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

Immune Checkpoint Blockade in Cancer Therapy:

*New insights into therapeutic mechanisms and opportunities for **Cures***

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SITC: Advances in Cancer Immunotherapy

San Antonio

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Disclosures

Consultant

Achelois, Apricity Health, BioAtla, Codiak Biosciences, Dragonfly Therapeutics, Jounce Therapeutics, Lave Therapeutics, Lytix Therapeutics, Polaris

Stock Ownership (<5%)

Adaptive Biotechnologies, BioAtla, BioNtech, Codiac Biosciences, Jounce Therapeutics Marker Therapeutics, Polaris

I will not discuss off label use and/or investigational use in my presentation.

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CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

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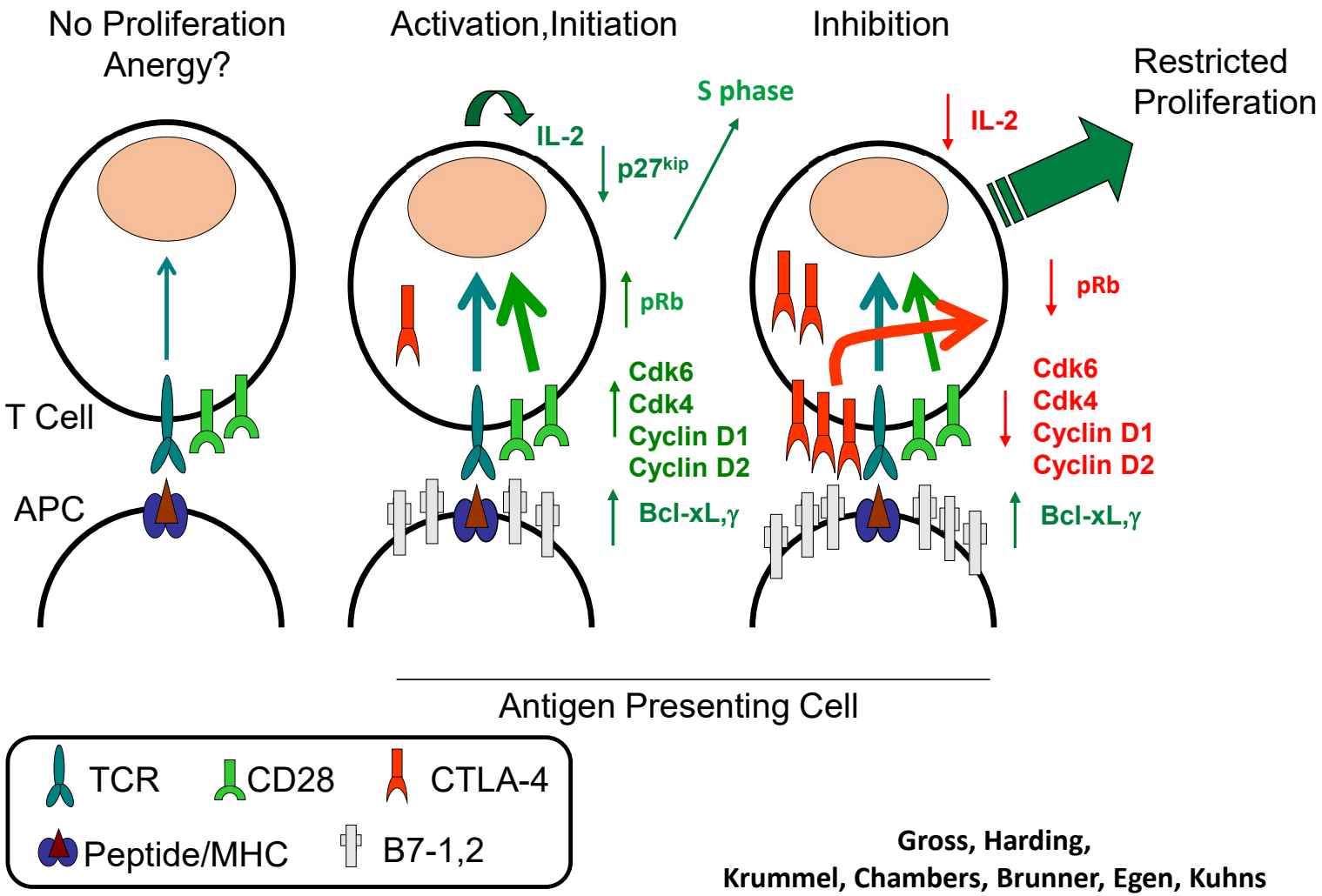
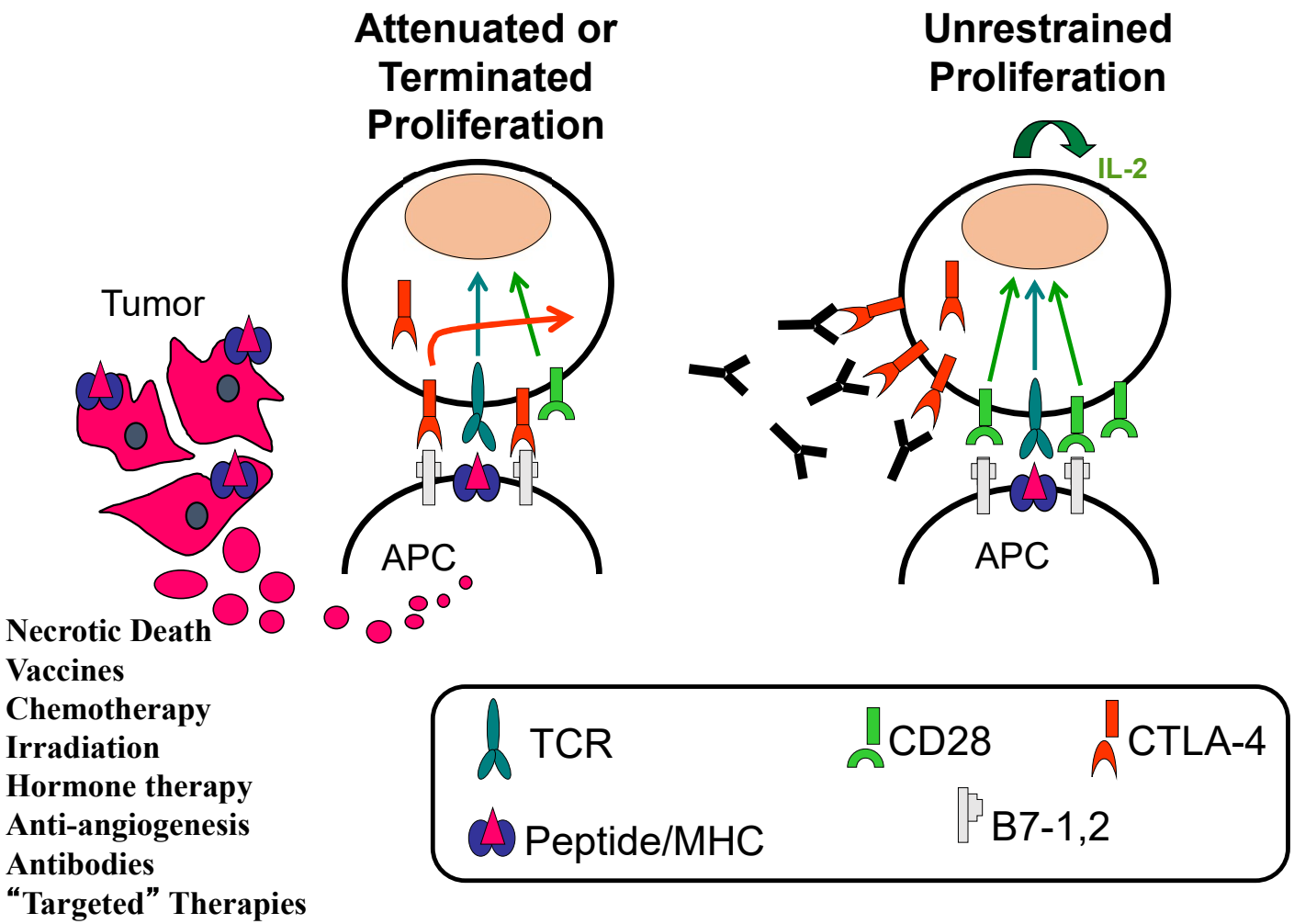
Dynamic Integration of TCR and Costimulatory Signals

circa 1996



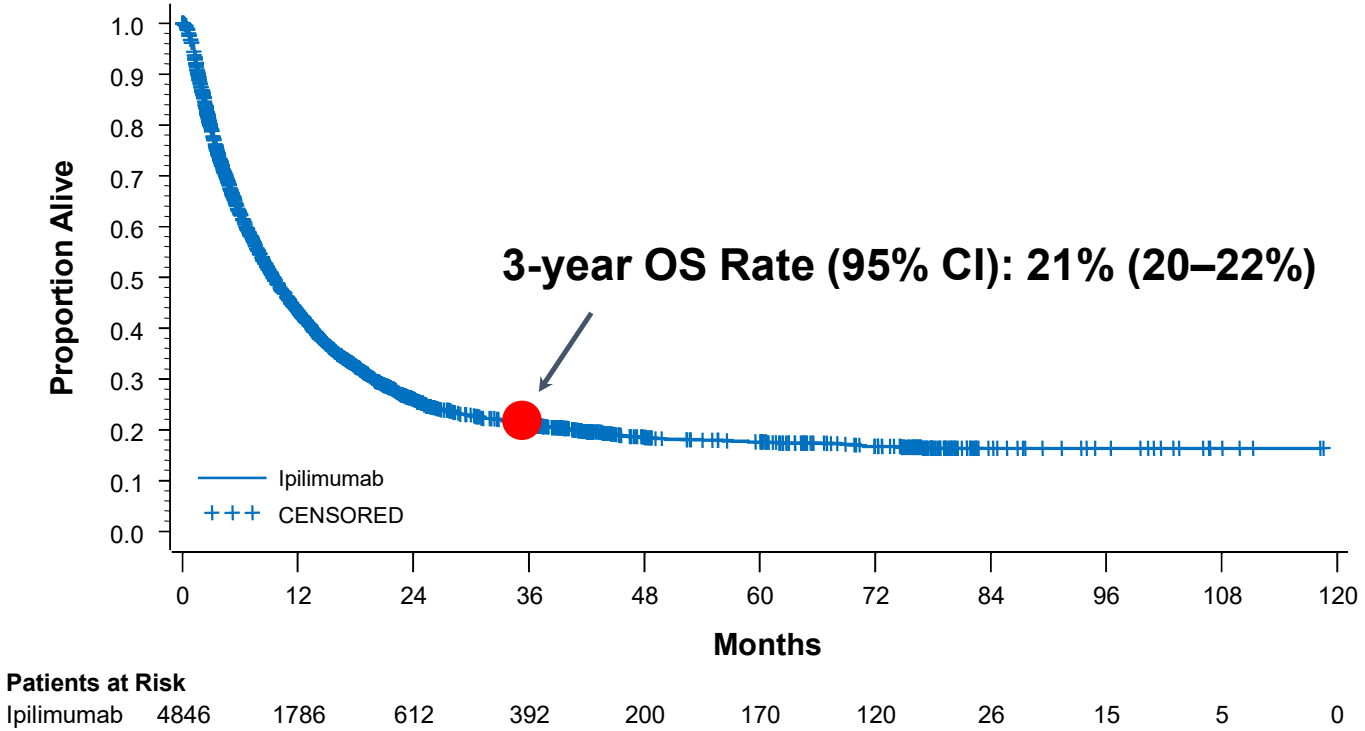
Gross, Harding,
Krummel, Chambers, Brunner, Egen, Kuhns

