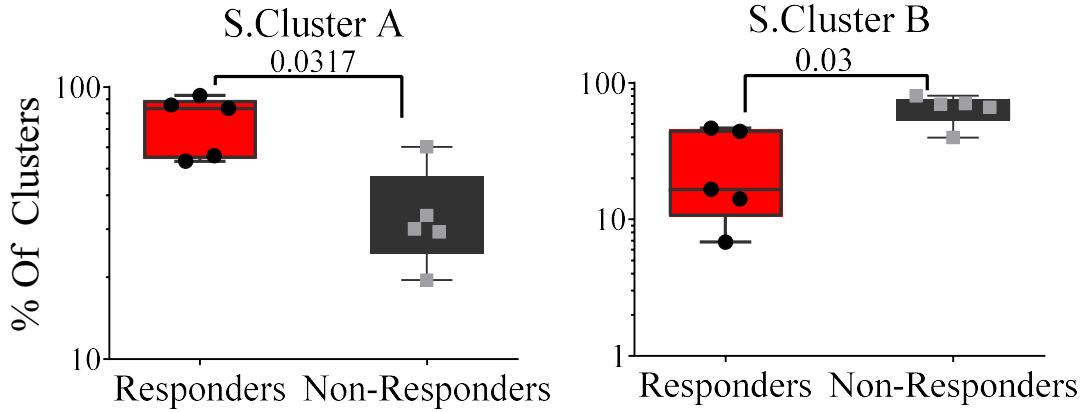
CD8+ CD39- CD69- cells infused is associated with better patient survival p.tx

Validated by Flow Cytometry
DN : CD39- CD69-
I.P : Infusion Product
PFS: Progression Free Survival
MSS: Melanoma Specific Survival
N = 54 patient infusion products



