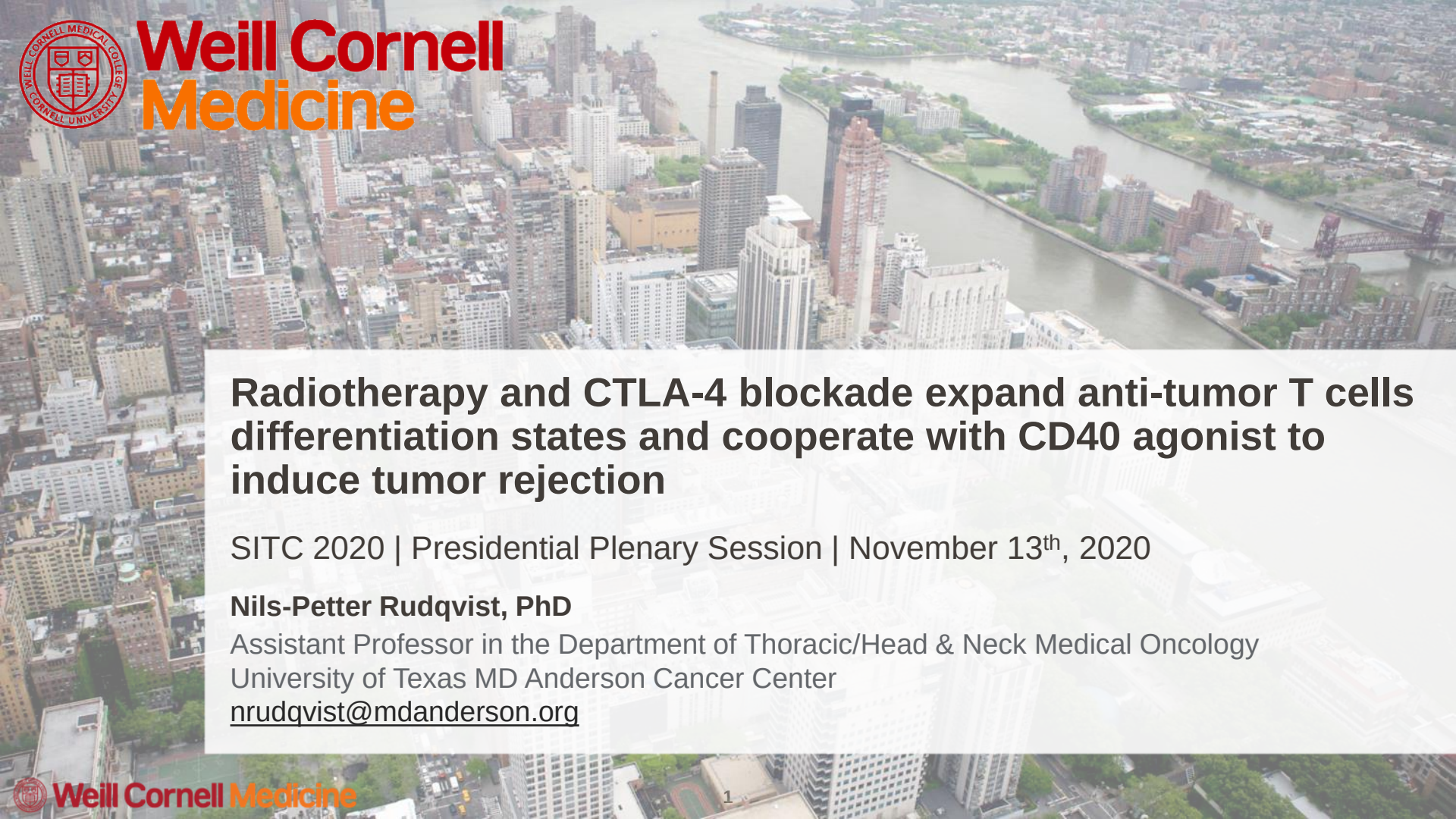


Radiotherapy and CTLA-4 blockade expand anti-tumor T cells differentiation states and cooperate with CD40 agonist to induce tumor rejection