CTLA-4 Blockade
Enhances Tumor-Specific Immune Responses



Ipilimumab (anti-CTLA-4) in Metastatic Melanoma

(pooled data from 4846 patients)

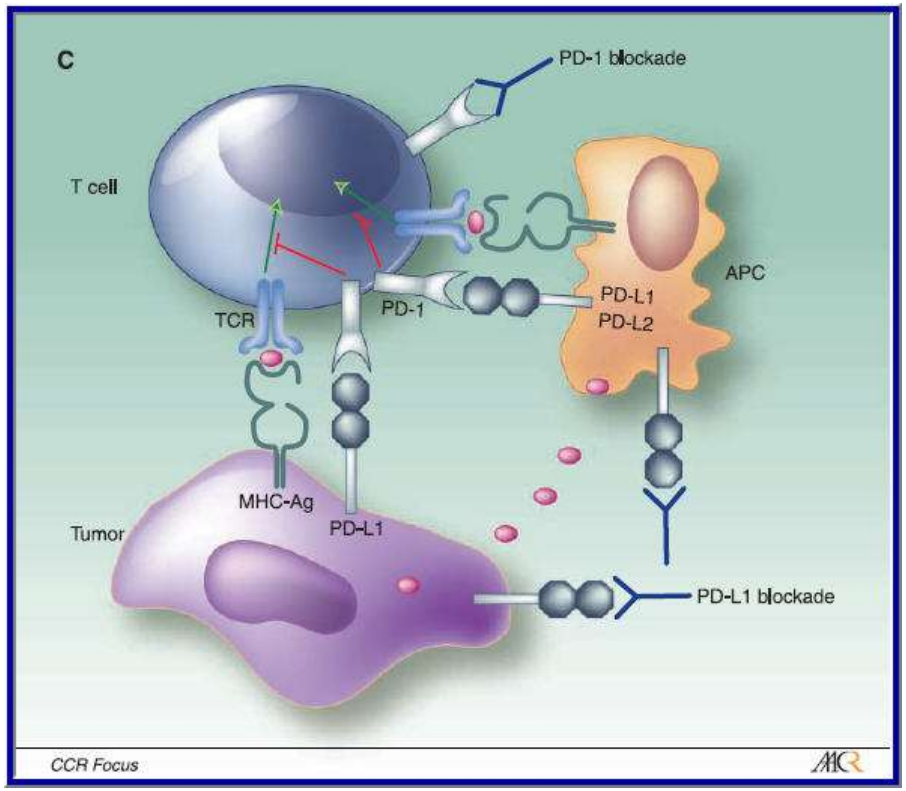


Patients at Risk

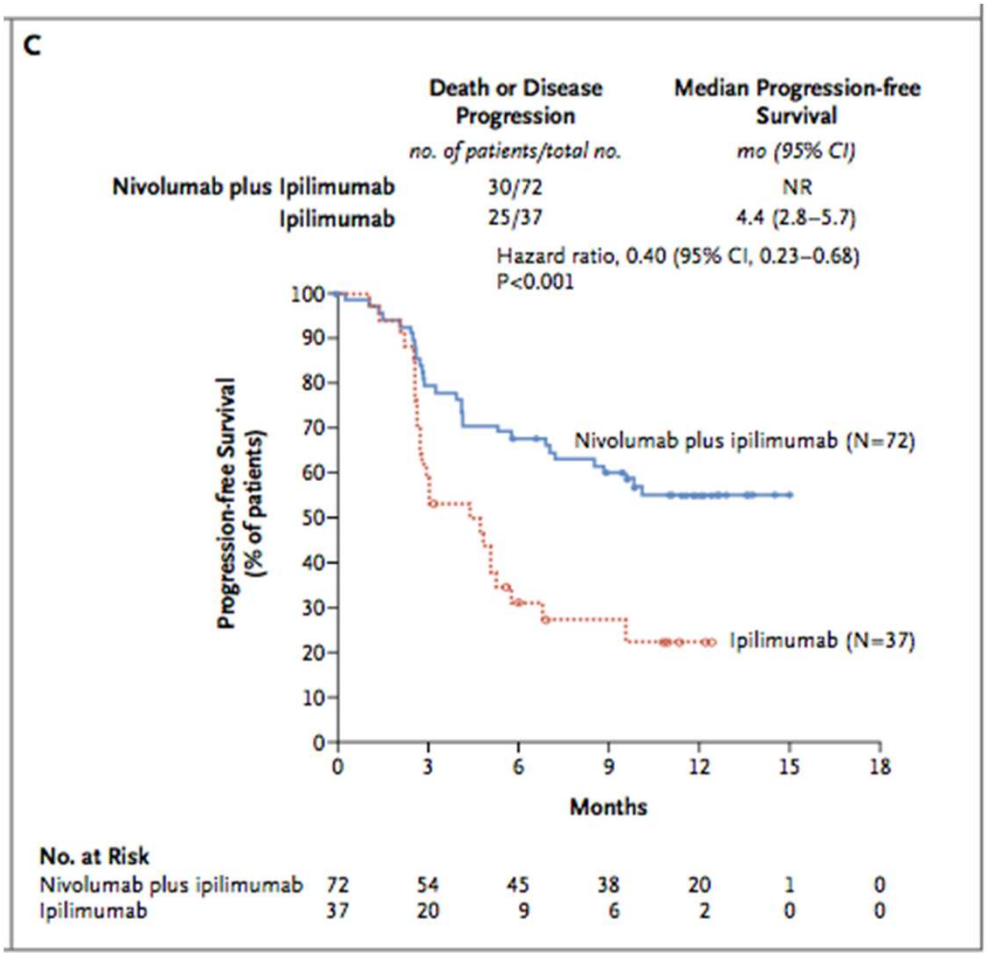
Ipilimumab	4846	1786	612	392	200	170	120	26	15	5	0

Schadendorf JCO 2015

Programmed Death 1
(PD-1)



Ipi/Nivo vs. Ipi in Metastatic Melanoma



Hodi NEJM 2015

FDA-Approvals of Immune Checkpoint Inhibitors
(by cancer type)

Melanoma
- **Ipilimumab (2011)**
- Nivolumab (2014)
- Ipilimumab + Nivolumab (2015)
- Pembrolizumab (2019)

Lung Carcinoma
- Nivolumab (2015)
- Pembrolizumab (2015)
- Atezolizumab (2016)
- Durvalumab (2018)

Renal Cell Carcinoma
- Nivolumab (2015)
- Ipilimumab + Nivolumab (2018)
- Avelumab (2019)

Colorectal Carcinoma
- Nivolumab (2017)
- Pembrolizumab (2017)
- Ipilimumab + Nivolumab (2018)

Head and Neck Squamous Cell Carcinoma
- Nivolumab (2016)
- Pembrolizumab (2016)

Lymphoma
- Nivolumab (2016)
- Pembrolizumab (2017)

Hepatocellular Carcinoma
- Nivolumab (2017)
- Pembrolizumab (2018)

Merkel Cell Carcinoma
- Avelumab (2017)
- Pembrolizumab (2018)

Gastric/Gastroesophageal Adenocarcinoma
- Pembrolizumab (2017)

Cervical Carcinoma
- Pembrolizumab (2018)

Breast Carcinoma
- Atezolizumab (2019)

Cutaneous Squamous Cell Carcinoma
- Cemiplimab (2018)

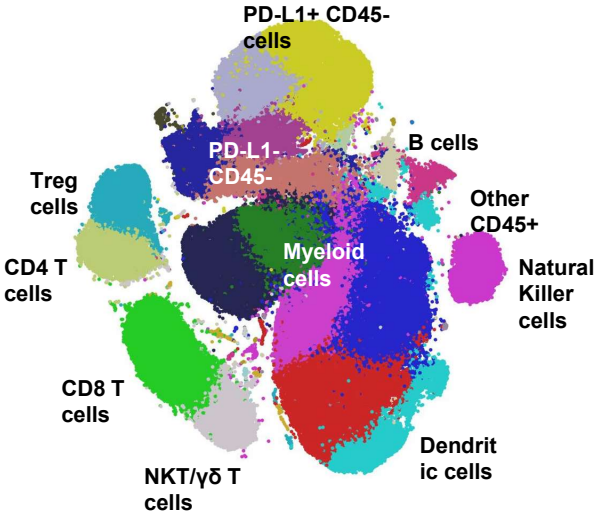
Esophageal Carcinoma
- Pembrolizumab (2019)

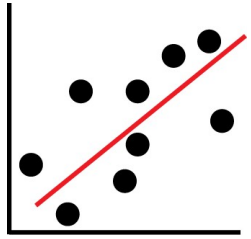
Uterine Carcinoma
- Pembrolizumab (2019)

Urothelial Carcinoma
- Atezolizumab (2016)
- Avelumab (2017)
- Durvalumab (2017)
- Nivolumab (2017)
- Pembrolizumab (2017)

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

Can we identify checkpoint blockade responsive T cell populations?





