Applying basic immunology to treat cancer

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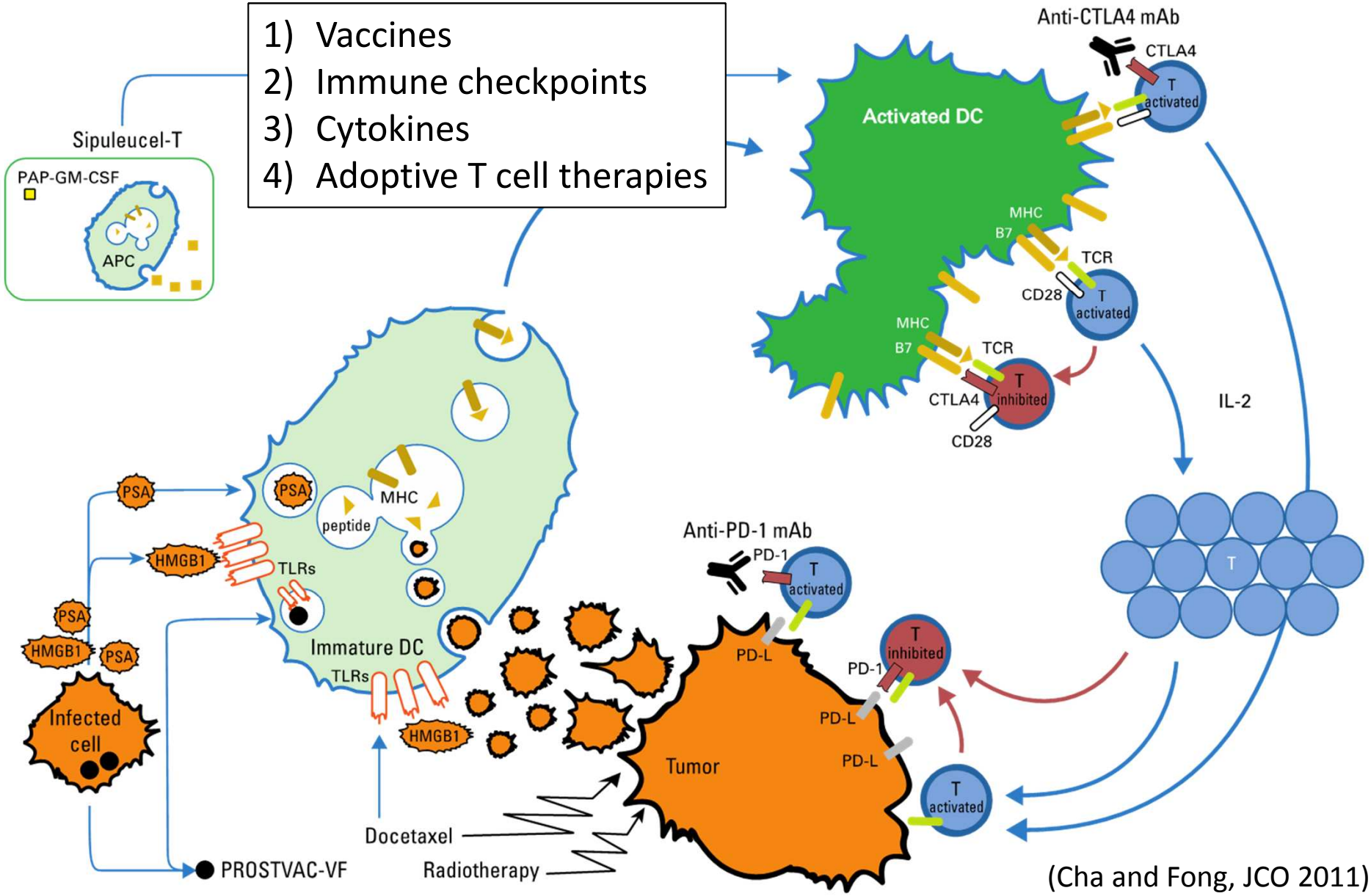
COI/disclosures

- We have received research support from Dendreon and Bristol Myer Squibb.
- Sipuleucel-T and Ipilimumab will be discussed in disease setting that are off-label and are investigational.

Approaches to cancer immunotherapy

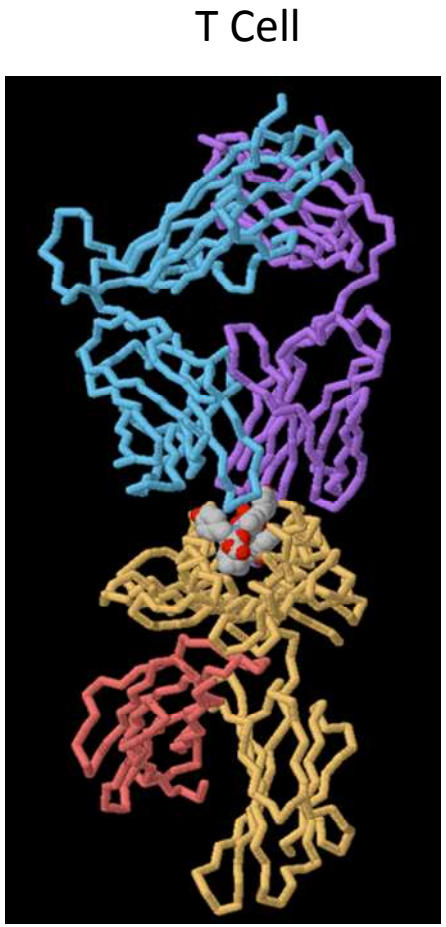
1) Vaccines
2) Immune checkpoints
3) Cytokines
4) Adoptive T cell therapies



(Cha and Fong, JCO 2011)

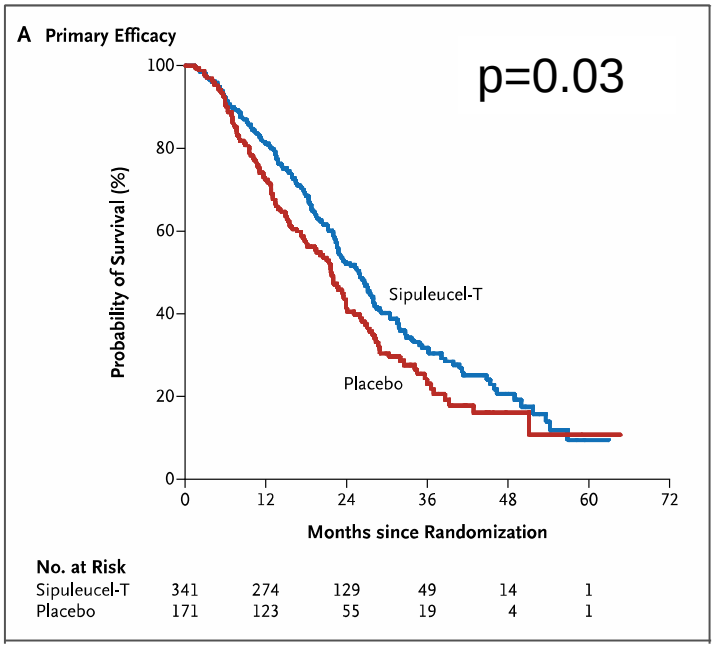
Candidate tumor antigens

Class	Antigen
Developmental:	Mage, Gage, Lage families
(cancer/testis)	NY-ESO-1
	telomerase
Viral:	EBV, HPV
Overexpressed:	Her2*neu*, CEA, Muc-1
Differentiation antigens:	Prostate Acid Phos, PSA, PSMA
	tyrosinase, gp100, Mart-1/Melan-A
Tumor specific:	Id, bcr-abl
	p53, *ras*
	Tumor specific mutations