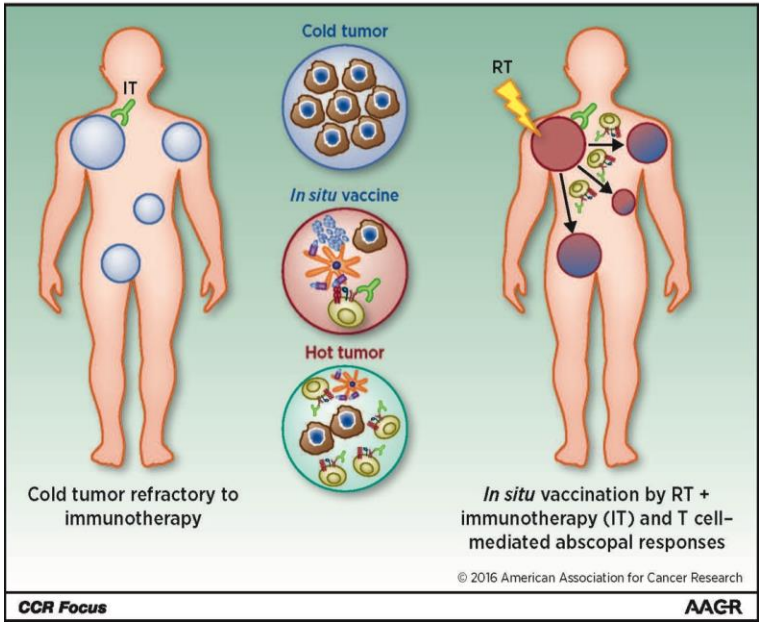
SITC 2020 | Presidential Plenary Session | November 13th, 2020

Nils-Petter Rudqvist, PhD

Assistant Professor in the Department of Thoracic/Head & Neck Medical Oncology
University of Texas MD Anderson Cancer Center
nrudqvist@mdanderson.org

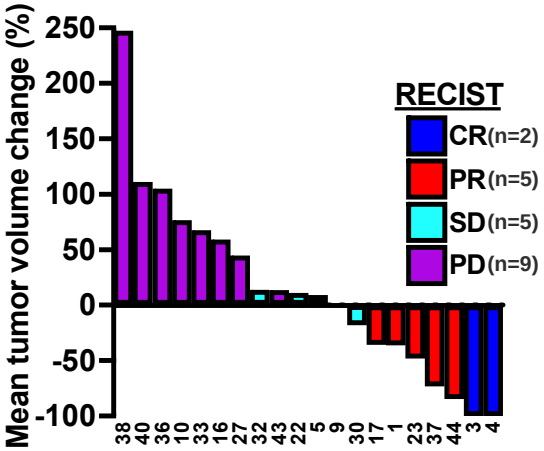
QUESTION

How to improve responses to checkpoint inhibitors?

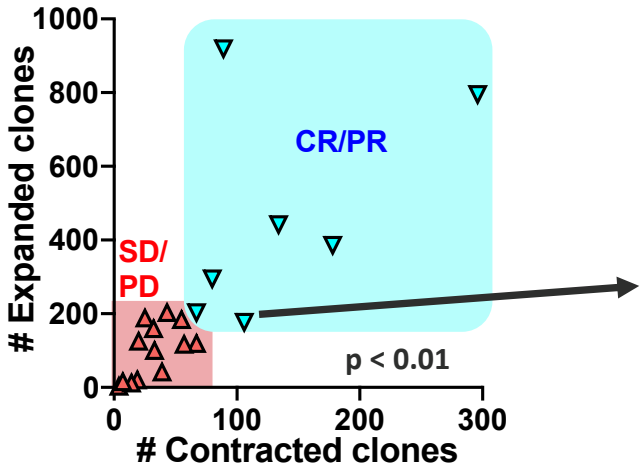


RT + CTLA-4 therapy induced an anti-tumor T cell response and clinical benefit in patients with metastatic NSCLC

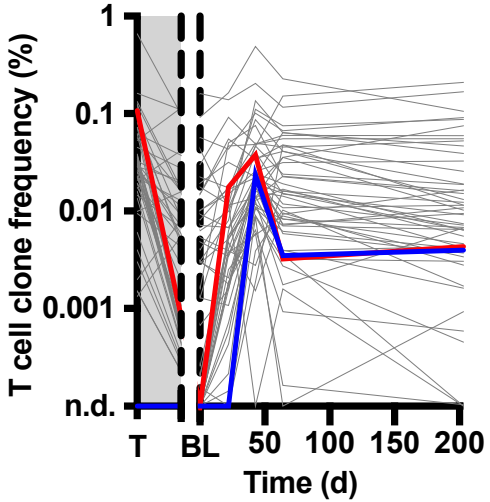
Average abscopal effect
Non-irradiated lesions



