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THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Immune Checkpoint Blockade in Cancer Therapy:

New insights into therapeutic mechanisms of anti-CTLA4 and anti-PD-1

Jim Allison, PhD

Regental Professor and Chair, Department of Immunology
Executive Director, Immunotherapy Platform
Co-Director, Parker Institute for Cancer Immunotherapy at MDACC
Olga Keith Weiss Distinguished University Chair for Cancer Research

Mechanistic Understandings and Misunderstandings

SITC 2020

November 14, 2020

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MDACC Immunotherapy Platform

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Prostate Cancer Foundation
Stand UP to Cancer

CANCER PREVENTION & RESEARCH
INSTITUTE OF TEXAS

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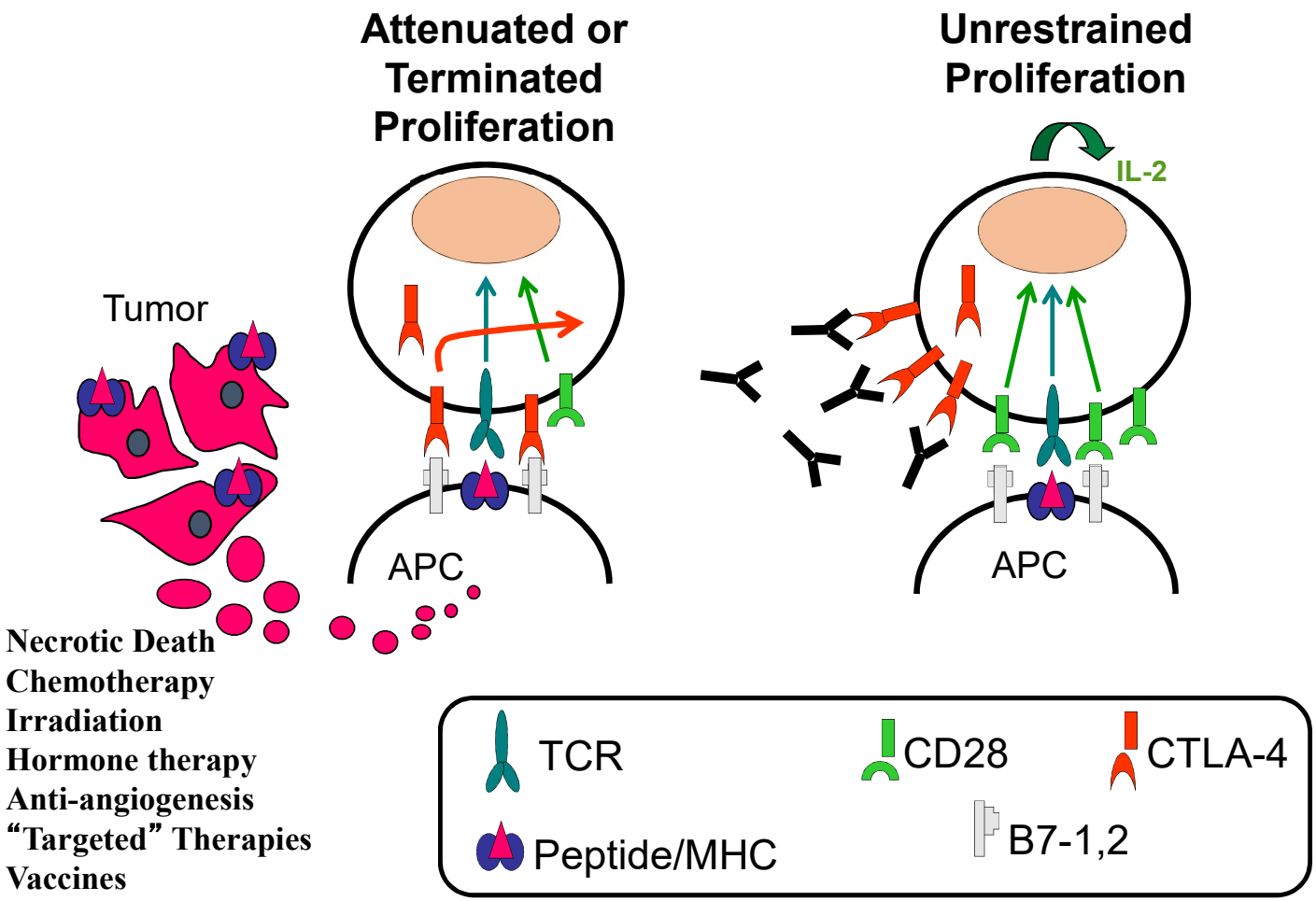
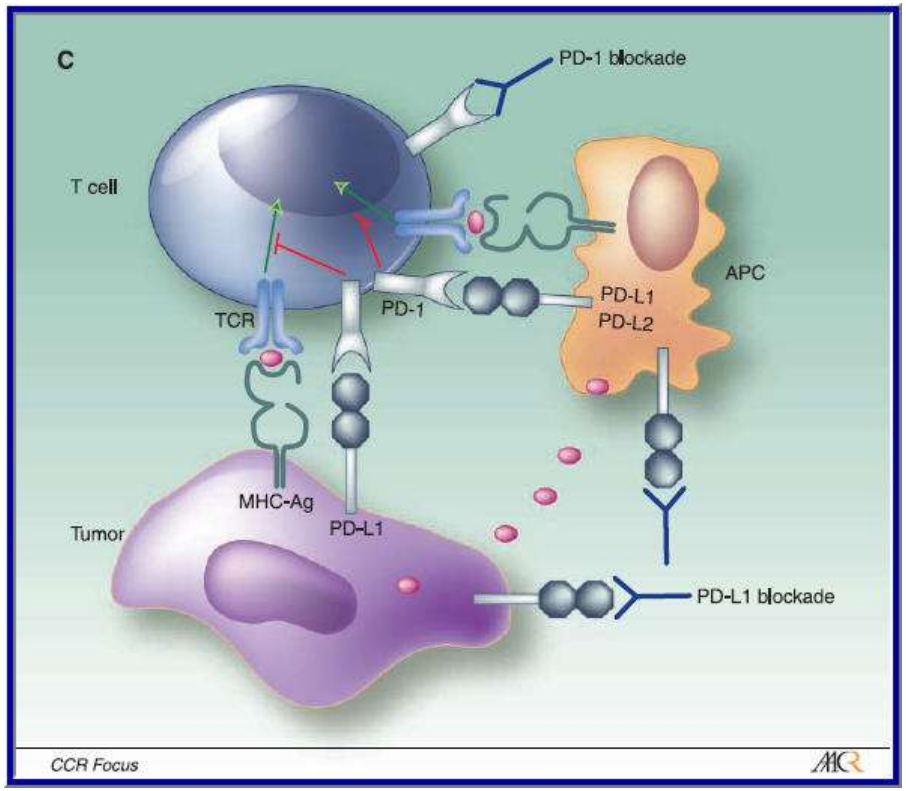
CTLA-4 Blockade
Enhances Tumor-Specific Immune Responses