CyTOF analysis of murine TILs (43 Parameters)

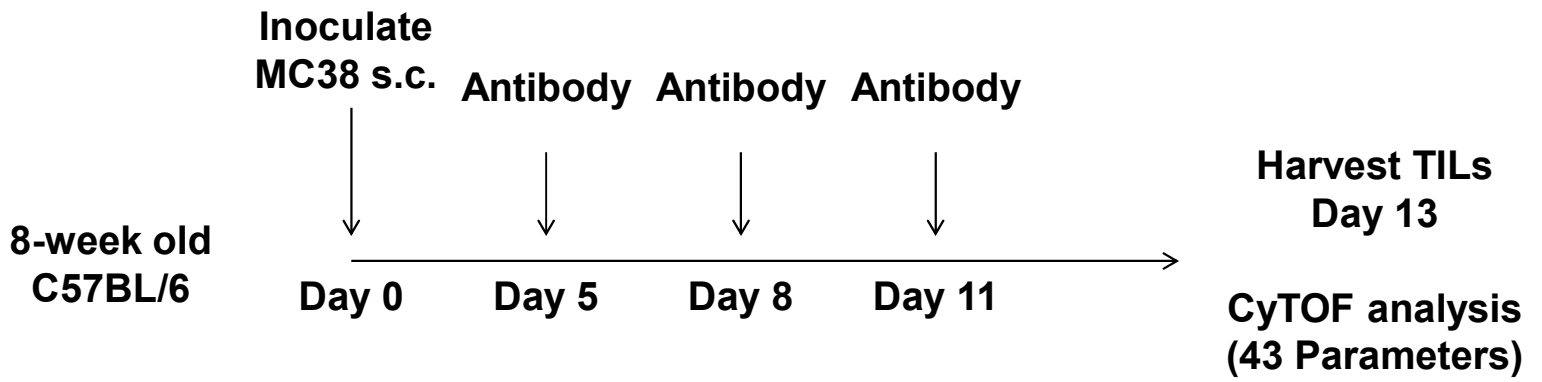
+/- checkpoint blockade

Unsupervised population identification

Identify associations with treatment and outcome

Spencer Wei

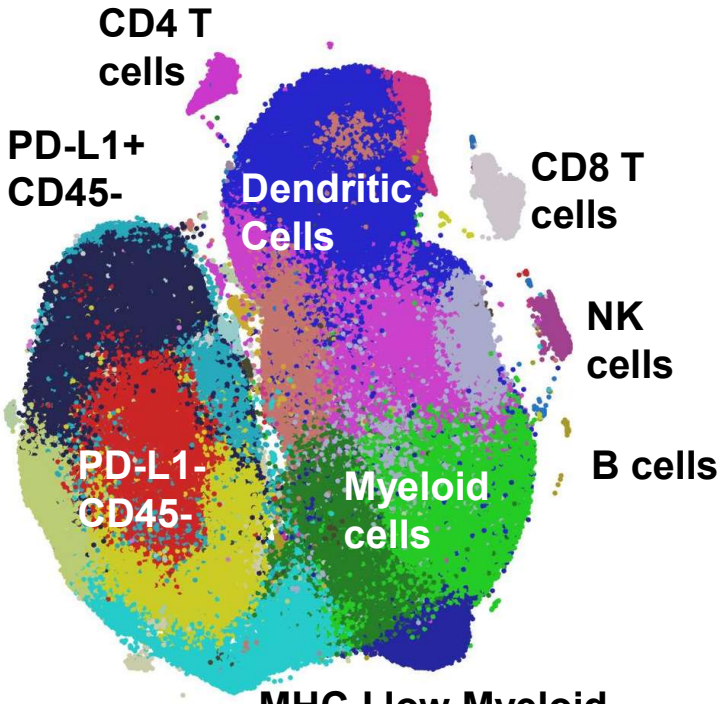
Mass cytometry analysis of MC38 TILs



Wei et al *Cell* 2017

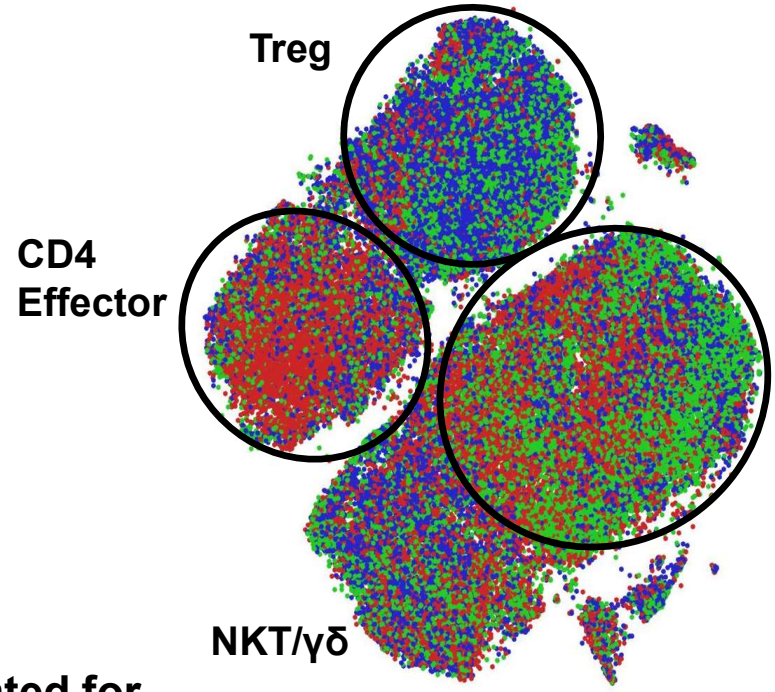
Mass Cytometry Analysis of MC38

Untreated



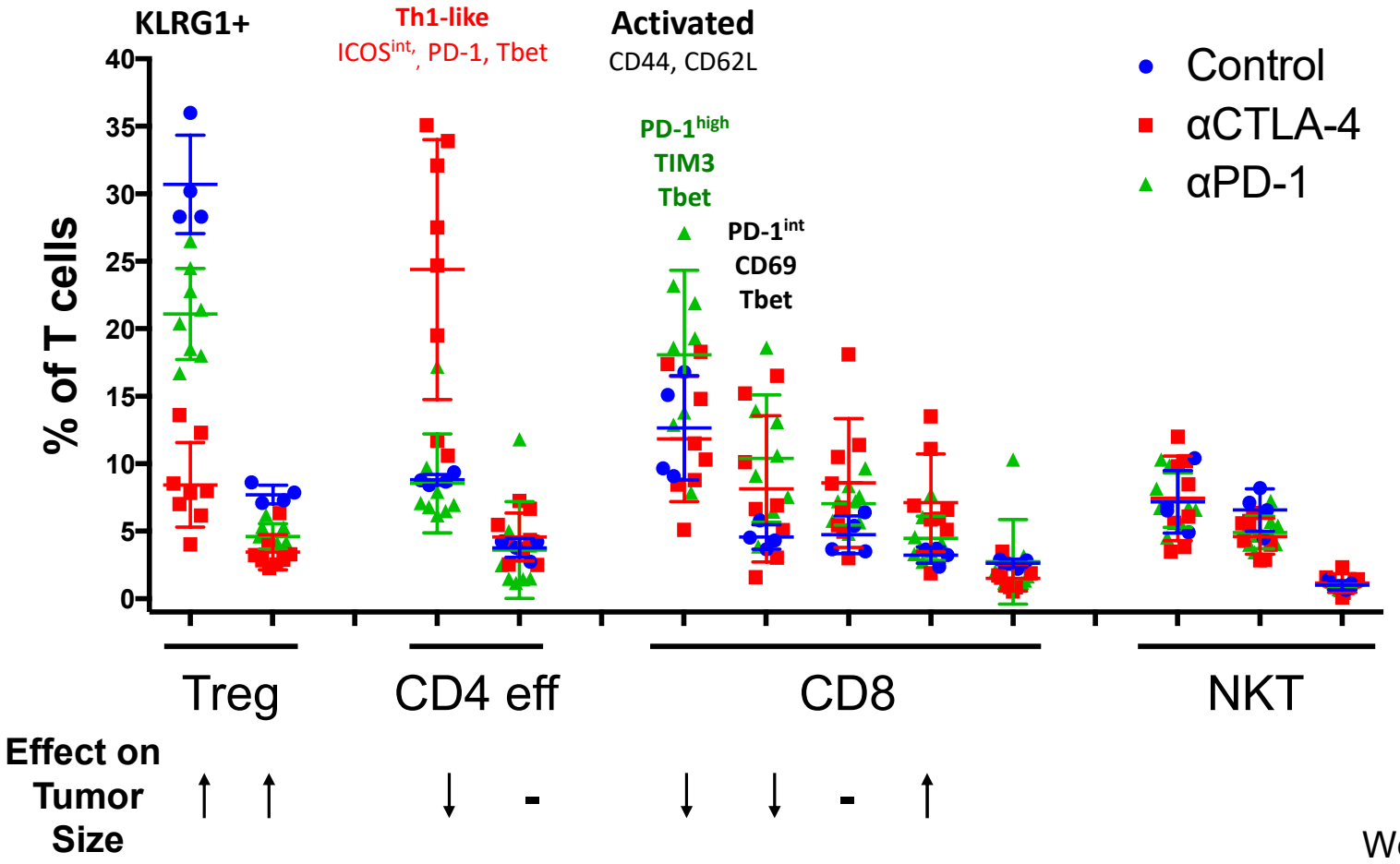
Gated for CD45+

Treated



Gated for CD45+, CD3ε+

Checkpoint blockade modulates MC38 infiltrating T cell population frequencies



Wei et al *Cell* 2017

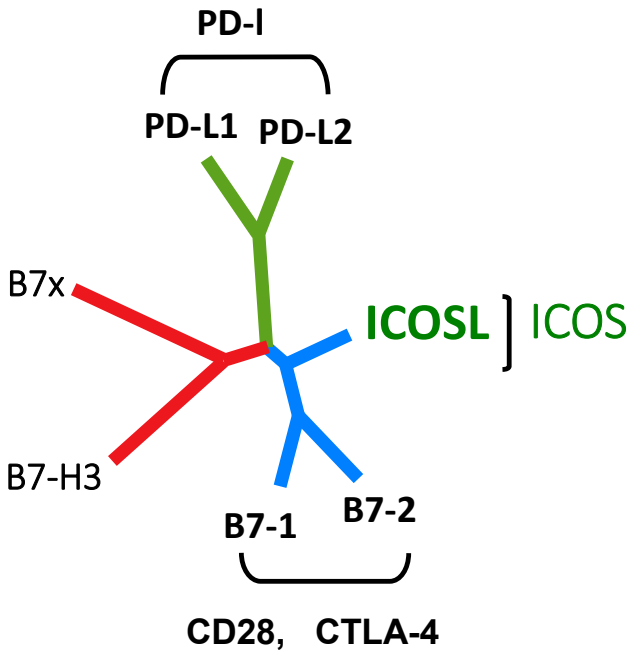
CELLULAR TARGETS OF CHECKPOINT BLOCKADE

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*



Identification of unusual ICOS+ Th1-like CD4 cells that arise after CTLA-4 Blockade