Early changes in the peripheral TCR repertoire in CR/PR patients



Anti-tumor T cells not present at baseline in blood of CR patient



HLA-A*24:01-KPNA2$_{peptide15}$
HLA-C*12:03-KPNA2$_{peptide16}$
Expanded TIL-TCRs

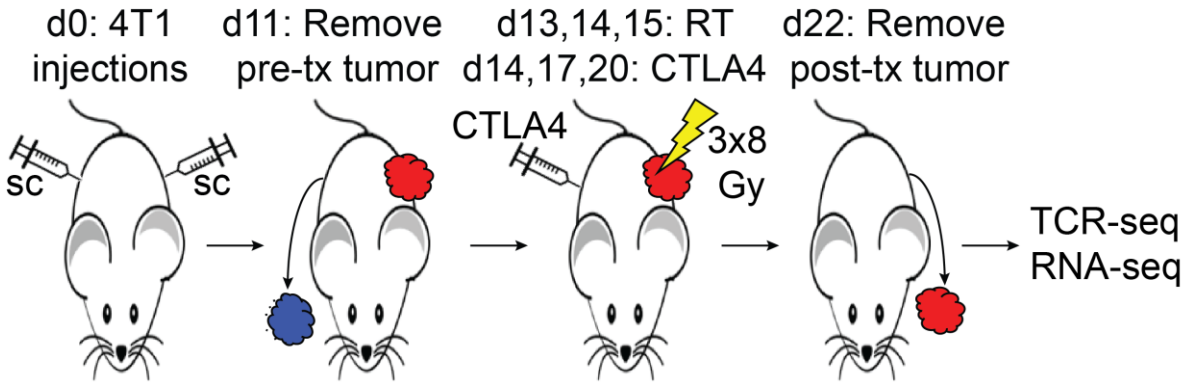
Formenti & Rudqvist, et al., Nat Med (2018)

QUESTION

How does RT + CTLA-4 blockade therapy shape the anti-tumor T cell response?

Investigated the effects of RT+CTLA-4 on the anti-tumor T cell response in 4T1 TNBC mouse model

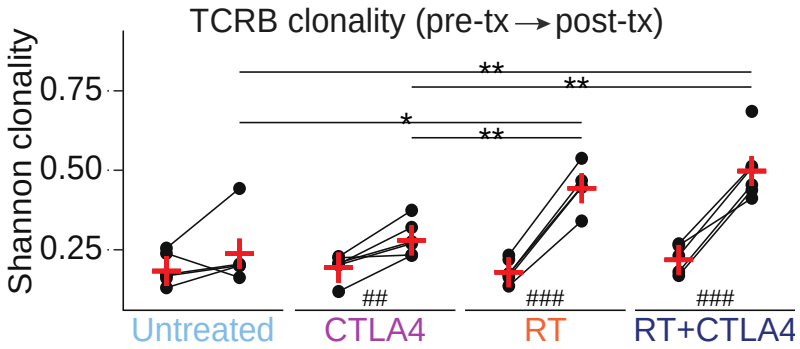
- Effects of RT+CTLA-4 in 4T1 tumors mirrors those in NSCLC
- Mice are treated in a similar way to patients with NSCLC
- Well characterized effects of RT+CTLA-4 in 4T1 tumors



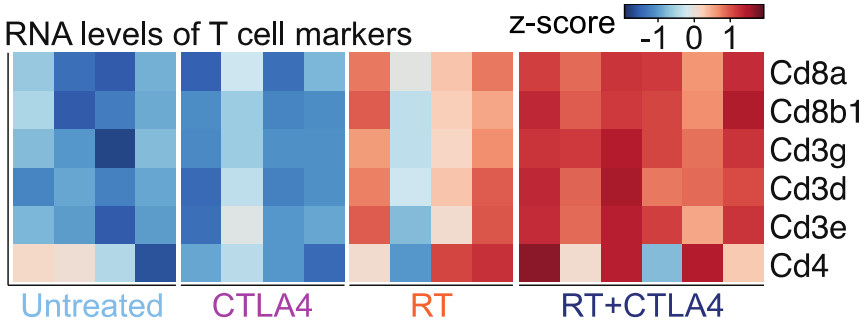
Demaria et al., Clin Cancer Res (2005)
Rudqvist et al., Cancer Immunol Res (2018)
Rudqvist et al., *in preparation*