Unsupervised scRNA analysis of TIL infusion products separates CRs and NRs

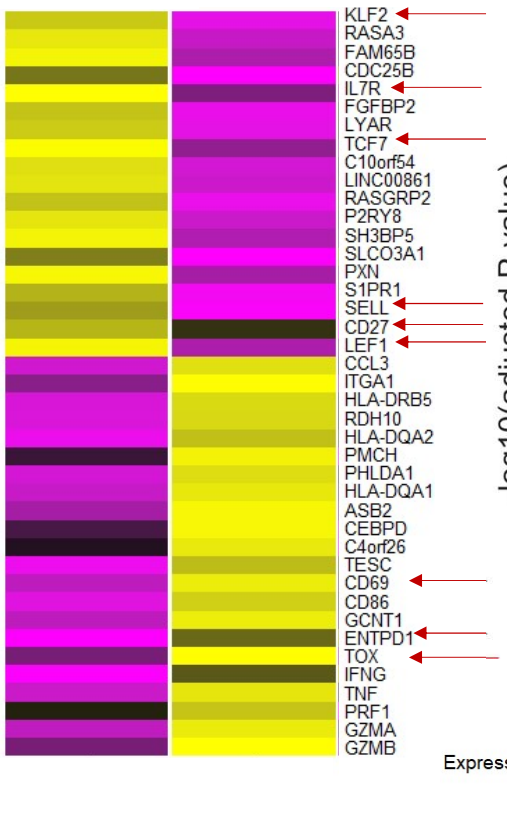




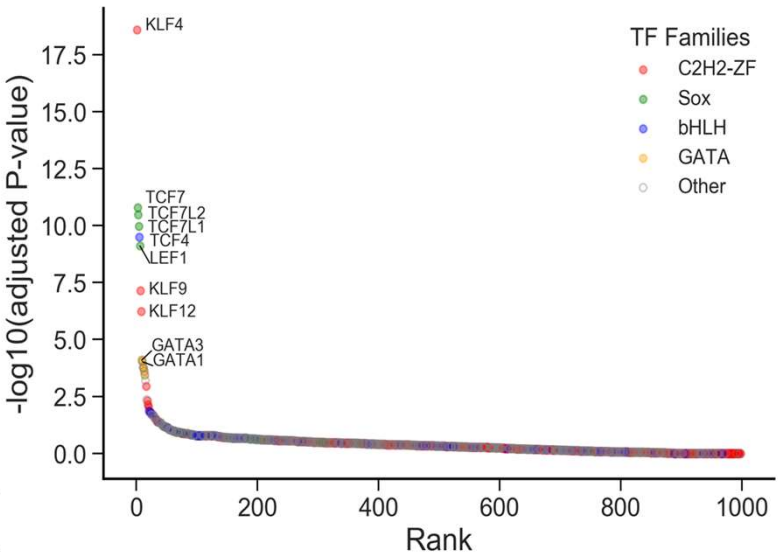
Wilcoxon Rank-Sum Test

Response cluster represents CD39- CD69- cells and enriches for key stemness factors

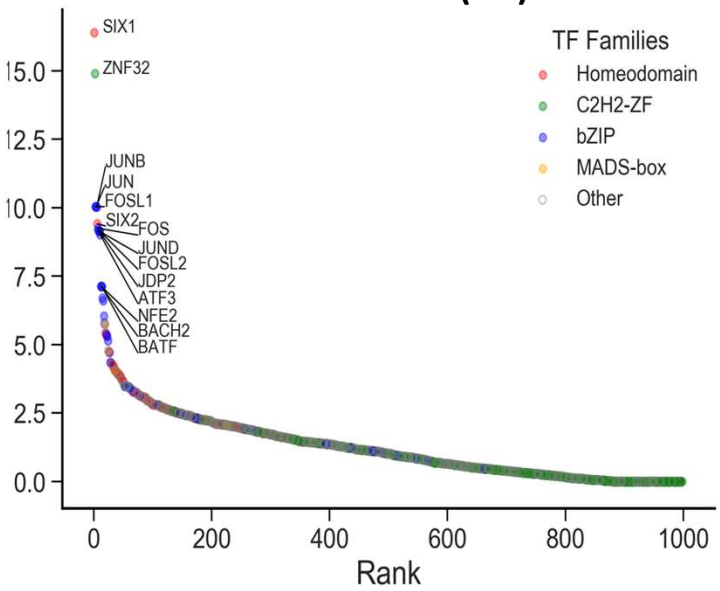
Top 20 differential genes each cluster



Transcription factor motifs enriched in CD39- CD69- (DN)