Clinical Studies

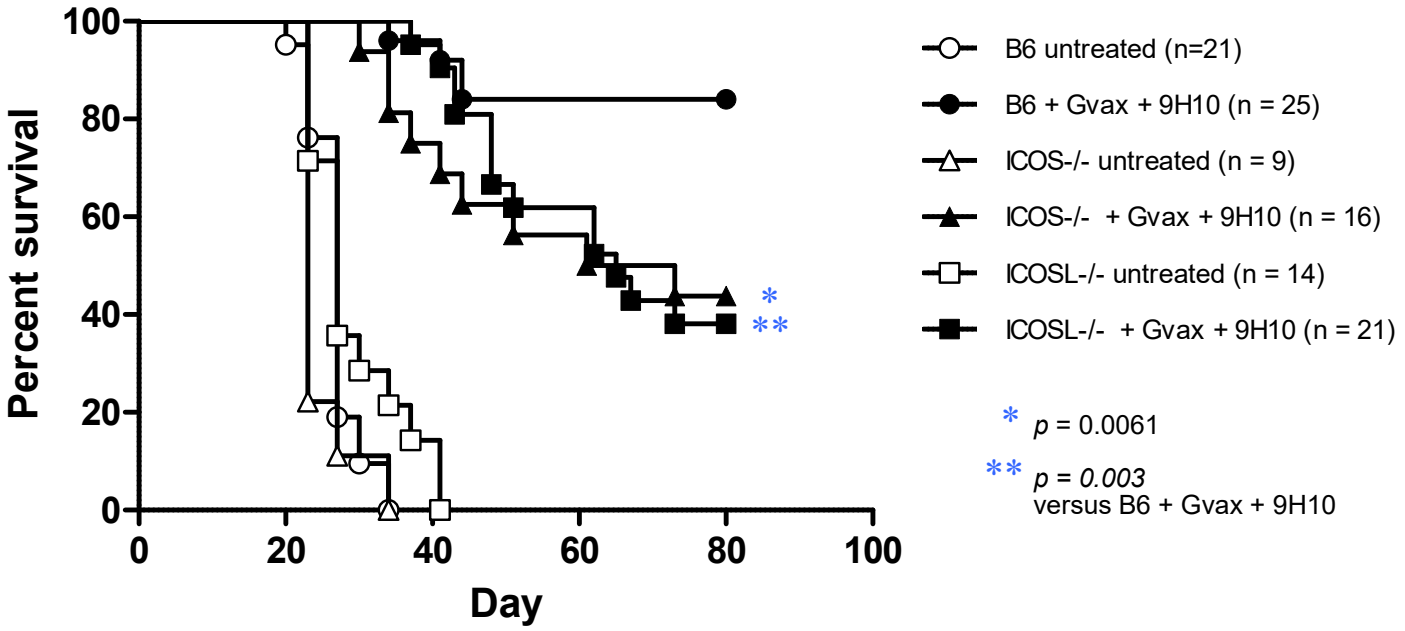
- 2-10 fold increase in tumor and blood after Ipi
- Contains tumor specific IFNγ– & TNFα–producing CD4 cells
- Sustained increase associated with longer survival
- *Pharmacodynamic marker of Ipi activity*

Mouse Studies

- Essential for optimal efficacy of CTLA-4 blockade
- Signaling via PI3K binding motif enhances Tbet expression
- Can be targeted to enhance efficacy of CTLA-4 blockade

Sharma

ICOS/ICOSL pathway is necessary for optimal anti-tumor responses in the setting of CTLA-4 blockade



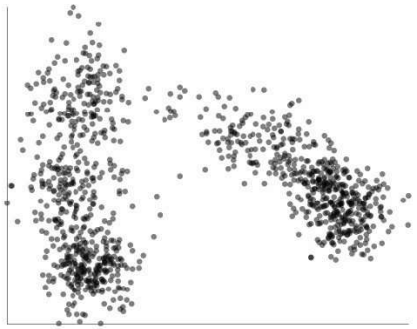
Fu et al., *Cancer Research, 2011*

Does negative costimulation effect the regulation of T cell differentiation?

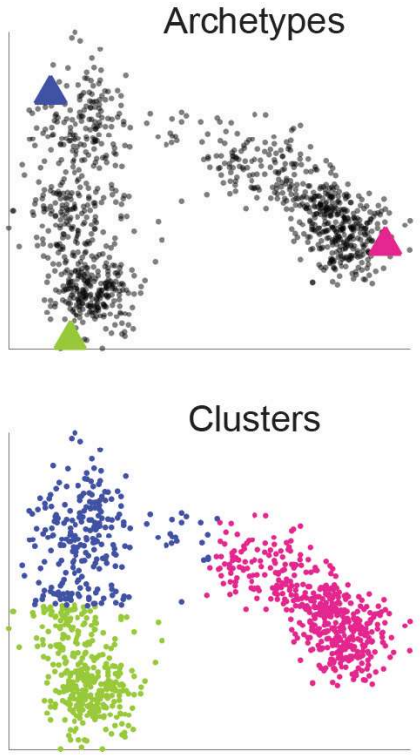
Comprehensive profiling of cell types in the absence of CTLA-4