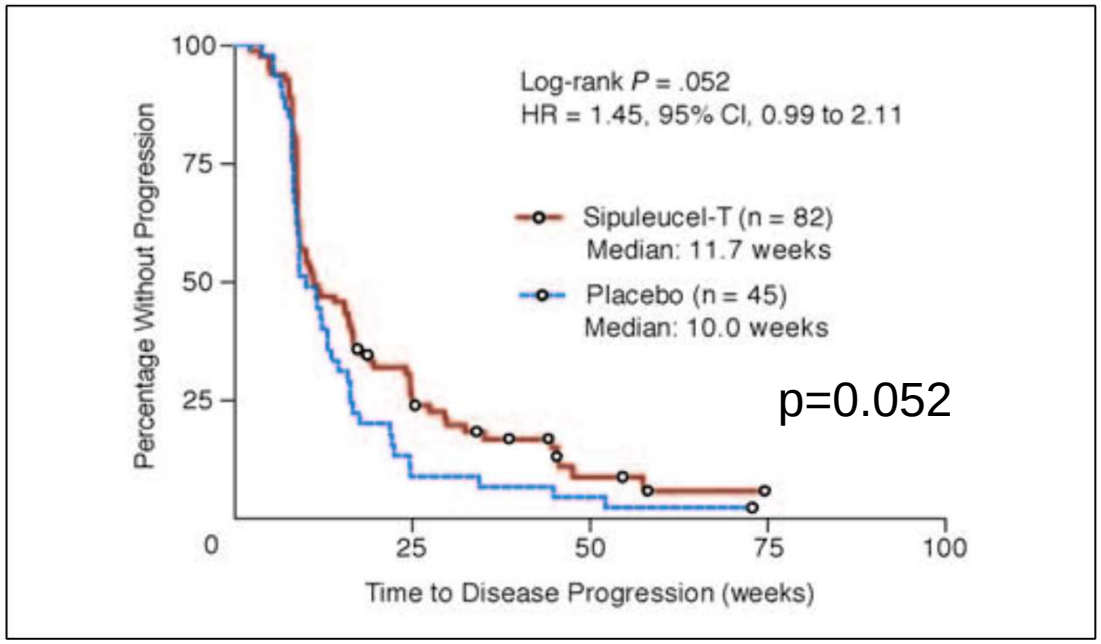


Sipuleucel-T improves overall survival in metastatic castration resistant prostate cancer (CRPC)

Overall Survival

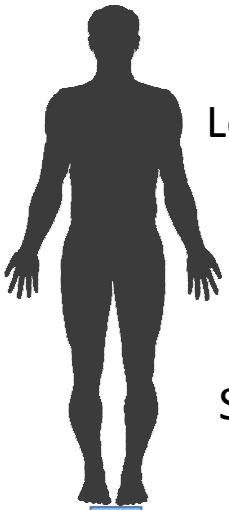


PFS



(Small JCO 2006, Kantoff NEJM 2010)

Sipuleucel-T treatment generates T cell responses in the prostate



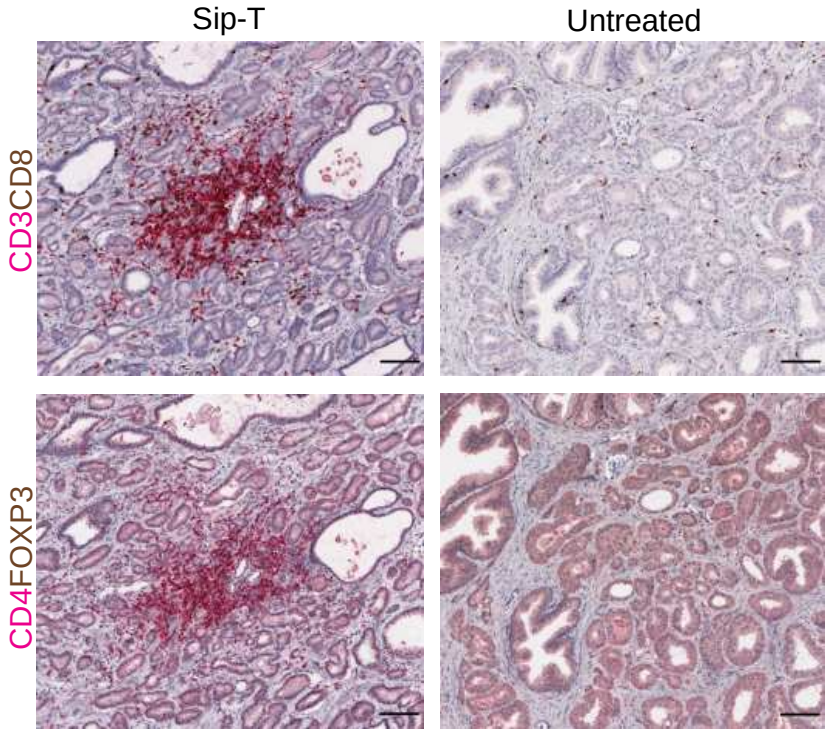
Leukapheresis

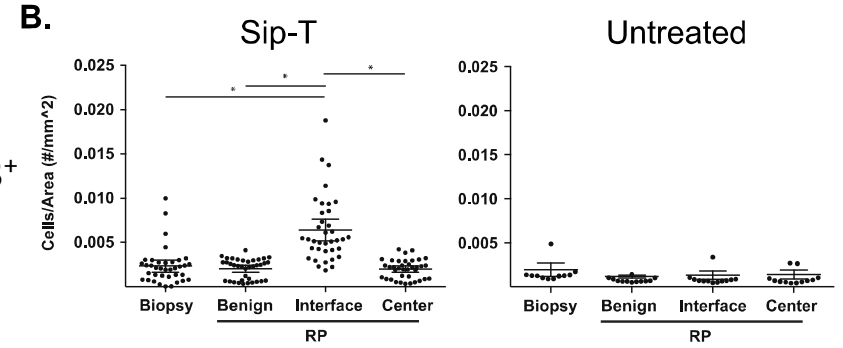
PBMC co-incubated with PAP/GM-CSF fusion