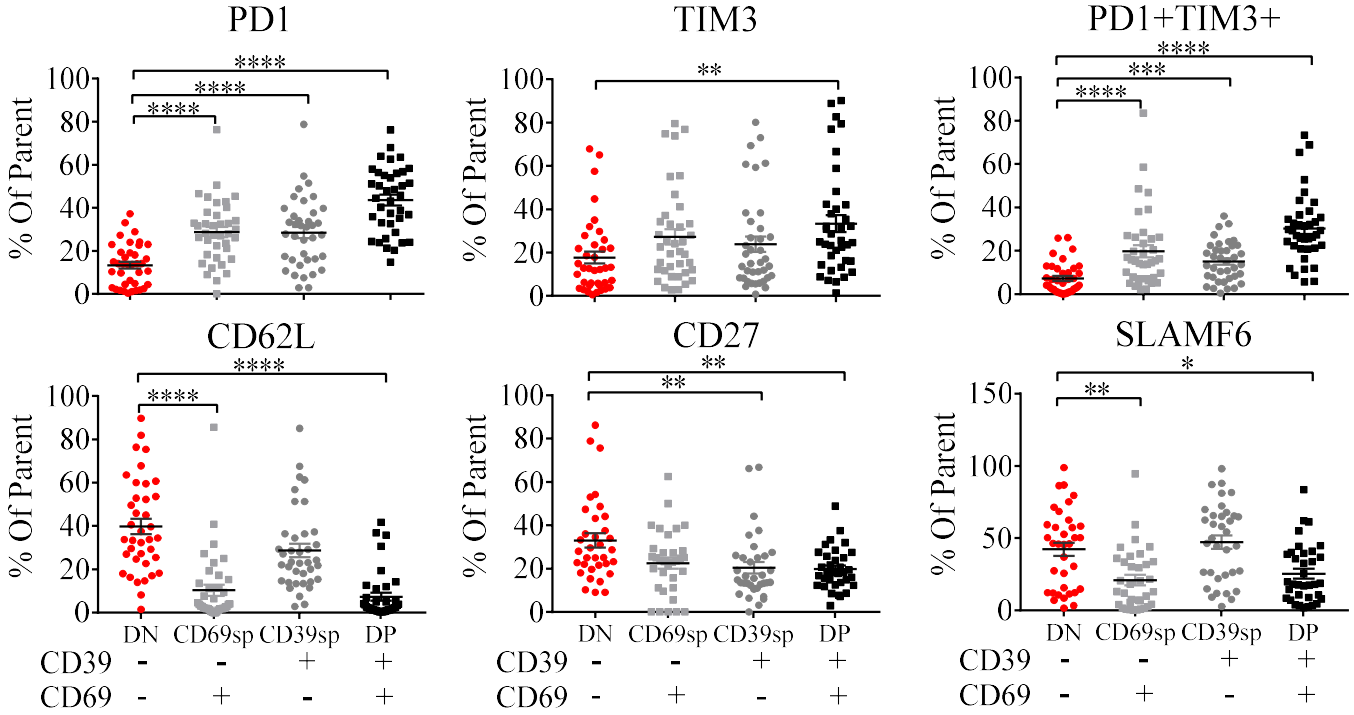


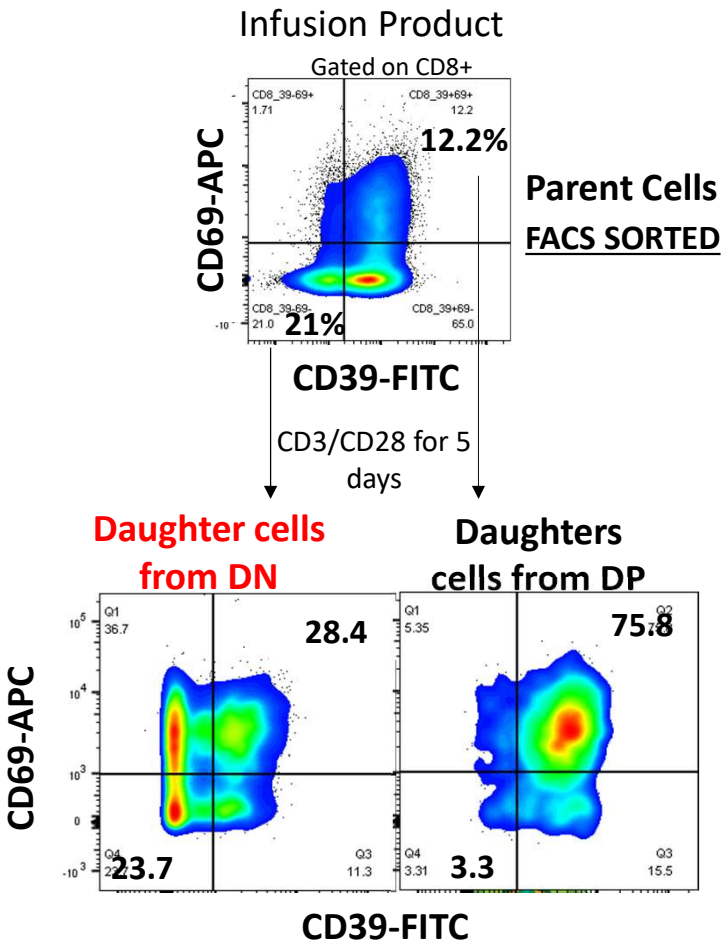
Transcription factor motifs enriched in CD39+ CD69+ (DP)



Epigenetic profiling of 4314 human transcription factor motifs for binding sites in sorted DN and DP populations by ATACseq