RT+CTLA-4 therapy induced clonal expansion and infiltration of T cells in tumors

TCR repertoire clonality increased by RT +/- CTLA-4 therapy

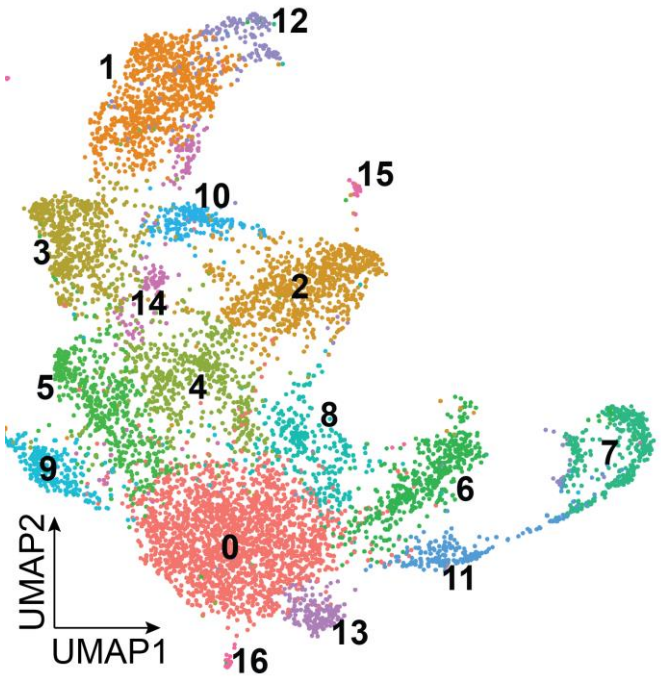


Increased infiltration of T cells in tumors by RT +/- CTLA-4 therapy



Rudqvist et al., *in preparation*

RT+CTLA-4 shifted the T cell compartment towards a Ifng^{+}Cd40lg^{+}Cd4^{+} and Ifng^{+}Tnf^{+}Cd8^{+} phenotype



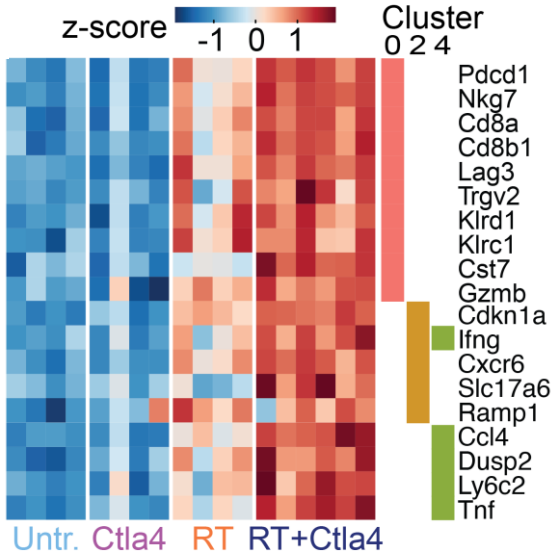
Cluster	Main phenotype	Key genes differentially expressed	Frequency of cells per cluster (%)			
			Untreated	CTLA4	RT	RT+CTLA4
0	Cd8	Gzmb, Lag3, Pd1, Prf1	30.4	17.7	35.4	18.5
1	Tregs	Ctla4, Cd25, Foxp3, Ox40	14.4	12.8	11.1	6.2
2	Cd4	Cd40lg, Ifng	7.1	16.3	3.6	15.0
3	Cd4		11.3	9.1	4.7	5.4
4	Cd8	Cd69, Ifng, Tnf	2.7	6.8	4.5	16.1
5	Cd8	Ly6c	7.3	8.1	5.4	8.1
6	Cd8	Cdk4, Mcm genes	5.8	5.2	8.0	5.1
7	Cd8/Tregs	Cdk and Mcm genes, Ki67	3.8	4.6	5.5	4.5
8	Cd8	Ifng, Lag3	3.3	3.1	3.1	5.6
9	Cd8	Ifn-I genes	2.7	2.4	3.5	4.2
10	Cd4	Il4, Il5, Cd40lg, Gata3	2.0	4.3	1.1	3.1
11	Cd8	Ki67, Survivin	2.0	2.3	4.1	1.9
12	Tregs	Ctla4, Cd25, Foxp3, Ox40	2.7	3.2	2.4	1.4
13	Cd8	Gzm-genes, Prf1	1.8	2.0	3.3	2.2
14	Tregs	Foxp3	1.5	1.4	3.8	2.4
15	Cd4	Cd4, Cd40lg, Il13	0.7	0.4	0.3	0.2
16	Cd8		0.4	0.5	0.3	0.1