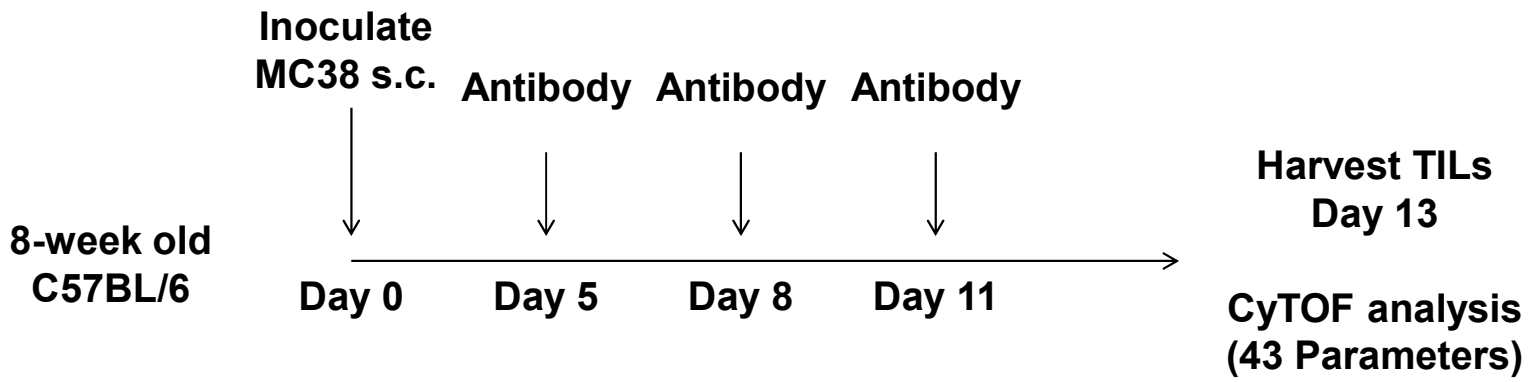


Programmed Death 1
(PD-1)



Anti-CTLA-4	Anti-PD-1
• Hard wired	• Induced resistance
• Targets CD28 pathway	• Targets TCR pathway
• Works during priming	• Works on differentiated T cells
• Expands clonal diversity	• Does not expand clonal diversity
• Responses often slow	• Responses usually rapid
• Primarily effects CD4 T cells	• Only effects CD8 T cells
• Can move T cells into “cold” tumors	• Does not move T cells into tumors
• Adverse events relatively frequent	• Adverse events less frequent
• Disease recurrence after response rare	• Disease recurrence after response significant