CD39- CD69- TILs represent a stem-like memory progenitor state



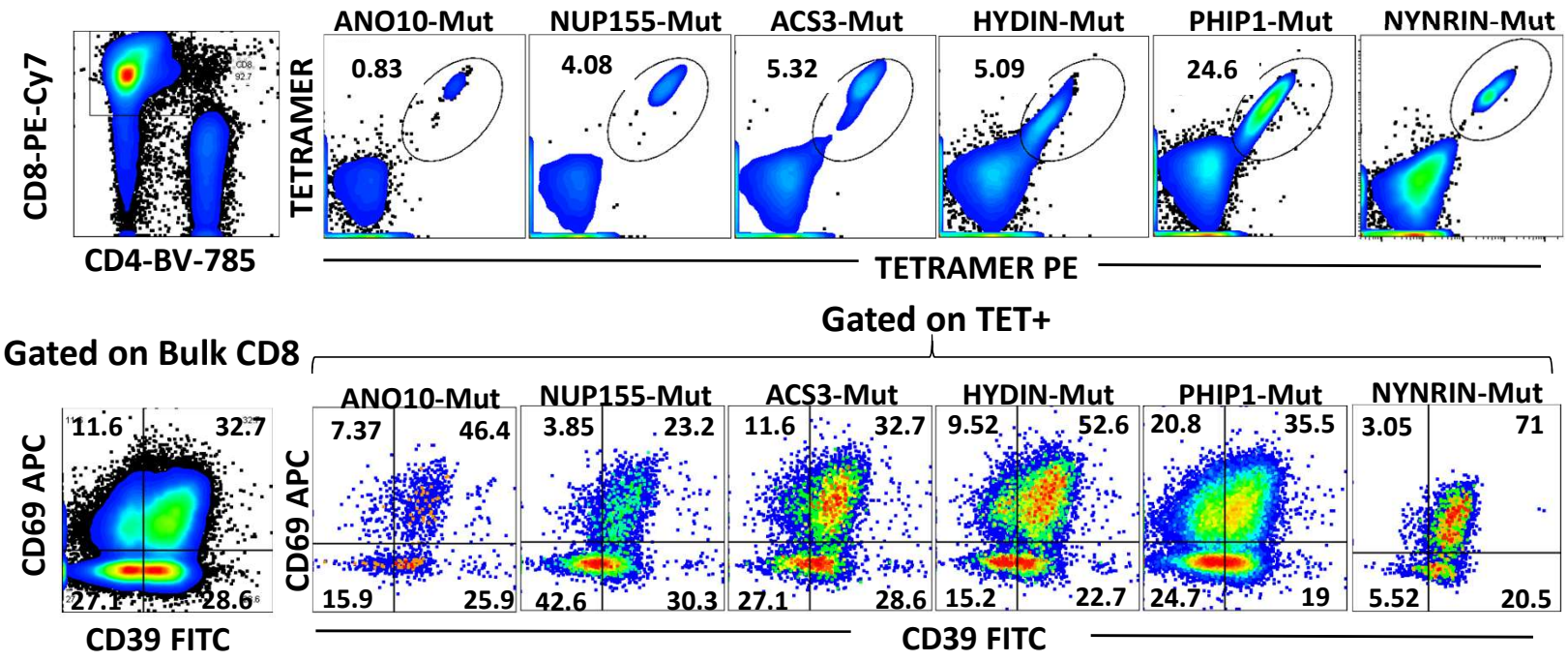


Can we find tumor-reactive neoantigen specific T cells within the CD39- CD69- DN subset?