Rudqvist et al., *in preparation*

T cell phenotype shifted in the tumors, but magnitude of infiltration important to understand response

Bulk mRNA levels of cluster-specific gene signatures

Bulk RNA-seq from post-tx tumors



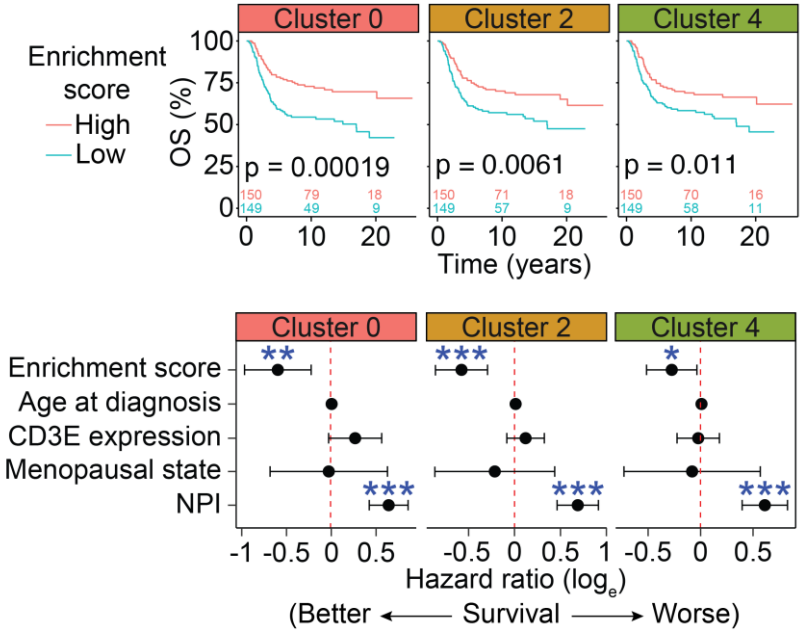
Cluster 0: Gzmb⁺Prf1⁺Pd1⁺Lag⁺Cd8⁺

Cluster 2: Ifng⁺Cd40lg⁺Cd4⁺

Cluster 4: Ifng⁺Tnf⁺Cd8⁺

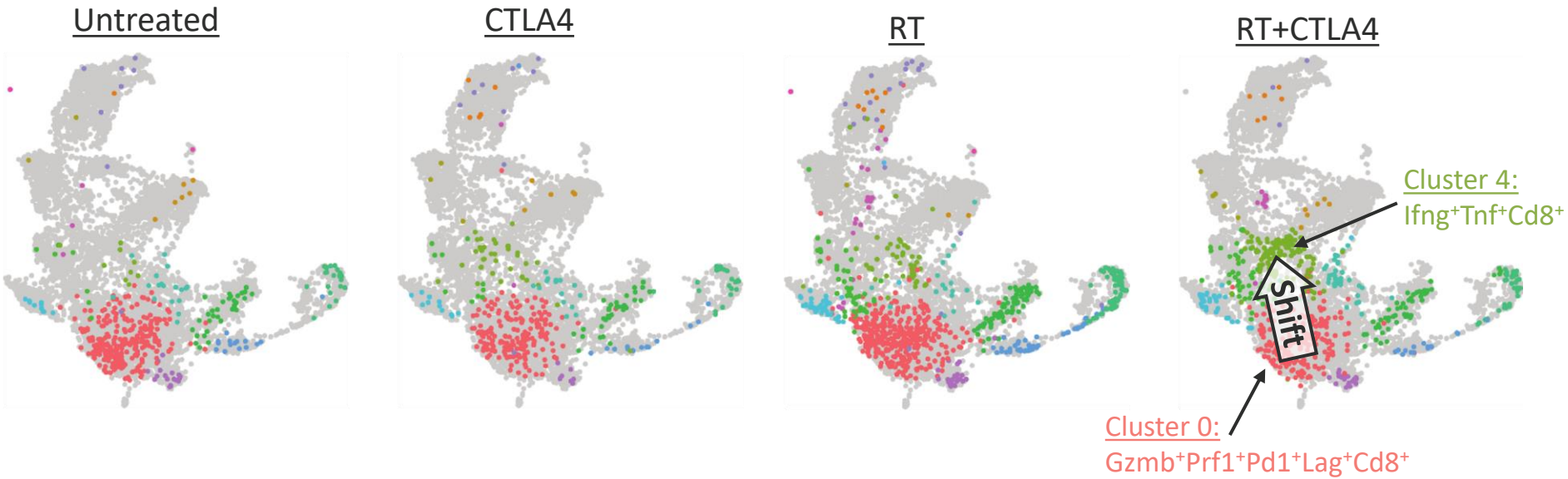
Enrichment of gene signatures in patients' TNBC tumors