Sipuleucel-T x 3

Radical Prostatectomy → Immunohistochemistry

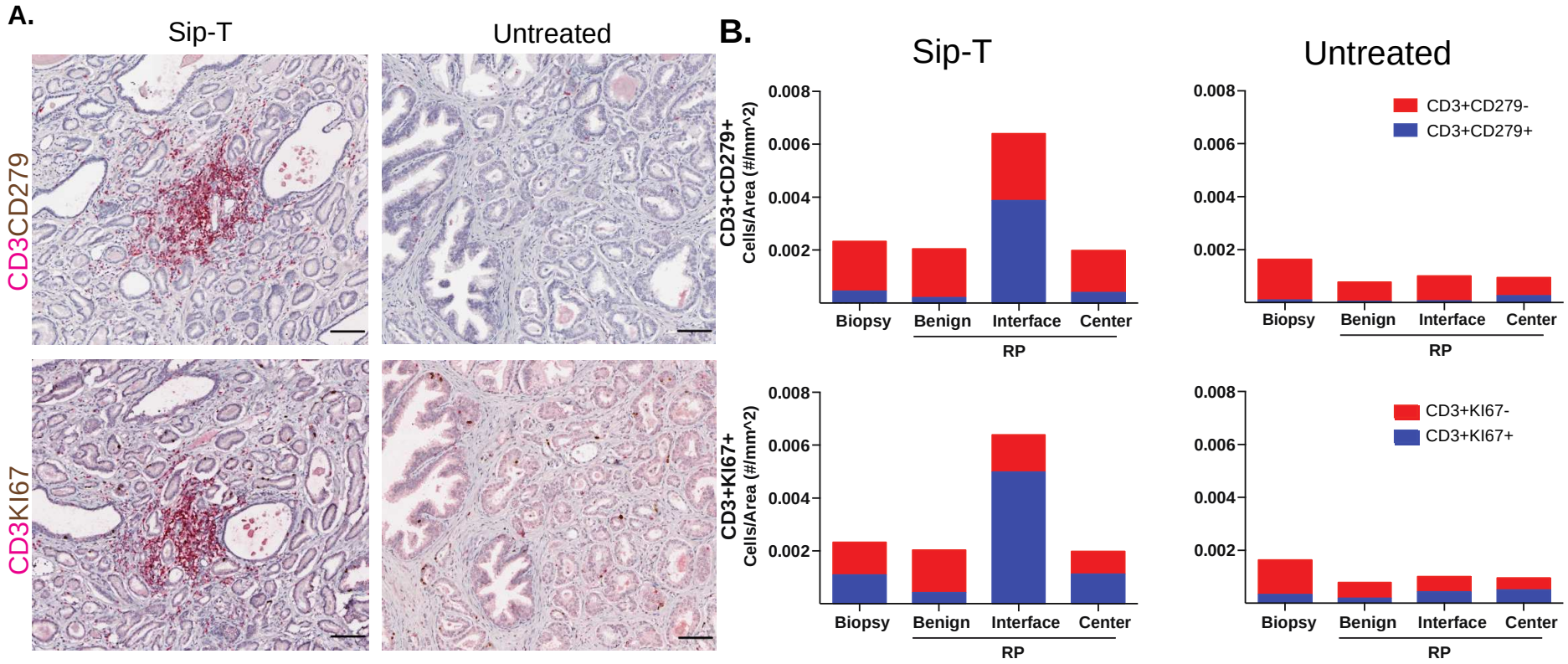
Blood → T Cell responses





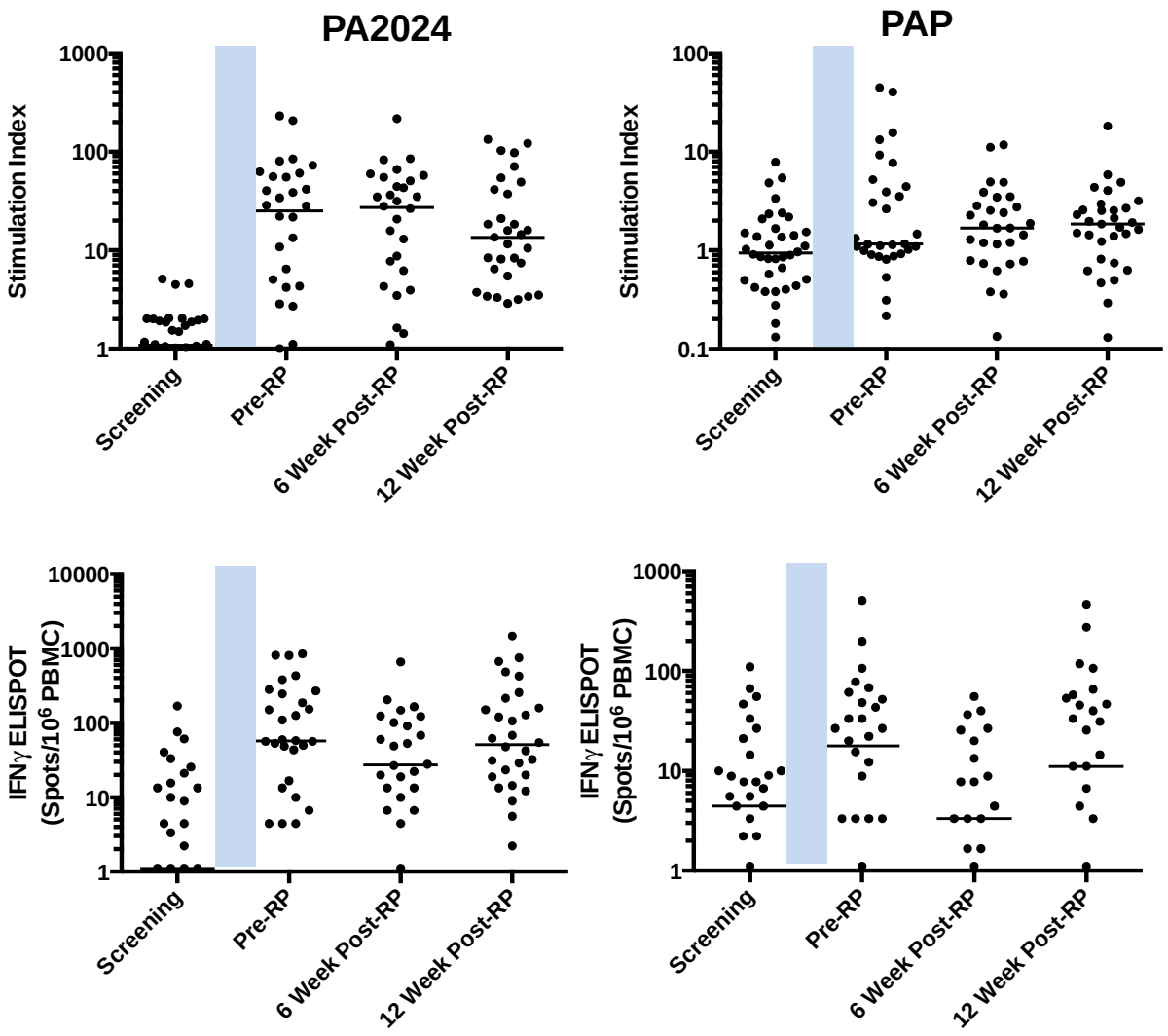
(Fong et al, JNCI 2014)

T cells at the interface express PD-1 and are proliferating



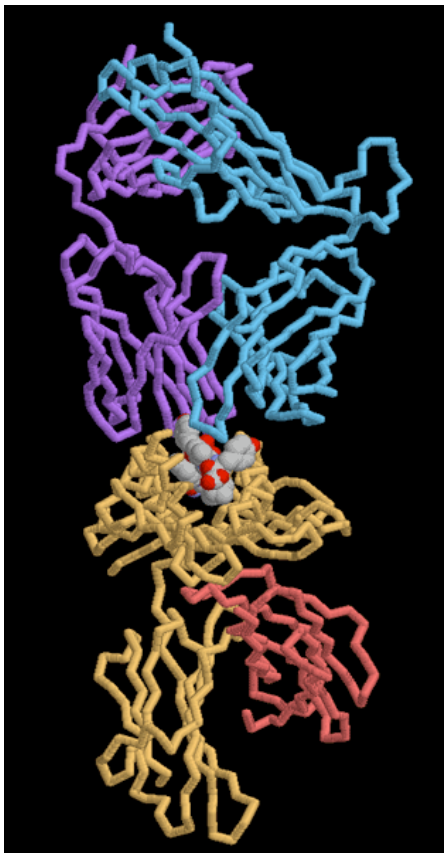
(Fong et al, JNCI 2014)