Recall that CD39- TILs are thought to be "bystander" TIL (Simoni et al, Nature, 2018)

CD39-CD69- stem-like phenotypic state can be detected within Neoantigen specific T cells from ACT Complete Responders

3733 CR

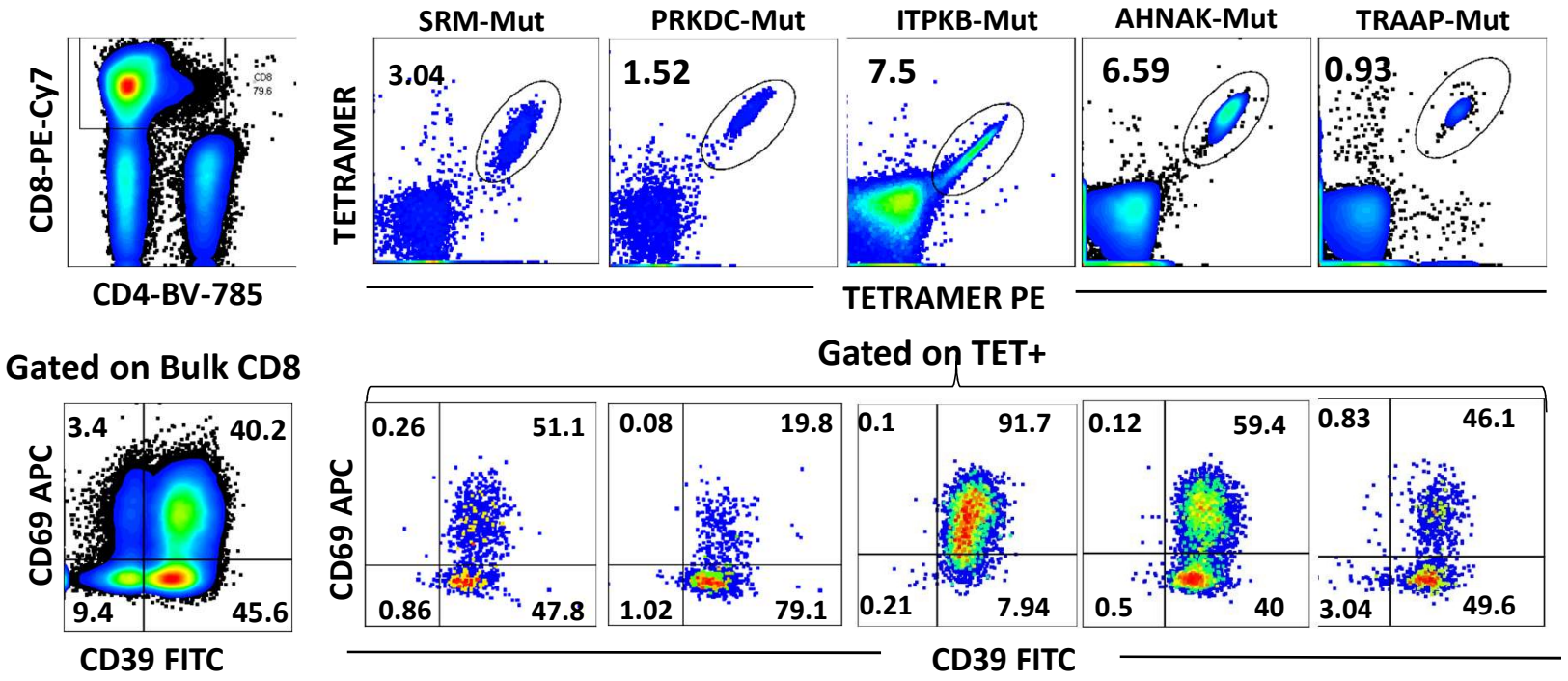


Amy Copeland,
Frank Lowery

Numbers indicate as a % of Tetramer gated CD8+ TILs

Lower levels of CD39-CD69- stem-like state within Neoantigen specific T cells from Non-Responders