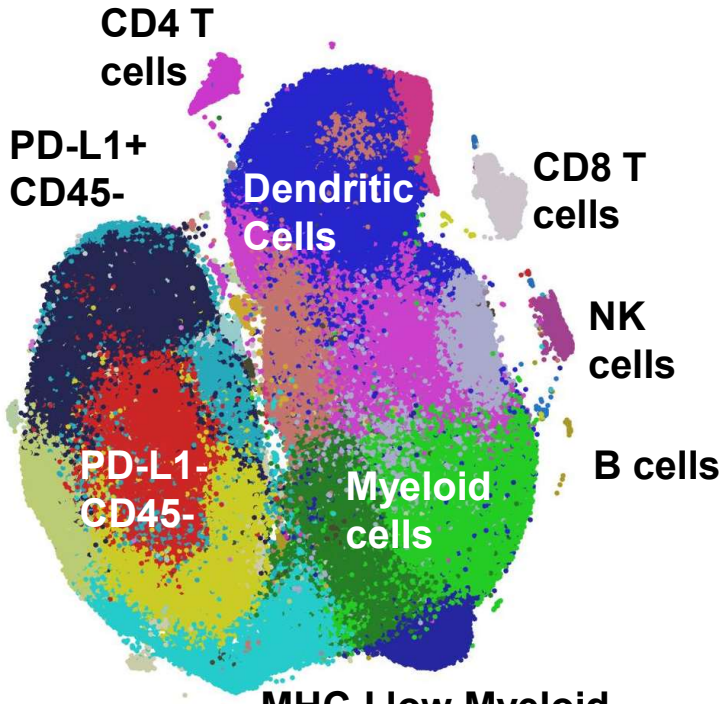
Mass cytometry analysis of MC38 TILs



Wei et al *Cell* 2017

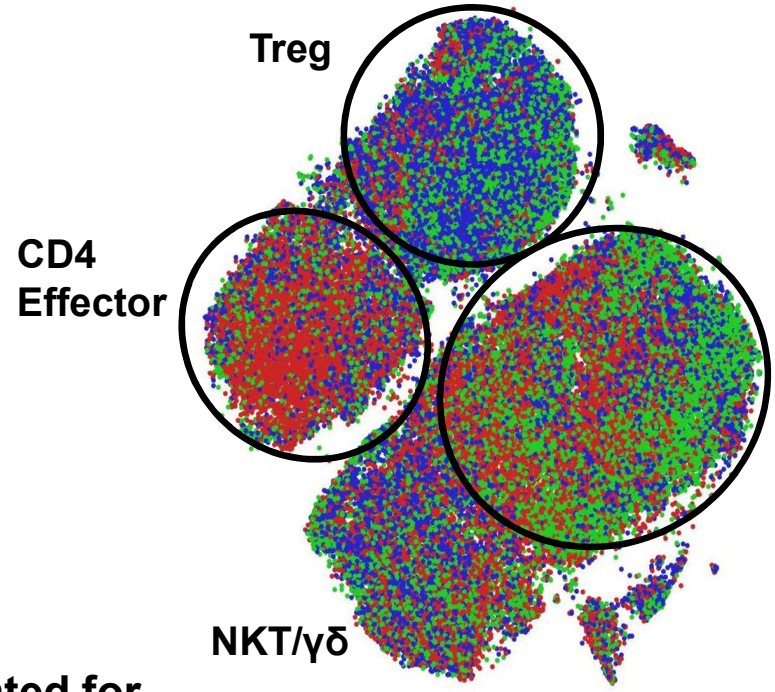
Mass Cytometry Analysis of MC38

Untreated



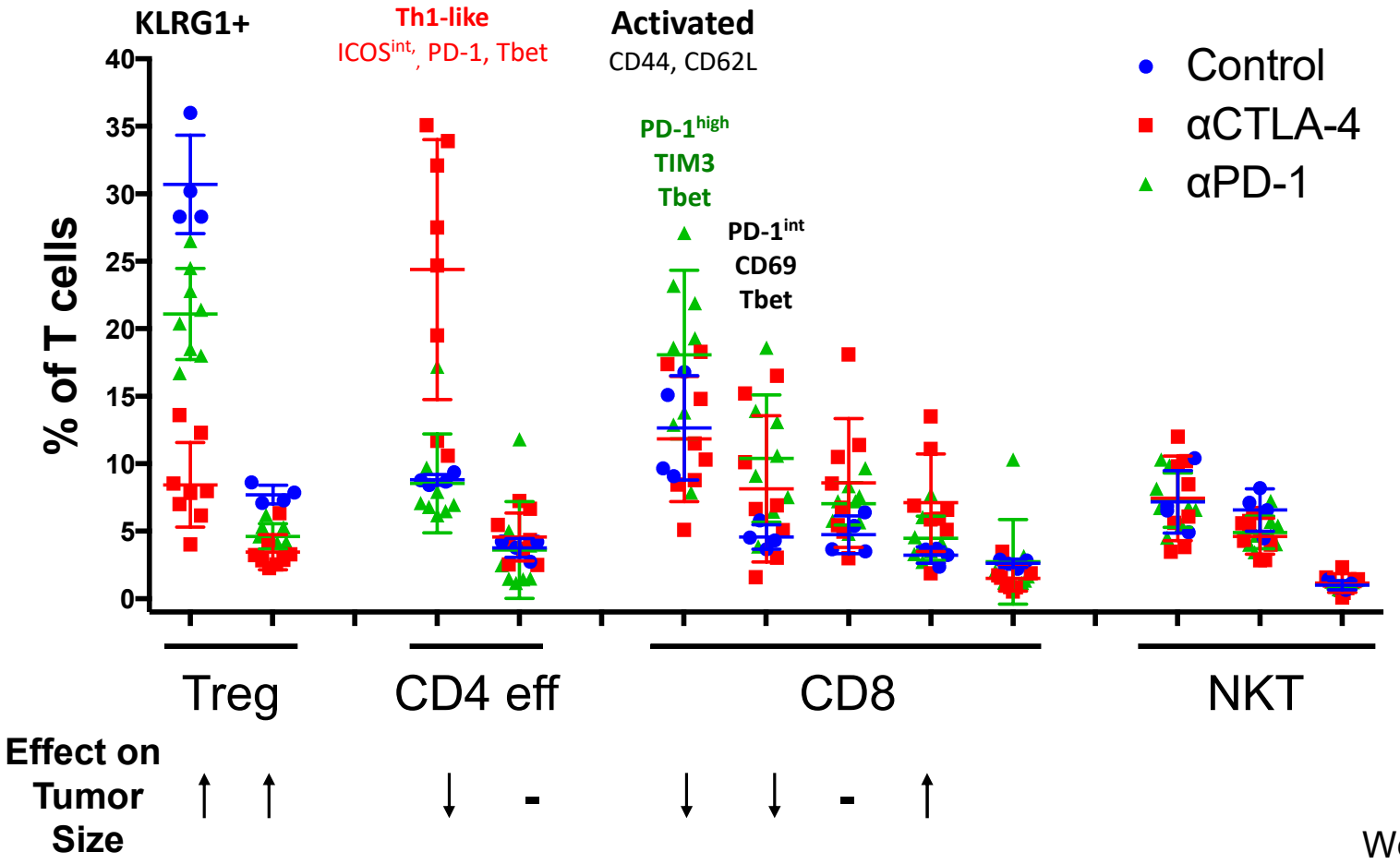
Gated for CD45+

Treated



Gated for CD45+, CD3ε+

Checkpoint blockade modulates MC38 infiltrating T cell population frequencies



Wei et al *Cell* 2017

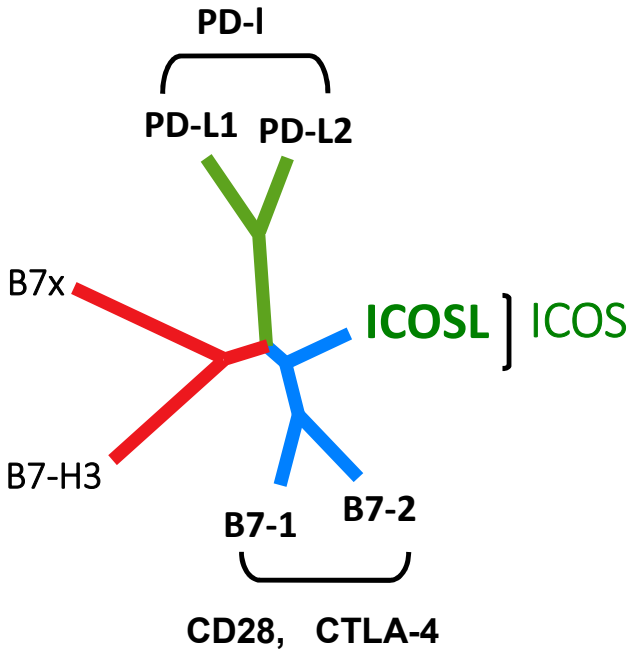
CELLULAR TARGETS OF CHECKPOINT BLOCKADE

Monotherapy:

- CTLA-4
  - CD4 ICOS+ Tbet+Th1-like Effector
  - CD8 Tbet+ EOMES+ Effector
- PD-1
  - CD8 Tbet+ EOMES+ Effector
  - CD8 Tbet+ PD-1++ Lag2++ Tim3++ “Exhausted”

Inducible Costimulator (ICOS)

- Member of CD28/CTLA-4 superfamily
- Usually associated with Tfh or Treg CD4 cells
- Role in cancer shown by Sharma (2006) *ICOS+Th1-like CD4 cells expanded by CTLA-4 blockade, critical for optimum efficacy*

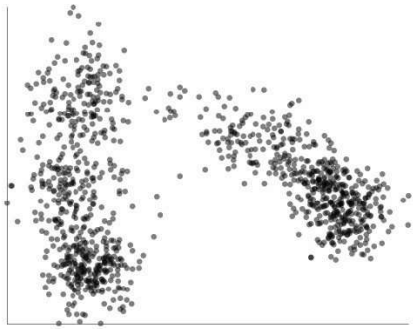


Does negative costimulation effect the regulation of T cell differentiation?