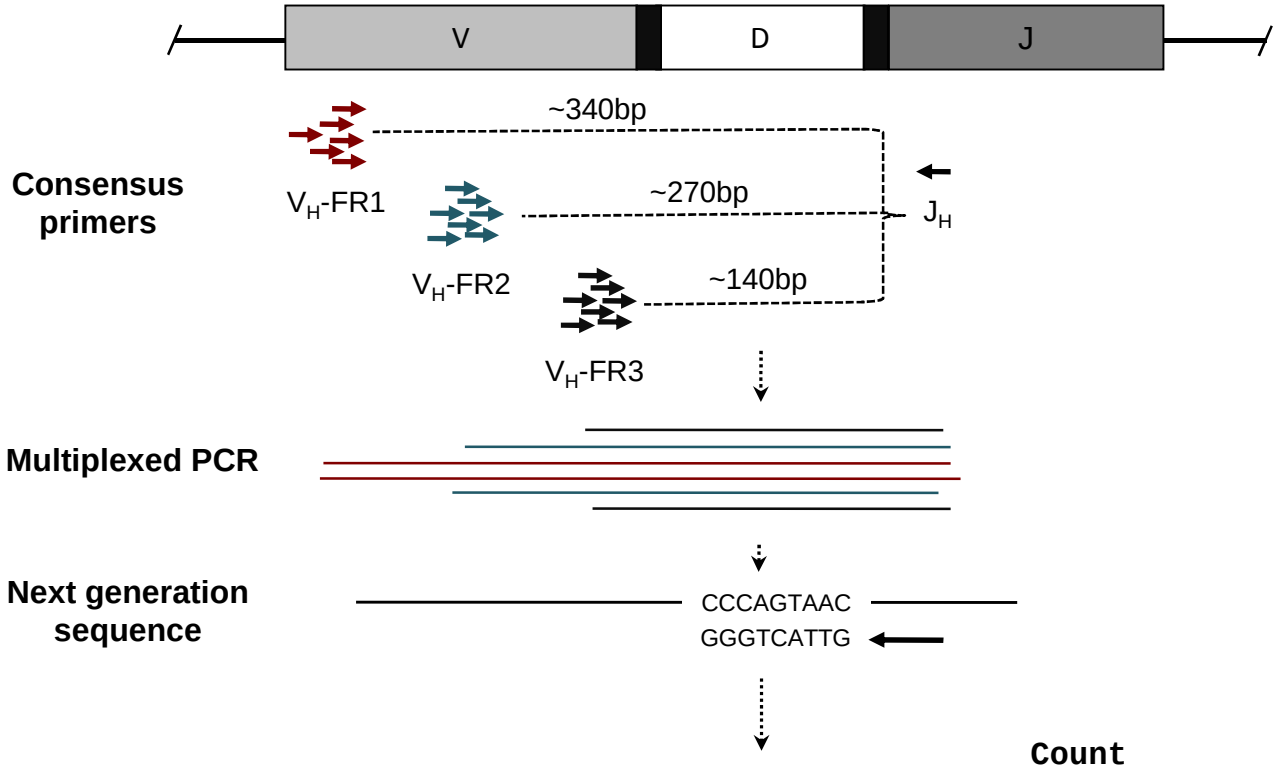
Neoadjuvant Sip-T induces circulating T cell responses



(Fong et al., JNCI 2014)

T cell clonotype tracking by TCRβ sequencing





10^{6}- 10^{8} Independent Sequence Reads Per Run

		Count
1	AAAGCGACATTGGGATCTGTCAGTTGTCATTCGCG	1321
2	GCGGTTTTGTAGAAGGTTAGGGGAATAGGTTAGAT	1122
3	TGAGTGGCTTAAGAATGTAAAATCTGGGATTATAG	901
4	TGTAGTAATCTCTGATTAACGGTGACGGTTTTAAG	534
5	GAAGAATAATTAAGAAAAAAGCACCCCTCGTCGCC	421
6	TAGAATTACCTACCGCGGTCCACCATACCTTCGAT	132
7	TATCGCGCCCACTCTCCCATTAGTCGGCAGAGGTG	113

(adapted from Aaron Logan)

Conclusions

- Neoadjuvant Sip-T recruits CD3 T cells to the tumor interface.
- Sip-T induces narrowing of the circulating T cell repertoire.
- Many of the circulating T cells induced by treatment can be found in the tumor tissue.
- Sip-T leads to a diversification of the T cells in the prostate.