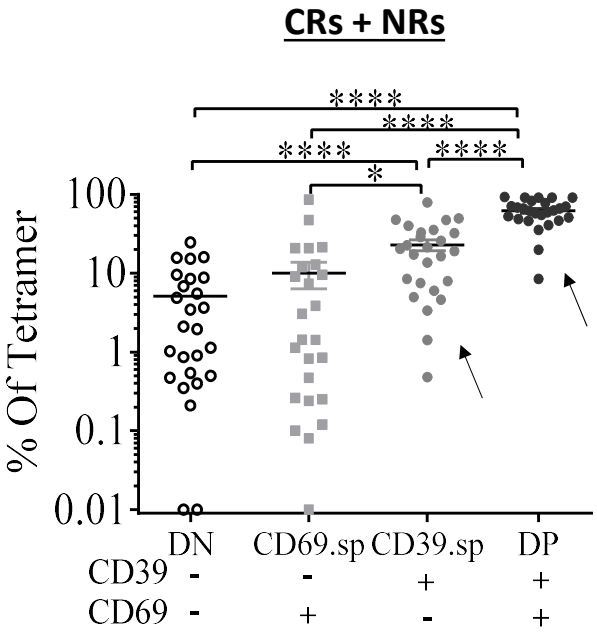
3645 NR



Amy Copeland,
Frank Lowery

Numbers indicate as a % of Tetramer gated CD8+ TILs

Majority of Neoantigen specific TILs are in terminally differentiated CD39+ CD69+ states..



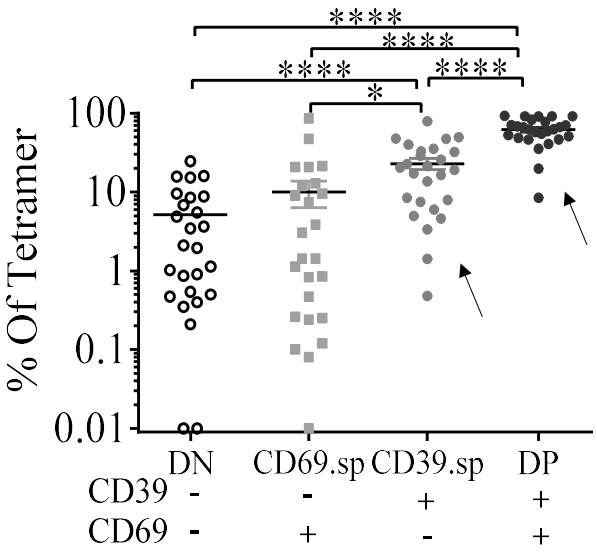
13 CR NeoAg, 13 NR NeoAg

CD39+ enriches for NeoAg TIL → Consistent with other studies and ours

Wilcoxon Rank-Sum Test adjusted by Bonferroni multiple corrections

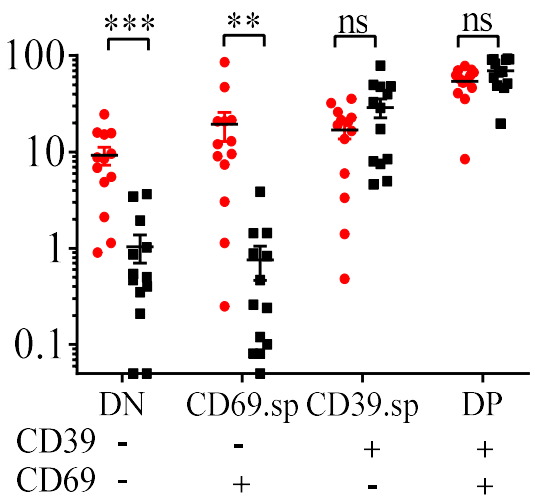
But.. ACT responders retained a pool CD39- Stem-like Neoantigen specific TILs