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

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

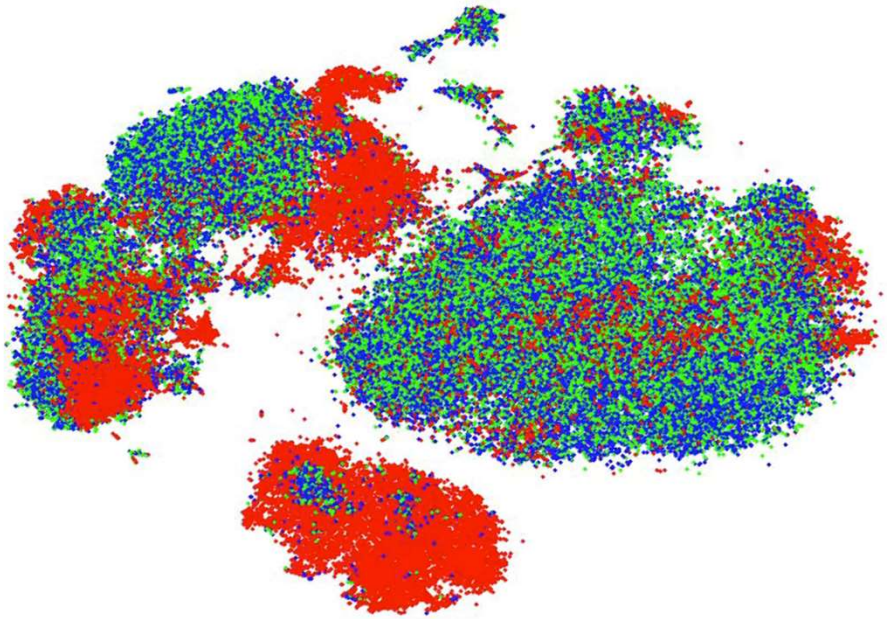


Single-cell data



Wei et al *Immunity* 2019

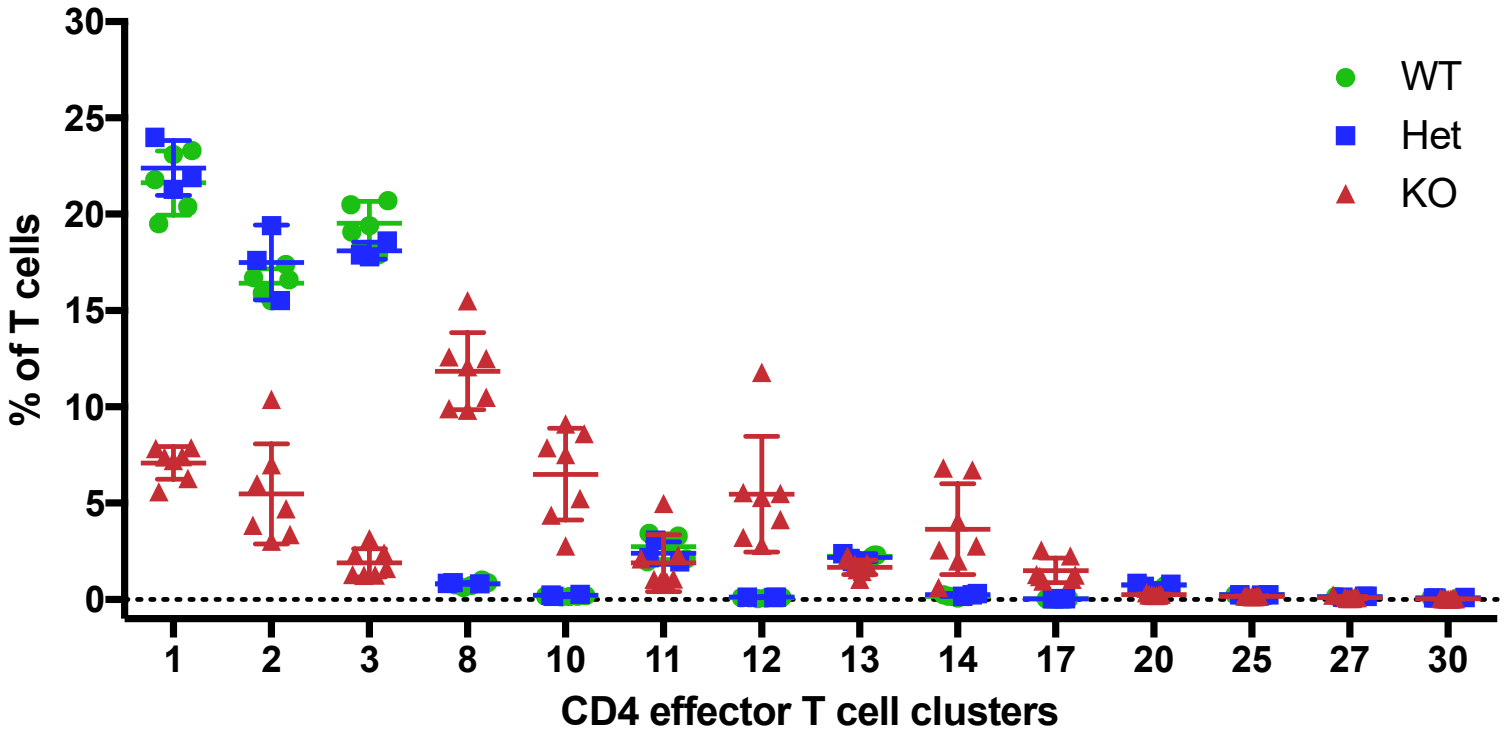
New T cell phenotypes arise in the absence of CTLA-4



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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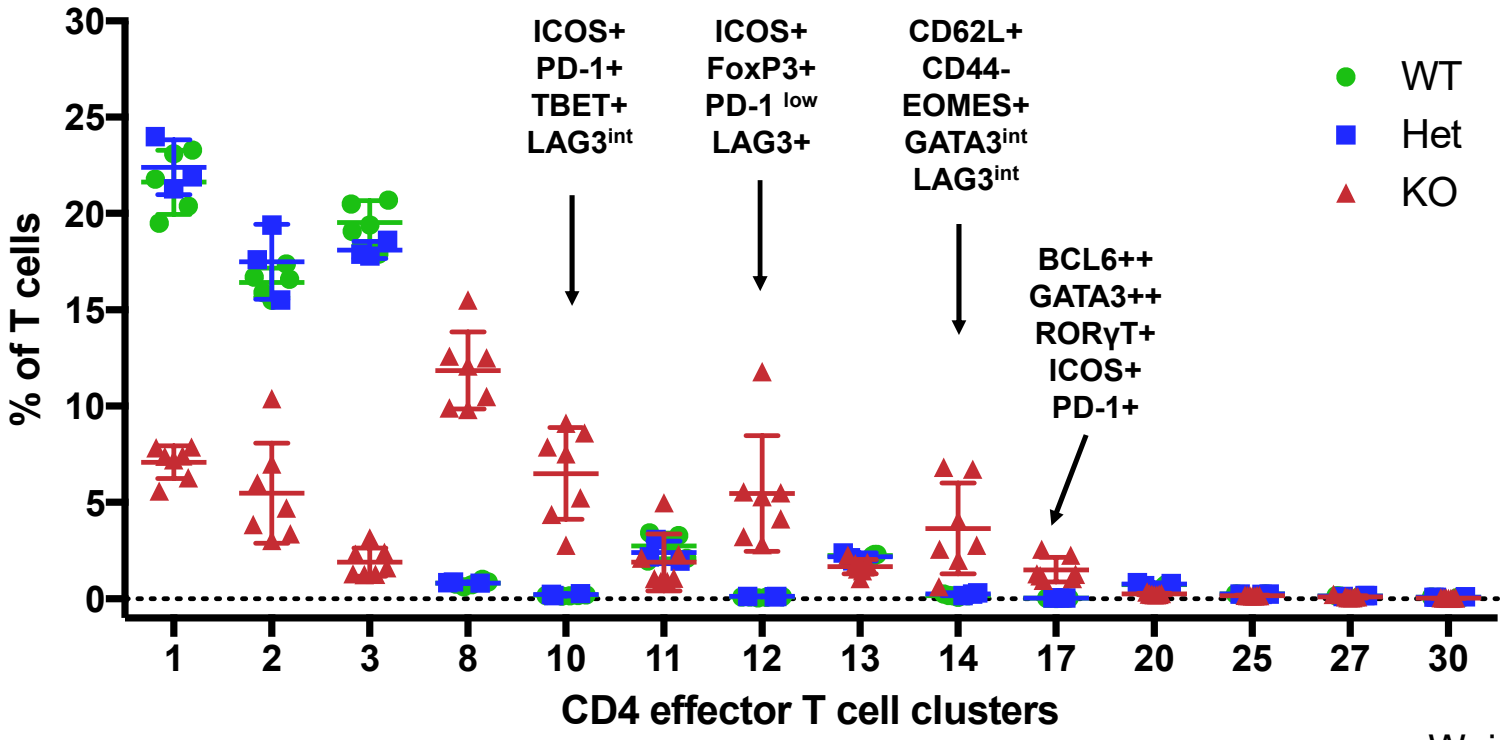
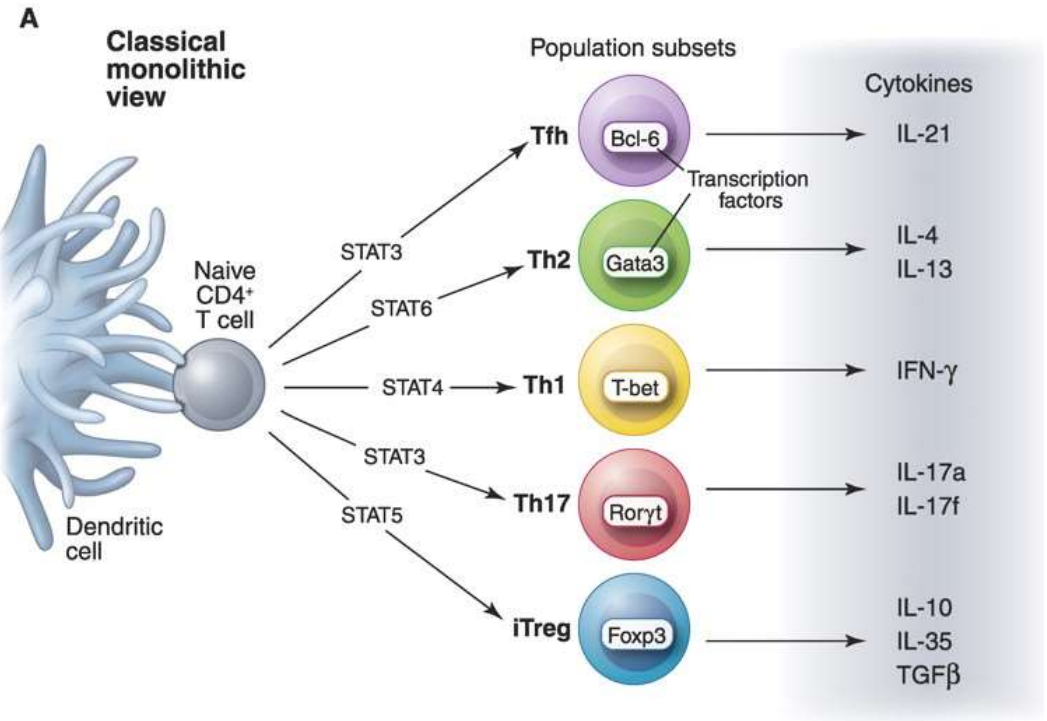
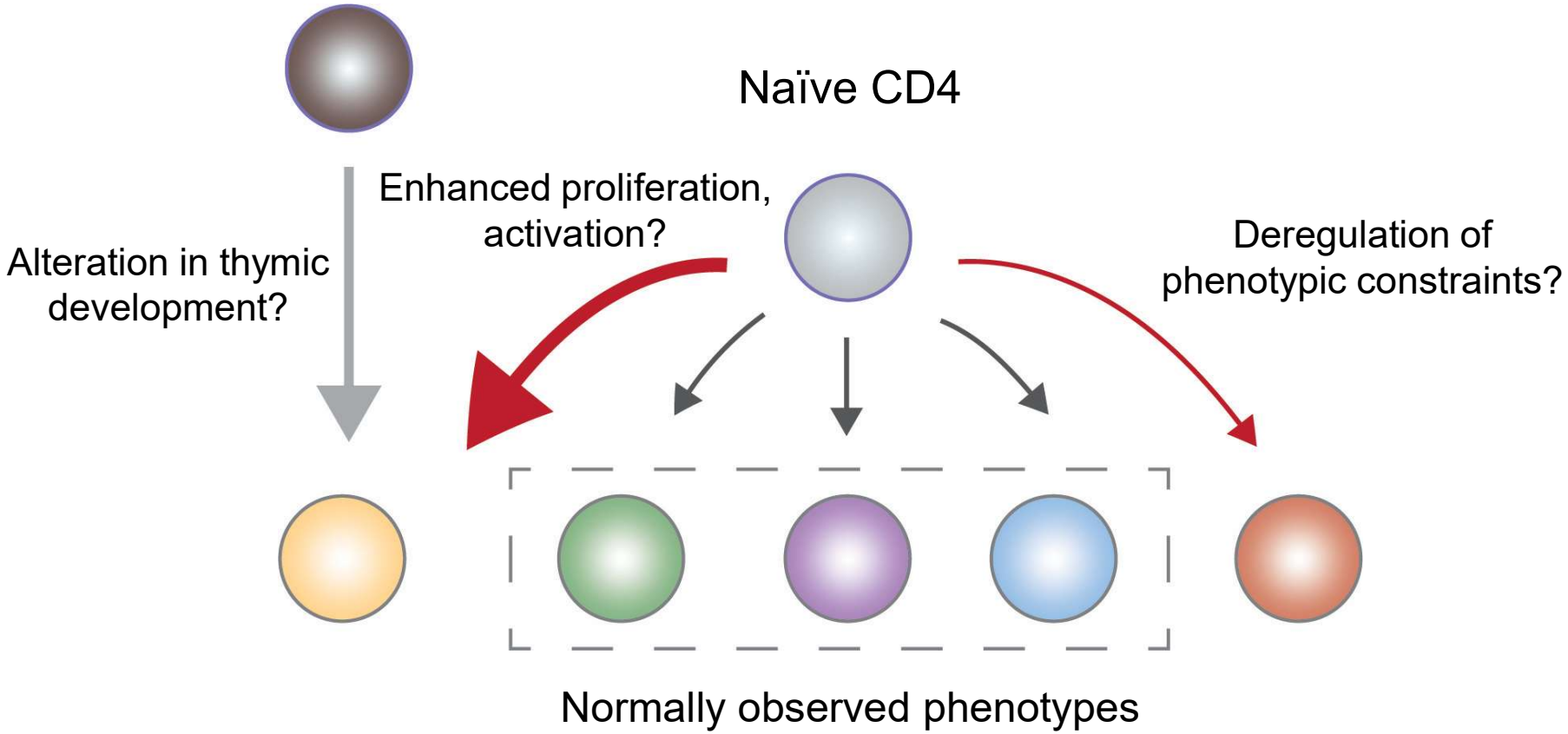