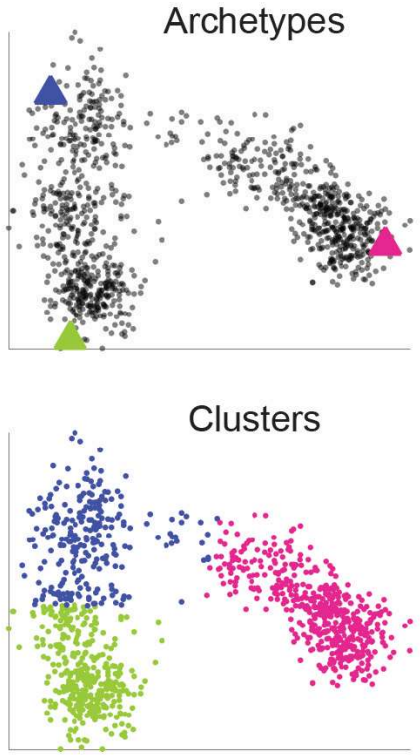
Comprehensive profiling of cell types in the genetic absence of CTLA-4 or PD-1

Mass cytometry analysis of
Ctla-4$^{-/-}$ and littermate controls

<u>39 Parameter T cell panel</u>
Activation, surface, lineage markers
Lineage transcription factors

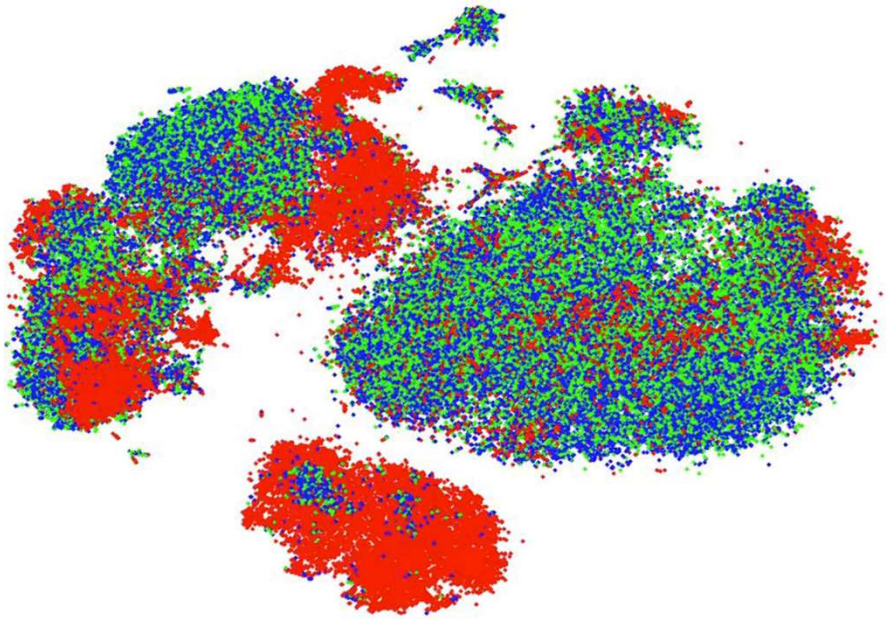


Single-cell data



Wei et al *Immunity* 2019

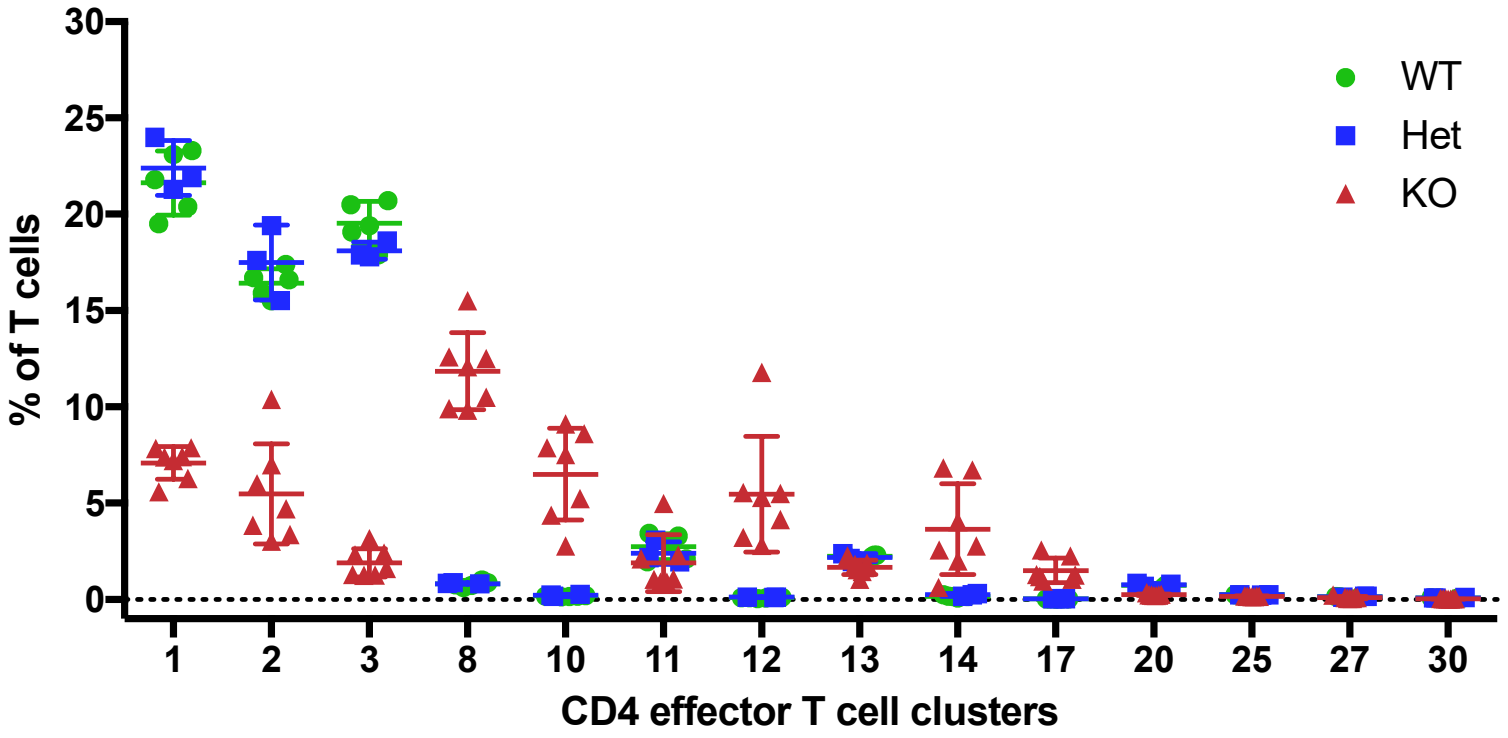
New T cell phenotypes arise in the absence of CTLA-4