CRs + NRs

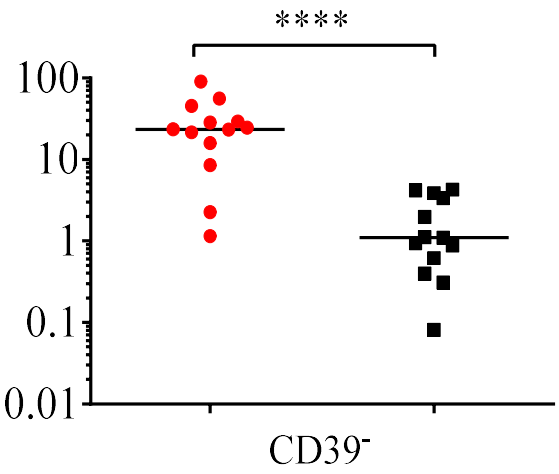


13 CR NeoAg, 13 NR NeoAg

CRs Vs. NRs



CRs Vs. NRs

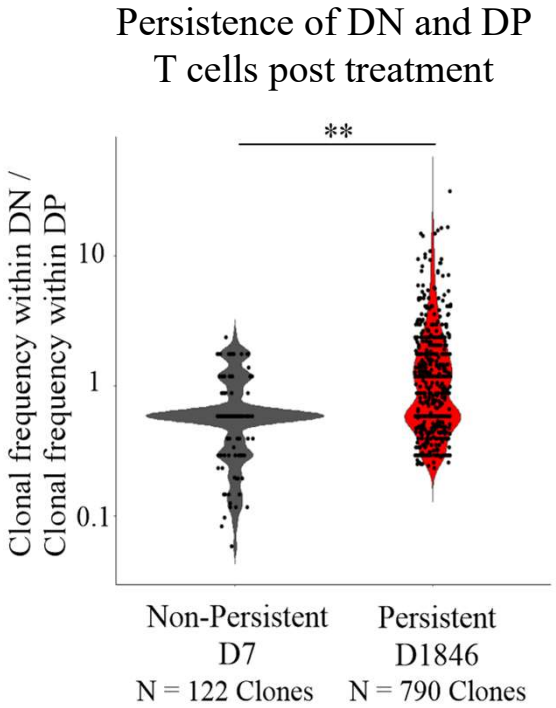


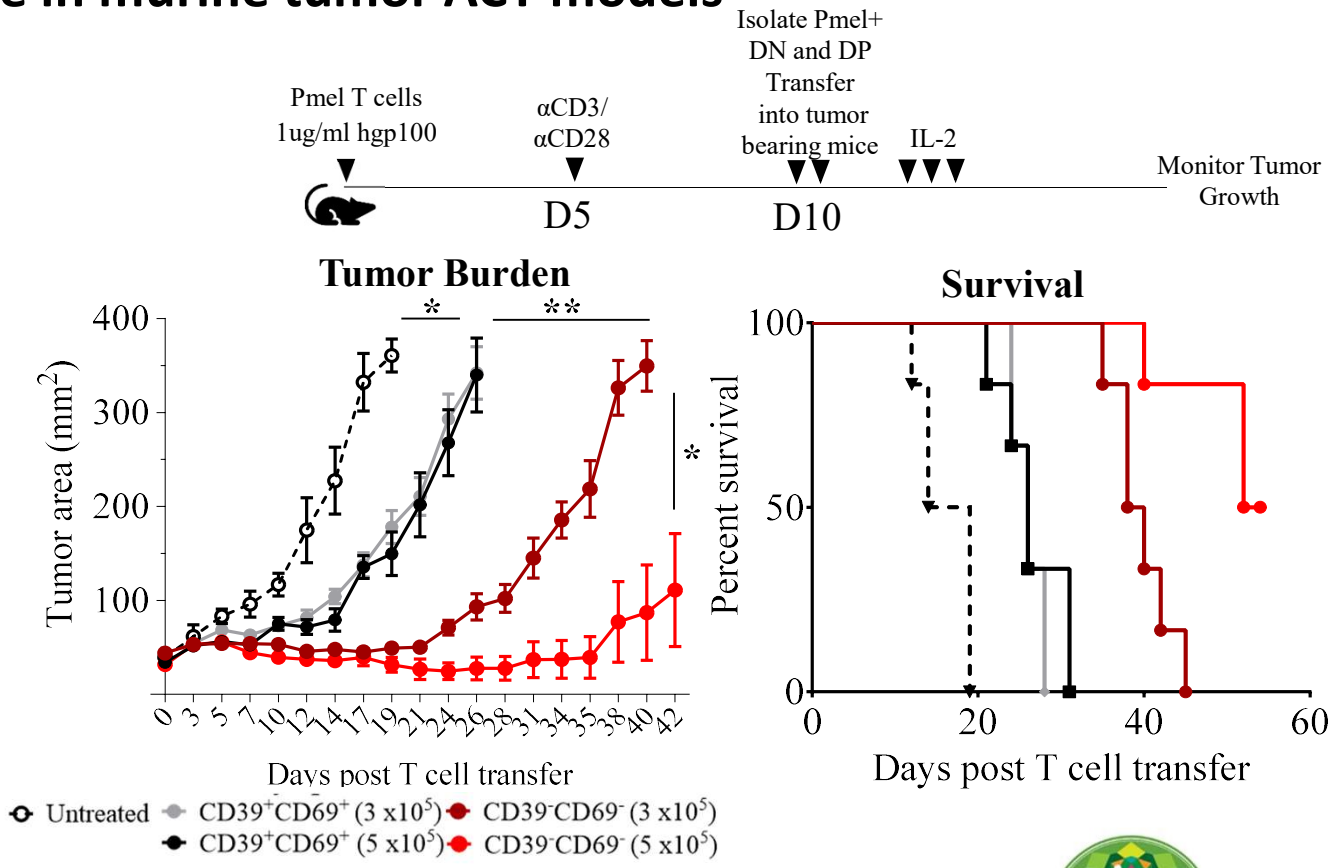
Note that we found no differences between CR's and NR's comparing