Wei et al *Immunity* 2019

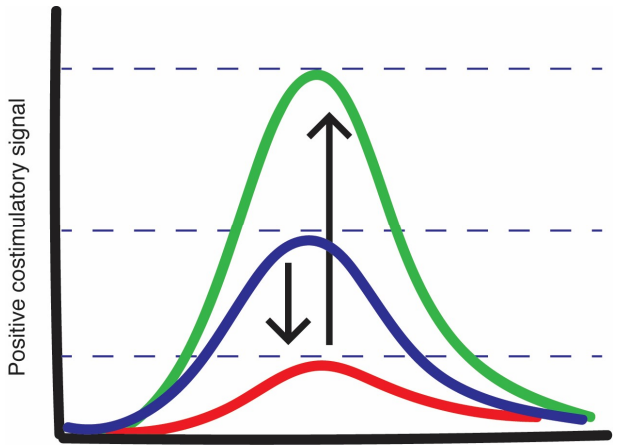
CD4 T cell differentiation is complex
How are phenotypes, lineages, and boundaries defined?



What underlies the generation of these subsets?



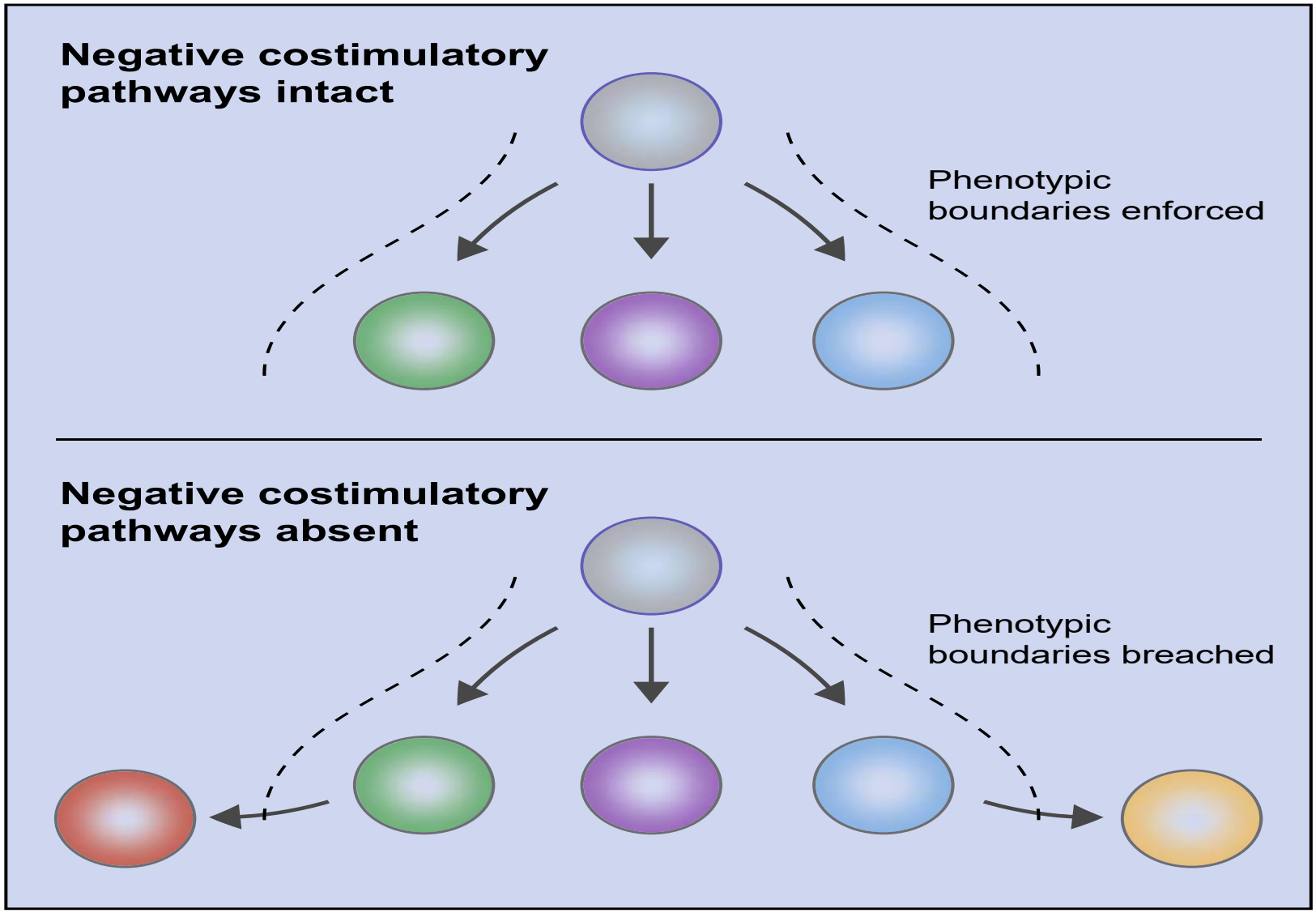
Does negative costimulation regulate T cell differentiation?



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

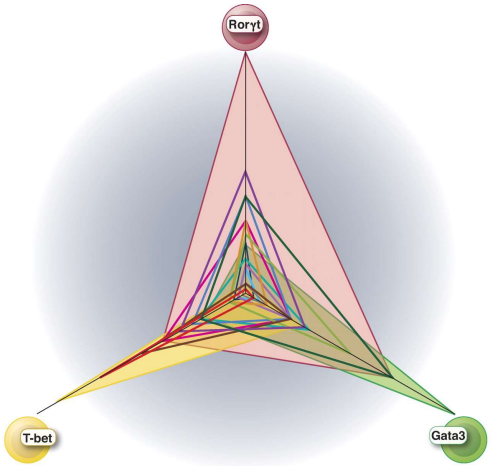
Maximum signal under normal conditions

Attenuated signal due to CTLA-4 regulation


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

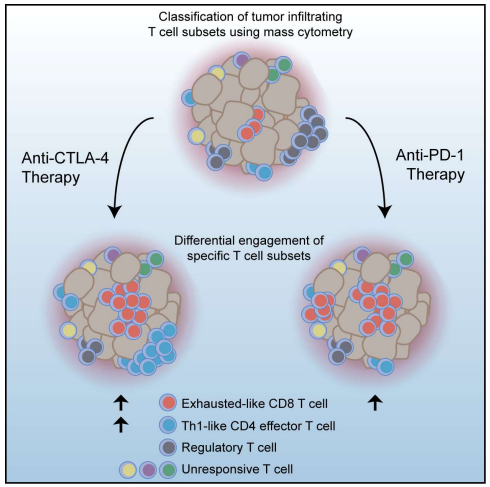
Potential implications

Evidence for a ‘nuanced model’ of T cell differentiation



O’Shea and Paul. *Science* (2010)

Role of T cell differentiation in mechanisms of immunotherapies



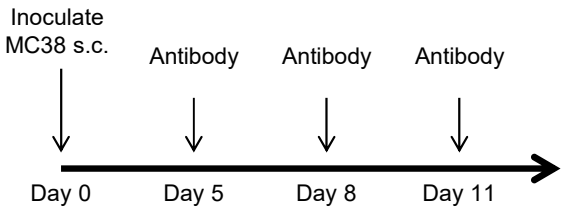
Wei et al. *Cell* (2017)

How do these cellular mechanisms interact?