T cells gated

Wei et al *Immunity* 2019

Multiple non-canonical CD4 T cell subsets arise in the absence of CTLA-4



Wei et al *Immunity* 2019

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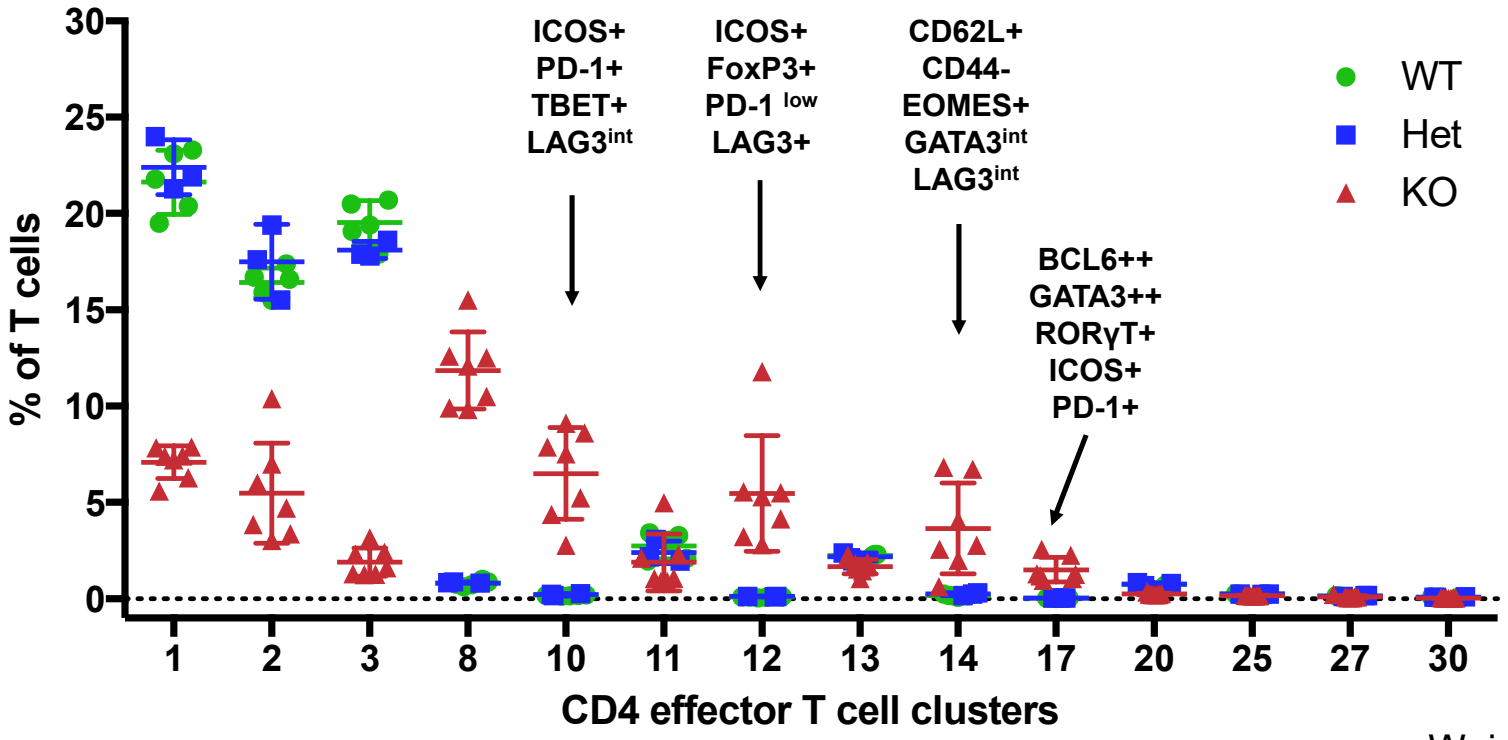
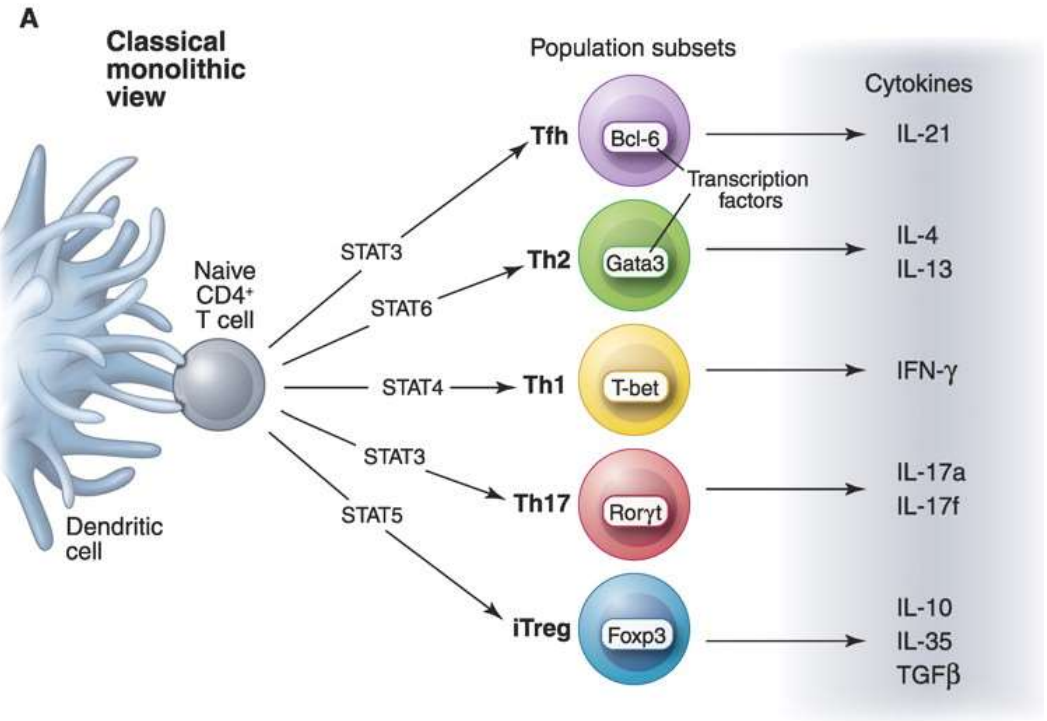
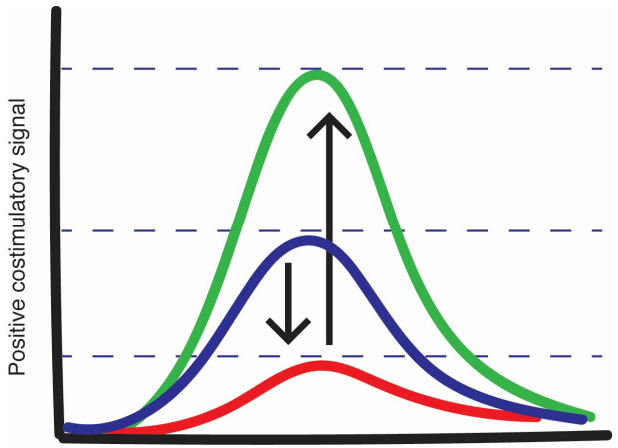


Wei et al *Immunity* 2019

CD4 T cell differentiation is complex
How are phenotypes, lineages, and boundaries defined?