Approaches to cancer immunotherapy

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2) Immune checkpoints
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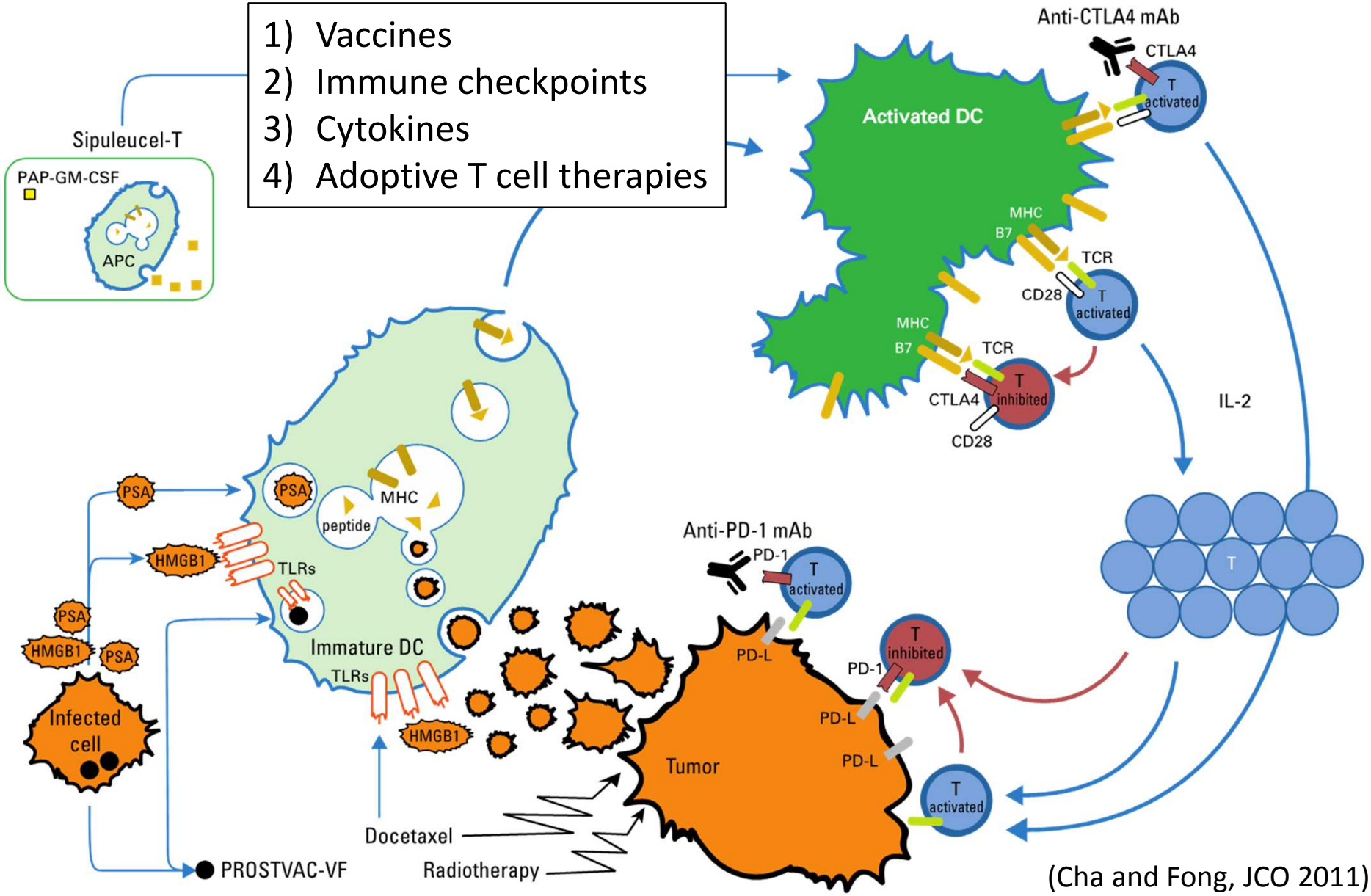
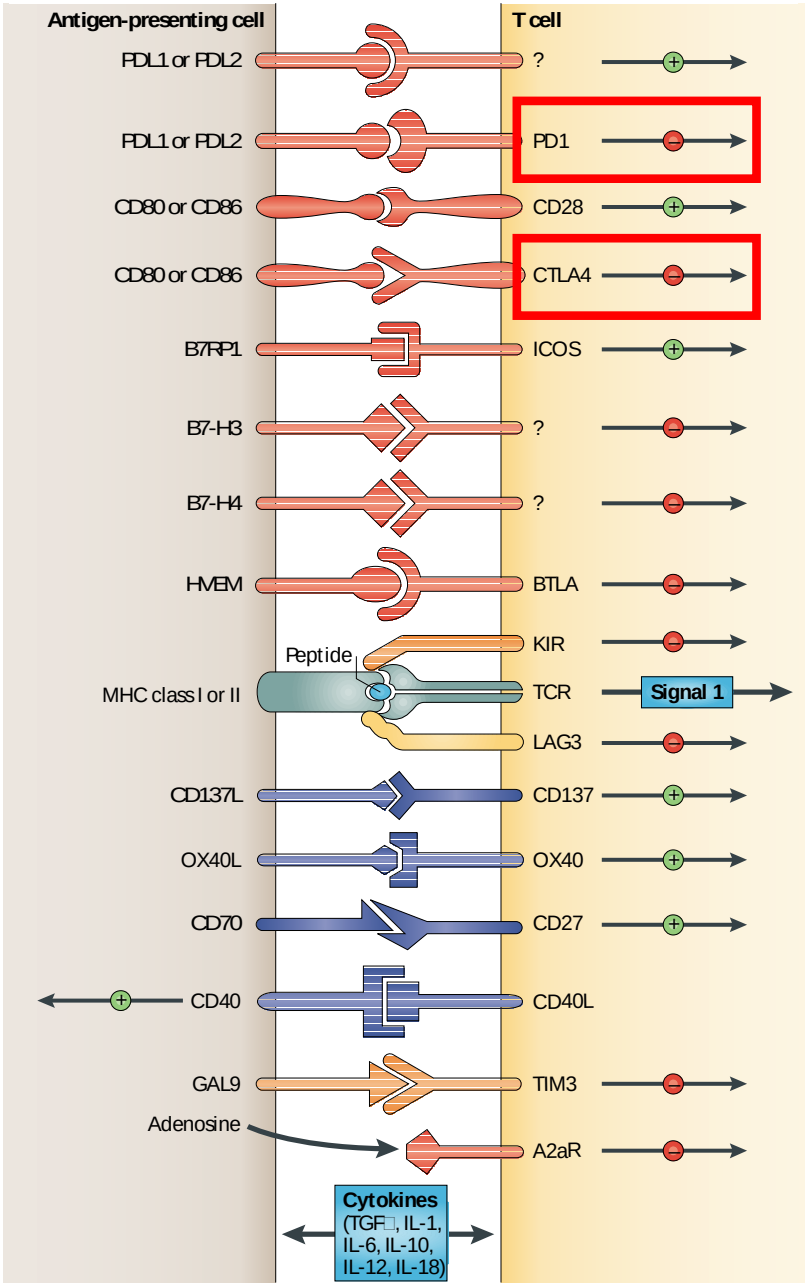


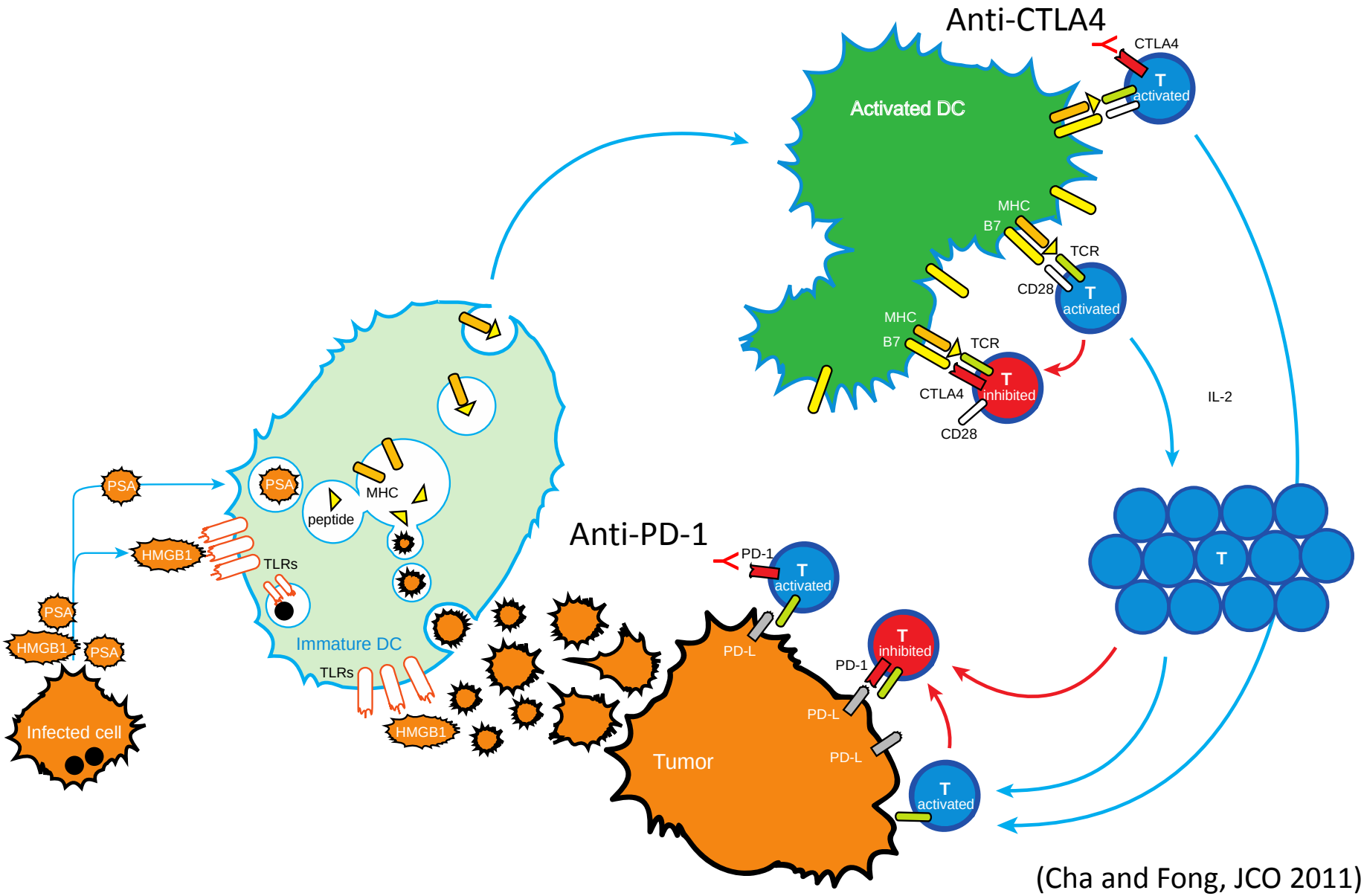
(Cha and Fong, JCO 2011)