METABRIC data



Rudqvist et al., *in preparation*

T cells that recognize the same antigen comes in different flavors (transcriptional states)

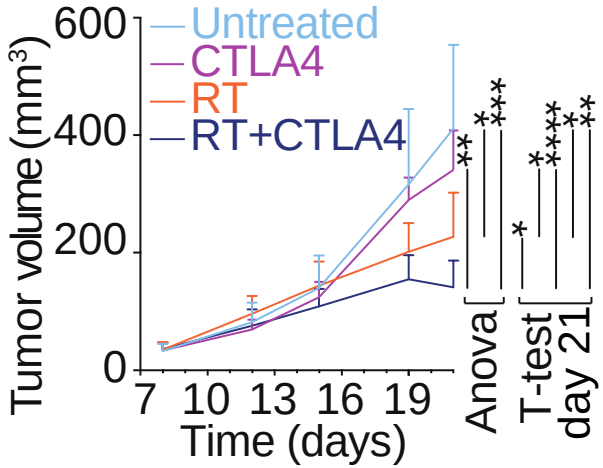


All non-grey T cells are specific to the same tumor-antigen
(The H-2-Ld restricted AH1-epitope; SPSYVYHQF)

Rudqvist et al., *in preparation*

QUESTION

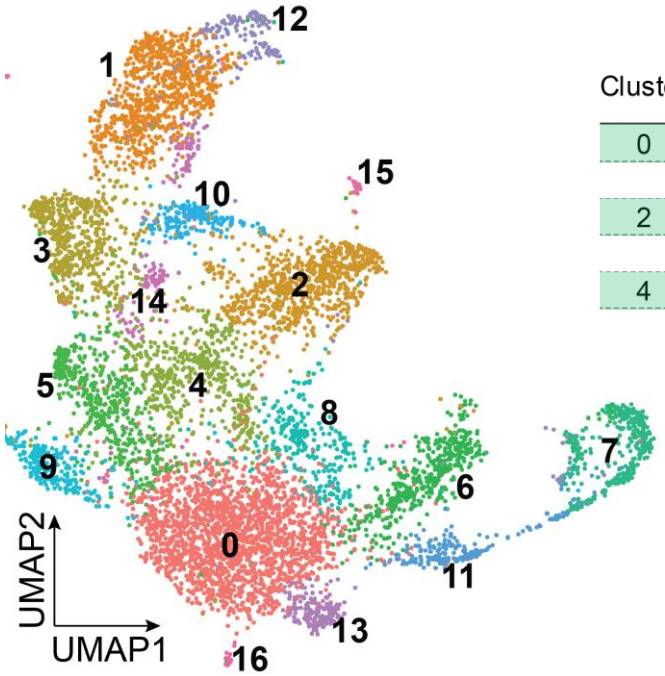
RT+CTLA-4 therapy elicits immune-mediated tumor control but rarely leads to complete rejection of 4T1 tumors



How can we improve it?