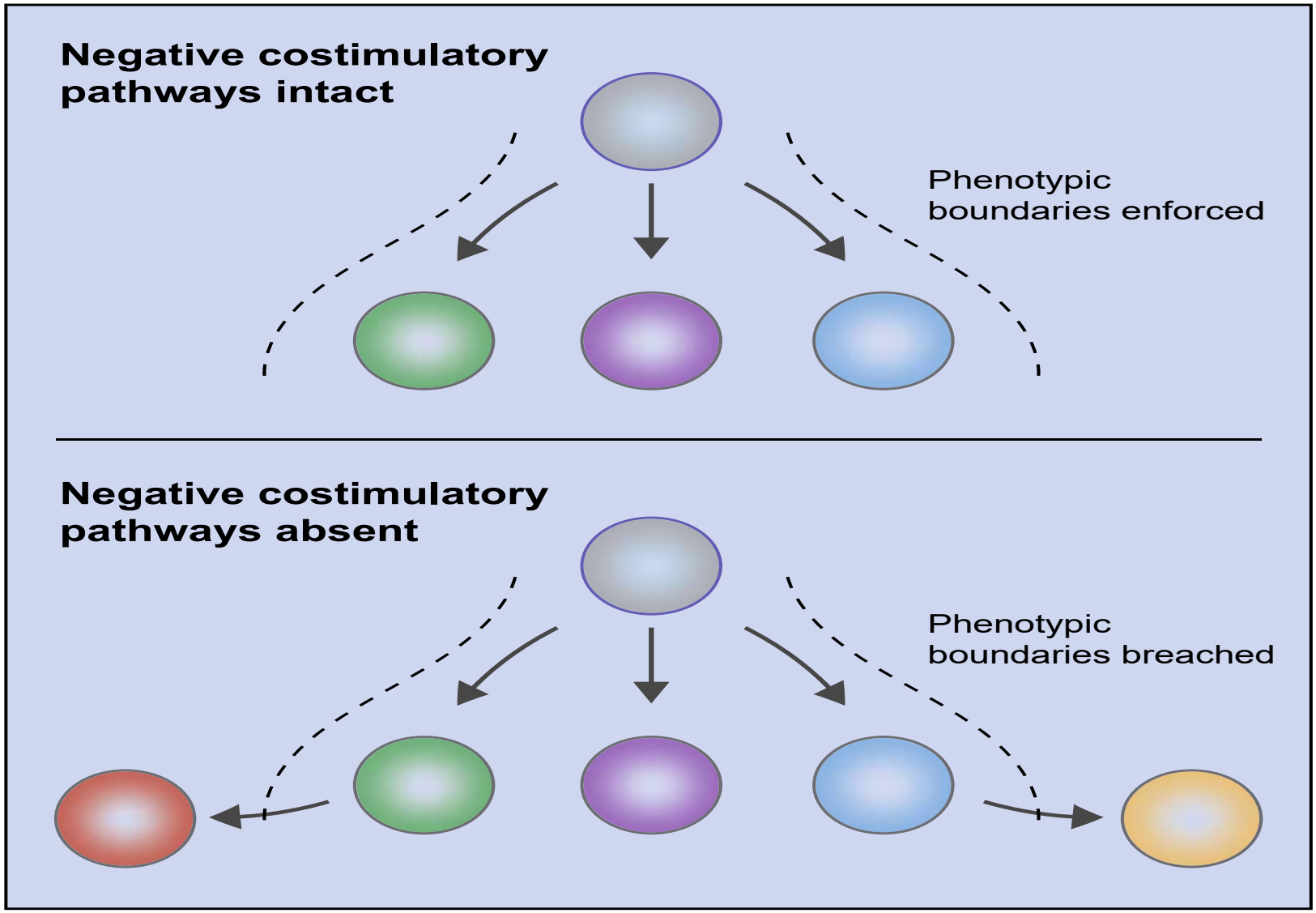
Does negative costimulation regulate T cell differentiation?



Maximum in the absence of CTLA-4?
⟶ **Effect on differentiation?**

Maximum signal under normal conditions

Attenuated signal due to CTLA-4 regulation


Negative costimulatory pathways intact
Phenotypic boundaries enforced
Negative costimulatory pathways absent
Phenotypic boundaries breached

Does negative costimulation effect the regulation of T cell differentiation?

Absence of CTLA-4

CD4: Appearance of atypical ICOS+ Th1 cells

CD8: No change in range of phenotypes

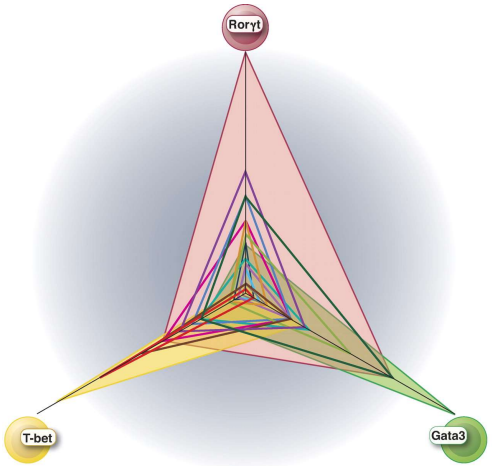
Absence of PD-1

CD4: No change in range of phenotypes

CD8: No change in range of phenotypes

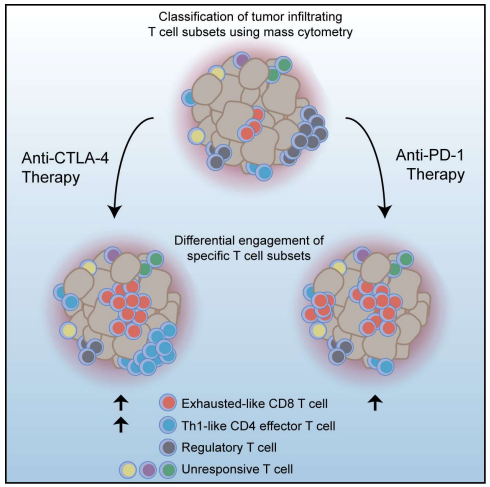
Potential implications

Evidence for a ‘nuanced model’ of T cell differentiation



O’Shea and Paul. *Science* (2010)

Role of T cell differentiation in mechanisms of immunotherapies



Wei et al. *Cell* (2017)

How do the cellular mechanisms of checkpoint blockade by CTLA-4 and interact?