Co-stimulation and co-inhibition



(Pardoll. NRC 2012)

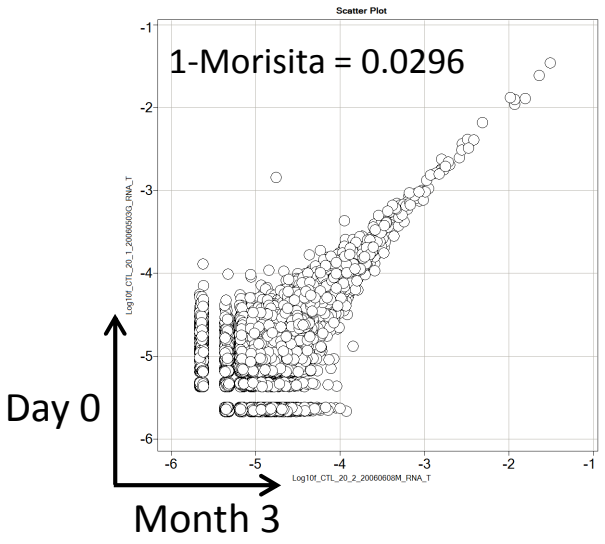
Checkpoint inhibitors rely on immune priming to endogenous tumor antigen



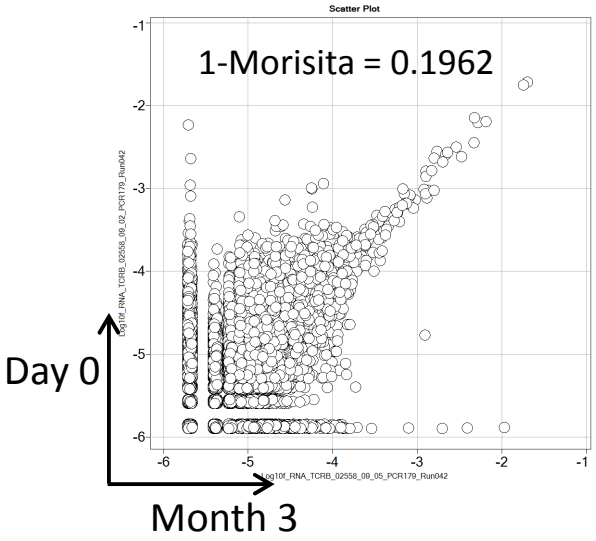
(Cha and Fong, JCO 2011)

CTLA-4 blockade induces remodeling of the T cell repertoire

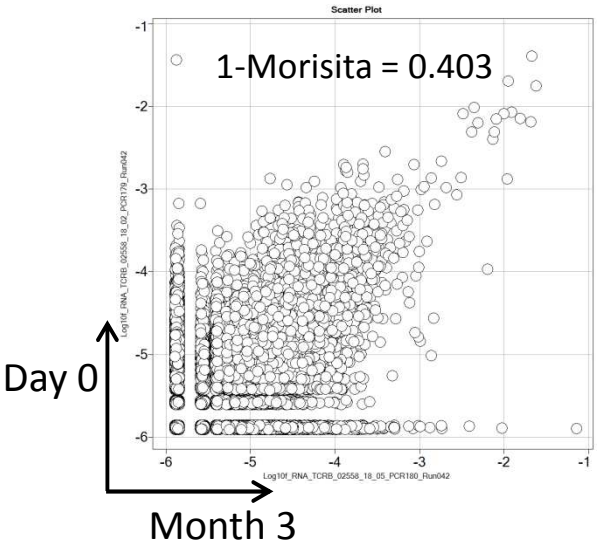
Untreated



Single treatment



3 treatments

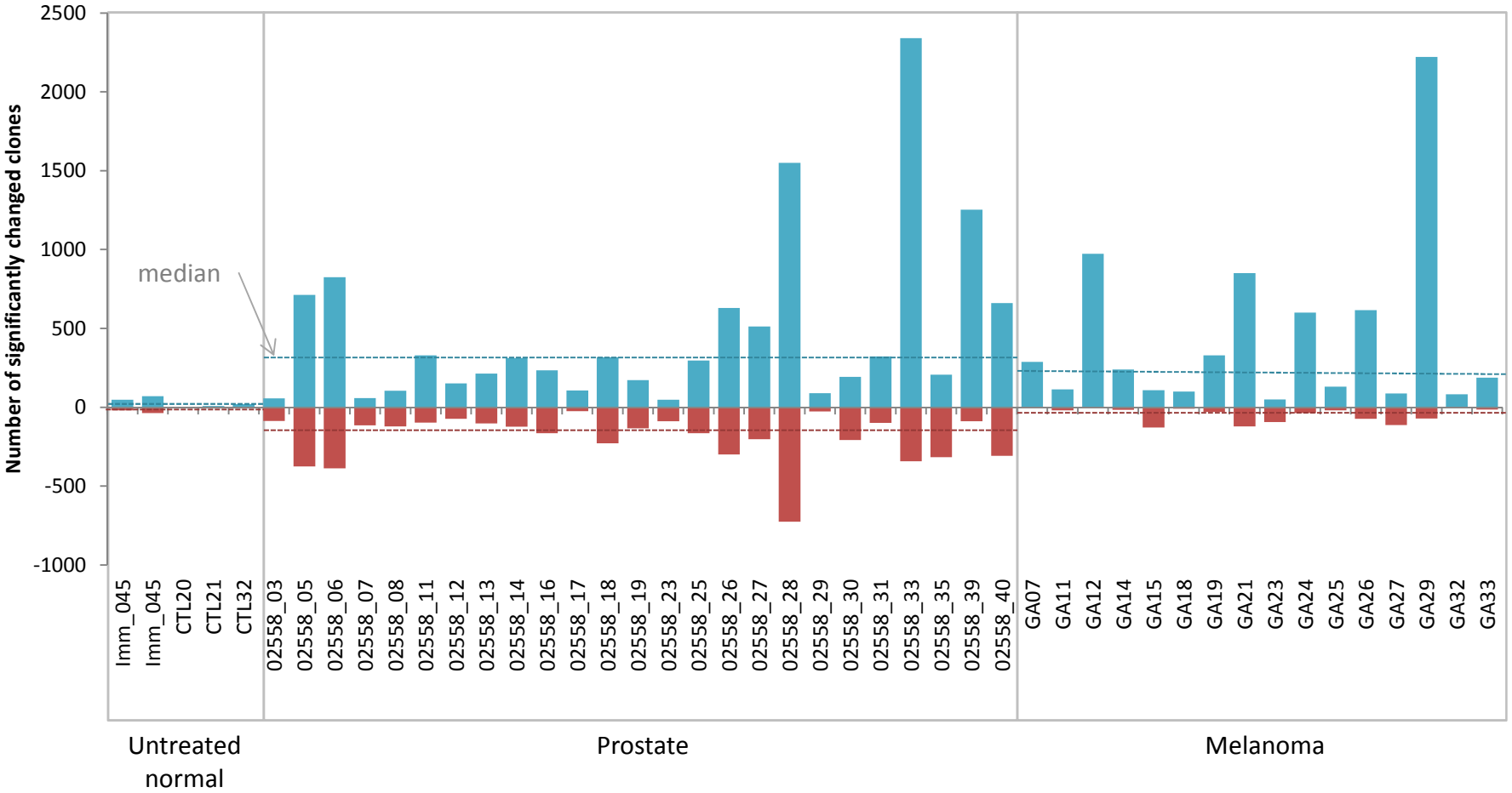


Morisita Distance: 0 (no change)-1

(Cha et al., Science TM 2014)