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

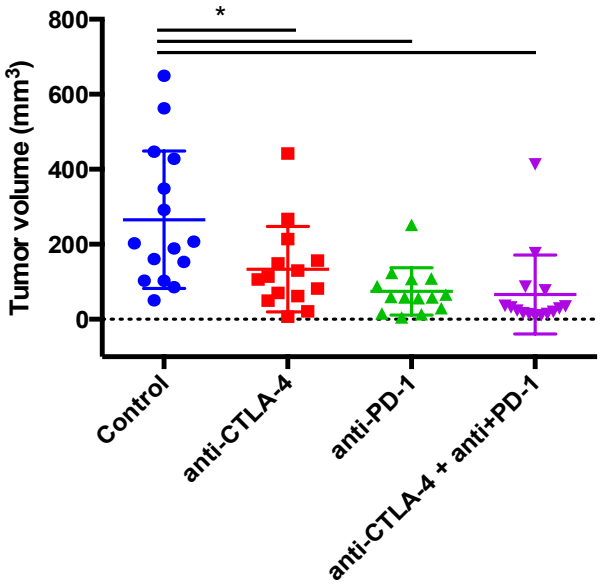
Mass cytometry analysis of MC38 TILs

C57BL/6 mice



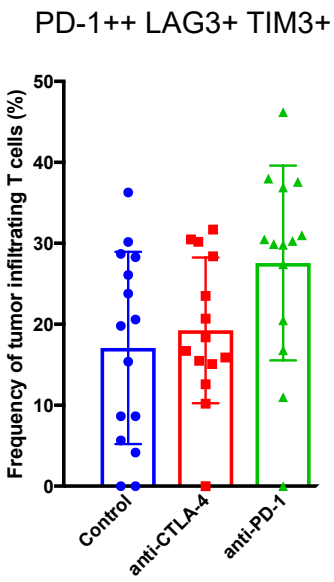
Harvest TILs Day 13

CyTOF analysis (43 Parameters)



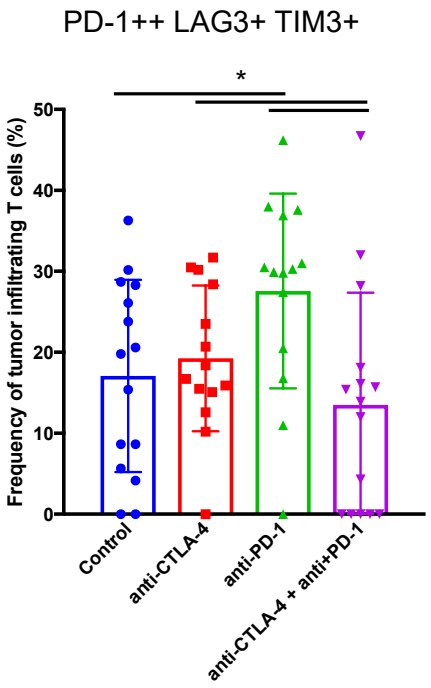
Wei et al *PNAS* 2019

Expansion of phenotypically exhausted CD8 T cells



Wei et al *PNAS* 2019

Combination therapy differentially affects CD8 subsets



Wei et al *PNAS* 2019

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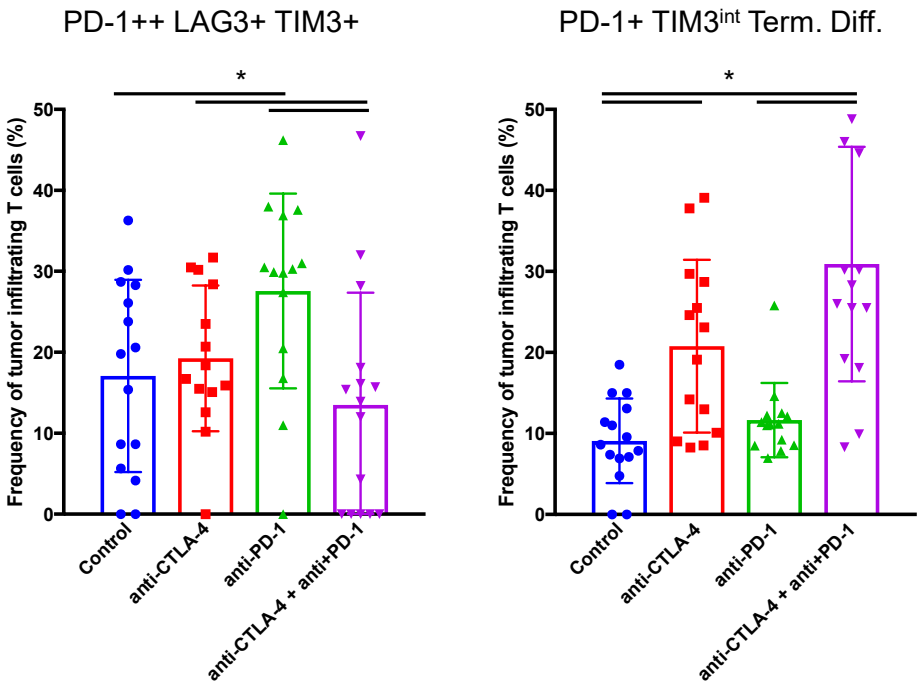
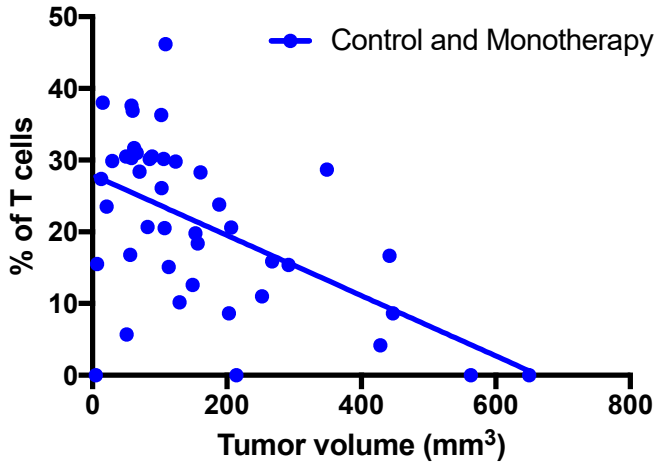


Wei et al in press *PNAS* 2019

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



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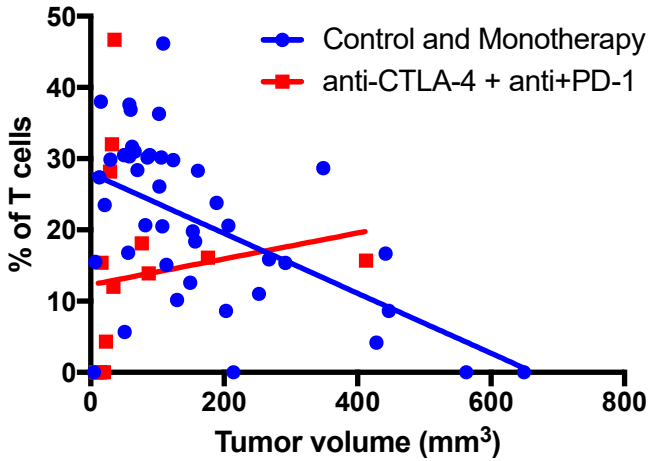
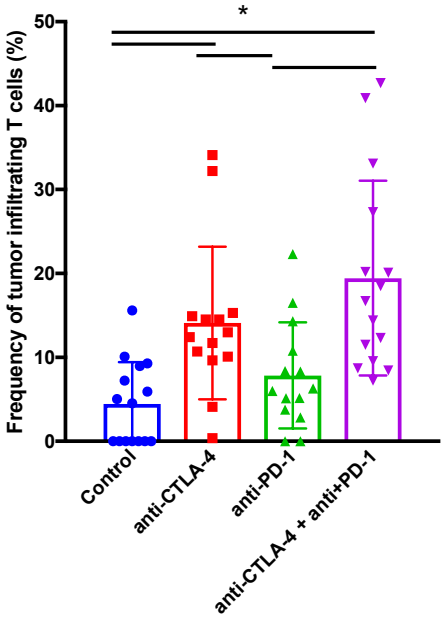


Wei et al in press *PNAS* 2019

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?

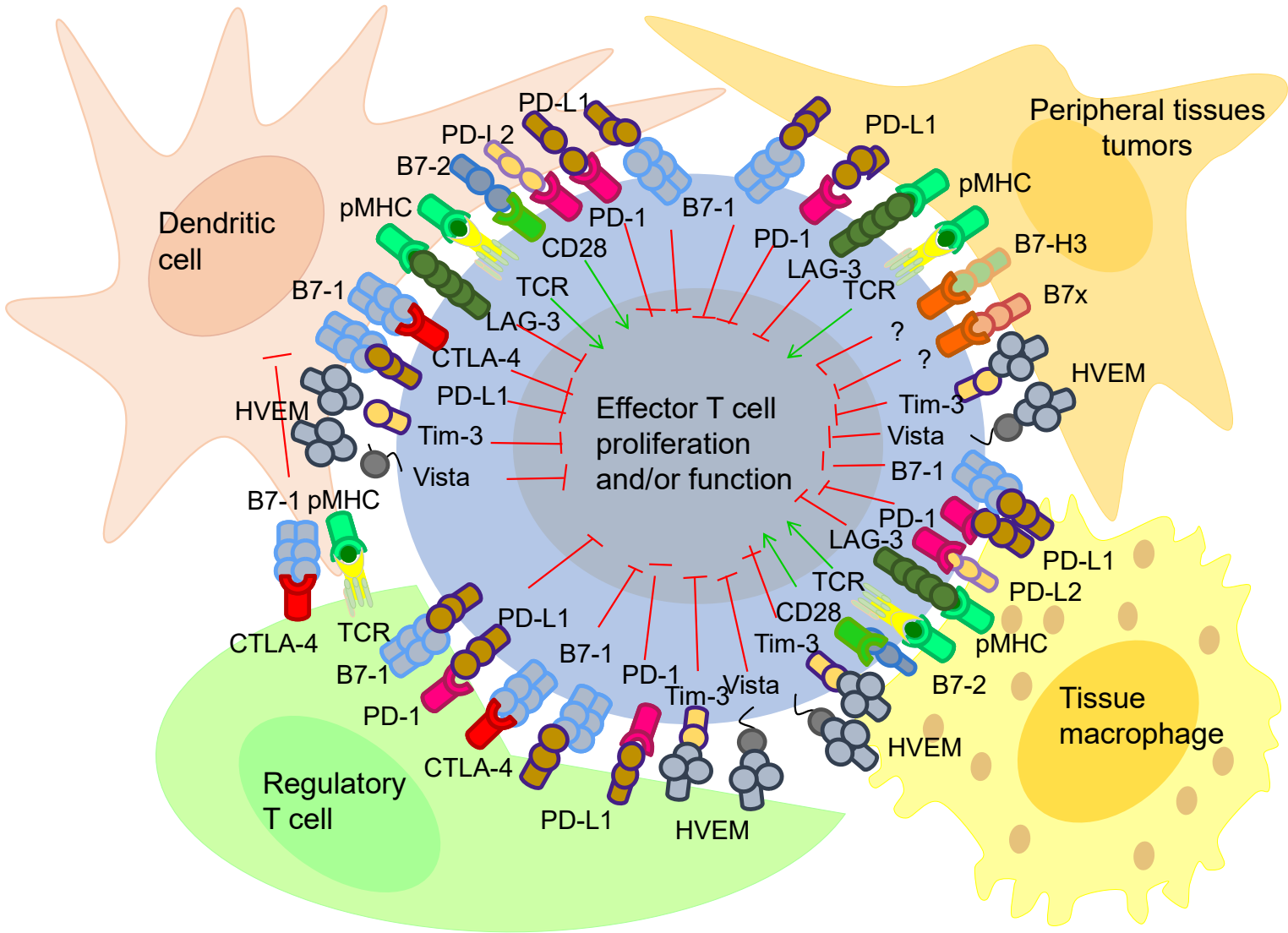
- Converted into CD8 effector T cells? *Unlikely, epigenetically fixed*