A + B = AB *or* A + B = C

Mass cytometry analysis of MC38 TILs

C57BL/6 mice

Inoculate MC38 s.c. — Day 0

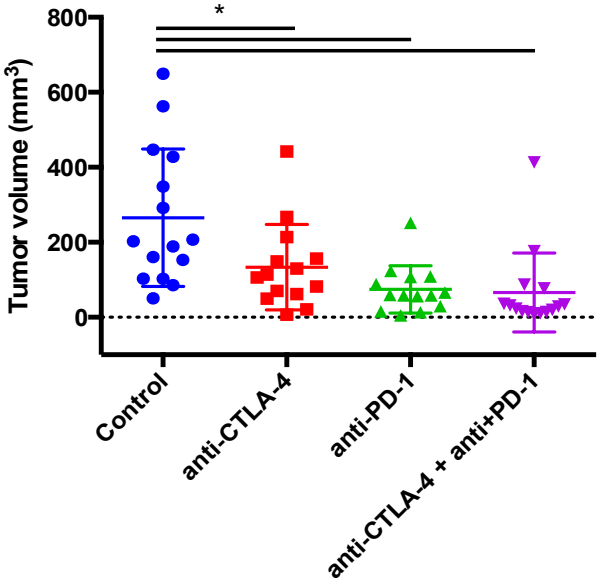
Antibody — Day 5

Antibody — Day 8

Antibody — Day 11

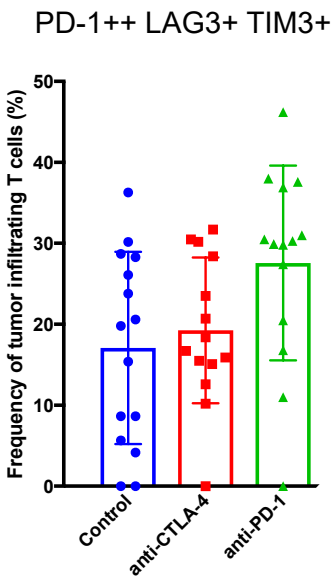
Harvest TILs Day 13

CyTOF analysis (43 Parameters)



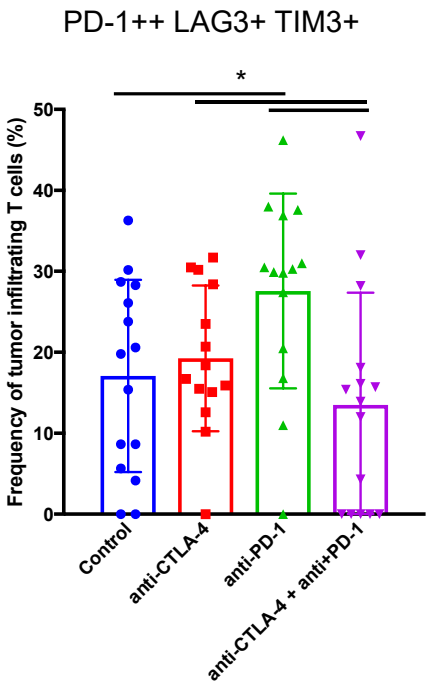
Wei et al *PNAS* 2019

Expansion of phenotypically exhausted CD8 T cells



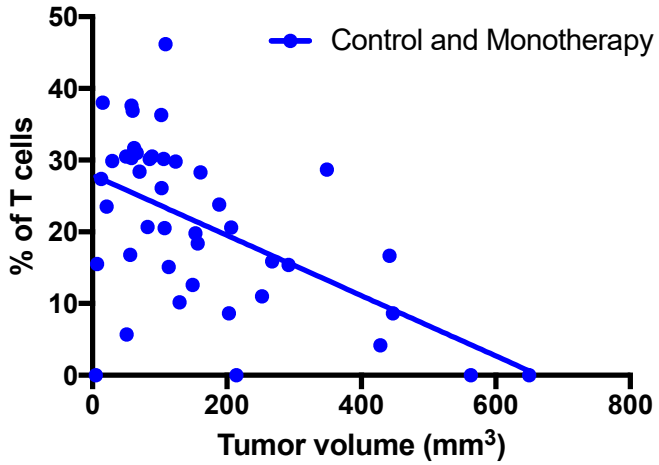
Wei et al *PNAS* 2019

Combination therapy differentially affects CD8 subsets



Wei et al *PNAS* 2019

Do phenotypically exhausted CD8 T cells have
the same function in the context of combination therapy?



Wei et al in press *PNAS* 2019

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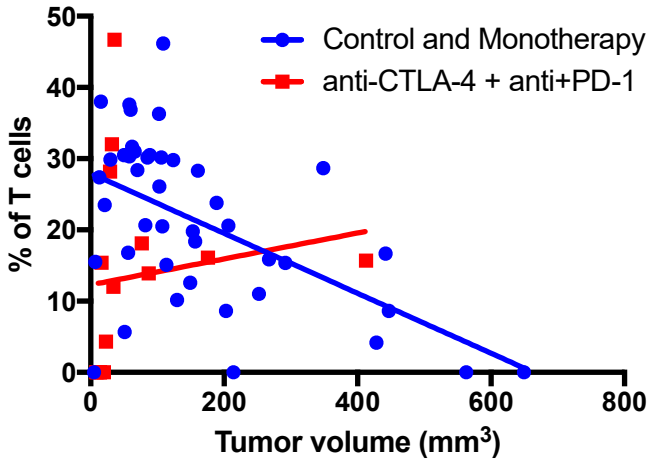