CTLA-4 blockade increases TCR diversity overall

Number of clones changing in abundance after CTLA-4 blockade (one month)

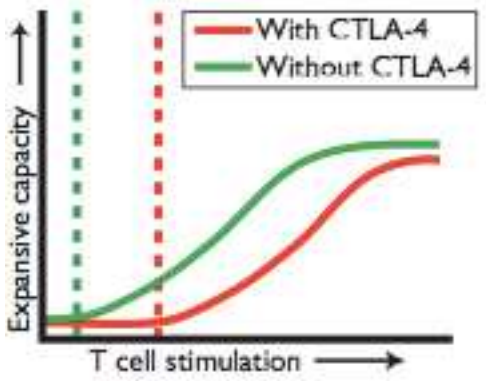


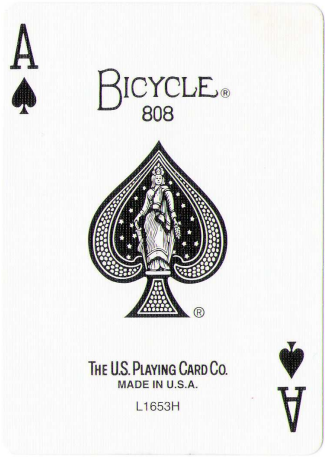
(Cha et al, Science TM 2014)

Model

- Threshold model: CTLA-4 helps set the threshold for T cell activation

  Prediction: Low avidity T cells would be allow to proliferate leading to increased increased TCR diverstiy.





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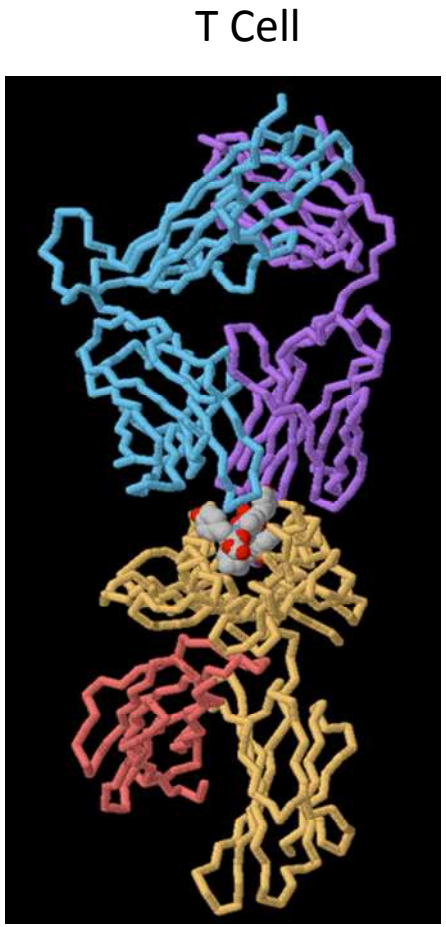
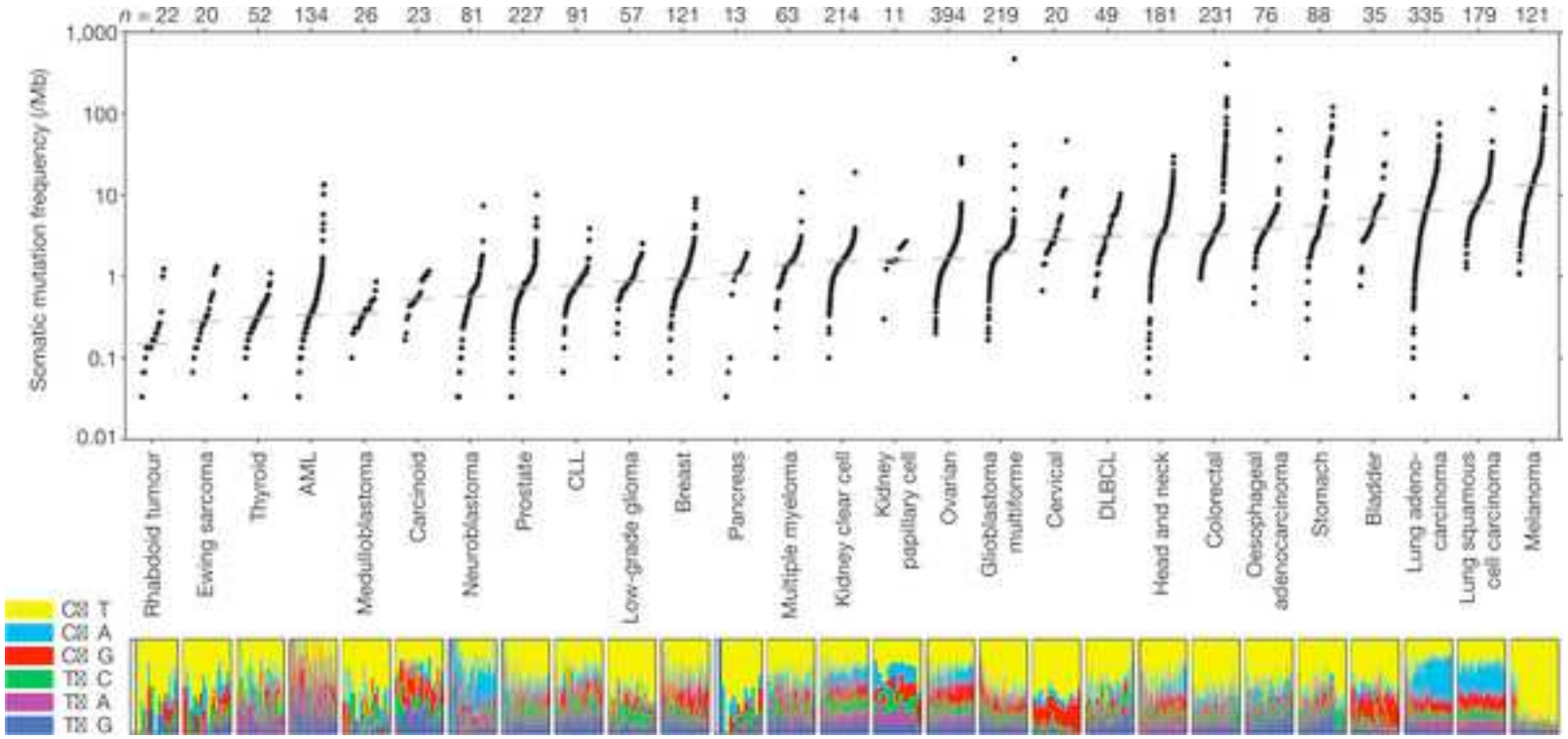
	Tumor specific mutations



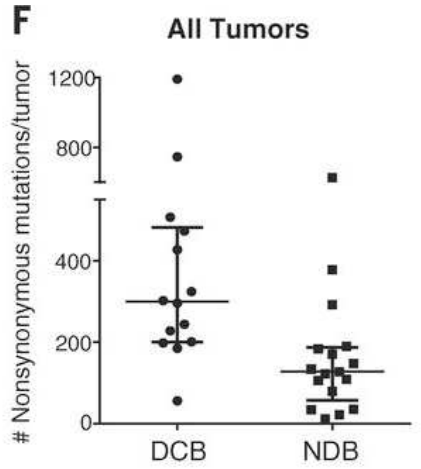
Why are these different cancers responding?