Rudqvist et al., *in preparation*

Actionable targets emerging from intratumoral T cell analysis

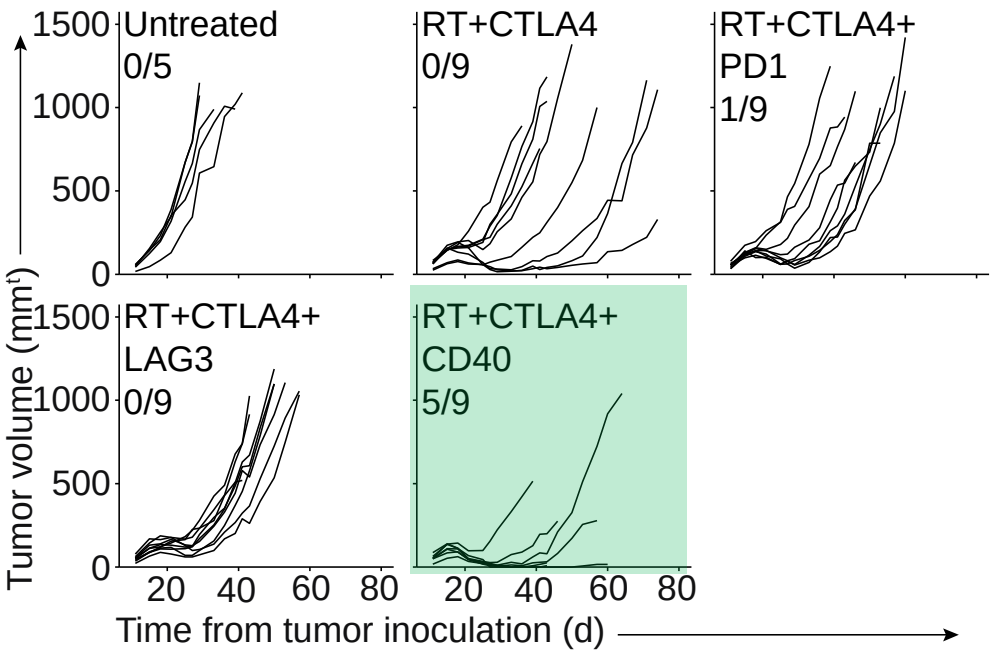


Cluster	Main phenotype	Key genes differentially expressed	Frequency of cells per cluster (%) Untreated	CTLA4	RT	RT+CTLA4	Intervention
0	Cd8	Gzmb, Lag3, Pd1, Prf1	30.4	17.7	35.4	18.5	◄Pd1, Lag3
2	Cd4	Cd40lg, Ifng	7.1	16.3	3.6	15.0	◄Cd40
4	Cd8	Cd69, Ifng, Tnf	2.7	6.8	4.5	16.1	