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*

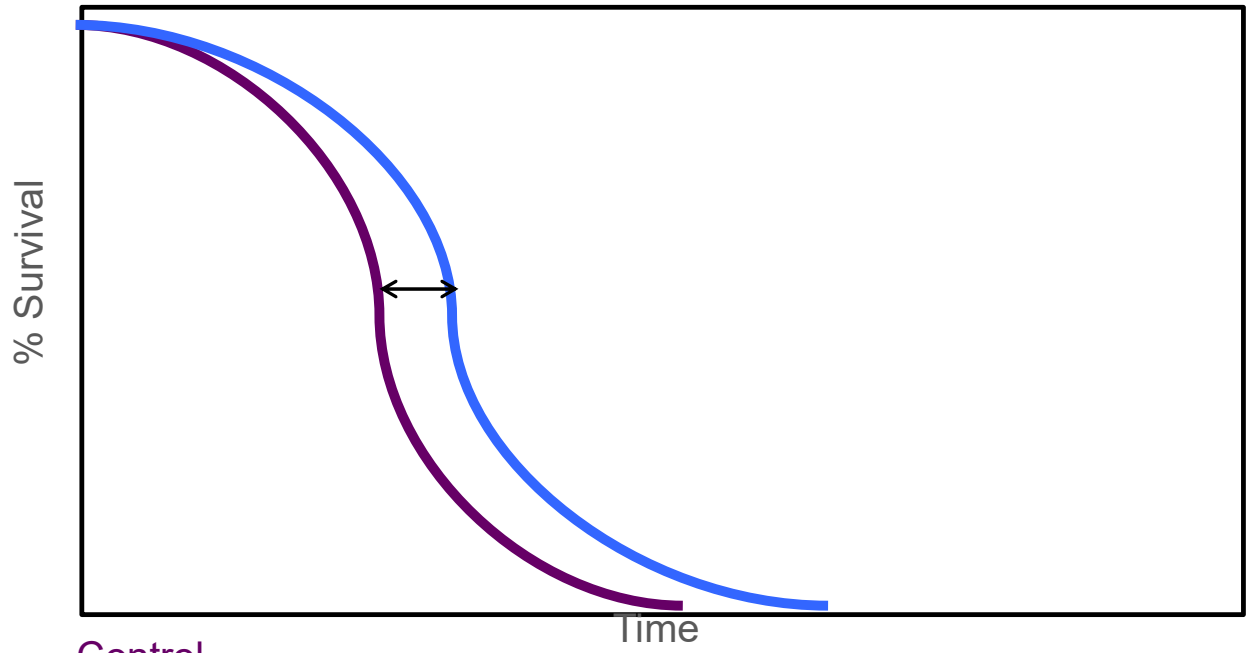
- Exhaustion of effectors prevented in presence of continued CD28 costimulation allowed by CTLA-4 blockade?


Dendritic cell
Peripheral tissues tumors
Tissue macrophage
Regulatory T cell
Effector T cell proliferation and/or function
PD-L1
PD-L 2
B7-2
pMHC
PD-1
B7-1
CD28
TCR
LAG-3
CTLA-4
HVEM
Tim-3
Vista
B7-1 pMHC
B7-H3
B7x
?
PD-L2

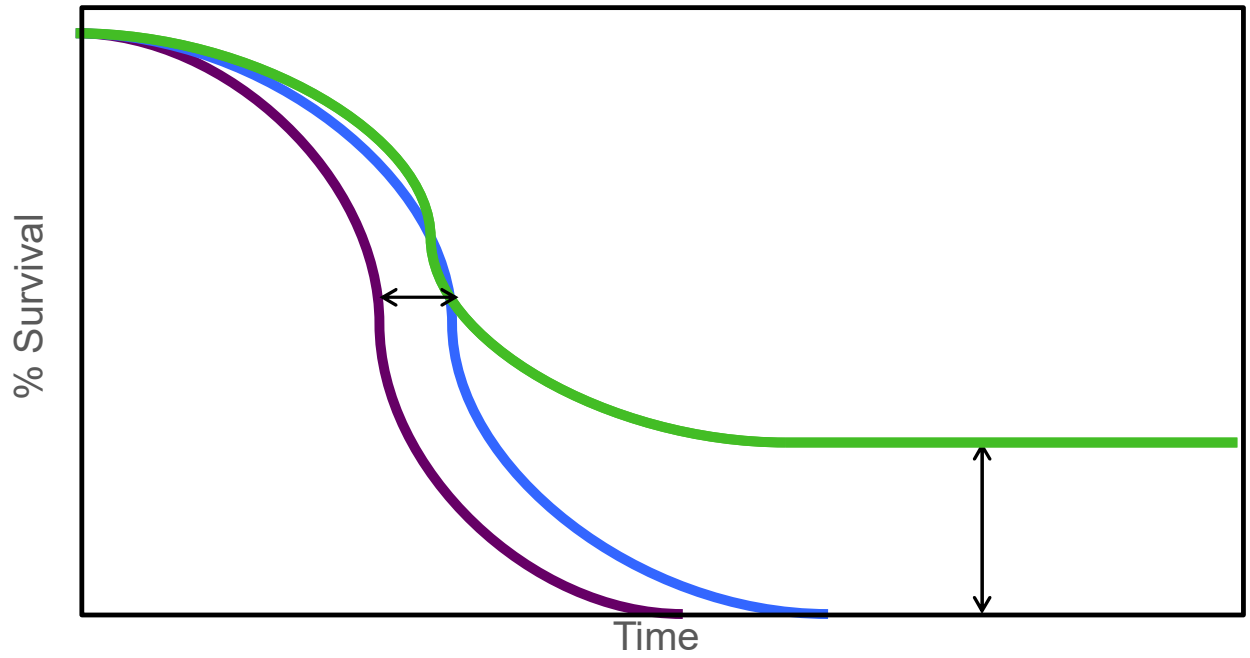
Combinations to enhance immune checkpoint targeting resulting in CURES

- Blocking multiple checkpoints (negative and positive)
- Conventional therapies
  - Chemotherpiy
  - ”Precision” Therapies
  - Radiation

Improving survival with combination therapy

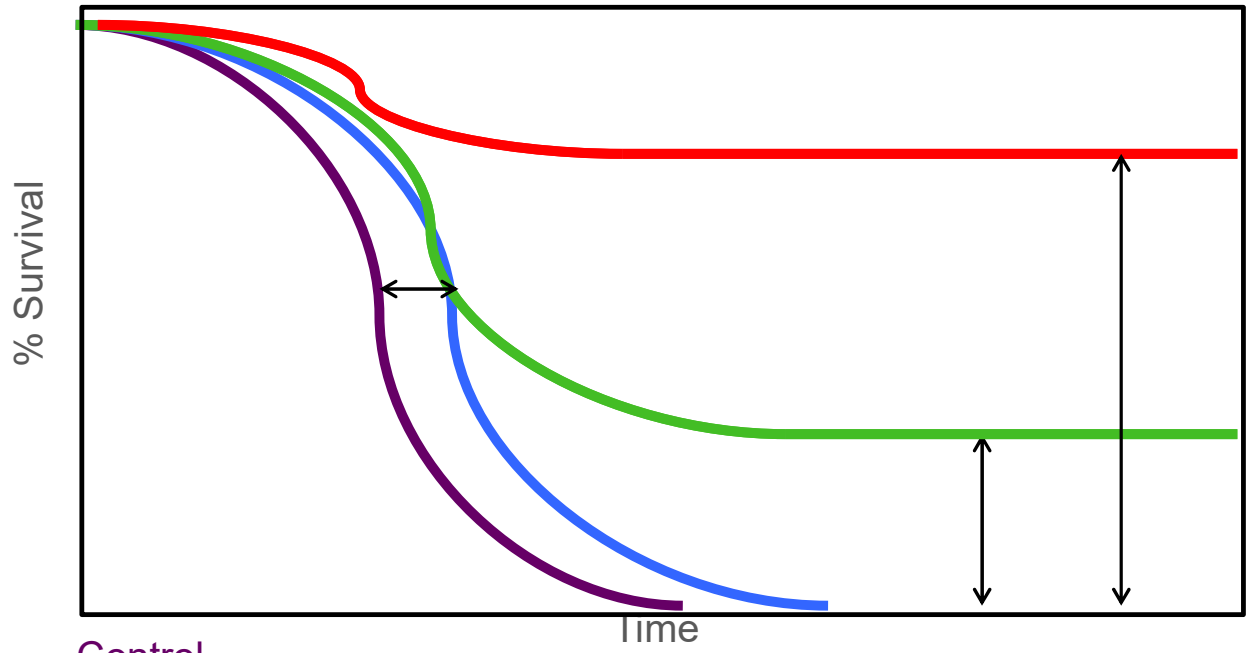


Improving survival with combination therapy



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

Improving survival with combination therapy



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