- Total Neoantigen TILs infused
- CD39+ NeoAg TILs infused
- Terminally differentiated CD39+ CD69+ NeoAg TILs infused

Wilcoxon Rank-Sum Test adjusted by Bonferroni multiple corrections

CD8+ CD39- CD69- stem-like T cells are associated with persistence and are curative in murine tumor ACT models





Ny-ESO TCR Transduced Clonotypes from patient infusion product compared between D7 and D1846

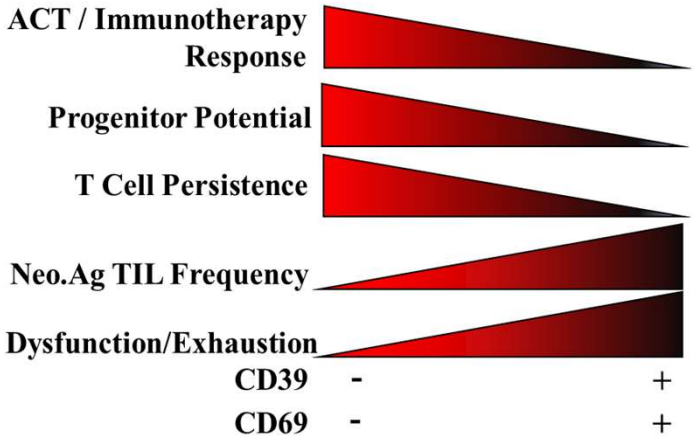
DN: CD39- CD69- DP:CD39+ CD69+

Devikala Guruswamy, Zhiya Yu

Summary

In this melanoma cohort there is an indication that TIL subsets enriched for tumor-reactivity (CD39+) appear distinct from TIL subsets associated with ACT response (CD39-) and TIL-persistence

Identifying or engineering tumor-reactive CD39- stem-like T cells might provide opportunities for improving T Cell immunotherapy



Acknowledgements

- **Frank J. Lowery**
- Amy Copeland
- Avi Sachs
- Victoria Hill
- Li Jia
- Rami Yoseph
- Jared Gartner
- Yong Li
- Biman Paria
- Maria Parkhurst
- Zhiya Yu
- Devikala Gurusamy
- Nikolaos Zacharakis
- Don White
- Arnold Mixon
- Shawn Farid
- Praveen Chatani
- Neil Parikh
- Members of Surgery Branch, NCI

Dr. Paul F. Robbins and Dr. Steven A. Rosenberg

Dr. Stephanie Goff, Surgery Branch
Dr. Michael Kelly, Single Cell Genomics Core
Dr. Gregoire Altan-Bonnet and lab, NCI

Pia Kvistborg, Netherlands Cancer Institute

NCI Director's Innovation Award 2018-2019