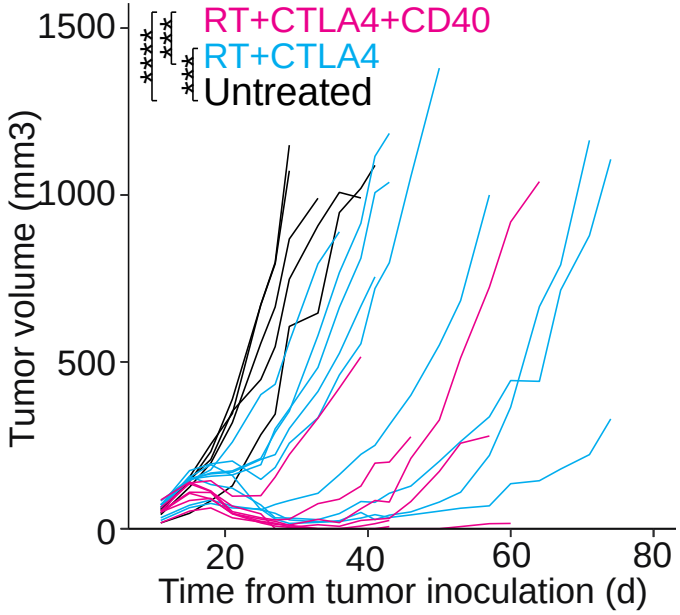
Rudqvist et al., *in preparation*

Only targeting CD40 improved tumor control by RT+anti-CTLA4

Individual tumor growth curves for mice with 4T1 tumors



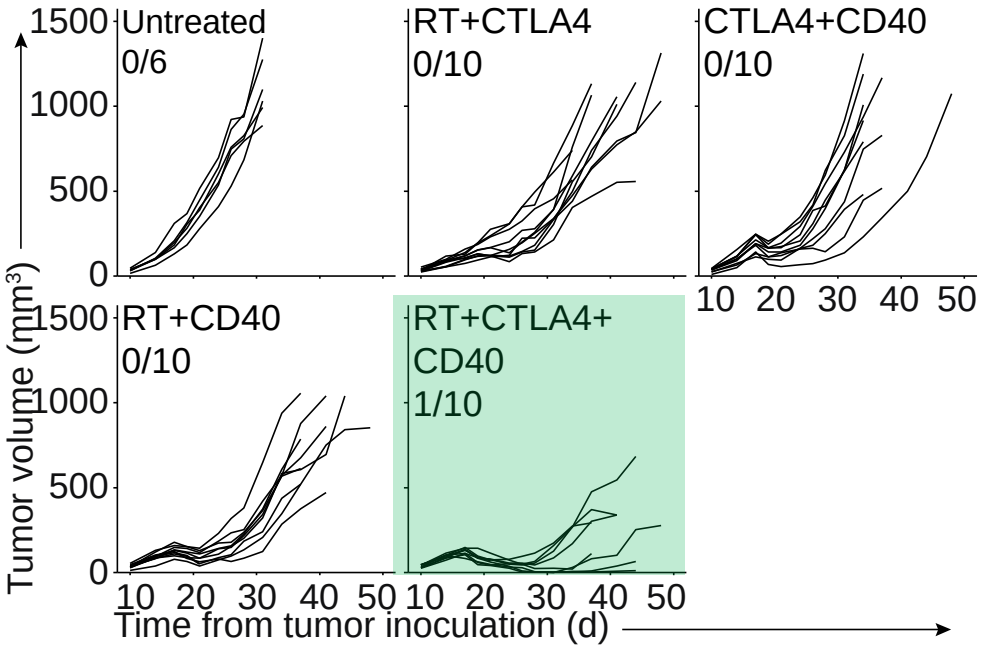
Combined tumor growth curves



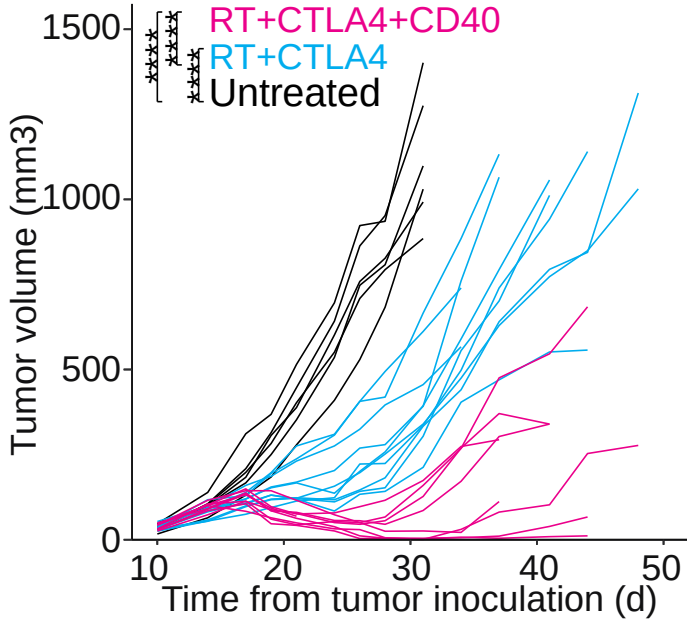
Rudqvist et al., *in preparation*

The triple combination is required for optimal tumor control

Individual tumor growth curves for mice with 4T1 tumors



Combined tumor growth curves



Rudqvist et al., *in preparation*

Conclusions

- RT increases T cell clonality and drives T cells into the tumor
- CTLA-4 blockade “unlocks” Th_1-like phenotype
- Together, RT+CTLA-4 cause a shift in the functional state of tumor-specific CD8 T cells (cytotoxic ⟹ cytokine producers)
- The best combination therapy is not always the most obvious one: anti-CD40 but not anti-PD1 improved tumor control by RT+CTLA-4

Weill Cornell Medicine

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