Wei et al in press *PNAS* 2019

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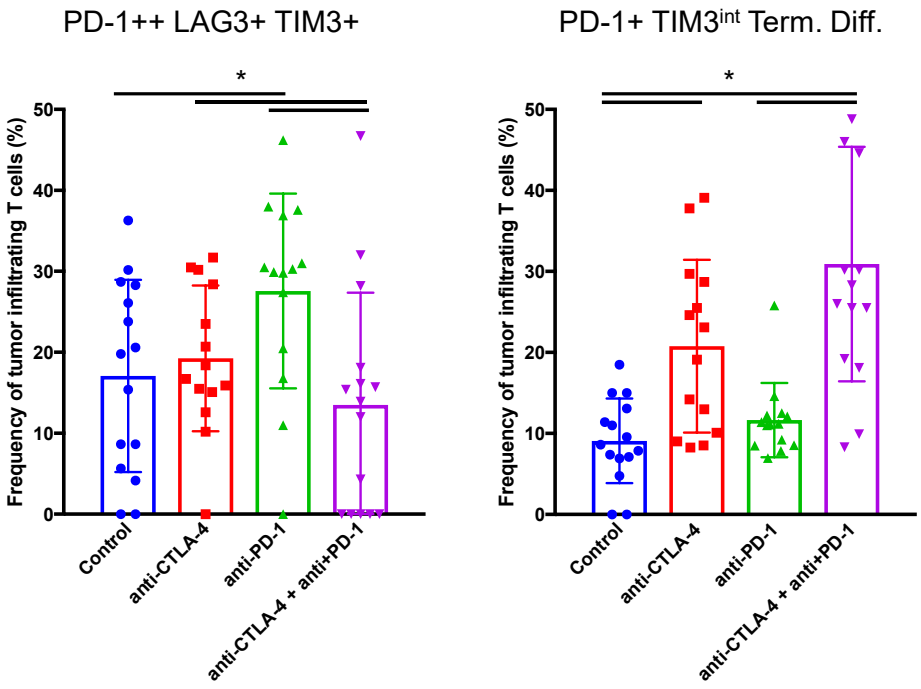
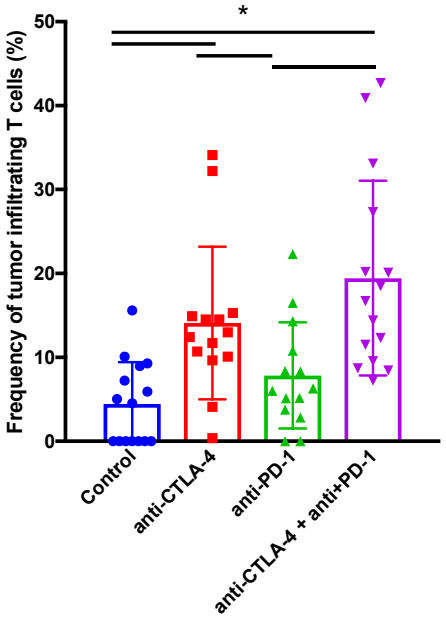


Wei et al in press *PNAS* 2019

Expansion of Th1-like CD4 T cells following combination therapy

PD-1^{+} ICOS^{int} TBET^{+}
Th1-like CD4 effector



Cellular Targets of Checkpoint Blaockade

Monotherapy:

- CTLA-4
  - CD4 ICOS+ Tbet+Th1-like Effector
  - CD8 Tbet+ EOMES+ KLRG-1+ Effector
- PD-1
  - CD8 Tbet+ EOMES+ KLRG-1+ Effector
  - CD8 Tbet+ PD-1++ Lag2++ Tim3++ “Exhausted”

Combination Therapy:

- CD4 ICOS+ Tbet+Th1-like Effector
- CD8 Tbet+ EOMES+ KLRG-1+ Effector

Cellular Targets of Checkpoint Blockade

What happens to “Exhausted” ($PD1^{hi}Lag3^{hi}Tim3^{hi}$) CD8 cells in presence of combination blockade of PD-1 and CTLA-4?

Cellular Targets of Checkpoint Blockade

What happens to “Exhausted” ($PD1^{hi}Lag3^{hi}Tim3^{hi}$) CD8 cells in presence of combination blockade of PD-1 and CTLA-4?

- Converted into CD8 effector T cells? *Unlikely, epigenetically fixed*

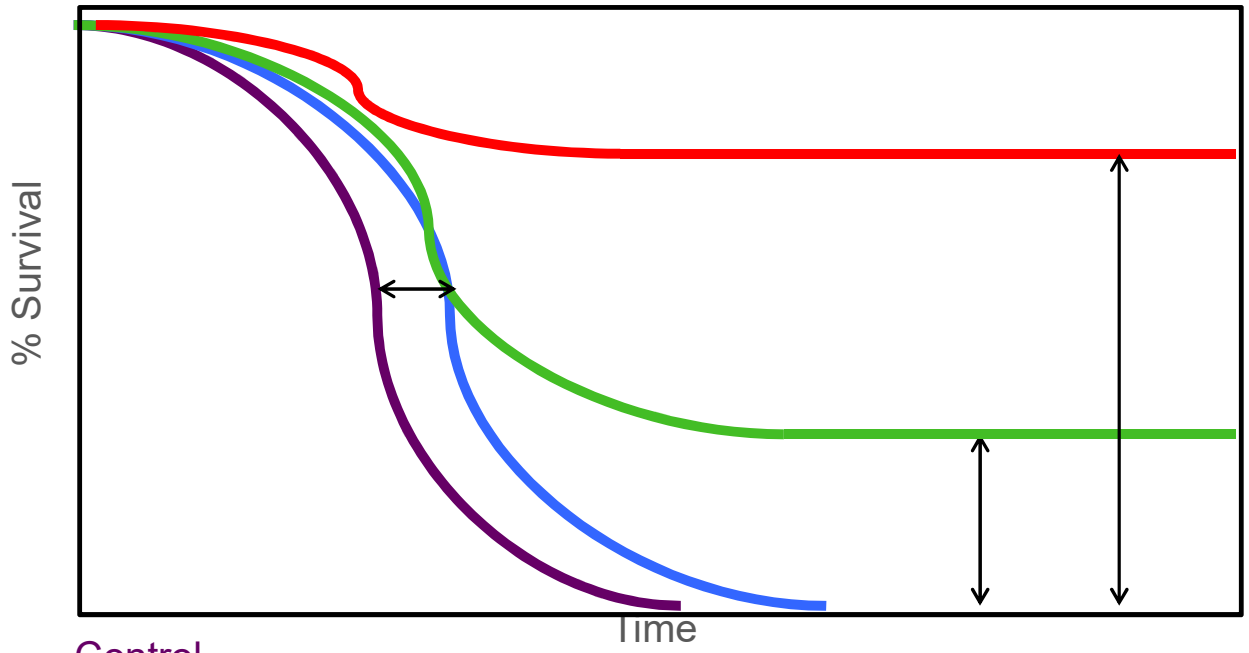
Cellular Targets of Checkpoint Blockade

What happens to "Exhausted" ($PD1^{hi}Lag3^{hi}Tim3^{hi}$) CD8 cells in presence of combination blockade of PD-1 and CTLA-4?

- Converted into CD8 effector T cells? *Unlikely, epigenetically fixed*

- Exhaustion of effectors prevented in presence of continued CD28 costimulation allowed by CTLA-4 blockade?

Improving survival with combination therapy



Control
Standard or other therapy
Immunotherapy (e.g.anti-CTLA4)
Combination