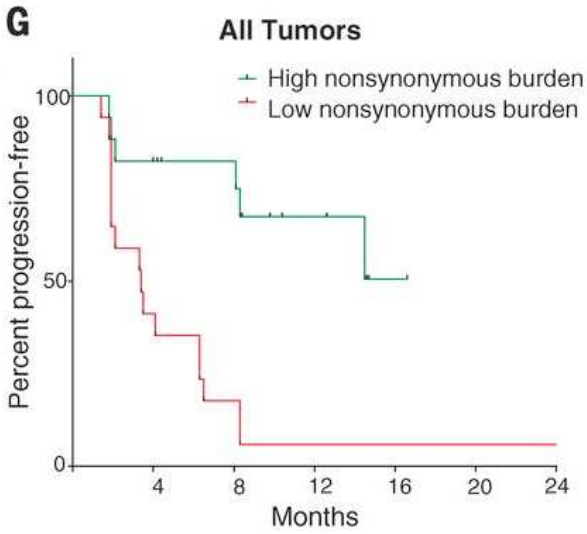


(Lawrence et al, Nat 2014)

Immune response to tumor mutations

- Non-small lung cancer patients treated with anti-PD-1
  - Durable clinical benefit (PR, SD at 6mos) or not
- Whole-exome sequence tumor
  - Enumerate the non-synonymous mutations

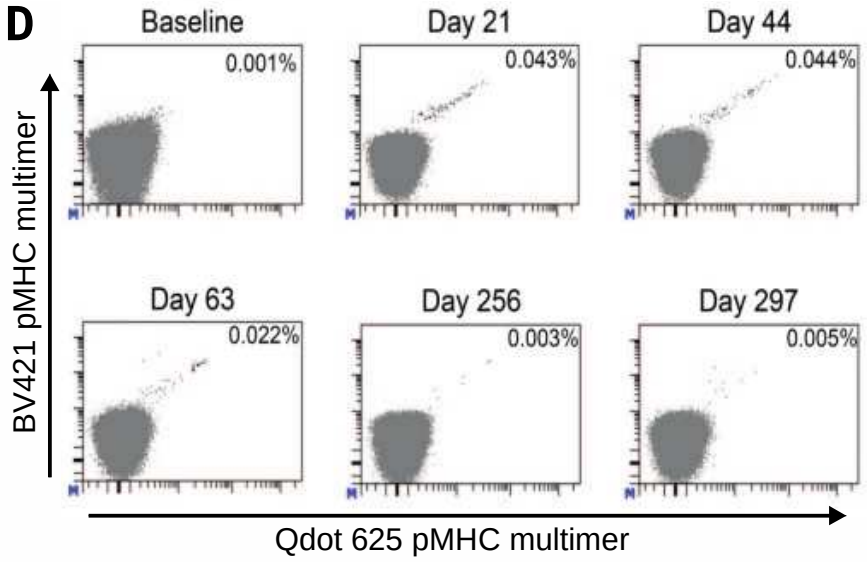




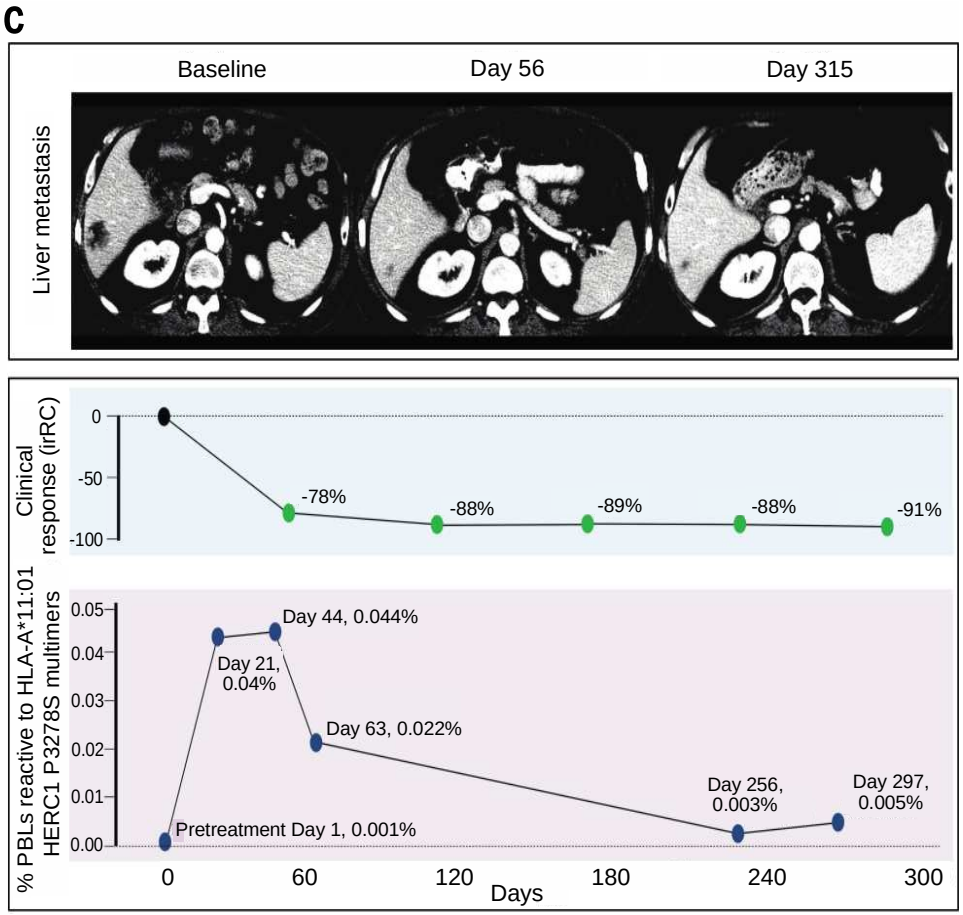
(Rizvi et al. Science 2015)

T cells recognizing neoantigens are expanded with treatment

- Identify candidate “neoantigens” by seeing which mutation will enhance binding to MHC
- Stain for these reactive T cells



WT- ASNAPSAAK
MUT-ASNASSAAK



(Rizvi et al. Science 2015)

Conclusions

- Cancer patients possess a more diverse T cell repertoire.
- CTLA-4 blockade induces remodeling of the T cell repertoire leading to greater T cell diversity.
- Tumor mutations can provide a pool of endogenous antigens against which T cell responses can respond.

Acknowledgements

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Sequenta
Malek Faham
Mark Klinger

Adaptive
David Hamm

Patients and their families.

NCI R01 CA163012
NCI R01 CA194511

Question 1

1) Cancer can stimulate:
   A. CD4 T cells
   B. Regulatory CD4 T cells
   C. CD8 T cells
   D. B cells
   E. All of the above

Question 2

2) Sources of tumor associated antigens can include

A. Differentiation antigens
B. Cancer/testis antgens
C. Overexpressed self antgens
D. Neoantigens derived from tumor associated mutations
E. All of the above